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ASYMMETRIC HOMOGENEOUS HYDROGENATION USING COMPLEXES OF RHODIUM(I) AND CHIRAL TERTIARY PHOSPHINES

WILLIAM F. MASLER III.

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ASYMMETRIC HOMOGENEOUS HYDROGENATION USING COMPLEXES OF RHODIUM(I) AND CHIRAL TERTIARY PHOSPHINES

by

WILLIAM F. MASLER, III

B. S., Bucknell University, 1969

A THESIS

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This thesis has been examined and approved.

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TO MY WIFE AND PARENTS

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ABSTRACT

ASYMMETRIC HOMOGENEOUS HYDROGENATION WITH RHODIUM(I) COMPLEXES OF CHIRAL TERTIARY PHOSPHINES

by

WILLIAM F. MASLER III

Asymmetric homogeneous hydrogenation with rhodium(I) complexes of chiral tertiary phosphines has been investigated.

Syntheses of the chiral phosphine ligands, (+)-neomenthyldiphenylphosphine (NMDPP), (-)-menthyldiphenylphosphine (MDPP), and (+)-1,2,2-trimethyl-1,3-bis(diphenylphosphinomethyl)cyclopentane (CAMPHOS) via diphenylphosphide displacement reactions are described. The reaction of aldehydes and ketones with diphenylphosphine oxides was explored. This reaction provided an alternate route to (+)-CAMPHOS dioxide. Experiments on the deoxygenation of hindered tertiary phosphine oxides demonstrated that reduction by both lithium aluminum hydride and trichlorosilane-amine mixtures caused fragmentation of the phosphine oxide. Hexachlorodisilane did not readily reduce the phosphine oxides studied.

Tertiary phosphine oxides were converted to tertiary phosphine sulfides via the tertiary phosphine dichloride. The tertiary phosphine sulfides were readily desulfurized

by either lithium aluminum hydride or by tris(dimethylamino)-phosphine to the parent tertiary phosphine.

Asymmetric homogeneous hydrogenations of α,β-unsaturated carboxylic acids with rhodium(I) complexes of (+)-NMDPP, (-)-MDPP, (+)-CAMPHOS, (-)-2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP), and (+)-o-anisylcyclohexylmethyl phosphine (ACMP) were studied.

The reduction substrates included four (Z)- and (E)-isomer pairs. Only with the (+)-NMDPP catalyst was it possible to define any obvious relationship between substrate structure and the absolute configurations of the products.

Product optical purities as high as 62% were recorded with the (+)-NMDPP catalyst. The chemical and optical yields of reduction products were generally lower with the (-)-MDPP catalyst than with the (+)-NMDPP catalyst.

The (+)-CAMPHOS catalyst readily reduced nearly all of the substrates employed, however, product optical purities were low. A rationale has been proposed to account for this observation.

The results of hydrogenations of the substrates with chiral catalysts prepared from (-)-DIOP, and (+)-ACMP have been presented for comparison of those ligands with (+)-NMDPP, (-)-MDPP, and (+)-CAMPHOS.

INTRODUCTION

The stereospecificity of biochemical transformations has long been a fascinating aspect of organic chemistry. Whereas the organic chemist is normally limited to the synthesis of racemic mixtures, biochemical systems are uniquely able to carry out reactions which are specific for a particular enantiomer.

For more than seventy years, chemists have attempted to accomplish asymmetric synthesis* without resorting to naturally occurring enzymes. Much of the pioneering work in asymmetric synthesis was performed by McKenzie who studied the addition of Grignard reagents to chiral esters of α-keto acids.[2] The results of these and other early studies were not interpreted satisfactorily until the work of Doering and Young[3], Mosher and LaCombe[4a,b], and later Prelog[5], and Cram and Abd Elhafez[6] had laid the foundation for a more rational understanding of the stereochemical course of asymmetric organic reactions.[7]

Since the early 1950's work on asymmetric synthesis has increased dramatically and this has added a new dimension to the array of synthetic techniques available to the organic chemist. Until recently, virtually every synthesis of an

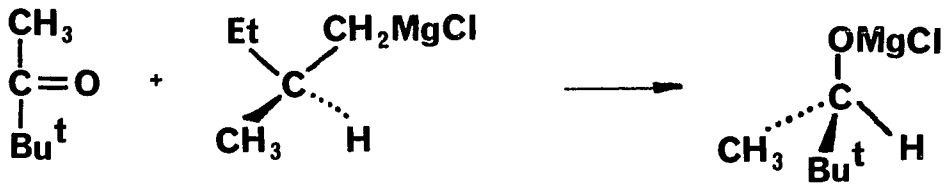
---

*Asymmetric synthesis has been defined as a reaction in which an achiral unit in an ensemble of substrate molecules is converted by a reactant into a chiral unit in such a manner that the stereoisomeric products are produced in unequal amounts. For almost all cases this amounts to saying that a prochiral unit is converted to a chiral unit.[1]

optically active natural product has required the often tedious and wasteful procedure of separating one stereoisomeric form by physical methods. In principle, asymmetric synthesis offers an attractive alternative procedure, that is, to introduce the correct chirality as the molecule is constructed.

Many of the available asymmetric synthetic techniques suffer the disadvantage that the chiral reagent is destroyed in the formation of the new chiral center. Asymmetric Grignard and Meerwein-Pondorf-Verley (MPV) reductions are examples where there is loss of chirality in the reagent (Figure 1). Catalytic asymmetric syntheses surmount the disadvantage associated with asymmetric syntheses in which the reagent chiral center is destroyed. Catalytic asymmetric syntheses also offer potential advantages over stoichiometric asymmetric syntheses, even those in which the chiral reagent can be recovered and recycled. Especially attractive are the related economic and environmental features that only a small investment of expensive chiral material is necessary and equally important, stoichiometric amounts of by-products are not produced. As chemists gain more insight into asymmetric synthesis, it should be possible to design and synthesize chiral catalysts which rival enzymes in their efficiency.

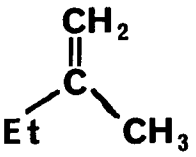
The development of chiral homogeneous hydrogenation catalysts has been a significant recent development in asymmetric synthesis. In order to more fully appreciate aspects of asymmetric hydrogenations using chiral homogeneous catalysts, it is important to consider what is known about

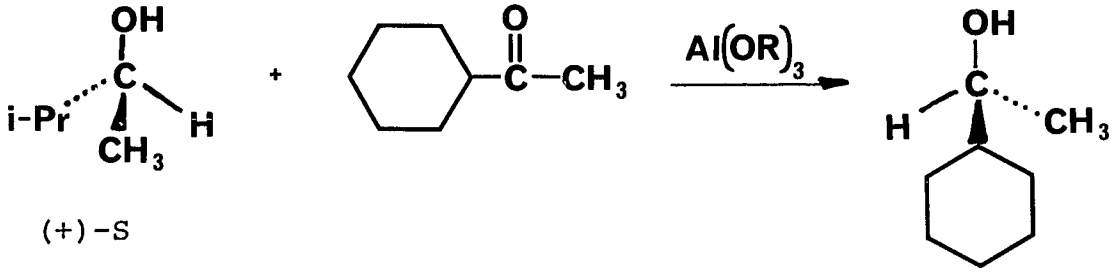


(+)-S

(+)-S
12% ee*

Asymmetric Grignard Reduction[2]





(+)-S

(+)-S
22% ee*

Asymmetric MPV Reduction[2]

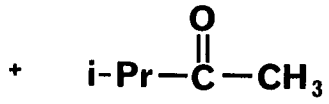


Figure 1. Asymmetric syntheses in which reagent chirality is lost.

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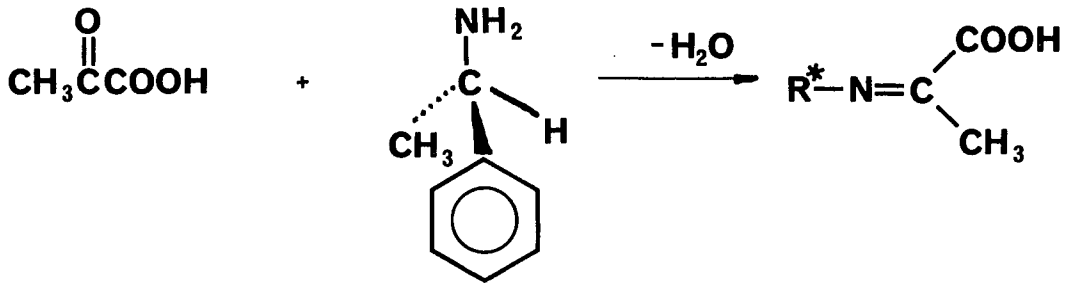
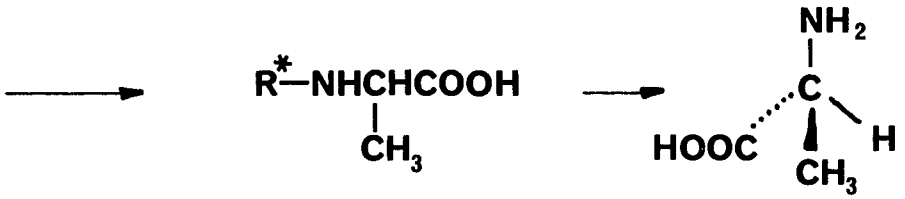
*The % ee is defined as %R-%S or vice versa.

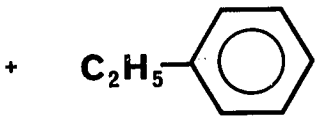
Figure 1. (continued)



(-)-S



Asymmetric Hydrogenolytic Transamination (+)-S, 81% ee



the mechanism and scope of hydrogenations in the presence of achiral homogeneous catalysts.

HISTORICAL

Nonenzymatic achiral homogeneous hydrogenation was first reported in 1938 by Calvin[8] who observed that chelate compounds of copper, cupric acetate and cuprous salicylaldehyde, in quinoline were catalysts for the homogeneous hydrogenation of the cupric ion and also quinone.[9] A year later Iguti made the discovery that the unstable rhodium complexes $[Rh(NH_3)_5(H_2O)]Cl_3$ and $[Rh(NH_3)_4Cl_2]Cl$ were able to activate molecular hydrogen.[10] Quinone was hydrogenated in aqueous solutions of the unstable complexes, but stable rhodium complexes such as $[Rh(NH_3)_6]Cl_3$ and $[Rh(en)_3]Cl_3$ had no activity. Rhodium trichloride was found to catalyze the reduction of quinone, fumaric acid, methylene blue, sodium nitrite, and hydroxylamine. The results of Iguti's study are suspect, however, as traces of metallic rhodium deposited under the reduction conditions could have caused the observed reductions.

Many of the early studies on homogeneous catalysis dealt with the "oxo" process, a hydroformylation reaction in which an olefin reacts with hydrogen and carbon monoxide in the presence of a cobalt metal catalyst or dicobalt octacarbonyl to give aldehyde products.[11]

$$RCH{=}CH_2 + H_2 + CO \xrightarrow{\text{catalyst}} RCH_2CH_2CHO$$

The catalyst was also found to reduce the carbon-carbon double bond of certain α,β-unsaturated compounds.

Evidence that the reduction process was homogeneous was provided by the observation that, unlike the usual heterogeneous catalysts, the cobalt catalyst in the "oxo" process was not poisoned by divalent sulfur.[8] Further evidence has been obtained to indicate that $Co_2(CO)_8$ is the effective catalyst in the hydroformylation process, moreover, that $Co_2(CO)_8$ reacts with molecular hydrogen to form hydridocobalt tetracarbonyl which has been shown to react with olefins to give aldehydes.[12,13,14]

$$Co_2(CO)_8 \xrightarrow{H_2} 2\ HCo(CO)_4$$

Many homogeneous hydrogenation reactions are known to occur in aqueous solution. For example, aqueous solutions of cobaltous cyanide readily absorb hydrogen at room temperature to the extent of approximately one hydrogen atom per cobalt atom. This system can effect the homogeneous hydrogenation of cinnamic acid and isatin and could also hydrogenate cyanide ion to methylamine.[15,16] This and other aqueous homogeneous hydrogenation systems are severely limited in applicability since only substrates with appreciable water solubility can be readily reduced.

Other homogeneous hydrogenation systems are known. Ethyleneplatinous chloride functions as a homogeneous catalyst at temperatures below -10° where ethylene is hydrogenated to ethane.[17] Homogeneous hydrogenation of the

ferric to the ferrous ion was observed for acidic solutions of rhodium(III).[18]

The homogeneous hydrogenation reaction, with the exception of the "oxo" process was more of an academic curiosity than a synthetically useful technique until the discovery in 1964 by Wilkinson and coworkers that 1,2,6-trichlorotripyridinerhodium(III) in aqueous pyridine solution was isomerized to trans-$[Rh(C_5H_5N)_4Cl_2]Cl$ in the presence of molecular hydrogen. A metal hydride intermediate was suggested as being involved. This hypothesis was supported by the observation that ethanol solutions of either rhodium trichloride or 1,2,6-trichlorotripyridinerhodium(III) containing 1-hexene took up hydrogen at room temperature and one atmosphere of pressure with the conversion of 1-hexene to n-hexane. The homogeneous nature of the reaction was demonstrated by the observation that sudden changes in the rate of reduction occurred if any metallic rhodium was formed.[19]

A more efficient catalytic system was obtained by forming the catalytic rhodium complex with a π acceptor ligand stronger than pyridine. In their initial studies, the Wilkinson group synthesized rhodium(III) complexes stabilized by triphenylphosphine. During the preparation of the rhodium(III)-triphenylphosphine complex it was found that when an excess of ligand was used, a rhodium(I) complex, $(Ph_3P)_3RhCl$ resulted. Tris(triphenylphosphine)rhodium(I) chloride and the corresponding bromide and iodide have

proven to be among the most effective homogeneous hydrogenation catalysts yet developed.[22]

Mechanism of Homogeneous Hydrogenation

Tris(triphenylphosphine)rhodium(I) chloride in benzene-ethanol solution at 25° was reported to activate molecular hydrogen at atmospheric pressure and was shown to give rapid reduction of 1-hexene and 1-hexyne.[20,21] Further studies by Wilkinson and coworkers demonstrated that isolated olefinic and acetylenic linkages were readily reduced.[22,23,24] The mechanism was considered in some detail, and a mechanism based on prior dissociation of the tris(triphenylphosphine)-rhodium(I) halide into a solvated complex and triphenylphosphine was initially postulated (Figure 2). Molecular weight measurements in benzene or chloroform suggested that tris-(triphenylphosphine)rhodium(I) chloride (1) dissociated reversibly to a solvated species 2 which slowly dimerized.

$$\underset{\underline{1}}{(Ph_3P)_3RhCl} + Solvent\ (S) \rightleftharpoons \underset{\underline{2}}{(Ph_3P)_2RhCl(S)} + Ph_3P$$

$$2\ \underset{\underline{2}}{(Ph_3P)_2RhCl(S)} \longrightarrow [(Ph_3P)_2RhCl]_2 + 2S$$

Figure 2. Dissociation and dimerization of Wilkinson's catalyst.

The view of dissociation taken by Wilkinson has been challenged by a number of groups. Shriver and coworkers[25] found that if molecular oxygen was excluded, tris-(triphenylphosphine)rhodium(I) chloride was not dissociated in benzene at concentrations from 2.4-5.8 x 10^{-3} M nor was it dissociated in dichloromethane at 3 x 10^{-2} M. Nuclear magnetic resonance (nmr) measurements have established that dissociation of $(Ph_3P)_3RhCl$ is very slight. Fourier transform nmr techniques have established that in a 5 x 10^{-2} M solution of $(Ph_3P)_3RhCl$ in CH_2Cl_2 dissociation took place only to the extent of about 3%.[26] Eaton and Suart obtained similar results.[27] Spectrophotometric measurements of benzene solutions of $(Ph_3P)_3RhCl$ allowed Arai and Halpern to calculate a dissociation constant of 1.4 ± 0.4 x 10^{-4} M at 25°.[28]

Wilkinson and coworkers postulated a mechanism for hydrogenation of alkenes and alkynes based on kinetic data for the reduction of 1-heptene, cyclohexene and 1-hexyne. They postulated a mechanism involving the dissociated, solvent saturated species $(Ph_3P)_2RhCl(S)$ as a key intermediate.

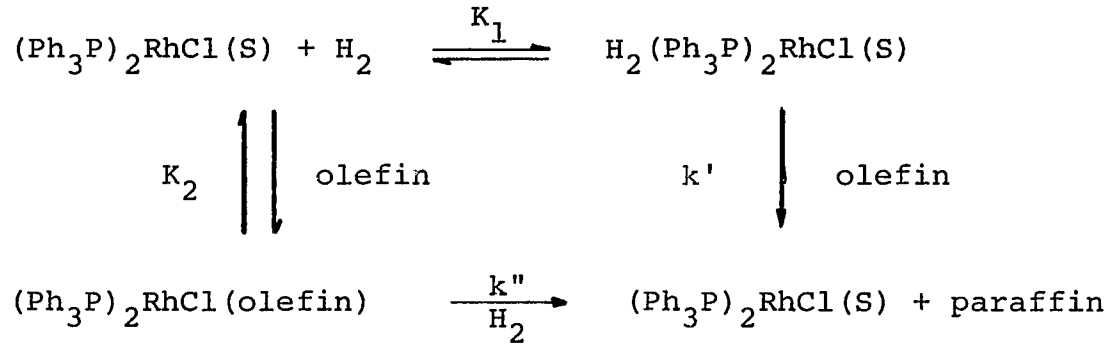


Figure 3. A proposed mechanism for hydrogenation by Wilkinson's catalyst.

It was envisioned that the rate-determining step could be either one or both of the two pathways shown in Figure 3. The olefin could add to the dihydride complex via the k' path, or, as it is usually described, a "hydride mechanism; alternatively hydrogen could add to the olefin complex via a so called "unsaturated mechanism" (k" path).

The Wilkinson group reported that the ethylene complex, $(Ph_3P)_2RhCl(C_2H_4)$, showed no reaction with hydrogen.[22] Osborn reported similar results with the analogous allene complex, $(Ph_3P)_2RhCl$(allene). On this basis it was concluded that the "unsaturate route" was unimportant.

Contrary to the reports of Wilkinson, Candlin and Oldham found that, indeed, the ethylene complex did catalyze the hydrogenation of olefins and acetylenes at rates comparable to those found for $(Ph_3P)_3RhCl$ (Table 1).[29] This was taken as evidence in support of the "unsaturate" mechanism. These workers observed stoichiometric reduction

Table 1. Relative rates of hydrogenation of olefins with two catalysts.

Substrate	Catalyst	
	$(Ph_3P)_3RhCl$	$(Ph_3P)_2RhCl(C_2H_4)$
	Rate	Rate
Cyclopentene	1.0[a]	1.05[a]
1-Hexene	0.45[a]	0.60[a]
Ethylene	1.0[b]	0.95[b]

a) The rates of reduction are normalized so that the rate of reduction of cyclopentene over $(Ph_3P)_3RhCl$ = 1.

b) The rates of reduction are normalized so that the rate of reduction of ethylene over $(Ph_3P)_3RhCl$ = 1.

$H_2(Ph_3P)_2RhCl(S)$

3

of 1-hexyne and 1-octene when using the preformed dihydride species 3. This observation was taken as evidence supporting the "hydride route" as a viable mechanistic pathway.[29]

Competition experiments have been used to probe the mechanism of hydrogenation.[29] It was noted that under a standard set of conditions, a series of terminal alkenes ranging from C_6 to C_{12} showed a relative rate of hydrogenation of 1.0 while C_6 to C_8 terminal alkynes showed relative rates of 0.85, yet when a mixture of 1-octene and 1-hexyne was hydrogenated in benzene, the alkyne was reduced 1.7 times as rapidly as the alkene. Individual rates, then, cannot be used to predict which substrate in a mixture will hydrogenate most rapidly. Of prime importance are the K values (Figure 3) for the complexation of the substrate with the catalyst. If the K_2 value is larger for the acetylene than for the olefin, then the acetylene will complex most of the available rhodium and will retard olefin reduction by either the "unsaturate" or "hydride routes". It is tempting to say then, that acetylene reduction proceeds by the "unsaturate route" but this is not necessarily the case if hydrogen transfer is the rate limiting step.

Supporting evidence for the existence of two hydrogenation mechanisms has come from competition experiments in different solvents. A competition figure, R*, is defined as the ratio of the hydrogenation rate of a substrate to that of a terminal olefin. Experimentally R* is obtained by determining the ratio of saturated products for

two substrates being competitively reduced. Competition figures for the reduction of 1-hexyne and 1-octene ranged from 1.7 in benzene to greater than 20 in 2,2,2-trifluoroethanol. Coordinating solvents such as nitromethane, dimethylformamide, or acetonitrile inhibited alkyne reduction, and this was interpreted as evidence that two mechanisms of hydrogenation operate and that the extent of participation by each mechanism is responsible for the difference in selectivity for reductions in various solvents. Candlin and Oldham found that when a mixture of 1-hexyne and 1-octene was reduced with a stoichiometric quantity of $H_2(Ph_3P)_2RhCl$ an R* value of 1.9 was obtained in benzene which compared well with an R* of 1.7 when the same reaction was carried out under catalytic conditions. When benzene-methanol was used as a solvent, the stoichiometric reduction gave an R* of greater than 10 while under catalytic conditions R* was only 2.6. This suggests that a high R* value might result if it were possible to direct, through the proper mixture of solvents, a reduction to go solely through the hydride route.[29]

Deuterium labeling studies have also been used to gain insight into the mechanism of reduction of unsaturated substrates with $(Ph_3P)_3RhCl$. Two groups have reported that there is no exchange between deuterium gas and solvent in solutions of $(Ph_3P)_3RhCl$ and benzene or benzene-alcohol.[22,30,31] At lower pressures in hydrogen and deuterium mixtures (ca. 15 cm pressure) very little HD was found in the gas phase over catalyst solutions which demonstrated that exchange was

slow compared to the rate of substrate reduction.

Deuteration of maleic and fumaric acids to meso- and dl-2,3-dideuterosuccinic acids respectively by $(Ph_3P)_3RhCl$ and D_2 provided evidence that deuteration, and by analogy hydrogenation occurred in a cis manner.[22] Confirmation of this conclusion was obtained by partially reducing 2-hexyne. Analysis of partially reduced material by glpc showed n-hexane and also 2-hexenes. The cis-2-hexene to trans-2-hexene ratio was about 20. Since cis-2-hexene is reduced more rapidly than trans-2-hexene the ratio of cis to trans hydrogenation rates must have been at least 20.[22] Hussey and Takeuchi have shown that addition of deuterium to norbornene occurs in an exo-cis manner.[32]

Specific deuteration of olefinic double bonds has been reported by Morandi and Jensen who reduced seventeen n-monoolefins using deuterium and $(Ph_3P)_3RhCl$.[33] cis-2-Decene, trans-2-decene, cis-3-decene, cis-4-decene, cis-5-decene, trans-5-decene, and all the α-olefins from decene through eicosene were reduced to the corresponding dideuteroalkanes. Mass spectral and nmr measurements indicated only the expected dideutero products, and no scrambling of deuterium was observed.

Wilkinson originally postulated that in the reaction sequence of Figure 4, both hydrides might be transferred simultaneously. More recently, however, evidence has been presented which suggests that the hydride transfer reaction is more likely to be a two-step process. Olefin isomeriza-

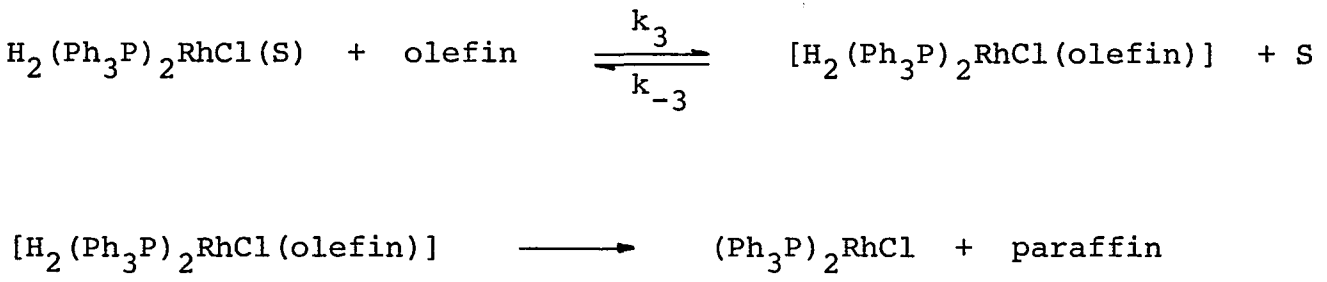
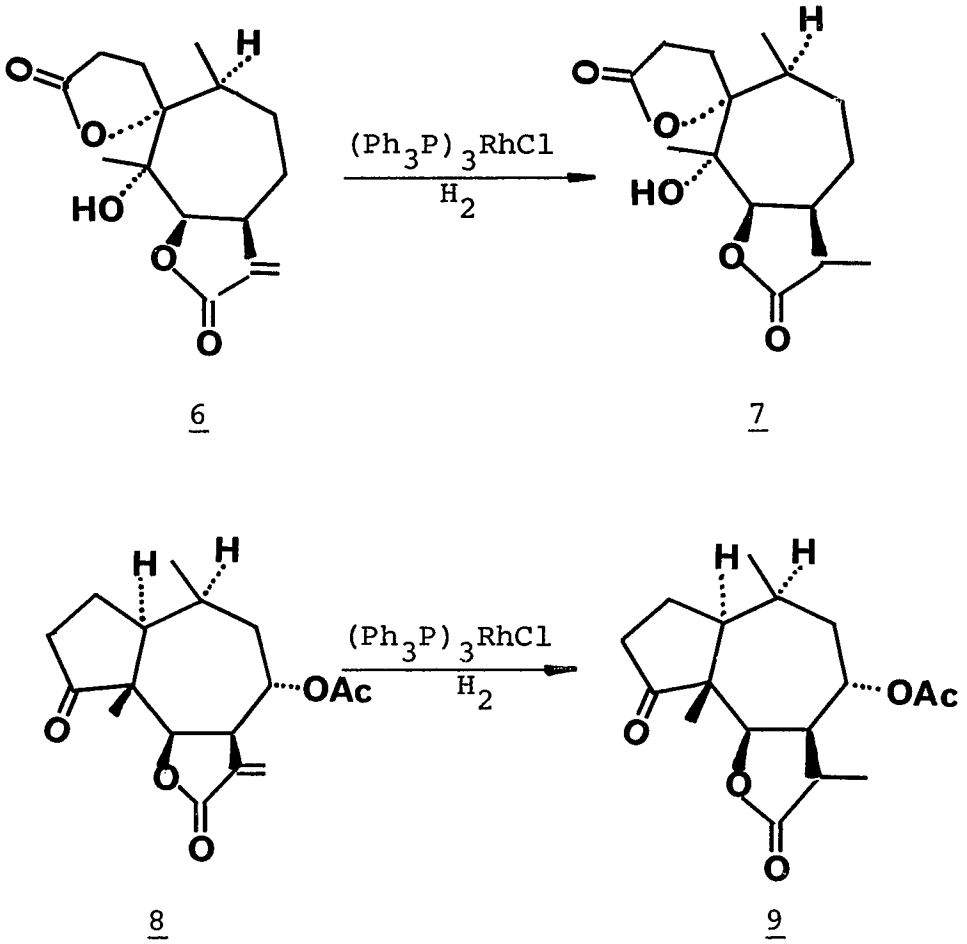


Figure 4. The "hydride" mechanism (simultaneous transfer of both hydrogens).

tion and hydrogen, deuterium, and tritium exchange have been used to support the intermediacy of a σ-alkyl hydride.

The double bonds in psilostachyine (6) and confertiflorin (8) are smoothly reduced by tris(triphenylphosphine)-chlororhodium(I) to give their dihydro derivatives (Figure 5). However, structurally similar damsin (4) undergoes isomerization to isodamsin (5) (Figure 6).[36] Damsin does not undergo isomerization to isodamsin in the presence of $(Ph_3P)_3RhCl$ alone, but only when hydrogen is also present (Figure 7). The isomerized product contained no deuterium when the reaction was carried out in the presence of EtOD. When damsin was allowed to react with a stoichiometric quantity of $RhD_2Cl(Ph_3P)_2$, the isolated isodamsin showed 0% incorporation of two deuterium atoms, and 58% incorporation of one deuterium. In the presence of a catalytic amount of $(Ph_3P)_3RhCl$ and deuterium gas, damsin gave isodamsin that was 70% undeuterated, 30% monodeuterated, and 0% dideuterated.

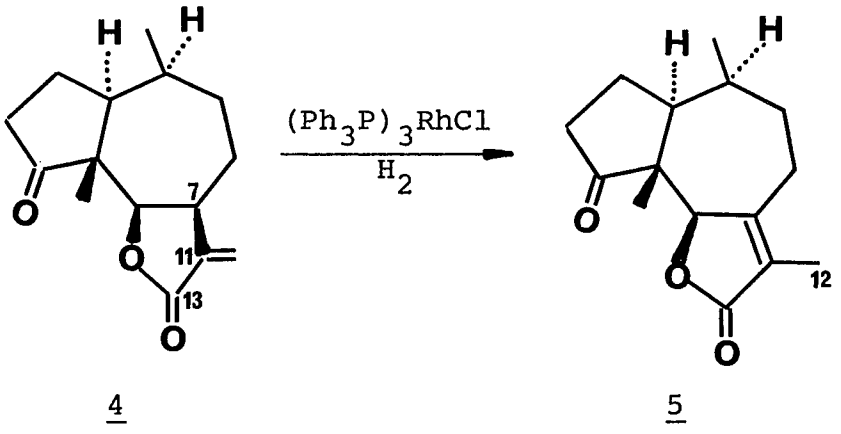
This complex behavior was explained as follows: reaction of damsin with the metal hydride gives an alkyl metal hydride which can undergo β-elimination to the metal hydride and isomerized olefin (Figure 7). Reaction of damsin with $RhD_2Cl(Ph_3P)_2$ leads to the introduction of one deuterium atom in damsin *via* the addition of Rh-D across the double bond. The resulting alkyl rhodium intermediate can undergo β-elimination to give monodeuterated isodamsin and $RhHDCl(Ph_3P)_2$. The reaction of the $RhHDCl(Ph_3P)_2$ with damsin gives isodamsin with the incorporation of either one



6 7

8 9

Figure 5. The hydrogenation of psilostachyine (6) and confertiflorin (8) over Wilkinson's catalyst.

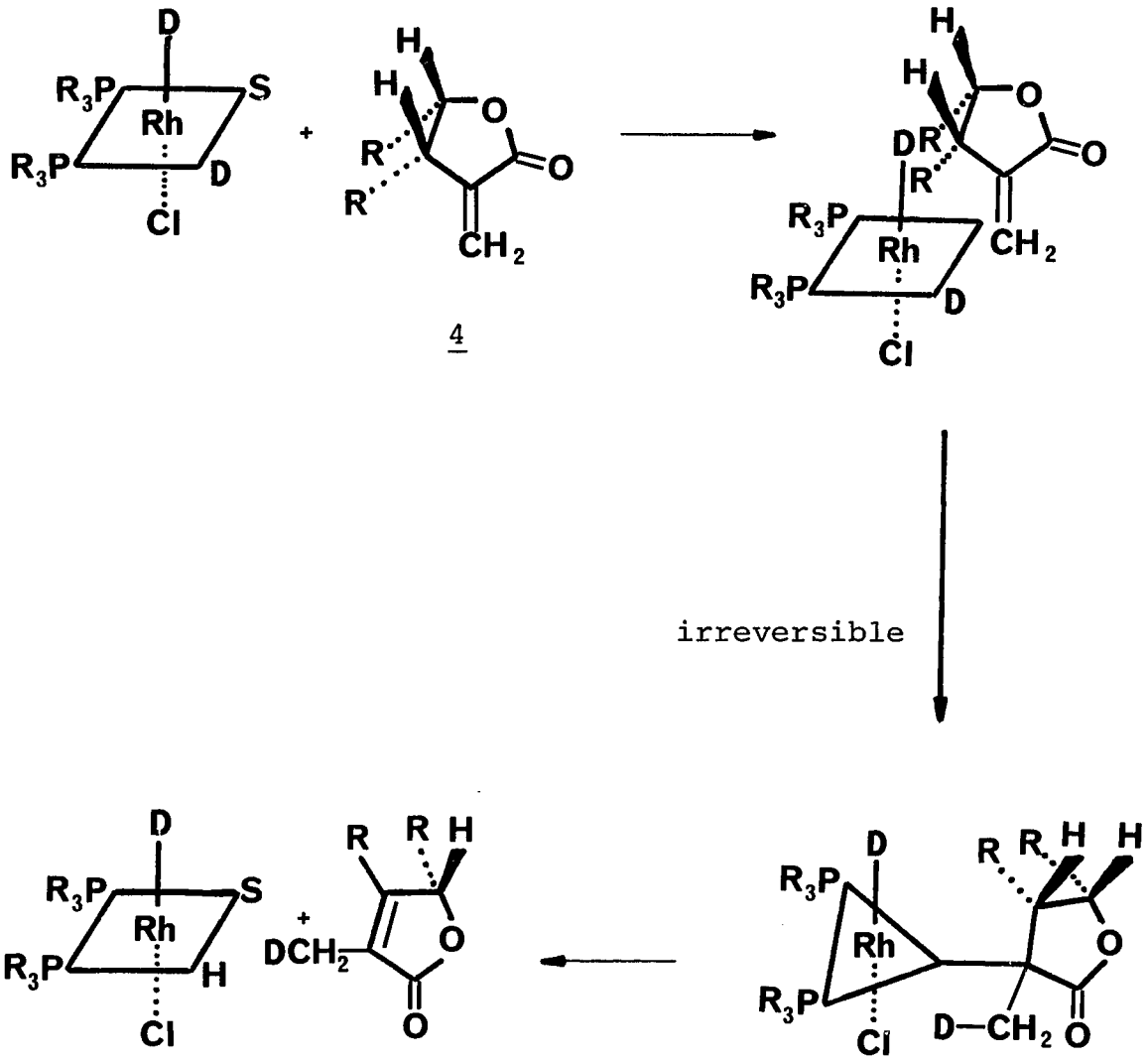


4 5

Figure 6. The isomerization of damsin (4) over Wilkinson's catalyst.

or no deuterium atoms. The deuterium isotope effect favors the transfer of hydrogen over deuterium and leads to the preferential formation of undeuterated isodamsin from $RhHDCl(Ph_3P)_2$. Further along the reaction coordinate, under catalytic conditions, $RhD_2Cl(Ph_3P)_2$ becomes replaced by $RhH_2Cl(Ph_3P)_2$. The observation that under stoichiometric conditions 42% of the isodamsin is monodeuterated and 58% is undeuterated as compared with 30% monodeuterated and 70% undeuterated isodamsin products under catalytic conditions reflects the relative contributions to the isomerization process by the three catalytic species, $RhD_2Cl(Ph_3P)_2$, $RhHDCl(Ph_3P)_2$, and $RhH_2Cl(Ph_3P)_2$. The contribution of $RhD_2Cl(Ph_3P)_2$ to the isomerization process in the stoichiometric reduction is greater than in the catalytic process and this leads to the differences observed in the product ratios. Similarly, the contributions of $RhHDCl(Ph_3P)_2$ and $RhH_2Cl(Ph_3P)_2$ in the stoichiometric process would be expected to be lower than for the catalytic isomerization. The absence of any dideuterated isodamsin implies that the initial hydrogen transfer is irreversible.

Augustine and Van Peppin observed a considerable amount of isomerization during the reduction of 4-t-butylmethylenecyclohexane to 4-t-butylmethylcyclohexane over $(Ph_3P)_3RhCl$ in benzene-ethanol or in ethanol alone.[37] Other cases of olefin isomerization have also been noted; Bond and Hillyard demonstrated that during the hydrogenation of cis-2-pentene, catalyzed by $(Ph_3P)_3RhCl$ in benzene-ethanol,



4

5

Figure 7. The mechanism postulated for isomerization of damsin (4) over Wilkinson's catalyst.

isomerization to trans-2-pentene took place.[38] Small amounts of isomeric 2-pentenes were found in the hydrogenation of 1-pentene. Isomerization of 1-octene to trans-2-octene in the latter stages of the hydrogenation of 1-octene in benzene-methanol was noted.[39]

Other cases of olefin isomerization over $(Ph_3P)_3RhCl$ alone have been observed but since these systems do not require molecular hydrogen, they are not likely to involve the dihydride complex.[39,40,41]

In contrast to some earlier studies, Hussey and Takeuchi did not find high specificity in the addition of hydrogen and deuterium to highly substituted cyclohexene substrates.[47] Deuterium addition to both 1,4-dimethyl and 1-methyl-4-isopropylcyclohexenes gave surprising results. The isomeric composition of the products was different and there was considerable deuterium scrambling. Exchange patterns were different for each cis-trans pair. The exchange patterns for a given substrate were the same in both benzene and benzene-ethanol. The results were rationalized by the hypothesis that the rate of transfer of deuterium to the highly substituted double-bonded carbon atoms is so slow that the stepwise character of the transfer is clearly reflected in the isomer and labeling patterns.

A mechanistic scheme has been proposed which embodies all the steps originally proposed by Wilkinson, but also accommodates the more recent evidence for this reaction (Figure 8).[23,36,46,47]

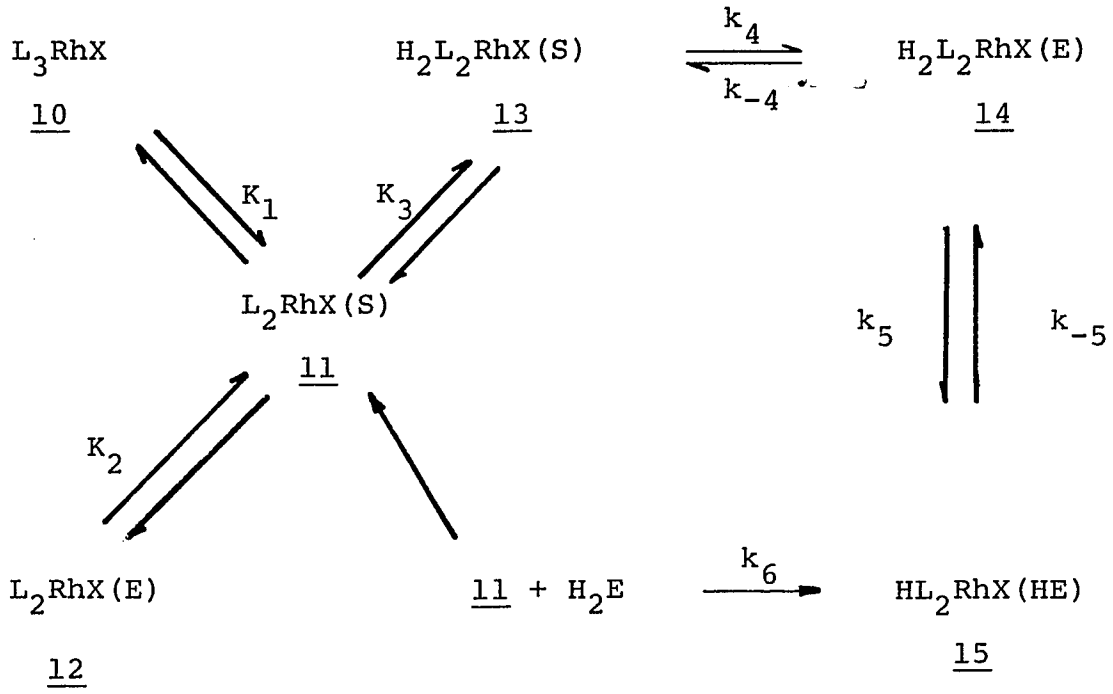


Figure 8. A postulated mechanism for hydrogenation of olefins over Wilkinson's catalyst.

Figure 8 accounts for the influence of the solvent (S), the ligand (L), and the ligand to rhodium ratio upon the dissociation of 10 and 11; the scheme also predicts variable effects of the alkene (E) through conversion of 11 to 12. The concentrations of the dihydro complex 13 and the π olefin complex 14 are seen to be dependent upon both the hydrogen concentration and the coordination potential of the olefin (E) vs. the solvent (S). As k_{-5} approaches k_6 in magnitude, the hydrogen transfer becomes observable as a two step process. This mechanism does not, however, account for hydrogenation by the "unsaturate route".

Data arising from the deuteration of styrene over $(Ph_3P)_3RhCl$ caused Smith and Shuford to argue for two catalyst

systems operating simultaneously.[42] In benzene or methylene chloride, only 1,2-dideuteroethylbenzene was formed. In chloroform or benzene-ethanol (3:1) exchange was found to occur. It was suggested that one catalyst accomplishes the cis addition of two deuterium atoms and the other causes deuterium to add reversibly with exchange. It was proposed that certain olefins may complex with one catalyst only, but others may complex with both, and further that solvent and substituent effects influence the extent to which an olefin interacts with each catalyst system. Smith and Shuford proposed that the monomeric dihydride complex 13 gave cis addition while the dimeric hydride complex 16 caused scrambling.

$$[H_2(Ph_3P)_2RhCl]_2$$

16

There is little direct evidence that the dimeric hydride 16 is involved in isomerization, moreover, several studies have shown it to be essentially inactive as a hydrogenation catalyst.[22,42]

Consideration of the hydrogenation of some vinylcyclopropanes has provided more evidence in support of the theory of stepwise transfer of hydrogen. Heathcock and Poulter found that when cyclopropylethylene was reduced with hydrogen and $(Ph_3P)_3RhCl$ in benzene three products resulted,

the expected ethylcyclopropane, but also n-pentane and 2-methylbutane in ratios of 85:14:1 (Table 2).[43] The results can be explained by invoking a two-step hydrogen transfer mechanism. If the first hydrogen is added α to the cyclopropane ring, an alkylrhodium(III) species results. This can collapse to give the expected alkylcyclopropane. If, however, the first hydrogen is added β to the cyclopropane ring, the resulting cyclopropylcarbinylrhodium species can rearrange by fission of the 1,2- or the 1,3-bond of the cyclopropane ring with the concurrent migration of the rhodium to form a homoallylrhodium compound prior to the transfer of the second hydrogen (Figure 9). The driving force for this rearrangement is, presumably, the assumed lower energy of the primary carbon-rhodium bond compared to that of the secondary carbon-rhodium bond.

The possibility that the observed products might have resulted from 1,4-addition was also considered but was thought to be an unlikely pathway since only trans-2-pentene was detected in the early stages of the reduction of cyclopropylethylene. This observation strengthens the assertion that the initial attack of the rhodium hydride takes place at the double bond rather than at the cyclopropane ring, however, it does not rule out 1,4-addition. Further support for the two-step mechanism for hydrogen transfer was gained by the study of the effect of alkyl groups on the cyclopropane hydrogenolysis. If the assumption is made that the primary alkylrhodium bond is of lower energy than a secondary or tertiary alkylrhodium bond, and further, that the addition

of Rh-H across the double bond is thermodynamically controlled, then the data in Table 2 support the proposed mechanism.

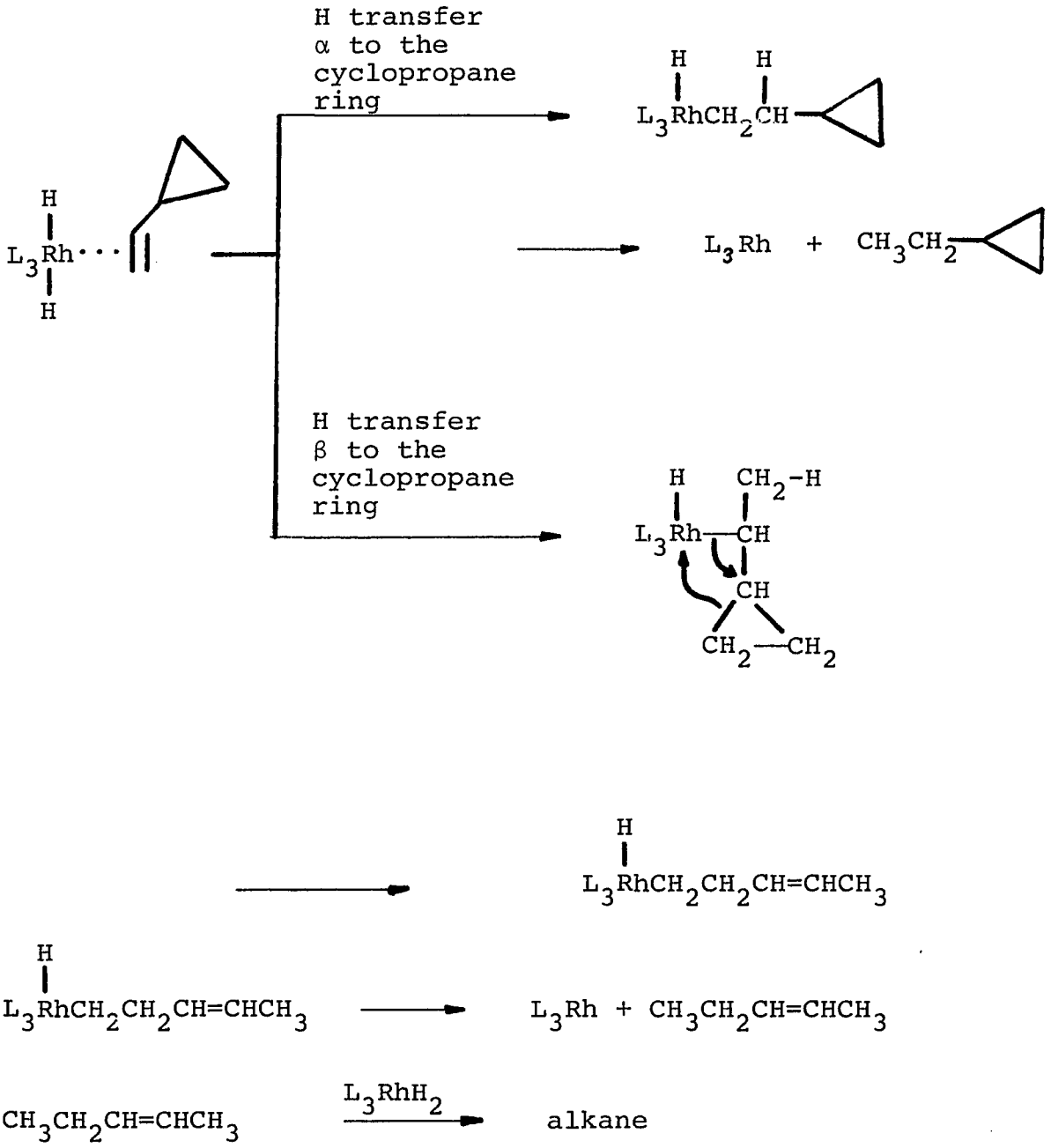


Figure 9. The reaction of cyclopropylethylene with Wilkinson's catalyst.

A 2-alkyl cyclopropylethylene would be expected to exhibit a greater degree of hydrogenolysis than a 1-alkylcyclopropylethylene (Table 2). In the former case a greater relative amount of addition of hydrogen β to the cyclopropane ring would be expected. That is, addition of hydrogen to the carbon α or β to the ring causes in both cases a secondary carbon-rhodium bond to result and both products would be of comparable energy, and one pathway should not be highly favored over the other. In the case of a 1-alkylcyclopropylethylene, addition of hydrogen α to the ring generates a primary carbon-rhodium bond which would be energetically favored over the tertiary carbon-rhodium bond formed when hydrogen is added β to the cyclopropane ring (Figure 10). Therefore, in the case of a 2-alkylcyclopropylethylene, because of energy considerations, a greater amount of the intermediate which undergoes rearrangement forms relative to the amount of a similar intermediate formed in the case of a 1-alkylcyclopropylethylene. In the latter case a primary alkylrhodium intermediate will probably almost exclusively result from the first hydrogen transfer.

From Table 2 it can be seen that a third type of product arises in some cases, in addition to the products resulting from simple hydrogenation of the olefin and from rearrangement to a homoallylic rhodium species followed by hydrogen transfer and hydrogenation of the resulting olefin. In the hydrogenation of cyclopropylethylene, the unusual product is 2-methylbutane; 1-cyclopropyl-2-methylethylene gives 2-methylpentane and bicyclo[3.1.0]hex-2-ene gives

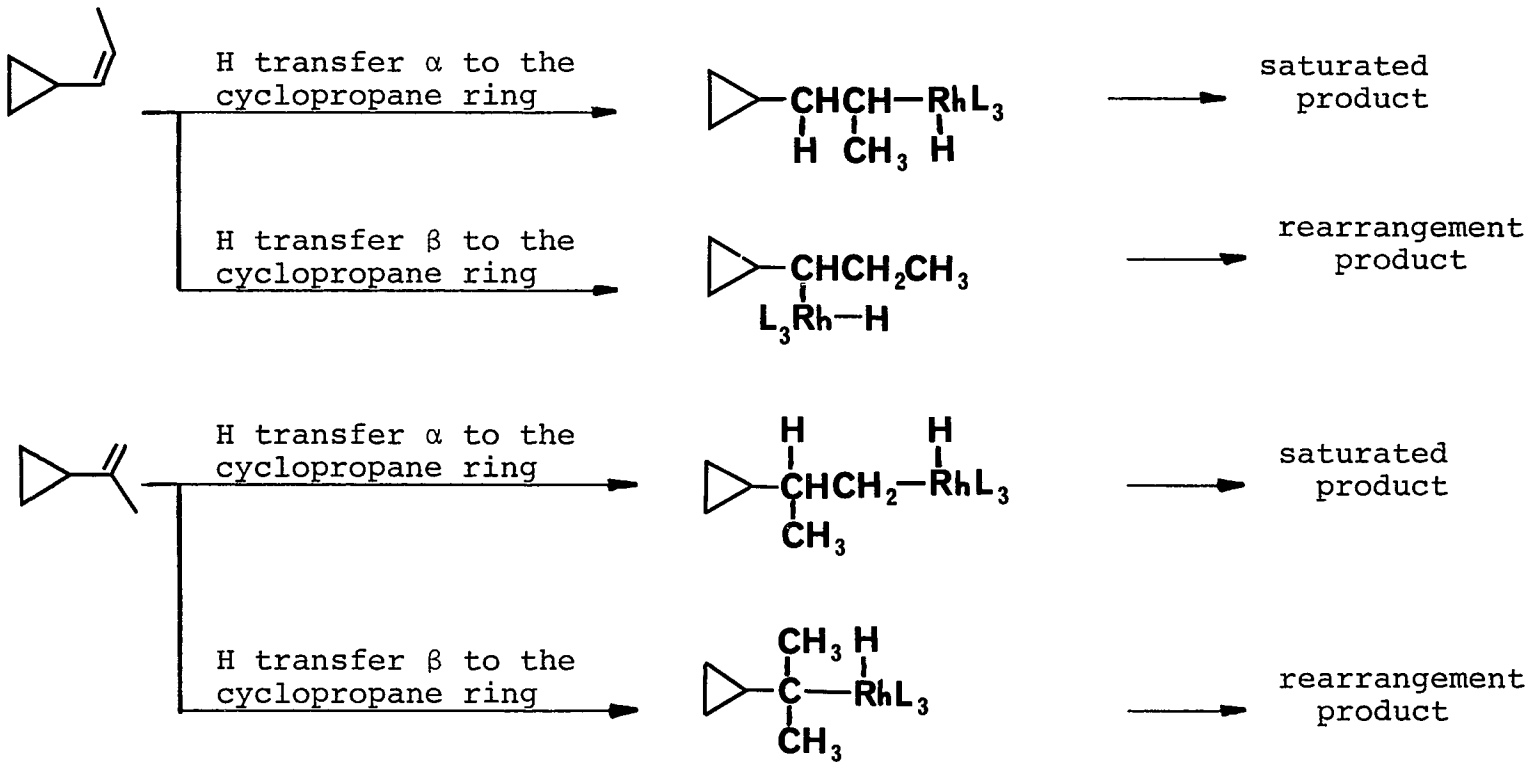


Figure 10. The hydrogenation of 1-alkyl and 2-alkylcyclopropylethylenes over Wilkinson's catalyst.

a) Both products are of approximately the same energy and the preferential formation of one should not be highly favored.

b) Hydrogen transfer to the ring gives a product of higher energy than transfer to the ring. The former product will be formed in a minor amount.

cyclohexane. These products can be viewed as arising from the addition of Rh-H across a double bond to give a secondary carbon-rhodium bond. Fission of the 2,3-bond of the cyclopropane with concurrent hydride transfer from the cyclopropane C-1 to the C-2 or C-3 position and migration of the rhodium gives an allyl-rhodium intermediate which can transfer hydrogen and give an olefin which is further hydrogenated to an alkane (Figure 11).

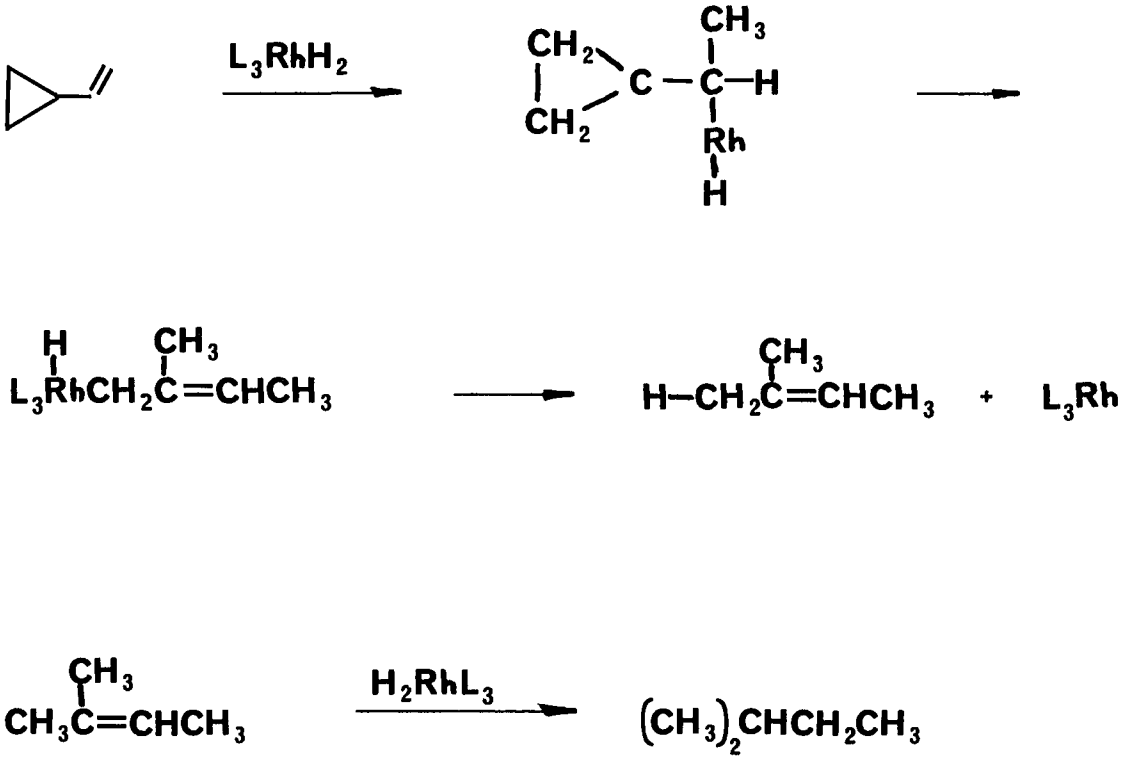
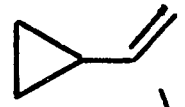
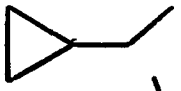
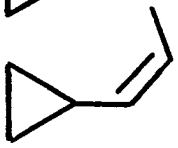
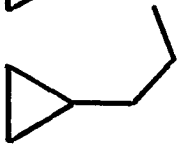
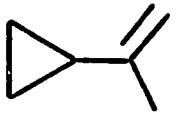
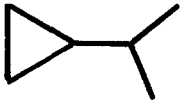
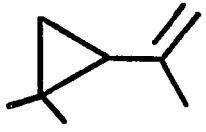
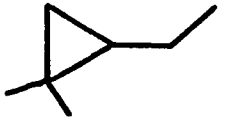
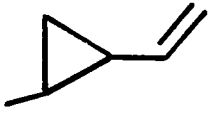
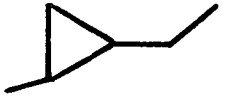
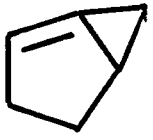
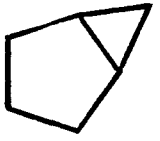
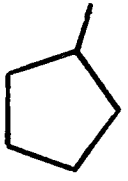
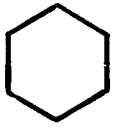
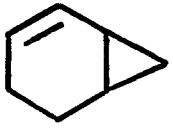
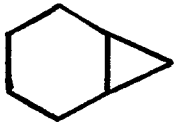
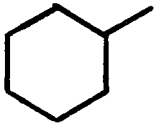


Figure 11. The rearrangement of a cyclopropylcarbinylrhodium hydride to an allylrhodium hydride.

Table 2. Hydrogenation of cyclopropylalkenes over $(Ph_3P)_3RhCl$ at 22-25°.[43]

Substrate	Products, %		
 	, 85;	$CH_3(CH_2)_3CH_3$, 14;	$(CH_3)_2CHCH_2CH_3$, 1
 	, 70;	$CH_3(CH_2)_4CH_3$, 27;	$(CH_3)_2CHCH_2CH_2CH_3$, 3
 	, 97;	$CH_3(CH_2)_2CH(CH_3)CH_3$, 1.5;	$CH_3CH_2CH=C(CH_3)_2$, 1.5
 	, 99;	$(CH_3)_3CH_2CH(CH_3)_2$, 1	
 	, 86;	$(CH_3)_2CHCH_2CH_2CH_3$, 11	
 	, 93;	 , 67;	 , 0.3
 	, 82;	 , 17	

Augustine and Van Peppen have concluded that the amount of double bond isomerization accompanying $(Ph_3P)_3RhCl$ catalyzed homogeneous hydrogenation is dependent on a number of factors: (a) the extent of prehydrogenation of the catalyst prior to introduction of the olefin, (b) the solvent system used, and (c) the presence of oxygen in the reaction mixture.[44,45]

Data collected by Augustine and Van Peppen show that prereduction of the catalyst before introduction of the substrate decreased isomerization drastically (Table 3).

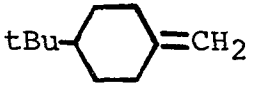
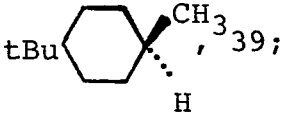
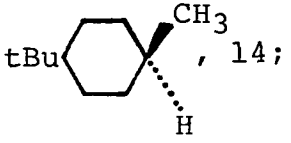
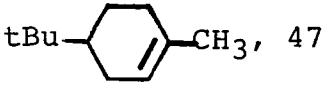
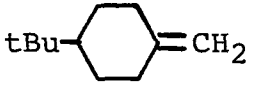
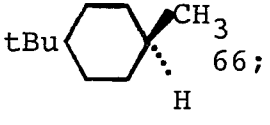
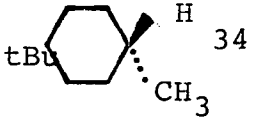
It was suggested that on presaturation of $(Ph_3P)_3RhCl$ with hydrogen the cis-dihydride described by Wilkinson is formed. The two hydrogens are then available for transfer to the olefin. With presaturation an alkylrhodium intermediate either will not be formed or its existence will be so transient as to preclude isomerization.[44]

In benzene-ethanol solvent these authors found that isomerization or deuterium scrambling took place, but in benzene alone, no exchange occurred. Other workers, however, have described deuterium exchange in benzene alone.[35,46,47]

The hypothesis that more than one catalytically active species is responsible for the varied results gained from the $(Ph_3P)_3RhCl$ catalyst system seems particularly attractive in light of data concerning the effect of oxygen.[44,48,

Oxygen has been found to have a significant effect on Wilkinson's catalyst. Van Bekkum and coworkers reported that small quantities of oxygen increased the activity of

Table 3. The isomerization of olefins over hydrogen presaturated and non-presaturated Wilkinson's catalyst.

Olefin	Catalyst[a]	Time, min.	Product %	Isomerized Olefins
1-heptene	NPS	15	heptane, 13; 1-heptene, 56	cis-2-heptene, 12; trans-2-heptene, 19
1-heptene	NPS	30	heptane, 17; 1-heptene, 47	cis-2-heptene, 16; trans-2-heptene, 20
1-heptene	PS	3	heptane, 18; 1-heptene, 81	——— ; trans-2-heptene, 1
1-heptene	PS	7	heptane, 29; 1-heptene, 70	——— ; trans-2-heptene, 1
	NPS	—	 39;  14;	 47
	PS	—	 66;  34	———

a) NPS refers to a non-presaturated catalyst, PS to a presaturated catalyst.

Wilkinson's catalyst.[89] In a system where 0.7 mole of oxygen was added per mole of rhodium, the rate of hydrogenation of cyclohexene was accelerated by a factor of 1.3. Acceleration factors from 1.5 to 4 were also observed.[89] The rate increase was explained as arising from the oxidation of one mole of triphenylphosphine to triphenylphosphine oxide which was thought to promote dissociation of $(Ph_3P)_3RhCl$ by removing the triphenylphosphine from the equilibrium, moreover, triphenylphosphine oxide was detected in solution.[89,90] Other authors have shown that Wilkinson's catalysts absorb one mole of oxygen to give a number of 1:1 rhodium:oxygen complexes.[88,91,92,93,94]

Oxidized catalysts, and not dissociated catalysts were considered by Augustine to be responsible for the observed rate increases.[44,48,49] The reaction of Wilkinson's catalyst with molecular oxygen showed a marked dependence on solvent. For example, one mole of $(Ph_3P)_3RhCl$ took up 1 mole of oxygen in benzene, 1.75 in methanol and 3 in ethanol. When one mole of oxygen was added to the prereduced $(Ph_3P)_3RhCl$ catalyst in ethanol-benzene an active catalyst was formed. This catalyst caused extensive isomerization, however, according to Augustine addition of oxygen to either the prereduced or to the non-prereduced $(Ph_3P)_3RhCl$ catalyst in benzene alone did not result in observable isomerization. The data are not clear cut, however, as Augustine, his statements to the contrary notwithstanding[44], has observed isomerization of olefins by an oxidized catalyst in benzene solution. The material

obtained from the oxidation of $(Ph_3P)_3RhCl$ in benzene was used to hydrogenate 1-heptene. A slow rate of hydrogen uptake was observed as was extensive isomerization.[49]

An effect of alcohol on the dissociation of $(Ph_3P)_3RhCl$ was also noted.[48] The addition of as little as 4% ethanol to a benzene solution of $(Ph_3P)_3RhCl$ completely inhibited the dissociation of a triphenylphosphine ligand in the presence of oxygen. However, upon hydrogenation of these solutions, triphenylphosphine and $H_2(Ph_3P)_2RhCl$ were formed. It was suggested that undissociated $(Ph_3P)_3RhCl$ could be the cause of olefin isomerization in ethanol-benzene. It may be that the suggested unsaturate route proceeds directly from undissociated $(Ph_3P)_3RhCl$ rather than <u>via</u> $(Ph_3P)_2RhCl$ or $(Ph_3P)_2RhCl(S)$.

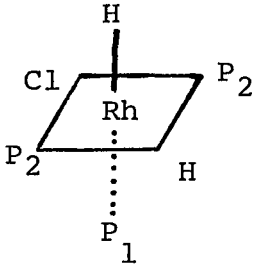
Triphenylphosphine in solution was found to inhibit the isomerization of olefins over oxidized catalysts.[49] A solution of $(Ph_3P)_3RhCl$ oxidized in ethanol took up 5 equivalents of hydrogen upon hydrogenation, while the catalyst oxidized in benzene solution took up 10-23 equivalence of hydrogen. Both oxidized catalysts caused some reduction of benzene to cyclohexane, but this activity was short lived. Both catalysts were effective in reducing 1-heptene and both catalysts caused extensive isomerization of the 1-heptene. The addition of one equivalent of triphenylphosphine to the catalyst which had been oxidized in either benzene or ethanol caused remarkable behavior; 2.5 equivalents of hydrogen were taken up and the reaction stopped. Benzene solvent was not hydrogenated to cyclohexane; the rate of hydrogenation for

the Ph_3P treated catalyst increased, and no olefin isomerization occurred. Augustine has suggested that the presence of free phosphine prevents isomerization by oxidized catalysts. Since phosphine cannot dissociate in ethanol solutions, isomerization takes place. In benzene, dissociation to a coordinatively unsaturated species and free triphenylphosphine takes place. The free phosphine then prevents olefin isomerization. No rationale for this behavior was advanced.

Other authors have stated that oxygen inhibits hydrogenation over $(Ph_3P)_3RhCl$.[22] It is clear, then, that the effect of oxygen on catalysis by tertiary phosphine-rhodium(I) catalysis is quite complex and may also be solvent dependent. The extent of oxidation and the ratio of hydrogen to oxygen may also be important.

The major component in CH_2Cl_2 solutions of $(Ph_3P)_3RhCl$ has been shown by ^{31}P nmr to be the tristriphenylphosphine species. The spectrum of the rhodium complex is unaffected by added ligand at 30°, and the only new resonance line that appears upon addition of excess ligand is that of the free ligand.[26] By the use of Fourier transform nmr a weak free phosphine resonance was detected in a solution of 0.05 M $(Ph_3P)_3RhCl$ in methylene chloride. The intensity was about 3% that of the principal species. As hydrogen was added to a solution of $(Ph_3P)_3RhCl$, a dihydride was formed which could be readily detected by proton nmr. From the nmr spectrum at -25° it was seen that the dihydride complex 17 was formed almost quantitatively and that it contained

three phosphine ligands. Structure 17 has been assigned to the dihydride complex. When the temperature was raised to 30° phosphine ligand dissociation at an appreciable rate was observed. At both -25° and 30°, P_2-Rh coupling was observed whereas P_1-Rh and P_1-P_2 couplings observed at -25° disappeared at 30°. It was concluded that only the P_1 phosphine was dissociating and that it returned to the coordination site from which it dissociated.



17

These studies have shown that $(Ph_3P)_3RhCl$ and $(Ph_3P)_3RhH_2Cl$ are the major species in solutions of tris-(triphenylphosphine)rhodium(I) chloride and hydrogen. This is consistent with the "hydride route" to hydrogenation in which the step subsequent to dissociation is coordination of the olefin to the site left vacant by P_1 (Figure 12).

Various groups have studied the effect of the ligand in homogeneous hydrogenations using rhodium(I)-tertiary phosphine catalysts. The catalysts have generally been made *in situ* by adding n moles of ligand to a labile rhodium(I)-olefin complex such as $[Rh(C_2H_4)_2Cl]_2$, $[Rh(COD)Cl]_2$

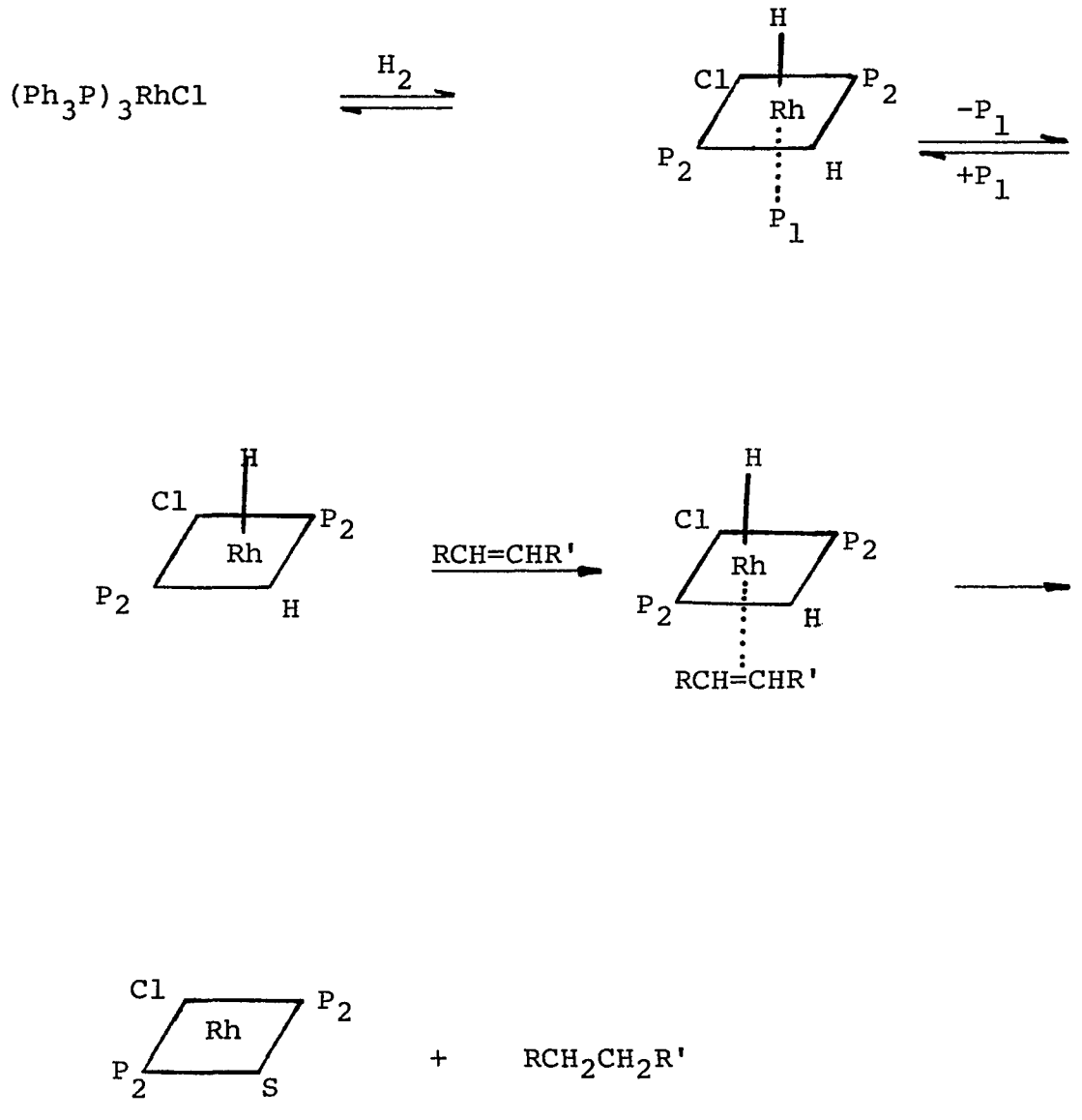


Figure 12. The hydride mechanism of olefin reduction based on the nmr study of Meakin, Jesson, and Tolman.[26]

$[Rh(1,5\text{-}C_6H_{10})Cl]_2$, or $[Rh(C_8H_{14})Cl]_2$.*

Changes in the electronic environment of the phosphorus of the phosphine ligands, produced by varying substituents on phenyl rings, caused considerable differences in the rates of catalytic hydrogenation observed with catalysts formed from these ligands. For example, at 25°, the catalytic activity of a catalyst made from tris(p-fluorophenyl)phosphine was much lower than the activity of catalysts made from either triphenylphosphine or tris-(p-methoxyphenyl)phosphine.[23] The electron releasing capability of the p-methoxyphenyl group was thought to increase the electron density about rhodium and favor the formation of the dihydride. Interestingly, substitution of more basic groups such as ethyl, butyl, or cyclohexyl for one or more of the phenyl groups of triphenylphosphine caused a decrease in activity. A rationale for this apparent contradiction has been proposed for tris(diphenylethylphosphine)rhodium(I) chloride. One phosphine ligand dissociates completely in solution to give the coordinatively unsaturated species bis(diphenylethylphosphine)rhodium(I) chloride but when the unsaturated species is hydrogenated to the dihydride, it reassociates to a catalytically inactive hexacoordinate compound. If only two moles of diphenylethylphosphine are used per mole of rhodium, then a catalytically active species is formed. Even under these conditions, however,

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*The olefins are abbreviated as follows: C_2H_4 = ethylene; COD = 1,5-cyclooctadiene; $1,5\text{-}C_6H_{10}$ = 1,5-hexadiene; C_8H_{14} = cyclooctene.

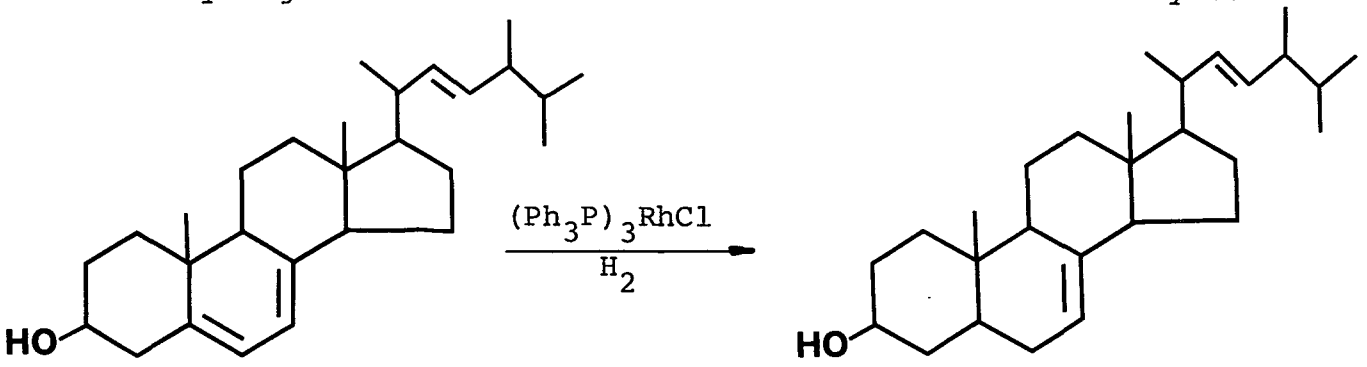
dimerization to an inactive species may occur. It has been suggested that catalysts made from alkylphosphines are less efficient than those made from arylphosphines under conditions where no reassociation can occur (Rh/L = 1/2) due to the fact that in these cases hydrogen transfer becomes the rate determining factor.[23] Steric factors have been suggested to play some role in determining the activity of the catalyst, and presumably, they affect the degree of dissociation of the catalyst and also its association to an inactive dimer.[23] A maximum activity is usually observed when the ligand to rhodium ratio is two.

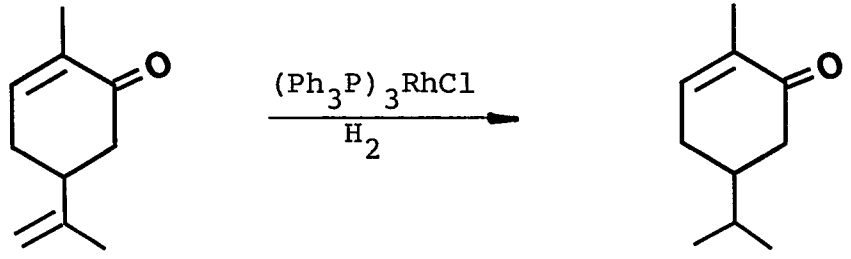
Scope of Reduction by Wilkinson's Catalyst

Much of the utility of rhodium(I)-tertiary phosphine catalysts lies in their specificity. These catalysts can reduce carbon-carbon double bonds in the presence of various functional groups. Mono- and disubstituted-olefins, cyclic mono- and dienes, and exocyclic methylene groups are reduced readily. Sterically hindered double bonds are reduced slowly, if at all. Table 4 shows some of the reductions that have been accomplished with a $(Ph_3P)_3RhCl$ catalyst (Wilkinson's catalyst).[50]

The carbon-carbon double bonds of α,β-unsaturated carboxylic acids, esters, nitro compounds, nitriles, ketones, and aldehydes have been reduced with Wilkinson's catalyst. Whereas many α,β-unsaturated compounds are reduced readily at room temperature and 1-3 atmospheres, some that are highly

Table 4. Hydrogenation of some olefins over Wilkinson's catalyst.





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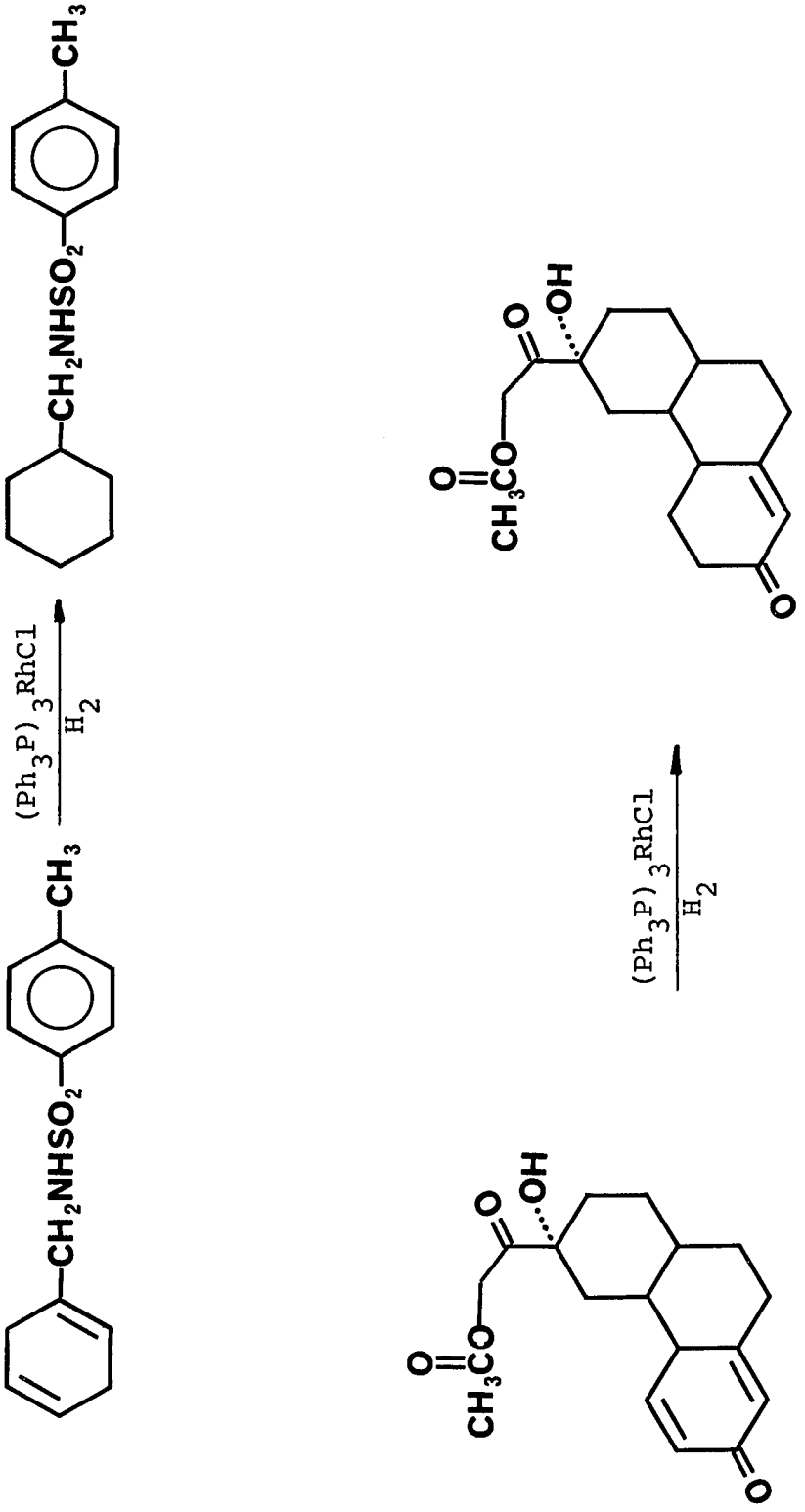

substituted require higher temperatures and pressures for complete reduction in a reasonable length of time (Table 5).

Benzyl cinnamate has been reduced quantitatively to benzyl-3-phenylpropanoate (with no hydrogenolysis). However, another ester, menthyl-α-phenylcinnamate could not be reduced at all, presumably due to steric hindrance.[51]

Unsaturated aldehydes can be reduced to saturated aldehydes by Wilkinson's catalyst.[24] In such an application, as can be seen in Table 5, a serious complication can be decarbonylation of the aldehyde (Figure 13). The decarbonylation reaction effectively destroys the catalyst by removing the solvent saturated precursor 18 of the dihydro complex 16. The carbonyl complex 19 does not activate molecular hydrogen under the mild conditions normally employed.[22] The decarbonylation reaction can be minimized by employing dilute catalyst solutions, prereducing the catalyst, and increasing the hydrogen pressure.[24]

$$\underset{\underline{18}}{(Ph_3P)_2RhCl(S)} \xrightarrow{R\text{-}CHO} \underset{\underline{19}}{(Ph_3P)_2Rh(CO)Cl(S)} + R\text{-}H$$

Figure 13. The decarbonylation of an aldehyde by Wilkinson's catalyst.

Quinones have been hydrogenated to enediones with tris(triphenylphosphine)rhodium(I) chloride.[52] For example, 1,4-naphthoquinone was rapidly reduced to 1,2,3,4-tetrahydro-1,4-dioxonaphthalene in 70% yield. The only other reported methods of synthesis gave 6 to 10.5% yields. The applica-

Table 5. Hydrogenation of α,β-unsaturated substrates with Wilkinson's catalyst.[51]

Substrate	Product(s)	Yield[a], %	Reduction[b], %
$PhCH=CHCO_2H$	$PhCH_2CH_2CO_2H$	85	100
(E)-$PhCH=C(CH_3)CO_2H$	$PhCH_2CH(CH_3)CO_2H$	83	100
(E)-$PhCH=C(Ph)CO_2H$	$PhCH_2CH(Ph)CO_2H$	85	100
cis-$HO_2CCH(CH_3)C=CHCO_2H$	$HO_2CCH(CH_3)CH_2CO_2H$	90	80
$PhCH=CHCO_2Et$	$PhCH_2CH_2CO_2Et$	93	100
3,4-$(CH_2O_2)C_6H_3CH=CH=CHNO_2$	3,4-$(CH_2O_2)C_6H_3CH_2CH_2NO_2$	84	100
$PhCH=CHCN$	$PhCH_2CH_2CN$	86	100
$PhCH=CHCOCH_3$	$PhCH_2CH_2COCH_3$	80	100
$PhCH=CHCHO$	$PhCH_2CH_2CHO$ (60%) + $PhCH_2CH_3$ (40%)	90	-

a) Yields are presumably isolated yields.

b) The percentage reduction was based on ir and nmr spectral analysis of the products.

bility of this method is limited, however, as quinones with higher oxidation potentials destroy the catalyst.

Nitro groups, easily reduced by heterogeneous catalysts, are unaffected by Wilkinson's catalyst. Allylic halides, however, seem to undergo hydrogenolysis.[50] When cinnamyl chloride was hydrogenated, the desired product, 1-chloro-3-phenylpropane was produced in 38% yield, β-methyl-styrene was formed in 35% yield, 1-phenylpropane was formed in 19% yield, and 10% of the starting material was recovered. Hydrogenolysis reactions, therefore, account for more than 50% of the product.

A serious limitation of heterogeneous catalysts has been their susceptability to poisoning, particularly by traces of divalent sulfur compounds. Homogeneous rhodium-(I)-phosphine catalysts are markedly resistant to such poisoning. For example, Hornfelt has shown Wilkinson's catalyst to be useful in the reduction of side chain unsaturation in thiophene derivatives.[53] Hydrogenations of 1-octene, dehydrolinalool, and ergosterol in the presence of what the authors describe as trace amounts of thiophenol proceeded readily.[54] The rate of hydrogenation was decreased when the concentration of thiophenol was increased to 1.25 times that of the catalyst. Nevertheless, reduction still proceeded at a synthetically useful rate. A very large excess of thiophenol (21 mol excess) severely depressed the hydrogenation rate (Table 6). Thiol poisoning is probably the result of an equilibrium between the normal catalyst species and a catalyst-thiophenol complex, with only the

Table 6. Hydrogenation[a] of olefins in the presence of divalent sulfur.[54]

Substrate	PhSH, mmol	H_2absorbed, mmol	Time, min.
1-heptene[b]	0.283	0.85	60
1-heptene[b]	0.0	3.1	60
1-heptene[b]	0.283	1.3	120
dehydrolinalool[c]	0.0	0.58	13
dehydrolinalool[c]	0.283	3.6	90
dehydrolinalool[c]	4.55	0.1	60
dehydrolinalool[c]	4.55	0.2	150

a) In all experiments 0.218 mmol of catalyst were used.

b) 3.51 Mmol of substrate were used.

c) 3.29 Mmol of substrate were used.

uncomplexed catalyst actually activating molecular hydrogen.

Sulfides do not seem to poison Wilkinson's catalyst. Ergosterol was completely hydrogenated in 5 hr in the presence of phenyl-n-propyl sulfide at a catalyst to substrate ratio of 1 to 2.32. Furthermore, allyl phenyl sulfide was hydrogenated to phenyl-n-propyl sulfide in 93% yield.[54]

Asymmetric Reductions

The discovery of rhodium-tertiary phosphine catalysts and the availability of optically active tertiary phosphine ligands[55,56] made inevitable the development of catalysts for catalytic asymmetric homogeneous hydrogenation.

The first catalytic asymmetric reduction was reported in 1968 when Knowles and Sebacky hydrogenated atropic and itaconic acids with a catalyst prepared from rhodium(III) and optically active tertiary phosphine ligands. The reaction of (-)-R-methylphenyl-n-propylphosphine and a methanolic solution of rhodium trichloride trihydrate gave trichlorotris(methylpropylphenylphosphine)rhodium(III). This catalyst, made with phosphine of 69% optical purity, was used to hydrogenate atropic acid to (+)-S-hydratropic acid with 15% ee. Similarly itaconic acid gave 2-methylsuccinic acid with 3% ee* (Figure 14).[57]

Heterogeneous catalysts modified by the addition of chiral substances have also been used to asymmetrically hydrogenate olefins, however, only a few effective chiral

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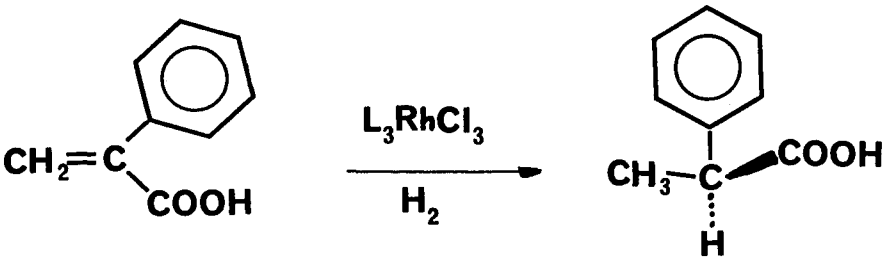
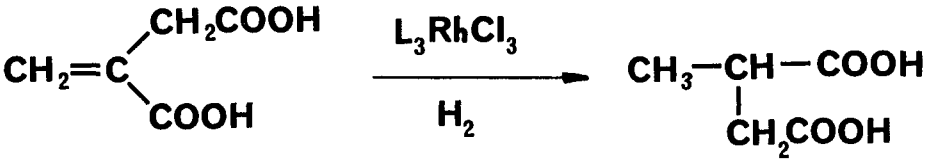
*No sign of rotation was given.



Atropic Acid

Hydratropic Acid
(+)-S, 15% ee



Itaconic Acid

2-Methylsuccinic Acid
3% ee

Figure 14. Hydrogenation of atropic and itaconic acids over trichlorotris (-)-S-methylphenylpropylphosphinerhodium.

heterogeneous catalyst systems have been found.[97] Palladium deposited on silk fibroin was used to asymmetrically hydrogenate 4-benzylidene-2-methyl-5-oxazolone to give, after hydrolysis, phenylalanine with optical purity as high as 35%.[58] The optical purity of the product was found to be dependent upon the origin of the fibroin and the chemical pretreatment used. Raney nickel has also been modified with active amino acids and other chiral reagents.[59] These catalysts have been used to reduce ketones asymmetrically, however, they suffer from some of the same limitations observed for the palladium on silk fibroin catalysts. For example, the optical purities of the products were found to be very dependent upon pH and the method of catalyst preparation. The best optical yields reported have been about 50% with methylacetoacetate as the substrate. Modified Raney catalysts have also been used to asymmetrically hydrogenate olefinic bonds.[60]

The generally low percent asymmetric synthesis in asymmetric heterogeneous hydrogenations may be due in part to a non-uniform distribution of chiral modifying agents over the catalytic surfaces. In the case of silk fibroin, metal clumping on the chiral support or dissociation of the metal from the fibroin may allow some reduction to occur in an achiral local environment.

Soluble chiral catalysts do not suffer from the same inborn defects that plague the chiral heterogeneous systems. Homogeneous catalysts can be better defined than their

heterogeneous counterparts and in catalytic complexes it is possible to modify the steric and electronic environment about the active site in a systematic manner to maximize the rate, yield, and in the case of chiral catalysts, hopefully, the optical purity. In catalysis by rhodium(I)-chiral tertiary phosphine catalysts the chiral ligands are coordinated directly to a central rhodium atom and impart to the metal the potential for diastereomeric interaction with unsaturated substrate molecules. This diastereomeric interaction of the substrate with the catalyst is responsible for asymmetric synthesis. Since each "active site" is in a chiral environment maximum efficiency should be realized.

In an early report by Horner and coworkers, α-ethylstyrene and α-methoxystyrene were reduced by hydrogen in the presence of a catalyst formed in situ from [Rh(1,5-hexadiene)Cl]$_2$ and (+)-S-methylphenyl-n-propylphosphine. The optical yields were 7-8% and 3-4%, respectively.[62]

A model was proposed to account for preferential formation of (+)-S-2-phenylbutane and (+)-R-1-methoxy-1-phenylethane. If one assumes that hydrogen transfer from a complex of the type H_2L_2RhCl(olefin) controls the asymmetric hydrogenation process then the model proposed by Horner (Figure 15) correlates the stereochemistry of the ligand and that of the chiral product.[62]

The model in Figure 15 suggests* that the phosphine ligands adjust their conformations to minimize their steric

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*Whether or not the model truly embodies the rationale of its success is not known.

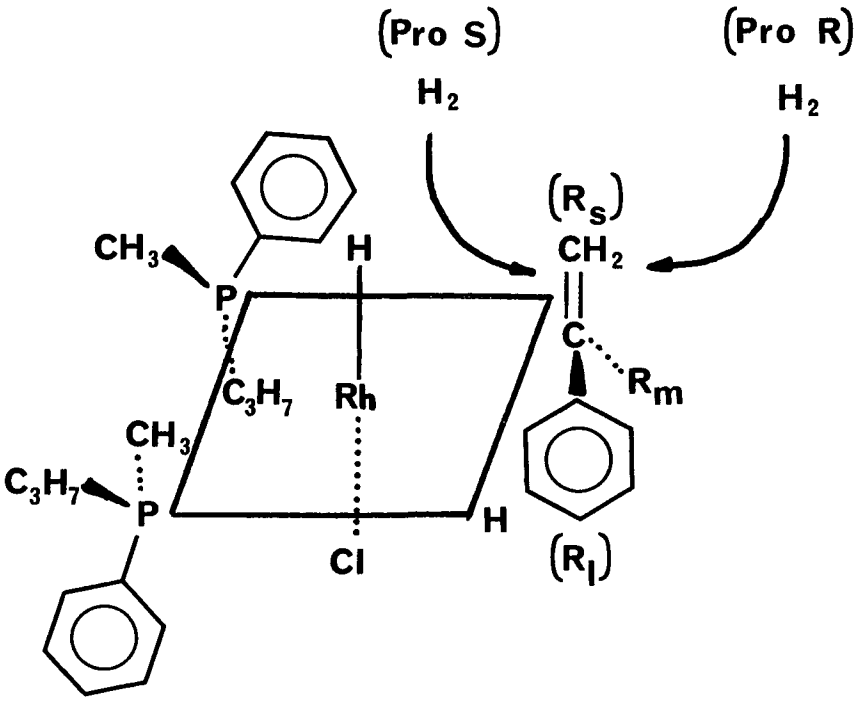


Figure 15. A model for the correlation of the stereochemistry of reduction products with that of the chiral ligand.[62]

interaction. If the approach of the olefin is the pathway of lowest energy, then where Rm is methyl, the S-isomer should be produced in excess. Where Rm is methoxy, the sequence rule priority but not the relative steric bulk of Rm changes. Thus the saturated product formed in excess is the R-isomer, but the same stereochemical model applies. This model also correctly predicts the formation of (+)-S-hydratropic acid from atropic acid.

Asymmetric homogeneous hydrogenation with a rhodium complex of a chiral amide has also been reported.[63] The chiral complex was prepared by reducing a solution of $(C_5H_5N)_3RhCl_3$ in (+)- or (-)-$PhCH(CH_3)NHCHO$ (or other chiral amides) with sodium borohydride. The complex in the chiral amide solvent was found to catalyze the asymmetric hydrogenation of methyl (E)-β-methylcinnamate. Hydrogenation in the presence of (+)-PhCHMeNHCHO (100% ee) gave an excess of (+)-S-methyl-3-phenylbutanoate (57% ee). In (-)-PhCHMeNHCHO (96% ee), (-)-R-methyl-3-phenylbutanoate (48% ee) was formed in excess as would be expected. The reaction is envisioned as proceeding via displacement of one of the pyridine ligands by the chiral amide solvent to form a catalytically active chiral borohydride complex (Figure 16).

The formulation in Figure 17 has been suggested as a representation of the half reduced state of the olefin during the hydrogenation process.

$$[(C_5H_5N)_3RhCl_3] \xrightarrow[PhCHMeNHCHO = L^*]{NaBH_4} [(C_5H_5N)_2L^*RhCl_2(BH_4)]$$

Figure 16. Formation of a catalytically active rhodium(III)-chiral amide complex.

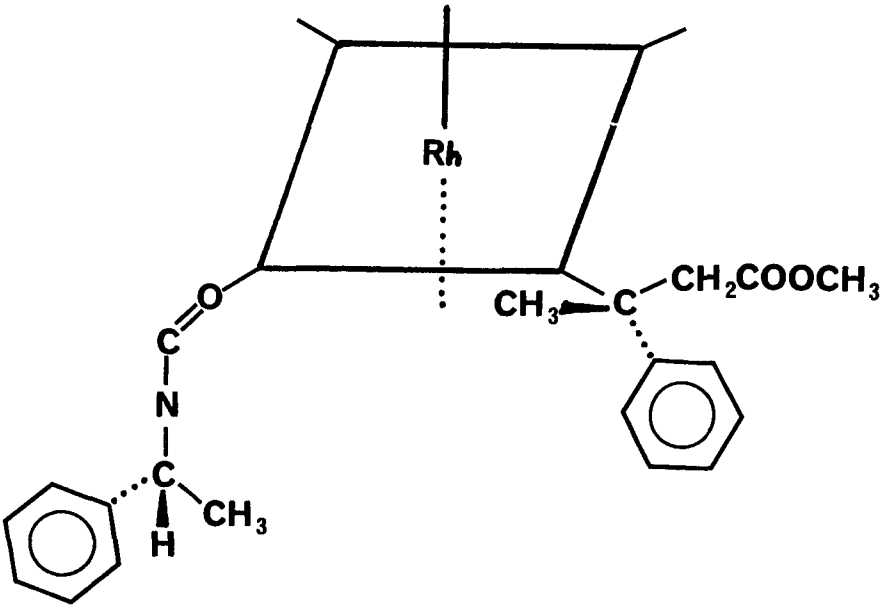


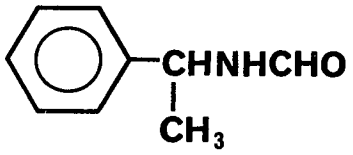
Figure 17. Representation of the half reduced state in the reduction of (E)-methyl-β-methylcinnamate.

The high asymmetric bias observed for this reaction is unusual. It is known that amides generally coordinate through the carbonyl oxygen[64] and a catalytic system with the chiral center four atoms removed from the metal would not be expected to give a product of high optical purity. However, some additional rigidity might be imposed on the complex by restricted rotation about the amide bond and this could accentuate the influence of the remote chiral center.

Initially, Abley and McQuillin used chiral amides as solvents and it was not determined that the asymmetric synthesis was really due to the formation of a discrete catalytic complex that incorporated the amide rather than to a less well defined asymmetric solvation by the chiral amide.[63] In a follow-up study the case for a discrete amide complex as a catalyst was supported by the observation that the degree of asymmetric induction was not diminished in dilute diethyleneglycol monoethyl ether solutions of the chiral amides.[65]

Abley and McQuillin hydrogenated both (E)- and (Z)-methyl-β-methylcinnamate with homogeneous catalysts prepared from a number of chiral amides and obtained optical purities ranging from 14 to 58% (Figure 18 and Table 7).[65]

It was observed that (Z)- and (E)-methyl-β-methyl-cinnamate both give the same sign and approximately the same magnitude of rotation. This could suggest, according to the authors that "...at the decisive stage the molecule has lost the olefin geometry." It was suggested that either the



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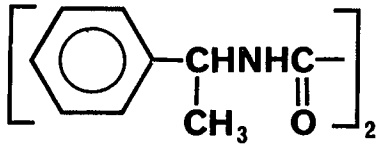

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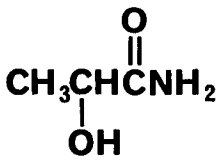

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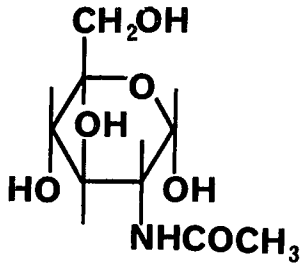

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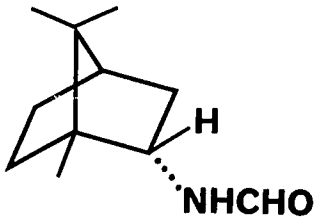

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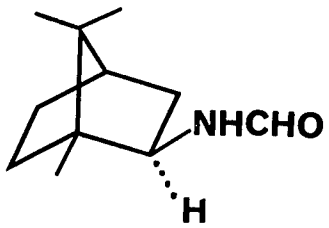

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Figure 18. Chiral amides ligands used in homogeneous hydrogenation reactions.

Table 7. Hydrogenation of (E)- and (Z)-methyl-β-methylcinnamate with rhodium(III)-borohydride complexes of chiral amides.

Substrate	Amide[a]	Optical Purity Amide, % ee	Solvent	Product D	Optical Purity Product, % ee
(E)-Methyl-β-methylcinnamate	(+)-20	100	A	+33	57
(E)-Methyl-β-methylcinnamate	(-)-20	96	A	-28	48
(E)-Methyl-β-methylcinnamate	(+)-20	100	B	+32	55
(E)-Methyl-β-methylcinnamate	(-)-21	---	C	+26	45
(E)-Methyl-β-methylcinnamate	(-)-22	92	A	- 9	15.5
(E)-Methyl-β-methylcinnamate	(+)-23	99	C	- 8	14
(Z)-Methyl-β-methylcinnamate	(-)-24	96	B	+26	45
(E)-Methyl-β-methylcinnamate	(-)-24	96	B	+23	40
(Z)-Methyl-β-methylcinnamate	(-)-25	100	B	+16	28
(E)-Methyl-β-methylcinnamate	(-)-25	100	B	+13	22

Solvents: A) With the amide as solvent at 60°. B) With the amide as a 5% solution in diethylene glycol monoethylether. C) With the amide as a 5% solution in diethylene glycol monoethylether-water (10:1).

a) The numbers refer to structures in Figure 18.

hydrogen transfer step determined the asymmetry or that of the spatial arrangements possible, one similar to A in Figure 19 was preferred to B for the (E)-isomer of the substrate. In the case of the (Z)-isomer of the substrate, D would be preferred over C.

The sequence of hydrogen addition to an olefin is not known, but the argument which Ableý and McQuillin proposed to rationalize the stereochemistry of the ligand with that of the product does not require a particular sequence of hydrogen addition. That is, addition of hydrogen to the tertiary center of the trisubstituted olefin would be expected to be slow compared to the addition of hydrogen to the secondary center, although this may not necessarily be the case if formation of the carbon-rhodium bond is thermodynamically controlled and the secondary carbon-rhodium bond is of lower energy than the tertiary carbon-rhodium bond. The stereochemical course of the reaction is most conveniently discussed in terms of addition of hydrogen to the olefin with the concurrent formation of a tertiary alkylrhodium intermediate.

The rationalization of the stereochemical outcome of the reductions was based on two assumptions, first; that the amide was coordinated "so that the smallest substituent group, hydrogen, projects toward the complex", and second; that the "smaller groups of the butanoate, i.e., $-CH_2CO_2CH_3$ or $-CH_3$, will be projected as to lie preferentially between the two smaller groups, H and M, of the (ligand) asymmetric

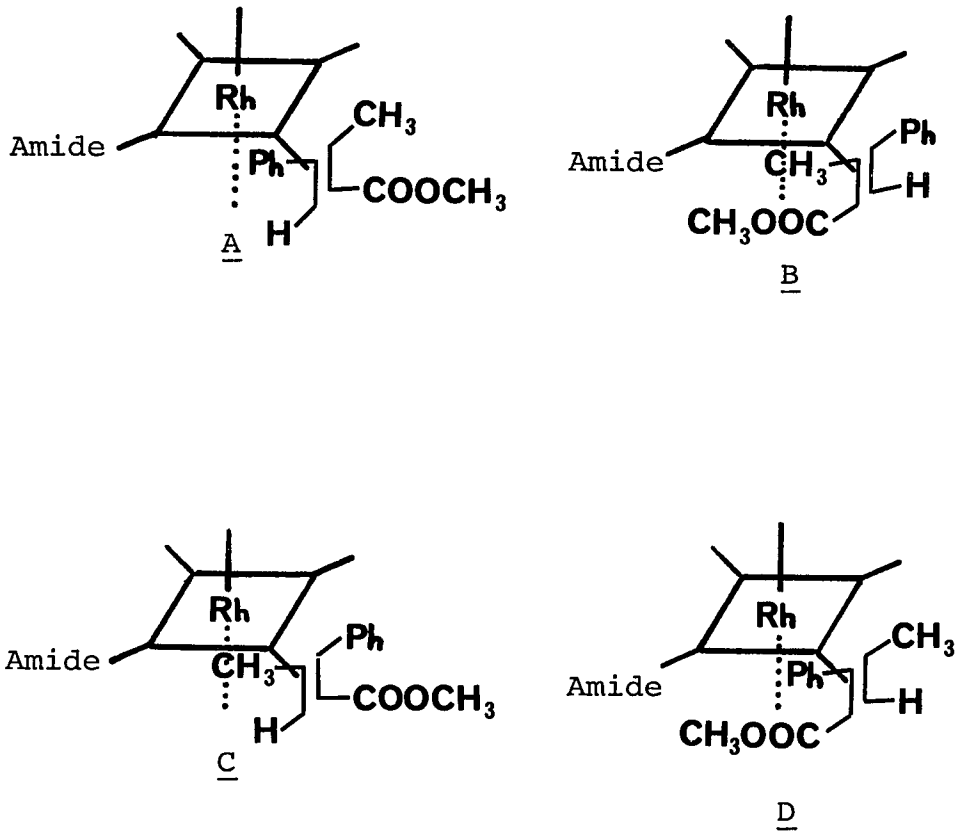


Figure 19. Four of the possible arrangements* of substrate and catalyst in the reduction of (E)- and (Z)-methyl-β-cinnamate with rhodium(III)-chiral amide complexes.

*Another set can be generated by rotating the olefin 180° about an axis perpendicular to the plane of asymmetry of the olefin.

carbon center, i.e., with the phenyl group remote." These assumptions, according to the authors, minimize both the steric compression of the coordinated amide and the steric compression between the amide and the butanoate substituent groups. In this way, the minimum activation energy is required to achieve the presumed transition state depicted in Figure 17.

Hydrogenolysis of the rhodium-carbon bond with retention of configuration leads to a product of the expected chirality.

The data supporting the stereochemical correlation rationale of McQuillin were generated using only two substrates, (E)- and (Z)-methyl-β-methylcinnamate, and, the (Z)-ester was reduced in the pressure of only two different ligands. It would be dangerous to infer that the correlation scheme will apply to olefins other than the isomeric methyl-β-methylcinnamates and ligands other than those used in the study.

Horner and Siegel have studied the homogeneous asymmetric hydrogenation of α-substituted styrene derivatives.[62,66] Phosphines of the general type CH_3PhPY (where Y was n-C_3H_7, i-C_3H_7, n-C_4H_9, or t-C_4H_9) were used to prepare the catalysts. The optical purities of the products were rather low (2-19%). Varying the temperature or the rhodium to phosphine ratio had little effect on the optical purity of the product. However, additives such as sodium ethoxide, ethanol, and acetone sometimes caused drastic changes in the stereochemical course of

the reaction which could not be rationalized with the stereo-correlation scheme outlined in a preliminary report (Figure 15).[62] Without additives there was a direct relationship between the absolute configuration of the chiral phosphine and the absolute configuration of the saturated alkane products. This relationship allowed Horner to assign the absolute configurations to two chiral products, $PhCH(i\text{-}Pr)CH_3$ and $PhCH(t\text{-}Bu)CH_3$.[66]

An unexpected result was recorded by Knowles who found that the reduction of atropic acid by a catalyst made from methylphenyl-n-propylphosphine was very sensitive to the ratio of phosphine to rhodium. At a ligand to rhodium ratio of 2, atropic acid was reduced to give a racemic product. When excess ligand was added, however, the rate of hydrogenation increased and the optical purity of the product rose to 23% at a phosphine to rhodium ratio of 16. On the other hand, 1-octene was readily reduced at a ligand to rhodium ratio of 2, but at a ratio of 16, the reaction was completely inhibited. The difference in behavior between 1-octene and atropic acid has been ascribed to a 1,4-addition of the ligand to the α,β-unsaturated acid to give a phosphonium salt. The phosphonium salt can function as a base and abstract a proton from the free unsaturated acid to form an atropate salt (Figure 20). Then the anion of the α,β-unsaturated acid rather than the free acid is reduced when the phosphine is present in large excess. Experimental evidence for this view of the reaction was the observation

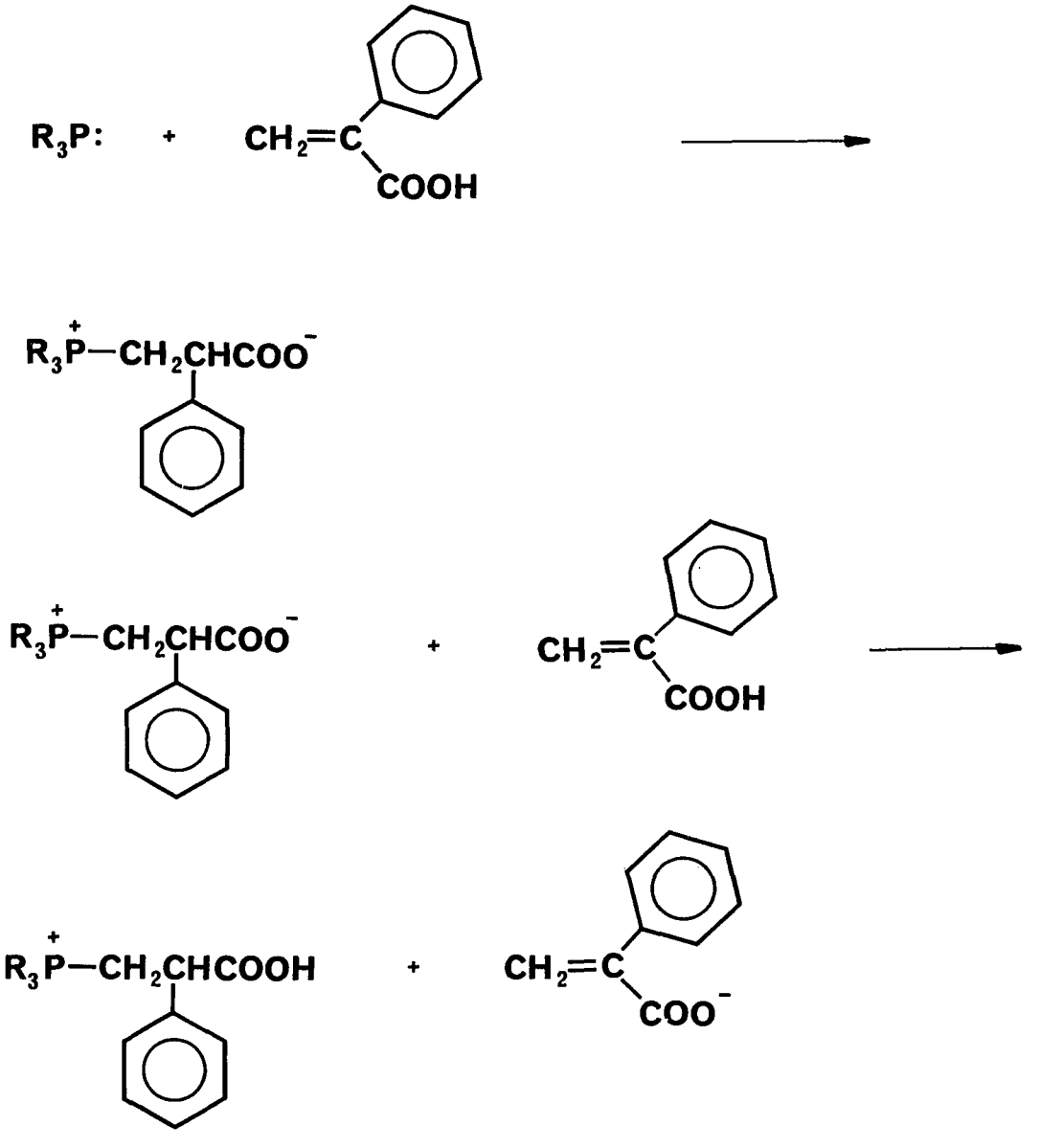


Figure 20. The reaction of a tertiary phosphine with atropic acid

that the addition of triethylamine to a hydrogenation mixture (Table 8) caused the same effects as excess phosphine.

Chirality at phosphorus in a tertiary phosphine ligand is not a necessary condition for asymmetric reduction by homogeneous rhodium(I)-phosphine catalysts. In principle, chirality anywhere in the ligand is sufficient to give the complex the potential for diastereomeric interactions with prochiral substrate molecules. That this is true has been experimentally demonstrated in this laboratory.[69] When (E)-β-methylcinnamic acid was hydrogenated (300 psi, 60°, 24 hr) in the presence of triethylamine (mol ratio Et_3N : substrate = 1:6) with a catalyst presumed to be tris(neomenthyldiphenylphosphine)rhodium(I) chloride. Chiral (+)-S-3-phenylbutyric acid (61% ee) was isolated in 80% yield. Other α,β-unsaturated acids and olefins were also asymmetrically reduced (Figure 21 and Table 9).[70]

A comparison of the effectiveness of various tertiary phosphine ligands chiral at both carbon and phosphorus (Figure 22) in hydrogenations of atropic acid (Table 10) shows that phosphines chiral at carbon can be more effective than those chiral at phosphorus in some cases.

The actual synthetic utility of rhodium-chiral tertiary phosphine catalysts made from phosphines chiral at phosphorus has been demonstrated by Knowles and coworkers.[68] Nearly complete stereospecificity in the synthesis of amino acid derivatives has been achieved. The Knowles group felt that the synthesis of chiral phosphines with

Table 8. Hydrogenation of atropic acid in the presence of excess phosphine[a] and triethylamine.[b]

R_3P:Rh	Et_3N:Rh	T°C	Relative Rate	Product Optical Purity, % ee
2:1	0	60	1	1
3:1	0	60	4	16.6
8:1	0	60	8	21.6
16:1	0	60	8	23.0
2:1	6	60	30	22.8
2:1	225	25	9	27.7

a) In all cases the phosphine was (-)-R-methylphenyl-n-propylphosphine.

b) All reactions were run at a substrate : rhodium rate of 232.

Table 9. Hydrogenation of α,β-unsaturated carboxylic acids and olefins over tris(neomenthyldiphenylphosphine)rhodium(I) chloride.

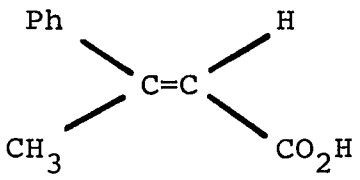
Substrate	Yield, %	Product Configuration	Optical Purity, % ee
(E)-β-Methylcinnamic Acid	80	(+)-S	61
(E)-α-Methylcinnamic Acid	80	(-)-R	52
Atropic Acid	82	(+)-S	28
α-Ethylstyrene	50	(-)-R	7
(Z)-β-Methylcinnamic Acid	80	(-)-R	20
(E)-α-Phenylcinnamic Acid	100	(+)-S	12
Itaconic Acid	100	(+)-R	6
Mesaconic Acid	(a)	-----	--
Citraconic Acid	88	-----	0

a) Mesaconic acid was not reduced under the conditions employed in this study.

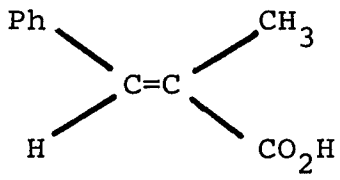
Table 10. Hydrogenation of atropic acid by chiral rhodium(I)-tertiary phosphine catalysts.

Configuration of Ligand	Ligand	Product Optical Purity, % ee	Configuration
(+)-S	2-Methylbutyldiphenylphosphine[70]	0.2	R
(+)-S	2-Phenylbutyldiphenylphosphine[70]	2.4	S
(-)-R	3-Phenylbutyldiphenylphosphine[70]	1.7	R
(+)-(1R,3S,4S)	NMDPP[70]	28	S
a	Methylphenyl-n-propylphosphine[67]	21	a
a	Methylphenyl-2-butylphosphine[67]	15	a
a	Methylisopropylphenylphosphine[67]	17.5	a
a	Cyclohexylmethylphenylphosphine[67]	3	a
(-)-(2R,3R)	DIOP[71]	63	S
(+)-R	ACMP[78]	1	a

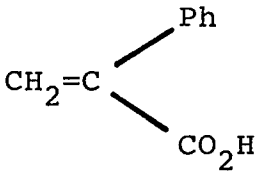
a) The sign and configuration were not stated.



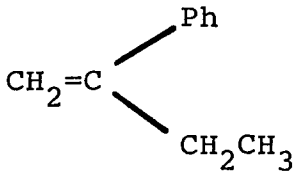
(E)-β-Methylcinnamic Acid



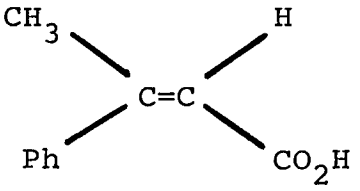
(E)-α-Methylcinnamic Acid



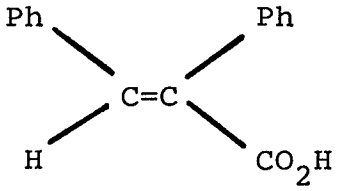
Atropic Acid



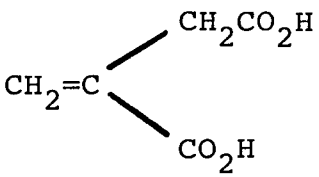
α-Ethylstyrene



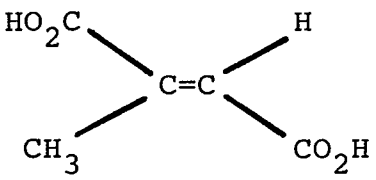
(Z)-β-Methylcinnamic Acid



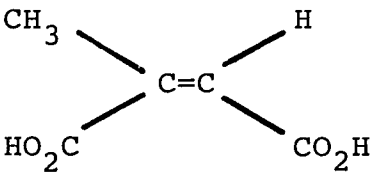
(E)-α-Phenylcinnamic Acid



Itaconic Acid

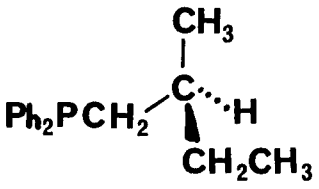


Mesaconic Acid

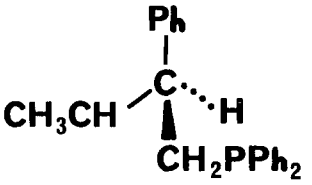


Citraconic Acid

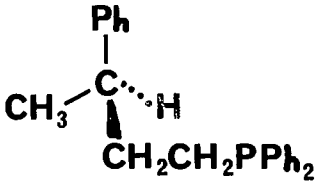
Figure 21. Substrates reduced by tris(neomenthyldiphenylphosphine)rhodium(I) chloride.



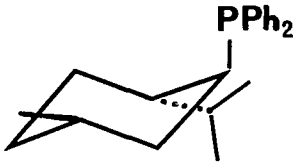
(+)-S-2-Methylbutyl-diphenylphosphine



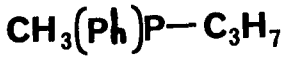
(+)-S-2-Phenylbutyl-diphenylphosphine



(-)-R-3-Phenylbutyl-diphenylphosphine



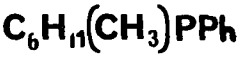
(+)-(1R, 3S, 4S)-NMDPP



Methylphenyl-n-propylphosphine

Methylphenyl-2-butylphosphine

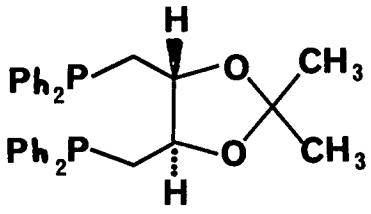
Methylisopropylphenylphosphine



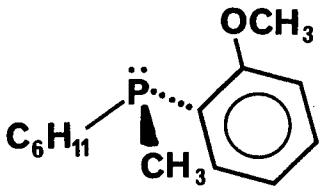
Cyclohexylmethylphenyl-phosphine

Figure 22. Chiral phosphine ligands used in asymmetric homogeneous hydrogenations.

Figure 22. (continued)



(-)-(2R, 3R)-DIOP



(+)-R-ACMP

R groups chosen to accentuate the difference between the small, medium, and large groups on phosphorus would not be fruitful. Instead, they devised a synthetic route to chiral phosphines containing a methoxy group which they hypothesized could function as a hydrogen bonding site between the catalyst complex and suitable substrate molecules. Such an attractive force between the substrate and the chiral catalyst would be expected to lend greater rigidity to the catalyst-substrate association and could lead to increased stereoselectivity. The catalyst prepared from one of these phosphines, o-anisylcyclohexylmethylphosphine (ACMP) was used in the asymmetric homogeneous hydrogenation of α-acylaminoacrylic acids; α-acylamino acids were prepared in yields of 85-90% and with up to 90% optical purity (Table 11).[68]

From Table 11 it is obvious that there is great variation in product optical purity with variations in the substrate and phosphine structures. The importance of matching substrates with chiral catalysts to obtain maximum chemical yield and optical purity cannot be too highly stressed.

In their initial studies the Knowles group used a rhodium(III) catalyst, trichlorotris(methylpropylphenylphosphine)rhodium(III).[57] It is easy to envision rhodium(I) species as also being involved due to the reversible oxidation shown in Figure 23.

Table 11. Reduction of some α-acylaminoacrylic acids with rhodium(I)-tertiary phosphine catalysts.

Chiral Phosphine				Substrate		
	R_2			$R_4CH=C(NHCOR_5)CO_2H$		
R_1-P-R_3						
R_1	R_2	R_3	Phosphine % ee	R_4	R_5	Product Optical Purity, % ee
o-Anisyl	Me	Ph	95	3-MeO-4-(OH)C_6H_3	Ph	58[b]
Me	Ph	n-Pr	90	3-MeO-4-(OH)C_6H_3	Ph	28[c]
Me	Ph	i-Pr	90	3-MeO-4-(OH)C_6H_3	Ph	28[c]
m-Anisyl	Me	Ph	80	3-MeO-4-(OH)C_6H_3	Ph	1[c]
o-Anisyl	C_6H_{11}	Me	95	3-MeO-4-(OH)C_6H_3	Ph	87[d]
o-Anisyl	C_6H_{11}	Me	95	3-MeO-4-(OH)C_6H_3	Ph	90[e]
C_6H_{11}	Me	Ph	75	3-MeO-4-(OH)C_6H_3	Ph	32[c]
o-Anisyl	Ph	i-Pr	80	3-MeO-4-(OH)C_6H_3	Ph	1[c]
o-Anisyl	Me	Ph	95	3-MeO-4-(OAc)C_6H_3	Me	55[b]
o-Anisyl	Me	n-Pr	95	3-MeO-4-(OAc)C_6H_3	Me	20[c]
o-Anisyl	C_6H_{11}	Me	90	3-MeO-4-(OAc)C_6H_3	Me	77[f]
o-Anisyl	C_6H_{11}	Me	95	3-MeO-4-(OAc)C_6H_3	Me	85[d]
o-Anisyl	C_6H_{11}	Me	95	3-MeO-4-(OAc)C_6H_3	Me	88[e]
o-Anisyl	C_6H_{11}	Me	95	Ph	Me	85[d]
o-Anisyl	C_6H_{11}	Me	95	Ph	Ph	85[d]
o-Anisyl	C_6H_{11}	Me	95	H	Me	60[d]

FOOTNOTES

a) The % ee was determined by direct comparison of the total reaction mixture with a blank from authentic acylated amino acid in order to avoid enrichment from workup or contribution by the catalyst.

b) The reductions were run in a stirred autoclave in methanol at 55 psi (absolute) of H_2 at 500° with 1 equivalent of NaOH. The catalyst to substrate mol ratio was 1 to 3000.

c) The reduction was run in a Parr shaker in methanol at 55 psi (absolute) at 25°.

d) The reduction was run in a Parr shaker in 95% ethanol at 10 psi (absolute).

e) The reduction was run in a Parr shaker in isopropanol.

f) The reduction was run as described in b with 0.05% triethylamine instead of NaOH.

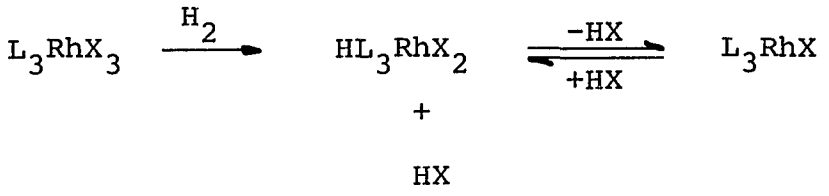


Figure 23. The reversible oxidation of L_3RhX.

In later studies, however, the <u>in situ</u> preparation of rhodium(I) catalysts proved to be experimentally easier. When phosphine ligands were added to a solution of $[Rh(diene)Cl]_2$ the chloride bridges were cleaved and a catalytic species was generated. Two ligands per rhodium have been shown to give optimum results. Preparation of the catalyst from $[Rh(1,5\text{-hexadiene})Cl]_2$ and o-anisylcyclohexylmethylphosphine (ACMP) gave results identical to those obtained from the crystalline, air stable, cationic complex $[Rh(1,5\text{-cyclooctadiene})(ACMP)_2]^+BF_4^-$ or BPh_4^-.[68] These data suggest that the <u>in situ</u> catalyst is also a cationic catalyst.

The Knowles group has continued its study of catalysts with ligands chiral at phosphorus and has prepared a series of chiral phosphines and cationic catalysts of the type $Rh(diene)L_2^+$, X^-, the most effective of which was 1,5-cyclooctadiene-bis(<u>o</u>-anisylcyclohexylmethylphosphine)rhodium(I) tetrafluoroborate. It was used to reduce α-acetamidocinnamic acid to N-acetylphenylalanine with optical purity as high

as 88%. A dependence on temperature and pressure was seen, but there was no significant difference in the product optical purity in going from methanol to isopropanol solvent. The free acid and the anion gave products of approximately the same optical purity (Table 12).[78]

Dang and Kagan have made the observation that the catalytic complex L_2H_2RhCl(olefin) is actually composed of a pair of enantiomers (Figure 24).[72] Resolution of the racemic catalyst complex into the two enantiomeric forms, while it would give a chiral catalyst, was considered not to be feasible experimentally. Rather than to resolve a complex which would be chiral at rhodium, these workers, like others, chose to use chiral ligands to impart chirality to the complex. Chiral diphosphine ligands were chosen for the study because of their ability to chelate the metal atom and give a more rigid complex than would be expected for monophosphine ligands. The ligands possessed two equivalent phosphorus atoms, thereby avoiding any possibility of geometrical isomerism about rhodium.[72]

Very high optical yields of α-acylamino acids have been realized using a diphosphine ligand containing multiple chiral centers. Catalysts containing (-)-DIOP, (-)-2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)-butane (26), prepared from (+)-ethyl tartrate, have been used to reduce α-acylaminoacrylic acids to α-acylamino acids in optical purity as high as 72%. Atropic acid was hydrogenated to (+)-S-hydratropic acid with 63% optical purity,

Table 12. Hydrogenation of a α-acetamidocinnamic acid with $[Rh(COD)(ACMP)]^+ BF_4^-$.[79]

Solvent	Added Base	T°C	Absolute Pressure, Atm.	Approximate Relative Rate	Product Optical Purity, % ee
i-PrOH, 88%	No	25	27	1.5	55
i-PrOH, 88%	No	25	3.5	1.0	80.5
i-PrOH, 88%	No	25	0.7	0.13	87.0
i-PrOH, 88%	No	50	3.5	2.0	80.5
MeOH	Yes	50	3.5	0.7	56
MeOH	Yes	25	3.5	0.3	79
MeOH	Yes	0	3.5	0.1	79
MeOH	Yes	25	21	0.5	88
MeOH	No	25	3.5	1.0	71

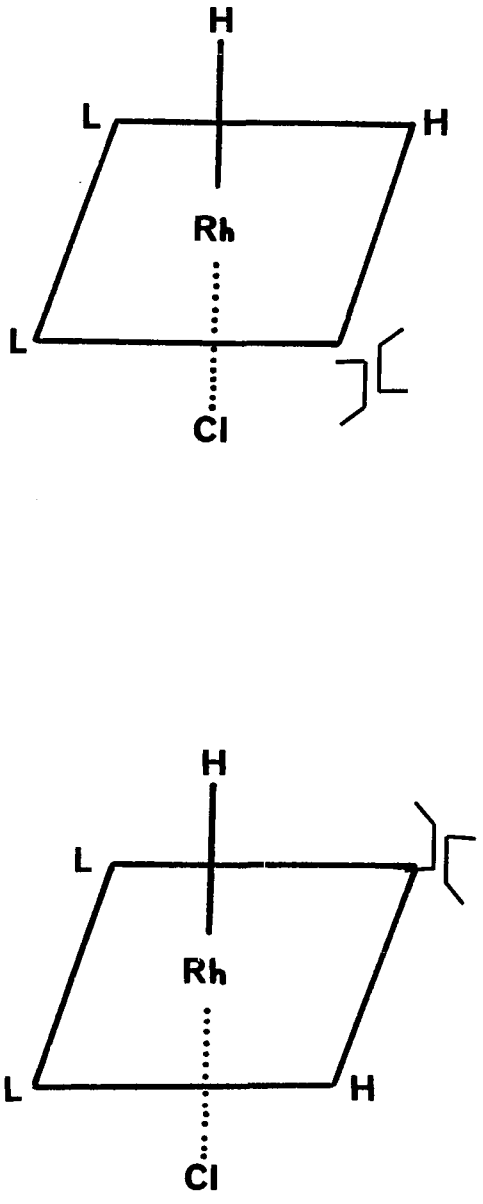
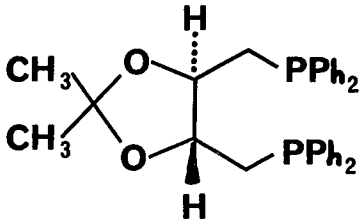


Figure 24. Enantiomeric forms of the complex L_2H_2RhCl-(olefin).

but interestingly, methyl atropate was hydrogenated to methyl hydratropate in only 7% optical purity and having the opposite configuration.[71]

Two ligands were studied initially; DIOP, (+)- or (-)-2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (26) and the open chain analog, (+)- or (-)-2,3-dimethoxy-1,4-bis(diphenylphosphino)butane (27). DIOP was preferred over the open chain analog due to the greater ease of purification of the former. The high stereoselectivity observed in reductions employing DIOP as a ligand may be attributable in part to the greater rigidity imparted to the chelate by the trans configuration of the dioxolane ring.



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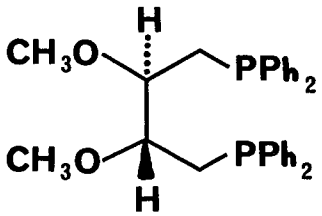

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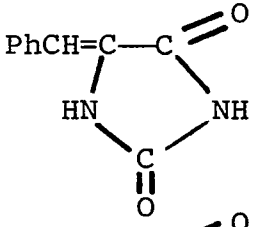
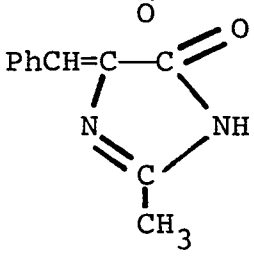
Kagan formed his catalyst, Rh(DIOP)Cl(S), in situ from 1 mole of $[Rh(cyclooctene)_2Cl]_2$ and two moles of (-)-DIOP ligand in benzene-ethanol (1:2). Various α-acylaminoacrylic acids were hydrogenated at room temperature and one atmosphere pressure in optical purities ranging from 22 to 80% (Table 13).[72]

Table 13. Hydrogenation of α-acylaminoacrylic acids over Rh(DIOP)Cl(S).

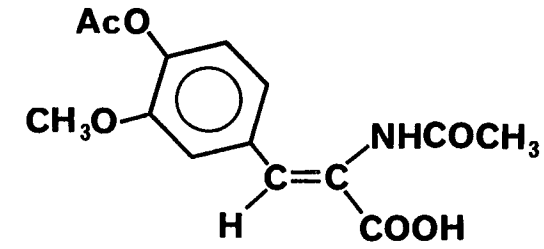
Substrate	Substrate Rh	Synthetic Yield, %	Configuration	Product Optical Purity % ee
$PhCH{=}C(NHCOCH_3)CO_2H$	540	95	R	72
$PhCH{=}C(NHCOPh)CO_2H$	200	96	R	64
$PhCH{=}C(NHCOCH_3)CO_2CH_3$	150	90	R	55
$PhCH{=}C(NHCOCH_3)CONH_2$	75	72	R	71
	---	N.R.	-	--
	---	N.R.	-	--
$CH_2{=}C(NHCOCH_3)CO_2H$	150	96	-	73
$4\text{-}(OH)C_6H_4CH{=}C(NHCOCH_3)CO_2H$	100	92	-	80
$3,4\text{-}(CH_2O_2)C_6H_3CH{=}C(NHCOPh)CO_2H$	50	97	-	79
$4\text{-}(OH)C_6H_4CH{=}C(NHCOPh)CO_2H$	80	95	-	62
$(CH_3)_2CHCH{=}C(NHCOPh)CO_2H$	75	98	-	22
$(CH_3)_2C{=}C(NHCOPh)CO_2H$	--	N.R.	-	--

An interesting feature of the DIOP system is that added base has little effect on the hydrogenation of α-acylaminoacrylic acids. The rate of hydrogenation of α-acetamidocinnamic acid, a trisubstituted olefin, was greater, under the same conditions, than that of a disubstituted olefin, atropic acid. In contrast to the results of other groups who have shown that substrates with free carboxyl groups generally gave higher optical yields than those substrates without the free carboxyls, the Kagan group discovered that in the reduction of α-acetamidocinnamic acid with the DIOP catalyst, a free carboxylic acid function did not seem to be a critical structural feature. The methyl ester and amide of α-acetamidocinnamic acid also gave high optical purities on hydrogenation. The high stereoselectivity of the reaction, according to Kagan, may be due to a loose coordination between the transition metal and the enamide function since the hydrogenation of 1-acetamido-1-phenylpropene proceeds to give a saturated product in 95% yield and 78% optical purity.[72] Kagan has not speculated on the precise nature of the coordination.

The work of Knowles and coworkers has clearly shown the great change in optical yields with variations in the structure of the chiral ligand. Kagan, too, has demonstrated the delicate relationship between ligand structure and reduction stereochemistry with various modifications of DIOP. When the phenyl groups of DIOP were replaced by m-tolyl groups, the hydrogenation of α-acetamidocinnamic acid gave

the expected N-acetyl-R-phenylalanine, but with an optical yield lowered to 39%.[72] In the Rh(DIOP)Cl(S) catalyzed hydrogenation of 3-methoxy-4-acetoxyphenyl-α-acetamidoacrylic acid (28) to the saturated dopa derivative 29, Kagan achieved 90% ee (D configuration).[73] Unexpectedly, when 28 was hydrogenated with the catalyst prepared from the modified DIOP 30, a reversal of stereochemistry was observed and the saturated dopa derivative 29 was obtained (35% ee, L configuration).[73] This example serves to underscore the fact that the theory of asymmetric homogeneous hydrogenation has not been developed fully enough to allow one to predict the stereochemical outcome of a reduction with any degree of certainty.

A potentially useful development in the field of homogeneous catalysis has been the development of insolubilized catalytically active transition metal complexes. These complexes exhibit some features of both homogeneous and heterogeneous catalysts. The catalyst need not be destroyed during product workup, and greater air stability of the catalyst is observed. In addition, solvent channels in the polymer support allow soluble substances to enter and leave the reaction site; the pores of the polymer are capable of excluding certain olefins on the basis of molecular size from the reaction sites.[74,75,76] Perhaps most important for the industrial chemist is the fact that polymer supported homogeneous catalysts readily lend themselves to continuous flow processes and are not limited



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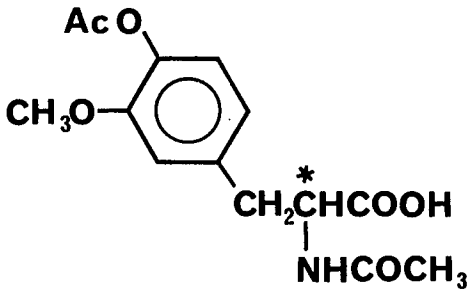

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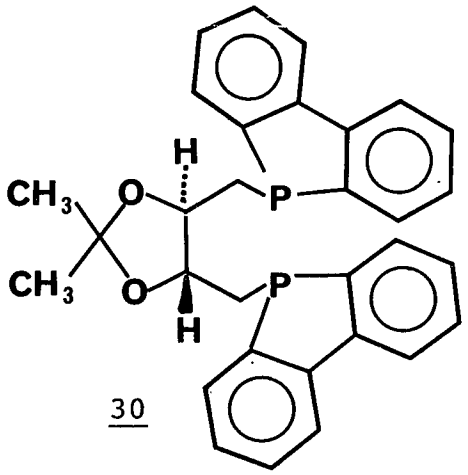

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to more inefficient batch processes as are their soluble counterparts.

Grubbs and Kroll found that when chloromethylated polystyrene beads were treated with lithium diphenylphosphide 80% of the chlorine atoms were replaced to give a polymer containing tertiary phosphine groups. This polymer was then equilibrated with tris(triphenylphosphine)rhodium-(I) chloride to give an insolubilized catalyst.[74]

The insolubilized catalyst was used to hydrogenate a variety of olefins, and the relative rates of hydrogenation were compared to the rates of hydrogenation of the same olefins over Wilkinson's catalyst (Table 14). The rate of reduction was found to be dependent upon the molecular size of the olefin. A decreased rate for large olefins was attributed to their exclusion from the catalytically active sites due to restrictions in the size of the solvent channels caused by random crosslinks in the polymer. This observation tends to confirm that the major portion of the reduction takes place inside the polymer beads.[74] The insolubilized catalyst could be recovered by filtration and used many times.

Kagan has used an ingenious modification of this system to insolubilize a rhodium complex of DIOP. A Merrifield resin[77] was allowed to react with dimethylsulfoxide to convert the chloromethyl groups to aldehyde groups. The aldehyde resin was then allowed to react with (+)-1,4-ditosylthreitol to give an acetal resin. Displacement of the tosyl groups by sodium diphenylphosphide gave a phosphinated resin. Reaction of the phosphinated resin with μ-dichlorotetraethylenedirhodium(I) gave an active catalyst (Figure 25).[95]

The insolubilized DIOP catalyst was found to be rather poor for asymmetric hydrogenation; the hydrogenation of α-ethylstyrene proceeded readily, but gave (-)-R-2-phenylbutane with an optical purity of only 1.5%. Methyl atropate was hydrogenated to (+)-S-methylhydratropate (2.5%

Table 14. Relative rates of hydrogenation for various olefins over insolubilized homogeneous catalyst vs. Wilkinson's catalyst.

Olefin	Insolubilized Catalyst Relative Rate	(Ph P) RhCl Relative Rate
Cyclohexene	1	1.0
Hexene	2.55	1.4
Δ^2 Cholestene	0.0312	0.715
Octadecene (isomer mixture)	0.485	0.715
Cyclooctene	0.396	1.01
Cyclododecene (*cis* and *trans*)	0.225	0.667

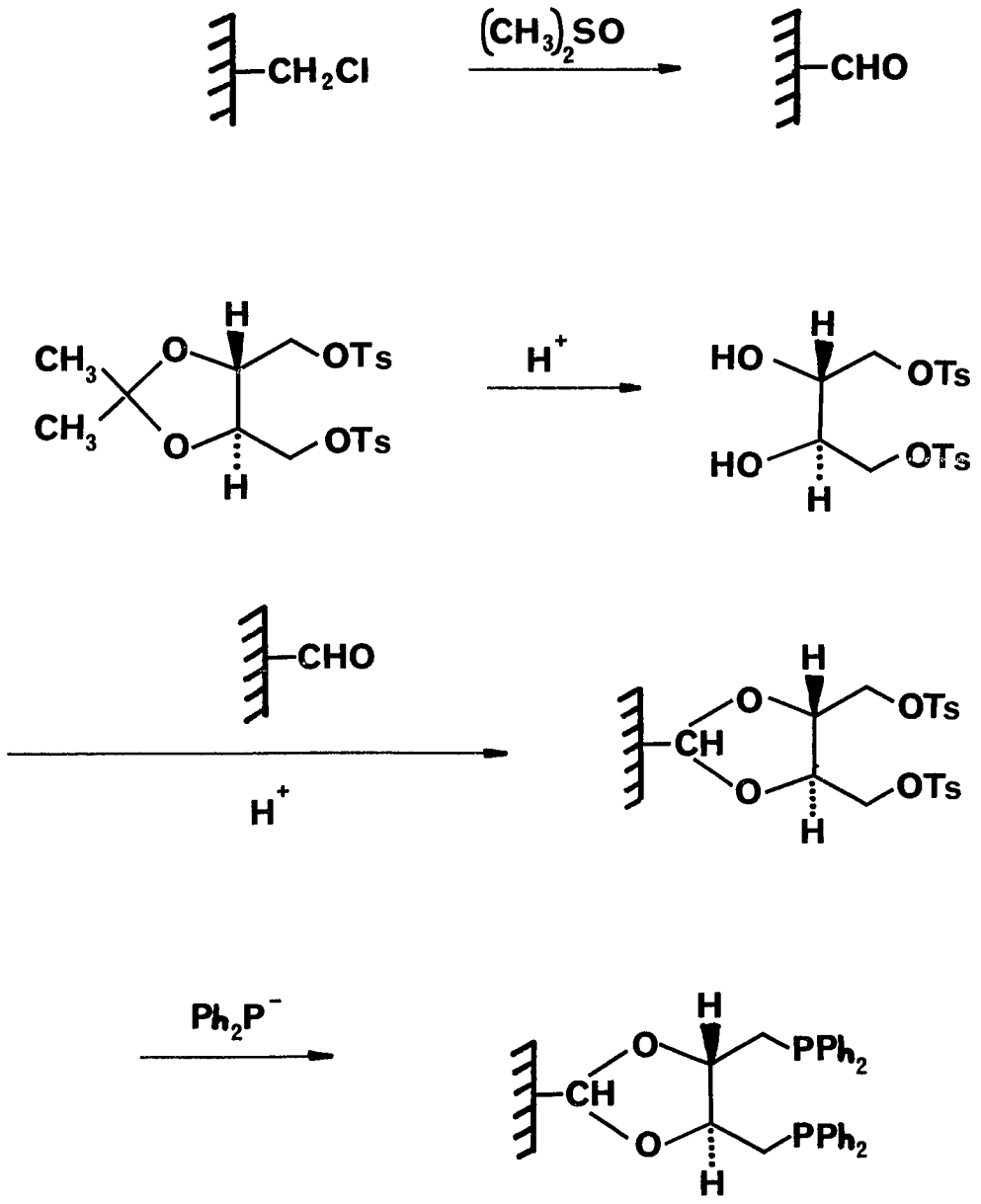


Figure 25. Synthesis of insolubilized DIOP.

ee). Soluble DIOP catalyst gave 15 and 17% ee, respectively, for the same reductions. The optical purity of the products was lower when recovered insolubilized catalyst was used. Kagan was unable to reduce α-acetamidocinnamic acid in ethanol-benzene with the insolubilized catalyst, presumably due to the hydrophobic nature of the polymer support which causes it to shrink in hydroxylic solvents.

Far better results were obtained for the asymmetric hydrosilylation of olefins over the insolubilized catalyst. Acetophenone, for example, was hydrosilylated with phenyl-naphthylsilane and the insolubilized catalyst. The product was hydrolyzed with HCl to give (-)-S-phenylmethylcarbinol (58% ee). Similar results were obtained for the homogeneous catalyst. Using diaryl or arylalkyl silanes, yields from 52-100% and optical purities of from 6.5-58.5% were realized (Table 15).[95]

Homogeneous rhodium(I)-chiral tertiary phosphine catalysts have been used to hydrogenate ketones, to hydrosilylate ketones and imines and to hydroformylate olefins.

Optical yields as high as 56% have been recorded in the direct asymmetric hydrogenation of ketones with $[Rh(COD)(ACMP)_2]^+ BF_4^-$.[80] Catalyst turnover ratios of over 1000 were observed and it was found that the reaction was quite dependent on the choice of solvent and water content. For example, the hydrogenation of 2-octanone in ethanol gave the (+)-S-carbinol with 1.6% ee; in DMF the R-carbinol was observed in 5.1% ee, and in acetic acid the R-carbinol

Table 15. A comparison of asymmetric synthesis of alcohols by hydrosilylation of ketones.[a] Insolubilized DIOP catalyst vs. solution DIOP catalyst.

Ketone	Silane	Ketone/Rh	Time, hr	Product Optical Purity % ee[b]	Product Optical Purity % ee[c]
Acetophenone	$H_2SiPhCH_3$	25	42	12	13
Acetophenone	$H_2SiPhCH_3$	25	26	8	--
Acetophenone	H_2SiPh_2	35	24	29	28
Acetophenone	H_2SiPh_2	35	18	22.5	--
Acetophenone	$H_2SiPh(C_{10}H_7)$	33	45	58.5	58
Acetophenone	$H_2SiPh(C_{10}H_7)$	20	24	55	58
Acetophenone	$H_2SiPh(C_{10}H_7)$	25	30	52	--
Phenylisopropyl ketone	$H_2SiPhCH_3$	25	48	6.5	20
Phenylisopropyl ketone	H_2SiPh_2	25	48	28	35

a) In all cases, the hydrosilylated product was hydrolyzed to the alcohol. The (-)-S-carbinol was obtained in every case.

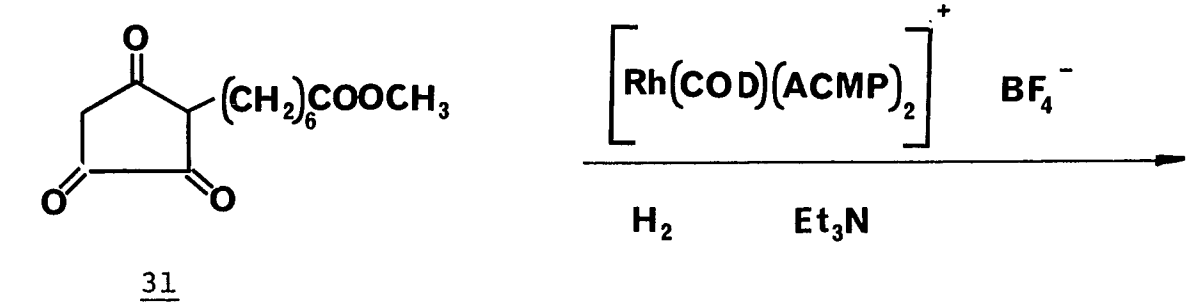
b) The reductions were performed with the insolubilized catalyst.

c) The reductions were performed with the soluble catalyst.

was observed in 12.0% ee. In varying the water content of the isobutyric acid solvent in the hydrogenation of 2-octanone from 0.1 to 8%, the optical yield dropped from 13.9% to 5.3%.

The synthetic utility of asymmetric homogeneous hydrogenation of ketones was demonstrated by Sih and coworkers.[96] The readily available starting material 2-(6-carbomethoxyhexyl)cyclopentane-1,3,4-trione (31) was hydrogenated in the presence of 1,5-cyclooctadiene-bis(o-anisylcyclohexylmethylphosphine)rhodium(I) tetrafluoroborate and triethylamine in methanol to give by direct crystallization 2-(6-carbomethoxyhexyl)-4-R-hydroxycyclopentane-1,3-dione (32) in 68% ee (Figure 26). This compound was converted to prostaglandin E_1 *via* a series of steps. The 68% ee reported does not accurately represent the optical yield of the reduction since the product was isolated by crystallization, the chemical yield was less than 50%, and the mother liquors from the crystallization were inactive.

A cationic complex $[Rh\{R\text{-}(PhCH_2)MePhP\}_2H_2S_2]^+ ClO_4^-$ prepared from $[Rh\{R\text{-}(PHCH_2)MePhP\}_2(NBD)]^+ ClO_4^-$ (NBD = norbornadiene) was used to hydrosilylate several alkylphenylketones. Optical yields ranging from 5 to 62% were reported, the most impressive being those for acetophenone (31.6% ee), ethylphenylketone (43.1% ee) and t-butylphenylketone (61.8% ee) when hydrosilylation was accomplished with phenyldimethyl-



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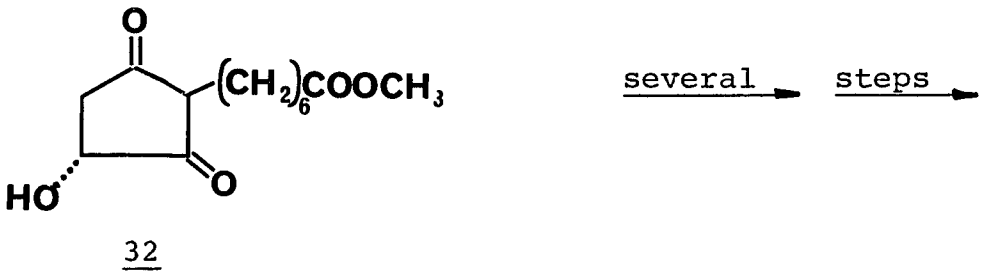

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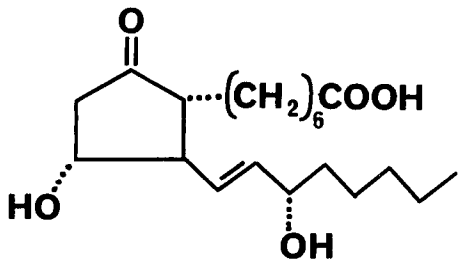


PGE_1

Figure 26. Asymmetric homogeneous hydrogenation of a ketone in the synthesis of prostaglandin E_1.

silane. Trimethylsilane gave lower optical yields.[81]

Asymmetric hydrosilylation of imines followed by hydrolysis of the N-silylamine yields chiral amines.[82] Kagan hydrosilylated a series of prochiral imines with both polymethylhydrogensiloxane and diphenylsilane over the catalyst Rh(DIOP)Cl(S) (Table 16). Product optical purities varied with the temperature, and low temperatures were found to give the highest optical yields.[82]

A number of groups have studied the hydroformylation of olefins over chiral rhodium(I)-tertiary phosphine catalysts.[83,84,85,86,87] A representative study is that of Stern and coworkers who studied hydroformylation of styrene to hydrotropaldehyde over a catalyst formed in situ from $Rh(C_2H_4)_2Cl_2$ and (+)-DIOP.[87] The optical yield was sensitive to temperature, pressure of the hydrogen and carbon monoxide, and phosphine concentration. Both hydrotropaldehyde and hydrocinnamaldehyde were produced. The best optical yield was 16% (Figure 27). Olefins have been hydroformylated over asymmetric homogeneous catalysts to yield chiral aldehydes in up to 27% ee (Table 17).

Table 16. Hydrosilylation of imines over Rh(DIOP)Cl(S).

Substrate	Silane	Product Configuration	Product Optical Purity, % ee
$PhC(CH_3)=NCH_2Ph$	H_2SiPh_2	S	50
$PhC(CH_3)=NCH_2Ph$	$(-SiH(CH_3)O-)_n$	S	3.4
$PhC(CH_3)=NPh$	H_2SiPh_2	S	40
$PhC(CH_3)=NPh$	$(-SiH(CH_3)O-)_n$	S	47
$PhCH_2C(CH_3)=NCH_2Ph$	H_2SiPh_2	S	11.5
$PhCH_2C(CH_3)=NCH_2Ph$	$(-SiH(CH_3)O-)_n$	S	13.8

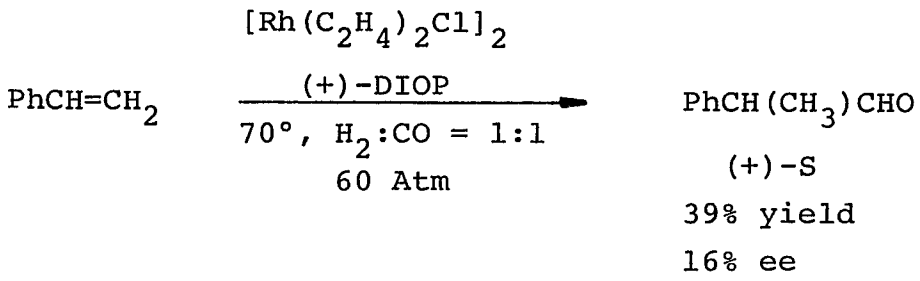


Figure 27. Hydroformylation of styrene over Rh(DIOP)Cl(S) and H_2/CO.

Table 17. Hydroformylation of olefins over chiral rhodium(I)-tertiary phosphine catalysts.

Substrate	Chiral Phosphine	Product	Product Optical Purity, % ee	Reference
$PhCH=CH_2$	(+)-R-$(PhCH_2)MePhP$	(+)-S-PhCHMeCHO	17.5	83
$PhCH=CH_2$	(+)-NMDPP	(+)-S-PhCHMeCHO	low[a]	84
$PhC(Et)=CH_2$	(+)-NMDPP	(+)-R-$PhCHEtCH_2CHO$	low[a]	84
$PhOCH=CH_2$	(+)-NMDPP	(-)-R-PhOCHMeCHO	low[a]	84
$PhCH=CH_2$	(-)-DIOP	(-)-R-PhCHMeCHO	3.8	86
$PhC(Me)=CH_2$	(-)-DIOP	(-)-R-$PhCMeCH_2CHO$	1.7	86
$PhCH=CH_2$	(-)-DIOP	(-)-R-CHMeCHO	25.2	86
$PhCH=CHCH_3$	(-)-DIOP	(-)-R-$PhCH_2CHMeCHO$	15.5	86
$PhCH=CH_2$	(+)-DIOP	(+)-S-PhCHMeCHO	16	87
cis-$CH_3CH=CHCH_3$	(+)-DIOP	( )-S-$CH_3CH_2CHMeCHO$	27	85

a) The optical purity was less than 2% ee.

RESULTS AND DISCUSSION

The work described was directed toward the synthesis of chiral catalysts for asymmetric homogeneous hydrogenation. Efficient syntheses for the chiral phosphine ligands, (+)-neomenthyldiphenylphosphine (NMDPP), its epimer (-)-menthyldiphenylphosphine (MDPP), and (+)-CAMPHOS were to be developed. The three phosphine ligands were to be used to form soluble rhodium(I) catalysts and the reduction of a series of α,β-unsaturated carboxylic acid substrates was to be investigated. The investigation was designed to encompass an unexplored area of asymmetric homogeneous hydrogenation, the effect of olefin geometry on the stereochemical outcome of the reductions. Furthermore, the epimeric nature of (+)-NMDPP and (-)-MDPP provided an opportunity to explore the relationship of one chiral center in two diastereomeric ligands to the stereochemistry of the reduction products. The products of the olefin reductions with catalysts made from (+)-NMDPP, (-)-MDPP, and (+)-CAMPHOS were to be compared to the products of olefin reduction by catalysts made from (-)-DIOP and ACMP. The latter two ligands have both given impressive results, especially in the reduction of α-acylaminoacrylic acids.

Synthesis of Chiral Phosphine Ligands

The earliest method of preparation of an optically active phosphorus compound was by resolution of a phosphine oxide. Meisenheimer resolved ethylmethylphenylphosphine oxide as the d-bromocamphor sulfonate salt.[99] Optically active phosphine oxides have also been prepared from resolved quaternary phosphonium salts[100] by reaction with sodium hydroxide[101] or by a Wittig sequence.[102] Optically active phosphines have been obtained by cathodic reduction of chiral quaternary phosphonium salts[103] or by trichlorosilane reduction of chiral phosphine oxides.[104]

These methods of synthesis of chiral phosphines all are intrinsically limited. The groups attached to phosphorus must be present prior to resolution and furthermore, the preparation of phosphine oxides and phosphines from quaternary phosphonium salts by chemical or electrochemical cleavage reactions requires that one of the groups bonded to phosphorus be substantially easier to cleave than the other three.

A newer synthetic approach that overcomes some of the difficulties inherent in earlier methods has been described by Mislow.[105] It involves a modification of the procedure used by Andersen to prepare chiral sulfoxides.[106] Unsymmetrically substituted phosphinyl halides were esterified with (-)-menthol, and the resulting diastereomeric phosphinates were separated by fractional crystallization.

Displacement of the menthyloxy group by an appropriate Grignard reagent gave chiral tertiary phosphine oxides. The tertiary phosphine oxides were reduced to the phosphines by one of several methods; trichlorosilane (retention of configuration), trichlorosilane and a weakly basic amine (retention), trichlorosilane and a strongly basic amine (inversion), and hexachlorodisilane (inversion). While it does not circumvent a classical resolution step, the Mislow approach does introduce greater flexibility since a number of chiral phosphines can be obtained from a single resolved precursor. Unfortunately the multistep synthesis of the diastereomerically pure menthyl phosphinate gives an overall yield of only about 10% (Figure 28).

Letsinger has developed a more direct method of preparation of menthyl phosphinates, however, the yield of the crucial diastereomerically pure menthyl phosphinate was only about 8% (Figure 29).[107a,b]

Synthesis of (+)-Neomenthyldiphenylphosphine and (-)-Menthyldiphenylphosphine

In the present research the synthesis of tertiary phosphine ligands having chiral carbon atoms was investigated. Rhodium(I) complexes of such ligands, like those from ligands chiral at phosphorus should, in principle, catalyze asymmetric hydrogenations. In addition to exploring this question further, the experimental complexities and relatively low yields obtained in the synthesis of diastereomerically pure menthyl phosphinates provided an added incentive to search

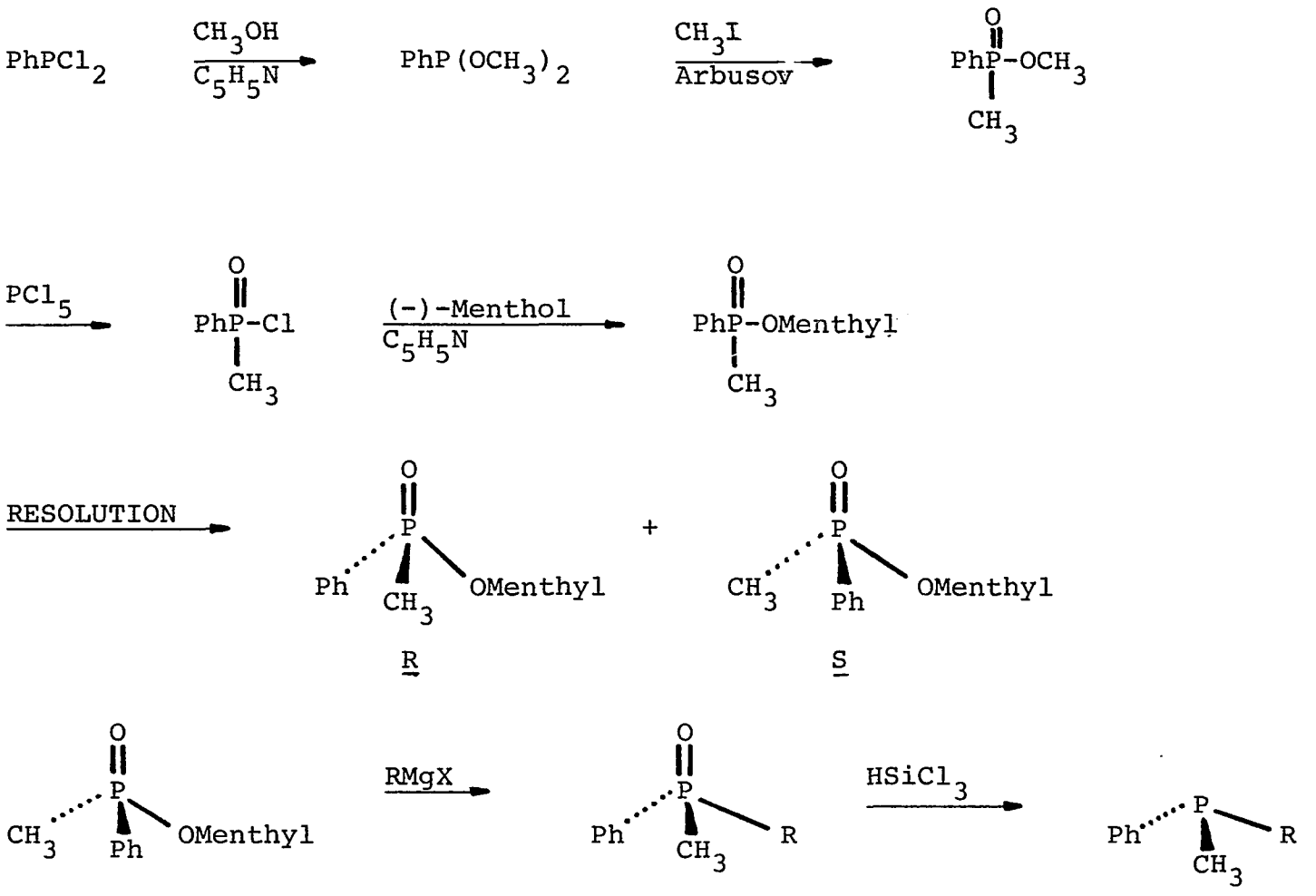


Figure 28. The synthesis of chiral phosphine oxides by reaction of Grignard reagents with diastereomerically pure menthyl phosphinates.

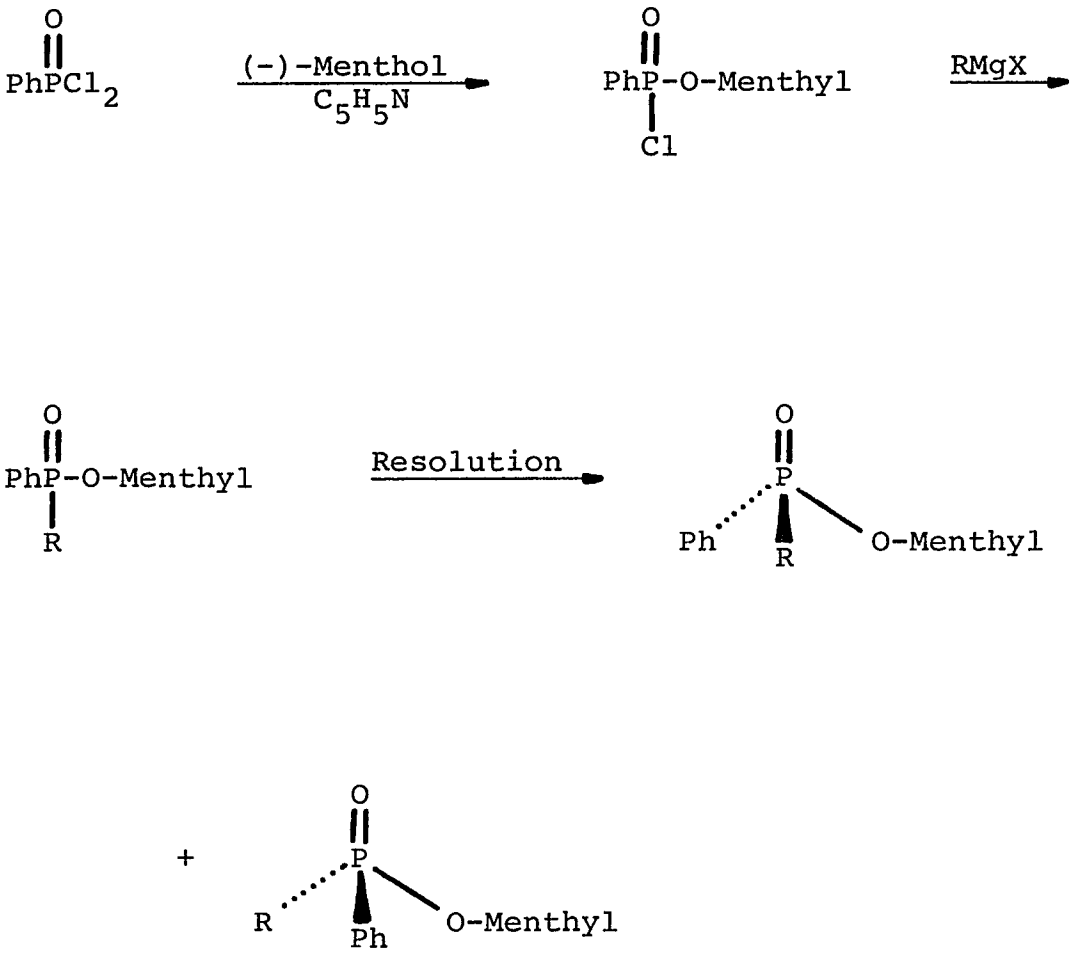


Figure 29. A modified procedure for the preparation of diastereomerically pure menthyl phosphinates.

for alternatives. It was hoped that efficient syntheses of phosphines with chirality remote from phosphorus could be found and that these compounds would be effective ligands for asymmetric homogeneous hydrogenations.

Burnett has already demonstrated in a preliminary study that rhodium(I) complexes of certain tertiary phosphines chiral at carbon indeed do asymmetrically reduce prochiral olefins.[69] Chiral phosphine ligands were prepared from chiral alkyl halides by halide displacement with the diphenylphosphide anion. For example, lithium diphenylphosphide was used to prepare (+)-S-2-methylbutyldiphenylphosphine (33), (+)-S-2-phenylbutyldiphenylphosphine (34), (-)-R-3-phenylbutyldiphenylphosphine (35), (+)-R-2-octyldiphenylphosphine (36) (stereochemistry presumed but not proved), and (+)-neomenthyldiphenylphosphine (39) from the appropriate chloride or bromide (Figure 30).

(+)-Neomenthyldiphenylphosphine proved to be the most promising of all the ligands studied by Burnett. Optical purities of reduction products as high as 61% ee were recorded.[69] (+)-NMDPP seemed to be an excellent ligand for study since the precursor, (-)-menthol, a natural product, was inexpensive, available in quantity and with an optical purity approaching 100%. In addition, this chiral phosphine ligand was produced in a two step reaction sequence rather than a five or seven step sequence as was required for phosphines chiral at phosphorus.

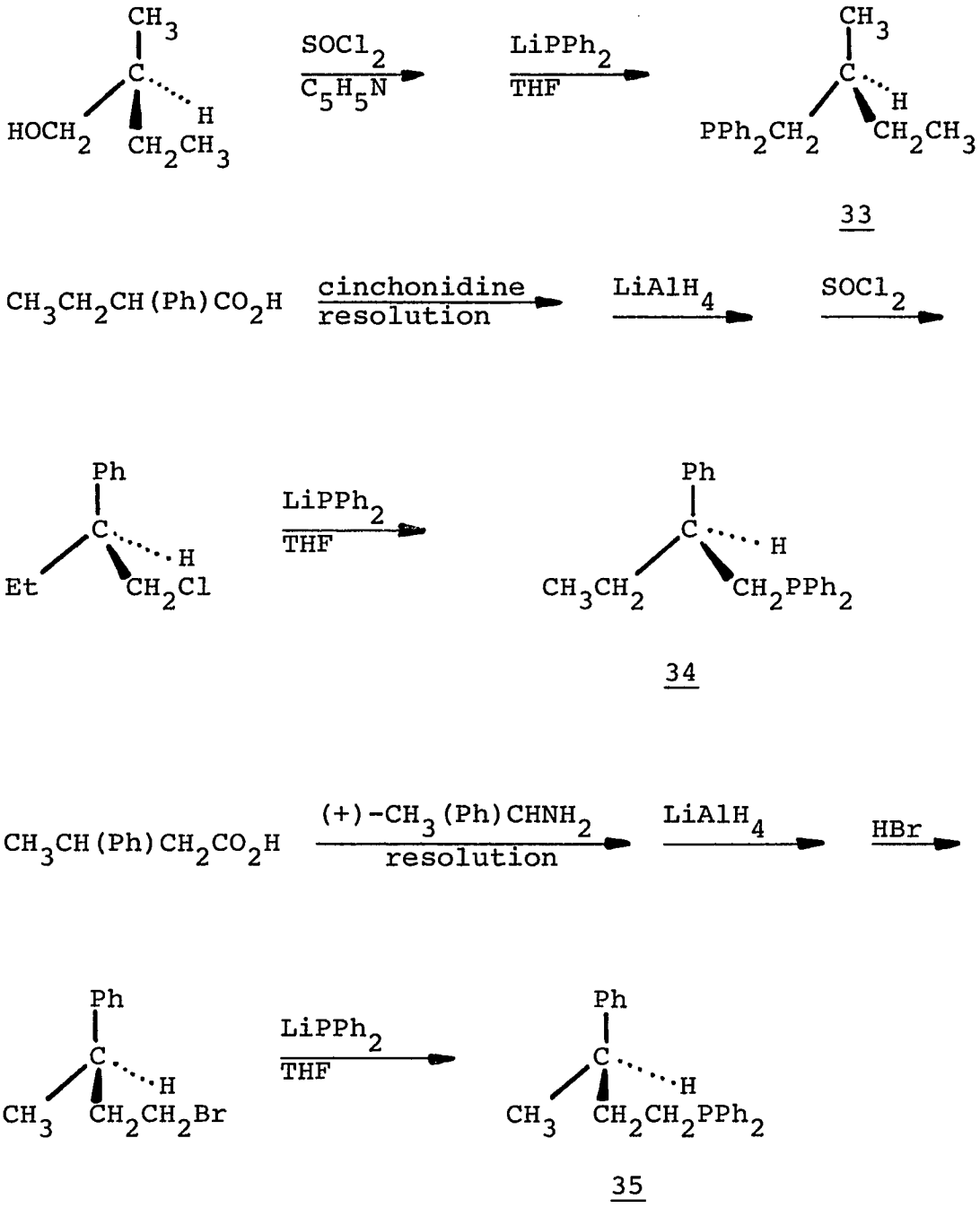
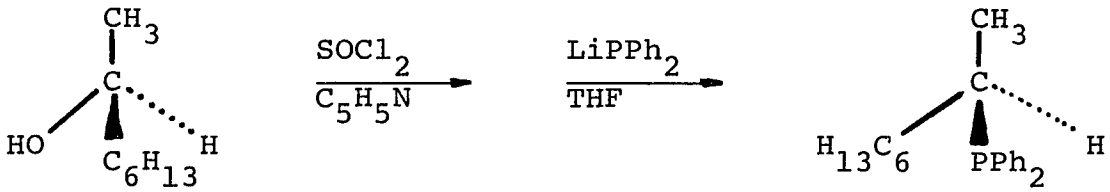


Figure 30. Synthesis of some tertiary phosphines that are chiral at carbon.

Figure 30. (continued)



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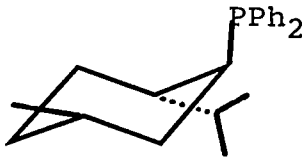

39

(+)-NMDPP was found to be unexpectedly difficult to synthesize, however. Several complications were encountered. First, displacement of halogen from (-)-menthyl chloride by lithium diphenylphosphide (prepared from chlorodiphenylphosphine and lithium in tetrahydrofuran), which proceeded readily at room temperature with some other primary and secondary halides, was very slow and prolonged reaction times and elevated temperatures were required to effect complete reaction. Second, the yield of tertiary phosphine product was lowered due to a competing elimination reaction in which the phosphide anion functions as a base rather than a nucleophile. Third, the product was contaminated with two tenacious impurities, 4-hydroxybutyldiphenylphosphine (from the ring opening of the tetrahydrofuran solvent by lithium diphenylphosphide) and (+)-neomenthyldiphenylphosphine oxide (NMDPP oxide) arising, most likely from air oxidation of (+)-NMDPP during workup.

Chlorodiphenylphosphine has been shown to react with alkali metals and magnesium in tetrahydrofuran solution to give 4-hydroxybutyldiphenylphosphine.[109] The ring opening reaction is specific for tetrahydrofuran; dioxane and aliphatic ethers are not affected. In the present study, on the other hand, sodium diphenylphosphide prepared from diphenylphosphine and sodium metal in either tetrahydrofuran or liquid ammonia gave no detectable ring opening of the tetrahydrofuran solvent, and this became our method of choice for the preparation of alkali metal phosphides.

The reaction of (-)-menthyl chloride with sodium diphenylphosphide in tetrahydrofuran required 48-54 hr at reflux temperature to achieve complete reaction. The elimination side reaction was still observed (Figure 31). However, the by-products (isomeric menthenes and diphenylphosphine) arising from the elimination reaction were easily removed by distillation. (+)-NMDPP oxide proved to be a very tenacious impurity, but careful crystallization of the phosphine from deoxygenated ethanol gave (+)-NMDPP in up to 95% purity. The phosphine was particularly sensitive to air oxidation in solution. The overall conversion of (-)-menthylchloride to (+)-NMDPP was about 34% not counting the (+)-NMDPP oxide produced.

The reaction of sodium diphenylphosphide with (+)-neomenthyl chloride (42) to give (-)-menthyldiphenylphosphine (43) proceeded much more readily than the corresponding reaction with (-)-menthyl chloride. This was as expected, since molecular models suggest that the steric interactions between the (+)-neomenthyl chloride and the incoming nucleophile are less severe than in the case of attack on (-)-menthyl chloride. As expected, the yield of (-)-MDPP was lower than the yield of (+)-NMDPP because elimination is a more serious competitive process in the case of (+)-neomenthyl chloride.* (-)-MDPP was easily purified by crystallization from ethanol, and a purity of 98% was attainable

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*The trans-diaxial relationship between the halogen and the hydrogens at C-2 and C-4 can account for the relative ease with which (+)-neomenthyl chloride undergoes E2 elimination.

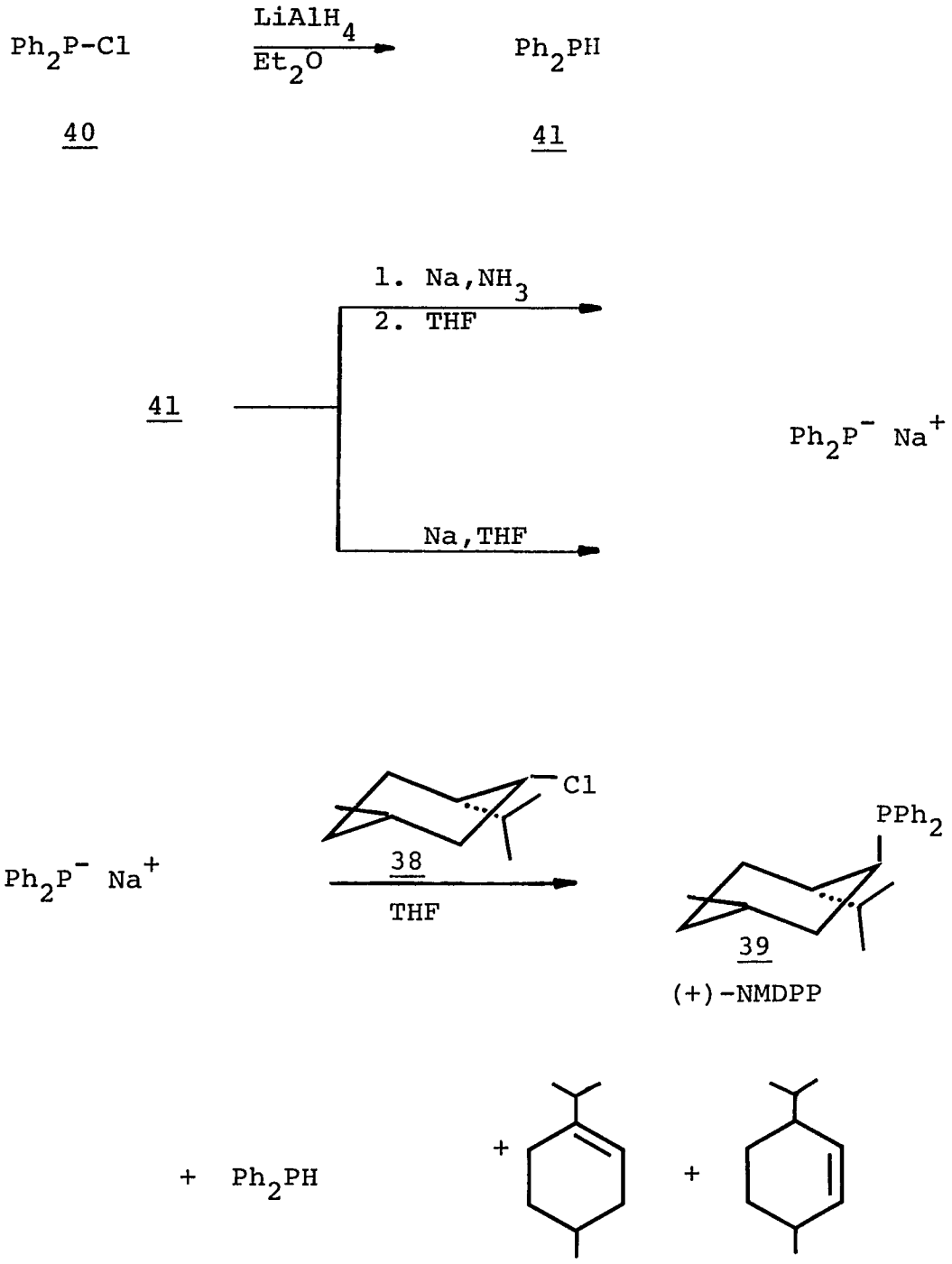


Figure 31. Synthesis of (+)-neomenthyldiphenylphosphine, (+)-NMDPP.

with one crystallization (Figure 32). The overall conversion of (+)-neomenthyl chloride to (-)-MDPP was 25-30%.**

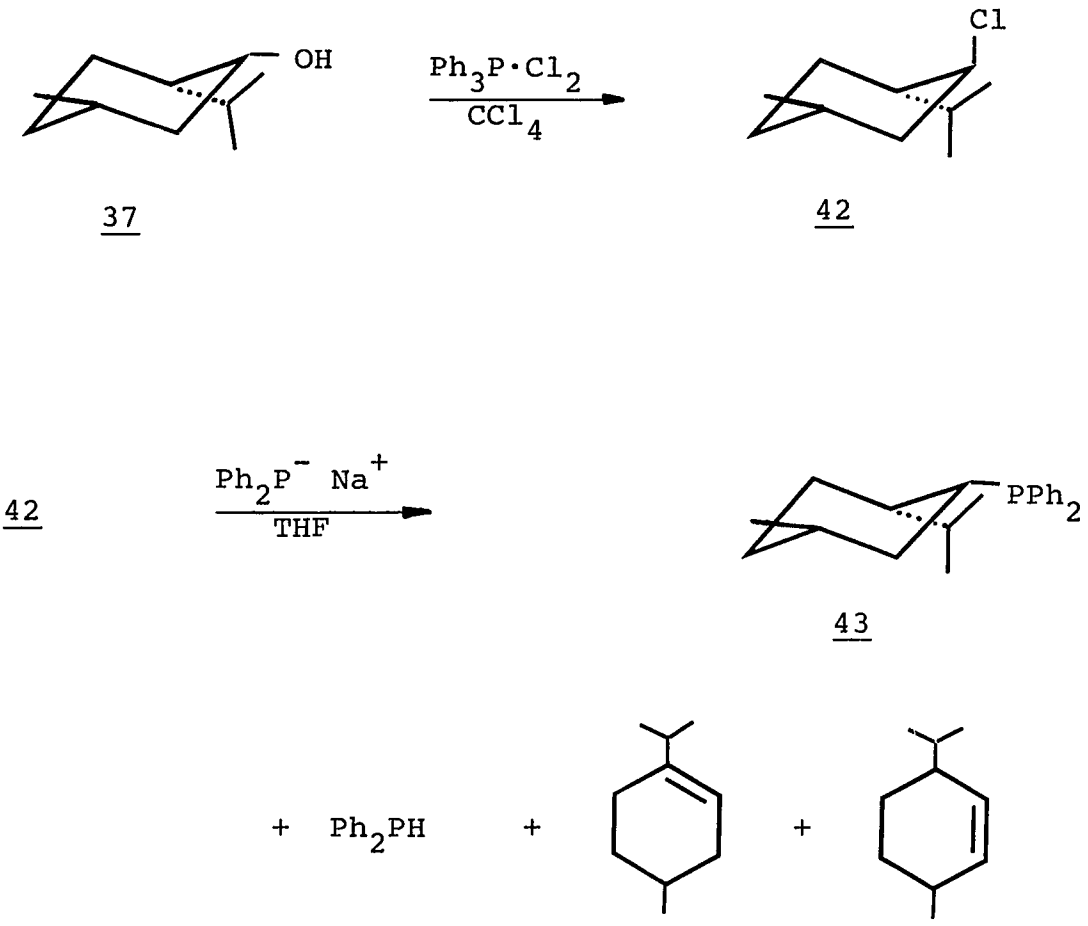
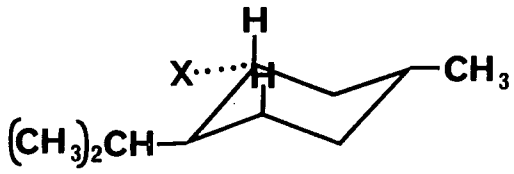


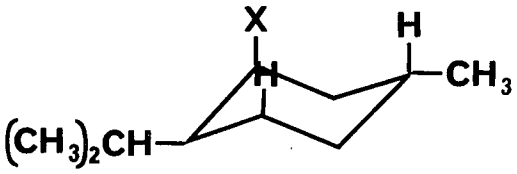
Figure 32. Synthesis of (-)-menthyldiphenylphosphine, (-)-MDPP.

**The diphenylphosphine elimination by-product from both the (+)-NMDPP and (-)-MDPP syntheses could be recovered and reused.

Displacement reactions of the diphenylphosphide anion at both saturated carbon and at vinylic centers have been studied. Vinyl halides undergo stereospecific displacement with retention of configuration to give vinyldiphenylphosphines.[111,112,113] As part of this study and in collaboration with others, nucleophilic displacement of halide ion from saturated carbon by the diphenylphosphide anion has been shown to occur with inversion of configuration at carbon as in related Sn2 displacements.[110] The reaction of (-)-menthyl chloride or (-)-menthyl bromide with lithium, sodium, or potassium diphenylphosphide provided a compound which has been shown by 220 MHz proton nmr and by ^{13}C nmr to have the neomenthyldiphenylphosphine structure. Treatment of (+)-neomenthyl chloride with an alkali metal phosphide was shown to give the epimeric phosphine (-)-menthyldiphenylphosphine (Figure 33).



(-)-MDPP and
(-)-MDPP oxide



(+)-NMDPP and
(+)-NMDPP oxide

X = Ph_2P- and $Ph_2\overset{O}{\overset{\|}{P}}-$

Figure 33. Conformational analysis of (-)-MDPP, (-)-MDPP oxide, (+)-NMDPP, and (+)-NMDPP oxide.

In conjunction with the syntheses of (-)-MDPP and (+)-NMDPP the relative effectiveness of lithium, sodium, and potassium diphenylphosphides was determined using (-)-menthyl chloride as the substrate. Under a standard set of conditions sodium diphenylphosphide gave the highest yield of (+)-NMDPP. The ratios of the yields of (+)-NMDPP were 1.0:1.55:1.16 for lithium, sodium, and potassium diphenylphosphide, respectively. Additionally, it was found that there was at least one by-product present in the lithium diphenylphosphide reaction that was not found in the other two, possibly 4-hydroxybutyldiphenylphosphine although this was not rigorously confirmed.

In the synthesis of (+)-NMDPP considerable quantities of (+)-NMDPP oxide were formed, presumably due to the oxidation of (+)-NMDPP during the workup. The crude oxide could be isolated by fractional crystallization, but frequently the oxide was contaminated with diphenylphosphine, diphenylphosphine oxide and some (+)-NMDPP. Purification of the crude oxide was accomplished by oxidation of the diphenylphosphine and diphenylphosphine oxide to diphenylphosphinic acid (with either bromine water or hydrogen peroxide) followed by extraction of the diphenylphosphinic acid into aqueous base.

Of course, this procedure also oxidized any (+)-NMDPP present to (+)-NMDPP oxide.* Consequently methods of con-

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*All the phosphines used in this study (except ACMP and DIOP) were also characterized as their oxides. The oxides were formed by oxidation of the phosphine with bromine water or hydrogen peroxide.

verting (+)-NMDPP oxide to (+)-NMDPP were explored. Trichlorosilane-tertiary amine reductions of phosphine oxides to phosphines have been reported to proceed readily and in high yield.[104]

Studies on a model compound, cyclohexyldiphenylphosphine oxide revealed that with a tenfold excess of trichlorosilane and N,N-dimethylaniline at 100°, cyclohexyldiphenylphosphine oxide was reduced quantitatively to the phosphine in 18 hr. Under the same conditions, however, (+)-NMDPP oxide was only 61% reduced after 20 hr. After 146.5 hr, reduction of (+)-NMDPP oxide to (+)-NMDPP was complete. Isolated yields as high as 56% were obtained. The severe steric hindrance of (+)-NMDPP oxide may account for the strenuous conditions required to effect complete reduction to the phosphine. The behavior of (-)-MDPP oxide was similar. After 89.5 hr, under the conditions described above, the conversion of (-)-MDPP oxide to (-)-MDPP was 96.5% complete.

Synthesis of (+)-CAMPHOS

(+)-CAMPHOS (47), (+)-(1R,3S)-1,2,2-trimethyl-1,3-bis(diphenylphosphinomethyl)cyclopentane was chosen as a target ligand for a number of reasons. First, as a diphosphine it has the ability to chelate a metal, and such a chelate would not undergo epimerization equilibria relative to chirality at rhodium.[137] Second, the diphosphine will form a bicylic structure when coordinated to rhodium and this would be ex-

pected to exhibit a greater degree of rigidity than a monocyclic diphosphine complex or a complex formed with monophosphine ligands. Third, the starting material, (+)-camphoric acid, is inexpensive, available in quantity, and in nearly 100% optical purity.

(+)-Camphoric acid (44) was reduced to 1,2,2-trimethyl-1,3-bis(hydroxymethyl)cyclopentane (45) with lithium aluminum hydride in ether. In the initial attempts to synthesize CAMPHOS many procedures were used in an attempt to halogenate the diol 45. Among the methods tried were thionyl chloride and pyridine, phosphorus pentachloride, triphenylphosphine dibromide in N,N-dimethylformamide, triphenylphosphine and carbon tetrachloride, tris(dimethylamino)phosphine and bromine, o-phenylenephosphorochloridite and bromine, tris-(dimethylamino)phosphine and carbon tetrachloride, and tri-n-octylphosphine and carbon tetrachloride. None of these methods met with any success. The attempts to synthesize the dibromide, 1,2,2-trimethyl-1,3-bis(bromomethyl)cyclopentane resulted in the isolation of a thermally unstable product. Reactions leading to the corresponding dichloride gave products which could not be adequately characterized by ir and nmr.

Reaction of 1,2,2-trimethyl-1,3-bis(hydroxymethyl)-cyclopentane (45) with p-toluenesulfonyl chloride in pyridine converted the diol into the ditosylate 46 in nearly quantitative yield. Sn2 displacement reactions by chloride on neopentyl tosylate have been shown to give good yields of

neopentyl chloride.[114] When 1,2,2-trimethyl-1,3-bis-(hydroxymethyl)cyclopentane ditosylate (46) was allowed to react with sodium chloride in hexamethylphosphoramide only N,N-dimethyl-p-toluenesulfonamide was isolated. The reaction of 46 with lithium chloride in ethoxyethanol was exothermic and HCl was evolved. However, the isolated product contained an olefinic linkage. In N,N-dimethylformamide, lithium chloride and 46 gave a product which decomposed on distillation.

Initial work on the synthesis of CAMPHOS (47) by displacement on its ditosylate precursor with the diphenyl phosphide anion did not seem promising. The reaction of lithium diphenylphosphide and 46 gave no CAMPHOS.* However, when potassium diphenylphosphide in tetrahydrofuran was used, in place of the lithium reagent, (+)-CAMPHOS 47 was formed.** The reaction of 46 with potassium diphenylphosphide is initially exothermic, however the reaction does not go to completion. Heat must be applied to effect complete reaction. It is likely that the less hindered α-tosylate group is displaced or eliminated readily at room temperature, but the neopentyl-like β-tosylate group requires more strenuous conditions to effect displacement (Figure 34).

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*Subsequent to this work, J. Solodar (Monsanto) reported in a private communication that he has observed skeletal rearrangement in the reaction of lithium diphenylphosphide with 46.[115]

**In conjunction with the study of the preparation of phosphines by halide and tosylate displacement, a number of achiral model compounds were synthesized including cyclohexyldiphenylphosphine, n-decyldiphenylphosphine, and neopentyldiphenylphosphine.

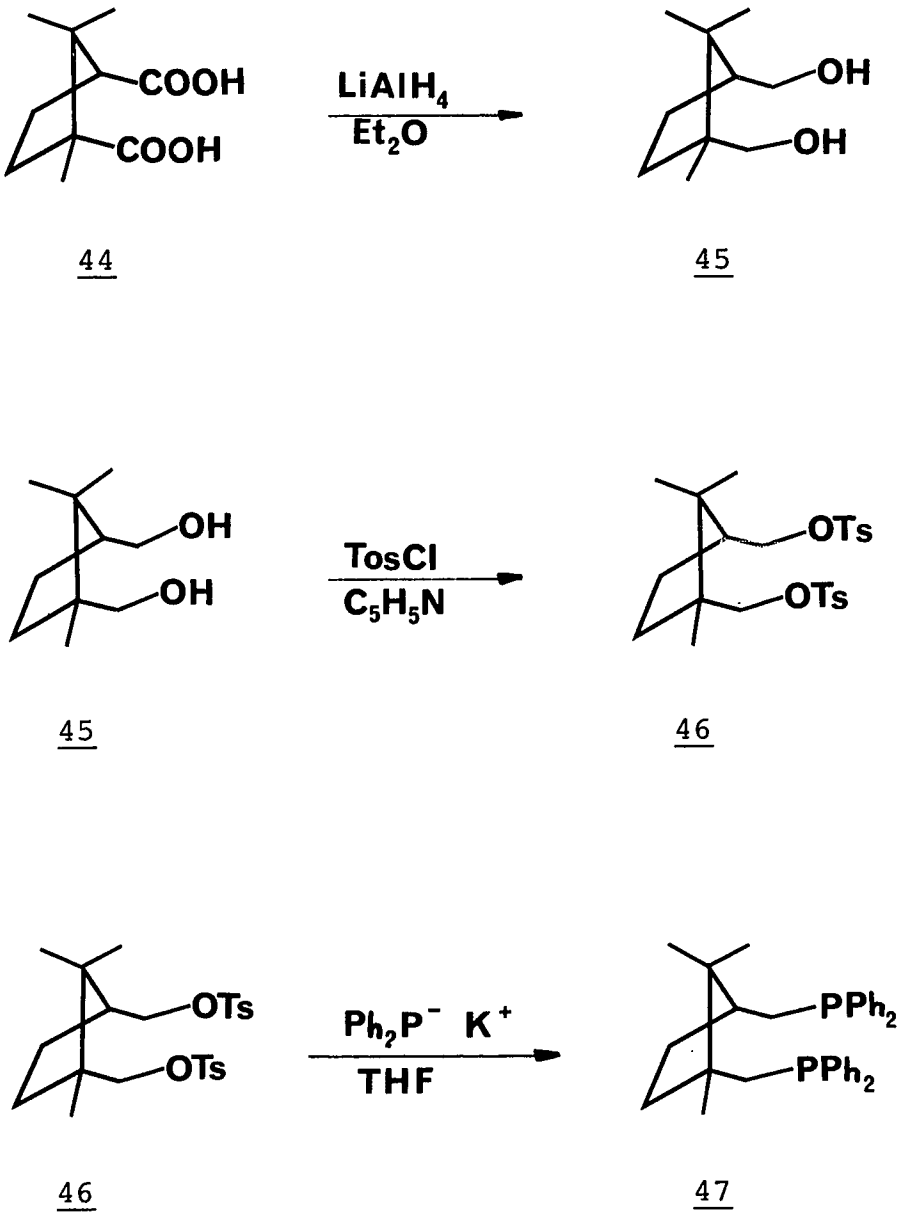

Figure 34. Synthesis of (+)-CAMPHOS (47) from (+)-camphoric acid (44).

The phosphide displacement reaction gives rise to a number of by-products, including diphenylphosphine, which were removed by vacuum distillation. A fraction boiling higher than diphenylphosphine [bp 220-250° (0.25 mm)] was isolated. It was presumed that the by-products were a monophosphine and its oxide resulting from elimination of the α-tosylate group and displacement of the β-tosylate (rigorous characterization of the by-products was not pursued). Glpc analysis (column A, 235°) showed two major components (retention times 75 and 165 sec). The less strongly retained component probably was a monophosphine, and the more strongly retained component was probably the monophosphine oxide. The ir spectrum of the mixture showed a strong band at 1190 cm^{-1} which corresponds to P=O. The observation of absorptions due to vinylic protons (δ 4.50 and 5.14) in the nmr spectrum of the mixture also supports the hypothesis that monophosphine by-products were produced.

(+)-CAMPHOS is a viscous oil and it could not be purified by distillation or crystallization. Crude (+)-CAMPHOS was distilled to remove lower boiling impurities. Based on the nmr spectrum, the pot residue consisted primarily of (+)-CAMPHOS and (+)-CAMPHOS dioxide. It was purified by column chromatography on silica gel or alumina, eluting the purified (+)-CAMPHOS with benzene.

An alternate route to (+)-CAMPHOS seemed desirable, and with this in mind, an unusual reaction of aldehydes and ketones with phosphines was explored. Phosphine, PH_3, reacts with dry formaldehyde at 100° under pressure to give tris-(hydroxymethyl)phosphine.[116] If the carbon chain of the

aldehyde is branched, then steric factors may stop the reaction at an earlier stage (Figure 35).

$$PH_3 + HCHO \xrightarrow{100°} P(CH_2OH)_3$$

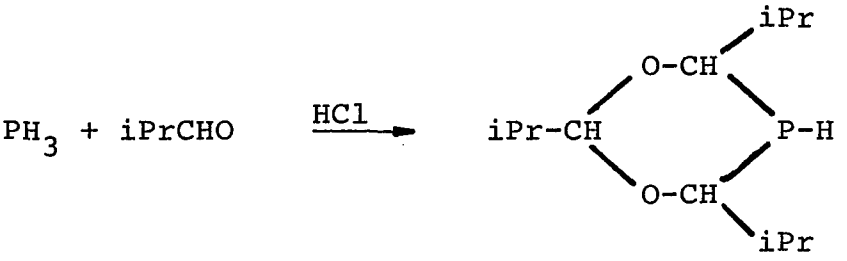

Figure 35. Reaction of phosphine with formaldehyde and 2-methylpropanal.

Ketones and aromatic aldehydes behave in a manner similar to branched aldehydes, however, addition may be complicated by rearrangement to phosphine oxides (Figure 36).

$$R_2CO + PH_3 \xrightarrow{HCl,\ conc.} R_2CHP(O)H_2$$ [117]

$$ArCHO + PH_3 \xrightarrow[ether]{HCl\ in} ArCH_2P(O)(CHOHPh)_2$$ [118]

Figure 36. Reaction of phosphine with ketones and aromatic aldehydes.

Buckler and Epstein have extended the reaction of phosphine with carbonyl compounds to synthesize tertiary phosphine oxides from aldehydes or ketones and dialkyl or diaryl phosphines.[119]

Little work has been carried out on the mechanism of addition of secondary phosphines to aldehydes and the accompanying rearrangement to tertiary phosphine oxides. It seems likely that the mechanism involves hydride transfer, and possibly a phosphorane intermediate. Developing carbonium character at the carbonyl carbon and formation of a phosphorus-oxygen double bond likely contribute the driving force for the reaction. Several reasonable mechanisms can be postulated to account for the observed addition and rearrangement, among them a dimeric structure with a six membered ring; however, a more likely mechanism is one similar to that written for the acid promoted rearrangement of epoxides to aldehydes or ketones (Figure 37).

The scope of this reaction was studied in order to determine whether it would be suitable for the synthesis of chiral phosphine oxides. Cyclohexyldiphenylphosphine oxide was formed in good yield from diphenylphosphine and cyclohexanone in concentrated HCl. The conversion of 4-t-butylcyclohexanone to 4-t-butylcyclohexyldiphenylphosphine oxide proceeded readily. The 4-t-butylcyclohexyldiphenylphosphine oxide was shown to be a mixture of cis and trans isomers by glpc analysis. The isomers could be separated by fractional crystallization.

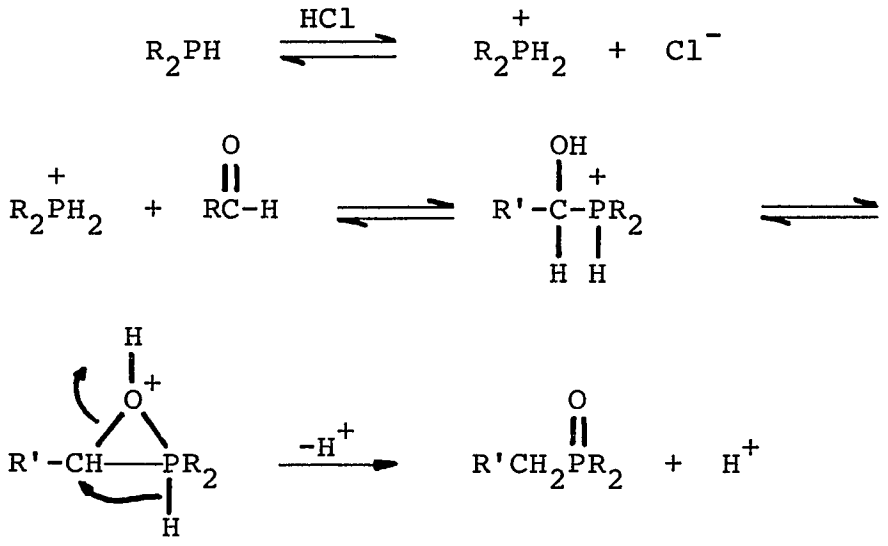

Figure 37. The acid promoted reaction of a secondary phosphine with an aldehyde

Hindered ketones did not react as readily as unhindered ketones. 2-Methylcyclohexanone gave only a low yield of 2-methylcyclohexyldiphenylphosphine oxide. Both (-)-menthone and (+)-camphor appeared to be unreactive under the conditions used in this study; no phosphine oxides were isolated.

A hindered aldehyde, 2,2-dimethylpropanal, did react readily with diphenylphosphine and HCl to give neopentyldiphenylphosphine oxide, so it was expected that (+)-1,2,2-trimethylcyclopentane-1,3-dicarboxaldehyde would react under similar conditions to give (+)-CAMPHOS dioxide.

(+)-Camphor (48) was oxidized to (+)-2,3-bornanedione (49) after the procedure of Marguet.[120] Reduction of the α-diketone with lithium aluminum hydride gave exo-exo-2,3-

bornanediol (50).[121] The glycol was cleaved to (+)-1,2,2-trimethylcyclopentane-1,3-dicarboxaldehyde (51) with lead tetraacetate.[122] The dialdehyde and diphenylphosphine were allowed to react in concentrated HCl to give (+)-CAMPHOS dioxide (52) (Figure 38).

It was envisioned that (+)-CAMPHOS dioxide (52) would be reduced to (+)-CAMPHOS (47) by trichlorosilane, hexachlorodisilane, or lithium aluminum hydride. However, in related reduction studies with (+)-NMDPP oxide and neopentyldiphenylphosphine oxide (NPDPP oxide) it was found that cleavage of the alkyl group by trichlorosilane-amine mixtures to give diphenylphosphine was a serious side reaction. The cleavage reaction was first noted in the reduction of (+)-NMDPP oxide with trichlorosilane and N,N-dimethylaniline when reaction times of about 200 hr were used. No cleavage, or only trace amounts of cleavage, were seen when reaction times of less than 150 hr were used. The cleavage reaction was more serious in the reduction of neopentyldiphenylphosphine oxide than with (+)-NMDPP oxide. In one experiment (at 80° with a tenfold excess of trichlorosilane and N,N-dimethylaniline) after 3.5 hr glpc analysis showed that 59% of the oxide had been converted to diphenylphosphine.*

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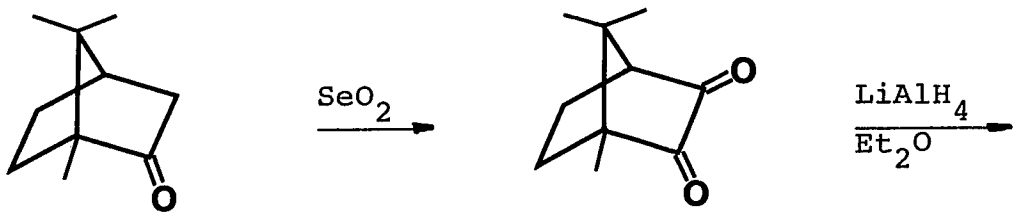
*Analyses of the phosphine oxide reductions were performed by glpc. In only one experiment was there circumstantial evidence for aryl group cleavage (an additional glpc peak with what was considered to be an appropriate retention time). However, aryl group cleavage cannot be ruled out in the other experiments with confidence.



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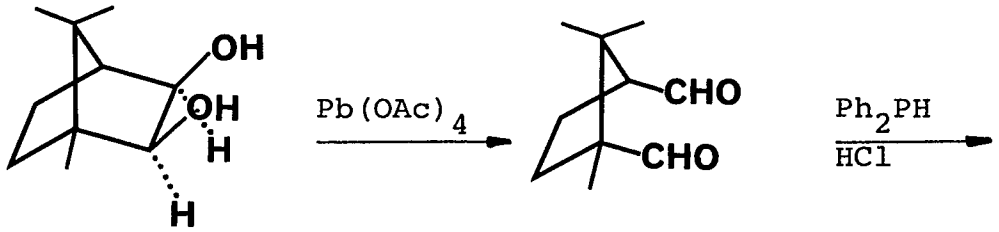

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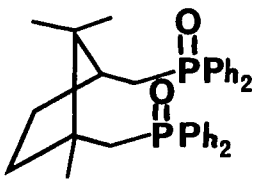

52

Figure 38. Synthesis of (+)-CAMPHOS dioxide (52) from (+)-camphor (48).

Other workers have successfully deoxygenated 3° phosphine oxides to phosphines using trichlorosilane and amines and have not commented on alkyl or aryl group cleavage as a complicating side reaction. The mechanisms and stereochemistry of such reactions have been studied in considerable detail. For example, Horner has proposed mechanisms to account for the observation that chiral phosphine oxides are reduced to phosphines with inversion of configuration by trichlorosilane and triethylamine, whereas with trichlorosilane and either N,N-diethylaniline or pyridine, the reduction takes place with retention of configuration (Figure 39).[104]

As mentioned previously, in developing a useful synthesis of optically active phosphines of known absolute configuration, Mislow and coworkers studied the reduction of acyclic phosphine oxides with trichlorosilane-tertiary amine mixtures.[124] Phosphine oxides could be reduced to phosphines with either predominant retention or inversion of configuration depending upon the tertiary amine used. Strongly basic amines (pKa < ca. 5) gave predominant inversion, and weak bases (pKa > ca. 7) gave predominant retention of configuration. These results were shown to be consistent with the reaction of the strong base with trichlorosilane to give a perchloropolysilane. The perchloropolysilane then could reduce the phosphine oxide to a phosphine with inversion of configuration (Figure 40).

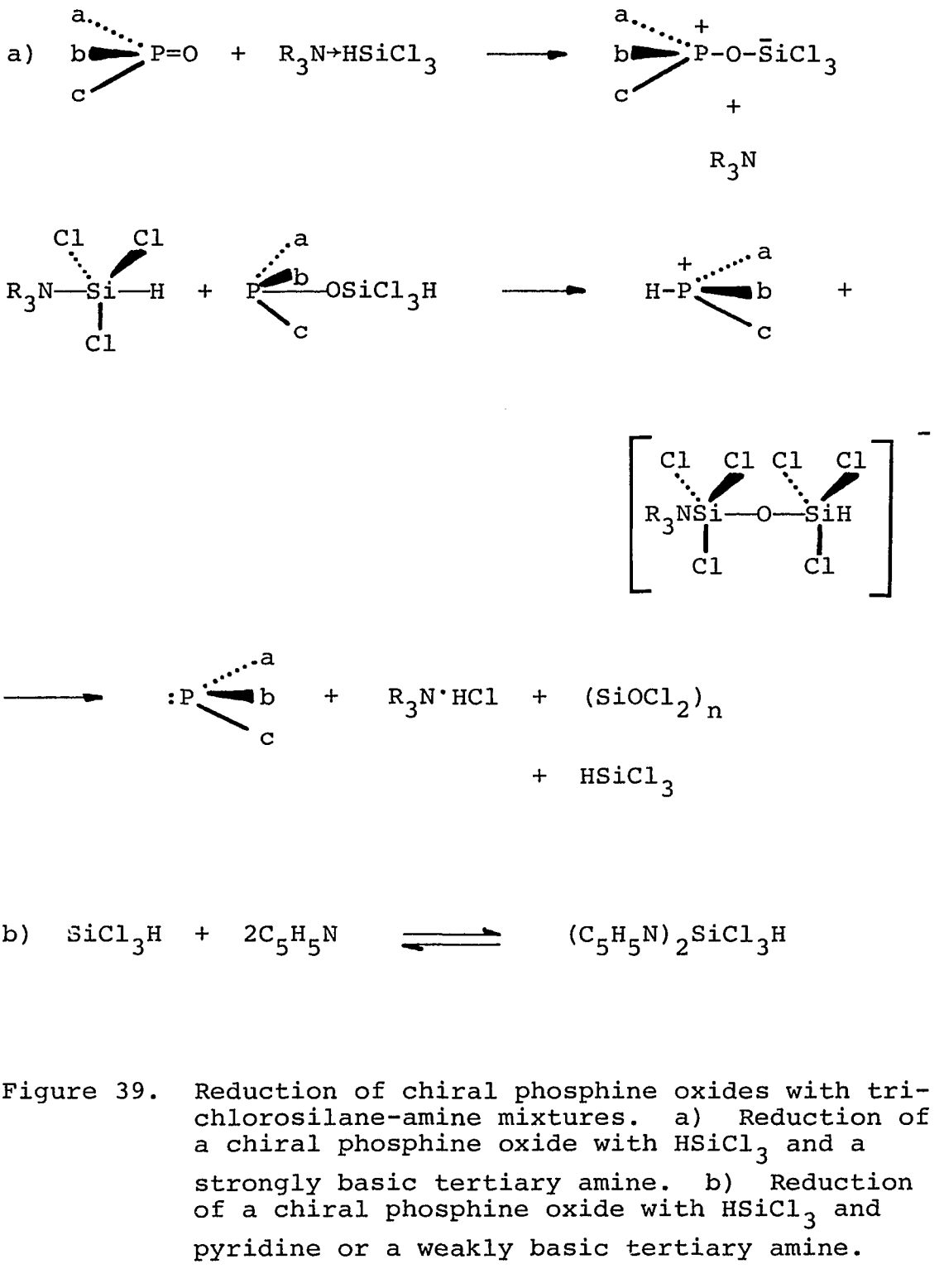

Figure 39. Reduction of chiral phosphine oxides with trichlorosilane-amine mixtures. a) Reduction of a chiral phosphine oxide with $HSiCl_3$ and a strongly basic tertiary amine. b) Reduction of a chiral phosphine oxide with $HSiCl_3$ and pyridine or a weakly basic tertiary amine.

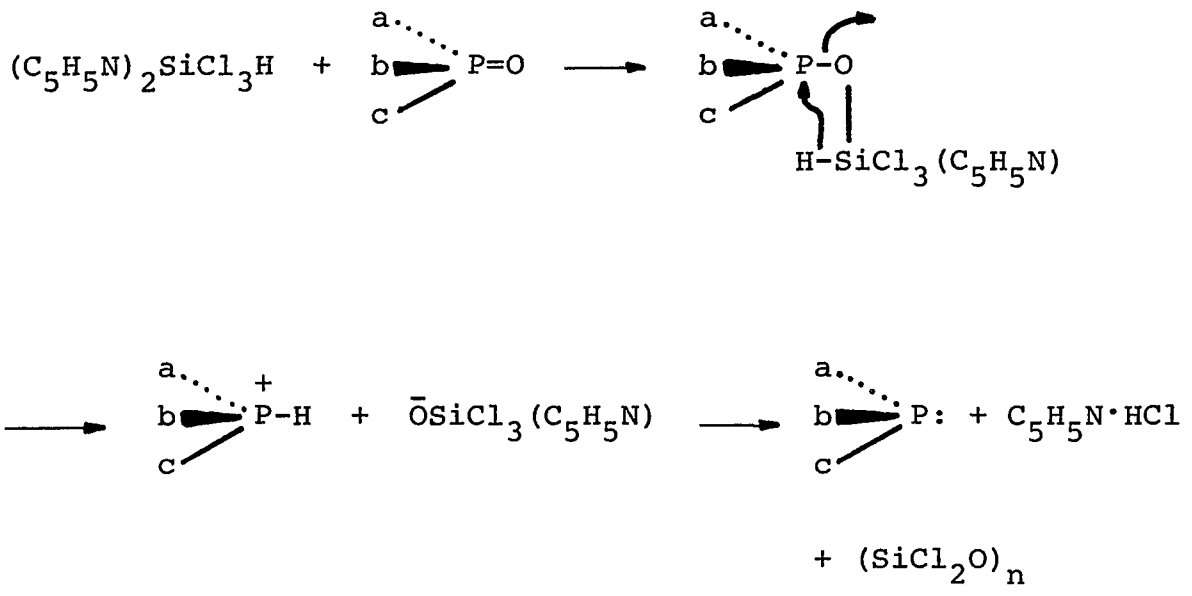

Figure 39. (continued)

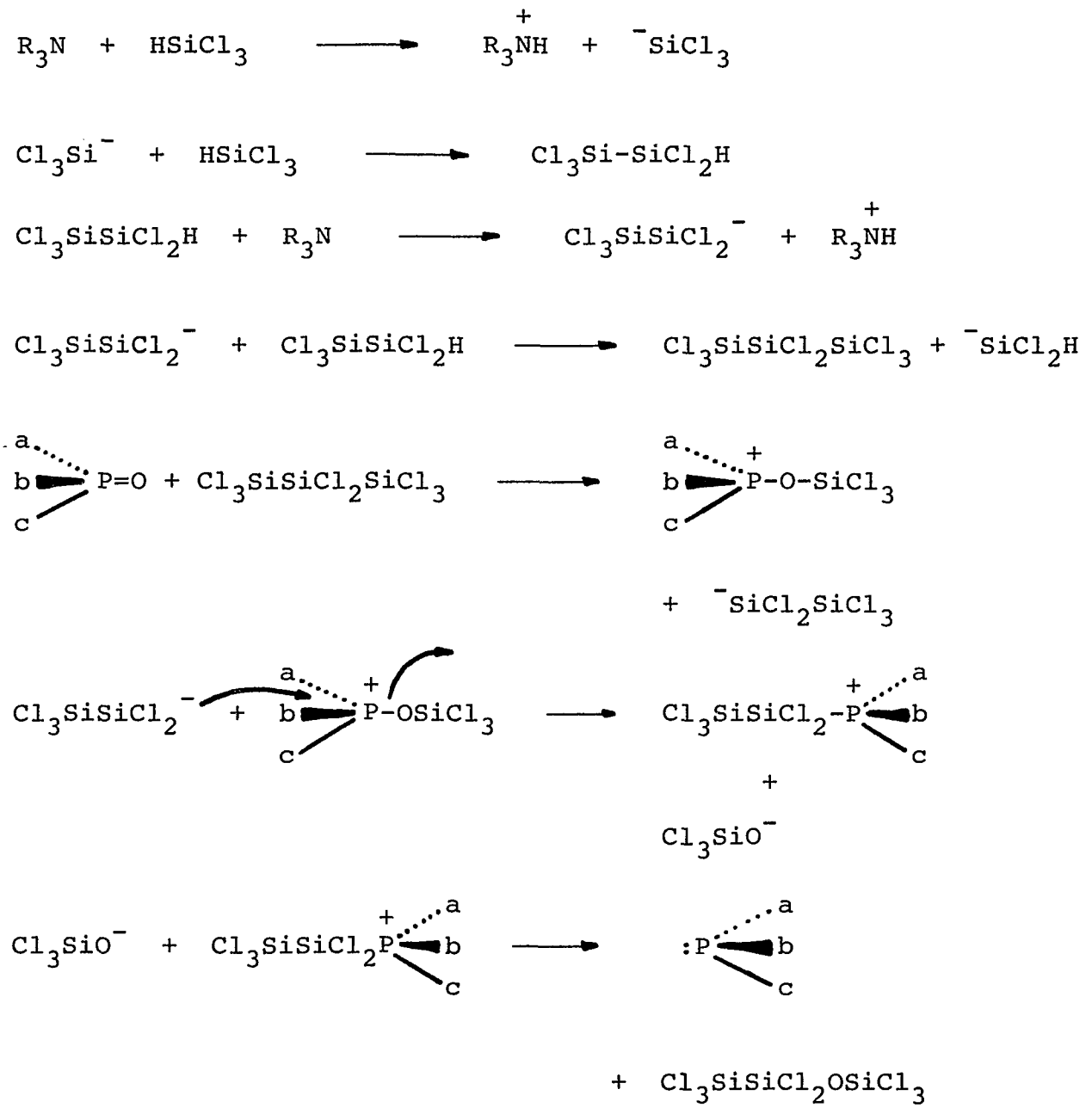

Figure 40. Reduction of chiral phosphine oxides with perchloropolysilanes.

In the reduction of rather hindered phosphine oxides such as (+)-NMDPP oxide and neopentyldiphenylphosphine oxide with trichlorosilane the cleavage of an alkyl group may be preferred to reduction because of steric hindrance. If the transfer of hydride from the reagent to phosphorus is energetically unfavorable, an alkyl group may instead be cleaved to an alkane and a trichlorosilyl ester of a phosphinous acid. The ester can then undergo further reaction with trichlorosilane to give a secondary phosphine and a siloxane (Figure 41).

Due to the cleavage reactions observed with (+)-NMDPP oxide and neopentyldiphenylphosphine oxide, trichlorosilane was considered to be an inappropriate reagent for the reduction of (+)-CAMPHOS dioxide (52) to (+)-CAMPHOS (47).

Lithium aluminum hydride has been used to reduce tertiary phosphine oxides to the corresponding phosphines.[125,131] Dioxane and high boiling aliphatic ethers have been most commonly used as solvents. The reduction of triphenylphosphine oxide by lithium aluminum hydride in dioxane or tetrahydrofuran gave phenyl cleavage to produce diphenylphosphine. However, only reduction to triphenylphosphine was observed in high boiling aliphatic ether solvents.[123]

In this study it has been noted that while lithium aluminum hydride caused cleavage* of neomenthyldiphenylphosphine oxide, cyclohexyldiphenylphosphine oxide, and neopentyl-

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*Again, as noted in the footnote on page 110 the possibility of some aryl as well as alkyl cleavage cannot be rigorously excluded on the basis of the available evidence (see also the footnote on page 119).

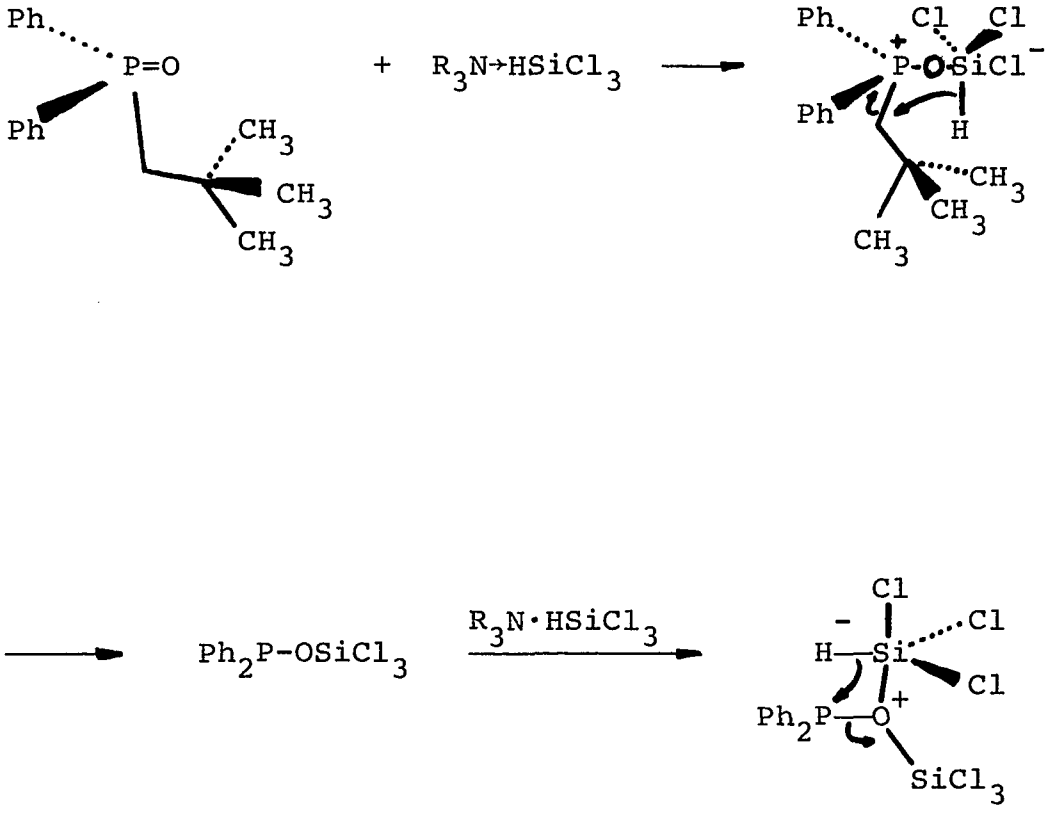

Figure 41. Reaction of neopentyldiphenylphosphine oxide (NPDPP oxide) with trichlorosilane and N,N-dimethylaniline.

diphenylphosphine oxide, no alkyl cleavage occurred during the reduction of n-decyldiphenylphosphine oxide to n-decyldiphenylphosphine. The behavior of the various phosphine oxides with lithium aluminum hydride can be better understood by first considering the mechanism of reduction.

Mislow has proposed a reversible addition of lithium aluminum hydride to phosphine oxides followed by pseudorotation of the intermediate phosphorane to accommodate the observation that optically active phosphine oxides are virtually completely racemized by lithium aluminum hydride before more than 10% of the oxide has been reduced to the phosphine (Figure 42).[132] The chiral phosphine product was configurationally stable under the reaction conditions employed.

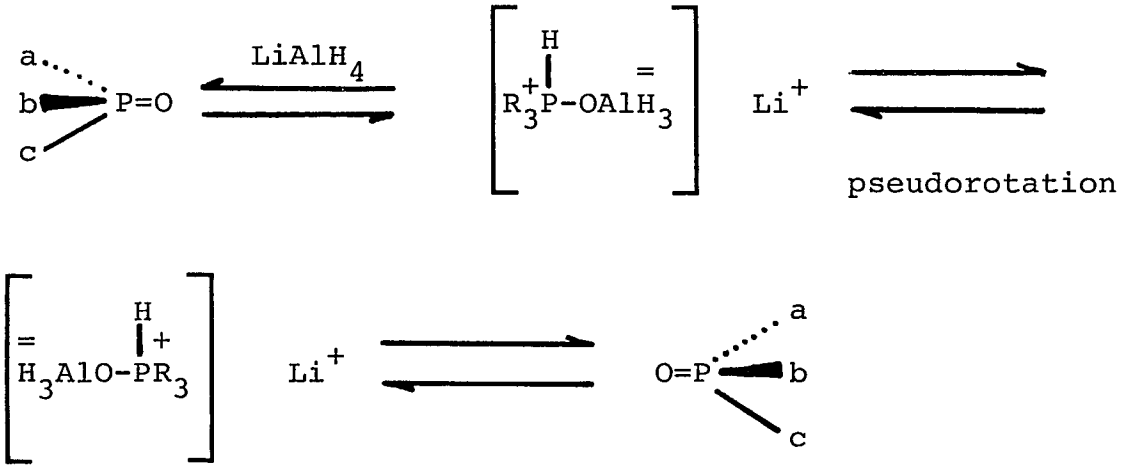

Figure 42. Racemization of a chiral phosphine oxide with lithium aluminum hydride.

The formation of an intermediate phosphorane in the lithium aluminum hydride reduction of chiral phosphine oxides can account for the observed racemization. Difficulty in forming an intermediate phosphorane in the case of hindered phosphine oxides may account for the observed cleavage of alkyl or aryl groups. Steric blocking due to branching β- to phosphorus may be sufficient to cause addition of $H\text{-}AlH_3$ across the phosphorus-oxygen double bond to be less favorable than the hydride cleavage of an alkyl or aryl group to a hydrocarbon and an aluminum salt of a hydroxyphosphine. Attack of hydride either inter- or intramolecularly on the aluminum salt of the hydroxyphosphine with concurrent displacement of an oxyaluminum hydride would give the secondary phosphine (Figure 43).

The above rationale can explain the observation that hindered phosphine oxides such as NMDPP oxide and NPDPP oxide suffer cleavage, while the relatively unhindered n-decyldiphenylphosphine oxide was reduced much more cleanly to the parent phosphine than the other phosphine oxides studied.* The behavior of lithium aluminum hydride with hindered phosphine oxides suggested that lithium aluminum hydride would not be a suitable reducing agent for (+)-CAMPHOS dioxide.

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*In the lithium aluminum hydride reduction of n-decyldiphenylphosphine oxide there was no evidence for cleavage of the alkyl group, however glpc analysis suggested that there was a small amount of aryl group cleavage.

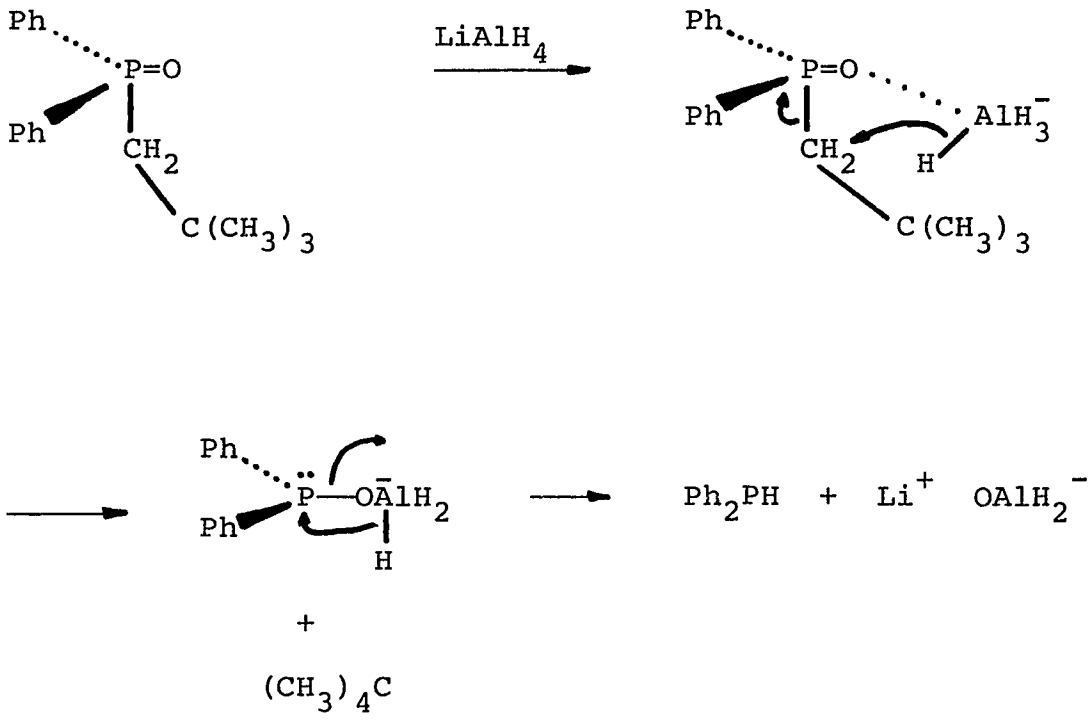


Figure 43. Cleavage of an alkyl group from NPDPP oxide by lithium aluminum hydride.

The hexachlorodisilane reduction of phosphine oxides, which works exceptionally well for the synthesis of many phosphines[124], did not prove to be a highly efficient method of synthesis of hindered phosphines. Neomenthyldiphenylphosphine oxide was only 81% reduced by a 30% excess of hexachlorodisilane after 73.5 hr at 100°. Neopentyldiphenylphosphine oxide proved to be even more difficult to reduce; only 83% reduction by a greater than 3 fold excess of hexachlorodisilane occurred in 212 hr at room temperature (Table 18). Because of the similar hindered nature of (+)-CAMPHOS dioxide another method of converting the dioxide (52) to CAMPHOS was sought.

The greater ease of reduction of phosphine sulfides relative to phosphine oxides prompted consideration of their use in the circuitous synthesis of CAMPHOS from camphor. Phosphine sulfides have been reduced to phosphines by lithium aluminum hydride in dibutyl ether[125], sodium hydride melts[125], sodium in toluene/naphthalene[126], sodium in toluene[126], iron metal[127], Raney nickel[125], tri-n-butylphosphine[128], lithium aluminum hydride in dioxane[129], and hexachlorodisilane.[130]

Phosphine sulfides can be prepared from phosphine oxides via phosphine dichlorides. For example, triphenylphosphine oxide has been converted to triphenylphosphine dichloride by reaction with phosphorus pentachloride.[125] In the present study triphenylphosphine dichloride was found to react with hydrogen sulfide gas to give triphenylphosphine sulfide in 85% yield. Similarly neopentyldiphenylphosphine

Table 18. Reduction of neopentyldiphenylphosphine oxide (NPDPP oxide) with hexachlorodisilane.[a]

Si_2Cl_6:NPDPP Oxide	Time,hr	Analysis[b] NPDPP	Analysis[b] NPDPP Oxide
1.3:1	1.33	22.2	77.8
2.33:1	4.25	26.6	73.4
2.33:1	19.	59.5	40.5
1.58:1	209.5	30.1	69.6
3.16:1	212	79.7	20.3
4.75:1	14.5	84.5	15.5

a) All reductions were performed in chloroform at room temperature

b) Analyses were performed by glpc (column A, 215°) and are corrected for response ratio, NPDPP:NPDPP Oxide = 1:1.20.

sulfide (43%), (-)-menthyldiphenylphosphine sulfide (57%), (+)-neomenthyldiphenylphosphine sulfide (45%) and (+)-CAMPHOS disulfide (54) (39%) were synthesized (Figure 44).

Experiments were conducted with NPDPP sulfide and other tertiary phosphine sulfides as models for the (+)-CAMPHOS disulfide reduction. Both lithium aluminum hydride in dioxane and tris(dimethylamino)phosphine were effective desulfurizing agents. The lithium aluminum hydride reduction of (+)-CAMPHOS disulfide gave, after chromatography, a 22% yield of (+)-CAMPHOS. The desulfurization of (+)-CAMPHOS disulfide by tris(dimethylamino)phosphine which proceeded readily at 130° could not be monitored by TLC since the tris(dimethylamino)phosphine and tris(dimethylamino)phosphine sulfide interferred with the analysis. A parallel reaction of neopentyldiphenylphosphine sulfide with tris(dimethylamino)phosphine was run and the rate of desulfurization of this model compound was followed by glpc analysis. When the NPDPP sulfide had been converted completely to NPDPP, the (+)-CAMPHOS disulfide reduction was worked up to give, after chromatography (+)-CAMPHOS (56%). The (+)-CAMPHOS synthesized from camphor (Figures 38 and 44) via the desulfurization route was identical to that synthesized by the tosylate displacement method. The ir and nmr spectra were superimposable and the optical rotations of the (+)-CAMPHOS samples prepared by the three methods were nearly identical.

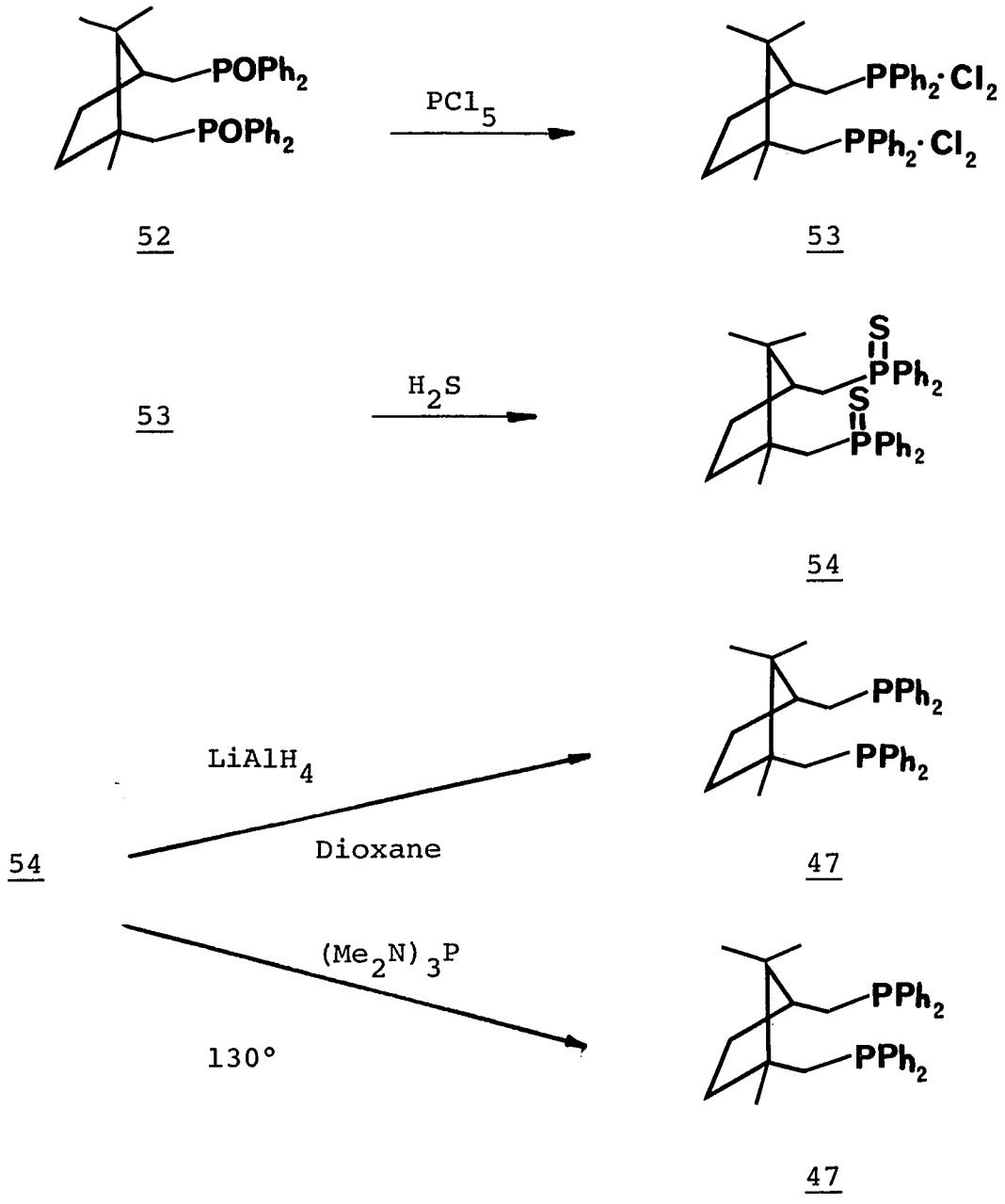


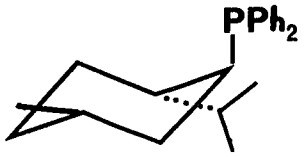
Figure 44. Conversion of (+)-CAMPHOS dioxide (52) to (+)-CAMPHOS disulfide (54) and desulfurization to (+)-CAMPHOS (47).

As a further test of identity, when (E)-α-methylcinnamic acid was reduced using a catalyst made from $[Rh(COD)Cl]_2$ and (+)-CAMPHOS synthesized by the displacement method (Figure 34), the absolute configuration and optical purity of the product was the same as that for a reduction product prepared using a catalyst made with (+)-CAMPHOS synthesized by the circuitous camphor-desulfurization route.

Asymmetric Homogeneous Hydrogenations

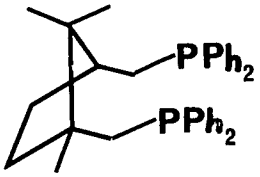
In this study synthetic procedures were developed for the chiral phosphine ligands (+)-neomenthyldiphenylphosphine (39), (-)-menthyldiphenylphosphine (43), and (+)-CAMPHOS (47). For comparison, (-)-DIOP (26) was prepared according to the procedure of Kagan.[72] The preformed catalyst $[Rh(COD)(ACMP)_2]^+ BF_4^-$ was graciously supplied to us by Dr. W. S. Knowles (Figure 45).

The substrates, atropic acid, (E)- and (Z)-α-methylcinnamic acid, (E)- and (Z)-α-phenylcinnamic acid, (E)- and (Z)-β-methylcinnamic acid, itaconic, mesaconic, and citraconic acids (Figure 46) were chosen for several reasons: a) The optical yields in asymmetric reductions of α,β-unsaturated carboxylic acids by rhodium(I)-chiral phosphine catalysts are uniformly higher than in systems where the unsaturated substrate lacks the carboxylic acid functions. b) The maximum rotations and absolute configurations of the saturated acid products have been documented. c) The (E) and (Z) relationships between several of the substrates

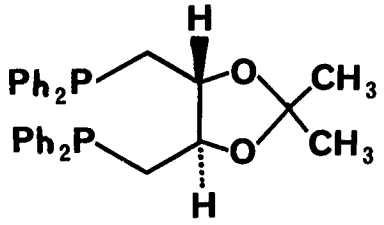


(+)-NMDPP

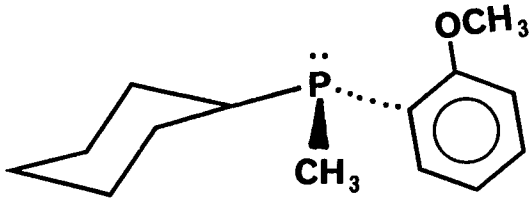
(-)-MDPP



(+)-CAMPHOS

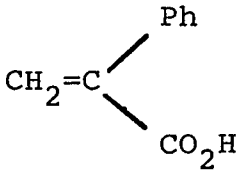


(-)-DIOP

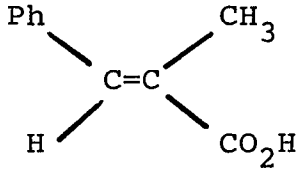


(+)-ACMP

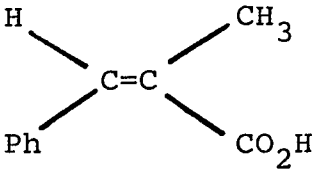
Figure 45. Chiral tertiary phosphine ligands used in this study.



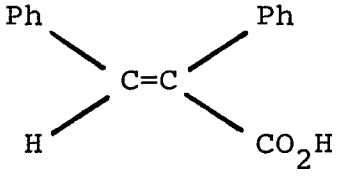
Atropic Acid



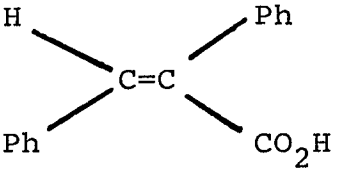
(E)-α-Methylcinnamic Acid



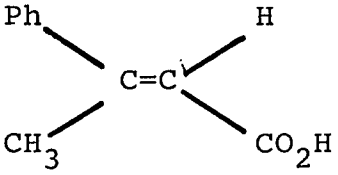
(Z)-α-Methylcinnamic Acid



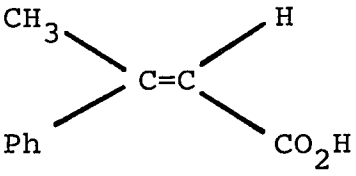
(E)-α-Phenylcinnamic Acid



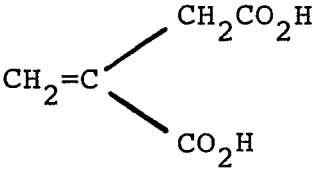
(Z)-α-Phenylcinnamic Acid



(E)-β-Methylcinnamic Acid

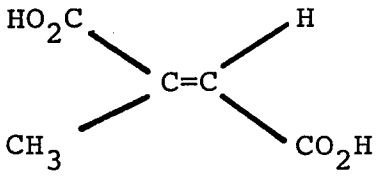


(Z)-β-Methylcinnamic Acid

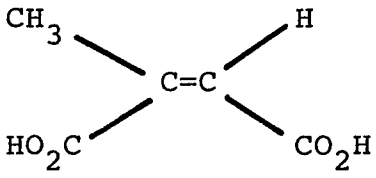


Itaconic Acid

Figure 46. α,β-Unsaturated carboxylic acid substrates used in this study.



Mesaconic Acid



Citraconic Acid

Figure 46. (continued)

allowed us a unique opportunity to observe what effect, if any, the olefin geometry would have on the stereochemical outcome of the asymmetric reductions. It was hoped that the data obtained from these reductions would provide new insight into the process of asymmetric homogeneous hydrogenation.

The chiral catalysts were formed *in situ* according to a modification of the procedure of Djerassi and Gutzwiller for Wilkinson's catalyst (Figure 47).[133]

$$6Ph_3P + [Rh(C_2H_4)_2Cl]_2 \xrightarrow[C_2H_5OH]{C_6H_6} 2(Ph_3P)_3RhCl$$

Figure 47. The procedure of Djerassi and Gutzwiller for the preparation of Wilkinson's catalyst.

The modification used in this study involved the use of μ,μ'-dichloro-bis(1,5-cyclooctadiene)dirhodium(I) rather than μ,μ'-dichlorotetraethylenedirhodium(I) because the former could be synthesized easily in nearly quantitative yield. The cyclooctadiene complex was easier to purify by crystallization than the ethylene complex, and it displayed greater stability during storage.

Knowles and coworkers have presented some evidence that the reaction of chiral phosphines with rhodium(I)-diene complexes generates a cationic species. With respect to asymmetric reductions it has been demonstrated that a preformed cationic complex behaves in a stereochemical sense

the same as a catalyst complex formed in situ from a rhodium(I)-diene complex.[68] From the data in this thesis it has not been possible to determine with certainty whether or not a cationic complex was involved in the reductions studied. However, only slight differences in product optical purities have been observed in reductions where $[Rh(COD)Cl]_2$ was used with (+)-NMDPP in place of $[Rh(C_2H_4)_2Cl]_2$. These data suggest that a cationic complex is not involved at least in the case where (+)-NMDPP is the ligand and high ligand loadings are maintained.

In Burnett's work with the rhodium(I)-(+)-NMDPP catalyst it was noted that the optical purities of the saturated products increased when an excess of phosphine ligand was employed.[70] The presence of excess phosphine in hydrogenations of atropic acid resulted in saturated products of higher optical purity than when excess phosphine was not used. Knowles[67] has shown that in reductions of atropic acid with a catalyst made from methylphenylpropylphosphine, the phosphine undergoes a 1,4-addition to the α,β-unsaturated acid to form a betaine which abstracts a proton from the atropic acid. The atropic acid anion then undergoes reduction to hydratropic acid. The optical purity of the product has been shown to increase with increasing phosphine concentration. Presumably, (+)-NMDPP reacts with atropic acid in a manner analogous to that of methylphenylpropylphosphine, and this can account for the increase in product optical purity with added phosphine.

The reaction of excess ligand with other more hindered α,β-unsaturated acids is probably not as facile as with atropic acid, and hindered ligands such as (+)-NMDPP and (-)-MDPP may not readily undergo this reaction, so another rationale might be needed to account for the increase in product optical purity with added ligand.

Optical purities of reduction products have been shown to be dependent upon the amount of phosphine ligand present. In one case the optical purity of a saturated product was lowered when less than the theoretically required ratio of two ligands per rhodium was present. In the case where one ligand per rhodium was present, the optical purity of the product was half the value of that for the system where the ligand to rhodium ratio was two.*[68]

In the course of the present investigation it was found that both (+)-NMDPP and (-)-MDPP are particularly sensitive to air oxidation in solution. The optical purities recorded in the reductions of α,β-unsaturated carboxylic acids with the (+)-NMDPP catalyst were not maximum values when the ligand to rhodium ratio was 3.07 (more than 50% in excess of the theoretically required two ligands per rhodium). This can be attributed to air oxidation of the ligand in

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*The observation that a decrease in the ligand to rhodium ratio of 50% caused a corresponding 50% loss of stereoselectivity was almost certainly fortuitous and no general inferences concerning the additivity of the ligand influence should be drawn.

solution so that less than the theoretically required ratio of two ligands per rhodium was present during hydrogenation.

Conditions were employed in this study to minimize the effect of air oxidation of the ligands. The 1:1 v/v benzene-ethanol solvent was deoxygenated with nitrogen immediately prior to use, and an effort was made to limit, as much as possible, the contact of air with solutions of catalyst and substrate. To minimize the effect of any oxidation which did take place, a large excess of phosphine ligand was employed.

The preliminary data collected by Burnett using (+)-NMDPP (Table 19) compares favorable with the data of this study (Table 20), although the reductions were performed under slightly different conditions.

Some interesting observations, pointing toward trends, were observed in the initial work on catalysis by the rhodium(I)-(+)-NMDPP system.[134] If the α,β-unsaturated acid is viewed as in Figure 48 then when R was large (phenyl) hydrogenation produced a saturated product in higher optical purity then was the case when R' was large. This is to say that the (E)-isomers of the substituted cinnamic acids used in this study always gave products of higher optical purity then the corresponding (Z)-isomers. As R" was increased in size from hydrogen to methyl to phenyl the optical purities of the products decreased irrespective of the nature of R and R'.

Table 19. Hydrogenation of α,β-unsaturated carboxylic acids with tris(neomenthyldiphenylphosphine)rhodium(I) chloride (from Burnett).[70,a,b,c]

Substrate	Mole Ratio NMDPP/Rh	Reduction, %[d]	Yield, %[e]	Product Configuration	Product Optical Purity % ee
Atropic Acid	3.07 (3.37)	100	82	S	17 (28)[f]
(E)-α-Methylcinnamic Acid	3.07 (3.37)	100	80	R	44 (52)[f]
(E)-α-Phenylcinnamic Acid	3.07	100	100	S	12
(E)-β-Methylcinnamic Acid	3.07 (3.37)	100	80	S	52 (61)[f]
(Z)-β-Methylcinnamic Acid	3.07	20 (100)[g]	80[g]	R	20
Itaconic Acid	3.07	100	100	R	6
Mesaconic Acid	3.07	40 (95)[h]	88	-	0
Citraconic Acid	3.07	0	---	-	--

FOOTNOTES

a) A substrate to rhodium ratio of 100 was maintained throughout these experiments.

b) A substrate to triethylamine mol ratio of 6.2 was used throughout these experiments.

c) All reductions were performed in a medium pressure Parr apparatus at 300 psi and 60° in 100 ml 1:1 v/v ethanol-benzene.

d) The % reduction was determined on the crude acid product by nmr spectroscopy.

e) The % yield refers to isolated yield. The liquid products were purified by distillation, the solid products were not purified.

f) Values in parentheses represent values obtained with 0.3 equivalents of added (+)-NMDPP; ligand: Rh = 3.37.

g) (Z)-β-Methylcinnamic acid was only 20% reduced after 24 hr but was reduced quantitatively in 144 hr. The data are for the 144 hr reduction.

h) After 24 hr citraconic acid was only 40% reduced. After 72 hr it was 95% reduced, 5% starting material. The data are for the 72 hr reduction.

Table 20. Asymmetric homogeneous hydrogenation of α,β-unsaturated carboxylic acids with the rhodium(I)-(+)-NMDPP catalyst complex.[a]

Substrate	Mole Ratio Substrate/Rh	Reduction, %[b]	Yield, %[c]	Product Configuration	Product Optical Purity % ee
Atropic Acid[d]	435	100	49.2	(+)-S	29.6
(E)-α-Methylcinnamic Acid	375	100	90.3	(-)-R	60.0
(Z)-α-Methylcinnamic Acid	375	29	(e)	(-)-R	25.2
(E)-α-Phenylcinnamic Acid	185	100	88.5	(+)-S	34.4
(Z)-α-Phenylcinnamic Acid	185	100	92.0	(+)-S	9.1
(E)-β-Methylcinnamic Acid	375	100	72.3	(+)-S	61.8
(Z)-β-Methylcinnamic Acid	375	100	80.5	(-)-R	31.2
Itaconic Acid	375	100	85.0	(+)-R	8.1
Mesaconic Acid	375	100	67.0	(+)-R	5.8
Citraconic Acid	375	10	(f)	-----	----

FOOTNOTES

a) All reactions were carried out in a medium pressure Parr apparatus for 24 hr at 300 psi hydrogen at 60°C in 200 ml 1:1 v/v deoxygenated ethanol-benzene with a substrate to triethylamine mol ratio of 6.25.

b) The % reduction was determined on the crude reduced acids by nmr spectroscopy.

c) The yield data are for distilled products where the product was a liquid and for crude products where the product was a solid.

d) The substrate to triethylamine mol ratio was 7.35.

e) (Z)-α-Methylcinnamic acid (25 mmol) gave a mixture of saturated acid (29%) and starting material (71%), 3.85 g. The mixture was purified to 76.8% saturated product for the determination of the optical rotation.

f) Citraconic acid (25 mmol) gave a mixture of saturated product (10%) and starting material (90%), 2.8 g. A rotation was not taken.

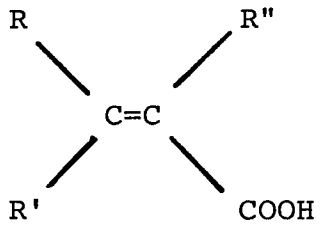

Figure 48. A general representation of the α,β-unsaturated acids used in the study.

Burnett found that with respect to the representation in Figure 48 the substituent on the carbon α to the carboxyl group seemed to control the stereochemistry of hydrogen addition. When R" was H, then the catalyst added hydrogen preferentially "from above the plane of the page", while when R" was methyl or phenyl hydrogen was added "from below the plane of the page".

On the basis of Burnett's preliminary observations it was expected that (Z)-α-methylcinnamic acid would add hydrogen to give (-)-R-2-methyl-3-phenylpropanoic acid. Similarly (Z)-α-phenylcinnamic acid was predicted to add hydrogen to give (+)-S-2,3-diphenylpropanoic acid. Both of these predictions were borne out experimentally (Figure 49).

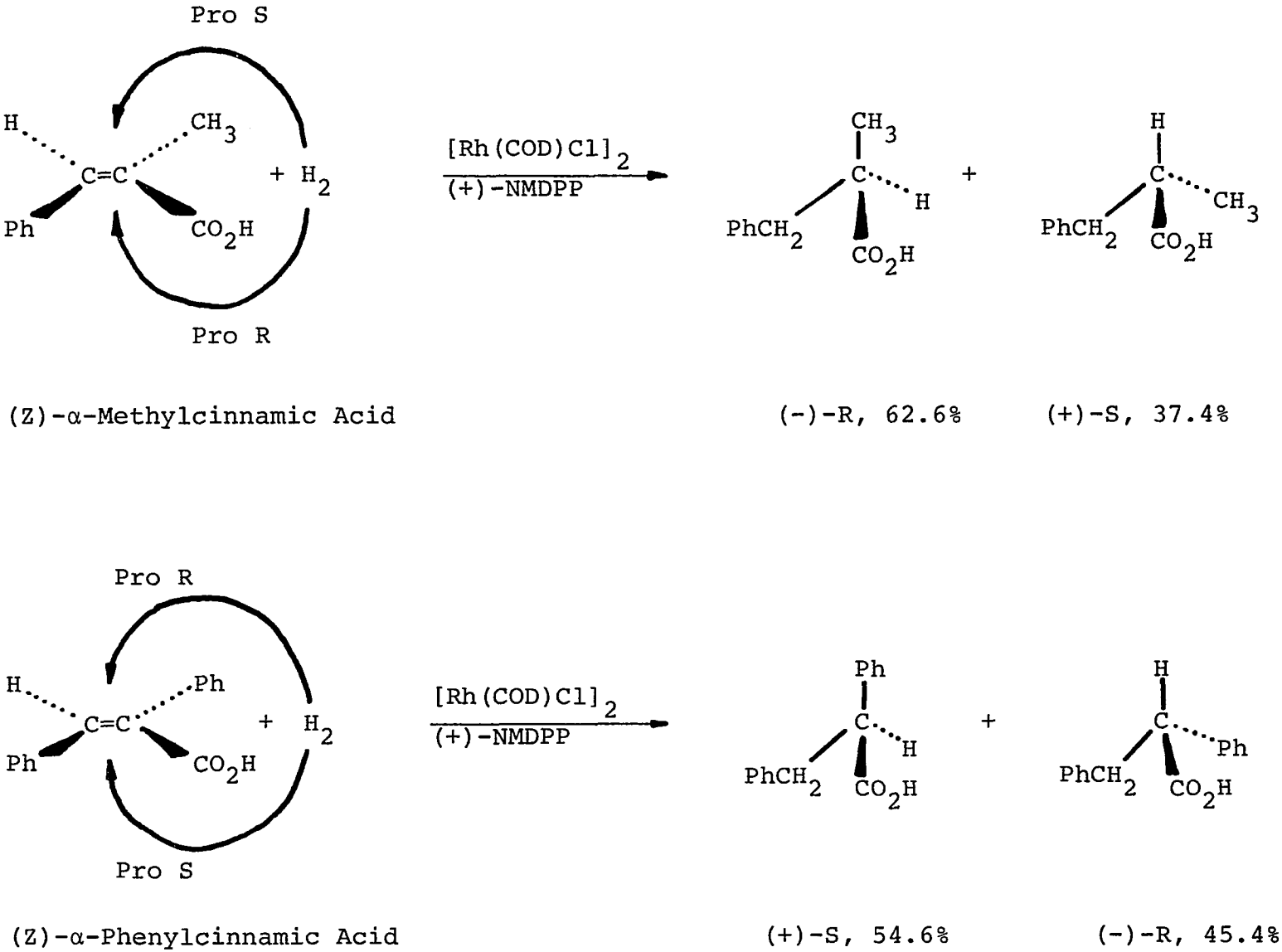

Figure 49. The stereochemistry of the reduction of (Z)-α-methylcinnamic acid and (Z)-α-phenylcinnamic acid with the rhodium(I)-(+)-NMDPP catalyst.

Burnett observed in the reductions of (E)- and (Z)-β-methylcinnamic acid with the (+)-NMDPP catalyst that higher stereoselectivity was recorded for the (E)-isomer (61% ee) than for the (Z)-isomer (20% ee). In this study, using the (+)-NMDPP catalyst, results with the (E)- and (Z)-α-methylcinnamic acids and the (E)- and (Z)-α-phenylcinnamic acids have paralleled Burnett's preliminary observation. In the reduction of the diastereomeric α-methylcinnamic acids, the (E)-isomer was reduced to (-)-R-2-methyl-3-phenylpropanoic acid in 60% ee, while the (Z)-isomer gave the (-)-R product in only 25.2% ee. (E)-α-Phenylcinnamic was reduced to (+)-S-2,3-diphenylpropanoic acid (34.4% ee), while (Z)-α-phenylcinnamic acid also gave (+)-S-2,3-diphenylpropanoic acid, but in only 9.1% ee.

The reduction of the three diacids, itaconic, mesaconic, and citraconic acids gave somewhat ambiguous results. Burnett reduced itaconic acid to (+)-R-2-methylsuccinic acid in 6% ee; mesaconic acid could not be reduced at all, and citraconic acid was reduced with difficulty to racemic 2-methylsuccinic acid.[135] In the present study, itaconic acid was reduced to (+)-R-2-methylsuccinic acid in 8.1% ee. Mesaconic acid, which Burnett was unable to reduce, was reduced in this study to (+)-R-2-methylsuccinic acid in 5.8% ee. Citraconic acid, which was reduced with some difficulty by Burnett, could not be reduced under the conditions employed in this study. When applied to itaconic acid, the trends followed by the α- and β-substituted cinnamic acids

lead to the prediction that reduction should give (-)-S-2-methylsuccinic acid. Experimentally, the (+)-R acid is formed in excess. Prediction of the stereochemical outcome of the reductions of both mesaconic and citraconic acids is confused because the two carboxylic acid functions allow two orientations with respect to Figure 48 (as amplified below). When R" is methyl then the correlation scheme predicts correctly the product stereochemistry. When R" is hydrogen the scheme fails.

The stereochemical model used to predict the major reduction pathway in the hydrogenation of α,β-unsaturated acids by the (+)-NMDPP catalyst is based on the premise that the substituent attached to the carbon α to the carboxyl group controls the overall stereochemistry of the reduction process. With the substrate oriented as in Figure 48, when R" was hydrogen, catalyzed hydrogenation took place preferentially "from above the plane of the page". When R" was larger than hydrogen, the preferential addition of hydrogen took place "from below the plane of the page". This model is ambiguous, however, for mesaconic and citraconic acids, which by virtue of two carboxyl groups, can be oriented in two possible modes with respect to the Figure 48. One mode correctly predicts the stereochemistry of addition and other mode fails. It is reasonable to say that the model is either inappropriate or it has been insufficiently developed to predict the stereochemistry of hydrogenation for the dicarboxylic acids studied.

It would be interesting to examine asymmetric hydrogenations of phenyl fumaric acid, and, if it could be obtained and did not isomerize under the reaction conditions, phenylmaleic acid. It is possible that in a substituted fumaric or maleic acid the more highly substituted α carbon controls the stereochemistry of the hydrogen addition. If this is the case, then with respect to Figure 48 phenyl is R" and hydrogen would be expected to be transferred to give (-)-S-phenylsuccinic acid preferentially in both cases.

An abbreviated study was conducted to determine the effect of varying solvent composition on the reduction of (E)-α-methylcinnamic acid by the (+)-NMDPP catalyst (Table 21). Benzene-ethanol (1:1, v/v) was shown to give optimum results. When the solvent ratio was changed to 3:1 (benzene-ethanol) the reduction did not go to completion in 24 hr. Analysis by nmr showed that the starting material was only 83% reduced. However, the optical purity of the distilled product was only 2% lower than that obtained in the 1:1 solvent. Hydrogenation did not occur readily in pure benzene, and the unsaturated starting material was only 13% reduced after the standard 24 hr reduction period. In 2-butanone, reduction took place to the extent of only 40% and the optical purity of the product dropped to 26.5% ee from 60% ee in 1:1 benzene-ethanol.

A possible explanation for the observed behavior is that varying the solvent may affect the dissociative equilibrium between tris(neomenthyldiphenylphosphine)rhodium(I)

Table 21. The influence of solvents on the reduction of (E)-α-methylcinnamic acid by the rhodium(I)-(+)-NMDPP catalyst system.[a,b]

Solvent	Reduction, %[c]	Yield, %[d]	Configuration	Product Optical Purity % ee
1:1 Benzene-Ethanol	100	90.3	(-)-R	60.0
3:1 Benzene-Ethanol	83	67.0	(-)-R	58.0
Benzene	13	(e)	-	-
2-Butanone	40	(f)	(-)-R	26.5
1:1 Benzene-Ethanol[g]	100	71.0	(-)-R	56.3

a) All reductions were carried out in a medium pressure Parr apparatus for 24 hr at 300 psi hydrogen at 60° in 200 ml deoxygenated solvent with 25 mmol of substrate and a substrate: catalyst ratio of 375. The substrate to triethylamine mol ratio was 6.25.

b) The author wishes to express his gratitude to Ms. Susan J. Hathaway who collected the data for all but the first entry in this table.

c) The % reduction was based on nmr analysis of the crude reduction products.

d) The % yield was based on the distilled product.

e) Reduction of 25 mmol of substrate, after workup gave 3.25 g of a crystalline product which was shown by nmr to be 13% reduced.

f) Data necessary to calculate the % yield were not obtained.

g) In this experiment 25 mmol of substrate and 25 mmol of triethylamine were used.

chloride and the coordinatively unsaturated or solvent saturated species $(NMDPP)_2RhCl$ or $(NMDPP)_2RhCl(S)$. If a change in solvent were to shift the equilibrium to greatly favor the tris(phosphine) species, reduction might be expected to be exceedingly slow.

The observed decrease in the optical purity of the saturated product formed in 2-butanone can be ascribed to a difference in the solvation of the catalyst complex, the olefin, or both, by the polar ketone solvent as compared to the solvation in 1:1 benzene-ethanol.

Much room for additional work exists here, and it should be possible through the proper choice of solvents to maximize both the chemical yield and optical purity of the products of asymmetric homogeneous hydrogenations.

An experiment was performed in which a 1:1 ratio of substrate, (E)-α-methylcinnamic acid, to triethylamine was used rather than the usual 6.25:1 ratio. This was done to determine whether the course of the reduction would be significantly affected by increasing the base concentration so that the substrate would be present in the reduction only as the anion. The last entry in Table 20 shows that the effect of increased base concentration was to lower the product optical purity by nearly 4%. This experiment demonstrates that higher asymmetric bias in the homogeneous hydrogenation of at least one α,β-unsaturated acid with the rhodium(I)-(+)-NMDPP catalyst is achieved when less than one equivalent of base is present. Reduction of (E)-β-

methylcinnamic acid under the standard conditions employed in this study except that no triethylamine was added resulted in only 20% reduction.

(+)-NMDPP and (-)-MDPP are diastereomeric ligands, specifically, epimers. An interesting question concerning the behavior of these ligands involves the relative effects of the three asymmetric centers in each molecule. If the stereochemical control of the reduction were exerted primarily by the asymmetric center nearest to phosphorus, and presumably nearest to rhodium, that at C-3 then these catalysts would be expected to behave as "pseudo-enantiomers". Asymmetric homogeneous hydrogenation by chiral phosphine catalysts, where the ligands in one reduction are enantiomeric to the ligands in the other reduction, would necessarily give products with the same magnitude of rotation, but different in sign. However, if chiral centers more remote from phosphorus also appreciably influence the reduction, then the relative behavior of a catalyst made with (+)-NMDPP compared to one made from (-)-MDPP would be unpredictable. The two catalysts might induce the same or different stereochemistry, and the same or different degrees of asymmetric synthesis might be observed.

The results of the present study show that the (+)-NMDPP and (-)-MDPP catalysts do, indeed, display divergent behavior both in terms of catalytic activity of their complexes and the qualitative and quantitative stereochemistry of the hydrogenations these complexes catalyze. Under

identical conditions, the chemical yield of reduction products was uniformly lower with the (-)-MDPP catalyst than with the (+)-NMDPP catalyst. A number of rationales to account for this observation can be postulated. Construction of molecular models seems to indicate that (-)-MDPP is less hindered than (+)-NMDPP, and on this basis it would be expected to form a more stable complex with rhodium than would (+)-NMDPP. The high ligand loadings used in this study (L : Rh = 15 : 1) may have forced the equilibrium between the tris(menthyldiphenylphosphine)rhodium(I) chloride and the coordinatively unsaturated species $Rh(MDPP)_2Cl$ or the solvent saturated species $Rh(MDPP)_2Cl(S)$ far to the left, causing the addition of hydrogen to olefinic substrates to be an exceedingly slow process (Figure 50).

$$[Rh(COD)Cl]_2 \xrightarrow[\text{large excess}]{L^*} Rh(L^*)_3Cl \rightleftharpoons Rh(L^*)_2Cl + L^*$$

Figure 50. The effect of excess ligand on the dissociation of $Rh(L^*)_3Cl$ (L^* = chiral ligand).

If the low rate of reduction was caused by inhibition of the dissociation of the tris(menthyldiphenylphosphine)-rhodium(I) chloride by the high ligand concentrations, then a preformed cationic complex such as $[Rh(COD)(MDPP)_2]^+ BF_4^-$ would obviate this difficulty. The syntheses of two cationic complexes of rhodium(I) and (-)-MDPP were attempted. Neither $[Rh(COD)(MDPP)_2]^+ BF_4^-$ or $[Rh(COD)(MDPP)_2]^+ PF_6^-$ could be

isolated from the reaction mixtures.

Another possibility is that while models predict (-)-MDPP to be less hindered at phosphorus than (+)-NMDPP, the geometry of the (-)-MDPP ligand may be such that it induces such steric constraints on the coordination of olefins to the complex, that the trisubstituted alkenes employed in this study could not readily coordinate. This could account for the low rate of reduction.

Striking differences in stereochemical behavior between in situ preparations of the (-)-MDPP (Table 22) and the (+)-NMDPP catalyst (Table 20) were observed. Atropic acid was reduced to the saturated acid by both the (+)-NMDPP and the (-)-MDPP catalysts, however, while the former gave (+)-S-2-phenylpropanoic acid in 29.6% ee, the latter gave a racemic product. While the (-)-MDPP catalyst generally gave products of much lower optical purity than the (+)-NMDPP catalyst, there was a notable exception that provides further evidence of the unpredictable behavior of the two ligands. With itaconic acid the (+)-NMDPP catalyst gave (+)-R-2-methylsuccinic in 8.1% ee, but the (-)-MDPP catalyst system (which gave a racemic product in the reduction of atropic acid) produced (+)-R-2-methylsuccinic acid in 18.1% ee, the highest optical purity recorded for this reaction with any catalyst studies thus far.

Another "spot variation" in (-)-MDPP catalyst behavior as compared to that of the (+)-NMDPP catalyst was revealed by reductions of isomeric pairs of (Z)- and (E)-

Table 22. Reduction of α,β-unsaturated carboxylic acids with the Rhodium(I)-(-)-MDPP catalyst complex.[a]

Substrate	Mole Ratio Substrate/Rh	Reduction, %[b]	Yield, %[c]	Configuration	Product Optical Purity % ee
Atropic Acid[d]	435	100	61.5	-	0.0
(E)-α-Methylcinnamic Acid	375	67	(e)	(+)-S	16.8[i]
(Z)-α-Methylcinnamic Acid	375	16	(f)	-	0.0[f,i]
(E)-α-Phenylcinnamic Acid	185	25	(g)	(-)-R	27.2[g,i]
(Z)-α-Phenylcinnamic Acid	185	23	(h)	(+)-S	3.2[h,i]
(E)-β-Methylcinnamic Acid	375	38	(j)	(+)-S	1.2[j,i]
(Z)-β-Methylcinnamic Acid	375	77	(k)	(+)-S	30.6[k,i]
Itaconic Acid	375	100	91	(+)-R	18.1[ℓ]
Mesaconic Acid	375	50	(m)	(-)-S	7.2[m,i]
Citraconic Acid	375	60	(n)	(-)-S	10.8[n,i]

FOOTNOTES

a) All reactions were carried out in a medium pressure Parr apparatus for 24 hr at 300 psi hydrogen at 60° in 200 ml 1:1 v/v deoxygenated ethanol-benzene with a substrate to triethylamine mol ratio of 6.25.

b) The % reduction was determined by nmr analysis of the crude products.

c) The % yield was determined on the distilled product for liquid products and on the crude product for solids.

d) The substrate to triethylamine mol ratio was 7.35.

e) Reduction of 25 mmol of (E)-α-methylcinnamic acid gave a mixture of saturated acid (67%) and starting material (33%), 3.9 g. The mixture was purified to 94.4% saturated acid for the determination of the rotation.

f) Reduction of 25 mmol of (Z)-α-methylcinnamic acid gave a mixture of saturated acid (16%) and starting material (84%), 3.9 g. The rotation was determined on the crude product.

g) Reduction of 12.5 mmol of (E)-α-phenylcinnamic acid gave a mixture of saturated acid (25%) and starting material (75%), 2.6 g. The rotation was determined on the crude product.

h) Reduction of 12.5 mmol of (Z)-α-phenylcinnamic acid gave a mixture of saturated acid (23%) and starting material (77%), 2.6 g. The rotation was determined on the crude product.

i) The optical rotation measurement assumes no contribution by the starting material other than a dilution effect.

j) Reduction of 25 mmol of (E)-β-methylcinnamic acid gave a mixture of saturated acid (37.5%) and starting material (62.5%), 3.5 g. The optical rotation was taken on the crude product.

k) Reduction of 25 mmol of (Z)-β-methylcinnamic acid gave a mixture of saturated acid (77%) and starting material (23%). The optical rotation was measured on a sample of 85% purity (15% starting material).

FOOTNOTES (continued)

ℓ) The optical rotation was measured on the crude product.

m) Reduction of 25 mmol of mesaconic acid gave a mixture (2.8 g) of saturated acid (50%) and starting material (50%). The optical rotation was measured on the crude product.

n) Reduction of 25 mmol of mesaconic acid gave a mixture (0.7 g) of saturated acid (60%) and starting material (40%). The optical rotation was measured on the crude product.

α,β-unsaturated acids. With the rhodium(I)-(+)-NMDPP catalyst system a substrate with a trans-phenyl-carboxyl relationship always gave a product of higher optical purity than a substrate with a cis-phenylcarboxyl relationship. Similarly, when reduced with the rhodium(I)-(-)-MDPP catalyst, (E)-α-methylcinnamic acid gave (+)-S-2-methyl-3-phenyl propanoic acid in 16.8% ee while the (Z)-α-methylcinnamic acid gave a racemic product. (E)-α-Phenylcinnamic acid was reduced to (-)-R-2,3-diphenylpropanoic acid (27.2% ee) while (Z)-α-phenylcinnamic acid gave the (+)-S-saturated product (3.2% ee). Thus the four experiments with the α-substituted cinnamic acids and the (-)-MDPP catalyst all gave results in accordance with the trend observed for the (+)-NMDPP catalyst. However, (E)-β-methylcinnamic (trans-phenyl carboxyl relationship) was reduced by the (-)-MDPP catalyst to (+)-S-3-phenylbutyric acid (1.2% ee) while (Z)-β-methylcinnamic acid (cis-phenyl-carboxyl) also gave (+)-S-3-phenylbutyric acid, but in 30.6% ee.

The results shown in Table 23 summarize the differences between the two catalysts.

CAMPHOS was particularly attractive as a chiral ligand. As described previously, CAMPHOS was available via a three step sequence from commercially available, inexpensive, and optically pure (+)-camphoric acid, and it was synthesized by reactions not affecting the asymmetric centers. CAMPHOS contains two asymmetric centers, and the diphosphine can act as a chelating agent forming a bicyclic complex when coordi-

Table 23. A comparison of the stereochemistry of products of reduction of α,β-unsaturated acids by the rhodium(I)-(+)-NMDPP and (-)-MDPP catalysts.

Substrate	(-)-MDPP Catalyst Product Configuration	(-)-MDPP Catalyst % ee	(+)-NMDPP Catalyst Product Configuration	(+)-NMDPP Catalyst % ee
Atropic Acid	-	0.0	(+)-S	29.6
(E)-α-Methylcinnamic Acid	(+)-S	16.8	(-)-R	60.0
(Z)-α-Methylcinnamic Acid	-	0.0	(-)-R	25.2
(E)-α-Phenylcinnamic Acid	(-)-R	27.2	(+)-S	34.4
(Z)-α-Phenylcinnamic Acid	(+)-S	3.2	(+)-S	9.1
(E)-β-Methylcinnamic Acid	(+)-S	1.2	(+)-S	61.8
(Z)-β-Methylcinnamic Acid	(+)-S	30.6	(-)-R	31.2
Itaconic Acid	(+)-R	18.1	(+)-R	8.1
Mesaconic Acid	(-)-S	7.2	-	-
Citraconic Acid	-	-	(+)-R	5.9

nated to rhodium. Such a complex would be expected to be more rigid, and perhaps more likely to display greater asymmetric bias than acyclic or monocyclic complexes. Additionally, monophosphine ligands and by analogy diphosphine ligand s remain bonded to the rhodium metal, and do not undergo epimerization equilibria relative to the rhodium chirality.[137]

However, the optical purities of the products of reduction of α,β-unsaturated acids by the rhodium(I)-(+)-CAMPHOS catalyst system were lower than those for the rhodium-(I)-(+)-NMDPP catalyst system. With the (+)-CAMPHOS catalyst, atropic acid was hydrogenated to (+)-S-2-phenylpropanoic acid (6% ee). In contrast, atropic acid was hydrogenated to (+)-S-2-phenylpropanoic acid with 29.6% ee with the (+)-NMDPP catalyst. The highest optical purities recorded for the (+)-CAMPHOS system were in reductions of (E)-α-methylcinnamic acid. (+)-CAMPHOS prepared by the displacement method was used to form a rhodium(I) catalyst which reduced (E)-α-methylcinnamic acid to (-)-R-2-methyl-3-phenylpropanoic acid in 15.2% ee. (+)-CAMPHOS prepared by the tris(dimethylamino)-phosphine desulfurization of (+)-CAMPHOS disulfide used under conditions identical to those of the above experiment gave (-)-R-2-methyl-3-phenylpropanoic acid in 15.4% ee (Table 24).

While the (+)-NMDPP catalyst generally displayed higher asymmetric bias in the reduction of α,β-unsaturated acids than did the (+)-CAMPHOS catalyst there were two exceptions. Both the (+)-NMDPP and the (+)-CAMPHOS catalysts reduced (Z)-α-phenylcinnamic acid to (+)-S-2,3-diphenyl-

Table 24. Asymmetric homogeneous hydrogenation of α,β-unsaturated carboxylic acids with the Rhodium(I)-(+)-CAMPHOS catalyst.[a]

Substrate	Mole Ratio Substrate/Rh	Reduction, %[b]	Yield, %[c]	Configuration	Product Optical Purity % ee
Atropic Acid[d]	435	100	69	(+)-S	6.05
(E)-α-Methylcinnamic Acid	375	100	93	(-)-R	15.2[e]
(Z)-α-Methylcinnamic Acid	375	100	88	(+)-S	11.0
(E)-α-Phenylcinnamic Acid	185	100	88	(+)-S	11.8
(Z)-α-Phenylcinnamic Acid	185	100	88	(+)-S	13.9
(E)-β-Methylcinnamic Acid	375	100	78	(+)-S	9.7
(Z)-β-Methylcinnamic Acid	375	100	90	(-)-R	11.4
Itaconic Acid	375	100	74	(+)-R	10.7
Mesaconic Acid	375	100	79	(+)-R	1.8
Citraconic Acid	375	14	(f)	-	-

FOOTNOTES

a) All reactions were carried out in a medium pressure Parr apparatus for 24 hr at 300 psi hydrogen at 60° in 200 ml 1:1 v/v deoxygenated ethanol-benzene with a substrate to triethylamine mol ratio of 6.25.

b) The % reduction was determined on the crude reduced acids by nmr spectroscopy.

c) The yield data were based on distilled products when the product was a liquid and on crude product when the product was a solid.

d) The substrate to triethylamine mol ratio was 7.35.

e) Under identical conditions, (+)-CAMPHOS ligand from the desulfurization of (+)-CAMPHOS disulfide with tris-dimethylamino)phosphine resulted in (-)-R-2-methyl-3-phenylpropanoic acid in 15.4% ee.

f) A crude solid (2.1 g) was isolated and was shown by nmr to be 14% 2-methylsuccinic acid. The balance was starting material. The optical rotation of the product was not determined.

propanoic acid. With (+)-NMDPP, 9.1% ee was recorded, while with (+)-CAMPHOS, the saturated acid was obtained in 13.9% ee. In the reduction of itaconic acid, both ligands induced the formation of (+)-R-2-methylsuccinic acid. With (+)-NMDPP 8.1% ee was recorded, and with (+)-CAMPHOS 10.7% ee was obtained. This evidence points to a need to individually tailor chiral ligands to match substrate molecules for it is most unlikely that any one ligand will be developed that will display high asymmetric bias with all unsaturated substrates.

The low optical purities resulting from reductions with the (+)-CAMPHOS system may be in part due to geometrical isomerism about rhodium. The complex H_2L_2RhCl(olefin) exists as two enantiomeric forms (Figure 51).

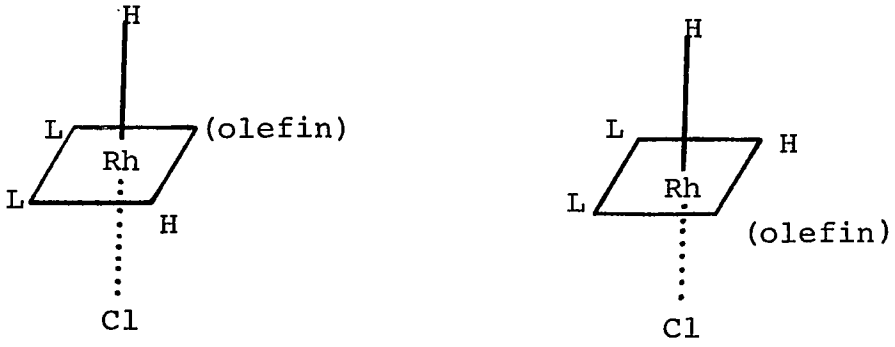

Figure 51. The two enantiomeric forms of H_2L_2RhCl(olefin).

When external chirality is introduced into the complexes of Figure 51 by substituting chiral ligands for the achiral L, the two previously enantiomeric forms become diastereomeric and each diastereomer must experience interactions of different energies with a prochiral olefin. The situation is further complicated in the case of the (+)-CAMPHOS catalyst which can exist in four diastereomeric forms due to geometrical isomerism (Figure 52). These diastereomers will be present in unequal amounts. Each of the diastereomeric catalyst forms will interact differently with a prochiral olefin, and each diastereomeric complex will display a different degree of asymmetric bias. The existence of several catalyst species does not necessarily require that the catalyst display low stereoselectivity, however.

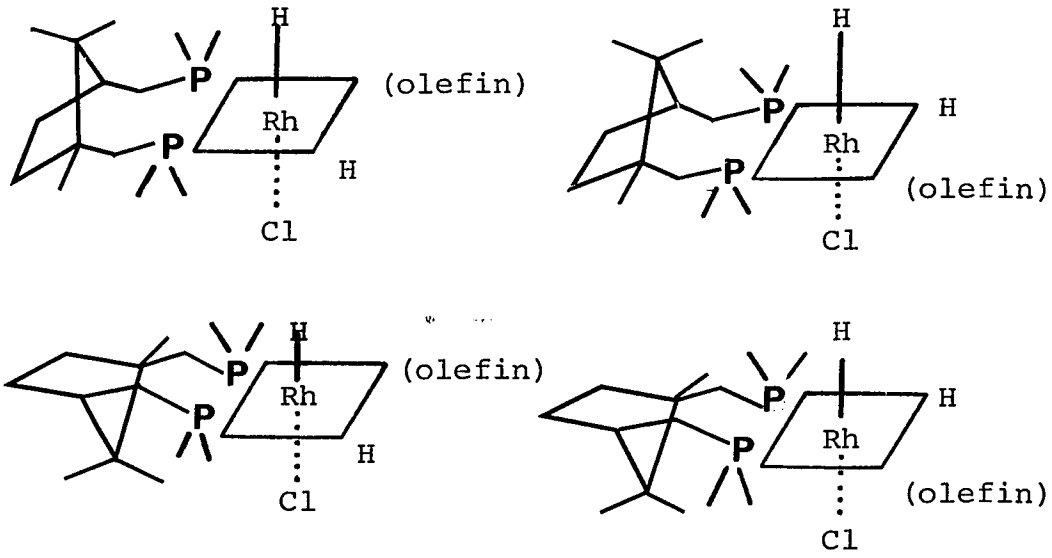

Figure 52. A representation of four of the diastereomeric forms of H_2(CAMPHOS)RhCl(olefin).

The low stereoselectivity observed in asymmetric hydrogenations with the (+)-CAMPHOS ligand may be due to several factors. In order to achieve high stereoselectivity, the prochiral olefin must undergo diastereomeric interactions of significantly different energy so that transfer of hydrogen from the catalyst to the substrate takes place predominantly to the re or si face of the olefin. A number of situations are possible in the case of (+)-CAMPHOS: a) Four diastereomeric catalyst complexes are formed and they will necessarily undergo interactions of different energies with the prochiral substrate. The low observed stereoselectivity could result from two of the complexes giving a product of high optical purity with one configuration, and the other two complexes giving a product of the opposite configuration, so that the resulting mixture was of low optical purity. Of course, it is possible that all four complexes give products of low optical purity. Other possibilities, not limited to the following, also exist. b) The diastereomeric complexes are formed in different amounts, and the complex formed in the largest amount could be responsible for the majority of the reduction. c) The rates of hydrogenation by the diastereomeric complexes will necessarily be different; although the magnitude of the difference may be small, it is conceivable that one or more of the diastereomeric complexes could be responsible for all or nearly all of the reduction if its rate of hydrogenation is much greater than that of the other diastereomers.

Kagan has attributed the high stereoselectivity of the DIOP catalyst, at least in part, to the absence of geometrical isomerism about rhodium since the phosphorus atoms of DIOP (26) are equivalent. The phosphorus atoms in (+)-CAMPHOS are not equivalent. There are still other differences between (+)-CAMPHOS and DIOP which may contribute to the lower stereoselectivity observed in reductions with the (+)-CAMPHOS catalyst. The chelate formed by DIOP is a seven membered ring, while that formed by (+)-DIOP has eight members and should be less rigid than the DIOP chelate. Further lack of rigidity in the (+)-CAMPHOS can be traced to the cis stereochemistry of the diphenylphosphinomethyl groups. In DIOP, the diphenylphosphinomethyl groups are fixed in a trans configuration by the dioxolane ring and this probably results in a more conformationally biased chelate ring than is the case for the (+)-CAMPHOS chelates with their cis-diphenylphosphinomethyl groups.

It should be noted that the "high stereoselectivity" referred to in the DIOP reductions is a relative term, and in fact, in all cases except two, the monophosphine (+)-NMDPP was a superior ligand to (-)-DIOP. The (-)-DIOP catalyst displayed higher stereoselectivity than the (+)-CAMPHOS catalyst in all reductions except that of (Z)-α-phenylcinnamic acid (Tables 21, 24, and 25).

Unusually high stereoselectivity in asymmetric reductions with DIOP has been observed with α-acylaminoacrylic substrates. Optical purities as high as 90% have been re-

Table 25. Asymmetric homogeneous hydrogenation of α,β-unsaturated carboxylic acids with the rhodium(I)-(-)-DIOP catalyst.[a,b,e]

Substrate	Mole Ratio Substrate/Rh	Yield, %[c]	Configuration	Product Optical Purity % ee
Atropic Acid[d]	435	70	(+)-S	43.9
(E)-α-Methylcinnamic Acid	375	81	(+)-S	24.6
(Z)-α-Methylcinnamic Acid	375	74	(-)-R	33.0
(E)-α-Phenylcinnamic Acid	185	89	(-)-R	14.9
(Z)-α-Phenylcinnamic Acid	185	68	(+)-S	1.0
(E)-β-Methylcinnamic Acid	375	85	(-)-R	13.5
(Z)-β-Methylcinnamic Acid	375	81	(+)-S	28.0

FOOTNOTES

a) All reactions were carried out in a medium pressure Parr apparatus for 24 hr at 300 psi hydrogen at 60° in 200 ml 1:1 v/v deoxygenated benzene-ethanol with a substrate to triethylamine mol ratio of 6.25.

b) The author wishes to express his gratitude to Ms. Susan J. Hathaway who collected the data in this table.

c) In all cases, reduction of the substrate was quantitative (determined by nmr). Yield refers to isolated yield, distilled in the case of liquid products, crude in the case of solids.

d) The substrate to triethylamine mol ratio was 7.35.

e) In all cases the mol ratio of (-)-DIOP to rhodium was 1.5.

corded.[73] It is most likely that these results are due to some attractive interaction between the substrate and the chiral ligand, possibly in the form of hydrogen bonding between the enamide function of the substrate and the dioxolane oxygens of the ligand. This interaction is not possible with the α,β-unsaturated acids used in this study and this probably results in the lower asymmetric bias observed for these substrates. The results of hydrogenations over $[Rh(COD)(ACMP)_2]^+ BF_4^-$ also suggest that hydrogen bonding plays an important role in the reductions of α-acylaminoacrylic acids over the ACMP catalyst. Optical purities of greater than 80% have been recorded in the reduction of α-acylaminoacrylic acids where hydrogen bonding between the substrate and the anisyl group of the ligand is possible. Much lower optical purities resulted from the reduction of the α,β-unsaturated acids used in this study (Table 26).

In conclusion, the goals set for this study have been met. Efficient syntheses for (+)-NMDPP, (-)-MDPP, and (+)-CAMPHOS have been developed. The use of these ligands in asymmetric homogeneous hydrogenations has been studied. The differences between the epimeric ligands (+)-NMDPP and (-)-MDPP have been elaborated, and (+)-CAMPHOS has been compared to another diphosphine, (-)-DIOP. For comparison, some of the substrates reduced by catalysts made from the above ligands were reduced by a cationic catalyst made from the ligand ACMP. The process of asymmetric catalytic homogeneous hydrogenation is clearly quite complex, and the behavior of

Table 26. Asymmetric homogeneous hydrogenation of α,β-unsaturated carboxylic acids with $[Rh(COD)(ACMP)_2]^+ BF_4^-$. [a,b]

Substrate	Yield, %[c]	Configuration	Product Optical Purity % ee
Atropic Acid[d]	--	-	1
(E)-α-Methylcinnamic Acid	88	(-)-R	12.1
(Z)-α-Methylcinnamic Acid	88	(-)-R	23.5
(E)-α-Phenylcinnamic Acid	85	(+)-S	24.4
(Z)-α-Phenylcinnamic Acid	93	(-)-R	1.5
(E)-β-Methylcinnamic Acid	85	(+)-S	37.1
(Z)-β-Methylcinnamic Acid	81	(-)-R	13.2

FOOTNOTES

a) All reductions except for atropic acid were carried out in a medium pressure Parr apparatus for 24 hr at 300 psi hydrogen at 60° in 200 ml deoxygenated 1:1 v/v benzene-ethanol with a substrate to rhodium ratio of 362. The substrate to triethylamine mol ratio was 6.25.

b) The author wishes to express his gratitude to Ms. Susan J. Hathaway who collected the data for the last four entries in this table.

c) In all cases reduction of the substrate was quantitative (determined by nmr). Yield refers to isolated yield, distilled in the case of liquid products, crude in the case of solids.

d) No data other than the optical purity of the product were given (ref. 78).

these catalysts toward prochiral substrates cannot be predicted.

In addition to the above findings a new route to chiral phosphines from chiral aldehydes and unhindered chiral ketones was developed and an unusual cleavage of alkyl or aryl groups from hindered tertiary phosphine oxides by trichlorosilane and N,N-dimethylaniline was discovered.

However, much work remains to be done. The trichlorosilane cleavage reaction merits further study. A simple modification of (+)-NMDPP could render it an especially efficient ligand for reduction of α-acylaminoacrylic acids. If di-o-anisylphosphine were substituted for diphenylphosphine in the (+)-NMDPP preparation, neomenthyldi-o-anisylphosphine would result. The o-methoxy groups could hydrogen bond to the substrate molecules and higher stereoselectivity might result. (+)-CAMPHOS could be modified similarly. Another area which bears investigation is the synthesis of iso-CAMPHOS. (+)-Camphoric acid can be converted with acid to isocamphoric acid.[138] Iso-camphoric acid can be converted to iso-CAMPHOS in three steps (Figure 53).

The diphenylphosphinomethyl groups of iso-CAMPHOS bear a trans relationship to each other. It is possible that iso-CAMPHOS would form a more rigid chelate structure with rhodium than CAMPHOS and increased stereoselectivity could result.

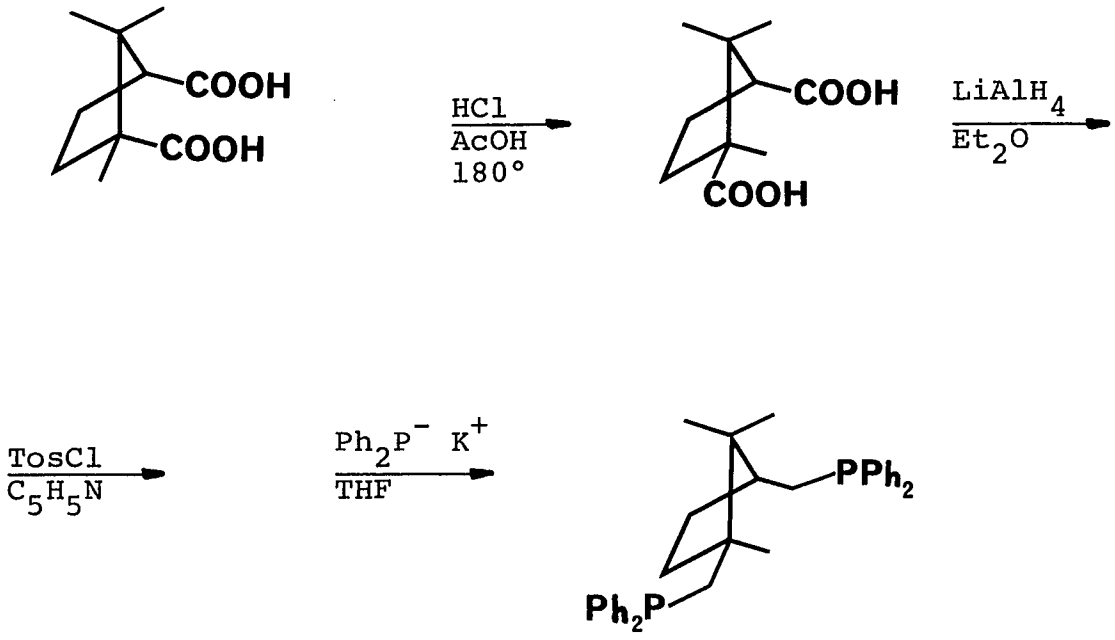

Figure 53. The synthesis of iso-CAMPHOS.

Finally, a unified theory of asymmetric homogeneous hydrogenation does not exist. While the chemist may have some vague guidelines to aid in his matching of substrate and catalyst, the choice remains largely empirical. The development of a quantitative relationship between substrate and ligand or catalyst structure will allow the realization of a goal set more than seventy years ago when work on asymmetric synthesis began. With a working knowledge of structure-activity relationships, it will be possible to design and synthesize chiral catalysts with stereochemical efficiency rivaling that of enzyme systems.

EXPERIMENTAL

General

Gas-liquid Partition Chromatographic Analyses (glpc) were performed on a Varian Aerograph Model 90-P gas chromatograph coupled to a Sargent Welch Model SRG recorder with Disc integrator. Helium was used as the carrier gas. Table 27 lists the analytical columns and retention times for the compounds used in this study.

Infrared Spectra (ir) were recorded on a Perkin-Elmer 337 grating spectrophotometer and calibrated using the 1601.4 and 906.7 cm^{-1} bands of polystyrene. The spectra of liquids were obtained neat, while those of solids were taken as mulls.

Nuclear Magnetic Resonance Spectra (nmr) were obtained on a Jeolco Model JNM-MH 100, 100 MHz nmr. All 100 MHz spectra are numbered less than 3000. A Varian Model A-60 Spectrometer was used to record 60 MHz nmr spectra. All 60 MHz spectra are numbered greater than 3000. Chemical shifts are reported in relative to internal tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants are given in Hertz.

Elemental Analyses were performed on an F and M Model 185 Carbon, Hydrogen, Nitrogen Analyzer.

Table 27. Gas chromatographic retention times for compounds used in this study.[a]

Compound	Column	Temp. °C	Retention Time, sec
Triethylphosphonoacetate	A	130	106
(E)-Ethyl-β-methylcinnamate	A	150	120
	C	150	314
(Z)-Ethyl-β-methylcinnamate	A	150	82
	C	150	232
Diphenylphosphine	A	175	76[b]
	A	210	22[b]
	A	250	7.5[b]
(-)-Menthyl chloride	B	180	196
Menthenes (2)	B	180	90,106
(+)-NMDPP	A	230	68[b]
	A	235	60[b]
(+)-NMDPP oxide	A	230	120[b]
	A	235	112[b]
(+)-Neomenthyl chloride	B	180	196[b]
(-)-MDPP	A	235	76[b]
(-)-MDPP oxide	A	235	120[b]
(-)-MDPP sulfide	A	235	188[c]
(-)-2,3-Bornanedione	B	210	450
(+)-1,2,2-Trimethylcyclopentane-1,3-dicarboxaldehyde	B	210	360
Diethyl-2,3-O-isopropylidene-L-tartrate	A	105	202

Table 27. (continued)

Compound	Column	Temp. °C	Retention Time, sec.
Neopentyl tosylate	A	175	112
Neopentyldiphenylphosphine	A	175	142
	A	214	52[b]
Neopentyldiphenylphosphine oxide	A	214	120[b]
	A	235	56[b]
Neopentyldiphenylphosphine sulfide	A	215	166[b]
Cyclohexyldiphenylphosphine	A	230	42[b]
Cyclohexyldiphenylphosphine oxide	A	235	82[b]
Tris(dimethylamino)phosphine	A	145	38
Tris(dimethylamino)phosphine sulfide	A	150	90
Triphenylphosphine oxide	A	225	224[c]
Triphenylphosphine sulfide	A	225	254[c]
Triphenylphosphine	A	225	82[c]
n-Decyldiphenylphosphine	A	250	68[b]
n-Decyldiphenylphosphine oxide	A	250	158[b]
4-t-Butyldiphenylphosphine oxide (*cis* and *trans*)	A	235	158[b],240[b]

Table 27. (continued)

Column A: 5' x 1/4" 3% SE-30 on Varaport 30, 80-100 mesh.

Column B: 10' x 1/4" 15% Carbowax 20M on Chromosorb P, 60-80 mesh.

Column C: 5' x 1/4" 20% QF-1 on Chromosorb W, AW/DMCS, 80-100 mesh.

a) The helium flow rate in all cases was 50 ml/min.

b) The retention time is relative to an internal standard of benzene.

c) The retention time is relative to an internal standard of chloroform.

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

Optical Rotations were determined on a Carl Zeiss Photoelectric Precision Polarimeter, 0.005°, equipped with a deuterium light source and filtered to give readings at 578, 546, 435, 405 and 365 nm. Rotations are reported at the sodium-D line (589 nm) and were calculated from the Drude equation.

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

Compounds unless otherwise noted were purchased from commercial sources and were used as received.

Dry Solvents: Diethyl ether (Fisher Anhydrous Ether) was dried over sodium wire.

Tetrahydrofuran (THF) was distilled from lithium aluminum hydride and was stored over molecular sieves.

Dioxane was purified according to the procedure of Vogel[174] and was stored over molecular sieves.

Dimethoxyethane was dried over molecular sieves.

Benzene was dried by distillation (80°). Water was removed as an azeotropic forerun (69°).

Pyridine was dried by refluxing over and distilling from potassium hydroxide pellets. The distilled pyridine was stored over potassium hydroxide pellets.

Hydrogenations. Catalyst solutions were prereduced in the stirred low pressure hydrogenator described by Masler et al.[175] The unsaturated carboxylic acids were hydrogenated using a Parr Model 4501 Medium Pressure Hydrogenator.

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

Preparation of Ethyl Atropate. Sodium ethoxide was prepared by dissolving sodium metal (23.0 g, 1.0 mol) in absolute ethanol (200 ml). When the sodium had dissolved, the mixture was concentrated to dryness and the solid sodium ethoxide was treated with diethyl oxalate (180 g, 1.24 mol) and benzene (400 ml). Ethylphenylacetate (164 g, 1.0 mol) was added slowly to the stirred benzene solution. After about one hour the reaction mixture solidified and was allowed to stand overnight.

The salt was collected by filtration and was washed well with ether. The salt was neutralized with 10% HCl and the resulting oil was extracted into ether. The ether solution was concentrated, (the temperature must be kept below 45° at this point to avoid decomposing the intermediate keto ester) and the concentrate was then treated with a solution of formaldehyde (140 ml, of a 37% solution) in water (400 ml). The mixture was cooled in ice and a solution of potassium carbonate (80 g, 0.58 mol) in water (75 ml) was added slowly so that the temperature of the mixture did not rise above 16°. At the end of the addition, the reaction mixture was allowed to stir at room temperature.

After 4 hr, the oil which had formed was extracted with ether, dried ($MgSO_4$) and concentrated to give crude ethyl atropate. The crude product was distilled and the fraction with bp 88-92° (0.25 mm) was collected, yield, 99 g (56.2%).

Preparation of Atropic Acid from Ethyl Atropate. Ethyl atropate (89 g, 0.505 mol) and a solution of sodium hydroxide (80.0 g, 2.0 mol) in water (600 ml) were heated together and allowed to reflux for 2.5 hr. The clear solution was allowed to cool to room temperature and was acidified with the calculated quantity of HCl. Atropic acid precipitated from solution, was collected by filtration and dried in air. The crude acid was recrystallized by stirring an ethanol-water solution of the crude acid in an ice bath. Two crops of crystals were collected to yield 47 g (63.8%) of product; mp 104-106°; lit.[139] mp 106-107°; ir (20403, nujol) 1690 (C=O), 900 cm^{-1} (C-O); nmr (15446, $CDCl_3$) δ 5.89 (d, 1, J=1 Hz, C=C<u>H</u>), 6.43 (d, 1, J=1 Hz, C=C<u>H</u>), 7.28 (m, 5, Ph), 11.70 (s, 1, CO_2<u>H</u>).

Preparation of (E)-α-Methylcinnamic Acid.[140] A mixture of benzaldehyde (106 g, 1.0 mol), propionic anhydride (160 g, 1.23 mol) and sodium acetate (82 g, 1.0 mol) was heated and allowed to reflux for 32 hr. The reaction mixture was poured onto ice and water (1.2 ℓ) and was made acidic with HCl. The crude acid was extracted into ether and the ether solution was washed well with water. The ether solution was then extracted with a solution of NaOH (80 g, 2.0 mol) in water (1 ℓ) and the aqueous solution was separated and washed with ether. The aqueous solution was acidified and the product separated as an oil which was extracted into ether. The ether layer was separated, washed with water and dried ($MgSO_4$). Concentration gave crude α-

methylcinnamic acid as an oil which crystallized on standing. The crude acid was crystallized from 60-80° petroleum ether to give 100 g of acid, (61.7%) mp 80-81°; lit.[141] mp 81-82°; nmr (16612, $CDCl_3$) δ 2.05 (d, 3, J=1.5 Hz, CH_3), 7.13 (s, 5, Ph), 7.58 (q, 1, J=1.5 Hz, C=CH).

Preparation of (Z)-α-Methylcinnamic Acid by Photolytic Isomerization of (E)-α-Methylcinnamic Acid. A solution of (E)-α-methylcinnamic acid (45 g, 0.278 mol) in 400 ml of benzene was irradiated in a quartz flask inside a "Srinivasen type" photochemical reactor (128 watts) for 6 days. The reaction mixture was then concentrated to dryness and the resulting yellow oil was taken up in 30-60° petroleum ether (425 ml). Seeding with (Z)-α-methylcinnamic acid caused slow crystallization at room temperature. The slightly brown crystals were filtered (8.0 g, 17.8%) and recrystallized from cyclohexane (100 ml) with decolorization by Norit to give white prisms, 7.0 g (15.5%), mp 91-92.5°; lit.[142] mp 91-92°; nmr (16386, $CDCl_3$) δ 2.05 (d, 3, J=1.5 Hz, CH_3), 6.75 (q, 1, J=1.5 Hz, C=CH), 7.20 (s, 5, Ph).

The mother liquor from the first crystallization was concentrated to dryness and an additional 10 g of (E)-α-methylcinnamic acid was added. The crude mixture of acids was dissolved in benzene (400 ml) and was again photolyzed (workup and purification as above) to give an additional 7.5 g of (Z)-α-methylcinnamic acid. This procedure can be repeated to give more (Z)-acid. Ethanol can also be used as a solvent for the photolysis.

Preparation of (E)-α-Phenylcinnamic Acid. A mixture of benzaldehyde (60 g, 0.57 mol), phenylacetic acid (55 g, 0.44 mol), triethylamine (40 ml), and acetic anhydride (115 ml, 115 g, 1.07 mol) was heated on a steam bath for 20 hr. The reaction mixture was poured into 10% HCl (500 ml) and the organic layer was extracted with 1 ℓ of 2.5% sodium hydroxide. The aqueous phase was withdrawn and was kept separate from the other base extracts. The organic layer was then extracted 4 times with 400 ml of 2.5% sodium hydroxide. The four base extracts were combined, washed with ether and then were acidified to pH 4-4.5 with acetic acid. The original 1 ℓ aqueous phase was treated in the same way. The 1 ℓ extract gave no precipitate, but the 1600 ml base extract gave a large amount of (E)-α-phenylcinnamic acid. The (E)-acid was removed by filtration and dried in vacuo over KOH. Then both aqueous solutions were acidified with HCl. On cooling at 5° overnight (Z)-acid separated as crystals which were filtered and recrystallized from 40% ethanol to give pure (Z)-acid, mp 137-138°, mp lit.[141] 137-138°, yield 7.0 g (7.0%).

The crude (E)-acid, 82.1 g was crystallized from 1:1 benzene: 100-115° petroleum ether to give (E)-α-phenylcinnamic acid as white needles, 70.0 g, (70.5%), mp 173-174°, mp lit.[143] 172°.

Preparation of (Z)-α-Phenylcinnamic Acid by Photolytic Isomerization of (E)-α-Phenylcinnamic Acid. A benzene solution of (E)-α-phenylcinnamic acid (40.0 g, 0.179 mol) in a 500 ml quartz flask was photolyzed for 8 days in a "Srinivasen type" photochemical reactor with 2537 Å light (128 watts).

The acid was extracted into a solution of sodium hydroxide (15 g, 0.38 mol) and water (1500 ml). The aqueous layer was separated and acidified to approximately pH 5 with acetic acid. The (E)-acid which precipitated was isolated by filtration and dried. The filtrate was acidified with HCl and the precipitated (Z)-acid was filtered and dried in vacuo to give (Z)-α-phenylcinnamic acid 17.5 g (43.7%).

Preparation of Triethylphosphonoacetate. Triethylphosphite (100 g, 0.602 mol) was warmed to about 100° under a nitrogen atmosphere. Ethylbromoacetate (100 g, 0.6 mol) was added dropwise; there was an exothermic reaction. The external heat was removed and ethyl bromide (bp 38°) was distilled as it formed (60 g was collected). The product was isolated by distillation of the residue and two fractions were collected, bp 145-146° (11 mm), 107.5 g and bp 146-155° (11 mm), 5.5 g, bp lit.[144] 135-145° (8-10 mm). Analysis by glpc (column A, 130°) indicated that the fractions were of comparable purity. Yield, 113 g (84.3%); ir (21446, neat) 2990 (C-H), 1720 (C=O), 1270 (P=O), 1160 (P-O-ethyl), 1030 cm^{-1} (P-O-C); nmr (1575, neat), δ 1.32 (m, 9, $C\underline{H}_3$), 3.02 (d, 2, $\underline{J}$=22 Hz, P-$C\underline{H}_2$), 4.25 (m, 6, $C\underline{H}_2$-CH_3).

Preparation of Ethyl-β-Methylcinnamate from Triethylphosphonoacetate and Acetophenone. Triethylphosphonoacetate (112 g, 0.5 mol) was added dropwise to a cooled suspension of sodium hydride (50% dispersion in nujol, 24 g, 0.5 mol) in dry dimethoxyethane (500 ml) so that the temperature did not rise above 30°. The reaction mixture was allowed to stir for 1 hr at room temperature and then acetophenone (60 g, 0.5 mol) was added dropwise so that the temperature remained below 30°. The reaction mixture was stirred for 2 hr at room temperature and then at 50° for 2 hr. After cooling, the reaction mixture was treated with water (40 ml) and sodium chloride was added to decrease the solubility of the dimethoxyethane. The reaction mixture was extracted with ether and the ether was concentrated to give a brown oil, 88 g. The aqueous layer was continuously extracted with ether for 8 hr and the ether extract was concentrated to give an additional 8 g of crude oily product. The oil was distilled, bp 75-83° (0.05 mm), yield, 70 g, (73.6%). Analysis by glpc (column A, 150°; column C, 150°) showed the presence of the two isomers in a ratio of 9:1. The distillate was analyzed by nmr which showed the presence of two isomers in a ratio of 9:1 with the (E)-isomer being the predominant one. nmr (1639, neat) (E)-isomer: δ 1.25 (t, 3, (CH_2-$C\underline{H}_3$), 2.64 (s, 3, C=CC$\underline{H}_3$), 4.28 (q, 2, $C\underline{H}_2$-CH_3), 6.32 (s, 1, C=C$\underline{H}$), 7.52 (m, -*, Ph); (Z)-isomer: δ 1.00 (t, 3, CH_2-$C\underline{H}_3$), 2.08 (s, 3, C=CC$\underline{H}_3$), 4.12 (q, partially obscured, $C\underline{H}_2$-CH_3), 6.04 (s, 1, C=C$\underline{H}$), 7.52 (m, -*, Ph).

*The aromatic signals for the (E)- and (Z)-isomers overlapped and it was not possible to integrate the signals separately.

Preparation of (E)-β-Methylcinnamic Acid by Hydrolysis of Ethyl-β-Methylcinnamate. Ethyl-β-methylcinnamate (70 g, 0.37 mol) was heated with a solution of potassium hydroxide (33 g, 0.5 mol) in water (300 ml) and the reaction mixture was allowed to reflux for 2 hr. The reaction mixture was allowed to cool and was extracted with ether. The aqueous solution was acidified with HCl and the resulting clear oil was extracted into ether (2 x 150 ml). The ether was dried (Na_2SO_4) and concentrated to give a white crystalline product which was crystallized from 3:1, heptane:ethyl acetate (350 ml) to give white prisms, yield 30.9 g (52%), mp 96-97°; lit.[145] mp 98.5°; nmr (16423, CS_2) δ 2.09 (d, 3, $\underline{J}$=1.5 Hz, C=CC$\underline{H}_3$), 5.56 (q, 1, $\underline{J}$=1 Hz, C=C$\underline{H}$), 6.92 (m, 5, Ph). Two more crops of crystals were collected, 20.3 g (34.2%) mp 80-90°. The melting point range suggests that the crystalline material was a mixture of both (Z)- and (E)-isomers.[145]

Preparation of Ethyl-3-hydroxy-3-phenylbutanoate From Ethylbromoacetate and Acetophenone.[146] Zinc dust (52 g, 0.80 mol) was activated by washing successively with 2% HCl, water, absolute ethanol, acetone, and dry ether. The activated dust was stirred under nitrogen with a mixture of acetophenone (90 g, 0.75 mol), trimethylborate (190 ml) and tetrahydrofuran (190 ml). The reaction mixture was held at room temperature and about 10% of the total amount of ethylbromoacetate (130 g, 0.78 mol) was added. The reaction mixture was stirred and heated gently to start the reaction. Once the reaction had begun the rate of addition of the

ethylbromoacetate was adjusted so that a gentle reflux was maintained. The reaction mixture was allowed to stir overnight and was then treated with glycerol (190 ml) followed by the slow addition of concentrated ammonia (190 ml). The resulting two layers were separated and the aqueous portion was extracted with ether. The ether extract and the organic layer were combined, washed successively with water and saturated salt, dried ($MgSO_4$), and concentrated to give 135.2 g (86.5%) of crude ethyl-3-hydroxy-3-phenylbutanoate which was not purified, but was immediately used in the next step.

Preparation of (E)-β-Methylcinnamic Acid From Ethyl-3-hydroxy-3-phenylbutanoate. Ethyl-3-hydroxy-3-phenylbutanoate (135.2 g, 0.65 mol) was dissolved in benzene (300 ml); phosphorus oxychloride (3 ml) was added and the mixture was heated and allowed to reflux. The water which formed was removed with a Dean-Stark trap. When water formation ceased, the heat was removed and the reaction mixture was allowed to cool before it was washed with saturated sodium bicarbonate and saturated sodium chloride. The organic phase was dried ($MgSO_4$) and concentrated to give a crude brown oil which was distilled. The fraction bp 90-98° (0.4 mm) was collected (83.0 g).

The ester was hydrolyzed in a solution of potassium hydroxide (75 g) and water (500 ml) at reflux temperature for 1.5 hr. The reaction mixture was allowed to cool and was acidified with HCl. The precipitated acid was isolated

by filtration, dried, and was crystallized from carbon disulfide (150 ml) to give two crops of white crystals, 49.2 g (42.8%), mp 95-97°; lit.[145] mp 98.5°.

Preparation of (Z)-β-Methylcinnamic Acid by Photolytic Isomerization of (E)-β-Methylcinnamic Acid. A solution of (E)-β-methylcinnamic acid (44.0 g, 0.272 mol) in benzene (400 ml) was irradiated (in a quartz flask) with 2537 Å light (128 watts) in a "Srinivasen type" photochemical reactor for a period of 6 days. The reaction mixture was concentrated to dryness and the crude product was crystallized from carbon disulfide (264 ml, 6 ml/g) at room temperature. Long needles of (Z)-β-methylcinnamic acid were produced; 7.2 g (16.3%); mp 129-132°, mp lit.[145] 131.5°; nmr (16433, d^6 acetone) δ 2.11 (d, 3, C=CC$\underline{H}_3$), 5.85 (q, 1, C=C$\underline{H}$), 7.17 (s, 5, Ph). The mixture of (Z)- and (E)-acids obtained by concentrating the mother liquor from the crystallization was dissolved in benzene (400 ml) and an additional 20 g of crude (E)-acid was added. The residual mixture was photolyzed again and worked up as above to give 15.0 g of (Z)-acid, mp 129-132°. This procedure can be repeated to give more (Z)-acid. Before using the (Z)-β-methylcinnamic acid for hydrogenations it was crystallized from 60-80° petroleum ether-ethyl acetate, 3:2 (4 ml/g) to remove traces of carbon disulfide; mp 131-132°.

Preparation of Diphenylphosphine by Lithium Aluminum Hydride Reduction of Chlorodiphenylphosphine.[147] Under a nitrogen atmosphere freshly distilled chlorodiphenylphosphine (340 g, 1.54 mol) in dry ether (550 ml) was added dropwise to an ice cold solution of lithium aluminum hydride (0.465 mol, 118 ml of a 3.9 M solution) in dry ether (650 ml). The reaction mixture was allowed to warm to room temperature and was stirred overnight at room temperature. The mixture was cooled in ice, and water (83.5 ml) was added dropwise. The reaction mixture was then heated and allowed to reflux for 1 hr. The ether layer was separated and filtered quickly (contact with air must be minimized). The sticky white precipitate was washed with ether and the ether solutions were combined. The precipitate was dissolved in 10% HCl and the acid solution was extracted with ether. The ether layers were combined, dried ($CaCl_2$) and then concentrated. Distillation gave a clear colorless liquid bp 105-117° (1.2 mm), yield, 238 g (83.2%). Analysis by glpc (column A, 175°) showed only diphenylphosphine and no diphenylphosphine oxide; ir (20068, neat) 2295 cm^{-1} (P-H).

Preparation of (-)-Menthyl Chloride from (-)-Menthol.[148] Lucas reagent was prepared by dissolving zinc chloride (908 g, 6.68 mol) in concentrated HCl (616 ml, 5.44 mol). The Lucas reagent was placed in a 2.0 ℓ Morton flask equipped with a mechanical stirrer and (-)-menthol (312 g, 2.0 mol) was added. The heterogeneous mixture was stirred for 5.0 hr at 35 ± 2° and then the (-)-menthyl chloride was extracted into petroleum

ether (30-60°, 600 ml). The solution of (-)-menthyl chloride was stirred over concentrated H_2SO_4 (4 x 100 ml) to remove alkenes. The petroleum ether solution was washed with saturated sodium bicarbonate and water and then was dried (Na_2SO_4). Concentration and distillation gave (-)-menthyl chloride 290 g (85.1%), bp 76-80° (8 mm) bp lit.[148] 100-101.5° (21 mm); $[\alpha]_D^{25}$ -45.5° (c 2.21, heptane); lit.[149] $[\alpha]_D^{20}$ -49.6° (neat liquid, ℓ = 10 cm).

Preparation of (+)-Neomenthyldiphenylphosphine From (-)-Menthyl Chloride and Sodium Diphenylphosphide. Sodium metal (34.5 g, 1.5 mol) was added in small pieces to 1.5 ℓ of anhydrous ammonia under a nitrogen atmosphere. Over a 1 hr period Ph_2PH (279 g, 1.5 mol), diluted to 600 ml with dry THF, was added to the sodium in ammonia solution (hydrogen evolution). The resulting red solution of sodium diphenylphosphide was allowed to warm to room temperature to expel the ammonia. A solution of (-)-menthyl chloride 262 g, 1.5 mol, $[\alpha]_D^{22}$ -49.1° (c 2.15, heptane), diluted to 800 ml with dry THF was added in one portion. The reaction mixture was heated at reflux for 54 hr. The resulting light orange solution was treated with 250 ml of water. The organic layer was separated, washed with water, concentrated, and vacuum distilled until crystal formation was observed in the distillation condenser about 160° (1 mm). The forerun was saved for recovery of diphenylphosphine. The pot residue (260 g) was carefully recrystallized from 95% ethanol (deoxygenated with N_2) using 16 ml of solvent/g of crude phosphine

and very slow cooling. The first crop of crystals (130.5 g) contained 85% NMDPP (glpc, column A, 235°) and 15% NMDPP oxide. The mother liquors were cooled further and yielded 46 g of crystals (94-95%, NMDPP), $[\alpha]_D^{23}$ + 94.4° (c 1.26, CH_2Cl_2), mp 96-99°*; ir (nujol) 1435 (P-phenyl), 1175 cm^{-1} (w, P=O impurity); nmr (16615, $CDCl_3$, δ 0.40-1.00 (m, 10), 1.00-2.00 (m, 8), 2.98 (s, broad, 1), 6.80-7.80 (m, 10).

Anal. Calcd for $C_{22}H_{29}P$: C, 81.44; H, 9.01. Found: C, 81.51; H, 9.10.

The mother liquor from the second crop of crystals was concentrated and cooled to give an additional 21 g of crystals 75% NMDPP, 10% NMDPP oxide, 15% $Ph_2P(O)H$. The total conversion of menthyl chloride to NMDPP was about 34%, not including the amount of NMDPP oxide produced. Careful recrystallization can provide high-purity NMDPP (95%), but the oxide is a tenacious impurity. Oxide does not interfere in the conversion of NMDPP to Rh(I) complexes of the Wilkinson type by displacement on μ-alkene Rh(I) precursors.[69]

Preparation of (+)-NMDPP Oxide by Oxidation of (+)-NMDPP.[150] A benzene (50 ml) solution of crude NMDPP (5.0 g, 66.5% NMDPP, 13.1% NMDPP oxide and 20.4% diphenylphosphine oxide) was treated with a mixture of 10% sodium hydroxide (40 ml) and 30% hydrogen peroxide (10 ml). The reaction mixture was stirred for 17.5 hr and then the benzene layer

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*Melting points of NMDPP samples vary slightly from preparation to preparation depending upon the amount of oxide present.

was separated, washed with water, dried and concentrated to give crude NMDPP oxide, yield 3.3 g (79.8%). The crude material was crystallized from xylene to give 2.2 g (53%) of purified NMDPP oxide, mp 216-217°; $[\alpha]_D^{24}$ +54.5° (c 1.40, absolute EtOH).

Preparation of (+)-NMDPP by Trichlorosilane Reduction of (+)-NMDPP Oxide. Neomenthyldiphenylphosphine oxide (5.0 g, 14.7 mmol), N,N-dimethylaniline (18.2 g, 0.15 mol), trichlorosilane (20.2 g, 0.15 mol), and xylene (50 ml) were sealed in a glass reaction vessel. The reaction mixture was heated at 100° for 8 days. The reaction vessel was opened and the contents were transferred to a 3-necked flask under nitrogen. The flask was cooled in ice and 30% potassium hydroxide was added cautiously with mechanical stirring until there were two clear layers. The aqueous layer was withdrawn and deoxygenated benzene (50 ml) was added. The resulting organic phase was washed with HCl and water, dried (Na_2SO_4) and concentrated. The residue was crystallized from deoxygenated ethanol (40 ml) to give 2.65 g (55.6%) of phosphine (in two crops) of better than 98% purity by glpc (column A, 235°); $[\alpha]_D^{24}$ +90.5° (c 1.06, CH_2Cl_2).*

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*The optical rotation recorded for (+)-NMDPP produced by this reduction was somewhat lower than that observed for (+)-NMDPP prepared by the displacement method and may be due to air oxidation of the methylene chloride solution of (+)-NMDPP used to measure the optical rotation.

Attempted Reduction of Neomenthyldiphenylphosphine Oxide by Hexachlorodisilane. Neomenthyldiphenylphosphine oxide (200 mg, 0.555 mmol), hexachlorodisilane (1.94 g, 0.722 mmol), and xylene (3 ml) were sealed in a glass reaction vessel and heated at 100°. After 73.5 hr the ampoule was cooled and opened. The reaction mixture was diluted with benzene (15 ml) and then 30% potassium hydroxide was added until two clear layers resulted. The organic layer was washed with 10% HCl and water and was then concentrated. The product was analyzed by glpc (column A, 235°) and was found to be composed of neomenthyldiphenylphosphine (80.8%) and neomenthyldiphenylphosphine oxide (19.2%).

Attempted Lithium Aluminum Hydride Reduction of NMDPP Oxide.[123,125] A suspension of lithium aluminum hydride (0.50 g, 53 mmol) in dry tetrahydrofuran (25 ml) was treated with a solution of neomenthyldiphenylphosphine oxide (1.4 g, 4.1 mmol) in dry tetrahydrofuran (25 ml). The reaction mixture was held under nitrogen, heated, and allowed to reflux. After 24 hr the reaction mixture was allowed to cool and was treated by the successive addition of water (0.5 ml), 15% sodium hydroxide (0.5 ml), and water (1.5 ml). The inorganic salts were removed by filtration and the tetrahydrofuran solution was concentrated. Analysis of the crude product by glpc (column A, 250°) showed that the crude product was a complex mixture of at least 7 components.

Preparation of Neomenthyldiphenylphosphine Sulfide from (+)-Neomenthyldiphenylphosphine Oxide. A mixture of crude (+)-NMDPP oxide (24.7 g, 72.5 mmol) and phosphorous pentachloride (15.1 g, 72.5 mmol) in chloroform (200 ml) was heated under a nitrogen atmosphere for 4 hr. The black reaction mixture was concentrated to dryness and the residue was dissolved in tetrahydrofuran (150 ml) and treated with hydrogen sulfide gas for 1.0 hr then concentrated to dryness. The residue was dissolved in ethanol (300 ml) and treated with Norit. The filtered, decolorized solution yielded NMDPP sulfide as white needles. Two crops gave 11.5 g (44.5%); mp 145.5-147°; $[\alpha]_D^{22}$ +41.7° (c 2.49, $CHCl_3$); ir (21344, nujol) 1087 cm^{-1} (P=S); nmr (1470, $CDCl_3$) δ 0.54 (d, 3, J=6 Hz), 0.74 (m, 6), 1.00-3.10 (m, 9), 3.45 (sextet, 1), 7.60 (m, 6), 8.35 (m, 4).

Anal. Calcd for $C_{22}H_{29}PS$: C, 74.12; H, 8.20. Found: C, 74.23; H, 8.27.

Preparation of (+)-Neomenthyl Chloride from (-)-Menthol.[151] Triphenylphosphine (515 g, 1.96 mol) was dissolved in carbon tetrachloride (1500 ml) and the solution was cooled in an ice bath. Methylene chloride (400 ml) was cooled in a dry ice-isopropanol bath and chlorine gas was passed in until 139 g (1.96 mol) had dissolved. The chlorine solution was added to the triphenylphosphine solution dropwise under a nitrogen atmosphere. At the end of the chlorine addition, the solution was allowed to cool to ice bath temperature and (-)-menthol (273 g, 1.75 mol) in

carbon tetrachloride (600 ml) was added over 1.5 hr. At the end of the addition, the reaction mixture was allowed to stand at room temperature for 49 hr. The reaction mixture was then poured onto ice and stirred. The triphenylphosphine oxide which separated was removed by filtration and washed well with petroleum ether (30-60°). The organic layers were dried (Na_2SO_4); the solvents were removed at atmospheric pressure through a 30 cm vigreux column, and the crude (+)-neomenthyl chloride was then distilled. The fractions bp 56-63° (8 mm), 63-70° (8 mm), 70-78° (8 mm), and 78-82° (8 mm) were collected. The first three fractions contained considerable amounts of menthenes; the fourth was nearly pure (+)-neomenthyl chloride.* The first three fractions were combined, dissolved in petroleum ether (30-60°, 200 ml) and were washed successively with H_2SO_4 (3 x 100 ml), saturated sodium bicarbonate (2 x 100 ml) and water (100 ml). The petroleum ether solution was dried, concentrated and re-distilled; the fraction bp 72-76° (8 mm) was collected. The total yield of (+)-neomenthylchloride was 159 g (52%); $[\alpha]_D^{25}$ +47.3° (c 3.08, heptane) lit.[152] $[\alpha]_D^{25}$ +53.7° (c 1.27, n-octane).

Preparation of (-)-Menthyldiphenylphosphine from (+)-Neomenthyl Chloride and Sodium Diphenylphosphide. Sodium metal (23.0 g, 1.0 mol) was added in small pieces to 1 ℓ of anhydrous ammonia under a nitrogen atmosphere. When the sodium was dissolved, a solution of Ph_2PH (186 g, 1.0 mol),

*The fractions were analyzed by glpc (column B, 180°).

diluted to 400 ml with anhydrous THF, was added dropwise. An additional 400 ml of THF was added after addition of the Ph_2PH solution was complete. The red solution was then allowed to warm to room temperature. The resulting solution was warmed slightly to expel all of the ammonia, and was then cooled in an ice bath. A solution of (+)-neomenthyl chloride [159 g, 0.91 mol, $[\alpha]_D^{22}$ +47.3° (c 3.08, heptane), diluted to 400 ml with anhydrous THF] was added over a 1 hr period. The reaction mixture was allowed to warm to room temperature slowly, was stirred at room temperature for 3 hr, and then was heated at reflux for 2 hr.

At the end of the reflux period, 200 ml of water was added to the light yellow reaction mixture. The organic layer was separated, washed with water, dried ($NaSO_4$), concentrated, and vacuum distilled (1 mm) until crystal formation was observed in the distillation condenser. The distillate was saved for recovery of diphenylphosphine. The pot residue weighed 95.0 g and was shown by glpc (column A, 235°) to be mainly menthyldiphenylphosphine. The total conversion of neomenthyl chloride to MDPP was about 25-30%. The crude phosphine was recrystallized from 475 ml of deoxygenated ethanol to give white crystals (27.8 g) which were isolated by vacuum filtration and dried under vacuum over P_2O_5. These crystals were shown by glpc to be 98% menthyldiphenylphosphine, $[\alpha]_D^{22}$ -93.9° (c 1.67, CH_2Cl_2), mp 57.5-58.5°. On further cooling the mother liquor yielded an additional 25.5 g of crystals, 96% MDPP by glpc. The following analyses were

performed on the 98% phosphine: ir (nujol) 1430 (P-phenyl), 1175 cm^{-1} (w, P=O of the oxide); nmr (2298, $CDCl_3$) δ 0.40-1.44 (m, 14), 1.44-1.92 (s, broad, 3), 1.96-2.30 (s, broad, 1), 2.90 (sextet, 1, J=ca. 6 Hz), 6.84-7.56 (m, 10).

Anal. Calcd for $C_{22}H_{29}P$: C, 81.44; H, 9.01. Found: C, 81.72; H, 9.17.

Preparation of (-)-MDPP Oxide by Oxidation of (-)-MDPP.[156] The mother liquor from the crystallization of the second crop of (-)-MDPP was concentrated to dryness and dissolved in chloroform. The stirred solution was treated with bromine water until an orange color persisted. The organic layer was separated, and washed with sodium hydroxide (5%) and water, dried and concentrated to give crude (-)-MDPP oxide. The crude MDPP oxide was recrystallized from toluene to give white crystals, mp 183.5-185°; $[\alpha]_D^{25}$ -87.4° (c 1.74, absolute ethanol).

Attempted Preparation of (-)-MDPP Oxide from (-)-Menthone and Diphenylphosphine. Diphenylphosphine (6.0 g, 32 mol), (-)-menthone (5.0 g, 32 mmol) and concentrated HCl (100 ml) were heated and allowed to reflux under nitrogen for 3 hr. The reaction mixture was allowed to cool and was extracted with chloroform (2 x 50 ml). The chloroform extracts were combined, dried (K_2CO_3) and concentrated. Analysis by glpc (column A, 235°) showed diphenylphosphine, diphenylphosphine oxide, but no menthyldiphenylphosphine oxide.

Preparation of (-)-Menthyldiphenylphosphine by Trichlorosilane Reduction of (-)-MDPP Oxide. (-)-Menthyldiphenylphosphine oxide (200 mg, 0.56 mmol), N,N-dimethylaniline (67 mg, 5.6 mmol), trichlorosilane (752 mg, 5.6 mmol) and xylene (3 ml) were sealed in a glass reaction tube and heated at 100°. After 90 hr the tube was opened and the mixture was diluted with an equal volume of benzene and then 20% sodium hydroxide (deoxygenated) was added dropwise until there were two clear layers. The organic layer was washed with 10% HCl and water and dried (Na_2SO_4). Analysis by glpc (column A, 235°)showed menthyldiphenylphosphine (96.5%) and menthyldiphenylphosphine oxide (3.5%).

Preparation of (-)-Menthyldiphenylphosphine Sulfide from (-)-MDPP Oxide. Phosphorus pentachloride (6.12 g, 29.4 mmol), and (-)-menthyldiphenylphosphine oxide (10.0 g, 29.4 mmol) in benzene (100 ml) were heated under a nitrogen atmosphere for 3 hr. The reaction mixture was concentrated, dissolved in dry tetrahydrofuran, and treated with hydrogen sulfide for 45 min. The reaction mixture was then concentrated to give a light brown oil which crystallized on cooling. The product was recrystallized from ethanol (200 ml) to give in three crops, (-)-menthyldiphenylphosphine sulfide, 5.8 g (55.7%), mp 185-187°; $[\alpha]_D^{27}$ -87.3° (c 2.3, $CHCl_3$); ir (2104l, nujol), 1090 cm^{-1} (P=S); nmr (1473, $CDCl_3$) δ 0.38 (d, 3, J=8 Hz), 0.78 (t, 6, J=4 Hz), 0.92-2.20 (m, 8), 2.85 (septet, distorted, 1), 7.58 (m, 6), 8.30 (m, 4).

Anal. Calcd for $C_{22}H_{29}PS$: C, 74.12; H, 8.20. Found: C, 74.44; H, 8.48.

Preparation of (+)-1,2,2-Trimethyl-1,3-bis(hydroxymethyl)cyclopentane by Lithium Aluminum Hydride Reduction of (+)-Camphoric Acid. A solution of (+)-camphoric acid (100 g, 0.5 mol) in dry ether (800 ml) was added to lithium aluminum hydride (1.0 mol, 255 ml of a 3.9 M ether solution, diluted with 600 ml of additional dry ether) at 0°. The reaction mixture was allowed to warm to room temperature and was stirred overnight. Water (38 ml), 15% sodium hydroxide (38 ml) and water (114 ml) were added successively and the resulting mixture was heated at reflux for 1 hr. The ether layer was separated, dried ($MgSO_4$) and concentrated to give white crystals 60.2 g (70%), mp 120-128°. Recrystallization from benzene (325 ml) gave, in two crops, 58.9 g of white crystals, mp 134-136°; $[\alpha]_D^{18.5}$ +62° (c 2.03, ethanol); ir (21415, nujol) 3260 (OH), 1040, 1075 cm^{-1} (C-O); nmr (16342, $CDCl_3$) δ 0.75 (s, 3), 0.97 (s, 6), 1.24-2.15 (m, 7), 3.15-3.65 (m, 4).

Preparation of (+)-1,2,2-Trimethyl-1,3-bis(hydroxymethyl)cyclopentane Ditosylate from (+)-1,2,2-Trimethyl-1,3-bis(hydroxymethyl)cyclopentane. 1,2,2-Trimethyl-1,3-bis-(hydroxymethyl)cyclopentane (40 g, 0.23 mol) from the LAH reduction of (+)-camphoric acid was dissolved in 550 ml of purified pyridine and cooled in ice-menthanol at -8°. p-Toluenesulfonyl chloride (60 g, 0.82 mol) was added in portions so that the temperature remained below 5°. The

resulting reaction mixture was placed in a refrigerator overnight. The tosylate was isolated by pouring the reaction mixture onto an ice-water slurry (1500 ml). After filtration it was washed successively with water, 10% hydrochloric acid and water again. The crystals were dried and recrystallized from 690 ml of benzene-heptane (80:20 by volume) by dissolving first in the full amount of solvent and then evaporating to 400 ml. The yield, including a second crop from the mother liquor was 106 g (96%), mp 145-147°, $[\alpha]_D^{18.5}$ +19.2 (c 2.36, $CHCl_3$); ir (21413, nujol) 1350 (SO_2), 1190, 1180 cm^{-1} (SO_2-O); nmr (16343, $CDCl_3$) δ 0.57 (s, 3), 0.87 (s, 6), 1.06-2.10 (m, 5), 2.33 (s, 6), 3.65 (d, 2, J=3 Hz), 3.80 (q, distorted, 2), 7.20 (q, 4, J_{AB}=8 Hz, Δν=26 Hz).

Preparation of (+)-CAMPHOS from 1,2,2-Trimethyl-1,3-bis(hydroxymethyl)cyclopentane Ditosylate and Potassium Diphenylphosphine. A solution of potassium diphenylphosphide was prepared under nitrogen by adding potassium metal (15.6 g, 0.4 mol) to a solution of diphenylphosphine (65.1 g, 0.350 mol) in dry tetrahydrofuran (800 ml). When the evolution of hydrogen had nearly ceased, the reaction mixture was heated and allowed to reflux for 1 hr. After cooling, excess potassium metal was removed with forceps.

The ditosylate 46 (75.0 g, 0.156 mol) was added in three equal portions over about 10 min. An exothermic reaction resulted. Heat was applied to maintain a gentle reflux for 24 hr. The orange reaction mixture was cooled to room temperature and water (200 ml) was added; two clear

layers separated. The organic layer was washed with saturated sodium chloride (3 x 200 ml), dried ($MgSO_4$), concentrated, and distilled to remove all material boiling below 250° (0.25 mm). The pot residue solidified into a clear glass, crude yield, 46.3 g (58.5%). Chromatography on silica gel, eluting with deoxygenated benzene, gave an oil, $[\alpha]_D^{23}$ +98.2° (c 2.22, CH_2Cl_2); ir (neat) 1435 (P-phenyl), 1180 cm^{-1} (w, P=O, oxide impurity)*; nmr (1451, $CDCl_3$) 0.82 (d, 9), 0.9-2.6 (m, 9), 7.1-7.8 (m, 20).

Preparation of (+)-CAMPHOS Dioxide by Oxidation of (+)-CAMPHOS. A sample of crude (+)-CAMPHOS (1.0 g, 1.97 mmol) from the displacement reaction in chloroform (50 ml) was added in one portion to a mixture of 30% hydrogen peroxide (3 ml) in 10% sodium hydroxide (10 ml). The reaction mixture was allowed to stir at room temperature for 2 hr. The chloroform layer was separated and washed with water. The chloroform solution was dried ($MgSO_4$) and concentrated to give a white viscous product which was crystallized from xylene (20 ml) to give (+)-CAMPHOS dioxide as white crystals, yield 0.7 g (65.6%), mp 206-214°. A second crystallization from xylene gave material with mp 208-214°, $[\alpha]_D^{20}$ +34.2° (c 2.00, $CHCl_3$).

A sample of (+)-CAMPHOS dioxide prepared by the aldehyde route showed a mp of 215-217°, and $[\alpha]_D^{20}$ +34.3

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*The weak band at 1180 cm^{-1} was presumably due to a small amount of phosphine oxide impurity present.

(c 1.56, $CHCl_3$).

Preparation of (-)-2,3-Bornanedione by Selenium Dioxide Oxidation of (+)-Camphor.[120] A mixture of d-camphor (83.5 g, 0.55 mol) and acetic anhydride (67 ml) was stirred mechanically under nitrogen. Selenium dioxide (60 g, 0.54 mol) was added and then the reaction mixture was heated and allowed to reflux for 2 hr after which time more selenium dioxide (20.0 g, 0.18 mol) was added and refluxing was continued for an additional 4.0 hr. Then the reaction mixture was allowed to stir at room temperature overnight. Acetic acid (100 ml) was added and the reaction mixture was filtered through a 50-75 μ fritted-glass filter. The selenium collected on the filter was washed with acetic acid (4 x 50 ml) and the acetic acid filtrate was concentrated. The concentrate was made basic (pH 9-10) with 30% aqueous potassium hydroxide and was then steam distilled. The steam distillate containing 2,3-bornanedione was extracted with 1,2-dichloroethane. The extract was dried (Na_2SO_4) and concentrated to give 2,3-bornanedione as a bright yellow crystalline solid, 82.0 g, (90%). Analysis by glpc (column B, 210°) showed only minor amounts of impurities. A small sample was sublimed, mp 195-197°; mp lit.[120] 198°; $[\alpha]_D^{21}$ -95.2° (c 2.04, $CHCl_3$); lit.[120] $[\alpha]_D$ -110° (c 1.9, $CHCl_3$); ir (20883, nujol) 1750, 1770 cm^{-1}(C=O); nmr (1554, $CDCl_3$) δ 0.95 (s, 3, C-C$\underline{H}_3$), 1.14 (s, 6, C-C$\underline{H}_3$), 1.44-2.45 (m, 4, C$\underline{H}_2$-C$\underline{H}_2$), 2.65 (d, 1, $\underline{J}$=6 Hz, C-$\underline{H}$).

Preparation of (-)-exo-exo-2,3-Bornanediol by Lithium Aluminum Hydride Reduction of (-)-2,3-Bornanedione.[121a] Under a nitrogen atmosphere, a mechanically stirred suspension of lithium aluminum hydride (17.3 g, 0.455 mol) in dry ether (300 ml) was cooled in a Dry ice-acetone bath. To the hydride suspension was added a solution of (-)-2,3-bornanedione (96.0 g, 0.578 mol) in dry ether (1000 ml) over 1 hr. The stirred mixture was kept at Dry ice-acetone temperature overnight and then water (40 ml) and 10% sulfuric acid (250 ml) were added dropwise. The organic layer was separated, washed with 10% HCl, saturated sodium bicarbonate, and water. The aqueous layer was extracted with ether (250 ml) and the ether was then washed with 10% HCl, saturated sodium bicarbonate, and water. The two organic layers were combined, dried (Na_2SO_4) and concentrated to give a white crystalline solid, 95.5 g (97.2%). The crude diol was crystallized from hot heptane (1600 ml) to give, in two crops, white crystals, 79.5 g (80.9%); mp 259-260°; mp lit.[121a] 262-263°; $[\alpha]_D^{24}$ -16.7° (c 6.94, EtOH); lit.[121b] $[\alpha]_D$ -17.7 (c 6.75, EtOH); ir (20696, nujol) 3350 (OH), 1260, 1088 cm^{-1} (C-O); nmr (16266, $CDCl_3$ + TFA) δ 0.79-1.22 (m, 11), 1.22-1.92 (m, broad, 3), 3.78 (q, 2, J=7 Hz, $\Delta\nu$=14 Hz).

Preparation of Lead Tetraacetate. Lead tetraacetate was prepared by the method of Fieser and Fieser.[153]

Preparation of (+)-1,2,2-Trimethylcyclopentane-1,3-dicarboxaldehyde by Oxidative Cleavage of (-)-exo-exo-2,3-Bornanediol.[122] A mechanically stirred solution of (-)-exo-exo-2,3-bornanediol (60.0 g, 0.353 mol) in a mixture of benzene (450 ml) and acetic acid (45 ml) was treated with freshly prepared lead tetraacetate (160 g, 0.360 mol) at a rate such that the temperature of the reaction was maintained between 35 and 40° (about 90 min were required). The reaction mixture was stirred an additional 90 min and then ether (600 ml) was added. The lead acetate by-product was removed by filtration and was washed with ether (200 ml). The ether fractions were combined and washed successively with water (3 x 250 ml), saturated sodium bicarbonate (3 x 150 ml), and water again (250 ml). The ether solution was dried (Na_2SO_4) and concentrated to give a white crystalline solid, 52.4 g (88.6%) mp about 96-102° (not sharp); mp lit.[122] 98°, (not sharp). Analysis by glpc (column B, 210°) showed that the dialdehyde was contaminated only by a small amount of material with a much shorter retention time. $[\alpha]_D^{18}$ +112° (c 10.05, benzene)*; lit.[122] $[\alpha]_D^{20}$ +95.13 (c 10, benzene); ir (20956, nujol) 2720 (CHO), 1720 cm^{-1} (C=O); nmr (699, $CDCl_3$) δ 1.00 (s, 3), 1.12 (s, 3), 1.28 (s, 3), 1.40-3.00 (m, 5), 9.80 (s, 1), 9.90 (d, 1, J=3 Hz).

*A sample of dialdehyde from another preparation, purified by sublimation had an $[\alpha]_D^{21}$ of +94.4° (c 11.13, benzene).

Preparation of (+)-CAMPHOS Dioxide from (+)-1,2,2-Trimethylcyclopentane-1,3-dicarboxaldehyde and Diphenylphosphine. A mixture of diphenylphosphine (3.8 g, 2.04 mmol), (+)-1,2,2-trimethylcyclopentane-1,3-dicarboxaldehyde (1.7 g, 1.01 mmol), and concentrated HCl (30 ml) was heated under nitrogen and allowed to reflux for 14 hr. The reaction mixture was allowed to stand overnight at room temperature and was then extracted with chloroform (50 ml). The chloroform extract was treated with bromine water until an orange color persisted and was then washed with 2% sodium thiosulfate (50 ml), saturated $NaHCO_3$ (2 x 50 ml) and water (50 ml). The chloroform solution was dried (Na_2SO_4) and concentrated. After standing for two days the concentrate changed from an oil to gummy off-white crystals. The crude product was crystallized from xylene to give white crystals, 1.9 g (34.8%); mp 210-214°; $[\alpha]_D^{21}$ +30.4° (c 1.54, $CHCl_3$); ir (20753, nujol), 1435 (P-phenyl), 1183 cm^{-1} (P=O); nmr (16194, $CDCl_3$) δ 0.78 (d, 6), 0.94 (s, 3), 1.58 (m, 4), 1.75-2.53 (m, 5), 7.15-8.05 (m, 20).

Attempted Reduction of (+)-CAMPHOS Dioxide with Trichlorosilane. A mixture of (+)-CAMPHOS dioxide $[\alpha]_D^{21}$ +30.4° (c 1.54, $CHCl_3$), (1.0 g, 1.85 mmol), N,N-dimethylaniline (2.42 g, 20 mmol), trichlorosilane (2.71 g, 20 mmol) and xylene (20 ml) were sealed in a glass reaction vessel and were heated at 100°. After 70 hr the reaction vessel was opened and the contents were diluted with benzene (50 ml). The reaction mixture was cooled to 0° and was treated

by the dropwise addition of 30% potassium hydroxide until there were two clear layers. The organic layer was separated and washed successively with water, 10% HCl, and water. The organic layer was separated, dried (Na_2SO_4) and concentrated to give a yellow oil from which CAMPHOS could not be isolated.*

Preparation of (+)-CAMPHOS Disulfide from (+)-CAMPHOS Dioxide. Phosphorus pentachloride (20.0 g, 96 mmol) was added in 0.5 to 1 g portions to a solution of (+)-CAMPHOS dioxide (20.0 g, 38.5 mmol) in dry acetonitrile (200 ml). The reaction mixture was heated and allowed to reflux for 45 min and was then allowed to cool and stir overnight. The reaction mixture was concentrated to dryness, dissolved in dry acetonitrile, treated with gaseous hydrogen sulfide for 35 min, and finally was allowed to stand for 1 hr. It was then concentrated, and the residue was crystallized from ethanol (200 ml). (+)-CAMPHOS disulfide was isolated in two crops; as tiny white plates; 8.2 g (38.7%) mp 204-205°; $[\alpha]_D^{18.5}$ +14.8° (c 2.94, $CHCl_3$); ir (21414, nujol) 1100 cm^{-1} (P=S); nmr (1504, $CDCl_3$) δ 0.80 (d, 9), 1.25-1.95 (m, 4), 2.05-3.05 (m, 5), 7.64 (s, 12), 8.04 (m, 8).

Anal. Calcd for $C_{39}H_{38}P_2S_2$: C, 71.30; N, 6.69. Found: C, 72.06; N, 6.87.

Preparation of (+)-CAMPHOS by Reduction of (+)-CAMPHOS Disulfide with Tris(dimethylamino)phosphine. A

*This reduction was carried out early in our attempt to synthesize CAMPHOS and before our methods of purification were perfected. It may be possible using column chromatography to isolate CAMPHOS from this reaction.

mixture of (+)-CAMPHOS disulfide (0.5 g, 0.975 mmol) and tris(dimethylamino)phosphine (2.5 g, 15.4 mmol) in xylene (10 ml) was heated at 130° for 10 hr. The reaction mixture was concentrated and analyzed by glpc (column A, 150°) which showed that tris(dimethylamino)phosphine sulfide had formed. The reaction mixture was further concentrated by distillation at reduced pressure to remove unreacted tris(dimethylamino)-phosphine and the residue was chromatographed on 10 g of basic alumina (Brockman activity I) in a 1.0 cm column using benzene as the eluent. The first two 4 ml fractions of benzene eluent were discarded, but the second two 4 ml fractions contained only (+)-CAMPHOS (by TLC on alumina, benzene eluent). The fractions containing (+)-CAMPHOS were combined, concentrated and dried in a vacuum. A slightly yellow viscous oil was obtained, yield 0.25 g, (56.2%); $[\alpha]_D^{22}$ +99.0° (c 2.02, CH_2Cl_2); ir (21648, neat), no bands at 1175 or 1100 cm^{-1} (P=O or P=S); nmr (2148, $CDCl_3$) δ 0.80 (d, 9), 1.0-2.04 (m, 7), 2.16 (d, 2, J=4 Hz), 7.00-7.34 (m, 20).

Preparation of (+)-CAMPHOS by Reduction of (+)-CAMPHOS Disulfide with Lithium Aluminum Hydride. A mixture of (+)-CAMPHOS disulfide (0.50 g, 0.88 mmol) and lithium aluminum hydride (0.20 g, 5.3 mmol) in dry dioxane (25 ml) was heated and allowed to reflux under an atmosphere of nitrogen. After a period of 30 hr, a parallel reduction of neopentyldiphenylphosphine sulfide, used as an indicator, was shown to be only 58% complete, so additional lithium

aluminum hydride (148 mg, 3.9 mmol, 1.0 ml of a 3.9 M solution in ether) was added to the CAMPHOS and the reaction mixture was heated and allowed to reflux for an additional 24 hr. The CAMPHOS reaction mixture was allowed to cool and was treated with 10% HCl (10 ml). The product was extracted into ether (25 ml) and the organic layer was separated, dried ($MgSO_4$) and concentrated. The last traces of solvent were removed at room temperature and 0.01 mm pressure to give a viscous oil, 0.42 g (94.5%); $[\alpha]_D^{22}$ +78.8° (c 2.17, CH_2Cl_2). The TLC on alumina (benzene eluent) showed three spots. The crude product was chromatographed on alumina (20 g, Brockman activity I) with benzene eluent. The fractions from 21-65 ml showed only CAMPHOS by TLC and were concentrated (rotary evaporator) to give 100 mg of a viscous oil (22.5% yield); $[\alpha]_D^{21}$ +95.6° (c 2.09, CH_2Cl_2); ir (21649, neat) no bands at 1175 or 1100 cm^{-1} (P=O or P=S). The ir spectrum was identical to that of (+)-CAMPHOS made by the displacement method. Nmr (2140, $CDCl_3$) δ 0.80 (d, 9), 1.0-2.04 (m, 7), 2.18 (d, 2, J=4 Hz), 7.08-7.70 (m, 20).

Preparation of Dimethyl-2,3-O-Isopropylidene-L-Tartarate from (+)-Tartaric Acid. A mixture of (+)-tartaric acid (252.5 g, 1.68 mol), 2,2-dimethoxypropane (768 g, 5.76 mol, 99% purity), p-toluenesulfonic acid (1.0 g) and cyclohexane (1250 ml) was heated and allowed to reflux for 46 hr with mechanical stirring and the exclusion of moisture. The reaction mixture was then allowed to stand at room temperature overnight. The acetone-cyclohexane azeotrope (bp 53°)

and the methanol-cyclohexane azeotrope (bp 54.5°) were removed by slow distillation through a 14 inch Vigreux column. Distillation was continued until 1900 ml had been collected (head temperature 73°). The reaction mixture was concentrated and the concentrate was stirred with 2.5 g of anhydrous potassium carbonate (the color changed from dark to light red). The potassium carbonate was removed by filtration, washed with a little menthanol and the product was distilled. The fractions with bp 90-97° (0.1-0.05 mm) were collected. Yield 312 g (86%); $[\alpha]_D^{18.5}$ -44.2° (c 10.29, $CHCl_3$); lit.[154] $[\alpha]_D^{20}$ -49.4° (neat); ir (21462, neat) 1770 (C=O), 1390 (gem-dimethyl), 1210 (C-O), 1110 cm^{-1} (C-O, dioxolane); nmr (1613, $CDCl_3$) δ 1.55 (s, 6, $C(CH_3)_2$), 3.82 (s, 6, CO_2CH_3), 4.84 (s, 2, C-H).

Preparation of (+)-2,3-O-Isopropylidene-L-Threitol from Dimethyl-2,3-O-Isopropylidene-L-Tartrate.[155] A solution of lithium aluminum hydride (565 ml of a 3.9 M solution, 2.22 mol, diluted further with 1 ℓ of dry ether) was cooled in an ice bath under nitrogen. Dimethyl-2,3-O-isopropylidene-L-tartrate (218 g, 1.0 mol) in dry ether (500 ml) was added over a period of 1.5 hr. The cooling bath was removed and the mixture was heated and allowed to reflux for 2 hr after which it was allowed to stir at room temperature for an additional 3 hr. The reaction mixture was cooled in an ice bath and ethyl acetate (100 ml), water (85 ml), 15% sodium hydroxide (85 ml), and water (3 x 85 ml) were added successively. The precipitate which formed was filtered,

washed with ether and then extracted in a soxhlet apparatus with ether for 96 hr. The ether filtrate washings, and soxhlet extract were combined, dried ($MgSO_4$), concentrated and distilled. Two fractions of comparable purity were collected, bp 112-115° (0.5-0.3 mm) and bp 115-117° (0.3 mm); yield, 141.7 g (87.5%); $[\alpha]_D^{15}$ +4.23 (c 5.32, $CHCl_3$); lit.[155] $[\alpha]_D^{20}$ +4.1° (c 5, $CHCl_3$); nmr (1666, $CDCl_3$) δ 1.40 (s, 6, $C(C\underline{H}_3)_2$, 3.80 (d, 4, $CH\text{-}C\underline{H}_2\text{-}O$), 4.02 (s, 2, $O\underline{H}$), 4.40 (t, 2, $C\underline{H}\text{-}CH_2\text{-}O$). The product could be further purified by crystallization from diisopropyl ether (4 ml/g).

Preparation of 1,4-Ditosyl-2,3-O-Isopropylidene-L-Threitol from 2,3-O-Isopropylidene-L-Threitol.[154] A solution of 2,3-O-isopropylidene-L-threitol (8.4 g, 0.0519 mol) in dry pyridine (55 ml) was cooled to -10° in an ice-methanol bath. p-Toluenesulfonyl chloride (21.0 g, 0.107 mol) was added in one portion. The reaction mixture was stirred until all the toluenesulfonyl chloride went into solution and was then allowed to stand for 12 hr at 5°. Water (90 ml) was added and a tan oil came out of solution. The oil crystallized when a small sample was rubbed on a porous plate and the material was used to induce crystallization of the rest of the oil. The crude product was isolated by filtration, washed with water, and then a little absolute ethanol. It was dried in vacuo and then was crystallized from absolute ethanol (65 ml) to give white crystals, 20.3 g (83%), mp 90-91°, mp lit.[154] 91-92°; a second crop of 0.4 g was isolated upon cooling the mother

liquor; $[\alpha]_D^{19}$ -12.3° (c 5.03, $CHCl_3$); lit.[154] $[\alpha]_D^{26.5}$ -12.4 (c 5, $CHCl_3$); nmr (1562, $CDCl_3$) δ 1.28 (s, 6, $C(CH_3)_2$), 2.48 (s, 6, $ArCH_3$), 4.16 (d, broad, 6, $TsO-CH_2-CH-$), 7.78 (q, 8, J=8 Hz, Δν=46 Hz, Aromatic).

Preparation of (-)-DIOP from 1,4-Ditosyl-2,3-O-Isopropylidene-L-Threitol.[72] A solution of potassium diphenylphosphide was prepared under nitrogen by adding, in one portion, potassium metal (4.29 g, 0.11 mol) to a solution of diphenylphosphine (20.4 g, 0.11 mol) in dry tetrahydrofuran (100 ml). The reaction was exothermic and after about 1 hr of stirring only a few tiny pieces of potassium metal remained. A solution of 1, 4-ditosyl-2,3-O-isopropylidene-L-threitol in dry tetrahydrofuran was added over about 0.5 hr. There was an exothermic reaction and a thick mixture formed. The mixture was stirred for 2 hr at room temperature then water (25 ml) and solid sodium chloride (to decrease the solubility of the tetrahydrofuran in the aqueous phase) were added. The organic layer was separated, dried ($MgSO_4$), and concentrated to a viscous oil. The oil was dissolved in ethanol (60 ml) and cooled at 5° to produce crystals. The product was filtered and recrystallized twice from ethanol (150 ml each time) to give fine white crystals, yield 11.3 g (45.4%), mp 88-90°, mp lit.[72] 88-89°, $[\alpha]_D^{13}$ -12.2° (c 4.76, benzene) lit.[72] $[\alpha]_D^{22}$ -12.3° (c 4.57, C_6H_6); nmr (1701, $CDCl_3$) δ 1.36 (s, 6, $C(CH_3)_2$), 2.44 (d, 4, J=5 Hz, CH_2), 4.05 (q, 2, CH), 7.48 (m, 20, Ph).

Cooling the mother liquor from the last crystallization gave an additional 1.1 g of phosphine, mp 82-85°, total yield 12.4 g, (49.8%).

Preparation of Neopentyl Tosylate from Neopentyl Alcohol.[156] An ice cold solution of neopentyl alcohol (10.0 g, 114 mmol) in pyridine (100 ml) was treated with p-toluenesulfonyl chloride (29.4 g, 150 mmol) in portions so the temperature of the reaction mixture did not rise above 0°. The reaction mixture was allowed to stir at 0° for 2 hr, then at room temperature for 2 hr, and finally at 5° in a refrigerator overnight. The reaction mixture was poured onto water (300 ml) and the product was extracted into benzene (200 ml). The benzene solution was washed successively with water (3 x 100 ml), 10% HCl (3 x 50 ml), saturated sodium bicarbonate (2 x 50 ml), and water (100 ml). It was then dried ($MgSO_4$) and concentrated to a clear colorless oil which crystallized in a refrigerator. The crude tosylate was recrystallized from warm ethanol (50 ml) to give 22.0 g of product. The mother liquors were concentrated to dryness and the residue was crystallized from ethanol (20 ml) to give an additional 4.2 g of tosylate. The total yield of tosylate was 26.2 g (95%) mp 47-48°, mp lit.[156] 48-49°, nmr (1269, $CDCl_3$) δ 0.92 (s, 9, $C(C\underline{H}_3)_3$), 2.48 (s, 3, $ArC\underline{H}_3$), 3.72 (s, 2, $C\underline{H}_2$) 7.68 (q, 4, $\underline{J}$=8 Hz, $\Delta\nu$=44 Hz, Aromatic).

Preparation of Neopentyldiphenylphosphine from Neopentyl Chloride and Sodium Diphenylphosphide. Sodium diphenylphosphide was prepared under a nitrogen atmosphere by slowly adding a solution of diphenylphosphine (3.72 g, 0.2 mol) in dry tetrahydrofuran (75 ml) to a solution of sodium metal (4.6 g, 0.2 mol) in anhydrous ammonia (250 ml). The ammonia was allowed to evaporate at room temperature and neopentyl chloride (21.2 g, 0.2 mol) in dry tetrahydrofuran (75 ml) was added over 0.5 hr. The reaction mixture was heated and allowed to reflux for 5 hr. It was then allowed to cool and was treated with water (100 ml). The organic layer was separated, washed with water (50 ml), dried (Na_2SO_4) and concentrated. The product was distilled and the fraction bp 131-133° (0.6 mm) was collected, yield 39.4 g (77%). Analysis by glpc (column A, 214°) showed only traces of impurities; nmr (666, neat) δ 1.00 (s, 9, $C(C\underline{H}_3)_3$), 2.13 (d, 2, $\underline{J}$=1 Hz, $C\underline{H}_2$-P), 7.05-7.65 (m, 10, Ph).

Preparation of Neopentyldiphenylphosphine Oxide from 2,2-Dimethylpropanal and Diphenylphosphine.[157] 2,2-Dimethylpropanal (17.2 g, 0.2 mol) and diphenylphosphine (37.2 g, 0.2 mol) were heated together with concentrated HCl (660 ml, 8.0 mol) and allowed to reflux for 18 hr. The reaction mixture was allowed to cool and was then extracted with chloroform. Analysis by glpc (column A, 214°) showed that a considerable amount of unreacted diphenylphosphine remained. The reaction mixture was concentrated and more 2,2-dimethylpropanal (8.6 g, 0.1 mol) and concentrated HCl (330 ml, 4.0

mol) were added. It was then stirred under nitrogen for 30 min and then was heated and allowed to reflux for 4 hr. At the end of this time it was extracted with chloroform and the chloroform extract was treated with hydrogen peroxide (30%) and 10% aqueous potassium hydroxide until glpc showed the presence of no more diphenylphosphine or diphenylphosphine oxide in the chloroform phase. The chloroform layer was washed with saturated sodium bicarbonate and water and was dried ($MgSO_4$) and concentrated to give crude neopentyldiphenylphosphine oxide, 32.9 g (60.5%). The crude product was crystallized from diisopropyl ether (800 ml) to give white needles, mp* 154-158° mp lit.[158] 164°; ir (20983, nujol) 1440 (P-phenyl), 1180 cm^{-1} (P=O); nmr (16613, $CDCl_3$), δ 1.08 (s, 9, $C(C\underline{H}_3)_3$), 2.35 (d, 2, $\underline{J}$=1 Hz, $C\underline{H}_2$-P), 7.22-8.05 (m, 11, Ph).*

Attempted Preparation of Neopentyldiphenylphosphine by Trichlorosilane Reduction of Neopentyldiphenylphosphine Oxide. A mixture of neopentyldiphenylphosphine oxide (1.0 g, 3.68 mmol), trichlorosilane (2.48 g, 18.4 mmol), N,N-dimethylaniline (2.23 g, 18.4 mmol) and benzene (5 ml) was sealed in a glass reaction vessel and heated at 100°. At

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*The large difference between the literature mp and the observed mp is probably due to the presence of some diphenylphosphinic acid. The nmr spectrum shows 11 rather than 10 protons in the aromatic region and this tends to support the above hypothesis. It is likely that bicarbonate is not a strong enough base to extract all the diphenylphosphinic acid from the chloroform solution into the aqueous phase during workup.

the end of 8 hr the reaction mixture was diluted under nitrogen with benzene (10 ml) and was treated with 30% potassium hydroxide until two clear layers were obtained. The organic phase was washed with water, 10% HCl, and water. The benzene layer was dried (Na_2SO_4) and concentrated. Analysis by glpc (column A, 214°) showed neopentyldiphenylphosphine and diphenylphosphine from cleavage of the alkyl group. Less strenuous conditions gave cleavage and also showed incomplete reduction.

Attempted Reduction of Neopentyldiphenylphosphine Oxide with Hexachlorodisilane. A solution of neopentyldiphenylphosphine oxide (272 mg, 1.0 mmol) in chloroform (5 ml) was treated with hexachlorodisilane (353 mg, 1.3 mmol) and allowed to stir at room temperature under nitrogen for 80 min. The reaction mixture was cooled to 0° and treated cautiously with 30% potassium hydroxide (2.5 ml). When there were two clear layers, the chloroform layer was separated. Analysis by glpc (column A, 214°) showed incomplete reduction, neopentyldiphenylphosphine, 25.6%; neopentyldiphenylphosphine oxide, 74.4%. In a series of experiments and employing higher temperatures (to 65°), longer reaction times (to 28 hr) and hexachlorodisilane in up to 4.75 times the amount theoretically required to effect reduction, the maximum phosphine to oxide ratio recorded was 9:1.

Attempted Lithium Aluminum Hydride Reduction of Neopentyldiphenylphosphine Oxide in Diisopropyl Ether.[123,125] A mixture of neopentyldiphenylphosphine oxide (1.0 g, 3.68 mmol) and lithium aluminum hydride (0.16 g, 3.68 mmol) in diisopropyl ether (20 ml) was heated under nitrogen and allowed to reflux. After 7.5 hr the reaction mixture was allowed to cool and was treated by the successive addition of water (160 µl), 15% sodium hydroxide (160 µl) and water (480 µl). The inorganic salts were removed by filtration and washed well with diisopropyl ether. The diisopropyl ether solution was concentrated and the crude product was analyzed by glpc (column A, 215°) and found to be incompletely reduced. A compound with a retention time corresponding to that of diphenylphosphine suggested that there had been cleavage of the alkyl group. Cleavage of the aryl group is possible but was not detected under our analysis conditions. An analogous reaction in di-n-butyl ether gave similar results.

Preparation of Neopentyldiphenylphosphine Sulfide from Neopentyldiphenylphosphine Oxide. Neopentyldiphenylphosphine oxide (6.8 g, 25 mmol) and phosphorus pentachloride (5.2 g, 25 mmol) were stirred in benzene (100 ml), heated, and allowed to reflux. After 2.5 hr the reaction mixture was allowed to cool and the resulting heavy yellow oil was washed with benzene (3 x 50 ml). Concentration gave a viscous yellow oil which was dissolved in dry tetrahydrofuran and treated with gaseous hydrogen sulfide for 1 hr.

The reaction mixture was stoppered, allowed to stir at room temperature for 1/2 hr, and was then concentrated to give tan crystals, 5.65 g. The crude product was crystallized from ethanol to give white crystals, 3.1 g (43%); mp 138-138.5°; ir (20982, nujol) 1100 cm^{-1} (P=S); nmr (770, $CDCl_3$) δ 1.08 (s, 9, $C(C\underline{H}_3)_3$), 2.64 (d, 2, $\underline{J}$=10 Hz, $C\underline{H}_2$-P), 7.52 (m, 6, Aromatic), 8.00 (m, broad, 4, Aromatic).

Anal. Calcd for $C_{17}H_{21}PS$: C, 70.80; H, 7.34. Found: C, 71.03; H, 7.40.

Preparation of Neopentyldiphenylphosphine by Desulfurization of Neopentyldiphenylphosphine Sulfide with Tris(dimethylamino)phosphine.[128] A solution of neopentyldiphenylphosphine sulfide (0.5 g, 1.73 mmol) and tris(dimethylamino)phosphine (2.4 g, 14.5 mmol) in xylene (10 ml) was heated at 130° for 10 hr. The reaction mixture was then analyzed by glpc (column A, 214°) which showed that complete reduction to neopentyldiphenylphosphine had occurred.

Preparation of Neopentyldiphenylphosphine by Reduction of Neopentyldiphenylphosphine Sulfide with Lithium Aluminum Hydride.[129] A mixture of neopentyldiphenylphosphine (0.5 g, 1.73 mmol) and lithium aluminum hydride (0.2 g, 5.27 mmol) in dry dioxane (25 ml) was heated and allowed to reflux under a nitrogen atmosphere for 30 hr. The reaction mixture was allowed to cool and 10% HCl (10 ml) was added. The product was extracted into ether (25 ml) and the organic phase was dried ($MgSO_4$) and concentrated. Analysis of the concentrate by glpc (column A, 214°) showed neopentyldiphenylphosphine (58%) and neopentyldiphenylphos-

phine sulfide (42%).

Preparation of Neopentyldiphenylphosphine from Neopentyldiphenylphosphine Sulfide by Lithium Aluminum Hydride Reduction.[129] A solution of lithium aluminum hydride (0.13 g, 3.5 mmol, 0.90 ml of a 3.9 M solution in ether) was added to dry dioxane (75 ml) and the ether was removed by distillation (25 ml of distillate was collected). Neopentyldiphenylphosphine sulfide (1.0 g, 3.5 mmol) in dry dioxane (10 ml) was added slowly to the lithium aluminum hydride solution. The reaction mixture was heated and allowed to reflux. After 25.5 hr at reflux and 48 hr at room temperature, a small sample was removed, treated with HCl and analyzed by glpc (column A, 215°) which showed incomplete reduction. After a total of 7 days at reflux temperature the remaining reaction mixture was treated with 10% HCl and saturated sodium chloride. The organic layer was separated and washed successively with saturated sodium bicarbonate and saturated sodium chloride. The organic phase was dried ($MgSO_4$) and concentrated to give an oil. The oil was dissolved in chloroform and analyzed glpc which showed four products: diphenylphosphine (trace), neopentyldiphenylphosphine (94.2%),

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*The percentage figures assume a response ratio of unity. It is likely that neopentyldiphenylphosphine sulfide has a smaller response than the phosphine.

neopentyldiphenylphosphine oxide (3.5%), neopentyldiphenylphosphine sulfide (2.3%).*

Preparation of Cyclohexyldiphenylphosphine from Cyclohexyl Bromide and Sodium Diphenylphosphide. A solution of sodium diphenylphosphide was prepared by slowly adding diphenylphosphine (40.4 g, 0.217 mol) in dry tetrahydrofuran (75 ml) to a solution of sodium metal (5.3 g, 0.23 mol) in anhydrous ammonia (250 ml). Cyclohexyl bromide (47 g, 0.288 mol) in dry tetrahydrofuran (75 ml) was added dropwise. There was an immediate and vigorous reaction. At the end of the addition, the reaction mixture had warmed to room temperature and nearly all the ammonia had been expelled. The reaction mixture was allowed to stir at room temperature for 2 hr and was then treated with water (75 ml). The organic layer was separated, washed with water (75 ml), dried ($NaSO_4$), and concentrated. The concentrate was distilled and the fraction bp 147-164° (0.3 mm) was collected, yield 28.7 g (48.5%). Analysis by glpc (column A, 250°) showed only traces of impurities. The cyclohexyldiphenylphosphine was crystallized from ethanol to give white needles, as rosettes, mp 59.5-60.5°, mp lit.[159] 60-61°.

Preparation of Cyclohexyldiphenylphosphine Oxide from Cyclohexanone and Diphenylphosphine.[157] Freshly distilled

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*The percentage figures assume response ratios of unity. The response ratio of neopentyldiphenylphosphine neopentyldiphenylphosphine oxide is 1:1.2. The response ratio for neopentyldiphenylphosphine sulfide has not been calculated.

cyclohexanone (9.8 g, 0.1 mol), diphenylphosphine (18.6 g, 0.1 mol), and concentrated HCl (330 ml, 4.0 mol) were heated under nitrogen and allowed to reflux for 2 hr. The reaction mixture was allowed to cool to room temperature and was then stirred for 4 hr. The CHDPP oxide was extracted into chloroform (2 x 75 ml); the chloroform was dried (K_2CO_3) and concentrated to give CHDPP oxide as a white solid, 27.3 g, (99.5%). The crude product was recrystallized from hexane (70 ml) and ethyl acetate (250 ml) to yield, in two crops, cyclohexyldiphenylphosphine oxide, as white needles, 19.0 g (69.5%), mp 164-166°, mp lit.[160] 165-166°; nmr (16619, $CDCl_3$) δ 0.84-1.92 (m, broad, 10), 1.93-2.48 (m, broad, 1), 6.92-7.83 (m, 10).

Preparation of Cyclohexyldiphenylphosphine by Trichlorosilane Reduction of Cyclohexyldiphenylphosphine Oxide. Cyclohexyldiphenylphosphine oxide (250 mg, 0.92 mmol), N,N-dimethylaniline (1.21 g, 10 mmol), trichlorosilane (1.35 g, 10 mmol) and xylene (2.5 ml) were sealed in a glass ampoule and heated at 100°. At the end of 18 hr, the ampoule was opened and the contents were treated with 20% sodium hydroxide (5 ml). The layers were separated and the organic phase was washed with 20% sodium hydroxide (5 ml), 10% HCl (2 x 5 ml), and water (2 x 5 ml). The organic layer was separated, dried ($NaSO_4$) and concentrated to give crude phosphine. Analysis by glpc (column A, 235°) showed only cyclohexyldiphenylphosphine.

Attempted Preparation of Cyclohexyldiphenylphosphine by Lithium Aluminum Hydride Reduction of Cyclohexyldiphenyl phosphine Oxide.[123,125] Cyclohexyldiphenylphosphine oxide (2.74 g, 10 mmol) in dry tetrahydrofuran (25 ml) was added dropwise to a suspension of lithium aluminum hydride (0.5 g, 52.6 mol) in dry tetrahydrofuran. The reaction mixture was held under nitrogen, heated, and allowed to reflux. At the end of 24 hr the reaction mixture was allowed to cool and was treated by the successive addition of water (0.5 ml), 15% sodium hydroxide (0.5 ml) and water (1.5 ml). The white precipitate was removed by filtration and was washed with tetrahydrofuran. The solution containing the product was analyzed by glpc (column A, 250°) and was found to be a complex mixture of products.

Preparation of Tris(dimethylamino)phosphine.[161] Under a nitrogen atmosphere anhydrous dimethylamine was bubbled through an externally cooled solution of phosphorus trichloride (68.7 g, 0.5 mol) at a rate such that the temperature of the reaction mixture did not rise above 15° (5 hr). The cooling bath was then removed and the reaction mixture was allowed to stir overnight under nitrogen. The reaction mixture was then filtered and the white precipitate of dimethylamine hydrochloride was washed well with ether. The ether filtrate was concentrated to give tris(dimethylamino)phosphine, 63.0 g (77.5%). Analysis by glpc (column A, 150°) indicated that the product was contaminated only by traces of ether and tris(dimethylamino)phosphine oxide.

Preparation of Tris(dimethylamino)phosphine Sulfide.[162] A solution of tris(dimethylamino)phosphine (8.15 g, 0.05 mol) in heptane (50 ml) was treated with sulfur (1.6 g, 0.05 g-atom) in small portions over 10 min. The reaction mixture was heated and allowed to reflux for 2.0 hr. Analysis by glpc (column A, 150°) showed that the reaction had gone to completion. The reaction mixture was filtered and concentrated to give 9.5 g (97%) of nearly pure tris(dimethylamino)-phosphine sulfide. Analysis by glpc (column A, 150°) showed the title compound contaminated by only traces of impurities. Ir (21005, neat) 975 (P=S), 740, 720 cm^{-1} (P-N).

Preparation of Triphenylphosphine Sulfide from Triphenylphosphine Oxide.[125] Under a nitrogen atmosphere a solution of triphenylphosphine oxide (20.0 g, 72 mmol) in chloroform (100 ml) was treated with phosphorus pentachloride (16.7 g, 80 mmol). There was a slightly exothermic reaction, and when this subsided, the reaction mixture was heated and allowed to reflux. After 11.5 hr the reaction mixture was allowed to cool and was then concentrated to dryness. Dry acetonitrile (100 ml) was added and the stirred reaction mixture was treated with gaseous hydrogen sulfide for 30 min. The reaction mixture was concentrated and the residue was crystallized from ethanol (500 ml) to give white crystals, in two crops, 18.0 g (85%); mp 161-162.5°; mp lit.[163] 161°.

Preparation of Triphenylphosphine by Desulfurization of Triphenylphosphine Sulfide with Tris(dimethylamino)phosphine. Triphenylphosphine sulfide (2.5 g, 8.5 mmol) and tris(dimethylamino)phosphine (5.0 g, 25.6 mmol) were sealed in a glass reaction vessel and heated at 120° for 48 hr. The tube was opened and analysis of the contents by glpc (column A, 225°) showed that the reduction was complete. The reaction mixture was poured onto methanol (40 ml), cooled in a refrigerator at 5°C and seeded with a crystal of triphenylphosphine. The crystallized phosphine was isolated by filtration and dried, yield, 1.4 g (62.8%), mp 78-79°, mp lit.[164] 79°.

Preparation of n-Decyldiphenylphosphine by Lithium Aluminum Hydride Reduction of n-Decyldiphenylphosphine Oxide.[123,125] To a suspension of lithium aluminum hydride (0.5 g, 53 mmol) in dry tetrahydrofuran (25 ml) was added n-decyldiphenylphosphine oxide (3.42 g, 10 mmol) in dry tetrahydrofuran (25 ml). The reaction mixture was held under a nitrogen atmosphere and heated and allowed to reflux. After 24 hr the reaction mixture was allowed to cool to room temperature and was treated cautiously with water (0.5 ml), 15% sodium hydroxide (0.5 ml) and water (1.5 ml). The inorganic salts were removed by filtration and the tetrahydrofuran solution of the product was concentrated. Analysis by glpc (column A, 250°) showed that the major product was the expected phosphine. No diphenylphosphine by-product was detected, and this observation indicates that there was no cleavage of the alkyl group. A minor amount of a by-product

was observed, and its retention time (15 sec relative to an internal standard of benzene) suggests that some cleavage of an aryl group may have occurred.

Preparation of 4-t-Butylcyclohexyldiphenylphosphine Oxide from 4-t-Butylcyclohexanone and Diphenylphosphine.[157] Diphenylphosphine (6.0 g, 0.0324 mol), 4-t-butylcyclohexanone (5.0 g, 0.0324 mol) and concentrated HCl (100 ml) were heated together and allowed to reflux under nitrogen for 3 hr. The reaction mixture was allowed to cool and was then extracted with chloroform (2 x 50 ml). The chloroform extracts were combined and dried (K_2CO_3). The chloroform solution was concentrated to give the title compound, 10.5 g (95.5%). Analysis by glpc indicated that both the cis- and trans-isomer were present (column A, 235°). A 1.0 g sample of the crude oxide was crystallized from hexane and ethyl-acetate (3:1) and was found to be greatly enriched in the epimer which had the shorter retention time. Another sample (4.0 g) was crystallized twice from xylene to give one isomer (with the shorter retention time); 0.45 g, mp 193-194°; nmr (16618, $CDCl_3$) δ 0.83 (s, 9), 0.96-2.18 (m, 9), 2.22-2.65 (m, broad, 1), 6.94-7.83 (m, 10).

Attempted Preparation of Bornyldiphenylphosphine Oxide from (+)-Camphor and Diphenylphosphine.[157] Under a nitrogen atmosphere diphenylphosphine (6.1 g, 33 mmol) was added to a stirred mixture of d-camphor (5.0 g, 33 mmol) and concentrated HCl (100 ml). The reaction mixture was heated and allowed to reflux for 1.5 hr. The solution was

allowed to cool and was extracted with chloroform (2 x 50 ml). The chloroform layer was separated, washed with saturated sodium bicarbonate, water, dried and concentrated. Analysis of the product by glpc (column A, 235°) showed only diphenylphosphine and diphenylphosphine oxide.

Preparation of μ-Dichlorotetracyclooctenedirhodium-(I).[165,166] A mixture of rhodium trichloride trihydrate (1.0 g, 4.02 mmol) and cyclooctene (3 g, 27.2 mmol) in absolute ethanol (20 ml) was stirred for 5 days. The product was isolated by filtration; yield 0.72 g (50%) of a brick red solid.

Preparation of Bis(1,5-cyclooctadiene)-μ,μ'-dichlorodirhodium(I).[167] A mixture of rhodium trichloride trihydrate (2.5 g, 9.5 mmol) and 1,5-cyclooctadiene (5.0 ml) in ethanol (75 ml) was heated and allowed to reflux for 3 hr. The yellow-orange crystalline product was filtered and washed with a little ethanol; yield 2.0 g (85%). The crude product was crystallized from acetic acid (90 ml/g) to give orange crystals, 1.7 g (72.5%); mp 248-251°; mp lit.[167] 256°.

Preparation of 1,5-Cyclooctadiene bis(neomenthyldiphenylphosphine) Rhodium(I) Tetrafluoroborate.[168] Under a nitrogen atmosphere, (+)-NMDPP, 91% pure (870 mg, 2.44 mmol) was added to a slurry of bis(1,5-cyclooctadiene)-μ,μ'-dichlorodirhodium(I) in deoxygenated methanol (100 ml). After about 20 min complete solution was effected and the reaction mixture was treated with sodium tetrafluoroborate

(246 mg, 2.44 mmol) in water (5 ml) and was allowed to stir for 30 min. The reaction mixture was concentrated and the residue was crystallized from 15 M aqueous acetic acid (23 ml) as orange prisms (0.33 g). The product was filtered and 5 ml of 10.5 M acetic acid was added to the filtrate. A yellow solid separated and was redissolved by heating. Upon cooling orange prisms were formed (0.60 g). The total yield of product was 0.93 g (80.8%); mp 150-153°.

Catalytic hydrogenations were carried out using three sets of conditions.

A) A catalyst solution was prepared by stirring under hydrogen (3.5 atm) for 30 min a mixture of $Rh(COD)Cl_2$ (16.6 mg, 33.7 μmol) and a chiral phosphine [171 mg, 0.5 mmol for (+)-NMDPP; 122 mg, 0.25 mmol for (+)-CAMPHOS] in 1:1 v/v benzene-ethanol (100 ml) which had been freshly deoxygenated with nitrogen.

The prereduced catalyst solution was added to a solution of 25 mmol of the substrate (except in the case of atropic acid reductions where 29.4 mmol was used) and triethylamine (0.4 g, 4 mmol) in freshly deoxygenated 1:1 benzene-ethanol (100 ml). The reaction mixture was hydrogenated at 300 psi and 60 ± 5°C for 24 hr.

B) Prereduced catalyst solution was prepared in exactly the same manner as Procedure A and was added to a solution of the substrate (12.5 mmol) and triethylamine (0.2 g, 2 mmol) in freshly deoxygenated 1:1 benzene-ethanol (100 ml). The reaction mixture was hydrogenated at 300 psi

and 60 ± 5°C for 24 hr.

C) A catalyst solution was prepared by stirring under hydrogen (3.5 atmosphere pressure) for 30 min a mixture $[Rh(COD)Cl]_2$ (33.2 mg, 67.5 mol) and a chiral phosphine [342 mg, 1 mmol for (+)-NMDPP; 244 mg, 0.5 mmol for (+)-CAMPHOS] in 1:1 benzene-ethanol (100 ml) which had been freshly deoxygenated with nitrogen.

The catalyst solution was added to a solution of the substrate (25 mmol) and triethylamine (0.4 g, 4 mmol) in freshly deoxygenated 1:1 benzene-ethanol (100 ml). The reaction mixture was hydrogenated at 300 psi and 60 ± 5°C for 24 hr.

Three different workups were employed.

D) For the reductions of atropic acid, (E)- and (Z)-α-methylcinnamic acids and (E)- and (Z)-β-methylcinnamic acids the reaction mixture was concentrated to dryness and the residue was partitioned between 10% sodium hydroxide (50 ml) and methylene chloride (50 ml). The aqueous layer was separated, washed with ether, and then was acidified with HCl. The organic acid was extracted into ether (2 x 30 ml), dried ($MgSO_4$) and concentrated to give a crude liquid product. The crude product was analyzed by nmr and then distilled in vacuo. An optical rotation measurement was taken on the distilled product.

E) For the reductions of (E)- and (Z)-α-phenylcinnamic acids, the reaction mixture was concentrated to dryness and the residue was partitioned between 5% sodium hydroxide

(100 ml) and methylene chloride (50 ml). The aqueous layer was separated, washed with ether, and then was acidified with HCl. The organic acid was extracted into ether (2 x 30 ml), dried ($MgSO_4$) and concentrated to give a crude solid product. The crude product was analyzed by nmr and an optical rotation measurement was taken on the crude material.

F) For the reductions of itaconic, citraconic and mesaconic acids, the reaction mixture was concentrated to dryness and the residue was partitioned between 10% sodium hydroxide (25 ml) and methylene chloride (50 ml). The aqueous layer was separated, washed with ether and then saturated with solid sodium chloride. The solution was acidified and the organic acid was extracted into ether (3 x 30 ml). The ether extracts were combined, dried ($MgSO_4$) and concentrated to give a crude solid product. The crude product was analyzed by nmr and an optical rotation measurement was taken on the crude material.

Reduction of Atropic Acid with the (+)-NMDPP Catalyst. Using a slight modification of reduction procedure A atropic acid (4.0 g, 29.4 mmol rather than the usual 25 mmol) was reduced to (+)-2-phenylpropanoic acid.

Workup procedure D was employed to give crude 2-phenylpropanoic acid, 3.6 g (88.5%). Analysis by nmr (16395, $CDCl_3$) indicated complete reduction.

The crude acid was distilled, bp 148.5-149° (10 mm) to give a clear colorless oil, 2.0 g (49.2%). Analysis by nmr (16396, $CDCl_3$) showed pure 2-phenylpropanoic acid; $[\alpha]_D^{16}$ +22.6° (c 8.03; $CHCl_3$). This corresponds to 29.6% ee of the (+)-S-isomer based on a maximum $[\alpha]_D^{25}$ of +76.1°.[169]

Reduction of (E)-α-Methylcinnamic Acid with the (+)-NMDPP Catalyst. (E)-α-Methylcinnamic acid (4.05 g, 25 mmol) was reduced to 2-methyl-3-phenylpropanoic acid using reduction procedure A.

Workup procedure D was employed to give crude 2-methyl-3-phenylpropanoic acid, 3.85 g (94%). Analysis by nmr (16512, $CDCl_3$) indicated complete reduction.

The crude acid was distilled, bp 99-107° (0.4 mm); $[\alpha]_D^{19}$ -16.2° (c 11.59, benzene); yield, 3.7 g (90.3%). This corresponds to 60% ee of the (-)-R-isomer based on a maximum $[\alpha]_D^{20}$ of +27.02°.[170]

Reduction of (Z)-α-Methylcinnamic Acid with the (+)-NMDPP Catalyst. (Z)-α-Methylcinnamic acid (4.05 g, 25 mmol) was reduced to 2-methyl-3-phenylpropanoic acid using reduction procedure A.

Workup procedure D, modified as below, was employed to give a mixture of starting material and 2-methyl-3-phenylpropanoic acid, 3.5 g. Analysis by nmr (16471, $CDCl_3$) indicated 29% reduction. The crude acid mixture from workup D was triturated with pentane and the pentane extract was filtered and concentrated. Some crystalline starting material was removed by filtration of the residue through fritted glass.

Analysis of the filtrate by nmr (16476, $CDCl_3$) indicated the product was composed of 77% 2-methyl-3-phenylporpanoic acid and 23% starting material. $[\alpha]_D^{17}$ -5.21° (c 11.24, benzene). This corresponds to 25.2% ee of the (-)-R-isomer based on a maximum $[\alpha]_D^{20}$ of +27.02° [170] and assuming no contribution to the rotation by the starting material.

Reduction of (E)-α-Phenylcinnamic Acid with the (+)-NMDPP Catalyst. (E)-α-Phenylcinnamic acid (5.6 g, 25 mmol) was reduced to 2,3-diphenylpropanoic acid, 5.0 g (88.5%), using reduction procedure C and workup procedure E.

Analysis by nmr (16479, $CDCl_3$) showed reduction to be complete. The specific rotation, $[\alpha]_D^{17}$ +48.2° (c 5.18, benzene), corresponded to a 34.4% ee of the (+)-S-isomer based on a maximum $[\alpha]_D^{20}$ of +140.8°.[171]

Reduction of (Z)-α-Phenylcinnamic Acid with the (+)-NMDPP Catalyst. (Z)-α-Phenylcinnamic acid (2.8 g, 12.5 mmol) was reduced to 2,3-diphenylpropanoic acid, 2.6 g (92%), using reduction procedure B and workup procedure E.

Analysis by nmr (16505, $CDCl_3$) indicated complete reduction. The specific rotation, $[\alpha]_D^{20}$ +12.8° (c 5.05, benzene), corresponded to a 9.1% ee of the (+)-S-isomer based on a maximum $[\alpha]_D^{20}$ of +140.8°.[171]

Reduction of (E)-β-Methylcinnamic Acid with the (+)-NMDPP Catalyst. (E)-β-Methylcinnamic acid (4.05 g, 25 mmol) was reduced to (+)-3-phenylbutyric acid using reduction procedure A.

Workup procedure D was employed to give crude 3-phenylbutyric acid, 3.5 g (85.5%). Analysis by nmr (16415, $CDCl_3$) showed complete reduction.

The crude acid was distilled, bp 108-112° (1.2 mm); $[\alpha]_D^{18}$ +34.9° (c 12.08, benzene); yield, 3.0 g (73.2%). This corresponds to 61.8% ee of the (+)-S-isomer based on a maximum $[\alpha]_D^{25}$ of +56.5°.[172]

Reduction of (Z)-β-Methylcinnamic Acid with the (+)-NMDPP Catalyst. (Z)-β-Methylcinnamic acid (4.05 g, 25 mmol) was reduced to 3-phenylbutanoic acid, 3.7 g (90.2%), using reduction procedure A and workup procedure D.

Analysis by nmr (16475, $CDCl_3$) indicated complete reduction.

The crude product was distilled bp 102-108° (0.05 mm); yield, 3.3 g (80.5%); $[\alpha]_D^{17}$ -17.6° (c 12.14, benzene); corresponding to 31.2% ee of the (-)-R-isomer based on a maximum $[\alpha]_D^{25}$ of -56.5°.[172]

Reduction of Itaconic Acid with the (+)-NMDPP Catalyst. Itaconic acid (3.25 g, 25 mmol) was reduced to (+)-2-methylsuccinic acid using reduction procedure A.

Workup procedure F was employed to give crude 2-methylsuccinic acid, 2.8 g (85%). Analysis by nmr (16449, d^6 acetone) indicated complete reduction. The specific rotation, $[\alpha]_D^{17}$ +1.39° (c 10.93, absolute ethanol), corresponded to 8.1% ee of the (+)-R-isomer based on a maximum $[\alpha]_D^{20}$ of 17.09°.[173]

Reduction of Mesaconic Acid with the (+)-NMDPP Catalyst. Mesaconic acid (3.25 g, 25 mmol) was reduced to 2-methylsuccinic acid using reduction procedure A and workup procedure F.

Analysis of the crude product (2.2 g, 67%) by nmr (16470, d^6 acetone) indicated complete reduction. The specific rotation, $[\alpha]_D^{16}$ +1.0° (c 11.69, absolute ethanol), corresponded to 5.85% ee of the (+)-R-isomer based on a maximum $[\alpha]_D^{20}$ of +17.09.[173]

Reduction of Citraconic Acid with the (+)-NMDPP Catalyst. Citraconic acid (3.25 g, 25 mmol) was hydrogenated using reduction procedure A and workup procedure F.

Analysis of the crude product (2.8 g) by nmr (16460, d^6 acetone) indicated 10% reduction. No further analysis was attempted.

Reduction of Atropic Acid with the (-)-MDPP Catalyst. Atropic acid (4.0 g, 29.4 mmol) was reduced to 2-phenylpropanoic acid, 3.4 g (83.6%) using reduction procedure A and workup procedure D.

Analysis of the crude acid by nmr (16508, $CDCl_3$) indicated complete reduction.

The crude product was distilled by 145-147° (10 mm); yield 2.5 g (61.5%); $[\alpha]_D^{17}$ 0.0° (c 8.23, $CHCl_3$). The product was racemic.

Reduction of (E)-α-Methylcinnamic Acid with the (-)-Catalyst. (E)-α-Methylcinnamic acid (4.05 g, 25 mmol) was reduced to (+)-2-methyl-3-phenylpropanoic acid, 3.9 g (95%)

using reduction procedure A and workup procedure D.

Analysis of the crude acid by nmr (16534, $CDCl_3$) showed 66.7% reduced product, the balance being starting material.

The crude product was distilled bp 92-94° (0.02 mm); yield, 1.8 g. Analysis of the distillate by nmr (16538, $CDCl_3$) showed the distillate to be 94.4% 2-methyl-3-phenylpropanoic acid; the balance was starting material, $[\alpha]_D^{21}$ +4.3° (c 11.08, benzene). This corresponds to 16.8% ee of the (+)-S-isomer based on a maximum $[\alpha]_D^{20}$ of +27.02° [170] and assuming only a dilution effect by the starting material.

Reduction of (Z)-α-Methylcinnamic Acid with the (-)-MDPP Catalyst. (Z)-αMethylcinnamic acid (4.05 g, 25 mmol) was reduced to 2-methyl-3-phenylpropanoic acid using reduction procedure A and workup procedure D.

A white solid (3.90 g) was isolated and analyzed by nmr (16547, $CDCl_3$) which indicated 16.3% reduction; the balance was starting material. The specific rotation $[\alpha]_D^{17}$ 0.0° (c 11.07, benzene) showed a racemic product (assuming the starting material has only a dilution effect).

Reduction of (E)-α-Phenylcinnamic Acid with the (-)-MDPP Catalyst. (E)-α-Phenylcinnamic acid (2.8 g, 12.5 mmol) was reduced to (-)-2,3-diphenylpropanoic acid using reduction procedure B and workup procedure E.

The crude acid product (2.6 g) was analyzed by nmr (16548, $CDCl_3$) which showed 25% reduction. The specific rotation $[\alpha]_D^{17}$ -9.51° (c 5.27, benzene) corresponded to

27.2% ee of the (-)-R-isomer based on a maximum $[\alpha]_D^{20}$ of +140.8° [171] and assuming the starting material has only a dilution effect.

Reduction of (Z)-α-Phenylcinnamic Acid with the (-)-MDPP Catalyst. (Z)-α-Phenylcinnamic acid (2.8 g, 12.5 mmol) was reduced to (+)-2,3-diphenylpropanoic acid using reduction procedure B and workup procedure E.

The crude acid product (2.6 g) was analyzed by nmr (16550, $CDCl_3$) which showed 22% reduction. The specific rotation, $[\alpha]_D^{17}$ +1.04° (c 5.64, benzene), corresponded to 3.2% ee of the (+)-isomer based on a maximum $[\alpha]_D^{20}$ of +140.8° [171] and assuming the starting material has only a dilution effect.

Reduction of (E)-β-Methylcinnamic Acid with the (-)-MDPP Catalyst. (E)-β-Methylcinnamic acid (4.05 g, 25 mmol) was reduced to (+)-3-phenylbutyric acid using reduction procedure A and workup procedure D.

The crude acid product (3.5 g) was analyzed by nmr (16548, $CDCl_3$) which showed 37.5% reduction; the balance was starting material. The specific rotation of the crude material, $[\alpha]_D^{18}$ +0.26° (c 12.14, benzene), corresponded to 1.2% ee of the (+)-S-isomer based on a maximum $[\alpha]_D^{25}$ of +56.5° [172] and assuming the starting material has only a dilution effect.

Reduction of (Z)-β-Methylcinnamic Acid with the (-)-MDPP Catalyst. (Z)-β-Methylcinnamic acid (4.05 g, 25 mmol) was reduced to (+)-3-phenylbutyric acid using reduction procedure A and workup procedure D.

The crude product (3.95 g) was analyzed by nmr (16543, $CDCl_3$) which showed 76.8% reduction; the balance was starting material.

The crude product was distilled, bp 108-109° (0.2 mm); yield 1.6 g; analysis by nmr (16545, $CDCl_3$) showed 85% 3-phenylbutyric acid; the balance was starting material. The specific rotation, $[\alpha]_D^{16}$ +14.7° (c 12.32, benzene), corresponded to 30.6% ee of the (+)-S-isomer based on a maximum $[\alpha]_D^{25}$ of +56.5° [172] and assuming the starting material has only a dilution effect.

Reduction of Itaconic Acid with the (-)-MDPP Catalyst. Itaconic acid (3.25 g, 25 mmol) was hydrogenated using reduction procedure A and workup procedure F.

A crude off-white solid (3.0 g, 91%) was isolated and was shown by nmr (16663, d^6 acetone) to be completely reduced.

The specific rotation $[\alpha]_D^{22}$ +3.09° (c 10.82, absolute ethanol) corresponds to 18.1% ee of the (+)-R-isomer based on a maximum $[\alpha]_D^{20}$ of +17.09°.[173]

Reduction of Mesaconic Acid with the (-)-MDPP Catalyst. Mesaconic acid (3.25 g, 25 mmol) was hydrogenated using reduction procedure A and workup procedure F. An off-white crystalline solid (2.8 g) was isolated and was shown by nmr (16705, d^6 acetone) to be 50% reduction product with the

balance starting material.

The specific rotation $[\alpha]_D^{23}$ -0.61° (c 10.92, absolute ethanol) corresponds to 7.2% ee of the (-)-S-isomer based on a maximum $[\alpha]_D^{20}$ of +17.09° and assuming only a dilution effect by the starting material.[173]

Reduction of Atropic Acid with the (+)-CAMPHOS Catalyst. Using a slight modification of procedure A, atropic acid (4.00 g, 29.4 mmol rather than the usual 25 mmol) was reduced to (+)-2-phenylpropanoic acid.

Workup procedure D was employed to give crude 2-phenylpropanoic acid. Analysis by nmr (16406, $CDCl_3$) indicated complete reduction.

The crude acid was distilled, bp 147-149° (10 mm); yield, 2.8 g (69%). The specific rotation, $[\alpha]_D^{17}$ +4.6° (8.24, $CHCl_3$), corresponded to a 6.05% ee of the (+)-S-isomer based on a maximum $[\alpha]_D^{25}$ of +76.1°.[169]

Reduction of (E)-α-Methylcinnamic Acid with the (+)-CAMPHOS Catalyst. (E)-α-Methylcinnamic acid (4.05 g, 25 mmol) was reduced to (-)-2-methyl-3-phenylpropanoic acid using a modification of reduction procedure A whereby $[Rh(C_8H_{14})_2Cl]_2$ (48.5 mg, 67.5 mmol) was used rather than $[Rh(COD)Cl]_2$.

Workup procedure D was employed to give crude 2-methyl-3-phenylpropanoic acid, 3.75 g (91.5%). The oil was distilled, bp 108-110° (0.25 mm), yield 3.55 g (86.5%). The specific rotation, $[\alpha]_D^{19}$ -4.10° (c 10.94, benzene), cor-

responded to 15.2% ee of the (-)-R-isomer based on a maximum $[\alpha]_D^{20}$ of +27.02°.[170]

Reduction of (E)-α-Methylcinnamic Acid with the (+)-CAMPHOS Catalyst.* (E)-α-Methylcinnamic (4.05 g, 25 mmol) was reduced to (-)-2-methyl-3-phenylpropanoic acid using reduction procedure A and workup procedure D.

Analysis of the crude 2-methyl-3-phenylpropanoic acid (4.05 g, 98.8%) by nmr (16546, $CDCl_3$) indicated complete reduction.

The crude acid was distilled, bp 105-106° (0.2 mm); yield 3.8 g (92.7%). The specific rotation, $[\alpha]_D^{17}$ -4.16° (c 11.39, benzene), corresponded to 15.4% ee of the (-)-R-isomer based on a maximum $[\alpha]_D^{20}$ of +27.02°.[170]

Reduction of (Z)-α-Methylcinnamic Acid with the (+)-CAMPHOS Catalyst. (Z)-α-Methylcinnamic acid (4.05 g, 25 mmol) was reduced to 2-methyl-3-phenylpropanoic acid using reduction procedure A and workup procedure D.

Analysis of the crude 2-methyl-3-phenylpropanoic acid (3.6 g, 87.8%) by nmr (16484, $CDCl_3$) indicated complete reduction.

The crude acid was distilled, bp 105-111° (0.4 mm); yield 3.4 g (83%). The specific rotation, $[\alpha]_D^{18}$ +6.22° (c

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*The (+)-CAMPHOS used to prepare the catalyst was obtained by desulfurization of (+)-CAMPHOS disulfide with tris(dimethylamino)phosphine.

12.60, benzene), corresponded to an 11% ee of the (+)-S-isomer based on a maximum $[\alpha]_D^{20}$ of +27.02°.[170]

Reduction of (E)-α-Phenylcinnamic Acid with the (+)-CAMPHOS Catalyst. (E)-α-Phenylcinnamic acid (2.8 g, 12.5 mmol) was reduced to 2,3-diphenylpropanoic acid using reduction procedure B and workup procedure E.

Analysis of the crude 2,3-diphenylpropanoic acid, 2.5 g (88.4%) by nmr (16507, $CDCl_3$) indicated complete reduction. The specific rotation $[\alpha]_D^{20}$ +16.6° (c 5.005, benzene), corresponded to 11.8% ee of the (+)-S-isomer based on a maximum $[\alpha]_D^{20}$ of 140.8°.[171]

Reduction of (Z)-α-Phenylcinnamic Acid with the (+)-CAMPHOS Catalyst. (Z)-α-Phenylcinnamic acid (2.8 g, 12.5 mmol) was reduced to 2,3-diphenylpropanoic acid using reduction procedure B and workup procedure E.

Analysis of the crude 2,3-diphenylpropanoic acid, 2.5 g (88.4%) by nmr (16508, $CDCl_3$) indicated complete reduction. The specific rotation, $[\alpha]_D^{20}$ +19.6° (c 5.047, benzene), corresponded to 13.8% ee of the (+)-S-isomer based on a maximum $[\alpha]_D^{20}$ of +140.8°.[171]

Reduction of (E)-β-Methylcinnamic Acid with the (+)-CAMPHOS Catalyst. (E)-β-Methylcinnamic acid (4.05 g, 25 mmol) was reduced to (+)-3-phenylbutyric acid, using reduction procedure A and workup procedure D.

The crude acid, 3.5 g (85.3%), was analyzed by nmr (16428, $CDCl_3$) which indicated complete reduction.

The crude product was distilled, bp 109-113° (0.15 mm); yield 3.2 g (78%). The specific rotation, $[\alpha]_D^{18}$

+5.52° (c 12.11, benzene), corresponded to 9.7% ee of the (+)-S-isomer based on a maximum $[\alpha]_D^{25}$ of -56.5°.[172]

Reduction of (Z)-β-Methylcinnamic Acid with the (+)-CAMPHOS Catalyst. (Z)-β-Methylcinnamic acid was reduced to 3-phenylbutanoic acid using reduction procedure A and workup procedure D.

Analysis of the crude 3-phenylbutyric acid, 3.9 g (95%) by nmr (16492, $CDCl_3$) indicated complete reduction.

The crude acid was distilled, bp 108-111° (0.05 mm); yield, 3.7 g (90.2%), $[\alpha]_D^{18}$ -6.46° (c 12.30, benzene), corresponding to 11.4% ee of the (-)-R-isomer based on a maximum $[\alpha]_D^{25}$ of -56.5°.[172]

Reduction of Itaconic Acid with the (+)-CAMPHOS Catalyst. Itaconic acid (3.25 g, 25 mmol) was reduced to 2-methylsuccinic acid using reduction procedure A and workup procedure F.

Analysis of the crude 2-methylsuccinic acid, 2.45 g (74.3%) by nmr (16480, $CDCl_3$) indicated that reduction was complete. The specific rotation, $[\alpha]_D^{19}$ +1.83° (c 12.9, absolute ethanol), corresponded to 10.8% ee of the (+)-R-isomer based on a maximum $[\alpha]_D^{20}$ of 17.09°.[173]

Reduction of Mesaconic Acid with the (+)-CAMPHOS Catalyst. Mesaconic acid (3.25 g, 25 mmol) was reduced to 2-methylsuccinic acid using reduction procedure A and workup procedure F.

Analysis of the crude 2-methylsuccinic acid, 2.6 g, (78.8%) by nmr (2014, d^6 acetone) showed reduction to be complete. The specific rotation, $[\alpha]_D^{17}$ +0.32° (c 11.6, absolute ethanol), corresponded to 1.8% ee of the (+)-R-isomer based on a maximum $[\alpha]_D^{20}$ of 17.09°.[173]

Reduction of Citraconic Acid with the (+)-CAMPHOS Catalyst. Citraconic acid (3.25 g, 25 mmol) was hydrogenated using reduction procedure A. Workup procedure F gave crude 2-methylsuccinic acid, 2.1 g. Analysis by nmr (16405, d^6 acetone) showed 14% reduction. No further analysis was attempted.

Reduction of Atropic Acid with the (-)-DIOP Catalyst. Using a slight modification of procedure A, atropic acid (4.0 g, 29.4 mmol rather than the usual 25 mmol) was reduced to (+)-2-phenylpropanoic acid. Workup procedure D was employed.

The crude acid product (3.7 g, 91%) was analyzed by nmr (16414, $CDCl_3$) and was shown to be completely reduced.

The crude acid was distilled, bp 145-146° (10 mm); yield, 2.85 g (70.2%). The specific rotation, $[\alpha]_D^{18}$ +33.4° (c 8.35, $CHCl_3$), corresponded to 43.9% ee of the (+)-S-isomer based on a maximum $[\alpha]_D^{25}$ of 76.1°.[169]

Attempted Reduction of (E)-α-Methylcinnamic Acid with the (-)-DIOP Catalyst. An attempt was made to reduce (E)-α-methylcinnamic acid (4.05 g, 25 mmol) by procedure A. Workup procedure D was employed and a white crystalline solid was isolated. Analysis by nmr (16440, $CDCl_3$) indicated no re-

duction had taken place. The recovery of starting material was 2.6 g (64.2%).

Reduction of (E)-α-Methylcinnamic Acid with the (-)-DIOP Catalyst. (E)-α-Methylcinnamic acid (4.05 g, 25 mmol) was reduced to (+)-2-methyl-3-phenylpropanoic acid using a modification of reduction procedure A whereby 50 mg of (-)-DIOP rather than 122 mg were used. Workup procedure D was employed to give a crude product (3.9 g, 95%) which was analyzed by nmr (16447, $CDCl_3$) and was shown to be completely reduced.

The crude acid was distilled, bp 93-99° (0.05 mm); yield 3.4 g (83%). The specific rotation $[\alpha]_D^{19}$ +6.95° (c 11.91, benzene), corresponded to 25.8% ee of the (+)-S-isomer based on a maximum $[\alpha]_D^{20}$ of +27.02°.[170]

Reduction of (E)-α-Methylcinnamic Acid with $[Rh(COD)(ACMP)_2]^+BF_4^-$. (E)-α-Methylcinnamic acid (4.05 g, 25 mmol) was reduced by a modification of procedure A whereby 50 mg, 69.2 μmol of preformed catalyst $[Rh(COD)(ACMP)_2]^+BF_4^-$ was used. Workup procedure D gave 2-methyl-3-phenylpropanoic acid.

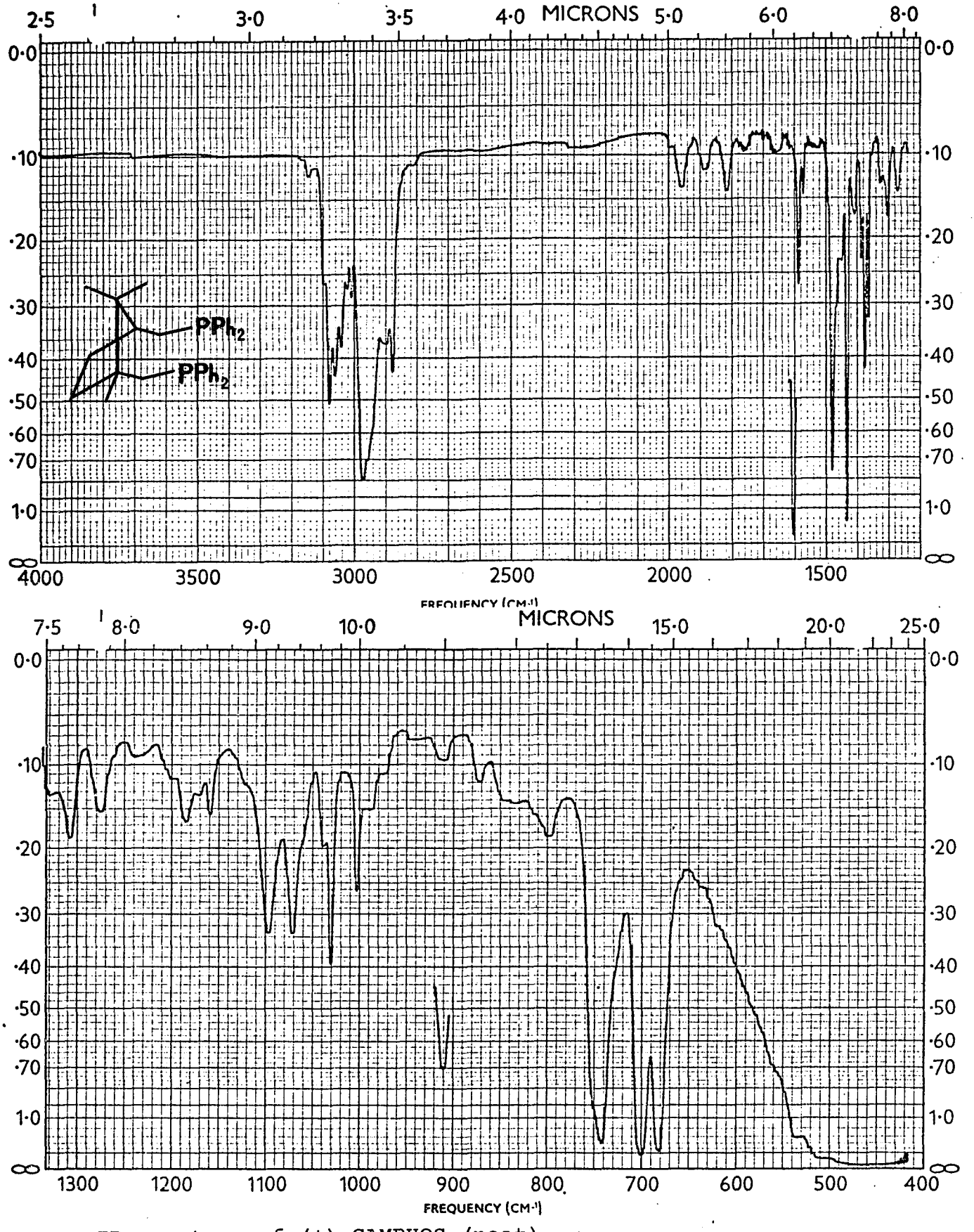
The crude product (3.8 g, 94%) was analyzed by nmr (16662, $CDCl_3$) and was shown to be completely reduced.

The crude acid was distilled, bp 99-102° (0.5 mm); yield, 3.6 g (88%). The specific rotation, $[\alpha]_D^{22}$ -3.26 (c 11.87, benzene), corresponded to 12.1% ee of the (-)-R-isomer based on a maximum $[\alpha]_D^{20}$ of +27.02°.[170]

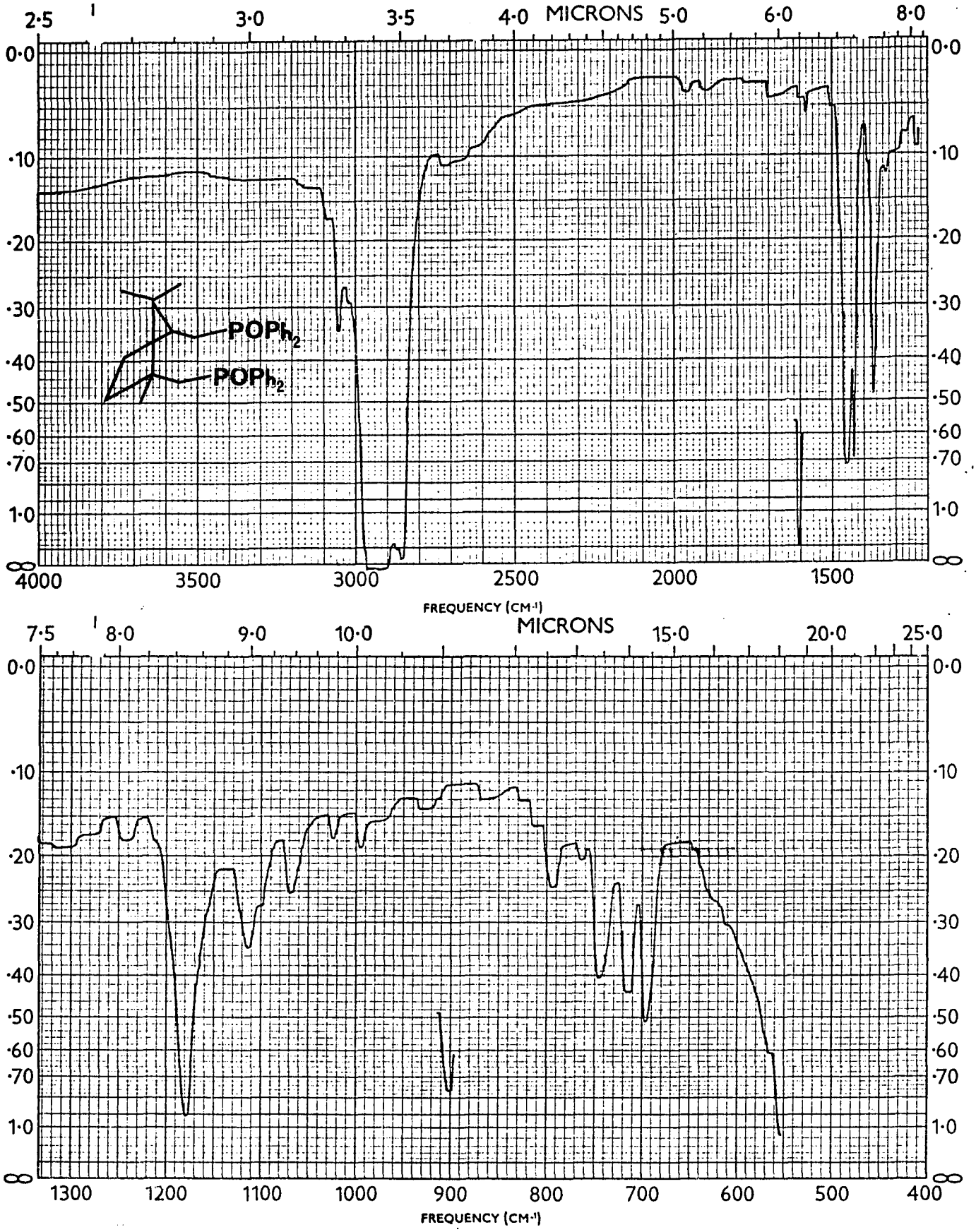
Reduction of (Z)-α-Methylcinnamic Acid with [Rh(COD)$(ACMP)_2]^+BF_4^-$. (Z)-α-Methylcinnamic acid (4.05 g, 25 mmol) was reduced by a modification of procedure A whereby 50 mg, 69.2 μmol of preformed catalyst $[Rh(COD)(ACMP)_2]^+BF_4^-$ was used. Workup procedure D gave 2-methyl-3-phenylpropanoic acid.

The crude product (3.95 g, 97.5%) was analyzed by nmr (16673, $CDCl_3$) and was shown to be completely reduced.

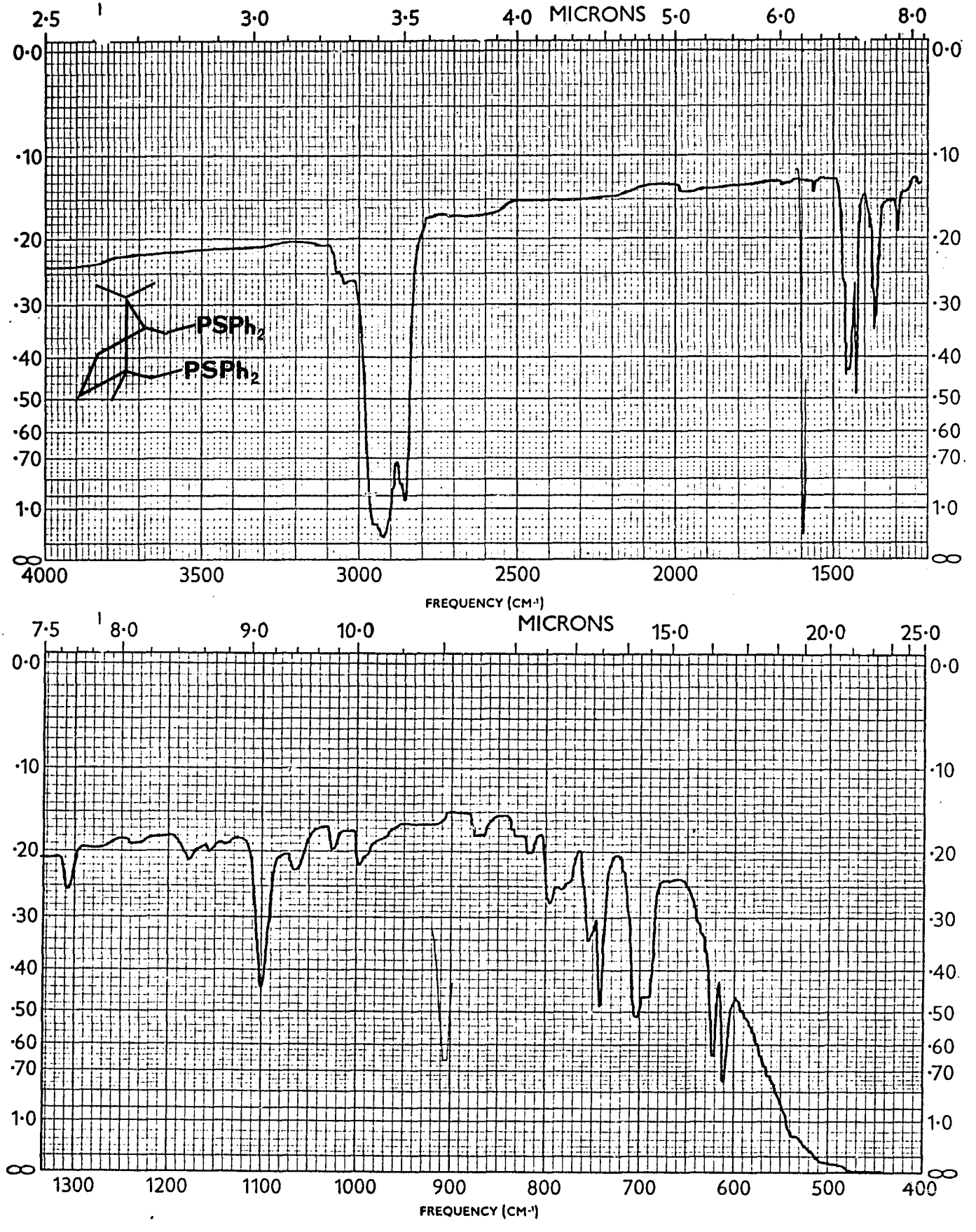
The crude acid was distilled, bp 105-107° (0.2 mm); yield 3.6 g (88%). The specific rotation $[\alpha]_D^{22}$ -6.35° (c 11.53, benzene), corresponded to 23.5% ee of the (-)-R-isomer based on a maximum $[\alpha]_D^{20}$ of 27.02°.[170]



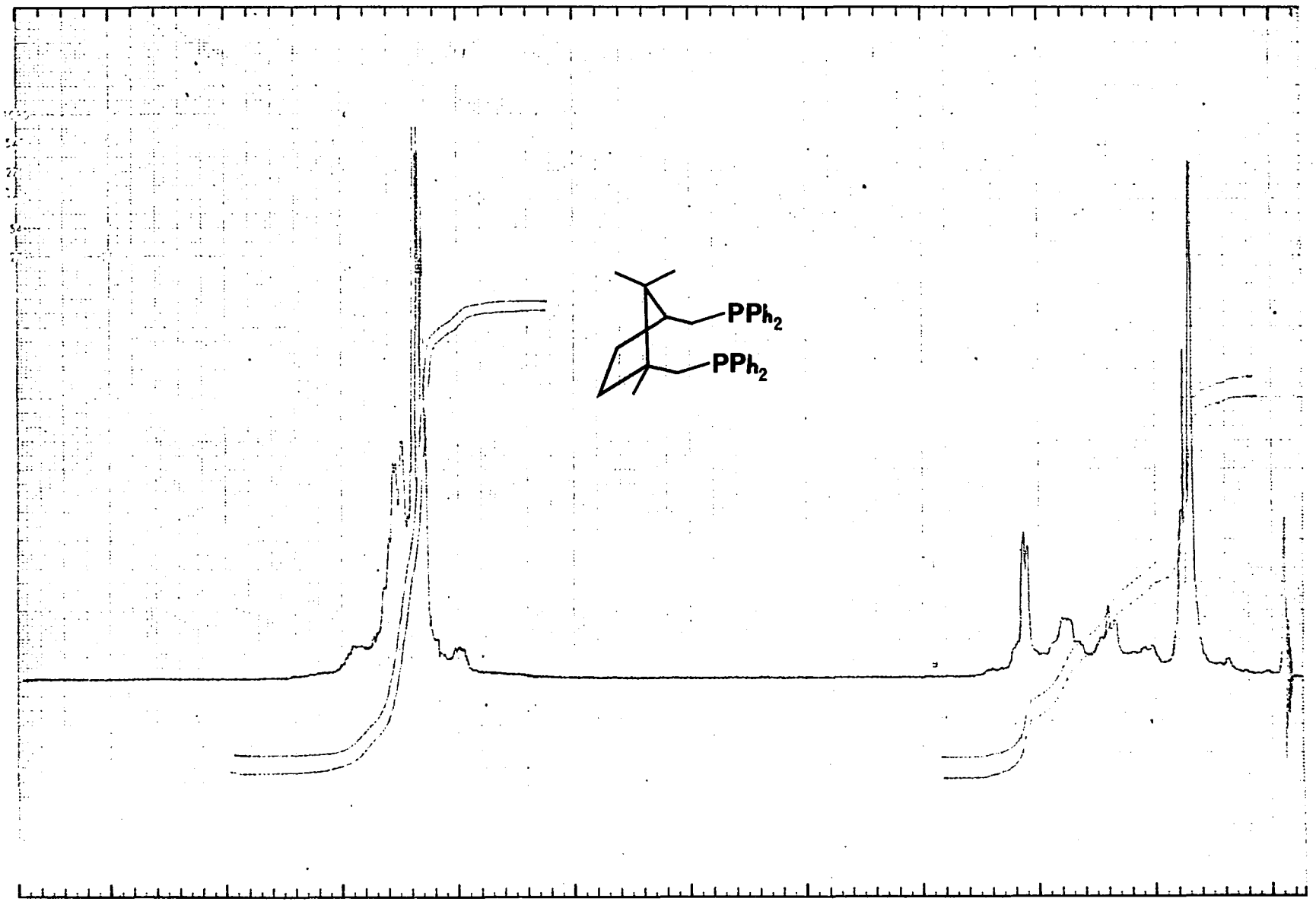
IR spectrum of (+)-CAMPHOS (neat).



IR spectrum of (+)-CAMPHOS dioxide (nujol).



IR spectrum of (+)-CAMPHOS disulfide (nujol).



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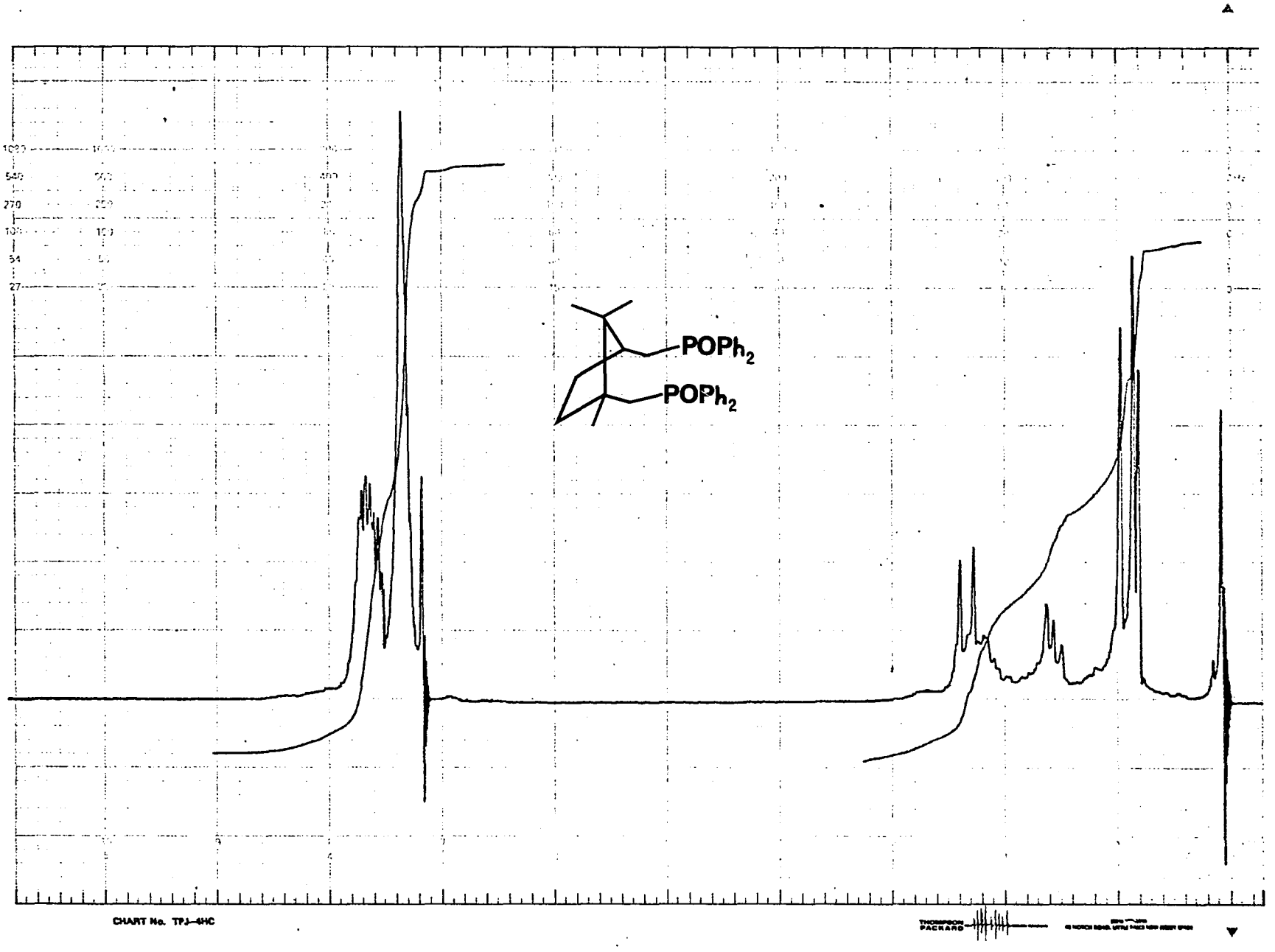
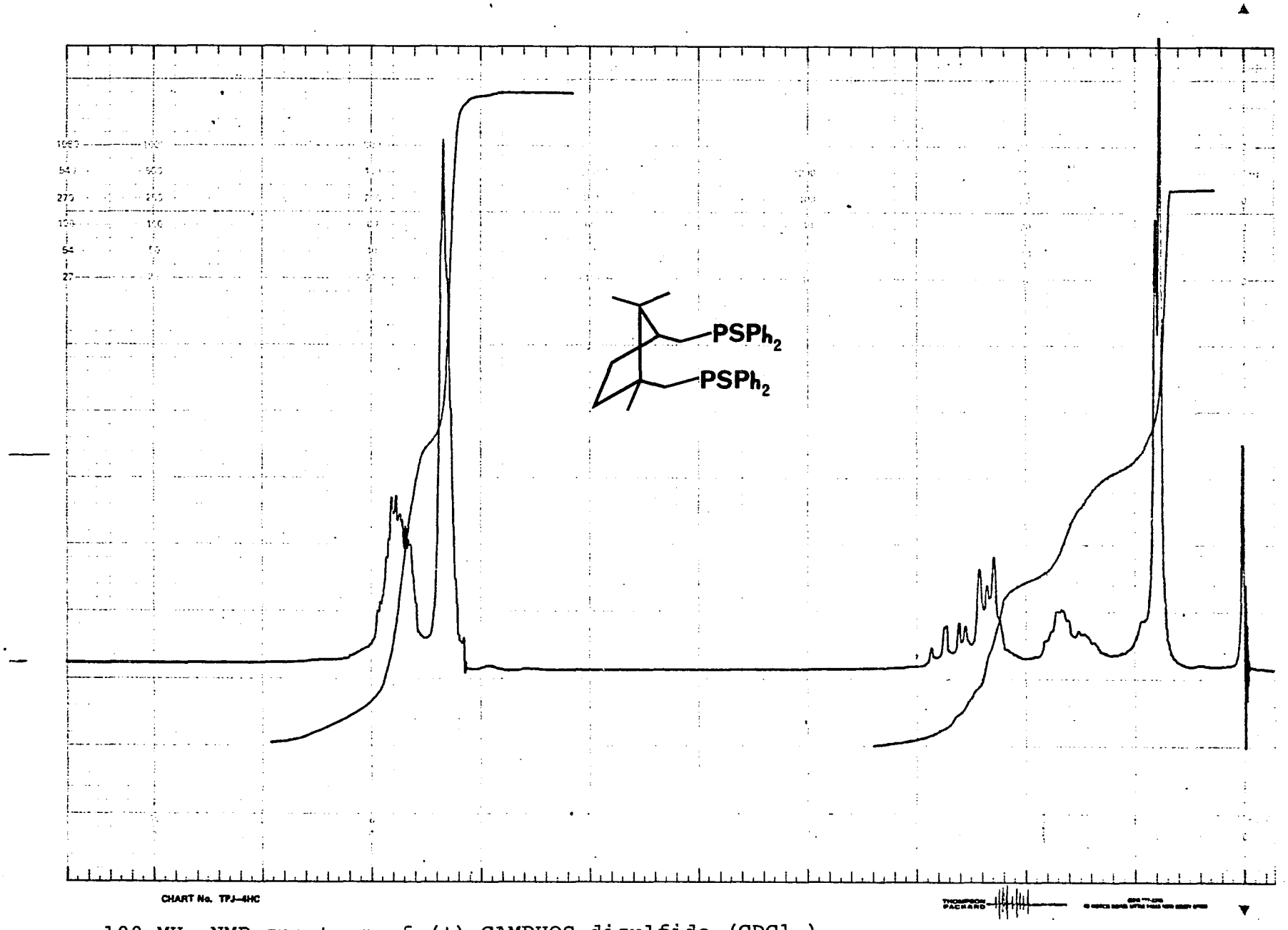
100 MHz NMR spectrum of (+)-CAMPHOS ($CDCl_3$).



100 MHz NMR spectrum of (+)-CAMPHOS dioxide ($CDCl_3$).



100 MHz NMR spectrum of (+)-CAMPHOS disulfide ($CDCl_3$).

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