Asymmetric Hydrogenation with Rhodium(I)-Chiral Diphosphinites. The Effect of the Dimethylamino Group of the Ligand on the Asymmetric Induction

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New chiral diphosphinites were prepared starting from (+)-diethyl tartrate. The asymmetric hydrogenation of dehydroamino acids, itaconic acid and dehydrodipeptides was studied using Rh(I)-diphosphinite catalysts. In the hydrogenation of dehydroamino acid derivatives, an introducion of ω-(dimethylamino)alkyl group in the ligands did not raise the optical yield. By the use of Rh(I)-diphosphinite having 3-(dimethylamino)propyl group, the inversion of the preferred product was observed. Itaconic acid can be hydrogenated in a good optical yield (76% e.e.) by use of the diphosphinite having 2-(dimethylamino)ethyl group. The diphosphinites having ω-dimethylamino group gave high optical yields in the case of dehydrodipeptides with a chiral center. Especially Rh(I)-catalysts coordinated by diphosphinites with 4-methyl or 4-methoxyl group on the phenyl ring of the ligand gave excellent stereoselectivities (more than 98% d.e.) in the case of Ac-ΔPhe-(*S*)-Phe-OH. The effect of these new chiral diphosphinites on the asymmetric hydrogenation of dehydroamino acids, itaconic acid and dehydrodipeptides was discussed in terms of the stereocontrol induced by electrostatic interaction between the dimethylamino group of the ligand and the substrate and by the steric interaction between the ligand and the substrate.

Recently, asymmetric hydrogenation of prochiral olefins has been studied very actively using many chiral ligands. In the hydrogenation of dehydroamino acid derivatives, several ligands could give high enough optical yields to be practically applied for amino acid production.[1]

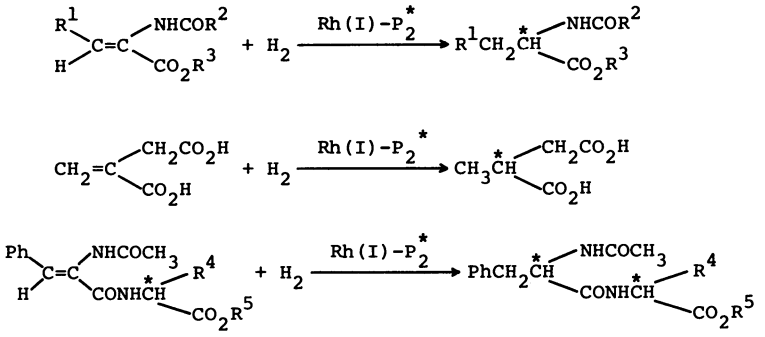
Since most of these ligands were designed to control the asymmetric induction only by the steric interaction between the substrate and phenyl groups on phosphorus atoms of the ligand,[2] the efficiency of these ligands seems to depend strongly on the structure of olefins.[3]

We intended to introduce both electrostatic and steric effects into the asymmetric hydrogenation of olefinic compounds. The electrostatic interaction between ligand and olefin will serve more significantly to discriminate the prochiral face of the substrate. So we prepared new chiral diphosphinites with pyrrolidine moiety, some of them having ω-(dimethylamino)alkyl substituent on the pyrrolidine ring. The dimethylamino group is expected to interact with a carboxyl group of prochiral olefins. These diphosphinites were used for asymmetric hydrogenation of dehydroamino acid derivatives, itaconic acid and dehydrodipeptides.[4] The result of itaconic acid and dehydrodipeptides strongly suggested that an electrostatic effect contributed to the stereoselection (Scheme 1).

Result and Discussion

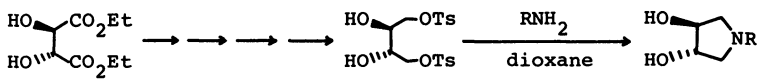
The preparative route to the diphosphinites (**1**—**5**) is shown in Scheme 2. 1,4-Di-*O*-tosyl-L-threitol was induced from (+)-diethyl tartrate by conventional method.[5] *N*-Substituted (*S,S*)-3,4-pyrrolidinediols were obtained by the reaction of the corresponding amine and 1,4-di-*O*-tosyl-L-threitol. These diols were easily converted to the diphosphinites (**1**—**5**) by the reaction with chlorodiarylphosphine in the presence of triethylamine.[6] Diphosphinite (**1**) is a carbon analog of **2** and is expected to show a similar steric effect to that of **2**.

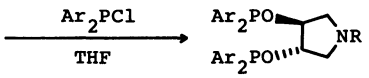
The result of asymmetric hydrogenation of dehydroamino acid derivatives with Rh(I)-diphosphinite (**1**—**3**) catalysts are summarized in Table 1. Rh(I)-diphosphinite (**1**—**3**) catalysts gave low optical yields. In

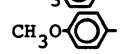


Scheme 1.

the hydrogenation of α-acetamidocinnamic acid, diphosphinite (**1**) without dimethylamino group, gave (*S*)-product in a higher optical yield than that with **2** (29% e.e. and 16% e.e., respectively). In the case of other *N*-acyl dehydroamino acids, diphosphinite (**1**) also gave (*S*)-product in higher optical yields than those with diphosphinite (**2**). It is noted that diphosphinite (**3**), which has a longer aminoalkyl group than **2**, gave (*R*)-product although the absolute configrations of the diphosphinites (**1**—**3**) are the same. The inversion of

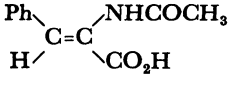
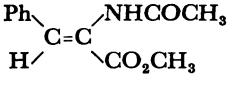
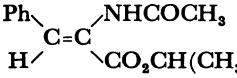
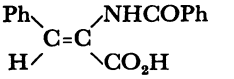
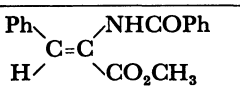
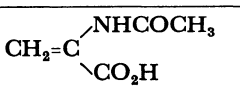




diphosphinite	Ar	R
1	Ph	$CH_2CH_2CH(CH_3)_2$
2	Ph	$CH_2CH_2N(CH_3)_2$
3	Ph	$CH_2CH_2CH_2N(CH_3)_2$
4		$CH_2CH_2N(CH_3)_2$
5		$CH_2CH_2N(CH_3)_2$

Scheme 2.

TABLE 1. ASYMMETRIC HYDROGENATION OF DEHYDROAMINO ACID DERIVATIVES USING Rh(I)-DIPHOSPHINITE (**1**—**3**) CATALYSTS[a]

Substrate[b]	Diphosphinite[c]	Time / min	Conversion / %	% e.e.	Configuration
	**1**	20	100	29	*S*
	1	50	100	5	*S*[e]
	2	720	100	16	*S*
	2	90	100	4	*S*[e]
	3	60	100	13	*R*
	3	90	100	10	*R*[e]
	**1**	20	100	27	*S*
	2	very slow		—	—
	3	600	100	35	*R*
	**1**	11	100	3	*S*
	3	1500	65	2	*R*
	**1**	40	100	40	*S*
	2	720	100	19	*S*
	3	180	100	1	*R*
	**1**	50	100	28	*S*
	3	120	100	4	*R*
	**1**	10	100	19	*S*
	2	90	100	6	*S*
	3	70	100	9	*R*

a) Hydrogenations were performed in ethanol-benzene (2/1) under atmospheric hydrogen pressure at 20 °C. b) Substrate/Rh=100. c) Diphosphinite/Rh=1.5. d) Optical yields (% e.e.) were calculated from the specific rotation of the product and that of optically pure substance: *N*-acetyl-(*S*)-phenylalanine, $[\alpha]_D^{26}$ +46.0° (*c* 1.0, EtOH);[1a] *N*-acetyl-(*S*)-phenylalanine methyl ester, $[\alpha]_D^{25}$ +15.9° (*c* 2.0, MeOH);[13] *N*-acetyl-(*S*)-phenylalanine isopropyl ester, $[\alpha]_D^{25}$ +76.1° (*c* 1.0, $CHCl_3$);[13] *N*-benzoyl-(*S*)-phenylalanine, $[\alpha]_D^{27}$ −40.3° (*c* 1.0, MeOH);[1a] *N*-benzoyl-(*S*)-phenylalanine methyl ester, $[\alpha]_D^{25}$ −45.3° (*c* 1.3, 95% EtOH);[18] *N*-acetyl-(*R*)-alanine, $[\alpha]_D^{26}$ +66.3° (*c* 2.0, H_2O).[1a] e) Addition of triethylamine (NEt_3/Rh=10).

the preferred product using diphosphinite (**3**) was also observed in the reaction of esters. This inversion in the system of **3** is considered to arise mainly from the change of the conformation of phenyl group on phosphorus atoms by the steric repulsion between the dimethylamino group and the phenyl groups. The results obtained indicate that the diphosphinite with a longer aminoalkyl group lowered the (*S*)-selectivity in the reaction of dehydroamino acid derivatives.

The rate of the hydrogenation with Rh(I)-diphosphinite (**2** or **3**) catalyst was much slower than that with Rh(I)-diphosphinite (**1**) catalyst, especially for dehydroamino acid esters. The suppression of the hydrogenation of esters would be ascribed to the coordination of the dimethylamino group onto rhodium and the weaker coordination ability of esters onto rhodium than that of carboxylic acids. The reaction was also suppressed by the presence of bulky alkyl substituent in the dehydroamino acid ester. The results of the hydrogenation of dehydroamino acids make it unlikely that any electrostatic interaction exists between carboxyl group of the substrate and the dimethylamino group of the ligand in the rhodium complex.

The low stereoselectivity by Rh(I)-diphosphinite (**1**—**3**) catalysts can be explained by the presence of several kinds of Rh(I) species in the reaction systems. ^{31}P NMR spectra of Rh(I)-diphosphinite (**2** or **3**)-α-acetamidocinnamic acid systems showed the presence of several Rh(I) species in the solution (Fig. 1). The different ^{31}P NMR patterns of the two systems (**2** and **3**), as well as CD spectra (*vide infra*), suggest the presence of different rhodium species in each system which has a different stereoselectivity.

Triethylamine addition into rhodium-chiral diphosphine systems increased the optical yields of hydrogenation of *N*-acyl dehydroamino acids.[7] It is thought that triethylamine deprotonates a carboxyl group of the substrate on rhodium. In our diphosphinite (**1**—**3**) systems, however, the addition of triethylamine lowered the optical yield of the hydrogenation of α-acetamidocinnamic acid (Table 1). Amine addition increased the intensity of the absorptions corresponding to d-d transition and CT transition of the rhodium complex for both systems (**2** and **3**). The intensity of the CD spectrum was reduced by the amine addition in the system of Rh(I)-(**2**)-α-acetamidocinnamic acid while the intensity was increased by the additive amine in the system of **3** (Fig. 2). The different effect of the additive amine on the CD spectra of the two systems would indicate that the main Rh(I) species have different coordination manners for these two diphosphinite systems.

We applied the diphosphinite (**1**—**3**) catalysts to itaconic acid (α-methylenesuccinic acid) which has a structure similar to α-acetamidoacrylic acid. Itaconic acid is considered to be more suitable to examine the effect of electrostatic interaction because of the presence of two carboxyl groups in the molecule. The dimethylamino group of **2** and **3** may interact electrostatically with β-carboxyl group of itaconic acid to enable the three points' recognition of the prochiral face of itaconic acid. As shown in Table 2, Rh(I)-diphosphinite (**2** and **3**) catalysts gave much higher optical yields for itaconic acid than those of α-acetamidoacrylic acid. It is noted that diphosphinite (**2**) gave the highest optical yield (66% e. e.) among the ligands examined; the optical yield increased to 76% e.e. by lowering the reaction temperature (−20 °C).[8] Since the catalyst of **1**, sterically similar to **2**, gave a lower optical yield (42% e. e.) than the catalyst of **2**, the above results would indicate the enhancement of the stereoselectivity by the dimethylamino group of **2** in the reaction of itaconic acid. The

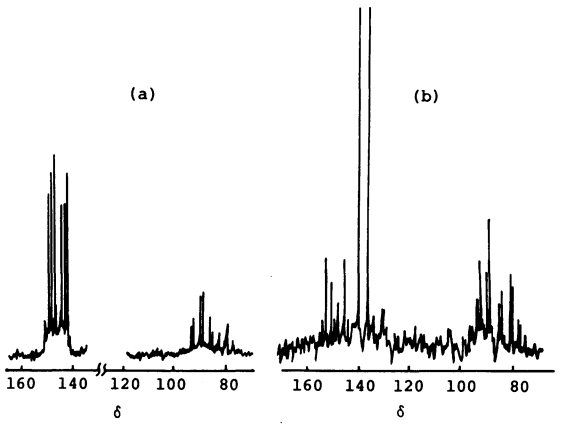


Fig. 1. ^{31}P NMR spectra of Rh(I)-diphosphinite (**2**)- or (**3**)-α-acetamidocinnamic acid systems in methanol solution.

(a): [Rh(Ph,H)C=C(NHCOCH$_3$,CO$_2$H)(**2**)]$^+$BF$_4^-$,

(b): [Rh(Ph,H)C=C(NHCOCH$_3$,CO$_2$H)(**3**)]$^+$BF$_4^-$.

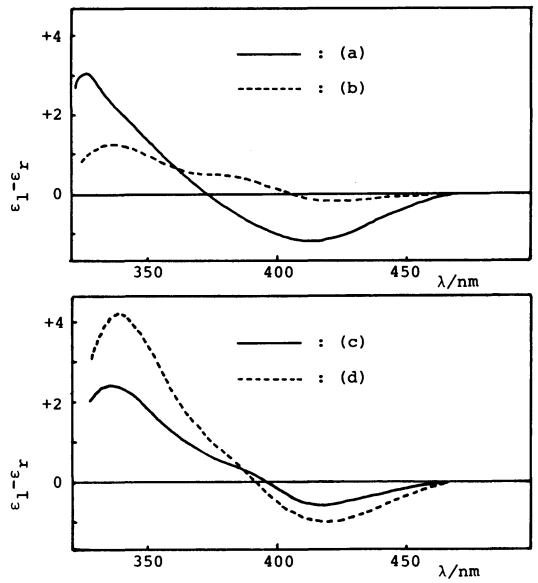


Fig. 2. CD spectra of Rh(I)-diphosphinite (**2**)- or (**3**)-α-acetamidocinnamic acid systems in methanol solution.

(a): [Rh(Ph,H)C=C(NHCOCH$_3$,CO$_2$H)(**2**)]$^+$BF$_4^-$,

(b): (a)+NEt$_3$,

(c): [Rh(Ph,H)C=C(NHCOCH$_3$,CO$_2$H)(**3**)]$^+$BF$_4^-$,

(d): (c)+NEt$_3$.

TABLE 2. ASYMMETRIC HYDROGENATION OF ITACONIC ACID USING Rh(I)-DIPHOSPHINITE (1—3) CATALYSTS[a]

Diphosphinite[b]	Temp °C	Time min	Conversion %	% e.e.[c]	Configuration
1	0	12	100	42	*R*
1	0	36	100	29	*R*[d]
1	−20	180	100	52	*R*
2	0	9	100	66	*R*
2	0	26	100	25	*R*[d]
2	−20	180	100	76	*R*
3	0	30	100	45	*R*
3	0	18	100	14	*R*[d]

a) Hydrogenations were performed in ethanol under atmospheric hydrogen pressure. Itaconic acid/Rh = 100. b) Diphosphinite/Rh = 1.5. c) Optical yields (% e.e.) were calculated from the specific rotation of the product and that of optically pure (*R*)-3-methylsuccinic acid: $[\alpha]_D^{21}$ +16.88° (*c* 2.16, EtOH).[19] d) Addition of triethylamine (NEt_3/Rh = 10).

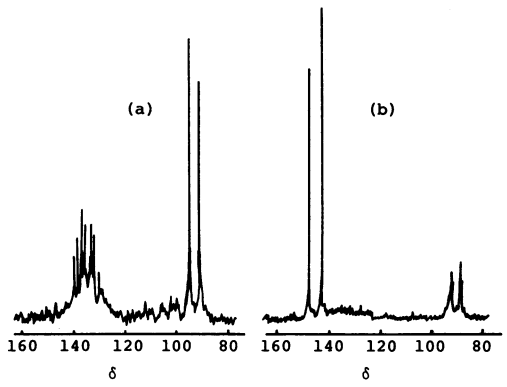


Fig. 3. ^{31}P NMR spectra of Rh(I)-diphosphinite (**2**)-itaconic acid systems in methanol solution.
(a): $[Rh(CH_2{=}C(CH_2CO_2H)CO_2H)(\mathbf{2})]^+BF_4^-$,
(b): (a) + NEt_3.

catalyst of **3** gave lower optical yield (45% e. e.). This decrease in the (*S*)-selectivity is in accord with the results of the hydrogenation of dehydroamino acid derivatives in the system of **3**.

In the reaction of itaconic acid, addition of triethylamine (NEt_3/Rh=10) lowered drastically the optical yield. The ^{31}P NMR spectrum of Rh(I)-diphosphinite (**2**)-itaconic acid system showed the presence of several Rh(I) species in the solution, but the addition of amine simplified the spectrum and no P-P coupling was observed (Fig. 3). These are explained by the competitive coordination between the diphosphinite and amine onto rhodium. Amine addition increased the intensity of absorption spectra in the systems of **1** and **2**, and the intensity of CD spectra also increased in both systems (Fig. 4). These would correspond to the competitive coordination between the diphosphinite and amine. Thus the addition of triethylamine weakened the stereocontrol by the diphosphinite to result in the decrease of the optical yield. On the other hand, it is also possible that triethylamine deprotonates the carboxyl

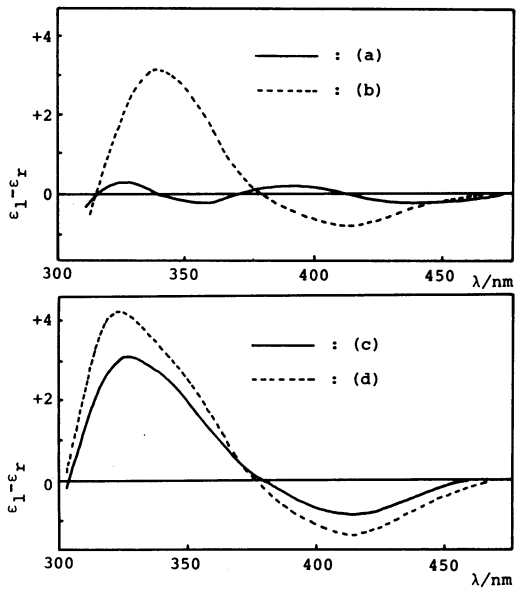


Fig. 4. CD spectra of Rh(I)-diphosphinite (**1**)- or (**2**)-itaconic acid systems in methanol solution.
(a): $[Rh(CH_2{=}C(CH_2CO_2H)CO_2H)(\mathbf{1})]^+BF_4^-$,
(b): (a) + NEt_3,
(c): $[Rh(CH_2{=}C(CH_2CO_2H)CO_2H)(\mathbf{2})]^+BF_4^-$,
(d): (c) + NEt_3.

group of itaconic acid, as is supposed in the hydrogenation of dehydroamino acid.[7] The reaction of monosodium salt of itaconic acid gave lower optical yield in methanol than the reaction of itaconic acid in the absence of amine in methanol (25% e. e. and 51% e. e., respectively). Therefore, the presence of itaconate anion does not serve to raise the optical yield unless the interaction exists between itaconate anion and the ligand.

As mentioned previously, several Rh(I) species are present in the solution to lower the optical yield. In order to decrease the number of Rh(I) species in the solution, the following diphosphinites (**4** and **5**) were examined. They have an electron-donating group (4-methyl or 4-methoxyl group) on the phenyl group on phosphorus atom and are expected to coordinate more strongly onto rhodium. As shown in Table 3, the reaction rate increased strikingly in the case of α-acetamidocinnamic acid by the introduction of the electron-donating substituent on the phenyl group, though the optical yield did not change so much. On the other hand, the reaction rate in the hydrogenation of itaconic acid was almost unchanged, but the optical yield slightly decreased as the coordination of diphosphinites onto rhodium became stronger. This different behavior seems to indicate that the coordination mode of the substrates was different between itaconic acid[9] and dehydroamino acid.

The electrostatic interaction between diphosphinite (**2**) and itaconic acid was expected, but considered to be not strong enough to allow the precise discrimination of the prochiral face of itaconic acid. In the case of dehydrodipeptides,[10] the carboxyl group of the sub-

Table 3. Asymmetric hydrogenation of α-acetamidocinnamic acid and itaconic acid using Rh(I)-diphosphinite (**2**, **4**, and **5**) catalysts

Substrate	Diphosphinite	Solvent	Temp °C	Time min	Conversion %	% e.e.	Configuration
Ph, $NHCOCH_3$; C=C; H, CO_2H	**2**	EtOH/Bz(2/1)	20	720	100	16	*S*
	4	EtOH/Bz(2/1)	20	120	100	16	*S*
	5	EtOH/Bz(2/1)	20	9	100	22	*S*
$CH_2=C$, CH_2CO_2H, CO_2H	**2**	EtOH	0	9	100	66	*R*
	4	EtOH	0	12	100	63	*R*
	5	EtOH	0	11	100	53	*R*

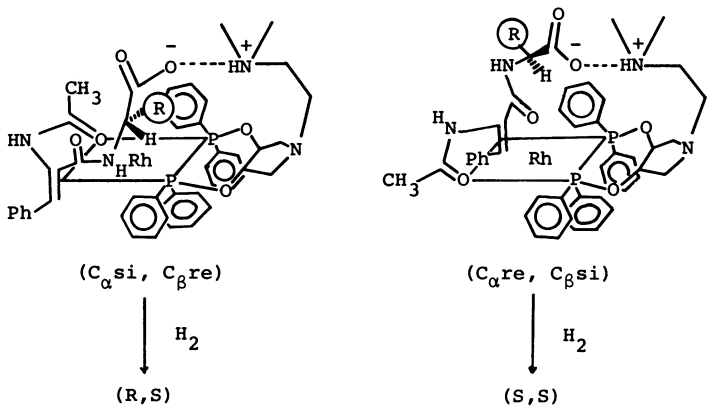
Table 4. Asymmetric hydrogenation of dehydrodipeptides using Rh(I)-diphosphinite (**1**—**5**) catalysts[a]

Dihydrodipeptide[b]	Diphosphinite[c]	Temp °C	Time min	Conversion %	(*S*)/(*R*) or (*S*,*S*)/(*R*,*S*)	% e.e. or % d.e.
Ph, $NHCOCH_3$; C=C; H, $CONHCH_2CO_2H$ (Ac-⊿Phe-Gly-OH)	**1**	20	20	100	74/26	48
	2	20	30	100	67/33	34
	3	20	20	100	58/42	16
Ph, $NHCOCH_3$; C=C; H, $CONHCH(CH_2Ph)CO_2H$ (Ac-⊿Phe-(*S*)-Phe-OH)	**1**	20	120	92	79/21	58
	2	20	180	71	95/ 5	90
	3	20	120	91	93/ 7	86
	4	20	45	100	>99/<1	>98
	5	20	15	100	>99/<1	>98
Ph, $NHCOCH_3$; C=C; H, $CONHCH(CH_3)CO_2H$ (Ac-⊿Phe-(*S*)-Ala-OH)	**1**	20	20	100	68/32	36
	2	20	30	100	94/ 6	88
	3	20	30	100	91/ 9	82
	5	20	30	100	98/ 2	96
Ph, $NHCOCH_3$; C=C; H, $CONHCH(CH_2Ph)CO_2CH_3$ (S) (Ac-⊿Phe-(*S*)-Phe-OMe)	**1**	20	180	100	51/49	2
	2	40	50 h	0	—	—
	3	40	30 h	20	—	—
	5	40	8 h	0	—	—

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

strate is expected to interact more easily with the dimethylamino group of the ligands. Accordingly, our diphosphinite catalysts were applied to the asymmetric hydrogenation of dehydrodipeptides (Table 4). The reaction of Ac-⊿Phe-Gly-OH, using diphosphinite (**2** and **3**) catalysts, having the dimethylamino group, proceeded as rapidly as the reaction with diphosphinite (**1**). These results present an interesting contrast with the reaction of dehydroamino acid derivatives using diphosphinites with the dimethylamino group. Diphosphinites (**2** and **3**) gave (*S*,*S*)-products with high stereoselectivity in the reaction of Ac-⊿Phe-(*S*)-Phe-OH (90% d.e. and 86% d.e., respectively), while diphosphinite (**1**) gave the product with much lower stereoselectivity (58% d.e.). These results indicate the effect of the dimethylamino group on the asymmetric induction. Introduction of the electron-donating substituent on the phenyl group of the diphosphinite (**2**) increased the reactivity and gave an extremely high stereoselectivity (more than 98% d. e. with both **4** and **5**). The presence of the dimethylamino group in the ligand induced also high stereoselectivity (96% d. e. with **5**) in the reaction of Ac-⊿Phe-(*S*)-Ala-OH, while diphosphinite (**1**) gave only low stereoselectivity (36% d. e.). In the case of Ac-⊿Phe-(*S*)-Phe-OMe, the reactivity was extremely low using diphosphinites (**2** and **5**) with the dimethylamino group, as was observed in the reaction of dehydroamino acid esters. Hydrogenation took place smoothly using diphosphinite (**1**) without dimethylamino group, but the stereoselectivity was very low. This striking difference between the reaction of Ac-⊿Phe-(*S*)-Phe-OH and that of Ac-⊿Phe-(*S*)-Phe-OMe will further support the electrostatic interaction between the carboxyl group of the dipeptide and the dimethylamino group of the ligand.

These results indicate the importance of the chiral center in the substrate, as well as the dimethylamino group of the ligand for asymmetric induction (Scheme 3). The electrostatic interaction between the dimethylamino group of the ligand and the carboxyl group of the dipeptide will play a role to fix the substrate onto rhodium. In the case of dehydrodipeptide with a chiral center, coordination of the substrate onto rhodium by the ($C_\alpha$si, $C_\beta$re) face of the double bond is unfavorable because of the steric repulsion between the substituent on the chiral carbon of the substrate and the phenyl



Scheme 3.

group of the ligand. So the coordination by the (Cαre, Cβsi) face becomes favorable, resulting in the predominant (*S*, *S*)-product formation. That is to say, the electrostatic interaction emphasized the steric effect of the chiral center of the dipeptide, resulting in the high stereoselective induction.

For dehydrodipeptides with (*R*)-chiral center, (*R*, *R*)-product was formed in a high stereoselectivity instead of (*S*, *R*)-isomer.[11]

In the case of dehydroamino acids, the dimethylamino group in the ligand and the carboxyl group of the substrate are too distant to interact strongly enough to increase the optical yield. On the other hand, in the case of itaconic acid, the carboxyl group of the substrate would interact with the dimethylamino group of the ligand to give high optical yield. Furthermore, in the case of dehydrodipeptides with a chiral center, the electrostatic interaction fixed the substrate onto rhodium to induce excellent stereoselectivity by emphasizing the steric effect. The detailed study of the asymmetric hydrogenations of dehydrodipeptides and dehydrooligopeptides is in progress using diphosphinite systems. Our ligand with the dimethylamino group will be applied for more complex substrates with many functional groups.

Experimental

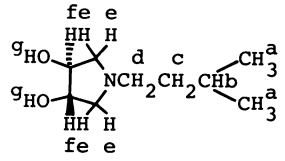
^{1}H NMR spectra were recorded on Hitachi R-24 High Resolution NMR spectrometer (60 MHz) with tetramethylsilane as internal standard. ^{31}P NMR spectra were recorded on a JEOL JNM-FX60Q spectrometer with triphenylphosphine as external standard (6.2 ppm). CD spectra were recorded on a JASCO J-40A spectropolarimeter. Optical rotations were measured with a UNION PM101 automatic digital polarimeter.

Materials. α-Acetamidocinnamic acid, α-acetamidoacrylic acid, and itaconic acid were purchased as commercial products. α-Benzoylaminocinnamic acid,[12] methyl α-acetamidocinnamate,[13] isopropyl α-acetamidocinnamate,[13] methyl α-benzoylaminocinnamate,[13] *N*-acetyl dehydrophenylalanylglycine,[14] *N*-acetyl dehydrophenylalanyl-(*S*)-phenylalanine,[14] *N*-acetyl dehydrophenylalanyl-(*S*)-alanine,[14] and *N*-acetyl dehydrophenylalanyl-(*S*)-phenylalanine methyl ester[10c] were prepared by the conventional methods. All substrates except α-acetamidoacrylic acid and itaconic acid were purified by repeated recrystallization.

Ethanol and methanol were dried and distilled over magnesium and stored under nitrogen. Tetrahydrofuran, diethyl ether, dioxane, triethylamine, and benzene were dried and distilled over sodium and stored under nitrogen. 1,4-Di-*O*-tosyl-L-threitol was prepared through four steps from (+)-diethyl tartrate.[5] Chlorodi-*p*-tolylphosphine and chlorobis(4-methoxyphenyl)phosphine were prepared by the reaction of corresponding Grignard reagent and sodium diethyl phosphite followed by hydrolysis and chlorination with phosphorus trichloride.[15]

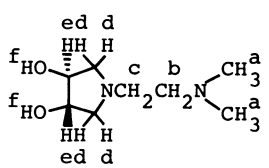
$[Rh(cod)_2]^+BF_4^-$(cod: 1,5-cyclooctadiene) was prepared by a conventional method and stored under nitrogen.[16]

Preparation of Diphosphinites. (3S,4S)-N-Isopentyl-3,4-pyrrolidinediol (6): Isopentylamine (4 cm^3, 3.4×10^{-2} mol) and 1,4-di-*O*-tosyl-L-threitol (4.8 g, 1.1×10^{-2} mol) were reacted in dioxane (6 cm^3) under reflux with stirring for 20 h under nitrogen. The reaction mixture was evaporated under reduced pressure, and the residual solid was extracted with THF in an ice-water bath. The extract was evaporated to dryness under reduced pressure. Recrystallization of the residue from diethyl ether with hexane gave 650 mg of pale yellow crystals containing a small amount of ammonium salt and unchanged amine. (85 mol% purity, 34% yield) This diol was used for the preparation of diphosphinite (**1**) without further purification. ^{1}H NMR ($CDCl_3$) δ=0.87 (6H, d, H^a), 1.38 (3H, br m, H^b, H^c), 2.33—3.11 (6H, m, H^d, H^e), 4.11 (2H, br t, H^f), 4.87 (2H, s, H^g).



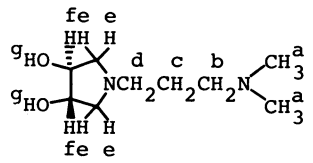
6

(3S,4S)-N-[2(Dimethylamino)ethyl]-3,4-pyrrolidinediol (7): *N*,*N*-Dimethylethylenediamine (18.2 g, 2.1×10^{-1} mol) and 1,4-di-*O*-tosyl-L-threitol (30 g, 6.9×10^{-2} mol) were reacted in dioxane and the product was treated in the manner described above. The crude diol was purified by short column chromatography of neutral alumina (ethanol eluent) and recrystallization from THF. In this way, the diol was obtained as white crystals. (2.4 g, 20% yield) $[\alpha]_D^{25}$ +2.9° (*c* 0.90, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=2.22 (6H, s, H^a), 2.43—3.10 (8H, m, H^b, H^c, H^d), 4.02 (2H, br t, H^e), 4.87 (2H, s, H^f).



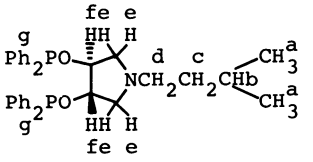
7

(3S,4S)-N-[3-(Dimethylamino)propyl]-3,4-pyrrolidinediol (8): *N,N*-Dimethyl-1,3-propanediamine (4.2 cm³, 3.3×10⁻² mol) and 1,4-di-*O*-tosyl-L-threitol (4.8 g, 1.1×10⁻² mol) were reacted in dioxane and the product was treated in the manner described previously. The crude diol was obtained as oily material containing a small amount of ammonium salt and unchanged amine (530 mg, 93 mol% purity, 25% yield); this diol was used without further purification in the preparation of the diphosphinite (**3**). ^{1}H NMR ($CDCl_3$) δ= 1.66 (2H, br m, H^c), 2.20 (6H, s, H^a), 2.20—3.08 (8H, m, H^b, H^d, H^e), 4.07 (2H, br t, H^f), 4.97 (2H, s, H^g).



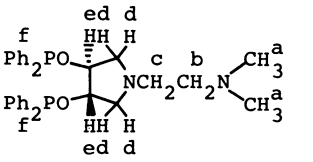
8

(3S,4S)-N-Isopentyl-3,4-bis(diphenylphosphinooxy)pyrrolidine (1): The phosphinitation of the diol (**6**) was performed in 2 steps because of the contamination by impurities (ammonium salt and amine). To the solution of the diol (**6**) (490 mg, 2.82×10⁻³ mol) and triethylamine (1.3 cm³, 9.3×10⁻³ mol) in THF (30 cm³), chlorodiphenylphosphine (0.6 cm³, 3.3×10⁻³ mol) in THF (5 cm³) was added dropwise in 3 h with stirring in an ice-water bath. After the addition, the mixture was stirred for 1.5 h at 0 °C. The white precipitate was filtered off and the filtrate was evaporated to dryness under reduced pressure. ^{1}H NMR of the oily residue indicated the formation of monophosphinite and diphosphinite (**1**). This oily product was further phosphinitated and treated as before. The resulting oily product was extracted with ether, and the ether extract was concentrated. Addition of hexane to the ether solution gave white precipitate of diphosphinite (**1**) at −50 °C. Repeated recrystallization from ether–hexane gave pure diphosphinite (**1**) as white crystals. (1.05 g, 68% yield) mp 54.5—57.2 °C (corr); $[\alpha]_D^{25}$ +59.8° (*c* 0.48, C_6H_6); ^{1}H NMR ($CDCl_3$) δ=0.86 (6H, d, H^a), 1.34 (3H, br m, H^b, H^c), 2.31—3.13 (6H, m, H^d, H^e), 4.65 (2H, br m, H^f), 7.40 (20H, m, H^g). Found: C, 72.66; H, 6.86; N, 2.62; P, 11.61. Calcd for $C_{33}H_{38}NP_2O_2$: C, 73.18; H, 6.88; N, 2.58; P, 11.43.



1

(3S,4S)-N-[2-(Dimethylamino)ethyl]-3,4-bis(diphenylphosphinooxy)pyrrolidine (2): Chlorodiphenylphosphine (0.65 cm³, 3.6×10⁻³ mol) in THF (3 cm³) was added dropwise to the solution of the diol (**7**) (310 mg, 1.7×10⁻³ mol) and triethylamine (0.5 cm³, 3.6×10⁻³ mol) in THF (20 cm³) in 30 min with stirring in an ice-water bath. After the addition, the mixture was stirred for 3 h at 0 °C. The white precipitate was filtered off and the filtrate was evaporated to dryness under reduced pressure. The oily residue was purified by recrystallization from ether–hexane, and the pure diphosphinite was obtained as white crystals having a melting point near the r.t. (610 mg, 63% yield) $[\alpha]_D^{25}$ +55.4° (*c* 0.97, C_6H_6); ^{1}H NMR ($CDCl_3$) δ=2.22 (6H, s, H^a), 2.41—3.17 (8H, m, H^b, H^c, H^d), 4.64 (2H, br m, H^e), 7.41 (20H, m, H^f).

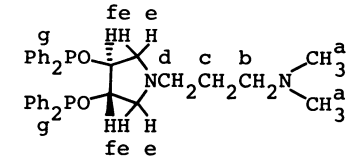


2

Found: C, 70.70; H, 6.94; N, 5.25; P, 11.59. Calcd for $C_{32}H_{36}N_2P_2O_2$: C, 70.83; H, 6.68; N, 5.16; P, 11.41.

(3S,4S)-N-[3-(Dimethylamino)propyl]-3,4-bis(diphenylphosphinooxy)pyrrolidine (3): The phosphinitation of the diol (**8**) was performed in 2 steps. To the solution of the diol (**8**) (530 mg, 2.8×10⁻³ mol) and triethylamine (1.2 cm³, 8.6×10⁻³ mol) in THF (30 cm³), chlorodiphenylphosphine (0.5 cm³, 2.8×10⁻³ mol) in THF (5 cm³) was added dropwise in 30 min with stirring in an ice-water bath. The resulting mixture was further stirred for 30 min at 0 °C. Filtration of the reaction mixture followed by evaporation of the filtrate gave oily monophosphinite. The monophosphinite was further phosphinitated with 0.5 cm³ of chlorodiphenylphosphine and 1.2 cm³ of triethylamine, and treated as before. The oily product was purified by recrystallization from ether–hexane and pure diphosphinite (**3**) was obtained as a colorless oil. (800 mg, 57% yield) $[\alpha]_D^{25}$ +56.0° (*c* 0.31, C_6H_6); ^{1}H NMR ($CDCl_3$) δ=1.61 (2H, m, H^c), 2.17 (6H, s, H^a), 2.17—3.13 (8H, m, H^b, H^d, H^e), 4.64 (2H, br, m, H^f), 7.44 (20H, m, H^g).

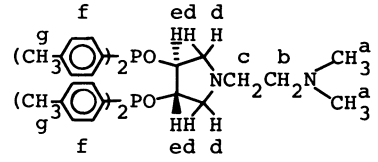
Found: C, 71.20; H, 6.98; N, 4.91; P, 11.08. Calcd for $C_{33}H_{38}N_2P_2O_2$: C, 71.20; H, 6.88; N, 5.30; P, 11.12.



3

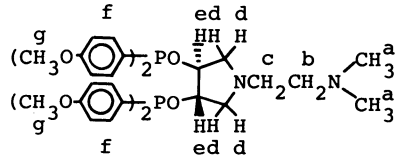
(3S,4S)-N-[2-(Dimethylamino)ethyl]-3,4-bis(di-p-tolylphosphinooxy)pyrrolidine (4): To the solution of the diol (**7**) (500 mg, 2.9×10⁻³ mol) and triethylamine (2.8 cm³, 20×10⁻³ mol) in THF (50 cm³), chlorodi-*p*-tolylphosphine (1.9 g, 7.6×10⁻³ mol) in THF (15 cm³) was added dropwise in 2 h with stirring at −30 °C. The mixture was further stirred for 2 h at 0 °C. Similar treatment of the reaction mixture to the case of (**2**) and recrystallization of the product from ether–hexane gave pure diphosphinite (**4**) as white needles. (780 mg, 45% yield) mp 74.5—76.5 °C (corr); $[\alpha]_D^{25}$ +60.4° (*c* 0.51, C_6H_6); ^{1}H NMR ($CDCl_3$) δ=2.18—3.09 (26H, m, H^a, H^b, H^c, H^d), 4.52 (2H, br m, H^e), 6.96—7.44 (16H, m, H^f).

Found: C, 72.48; H, 7.59; N, 4.57; P, 10.16. Calcd for $C_{36}H_{44}N_2P_2O_2$: C, 72.22, H, 7.40; N, 4.67; P, 10.34.



4

(3S,4S)-N-[2-(Dimethylamino)ethyl]-3,4-bis[bis(4-methoxyphenyl)phosphinooxy]pyrrolidine (5): To the solution of the diol (**7**) (600 mg, 3.4×10⁻³ mol) and triethylamine (5.5 cm³, 40×10⁻³ mol) in THF (50 cm³), chlorobis(4-methoxyphenyl)phosphine (2.2 g, 7.8×10⁻³ mol) in THF (15 cm³) was added dropwise in 2 h with stirring at −30 °C. The mixture was further stirred for 30 min at 0 °C. Similar treatment of the reaction mixture to the case of **2** and recrystallization of the product from ether–hexane gave pure diphosphinite (**5**) as white crystals. (1.67 g, 47% yield) mp 62.8—65.7 °C (corr); $[\alpha]_D^{25}$ +58.9° (*c* 0.95, C_6H_6); ^{1}H NMR ($CDCl_3$) δ=2.17 (6H, s, H^a) 2.33—3.06 (8H, M, H^b, H^c, H^d), 3.72 (12H, s, H^g), 4.43



5

(2H, br, m, H^e), 6.57—7.48 (16H, m, H^f).

Found: C, 65.27; H, 6.77; N, 4.03; P, 9.16. Calcd for $C_{36}H_{44}N_2P_2O_6$: C, 65.24; H, 6.96; N, 4.22; P, 9.36.

Hydrogenation Procedure. Dehydroamino Acid Derivatives and Itaconic Acid: Typically, $[Rh(cod)_2]^+BF_4^-$ (4.1 mg, 1.0×10^{-5} mol) and a diphosphinite (1.5×10^{-5} mol) were dissolved in a solvent (3 cm^3) under nitrogen and the solution was stirred at r.t. for 5 min. This catalyst solution was transferred into the hydrogenation flask containing the substrate (1.0×10^{-3} mol) and a solvent (7 cm^3) by a narrow stainless steel tube under nitrogen. After the solution was stirred for 1 h at r. t. under nitrogen, degassing under reduced pressure and filling the flask with hydrogen were repeated several times, quickly. The resultant solution was stirred vigorously until the required amount of hydrogen had been absorbed. The reaction mixture was worked up by the conventional method[17] and the optical yield was determined polarimetrically. In the case of itaconic acid, hydrogen was introduced after stirring of the mixture for 5 min under nitrogen.

Dehydrodipeptides: $[Rh(cod)_2]^+BF_4^-$ (4.1 mg, 1.0×10^{-5} mol) and a diphosphinite (1.5×10^{-5} mol) were dissolved in ethanol (2 cm^3) under nitrogen and the solution was stirred at r. t. for 5 min. This catalyst solution was transferred into the hydrogenation flask containing a dehydrodipeptide (5.0×10^{-4} mol) and ethanol (3 cm^3) by a narrow stainless steel tube under nitrogen, and the hydrogenation procedure described above was carried out. The reaction mixture was worked up by the conventional method[10] and the optical yield was determined by ^1H NMR usig a shift reagent ($Eu(tfc)_3$).

^{31}P NMR Spectra. The Typical Procedure for Preparation of the Sample: The solution of $[Rh(cod)_2]^+BF_4^-$ (37 mg, 9.1×10^{-5} mol) and a diphosphinite (9.1×10^{-5} mol) in methanol (1 cm^3) containing 10% of an internal lock (CD_3OD or C_6D_6) in a Schlenk tube was degassed by a freeze and thaw cycle. Hydrogen was introduced and the solution was stirred at r. t. for the time necessary for removing the coordinated cod. Then the solution was evacuated by three freeze and thaw cycles and transferred into a Schlenk tube containing a substrate (1.8×10^{-3} mol) with a narrow stainless steel tube under nitrogen, further degassed by the above procedure, and stirred at r. t. for 30 min. Finally, the solution was transferred into a NMR tube and the tube was sealed under nitrogen.

CD Spectra. The Typical Procedure for Preparation of the Sample: The stock solution of $[Rh(cod)_2]^+BF_4^-$ (8.1 mg, 2.0×10^{-5} mol) and a diphosphinite (2.4×10^{-5} mol) in methanol (20 cm^3) was evacuated by two freeze and thaw cycles. The solution (2.5 cm^3) was treated as described above and transferred into a Schlenk tube containing the methanol solution of a substrate (2.5×10^{-5} mol, 2.5cm^3), further degassed, and stirred at r. t. for 30 min. The resultant solution was transferred into a 10 mm cell under nitrogen.

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