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EFFECTIVE ASYMMETRIC HYDROGENATION OF DEHYDRODIPEPTIDES WITH RHODIUM(I)-NEW CHIRAL DIPHOSPHINITE SYSTEMS

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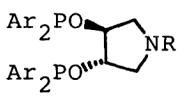
Rh(I)-new chiral diphosphinite systems with terminal amino groups were very effective for asymmetric hydrogenation of dehydrodipeptides with free carboxyl group and a chiral carbon. The effectiveness of the diphosphinite catalysts strongly suggests the contribution of electrostatic effect to asymmetric induction.

For the past decade, many effective chiral ligands for asymmetric hydrogenation were synthesized and several ligands gave high optical yields more than 95% e.e. for dehydroamino acid derivatives.[1] Most of these ligands are designed to control the asymmetric induction only by steric factor and the stereoselectivity depends on the structure of olefinic substrates.[2]

In the case of complex substrate with several functional groups it is difficult to discriminate the prochiral face by steric effect alone. We intended to introduce the electrostatic factor, as well as the steric factor, in the catalytic asymmetric reaction to enable more precise discrimination of the prochiral face of substrates. Accordingly, we prepared new chiral diphosphinites (1-5) containing pyrrolidine moiety, some of them (2, 3, and 5) having a dimethylamino group at the end of alkyl substituent of the pyrrolidine ring (vide infra). This terminal dimethylamino group is expected to interact with carboxyl group of the substrates. We have studied the asymmetric hydrogenation of itaconic acid and dehydroamino acid derivatives with Rh(I)-diphosphinite (1-5) systems and found that diphosphinite (2) with the terminal amino group gave a moderately high optical yield in the case of itaconic acid.[3] The carboxyl groups of these substrates were considered to be too distant from the terminal amino group of the ligand to enable the strong interaction between them.



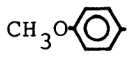
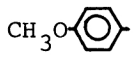
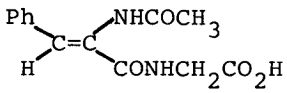
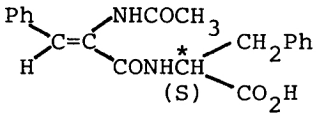
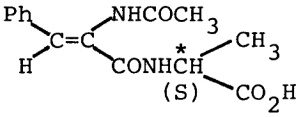
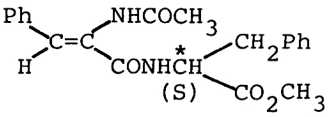
	R	Ar	$[\alpha]_D$
1	$CH_2CH_2CH(CH_3)_2$	Ph	+59.8°(c 0.48, C_6H_6)
2	$CH_2CH_2N(CH_3)_2$	Ph	+55.4°(c 0.97, C_6H_6)
3	$CH_2CH_2CH_2N(CH_3)_2$	Ph	+56.0°(c 0.31, C_6H_6)
4	$CH_2CH_2CH(CH_3)_2$		+53.3°(c 0.27, C_6H_6)
5	$CH_2CH_2N(CH_3)_2$		+58.4°(c 0.95, C_6H_6)

Table 1. Asymmetric Hydrogenation of Dehydrodipeptides with Rh(I)-Diphosphinite (1-5) Systems

Dehydrodipeptide	Diphosphinite	Temp (°C)	Time (min)	Conv. (%)	(S)/(R), (S,S)/(R,S), or (S,R)/(R,R)	% e.e. or % d.e.
 (Ac-ΔPhe-Gly-OH)	1	20	20	100	74/26	48
	2	20	30	100	67/33	34
	3	20	20	100	58/42	16
 (Ac-ΔPhe-(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	120	84	82/18	64
	5	20	15	100	>99/<1	>98
(Ac-ΔPhe-(R)-Phe-OH)	5	20	16 h	90	7/93	86
 (Ac-ΔPhe-(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
(Ac-ΔPhe-(R)-Ala-OH)	2	20	50	100	4/96	92
	5	20	25	100	7/93	86
 (Ac-ΔPhe-(S)-Phe-OMe)	1	20	180	100	51/49	2
	2	40	50 h	0	———	—
	3	40	30 h	20	———	—
	4	20	60	100	55/45	10
	5	40	8 h	0	———	—

Diphosphinite/Rh = 1.5, Dehydrodipeptide/Rh = 50, P_{H_2} = 1 atm, Solvent = EtOH

We have applied these Rh(I)-diphosphinite (1-5) systems to the asymmetric hydrogenation of dehydrodipeptides.[4] Dehydrodipeptides with terminal carboxyl group are expected to interact more easily with the terminal amino group of the diphosphinites (2, 3, and 5).

The diphosphinites were prepared from N-substituted (S,S)-pyrrolidine diols and chlorodiphenylphosphine or chlorodi(4-methoxyphenyl)phosphine by the conventional method.[5] Rhodium catalysts were prepared in situ from $[Rh(COD)_2]^+BF_4^-$ and a diphosphinite. The hydrogenations were monitored by the absorption of H_2 and the

conversion and optical yield were determined by ^{1}H NMR.

The results of the asymmetric hydrogenation of dehydrodipeptides with Rh(I)-diphosphinite (1-5) systems are summerized in Table 1. In the hydrogenation of Ac-ΔPhe-Gly-OH, rhodium catalyat coordinated with diphosphinite (1) without terminal amino group gave highest optical yield (48% e.e.) among the ligands examined. Diphosphinites having terminal amino groups lowered the (S)-selectivity as the alkyl chain extended. This result agreed wuth those for dehydroamino acid derivatives.[3)]

In the case of Ac-ΔPhe-(S)-Phe-OH, diphosphinite (2 and 3) gave (S,S)-product with high stereoselectivity (90% d.e. and 86% d.e., respectively). But diphosphinite (1), a carbon analogue of 2, gave lower stereoselectivity (58% d.e.). This result would indicate the contribution of the terminal amino group in asymmetric induction, and it is suggested that the electrostatic interaction between the terminal amino group in the ligand and the carboxyl group in dehydrodipeptide serves to fix the substrate on rhodium, It is noted that diphosphinite (5) with 4-methoxyphenyl group on phosphorous atom, an analogue of 2, gave an excellent stereoselectivity of more than 98% d.e. and the reaction completed in a short time (15 min). This phenomenon can be ascribed to the strong coordination of 5 onto rhodium, for 4-methoxyphenyl group raised the electron density on phosphorous atom. The asymmetric hydrogenation of Ac-ΔPhe-(S)-Ala-OH with Rh(I)-diphosphinite (1, 2, 3, and 5) systems gave results similar to those for Ac-ΔPhe-(S)-Phe-OH, and diphosphinite (5) gave a (S,S)-product with very high optical yield (96% d.e.), while diphosphinite (1) without terminal amino group gave low optical yield (36% d.e.).

Above results indicate the importance of the chiral center in the substrate for asymmetric induction. We have also examined the hydrogenation of dehydrodipeptides with a (R)-chiral center using 2 or 5, and observed an extremely strong double asymmetric induction. In the reaction of Ac-ΔPhe-(R)-Phe-OH, diphosphinite (5) gave (R,R)-isomer with high stereoselectivity (86% d.e.). As for Ac-ΔPhe-(R)-Ala-OH too, diphosphinite (2 and 5) gave (R,R)-product with 92% d.e. and 86% d.e., respectively. This specific dependence of the asymmetric induction on the chiral center in the substrate leading to high stereoselectivity has not been reported in the catalytic asymmetric hydrogenation. This phenomenon may be ascribed to the flexibility of the chelate ring and the electrostatic interaction between the ligand and substrate in the present diphosphinite systems.

In the case of Ac-ΔPhe-(S)-Phe-OMe, the presence of a terminal amino group in the ligand (2, 3, or 5) lowered the reactivity extremely, and diphosphinites with dimethylaminoethyl group (2 and 5) gave no hydrogenated product. This low reactivity of Ac-ΔPhe-(S)-Phe-OMe would be caused by the coordination of the terminal amino group in the ligand onto the other rhodium species to prevent the hydrogenation of the ester. On the other hand, hydrogenation of the ester occurred smoothly with rhodium catalyst coordinated with diphosphinite (1 or 4), but the stereoselectivity was very low. This striking difference between the reaction of Ac-ΔPhe-(S)-Phe-OH and that of Ac-ΔPhe-(S)-Phe-OMe will support the electrostatic interaction between the carboxyl group of dipeptide and the terminal amino group of the ligand.

Present diphosphinites having terminal amino groups (2, 3, and 5) are very effective for the asymmetric hydrogenation of dehydrodipeptide containing free

carboxyl group and a chiral carbon, and especially ligand (5) gave an excellent stereoselectivity. These high stereoselectivities suggest that the electrostatic interaction between ligand and substrate as well as steric interaction enable the precise discrimination of prochiral face. These results must be useful for designing new chiral catalyst.

References

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3) For example, the asymmetric hydrogenation of α-acetamidocinnamic acid with Rh(I)-diphosphinite (1, 2, and 3) systems gave following results: 1 29% e.e. [S], 2 16% e.e. [S], 3 13% e.e. [R]. In the case of itaconic acid with Rh(I)-diphosphinite (1, 2, and 3) systems diphosphinite (2) gave the highest optical yield : 1 51% e.e. [R], 2 65% e.e. [R], 3 45% e.e. [R].

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