1,2-Bis(diphenylphosphino)-1-cyclohexylethane. A New Chiral Phosphine Ligand for Catalytic Chiral Hydrogenations

Dennis P. Riley* and Robert E. Shumate

The Procter & Gamble Company, Miami Valley Laboratories, Cincinnati, Ohio 45247

Received September 8, 1980

The new chiral bidentate phosphine ligand (*R*)-1,2-bis(diphenylphosphino)-1-cyclohexylethane ((*R*)-Cycphos) has been prepared. The rhodium(I) cationic complex of this phosphine serves as an effective homogeneous asymmetric hydrogenation catalyst for the reduction of (*Z*)-α-amidoacrylic acids at ambient temperature and pressure. Optical yields for the corresponding (*S*)-α-amino acid derivatives that are produced are generally above 90%. The success of this ligand in giving higher optical yields than those obtained from other structurally analogous phosphines is rationalized in terms of the bulky cyclohexyl substituent affording a more stereochemically rigid chelating phosphine.

During the last several years many rhodium(I) complexes containing novel chiral phosphine ligands have been reported to function effectively as chiral hydrogenation catalysts.[1] Paralleling these synthetic developements have been advances in the understanding of the chemical and stereochemical mechanisms of these asymmetric homogeneous hydrogenation catalysts.[2] From such studies, an important point has emerged; namely, those phosphines giving more stereochemically rigid complexes generally function as better (higher optical yields) chiral catalysts. For example, chiral bidentate phosphine ligands are better for generating chirality than monodentate phosphines, and bidentate phosphines yielding five-membered chelate rings (Dipamp, 1,2-ethanediylbis[(2-methoxyphenyl)phenyl]-phosphine;[3] (*R*)-prophos (**1a**);[4] (*S*)-Chiraphos, 2,3-bis(diphenylphosphino)butane;[5] (*R*)-Phenphos (**1c**)[6]) are generally better catayst for generating optical activity from reduction of (*Z*)-α-amidoacrylic acids than those derived from chiral phosphines containing seven-membered chelate rings [Diop, 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis-(diphenylphosphino)butane].[7]

Recently, the work of Bosnich et al.[4,5] has shown that a five-membered chelate ring-forming phosphine containing the chirality on a ring backbone carbon (as opposed to the phosphorus) can function as a chiral hydrogenation catalyst. The success of these catalysts is believed to be due to the constraint of the chelate ring to one conformation by the barrier to inversion arising from the equatorial methyl substituent; thus a "rigid" phosphine and consequently a fixed phenyl group orientation are present. The fixed phenyl groups then provide a mechanism for enantiofacial discrimination between the substituents on the coordinated prochiral olefin and the catalyst.[2g] This stereochemical effect is the suspected source of the high selectivities observed for these catalysts.

This work prompted us to investigate whether better and more versatile rhodium phosphine catalysts could be synthesized on the basis of such stereochemical considerations. The prototype catalyst we chose to model was the [Rh((*R*)-Prophos)]$^+$ catalyst.[4] Figure 1a shows the predicted solution structure of the (*R*)-Prophos rhodium (I) catalyst (based on solid-state X-ray data[2g] and from theoretical considerations[8]) in which the methyl group is in the equatorial position. Our primary consideration was that a better catalyst would be one in which the equilibrium concentration of the less stable axial conformer would be diminished. This could be achieved by replacing the methyl with a much more bulky three-dimensional group; e.g., *tert*-butyl, isopropyl, or cyclohexyl. Another more practical constraint was that a relatively straightforward method of synthesis of such a chiral ligand should be possible.

The naturally occurring (*S*)-(+)-mandelic acid was investigated as a potentially useful starting material because it is readily available for conversion to a chiral diphosphine by established procedures and because the phenyl ring could be reduced to a cyclohexyl, affording a very bulky three-dimensional group on the chiral chelate ring; thus, in effect, the methyl of (*R*)-prophos is replaced with a cyclohexyl. This new ligand [(*R*)-Cycphos (**1b**)] is readily synthesized in optically pure form from (+)-mandelic acid in over 30% yield by using the basic procedure of Bosnich et al.[4,5] In addition, the opposite isomer, (*S*)-Cycphos, can be synthesized similarly from (−)-mandelic acid. Significantly, when complexed to Rh(I), an excellent asymmetric hydrogenation catalyst results with either chiral phosphine.

The synthesis of this new phosphine ligand and the optical yields obtained from the reduction of typical prochiral olefinic substrates are reported herein. In addition, the optical yield results obtained with this ligand and with other related chiral catalysts are compared and discussed.

Results

Synthesis. This new chiral phosphine ligand, (*R*)-Cycphos, was synthesized as shown in Figure 2 by standard methods[4-6] in over 30% overall yield. The key step in this sequence is the displacement of the tosylates with lithium diphenylphosphide. In order to maximize this step by

(1) (a) Valentine, D.; Scott, J. W. *Synthesis* **1978**, 329. (b) Lauer, M.; Samuel, O.; Kagan, H. B. *J. Organomet. Chem.* **1979**, *177*, 309-12. (c) Pino, P.; Consiglio, G. In "Fundamental Research in Homogeneous Catalysts"; Tsutsui, M., Ed.; Plenum: New York, 1979; Vol. III, p 519.

(2) (a) Halpern, J.; Riley, D. P.; Chan, A. S. C.; Pluth, J. J. *J. Am. Chem. Soc.* **1977**, *99*, 8055. (b) Chan, A. S. C.; Pluth, J. J.; Halpern, J. *Inorg. Chim. Acta* **1979**, *37*, L477. (c) Slack, D. A.; Greveling, I.; Baird, M. C. *Inorg. Chem.* **1979**, *18*, 3125 (1979). (d) Brown, J. M.; Murrer, B. A. *Tetrahedron Lett.* **1979**, *50*, 4859. (e) Brown, J. M.; Chaloner, P. A.; Nicholson, P. N. *J. Chem. Soc., Chem. Commun.* **1978**, 646. (f) Halpern, J.; Chan, A. S. C.; Riley, D. P.; Pluth, J. J. *Adv. Chem. Ser.* **1979**, *No. 173*, 16-25. (g) Knowles, W. S.; Vineyard, B. D.; Sabacky, M. J.; Stults, B. R. In "Fundamental Research in Homogeneous Catalysts"; Tsutsui, M., Ed.; Plenum: New York, 1979; Vol. III, p 537. (h) Detellier, C.; Gelbard, G.; Kagan, H. M. *J. Am. Chem. Soc.* **1978**, *100*, 7556. (i) Chan, A. S. C.; Halpern, J. H. *J. Am. Chem. Soc.* **1980**, *102*, 838. (j) Brown, J. M.; Chaloner, P. A. *J. Am. Chem. Soc.* **1980**, *102*, 3040.

(3) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5046.

(4) Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1978**, *100*, 5491.

(5) Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1977**, *99*, 6262.

(6) King, R. B.; Bakos, J.; Hoff, C. D.; Marko, L. *J. Org. Chem.* **1979**, *44*, 1729.

(7) Kagan, H. B.; Dang, T.-P. *J. Am. Chem. Soc.* **1972**, *94*, 6429.

(8) DeHayes, L. J.; Busch, D. H. *Inorg. Chem.* **1973**, *12*, 1505.

0022-3263/80/1945-5187$01.00/0

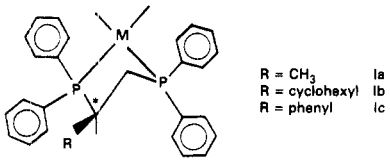


Figure 1. Preferred equatorial conformational structure of the known chiral chelate, ring-substituted, 1,2-bis(diphenylphosphino)ethane-type phosphine ligands.

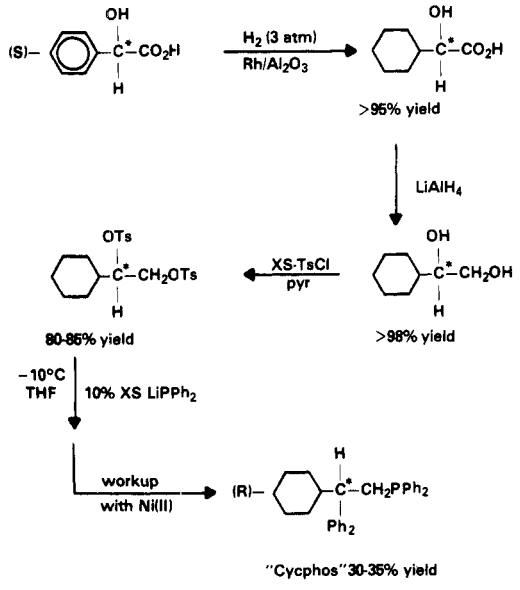


Figure 2. General synthetic scheme utilized for the preparation of (*R*)-Cycphos.

discouraging elimination, we found that the best yields were obtained by carrying out the displacement reaction at −10 °C with a slight excess of lithium diphenylphosphide.[4,5] Other diphenylphosphide salts were tried, e.g., sodium diphenylphosphide and potassium diphenylphosphide, but the yields were diminished, and the product phosphines had lower optical rotations.

Hydrogenations and Catalyst Removal. Using the cationic rhodium phosphine complex [Rh((*R*)-Cycphos)(norbornadiene)]PF_6 as a convenient catalyst precursor, we have studied the asymmetric hydrogenation of a number of olefinic and ketonic substrates. Table I lists the substrates that were reduced by using the (*R*)-Cycphos-based Rh catalyst.

The reductions were carried out in a number of solvents, including methanol, tetrahydrofuran, ethyl acetate, and dichloromethane. In all cases the rates and optical yields were somewhat sensitive to solvent effects. The reduction of the (*Z*)-α-amidoacrylic acid substrates was generally very fast at 25 °C and 1 atm of H_2. Turnover numbers ranged from as high as several hundred reciprocal hours for the least sterically encumbered olefin, α-acetamidoacrylic acid, to as low as 1 h^{-1} for the more sterically encumbered olefin, α-acetamido-β-indolylacrylic acid.

Typically, catalyst to substrate ratios of 1:125 were employed for conveniently high reaction rates, but catalyst to substrate ratios as low as 1:1000 were successfully employed with no effect on the optical yield. But since the catalyst solutions are air sensitive, one needs to rigorously exclude oxygen at these low catalyst levels.

One important aspect of the evaluation of a chiral reduction catalyst is the need for monitoring chemical and optical purities of the products. Chemical purities of the products were routinely monitored by ^1H NMR spectral and thin-layer chromatographic analyses. However, an early problem we encountered was in obtaining reproducibly accurate optical yields. The optical yields were routinely determined by measuring the optical rotation of the product and comparing it to the rotation of the pure enantimorph. This method is proper if it is assumed that no interfering species, such as residual chiral phosphines, are present. In some cases the parent phosphines have specific rotations of several hundred degrees, compared to 10–20° in the products. Since there was no accepted or standardized method for removing chiral catalyst residue when we began this work, we attempted to ascertain if a general method could be devised that would eliminate any potential phosphine interference problems.

Of the published separation methods, we found that most do not remove the rhodium–phosphine contaminants reproducibly. For example, the cation-exchange procedure in ref 4 and 5 does not diminish the rhodium phosphorus content of a typical hydrogenation batch on workup if the solutions are exposed to air prior to workup. By this method the rhodium and phosphorus levels are unchanged as monitored by atomic absorption (parts per billion accuracy) and phosphorus microanalysis (parts per million accuracy). Other methods of separation such as formation of an aqueous solution of the salt of an α-amide acid and filtration do not remove the rhodium–phosphine material effectively or reproducibly.

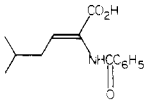
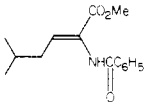
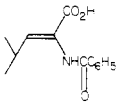
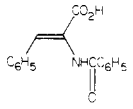
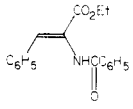
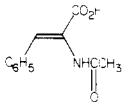
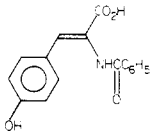
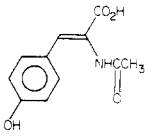
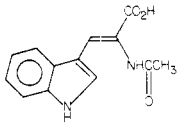
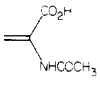
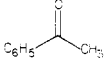
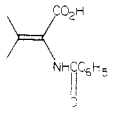
The removal of any interfering species without changing the distribution of optical isomers is most important. To use a crystallization technique or other such physical techniques runs the risk of selectively enriching one enantiomer over the other. We found that when acids are used as the substrate, an extraction method effectively removes the catalyst.[6] The method involved simply extracting an ether or dichloromethane solution of the reaction product mixture with an aqueous 1 N sodium hydroxide solution. The rhodium–phosphine species are retained in the organic layer. The inverse of this procedure—extraction of the basic aqueous layer with organic solvent—is not as reproducibly effective. For removal of the contaminants when esters were used, we found that simple chromatography on silica gel or neutral alumina worked effectively. For ketones, either chromatography on silica gel or distillation of the product alcohols proved to be an effective method of workup.

To test whether the workup procedures actually affected the optical yields, we carried out chiral ^1H NMR shift experiments[9,10] on several of the purified α-amide acid products as their methyl esters (diazomethane used for esterification) both before and after the catalyst workup procedure was performed. In this way it was shown that no effect on the optical yield results from the workup procedure. Interestingly, if the optical rotation measurements were made before the catalyst was removed, the optical yields were seen in some instances to deviate by as much as 10% from the actual optical yield when a 1:125 catalyst–substrate ratio was employed with both (*R*)-Prophos and (*R*)-Cycphos.

Optical Yields. In Table I are listed the optical yields obtained from the hydrogenations at 25 °C and 1 atm of hydrogen pressure of the substrates listed. The (*R*)-Cycphos ligand is capable of generating uniformly high optical yields generally in any of 90% for the reduction of the (*Z*)-α-amidoacrylic acid substrates. And as with (*R*)-Prophos, the (*R*)-Cycphos-based catalyst generates (*S*)-amino acids derivatives with the (*Z*)-α-amidoacrylic acid

(9) Goering, H. L.; Eikenberry, J. N.; Koermer, G. S.; Lattimer, C. J. *J. Am. Chem. Soc.* **1974**, *96*, 1493.
(10) Whitesides, G. M.; Lewis, D. W. *J. Am. Chem. Soc.* **1971**, *93*, 5914.

Table I. Optical Yields (%)

substrate	amino acid	solvent			
		THF	MeOH	EtOAc	CH_2Cl_2
	L-2-amino-5-methylhexanoic acid	90	94	95, 94[a]	91, 92[a]
	L-2-amino-5-methylhexanoic acid		86	84	90
	L-leucine	89	90	94, 94[a]	
	L-phenylalanine	94	90, 88[b]	93, 92[a]	
	Lphenylalanine	90	88, 89[b]	87	
	L-phenylalanine	83	84	91	
	L-tyrosine	98		96	
	L-tyrosine	90	80	88	
	L-tryptophan		81	83	87
	L-alanine	87	93	96	
	hydratropic acid		8[e]		
	1-phenylethanol		6[d]		
$H_3CC(O)CO_2Me$	lactic acid		very low[e]		
	L-valine		43[f]		

[a] 50 atm of H_2 pressure, other conditions unchanged. [b] NEt_3 added, base/Rh = 5. [c] Reaction time 20 h at 50 °C and 100 atm with NEt_3/Rh = 5. Percent conversion = 75. [d] Reaction time 140 h at 25 °C and 100 atm with NEt_3/Rh = 5. Percent conversion = 71. [e] Reaction time 140 h at 25 °C and 100 atm with NEt_3/Rh = 5. Percent conversion = 65. [f] Reaction time 100 h at 25 °C and 100 atm.

substrates. Also the ester of an acrylic acid does not result in as high an optical yield as the corresponding acid substrate. Finally, the optical yields do show a slight solvent dependence; surprisingly, even very poor donor or noncoordinating solvents give high optical yields. For example, ethyl acetate or even dichloromethane serves as an excellent solvent for these reactions with no diminishing of the chemical rate.

With several of the α-amidoacrylic acid substrates (Table I) the effect of hydrogen pressure on optical yields was also investigated. Pressures as high as 50 atm did not result in any significant change in the optical yields as

Table II. Effect of Temperature on Optical Yield[a]

temp, K	optical yield, % (R)-Prophos	(R)-Cycphos
283	90.8 ± 0.2	91.8 ± 0.1
293	89.7 ± 0.1	91.0 ± 0.1
303	89.1 ± 0.1	90.2 ± 0.2
313	87.4 ± 0.1	89.9 ± 0.1
323	87.0 ± 0.2	89.3 ± 0.2
333	84.9 ± 0.2	88.0 ± 0.1
343	84.2 ± 0.3	86.9 ± 0.1
353	82.4 ± 0.2	85.8 ± 0.1

[a] All values are the average of three trials, with the values all falling in the range noted.

compared to results obtained at 1 atm of hydrogen pressure. Consequently, increased hydrogen pressure could be used to decrease the reaction times without any deleterious effects on optical yield.

When other substrates such as the ketones or 2-phenylpropenoic acid were used, it was found that the catalyst was much less active for their reduction. In fact, very long reaction times and higher temperatures (50 °C) and pressures (100 atm) generally resulted in only a slight reduction of these substrates. But addition of triethylamine (5:1 base/Rh) resulted in much greater catalyst activity for these substrates, with 100% conversions being achieved in some instances under the same conditions which in the absence of base give poor conversions. The $[Rh(Cycphos)]^+$ catalyst gives only very low enantiomeric excesses with these substances though. A few representative examples are shown in Table I.

The temperature dependence of the optical yield for the (R)-Prophos- and (R)-Cycphos-based catalyst systems was also studied for reaction 1. The reaction was carefully

$$(Z)\text{-}C_6H_5CH{=}C(CO_2H)(NHCOC_6H_5) \xrightarrow[\text{chiral catalyst, } n\text{-BuOH}]{\text{1 atm of } H_2} \text{L-}C_6H_5CH_2CH(CO_2H)(NHCOC_6H_5) \quad (1)$$

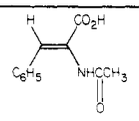
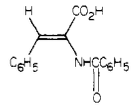
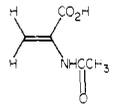
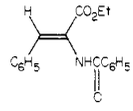
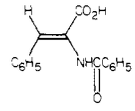
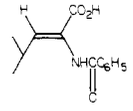
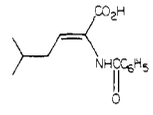
studied in 1-butanol which has a higher boiling point than the commonly used solvents, and this made it possible to obtain data over a greater temperature range. The specific rotations were measured accurately and reproducibly to ±0.1 °C by using a thermostated polarimeter cell compartment for a series of runs over the temperature range 10–80 °C with both the (R)-Cycphos and (R)-Prophos rhodium-based catalysts. Table II shows the optical yield results with each point reproduced in triplicate. A regular decrease in the optical yield results with both catalysts. A plot of optical yield vs. temperature for the two catalysts gives a nearly linear decrease in optical yield with temperature for each catalyst. A least-squares fit of these results gives a straight line exhibiting a correlation coefficient of 0.99. The slope of the (R)-Prophos catalyst was approximately 1.5 times as large as that for the (R)-Cycphos catalyst.

Discussion

As can be seen in Table I, the optical yields obtained with (R)-Cycphos are very high (generally in excess of 90%) for the production of natural amino acid derivatives from the class of (Z)-α-aminoacrylic acid substrates. In fact, the (R)-Cycphos-based catalyst appears to be about as successful as the Dipamp catalyst of Knowles et al.[3] for generating optical activity within this class of prochiral olefins.

One feature of the $[Rh((R)\text{-Cycphos})]^+$-based catalyst was its relative inability to reduce ketones effectively.

Table III. Optical Yields[a]

substrate	(R)-Cycphos	(R)-Prophos[b]	(S)-Phenphos[c]
	83 (84)[d]	83 (85)[d]	78
	93 (94)[d]	88 (89)[d]	84
	96[e] (87)[d]	86[e] (87)[d]	
	88	83.5	86
	92 (91)[d]	85 (81)	
	91[e]	79[e]	
	94 (90)[d]	86 (83)[d]	

[a] The solvent for all reductions was MeOH unless noted otherwise. [b] Data from this work. [c] Data from ref 6 were identical with our own data. [d] Data in parentheses are from experiments with THF as hydrogenation solvent. [e] EtOAc solvent.

While ketones are known to be notoriously difficult to reduce in high optical yield, the $[Rh((R)\text{-Cycphos})]^+$ complex did not function as a hydrogenation catalyst unless added base was present. This base effect has been noted previously and is likely due to the generation of a different catalyst species in solution.[11] In all cases, only low optical yields were obtained from the ketone reductions. While a great rate enhancement was observed with added base for these ketones and less activated olefinic substrates, the effect of added amine on the rate and on the optical yield for the reduction of both the (Z)-α-benzamido-β-phenylacrylic acid and its ethyl ester was negligible.

The tetrasubstituted olefin β,β′-dimethyl-α-benzamidoacrylic acid was reduced cleanly to the α-benzamido-L-valine in moderate optical excess. This result is significant, for this is only the second[12] reported successful trial at reducing a tetrasubstituted olefin, yielding a chiral product with a chiral homogeneous catalyst. Indeed, Kagan et al. have reported that the neutral Rh(Diop)Cl-based catalyst was unsuccessful at reducing this particular tetrasubstituted olefin.[7]

Our original premise for the synthesis of this new phosphine was that steric bulk on the chelate-ring backbone will give added rigidity, maintain a greater equilibrium concentration of the equatorial conformer in solution and hence result in higher optical yields than are obtained with other phosphines in this class. The (R)-Cycphos

(11) (a) Hayashi, T.; Mise, T.; Kumada, M. *Tetrahedron Lett.* **1976**, 4351–4. (b) Heil, B.; Toros, S.; Bakos, J.; Marko, L. *J. Organomet. Chem.* **1979**, *175*, 229–32.
(12) Achiwa, K. *Tetrahedron Lett.* **1978**, 2583.

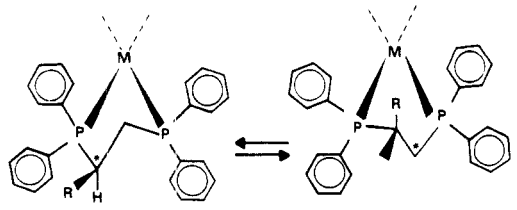


Figure 3. Two possible unique conformational structures can arise upon coordination of a chiral chelate ring-substituted bidentate phosphine ligand.

ligand allows us to compare optical yield data with those of other chiral phosphine ligands (where R is methyl (1a) or phenyl (1c)] containing the chiral center on a carbon of the five-membered chelate ring and, thus, test this premise.

In Table III are listed some comparisons of optical yield results with these three ligands. The (*R*)-Prophos data are from our work, since the Prophos literature results were not obtained in methanol and also since the possibility of optical yield differences might result due to the use of different catalyst removal procedures. It it readily apparent that the Cycphos ligand is generally the superior ligand with regard to optical yields, while Prophos is, in general, somewhat better than Phenylphos. It is especially attractive to attribute the observed optical yield results to the fact that the most sterically rigid chelate ring will provide the highest optical yields. On the basis of such stereochemical arguments, the bulkiest R group will provide the greatest steric barrier to inversion arising from the substituent's interaction with adjacent methylene protons. In addition, it is also expected that the equilibrium constant for the chelate ring inversion process shown in Figure 3 will be larger for the bulkier group. Thus, we might reasonably predict that the optical yields would follow the order Cycphos > Phenphos > Prophos.

The observed optical yields do not always follow this trend. Since the cyclohexyl group is the bulkiest R group, it clearly would be expected to have a larger equilibrium concentration of the more stable equatorial conformer B (Figure 3), and, perhaps as importantly, the activation energy barrier to inversion would be the highest. The optical yield results do support this conclusion. The comparison between Prophos and Phenylphos is not as clear. The equilibrium for each of these ligands is expected to favor the equatorial B form, but it is not clear why the Phenphos functions as a poorer chiral catalyst, especially since the phenyl substituent is larger.

The observed reaction rates for the (*R*)-Cycphos-based catalyst are virtually the same as those we found, and as were was reported, for (*R*)-Prophos. Apparently, the cyclohexyl has little effect on steric bulk about the remaining coordination sites on the metal, since the observed chemical rates are virtually the same for the two systems. Consequently, optical yields can be improved with no loss in chemical rates. Also, it is interesting to note that the (*Z*)-(*p*-hydroxyphenyl)-α-amidoacrylic acids have much slower rates (turnover numbers ~5–10 h^{-1}) than the corrsponding β-phenyl derivatives (turnover numbers ~150–200 h^{-1}). This large rate difference cannot be simply a steric effect but must also reflect coordination ability differences of the substrates arising from electronic effects. Finally, the less activated substrates, e.g., ketones, require higher temperatures and pressures to attain reasonable reaction rates.

The temperature dependence of the optical yields was studied (Table II) to determine the extent to which the two catalysts derived from Cycphos and Prophos were susceptible to temperature changes. Since the rates of reaction increase with temperature, an increase in reaction temperature without loss of optical yield is desirable. The results of this study show that the optical yields obtained with the Cycphos-based catalyst are less susceptible to temperature changes than are those from Prophos. This is consistent with the view that the Cycphos ligand is more rigid than the Prophos and is, as a result, somewhat less susceptible to thermal effects.

Our results reinforce the argument that increased stereorigidity within a class of chiral phosphine-based hydrogenation catalysts is an important factor for achieving consistently high optical yields from the reduction of a class of prochiral substrates. There are, of course, other secondary effects such as substrate interaction, solvent, temperature, and even pressure[13] that are superimposed on the effects due to the chiral phosphine-generated positional fixedness of the phosphorus phenyl groups. But the rationale described here should be considered for the synthesis of other asymmetric catalysts where the dual goal of fast reaction rates and high optical yields is desired.

Experimental Section

(A) Instrumentation. All ^1H NMR spectra were recorded on a Varian T-60 spectrometer, and optical rotations were obtained at 589 and 546 nm on a Rudolph Autopol III automatic polarimeter.

(B) Reagents. (*S*)-(+)-Mandelic acid was purchased from Sigma Chemical Co.; α-acetamidoacrylic acid, acetophenone, 2-butanone, pyruvic acid, methyl pyruvate, and *p*-toluenesulfonyl chloride were purchased from Aldrich Chemical Co. Rh/Al_2O_3 was purchased from Strem Chemical Co. The other (*Z*)-α-amidoacrylic acid substrates were prepared by standard Erlenmeyer azlactone procedures,[14] were recrystallized until colorless, sharp melting crystals were obtained, and were found pure by TLC. The (*Z*)-α-acetamido-β-indolylacrylic acid was prepared by the method of ref 15. The esters of the α-amidoacrylic acids were prepared by the method of ref 3 by using refluxing anhydrous alcohol and NaOAc to open the corresponding azlactone directly to the ester. The atropic acid was prepared from ref 16. All substrates were confirmed to be pure by ^1H NMR and TLC before use. All NMR shift reagents were obtained from Norell Chemical Co.

(C) Products. Table IV lists each chiral product with its specific rotation and literature reference. The (*S*)-2-α-benzamido-5-methylhexanoic acid optical yields were obtained via chiral shift studies[9] with the methyl ester from the direct reduction of the ester substrate or from esterification of the acid product with diazomethane. The shift reagent used was the optically active tris[3-(heptafluorobutyryl)-*d*-camphorato]europium(III), Eu(hfbc)$_3$.[9] The optimum shift reagent to ester ratio was 3.1–3.3/1. This ratio gave clean baseline separation of orthophenyl hydrogen peaks.

(D) (*S*)-(+)-Hexahydromandelic Acid.[25] (*S*)-(+)-Mandelic acid (76.0 g) was dissolved in 400 mL of methanol containing 5

(13) O'Jima, I.; Kogure, T.; Yoda, N. *Chem. Lett.* **1979**, 495.
(14) (a) Baltazzi, E.; Robinson, R. *Chem. Ind. (London)* **1954**, 191. (b) Baltazzi, E. *Q. Rev., Chem. Soc.* **1955**, *9*, 150.
(15) Hengartner, U.; Valentine, D., Jr.; Johnson, K. K.; Larscheid, M. E.; Pigott, F.; Scheidl, F.; Scott, J. W.; Sun, R. C.; Townsend, J. M.; Williams, T. H. *J. Org. Chem.* **1979**, *44*, 3741.
(16) Raper, H. S. *J. Chem. Soc.* **1923**, 2557.
(17) Williams, M. W.; Young, G. T. *J. Chem. Soc.* **1963**, 885.
(18) Goodman, M.; Levine, L. *J. Am. Chem. Soc.* **1964**, *86*, 3920.
(19) Fischer, E. *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 3642.
(20) Schuller, W. H.; Nieman, C. *J. Am. Chem. Soc.* **1952**, *74*, 4633.
(21) Aviron-Violet, P.; Colleuille, Y.; Varagnat, J. *J. Mol. Catal.* **1979**, *5*, 41.
(22) Nagai, U.; Shishido, T.; Chiba, R.; Mitsuhashi, H. *Tetrahedron* **1965**, *21*, 1701.
(23) Purdie, T.; Irvine, J. C. *J. Chem. Soc.* **1899**, 483.
(24) Fox, S. W.; Pettinga, C. W.; Holverson, J. S.; Wax, H. *Arch. Biochem.* **1950**, *25*, 21.
(25) Stocker, J. H. *J. Org. Chem.* **1962**, *27*, 2288.

Table IV

product	specific rotation	ref
L-2-benzamido-5-methylhexanoic acid	$[\alpha]^{25}_D$ +20.4° (c 1, N NaOH)	this work
methyl L-2-benzamido-5-methylhexanoate	$[\alpha]^{25}_D$ −17.6° (c 1, MeOH)	this work
N-benzoyl-(*S*)-leucine	$[\alpha]^{25}_D$ −6.9° (c 2.6, EtOH)	8
N-benzoyl-(*S*)-phenylalanine	$[\alpha]^{27}_D$ −40.3 (c 1, MeOH)	5
	$[\alpha]^{25}_D$ +38.74° (c 1.6, dioxane)	18
N-acetyl-(*S*)-phenylalanine	$[\alpha]^{20}_D$ +40.1° (c 1, MeOH)	3
N-benzoyl-(*S*)-tyrosine	$[\alpha]^{20}_D$ +19.25° (c 8, 1 N KOH)	19
	$[\alpha]^{29}_D$ +18.24° (c 5.2, 0.2 N KOH)	20
N-acetyl-(*S*)-tyrosine	$[\alpha]^{27}_D$ +51.5° (c 1, MeOH)	5
N-acetyl-(*S*)-tryptophan	$[\alpha]^{15}_D$ +25° (c 1, 95% EtOH)	21
N-acetyl-(*R*)-alanine	$[\alpha]_D$ +66.5 (c 2, H_2O)	4, 7
N-benzoyl-(*S*)-phenylalanine ethyl ester	$[\alpha]^{26}_D$ −42.7° (c 1, MeOH)	5
(*S*)-1-phenylethanol	$[\alpha]^{23}_D$ −52.5° (c 2.27, CH_2Cl_2)	22
(*S*)-methyl lactate	$[\alpha]^{19}_D$ 8.25° (neat)	23
(*S*)-2-phenylpropanoic acid	$[\alpha]_D$ +81.1° (c 3.1, EtOH)	16
N-benzoyl-(*S*)-valine	$[\alpha]_D$ +21.8° (c 4.9, 95% EtOH)	24

mL of glacial acetic acid. The phenyl ring was entirely reduced in the presence of 5% rhodium-on-alumina catalyst under 100 psi of H_2 pressure in 10 h. Following filtration of the solution through Celite to remove the catalyst, the methanol was removed via a rotary evaporator. The white solid was dissolved in 1 L of hot diethyl ether and filtered while hot. The volume of the solution was reduced to ~400 mL, and 250 mL of cyclohexane was added. The ether was then removed, and the resultant cyclohexane solution was stored several hours in the refrigerator. White crystals of the desired product formed and were collected via filtration. The solid was dried overnight in vacuo at 40 °C. A 71-g sample of hexahydromandelic acid was obtained for a 90% yield: mp 128–129 °C (lit.[25] mp 129 °C); $[\alpha]^{23}_D$ +23.5° (c 1, HOAc) [lit.[25] $[\alpha]^{23}_D$ −25.5 (c 1.1, HOAc) for the *R* isomer].

(*S*)-Cyclohexyl-1,2-ethanediol.[4] (*S*)-(+)-Hexahydromandelic acid (195 g, 1.23 mol) in dry THF (1 L) was added dropwise over a period of 2 h to a stirred suspension of lithium aluminum hydride (107 g, 2.82 mol) in 2 L of dry THF at 0 °C. After the addition was complete, the solution was warmed to 25 °C and then refluxed for an additional 2 h. The reaction was then cooled to room temperature and the excess LAH carefully quenched by dropwise addition of 175 mL of H_2O, followed by 21.5 mL of 4 N NaOH and finally 400 mL of H_2O. The mixture was then refluxed for 1 h and filtered. The alumina cake was washed five times with 800-mL portions of boiling THF. The filtrates were combined and reduced to dryness to yield a yellowish oil. This oil was dissolved in 1.5 L of hot diethyl ether. To this solution were added $MgSO_4$ and activated charcoal. The solution was filtered and the filtrate reduced to dryness to give a colorless oil which on being allowed to stand crystallized to give the desired diol. The yield was 176 g (1.22 mol) for a 99% yield. The IR spectrum showed complete reduction. This material was then used directly to prepare the ditosylated alcohol.

(*S*)-Cyclohexyl-1,2-bis(*p*-toluenesufonyloxy)ethane. The previous diol (176 g, 1.22 mol) was dissolved in 125 mL of dry pyridine, and this solution was then added dropwise over 0.5 h to an ice-cold solution containing 530 g (2.8 mol) of *p*-toluenesulfonyl chloride in dry pyridine. The solution was stirred at 0 °C for 6 h, by which time white needles of pyridine hydrochloride had formed. The reaction was then stirred at 25 °C for an additional 18 h. At this point several small portions of ice were added with vigorous shaking to destroy excess TsCl. The product was then poured onto 2.5 L of ice, 520 mL of concentrated HCl (12 N) was added, and the mixture was stirred vigorously for 1 h. The solid was collected by filtration and washed with copious amounts of water. The solid was redissolved in 1.6 L of CH_2Cl_2 and washed twice with 400 mL of 5 N HCl and then once with 600 mL of H_2O. The organic layer was dried over $HgSO_4$ and activated charcoal added. The solution was filtered through Celite, the volume was reduced by half, and then, while hot (~40 °C), cyclohexane (1 L) was added to the cloudy precipitate. The solution was allowed to cool slowly upon which a solid mass of white crystals formed. After the mixture was stored at 0 °C for several hours, the product was collected by filtration to yield 445 g of the desired ditosylate, $[\alpha]^{23}_D$ +3.7° (c 1.5, $CHCl_3$). The yield was 80%, the product ^1H NMR was consistent, and a satisfactory elemental analysis was obtained. Anal. Calcd for $C_{22}H_{28}O_6S_2$: C, 58.38; H, 6.24; S, 14.17. Found: C, 58.90; H, 6.41; S, 14.0.

(*R*)-1,2-Bis(diphenylphosphino)cyclohexylethane ((*R*)-Cycphos). A solution containing 45.3 g (0.1 mol) of the preceeding ditosylate dissolved in 200 mL of dry degassed THF was added dropwise under N_2 over 1 h to an ice-cold, stirred solution containing 0.35 mol of lithium diphenylphosphide.[5] After the addition was complete, the solution was stirred for an additional hour at 25 °C. Degassed H_2O (250 mL) was then added and the THF distilled off under vacuum. This produced a white oily residue which was frozen (to inhibit aerial oxidation of the phosphine) and extracted while cold under N_2 with three 200-mL portions of cold diethyl ether. The ether was then added directly with vigorous stirring to a degassed solution containing 21.7 g of Ni-$(ClO_4)_2 \cdot 6H_2O$ in 50 mL of absolute EtOH. A deep red solution forms, to which was added slowly a hot saturated ethanolic solution containing 21.7 g of sodium thiocyanate. The solution turned deep reddish-brown and was stirred for 2 h. The ether was then removed on a rotary evaporator, and the remaining ethanol solution was heated to boiling to dissolve all the solids. While the solution was kept warm, diethyl ether was added (~2–3 L) to precipitate the red-brown Ni(Cycphos)$_2$ thiocyanate complex. The solid was then recrystallized from hot 95% EtOH, collected by filtration, and dried in vacuo to yield 21.7 g (34%) of nickel complex.

The nickel complex (21.7 g) was slurried under N_2 in 100 mL of refluxing 95% ethanol. To this hot solution was added at a brisk dropwise rate 6.1 g of NaCN in 75 mL of H_2O. The solution was refluxed for an additional hour, after which a yellow-orange solution forms along with globules of an oil. While cold, the water was extracted with 2 portions of 250 mL of Et_2O. The Et_2O was removed on a rotary evaporator. The oily solid was dissolved under N_2 in 150 cm^3 of hot absolute EtOH and then filtered. When the mixture cooled, a white solid mass formed and was collected by filtration and dried in vacuo. The yield of crude product was 17.7 g (32% from the ditosylate). This was recrystallized under N_2 from a minimum volume of hot absolute EtOH (~110 mL) to yield 11.7 g of white needles. A second crop of the same optical rotation was later collected to afford a total yield of 13.7 g (25% yield from the ditosylate); $[\alpha]^{25}_D$ +103.3° (c 1, THF under N_2). Subsequent recrystallizations did not change the rotation. Anal. Calcd for $C_{32}H_{34}P_2$: C, 79.97; H, 7.13; P, 12.89. Found: C, 80.07; H, 7.06; P, 13.01.

[Rh((*R*)-Cycphos)(NBD)]PF_6. This complex was prepared by an adaptation of the method developed in ref 26. In a typical preparation, 2.0 g of the Rh dimer [(Rh(NBD)Cl)$_2$] was dissolved in acetone under N_2 and 2.2 g of $AgPF_6$ added. The AgCl was filtered off, and the phosphine (4.1 g) was added slowly. The volume of the acetone solution was then reduced to 15 mL and the solution filtered through Celite. Then, while hot, methanol was added (50 mL), and upon removal of more solvent in vacuo and cooling, an orange precipitate formed. Two crops of the orange product were obtained, combined, washed with Et_2O, and

(26) Schrock, R. R.; Osborn, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 2397.

dried in vacuo. The total yield was 5.4 g (74% yield based on starting phosphine). Anal. Calcd for $C_{39}H_{42}P_3F_6Rh$: C, 57.09; H, 5.16; P, 11.32. Found: C, 56.63; H, 5.40; P, 11.01.

(E) Hydrogenation Procedure. All solvents used for the hydrogenations were dried and degassed prior to use. In all cases the procedure involved loading the weighed substrate (~2 g) and catalyst precursor, [Rh((*R*)-Cycphos)(NBD)]PF_6, into a dimpled flask which was transferred to an inert-atmosphere glovebox. To the flask was added the desired amount of solvent (generally 30 mL). The flask (sealed via a stopcock) was then transferred to the hydrogenation line. After several pump/purge cycles, the hydrogenations were begun via vigorous shaking. Reactions were allowed to go to completion via monitoring the H_2 uptake.

The workup of an acid product was carried out by removing all the solvent on a rotary evaporator and then dissolving the residue in CH_2Cl_2 or other suitable (non-water-miscible) solvent. The organic layer was then extracted once with 1 N NaOH solution. The organic phase that contains the catalyst residues can be discarded. The organic layer was filtered to remove any suspended material and then acidified with concentrated HCl. The water layer was then extracted with Et_2O or other suitable organic solvent, and this organic layer was then dried over Na_2SO_4. Filtration followed by removal of all solvent afforded solid (generally crystalline) products which were then weighed directly to obtain optical rotations and also ^1H NMR spectra. For some of the acids (*N*-acetylalanine and *N*-acetyltyrosine) which are H_2O soluble, the neutralization step is followed by removal of all H_2O. The solid residue is then extracted with an organic solvent (EtOAc) to dissolve the product and leave the NaCl behind.

For esters and alcohol products, the catalyst removal was effected by silica gel chromatography using 30% EtOAc in hexanes as the eluent.

Acknowledgment. We thank Dr. Douglas Hager for many useful discussions.

Registry No. (*S*)-Mandelic acid, 17199-29-0; (*S*)-hexahydromandelic acid, 61475-31-8; (*S*)-cyclohexyl-1,2-ethanediol, 61414-09-3; (*S*)-cyclohexyl-1,2-bis(*p*-toluenesulfonyloxy)ethane, 75421-30-6; (*R*)-cycphos, 75421-31-7; L-2-amino-5-methylhexanoic acid, 31872-98-7; L-leucine, 61-90-5; L-phenylalanine, 63-91-2; L-tyrosine, 60-18-4; L-tryptophan, 73-22-3; L-alanine, 56-41-7; hydratropic acid, 492-37-5; 1-phenylethanol, 98-85-1; lactic acid, 50-21-5; L-valine, 72-18-4; (*Z*)-2-benzamido-5-methyl-2-hexenoic acid, 75421-32-8; methyl (*Z*)-2-benzamido-5-methyl-2-hexenoate, 75421-33-9; (*Z*)-2-benzamido-4-methyl-2-pentenoic acid, 64896-31-7; (*Z*)-2-benzamido-3-phenyl-2-propenoic acid, 26348-47-0; ethyl (*Z*)-2-benzamido-3-phenyl-2-propenoate, 26348-46-9; (*Z*)-2-acetamido-3-phenyl-2-propenoic acid, 55065-02-6; (*Z*)-2-benzamido-3-(*p*-hydroxyphenyl)-2-propenoic acid, 64896-32-8; (*Z*)-2-acetamido-3-(*p*-hydroxyphenyl)-2-propenoic acid, 64896-33-9; (*Z*)-2-acetamido-3-(3-indolyl)-2-propenoic acid, 70082-70-1; 2-acetamidopropenoic acid, 5429-56-1; 2-phenylpropenoic acid, 492-38-6; 1-phenylethanone, 98-86-2; methyl 2-oxopropanoate, 600-22-6; 2-benzamido-3-phenyl-2-butanoic acid, 1738-64-3; (*R*)-prophos, 67884-32-6; L-2-benzamido-5-methylhexanoic acid, 75421-34-0; methyl L-2-benzamido-5-methylhexanoate, 75421-35-1; Ni(cycphos)$_2$ thiocyanate complex, 75421-74-8; [Rh((*R*)-cycphos)(NBD)]PF_6, 75421-76-0; $(Rh(NBD)Cl)_2$, 12257-42-0.

Cyclopropanation of Ester Enolates by π-Allylpalladium Chloride Complexes

Louis S. Hegedus,* W. H. Darlington, and Charles E. Russell

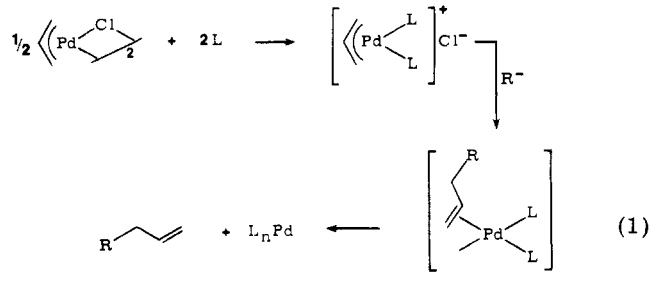
Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

Received August 18, 1980

Branched ester enolates react with π-allylpalladium chloride complexes in the presence of Et_3N and HMPA to produce alkylated cyclopropanes. Labeling studies indicate the carbanion attacks the *central* carbon of the π-allyl complex.

Introduction

The reaction of π-allylpalladium halide complexes with stabilized carbanions in the presence of excess phosphine or in polar aprotic solvents such as Me_2SO results in allylic alkylation (eq 1).[1] With unsymmetrical π-allylpalladium



(1)

complexes, attack occurs at either or both of the terminal allylic carbons, depending on the specific carbanion and π-allylpalladium complex.[1c] This chemistry has found extensive application in organic synthesis and both inter-[2] and intramolecular[3] processes have been developed.

The generally accepted mechanism for this reaction involves external (without prior coordination) nucleophilic attack on a cationic π-allylpalladium complex generated by displacement of chloride by added ligand (or solvent) (eq 1).[1c,4,5] The limitation of this reaction to relatively stabilized ($pK_a < \sim 17$) anions may be due to the propensity of nonstabilized carbanions to attack the *metal* in preference to the allyl group,[6,7] resulting in reduction of the complex rather than alkylation. This restriction to stabilized carbanions is fairly general throughout organopalladium chemistry. Initially the palladium assisted al-

(1) (a) J. Tsuji, H. Takahashi, and M. Morikawa, *Tetrahedron Lett.*, 4387 (1965); (b) J. Tsuji, *Bull. Chem. Soc. Jpn.*, **46**, 1896 (1973); (c) B. M. Trost, L. Weber, P. E. Strege, T. J. Fullerton, and T. J. Dietsche, *J. Am. Chem. Soc.*, **100**, 3416 (1978).

(2) B. M. Trost, P. E. Strege, L. Weber, T. J. Fullerton, and T. J. Dietsche, *J. Am. Chem. Soc.*, **100**, 3426 (1978).

(3) (a) Y. Kitagawa, A. Itoh, S. Hashimoto, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, **99**, 3864 (1977); (b) B. M. Trost and T. R. Verhoeven, *ibid.*, **99**, 3867 (1977); (c) *ibid.*, **101**, 1595 (1979).

(4) B. Akermark and K. Zetterberg, *Tetrahedron Lett.*, 3733 (1975).

(5) B. Akermark, J-E. Backvall, A. Lowenburg, and K. Zetterberg, *J. Organomet. Chem.*, **166**, C33 (1979).

(6) S.-i. Murahashi, Y. Tamba, M. Yamamura, and N. Yoshimura, *J. Org. Chem.*, **43**, 4099 (1978).

(7) S.-i. Murahashi, M. Yamamura, and N. Mita, *J. Org. Chem.*, **42**, 2870 (1977).

0022-3263/80/1945-5193$01.00/0