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THE ASYMMETRIC HYDROGENATION OF α-KETO ESTERS CATALYZED BY RHODIUM(I) COMPLEXES WITH CHIRAL DIPHOSPHINE LIGANDS. ON THE CATALYTIC CYCLES AND THE MECHANISM OF ASYMMETRIC INDUCTION

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Summary

Asymmetric hydrogenations of n-propyl pyruvate and ketopantoyl lactone catalyzed by rhodium complexes with (—) DIOP and BPPM were carried out under a variety of conditions. It was found that i) the Schrock-Osborn mechanism was not operative in these reactions at all since no acceleration of the reaction rate by the addition of water (1%) was observed, ii) there was a clear difference between cationic and neutral (in situ) rhodium catalysts in their enantioselectivity, and iii) there was a remarkable solvent effect on the extent and direction of asymmetric induction. Possible mechanisms are discussed on the basis of these results.

Introduction

The asymmetric hydrogenation of ketones catalyzed by chiral rhodium complexes has been attracting much interest [1,2]. However, the optical yields attained in the reaction have been rather low so far for simple prochiral ketones. Recently, Hayashi et al. developed a special chiral ferrocenyldiphosphine which brought about the effective asymmetric hydrogenation when it was employed as a ligand in a rhodium catalyst, and high optical yields were realized for the hydrogenation of pyruvic acid [3] and amino ketones [4].

We found that neutral Wilkinson-type catalysts are quite effective for the hydrogenation of α-keto esters as a special case [5], and applied it successfully to the asymmetric synthesis of lactates [5] and D-(—)-pantoyl lactone [6]. The latter reaction has been further applied to the asymmetric synthesis of D-(+)-pantothenate following the biosynthetic route [6].

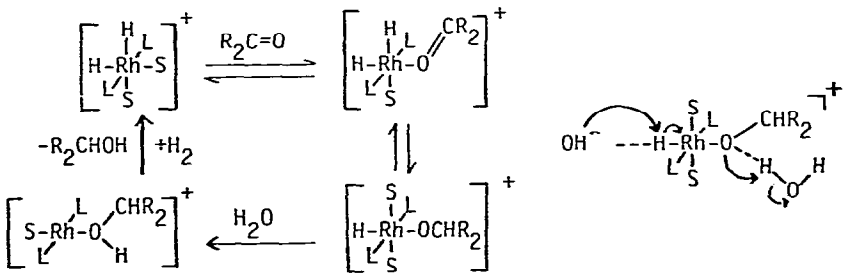
In order to clarify the more detailed features of the asymmetric hydrogenation of carbonyl compounds, we carried out the reaction of n-propyl pyruvate

and ketopantoyl lactone catalyzed by rhodium complexes with (—)DIOP and BPPM under a variety of conditions. We will describe here the results of our study on the catalytic cycles and the mechanism of asymmetric induction in the asymmetric hydrogenation of α-keto esters.

Results and discussion

As for the mechanism of the homogeneous hydrogenation of ketones catalyzed by phosphine-rhodium complex, the Schrock-Osborn mechanism has been widely accepted [7]. The most characteristic point of this mechanism is that the reaction involves a general acid-base catalysis by the adding water instead of the usual reductive elimination as shown in Scheme 1. Similar accelerating effects of added water on the rate of the asymmetric hydrogenation were also reported by Solodar [2]. It should be noted that Schrock, Osborn and Solodar employed monodentate phosphine ligands which form the complexes with *trans* configuration.

SCHEME 1.



In the first place, we looked at the effects of added water (1%) on the rate of the reaction on using cationic rhodium complexes with (—)DIOP [(—)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane] [8] and BPPM [(2*S*, 4*S*)-*N*-t-butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine] [9] as chiral ligands. Namely, the competitive hydrogenations of n-propyl pyruvate were carried out (see, Experimental). As Table 1 shows, the addition of water causes a decrease in the rate in every case examined. These results stand in sharp contrast to those of Schrock-Osborn and Solodar. Thus, the reaction does not follow the Schrock-Osborn mechanism at all. The differences may be due to the fact that we employed a *cis*-chelating ligand *. In Table 2 are summarized the effects of added water on the chemical and optical yields for the reactions catalyzed by either neutral or cationic complexes of (—)DIOP. As Table 2 clearly shows, the added water does not affect the optical yields.

Next, we investigated the solvent effects on the chemical and optical yields for neutral and cationic complex catalyzed reactions. The results on using n-propyl pyruvate are listed in Table 3. As is immediately seen from Table 3,

* As to the difference between the rhodium complexes with *trans*-ligands and those with *cis*-chelating ligands, see ref. 16.

TABLE 1

EFFECTS OF ADDING WATER ON THE RATE OF THE REACTION CATALYZED BY CATIONIC RHODIUM COMPLEXES [a]

$$CH_3COCOOn\text{-}Pr \xrightarrow[H_2]{Cat.\ *} CH_3\overset{*}{C}HCOOn\text{-}Pr \quad (OH)$$

Catalyst	Solvent	Conditions	Conversion(%) [b]
[((−)DIOP)Rh(COD)]$^+ClO_4^-$	MeOH	20°C, 3 h	46.2
	MeOH(H_2O 1%) [c]	20°C, 3 h	30.9
	THF	20°C, 3 h	34.3
	THF(H_2O 1%) [c]	20°C, 3 h	29.0
[(BPPM)Rh(COD)]$^+ClO_4^-$	MeOH	20°C, 3 h	93.6
	MeOH(H_2O 1%) [c]	20°C, 3 h	90.7
	THF	20°C, 3 h	55.2
	THF(H_2O 1%) [c]	20°C, 3 h	37.5

[a] All reactions were run with 0.5 mol% of catalyst under an initial hydrogen pressure of 20 atm. [b] GLC analysis. [c] Volume per cent.

an aprotic solvent such as benzene and tetrahydrofuran gave better results than did methanol, especially with neutral catalysts. Methanol not only decreases the optical yield but also remarkably decreases the rate. This phenomenon seems rather unusual since methanol is a commonly used solvent for hydrogenations catalyzed by Wilkinson-type rhodium complexes and gives good results. Both neutral catalysts with (−)DIOP and those of BPPM prefer the formation of (*R*)-lactate. However, the formation of (*S*)-lactate is favored on using the cationic (−)DIOP complex. In the case of BPPM catalyst, such an inversion

TABLE 2

EFFECTS OF ADDING WATER ON THE CHEMICAL AND OPTICAL YIELDS OF THE REACTION WITH NEUTRAL AND CATIONIC RHODIUM CATALYSTS [a]

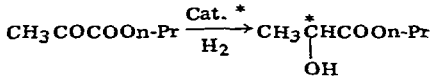
$$CH_3COCOOn\text{-}Pr \xrightarrow[H_2]{Cat.\ *} CH_3\overset{*}{C}HCOOn\text{-}Pr \quad (OH)$$

Catalyst	Solvent	Conversion(%) [b]	Optical Purity(% e.e) [c]
[(−)DIOP]Rh(S)Cl	MeOH	57	24.9 (*R*)
	MeOH(H_2O 1%) [d]	55	24.7 (*R*)
	THF	100	41.9 (*R*)
	THF(H_2O 1%) [d]	91	40.1 (*R*)
[((−)DIOP)Rh(COD)]$^+ClO_4^-$	MeOH	100	24.4 (*S*)
	MeOH(H_2O 1%) [d]	98	24.0 (*S*)
	THF	99	19.4 (*S*)
	THF(H_2O 1%) [d]	98	22.1 (*S*)

[a] Reactions were run with 0.5 mol% of catalyst at 20°C and 20 atm (initial pressure) of hydrogen for 24 h (neutral catalysts) or 20 h (cationic catalyst). [b] GLC analysis. [c] Optical purity was determined on the basis of the maximum rotation of the pure enantiomer, $[\alpha]_D^{18} -12.1°$ (neat) [20]. [d] Volume per cent.

TABLE 3

SOLVENT EFFECTS ON THE CHEMICAL AND OPTICAL YIELDS IN THE ASYMMETRIC HYDROGENATION OF n-PROPYL PYRUVATE WITH NEUTRAL AND CATIONIC RHODIUM CATALYSTS [a]

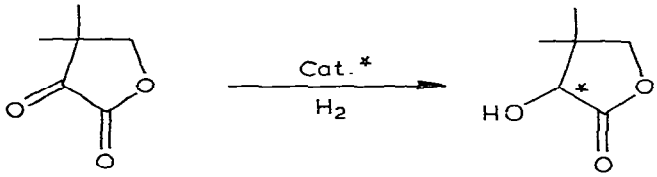


Catalyst	Solvent	Conversion(%) [b]	Optical Purity (% e.e.) [c]
[(—)DIOP]Rh(S)Cl	MeOH	57	24.9 (*R*)
	THF	100	41.9 (*R*)
	C_6H_6	100	34.7 (*R*)
(BPPM)Rh(S)Cl	MeOH	65	67.4 (*R*)
	THF	98	75.8 (*R*)
	C_6H_6	98	75.8 (*R*)
[((—)DIOP)Rh(COD)]$^+ClO_4^-$	MeOH	100	24.4 (*S*)
	THF	99	19.4 (*S*)
	C_6H_6	99	15.5 (*S*)
[(BPPM)Rh(COD)]$^+ClO_4^-$	MeOH	100	20.2 (*R*)
	THF	99	33.4 (*R*)
	C_6H_6	99	37.2 (*R*)

[a] Reactions were run with 0.5 mol% of catalyst at 20°C and 20 atm (initial pressure) of hydrogen for 24 h (neutral catalyst) or 20 h (cationic catalyst). [b] GLC analysis. [c] Optical purity was determined on the basis of the maximum rotation of the pure enantiomer, $[\alpha]_D^{18}$ —12.1° (neat) [20].

TABLE 4

SOLVENT EFFECTS ON THE CHEMICAL AND OPTICAL YIELDS IN THE ASYMMETRIC HYDROGENATION OF KETOPANTOYL LACTONE WITH NEUTRAL AND CATIONIC RHODIUM CATALYSTS [a]



Catalyst	Solvent	Conversion(%) [b]	Optical Purity(% e.e.) [c]
[(—)DIOP]Rh(S)Cl	MeOH	5.2	16.7 (*R*)
	THF	37.8	40.1 (*R*)
	C_6H_6	38.8	34.2 (*R*)
(BPPM)Rh(S)Cl	MeOH	6.2	26.6 (*R*)
	THF	99.5	80.7 (*R*)
	C_6H_6	100.0	86.7 (*R*)
[((—)DIOP)Rh(COD)]$^+ClO_4^-$	MeOH	60.3	6.3 (*S*)
	THF	100.0	2.6 (*R*)
	C_6H_6	99.4	18.7 (*R*)
[(BPPM)Rh(COD)]$^+ClO_4^-$	MeCH	19.2	15.7 (*S*)
	THF	86.9	8.0 (*R*)
	C_6H_6	99.5	53.5 (*R*)

[a] All reactions were run with 1.0 mol% of catalyst at 30°C and 50 atm (initial pressure) of hydrogen for 48 h. [b] GLC analysis. [c] Optical purity was determined on the basis of the maximum rotation of the pure enantiomer, $[\alpha]_D^{25}$ —50.7° (*c* 2.05, H_2O) [21].

of configuration is not observed, but the optical yields are remarkably decreased. As a whole, the results indicate that the chlorine ligand of the neutral complexes plays a significant role in the induction of asymmetry in these reactions. During the course of our work, a similar marked difference in enantioselectivity, mainly due to the presence or absence of the chlorine ligand, was reported by Tőrös, Heil and Markó in the asymmetric hydrogenation of acetophenone catalyzed by (+)DIOP-rhodium complexes [10].

Results on using ketopantoyl lactone as substrate are listed in Table 4. As ketopantoyl lactone has a rigid cyclic structure, this substrate is probably a more appropriate probe than n-propyl pyruvate for understanding the mechanism of asymmetric induction in the coordination sphere of catalyst. In fact, we could observe very remarkable solvent effects, especially for the cationic BPPM complex catalyst. Namely, the optical yield varies markedly as the coordinating solvent changes, and in methanol, which is a poorly coordinating solvent, the direction of asymmetric induction is reversed to *S*.

These results strongly indicate that solvent molecule plays an important role in the coordination sphere of the cationic rhodium complex and that the complex coordinated with a solvent molecule acts as the true catalyst. At the same time, the significant effect of the chlorine ligand in the neutral complex is also clearly shown in this case.

As for the solvent effects, Sinou and Kagan reported [11] an inversion of configuration due to a change of the solvent from benzene to ethanol in the asymmetric hydrogenation of α-acetamido-β-methylstyrene with a neutral (+)DIOP-rhodium complex as catalyst. As they proposed, a cationic species would be generated in ethanol. But, it should be noticed that α-acetamido-β-methylstyrene is a strongly coordinating substrate because it can act as bidentate ligand which has a large binding constant. Thus, in the presence of such a strongly binding ligand, a polar protic solvent, ethanol, may help the dissociation of the chlorine ligand to the outer sphere of the rhodium complex as counter anion, while a non-polar aprotic solvent, such as benzene, may not. On the other hand, carbonyl compounds are by far a more weakly coordinating substrate, compared with bidentate olefinic substrates *. Accordingly, it is reasonable to assume that the neutral catalysts do not release the chlorine ligand in methanol, in contrast to the case of α-acetamido-β-methylstyrene. Nevertheless, the observed marked decrease in the catalytic activity of neutral catalysts with (—)DIOP and BPPM may suggest the partial generation of another catalyst species in methanol. Solodar also reported [2] solvent effects on the reduction of 2-octanone catalyzed by a cationic rhodium complex with chiral mono-dentate phosphine ligands. However, these observations have as yet found no explanation.

Before discussing the possible mechanism of asymmetric induction, it is of some importance to mention the molecular structure of the catalysts. On the

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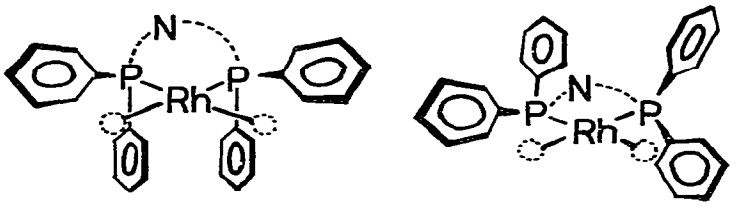
* In fact, the formation of a substrate-rhodium complex, $[(BPPM)Rh(CH_3COCOOn\text{-}Pr)]^+ClO_4^-$, could not be detected at all in the ^{31}P NMR spectrum of the mixture of $[(BPPM)Rh(CD_3OD)_n]^+ClO_4^-$ and large excess of n-propyl pyruvate in methanol-d_4, whereas that of the corresponding substrate-rhodium complex, $[(BPPM)Rh(CH_2 = C(COOH)NNCOMe)]^+ClO_4^-$, was readily observed [12].

basis of a stereochemical inspection using CPK models, there are only two possible conformations for the rhodium complex with BPPM or PPPM [(2*S*, 4*S*)-*N*-pivaloyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine] [13], in contrast to the DIOP-rhodium complex, which has several possible conformations. The simplified drawings are shown below:



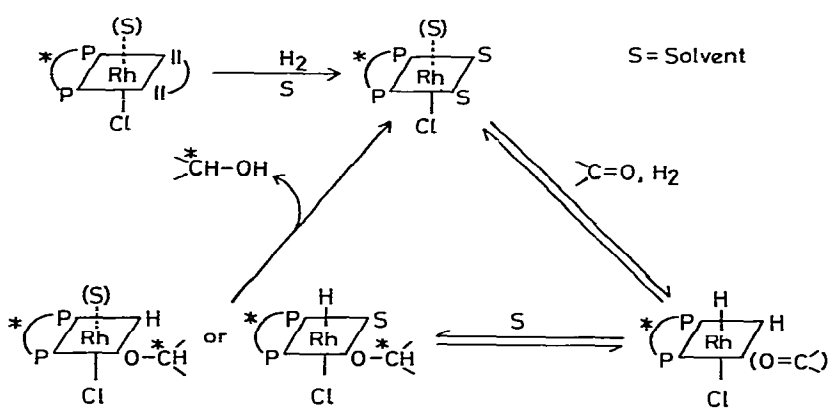
Conformation B Conformation A

The conformation A is closely similar to the structure of (DIOP)IrCl(COD) [COD = 1,5-cyclooctadiene] which was determined by Kagan et al. [14]. But this conformation seems ineffective for asymmetric induction because of its symmetrical coordination sphere. The conformation B is somewhat similar to the model proposed by Glaser [15]. This conformation has a highly asymmetrical coordination sphere and we believe that only conformation B plays a significant role in the asymmetric induction. In fact, the X-ray analysis of $[(PPPM)Rh(COD)]^+ClO_4^-$ has revealed that the complex takes the conformation B in the crystalline state, as shown in Figure 1 [16]. As is understood from Figure 1, the upper apical site is conjested by the *ortho* hydrogens of two edge phenyls while the lower apical site is vacant enough to accept the coordination of solvent molecule. As all the stereochemical situations in the coordination sphere of $[(BPPM)Rh(COD)]^+ClO_4^-$ must be virtually the same as those of $[(PPPM)Rh(COD)]^+ClO_4^-$, we can now discuss the possible mechanisms of the given reactions catalyzed by BPPM-rhodium complexes, having an image of the structure of the catalyst.

Scheme 2 illustrates a possible catalytic cycle of the neutral complex. The most significant point of the mechanism is that the chlorine ligand occupies the lower apical site throughout the reaction.

SCHEME 2.

PROPOSED CATALYTIC CYCLE OF NEUTRAL RHODIUM COMPLEX



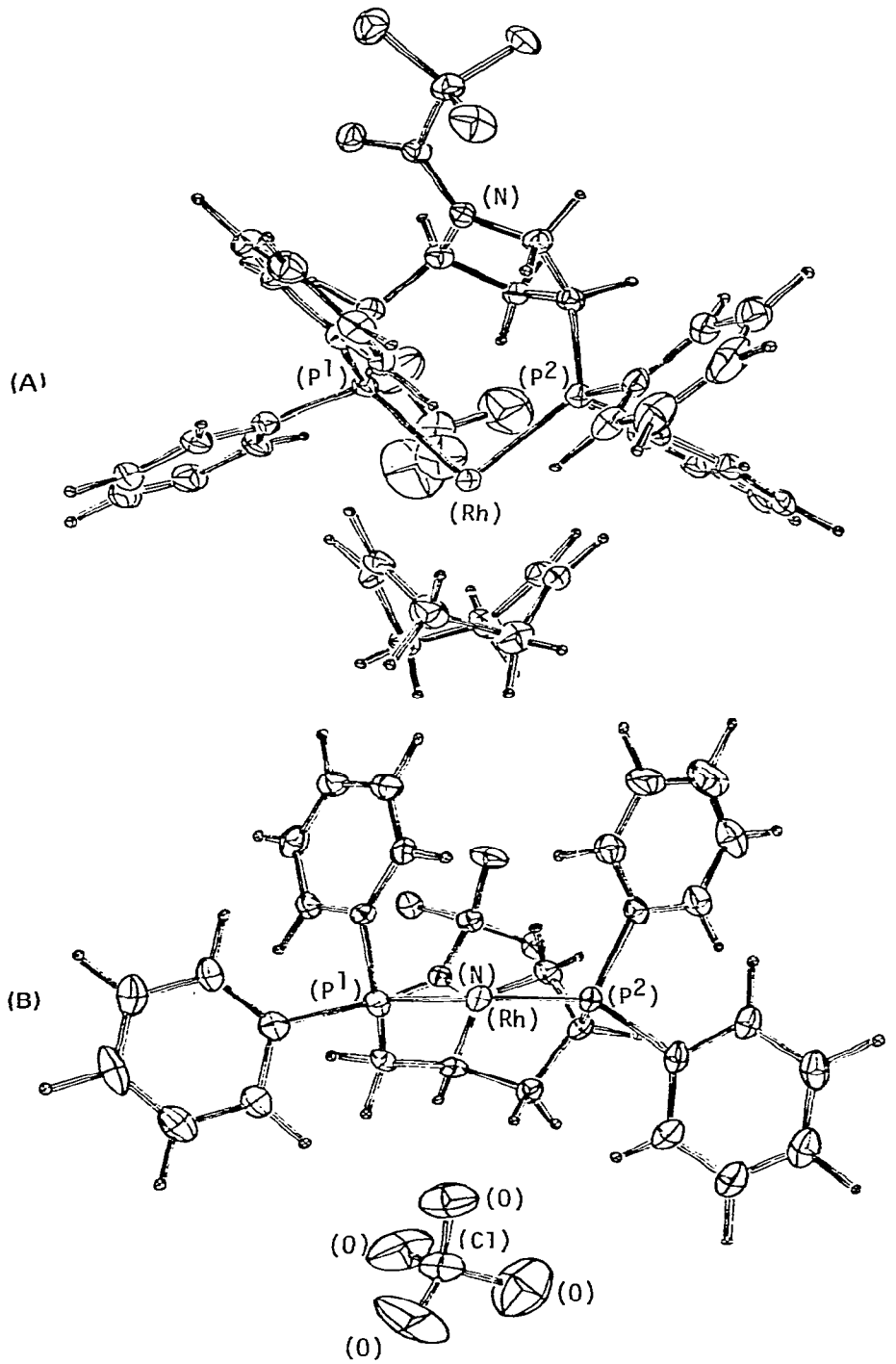


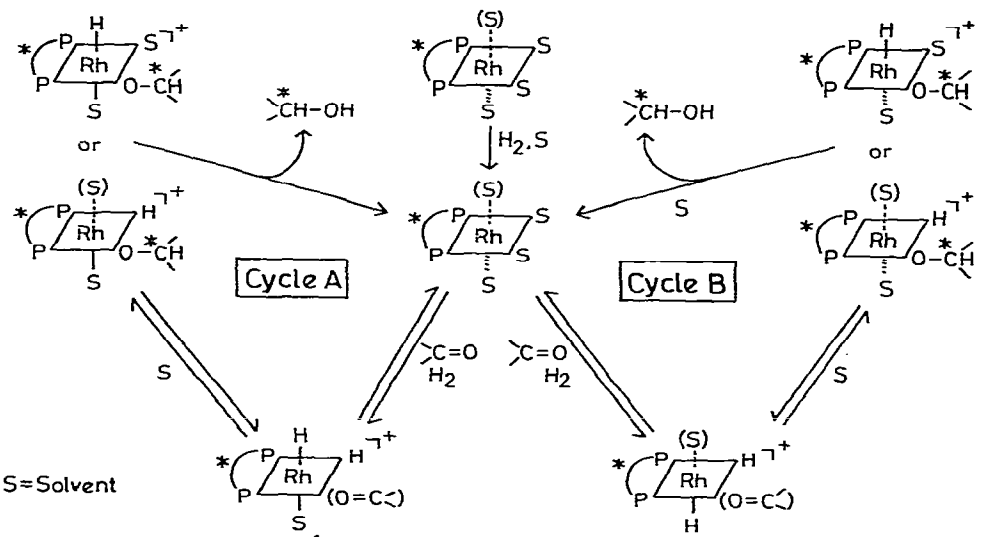
Fig. 1. Perspective views of $[(PPPM)Rh(COD)]^{+}ClO_4^{-}$. 1,5-Cyclooctadiene is omitted for simplicity in B.

The proposed mechanism involves a) oxidative addition of molecular hydrogen to a rhodium(I) species, b) formation of the substrate-rhodium(III)-dihydride intermediate, c) hydrogen migration giving an alkoxyrhodium(III)-hydride intermediate and d) reductive elimination of the product alcohol to regenerate the rhodium(I) species.

Similarly, Scheme 3 illustrates possible catalytic cycles of the cationic complexes. Although the proposed catalytic cycles involve essentially the same unit reactions, these are different with each other from the stereochemical point of view.

SCHEME 3.

PROPOSED CATALYTIC CYCLES OF CATIONIC RHODIUM COMPLEXES



The catalytic cycle A is the one for the catalyst species in strongly coordinating solvents such as benzene, in which benzene acts as η^2 ligand. The unusually strong interaction between a cationic rhodium complex with a *cis*-chelating diphosphine and aromatic compounds was revealed by Halpern et al. [17]. In this case the solvent molecule surely occupies the lower apical position throughout the reaction like the chlorine ligand of the neutral catalyst. In fact, as Table 4 shows, the asymmetric hydrogenation of ketopantoyl lactone with the cationic BPPM-rhodium catalyst in benzene gave (*R*)-pantoyl lactone with 53.5% e.e., which is comparable to the enantioselectivity of the neutral catalyst.

On the other hand, the catalytic cycle B is the one for the catalyst species in poorly coordinating solvents such as methanol. In this case, a diastereomeric mixture of the dihydride intermediates may be formed, and the one with lower apical hydrogen is rather favorable because of the vacancy of the lower apical site. It should be noted that the steric requirements of the favorable species in the catalytic cycle B are opposite to those in catalytic cycle A as far as the enantioface selection is concerned. Actually, as Table 4 shows, an inversion of

configuration takes place when the reaction is carried out in methanol, which gives (*S*)-pantoyl lactone. The ratio of the two dihydride intermediates in catalaytic cycle B is supposed to be very sensitive to the coordinating power of the solvent employed.

Although the proposed mechanism of asymmetric induction in the coordination sphere of BPPM-rhodium complexes is not necessarily applicable to the DIOP-rhodium complexes, the results obtained in the present study may suggest a similarity in these two systems.

Experimental

Measurements

Melting points and boiling points were uncorrected. Optical rotations were measured with a Union PM 201 automatic digital polarimeter. Analytical gas chromatography (GLC) was carried out on a Shimadzu GC-3BF using a column packed with 3% PEG-20M on Chromosorb W.

Materials

$[Rh(COD)Cl]_2$ was prepared from rhodium trichloride trihydrate and 1,5-cyclooctadiene [18]. BPPM was prepared from L-hydroxyproline in accordance with a previously reported method [8]. (—)DIOP was commercially available from Strem Chemicals Inc. n-Propyl pyruvate was prepared by azeotropic esterification of pyruvic acid. Ketopantoyl lactone was prepared by the oxidation of DL-pantoyl lactone with bromine in carbon tetrachloride in 96% yield by a modified method of Broquet and Bedin [19]. All the solvents used were degassed and stored under argon.

Preparation of the neutral catalysts

The neutral catalysts were prepared in situ by the reaction of $[Rh(COD)Cl]_2$ with the chiral diphosphine, BPPM or (—)DIOP, in a degassed solvent at ambient temperature.

Preparation of the cationic catalysts

The preparation of $[(BPPM)Rh(COD)]^+ClO_4^-$. Et_2O is described. To a solution of Rh(COD)(acac) [acac = acetylacetonato] (233 mg, 7.50×10^{-4} mol) in 1.0 ml of tetrahydrofuran under argon was added 70% perchloric acid (107 mg, 7.45×10^{-4} mol), and the mixture was stirred for 30 min at ambient temperature. Then, BPPM (402 mg, 7.26×10^{-4} mol) in 1.0 ml of tetrahydrofuran was added to the mixture. After stirring for 1.5 h at ambient temperature, 10 ml of diethyl ether was added and the resulting orange solid was collected by filtration, washed with diethyl ether and dried in a vacuum. $[(BPPM)Rh(COD)]^+ClO_4^-$. Et_2O was obtained in 98% yield (665 mg).

Competitive hydrogenation of n-propyl pyruvate

In a typical experiment, two 10 ml glass ampoules containing a magnetic stirring bar and a mixture of $[(BPPM)Rh(COD)]^+ClO_4^-$. Et_2O (13 mg, 1.3×10^{-5} mol), n-propyl pyruvate (325 mg, 2.5×10^{-3} mol) and tetrahydrofuran (1 ml) in each one, were prepared and 10 μl of water was added to one of the

ampoules. Then, both the ampoules were placed in a 100 ml autoclave, which was purged three times by filling (30 atm) and evacuating with hydrogen. The competitive hydrogenation was carried out at 20°C for 3 h under an initial hydrogen pressure of 20 atm with stirring. The conversion of the reaction was estimated by GLC analysis.

The reactions using other solvents and/or [(—)DIOPRh(COD)]$^{+}ClO_4^{-}$ as catalyst were performed in a similar manner.

Asymmetric hydrogenation

All the asymmetric hydrogenations of n-propyl pyruvate were run with 1.5×10^{-2} mol of the substrate and 7.6×10^{-5} mol of a rhodium catalyst using BPPM or (—) DIOP as chiral ligand in 4 ml of a solvent at 20°C for 20—24 h under an initial hydrogen pressure of 20 atm in a 100 ml stainless autoclave. For the measurement of optical rotation, the neat samples obtained by the direct distillation of the reaction mixture were used.

Similarly, all the asymmetric hydrogenations of ketopantoyl lactone were run with 1.0×10^{-2} mol of the substrate and 1.0×10^{-4} mol of a rhodium catalyst in 8 ml of solvent at 30°C for 48 h under an initial hydrogen pressure of 50 atm. For the measurement of optical rotation, the aqueous solutions (*c* 2.00—2.10) of the crystalline samples obtained by the direct distillation of the reaction mixture were used. When the conversion of the reaction was low, the distilled mixture of pantoyl lactone and ketopantoyl lactone was used for the measurement, in which the amount of pantoyl lactone was readily determined on the basis of GLC analysis since no by-product was produced, and the optical yield was estimated based on the concentration of pantoyl lactone.

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