Asymmetric Reactions. X. Asymmetric Hydrogenation Catalyzed by Bis(dimethylglyoximato)cobalt(II)-Chiral Cocatalyst (Amino Alcohol) System

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The catalytic asymmetric hydrogenations of α-diketones, α-keto carboxylates, α-(acylamino)acrylates, α-phenylacrylophenone, and α-phenylacrylate were examined with bis(dimethylglyoximato)cobalt(II)–chiral cocatalyst (amino alcohol) and with simple achiral base coordinated bis(dimethylglyoximato)cobalt(II)–chiral cocatalyst (amino alcohol) systems. These gave corresponding optically active reduction products, and in some cases, optically active reductive dimerization products. High degrees of enantioselectivities (≈78%) are achieved in the hydrogenation of α-diketones. Evidence for non-binding of chiral base to cobalt complexes was presented in the case of latter system, *i.e.*, it was shown that the catalytic site and the enantioselectivity-determining site are separated in this system, as in enzymes. The importance of protonated chiral bases for enantioselection was also shown. Based on these results and the stereochemical correlations between structures of the chiral bases and those of the products, a mechanism for this asymmetric hydrogenation was proposed.

Considerable attention has recently been paid to metal complex-catalyzed asymmetric hydrogenation.[1,2] Most of the researches in this area concentrate on the chiral phosphine rhodium complexes which have given successful results in the asymmetric hydrogenation of olefinic compounds.[1,2] In spite of the obvious advantages of being easily accessible and versatile, catalytic asymmetric hydrogenation using cobalt complexes and/or chiral cocatalysts has scarcely been studied.[3–6]

From the viewpoint of chemical evolution, the authors began to study asymmetric hydrogenation with one of the simplest catalysts, cyanocobalt–chiral amine systems.[3,4] The limitations of these systems suggested that we should use a complex whose framework is stable during the reaction. On the other hand, bis(dimethylglyoximato)cobalt(II) complex (Fig. 1)[7]

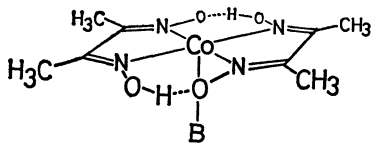


Fig. 1. Bis(dimethylglyoximato)cobalt(II).

was shown to be an effective catalyst for hydrogenation of activated olefinic compounds, α-diketones, α-keto carboxylates, and unsaturated nitrogen compounds.[8,9] We expected that a polyfunctional asymmetric substance bound weakly to cobalt or dimethylglyoxime ligand could draw a substrate into the reaction center with an attractive interaction and should bring about asymmetric induction. Thus, we have found two unique and excellent catalyst systems, bis(dimethylglyoximato)cobalt(II)–chiral amino alcohol and achiral base coordinated bis(dimethylglyoximato)-cobalt(II)–chiral amino alcohol, which catalyze asymmetric hydrogenation of α-diketones, α-keto carboxylates, and olefinic compounds. These have, in part, been communicated previously.[5]

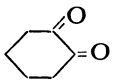
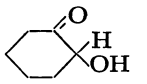
The purpose of this paper is to describe more detailed results and the mechanism of this asymmetric hydrogenation which revealed the unique characteristic of these systems: the catalytic site and the enantioselectivity-determining site are separated, as in enzymes.

Results and Discussion

Catalytic Asymmetric Hydrogenation of α-Keto Carbonyl Compounds and Olefinic Compounds with Bis(dimethylglyoximato)cobalt(II)–Chiral Base System. (a) Substrate Study: Catalytic hydrogenations of various keto carbonyl compounds were examined using bis(dimethylglyoximato)cobalt(II)–quinine under an atmospheric pressure of hydrogen in benzene solution. α-Diketones and α-keto carboxylates were catalytically hydrogenated with this catalyst system to give the corresponding optically active reduction products as shown in Table 1. However, β-keto carboxylates, α-keto carboxamides, and 1,4-dibenzoylbenzene resisted reduction under the given conditions.

Asymmetric hydrogenation of benzil gave *S*(+)-benzoin almost quantitatively with 71% optical yield at 10 °C. The carbonyl group adjacent to the phenyl group of methyl phenyl diketone was preferentially reduced to give *S*(+)-α-hydroxy-α-phenylacetone in 56% optical yield. This compound was shown to racemize under the reaction conditions, and the true enantioselectivity (about 67%) was obtained by extrapolation of the linear log $[\alpha]_D$ *vs.* reaction time to $t=0$. The hydrogenation of biacetyl gave not only the simple reduction product, but also reductive dimerization products. The simple reduction product, acetoin, and reductive dimerization products, 3,4-dihydroxy-3,4-dimethyl-2,5-hexanedione, were separated by silica gel column chromatography. The ratio of *erythro* isomer (78%) and *threo* isomer (22%) in the dimerization products was determined from the intensities of NMR signals of C–CH_3 [δ 1.25 (*erythro*) and δ 1.30 (*threo*)] and CH_3CO [δ 2.36 (*erythro*) and δ 2.23 (*threo*)].[10] Reduction of 1,2-cyclohexanedione gave 2-hydroxycyclohexanone with $[\alpha]_D$ −2.44° in 54% chemical yield. The optical yield can not be

Table 1. Asymmetric hydrogenation of α-ketocarbonyl compounds catalyzed by $Co(dmg)_2$-quinine[a]

Substrate	S/Co[g]	Reaction temp °C	Products: Structure	Yield/%	$[\alpha]_D$/°	Optical yield/%	Conf.
PhCOCOPh (1)	10	30	PhCHCOPh (7) OH	99	+73[h]	61.6	*S*
			PhCHCOCH$_3$ (8) OH	87—88	+88.8[b]	56.1	*S*
PhCOCOCH$_3$ (2)	10	R.T.	PhCOCHCH$_3$ (9) OH	7— 8			
			CH$_3$CHCOCH$_3$ (10) OH		−2.0[c]	2.5	*R*
CH$_3$COCOCH$_3$ (3)	10	30	[CH$_3$ -COH COCH$_3$]$_2$ *erythro* (11-E)	42.9			
			threo (11-T)	12.1	−33[d]		
 (4)	10	R.T.	 (12)	54	−2.44		
			PhCHCOOC$_2$H$_5$ (13) OH	32	+28.2[e]	13.7	*S*
PhCOCOOC$_2$H$_5$ (5)	20	30	[Ph -COH COOC$_2$H$_5$]$_2$ (14)	54			
5	10	15	13	71—73	+40	19.5	*S*
			14	20—23			
			PhCHCOOCH(CH$_3$)$_2$ (15) OH	62	+18[f]	11.4	*S*
PhCOCOOCH(CH$_3$)$_2$ (6)	10	15	[Ph -COH COOCH(CH$_3$)$_2$]$_2$ (16)	24			

a) Catalytic hydrogenation was carried out in benzene under the atmospheric pressure of hydrogen. In every experiment, equimolar amounts of quinine (Q*) and its HCl salt (Q*HCl) were used (Q*/Co=Q*HCl/Co=1). b) Specific rotation of pure *R*(−)-α-hydroxy-α-phenylacetone, $[\alpha]_D^{20}$ −158.3° (*c* 2.5, ethanol).[11] c) Specific rotation of pure (*R*(−)-acetoin, $[\alpha]_D$ −82° (*c* 0.844, water)[12] d) This value was based upon the concentration of *threo* derivative calculated from the ratio of *threo* to *erythro*. e) Specific rotation of pure ethyl *S*(+)-mandelate, $[\alpha]_D^{20}$ +205.1° (*c* 0.7, carbon disulfide).[13] f) Specific rotation of mandelic acid derived by hydrolysis of the product (isopropyl mandelate); Specific rotation of pure *S*(+)-mandelic acid, $[\alpha]_D^{20}$ +157.5 (*c* 2.1875, water)[14] g) S/Co: molar ratio of substrate to cobalt. h) Specific rotation of pure benzoin, $[\alpha]_D$ ±118.5 (*c* 1, acetone).[15]

determined because the optically pure enantiomer is unknown. Hydrogenation of ethyl phenylglyoxylate and isopropyl phenylglyoxylate gave ethyl *S*(+)-mandelate and isopropyl *S*(+)-mandelate in optical yields of 19.5 and 11.4%, respectively. In these cases, reductive dimerization products which had positive rotation were also obtained. The yields of reductive dimerization products increase with increasing molar ratio of substrate to cobalt. The details of these reductive dimerizations will be published separately.

Catalytic asymmetric hydrogenations of olefinic compounds were also carried out in benzene solution. The reaction products were purified by distillation, except for the case of methyl (*S*)-*N*-(phenylacetyl)-alaninate (**23**). All these samples were checked by ^{1}H NMR. Optical yields were calculated from the specific rotations of the products by reference to the maximum optical rotation reported in the literature, except for **23** which was obtained by methylation of (*S*)-*N*-(phenylacetyl)alanine ($[\alpha]_D$ −30°)[19] with diazomethane, $[\alpha]_D$ −56.9° (*c* 2, methanol) (see experimental part). The results are shown in Table 2. Olefinic double bonds of both the olefinic ketone and olefinic carboxylates are chemospecifically hydrogenated with this catalyst system to give the corresponding saturated optically active ketone and carboxylates.

In general, the optical yields with the substrates carrying acyl groups were much higher than those with the substrates carrying alkoxycarbonyl groups (Tables 1 and 2).

(b) Effect of Solvent: Catalytic hydrogenation of benzil was examined in several solvent systems (Table

Table 2. Asymmetric hydrogenation of olefinic compounds catalyzed by $Co(dmg)_2$-quinine

Substrate	S/Co[a]	Reaction temp °C	Products: Structure	Yield/%	$[\alpha]_D$/°	Conf.	Optical yield/%
$H_2C=C(Ph)(COOCH_3)$ (**17**)	9	R.T.[b]	$H_3C-CH(Ph)(COOCH_3)$ (**21**)	80	+7.7[c]	*S*	7.1
$H_2C=C(Ph)(COOCH_3)$	17	9	$H_3C-CH(Ph)(COOCH_3)$	92	+11.3	*S*	10.4
$H_2C=C(NHCOCH_3)(COOCH_3)$ (**18**)	8.4	R.T.	$H_3C-CH(NHCOCH_3)(COOCH_3)$ (**22**)	62	−17.0[d]	*S*	18.5
$H_2C=C(NHCOCH_2Ph)(COOCH_3)$ (**19**)	8	R.T.	$H_3C-CH(NHCOCH_2Ph)(COOCH_3)$ (**23**)	60	−4.0	*S*	7.0
$H_2C=C(Ph)(COPh)$ (**20**)	10	R.T.	$H_3C-CH(Ph)(COPh)$ (**24**)	95	+99.4[e]	*S*	49.2

a) Molar ratio of substrate to cobalt complex. b) Room temperature. c) Optical rotation of pure (*S*)-isomer; $[\alpha]_D$ +109.2° (*c* 6.2, toluene).[16] d) Optical rotation of pure (*S*)-isomer; $[\alpha]_D$ −91.7° (*c* 2, water).[17] e) Optical rotation of pure (*S*)-isomer; $[\alpha]_D$ +202° (*c* 3.5, chloroform).[18]

Table 3. Effect of solvent on the asymmetric hydrogenation of benzil catalyzed by $Co(dmg)_2$-quinine[a]

Run	S/Co[b]	B/Co[c]	Solvent (ratio)[d]	Yield %	$[\alpha]_D^{21}$/°	Optical yield/%
1	5	3	M	98.5	+10.3	8.7
2	20	3	M/B (1.4)	99.0	+27.8	23.5
3	50	3	M/B (1.07)	85.0	+33.5	28.3
4	20	1	M/B (1.4)	96.5	+29.7	25.1
5	20	2	M/B (1.4)	99.0	+30.2	25.5
6	20	2	M/B (0.43)	96.5	+50.1	42.3
7	20	2	A	96.0	+12.0	10.1
8	20	2	THF	95.5	+42.6	36.0
9	20	2	THF/B(0.6)	97.0	+59.0	49.8
10	10	2	B	98.0	+72.7	61.4

a) Hydrogenation was carried out under the atmospheric pressure of hydrogen at room temperature. In this series of experiments eqimolar amounts of quinine(Q*) and its HCl salt (Q*HCl) were used. b) Molar ratio of substrate to cobalt. c) Molar ratio of quinine to cobalt. d) Ratio of solvents in volume; M=methanol, B=benzene, A=acetone, THF=tetrahydrofuran. e) Specific rotations were measured in acetone (*c*=2—5). The specific rotation of optically pure benzoin, $[\alpha]_D$ ±118.5° (*c* 1, acetone).[15]

3). As is seen from Table 3, the optical yield increases with decreasing polarity of the solvent used. The reaction in benzene gave maximum optical yield under the given conditions. The carbonyl and hydroxyl groups in the solvent molecules decrease the enantioselectivity considerably, suggesting that these groups are concerned with the enantioselection mechanism.

(c) Effect of Temperature and Activation Parameters: The enantioselectivities and pseudo-first-order rate constants were determined at 10°, 20°, and 30 °C in the $Co(dmg)_2$–quinine catalyzed hydrogenation of benzil. The results are summarized in Table 4. From the Arrhenius plot of the rate constants, the apparent activation energy (ΔE_a^*) and the activation entropy (ΔS^*) were estimated to be 8.3 kcal/mol and −50 eu, respectively. Plotting logarithms of the enantiomeric ratio (*S*-isomer/*R*-isomer) *vs.* $1/T$ gave fairly good linearity. From the slope and the intercept at $1/T=0$, the difference between the activation enthalpies for the formation of *R*-isomer and that of

Table 4. Enantioselectivities and pseudo-first-order rate constants in variation of temperatures in the hydrogenation of benzil[a]

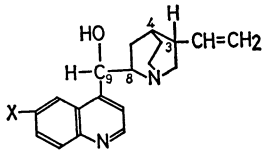
Reaction temp °C	Chemical yield	Rate constant, k/min^{-1}	$[\alpha]_D^{21}$/°	Optical yield/%
10	95	5.2×10^{-3}	+94	70.9
20	95	9.1×10^{-3}	+79	66.7
30	99	1.4×10^{-2}	+73	61.6

a) Hydrogenation was carried out in benzene under the atmospheric pressure of hydrogen. Reaction conditions: $Co(DMG)_2$, 2.1×10^{-2} mol dm^{-3}; quinine, 2.1×10^{-2} mol dm^{-3}; quinine hydrochloride, 2.1×10^{-2} mol dm^{-3}; benzil, 2.1×10^{-1} mol dm^{-3} in benzene.

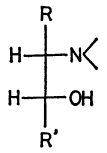
Table 5. Effect of structural variation of chiral amine on the asymmetric hydrogenation of benzil[a)]

Run	Amine	Solvent (ratio)	Yield %	$[\alpha]_D^{21}$/°	Optical yield/%	Conf.[b)]
1	Quinine	T/B (0.6)[c)]		+40.0	33.8	*S* (+)
2	Quinidine	T/B (0.64)	92	−39.4	33.2	*R* (−)
3	Cinchonidine	T/B (0.64)	98	+39.9	33.7	*S* (+)
4	Quinidine	B	95	−56.0	47.3	*R* (−)
5	Ephedrine	M/B (0.36)	99.5	+12.6	10.6	*S* (+)
6	Ephedrine	B	94	+19.8	16.7	*S* (+)
7	*Ψ*-Ephedrine	B	96	−9.2	7.8	*R* (−)
8	*N*-Methylephedrine	B	95	+33.2	28.0	*S* (+)
9	(1*R*,2*S*)-ADPE[e)]	B (5—7 °C)	89	+8.3	7.0	*S* (+)
10	(1*S*,2*S*)-ADPE[g)]	B[d)]	90	−2.0	1.7	*R* (−)
11	(1*R*,2*S*)-MADPE[f)]	B[d)]	98	+15.4	13.0	*S* (+)
12	Brucine	T/B (0.64)	96	−1.55	1.3	*R* (−)
13	*O*-Acetylquinine	T/B (0.6)	99	−5.35	4.5	*R* (−)
14	*S*(−)-α-Methylbenzylamine	T/B (0.6)	95	0.00	0	

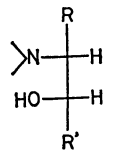
a) In this series of experiments free bases were used (Base/Cobalt=2; Substrate/Cobalt=20). Hydrogenation was carried out under atmospheric pressure of hydrogen at room temperature. b) Configuration of predominant isomer. c) T=tetrahydrofuran; B=benzene; M=methanol. d) Benzene solution containing a small amount of methanol. e) (1*R*,2*S*)-2-Amino-1,2-diphenylethanol. f) (1*R*,2*S*)-2-Dimethylamino-1,2-diphenylethanol.[27] g) (1*S*,2*S*)-2-Amino-1,2-diphenylethanol.



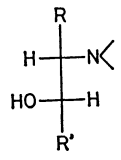
Quinine (X=OCH_3)
Quinidine (X=OCH_3)
Cinchonidine (X=H)



Quinine
Cinchonidine
Ephedrine
(R=CH_3, R′=Ph)
(1*R*,2*S*)-ADPE
(R=R′=Ph)



Quinidine



ψ-Ephedrine
(R=CH_3, R′=Ph)
(1*S*,2*S*)-ADPE
(R=R′=Ph)

Fig. 2. Structures and Fischer projections of chiral amino alcohols.

S-isomer ($\Delta\Delta H^{*}_{R\text{-}S}$), and the corresponding entropy difference of activation ($\Delta\Delta S^{*}_{R\text{-}S}$) were estimated to be 2.9 kcal/mol and 6.5 eu, respectively. It should be mentioned that in spite of the rather large difference in activation enthalpies, activation free energy difference became rather small ($\Delta\Delta G^{*}_{R\text{-}S}$=1.1 kcal/mol at 10 °C) since the contribution of the activation entropy term of the same sign is also large ($T\cdot\Delta\Delta S^{*}_{R\text{-}S}$=1.8 kcal/mol).

(d) Effect of Structure of Chiral Amines: In order to obtain some information on the structural parts which have effective interactions in enantioselection, several amines were tested for this catalytic asymmetric hydrogenation of benzil. Only free bases were used in this series of experiments. The results are shown in Table 5; the structures of chiral amines needed for this explanation are shown in Fig. 2. Quinine, quinidine, and cinchonidine have the same configuration at C_3 and C_4 (3*R*,4*S*).[20] The configuration at C_8 and C_9 of quinine and cinchonidine is (8*S*,9*R*), while that of quinidine is (8*R*,9*S*).[20] (−)-Ephedrine,[21] (−)-*N*-methylephedrine,[22] (1*R*,2*S*)-2-amino-1,2-diphenylethanol[23] have the same configurations as quinine at carbon atoms which are attached to amino and hydroxyl groups, *i.e.*, (C_N–*S*,C_{OH}–*R*). *Ψ*-Ephedrine,[24] and (1*S*,2*S*)-2-amino-1,2-diphenylethanol[23] have the (C_N–*S*,C_{OH}–*S*) configuration.

The results indicate that the chiral structure at C_3 and C_4 of quinine, quinidine, and cinchonidine does not affect enantioselectivity (runs 1—4), and that the configuration of predominant isomer is unequivocally determined by those of the vicinal carbons which are attached to amino and hydroxyl groups, *i.e.*, (C_N–*S*,C_{OH}–*R*) and (C_N–*R*,C_{OH}–*S*) give *S*(+)- and *R*(−)-benzoin, respectively. Brucine and *O*-acetylquinine gave extremely low enantioselectivity and moreover, *S*(−)-α-methylbenzylamine could not bring about asymmetric hydrogenation. These facts show again that the hydroxyl group of chiral amines plays an extremely important role in the enantioselection, as already pointed out in a previous section (b). The enantioselectivity of chiral amino alcohol seems to increase in the order of primary, secondary, and tertiary amines.

Asymmetric Hydrogenation Catalyzed by a Conjugated System Composed of Achiral Base Coordinated Bis(dimethylglyoximato)cobalt(II) and Chiral Amino Alcohols (Cocata-

Table 6. Asymmetric hydrogenation of benzil catalyzed by $Co(dmg)_2$·B-Q* [a]

Run	Base	Reaction temp °C	B/Co[c]	Q*/Co[d]	Q*HCl/Co[e]	Benzoin $[\alpha]_D^{22}$/°	Benzoin O.Y.[f] %	Benzoin Conf.	V[g] 10^{-3} s^{-1}
1	Quinidine	R.T.	0	2	0	−56	47.3	*R*	
2	BA[b] Quinidine	26—27	1	1	0	−57	48.1	*R*	6.0
3	BA Quinidine	30	1	3	0	−60	50.6	*R*	12.0
4	Quinine	30	0	1	1	+73	61.6	*S*	1.5
5	BA Quinine	30	1	1	0	+54	45.6	*S*	
6	BA Quinine	30	1	1	1	+72.3	61.0	*S*	13.6
7	Ph_3P Quinine	R.T.	1	1	1	+72.8	61.4	*S*	0.3
8	Pyridine Quinine	30	1.5	1	1	+67.1	56.6	*S*	2.5
9	BA Quinine	−10	1	1	1	+92	77.6	*S*	

a) Every experiment was carried out in benzene solution except for run 9 (in mesitylene); Substrate/Cobalt=10. b) BA: benzylamine. c) B: achiral base. d) Q*: chiral amino alcohol. e) Q*HCl: hydrochloride of Q*. f) O.Y.: optical yield. g) V: initial velocity (H_2 moles consumed/s/mol of catalyst). h) In every case, chemical yield was almost quantitative.

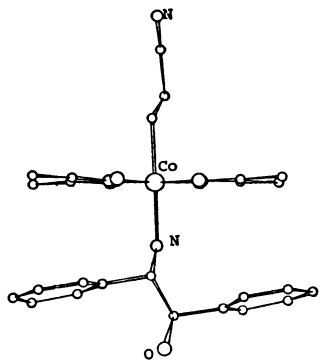


Fig. 3. Perspective view of **25** looking along equatorial plane.[26]

lysts). (a) Evidence for Non-binding of Chiral Base to Cobalt Complexes: Our primary concern is to disclose the mechanism by which chiral amine brings about asymmetric induction. Two dimethylglyoxime monoanions are in planar coordination to cobalt. If chiral amine would coordinate to cobalt, the catalytically active site must be at the site trans to the chiral amine which can not interact with the substrate directly. All attempts to isolate a quinine or quinidine coordinated complex were unsuccessful. However, (1*R*, 2*S*)-2-amino-1,2-diphenylethanol coordinated (2-cyanoethyl)bis(dimethylglyoximato)cobalt(III) (**25**) was isolated. From NMR and circular dichroism spectra of the complex and from the importance of the hydroxyl group of chiral amine, asymmetric induction had, first, been assumed to be brought about by an asymmetric field induced at the site trans to chiral axial base through hydrogen bonding between the oxygen of the dimethylglyoxime ligand and the hydroxyl group of chiral amino alcohol. However, X-ray analysis of the complex (**25**) revealed that the amino nitrogen and the hydroxyl group of amino alcohol are fully transoid; there exists no hydrogen bonding between the oxygen of the inplane ligand and the hydroxyl group of amino alcohol and also no significant asymmetric distortion of the inplane ligand (Fig. 3).[25] The optical yields increase in the order of primary, secondary, and tertiary amines. This order is consistent with that of the difficulty in coordination of the amine. Such results suggested the possibility that asymmetric induction was brought about by an amino alcohol molecule other than that coordinated to the cobalt atom. Thus, asymmetric hydrogenation was examined in the presence of both chiral amino alcohol and an achiral simple base such as benzylamine, pyridine, and triphenylphosphine. The results are summarized in Table 6. A comparison of runs 4 and 6 (or 1 and 2) shows the optical yields did not decrease, while the reaction rates were extremely enhanced on addition of benzylamine to bis(dimethylglyoximato)cobalt(II)–quinine or –quinidine system. The reaction rates increase in the order of increasing electron donor ability of the achiral simple base added. This seems to suggest that the achiral simple base is coordinated to a cobalt atom. The rate acceleration made it easy to react at a lower temperature. At −10 °C in mesitylene the optical yield reached 78%.

In order to obtain more precise information on the coordinated base, the circular dichroism was examined. If an optically active amine is coordinated to a cobalt atom, the CD band due to vicinal effect[26] of the amine should be observed in the d-d transition region of cobalt. The CD spectra of mixtures of methylbis(dimethylglyoximato)cobalt(III) and quinidine were measured for various molar ratios (Fig. 4). The CD Cotton effect in the d-d transition region of cobalt increased with the increasing molar ratio of quinidine to cobalt complex, showing an equilibrium between the states of quinidine coordinated and non-coordi-

Table 7. Effect of HCl salt on the asymmetric hydrogenation of benzil[a)]

Run	Solvent (ratio)	BA[b)]	Q*[c)]	Q*HCl	BHCl (BHCl/Co)	$[\alpha]_D^{22}$/°	O.Y./%	$\frac{V}{10^{-3}\ s^{-1}}$
1	Benzene	1	1	0	0	+54	45.6	9
2	Benzene	1	0	1	0	+70	59.0	6.5
3	Benzene	1	1	1	0	+72.3	61.0	13.6
4	B/M(4/1)[d)]	1	0	1	0	+33.6	28.4	6.5
5	B/M(4/1)	1	0	1	Quinuclidine HCl (1)	+8.6	7.3	7.6

a) The reaction was carried out under the atmospheric pressure of hydrogen at about 30 °C. b) BA: benzylamine. c) Q*: quinine. d) B/M: a mixture of benzene and methanol.

Table 8. Effect of HCl salt on the asymmetric hydrogenation of α-phenylacrylophenone[a)]

Run	Reaction temp °C	BA	Q*	Q*HCl	$[\alpha]_D$/°	O.Y./%	$\frac{V}{10^{-3}\ s^{-1}}$
1	R.T.	0	1	1	+99.4	49	—
2	30	1	1	0	+20.2	10	13
3	30	1	0	1	+91.4	45	11

a) The reaction was carried out in benzene. See also the footnotes of Tables 6 and 7.

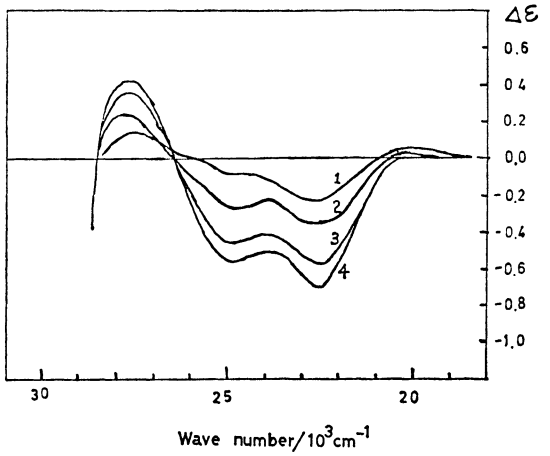


Fig. 4. CD Spectra of dichloromethane solutions of $CH_3Co(dmg)_2$ (A) and quinidine (B) in variation of molar ratio of (B) to (A).
Spectrum 1: $[A]=[B]=10^{-3}$ mol/l,
Spectrum 2: $[A]=10^{-3}$ mol/l; $[B]=1.5\times10^{-3}$ mol/l,
Spectrum 3: $[A]=10^{-3}$ mol/l; $[B]=4\times10^{-3}$ mol/l,
Spectrum 4: $[A]=10^{-3}$ mol/l; $[B]=8\times10^{-3}$ mol/l.

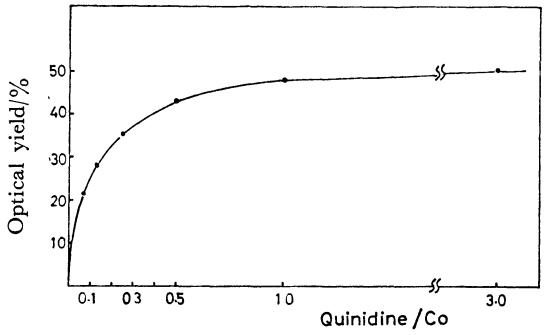


Fig. 5. Non-linear correlation between optical yields and molar ratio of quinidine to $Co(dmg)_2$ in the hydrogenation of benzil catalyzed by $Co(dmg)_2$·benzylamine-quinidine.

nated to the cobalt complex. Addition of an equimolar amount of benzylamine to the above system erased the Cotton effect. This clearly indicates that benzylamine coordinates selectively to cobalt in the system:

$$[CH_3Co(dmg)_2\cdot Q^* \rightleftarrows CH_3Co(dmg)_2 + Q^*] \xrightarrow{PhCH_2NH_2} CH_3Co(dmg)_2\cdot NH_2CH_2Ph + Q^*$$

However, the results still do not rule out the possibility that the amino alcohol have some interaction with some part of the ligands. In order to check this possibility, we studied the change in optical yield with variation of molar ratio of quinidine to cobalt complex in the hydrogenation of benzil by this system. If chiral amine and cobalt complex have a 1:1 interaction or binding, then the optical yields will increase linearly up to the ratio of Q*/Co=1. However, the results do not show a linear correlation (Fig. 5). These results clearly indicate that this enantioselection is brought about by chiral amino alcohol which does not bind firmly to any part of the complex. This fact is quite surprising in view of how asymmetric induction is brought about.

(b) Importance of Protonated Chiral Base for Enantioselection, and Mechanism of Asymmetric Hydrogenation: As is seen from Table 7, when free quinine only is used as the chiral substance in the hydrogenation of benzil, the optical yield is only 46%. However, when the hydrochloride of quinine is used, the optical yield becomes much higher. The optical yield increases a little more when both free quinine and its hydrochloride salt are used. Moreover, the addition of hydrochloride of achiral quinuclidine caused a remarkable decrease in enantioselectivity. A similar effect of hydrochloride salt was also observed in the hydrogenation of α-phenylacrylophenone (Table 8). These facts suggest that protonated chiral amino alcohol plays a decisive role in this enantioselection and also that the proton pulled out of the hydridobis(dimethylglyoxi-

Table 9. Effect of tertiary amines on the asymmetric hydrogenation of benzil with $Co(dmg)_2 \cdot BA\text{-}Q^*$

Run	Reaction temp/°C	BA[a]	Q_1^*	Q_1^*HCl[b]	Q_2^*[c]	Tertiary base(B/Co)	Optical yield/%	Conf.	V[d] 10^{-3} s^{-1}
1	30	1	1	1	0	0	61.0	*S*	13.6
2	30	1	1	1	0	Pyridine (2)	61.0	*S*	10.0
3	30	1	1	1	0	$(n\text{-}C_6H_{13})_3N$ (2)	58.0	*S*	11.1
4	R.T.	1	1	1	0	$(C_2H_5)_3N$ (2)	51.8	*S*	14.9
5	30	1	1	1	0	Quinuclidine (2)	8.5	*S*	
6	30	1	1	0	0	0	45.6	*S*	9.0
7	27	1	0	0	1	0	48.1	*R*	6.0
8	30	1	0	0	3	0	51.0	*R*	12.0
9	30	1	0	0	1	$(n\text{-}C_6H_{13})_3N$ (1)	37.0	*R*	8.2
10	30	1	0	0	1	$(C_2H_5)_3N$ (1)	32.0	*R*	9.9
11	30	1	0	0	1	Quinuclidine (1)	12.0	*R*	10.6

a) BA: benzylamine. b) Q_1^*: quinine, Q_1^*HCl: hydrochloride of quinine. Q_2^*: quinidine. d) V: initial velocity (H_2 moles consumed/s/mol of catalyst). For reaction conditions see the footnote of Table 6.

Table 10. Asymmetric hydrogenation of benzil catalyzed by $Co(dmg)_2 \cdot B$-bulky chiral base

Run	Base	Reaction temp/°C	B/Co[a]	B*/Co[b]	$[\alpha]_D$/°	Optical yield/%	Conf.	V[c] 10^{-3} s^{-1}
1	*N*-Methylephedrine	R.T.	0	1	+33.2	28.0	*S*	
2	[Benzylamine / *N*-Methylephedrine	30	1	1	+9.1	7.7	*S*	5.0
3	[Pyridine / *N*-Methylephedrine	30	1	1	+18.2	15.4	*S*	0.7
4	[Triphenylphosphine / *N*-Methylephedrine	30	1	1	+51.0	43.0	*S*	0.2
5	(1*R*,2*S*)-MADPE	R.T.	0	1	+15.4	13.0	*S*	
6	[Benzylamine / (1*R*,2*S*)-MADPE	30	1	1	+1.3	1.1	*S*	7.1

a) Molar ratio of B(non-chiral base) to cobalt. b) Molar ratio of bulky chiral base(B*) to cobalt. c) V: initial velocity, see the footnot of Table 6. d) (1*R*,2*S*)-2-Dimethyl-amino-1,2-diphenylethanol.[27]

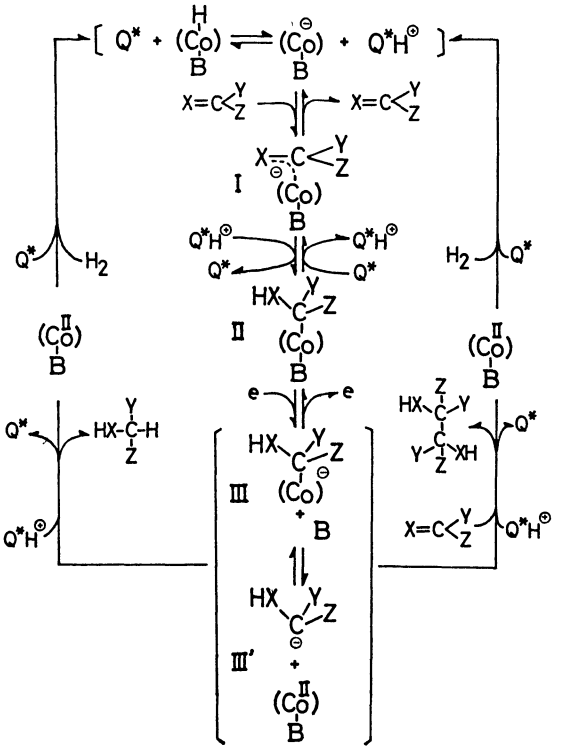
mato)cobalt complex by the amine reacts with substrate or substrate-bound complexes in a bound state. Addition of an achiral base stronger than the chiral base gives a protonated achiral base (t-BH^+), in competition with the formation of a protonated chiral base (B^*H^+). This is expected to cause a decrease in enantioselectivity. As expected, addition of a

$$[B^* + t\text{-}B + HCo(dmg)_2 \cdot B \rightleftharpoons Co(dmg)_2 \cdot B^- + B^*H^+ + t\text{-}B \rightleftharpoons Co(dmg)_2 \cdot B^- + B^* + t\text{-}BH^+]$$

stronger base to the system caused a remarkable decrease in enantioselectivity (Table 9). Even though these tertiary amines have almost the same basicity, their effects on the enantioselectivities are considerably different. The differences can be understood in terms of steric hinderances which prevent these protonated bases from approaching the reaction center. The same kind of steric effect is observed in cases of sterically hindered chiral amine (Table 10). On using quinine or quinidine, whose effective bulk around nitrogen atom is relatively small owing to the cage structure, optical yields did not vary with achiral weak bases such as benzylamine, pyridine, and triphenylphosphine. However, when *N*-methylephedrine was used as the chiral base, optical yields varied remarkably with variation of the above achiral bases. In this case, even a small amount of a protonated simple base (for example, dissociated benzylamine) or hydride complex seems to compete seriously. Thus, a fairly good result is obtained using triphenylphosphine as the axial base which has very low basicity toward protons.

Thus, protonated chiral amino alcohol must recognize enantiotopic face on giving its proton to the substrate or substrate-bound complexes. This, in turn, requires an electron donor at some stages. The species must be a Co(I) anion which is released by abstraction of H^+ from a hydride complex. The rate accelerations with increasing basicity and with addition of proton sources are in accord with the mechanism comprised of an electron donor [Co(I) anion] and a proton donor. In addition, the catalytic hydrogenation by this system has been shown to proceed through an α-alkyl complex, followed by the reductive cleavage of Co–C bond with a Co(I) anion.[9,28] The mechanism of this hydrogenation is schematically delineated in Scheme 1.

A hydridobis(dimethylglyoximato)cobalt complex is produced by the reaction of bis(dimethylglyoximato)-cobalt(II)–base and molecular hydrogen. The hydride complex dissociates into proton and Co(I) anion with an aid of a basic solute in equilibrium. The proton is captured by bases in this system. The substrate



Scheme 1. Catalytic cycle in the hydrogenation with $Co(dmg)_2$·B-Q*.
Electron (e) is supplied from hydrogen probably *via* (Co^{I})·B^{-}. (Co), B, and Q* represent bis(dimethylglyoximato)cobalt, axial base and chiral cocatalyst (chiral amino alcohol), respectively.

gains an electron from the Co(I) anion to give an intermediate (anionic alkyl complex or radical anion) which undergoes the attack of the protonated base to give an alkyl complex (II). The reaction of the alkyl complex (II) with the electron donor, Co(I) anion, will form the reduced state of the alkyl complex, III, and/or carbanion, III'. The subsequent attack of the protonated base, Q^*H^+, and/or the protonated basic solute including the hydridobis(dimethylglyoximato)cobalt complex will give the simple reduction product. But if the reduced state of the alkyl complex or carbanion (III or III') undergoes the attack of another substrate followed by protonation, the reductive dimerization product may be formed. Enantioselection will take place in two stages when Q^*H^+ gives its proton to the intermediates I and III and/or III'. The latter stage of enantioselection will be more important for the following reasons. The former stage was shown to be in an equilibrium;[9] also, deuterium cleavage of optically pure [(*R*)-1-(methoxycarbonyl)ethyl](pyridine)bis(dimethylglyoximato)cobalt(III), which was easily derived by displacement of the axial base of [(*R*)-1-(methoxycarbonyl)ethyl] [*R*(+)-methylbenzylamine]bis(dimethylglyoximato)cobalt(III)[29] with pyridine, gave the inversion product predominantly, but the stereoselectivity was extremely low (lower than 1%).[30] This result implies that the reduced state of alkyl complex III is also in an equilibrium with carbanion III'.

Before presenting the mechanism of chiral recognition it is necessary to discuss the conformations of alkyl complexes or carbanions ejected from the reduced state of alkyl complexes. They will be able to exist in two forms of rotamers with respect to the rotating axis of C_α–COR' bond:

Transoid (*T*) Cisoid (*C*)

One is the rotamer in which substituents, R and R' are transoid, and the other is one in which they are cisoid. The stability of each form will be determined by the balance of the attractive interaction between O and HX, and the repulsive interaction between R and R'. Considering that Q^*H^+ selects the favored chirality of two enantiomers (or the favored prochiral face of carbanion) in the more stable rotamer (*T* or *C*) to furnish its proton, we can predict the configuration of the predominant enantiomer in all the cases examined.

In cases of substrates having large substituents such as benzil and α-phenylacrylophenone, two substituents have to situate in trans form, because of the large steric repulsion between these groups. Protonated quinine will approach the reduced alkyl complex (III) or carbanion (III') with an attractive interaction between the OH group of quinine and carbonyl group of substrate and also between the positive charge of protonated quinine and the negative charge of reduced alkyl complexes or carbanion (Fig. 6). The assumption of the attractive interaction between the hydroxyl group of amino alcohol and the carbonyl group of the substrate may be substantiated by solvent

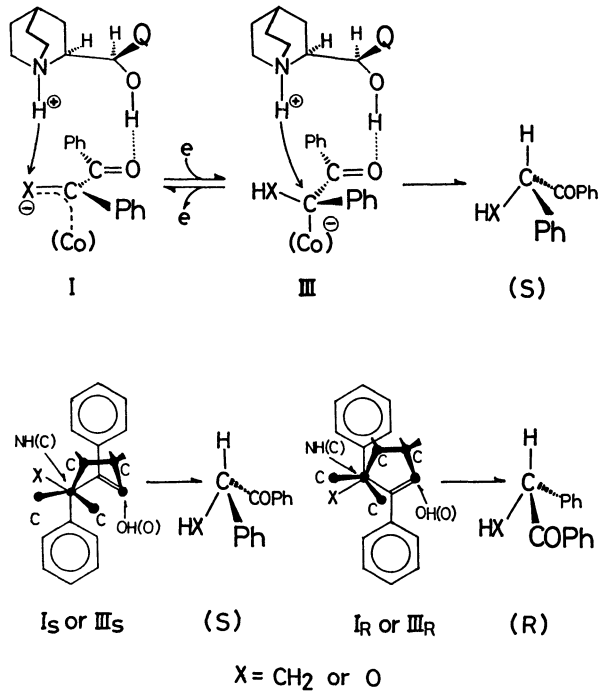


Fig. 6. A proposed mechanism for enantioselection in the hydrogenation of benzil, α-phenylacrylophenone, and methyl phenyl diketone.

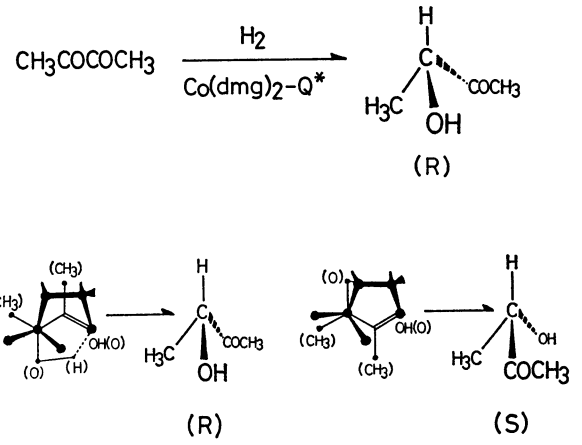


Fig. 7. A proposed mechanism for enantioselection in the hydrogenation of biacetyl.

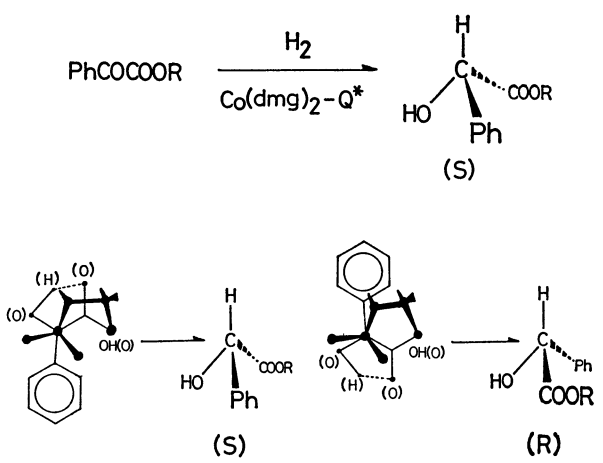


Fig. 8. A proposed mechanism for enantioselection in the hydrogenation of phenylglyoxylates.

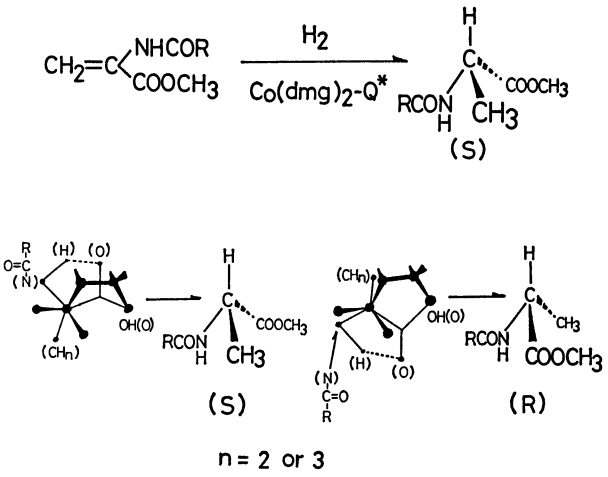


Fig. 9. A proposed mechanism for enantioselection in the hydrogenation of dehydroalanine derivatives.

effect: that solvents having hydroxyl and carbonyl groups decrease enantioselectivity, and also by the importance of hydroxyl group of chiral amine for the enantioselection. Is (or IIIs) and Ir (or IIIr) are the projections which are obtained by viewing I (or III) from above. As is seen, an approach like Is (or IIIs) which gives the predominant enantiomer (*S*) is well fitting and has no substantial repulsion, while the other (*R*) will result in a serious repulsion because the substituents around the reaction site are nearly eclipsed. In cases of the substrates having small substituents or substituents compelled to be in cisoid form, such as biacetyl and 1,2-cyclohexanedione, hydrogen bonded cis form will be favored. Thus, the attack of protonated quinine to the cis form (***C***) will reasonably be assumed in cases of substrates having small substituents or substituents compelled to be in cis form. The transition state which gives *R* isomer is more stable than that giving *S* isomer (Fig. 7). The same explanation will be made in the cases of α-keto carboxylates and α-(acylamino)acrylates (Figs. 8 and 9). Although only quinine was used for the explanation of the enantioselection mechanism, the enantioselectivity of other chiral amino alcohols can also be explained in the same way.

Features and Limitations of This Catalyst System. Thus, the attempt to overcome the shortcomings of the previously studied catalyst system, the cyanocobalt–chiral amine system, have led us to explore a unique catalyst system, bis(dimethylglyoximato)cobalt(II)·B–chiral amino alcohol system, which resembles enzymes. The catalytic site and the enantioselectivity-determining site of this catalytic system are separated: bis(dimethylglyoximato)cobalt complex and chiral amino alcohol are considered to correspond to NAD (or NADP) and apoenzyme, respectively. This makes it possible to improve these two catalytic features almost independently. In fact, catalytic activity was enhanced by increasing electron density on cobalt atom without decreasing enantioselectivity, when the chiral base used was the same.

On the other hand, enantioselection of this catalytic system is performed when the chiral proton carrier gives the proton. In consequence, the existence of achiral proton carrier makes enantioselectivity lower. This is an inherent shortcoming of this catalytic system. However, this is not one which is impossible to overcome: Directed proton transfer with complete enantioselectivity seems to be involved in biological redox systems.

Another aspect is concerned with kinetic parameters. As described in a previous section, in spite of the rather large difference of activation enthalpies ($\Delta\Delta H^{*}_{R\text{-}S}=2.9$ kcal/mol), the activation free energy difference becomes rather small ($\Delta\Delta G^{*}_{R\text{-}S}=1.1$ kcal/mol at 10 °C) because of large difference in activation entropy term which has the same sign. If it would be possible to make the entropy term zero, almost complete enantioselectivity (99%) should be achieved. Thus, controlling the entropy term is an essential problem to be solved.

Experimental

Melting points were measured by a Yanagimoto micro-melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a JEOL JNM-4H-100 spectrometer, using TMS as the internal standard.

Gas liquid chromatography was performed on a Shimadzu GC-4CM using 10% PEG 4000-Celite column. Optical rotations were measured on a Carl Zeiss photoelectric precision polarimeter. Circular dichroism spectra were measured by JASCO ORD/UV-5 spectrometer. Infrared spectra were taken on a Hitachi EPI-G2 spectrophotometer.

General Procedure for Asymmetric Hydrogenation Catalyzed by Bis(dimethylglyoximato)cobalt(II)–Puinine. A 200 ml flask which have a side neck with a rubber cap was used as the reaction vessel. To a methanol (10 ml) solution of $CoCl_2 \cdot 6H_2O$ (0.25 g) was added a hot solution of dimethylglyoxime (0.244 g) in methanol (14 ml) under nitrogen atmosphere with stirring. The solution was stirred for 5—10 min and then 1 ml of 2.35 mol dm^{-3} sodium methoxide solution was added to this solution. After 1—2 min, a degassed methanol solution of an equimolar mixture of quinine and quinine hydrochloride (which is prepared by adding 0.46 ml of 2.35 mol dm^{-3}-sodium methoxide solution to a solution of quinine $HCl \cdot 2H_2O$ (0.84 g) in methanol (5 ml)) was added to the above reaction vessel. The reaction vessel was connected to a gas burret and a vacuum system through a three-way tap. Methanol in the resulting catalyst solution was evaporated under a reduced pressure with warming and stirring to a wet paste (in this case, caution should be taken not to dry the catalyst). To this paste 10 ml of degassed benzene was added by a syringe under atmospheric pressure of hydrogen, and the mixture was then evaporated again to a wet paste under a reduced pressure in order to eliminate the residual methanol (the above caution should be repeated). To the resulting catalyst was added a degassed benzene solution of substrate with a syringe under atmospheric pressure of hydrogen; hydrogenation was then initiated with vigorous stirring. After the theoretical amount of hydrogen was absorbed, about 300 ml of benzene or ether was added to the reaction mixture, and then successively washed with water (several times), 6 mol dm^{-3} or dilute hydrochloric acid (several times), and water. The organic layer was dried over anhydrous sodium sulfate, and concentrated under a reduced pressure to give the corresponding reduction products.

Asymmetric Hydrogenation of Benzil. In this case, the crude product obtained according to the general procedure was shown to contain substantially no impurity by TLC and GLPC; optical rotation was therefore measured without further purification. The IR and NMR spectra were identical with those of the authentic sample (benzoin). Yields were almost quantitative (Tables 1 and 3).

Asymmetric Hydrogenation of Methyl Phenyl Diketone. After carrying out the usual workup (general procedure) described above, 1.4 g of a syrupy product was obtained from 1.48 g of methyl phenyl diketone. The reaction products were adsorbed on a silica-gel column (Kiesel gel H, Merck) and successively eluted by hexane, benzene, and ethyl acetate. α-Hydroxy-α-phenylacetone (**8**) and α-hydroxypropiophenone (**9**) were thus isolated and characterized by NMR as follows. **8**: NMR ($CDCl_3$) δ 7.20 [s, 5H, phenyl], 5.05 [s, 1H, α-CH–], 3.70 [s, 1H, OH], 2.05 [s, 3H, $COCH_3$]. $[\alpha]_D^{22}$ +88.8° (*c* 2.3, ethanol). TLC R_f 0.27 (benzene/hexane/ethyl acetate=4.5/4.5/1). **9**: NMR ($CDCl_3$) δ7.85 [2H, ortho H of phenyl], 7.20 [mc, 3H, metha and para H of phenyl], 5.00 [q, 1H α-CH–], 1.45 [d, 3H, methyl). TLC R_f 0.41 (benzene/hexane/ethyl acetate=4.5/4.5/1). The ratio of **8** and **9** was determined by NMR of the crude products.

Asymmetric Hydrogenation of Biacetyl. The catalyst was prepared according to the general procedure, except for using twice the amounts of the reagents. To the catalyst was added a solution of 1.81 g of biacetyl in 50 ml of benzene. The mixture was stirred under the atmospheric pressure of hydrogen. The reaction was stopped when 97 ml of hydrogen was absorbed (this took 2 h). The reaction mixture was adsorbed on a silica-gel column (40 g of Wako gel C-200) and eluted by ether/petroleum ether (2/1). The eluate was checked by thin layer chromatography. The first fraction contained biacetyl; the next ones contained *erythro*- and *threo*-3,4-dihydroxy-3,4-dimethyl-2,5-hexanedione (**11**-E and **11**-T). The fractions containing reductive dimerization products were combined and concentrated under a reduced pressure to give 1.0 g of a syrup. The syrup was dissolved in benzene and the optical rotation was measured. The ratio of *threo* and *erythro* products was determined from the intensities of NMR signals of C–CH_3 and CH_3CO to be 22/78. From the ratio and the optical rotation of the mixture (**11**-E and **11**-T), the specific rotation of **11**-T produced was determined: $[\alpha]_D$ −33° (*c* 2.02, benzene). The fractions containing only acetoin were combined. The solvent was evaporated by bubbling N_2 gas into the eluate. The residue was distilled at 25—25.5 °C/29 mmHg (1 mmHg=133.322 Pa.) $[\alpha]_D$ −2° (*c* 0.8, water). From the optical rotation, the optical yield was calculated by reference to that of the optically pure acetoin.[12] Optical yield, 2.5%.

Asymmetric Hydrogenation of 1,2-Cyclohexanedione. The reaction was performed according to the general procedure, except for using benzene/methanol (4/1) as a solvent. After a theoretical amount of hydrogen was absorbed, the reaction mixture was extracted with chloroform and the chloroform layer was washed with NaCl-saturated water, dil HCl and water, successively. The chloroform layer was dried over anhydrous sodium sulfate, and concentrated under a reduced pressure to give a syrup which crystallized gradually. $[\alpha]_D$ −2.44° (*c* 0.35, chloroform).

Asymmetric Hydrogenation of Ethyl Phenylglyoxylate. After carrying out the general procedure, 1.6 g of a syrupy product was obtained from 1.78 g of ethyl phenylglyoxylate. The yields of ethyl mandelate and reductive dimerization products were calculated by ^1H NMR spectra and yield of the crude product. The crude product crystallized partially (about 0.31 g), mp 118—121 °C; it was recrystallized by hexane to give cubic crystals, mp 124 °C. Found: C, 67.02; H, 6.10; MS *m/e* 359[$(M+1)^+$]. Calcd for $C_{20}H_{22}O_6$: C, 67.02; H, 6.15. ^1H NMR ($CDCl_3$) δ 7.15 [10H, phenyl], 5.07 [s, 2H, OH], 4.30 [q, 4H, $-CH_2-$], 1.27 [t, 6H, methyl]. The syrup obtained after removal of crystals (by filtration) was chromatographed on a silica-gel column using hexane–benzene (with increasing polarity of the solvent) as the solvent, giving ethyl phenylglyoxylate (0.3 g), dimerization products (0.06 g), and ethyl mandelate (0.42 g). The specific rotations of ethyl mandelate are given in Table 1.

Asymmetric Hydrogenation of Isopropyl Phenylglyoxylate. After carrying out the general procedure, the crude products were adsorbed on a silica-gel column (Kiesel gel H, Merck) and eluted by hexane/benzene; the polarity of the solvent was gradually increased. Diisopropyl α,α′-diphenyltartrate and isopropyl mandelate were thus isolated and characterized by ^1H NMR spectra. ^1H NMR of diisopropyl α,α′-diphenyltartrate ($CDCl_3$) δ 7.02 [m, 10H, phenyl], 5.1 [q, 2H, methine H of isopropyl], 4.9 [s, 2H, OH], 1.14 [t, 12H, methyl]. ^1H NMR of isopropyl mandelate ($CDCl_3$) δ 7.35 [m, 5H, phenyl], 5.09 [s, 1H, methine H of α-carbon], 5.02 [m, 1H, methine H of isopropyl], 3.4 [broad s, 1H, OH], 1.28 [d, 3H, methyl], 1.11 [d, 3H, methyl].

Isopropyl mandelate thus isolated was hydrolyzed by refluxing with 4 mol dm^{-3}-sulfuric acid for 24 h. The reaction mixture was made alkaline and washed with benzene.

The aqueous layer was acidified and extracted with benzene. The organic layer was washed with water, and concentrated *in vacuo* to give 0.1 g of mandelic acid, $[\alpha]_D$ +18° (*c* 2.0, water).

Asymmetric Hydrogenation of Methyl α-(Acetylamino)acrylate. After carrying out the usual workup (general procedure), an oily product was obtained which was chromatographed on a silica-gel column using ether as a solvent. 0.8 g of an oily substance (*N*-acetylalanine methyl ester) was obtained starting from 1.2 g of the substrate; this was further purified by distillation at 70—82 °C/1—2 mmHg, 0.4 g, $[\alpha]_D$ −17.2° (*c* 1.2, water).

Asymmetric Hydrogenation of Methyl α-(Phenylacetylamino)acrylate. 187 ml of hydrogen was absorbed for 2.2 h. The reaction mixture was treated as usual (general procedure) to give 1 g of *N*-(phenylacetyl)alanine methyl ester (starting from 1.67 g of substrate), $[\alpha]_D$ −4° (*c* 2, methanol). The IR and ^{1}H NMR spectra of the product were identical with those of the authentic sample prepared by the reaction of (*S*)-*N*-(phenylacetyl)alanine with diazomethane.

(S)-N-(Phenylacetyl)alanine Methyl Ester. (*S*)-*N*-(Phenylacetyl)alanine was esterified with diazomethane. The crude product was purified by recrystallization from ether–petroleum ether, mp 68.5—70.5 °C, $[\alpha]_D$ −56.9° (*c* 2, methanol). ^{1}H NMR ($CDCl_3$) δ 7.30 [s, 5H, phenyl], 6.32 [broad d, 1H, NH], 4.57 [qt, 1H, CH], 3.68 [s, 3H, OCH_3], 3.57 [s, 2H, CH_2], 1.34 [d, 3H, C-CH_3]. IR (KBr), 3340 cm^{-1} (NH), 1745 cm^{-1} (ester), 1640 cm^{-1} (amide).

Asymmetric Hydrogenation of Methyl 2-Phenyl-2-propenoate. After carrying out the usual workup (general procedure), 2.5 g of a syrup was obtained from 2.7 g of substrate, $[\alpha]_D$ +7.7° (*c* 6.2, toluene). This was distilled at 67—68 °C/2 mmHg and 0.9 g of purified product (methyl 2-phenylpropanoate) was obtained, $[\alpha]_D$ +11.5° (*c* 6.2, toluene).

Asymmetric Hydrogenation of α-Phenylacrylophenone. After carrying out the usual workup (general procedure) 1.9 g of a syrup (crude α-phenylpropiophenone) was obtained from 2 g of substrate, $[\alpha]_D$ +88.6° (*c* 3.5, chloroform). The syrup was distilled at 115—116 °C/1 mmHg, 1.0 g $[\alpha]_D$ +99.4° (*c* 3.57, chloroform).

Reaction Rate. A 200 ml Erlenmeyer flask which has a side neck with a rubber cap was used as the reaction vessel. The catalyst was prepared according to the general procedure using $CoCl_2 \cdot 6H_2O$ (0.25 g), dimethylglyoxime (0.244 g), and quinine $HCl \cdot 2H_2O$ (0.84 g) (a half of which was neutralized with sodium methoxide). To the reaction vessel containing the catalyst was added a degassed benzene solution (50 ml) of benzil (2.24 g) by a syringe. The reaction was initiated with vigorous stirring. The reaction temperature was maintained constant within ±0.2 °C. The quantity of hydrogen absorbed was measured by a gas burret. The pseudo-first-order rate constants are listed in Table 4.

General Procedure for Asymmetric Hydrogenation Catalyzed by a Conjugated System Composed of Achiral Base Coordinated Bis(dimethylglyoximato)cobalt(II) and Chiral Amino Alcohols. To a methanol solution (10 ml) of $CoCl_2 \cdot 6H_2O$ (0.25 g) was added a hot solution of dimethylglyoxime (0.244 g) in methanol (14 ml) under nitrogen atmosphere with stirring. The solution was stirred for 5—10 min and then 1 ml of 2.35 mol dm^{-3}-sodium methoxide solution was added to this solution. After 1—2 min, achiral base, additives, and a degassed methanol solution of equimolar mixture of quinine and quinine hydrochloride (which is prepared by adding 0.46 ml of 2.35 mol dm^{-3}-sodium methoxide solution to a solution of quinine $HCl \cdot 2H_2O$ (0.84 g) in methanol (5 ml)) were added to the above reaction vessel, one by one. The procedure hereafter was the same as in the "General Procedure for Asymmetric Hydrogenation Catalyzed by Bis(dimethylglyoximato)cobalt(II)–Quinine."

Circular Dichroism Study. To each methanol solution of 9.15 g of methyl(dimethyl sulfide)bis(dimethylglyoximato)cobalt(III)[31] 8.1 mg (1 molar equivalent), 12.1 mg (1.5 molar equivalent), 32.4 mg (4 molar equivalent), or 64.8 mg (8 molar equivalent) of quinidine was added. The resulting solution was evaporated *in vacuo* to dryness. The residue was dissolved in methanol and the resulting solution was again evaporated *in vacuo* to dryness. The procedure was repeated several times, during which dimethyl sulfide was completely expelled. Circular dichroism spectrum of 25 ml dichloromethane solution of each sample thus prepared was measured by JASCO ORD/UV-5 Spectrometer. The results are shown in Fig. 4.

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