Asymmetric Synthesis. Production of Optically Active Amino Acids by Catalytic Hydrogenation

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Received February 1, 1977

Abstract: The ligand (2*S*, 3*S*)-bis(diphenylphosphino)butane ((*S*,*S*)-chiraphos) has been prepared. The rhodium(I) complex of this phosphine acts as an efficient homogeneous hydrogenation catalyst at ambient temperature and pressure for α-*N*-acylaminoacrylic acids. This catalyst gives leucine and phenylalanine in essentially complete optical purity; alanine, DOPA, and tyrosine are obtained in 91, 83, and 92% optical purity, respectively.

The discovery that the $[Rh(Ph_3P)_3Cl]$ complex and related derivatives were efficient homogeneous hydrogenation catalysts for a range of olefin substrates[1] provided systems which could potentially be modified into asymmetric catalysts. Early attempts at using these modified systems for asymmetric hydrogenation provided interesting but mixed results;[2-5] the optical yields were generally low and were capricious in that apparently trivial changes in the substrates caused large changes in the optical yield and, in some cases, a switch in the sense of discrimination occurred. All of these initial attempts used unidentate phosphines, most with chiral phosphorus centers, others with an achiral phosphorus center, but with the chirality residing at the alkyl substituents of the phosphine.

Except for one case, which we discuss later, the rather modest optical yields obtained with these unidentate ligands are probably connected with their conformational lability when complexed to the rhodium atom. For reasons which we discussed in the previous paper,[6] this conformational lability tends to "wash out" the chiral preference of the coordinated (prochiral) substrate.

More recently, a number of catalytic systems incorporating chiral bidentate phosphine and phosphite ligands have been reported.[7-10] These generally give higher optical yields and, in one case,[10] very high optical yields were reported. While not having the same conformational freedom as the unidentate systems, the bidentate systems so far studied are all potentially highly flexible systems having, except for one case,[10] seven-membered chelate rings which, at least in principle, may adopt numerous conformations.

The purpose of this paper is to describe a bidentate phosphine ligand which, when coordinated to a metal atom, adopts a rigid, unique chiral conformation. Apart from this, two other factors were considered in designing this ligand. Firstly, its accessibility and ease of preparation and, second, its ability to give consistently high optical yields for a wide range of substrates. This latter demand is to some extent contradictory, for as the substrate and chiral catalyst approach a "lock and key" compatability, the range of acceptance for the two diminishes; that is, the substrate and catalyst become specific. Despite this, we describe a catalytic system, which, under ambient conditions, produces acylated amino acids in consistently high optical yields with turnover numbers which range from 3×10^{-2} to 6×10^{-4} s^{-1}, which gives two amino acids in essentially complete optical purity, and the chemical conversion is quantitative for all substrates.

1. Stereochemical Considerations

It is well known that saturated five-membered chelate rings adopt a puckered chiral conformation.[11] In the absence of C substitution and when the donor atoms are symmetrically substituted then such a ring rapidly interconverts from one chiral conformation to the other[12] (Figure 1). If, however, the aliphatic link is substituted and thereby an asymmetric carbon center is produced, the chelate ring may be fixed into a single, static chiral conformation by the requirement that the substituent be equatorially disposed. There is a further consequence arising from the fixed chirality of the ring; the substituents on the donor atoms are distinguished by the circumstance that these adopt fixed quasi-axial and -equatorial dispositions. Thus a chiral substituent transmits its chirality to the ring, which, in turn, disposes the donor atom substituents in such a way that the whole molecular framework is twisted into a single chiral conformation. A prochiral olefin coordinated to a metal incorporating such a ring system will therefore be discriminated largely by the chiral arrangement of the donor atom substituents despite the fact that the actual chiral center resides on a distant chiral carbon center. It is on these principles that we have chosen the chiral ligand, (2*S*,3*S*)-bis(diphenylphosphino)butane ((*S*,*S*)-chiraphos) (Figure 2), which is prepared from a readily available starting material and avoids the somewhat tedious procedures for preparing chiral phosphines.

2. Preparations

The method of preparation of the diphosphine is shown in Figure 3. Tosylation of (2*R*,3*R*)-butanediol proceeds quantitatively,[13] but the reaction between the ditosyl derivative and lithium diphenylphosphide can be troublesome unless appropriate conditions are maintained. The obvious complications associated with elimination and loss of configurational integrity through neighboring group participation tend to dominate in the reaction as the dilution and temperature are increased. Even at the optimum conditions devised, elimination and some loss of optical activity occurs; the isolated yield of pure (*S*,*S*)-chiraphos is 20–30%. The phosphine was separated from the side products of the reaction as an insoluble nickel(II) complex and then was obtained free of the metal by the action of cyanide ions. After two recrystallizations from ethanol, optically pure (*S*,*S*)-chiraphos was obtained as large white plates (mp 109 °C). The product is indefinitely stable as the solid, but is oxidized by air in solution.

Two catalytic precursors, [Rh((*S*,*S*)-chiraphos) (COD)]ClO_4 and [Rh((*S*=*S*)-chiraphos) (NBD)]ClO_4 (COD = 1,5-cyclooctadiene, NBD = norbornadiene), were isolated and characterized from the reaction[14]

$$[Rh(diene)(acac)] + (S,S)\text{-chiraphos} \xrightarrow[THF]{HClO_4} [Rh((S,S)\text{-chiraphos})(diene)]ClO_4 + Hacac$$

or more expeditiously by the reaction[14]

$$[Rh(diene)_2]ClO_4 + (S,S)\text{-chiraphos} \rightarrow [Rh((S,S)\text{-chiraphos})(diene)]ClO_4 + diene$$

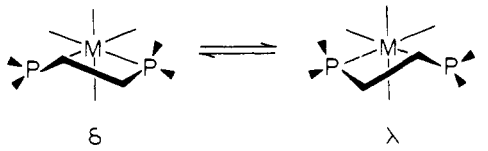


Figure 1. The chiral δ and λ conformations of a saturated five-membered chelate ring.

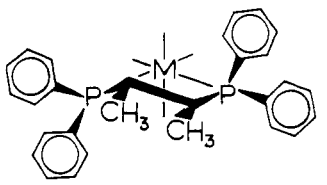


Figure 2. The preferred conformation of the (*S,S*)-chiraphos chelate ring.

Of the two diene complexes containing (*S,S*)-chiraphos, the more reactive derivative (NBD) was used for hydrogenation. This orange-red compound retains its catalytic properties indefinitely if it is kept at 0 °C in a sealed system under nitrogen. If left exposed to air at room temperature, it slowly loses its catalytic activity even though the appearance is not observably different. Catalytic activity ceases if the solvent contains peroxides or if it is exposed to oxygen.

3. Stereochemistry

Since the basis for the design of the (*S,S*)-chiraphos ligand assumed that the presence of methyl groups would fix the conformation of the complexed ligand, it was important to establish that this is so. A single crystal x-ray (absolute) structural determination[15] of the [Rh((*S,S*)-chiraphos)(COD)]ClO_4·THF complex shows that the total structure is essentially that predicted; the chiral centers are *S* and the methyl groups are equatorially disposed to give a δ-chelate ring (Figure 2).

That this conformational structure of the phosphine ligand persists in solution is supported by the following evidence. The proton NMR spectra of the [Rh((*S,S*)-chiraphos)(COD)]$^+$ and [Rh((*S,S*)-chiraphos)(NBD)]$^+$ ions show resonances which are broadened by long- and short-range coupling from phosphorus, rhodium, and hydrogen nuclei, but, in both cases, the vinylic protons of the dienes occur as broad, equally intense doublets at around δ 5. If it is assumed that the chemical shifts of the four vinylic protons are differentiated principally by the phenyl rings of the coordinated phosphine, then the observation of a doublet for the vinylic diene protons supports the view that the (*S,S*)-chiraphos chelate ring is static (on an ^1H NMR time scale), for, in the static case, the phenyl rings of each phosphorus atom are interchanged by a twofold axis. It follows that if it is the methyl groups which maintain the conformation of the (*S,S*)-chiraphos chelate ring, then their replacement by hydrogen atoms should produce a fluxional ring system (Figure 1) and the vinylic protons of the dienes should become equivalent on a ^1H NMR time scale. Indeed, the vinylic proton resonances of each of the [Rh(diphos)(COD)]$^+$ and [Rh(diphos)(NBD)]$^+$ ions (diphos = 1,2-bis(diphenylphosphino)-ethane) show a single broad vinylic proton resonance, which occurs at a chemical shift between the doublets observed for the corresponding (*S,S*)-chiraphos complexes (Figure 4). While this NMR argument does not constitute proof for the structure in solution, it, together with the crystal structure, provides plausible support for our initial assumptions.

4. Hydrogenation

When [Rh((*S,S*)-chiraphos)(NBD)]ClO_4 is suspended in either ethanol, tetrahydrofuran, benzene, dioxane, or ethanol-water mixtures and placed under an atmosphere of hydrogen, the orange-red complex rapidly dissolves to give a straw-yellow solution which probably contains the [Rh((*S,S*)-chiraphos)$(H)_2$(solvent)$_2$]$^+$ ion.[16] It is this species which is capable of hydrogenating a variety of olefins under catalytic conditions.

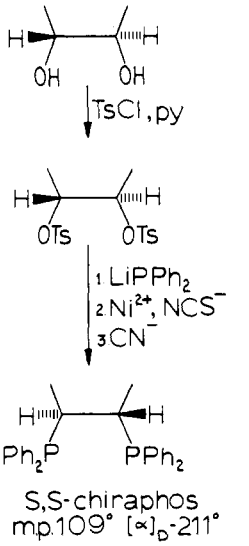


Figure 3. An outline of the preparation of (*S,S*)-chiraphos.

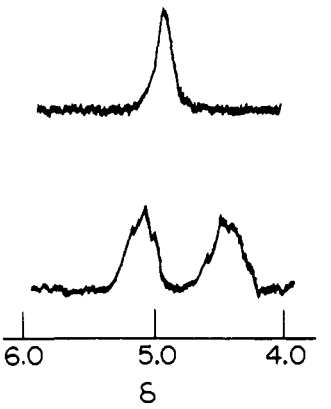
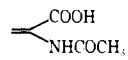
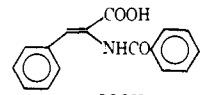
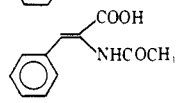
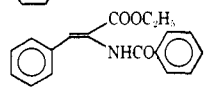
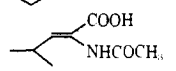
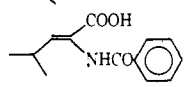
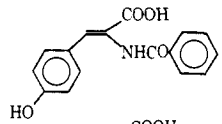
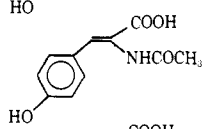
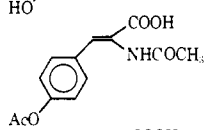
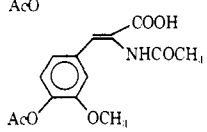


Figure 4. ^1H NMR spectra of [Rh(diphos)(COD)]ClO_4 (upper spectrum) and that of [Rh((*S,S*)-chiraphos)(COD)](ClO_4·THF (lower spectrum) in $CDCl_3$ at 30 °C. The resonances due to the vinylic protons of COD in the two cases are shown.

We have chosen to investigate the asymmetric hydrogenation of a series of α-*N*-acylaminoacrylic acids, since these are converted to *N*-acylamino acids. All the α-*N*-acylaminoacrylic acids were prepared[17] by methods which exclusively give the *Z* configuration. The catalyst to substrate ratio was usually 1:100, but hydrogenation proceeded even at a ratio of 1:1000 although, under these conditions, some care is needed to exclude traces of oxygen. For a 100:1 ratio of substrate to catalyst, the hydrogenation time for the present substrates spanned 45 min for α-acetamido-β-isopropylacrylic acid and 1 day for α-benzamido-β-(*p*-hydroxyphenyl)acrylic acid under 1 atm of hydrogen at 25 °C.

Since the optical yields we report are exceptionally high, we have taken some care to ensure that the correct rotations for the products were used. For this purpose we have prepared all the pertinent acylated amino acids as optically pure crystals. The values for the optical rotations are collected in the Experimental Section; most agree with comparable reported values, but some do not. In order to avoid enantiomer enrich-

Table I. Optical Yields (%)[a]

Amino acid	Substrate	Solvent THF	EtOH	Other
Alanine		88	91	
Phenylalanine		99	95	
		74	89	
		83		
Leucine		100	93	
		87	72	88 (benzene)
Tyrosine		92		84 (dioxane)
		80	88	91 (1:1, EtOH/H_2O) 78 (MeOH)
		74	88	
DOPA		80	83	

[a] All the acylated amino acids produced by (*S,S*)-chiraphos have the *R* configuration.

ment of the products, the following procedure was adopted. After the hydrogenation in THF, dioxane, or benzene was complete, the solvent was removed at 30 °C under reduced pressure, the residue was taken up in methanol, and ion-exchange resin (H^+ form) was added to remove the cationic catalyst. The resin was removed and the rotations were measured at five wavelengths. If the hydrogenation was done in ethanol or 50% ethanol–water, the resin was added directly to the reaction mixture and the rotations were taken in these solvents. The values were compared, in each case, with identically prepared solutions of the optically pure *N*-acylamino acids.[18] The results were reproducible to within 1%. The solutions from the products of hydrogenation were then evaporated to dryness, and the crystalline products were isolated and identified by NMR. Rotations of the isolated products tended to be higher than obtained by the above method, but the values depended on the optical purity and the nature of the product.

The results are given in Table I and are remarkable in a number of respects. Firstly, the (*S,S*)-chiraphos catalyst always gives *R*-amino acid derivatives, and second, the optical yields for all nine substrates are very high. Third, two amino acids, leucine and phenylalanine, are obtained optically pure within the detectability of our method; the other three, alanine, tyrosine, and DOPA, can be obtained in 91, 92, and 83% optical purity, respectively. Finally, the optical yield is sensitive to both the *N*-acyl and β-vinylic substituent and also to the solvent that is used. In free energy terms, the solvent variations

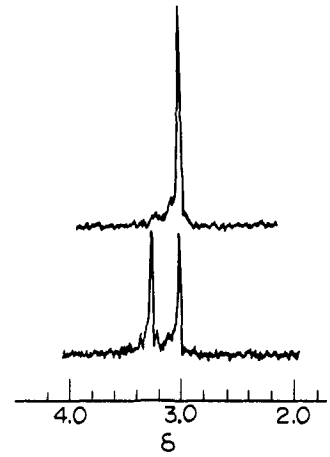


Figure 5. The ^1H NMR spectra, in the benzylic proton region, of *N*-benzoyl[(2*R*,3*R*)-$^2H_2$]phenylalnine (upper curve) and *N*-benzoyl[(2*R*,*S*,3*R*)-$^2H_2$]phenylalanine (lower curve) in D_2O containing NaOD at 30 °C. (Reference: HOD assuming δ 4.7 for this signal; concentration 100 mg in 0.4 mL.)

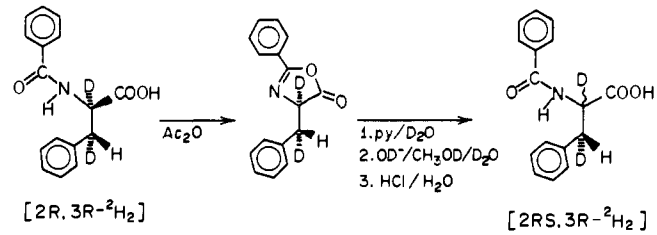


Figure 6. An outline of the method of racemizing the α-carbon center of *N*-benzoylphenylalanine via the oxazolone.

are quite large because of the exponential variation of ΔG with optical yield; for example, a change for 0 to 90% in optical yield is equivalent to a change from 90 to 100% optical yield in free energy terms.

5. Asymmetric Deuteration

The hydrogen transfer from the metal to the substrate in these soluble rhodium catalysts is a two-step process[19] involving first the addition of (formally) a hydride to the olefin to produce a rhodium alkyl bond, which is then (rapidly) cleaved by the insertion of (formally) a proton into the metal alkyl bond. Despite the two-step mechanism, the process appears to be completely stereospecific in that only cis hydrogen addition to the olefins is observed.[1] If this is so for the present system, then since phenylalanine and leucine are hydrogenated optically pure, it should be possible to generate pure chiral β-carbon centers by the addition of deuterium. These experiments were performed on the appropriate phenylalanine and leucine precursors in solvents which gave optically pure products. The phenylalanine case, which gives the simpler proton NMR, is described.

Figure 5 shows the NMR of the deuterated benzoylphenylalanine in the benzylic proton region (upper spectrum). The single benzylic proton signal of the deuterated material is consistent with stereospecific (cis) addition. This is confirmed by the two proton signals which are observed after the α center is racemized. The method of racemization is summarized in Figure 6 and proceeds smoothly under the appropriate conditions. Since the optical rotation of the deuterated benzylic center, after the α center has been racemized, is the same sign as that of the initial deuterated material (with a chiral α center), we have taken some care to ensure the validity of the value. Thus the deuterated material was subjected to several cycles of the α-center racemization process; the rotation of the crystallized product was checked after each cycle. After two

cycles, a constant rotation was observed which did not change upon fractional crystallization. The above chiral deuterium incorporations may prove to be a convenient method for obtaining these materials for the study of biogenesis.[20]

The leucine precursor is deuterated in an analogous way, and in this case, the deuterium appears only at the α and β centers. The γ-carbon atoms carry no deuterium, implying, as expected, that no double bond migration occurs during deuteration.

6. Discussion

The effectiveness of the present catalyst in asymmetric hydrogenation of the amino acid precursors is almost certainly connected with the conformational rigidity of the chelated diphosphine ligand. More precisely, it seems probable that it is the dissymmetric orientation of the phenyl groups, held so by the puckered chelate ring, which is the major source of diastereotopic interaction[21] with the prochiral substrates. These phenyl groups, although capable of somewhat restricted rotation about the phosphorus–carbon bonds, present the prochiral substrates with a dissymmetric array of potential interactions which cause one face of the olefinic substrates to be preferentially coordinated over the other by virtue of the interactions of the vinylic substituents with the phenyl groups. Once coordinated via the preferred olefinic face, the substrate is hydrogenated stereospecifically cis-endo; that is, the hydrogen adds to the olefinic face coordinated to the metal. This cis-endo addition of hydrogen is thus capable of producing chiral centers at both the α and β positions of the present substrates. Given the observation that (*R*)-*N*-acylamino acids are produced, and that cis-endo hydrogen transfer occurs, the preferred facial coordination of the olefinic substrates is known. It is not apparent from molecular models, however, that (*S,S*)-chiraphos in its assumed conformation should prefer coordination of the α-si,β-re face of the present substrates. The ambiguity arises, in part, because the substrates may adopt a number of (unknown) rotameric conformations which will have varying degrees of diastereotopic interaction. Unless the population average of these putative rotamers is known, or can be calculated, speculation on the intimate details of the discrimination is fanciful.

The situation is even more complicated than just the nature of the internal interactions for, as we have seen, quite large solvent effects are observed. Thus a complete description of the chiral discrimination would also require an examination of the dissymmetry of the immediate solvation sphere as well as the solvent-incorporated coordination sphere. Despite these effects, however, (*S,S*)-chiraphos gives (*R*)-*N*-acylamino acids in all cases studied and the optical yields are high irrespective of the solvent. Thus although the solvent effects are colligative and large in free energy terms, they are effects which are superimposed on the intrinsic (solvent free) bias of the chiral ligand.

The premise of the present work was that the rigidity of the (*S,S*)-chiraphos chelate ring would enhance the dissymmetric bias over comparable systems without this rigidity. We therefore comment briefly on a recent report[10] which observed that the rhodium(I) complex of 1,2-bis(*O*-anisylphenylphosphino)ethane asymmetrically hydrogenated some of the present substrates in exceptionally high optical yields. The chirality of the puckered five-membered chelate ring of this system is determined by the differences which may arise between the *O*-anisyl and phenyl groups. Experience suggests[22] that such a difference alone would not be capable of fixing the ring conformation to any practical degree of stability. If this is the case, then either this system has interactions with the substrates which are different from those of the present system or the conformation is stabilized by a special effect. In view of the present results and those obtained with nonrigid ligands,[23,24] we think it probable that the chelate ring chirality is fixed by coordination of the oxygen atoms of the *O*-anisyl groups. That is, the phosphine may act as a quadridentate ligand (or as a tridentate during hydrogenation), where the chirality is fixed by the oxygen atoms occupying the two apical octahedral positions in the preferred cis-α topology.[25,26] If this is so, this ligand and (*S,S*)-chiraphos bear a structural similarity upon coordination to rhodium(I). This coordination may also explain the effectiveness of certain unidentate *O*-anisyl phosphines.[4]

We believe that the success of the fairly simple ideas adumbrated in this paper is its most important observation for it may provide the basis for the rational design of other readily prepared ligands, the structures of which could be "tuned" to other prochiral substrates. The rationalization for the design of (*S,S*)-chiraphos and the optical yields obtained with the present substrates suggests that predictions about optical yields and the chirality of the products obtained with related phosphines can be made. For example, we have prepared (*R*)-prophos, (*R*)-1,2-bis(diphenylphosphino)propane, which according to the present rationalization should give the "natural" hand of the amino acids with similar optical yields to those obtained with (*S,S*)-chiraphos. Indeed it does.[27]

7. Experimental Section

A. Instrumentation. Routine ^{1}H NMR spectra were recorded with a Varian T60 spectrometer and optical rotations were obtained with a Perkin-Elmer 141 polarimeter.

B. Substrates. α-Acetamidoacrylic acid was purchased from Aldrich Chemical Co. The other substrates, α-acetamidocinnamic acid,[28] α-benzamidocinnamic acid,[29] ethyl α-benzamidocinnamate,[30] β-isopropyl-α-acetamidoacrylic acid,[31] β-isopropyl-α-benzamidoacrylic acid,[32] α-benzamido-4-hydroxycinnamic acid,[33] α-acetamido-4-hydroxycinnamic acid,[34] α-acetamido-4-acetoxycinnamic acid,[35] and α-acetamido-3-methoxy-4-acetoxycinnamic acid[36] were prepared by standard Erlenmeyer procedures, sometimes with minor modifications of the published directions. All the substrates were crystallized until pure colorless crystals were obtained. All had their melting points and ^{1}H NMR spectra taken before use.

C. Amino Acid Derivatives. *N*-Acetyl-(*S*)-tyrosine was obtained from U.S. Biochemical Corporation and *N*-acetyl-(*R*)-alanine and *N*-acetyl-(*S*)-phenylalanine were purchased from Sigma Chemical Co. We thank Dr. W. S. Knowles of Monsanto Co. for a gift of *N*-acetyl-3-(4-acetoxy-3-methoxyphenyl)-(*S*)-alanine. All other amino acid derivatives were prepared from the optically pure amino acids by standard Schotten–Bauman procedures. The specific rotations of the optically pure amino acid derivatives and solvents from which each was crystallized are summarized in Table II. Each was obtained as colorless, well formed crystals and the derivatives giving the quoted rotations were used as a standard for obtaining the optical purity of the hydrogenation products.

D. Preparation of the Ligand. (+)-(2*R*,3*R*)-Butanediol di-*p*-toluenesulfonate (90 g) was prepared [13] from (−)-(2*R*,3*R*)-butanediol (22 g; $[\alpha]^{27}_D$ −12.5°, neat). The crude air-dried product was dissolved in CH_2Cl_2 (400 mL) and was washed with 1 N HCl (two 100-mL portions) and then with H_2O (100 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to a clear oil. On cooling at 5 °C for several hours, the oil crystallized. It was collected and washed with 30–60 °C petroleum ether and stored over KOH in a desiccator: $[\alpha]^{25}_D$ +35.6° (0.92, $CHCl_3$); lit.[13] $[\alpha]^{25}_D$ +37.2° (2.105, $CHCl_3$).

(−)-(2*S*,3*S*)-Bis(diphenylphosphino)butane ((*S,S*)-chiraphos). To a 1-L round-bottom, three-neck flask equipped with a 250-mL dropping funnel, a reflux condenser, and nitrogen inlet was added recrystallized triphenylphosphine (95 g) in dry tetrahydrofuran (300 mL). Dry nitrogen was passed over the magnetically stirred solution at 25 °C, as thin, finely cut strips of lithium metal (5.0 g) were added to the solution. The solution soon turned a deep orange-red color as $LiPPh_2$ formed with the liberation of heat. The temperature rose to ~55 °C over 1 h and then slowly cooled to 25 °C over the next 2 h. At this stage a small amount of lithium remains, but the reaction is essentially complete. The lithium phenyl was decomposed by the

Table II.

Amino acid derivative	Specific rotation	Crystallization solvent	Ref
N-Acetyl-(*R*)-alanine	$[\alpha]_D^{26}$ +66.3° (2.0, H_2O)	*a*	37
N-Acetyl-(*S*)-phenylalanine	$[\alpha]_D^{26}$ +46.0° (1.0, EtOH)	*a*	38
N-Benzoyl-(*S*)-phenylalanine	$[\alpha]_D^{27}$ −40.3° (1.0, MeOH)	H_2O	39
N-Benzoyl-(*S*)-phenylalanine ethyl ester	$[\alpha]_D^{26}$ −42.7° (1.0, MeOH)	EtOH–H_2O	
N-Acetyl-(*S*)-leucine	$[\alpha]_D^{26}$ −23.2° (1.0, EtOH)	$CHCl_3$–hexane	40
N-Benzoyl-(*R*)-leucine	$[\alpha]_D^{26}$ +10.1° (2.0, MeOH)	H_2O	41
N-Benzoyl-(*S*)-tyrosine	$[\alpha]_D^{26}$ −36.0° (1.0, MeOH)	EtOH–H_2O	42
N-Acetyl-(*S*)-tyrosine	$[\alpha]_D^{27}$ +51.5° (1.0, MeOH)	H_2O	43
O,*N*-Diacetyl-(*S*)-tyrosine	$[\alpha]_D^{27}$ +45.4° (1.5, MeOH)	H_2O	43
N-Acetyl-3-(4-acetoxy-3-methoxyphenyl)-(*S*)-alanine	$[\alpha]_D^{20}$ +40.7° (1.0, MeOH)	H_2O	10

[a] Used as received.

dropwise addition of freshly distilled *tert*-butyl chloride (33 g) over a period of 45 min. The now clear orange-red solution was brought to boil for 5 min and then was cooled to −4 °C in an acetone–ice bath.

(+)-(2*R*,3*R*)-Butanediol di-*p*-toluenesulfonate (35 g) in dry tetrahydrofuran (100 mL) was then added dropwise over 1 h to the cold, stirred solution. After the addition was complete, the resulting solution was allowed to rise to 25 °C and was stirred at this temperature for 30 min. Water (300 mL), purged with nitrogen, was then added and the tetrahydrofuran was distilled off under reduced pressure to give an oily colorless residue. The residue was extracted, under nitrogen, with ether (two 150-mL portions) and then dried over Na_2SO_4. The ethereal extracts were filtered, under nitrogen, into a solution of nickel perchlorate hexahydrate (15 g) in ethanol (50 mL). The Na_2SO_4 remaining on the filter was thoroughly washed with ether, which was added to the nickel solution. An oily, red-brown deposit formed, but occasionally yellow crystals of [Ni((*S*,*S*)-chiraphos)$_2$](ClO$_4$)$_2$ were produced. This is best ignored, for this isolated solid tends to be pyrophoric on storage because, we suppose, diphenylphosphine (Ph_2PH) is to some extent coordinated to the fifth position of the nickel ion. To the oily (or crystalline) mixture was added sodium thiocyanate (15 g) in hot ethanol (50 mL) and the solution was vigorously stirred for several hours until a homogeneous yellow-brown crystalline solid of [Ni((*S*,*S*)-chiraphos)$_2$NCS]NCS formed. (The thiocyanate serves two purposes: the five-coordinate complex is very insoluble and NCS^- "locks up" the fifth coordination position which can be occupied by unidentate phosphines. These complexes tend to be more soluble and tend to be pyrophoric in the solid.) The solid was collected and washed thoroughly with ethanol and finally with ether.

The free phosphine was isolated as follows. The nickel complex (15 g) was suspended in 95% ethanol (150 mL) under nitrogen. The suspension was stirred and brought to the boil and then sodium cyanide (4 g) in water (20 mL) was added rapidly. The nickel complex slowly dissolved to give first a clear blood-red solution (probably [Ni((*S*,*S*)-chiraphos)(CN)$_3$]$^-$), which then turned a cloudy beige color. The hot solution was stirred until all of the starting complex had dissolved and a yellow slurry formed. It was then cooled in ice and the solid collected and washed successively with water (two 25-mL portions) and then quickly with ice-cold ethanol (25 mL). This beige-colored solid is the impure phosphine. It was dried at 25 °C and then was taken up in boiling absolute ethanol (~125 mL), and the hot solution was filtered through a frit under nitrogen. On standing at room temperature for 12 h, the filtrate deposited lustrous colorless plates of the phosphine. A second crystallization of this product from absolute ethanol (60 mL) gave large, colorless plates of optically pure (−)-(2*S*,3*S*)-bis(diphenylphosphino)butane, (*S*,*S*)-chiraphos (5.5 g): $[\alpha]^{27}_D$ −211° (1.5, $CHCl_3$); mp 108–109 °C (sealed tube under N_2). Further fractional crystallization did not change this rotation.

Anal. Calcd for $C_{28}H_{28}P_2$: C, 78.9; H, 6.6; P, 14.6. Found: C, 78.9; H, 6.7; P, 14.7.

E. Catalytic Precursors. The complexes [Rh(COD)Cl]$_2$[44] and [Rh(NBD)Cl]$_2$[45] were prepared by slight modifications of the literature methods. [Rh(NBD)(acac)] was prepared from the chloro-bridged dimer using Tl(acac). [Rh(COD)(acac)] was prepared from the dimer in CH_2Cl_2 mixed with Na_2CO_3 and acacH in water.[46]

[Rh((*S*,*S*)-chiraphos)(NBD)]ClO$_4$. Method 1. The complex [Rh(NBD)(acac)] (0.3559 g) and (*S*,*S*)-chiraphos (0.5165 g) were dissolved in dry, freshly distilled tetrahydrofuran (7.5 mL) under nitrogen. To this solution was added 70% perchloric acid (0.173 g; 1 equiv) in tetrahydrofuran (6 mL). The solution turned a deep red color at once. It was allowed to stand at 25 °C for 24 h and the orange-red crystals of the product were collected and washed with cold tetrahydrofuran (0.6 g). These crystals were dried in vacuo at 40 °C and then stored at 0 °C under nitrogen in a sealed container.

Method 2. The complex [Rh(NBD)Cl]$_2$ (0.35 g) and NBD (0.14 g) were dissolved in methylene chloride (15 mL) under nitrogen. Then silver perchlorate (0.315 g) was added, and the mixture was stirred for 1 h. It was then filtered and diluted with tetrahydrofuran (15 mL). The methylene chloride was removed under vacuum, whereupon orange needles of [Rh(NBD)$_2$]ClO$_4$[47] separated. These were collected and washed with cold tetrahydrofuran and then dried in vacuo to give 0.5 g of now rust-brown crystals.

The complex [Rh(NBD)$_2$]ClO$_4$ (0.290 g) and (*S*,*S*)-chiraphos (0.308 g) were dissolved in methylene chloride (5 ml) and tetrahydrofuran (5 mL) under nitrogen. Hexane (6 mL) was then added and, after the mixture was allowed to stand at 25 °C for 1 h and then for 2 h at 5 °C, the orange-red needles of [Rh((*S*,*S*)-chiraphos)(NBD)]ClO$_4$ were collected (0.43 g).

Anal. Calcd for [Rh($C_{28}H_{28}P_2$)(C_7H_8)]ClO$_4$: C, 58.3; H, 5.0; P, 8.6; Cl, 4.9. Found: C, 58.1; H, 5.2; P, 8.5; Cl, 4.7.

[Rh((*S*,*S*)-chiraphos)(COD)]ClO$_4$·THF. The complex [Rh(COD)(acac)] (0.180 g) and (*S*,*S*-chiraphos (0.244 g) were dissolved in pure tetrahydrofuran (4 mL) under nitrogen. To this solution was added 70% perchloric acid (0.080 g; 1 equiv) in tetrahydrofuran (1 mL). The resulting red solution was allowed to stand at 25 °C for 12 h and then the bright orange blocks of the product were collected. They were washed with cold tetrahydrofuran and air dried (0.4 g). The THF of crystallization was confirmed by NMR and by a crystal structure.[15]

Anal. Calcd for [Rh($C_{28}H_{28}P_2$)(C_8H_{12})]ClO$_4$·C_4H_8O: C, 59.4; H, 6.0; P, 7.7; Cl, 4.4. Found: C, 59.3; H, 6.0; P, 7.9; Cl, 4.4.

F. Hydrogenation Procedure. Tetrahydrofuran, dioxane, and benzene were refluxed over $LiAlH_4$ and freshly distilled before use. All solvents were purged with a stream of oxygen-free nitrogen for at least 15 min before use.

The requisite substrate (1–2 g) was accurately weighed into a two-neck round-bottom flask equipped with a serum cap. The weighed catalytic precursor, [Rh((*S*,*S*)-chiraphos)(NBD)]ClO$_4$, was then added and the flask was fitted to the hydrogenation manifold. The flask was then successively evacuated and filled with oxygen-free hydrogen. The required solvent (20–30 mL) was then injected through the serum cap via a syringe. The mixture was then vigorously stirred magnetically until the required amount of hydrogen had been absorbed. With many substrates the solution is a deep red color while the hydrogenation is proceeding but when hydrogen uptake ceases, the solution is a very light straw-yellow color. This is a useful way of monitoring some of the reactions. Presumably, the deep red color is due to the rhodium olefin complex and the light straw yellow color is due to[14] [Rh((*S*,*S*)-chiraphos)(H)$_2$]$^+$. When the hydrogenation was complete, two methods for the workup were used depending on the solvent used.

Method 1. For Tetrahydrofuran, Dioxane, and Benzene. The reaction mixture was pumped down under vacuum to an oil and then methanol was added and the solvent was pumped off again. This was repeated several times to ensure that none of the original solvent remained. The resulting yellow oil (sometimes a yellow solid) was dissolved in methanol (15 mL) and then dry Dowex 50W-X2 (200–400 mesh) cation (H^+ form) exchange resin (1–2 g) was added. The

mixture was stirred for 15 min, after which time a clear colorless supernatant solution remained as a result of the transference of the (yellow) catalyst onto the resin. The mixture was filtered into a volumetric flask and the resin was thoroughly washed with warm methanol. The filtrate was allowed to cool and then made up to the mark. An identical solution containing the optically pure product was prepared.

Method 2. For Methanol, Ethanol, and 50% Ethanol–Water. The ion-exchange resin was added directly to the hydrogenation solution and after 15 min, the resin was removed and the now clear solution was made up to a specified volume with the same solvent as was used for hydrogenation. The optical rotation was compared with an identical solution containing the optically pure product.

All the optical rotations of the products of hydrogenation (prepared by either method 1 or 2) and the corresponding blanks containing the optically pure amino acid derivatives were taken at 589, 578, 546, 436, and 365 mμ and the resulting optical purities as quoted in Table I are an average derived from these five wavelengths.

To check the results obtained by the above method, the solutions were pumped down and the products of hydrogenation isolated (generally in >90% yield). The optical rotations were again measured and the chemical identity of the products was checked by NMR. The rotations so obtained were in excellent agreement, and the NMR established that the expected products were obtained.[48]

G. Deuteration Experiments. *N*-Benzamido[2*R*,3*R*)-$^2H_2$]phenylalanine. α-Benzamidocinnamic acid (2.46 g) was deuterated in tetrahydrofuran (35 mL) using [Rh((*S*,*S*)-chiraphos)(NBD)]ClO_4 (70 mg). When the uptake of deuterium was complete (~7 h), the mixture was pumped to dryness. It was taken up in methanol and the catalyst was removed with ion-exchange resin. The filtrate was taken down to an oil in vacuo, and the oil was dissolved in sodium hydroxide (10 mL; 1 N) and carefully acidified with HCl to congo blue. The voluminous crystals were collected and thoroughly washed with water and then dried (2.3 g). This material has the same specific rotation as the product obtained from hydrogenation.

α-Carbon Racemization of *N*-Benzoyl[(2*R*,3*R*)-$^2H_2$]phenylalanine. *N*-Benzoyl[2*R*,3*R*)-$^2H_2$]phenylalanine (1.1 g) was dissolved in dry dioxane (50 mL) containing acetic anhydride (1.1 g; 98%) and the resultant solution was heated at reflux temperature for 2 h. The hot solution was then filtered and reduced to an oil under vacuum. This oil was dissolved in dry dioxane (15 mL) and D_2O (8 mL; 99.5%) followed by dry pyridine (8 drops) was added. The solution was stirred for 12 h under nitrogen and then was pumped down to an oil at 40 °C under vacuum. The oil was dissolved in CH_3OD (15 mL) containing 1.5 g of 40% NaOD in D_2O. This mixture was stirred for 5 h at 25 °C, during which time D_2O (20 mL) was periodically added. The solution was warmed to 40 °C and then acidified with dilute HCl to congo blue. After the mixture was allowed to stand at 5 °C for 2 h, the fine white crystals were filtered and washed with water and dried at 70 °C (0.9 g).

The product (0.9 g) was taken up in hot ethanol (10 mL) and filtered while hot, and then warm water (15 ml) added. After the solution was allowed to cool slowly and then allowed to stand at 5 °C for 12 h, the crystals were collected (0.8 g).

The racemization process and the crystallization were repeated on this material to give, finally, 0.6 g of pure *N*-benzoyl[(2*R*,*S*,3*R*)-$^2H_2$]phenylalanine. A 10% solution in dimethylformamide had a specific rotation of $[\alpha]^{25}_D + 0.50 \pm 0.05°$, which remained unchanged after a third racemization cycle and fractional crystallization from ethanol–water.

Acknowledgment. This work was supported by the National Research Council of Canada. We thank N. C. Payne for crystallographic information before publication.

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