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Effects of Solvent and Temperature on the 1,4-Asymmetric Induction in the Diastereoselective Hydrogenation of Dehydrodipeptides

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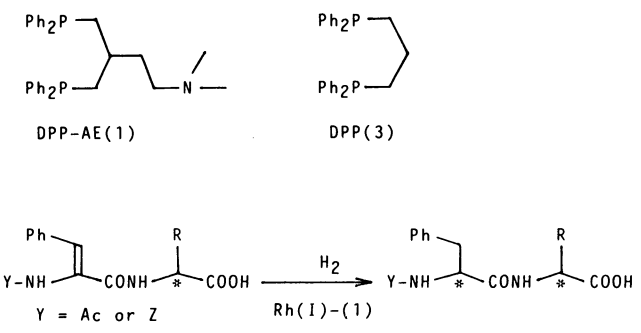
A study of the effets of solvent and temperature on the stereoselectivity of asymmetric hydrogenation of dehydrodipeptides has been made with Rh(I)-(DPP-AE) catalyst, in which an electrostatic interaction is possible between the dimethylamino group of the ligand and the carboxyl group of the substrate. The highest stereoselectivity was attained in the MeOH–water solvent, while aprotic solvents such as DMF and THF gave comparatively low selectivity and reactivity. With increasing the temperature from −40 °C to 80 °C in alcoholic solvent, the stereoselectivity increased to reach a maximum at 20—40 °C, then decreased. The effects of solvent and temperature on the stereoselectivity were discussed.

The asymmetric hydrogenation of olefinic compounds with Rh(I)–diphoshine catalysts has been widely studied and high enantio- or diastereoselectivity was obtained, especially in the case of the hydrogenation of α-dehydroamino acid derivatives.[1] The stereocontrol in these systems is caused by a large steric repulsion between substrate and chiral ligand coordinated to rhodium.[2] On the other hand, enzymes efficiently use attractive forces such as electrostatic interaction, hydrogen bonding, and van der Waals interaction in addition to simple steric repulsion in their highly stereoselective reactions.[3] Incorporation of such attractive interactions to a catalytic system will enhance stereoselectivity in the asymmetric reactions.

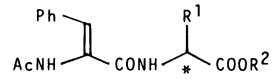
Previously, we have reported the application of Rh(I)–achiral diphosphine [2-[2-(dimethylamino)ethyl]-1,3-propanediyl]bis[diphenylphosphine] (DPP-AE(**1**)) system to the hydrogenation of dehydrodipeptides, where the dimethylamino group of the ligand was expected to interact electrostatically with carboxyl group of the substrate (Scheme 1).[4] The detailed examination showed that the presence of both amino group of the ligand and free carboxyl group of the substrate is essential for high stereoselectivity. The Rh(I)–**1** system showed highly selective 1,4-asymmetric induction for the hydrogenation of *N*-acetyl or *N*-benzyloxycarbonyl dehydrodipeptides. For example, the diastereomeric excess was 94% for the hydrogenation of Ac–ΔPhe–(*S*)-Phe–OH, and 92% for Z–ΔPhe–(*S*)-Val–OH, with the selectivity of (*S*,*S*). In the asymmetric reactions, solvent and/or temperature largely affects the stereoselectivity and the reactivity.[5] In this paper we describe the effects of solvent and temperature on the hydrogenation of dehydrodipeptides using this Rh(I)–DPP-AE system, to confirm the contribution of the electrostatic interaction and to establish the optimum conditions for obtaining high stereoselectivity.



Scheme 1.

Results and Discussion

Solvent Effect. The Rh(I)–DPP-AE catalyst system achieved a high stereoselective 1,4-asymmetric induction and afforded a predominant diastereomer with a (*S*,*S*)- or (*R*,*R*)-configuration corresponding to that of the chiral center in the substrate. The hydrogenation of *N*-acetyldehydrophenylalanylamino acids (Ac–ΔPhe–AA–OH (**2**); where AA is a chiral amino acid residue) gave higher stereoselectivities with an increase in polarity of alcoholic solvents (MeOH>EtOH>*i*-PrOH).[4] Therefore addition of water to methanol was expected to raise the stereoselectivity for the hydrogenation of dehydrodipeptides. As was expected, the selectivity of the reaction of **2a** or **2c** increased with an addition of proper amount of water to methanol, although the degree of increase was a little (96% diastereomeric excess for **2a** and 91% d.e. for **2c**) (Table 1). An excessive addition of water, however, lowered both the reactivity and stereoselectivity. Substrate **2a** having a highly hydrophobic amino acid residue afforded 71% d.e. in the 1:1 methanol–water. On the other hand, **2b** gave 77% d.e. even in the 19:1



Ac-dehydrodipeptides(2)
2a Ac-ΔPhe-(S)-Phe-OH; R^1 = $PhCH_2$, R^2 = H
2b Ac-ΔPhe-(S)-Ala-OH; R^1 = CH_3, R^2 = H
2c Ac-ΔPhe-(R)-Leu-OH; R^1 = $(CH_3)_2CHCH_2$, R^2 = H
2d Ac-ΔPhe-(S)-Ala-OMe; R^1 = CH_3, R^2 = CH_3

Table 1. Asymmetric Hydrogenation of Dehydrodipeptides with Rh(I)-DPP-AE System in Aqueous Methanol Solution

Solvent system	%d.e.[a] (time/h)		
	Dehydrodipeptide		
	2a	**2b**	**2c**
$MeOH/H_2O$			
10:0	94(0.5)	88(0.8)	87(1.5)
19:1		77(2)	
9:1		72(12)	91(1)
8:2		—(12)[b]	82(18)
7:3	96(0.5)		—(36)[c]
1:1	71(48)[d]		

The reaction was carried out at 20 °C under atmosheric hydrogen pressure. Dehydrodipeptide : **1** : Rh= 50 : 1.1 : 1. The conversion is 100% unless otherwise noted. The configuration of the predominant product was (*S,S*) for **2a** and **2b**, (*R,R*) for **2c**. a) Diastereomeric excess. b) Conversion was ca. 10%. c) Conversion was 55%. d) Conversion 88%.

methanol–water solution and the reaction was too slow in 8:2 methanol–water solution to determine the diastereoselectivity. Addition of excess water would prevent the electrostatic interaction between substrate and ligand, and also decrease the solubility of the substrates and hydrogen gas in the solvent.

The stereoselectivity and reactivity of **2b** and **2c** in aprotic solvents were rather lower than those in protic solvents (Table 2). The reaction of **2b** required 12 hours in DMF to complete and 20 hours in THF, while the reaction completed within 1 hour in methanol. These results indicated clearly that protic and polar solvent is necessary to obtain good selectivity and reactivity by this Rh(I)–DPP-AE catalyst system for dehydrodipeptides, although large increase of solvent polarity by addition of excess water would lower the selectivity because of the reduction of electrostatic interaction. This solvent effect is in contrast to the hydrogenation of acetamidocinnamic acid with Rh(I)-(*R*)-PheNOP system, which gave high selectivities in DMF or THF and the lowest in MeOH.[5b] On the other hand, the Rh(I)–BPPFA ((*S*)-1-[(*R*)-1,2-bis(diphenylphosphino)ferrocenyl]-*N,N*-dimethylethylamine) having a dimethylamino moiety showed a similar solvent dependence in the hydrogenation of acetamidocinnamic acid derivatives to that of the present Rh(I)–DPP-AE system: Rh(I)–BPPFA gave high selectivity in aqueous methanol rather than in methanol.[5e]

The high stereoselectivity in polar and protic solvents suggests that both proton-donating and proton-accepting characters of solvent affect the selectivity. A proton donor can convert amino group to ammonium cation and a proton acceptor can convert the carboxyl group to carboxylate anion. These ionizations are more feasible in polar solvents such as alcohol or mixture of alcohol–water than in less polar

Table 2. Asymmetric Hydrogenation of Dehydrodipeptides with Rh(I)–DPP-AE in Aprotic Solvents

Dehydrodipeptide	Solvent	Time/h	%d.e.
2b	THF	20	74 (*S,S*)
	DMF	12	65
	MeOH	0.8	88
	THF/H_2O[a]	12	78
2c	THF	3 days	68 (*R,R*)
	EtOH/THF[b]	0.5	86
	EtOH	4	78

The reaction was carried out under atmospheric hydrogen pressure at 20 °C for alcoholic solvents, at 25 °C for others. Dehydrodipeptide : **1** : Rh=50 : 1.1 : 1. Conversion was 100% in all cases. a) The THF : H_2O= 9 : 1. b) The EtOH : THF=9 : 1.

solvents. Here alcohols and water act as proton donor as well as proton acceptor, while THF acts only as proton acceptor. The hydrogenation of **2c** in EtOH–THF and **2b** in THF–H_2O afforded higher diastereoselectivity than in EtOH or THF respectively. These were ascribed to the better combination of proton-donating and proton-accepting solvents. It was concluded that the polarity and the proportion of the proton donor and proton acceptor characters of the solvents are important to affect the ionization of the amino and the carboxyl groups and the electrostatic interaction between them. In the present systems, MeOH–H_2O mixed solvent is the best.

We reported that addition of triethylamine to Rh(I)–DPP-AE system lowered the stereoselectivity.[4] The hydrogenation of **2a** with Rh(I)–DPP-AE in MeOH gave 94%d.e. and addition of amine in 10 molar ratio to the rhodium diminished the selectivity to 66% d.e. On the basis of the above consideration, the influence of addition of amine on selectivity was examined over the amine/Rh ratios from 0 to 50 at 20 °C (Fig. 1), since amine is supposed to be a good proton acceptor to favor the ionization of carboxyl group and to prevent the protonation of dimethylamino group. In the case of Rh(I)–DPP (**3**) system without the electrostatic interaction between ligand and substrate, a maximum selectivity was observed at the amine ratio of 10 to rhodium, and addition of 50 fold amine to rhodium reduced the diastereomeric excess to 22%. The increasing in the diastereoselectivity may be explained as an enhancement of the steric recognition of the substrate by catalyst through the axial coordination of the carboxylate unit formed by addition of amine. It was reported that addition of a small amount of amine increased the stereoselectivity in the hydrogenation of acetamidocinnamic acid or itaconic acid with the Rh(I)–diphosphine catalyst.[6] The Rh(I)–DPP-AE system showed a different behavior from the Rh(I)–DPP catalyst system. Increasing the amount of amine up to 10 molar to the rhodium caused the decrease of the stereoselectivity from 94% to about 60% d.e. By further addition of amine, however,

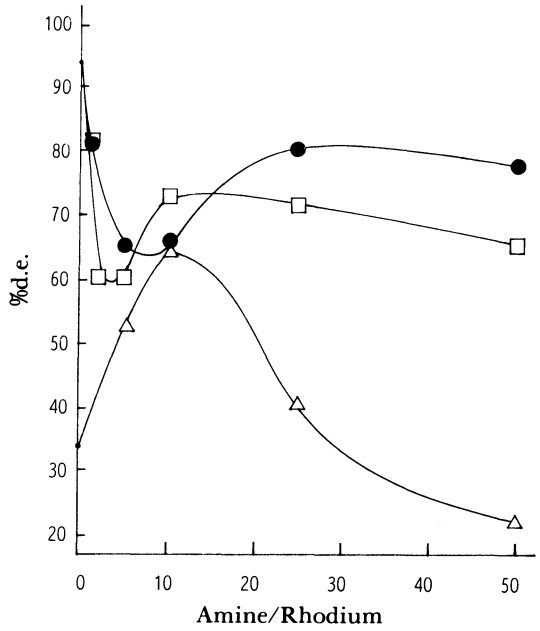


Fig. 1. The influence of amine on stereoselectivity of the hydrogenation of **2b** ●: DPP-AE–triethylamine, □: DPP-AE–*N*-methylmorpholine, △: DPP–triethylamine.

the selectivity turned to increase to reach a maximum (80% d.e. for triethylamine, 72% d.e. for *N*-methylmorpholine) at about 25 molar amine to the rhodium. The initial fall of selectivity was explained by the obstruction of the efficient electrostatic interaction between ligand (**1**) and substrate (**2a**) by the addition of amine. The formed triethylammonium cation will interact with carboxylate anion of the substrate in competition with the ammonium cation unit in the ligand, and suppress the interaction between ligand and substrate. The presence of relatively large amount of amine afforded a high stereoselectivity (80% d.e.), probably by the efficient axial coordination of the carboxylate anion of the substrate, but could not substitute the role of the amino group in DPP-AE catalyst which gave 94% d.e.

Temperature Effect. Generally, the stereoselectivity decreased simply with the elevation of the temperature for the hydrogenation of acetamidocinnamic acid derivatives using Rh(I) catalysts.[5a–d] The reversed trends were reported for some catalytic systems using DIPAMP (1,2-bis[(*o*-methoxyphenyl)phenylphosphino]-ethane) or DIOXOP (4-diphenylphosphino-2-diphenylphosphinomethyl-1,3-dioxolane).[6b,7] We examined the temperature effect of the Rh(I)–DPP-AE system on the hydrogenation of **2b** in MeOH, EtOH, and *i*-PrOH, in the temperature range from −40 °C to 80 °C (Fig. 2). Each plot of the selectivities against temperature showed a curve with a maximum. The optimal temperature shifted to the lower temperature with an increase in the polarity of solvent. EtOH and MeOH gave the maximum around ambient temperature, while *i*-PrOH shifted the maximum to higher temperature. The Arrhenius plot of the (*S,S*)/(*R,S*) ratio apparently showed the presence of at least two predominant active species. Assuming those two species we estimated the difference of activation enthalpies ($\Delta\Delta H^{\neq}$) and entropies ($\Delta\Delta S^{\neq}$) of the reaction in EtOH. The one catalyst species seems to operate at lower temperatures between −40 °C and 20 °C, and has the activation parameters, 16 kJ mol^{-1} of $\Delta\Delta H^{\neq}$ and 74 J deg^{-1} mol^{-1} of $\Delta\Delta S^{\neq}$. The another species seems to operate at higher temperatures between 20 °C and 80 °C, and has −3.9 kJ mol^{-1} of $\Delta\Delta H^{\neq}$ and 8.1 J deg^{-1} mol^{-1} of $\Delta\Delta S^{\neq}$. These activation parameters suggest that the enthalpy term of the former catalyst species selects (*R,S*) isomer, while its entropy term selects (*S,S*) isomer. On the other hand both enthalpy and entropy terms of the latter species select (*S,S*) isomer. The contribution of the entropy term to the stereocontrol of this Rh(I)–DPP-AE catalytic system at lower temperatures is large compared with that of chiral Rh(I) catalyst systems.[8] This fact suggests that the mode of coordination of substrate to catalyst affects largely the control of stereoselectivity. The electrostatic interaction provides an additional recognition point of substrate by catalyst and this interaction plays an important role to determine the mode of coordination at least in the lower temperature range and cause a large contribution of the entropy term to the stereocontrol. This temperature effect is rather similar to the temperature dependence of the heterogeneous systems, hydrogenolytic transamination between α-keto ester and chiral amine with $Pd(OH)_2$ on carbon.[5f] Temperature effects in EtOH were also examined for the hydrogenation of **2b** with DPP and of **2d** (methyl ester of **2b**) with DPP-AE (Fig. 3). Both systems have a similar steric circumstance to that of DPP-AE–**2b** system, but the electrostatic interaction cannot operate in these systems. Both showed stereoselectivities of about 50% d.e. between −40 °C

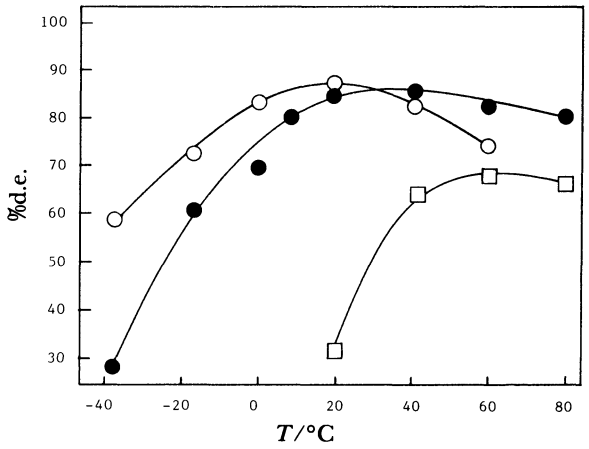


Fig. 2. The temperature dependence of the hydrogenation of **2b** with Rh(I)–DPP-AE system ○: MeOH; ●: EtOH, □: *i*-PrOH.

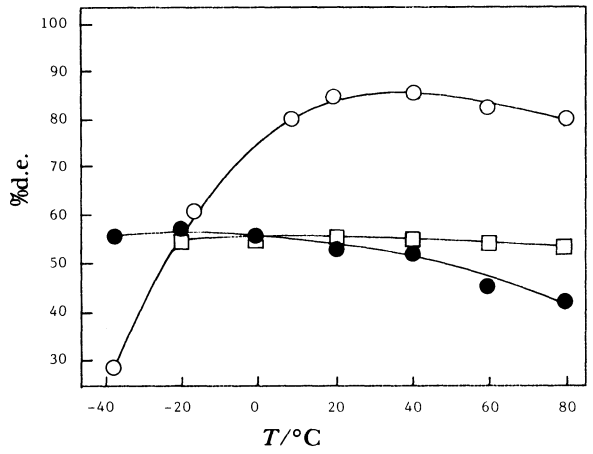


Fig. 3. The temperature dependence of the asymmetric induction in MeOH ○: DPP-AE-**2b**, □: DPP-AE-**2d**,●: DPP-**2b**.

and 80 °C. The $\Delta\Delta S^{\neq}$ was 0.85 J deg^{-1} mol^{-1} (−20 to 80 °C) for DPP-**2b** system, and 13 J deg^{-1} mol^{-1} (−20 to 20 °C), 7.4 J deg^{-1} mol^{-1} (20 to 80 °C) for DPP-AE-**2d** system. The absolute values of $\Delta\Delta S^{\neq}$ of these systems were smaller than that of DPP-AE-**2b** systems. At lower temperature the diastereoselectivity of these two systems are higher than that of DPP-AE system. This suggests that the electrostatic interaction works to increase (*R*,*S*) selectivity by lowering the temperature, although the predominant diastereomer is still (*S*,*S*).

We observed that the Rh(I)-DPP-AE (**1**) system gives the optimum conditions at ambient temperature in MeOH or MeOH-water mixed solvents in which the efficient electrostatic interaction is possible between ligand and substrate for hydrogenation of dehydrodipeptides. This catalytic system achieves highly stereoselective 1,4-asymmetric induction more than 90% d.e. regardless of the chiral amino acid residue in the dehydrodipeptides. Thus this method is useful for synthesis of chiral linear dipeptides.[9]

Experimental

Instrument. ^{1}H NMR spectra were recorded on a Hitachi R-24 or JEOL FX-90Q spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard.

Chemicals and Solvents. DPP-AE (**1**) was prepared in four steps starting from diethyl malonate and 2-chloro-*N*,*N*-dimethylethylamine.[5] DPP (**3**) was prepared from 1,3-dichloropropane and lithium diphenylphosphide. Dehydrodipeptides (**2a**—**2c**) were prepared from the azlactone of acetamidocinnamic acid[10] and corresponding chiral amino acid according to the method by Bergmann et al.[11] Dehydrodipeptide ester (**2d**) was obtained by the reaction of **2b** with MeOH-HCl. Alcohols were dried by refluxing over magnesium (MeOH and EtOH) or sodium (*i*-PrOH) and distilled under nitrogen. Tetrahydrofuran, triethylamine and *N*-methylmorpholine were dried over sodium and distilled, and DMF was dried over Molecular Sieves 4A and distilled. All solvents and amines were stored under nitrogen. NMR shift reagent, Eu(fod)$_3$, was used as purchased. $[Rh(nbd)_2]^+BF_4^-$ (nbd=norbornadiene) was used as the rhodium precursor.

Method of Hydrogenation. All hydrogenations were carried out under atmospheric hydrogen pressure. The catalyst was prepared in situ from the ligand and rhodium precursor. To this catalyst solution in a reaction vessel was added the substrate, and the mixture was stirred for 1 hour under nitrogen. The reaction vessel was immersed in a temperature-regulated bath and hydrogen was introduced. The reaction was monitored by the absorption of H_2 using a gas burette for the reaction above 0 °C. In the case of the reaction under −20 °C, the stopcock of the vessel was closed after introduction of hydrogen and stirring was continued for 1 to 3 days. After the reaction, the catalyst was removed with cation-exchange resin, Dowex 50, and the product was converted to its methyl ester in MeOH-HCl.

Determination of Diastereomeric Excess. ^{1}H NMR spectra of the methyl ester were measured in the presence of Eu(fod)$_3$. Two singlets of diastereotopic methyl protons in the methyl ester shifted in different degrees and the diastereomeric excess was determined based on the area of each signal.

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8) The calculated activation parameters of some Rh(I)

catalytic systems from reported temperature dependence are listed below.

Ligand	Substrate	$\Delta\Delta S^{\neq}$ $\Delta\Delta H^{\neq}$	Temp range/°C	Ref.
(*R*)-Prophos	Bz-ΔPhe-OH	−3.53, −8.17	10—80	5d
(*S,S*)-BDPP	Ac-ΔPhe-OH	−9.2 , −12	−20—70	5c
DIOXOP	Ac-ΔPhe-OH	53 , 15	0—100	6b
(*R,R*)-DIOP	Ac-ΔPhe-OH	−16 , −11	25—100	6b

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