furan-2(3*H*)-one (10). Dry triethylamine (107 mg, 0.147 mL, 1.05 mmol) was added via a syringe to alcohol **9** (220 mg, 0.88 mol) in 3.7 mL of CH_2Cl_2 at −5 °C to −10 °C under N_2 with stirring. The reaction mixture was stirred for 5 min and methanesulfonyl chloride (111 mg, 0.075 mL, 0.97 mmol) was added dropwise via a syringe over a 10-min period. The reaction mixture was stirred between 0 and −10 °C for 2.75 h, diluted with 100 mL of CH_2Cl_2, and washed with 15 mL of cold H_2O, 20 mL of 10% HCl, 20 mL of 10% $NaHCO_3$, and 15 mL of brine. The organic solution was dried ($MgSO_4$) and concentrated in vacuo to afford a quantitative yield of **10**: mp 89.5–90 °C; NMR ($CDCl_3$) δ 5.30–5.58 (m, 1 H), 4.59–4.92 (m, 1 H, CHOCO, unresolved), 4.42 (d, 2 H), 3.06 (s, 3 H); IR (KBr) 1765, 1340, 1360 cm^{-1}.

(3aβ,4aα,5α,9aβ)-3a,4a,5,6,7,9,9a-Octahydro-4a,5-dimethyl-3-methylenenaphtho[2,3-*b*]furan-2(3*H*)-one (1). DBU (0.191 g, 0.188 mL, 1.26 mmol) was added via a syringe over a 10-min period to sulfonate **10** (330 mg, 1.01 mol) in 4.5 mL of dry benzene under N_2 with stirring at room temperature. The reaction mixture was stirred for 3 h and then diluted with 150 mL of ether. The organic solution was washed with 10 mL of cold H_2O, 15 mL of cold 10% HCl, and 10 mL of cold brine, dried ($MgSO_4$), and concentrated in vacuo, giving an oil. Chromatography on silica gel G and elution with hexanes and ether–hexane solutions afforded (183 mg, 78%) of **1**: mp 95.5–96.2 °C; NMR (PhD_6) δ 6.01 (d, 1 H, J = ~1 Hz, H-13), 5.10–5.40 (m, 1 H, H-1), 4.96 (d, 1 H, J = 1 Hz, H-13), 3.70–4.05 (m, 1 H), 2.10–2.60 (m), 1.65–2.0 (m), 0.85–1.60 (m, 5 H), 0.67 (d, J = 6 Hz), 0.63 (s, 6 H); irradiation of the C-7 and C-9 hydrogens caused the multiplet at δ 3.70–4.05 to collapse to a singlet at δ 3.93; irradiation of the C-9 hydrogens caused the multiplet at δ 3.70–4.05 to collapse to a doublet at δ 3.93 ($J_{7,8}$ = 4–5 Hz); IR (CH_2Cl_2) 1770 cm^{-1}; mass spectrum m/e 232 (M), 217, 190, 145, 119, 105, 91, 79.

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.79; H, 8.58.

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Synthesis of Chiral Dipeptides by means of Asymmetric Hydrogenation of Dehydro Dipeptides

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Asymmetric hydrogenation of various dehydro dipeptides was carried out by using rhodium complex catalysts with a variety of chiral diphosphine ligands. The efficiency of chiral diphosphine ligands as well as the effect of the chiral center in the substrate on the catalytic asymmetric induction was studied. It was found that extremely high stereoselectivities for producing the *S,S*, *R,S*, *S,R*, or *R,R* isomer were achieved with the proper choice of chiral ligands although a considerably large double asymmetric induction was observed in some cases. Pyrrolidinodiphosphines, e.g., Ph-CAPP, *p*-BrPh-CAPP, BPPM, CBZ-Phe-PPM, and diPAMP, exhibited excellent stereoselectivities, whereas chiraphos, prophos, and BPPFA only gave poor results especially for the reaction of *N*-acyldehydro dipeptide which had a free carboxylic acid terminus. Stereoselective dideuteration was also successfully performed.

It is well-known that the general methods for the formation of peptide linkage are based on the coupling of two optically active amino acid components by using, e.g., the acyl chloride method, the acyl azide method, the mixed anhydride method, the carbodiimide method, and the enzyme method. These methods have been developed for the synthesis of naturally occurring polypeptides with minimum racemization.

Recently, it has been shown that significant modification of biological activities can be effected through inversion of configuration at one or more chiral centers or through replacement of one or more "natural" amino acid residue(s), by "unnatural" amino acid components in a biologically active polypeptide such as enkephalin, vasopressin, angiotensin II, gonadoliberin, and other hormones.[1] As an approach to the synthesis of chiral olgio- and polypeptides with desired structures, it is important to develop a facile device which gives a chiral building block for peptide synthesis other than the simple preparation of "unnatural" amino acids. As precursors of modified peptides, dehydro peptides are interesting candidates since catalytic asymmetric hydrogenation, in principle, can convert the dehydro amino acid residue into the amino acid residue with either *R* or *S* configuration. In this context, the asymmetric hydrogenation of dehydro dipeptides giving chiral dipeptides is a significant model reaction. We reported the preliminary results on the asymmetric synthesis of dipeptides by means of asymmetric hydrogenation catalyzed by chiral rhodium complexes in 1980,[2] and in the same year Kagan et al.,[3] and Onuma et al.[4] also reported similar results independently. Now, we will describe here a full account of our research on this approach to the synthesis of chiral dipeptides.

Results and Discussion

As the homogeneous asymmetric hydrogenation of dehydro-α-amino acids catalyzed by rhodium complexes with chiral diphosphine ligands has turned out to be quite effective for the synthesis of chiral α-amino acids,[5] it would

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Table I. Efficiency of Chiral Diphosphine Ligands in the Asymmetric Hydrogenation of Typical Dehydro Dipeptides[a]

entry	substrate	ligand	conditions: H_2 press, atm	conditions: temp, °C	conditions: time, h	% conversion[b]	dipeptide R,S/S,S[b] ratio
1	Bz-ΔPhe-(S)-Phe-OMe	p-BrPh-CAPP	1	40	3	100	99.2/0.8
2		(−)-BPPM	1	40	1	100	98.7/1.3
3		(+)-BPPM	1	40	1	100	0.9/99.1
4		(−)-DIOP	5	25	18	100	84.1/15.9
5		(+)-DIOP	5	25	18	100	16.4/83.6
6		diPAMP	10	50	15	100	2.2/97.8
7		chiraphos	5	40	10	82	85.1/14.9
8		prophos	5	40	10	99	4.1/95.9
9		BPPFA	5	40	10	51	18.7/81.3
10		dppb[b]	1	40	5	85	37.8/62.2
11	Ac-ΔPhe-(S)-Phe-OH	Ph-CAPP	5	40	20	100	98.0/2.0
12		(−)-BPPM	10	50	20	100	96.2/3.8
13		(+)-BPPM	10	50	20	97	0.6/99.4
14		(−)-DIOP	5	40	20	100	81.8/18.2
15		(+)-DIOP	5	40	20	89	5.9/94.1
16		diPAMP	5	50	20	86	1.4/98.6
17		chiraphos	10	50	20	96	39.1/60.9
18		prophos	10	50	20	95	18.8/81.2
19		BPPFA	50	50	20	23	61.2/38.8
20		dppb	10	50	20	99	34.1/65.9

[a] All reactions were run with 5.0×10^{-4} mol of the substrate and 5.0×10^{-6} mol of the catalyst. [b] Determined by HPLC (±0.1%).

Table II. Effect of Chiral Center in Dehydro Dipeptides on Stereoselectivity[a]

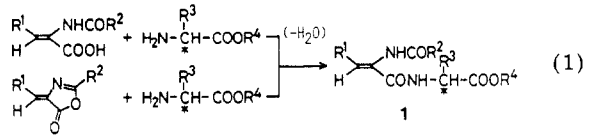
entry	ligand	substrate	Ac-Phe-Phe-OMe ratio: R,S/S,S[b]	Ac-Phe-Phe-OMe ratio: R,R/S,R[b]
1	CBZ-(S)-Phe-PPM (3a)	Ac-ΔPhe-(S)-Phe-OMe	98.0/2.0	
2	CBZ-(S)-Phe-PPM (3a)	Ac-ΔPhe-(R)-Phe-OMe		99.5/0.5
3	CBZ-(S)-Pro-PPM (3d)	Ac-ΔPhe-(S)-Phe-OMe	98.1/1.9	
4	CBZ-(S)-Pro-PPM (3d)	Ac-ΔPhe-(R)-Phe-OMe		99.5/0.5
5	CBZ-(S)-Val-PPM (3f)	Ac-ΔPhe-(S)-Phe-OMe	98.9/1.1	
6	CBZ-(S)-Val-PPM (3f)	Ac-ΔPhe-(R)-Phe-OMe		96.2/3.8

[a] All reactions were run with 5.0×10^{-4} mol the substrate and 5.0×10^{-6} mol of the catalyst at 40 °C and 1 atm of hydrogen for 2 h. Conversion was 100% for every case examined. [b] Determined by HPLC (±0.1%).

be a good test to examine the potential of the chiral rhodium catalysts in the asymmetric hydrogenation of dehydro dipeptides.

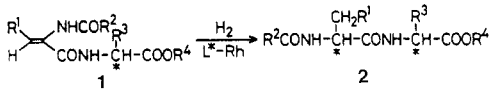
An interesting point involved in this reaction is how the chiral center of the dehydro dipeptide affects the way of asymmetric induction by the catalyst. Namely, if the optical purity of the newly forming chiral center is not affected by the already existing chiral center in the substrate, we can synthesize the dipeptides having desired configurations.

N-Acyldehydro dipeptides were readily prepared either by the condensation of an *N*-acyldehydro α-amino acid with an α-amino acid ester or by the reaction of the azlactone of the *N*-acyldehydro α-amino acid with an α-amino acid ester (eq 1).



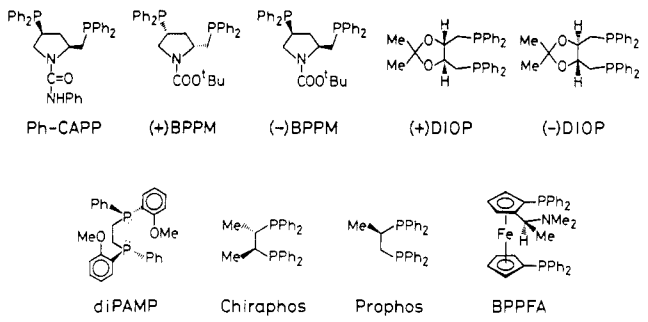
(1)

The asymmetric hydrogenation of *N*-acyldehydro dipeptides thus obtained was carried out (eq 2) by using



(2)

Chart I



Ph-CAPP (+)BPPM (−)BPPM (+)DIOP (−)DIOP

diPAMP Chiraphos Prophos BPPFA

rhodium complexes with a variety of chiral diphosphines (Chart I) such as *p*-BrPh-CAPP,[6] Ph-CAPP,[6] (−)-BPPM,[7] (+)-BPPM,[20] (−)-DIOP,[8] (+)-DIOP,[8] diPAMP,[9] chiraphos,[10] prophos,[11] BPPFA,[12] and CBZ-Phe-PPM[21] (vide infra). The chiral catalysts were prepared in situ from the chiral diphosphine ligand with $[Rh(NBD)_2]^+ClO_4^-$ (NBD = norbornadiene). Typical results are summarized in Tables I–V.

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Table III. Typical Results on the Asymmetric Hydrogenation of Dehydro Dipeptides

substrate	ligand[f]	conditions: H_2 press, atm	conditions: temp, °C	conditions: time, h	dipeptide[f] $R,S/S,S$[a] or $R,R/S,R$[b] ratio
Bz-ΔPhe-(*S*)-Phe-OMe	*p*-BrPh-CAPP	1	40	3	99.2/0.8
	(+)-BPPM	1	40	1	0.9/99.1
Bz-ΔPhe-(*S*)-Val-OMe	*p*-BrPh-CAPP	10	40	20	98.0/2.0
	diPAMP	10	40	24	1.0/99.0
Ac-ΔPhe-(*S*)-Phe-OMe	Ph-CAPP	1	40	46	99.0/1.0
	(+)-BPPM	1	40	1	0.6/99.4
Ac-ΔPhe-(*S*)-Phe-OH	Ph-CAPP	5	40	20	98.0/2.0
	(+)-BPPM	10	50	20	0.6/99.4
Ac-ΔPhe-(*S*)-Val-OH	Ph-CAPP	10	50	20	96.3/3.7
	diPAMP	10	50	20	3.0/97.0
Bz-ΔLeu-(*S*)-Phe-OMe	(−)-BPPM	1	40	24	95.3/4.7
	(+)-BPPM	1	40	16	3.6/96.4
Ac-ΔPhe-(*R*)-Phe-OMe	(−)-BPPM	1	40	2	99.6/0.4[b]
	(+)-BPPM	1	40	2	1.5/98.5[b]
Ac-ΔPhe-(*R*)-Phy-OMe	Ph-CAPP	5	40	20	97.4/2.6[b]
	diPAMP	10	40	24	2.6/97.4[b]
Bz-ΔPhe-(*R*)-Phe-OMe	CBZ-(*S*)-Phe-PPM	1	40	1	99.5/0.5[b]
Ac-Δ(Ac)Tyr-(*R*)-Ala-OMe[c]	Ph-CAPP	5	40	24	99.8/0.2[b]
Ac-Δ(AcO)(MeO)Phe-(*R*)-Ala-OMe[d]	Ph-CAPP	5	40	24	99.4/0.6[b]
Ac-Δ(F)Phe-(*S*)-Leu-OMe[e]	(+)-BPPM	5	40	64	0.9/99.1

[a] Determined by HPLC (±0.1%); *R,S/S,S* ratio unless otherwise noted. [b] *R,R/S,S*. [c] Ac(Tyr) = 4-acetyltyrosyl. [d] (AcO)(MeO)Phe = (3-methoxy-4-acetoxyphenyl)alanyl. [e] (F)Phe = (4-fluorophenyl)alanyl. [f] 100% conversion in all cases.

Table IV. Asymmetric Hydrogenation of Bz-ΔPhe-(*S*)-Phe-OMe by Using α-(Aminoacyl)-4-(diphenylphosphino)-2-[diphenylphosphino)methyl]pyrrolidine (3) as Chiral Ligand[a]

entry	ligand	time,[c] h	Bz-Phe-Phe-OMe[b] *R,S/S,S*[b] ratio
1	CBZ-(*S*)-Phe-PPM (3a)	1	98.0/2.0
2	CBZ-(*S*)-Ala-PPM (3b)	1	97.7/2.3
3	CBZ-(*R*)-Ala-PPM (3c)	1	97.6/2.4
4	CBZ-(*S*)-Pro-PPM (3d)	1	98.1/1.9
5	CBZ-(*R*)-Pro-PPM (3e)	18	83.0/17.0
6	CBZ-(*S*)-Val-PPM (3f)	1	96.2/3.8
7	CBZ-Gly-PPM (3g)	4	97.8/2.2
8	CBZ-(*S*)-Phe-(*S*)-Val-PPM (3h)	2	96.4/3.6

[a] All reactions were run with 5.0×10^{-4} mol of the substrate and 5.0×10^{-6} mol of the catalyst in 15 mL of ethanol. [b] All conversions were 100% as determined by HPLC (±0.1%). [c] The H_2 pressure was 1 atm and the temperature 40 °C in all cases.

As Table I shows, the efficiency of each chiral diphosphine ligand exhibited in the asymmetric hydrogenation of dehydro dipeptides is considerably different from that reported for the reaction of *N*-acyldehydro amino acids, especially in the case of chiraphos and BPPFA, which are known to realize much better enantioselectivity than DIOP for the dehydro amino acid case.[5,10,12] When Ac-ΔPhe-(*S*)-Phe-OH was employed as the substrate, chiraphos induced the *S* configuration (entry 17) and BPPFA led to the *R* configuration (entry 19) with low stereoselectivities; in both cases, the directions of asymmetric induction are opposite to those observed for α-acetamidocinnamic acid. Prophos brought about a good result for Bz-ΔPhe-(*S*)-Phe-*OMe* (entry 8) whereas it was no longer an excellent chiral ligand for Ac-ΔPhe-(*S*)-Phe-*OH* (entry 18). Pyrrolidinodiphosphines and diPAMP achieved extremely high stereoselectivities. There seems to be a trend that the chiral ligands which form seven-membered-ring chelate with rhodium give rise to much better results than those forming a rigid five-membered-ring chelate or a quasi-five-membered-ring chelate, except for diPAMP. The results may imply that the seven-membered-ring chelate has flexibility for "induced-fit" action like an enzyme, which is quite an important factor for a chiral complex catalyst used with a polyfunctionalized substrate.[13]

As for the influence of the chiral center in the substrate on asymmetric induction, fairly large double asymmetric induction was observed on using a dehydro dipeptide bearing a free acid terminus such as Ac-ΔPhe-(*S*)-Phe-OH (see entries 12 and 13 and entries 14 and 15). To realize the extent of double asymmetric induction more quantitatively, one has to look at not the difference of the relative amounts of diastereomers in percent but the ratio of two diastereomers, which is related to $\Delta\Delta G^{\ddagger}$: for BPPM, *R,S/S,S* ratio = 25.3 (entry 12, (−)-BPPM), *S,S/R,S* ratio = 165.7 (entry 13, (+)-BPPM); for DIOP, *R,S/S,S* ratio = 4.49 (entry 14, (−)-DIOP), *S,S/R,S* ratio = 15.9 (entry 15, (+)-DIOP). Thus, the extent of double asymmetric induction turns out to be more pronounced in BPPM rather than DIOP although the apparent difference in optical purities is much smaller in BPPM compared with that in DIOP. The results regarding to the double asymmetric induction indicate that the formation of *S,S* isomer is preferred in these systems. The experiment using an achiral diphosphine ligand, bis(diphenylphosphino)butane (dppb), gave the consistent results (entry 20); i.e., 31.8% asymmetric induction which favored the formation of the *S,S* isomer of Ac-Phe-Phe-OH was observed. On the other hand, when dehydro dipeptide methyl esters were employed, only a slight effect of the chiral center was observed as far as DIOPs were concerned.[18] E.g., for Bz-Phe-

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(18) All reactions were run with 5.0×10^{-4} mol of the substrate and 5.0×10^{-6} mol of the catalyst at 40 °C and 5 atm of hydrogen in ethanol for 12–24 h. It was found as a special case that the introduction of (*R*)-phenylglycine to the substrate caused an appreciable double asymmetric induction even when (+)- and (−)-DIOPs were employed: Ac-Phe-Phy-OMe: (+)-DIOP, *R,R/S,R* ratio of 5.1/94.9; (−)-DIOP, *R,R/S,R* ratio of 85.5/14.5.

Table V. Asymmetric Hydrogenation of Dehydro Dipeptides by Using CBZ-(*S*)-Phe-PPM (3a) as Chiral Ligand[a]

entry	substrate	time,[c] h	% conversion[b]	dipeptide *R,S/S,S*[b] ratio
1	Ac-Δ-Phe-(*S*)-Phe-OMe	2	100	97.9/2.1
2	Bz-Δ-Phe(*S*)-Val-OMe	3	100	98.2/1.8
3	Ac-Δ-Phe-(*S*)-Ala-OMe	1	99	98.3/1.7
4	Ac-Δ-Phe-(*S*)-Phe-OH	3	99	97.6/2.4
5	Ac-Δ-Phe-(*S*)-Val-OH	24	97	96.0/4.0

[a] All reactions were run with 5.0×10^{-4} mol of the substrate and 5.0×10^{-6} mol of the catalyst in 15 mL of ethanol. [b] Determined by HPLC (±0.1%). [c] The H_2 pressure was 1 atm and the temperature 40 °C in all cases.

Phe-OMe: (+)-DIOP, *R,S/S,S* ratio = 16.6/83.4; (−)-DIOP, *R,S/S,S* ratio = 84.2/15.8. For Ac-Phe-Ala-OMe: (+)-DIOP, *R,S/S,S* ratio = 7.9/92.1; (−)-DIOP, *R,S/S,S* ratio = 92.5/7.5. For Bz-Phe-Val-OMe: (+)-DIOP, *R,S/S,S* ratio = 20.6/79.4; (−)-DIOP, *R,S/S,S* ratio = 85.5/14.5.

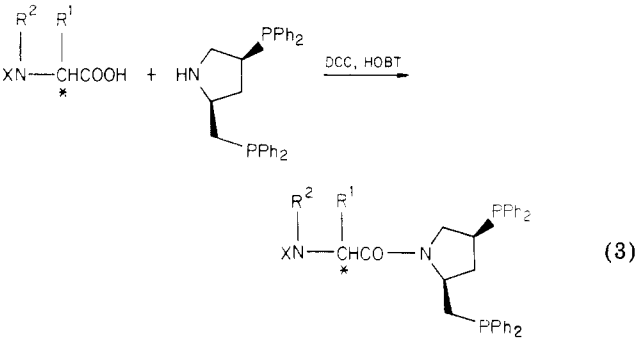
The results could be interpreted by assuming the exclusive coordination of the *N*-acyldehydro amino acid moiety with the rhodium complex in which the rest of the molecule, i.e., the α-amino ester moiety, is located in the outer sphere of the chiral coordination site: this may be the reason why virtually no double asymmetric induction was observed. However, a simple asymmetric hydrogenation using dppb as achiral ligand (entry 9) disclosed favorable formation of Bz-(*S*)-Phe-(*S*)-Phe-OMe with 24.4% asymmetric induction, which is consistent with the result with Ac-ΔPhe-(*S*)-Phe-OH as the substrate (entry 19). Accordingly, it seems that the results with DIOPs are rather exceptional. In this context, we further looked at the effect of the chiral center on the catalytic asymmetric induction by using Ac-ΔPhe-(*R*)-Phe-OMe and Ac-ΔPhe-(*S*)-Phe-OMe as substrates and CBZ-(*S*)-Phe-PPM (**3a**), CBZ-(*S*)-Val-PPM (**3f**) and CBZ-(*S*)-Pro-PPM (**3d**) as chiral ligands for the cationic rhodium complex. Results are listed in Table II. As Table II shows, there is only a slight difference between the two substrates in the percent asymmetric induction from a synthetic point of view since the reactions achieve quite high stereoselectivities, but there is a significant difference in $\Delta\Delta G^{\ddagger}$ since it was found that the *R,R/S,R* ratio is 3–4 times larger than the *R,S/S,S* ratio in every case examined. Moreover, similar results were obtained in the asymmetric hydrogenation of Ac-ΔPhe-(*R*)-Phe-OMe by using (−)-BPPM and (+)-BPPM as shown in Table III. Namely, the reaction using (−)-BPPM achieved 99.6% production of Ac-(*R*)-Phe-(*R*)-Phe-OMe while that using (+)-BPPM led to 98.5% production of the *S,R* isomer: *R,R/S,R* ratio = 249 for (−)-BPPM; *S,R/R,R* ratio = 65.7 for (+)-BPPM. Consequently, it can be said that there is a significant extent of double asymmetric induction for the reaction of the dehydro dipeptide methyl ester too, and DIOP's case is rather exceptional.

Table III summarizes typical results for the asymmetric hydrogenation of a variety of *N*-acyldehydro dipeptides with the use of pyrrolidinodiphosphines and diPAMP. As Table III shows, it is demonstrated that *R,S*, *S,S*, *S,R*, or *R,R* dipeptides with high optical purities can be readily synthesized by using these chiral ligands, and one recrystallization easily leads to optically pure dipeptides.

Since it turns out that the catalytic asymmetric hydrogenation can generate either the *S* or *R* configuration at the position of the dehydro amino acid residue, this method could be potentially useful for the specific labeling of a certain amino acid residue in a polypeptide. With regard to the regiospecific and stereoselective labeling of the amino acid residue, we carried out the dideuteration of Ac-ΔPhe-(*S*)-Ala-OMe with the use of the cationic rhodium complexes with (−)-BPPM and (+)-BPPM (Scheme I), which gave Ac-(*R,R*)-Phe-d_2-(*S*)-Ala-OMe (*R,R,S/S,S,S* ratio = 98.7/1.3) and Ac-(*S,S*)Phe-d_2-(*S*)-Ala-OMe (*R,R,S/S,S,S* ratio = 0.5/99.5), respectively, without any scrambling of deuterium.

As it has been shown that the introduction of deuterium to the chiral center of certain amino acids, e.g., 3-fluoro-2-deuterio-(*R*)-alanine,[19] changes the biological activity remarkably, the stereoselective dideuteration may provide a convenient device for this kind of modification of biological activity.

As pyrrolidinodiphosphines, e.g., Ph-CAPP, *p*-BrPh-CAPP, and BPPM, gave excellent stereoselectivities, we prepared a series of new chiral pyrrolidinodiphosphines in which the nitrogen atom of PPM[7,13] is linked up with a variety of α-aminoacyl groups by taking into account a possible connection to polymers, especially polyamides, which may serve as a good biomimetic model of reductase. α-AacPPMs (**3**; Aac = aminoacyl) were prepared by the condensation of PPM with an *N*-CBZ α-amino acid or an *N*-CBZ dipeptide in the presence of dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBT; eq 3; see Experimental Section).



(3)

3a, $R^1 = PhCH_2$; $R^2 = H$;
X = CBZ [CBZ-(*S*)-Phe-PPM]
b, $R^1 = Me$; $R^2 = H$;
X = CBZ [CBZ-(*S*)-Ala-PPM]
c, $R^1 = Me$; $R^2 = H$;
X = CBZ [CBZ-(*R*)-Ala-PPM]
d, $R^1, R^2 = (CH_2)_3$;
X = CBZ [CBZ-(*S*)-Pro-PPM]
e, $R^1, R^2 = (CH_2)_3$;
X = CBZ [CBZ-(*R*)-Pro-PPM]
f, $R^1 = i$-Pr; $R^2 = H$;
X = CBZ [CBZ-(*S*)-Val-PPM]
g, $R^1 = R^2 = H$;
X = CBZ [CBZ-Gly-PPM]
h, $R^1 = i$-Pr; R^2 = CBZ-(*S*)-Phe;
X = H [CBZ-(*S*)-Phe-(*S*)-Val-PPM]

Typical results on using Bz-ΔPhe-(*S*)-Phe-OMe as substrate are listed in Table IV, and Table V summarizes the results with CBZ-(*S*)-Phe-PPM (**3a**) as the chiral ligand for the reaction of several dehydro dipeptides. As Table

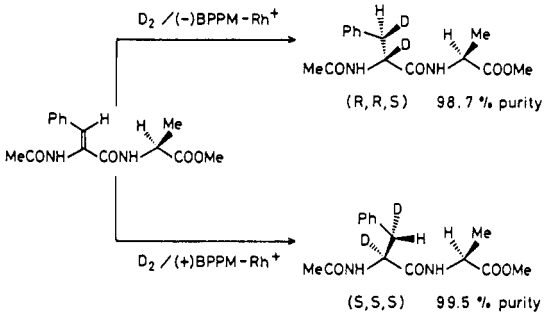
(19) (a) Kollonitsch, J.; Barash, L. *J. Am. Chem. Soc.* **1976**, *98*, 5591. (b) Dang, T.; Cheng, Y.; Walsh, C. *Biochem. Biophys. Res. Commun.* **1976**, *72*, 960.

Table VI. Physical Properties of Compound 3

ligand	yield, %	mp, °C	$[\alpha]^{20}_D$, deg	IR, cm^{-1} ν(C=O)	IR, cm^{-1} amide II	^{1}H NMR ($CDCl_3$) for $PhCH_2OCO$, δ
3a	91	73-77	−6.2 (c 0.504, $CHCl_3$)	1715, 1630	1530	5.04 (s)
3b	82	66-72	−20.6 (c 1.030, MeOH)	1715, 1635	1535	5.04 (s)
3c	90	65-69	−10.5 (c 1.004, MeOH)	1715, 1640	1530	4.93 (s)
3d	94	63-70	−19.7 (c 1.012, $CHCl_3$)	1705, 1650		4.88 (AB q, J = 12 Hz),[a] 5.01 (AB q, J = 13 Hz)[a]
3e	91	66-71	−19.9 (c 1.006, $CHCl_3$)	1700, 1645		4.60-5.18 (m)[a]
3f	92	63-68	−18.0 (c 1.007, $CHCl_3$)	1715, 1625	1530	5.05 (s)
3g	84	60-65	−15.3 (c 1.003, $CHCl_3$)	1725, 1650	1515	5.07 (s)
3h	91	76-80	−22.7 (c 1.007, $CHCl_3$)	1722, 1675, 1630	1540	5.03 (s)

[a] Rather complicated spectra can be ascribed to conformational isomers.

Scheme I. Stereoselective Dideuteration of Dehydro Dipeptide



IV shows (i) that the stereoselectivities attained by these α-AacPPMs are as high as those attained by other pyrrolidinodiphosphines and (ii) that there are not significant differences in stereoselectivities by changing the amino acid residue, except the case of CBZ-(*R*)-Pro-PPM (**3e**), which shows a lower stereoselectivity and a lower rate than CBZ-(*S*)-Pro-PPM (**3d**) and other α-AacPPMs. It should be noted that the reaction rate is considerably higher than that realized by other pyrrolidinodiphosphines such as Ph-CAPP and BPPM. These results may indicate a promising activity of the corresponding polymer-anchored catalyst, and our study on the catalysis of such polymer-anchored complexes will be reported elsewhere.

Experimental Section

Measurements. Melting points were uncorrected. Infrared spectra were recorded on a Hitachi 285 spectrophotometer by using samples as KBr disks. ^{1}H NMR spectra were measured with a Varian XL-100-15A, T-60, or EM-390 spectrometer with Me_4Si as the internal standard. ^{31}P NMR spectra were recorded on a Varian XL-100-15A by using H_3PO_4 as the external standard. Optical rotations were measured with a Union PM 201 polarimeter. High-pressure liquid chromatography (HPLC) analysis was carried out by using a TOYO SODA HLC-803 apparatus.

Materials. *N,N*-Dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBT) were used as purchased. α-Amino acids and *N*-CBZ α-amino acids were used as purchased. (*S*,*S*)-CBZ-Phe-Val-OH was prepared from *N*-CBZ-(*S*)-Phe and (*S*)-valine methyl ester by the conventional method using DCC and HOBT followed by hydrolysis. The azlactones of *N*-acyldehydro α-amino acids were prepared by a reported method.[14] *N*-Acyldehydro α-amino acids were prepared by the hydrolysis of the corresponding azlactones.[14] $[Rh(NBD)_2]^+ClO_4^-$ was prepared by the literature method.[10,15] (+)-DIOP, (−)-DIOP, chiraphos, prophos, and dppb were commercially available from Strem Chemicals Inc. (−)-BPPM,[7,13] Ph-CAPP,[6] *p*-BrPh-CAPP,[6] PPM,[7,13] and BPPFA[12] were prepared by following the reported methods. (+)-BPPM was prepared from unnatural (4*S*,2*R*)-hydroxyproline,[20] which was obtained by the transformation of natural (4*R*,2*S*)-hydroxyproline[16] by the same procedure as for (−)-BPPM.[7,13]

Preparation of α-AacPPMs(3). α-AacPPMs (Aac = aminoacyl) were prepared by the condensation of PPM with an *N*-CBZ α-amino acid or an *N*-CBZ dipeptide. The preparation of CBZ-(*S*)-Pro-PPM (**3d**) is typically described. A mixture of PPM (453 mg, 1.00 mmol), *N*-CBZ-(*S*)-Pro (274 mg, 1.10 mmol), DCC (271 mg, 1.31 mmol), and HOBT (176 mg, 1.30 mmol) in 3 mL of degassed dimethylformamide (DMF) was stirred at 0 °C for 12 h under argon. TLC analysis of the reaction mixture revealed the completion of the reaction. Then, degassed ethyl acetate (10 mL) was added to the reaction mixture, and the resulting white precipitate was filtered off. After the solvent was removed under reduced pressure, the residue was submitted to column chromatography on silica gel under argon. CBZ-(*S*)-Pro-PPM (**3d**) was obtained as colorless solid by ethyl acetate elution; 645 mg (94% yield).

Physical properties of α-AacPPMs **3a-h** thus obtained are listed in Table VI. Microanalytical data are as follows. **3a**: Anal. Calcd for $C_{46}H_{44}N_2O_3P_2{\cdot}H_2O$: C, 73.39; H, 6.16; N, 3.72. Found: C, 73.62; H, 6.02; N, 3.83. **3b**: Anal. Calcd for $C_{40}H_{40}N_2O_3P_2{\cdot}H_2O$: C, 71.00; H, 6.20; N, 4.14. Found: C, 71.19; H, 6.27; N, 4.09. **3c**: Anal. Calcd for $C_{40}H_{40}N_2O_3P_2$: C, 72.94; H, 6.12; N, 4.25. Found: C, 72.67; H, 6.29; N, 4.46. **3d**: Anal. Calcd for $C_{42}H_{42}N_2O_3P_2{\cdot}0.5H_2O$: C, 72.71; H, 6.25; N, 4.04. Found: C, 72.49; H, 6.24; N, 4.25. **3e**: Anal. Calcd for $C_{42}H_{42}N_2O_3P_2{\cdot}0.5H_2O$: C, 72.71; H, 6.25; N, 4.04. Found: C, 72.52; H, 6.38; N, 4.15. **3f**: Anal. Calcd for $C_{42}H_{44}N_2O_3P_2{\cdot}0.5\ H_2O$: C, 72.50; H, 6.52; N, 4.30. Found: C, 72.39; H, 6.46; N, 4.33. **3g**: Anal. Calcd for $C_{39}H_{38}N_2O_3P_2$: C, 72.66; H, 5.94; N, 4.35. Found: C, 72.39; H, 6.09; N, 4.57. **3h**: Anal. Calcd for $C_{51}H_{53}N_3O_4P_2{\cdot}H_2O$: C, 71.90; H, 6.51; N, 4.93. Found: C, 72.04; H, 6.39; N, 5.18.

Preparation of Dehydro Dipeptides 1. *N*-(*N*-Acetyldehydrophenylalanyl)-(*S*)-phenylalanine and *N*-(*N*-acetyldehydrophenylalanyl)-(*S*)-valine were prepared in accordance with the method of Doherty, Tietzman, and Bergmann[17] by reacting the azlactone of *N*-acetyldehydrophenylalanine with the sodium salts of (*S*)-phenylalanine and (*S*)-valine, respectively. *N*-(*N*-Benzoyldehydrophenylalanyl)-(*S*)-phenylalanine methyl ester, *N*-(*N*-benzoyldehydrophenylalanyl)-(*R*)-phenylalanine methyl ester, *N*-(*N*-benzoyldehydrophenylalanyl)-(*S*)-valine methyl ester, *N*-(*N*-acetyldehydrophenylalanyl)-(S)-phenylalanine methyl ester,

(20) An improved method for the preparation of (+)-BPPM starting from natural hydroxyproline recently reported by Stille's group is recommended since the transformation of natural hydroxyproline to an unnatural one is long and troublesome. See: Baker, G. L.; Fritschel, S. J.; Stille, J. R.; Stille, J. K. *J. Org. Chem.* **1981**, *46*, 2954.

(21) CBZ-Phe-PPM stands for (4*S*,2*S*)-*N*-[*N*-(benzyloxycarbonyl)-(*S*)-phenylalanyl]-4-(diphenylphosphino)-2-[(diphenylphosphino)-methyl]pyrrolidine.

N-(*N*-acetyldehydrophenylalanyl)-(*R*)-phenylalanine methyl ester, *N*-(*N*-benzoyldehydroleucyl)-(*S*)-phenylalanine methyl ester, *N*-(*N*-acetyldehydrophenylalanyl)-(*R*)-phenylglycine methyl ester, *N*-(*N*,*O*-diacetyldehydrotyrosyl)-(*R*)-alanine methyl ester, *N*-acetyl-*N*-[(3-methoxy-4-acetoxyphenyl)dehydroalanyl]-(*R*)-alanine methyl ester, and *N*-[*N*-acetyl-(4-fluorophenyl)dehydroalanyl]-(*S*)-leucine methyl ester were prepared either by reacting the azlactones of *N*-acyldehydro amino acids with chiral α-amino acid methyl esters in a manner similar to Bergmann's method[17] or by the coupling of *N*-acyldehydro α-amino acids with chiral α-amino acid methyl esters in the presence of DCC and HOBT.

As typical examples, the preparation of *N*-(*N*-benzoyldehydrophenylalanyl)-(*S*)-valine methyl ester (A) and that of *N*-(*N*,*O*-diacetyldehydrotyrosyl)-(*R*)-alanine methyl ester (B) are described.

Ester A. *N*-Methylmorpholin (4.25 g, 42 mmol) was added to the solution of (*S*)-valine methyl ester hydrochloride (6.71 g, 40 mmol) in dimethylformamide (50 mL), and the mixture was stirred for 10 min at 5 °C on an ice–water bath. Then, (*Z*)-α-benzamidocinnamic acid (10.69 g, 40 mmol) and DCC (8.66 g, 42 mmol) were added to it, and the mixture was stirred at 5 °C. After 1 h, the ice–water bath was removed, and the stirring was continued for another 24 h. Precipitated dicyclohexylurea was filtered off, and the solvent was evaporated under reduced pressure. The residue was dissolved in chloroform (200 mL), washed with 10% aqueous citric acid, water, 5% aqueous sodium bicarbonate, and water, and dried over anhydrous magnesium sulfate. Evaporation of the solvent left white residue, which was recrystallized from ethyl acetate to give colorless crystalline *N*-(*N*-benzoyldehydrophenylalanyl)-(*S*)-valine methyl ester: 9.47 g (62.5% yield); mp 199–200 °C; $[\alpha]^{25}_D$ −1.43° (*c* 1.13, $CHCl_3$).

Ester B. Triethylamine (2.03 g, 20 mmol) was added to the solution of (*R*)-alanine methyl ester hydrochloride (2.79 g, 20 mmol) in chloroform (150 mL) with stirring at ambient temperature. Then, 2-methyl-4-(*p*-acetoxybenzylidene)-2-oxazolin-5-one (4.91 g, 20 mmol) was slowly added, and the mixture was stirred overnight at ambient temperature. The reaction mixture was washed with saturated aqueous sodium chloride (4 × 50 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residual solid was recrystallized from ethyl acetate–chloroform to give colorless crystalline *N*-(*N*,*O*-diacetyldehydrotyrosyl)-(*R*)-alanine methyl ester: 4.17 g (60% yield); mp 158–159 °C; $[\alpha]^{25}_D$ −24.15° (*c* 1.002, $CHCl_3$).

Preparation of Chiral Catalyst Solution. The chiral catalysts were prepared in situ by the reaction of $[Rh(NBD)_2]^+ClO_4^-$ with chiral diphosphine in degassed solvent. Typically, 3.87 mg (1.0×10^{-5} mol) of $[Rh(NBD)_2]^+ClO_4^-$ and 6.30 mg (1.1×10^{-5} mol) of Ph-CAPP were dissolved in 5 mL of ethanol under argon. The complexes of other chiral diphosphine ligands were prepared in a similar manner.

Hydrogenation Procedure. Typically, *N*-(*N*-benzoyldehydrophenylalanyl)-(*S*)-phenylalanine methyl ester (214 mg, 5.0×10^{-4} mol) was hydrogenated in the presence of [(+)-BPPM-Rh(NBD)]$^+ClO_4^-$ in situ prepared (5.0×10^{-6} mol) in 15 mL of ethanol under an atmospheric pressure of hydrogen at 40 °C for 1 h. Then, Bosnich's workup[10] was employed to remove the catalyst, and the solution was further treated with a small amount of Norit. In order to determine the optical purity, the solution was submitted to HPLC analysis with a reversed-phase column packed with TOYO SODA LS 410K (ODS SIL) and with MeOH–H_2O (65/35) as the eluent, which indicated that the *S*,*S*/*R*,*S* ratio of the produced dipeptide was 99.1/0.9. After simple evaporation of the solvent, *N*-benzoyl-(*S*)-phenylalanyl-(*S*)-phenylalanine methyl ester was obtained: 99% yield (213 mg); $[\alpha]^{20}_D$ −46.76° (*c* 1.005, MeOH).

Acknowledgment. We are grateful to Dr. W. S. Knowles of Monsanto Co. for his generous gift of a chiral ligand, diPAMP.

Registry No. (*S*)-**1** (R^1, R^2 = Ph, R^3 = CH_2Ph, R^4 = Me), 80630-61-1; (*S*)-**1** (R^1 = Ph, R^2 = CH_3, R^3 = CH_2Ph, R^4 = H), 42291-22-5; (*R*)-**1** (R^1 = Ph, R^2 = Me, R^3 = CH_2Ph, R^4 = Me), 80165-37-3; (*S*)-**1** (R^1 = Ph, R^2 = Me, R^3 = CH_2Ph, R^4 = Me), 57986-20-6; (*S*)-**1** (R^1, R^2 = Ph, R^3 = iso-Pr, R^4 = Me), 79965-45-0; (*S*)-**1** (R^1 = Ph, R^2 = Me, R^3 = *iso*-Pr, R^4 = Me), 80657-81-4; (*S*)-**1** (R = *iso*-Pr, R^2 = Ph, R^3 = CH_2Ph, R^4 = Me), 80630-62-2; (*R*)-**1** (R^1 = C_6H_4pOAc, R^2 = Me, R^3 = Me, R^4 = Me), 80630-63-3; (*R*)-**1** (R^1 = 3-MeO-4-$AcOC_6H_3$, R^2 = Me, R^3 = Me, R^4 = Me), 80630-64-4; (*S*)-**1** (R^1 = C_6H_4pF, R^2 = Me, R^3 = CH_2CHMe_2, R^4 = Me), 80630-65-5; (*S*,*S*)-**2** (R^1, r^2 = Ph, R^3 = CH_2Ph, R^4 = Me), 60728-18-9; (*R*,*S*)-**2** (R^1, R^2 = Ph, R^3 = CH_2Ph, R^4 = Me), 80657-82-5; (*R*,*S*)-**2** (R^1 = Ph, R^2 = Me, R^3 = CH_2Ph, R^4 = H), 24809-18-5; (*S*,*S*)-**2** (R^1 = Ph, R^2 = Me, R^3 = CH_2Ph, R^4 = H), 10030-31-6; (*R*,*R*)-**2** (R^1 = Ph, R^2 = Me, R^3 = CH_2Ph, R^4 = Me), 32435-69-1; (*S*,*R*)-**2** (R^1 = Ph, R^2 = Me, R^3 = CH_2Ph, R^4 = Me), 62088-03-3; (*R*,*S*)-**2** (R^1 = Ph, R^2 = Me, R^3 = CH_2Ph, R^4 = Me), 32435-70-4; (*S*,*S*)-**2** (R^1 = Ph, R^2 = Me, R^3 = CH_2Ph, R^4 = Me), 2562-48-3; (*R*,*S*)-**2** (R^1, R^2 = Ph, R^3 = *iso*-Pr, R^4 = Me), 79965-48-3; (*S*,*S*)-**2** (R^1, R^2 = Ph, R^3 = *iso*-Pr, R^4 = Me), 74863-35-7; (*R*,*S*)-**2** (R^1 = Ph, R^2 = Me, R^3 = *iso*-Pr, R^4 = H), 79965-49-4; (*S*,*S*)-**2** (R^1 = Ph, R^2 = Me, R^3 = *iso*-Pr, R^4 = H), 23506-45-8; (*R*,*S*)-**2** (R^1 = *iso*-Pr, R^2 = Pr, R^3 = CH_2Ph, R^4 = Me), 80630-66-6; (*S*,*S*)-**2** (R^1 = *iso*-Pr, R^2 = Ph, R^3 = CH_2Ph, R^4 = Me), 80630-67-7; (*R*,*R*)-**2** (R^1 = C_6H_4pOAc, R^2 = Me, R^3 = Me, R^4 = Me), 80630-68-8; (*S*,*S*)-**2** (R^1 = C_6H_4pOAc, R^2 = Me, R^3 = Me, R^4 = Me), 80630-69-9; (*R*,*R*)-**2** (R^1 = 3-MeO-4-$AcOC_6H_3$, R^2 = Me, R^3 = Me, R^4 = Me), 80630-70-2; (*S*,*S*)-**2** (R^1 = 3-MeO-4-$AcOC_6H_3$, R^2 = Me, R^3 = Me, R^4 = Me), 80630-71-3; (*R*,*S*)-**2** (R^1 = C_6H_4pF, R^2 = Me, R^3 = CH_2CHMe_2, R^4 = Me), 80630-72-4; (*S*,*S*)-**2** (R^1 = C_6H_4pF, R^2 = Me, R^3 = CH_2CHMe_2, R^4 = Me), 80630-73-5; (*S*)-**3a**, 80630-74-6; (*S*)-**3b**, 80630-75-7; (*R*)-**3c**, 80630-76-8; (*S*)-**3d**, 80630-77-9; (*R*)-**3e**, 80630-78-0; (*S*)-**3f**, 80630-79-1; **3g**, 80630-80-4; (*S*,*S*)-**3h**, 80630-81-5; Ac-(*R*,*R*)-Phe-d_2)-(*S*)-Ala-OMe, 80630-82-6; Ac-(*S*,*S*)-Phe-d_2)-(*S*)-Ala-OMe, 80657-83-6; *N*-[(phenylmethoxy)carbonyl]-L-phenylalanine, 1161-13-3; *N*-[(phenylmethoxy)carbonyl]-L-alanine, 1142-20-7; *N*-[(phenylmethoxy)carbonyl]-D-alanine, 26607-51-2; 1-(phenylmethyl)(*R*)-1,2-pyrrolidinedicarboxylate, 6404-31-5; 1-(phenylmethyl)(*S*)-1,2-pyrrolidinedicarboxylate, 1148-11-4; *N*-[(phenylmethoxy)-carbonyl]-L-valine, 1149-26-4; *N*-[(phenylmethoxy)carbonyl]glycine, 1138-80-3; *N*-[*N*-[(phenylmethoxy)carbonyl]-L-phenylalanyl]-L-valine, 13123-00-7; PPM, 61478-29-3; L-valine methyl ester hydrochloride, 6306-52-1; (*Z*)-α-benzamidocinnamic acid, 26348-47-0; D-alanine methyl ester hydrochloride, 14316-06-4; 2-methyl-4-(*p*-acetoxybenzylidene)-2-oxazolin-5-one, 52507-17-2.