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

ROBERT EDWARD BURNETT
University of New Hampshire, Durham

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by

ROBERT EDWARD BURNETT

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This thesis has been examined and approved.

James D. Morrison, Research Director
Associate Professor of Chemistry

Robert E. Lyle
Professor of Chemistry

Kenneth K. Andersen
Professor of Chemistry

Charles M. Wheeler
Associate Professor of Chemistry

Albert B. Bennett, Jr.
Assistant Professor of Mathematics

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The author wishes to dedicate this thesis to his wife whose love and understanding made the completion of this work possible.

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ABSTRACT

ASYMMETRIC HOMOGENEOUS HYDROGENATION
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The asymmetric homogeneous hydrogenation of carbon-carbon double bonds with catalysts prepared from rhodium(I) complexes of chiral phosphines is discussed.

Five new chiral phosphines were synthesized by the reaction of lithium diphenylphosphide with optically active alkyl halides. A sixth ligand was synthesized from diphenylphosphinous chloride and optically active N-ethyl-α-methylbenzylamine. These ligands, which are chiral at carbon, have the general structure $Ph_2P\overset{*}{R}$.

When allowed to react with μ-dichlorotetraethylene-dirhodium(I) in ethanol-benzene, these phosphines form catalytically active species in solution, presumably of the type $(Ph_2P\overset{*}{R})_2RhCl$. Hydrogenation of 2-phenyl-1-butene and atropic acid with these catalysts gives optically active products in every case.

One of these complexes, tris(neomenthyldiphenylphosphine)rhodium(I) chloride, is exceptionally effective as an asymmetric homogeneous hydrogenation catalyst. Reduction of 2-phenyl-1-butene at room temperature under one atmosphere of hydrogen gives (-)-2-phenylbutane having 6.6% enantiomeric excess of the R isomer. Hydrogenation of a series of α,β unsaturated acids in a 1:1 ethanol-benzene solution of pre-reduced tris(neomenthyldiphenylphosphine)rhodium(I) chloride containing triethylamine is reported. The hydrogenations were carried out at 300 psi of hydrogen pressure, at 60° over a period of 24 hr. Mono- and disubstituted acrylic acids are reduced with remarkable stereoselectivity (12-52% e.e.). Dicarboxylic acids either do not reduce or reduce with low stereoselectivity (0-5% e.e.).

INTRODUCTION

The asymmetric hydrogenation of double bonds (C=O, C=N, C=C) may be divided into two main classes. The unsaturated compound may contain a chiral center, which causes hydrogen to add preferentially to one diastereotopic face of the double bond or the hydrogen may be transferred from a chiral catalyst through a diastereomeric transition state that preferentially adds to one of the enantiotopic faces of the achiral unsaturated compound.

A number of asymmetric hydrogenations have been attempted using metals deposited on dissymmetric supports as catalysts.[1-3] A typical example is the hydrogenation of an α,β-unsaturated carboxylic acid with palladium on silica gel that had been pretreated with an alkaloid and then all the alkaloid was leached out.[4] Hydrogenation of α-methylcinnamic acid over this catalyst gave chiral 2-methyl-3-phenylpropanoic acid (1.7-3.3% e.e.). If the palladium was deposited on a chiral polypeptide support, such as poly-S-leucine, the degree of asymmetric hydrogenation was greater[5] (Figure 1).

The hydrogenation of chiral unsaturated substances may result in the formation of an excess of one of the diastereomeric products. The asymmetric reduction of the

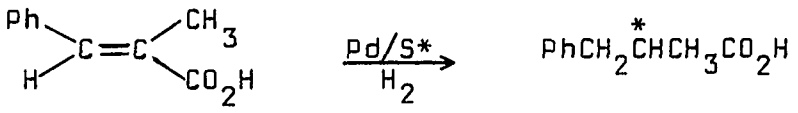


Figure 1. Hydrogenation of α-methylcinnamic acid with palladium deposited on a chiral support. S* is a polypeptide or silica gel pretreated with an alkaloid.

azomethine bond of imino-carboxylates has been extensively studied as a method for the asymmetric synthesis of amino acids, since chiral precursors are readily available from either the reaction of a chiral α-ketoester with an achiral amine or a chiral amine and an achiral α-ketoester[6] (Figure 2). The inducing chiral center can usually be re-

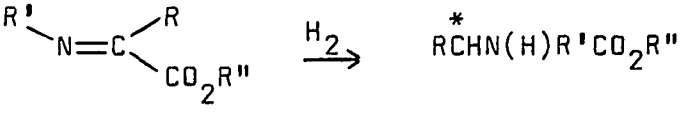


Figure 2. Hydrogenation of chiral imines. R' and/or R" chiral groupings.

moved by hydrolysis of the ester or hydrogenolysis of a benzylamine. The removal of the inducing center, as in the reduction of chiral esters of β-methylcinnamic acid, can provide a clearer understanding of the nature of the asymmetric hydrogenation process[7] (Figure 3).

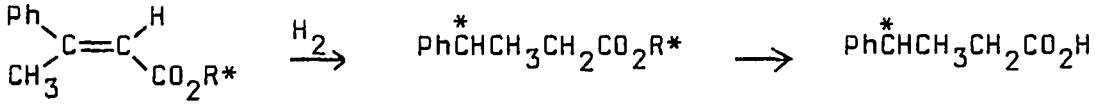


Figure 3. Hydrogenation of chiral esters of β-methylcinnamic acid with hydrolysis to the resulting chiral acid. R* is a chiral alcohol.

When Raney nickel was modified with chiral amino acids, e.g., S-alanine and S-glutamic acid, or chiral hydroxy acids, e.g., 2-R,3-R-tartaric acid, activated carbonyl compounds could be reduced with stereoselectivities typically from 0-27% e.e., and in the case of methyl acetoacetate as high as 50% e.e. has been observed.[8] The degree of asymmetric hydrogenation obtained with these catalysts, however, is generally sensitive to small changes in the pH, temperature, or method of preparation of the catalyst.

Recently the reduction of imine, alkene, and carbonyl double bonds by a soluble cobalt catalyst was reported.[9] When this catalyst was modified with quinine, benzil could be reduced to benzoin with up to 61.5% e.e. of the S isomer.[10] The homogeneous hydrogenation of carbonyl compounds has also been observed with tris(triphenylphosphine)trihydridoiridium-(III), $(Ph_3P)_3Ir(H)_3$,[11] and the cationic tetrakis(triphenylphosphine)rhodium(I) perchlorate, $(Ph_3P)_4Rh^+,ClO_4^-$,[12] however these systems have yet to be modified with chiral ligands.

The discovery in the past decade of very active rhodium-phosphine catalysts, coupled with the preparation of a number of tertiary chiral phosphines offered an excellent opportunity for the study of asymmetric hydrogenations. It is of importance to describe briefly the nature of the original Wilkinson catalyst, $(Ph_3P)_3RhCl$, as an introduction to the discussion of catalysts of this type containing chiral ligands.

In 1939, Iguti[13] reported the first activation of molecular hydrogen by soluble rhodium complexes. The catalytic reduction of quinone and fumaric acid was accomplished in aqueous solutions of $[Rh(NH_3)_5(H_2O)]Cl_3$ and $[Rh(NH_3)_4Cl_2]Cl$. However, traces of metallic rhodium were readily formed under these conditions and the possibility for heterogeneous catalysis shadows the credibility of these results.

It was not until 1964, when Gillard et al[14] began preparing similar complexes with pyridine that any real progress toward a mechanistic understanding of their role in homogeneous hydrogenations was achieved. It was observed that the preparation of trans$[Rhpy_4Cl_2]Cl$ (3) from 1,2,6-trichlorotripyridinerhodium(III) (1) was catalyzed by hydrogen (Figure 4). The reaction was presumed to proceed through a rhodium hydride intermediate (2).

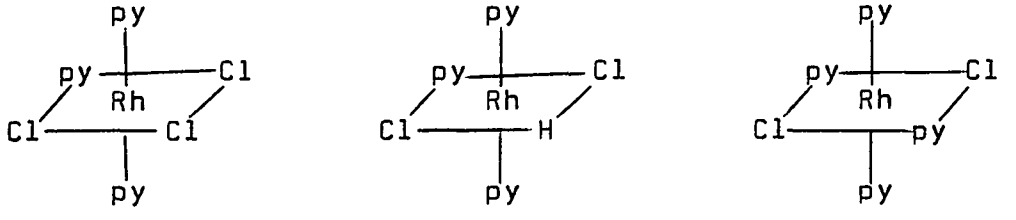


Figure 4. Hydride catalyzed preparation of trans$[Rhpy_4Cl_2]Cl$.

To test the credibility of such a hydride intermediate, the hydrogen catalyzed reduction of 1 to 3 was conducted in the presence of 1-hexene. The solution slowly took up molecular hydrogen and the olefin was converted to

n-hexane. Further experiments showed that when the reaction was stopped prior to complete reduction some of the olefin was isomerized to trans-2-hexene. These experiments only inferred the existence of 2, however they firmly established the catalytic activity of solutions of 1. This catalytic activity prompted similar investigations with rhodium complexes of tertiary phosphines.

Initial experiments were conducted using tris(triphenylphosphine)rhodium(III) trichloride (4).[15] It was later observed that the preparation of 4 in the presence of excess triphenylphosphine afforded the reduced complex tris(triphenylphosphine)rhodium(I) chloride (5)[16] (Equation 1).

(1) $(Ph_3P)_3RhCl_3 + Ph_3P \longrightarrow (Ph_3P)_3RhCl + Ph_3PCl_2$

(4) (5)

This new complex has proved to be a most effective catalyst for the homogeneous hydrogenation of a variety of olefins.[16-19] The rate of hydrogenation is comparable to that observed with Raney nickel or Adam's catalyst, but the selectivity is much greater. At normal temperatures and pressures: (a) terminal alkenes are reduced more rapidly than internal alkenes; (b) cis alkenes are reduced faster than the corresponding trans isomers; (c) trisubstituted olefins are reduced very slowly; (d) conjugated olefins are generally not reduced; (e) substrates which react with the catalyst to form rhodium(III) compounds are not hydrogenated.

Carbon-carbon double bonds can be selectively reduced in the presence of keto-[20,21], cyano-[17,18], nitro-[17,20], azo-[17], ester[17,22], carboxylic acid[17,22,23] and aldehyde[24] groups.

Some problems that are frequently encountered with heterogeneous catalysis, for example hydrogenolysis of labile groups and catalyst poisoning, especially by sulfur compounds, do not occur. Benzyl ethers[25], esters[25], amines[24] and thiols[26] are stable to hydrogenolysis with this catalyst. Mixed results have been obtained with halides. Benzyl bromide is unaffected, but treatment of cinnamyl chloride (6) with one equivalent of hydrogen produced a mixture of products (Figure 5) some of which resulted from hydrogenolysis.[20]

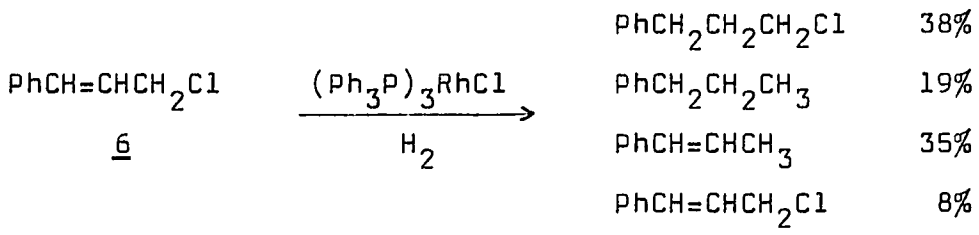


Figure 5. Hydrogenation of cinnamyl chloride with tris(triphenylphosphine)rhodium(I) chloride.

Allyl phenyl sulfide has been reduced to n-propyl phenyl sulfide with tris(triphenylphosphine)rhodium(I) chloride without any noticeable inhibition.[26] Addition of a large excess of thiophenol does inhibit the hydrogenation of olefins, probably by complexation with the catalyst. However, in the presence of a 2.5 molar excess of thiophenol hydrogenation proceeds at a reasonable rate (Table 1).

TABLE 1

RATE OF HOMOGENEOUS HYDROGENATIONS WITH $(Ph_3P)_3RhCl$ IN THE PRESENCE OF ADDED THIOPHENOL

Substrate Reduced	Molar Ratio $PhSH:(Ph_3P)_3RhCl$	Absorbed H_2 (ml)	Time (min)
1-octene	0	70	60
	2.5:1	19	60
dehydrolinalool[a]	0	80	13
	2.5:1	80	90
	42:1	5	120

(a) In dehydrolinalool, $(CH_3)_2C{=}CH(CH_2)_2C(OH)(CH_3)C{\equiv}CH$, reduction occurs at the triple bond.

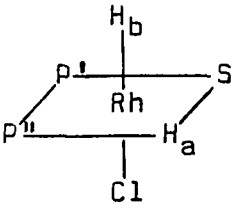
The fact that there is catalytic addition of hydrogen to an unsaturated substrate indicates that the catalytically active species must be able to activate both hydrogen and the substrate. Furthermore, the transfer of hydrogen in this activated species must be an energetically favored process. Any discussion of the mechanism should include the determination of (a) the catalytically active species; (b) the nature and the order in which these events take place; (c) the stereochemistry of hydrogen addition.

The apparent molecular weight of tris(triphenylphosphine)rhodium(I) chloride (5) in solution is constant, over a range of concentrations, and is about one half the expected value. Solutions of 5 do not show conductance and react quantitatively with carbon monoxide, ethylene, tetrafluroethylene and pyridine, forming complexes of the type

$(Ph_3P)_2Rh(Cl)L$ (L=CO, C_2H_4, C_2F_4 and C_5H_5N).[17] These results have been interpreted to mean that 5 dissociates completely in solution to form the coordinatively unsaturated bis(triphenylphosphine)rhodium(I) chloride (7) and triphenylphosphine and that 7 is the catalytically active species (Equation 2). The complex 7 reacts reversibly with

(2) $$\underset{(5)}{(Ph_3P)_3RhCl} \rightleftharpoons \underset{(7)}{(Ph_3P)_2RhCl} + Ph_3P$$

one equivalent of hydrogen to form a dihydrido-complex. The nmr spectrum of the dihydrido-complex is readily interpreted in terms of an octahedral cis dihydrido-complex structure (8), where H_a but not H_b shows a doublet characteristic of trans H-^{31}P coupling (Figure 6). Kinetic data could not

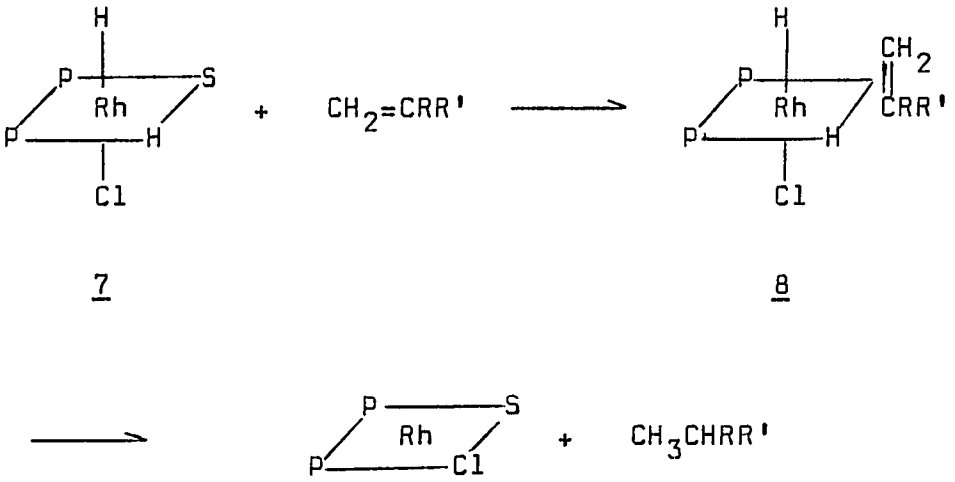


8

Figure 6. H_a trans to P' and cis to P", H_b cis to P' and P", P is Ph_3P, S is solvent.

distinguish between the formation of the olefin-hydrido complex (9) from attack of olefin on 8 or attack of hydrogen on the olefin complex. However, a series of experiments employing hydrogen, ethylene and solutions of tris(triphenyl-

phosphine)rhodium(I) chloride (5) demonstrated that the olefin-complex is inert to hydrogen while the dihydrido-complex (8) reacts readily with olefins to form 9 which then collapses to products (Figure 7).[17]



7 8

Figure 7. Attack of olefin on the dihydrido-complex. S is solvent; P is Ph_3P; R and/or R' are aryl, alkyl or hydrogen.

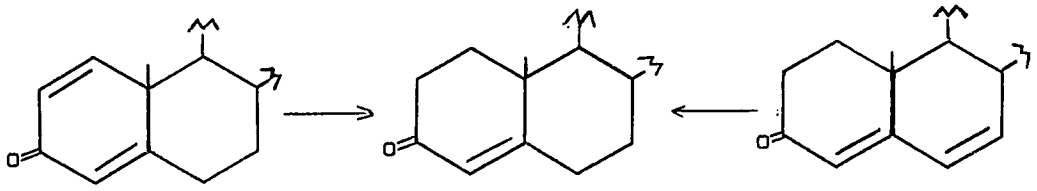
The addition of deuterium was shown to occur without scrambling. Therefore, the observation that the reduction of maleic acid with tris(triphenylphosphine)rhodium(I) chloride gave meso 1,2-dideuterosuccinic acid and that fumaric acid gave racemic 1,2-dideuterosuccinic acid showed that the addition occurred in a cis-concerted manner.[17] Further evidence for cis addition of deuterium was obtained by the partial reduction of 2-hexyne. The reaction was found to proceed stepwise to form alkene which is then further reduced to alkane. Analysis of the alkene portion showed that it contained greater than 95% of the cis isomer. This represents a minimum

value for the stereoselectivity, since the cis isomer is more rapidly reduced than the trans isomer.

Since the original work of the Wilkinson group, many other workers have utilized it in organic synthesis and as a result have more closely defined the scope and limitations of this catalyst system.

Djerassi and Gutzwiller[27] investigated the suitability of tris(triphenylphosphine)rhodium(I) chloride (5) for the hydrogenation of steroids. They observed that unhindered disubstituted double-bonds are selectively reduced in high yield. A striking example of this selectivity is the hydrogenation of $\Delta^{1,4}$ (9) and $\Delta^{4,6}$-androstadiene-3,17-diones (10) where both isomers afford only Δ^{4}-androstene-3,17-dione (11) (Equation 3).

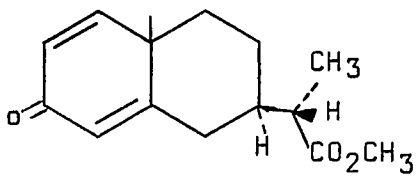
(3)



(9) (11) (10)

Similar examples of remarkable selectivity are the quantitative hydrogenation of only the 1,2 double-bond in 12[28] and the terminal double-bond in 13[29].

While psilostachyine (14) and confertiflorin (15) are readily hydrogenated by tris(triphenylphosphine)rhodium(I)



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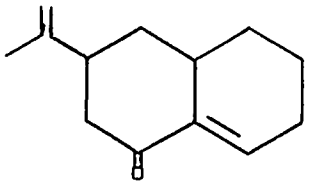
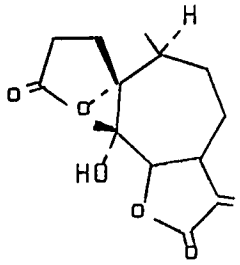


(13)

chloride, damsin (16) is not reduced but is instead isomerized to isodamsin (17).[30] Since the catalyst itself, in



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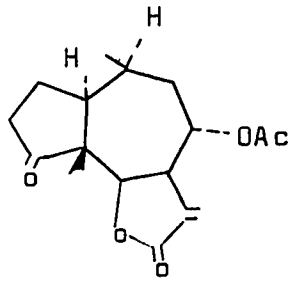

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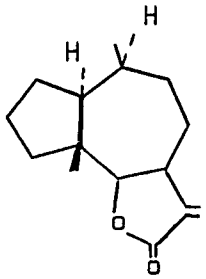
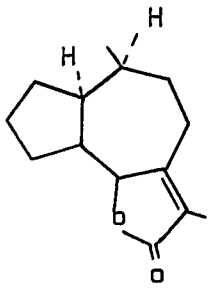


(16)



(17)

the absence of hydrogen, does not cause isomerization and since bis(triphenylphosphine)bis(dideutero)rhodium(III) chloride isomerizes damsin quantitatively to isodamsin-d_1,

the isomerization was postulated to proceed through an alkylrhodium hydride intermediate. Hydrogenation was postulated to also proceed through this intermediate.

Data for the reduction of a series of cyclopropylalkenes, summarized in Table 2, provides further evidence for an alkylrhodium hydride intermediate.[31] The isomerization is thought to proceed by rearrangement of a cyclopropylcarbinylrhodium hydride to the corresponding homoallylrhodium hydride which then dissociates to give the alicylic olefin (Figure 8).

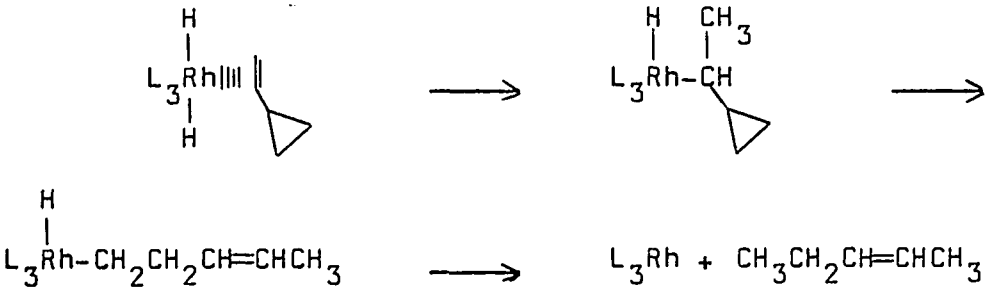
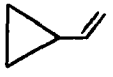
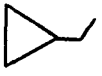
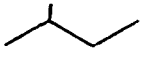
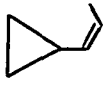
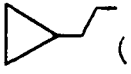
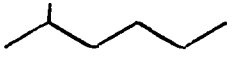
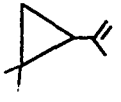
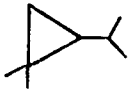
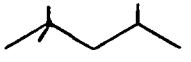
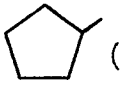
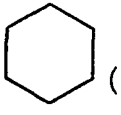
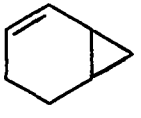
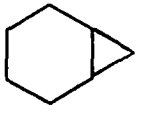
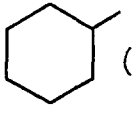


Figure 8. Rearrangement of cyclopropylcarbinylrhodium hydride to homoallylrhodium hydride. L=Ph_3 or Cl

The addition of deuterium to a variety of substances has been reported.[27,32-34] While this addition had previously been assumed to occur in a cis-concerted manner,[17] recent work has indicated that in certain cases, at least, with tris(triphenylphosphine)rhodium(I) chloride deuterium addition is sensitive to catalyst concentration, reaction time and solvent.[35] It was observed that styrene in benzene or methylene chloride afforded pure 1,2-dideuteroethylbenzene, changing the solvent to chloroform or 3:1 benzene-

TABLE 2

$(Ph_3P)_3RhCl$ CATALYZED REDUCTION OF CYCLOPROPYLALKENES

Substrate	Products (%)		
	 (85)	 (14)	 (1)
	 (70)	 (27)	 (3)
	 (99)	 (1)	
	 (93)	 (6.7)	 (0.3)
	 (82)	 (18)	

ethanol increased the amount of d_0 and d_1 ethylbenzene.[36] Other workers[37-40] also noted this solvent dependence. In benzene, reduction proceeded with a high degree of stereoselectivity, while the use of ethanol as a cosolvent promoted isomerization and deuterium scrambling. However, presaturation of a benzene-ethanol solution of 5 gave the active dihydrido species and triphenylphosphine. Therefore, the nonselectivity was postulated to result from an olefin complex of the undissociated tris(triphenylphosphine)rhodium(I) chloride.

Hussey and Takeuchi[41,42] in an elegant mechanistic study with a series of dimethylcyclohexenes showed that the attack of olefin on the dideutero(dihydrido)-complex (18) was reversible (Figure 9). The authors specify, however, that for most mono-and disubstituted double-bond systems, in a practical sense, the formation of complexes with 18 can be considered irreversible and the transfer of hydrogen can be considered to be concerted.

During the course of this investigation and in one case subsequent to its completion, a number of reports appeared describing similar work. The initial studies of asymmetric hydrogenation with soluble rhodium catalysts concentrated upon the use of tertiary phosphine ligands that were chiral at phosphorus. For example, the hydrogenation of α-ethylstyrene and α-methoxystyrene with a catalyst prepared from S-methylpropylphenylphosphine gave S-2-phenyl-

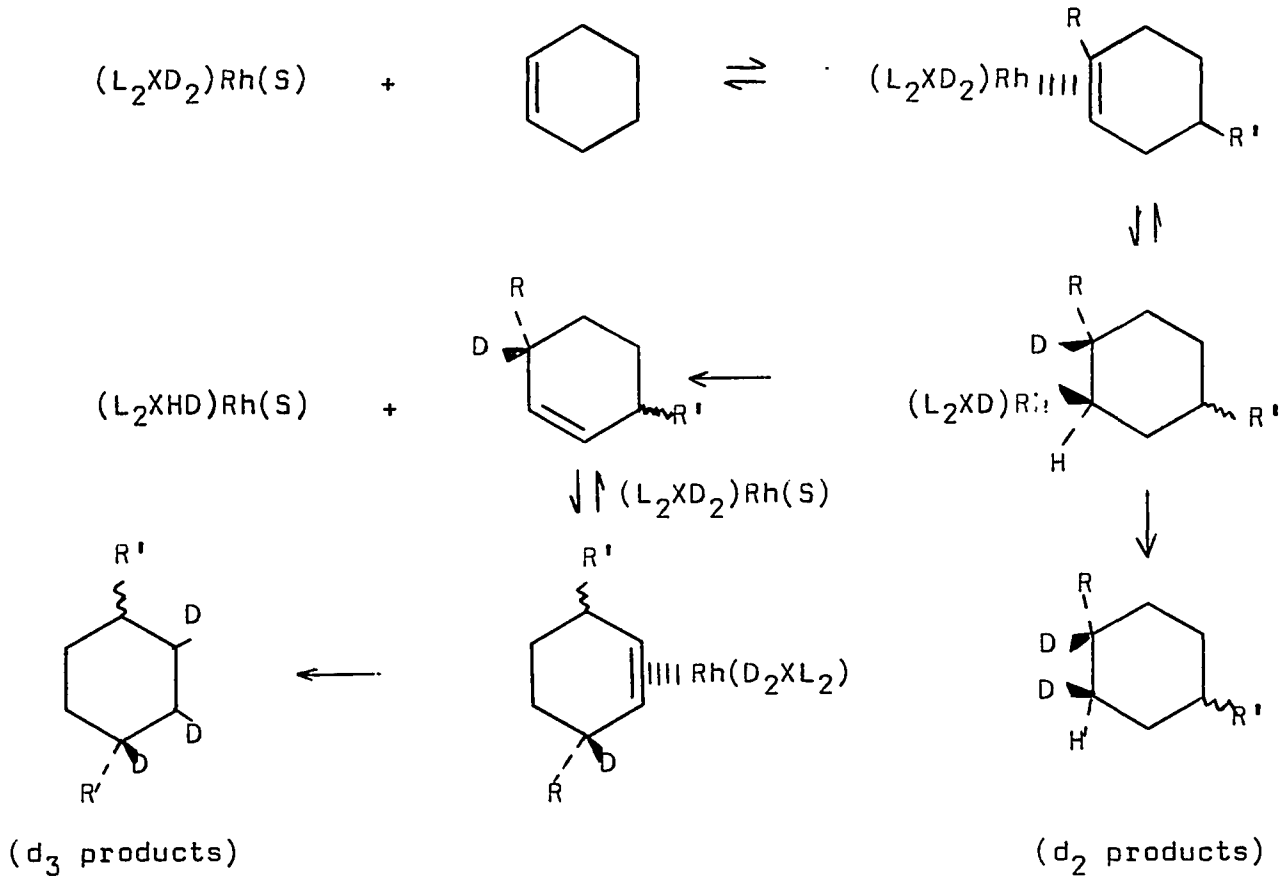


Figure 9. Modified mechanism for the hydrogenation of alkenes with tris(triphenylphosphine)rhodium(I) chloride.

butane (7-8% e.e.) and R-1-methoxy-1-phenylethane (3-4% e.e.) (Figure 10).[43]

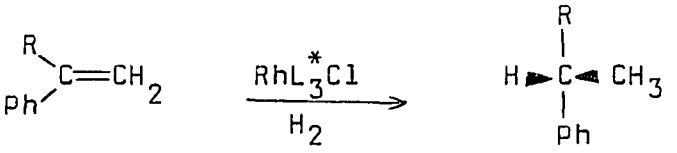


Figure 10. Asymmetric homogeneous hydrogenation of α-substituted styrenes; L* is S-methylpropylphenylphosphine, R is ethyl or methoxy.

This same catalyst was reported to reduce atropic and itaconic acids to 2-phenylpropanoic (21% e.e.) and 2-methylsuccinic acid (3% e.e.).[23] In a later study, atropic acid was hydrogenated with chiral catalysts prepared from methylphenylcyclohexyl, methylphenyl-sec-butyl, and methylphenylisopropylphosphine to give optically active 2-phenylpropanoic acid (3, 15 and 17.5% e.e.) (Figure 11).[44]

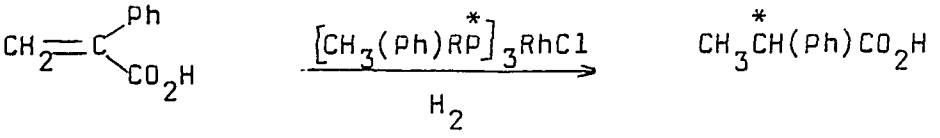
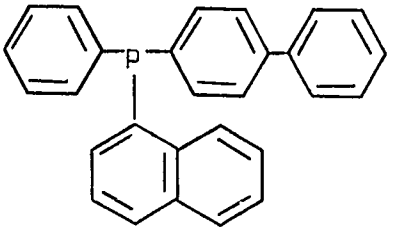


Figure 11. The homogeneous hydrogenation of atropic acid with chiral catalysts prepared from chiral methylphenylalkylphosphine; R is propyl, isopropyl, sec-butyl and cyclohexyl.

Other reductions of atropic acid with catalysts prepared from chiral 4-biphenyl-1-naphthylphenylphosphine (20),[45] phenyldi(2-methylbutyl)phosphine (21)[23] and 1,4-diphenylphosphine-2,3-isopropylidenebutanediol (22)[46] have been reported. With the triarylphosphine (20) no asymmetry was induced and



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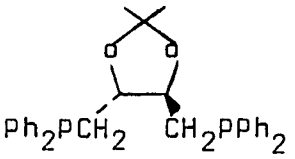


22

$PhP(CH_2\overset{*}{C}H(CH_3)CH_2CH_3)_2$

21

with the phenyldialkylphosphine (21) reduction gave 2-phenylpropanoic acid with only 1% enantiomeric excess. However, when the catalyst was prepared from the diphosphine (22), 2-phenylpropanoic acid of 63% enantiomeric excess was obtained. Similarly, the reduction of α-acetamidocinnamic acid and α-phenylacetamidoacrylic acid with a catalyst prepared from 22 gave R-N-acetylphenylalanine (72% e.e.) and N-phenylacetylalanine which gave R-alanine (68% e.e.) after hydrolysis.

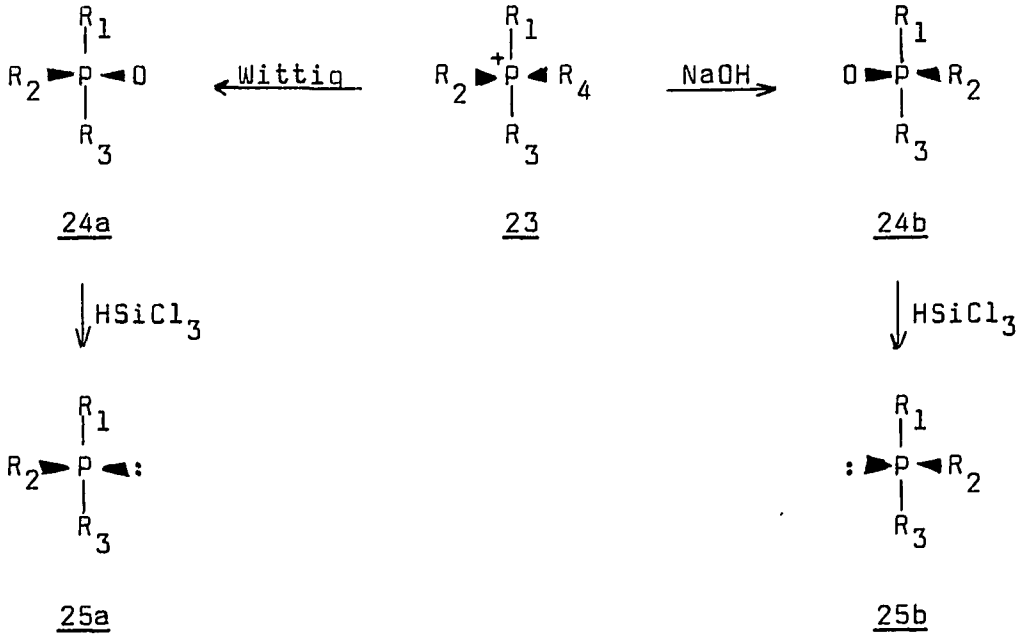
Rhodium(I) complexes containing pyridine and chiral amides have been used to catalyze the asymmetric hydrogenation of some α,β unsaturated esters.[47,48] The highest asymmetric induction was observed when (E)-β-methylcinnamic acid was hydrogenated with a catalyst prepared by the reduction of $(Py)_3RhCl_3$ with sodium borohydride in the presence of R-(+)-$PhCH_3CHNHCHO$.

RESULTS AND DISCUSSION

In investigating the possibility of modifying the Wilkinson catalyst with chiral phosphine ligands and the effect of such modification, the first major consideration has to be the availability of these chiral ligands. At the outset the use of tertiary phosphines, chiral at phosphorus, was considered since coordination would then occur at the chiral center and it seemed reasonable that this proximity might enhance any asymmetric bias.

Early synthetic routes to tertiary phosphines, chiral at phosphorus, ($R_1R_2R_3\overset{*}{P}$) (25) required the resolution of either the phosphine oxide ($R_1R_2R_3PO$) (24)[49] or, more commonly, the quarternary phosphonium salt ($R_1R_2R_3R_4P^+X^-$) (25)[50]. It was reported that conversion of 23 to the phosphine oxide (24) was accomplished by cleavage of R_4 with sodium hydroxide[51] or by the Wittig reaction[52] (Figure 12). Trichlorosilane reduction of 24 gave the chiral phosphine.[53] It was subsequently reported that cathodic reduction of 23 gave 25 directly.[54] Whatever the method of preparation, the starting material had to contain R_1, R_2 and R_3 prior to resolution. In addition, starting from 23 the ease of cleavage of R_4 must be significantly greater than that of the other three groups.

A second approach involved the reaction of Grignard



24a 23 24b

25a 25b

Figure 12. Preparation of chiral phosphines from resolved phosphonium salts.

reagents with diastereomerically pure menthyl phosphinates.[55] The resulting phosphine oxides could then be reduced with trichlorosilane. Although this sequence avoids the necessity of a classical resolution, the multi-step synthesis of the phosphinate (Figure 13) was accomplished in only 10% yield. Other workers[56] subsequently reported a more direct preparation of menthyl phosphinates (Figure 14), however, the yield of the diastereomerically pure phosphinate was still low (8%).

Because of these synthetic limitations, it was decided to utilize tertiary phosphines which were chiral at carbon and much more accessible. These phosphines could be prepared directly by reacting the appropriate chiral alkyl halide with lithium diphenylphosphide. While this reaction is well documented,[57] its use with chiral substrates had not

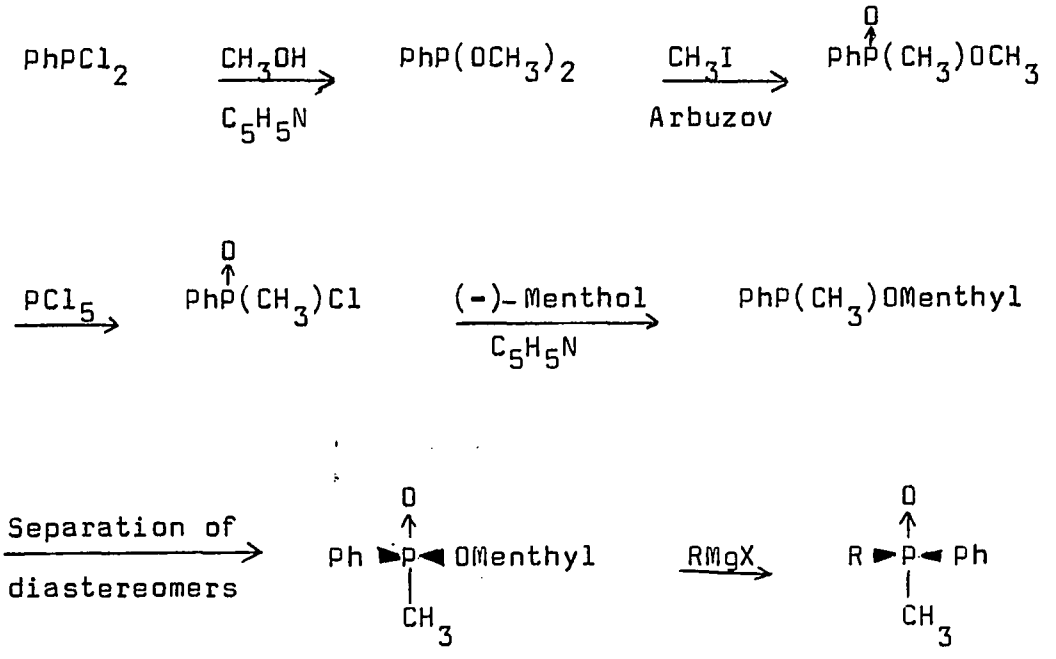


Figure 13. Preparation of chiral phosphine oxides by reaction of Grignard reagents with menthyl phosphinates.

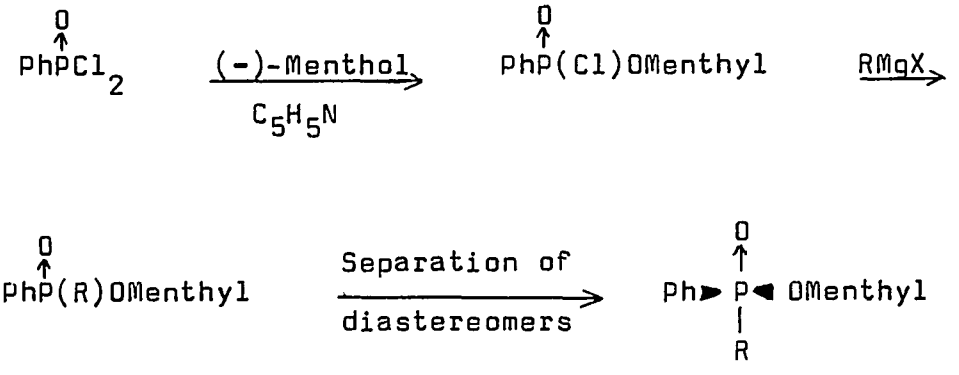
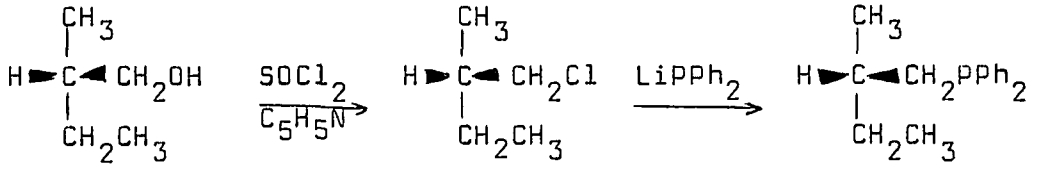


Figure 14. Modified preparation of menthyl phosphinates.

been reported previously. Since the only condition for asymmetric reduction of an unsymmetrical substrate is that the catalyst be chiral, ligands which are dissymmetric remote from phosphorus also fulfill the requirement.

The Preparation of Optically Active Phosphines

The preparation of S-(+)-2-methylbutyldiphenylphosphine (26) was effected from S-(+)-2-methyl-1-butanol (27) (Figure 15) in the following manner. The alcohol was converted to S-(+)-1-chloro-2-methylbutane (28) in 61% yield (90% e.e.) by reaction with thionyl chloride and pyridine. The chloride was allowed to react with lithium diphenylphosphide in tetrahydrofuran to give 26 in 54% yield.

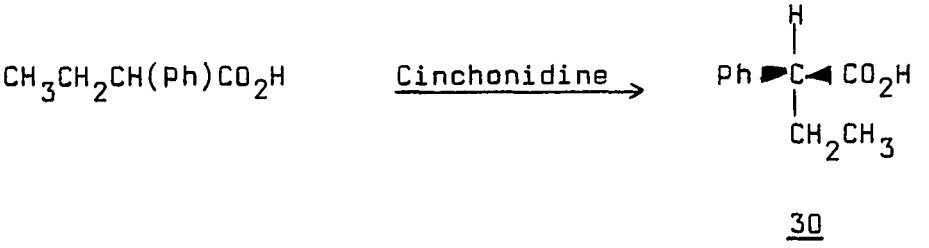


27 28 26

Figure 15. Preparation of S-(+)-2-methylbutyldiphenylphosphine.

S-(+)-2-Phenylbutyldiphenylphosphine (29) was prepared starting from 2-phenylbutanoic acid (Figure 16). Resolution of the racemic acid with cinchonidine gave S-(+)-2-phenylbutanoic acid (30) in 90% yield. Lithium aluminum hydride reduction of 30 gave S-(+)-2-phenyl-1-butanol (31) in 84% yield. The alcohol was converted to S-(+)-1-chloro-

2-phenylbutane (32) in 80% yield (97% e.e.) by reaction with thionyl chloride and pyridine. The chloride was allowed to react with lithium diphenylphosphide in tetrahydrofuran to give 29 in 52% yield.



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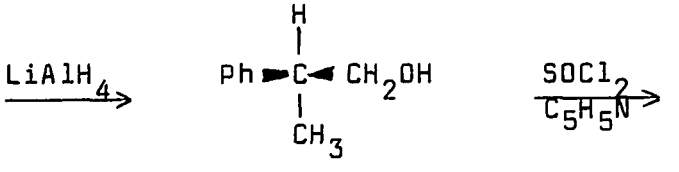

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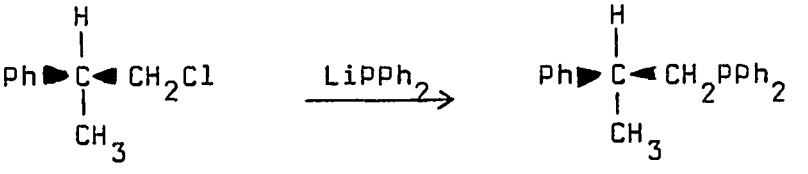


32 29

Figure 16. Preparation of S-(+)-2-phenylbutyldiphenylphosphine.

R-(-)-3-Phenylbutyldiphenylphosphine (33) was prepared starting from 3-phenylbutanoic acid (Figure 17). Resolution of the racemic acid with R-(+)-α-methylbenzylamine gave R-(-)-3-phenylbutanoic acid (34) in 70% yield. Lithium aluminum hydride reduction of 34 gave R-(-)-3-phenylbutanol (35) in 95% yield. The alcohol was converted to R-(-)-1-bromo-

3-phenylbutane (36) in 69% yield (90% e.e.) by reaction with 48% hydrobromic acid. The bromide was allowed to react with lithium diphenylphosphide in tetrahydrofuran to give 33 in 41% yield.

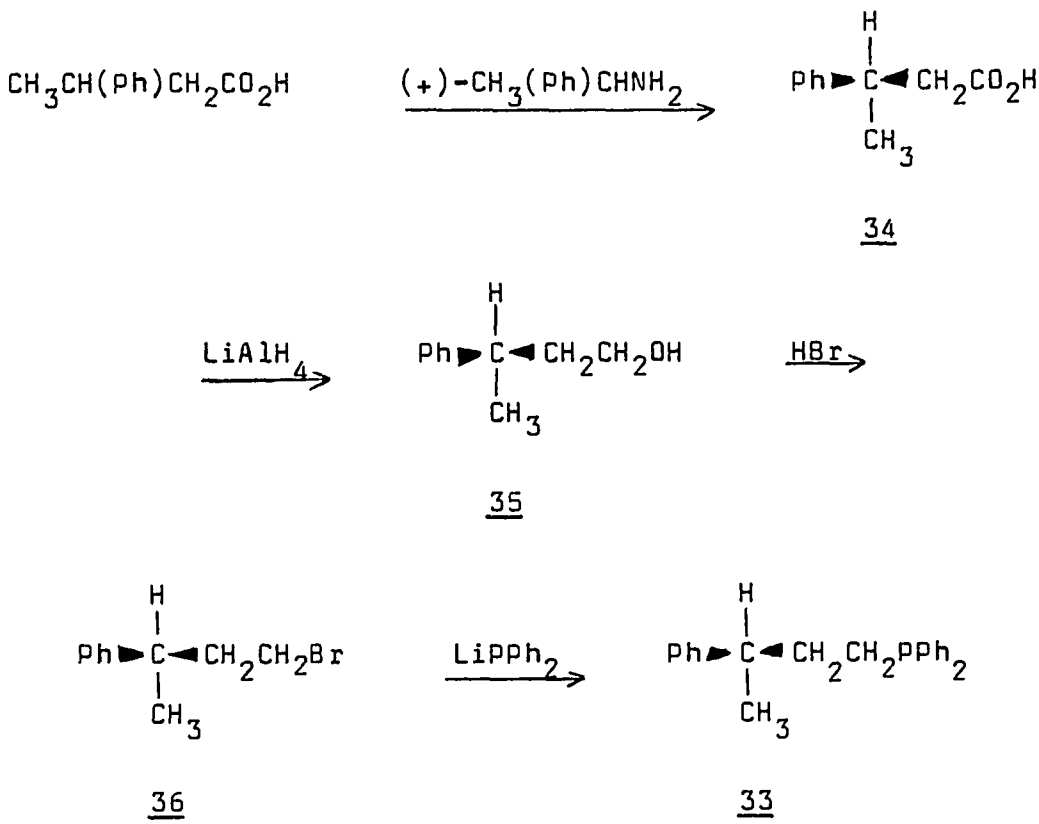
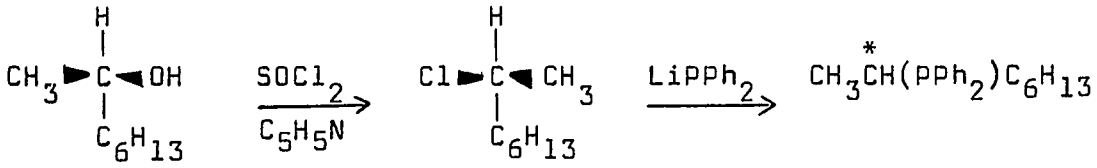


Figure 17. Preparation of R-(-)-3-phenylbutyldiphenylphosphine.

Optically active 2-octyldiphenylphosphine (37) was prepared starting from R-(-)-2-octanol (38) (Figure 18). In initial experiments, the alcohol was resolved as the hydrogen phthalate with R-(+)-α-methylbenzylamine, later in the investigation optically active 2-octanol became commercially available. The alcohol was converted to S-(+)-2-chlorooctane (39) in 44% yield (86% e.e.) by reaction with thionyl chloride

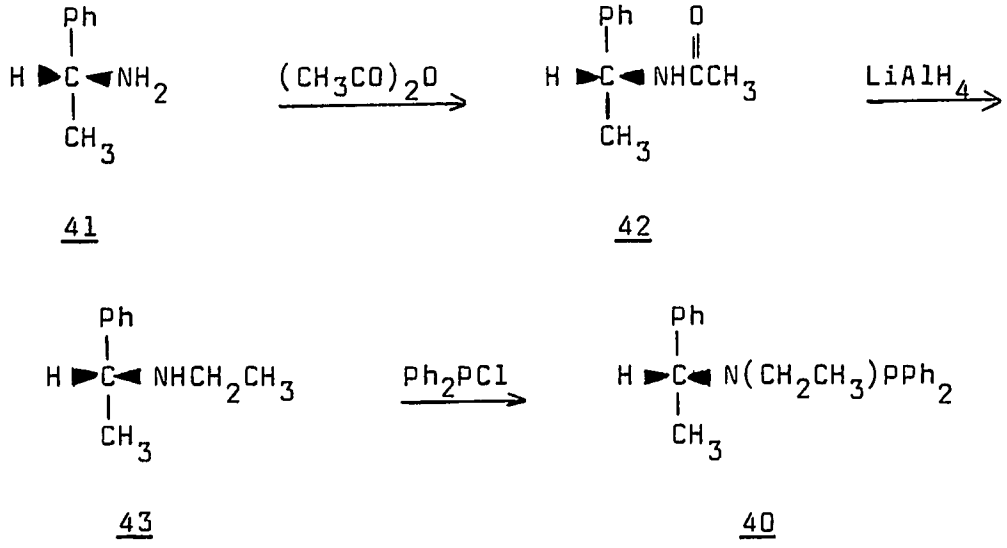
and pyridine. The chloride was allowed to react with lithium diphenylphosphide in tetrahydrofuran to give 37 in 37% yield.



38 39 37

Figure 18. Preparation of optically active 2-octyldiphenylphosphine.

R-(+)-N-Ethyl-N-(α-methylbenzyl)diphenylphosphinamide (40) was prepared starting from commercial R-(+)-α-methylbenzylamine (41) (93% e.e.) (Figure 19). The amine was con-



41 42 43 40

Figure 19. Preparation of R-(+)-N-ethyl-N-(α-methylbenzyl)-diphenylphosphinamide.

verted to R-(+)-N-(α-methylbenzyl)acetamide (42) in 78% yield by reaction with acetic anhydride. Lithium aluminum hydride

reduction of 42 gave R-N-ethyl-α-methylbenzylamine (43) in 46% yield. The secondary amine (43) was allowed to react with diphenylphosphinous chloride in ether to give 40 in 22% yield.

Optically active neomenthyldiphenylphosphine (44) was prepared starting from (-)-menthol (45) (98% e.e.) (Figure 20).

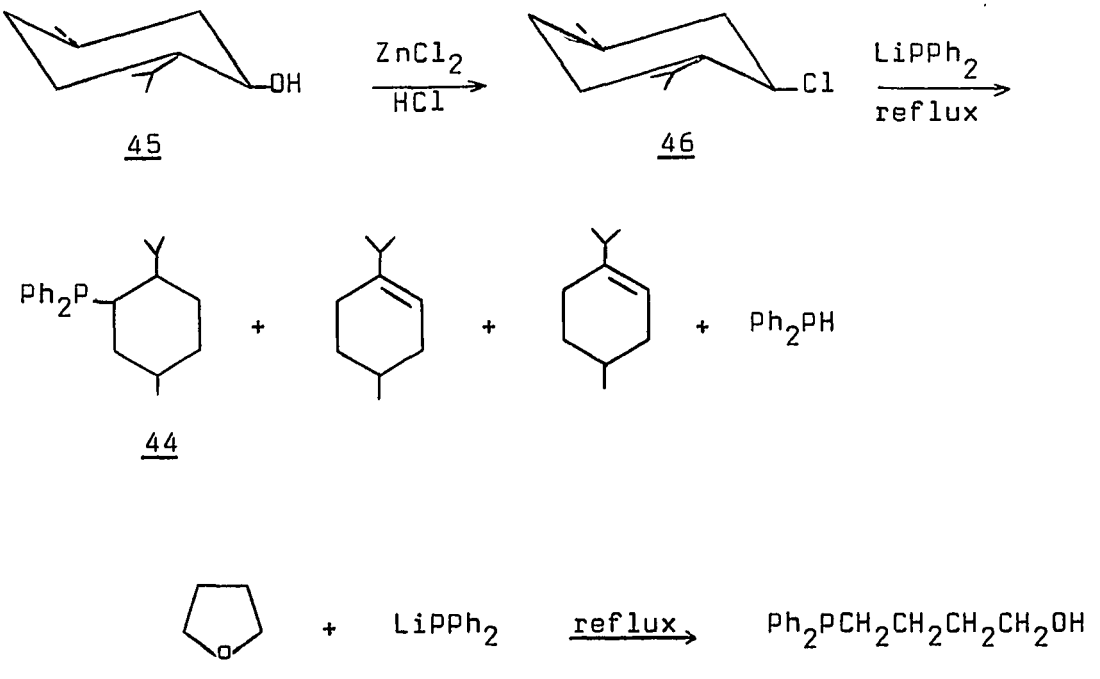


Figure 20. Preparation of optically active neomenthyldiphenylphosphine.

The alcohol was converted to (-)-menthyl chloride (46) by reaction with zinc chloride and 37% hydrochloric acid. The reaction of lithium diphenylphosphide with alkyl halides in tetrahydrofuran usually occurs readily at room temperature,

however, under these conditions reaction with menthyl chloride could not be accomplished. When the solution was heated to reflux, some displacement (10-15%) occurred, however, the major products resulted from either dehydrohalogenation or attack of the lithium diphenylphosphide on the tetrahydrofuran. Similarly, reaction with either menthyl bromide or menthyl tosylate gave only the isomeric menthenes, diphenylphosphine and 4-hydroxybutyldiphenylphosphine.

Bhacca[58] has tentatively concluded that the 220 MHz nmr spectrum of the benzyl salt of 44 is compatible with a neomenthyl configuration. If this is correct, the reaction of lithium diphenylphosphide with menthyl chloride proceeded with inversion of configuration at carbon to give neomenthyldiphenylphosphine.

In a variation of this procedure the lithium diphenylphosphide reagent was prepared in tetrahydrofuran and then the tetrahydrofuran was displaced by adding benzene and distilling to a boiling point of 80°. When menthyl chloride was allowed to react with the resulting benzene solution of the phosphide, the amount of dehydrohalogenation increased, but the absence of the 4-hydroxydiphenylphosphine by product as a contaminant simplified the purification of the phosphine.

Alternate syntheses from either menthyl lithium or menthyl Grignard were unsuccessful. Menthyl lithium[59] could not be prepared in this laboratory. The reaction of menthyl Grignard with diphenylphosphinous chloride gave, in low yield, a mixture of neomenthyldiphenylphosphine and another

compound believed to be menthyldiphenylphosphine.[47] This same compound was obtained when neomenthyl bromide was allowed to react with lithium diphenylphosphide.

Hydrogenation of 2-Phenyl-1-butene

The Wilkinson catalyst has become a valuable synthetic tool, largely because of the selectivity of its action and the absence of many of the side reactions of heterogeneous hydrogenations. The possibility that this catalyst might be modified with chiral tertiary ligands without loss of catalytic activity would in principle allow the asymmetric hydrogenation of appropriate alkenes. This would afford a direct synthesis of some optically active alkanes which are usually obtained by circuitous routes from resolved precursors. This work was concerned with developing a system which could realize this possibility using chiral ligands derived from readily available chiral precursors.

2-Phenyl-1-butene (48) was chosen as the substrate since it is the simplest aryl alkyl terminal olefin which can be reduced to an optically active alkane. The resulting 2-phenylbutane is a well known compound; both its absolute configuration and maximum rotation are known.[60]

The catalysts were prepared *in situ*, in a benzene-ethanol solution from μ-dichlorotetraethylenedirhodium(I) (49) and the chiral phosphine, according to the procedure used by Djerassi and Gutzwiller[61] for the Wilkinson

catalyst (Equation 4). The solution was prereduced with

$$(4) \qquad 6Ph_2P^*R + Rh_2Cl_2(C_2H_4)_4 \xrightarrow[C_2H_5OH]{C_6H_6} 2(Ph_2P^*R)_3RhCl$$

hydrogen for 0.5 hr to convert the catalyst to the active dihydrido species and then 2-phenyl-1-butene (48) was added.

Hydrogenation of 48 with catalysts prepared from 26, 29, 33, 37, 40 and 44 gave optically active 2-phenylbutane in every case. Data for these hydrogenations and for the hydrogenation of 48 with a catalyst prepared from S-(+)-methylpropylphenylphosphine (50) are compiled in Table 3.

TABLE 3

ASYMMETRIC HOMOGENEOUS HYDROGENATION OF 2-PHENYL-1-BUTENE WITH A RHODIUM CATALYST PREPARED FROM CHIRAL PHOSPHINES

Ligand	2-Phenylbutane Configuration	% e.e.
2-methylbutyldiphenylphosphine (26)	S	3.1
2-phenylbutyldiphenylphosphine (29)	R	4.0
3-phenylbutyldiphenylphosphine (33)	R	0.4
2-octyldiphenylphosphine (37)	R	0.5
N-Ethyl-N-(α-methylbenzyl)-phosphinamide (40)	S	1.2
neomenthyldiphenylphosphine (44)	R	6.6
methylpropylphenylphosphine[a] (50)	S	7-8

(a) See reference 43.

It is interesting that the catalyst prepared from neomenthyldiphenylphosphine (44) induced as much asymmetry as that prepared from S-(+)-methylpropylphenylphosphine (50) which is chiral at phosphorus. Furthermore, catalysts prepared from 2-phenylbutyldiphenylphosphine (29) 2-methyl-

butyldiphenylphosphine (26) which are asymmetric β to phosphorus are half as effective as 50. However, when the ligand is chiral ɣ to phosphorus, as in the case of 3-phenylbutyldiphenylphosphine (33), the asymmetric bias is considerably reduced. Similarly, with 2-octyldiphenylphosphine (37) which is chiral α to phosphorus, there is little bias, although in this case the interpretation is tenuous since the substituents on the asymmetric carbon are different from those present at the β and ɣ positions of 26, 29 and 33.

Catalysts prepared from phosphinamides have also been reported to reduce olefins.[42,62] These ligands are easily prepared from phosphinous chloride and secondary amines (Equation 5).

(5) $Ph_2PCl + 2RR'NH \longrightarrow Ph_2PNRR' + RR'NH\cdot HCl$

While these catalysts are reportedly less active than those prepared from tertiary phosphines, the number of available chiral amines makes this system especially attractive from the point of view of ligand synthesis. The reduction of 2-phenyl-1-butene (48) with a catalyst prepared from N-ethyl-N-(α-methylbenzyl)diphenylphosphinamide (40) could not be accomplished at low hydrogen pressures; however, hydrogenation at 6 atmospheres of pressure gave optically active 2-phenylbutane.

To ensure that the optical activity observed in these hydrogenations was due to the 2-phenylbutane and not to some undetected impurity, α-methylstyrene was hydrogenated under

the same conditions using a catalyst prepared from 2-octyldiphenylphosphine (37). The 2-phenylpropane that resulted had α_D 0.000.

In another experiment the tris(2-methylbutyldiphenyl)rhodium(I) chloride catalyzed reduction of 2-phenyl-1-butene (48) was stopped prior to completion. Analysis of the reaction mixture showed unreacted 48 and 2-phenylbutane, but no 2-phenyl-2-butene. Since the internal alkene is not hydrogenated under these conditions, it can be concluded that there was no rearrangement of the substrate.

These results show that modification of the Wilkinson catalyst with chiral phosphorus ligands can be achieved without loss of catalytic activity and that these catalysts are capable of inducing asymmetry. Furthermore, at least one phosphine ligand prepared from a readily available chiral compound, containing multiple centers of chirality, was as effective as ligands which are chiral at phosphorus. Also, in phosphines containing only one chiral carbon, the position of asymmetry relative to phosphorus may be important. Finally, the result obtained with the phosphinamide (40) indicates that further investigation of other chiral tertiary phosphorus compounds is warranted.

Hydrogenation of α,β Unsaturated Carboxylic Acids

While the experiments with 2-phenyl-1-butene were being conducted in this laboratory, Knowles and Sabacky[23] reported the asymmetric hydrogenation of atropic acid (51)

using a catalyst prepared from R-(-)-methylpropylphenylphosphine (50). It was reported that if the reduction was carried out in a benzene-ethanol solution containing triethylamine, (+)-hydratropic acid was obtained in 21% optical purity (Equation 6). When 51 was reduced without added amine

(6) $CH_2{=}C(CO_2H)H + H_2 \xrightarrow[(C_2H_5)_3N]{(MePrPhP)_3RhCl}$

51

$H{-}C(CH_3)(Ph)(CO_2H)$ + $Ph{-}C(CH_3)(H)(CO_2H)$

R-(-) 39.5% S-(+) 60.5%

the hydratropic acid obtained had only 1% optical purity.

Since ligands of the type Ph_2P^*R were comparable to 50 in their ability to induce asymmetry during the hydrogenation of 2-phenyl-1-butene, their utility for the asymmetric reduction of 51 was investigated. The hydrogenations were all carried out with added triethylamine according to the general procedure reported by Knowles and Sabacky.[44] The results are compiled in Table 4.

Neomenthyldiphenylphosphine was again observed to be as effective as those ligands which were chiral at phosphorus.

TABLE 4

ASYMMETRIC HOMOGENEOUS HYDROGENATION OF ATROPIC ACID WITH A RHODIUM CATALYST PREPARED FROM CHIRAL PHOSPHINES

Ligand	Atropic Acid Configuration	% e.e.
2-methylbutyldiphenylphosphine (26)	R	0.2
2-phenylbutyldiphenylphosphine (29)	S	2.4
3-phenylbutyldiphenylphosphine (33)	R	1.7
neomenthyldiphenylphosphine (44)	S	28.0[a]
phenylmethylpropylphosphine[b]		21.0
phenylmethyl-sec-butylphosphine[b]		15.0
phenylmethylisopropylphosphine[b]		17.5
phenylmethylcyclohexylphosphine[b]		3.0

(a) With 0.3 equivalents added phosphine.
(b) See reference 44.

Those ligands which contained one asymmetric carbon showed only a low stereoselectivity. While more data is desirable, it can be tentatively concluded that in using phosphines that are chiral at carbon and not phosphorus, those ligands which contain multiple centers of chirality are most effective.

The degree of asymmetric induction obtained in the hydrogenation of atropic acid with tris(neomenthyldiphenylphosphine)rhodium(I) chloride (52) prompted investigation of the reduction of other α,β unsaturated carboxylic acids. The results of this study are compiled in Table 5. Atropic, (E)-β-methylcinnamic and (E)-α-methylcinnamic acid were reduced with catalysts prepared from two different samples of neomenthyldiphenylphosphine, and different conditions were used in the two sets of experiments. In the first set, the acids were hydrogenated using a 50-1 substrate to catalyst

ratio and 0.3 equivalents of added neomenthyldiphenylphosphine. The optical purities of the resulting acids are given in parentheses in Table 5. The second set of hydrogenations were effected using a 100-1 substrate to catalyst ratio and no added phosphine. Within each set the results were reproducible.

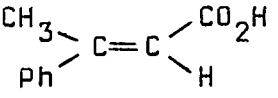
TABLE 5

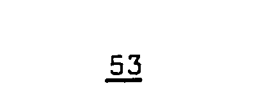
ASYMMETRIC HOMOGENEOUS HYDROGENATION
OF α,β UNSATURATED CARBOXYLIC ACIDS
WITH TRIS(NEOMENTHYLDIPHENYLPHOSPHINE)RHODIUM(I) CHLORIDE

Substrate	Configuration	% e.e.
atropic acid (51)	S	17 (28)[a]
(E)-β-methylcinnamic acid (53)	S	52 (61)[a]
(Z)-β-methylcinnamic acid (54)	R	20
(E)-α-methylcinnamic acid (56)	R	44 (52)[a]
(E)-α-phenylcinnamic acid (57)	S	12
itaconic acid (58)	R	6
citraconic acid (59)	-	0
mesaconic acid (60)	-	no reduction

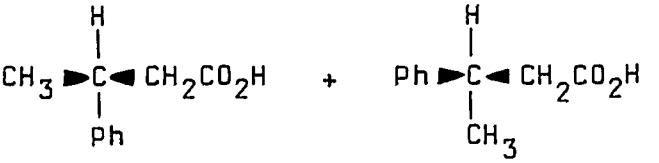
(a) With 0.3 equivalents added phosphine.

The hydrogenation of (E)-β-methylcinnamic acid (53) which has phenyl *trans* to carboxyl was an exceptionally stereoselective process. When the phenyl substituent was *cis* to the carboxyl group, as in (Z)-β-methylcinnamic acid (54), hydrogenation proceeded more slowly and the optical activity of the resulting 3-phenylbutanoic acid (55) was lower than it was with the E isomer (Equation 7).

(7) 

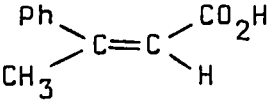


53

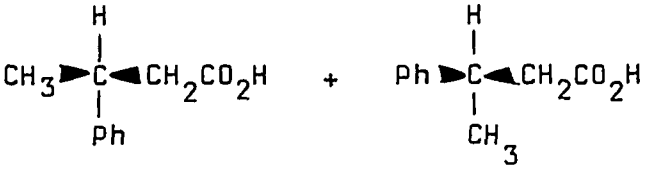


S-(+) 76%

R-(-) 24%



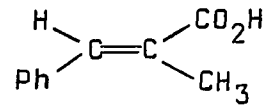
54



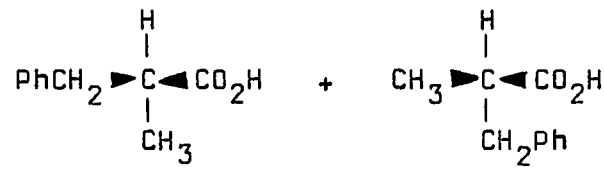
S-(+) 40%

R-(-) 60%

The hydrogenation of (E)-α-methylcinnamic acid (56) which has a trans phenyl-carboxyl relationship also proceeded with a high degree of asymmetric bias (Equation 8). The slightly lower optical yield obtained here compared with the reduction of 53 might be attributed to the presence of the

(8)  $\xrightarrow[H_2]{\underline{52}}$

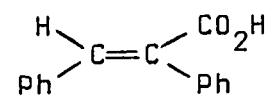
56



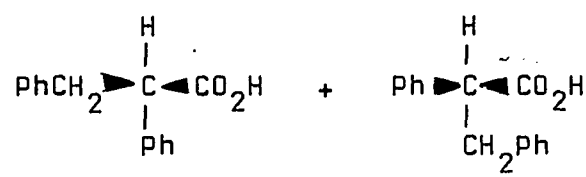
S-(+) R-(-)

28% 72%

methyl group at the α position. This is further exemplified in the reduction of (E)-α-phenylcinnamic acid (57) where the methyl of 53 has been replaced with a phenyl group (Equation 9).

(9)  $\xrightarrow[H_2]{\underline{52}}$

57



R-(-) S-(+)

44% 56%

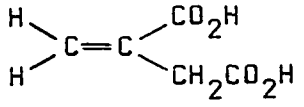
The 2,3-diphenylpropanoic acid obtained had an optical purity only one-third of that exhibited by 2-benzylpropanoic acid from the reduction of (E)-α-methylcinnamic acid (53).

The hydrogenation of itaconic acid (58) proceeded to give a quantitative yield of 2-methylsuccinic acid, which had a 6% enantiomeric excess of the R isomer. Under similar conditions mesaconic acid (60) was inert to hydrogenation and citraconic acid (59) afforded only 40% reduction. With a threefold increase in reaction time, the reduction of 59 was almost quantitative. Analysis of the resulting 2-methylsuccinic acid, however, showed that the reaction had proceeded without asymmetric induction.

When a sample of S-(+)-3-phenylbutanoic acid (65% e.e.) was carried through the hydrogenation sequence, the crude recovered acid had an apparent 63% e.e., but the distilled acid had a 65% e.e. of the S-(+) enantiomer. This experiment shows that the optical activity observed for the saturated carboxylic acids results entirely from an asymmetric reduction and not from subsequent asymmetric transformation (either racemization or enrichment) of the hydrogenated products. Furthermore, the slightly higher rotation observed for the distilled products is most probably due to the separation of impurities rather than to separation of the enantiomer in excess from racemate since one distillation raised the rotation to its original value. Moreover, simple distillation of optically active 3-phenylbutanoic acid does not change its rotation.

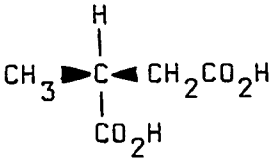
These results indicate that tris(neomenthyldiphenylphosphine)rhodium(I) chloride is a very effective catalyst for the asymmetric hydrogenation of α,β unsaturated

(10)



58

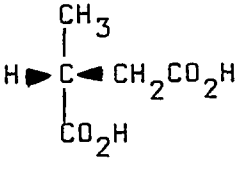
$\xrightarrow[H_2]{52}$



S-(-)

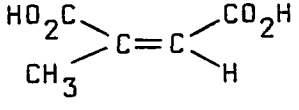
47%

+



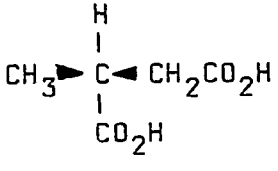
R-(+)

53%



59

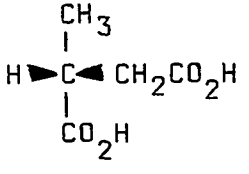
$\xrightarrow[H_2]{52}$



S-(-)

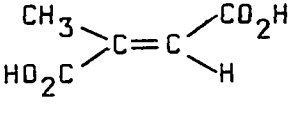
50%

+



R-(+)

50%

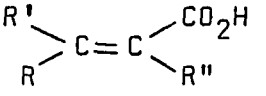


60

$\xrightarrow[H_2]{52}$

No Reduction

carboxylic acids. Furthermore, interpretation of the reduction of substituted acrylic acids using a model like 61 demonstrates some interesting trends. First, when R is a



61

large β substituent (53, 56) hydrogenation proceeds with considerable asymmetric induction. However, when R' is the large substituent at carbon-3 (54) the stereoselectivity is considerably reduced. A second important point is that as R" increases from hydrogen (53) to methyl (56) to phenyl (51, 57) hydrogenation proceeds with diminishing optical yield. Finally, with reference to 61, when carbon-2 is unsubstituted hydrogen is preferentially added from below the plane of the paper. Substitution of a methyl or phenyl group (R") at carbon-2, however, causes hydrogen transfer to occur preferentially from above the plane of the paper.

The purpose of this investigation was the development of a system for the asymmetric homogeneous hydrogenation of carbon-carbon double bonds. It was found that modification of the Wilkinson catalyst with chiral ligands gave such a system. It was further observed that phosphorus ligands chiral at carbon, and more accessible, were as effective as those which were chiral at phosphorus.

It remains for future investigators to determine if other homogeneous catalysts can be similarly modified or if

other substrates can be hydrogenated with asymmetric induction. The results of this thesis indicate that other ligands prepared from phosphines which contain multiple chiral centers should be studied. Furthermore, the result with N-ethyl-N-(α-methylbenzyl)diphenylphosphinamide suggests that other chiral phosphinamide and possibly phosphite ligands should be investigated.

EXPERIMENTAL

General

Methods

Melting Points: Melting points (mp) were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected.

Infrared Absorption Spectra: All infrared (ir) spectra were obtained using a Perkin-Elmer Model 337 grating spectrophotometer. The spectra of liquids were obtained as films between salt plates. The spectra of solids were obtained as mulls.

Nuclear Magnetic Resonance Spectra: All nuclear magnetic resonance (nmr) spectra were determined using a Varian Model A-60 Spectrometer.

Gas Liquid Partition Chromatography: Gas liquid partition chromatography (glpc) analyses were conducted using a Varian Aerograph 90-P Chromatograph. Phosphines were analyzed on a 5' x 1/4" 3% Silicone SE-30 on Varaport 30 column, 235°, flow rate 50 ml/min, retention times (R.T.) are relative to an internal benzene standard. 2-Phenyl-1-butene and 2-phenylbutane were analyzed on a 10' x 1/4" 5% STAP on Chromosorb G-AW/DMCS column, 150°, flow rate 50 ml/min, and had retention times of 432 sec and 240 sec, respectively, relative to air.

Optical Rotation Data: Optical rotations were determined on a Carl Zeiss Photoelectric Precision Polarimeter, 0.005^{o}, equipped with a mercury vapor 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 obtained 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, compounds 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 refluxed over and distilled from calcium hydride.

Benzene was dried by distillation (80^{o}). Any water was removed as an azeotropic forerun (69^{o}).

Pyridine was dried by refluxing over, and distilling from, potassium hydroxide pellets. The distilled product was stored over 4-A molecular sieves.

Hydrogenations: 2-Phenyl-1-butene was hydrogenated using a Parr model 3911 Low Pressure Hydrogenator. The unsaturated carboxylic acids were hydrogenated using a Parr model 4501 Medium Pressure Hydrogenator.

Preparation of Phosphines

Lithium Diphenylphosphide: This compound was prepared, under an atmosphere of nitrogen, from diphenylphosphinous chloride and lithium ribbon in anhydrous THF.[63,64]

S-(+)-2-Chlorooctane (39): Thionyl chloride (6g, 84mmol) was added slowly, with stirring, to a solution of (-)-2-octanol, (10g, 72mmol) α_D^{30} -6.69 (neat, l=1.0), 83% e.e. of the R isomer[65], in dry pyridine (6g, 77mmol). The temperature was maintained between 0 and -10°. The thick yellow paste which formed was stirred one hour with continued cooling before it was allowed to warm to room temperature. The reaction mixture was then heated at 80° for 5 hr to decompose the chlorosulfite ester. The flask was cooled and water (50ml) and ether (50ml) were added. The ethereal layer was drawn off and saved, and the aqueous layer was extracted with additional ether (2x50ml). The ethereal solutions were combined, washed with water (2.50ml), 5% sodium bicarbonate (1x50ml) and water (1x50ml), were dried ($MgSO_4$) and were concentrated. Distillation of the residue gave 5g (44%) of (+)-2-chlorooctane: bp 68-9° (22mm), α_D^{30} +27.96 (neat, l=1.0), 86% e.e. of the S isomer[66], nmr spectrum number 11128, ir spectrum number 16692. A glpc analysis gave only one peak (R.T. 4 min) (10' x 1/4" 10% Carbowax 20M on Chromosorb W, 110°, 120 ml/min).

(+)-2-Octyldiphenylphosphine (37): A solution of lithium diphenylphosphide (27mmol) in THF (50ml) was added,

dropwise, under a nitrogen atmosphere to a solution of (+)-2-chlorooctane (4g, 27mmol), α_D^{30} +27.96, 86% e.e. of the S isomer[66], in dry THF (25ml). After stirring an additional 2 hr the reaction mixture was concentrated and the residue was poured into water (50ml) and extracted with ether (4x25ml). The ethereal extracts were combined, washed with water (50ml), dried ($MgSO_4$) and concentrated. The residue was distilled to give 3.0g (37%) of (+)-2-octyldiphenylphosphine as a clear liquid bp 174-5° (0.6mm), $[\alpha]_D^{30}$ +19.67 (c 19.62, benzene), nmr spectrum number 5473, ir spectrum number 7960. A glpc analysis showed the compound to contain 90% phosphine (R.T. 72 sec) and 10% phosphine oxide (R.T. 180 sec).

R-(+)-N-(α-methylbenzyl)acetamide (42): R-(+)-α-Methylbenzylamine (30g, 0.25mol), α_D^{23} +35.73 (neat, l=0.5) 93% e.e. of the R isomer[67] was added slowly, with stirring, to acetic anhydride (41g, 0.4mol) which had been cooled to 10°. The temperature was maintained below 30°. The reaction mixture was then stirred 4 hr at room temperature and an additional 1.5 hr on a steam bath. When water (200ml) was slowly added, an oil formed, but it solidified upon cooling. Recrystallization from cyclohexane (4ml/g) provided 32g (78%) of R-(+)-N-(α-methylbenzyl)acetamide as white irridescent plates: mp 102-4°, $[\alpha]_D^{29}$ +129.4 (c 8.81, chloroform), nmr spectrum number 1119, ir spectrum number 2442.

R-N-Ethyl-α-methylbenzylamine (43): (+)-1-Methyl-

benzylacetamide (40g, 0.25mol), $[\alpha]_D^{29}$ +129.4 (c 8.81, chloroform) in dry THF (150ml) was slowly added to a stirred suspension of lithium aluminum hydride (5.6g, 0.15mol) in THF (100ml). The reaction mixture was then heated under reflux for 10 hr, cooled and hydrolyzed by successive additions of 50ml of water, 25ml of 15% sodium hydroxide and another 50ml of water. The inorganics were removed by filtration and the filtrate was dried ($MgSO_4$) and concentrated. The residue was distilled to afford 17g (46%) of R-N-ethyl-α-methylbenzylamine: bp 96-7° (18mm).

R-(+)-N-Ethyl-N-(α-methylbenzyl)diphenylphosphinamide (40): A solution of diphenylphosphinous chloride (11g, 0.05mol) in anhydrous ether (50ml) was added with stirring, under a nitrogen atmosphere, to a solution of R-N-ethyl-α-methylbenzylamine (16g, 0.1mol) in anhydrous ether (100ml). Stirring was continued for 0.5 hr, then the solution was filtered to remove the amine hydrochloride, and concentrated to give a white solid. Two recrystallizations from hot acetone-water gave 3.8g (22%) of R-(+)-N-ethyl-N-(α-methylbenzyl)diphenylphosphinamide: mp 74-5°, $[\alpha]_D^{25}$ +85.55 (c 10.66, benzene), nmr spectrum number 1121, ir spectrum number 3465. A glpc analysis gave only one peak (R.T. 156 sec).

R-(-)-3-Phenylbutyldiphenylphosphine (33): A solution of (-)-1-bromo-3-phenylbutane* (21.3g, 0.1mol), α_D^{26} -94.4 (neat, l=1), 90% e.e. of the *R* isomer[68] in THF

* Prepared from R-(-)-3-phenyl-1-butanol, see reference 79.

(50ml) was added slowly to a solution of lithium diphenylphosphide (0.1mol) in THF (100ml) and the reaction mixture was stirred overnight. The solvent was removed and the residue was poured into water (200ml). The aqueous mixture was extracted with ether (4x100ml). The ethereal extracts were combined, washed with water (1x50ml), dried ($MgSO_4$) and concentrated. Distillation of the residue afforded 13g (41%) of R-(-)-3-phenylbutyldiphenylphosphine as a clear liquid: bp 196-200° (0.8mm), $[\alpha]_D^{29}$ -39.94 (c 10.00, benzene), nmr spectrum number 9496, ir spectrum number 16694. A glpc analysis showed 99% phosphine (R.T. 180 sec) and 1% phosphine oxide (R.T. 384 sec).

S-(+)-2-Methylbutyldiphenylphosphine (26): A solution of (+)-1-chloro-2-methylbutane* (20g, 0.19mol), α_D^{31} +1.29 (neat, l=0.5), 90% e.e. of the S isomer[69] in THF (50ml) was slowly added to a solution of lithium diphenylphosphide (0.19mol) in THF (200ml). The reaction mixture was stirred overnight, concentrated, and the residue was poured into water (200ml). Ethereal extracts (3x100ml) of the aqueous mixture were dried ($MgSO_4$) and concentrated. The residue was distilled to afford 26g (54%) of S-(+)-2-methylbutyldiphenylphosphine: bp 149-50° (1.0mm), $[\alpha]_D^{31}$ +41.53 (c 19.40, benzene), nmr spectrum number 9455, ir spectrum number 10195. A glpc analysis showed 99% phosphine (R.T. 36 sec) and 1% phosphine oxide (R.T. 84 sec).

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* Prepared from S-(-)-2-methyl-1-butanol by R. W. Ridgway.

S-(+)-1-Chloro-2-phenylbutane (32): Thionyl chloride (16.6g, 0.14mol) was added slowly, with stirring, to a solution of (+)-2-phenyl-1-butanol*, (19.5g, 0.13mol), α_D^{27} +16.2 (neat, l=0.5), 97% e.e. of the S isomer[70], in dry pyridine (10.8g, 0.14mol). The temperature was maintained between 0° and -10°. The thick yellow paste which formed was stirred one hour with continued cooling and then it was heated at 80° for 1.5 hr. The reaction mixture was cooled, the upper layer of crude chloride was decanted, and the bottom layer was dissolved in water and extracted with ether. The upper layer and the ethereal extracts were combined and washed successively with 10% HCl, water, 5% $NaHCO_3$ and water. The ether solution was dried ($MgSO_4$), concentrated, and distilled giving 16.7g (80%) of (+)-1-chloro-2-phenylbutane: bp 51-3° (0.4mm), α_D^{27} +5.78 (neat, l=0.5), 97% e.e. of the S isomer[70], nmr spectrum number 11176, ir spectrum number 3782. A glpc analysis gave only one peak (R.T. 264 sec) (10' x 1/4" 5% STAP on Chromosorb G-AW/DMCS column, 210°, flow rate 60 ml/min).

S-(+)-2-Phenylbutyldiphenylphosphine (29): A solution of lithium diphenylphosphide (30mmol) in THF (30ml) was added, slowly, under a nitrogen atmosphere to a solution of (+)-1-chloro-2-phenylbutane (5g, 30mmol), 97% e.e. of the S isomer, in THF (20ml). After stirring an additional 2 hr,

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* Prepared from S-(+)-2-phenylbutanoic acid by R. A. Sakash.

the reaction mixture was concentrated and the residue poured into water and extracted with ether. The ethereal extracts were combined, dried ($NaSO_4$) and concentrated. The residue was distilled to give 4.9g (52%) of (+)-2-phenylbutyldiphenylphosphine: bp 173-5° (0.2mm), $[\alpha]_D^{32}$ +7.43 (c 20.09, benzene), nmr spectrum number 7345, ir spectrum number 16693. A glpc analysis showed 99% phosphine (R.T. 180 sec) and 1% phosphine oxide (R.T. 420 sec).

(-)-Menthyl Chloride (46): Menthyl chloride was prepared by the method of Smith and Wright[71] from zinc chloride (190g, 2.8mol) concentrated hydrochloric acid (246ml, 3.2mol of HCl), and (-)-menthol (156g, 1.0mol) $[\alpha]_D^{25}$ -49.3 (c 10.33, ethanol). The undistilled chloride 155g (90%) was used immediately.

Neomenthyldiphenylphosphine (44): A solution of (-)-menthyl chloride (34.8g, 0.2mol) in THF (50ml) was added in one portion, under a nitrogen atmosphere to a solution of lithium diphenylphosphide (0.2mol) in THF (200ml). After refluxing for 24 hr, the reaction mixture was concentrated and the residue extracted with dry pentane. The pentane extracts were concentrated and the residue distilled (0.2mm) to give fraction 1, 17g, bp 50-55°; fraction 2, 8.3g, bp 125-6°; and fraction 3, 11.0g, bp 164-8°. A glpc analysis showed fraction 1 to be diphenylphosphine (R.T. 12 sec), fraction 2 to be 4-hydroxybutyldiphenylphosphine (R.T. 60 sec) and fraction 3 to be 60% 4-hydroxybutyldiphenylphosphine, 35% neomenthyl-

diphenylphosphine (R.T. 144 sec) and 5% neomenthyldiphenylphosphine oxide (R.T. 288 sec). Fraction 3, which was a wax-like substance, was triturated with pentane and the pentane concentrated to give a white solid. This solid was washed with cold pentane, dissolved in pentane and precipitated by concentration to give 2g (3%) neomenthyldiphenylphosphine, as a white solid, mp 169-73°. A glpc analysis of this solid showed 96% neomenthyldiphenylphosphine and 4% neomenthyldiphenylphosphine oxide. As this compound is extremely sensitive to oxidation, it was used without further purification and characterization was accomplished as the phosphine oxide: mp 214-15°, $[\alpha]_D^{28}$ +51.7 (c 1.55, ethanol), nmr spectrum number 10865, ir spectrum number 16594.

In an attempt to increase the yield of phosphine, the following variations of the preceeding procedure were used. Menthyl bromide and menthyl tosylate were each allowed to react with lithium diphenylphosphide using the conditions described for the reaction with menthyl chloride. In both cases a glpc analysis of the undistilled product showed diphenylphosphine and 4-hydroxybutyldiphenylphosphine but no neomenthyldiphenylphosphine or neomenthyldiphenylphosphine oxide. In an attempt to eliminate contamination from 4-hydroxybutyldiphenylphosphide, which results from addition of the lithium diphenylphosphide to tetrahydrofuran, other solvent systems were tried. It was found that lithium diphenylphosphide was not readily prepared in other solvents, but the phosphide (0.1mol) could be prepared in a small

amount of THF (50ml) and then a higher boiling solvent added (300-400ml) and the THF removed by distillation. Menthyl chloride (0.1mol) was then added and the reaction conducted as previously described. When benzene was used as the higher boiling solvent, a glpc analysis of the undistilled reaction mixture showed diphenylphosphine (78%), 4-hydroxybutyldiphenylphosphine (4%), neomenthyldiphenylphosphine (12%) and neomenthyldiphenylphosphine oxide (4%). Distillation, bp 166-8^{o} (0.2mm), gave 2g of product that contained 4-hydroxybutyldiphenylphosphine (5%), neomenthyldiphenylphosphine (89%) and neomenthyldiphenylphosphine oxide (6%). When the same reaction was repeated using xylene as solvent, a glpc analysis of the undistilled product showed only diphenylphosphine.

Substrates for Asymmetric Hydrogenation Experiments

Atropic Acid (51): Ethyl oxalate (90g, 0.62mol) and ethyl phenylacetate (82.0g, 0.5mol) were successively added to sodium ethoxide (from 11.5g sodium) in benzene (200ml). After stirring for 0.5 hr the reaction mixture, which solidified, was set aside for 8 hr. The solid was collected by suction filtration, washed well with ether and acidified to Congo Red. The acidic solution was extracted with ether (3x150ml) and the ethereal extracts were dried ($MgSO_4$), and concentrated. To the residual oil was added 37% aqueous formaldehyde (70ml, 0.87mol) and water (200ml). The reaction mixture was then cooled in an ice bath and a solution of potassium carbonate (40g, 0.29mol) in water (75ml) was slowly

added to the stirred solution. After stirring 2 hr at room temperature, the crude ethyl atropate, which separated as an oil, was extracted with ether. The ethereal extracts were washed with water, dried ($MgSO_4$) and concentrated. The residue was distilled, bp 127-30° (15mm) to give 47g (53%) of ethyl atropate.

The ester was saponified by refluxing 4 hr with sodium hydroxide (40g, 1.0mol) and water (300ml). The basic mixture was acidified and the atropic acid was collected by filtration. Recrystallization from hot ethanol provided 38g (48%) of atropic acid as white crystals: mp 106-7° (lit[72] 106-7°), nmr spectrum number 11175, ir spectrum number 15013.

(E)-β-Methylcinnamic Acid (53): Ethyl-3-hydroxy-3-phenylbutanoate was prepared by the Reformatsky reaction[73] from acetophenone (60g, 0.50mol), ethyl bromoacetate (90g, 0.54mol), zinc metal (35g, 0.54g-atom of No. 10 mesh) and dry benzene (300ml). The crude ester was not purified but immediately dehydrated by refluxing with benzene (200ml) and phosphorus oxychloride (2ml) in a Dean-Stark apparatus until no more water was collected. The crude unsaturated ester was saponified by heating under reflux with potassium hydroxide (48g, 0.86mol) and water (200ml) for 6 hr. The mixture was washed with ether and acidified to provide a crude mixture of acids. Recrystallization from carbon disulfide (2ml/g) gave 33g (41%) of (E)-β-methylcinnamic acid as white crystals: mp 96-97.5° (lit[73] 98°), nmr spectrum number 10021, ir spectrum number 14983.

(Z)-β-Methylcinnamic Acid (54): (E)-β-Methylcinnamic acid was dissolved in benzene (200ml), and irradiated in a quartz tube for 24 hr in a "Srinivasen" type photochemical reactor using a 2537 Å light source (128 watt). The solvent was concentrated and the residue was recrystallized twice from carbon disulfide (6ml/g) to give 5g (50%) of (Z)-β-methylcinnamic acid as white prisms: mp 131-2° (lit[73] 131-2°), nmr spectrum number 11174.

Triphenylmethylphosphonium Iodide: Methyl iodide (156g, 1.1mol) was slowly added to a stirred solution of triphenylphosphine (272g, 1.0mol) in benzene (1000ml). The temperature was maintained below 35°. After stirring 3 hr at room temperature and 1 hr at 0°, the phosphonium salt, which had precipitated, was collected and air dried. The white solid was then dried 4 hr in a heated vacuum desiccator (75°, 0.2mm) to give 357g (89%) of triphenylmethylphosphonium iodide, mp 181-3°.

2-Phenyl-1-butene (48): A solution of n-butyllithium* in hexane (160ml of a 1.5M solution) was slowly added, under nitrogen, to a stirred solution of triphenylmethylphosphonium iodide (93g, 0.23mol) in ether (1000ml). The temperature was maintained below 10°. After stirring 2 hr at room temperature, a solution of propiophenone (25g, 0.18mol) in ether (50ml) was slowly added. After refluxing 4 hr, the reaction

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* A gift from Foote Mineral Company. Appreciation expressed to Dr. O. F. Beumel for arranging the gift.

mixture was set aside for 10 hr. The triphenylphosphine oxide, which precipitated, was removed by filtration and the filtrate was washed with water (2x500ml), dried ($MgSO_4$), and concentrated. The residue was distilled to give 11g (50%) of 2-phenyl-1-butene: bp 90-2° (40mm), nmr spectrum number 1120, ir spectrum number 16794. A glpc analysis showed only one peak.

Hydrogenations

μ-Dichlorotetraethylenedirhodium(I) (49): This compound was prepared by bubbling ethylene through a solution of rhodium trichloride trihydrate (5g, 20mmol) in water (10ml) and methanol (125ml) according to the procedure of Cramer[74]. The complex (3.0g, 41%) was obtained as a brick-red solid and was stored in a desiccator at 5°.

General Procedure For The Hydrogenation Of Unsaturated Carboxylic Acids With The Tris(neomenthyldiphenylphosphine)rhodium(I) Chloride Catalyst.

The catalyst was prepared by dissolving neomenthyldiphenylphosphine (0.0615g, 0.19mmol) and μ-dichlorotetraethylenedirhodium(I) (0.0120g, 0.031mmol) in 1:1 benzene - 95% ethanol (100ml). The yellow solution was filtered into the medium pressure hydrogenator and prereduced for 1 hr at 60 psi. The unsaturated acid (0.8-1.4g, 6.2mmol) and triethylamine (0.1g, 1.0mmol) were added and hydrogenation was effected at 60°C and 300 psi. After 24 hr the solvent was

concentrated, the residual oil was extracted with 5% sodium hydroxide (50ml) and the basic extract was filtered through Celite to remove the catalyst. The filtrate was acidified with 10% hydrochloric acid and extracted with ether. The ethereal extracts were dried ($MgSO_4$) and concentrated to afford the crude saturated acid. Rotations of solid products were taken on the crude material; rotations were taken on liquids after vacuum distillation. Purity was determined by nuclear magnetic resonance spectrometry.

Hydrogenation of Atropic Acid (51): Hydrogenation of atropic acid gave a quantitative yield of 2-phenylpropanoic acid. After distillation, bp 93-4° (0.25mm), an 82% yield of (+)-2-phenylpropanoic acid was obtained: $[\alpha]_D^{25}$ +11.91 (c 8.06, chloroform), 17% e.e. of the S isomer based on a maximum $[\alpha]_D^{25}$ of -76.1,[75] nmr spectrum number 10277.

Hydrogenation of (E)-β-Methylcinnamic Acid (53): Hydrogenation of (E)-β-methylcinnamic acid gave a quantitative yield of 3-phenylbutanoic acid. After distillation, bp 100-2° (0.3mm), an 80% recovery of (+)-3-phenylbutanoic acid was obtained: α_D^{25} +29.56 (neat, l=0.5), 52% e.e. of the S isomer based on a maximum α_D^{25} of -56.5,[68] nmr spectrum number 10276.

Hydrogenation of (Z)-β-Methylcinnamic Acid (54): After 24 hr (Z)-β-methylcinnamic acid was only 20% reduced, nmr spectrum number 10325. A second hydrogenation of (Z)-β-methylcinnamic acid for 144 hr afforded a quantitative yield of (-)-3-phenylbutanoic acid, $[\alpha]_D^{25}$ -11.51 (c 10.08,

benzene). After distillation, bp 106-7° (0.4mm) an 80% recovery of (-)-3-phenylbutanoic acid was obtained: $[\alpha]_D^{25}$ -11.35 (c 10.20, benzene), 20% e.e. of the R isomer based on a maximum $[\alpha]_D^{20}$ of -58.5,[68] nmr spectrum number 11136.

Hydrogenation of (E)-α-Methylcinnamic Acid (56): Hydrogenation of (E)-α-methylcinnamic acid afforded a quantitative yield of 2-benzylpropanoic acid, $[\alpha]_D^{25}$ -11.86 (c 10.43, benzene). After distillation, bp 108-9° (0.35mm), an 80% recovery of (-)-2-benzylpropanoic acid was obtained: $[\alpha]_D^{25}$ -11.94 (c 10.68, benzene), 44% e.e. of the R isomer[76] based on a maximum $[\alpha]_D^{20}$ of +27.06,[77] nmr spectrum number 10251.

Hydrogenation of (E)-α-Phenylcinnamic Acid (57): Hydrogenation of (E)-α-phenylcinnamic acid afforded a quantitative yield of (+)-2,3-diphenylpropanoic acid: $[\alpha]_D^{25}$ +17.0 (c 4.20, benzene), 12% e.e. of the S isomer based on $[\alpha]_D^{20}$ +140.8,[76] nmr spectrum number 10274.

Hydrogenation of Itaconic Acid (Methylenesuccinic Acid) (58): Hydrogenation of itaconic acid afforded a quantitative yield of (+)-2-methylsuccinic acid: $[\alpha]_D^{25}$ +0.95 (c 10.50, absolute ethanol), 5.6% e.e. of the R isomer based on a maximum $[\alpha]_D^{20}$ of +17.09,[78] nmr spectrum number 10324.

Hydrogenation of Citraconic Acid (Methylmaleic Acid) (59): After 24 hr citraconic acid was only 40% reduced, nmr spectrum number 10313. A second hydrogenation of citraconic acid for 72 hr afforded an 88% yield of crude material. Nmr

spectrum number 10347 showed the material to be 95% 2-methylsuccinic acid and 5% citraconic acid. The material had no optical rotation.

Attempted Hydrogenation of Mesaconic Acid (Methylfumaric Acid) (60): After 24 hr an nmr spectrum (number 11122) of the acid residue showed only unreacted mesaconic acid.

General Procedure For The Hydrogenation Of Atropic Acid (51) With Tris(alkyldiphenylphosphine)rhodium(I) Chloride Catalysts.

The catalysts were prepared by dissolving the chiral alkyldiphenylphosphine (0.187-0.243g, 0.75mmol) and μ-dichlorotetraethylenedirhodium(I) (0.048g, 0.125mmol) in 1:1 benzene - 95% ethanol (200ml). The solution was filtered into a medium pressure hydrogenator and prereduced for 2 hr at 60 psi. Atropic acid (2.0g, 13.5mmol) and triethylamine (0.3g, 3.0mmol) were added and hydrogenation was carried out at 60°C and 300 psi. After 18 hr the solvent was concentrated and the residual oil was extracted with 10% sodium hydroxide (50ml). The basic extract was filtered through Celite and then acidified with 10% hydrochloric acid. The crude 2-phenylpropanoic acid was extracted with ether and the ethereal solution was dried ($MgSO_4$), and concentrated. The residue was distilled under reduced pressure. Rotations were taken neat on the distilled 2-phenylpropanoic acid and

compared with a maximum α_D^{27} of +94.0.[79] Purity was determined by nuclear magnetic resonance spectrometry.

Hydrogenation of Atropic Acid with Tris(neomenthyldiphenylphosphine)rhodium(I) Chloride: A 70% yield of (+)-2-phenylpropanoic acid was obtained: bp 97-8° (0.20mm), α_D^{24} +26.5 (neat, l=0.5) 28% e.e. of the S isomer, nmr spectrum number 11113.

Hydrogenation of Atropic Acid with Tris(2-phenylbutyldiphenylphosphine)rhodium(I) Chloride: A 60% yield of (+)-2-phenylpropanoic acid was obtained: bp 97-8° (0.25mm), α_D^{25} -2.29 (neat, l=0.5) 2.4% e.e. of the S isomer, nmr spectrum number 11112.

Hydrogenation of Atropic Acid with Tris(3-phenylbutyldiphenylphosphine)rhodium(I) Chloride: A 75% yield of (-)-2-phenylpropanoic acid was obtained: bp 99-100° (0.35mm), α_D^{25} -1.64 (neat, l=0.5) 1.7% e.e. of the R isomer, nmr spectrum number 11116.

Hydrogenation of Atropic Acid with Tris(2-methylbutyldiphenylphosphine)rhodium(I) Chloride: A 60% yield of (-)-2-phenylpropanoic acid was obtained: bp 99-100° (0.30mm), α_D^{26} -0.14 (neat, l=0.5) 0.2% e.e. of the R isomer, nmr spectrum number 11114.

General Procedure For The Hydrogenation Of 2-Phenyl-1-butene (48) With Chiral Catalysts

Except as noted, the catalyst was prepared by

dissolving the chiral phosphine (0.374-0.486g, 1.5mmol) and μ-dichlorotetraethylenedirhodium(I) (0.096g, 0.25mmol) in 1:1 benzene - absolute ethanol (100ml). The solution was filtered into a hydrogenation flask and prereduced for 0.5 hr. 2-Phenyl-1-butene (3.0g, 22mmol) was added and the solution was hydrogenated at room temperature. The solution was then concentrated and pentane was added to precipitate most of the catalyst. The pentane solution was concentrated and the residue was distilled. In every case glpc analysis of the distilled samples of 2-phenylbutane showed only one peak. Rotations were taken on the distilled liquid and % enantiomeric excess (% e.e.) was based on a maximum α_D^{20} of -24.3.[68]

Hydrogenation of 2-Phenyl-1-butene with Tris(2-octylphenylphosphine)rhodium(I) Chloride: The olefin was hydrogenated over a period of 4 days under 1 atm of hydrogen. A 67% yield of (-)-2-phenylbutane was obtained: bp 72-4° (22mm), α_D^{32} -0.12 (neat, l=0.5), 0.5% e.e. of the R isomer.

Hydrogenation of 2-Phenyl-1-butene with Tris(neomenthyldiphenylphosphine)rhodium(I) Chloride: The catalyst was prepared by dissolving the phosphine (0.243g, 0.75mmol) and rhodium chelate (0.048g, 0.125mmol) in 1:1 benzene - absolute ethanol (50ml). The olefin was hydrogenated over a period of 7 days under 1 atm of hydrogen. A 50% yield of (-)-2-phenylbutane was obtained: bp 66-8° (17mm), α_D^{21} -1.62 (neat, l=0.2), 6.6% e.e. of the R isomer.

Hydrogenation of 2-Phenyl-1-butene with Tris(2-phenylbutyldiphenylphosphine)rhodium(I) Chloride: The olefin was hydrogenated over a period of 24 hr under 1 atm of hydrogen. A 73% yield of (-)-2-phenylbutane was obtained: bp 64-6° (12mm), α_D^{28} -0.96 (neat, l=0.5), 4% e.e. of the R isomer.

Hydrogenation of 2-Phenyl-1-butene with Tris(N-ethyl-N-1-methylbenzyldiphenylphosphinamide)rhodium(I) Chloride: The olefin was hydrogenated for a period of 39 hr under 7 atm of hydrogen. A 67% yield of (+)-2-phenylbutane was obtained: bp 48-50° (6mm), α_D^{27} +0.28 (neat, l=0.5), 1.2% e.e. of the S isomer.

Hydrogenation of 2-Phenyl-1-butene with Tris(3-phenylbutyldiphenylphosphine)rhodium(I) Chloride: The olefin was hydrogenated for a period of 24 hr under 4 atm of hydrogen. A 70% yield of (-)-2-phenylbutane was obtained: bp 43-4° (5mm), α_D^{29} -0.09 (neat, l=0.5), 0.4% e.e. of the R isomer.

Hydrogenation of 2-Phenyl-1-butene with Tris(2-methylbutyldiphenylphosphine)rhodium(I) Chloride: The olefin was hydrogenated for a period of 24 hr under 4 atm of hydrogen. A 75% yield of (+)-2-phenylbutane was obtained: bp 42-3° (5mm), α_D^{29} +0.75 (neat, l=0.5), 3.1% e.e. of the S isomer.

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