Asymmetric Hydrogenation of Dehydrodipeptides with Rhodium(I)-Chiral Diphosphinites. Selective (S,S)- and (R,R)-Product Formation by Double Asymmetric Induction

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In the hydrogenation of dehydrodipeptides, the effect of chiral center of the substrate ((S) or (R)) on the asymmetric induction was examined using the catalysts of Rh(I)-chiral diphosphinite containing pyrrolidine moiety (POP). The catalysts with POP's having the ω-(dimethylamino)alkyl group indicated an extremely large double asymmetric induction to give (S,S)- or (R,R)-product in high stereoselectivities, depending on the chiral center of the substrates. This result was ascribed to the electrostatic interaction between the ligand and substrate. POP's without ω-(dimethylamino)alkyl group gave (R,R)-product for (R)-substrate in a high stereoselectivity by the steric effect between the ligand and substrate, while for (S)-substrate, (S,S)-product was obtained in a low stereoselectivity.

In the catalytic asymmetric hydrogenation with Rh(I) catalysts, asymmetric induction is generally caused by the steric interaction between the ligand and the substrate on the rhodium species.[1] If the electrostatic interaction between the ligand and the substrate intensifies the stereocontrol, the chiral catalyst will be more widely applied to the asymmetric reactions.

The authors prepared new chiral diphosphinites with pyrrolidine moiety (POP's) from (+)-diethyl tartrate, which are listed in Table 1. Some of them have ω-(dimethylamino)alkyl substituent, which is expected to interact electrostatically with a carboxyl group of the substrate. They were applied to the asymmetric hydrogenation of olefinic compounds with a carboxyl group and proved to be very effective for the hydrogenation of dehydrodipeptides with (S)-chiral center.[2,3] In the reaction of dehydrodipeptides, the carboxyl group can approach the dimethylamino group of the ligand on rhodium species, causing a strong electrostatic interaction. In the reaction of Ac-ΔPhe-Gly-OH without a chiral center, however, only moderate optical yields were obtained.[2,3] This would indicate that the steric effect by the chiral center

of the dehydrodipeptides and the electrostatic interaction between the ligand and substrate lead to the high stereoselectivity in the Rh(I)-POP-catalyzed hydrogenation.

In this paper, we will describe how the chiral center ((S) and (R)) of dehydrodipeptides affects the stereoselectivity, leading to an extremely large double asymmetric induction in the Rh(I)-POP-catalyzed hydrogenation.

Results and Discussion

The catalysts of the diphosphinites (POP's) were examined for the asymmetric hydrogenation of dehydrodipeptides. POP-AE and POP-AP have ω-(dimethylamino)alkyl groups, which facilitate electrostatic interaction between the ligand and substrate. POP-IP is a carbon analogue of POP-AE, and the isopentyl group will have a similar steric factor to that of the 2-(dimethylamino)ethyl group of POP-AE. For p-Me-POP-AE, p-MeO-POP-AE, and p-MeO-POP-IP, the increasing in the electron density on the phosphorus atoms of the ligands will cause the stronger coordination of them onto rhodium. The results of asymmetric hydrogenations of dehydrodipeptides using Rh(I)-POP catalysts are summarized in Table 2. For the substrates with (S)-chiral center, POP's with ω-(dimethylamino)alkyl group showed good to excellent stereoselectivities. For Ac-ΔPhe-(S)-Phe-OH, the stereoselectivity with p-Me-POP-AE and p-MeO-POP-AE was near 100% d.e. POP's without dimethylamino group gave low or moderate optical yields. These results clearly indicated the contribution of the dimethylamino group of POP in the asymmetric induction.

From the hydrogenation of Ac-ΔPhe-Gly-OH and dehydrodipeptides with (S)-chiral center, the present POP's were considered to have (S)-selectivity.[2,3] Surprisingly, the hydrogenation of dehydrodipeptides with (R)-chiral center using POP's with dimethylamino group gave (R,R)-product with high optical yields (86—96% d.e.) instead of (S,R)-isomer. The reaction of Ac-ΔPhe-(R)-Phe-OH was much slower than that of Ac-ΔPhe-(S)-Phe-OH. Achiral 1,2-bis-

TABLE 1. CHIRAL DIPHOSHINITES (POP's)

Diphosphinite[a]	Ar	R
POP-AE	Ph	CH₂CH₂N(CH₃)₂
p-Me-POP-AE	CH₃—⟨O⟩—	CH₂CH₂N(CH₃)₂
p-MeO-POP-AE	CH₃O—⟨O⟩—	CH₂CH₂N(CH₃)₂
POP-AP	Ph	CH₂CH₂CH₂N(CH₃)₂
POP-IP	Ph	CH₂CH₂CH(CH₃)₂
p-MeO-POP-IP	CH₃O—⟨O⟩—	CH₂CH₂CH(CH₃)₂
POP-BZ	Ph	CH₂Ph

a) AE, AP, IP, and BZ represent alkyl group(R) of POP and denote dimethylaminoethyl, dimethyl-aminopropyl, isopentyl, and benzyl, respectively.

[bis(4-methoxyphenyl)phosphinooxy]ethane catalyst gave (S,S)- or (R,R)-product with low optical yields (20% d.e.) for Ac-ΔPhe-(S)-Ala-OH and Ac-ΔPhe-(R)-Ala-OH, respectively. These results indicate that the POP catalysts caused an excellent double asymmetric induction, leading to high stereoselectivity for both (S)- and (R)-substrate. This makes a striking contrast to the results reported with chiral diphosphines.[4]

It is further noted that POP's without dimethylamino group gave (R,R)-product in fairly high stereoselectivities (68—90% d.e.), though they gave low optical yields for (S,S)-isomer from (S)-substrates.

[Rh(p-MeO-POP-AE)(cod)]+BF4− was treated with an equimolar amount of perchloric acid in ethanol-methanol solution; this resulted in an orange-yellow precipitate. ¹H NMR spectra of this orange-yellow complex (A) in CD₃OD showed that the protonation occurred mainly at the ω-dimethylamino group of p-MeO-POP-AE. The hydrogenation with the complex (A) afforded much lower stereoselectivities for Ac-ΔPhe-(S)-Ala-OH and Ac-ΔPhe-(R)-Ala-OH (62% and 66% d.e., respectively) (Table 3). From these results, it is concluded that the dimethylamino group of POP plays an important role in the asymmetric induction by electrostatic interaction with a carboxyl group of the substrate. The result of the hydrogenation of Ac-ΔPhe-(S)-Ala-OMe with POP-AP supports the above conclusion: In the reaction of Ac-ΔPhe-(S)-Ala-OMe, Rh(I)-(POP-AP) catalyst gave a very low optical yield ((S,S)/(R,S)=46/54, 8% d.e.), while the same catalyst afforded a high diastereomeric excess ((S,S)/(R,S)=91/9, 82% d.e.) in the reaction of Ac-ΔPhe-(S)-Ala-OH.

(R)-Selectivity observed in the case of Ac-ΔPhe-(S)-

Ala-OMe by POP-AP was in accord with the reactions of dehydroamino acids using POP-AP where electrostatic interaction is not likely to function.[3]

Tertiary amine moiety of p-MeO-POP-IP was also converted to the ammonium type by treating [Rh(p-MeO-POP-IP)(cod)]+BF4− with HClO₄. The resulting complex (B) gave similar stereoselectivities for both (S)- and (R)-substrates to that for p-MeO-POP-IP complex (Table 3). Therefore, it is unlikely that nitrogen of the pyrrolidine ring contributed to the asymmetric induction. In the case of dehydrodipeptide esters, electrostatic interaction between the substrate and the ligand will be impossible. However, the double asymmetric induction with POP-IP was also observed for the esters with (R)-chiral center (Table 4). Therefore, it would be the steric effect of the POP's without dimethylamino group that produced a fairly large double asymmetric induction for (R,R)-products from (R)-substrates. In the reaction of the substrate with (R)-chiral center, methoxyl group on the ligand slightly lowered the (R,R)-selectivity, contrary to the results of the (S)-substrate (Tables 2 and 4), since strong coordination of the ligand onto rhodium increased (S)-selectivity inherent to the ligand.

As shown in Fig. 1, the system of Rh(I)-(p-MeO-POP-IP) containing Ac-ΔPhe-Ala-OH gave the same CD spectra irrespective of the chirality in the substrate. On the other hand, CD spectra of the system of Rh(I)-(p-MeO-POP-AE) containing Ac-ΔPhe-Ala-OH depended on the chirality of the substrate. This indicates that the substrate with (S)-chiral center coordinates onto rhodium in a different mode from that for the substrate with (R)-chiral center in the p-MeO-POP-AE system. That is to say, the dimethyl-

TABLE 2. Asymmetric hydrogenation of dehydrodipeptides using the catalysts of POP's[a]

Dehydrodipeptide[b]	Diphosphinite[c]	(S)				(R)			
		Time	Conversion	(S, S)/(R, S)	% d.e.	Time	Conversion	(S, R)/(R, R)	% d.e.
		min	%			min	%		
Ph⟩C-C⟨NHCOCH₃ / CONHCH⟨CH₂Ph / CO₂H	POP-AE	180	71	95/5	90				
	p-Me-POP-AE	45	100	>99/<1	>98				
	p-MeO-POP-AE	15	100	>99/<1	>98	16 h	90	7/93	86
	POP-AP	120	91	93/7	86				
(Ac-ΔPhe-Phe-OH)	POP-IP	120	92	79/21	58				
	p-MeO-POP-IP	120	84	82/18	64	20 h	76	9/91	82[d]
Ph⟩C-C⟨NHCOCH₃ / CONHCH⟨CH₃ / CO₂H	POP-AE	30	100	94/6	88	50	100	4/96	92
	p-MeO-POP-AE	30	100	98/2	96	25	100	7/93	86
	POP-AP	30	100	91/9	82	40	73	8/92	84
	POP-IP	20	100	68/32	36	30	100	5/95	90
(Ac-ΔPhe-Ala-OH)	p-MeO-POP-IP	25	100	69/31	38	16	100	7/93	86
	POP-BZ	40	100	66/34	32	40	100	16/84	68
	e)	40	100	60/40	20	40	100	40/60	20

a) Hydrogenations were performed in ethanol at 20 °C under atmospheric hydrogen pressure. b) Dehydrodipeptide/Rh=50. c) Diphosphinite/Rh=1.5. d) Reaction temp=40 °C. e) [Rh(1, 2-bis{bis(4-methoxyphenyl)phosphinooxy}ethane) (cod)]+BF4−.

TABLE 3. Asymmetric hydrogenation of Ac-ΔPhe-(S)-Ala-OH and Ac-ΔPhe-(R)-Ala-OH with the complex A and B[a]

Catalyst[b]	(S)				(R)			
	Time	Conversion	(S, S)/(R, S)	% d.e.	Time	Conversion	(S, R)/(R, R)	% d.e.
	min	%			min	%		
Complex A	30	100	81/19	62	30	100	17/83	66
Complex B	90	73	70/30	40	40	68	12/88	76

a) Hydrogenations were performed in ethanol at 20 °C under atmospheric hydrogen pressure. b) Ac-ΔPhe-Ala-OH-/Rh=50

TABLE 4.   ASYMMETRIC HYDROGENATION OF DEHYDRODIPEPTIDE ESTERS WITH THE CATALYSTS OF POP-IP AND p-MeO-POP-IP[a]

Dehydrodipeptide[b]	Diphosphinite[c]	(S)				(R)			
		Time	Conversion	(S, S)/(R, S)	% d.e.	Time	Conversion	(S, R)/(R, R)	% d.e.
		min	%			min	%		
Ph C=C NHCOCH₃ CONHCH CH₂Ph CO₂CH₃ (Ac-ΔPhe-Phe-OMe)	POP-IP	180	100	51/49	2				
	p-MeO-POP-IP	60	100	55/45	10	180	45	35/65	30
Ph C=C NHCOCH₃ CONHCH CH₃ CO₂CH₃ (Ac-ΔPhe-Ala-OMe)	POP-IP	20	100	59/43	16	25	100	17/83	66
	p-MeO-POP-IP					30	100	22/78	56

a) Hydrogenations were performed in ethanol at 20 °C under atmospheric hydrogen pressure.   b) Dehydrodipeptide/Rh=50.   c) Diphosphinite/Rh=1.5.
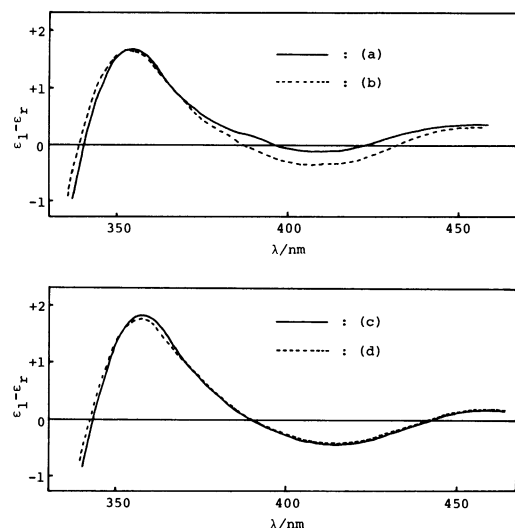

Fig. 1.   CD spectra of Rh(I)-(p-MeO-POP-AE) and Rh(I)-(p-MeO-POP-IP) systems in the presence of Ac-ΔPhe-Ala-OH in methanol solution. ([Rh]= 5.0×10⁴ mol dm⁻³, [POP]=6.0×10⁻⁴ mol dm⁻³, [Ac-ΔPhe-Ala-OH]=2.5×10⁻³ mol dm⁻³).
(a): Rh(I)-(p-MeO-POP-AE)-(Ac-ΔPhe-(S)-Ala-OH), (b): Rh(I)-(p-MeO-POP-AE)-(Ac-ΔPhe-(R)-Ala-OH), (c): Rh(I)-(p-MeO-POP-IP)-(Ac-ΔPhe-(S)-Ala-OH), (d): Rh(I)-(p-MeO-POP-AE)-(Ac-ΔPhe-(R)-Ala-OH).

amino group of the ligand could affect the step of prochiral face selection of the substrate by means of the electrostatic interaction with the carboxyl group of the substrate to emphasize the steric effect of the chiral center in the substrate.

In the reaction of Ac-ΔPhe-(S)-Ala-OH in ethanol, p-MeO-POP-AE afforded much higher optical yield than p-MeO-POP-IP, while similar optical yields were obtained by the above two diphosphinites in the reaction of Ac-ΔPhe-(R)-Ala-OH in ethanol. The hydrogenation of Ac-ΔPhe-(R)-Ala-OH in 2-propanol using p-MeO-POP-AE gave higher optical yield than that by p-MeO-POP-IP (86% and 78% d.e., respectively). This is because a decrease in the polarity of solvent can emphasize the electrostatic interaction between the ligand and substrate. But the difference in the optical yields between the two diphosphinites in 2-propanol was not large. So it is considered that the contribution of the electrostatic interaction for (R,R)-product

formation would be smaller than that for (S,S)-product formation.

As described so far, the present POP's with the dimethylamino group showed an excellent stereoselectivity in the hydrogenation of dehydrodipeptides with (S)- or (R)- chiral center by the extremely large double asymmetric induction. These phenomena will be ascribed mainly to the contribution of the electrostatic interaction to emphasize the stereocontrol for asymmetric induction. The steric interaction between the substituent on the chiral center of the substrate and the phenyl group on the phosphorus atom of the ligand evoked by the electrostatic interaction will affect the selection of the prochiral face of the substrate in coordination onto rhodium.[3] On the other hand, POP's without dimethylamino group indicated high (R)-selectivity in the reaction of the (R)-substrate due to the steric effect of the ligand, though the details of the stereocontrol are not clear in the present stage.

p-MeO-POP-AE and p-MeO-POP-IP were applied to the hydrogenation of Ac-ΔPhe-Asp-OH with two carboxyl groups capable of interaction with the ligand. p-MeO-POP-AE showed a double asymmetric induction in the case of both Ac-ΔPhe-(S)-Asp-OH and Ac-ΔPhe-(R)-Asp-OH, while with p-MeO-POP-IP the chirality newly formed was the same for both substrates. This would suggest the possibility of selecting the newly formed chirality of the product by utilizing the steric factor and/or electrostatic factor of the present POP catalysts. Furthermore, it will be fruitful to apply the present POP catalysts to other substrates, for example, dehydrodipeptides of Y-AA-ΔAA-OH type, or dehydrooligopeptides.

Experimental

Rh(I) catalysts were prepared in situ from [Rh(cod)₂]⁺BF₄⁻ and a diphosphinite (POP). The procedure of asymmetric hydrogenations and determination of the optical yields were the same as described previously.[3] CD spectra were measured by the method described previously.[3]

Materials.   All N-acetyl dehydrodipeptides were prepared by Bergmann's method.[5] Esterification of N-acetyl

dehydrodipeptides was performed by a conventional method.[4c] All solvents were dried, distilled, and stored under nitrogen. [Rh(cod)$_2$]$^+$BF$_4^-$ was prepared by a conventional method and stored under nitrogen.[6]

Preparation of Chiral Diphosphinites (POP-BZ and p-MeO-POP-IP).   (3S, 4S)-N-*Benzyl-3,4-pyrrolidinediol*: Benzylamine (30 cm^3, 27.5×10^{-2} mol) and 1,4-di-O-tosyl-L-threitol (24.2 g, 5.6×10^{-2} mol) were reacted in dioxane under nitrogen; the product was treated in the manner described previously.[3] (7.0 g, 64% yield) [α]$_D$+8.5° (c 2.07, CHCl$_3$); ^{1}H NMR δ=2.45—2.89 (4H, m, H^c), 3.55 (2H, s, H^b), 4.01 (2H, br t, H^d), 4.30 (2H, s, H^e), 7.18(5H, s, H^a).
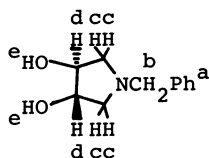
(3S,4S)-N-*Benzyl-3,4-bis(diphenylphosphinooxy)pyrrolidine* (POP-BZ): The diol (870 mg, 4.5×10^{-3} mol) and chlorodiphenylphosphine (2.2 g, 1.0×10^{-2} mol) were reacted in the presence of triethylamine (1.0 g, 1.0×10^{-2} mol); white crystals of POP-BZ were obtained by the work up described previously.[3] (1.8 g, 90% yield) [α]$_D$+50.4° (c 1.02, C$_6$H$_6$); ^{1}H NMR (CDCl$_3$) δ=2.53—3.11 (4H, m, H^c), 3.56 (2H, br s, H^b), 4.55 (2H, br m, H^d), 7.20 (25H, s, m, H^a, H^e).
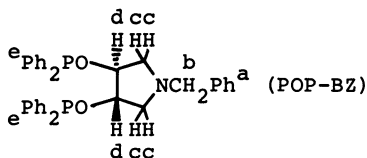

(3S,4S)-N-*Isopentyl-3,4-bis[bis(4-methoxyphenyl)phosphinooxy]-pyrrolidine* (p-MeO-POP-IP): (3S,4S)-N-Isopentyl-3,4-pyrrolidinediol (200 mg, 1.2×10^{-3}mol) and chlorobis(4-methoxyphenyl)phosphine (670 mg, 2.4×10^{-3} mol) were reacted in the presence of triethylamine (720 mg, 7.1×10^{-3} mol); white crystals of p-MeO-POP-IP were obtained by the procedure described previously.[3] (310 mg, 40% yield)[α]$_D^{20}$ +53.3° (c 0.27, C$_6$H$_6$); ^{1}H NMR (CDCl$_3$)δ=0.85 (6H, d, H^a), 1.31 (3H, br m, H^b, H^c), 2.24—3.00 (6H, m, H^d, H^e), 3.72 (12H, s, H^h), 4.46 (2H, br m, H^f), 6.75—7.48 (16H, m, H^g).
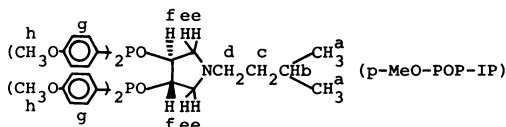

[Rh(1,2-bis{bis(4-methoxyphenyl)phosphinooxy}ethane) (cod)]$^+$ BF$_4^-$: To the solution of ethylene glycol (250 mg, 4.0×10^{-3} mol) and pyridine (700 mg, 8.8×10^{-3} mol) in THF (10 cm^3), chlorobis(4-methoxyphenyl)phosphine (2.4 g, 8.5×10^{-3} mol) was added dropwise in 1.5 h with stirring in an ice-water bath. The resulting mixture was stirred overnight at r.t. Filtration of the reaction mixture, followed by evaporation of the filtrate, gave an oily product containing monophosphinite. This oily product was phosphinitated with 520 mg of chlorobis(4-methoxyphenyl)phosphine and 600 mg of pyridine, and the same work up as above gave an oily product. This oil was purified from diethyl ether–hexane, and crude diphosphinite was obtained. (100 mg, 70 mol% purity) This diphosphinite and [Rh(cod)$_2$]$^+$BF$_4^-$ (54 mg, 1.3×10^{-4} mol) are dissolved in CH$_2$Cl$_2$ (5 cm^3) and the solution was stirred at r.t. for 1 h. Addition of ether (10 cm^3) to this solution gave a yellow precipitate, and yellow needles were obtained by recrystallization of this precipitate from CH$_2$Cl$_2$–THF–diethyl

ether (73 mg, 64% yield). ^{1}H NMR (CDCl$_3$) δ=3.74(20H, s, m, H^c, H^e), 4.27 (4H, br, H^a), 6.54—7.70 (20H, br m, H^b, H^d).
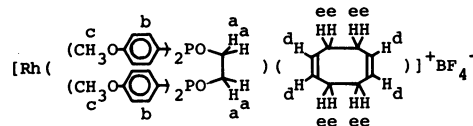
Rh Complex A: To the solution of the p-MeO-POP-AE (83 mg, 1.25×10^{-4} mol) and [Rh(cod)$_2$]$^+$BF$_4^-$ (47 mg, 1.15×10^{-4} mol) in ethanol (20 cm^3) and methanol (5 cm^3), HClO$_4$ (1.21×10^{-4} mol) was added as an ethanol solution. This solution was stirred for 15 min at r.t.; orange-yellow crystals precipitated from the solution. This mixture was concentrated by evaporation and filtrated under nitrogen. Yellow-orange crystals of complex A were dried under reduced pressure. (56 mg, 48% yield) ^{1}H NMR (CD$_3$OD): δ=2.76—3.58 (14H, s, br m, H^a, H^b, H^c, H^d), 3.84 (20H, br m, H^g, H^h), 5.05 (2H, br, H^e), 6.63—7.78 (20H, br m, H^f, H^i).

A
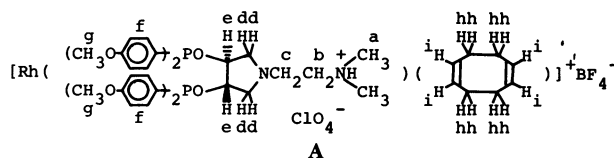
Rh Complex B: To the solution of p-MeO-POP-IP (70 mg, 1.05×10^{-4} mol) and [Rh(cod)$_2$]$^+$BF$_4^-$ (40 mg, 1.0×10^{-4} mol) in ethanol (10 cm^3), HClO$_4$ (1.05×10^{-4} mol) was added as an ethanol solution. This solution was stirred for 5 min at 0°C; yellow crystals separated from it. The remaining mixture was cooled to −20°C and filtrated under nitrogen. Crystals of complex B were dried under reduced pressure. (73 mg, 69% yield) ^{1}H NMR (CD$_2$Cl$_2$) δ=0.91 (6H, br d, H^a), 1.66 (3H, br, H^b, H^c), 3.74(26H, br m, H^d, H^e, H^h, H^i, H^j), 4.79 (2H, br, H^f), 6.36—7.70 (20H, br m, H^g, H^i).

B
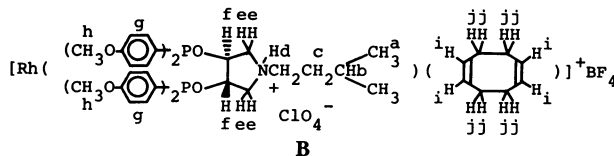
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