Asymmetric Hydrogenation Catalyzed by the (Achiral Base)bis(dimethylglyoximato)cobalt(II)-Chiral Cocatalyst System. The Preparation of a New Type of Chiral Cocatalyst and Its Application to the Asymmetric Hydrogenation of Methyl *N*-(Acetylamino)acrylate and Benzil[1)]

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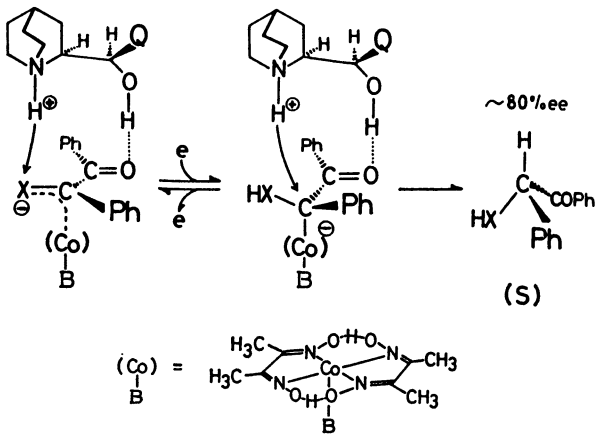
As a new type of chiral cocatalyst in the achiral base-coordinated bis(dimethylglyoximato)cobalt(II)–chiral cocatalyst system, tertiary amines with an amide group at α- or β-carbon were prepared, and asymmetric hydrogenation was examined by using them. The optical yield reached 34.5% enantiomeric excess(ee) by using *N*-[(2*S*,3*S*)-2-acetoxy-3-dimethylamino-3-phenylpropionyl]-(*R*)-α-methylbenzylamine; this is the highest value attained so far in the asymmetric hydrogenation of methyl *N*-(acetylamino)acrylate with this system. The enantioselectivity in the hydrogenation of methyl *N*-(acetylamino)acrylate was reversed with a configurational alteration of the α-methylbenzylamine moiety of *N*-[*N*,*N*-dimethyl-(*S*)-phenylalanyl]-α-methylbenzylamine, while it was not reversed in the hydrogenation of benzil by the configurational alteration. From these facts, it is deduced that the hydrogen bond between amide groups of the chiral amino carboxamides and methyl *N*-(acetylamino)acrylate may act as an attractive force to enhance the enantioselectivity of the asymmetric hydrogenation.

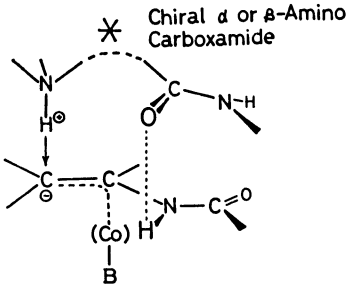
The authors have previously reported the asymmetric hydrogenation of α-diketones, α-keto carboxylates, and olefinic compounds catalyzed by an achiral base-coordinated bis(dimethylglyoximato)cobalt(II)–chiral base system (hereafter abbreviated as $Co(dmg)_2$·B–B*: B and B* are achiral and chiral bases respectively). This system resulted in high optical yields (up to 78%ee) and high reactivities for such α-diketone as benzil, but in low optical yields (up to 19%ee) and low reactivities for dehydro amino acid derivatives.[2)]

The catalytic system comprises two independent elementary processes, *i.e.*, electron-donation to a substrate by $[Co(dmg)_2 \cdot B]^-$ and proton-donation to a reduced state of the substrate by a protonated chiral base, of which only the proton-donation by the protonated chiral base is responsible for the asymmetric induction. Another important characteristic of this catalytic system is that the hydrogen bond between the hydroxyl group of the chiral base (chiral amino alcohol) and the carbonyl group of the substrate extremely enhances the enantioselectivity of the proton-donation reaction (Scheme 1).[1,2)]



Scheme 1.

Therefore, the chiral base can be modified arbitrarily so long as the characteristics are retained. If the hydrogen bond between amide groups of a chiral amine having a secondary amide group and a dehydro amino acid derivative will act as an effective attractive force in the enantioselective proton-donation steps, the chiral amine can be expected to afford better results for the enantioselective hydrogenation of dehydro amino acid derivatives (Scheme 2).



Scheme 2.

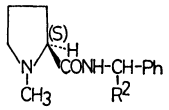
Here, we would like to describe the preparation of chiral tertiary amines bearing an alkylcarbamoyl group at the α- or β-carbon and the enantioselective hydrogenation of benzil and methyl *N*-(acetylamino)acrylate by their use of as cocatalysts.

Results and Discussion

Tertiary amines with an alkylcarbamoyl group at the α-carbon were prepared by the condensation of *N*-benzyloxycarbonyl derivatives of α-amino acids (L-phenylalanine, D-phenylglycine, L-isoleucine, and L-proline) with the corresponding amines (benzylamine, (*R*)- and (*S*)-α-methylbenzylamine), followed by reductive methylation. *N*-[(2*S*,3*S*)-3-dimethylamino-2-hydroxy-3-phenylpropionyl]-(*R*)-α-methylbenzylamine and its antipode were prepared by the condensation of (2*S*,3*R*)-2,3-epoxy-3-phenylpropionic acid and the (2*R*,3*S*)-isomer with (*R*)- and (*S*)-α-methylbenzylamine

Table 1. Structures and abbreviations of the chiral α- and β-amino carboxamides

(a) α-Amino carboxamides: $R^1\text{-}CH(N(CH_3)_2)\text{-}CONH\text{-}CH(R^2)\text{-}Ph$

R^1	Config.[a] of $R^1\text{-}CH<^{N}_{CO}$	R^2	Config. of $Ph\text{-}CH(R^2)\text{-}NH$	Abbreviation
$Ph\text{-}CH_2$	(*S*)	H		Pha-*S*,0
	(*S*)	CH_3	(*S*)	Pha-*S*,*S*
	(*S*)	CH_3	(*R*)	Pha-*S*,*R*
Ph	(*R*)	CH_3	(*S*)	Phg-*R*,*S*
$CH_3\text{-}CH(C_2H_5)$	(*S*)	CH_3	(*S*)	Il-*S*,*S*
		CH_3	(*S*)	Pr-*S*,*S*
		CH_3	(*R*)	Pr-*S*,*R*

(b) β-Amino carboxamides: $Ph\text{-}CH(OR)\text{-}CH(N(CH_3)_2)\text{-}CONH\text{-}CH(CH_3)\text{-}Ph$

Config. of CH-OR	Config. of CH-$N(CH_3)_2$	Config. of CH-CH_3	R	Abbreviation
(*R*)	(*R*)	(*S*)	H	DHP-(*R*,*R*)*S*
(*S*)	(*S*)	(*R*)	H	DHP-(*S*,*S*)*R*
(*S*)	(*S*)	(*R*)	CH_3-CO	DHP-*OAc*-(*S*,*S*)*R*

a) Configuration.

respectively (using the DCC method), followed by opening the epoxide ring by the use of dimethylamine (see Experimental section).

The structures and abbreviations of these amino carboxamides are listed in Table 1.

The asymmetric hydrogenation of benzil and methyl *N*-(acetylamino)acrylate with $Co(dmg)_2$·B-B* was carried out in benzene under an atmospheric pressure of hydrogen at room temperature by using these amino carboxamides as chiral cocatalysts (B*). The hydrogenation rate with $Co(dmg)_2$·BA is much faster than that with $Co(dmg)_2$·PPh_3 (BA and PPh_3 are abbreviations of benzylamine and triphenylphosphine respectively). However, triphenylphosphine was used as B when B* was the chiral α-amino carboxamides, since the optical yield of benzoin with benzylamine (5.7%ee) was considerably lower than that with triphenylphosphine (15.7%ee). The amine released in some stage of the catalytic cycle competes with chiral α-amino carboxamides in catching and in transferring the proton to a reduced state of the substrate. Because of the lower basicity of α-amino carboxamides, the competition is rather more serious when benzylamine is used as B than when triphenylphosphine[1,2] (which has a very low basicity toward proton) is so used. Both benzylamine and triphenylphosphine were employed when B* was the chiral β-amino carboxamides.

The results are summarized in Tables 2 and 3.

As the chemical yield of methyl *N*-acetylalaninate was lowered during isolation, and as the amount of the enantiomeric excess did not exceed that of the loss in chemical yield, the possibility of enantiomer enrichment during the isolation procedure was checked. The methyl *N*-acetylalaninate had no optical rotation such as was isolated after the treatment of the racemic one under the same conditions as in the catalytic hydrogenation. Therefore, it is evident that the optical activities of methyl *N*-acetylalaninate shown in Tables 2 and 3 are those brought about only by the asymmetric hydrogenation.

As may be seen in Table 2, the optical yields of methyl *N*-acetylalaninate were up to 17.2%ee and did not exceed that attained with the $Co(dmg)_2$–quinine system, but an interesting difference in the direction of stereoselectivities for benzil and methyl *N*-(acetylamino)acrylate was observed. The reaction using *S*-amino acid derivatives as the chiral cocatalysts gave *S*-benzoin predominantly, irrespective of the configuration of the α-methylbenzylamine moiety (Runs 1,2, 3,6, and 7), but the enantioselectivity of methyl *N*-acetylalaninate was reversed with a configurational change in the α-methylbenzylamine moiety (Runs 2 and 3). Furthermore, methyl *N*-acetylalaninate with the same configuration as that of the α-carbon of the α-amino carboxamides used as chiral cocatalysts was produced predominantly, except for Run 3.

The reversal of enantioselectivity by changing the configuration of α-methylbenzylamine (Runs 2 and 3 of methyl *N*-acetylalaninate) makes us imagine that the hydrogen bond between the amide groups of Pha-*S*,*R* and methyl *N*-(acetylamino)acrylate may be formed in the proton-donation steps; such a phenomenon may be brought about only when chiral α-amino carboxamides are able to be in a conformation suitable

Table 2. The asymmetric hydrogenation of benzil and methyl *N*-(acetylamino)acrylate with $Co(dmg)_2 \cdot PPh_3$-chiral α-amino carboxamides[a]

Run	Chiral carboxamides	Benzoin				Methyl *N*-acetylalaninate			
		Yield	$[\alpha]_D$/°	Config.	Optical yield/%ee	Yield/%	$[\alpha]_D$/°	Config.	Optical yield/%ee
1	Pha-*S*,0	q[b]	+12.8[c]	(*S*)	10.8	54.0	−7.7[d]	(*S*)	8.3
2	Pha-*S*,*S*	q	+12.7	(*S*)	10.8	75.3	−13.1	(*S*)	14.3
3	Pha-*S*,*R*	q	+19.5	(*S*)	16.4	50.6	+15.8	(*R*)	17.2
4	Phg-*R*,*S*	q	−3.5	(*R*)	3.0	53.3	+3.5	(*R*)	3.9
5	Il-*S*,*S*	q	+2.2	(*S*)	1.9	68.0	−1.6	(*S*)	1.8
6	Pr-*S*,*S*	q	+11.0	(*S*)	9.3	45.0	−5.6	(*S*)	6.1
7	Pr-*S*,*R*	q	+17.8	(*S*)	15.0	45.0	−6.4	(*S*)	7.0

a) The molar ratio of the substrate to cobalt was 10 : 1, while those of triphenylphosphine, the chiral α-amino carboxamide, and its hydrochloride to cobalt were all 1 : 1. b) Quantitative yield. c) Optically pure *S* isomer: $[\alpha]_D$ +118.5° (*c* 1, acetone). d) Optically pure *S* isomer: $[\alpha]_D$ −91.7° (*c* 2, water).

Table 3. The asymmetric hydrogenation of benzil and methyl *N*-(acethylamino)acrylate with $Co(dmg)_2 \cdot$B-chiral β-amino carboxamides[a]

Run	[Achiral base Chiral base	Benzoin				Methyl *N*-acetylalaninate			
		Yield	$[\alpha]_D$/°	Config.	Optical yield/%ee	Yield/%	$[\alpha]_D$/°	Config.	Optical yield/%ee
1	[BA DHP-(*R*,*R*)*S*	q	+26.4	(*S*)	22.2	55.3	−1.8	(*S*)	2.0
2	[BA DHP-(*R*,*R*)*S*·HCl[b]	q	+0.8	(*S*)	0.7				
3	[BA DHP-(*R*,*R*)*S* DHP-(*R*,*R*)*S*·HCl	q	−3.7	(*R*)	3.1				
4	[PPh_3 DHP-(*S*,*S*)*R*	q	−3.8	(*R*)	3.2	45.3	+5.5	(*R*)	6.0
5	[BA DHP-*OAc*-(*S*,*S*)*R* DHP-*OAc*-(*S*,*S*)*R*·HCl[b]	q	−1.4	(*R*)	1.2	47.0	+17.7	(*R*)	19.3
6	[PPh_3 DHP-*OAc*-(*S*,*S*)*R* DHP-*OAc*-(*S*,*S*)*R*·HCl					45.5	+31.6	(*R*)	34.5

a) The molar ratio of the substrate to cobalt was 10 : 1, while those of achiral base, the chiral β-amino carboxamide, and its hydrochloride to cobalt were all 1 : 1. b) Hydrochloride of the corresponding chiral β-amino carboxamide.

for hydrogen bonding between the amide groups of the chiral α-amino carboxamides and the substrates.

If the above consideration is reasonable, it is possible to explain the enantioselectivities (the configurations and optical yields of products) in terms of the following factors: I) the bulkiness and arrangement of substituents around the α-carbon atom of the α-amino acid moiety, II) the conformation of the chiral α-amino carboxamides, and III) the hydrogen bonding between the amide groups of the chiral α-amino carboxamides and the substrates. The configurations and optical yields of the products are determined by the I) and II) factors, while the reversal enantioselectivity and/or the relatively high optical yields are obtained when the III) factor brought about by the II) factor becomes predominant.

It is impossible here to infer what conformation of the chiral α-amino carboxamide, Pha-*S*,*R*, is most effective and suitable for hydrogen bonding between the amide groups of Pha-*S*,*R* and methyl *N*-(acetylamino)acrylate in the proton-donation steps.

As may be seen in Table 3, the optical yield of methyl *N*-acetylalaninate rose to 34.5%ee, which is the highest value attained so far in the asymmetric hydrogenation of methyl *N*-(acetylamino)acrylate with the $Co(dmg)_2 \cdot$B–B* system, and a marked difference in the enantioselectivities for benzil and for methyl *N*-(acetylamino)acrylate was observed. The optical yield of benzoin was 22.2%ee (Run 1), but that of methyl *N*-acetylalaninate was 6.2%ee at most (Runs 1 and 4) when chiral β-amino carboxamides used had a hydroxyl group. On the other hand, the optical yield of methyl *N*-acetylalaninate rose to 34.5%ee (Run 6), while that of benzoin was lowered to 1.1%ee (Run 5), when the chiral β-amino carboxamide used had no free hydroxyl group, but an acetoxyl group.

From these results it may be deduced that the hydroxyl group of DHP-(*R*,*R*)*S* and DHP-(*S*,*S*)*R* in Runs 1 and 4, and the amide group of DHP-*OAc*-(*S*,*S*)*R* in Runs 5 and 6, are operative in forming the hydrogen bond to the carbonyl group of benzil and to the amide group of methyl *N*-(acetylamino)acrylate respectively,

in their enantioselectivity-determining step.

The findings that the optical yield of benzoin was considerably lowered (Run 4) when triphenylphosphine was used as the achiral base, as compared with that using benzylamine (Run 1), and that the enantioselectivity was reversed by change from the presence of the hydrochloride of DHP-(*R,R*)*S* to its absence (Runs 1 and 3), differ from those observed when a simple chiral amino alcohol such as *N*-methylephedrine was employed as the chiral base of the $Co(dmg)_2$·B–B* system, although it is not evident why these differences are brought about.

In conclusion, new type of chiral cocatalysts, α- and β-amino carboxamides, were explored; of them, DHP-*OAc*-(*S,S*)*R* is one of the most promising chiral bases of the $Co(dmg)_2$·B–B*-catalyzed asymmetric hydrogenation of methyl *N*-(acetylamino)acryrate. It can also be mentioned that the hydrogen bond between the amide groups of DHP-*OAc*-(*S,S*)*R* and methyl *N*-(acetylamino)acrylate may play an important role in the asymmetric hydrogenation.

Experimental

The melting points were determined by a Yanagimoto micro-melting-point apparatus and were uncorrected. The IR spectra were recorded on a JASCO A-3 spectrometer. The NMR spectra were obtained on JEOL JNM-PMX60 and JNM-PS-100 spectrometers. The optical rotations were measured with a Perkin Elmer 241 polarimeter.

Preparation of Chiral α-Amino Carboxamides. The chiral α-amino carboxamides (Pha-*S,0*, Pha-*S,S* Pha-*S,R*; Phg-*R,S*; Il-*S,S* and Pr-*S,S* Pr-*S,R*) were prepared by essentially the same procedure. Benzylamide and (*R*)- or (*S*)-α-methylbenzylamides of *N*-benzyloxycarbonylated α-amino acids (purchased from the Peptide Institute, Osaka) were prepared from the corresponding amines and α-amino acid derivatives by a modified DCC method,[3] and then the reductive *N,N*-dimethylation or *N*-methylation of them with formalin[4] was carried out.

The preparation of Pha-*S,R* as a typical procedure and that of Phg-*R,S* as an exceptional one are shown below.

N-[N-*Benzyloxycarbonyl-(S)-phenylalanyl*]-*(R)-α-methylbenzylamine.* To a solution of *N*-benzyloxycarbonyl-(*S*)-phenylalanine (15.0 g, 50 mmol) and (*R*)-α-methylbenzylamine (purchased from Aldrich: $[\alpha]_D^{23}$ +38° (neat); 6.47 ml, 50 mmol) in DMF (100 ml) was added a solution of DCC (10.73 g, 52 mmol) and 1-hydroxybenzotriazole (7.43 g, 55 mmol) in DMF (100 ml) during 1 h on ice-cooling with stirring. The reaction mixture was then allowed to stand overnight at room temperature. The dicyclohexylurea separated out was filtered off, and the filtrate was concentrated *in vacuo* at 30—40 °C. The residue was dissolved in ethyl acetate (*ca.* 500 ml), and the solution was washed successively with a 1 mol dm^{-3}-hydrochloric acid (100 ml), a 1 mol dm^{-3}-sodium hydrogencarbonate solution (100 ml), and a sodium chloride solution (100 ml) and then dried over anhydrous sodium sulfate. The solution was concentrated to a half, and the crystals separated out were thoroughly dissolved on heating. To the solution was added petroleum ether carefully. 13.1 g of a first crop (needles) and from the filtrate after similar recrystallization, 3.15 g of a second crop (needles) were obtained: first crop, mp 135.0—146.0 °C, $[\alpha]_D^{22.0}$ +24.9° (*c* 1.018, $CHCl_3$) and second crop, mp 134.0—135.0 °C, $[\alpha]_D^{22.0}$ +24.1° (*c* 1.045, $CHCl_3$); IR (KBr) 3340 (NH), 1690 (carbamate C=O) and 1650 cm^{-1} (amide C=O); NMR ($CDCl_3$) δ=1.26 (3H, d, *J*=7 Hz, $C\underline{H}_3$–CH), 3.10 (2H, dd, Ph–$C\underline{H}_2$–CH), 4.40 (1H, q, Ph–CH_2–$C\underline{H}$), 5.00 (1H, quintet, *J*=7 Hz, CH_3–$C\underline{H}$), 5.08 (2H, s, Ph–$C\underline{H}_2$–O), 5.46 (1H, d, N$\underline{H}$), 5.90 (1H, d, N$\underline{H}$), 7.30 (15H, d, Ph).

N-[N,N-*Dimethyl-(S)-phenylalanyl*]-*(R)-α-methylbenzylamine, (Pha*-S,R*).* *N*-[*N*-Benzyloxycarbonyl-(*S*)-phenylalanyl]-(*R*)-α-methylbenzylamine (6.0 g, 15 mmol: the first crop obtained above) was dissolved in methanol (*ca.* 200 ml) on heating, and to the solution glacial acetic acid (0.85 ml, 15 mmol) was then added. Under a weak nitrogen-gas flow, the solution was poured into an Erlenmeyer flask (with a special neck stoppered with a silicone gum cap) in which a 10% palladium charcoal catalyst (1.0 g) has been placed. Setting up the equipment for hydrogenation, the flask was degassed and charged with hydrogen gas, and then hydrogenation was carried out under atmospheric pressure at room temperature with stirring. About a theoretical amount of hydrogen was absorbed during 1 h; then, after degassing and the introduction of hydrogen, 37% formalin (2.4 ml, 32 mmol) was injected through the silicone gum cap and the hydrogenation was continued overnight. About two equivalents of hydrogen were absorbed. The reaction mixture was then filtered through celite, and the filtrate was concentrated *in vacuo*. The residue was dissolved in ether (*ca.* 200 ml) and washed twice with sodium hydrogencarbonate solution, and then the ether layer was dried over anhydrous sodium sulfate. The solution was concentrated *in vacuo* to afford 4.26 g of crystalline materials. This was recrystallized from ether–petroleum ether to yield 2.90 g of a first crop (needles) and 0.98 g of a second crop (needles): first crop, mp 79.5—80.5 °C, $[\alpha]_D^{12.5}$ +72.0° (*c* 1.005, $CHCl_3$) and second crop, mp 78.0—79.0 °C, $[\alpha]_D^{22.0}$ +70.8° (*c* 1.016, $CHCl_3$); IR (KBr) 3300 (NH) and 1630 cm^{-1} (amide C=O); NMR ($CDCl_3$) δ=1.38 (3H, d, *J*=7 Hz, $C\underline{H}_3$–CH), 2.28 (6H, s, $N(C\underline{H}_3)_2$), 3.13 (3H, m, Ph–$C\underline{H}_2$–CH), 5.10 (1H, quintet, *J*=7 Hz, CH_3–$C\underline{H}$), 7.03 (1H, d, N$\underline{H}$), 7.28 (10H, d, Ph).

N-[N,N-*Dimethyl-(R)-phenylglycyl*]-*(S)-α-methylbenzylamine, (Phg*-R,S*).* The reductive *N,N*-dimethylation of *N*-[*N*-benzyloxycarbonyl-(*R*)-phenylglycyl]-(*S*)-α-methylbenzylamine gave *N,N*-dimethylated, *N*-monomethylated and deaminated products; the yield of the *N,N*-dimethylated product, Phg-*R,S*, among them was very low. Therefore, *N*-[*N*-methyl-(*R*)-phenylglycyl]-(*S*)-α-methylbenzylamine was prepared in a 75% yield by using an equimolar amount of formardehyde and stopping the reductive methylation when equimolar amount of hydrogen had been absorbed. The isolated *N*-methylated product was further *N*-methylated by the following procedure.

A solution of *N*-[*N*-methyl-(*R*)-phenylglycyl]-(*S*)-α-methylbenzylamine (6.5 g, 24 mmol), 37% formalin (2.17 ml, 29 mmol) and 88% formic acid (3.7 g, 71 mmol) was refluxed for 3.5 h. After cooling, the solution was acidified with conc hydrochloric acid and extracted with ether (*ca.* 50 ml). By making the water layer basic with sodium hydroxide, an oily material was separated out and then crystallized. The crystalline products were extracted with ether (100 ml), and the solution was dried over sodium sulfate. The solution was concentrated *in vacuo* to afford 5.82 g of crystalline products. This was recrystallized from ether-petroleum ether to yield 4.27 g of white needles: mp 92.5—93.5 °C, $[\alpha]_D^{12.5}$ −146.6° (*c* 1.006, $CHCl_3$); IR (KBr) 3300 (NH) and 1660 cm^{-1} (amide C=O); NMR ($CDCl_3$) δ=1.56 (3H, d, *J*=7 Hz, $C\underline{H}_3$–CH), 2.20 (6H, s, $N(C\underline{H}_3)_2$), 3.72 (1H, s, Ph–C$\underline{H}$–CONH), 5.15 (1H, quintet, *J*=7 Hz, CH_3–$C\underline{H}$), 7.24 (11H, m, N$\underline{H}$ and Ph).

The hydrochlorides of the α-amino carboxamides were

Table 4. Physical constants and elemental analyses of chiral α-amino carboxamides

Chiral α-amino carboxamides	Mp/°C	$[\alpha]_D$/°	Elemental analyses (%) C	H	N	
			C	H	N	(Calcd)
Pha-*S*,0	61.0—62.0	+3.6 (*c* 1.026, $CHCl_3$)	76.56	7.85	9.92	($C_{18}H_{22}N_2O$)
			75.76	7.68	9.69	(Found)
Pha-*S*,0·HCl	147.0—148.0	+35.7 (*c* 1.026, CH_3OH)				
Pha-*S*,*S*	77.0—78.0	−46.1 (*c* 1.005, $CHCl_3$)	76.99	8.16	9.45	($C_{19}H_{24}N_2O$)
			77.63	8.24	9.59	(Found)
Pha-*S*,*S*·HCl	170.0—171.0	−14.3 (*c* 1.041, CH_3OH)				
Pha-*S*,*R*	79.5—80.5	+72.0 (*c* 1.005, $CHCl_3$)	77.01	8.38	9.52	(Found)
Pha-*S*,*R*·HCl	206.0—207.0	+128.0 (*c* 1.028, CH_3OH)				
Phg-*R*,*S*	92.5—93.5	−146.6 (*c* 1.006, $CHCl_3$)	76.56	7.85	9.92	($C_{18}H_{22}N_2O$)
			77.08	8.22	10.00	(Found)
Phg-*R*,*S*·HCl	214.0—216.0 (dec)	−117.4 (*c* 1.007, CH_3OH)				
Il-*S*,*S*	95.5—98.5	−70.6 (*c* 1.034, $CHCl_3$)	73.80	9.29	10.76	($C_{16}H_{26}N_2O$)
			72.65	10.24	10.60	(Found)
Il-*S*,*S*·HCl[a]	200.0—201.0	−59.1 (*c* 1.280, CH_3OH)				
Pr-*S*,*S*[b]	58.0—60.0	−170.0 (*c* 0.165, CH_3OH)	72.38	8.68	12.07	($C_{14}H_{26}N_2O$)
			73.13	8.90	11.39	(Found)
Pr-*S*,*R*	85.5—87.0	−2.17 (*c* 0.277, CH_3OH)	72.15	8.91	12.01	(Found)

a) Very hygroscopic. b) Hydrochloride did not crystallize.

prepared by bubling dry hydrogen chloride gas into an ether solution of α-amino carboxamides and recrystallized from methanol–ethyl acetate or methanol–ether–ethyl acetate.

The physical constants and data of the elemental analyses of the chiral α-amino carboxamides and their hydrochlorides are summarized in Table 4.

Preparation of Chiral β-Amino Carboxamides.

N-[(2S,3R)-2,3-Epoxy-3-phenylpropionyl]-(R)-α-methylbenzylamine and Its Antipode. (*R*)-α-methylbenzylammonium (2*S*,3*R*)-2,3-epoxy-3-phenylpropionate and its antipode were prepared by Harada's method.[5]

To a suspension of (*R*)-α-methylbenzylammonium (2*S*, 3*R*)-2,3-epoxy-3-phenylpropionate ($[\alpha]_D^{24.0}$ +126.3° (*c* 1.001, 99% ethanol), lit,[5] $[\alpha]_D$ +125.5° (*c* 0.96, abs ethanol); 15.3 g, 54 mmol) in DMF (300 ml) was added a solution of DCC (11.2 g, 54 mmol) and 1-hydroxybenzotriazole (7.3 g, 54 mmol) in DMF (100 ml) during 1.5 h on ice-cooling with stirring. The reaction mixture gradually became homogeneous and then heterogeneous again. Stirring was continued overnight at room temperature. After the filtration of the precipitates, the filtrate was concentrated *in vacuo* at 30—40 °C. The residue was dissolved in ethyl acetate (*ca.* 800 ml), after which the solution was washed successively with a 10% citric acid solution (200 ml), a 4% sodium hydrogencarbonate solution (200 ml), and a sodium chloride solution (200 ml) and then dried over anhydrous sodium sulfate. The solution was subsequently concentrated to 500—600 ml, and the crystals separated out were dissolved thoroughly on heating. To the solution was added petroleum ether carefully. 10.2 g of a first crop (needles) and, from the filtrate, 3.3 g of a second crop (needles) were obtained: first crop, mp 168.0—169.0 °C, $[\alpha]_D^{23.0}$ +143.1° (*c* 0.997, $CHCl_3$) and second crop, mp 167.0—168.0 °C, $[\alpha]_D^{23.0}$ +143.2° (*c* 0.997, $CHCl_3$): IR (KBr) 3300 (NH) and 1660 cm^{-1} (amide C=O); NMR ($CDCl_3$) δ=1.50 (3H, d, J=6.5 Hz, $C\underline{H}_3$-CH), 3.50 (1H, d, J=2 Hz, Ph-C<u>H</u>-O), 3.68 (1H, d, J=2 Hz, C<u>H</u>-CONH), 5.07 (1H, quintet, J=6.5 Hz, CH_3-C<u>H</u>), 6.43 (1H, d, N<u>H</u>), 7.17 (10H, Ph).

Its antipode was likewise prepared from (*S*)-α-methylbenzylammonium (2*R*,3*S*)-2,3-epoxy-3-phenylpropionate (18.0 g, 63 mmol) to afford 14.4 g of a first crop (needles) and 2.3 g of a second crop (needles): first crop, mp 169.0—170.0 °C, $[\alpha]_D^{22.0}$ −144.5° (*c* 0.996, $CHCl_3$) and second crop, mp 167.0—168.0 °C, $[\alpha]_D^{22.0}$ −138.7° (*c* 0.990, $CHCl_3$).

N-[(2S,3S)-3-Dimethylamino-2-hydroxy-3-phenylpropionyl]-(R)-α-methylbenzylamine, (DHP-(S,S)R) and Its Antipode (DHP-(R,R)S). A suspension of the first and second crops of *N*-[(2*S*,3*R*)-2,3-epoxy-3-phenylpropionyl]-(*R*)-α-methylbenzylamine (13.1 g, 49 mmol) prepared above in a 50% dimethylamine aqueous solution (250 ml) was stirred for 4 h at room temperature. The undissolved crystals were then filtered off, and the filtrate was evaporated *in vacuo*. A crystalline mass was separated out when the water began to evaporate and was then filtered off. After drying, the crystals were recrystallized from benzene to yield 7.4 g of a first crop (needles): mp 157.0—157.5° C, $[\alpha]_D^{26.5}$ +52.7° (*c* 1.028, $CHCl_3$); IR (KBr) 3400 (NH), 3200 (OH) and 1660 cm^{-1} (amide C=O); NMR ($CDCl_3$) δ=1.40 (3H, d, J=7 Hz, $C\underline{H}_3$-CH), 2.26 (6H, s, $N(C\underline{H}_3)_2$), 3.59 (1H, d, J=5 Hz, N-C<u>H</u>-CH-CONH), 4.20 (1H, s, OH), 4.60 (1H, d, J=5 Hz, C<u>H</u>-CONH), 4.90 (1H, quintet, J=7 Hz, CH_3-C<u>H</u>), 6.75 and 7.20 (11H, m, N<u>H</u> and Ph); Found: C, 73.23; H, 7.76; N, 9.03%; Calcd for $C_{19}H_{24}N_2O_2$: C, 73.04; H, 7.74; N, 8.97% and 1.43 g of a second crop (needles): mp 157.0—157.5 °C, $[\alpha]_D^{26.0}$ +53.1° (*c* 1.018, $CHCl_3$). The crystals obtained above by the filtration of the reaction mixture were also recrystallized from benzene to yield 2.7 g of a third crop (needles): mp 156.5—157.5 °C, $[\alpha]_D^{26.0}$ +51.3° (*c* 1.082, $CHCl_3$).

Its antipode, DHP-(*R*,*R*)*S*, was likewise prepared from *N*-[(2*R*,3*S*)-2,3-epoxy-3-phenylpropionyl]-(*S*)-α-methylbenzylamine (14.0 g, 52 mmol) to afford 7.82 g of a first crop: mp 156.5—157.5 °C, $[\alpha]^{26.5}$ −52.7° (*c* 1.007, $CHCl_3$); Found: C, 72.32; H, 7.74; N, 8.88%, a second crop (1.37 g): mp 156.5—157.5 °C, $[\alpha]_D^{26.5}$ −52.9° (*c* 1.007, $CHCl_3$) and a third crop (3.18 g): mp 156.0—157.0 °C, $[\alpha]_D^{26.5}$ −51.1° (*c* 1.101, $CHCl_3$).

The hydrochloride of DHP-(*R*,*R*)*S* was prepared by the procedure described above from the first crop of DHP-(*R*, *R*)*S*: mp 211.5—212.5 °C, $[\alpha]_D^{20.0}$ −38.7° (*c* 1.004, CH_3OH).

N-[*(2S,3S)-2-Acetoxy-3-dimethylamino-3-phenylpropionyl*]-*(R)*-*α-methylbenzylamine, (DHP*-OAc-*(S,S)R)*. To a solution of the first crop of DHP-*(S,S)R* prepared above (2.0 g, 64 mmol) in dry ethyl acetate (150 ml) was added acetyl chloride (0.54 g, 64 mmol). The solution was allowed to stand for 2 d at room temperature and then concentrated *in vacuo*. The residue was solidified by scratching the flask with ether. The solids were filtered off and dissolved in water. The solution was washed with ether, and the aqueous layer was made basic with a sodium hydrogencarbonate solution. The solution was extracted with ether, and the ether layer was dried over anhydrous sodium sulfate. The solution was concentrated *in vacuo* to afford 1.8 g of a crystalline material. This was recrystallized from ether–petroleum ether to yield 1.35 g of needles: mp 83.0—84.0 °C, $[\alpha]_D^{23.0}$ +21.6° (*c* 1.008, $CHCl_3$); IR (KBr) 3400 (NH), 1725 (ester C=O) and 1675 cm^{-1} (amide C=O); NMR ($CDCl_3$) δ=1.46 (3H, d, J=7 Hz, $C\underline{H}_3$-CH), 2.03 (3H, s, $C\underline{H}_3COO$), 2.23 (6H, s, N-$(C\underline{H}_3)_2$), 3.89 (1H, d, J=7 Hz, N-C$\underline{H}$-CH-CONH), 5.03 (1H, quintet, J=7 Hz, CH_3-C$\underline{H}$), 5.78 (1H, d, J=7 Hz, C$\underline{H}$-CONH), 7.00 and 7.22 (10H, m, Ph), 7.62 (1H, d, N$\underline{H}$); Found: C, 70.28; H, 7.61; N, 7.78%; Cacld for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90%.

Its hydrochloride was prepared by the procedure described above: mp 212.0—213.0 °C (dec), $[\alpha]_D^{20.0}$ +48.6° (*c* 0.693, CH_3OH).

Hydrogenation of Benzil and Methyl N-*(Acetylamino)acrylate with the Co(dmg)*$_2$·*B-Chiral Amino Carboxamide System.* The preparation of the catalyst system and the hydrogenation of the two substrates with it were identical to those described in the previous paper[1] except for using the chiral amino carboxamide as the chiral base; hence, only the typical procedure of the isolation of methyl *N*-acetylalaninate in Run 2 of Table 2 is given below.

After theoretical amounts of hydrogen (1.5 g, 10.5 mmol of methyl *N*-(acetylamino)acrylate was used) had been absorbed, the benzene solution was filtered through a short (*ca.* 10 cm×1.5ϕ) silica-gel column (Wako gel C-300), and then the column was washed with ethyl acetate (*ca.* 300 ml). The filtrate was concentrated *in vacuo*, and the residue was dissolved in ether (*ca.* 100 ml). Into the ether solution dry hydrogen chloride gas was bubbled until the solution became acidic. The amorphous solid which separated out was filtered off, and the filtrate was concentrated *in vacuo* to 5—10 ml. The residual ether solution was again filtered through a short silica-gel column (similar to the one above), and the column was washed with ethyl acetate (*ca.* 300 ml). The filtrate was neutralized and dried over anhydrous sodium carbonate and sodium sulfate. The solution was concentrated *in vacuo*, and to the residue was added water (100 ml). The crystalline materials which separated out were filtered off through celite and washed with water (150 ml). The filtrate was concentrated *in vacuo*, the residue was dissolved in ether (100 ml), and the ether solution was dried over anhydrous sodium sulfate. After the concentration of the solution, 1.13 g (75.3% yield) of an oily product, $[\alpha]_D^{25.0}$ −12.0° (*c* 2.121, water) was obtained. This was distilled at 98—99 °C/3 mmHg to give 0.49 g of a colorless liquid: $[\alpha]_D^{25.0}$ −13.1° (*c* 2.091, water).

No contamination of the chiral α-amino carboxamide, Pha-*S,S*, in the distilled product was observed in the NMR spectra.

Examination of Enantiomer Enrichment during Isolation. 2.0 g of racemic methyl *N*-acethylalaninate were treated under the same conditions as were used for the hydrogenation in Run 2 of Table 2 and were then isolated by the procedure described above. 1.1 g of an oily material was thus obtained: $[\alpha]_D^{13.0}$ −0.1° (*c* 2.108, water). This was subsequently distilled at 99—101 °C/3 mmHg to give 0.4 g of a colorless liquid: $[\alpha]_D^{15.6}$ 0.0° (*c* 2.010, water).

The NMR spectra of the colorless liquid was identical to that observed above.

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