Asymmetric Hydrogenation with Chiral Aminophosphine–Rhodium Complexes[1] and Chiral Recognition by Bisphosphine–Rhodium Complexes in the Asymmetric Hydrogenation of Olefins through the Chiral Helical Conformation of Phenyl Groups on the Phosphorus Atom

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The asymmetric hydrogenation of α-acylaminocinnamic acids with the rhodium complex of (1*R*,2*R*)-1,2-bis(*N*-diphenylphosphino-*N*-methylamino)cyclohexane has been reported to give preferentially (*S*)-amino acids. On the contrary, it has been found that the enantiomeric (*R*)-amino acids are obtained by hydrogenation with the rhodium complex of (1*R*,2*R*)-1,2-bis(diphenylphosphinamino)cyclohexane. The study of the inversion of the stereoselectivity of the rhodium complex of (1*R*,2*R*)-1,2-bis(diphenylphosphinamino)cyclohexane by the *N*-methylation of the ligand in asymmetric hydrogenation has been described. From stereochemical considerations, the chiral helical conformation of the phenyl groups attached on the phosphorus in bisphosphine–rhodium complexes may be responsible for the induced chirality of the product of the hydrogenation. A complex with a left-handed helicity would give (*R*)-amino acid, and a complex with a right-handed helicity would give (*S*)-amino acid. The effects of the solvents and substrate structures on the optical yields are also discussed.

In recent years, the catalytic asymmetric hydrogenation of α-acylaminocinnamic acid has been investigated in order to obtain chiral α-amino acid. Considerable efforts have been devoted not only to developing new chiral ligands,[2] but also to studying the mechanism of asymmetric hydrogenations.[3] Only a few papers have been reported,[2a] however, about the correlation of the ligand structure to the chirality of the products.

The stereochemistry of the produced acylamino acids is reversed by the *N*-methylation of the ligand in the hydrogenation with the rhodium complex of the bis-aminophosphine, which has a 1,2-bis(diphenylphosphinamino)ethane skeleton.[4] For example, (1*R*,2*R*)-1,2-bis(diphenylphosphinamino)cyclohexane, (*R*,*R*)-I, has been found to be an effective ligand for the rhodium-catalyzed asymmetric hydrogenation of α-acylaminocinnamic acids to give preferentially (*R*)-amino acids. On the contrary, its *N*,*N*′-dimethyl derivative, (1*R*,2*R*)-1,2-bis(*N*-diphenylphosphino-*N*-methylamino)cyclohexane, (*R*,*R*)-II, has been reported to give preferentially (*S*)-amino acids under similar reaction conditions. In view of the subtlety of the structural divergence between these two ligands, the origin of this marked difference in stereoselectivity should be further explored. The stereochemical consideration suggests that the chiral inversion may be caused by the difference in the configuration of the nitrogen atom, by which the four phenyl groups are caused to be arranged in a reverse helical orientation in each (*R*,*R*)-I and (*R*,*R*)-II complex.

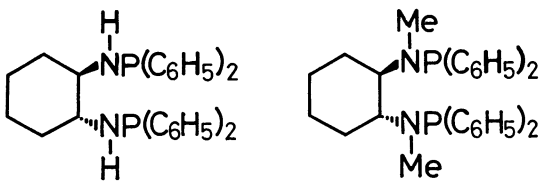
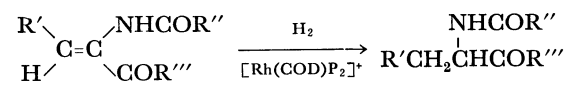


Fig. 1. Chiral aminophosphines, (*R*,*R*)-I (left) and (*R*,*R*)-II (right).

Results and Discussion

The α-acylaminocinnamic acids were hydrogenated with the cationic rhodium complexes of (*R*,*R*)-I, (*S*,*S*)-I, and (2*S*,3*S*)-2,3-bis(diphenylphosphinamino)butane, [(*S*,*S*)-III]. The results are summarized in Table 1.



Scheme 1.

Stereochemical Studies. As can be seen in Table 1, acylamino acids with an *R*-configuration were always obtained preferentially by the hydrogenation using the rhodium complex of (*R*,*R*)-I. On the other hand, the products with an *S*-configuration were preferentially obtained using either (*S*,*S*)-I or (*S*,*S*)-III as the chiral ligand. The most noticeable result is that *N*-acyl-(*S*)-amino acids were always obtained by using the (*R*,*R*)-II complex, contrary to the result obtained with the (*R*,*R*)-I complex. Moreover, it has previously been reported that the chiral inversion of the stereoselectivity by the *N*-methylation of the ligand is also observed in the rhodium complexes of (1*S*,2*S*)-1,2-bis(diphenylphosphinamino)-1,2-diphenylethane[4b] and (*R*)-1,2-bis(diphenylphosphinamino)propane.[4c] Therefore, the inversion may be an essential feature of these aminophosphine–rhodium complexes. The chiral inversion may be deduced as having the same origin, as the complex of (*S*,*S*)-I or (*S*,*S*)-III gives similar results in the hydrogenation, as has been described in the preceding paper.[1] In order to clarify the origin of the chiral inversion, the stereochemistry of these complexes has been considered.

As is shown in Fig. 2, the seven-membered chelate ring, consisting of the rhodium atom and two phosphorus atoms, may be considered to take predominantly a twist-chair conformation,[6] for the repulsion between the phenyl groups and the cyclohexane ring is reduced. By deduction by analogy, with the preferred conforma-

Table 1. Asymmetric hydrogenation[a] with chiral aminophosphine-rhodium complexes

Substrate R′	Substrate R″	Substrate R‴	Solvent[b]	Optical yield[c] (*R*,*R*)-I	(*S*,*S*)-I	(*S*,*S*)-III	(*R*,*R*)-II[d]	
C_6H_5	CH_3	OH	Methanol	32(*R*)	30(*S*)			
C_6H_5	CH_3	OH	Ethanol	41(*R*)	41(*S*)	45(*S*)	89(*S*)	92(*S*)
C_6H_5	CH_3	OH	2-Propanol	70(*R*)	71(*S*)	80(*S*)		
C_6H_5	CH_3	OH	Methanol/benzene	50(*R*)	50(*S*)			
C_6H_5	CH_3	OH	Ethanol/benzene	70(*R*)	72(*S*)	62(*S*)		
C_6H_5	CH_3	OH	2-Propanol/benzene	64(*R*)	63(*S*)	94(*S*)		
C_6H_5	C_6H_5	OH	Ethanol	43(*R*)	43(*S*)	32(*S*)	92(*S*)	
C_6H_5	C_6H_5	OH	2-Propanol	70(*R*)	70(*S*)	80(*S*)		
C_6H_5	C_6H_5	OH	Ethanol/benzene	62(*R*)	60(*S*)	69(*S*)		
C_6H_5	C_6H_5	OH	2-Propanol/benzene	49(*R*)	48(*S*)	93(*S*)		

a) Hydrogenation was carried out with 1 g of a substrate and 7 mg of a cationic rhodium complex. b) The ratio of the mixed solvent was 1:1 (v/v). c) Calculated on the basis of the following reported values for optically pure enantiomers: *N*-acetyl-(*S*)-phenylalanine $[\alpha]_D^{26}=+46.0°$ ($c=1.0$, C_2H_5OH),[5] *N*-benzoyl-(*S*)-phenylalanine $[\alpha]_D^{26}=-40.3°$ ($c=1.0$, CH_3OH).[5] The predominant configuration of the product is shown in parentheses. d) Quoted from Refs. 4b, c.

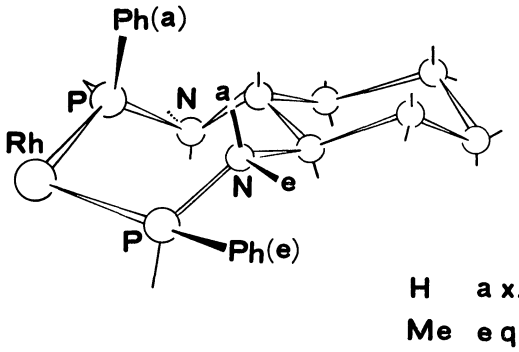


Fig. 2. The conformation of seven-membered chelate ring. The letters of a and ax. mean a *quasi*-axial position. The letters of e and eq. mean a *quasi*-equatorial position.

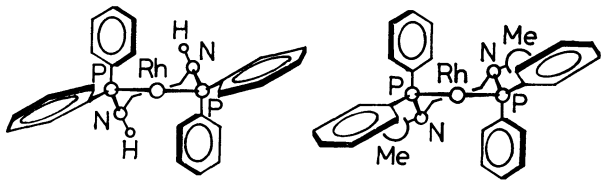


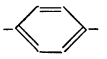
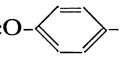
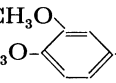
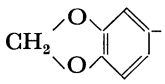
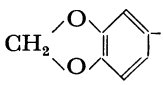
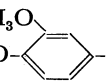
Fig. 3. Chiral skew conformation of four phenyl groups in the rhodium complex of (*R*,*R*)-I and (*R*,*R*)-II. The skeleton of the cycleohexane ring is omitted for simplicity.
Left: (*R*,*R*)-I complex, left-handed helicity; Right: (*R*,*R*)-II complex, right-handed helicity.

tion of piperazine derivatives,[7] the hydrogen atom on the nitrogen atoms in the (*R*,*R*)-I complex may occupy a *quasi*-axial position and so be $(R)_N$, and the methyl group in the (*R*,*R*)-II may occupy a *quasi*-equatorial position and so be $(S)_N$, in the twist-chair conformation. This inversion of the configuration around the nitrogen atoms, despite having the same configuration of $(R)_C$, may exert significant effects on the orientation of the *quasi*-equatorial phenyl groups. Affected by the substituent (H or CH_3) on the nitrogen atoms, the rotation of the *quasi*-equatorial phenyl groups in (*R*,*R*)-I complex and (*R*,*R*)-II complex may be restricted in a reverse direction, and the correlated rotation of the *quasi*-axial phenyl groups may give reverse helical conformations, as is shown in Fig. 3. That is, the four phenyl groups may be twisted in a left-handed orientation in the (*R*,*R*)-I complex and in a right-handed orientation in the (*R*,*R*)-II complex. These preferred conformations can also be satisfactorily understood in terms of the CPK molecular models.

The inversion of stereoselectivity in the asymmetric hydrogenation may be caused mainly by the difference in the helical conformation; the complex with left-handed helicity would give (*R*)-amino acids, while the complex with right-handed helicity would give (*S*)-amino acids. The hypothesis concerning the structural correlation between the helical conformation of phenyl groups and the chirality of the products may also be adopted in treating other results previously reported.[2a,b] The structure of the rhodium complex of (2*S*,3*S*)-2,3-bis(diphenylphosphino)butane has been determined by X-ray analysis.[8] This complex has the left-handed helicity and has been reported surely to give (*R*)-amino acids.[2b] The phenyl groups are skewed in a right-handed orientation in the rhodium complex of (*R*,*R*)-1,2-bis(*P*-phenyl-*o*-methoxyphenylphosphino)ethane,[2a] which has been reported certainly to give (*S*)-amino acids.

Solvent Effect. As is shown in Table 1, the optical yield of the products is dependent on the solvent used in the reaction. For the reaction carried out in an alcohol, such as methanol, ethanol, or 2-propanol, as well as in a mixed solvent of alcohol and benzene, the optical yield generally increases in this order: methanol<ethanol<2-propanol, and is higher in the mixed solvent than in alcohol, with the exception of the hydrogenation in the mixed solvent of 2-propanol and benzene with the (*S*,*S*)-I complex. The solvent may be supposed to play an important role in making a specific conformation of the catalyst more predominant. Thus, a solvent may be considered to contribute to fixing the specific conformation of the transition

Table 2. Asymmetric hydrogenation of α-acylaminocinnamic acid derivatives

Substrate			Optical yield[a]	
R′	R″	R‴	[Rh(COD)(*S*,*S*)-I]$^+$	[Rh(COD)(*S*,*S*)-III]$^+$
C_6H_5	CH_3	OH	72(*S*)	62(*S*)
C_6H_5	CH_3	NH_2	92(*S*)	94(*S*)
C_6H_5	C_6H_5	OH	60(*S*)	69(*S*)
C_6H_5	C_6H_5	NH_2	70(*S*)	80(*S*)
HO- 	CH_3	OH	53(*S*)	43(*S*)
AcO- 	CH_3	OH	56(*S*)	53(*S*)
CH_3O CH_3O- 	CH_3	OH	56(*S*)	42(*S*)
	CH_3	OH	49(*S*)	34(*S*)
	C_6H_5	OH	28(*S*)	13(*S*)
CH_3O AcO- 	CH_3	OH	48(*S*)	

a) Calculated on the basis of the following reported values for optically pure enantiomers: *N*-acetyl-(*S*)-tyrosine $[\alpha]_D^{27}=+51.5°$ ($c=1.0$, MeOH),[5] *O*,*N*-diacetyl-(*S*)-tyrosine $[\alpha]_D^{27}=+45.4°$ ($c=1.0$, MeOH),[5] *N*-acetyl-β-(3,4-dimethoxyphenyl)-(*S*)-alanine $[\alpha]_D=+46.2°$ ($c=5.0$, MeOH),[9] *N*-acetyl-β-(3,4-methylenedioxyphenyl)-(*S*)-alanine $[\alpha]_D^{18}=+53.4°$ ($c=1.8$, EtOH),[10] *N*-benzoyl-β-(3,4-methylenedioxyphenyl)-(*S*)-alanine $[\alpha]_D=-11.0°$ ($c=2.0$, *N*-NaOH),[11] *N*-acetyl-β-(4-acetoxy-3-methoxyphenyl)-(*S*)-alanine $[\alpha]_D^{20}=+40.7°$ ($c=1.0$, MeOH).[5]

state in a degree dependent upon its ability of coordination and its bulkiness.

Substrate Studies. Further studies were carried out on the hydrogenation of α-acylaminocinnamic acid derivatives with the rhodium complexes of (*S*,*S*)-I and (*S*,*S*)-III. The results are shown in Table 2.

As can be seen in Table 2, the optical yield depends greatly on the substrate structures. For the effects of substituents of α-acylaminocinnamic acid on the optical yield of the reaction, a tendency to obtain a higher optical yield is generally observed: 1) As for the phenyl group, the unsubstituted one is more advantageous than one with a substituent, such as a hydroxyl, alkoxyl, or acetoxyl group. 2) As for the carboxylic acid moiety, the carbamoyl derivative is more favorable compared with the parent carboxylic acid. Any substituent on the phenyl groups may prevent the substrate from approaching the catalytic rhodium complex. The hydrogenation of α-acetamidocinnamic acid and its amide with the (−)-DIOP–rhodium complex has been reported to give the corresponding product, with 82%e.e. and 71%e.e. respectively.[12] Therefore, the advantage of the carbamoyl group over the carboxyl group may be characteristic of this system.

Experimental

General. The measurements of the melting points, the ^{1}H-NMR, the optical rotations, and the apparatus used for hydrogenation were the same as those described in the preceding paper.[1] The liquid chromatograms were recorded on a Hitachi KLA-5 amino-acid analyzer.

Substrates and Solvents. The α-acetamidocinnamic acid,[13] α-benzamidocinnamic acid,[14] α-acetamido-3,4-dimethoxycinnamic acid,[15] α-acetamido-3,4-methylenedioxycinnamic acid,[13] α-benzamido-3,4-methylenedioxycinnamic acid,[16] α-acetamido-4-hydroxycinnamic acid,[17] α-acetamido-4-acetoxycinnamic acid,[18] and α-acetamido-4-acetoxy-3-methoxycinnamic acid[19] were prepared by standard Erlenmeyer procedures, sometimes with minor modifications of the published directions. The α-benzamidocinnamamide was prepared as follows: 2-phenyl-4-benzylidene-5-oxazolone (15.3 g) was allowed to react with liquid ammonia (20 ml) in a sealed tube at room temperature for one night. The ammonia was then removed by breaking the seal, and the residual crystals were recrystallized from methanol; 10.9 g; mp 165—166 °C, Found: C, 71.99; H, 5.34; N, 10.57%. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52%. The α-acetamidocinnamamide was prepared by a similar procedure; mp 197—198 °C. Found: C, 64.51; H, 5.92; N, 13.59%. Calcd for $C_{11}H_{12}O_2N_2$: C, 64.99; H, 5.92; N, 13.72%.

The solvents for hydrogenation were purified as has been described in the preceding paper.

*Preparation of (*R,R*)-I and Its Rhodium Complex.* (1*R*,2*R*)-1,2-Cyclohexanediamine was prepared according to the method of Asperger and Liu;[20] bp 76—78 °C (13 mmHg), $[\alpha]_D^{24}=-41.6°$ ($c=4.9$, C_6H_6). (*R*,*R*)-I and its cationic rhodium complex were prepared much like (*S*,*S*)-I, described in the preceding paper; mp 130—132 °C, $[\alpha]_D^{15}=-4.51°$ ($c=1.0$, C_6H_6). Found: C, 74.47; H, 6.65; N, 5.79; P, 12.81%. Calcd for $C_{30}H_{32}N_2P_2$: C, 74,67; H, 6.68; N, 5.81; P, 12.84%. [Rh(COD)(*R*,*R*)-I]$^+$$ClO_4^-$·1/2$CH_2Cl_2$; mp 142—145 °C (dec), Found: C, 55.87; H, 5.90; N, 3.30%. Calcd for $RhC_{38}H_{44}N_2P_2ClO_4\cdot 1/2CH_2Cl_2$:

C, 55.34; H, 5.43; N, 3.53%. The rhodium complex was stored in an ampoule under argon.

Hydrogenation Procedure. Hydrogenation was carried out by the method described in the preceding paper. Three methods for the isolation of the hydrogenation product were used, depending on the substrate, as follows: Method 1. For *N*-acetyltyrosine, *O*,*N*-diacetyltyrosine, and *N*-acetyl-*β*-(4-acetoxy-3-methoxylphenyl)alanine, the hydrogenation product was separated from the insoluble catalyst by extraction with water followed by concentration. Method 2. For *N*-acetylphenylalaninamide and *N*-benzoylphenylalaninamide, the product was hydrolyzed with concd hydrochloric acid by refluxing for 1 h. The solution was then filtered, and the filtrate was evaporated to dryness. The optical purity of the phenylalanine thus obtained was determined by means of a liquid chromatogram according to the Manning and Moore method.[21] Method 3. For the other compounds, the product was extracted with 0.5 mol dm^{-3} NaOH. The filtrate was acidified with dilute HCl and then repeatedly extracted with the mixed solvent of ether (5 ml) and dichloromethane (20 ml). The organic layer was dried over sodium sulfate and then evaporated to dryness.

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15) Prepared by a procedure similar to that given in Ref. 13, using the appropriate aldehyde and recrystallizing the acid from methanol.

16) Prepared as in Ref. 13. The acid was recrystallized from ethanol.

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18) Prepared as in Ref. 13. The acid was recrystallized from ethanol.

19) Prepared as in Ref. 13. The acid was recrystallized from methanol.

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