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Stereochemical Studies. LIX.[1] Asymmetric Transamination from (*S*)-α-Amino Acids. Synthesis of optically Active Amines by Chemical Transamination of (*S*)-α-Amino Acid Esters to Ketones[2]

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Asymmetric synthesis of optically active amines (**15**) by catalytic hydrogenation and chemical transamination of the Schiff bases (**10**) of (*S*)-α-amino acid esters (**8**) with ketones (**9**) was achieved. The effects of solvents and the ester moiety of chiral reagents on the asymmetric induction were examined, and (*S*)-(+)-2-amino-3-phenylpropane (**15a**) was prepared from (*S*)-valine *tert*-butyl ester and phenylacetone in 63% yield and 87% optical yield. The possible steric course of the asymmetric hydrogenation is discussed. The reduction of the Schiff bases (**10**) with sodium borohydride is also described.

Keywords——asymmetric transamination; (*S*)-α-amino acid; optically active amine; asymmetric hydrogenation; solvent effect; transposition of carbon–nitrogen double bond

Transamination, the transfer of an amino group from an amino acid to an α-keto acid, is one of the enzymic reactions catalyzed by pyridoxal phosphate. The conversion of pyruvic acid to (*S*)-alanine with (*S*)-glutamic acid, catalyzed by a pyridoxal phosphate-containing enzyme, is representative of this type of reaction. The scheme as shown in Chart 1 was

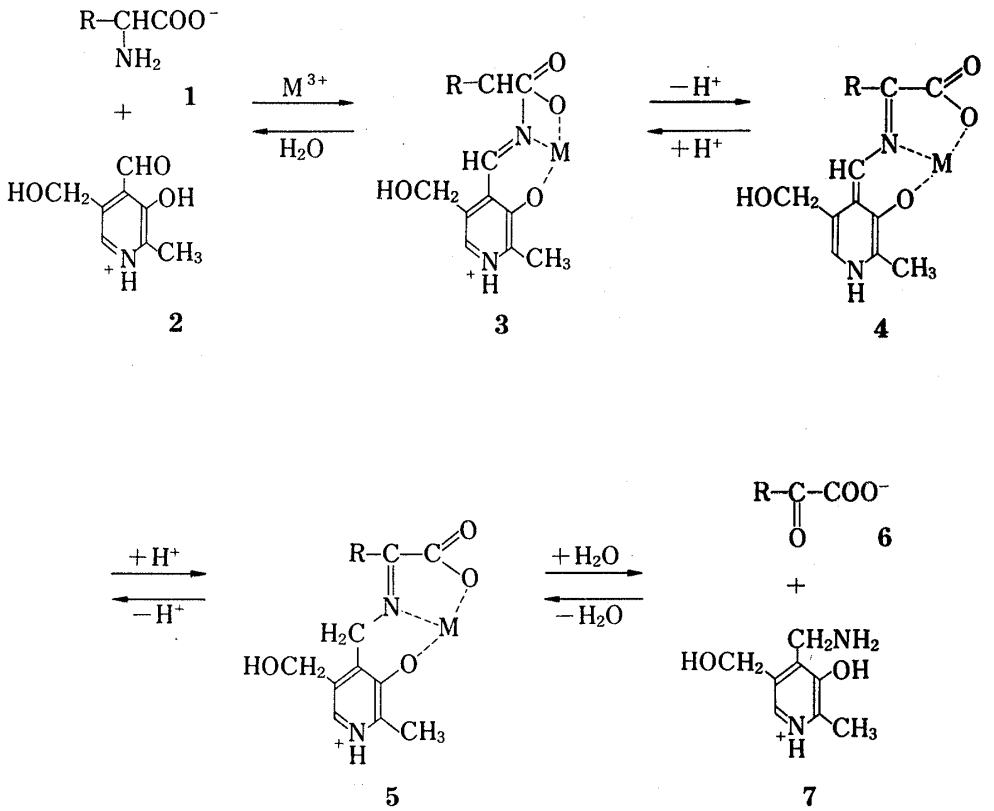

Chart 1

suggested to represent the reversible interconversion of an (*S*)-α-amino acid and an α-keto acid.[4] The enzyme provides an asymmetric environment for this conversion, and the transfer of a hydrogen atom from **4** to **3** proceeds with complete stereoselectivity, leading to the formation of an optically active α-amino acid.

Several asymmetric syntheses of α-amino acids and amines by chemical transamination have been reported.[5–11] Hiskey and Northrop[6] reported the synthesis of optically active α-amino acids by hydrogenation and subsequent hydrogenolysis of the Schiff base of α-keto acids with (*R*)-(+)- and (*S*)-(−)-α-phenethylamine. Harada *et al.*[8] reported many Hiskey-type asymmetric reactions and described the possible steric course of the asymmetric induction. However, in these cases[6–11] the chiral reagents used were restricted to benzylamine derivatives in which the benzylic carbon–nitrogen bond was hydrogenolyzed, thereby transferring the amino group into the new asymmetric center. More recently, Kuzuhara *et al.*[12] and Breslow *et al.*[13] synthesized chiral pyridoxamine analogs, and successively applied these reagents to the synthesis of optically active α-amino acids by nonenzymatic transamination.

We have already reported the efficient asymmetric synthesis of α-amino acids[14] by hydrogenation of the Schiff bases of α-keto ester with (*S*)-α-amino acid *tert*-butyl esters and subsequent oxidative decarboxylation including regio-specific fission of the carbon–nitrogen bond, and the synthesis of optically active amines[2] from ketones by chemical transamination using (*S*)-α-amino acid esters. The details of the work on the asymmetric synthesis of amines are the subject of this paper.

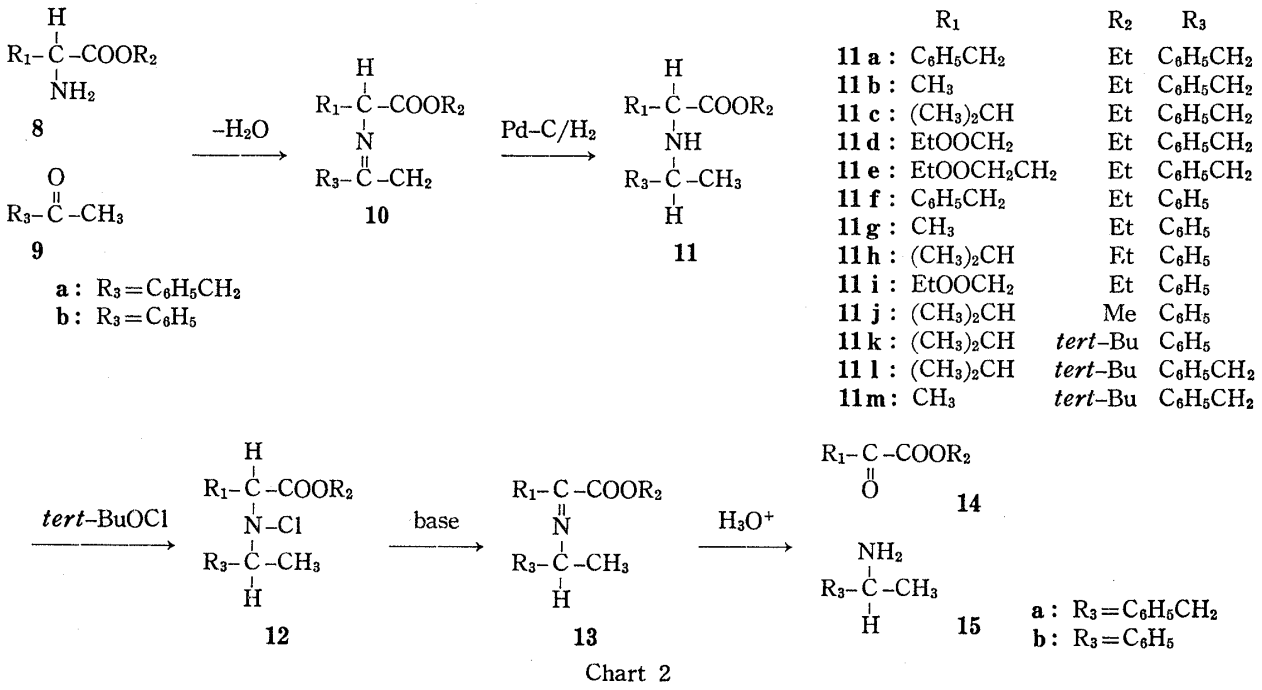

Chart 2

As shown in Chart 2, optically active amines (**15**) were synthesized from phenylacetone (**9a**) or acetophenone (**9b**) using (*S*)-α-amino acid esters such as the esters of (*S*)-alanine, (*S*)-valine, (*S*)-phenylalanine, (*S*)-aspartic acid, and (*S*)-glutamic acid. The acidic α-proton of the *N*-chloramino acid derivative (**12**) was regiospecifically removed to give exclusively **13**. This transposition of the carbon–nitrogen double bond from **10** to **13** is similar to the transamination model. Condensation of ketones (**9**) and (*S*)-α-amino acid ethyl esters (**8**) in benzene under azeotropic conditions afforded the Schiff bases (**10**), which, without isolation, were catalytically hydrogenated using 5% palladium on charcoal at room temperature in ethanol (initial pressure, 60 kg/cm²). The *N*-alkylated amino acid esters (**11**) were obtained as a mix-

ture of diasteromers in 32—91% and 20—30% yields, after silica gel chromatography, from **9a** and **9b**, respectively. Treatment of **11** with *tert*-butylhypochlorite[15] in ether at 0°C gave the *N*-chloramines (**12**), which were converted to the imines (**13**) by reaction with sodium ethoxide in ethanol, and subsequent hydrolysis with 5% sulfuric acid afforded amines (**15**) in 8—56% yields (50—80% from **11**). The optical yields of the resulting amines were 20—70%. The results are summarized in Tables I and II. In some cases, the diastereomers of **11** could be well separated by gas chromatography (GLC). Therefore, optical yields were calculated on the basis of GLC analysis, and agreed closely with experimental values based on the optical rotations of **15** and their benzoates. The two diastereomers of **11c** were isolated by silica gel column chromatography, and they were converted to optically pure benzoate of **15a** ((*S*)-(+)-benzoate of **15a** was obtained from the major diastereomer of **11c**, mp 159—160°C, $[\alpha]_D^{25}$ +72° (*c*=1, MeOH), lit.[16] mp 159—160°C, $[\alpha]_D^{25}$ +72° (*c*=1, MeOH)). These results mean that no racemization occurs during the overall reaction sequence.

Table I. Asymmetric Synthesis of 2-Amino-3-phenylpropane (**15a**)

Run	Chiral reagents used (*S*)-α-Amino acid ethyl esters	Product: 2-Amino-3-phenylpropane Chemical yield[a] (%)	$[\alpha]_D^{15}$ (°) (EtOH)	Optical yield[b] (%)	Benzoate $[\alpha]_D^{25}$ (°) (*c*=1, MeOH)	Benzoate Optical yield[b] (%)	Confign.	Optical yield[c] (%)
1	Ala	37	+22.7 (*c*=4.4)	66	+45.1	63	*S*	
2	Phe	25	+7.2 (*c*=3.0)	21	+16.6	23	*S*	
3	Val	56	+17.3 (*c*=5.4)	50	+38.0	53	*S*	48
4	Asp	40	+16.9 (*c*=5.2)	49	+38.0	53	*S*	
5	Glu	17	+21.7 (*c*=3.1)	63	+46.8	65	*S*	

a) Determined by GLC using naphthalene as the internal standard.
b) Optically pure (*S*)-(+)-**15a**, $[\alpha]_D^{15}$ +34.5° (*c*=10.62, EtOH). Optically pure (*S*)-(+)-benzoate of **15a**, $[\alpha]_D^{25}$ +72° (*c*=1, MeOH) (see ref. 16).
c) Determined based on GLC analysis of **11**.

Table II. Asymmetric Synthesis of α-Phenethylamine (**15b**)

Run	Chiral reagent used (*S*)-α-Amino acid ethyl esters	Product: α-Phenethylamine Chemical yield[a] (%)	$[\alpha]_D^{20}$ (°) (EtOH)	Optical yield[b] (%)	Benzoate $[\alpha]_D^{20}$ (°) (*c*=0.8, benzene)	Benzoate Optical yield[b] (%)	Confign.	Optical yield[c] (%)
1	Ala	20	−21.3 (*c*=1)	69	−37.3	71	*S*	68
2	Phe	13	−15.5 (*c*=1)	50	−29.0	55	*S*	48
3	Val	14	−15.4 (*c*=2.1)	50	−31.0	59	*S*	56
4	Asp	8	[d]		−23.8	45	*S*	51

a) Determined by GLC using 1,2,4,5-tetramethylbenzene as the internal standard.
b) Optically pure (*R*)-(+)-**15b**, $[\alpha]_D^{20}$ +31° (*c*=2.08, EtOH). Optically pure (*S*)-(−)-benzoate of **15b**, $[\alpha]_D^{20}$ −52.5° (*c*=0.79, benzene) (see ref. 17).
c) Determined based on GLC analysis of **11**.
d) **15b** was not isolated but was directly converted to the benzoate.

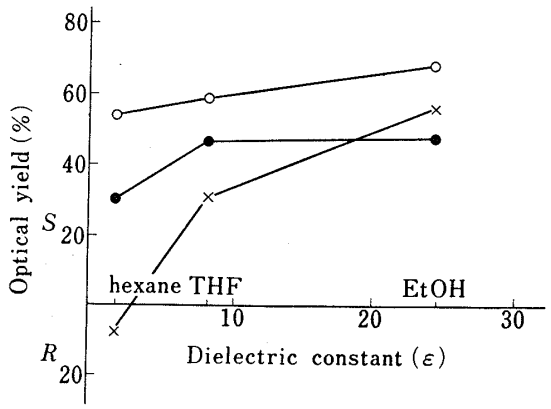

Fig. 1. Relationship between Optical Yields of Amines and Dielectric Constants of the Solvents

×, α-phenethylamine from (*S*)-Val–OEt and acetophenone;
○, α-phenethylamine from (*S*)-Ala–OEt and acetophenone;
●, 2-amino-3-phenylpropane from (*S*)-Val–OEt and phenylacetone. Optical yield was calculated based on GLC analysis of **11**.

Solvent Effects

The effects of solvents on this asymmetric induction were examined. The ketones used were phenylacetone and acetophenone, and the chiral reagents used were ethyl esters of (*S*)-alanine and (*S*)-valine. Schiff bases (**10**) were prepared as previously described, and the solvent effect on the asymmetric hydrogenation was studied by the use of ethanol, tetrahydrofuran (THF), and hexane. Optical yields were determined by GLC analysis of the crude **11**. Figure 1 shows the relationship between the optical yields and the dielectric constants of the solvents. Generally the optical yields decreased with decreasing dielectric constant of the solvent.

Effects of the Ester Moiety of (*S*)-α-Amino Acid Esters

Methyl, ethyl, and *tert*-butyl groups were used as the ester moiety of α-amino acid, and their steric effects on the asymmetric induction were studied. Reactions were carried out under the same conditions as previously described. Catalytic hydrogenation was conducted in ethanol as a solvent. The results (summarized in Table III) show that the optical yield increased remarkably with increasing bulkiness of the ester moiety. The best result (63% total yield, 87% optical yield) was obtained in the synthesis of (*S*)-(+)-2-amino-3-phenylpropane using (*S*)-valine *tert*-butyl ester.

Table III. Effects of the Ester Moiety of Chiral Reagents

Run	Chiral reagents used (*S*)-α-Amino acid esters	Ketones used	Product: Amine (**15**) Chemical yield[a]	[α]^{D} (°) (EtOH)	Optical yield (%)	Benzoate [α] (°)	Optical yield (%)	Confign.	Optical yield[g] (%)
1	Val–OMe	**9b**	12	−9.3[b]	30	−18.8[e]	36	*S*	31
2	Val–OEt	**9b**	14	−15.4[b]	50	−31.0[e]	59	*S*	56
3	Val–OBu-*tert*	**9b**	10	[c]		−45.0[e]	85	*S*	88
4	Val–OEt	**9a**	56	+17.3[d] (*c*=5.4)	50	+38.0[f]	53	*S*	48
5	Val–OBu-*tert*	**9a**	63	+30.0[d] (*c*=5.6)	87	+59.2[f]	83	*S*	81
6	Ala–OEt	**9a**	37	+22.7[d] (*c*=4.4)	66	+45.1[f]	63	*S*	
7	Ala–OBu-*tert*	**9a**	37	+29.3[d] (*c*=6.4)	85	+64.0[f]	89	*S*	

a) Determined by GLC.
b) *c*=1.0, measured at 20°C.
c) **15b** was not isolated but was directly converted to the benzoate.
d) Measured at 20°C.
e) *c*=0.8, benzene, measured at 20°C.
f) *c*=1.0, MeOH, measured at 25°C.
g) Determined based on GLC analysis of **11**.

Steric Course of Catalytic Hydrogenation of the Schiff Base

The absolute configuration of the amines (**15**) obtained using (*S*)-α-amino acid esters was (*S*). When the catalytic hydrogenation was carried out in a polar solvent, and a sterically large ester group was employed as a chiral reagent, high optical yields were obtained.

Harada *et al.*[8d-j] proposed a possible steric course for the hydrogenolytic asymmetric transamination. We have similarly deduced the steric course of this asymmetric reaction. Figure 2 shows the postulated conformations of the substrate in polar and in less polar solvents. In a polar solvent, structure A could be the preferred conformation, and hydrogenation occurs at the less hindered side to afford the (*S*)-amines as the major product. However, in a less polar solvent, the proportion of chelate structure B could increase, because electrostatic attraction between the substrate and the transition metal catalyst in a less polar solvent is stronger than that in a polar solvent, and the solvation of the substrate in a less polar solvent is weaker. Therefore, the optical yields of the resulting amines decreased with decreasing polarity of the solvent.

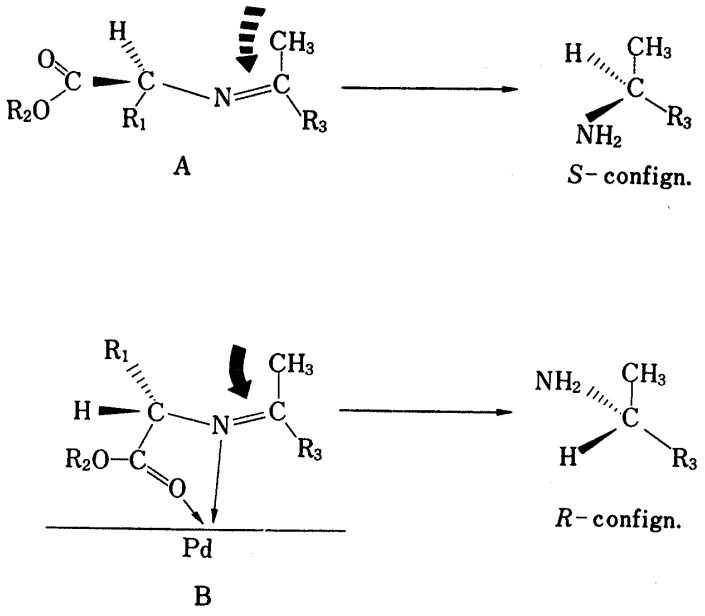

Fig. 2

Reduction of the Schiff Bases with Sodium Borohydride

Reduction of the Schiff bases with sodium borohydride was examined. The Schiff bases, prepared by the usual method, were reduced with $NaBH_4$ at 0°C for 3 h in ethanol. The reduced products (**11**) were isolated in 10—40% yields, and were converted to amines by the same reactions as previously described. When the diastereomers of **11** were separated by GLC, the optical yields were determined by GLC analysis of **11**. The results are summarized in Table IV. It was found that optical yields were lower than those obtained by catalytic hydrogenation.

Table IV. Asymmetric Synthesis of Amines (**15**) by Reduction of the Schiff Bases (**10**) with Sodium Borohydride

Run	Chiral reagent used: (*S*)-α-Amino acid esters	Ketones used	Product: Chemical yield (%)	Product: Optical yield (%)	Product: Confign.
1	Ala–OEt	**9b**	16[a]	52[c]	*S*
2	Val–OEt	**9b**	12[a]	10[c]	*S*
3	Ala–OEt	**9a**	23[b]	35[d]	*S*
4	Ala–OBu-*tert*	**9a**	28[b]	50[d]	*S*

a) Yield from **9b** to **11**.
b) Yield from **9a** to **15a**, determined by GLC.
c) Determined based on GLC analysis of **11**.
d) Determined based on optical rotation of **15a**.

Experimental[18]

Optically Active α-Amino Acid Esters——Prepared according to the reported procedure.[19a,b] (*S*)-Phenylalanine ethyl ester: bp 130—132°C (8 mmHg), $[\alpha]_D^{21}$ +22.8° (*c*=3.2, EtOH) (lit.[19b] bp 140—142°C (10 mmHg), $[\alpha]_D$ +23±1° (*c*=3.1, EtOH)). (*S*)-Aspartic acid diethyl ester: bp 110—112°C (5 mmHg), $[\alpha]_D^{20}$ −9.4° (neat) (lit.[19c] bp 126.5°C (11 mmHg), $[\alpha]_D^{20}$ −9.46° (neat)). (*S*)-Glutamic acid diethyl ester: bp 120—123°C (7 mmHg), $[\alpha]_D^{20}$ +7.43° (neat) (lit.[19c] bp 139—140°C (10 mmHg), $[\alpha]_D^{20}$ +7.34°C (neat)). (*S*)-Alanine ethyl ester: bp 58—60°C (15 mmHg), $[\alpha]_D^{20}$ +3.0° (*c*=3.8, EtOH) (lit.[19d] $[\alpha]_D$ +3° (*c*=3.94, EtOH)). (*S*)-Alanine *tert*-butyl ester: bp 57—58°C (17 mmHg), α_D −0.065° (*l*=0.1, neat). (*S*)-Valine methyl ester: bp 64—66°C (22 mmHg), $[\alpha]_D^{20}$ +38° (*c*=3.2, MeOH). (*S*)-Valine ethyl ester: bp 73—75°C (13 mmHg), $[\alpha]_D^{20}$ +33.6° (*c*=5, EtOH). (*S*)-Valine *tert*-butyl ester: bp 78°C (15 mmHg), $[\alpha]_D^{20}$ +25.6° (neat) (lit.[19e] bp 63°C (1.25 mmHg), $[\alpha]_D^{20}$ +25.5° (neat)).

Asymmetric Syntheses of (*S*)-(+)-2-Amino-3-phenylpropane ((*S*)-(+)-15a)——Reaction procedure for asymmetric synthesis of (*S*)-(+)-**15a** from (*S*)-alanine ethyl ester and phenylacetone (**9a**) (Table I, run 1) is described as an example. Other syntheses were conducted under the same conditions. A mixture of phenylacetone (2.44 g, 18.3 mmol) and (*S*)-alanine ethyl ester (2.14 g, 18.3 mmol) in 60 ml of benzene was stirred at reflux for 48 h using a Dean–Stark apparatus. The benzene was evaporated off *in vacuo* to afford an oily residue, which was dissolved in 50 ml of ethanol. The solution was hydrogenated using 1.0 g of 5% paladium on charcoal at room temperature for 16 h (initial pressure, 60 kg/cm²). The catalyst was filtered off and the filtrate was concentrated *in vacuo* to give an oil, which was purified by silica gel column chromatography (ether–hexane, 2: 3) to afford **11b** (2.56 g, 59%) as an oil. Nuclear magnetic resonance (NMR) (in $CDCl_3$): 1.0 (3H, d, *J*=6 Hz, $CH_2CHC\underline{H}_3$), 1.24 (3H, d, *J*=7 Hz, $C\underline{H}_3CHCOOEt$), 1.29 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 1.88 (1H, s, NH), 2.3—3.0 (3H, m, $C_6H_5C\underline{H}_2C\underline{H}CH_3$), 3.4 (1H, q, *J*=7 Hz, $C\underline{H}COOEt$), 4.15 (2H, q, *J*=7 Hz, $C\underline{H}_2CH_3$), 7.2 (5H, m, C_6H_5). IR ν_{max}^{film} cm^{-1}: 1740.

A solution of *tert*-butylhypochlorite (0.98 g, 9 mmol) in 5 ml of dry ether was added to a solution of **11b** (2.0 g, 8.5 mmol) in 10 ml of dry ether at 0°C. The mixture was stirred at 0°C for 0.5 h, then a solution of sodium ethoxide (prepared from 0.275 g of sodium (0.012 gram atom) and 10 ml of ethanol) was added. The mixture was stirred at 40°C for 1 h, then the solvent was evaporated off *in vacuo*. A 15 ml aliquot of 5% sulfuric acid was added to the residue, and stirring was continued for 2 h at room temperature. The mixture was washed with ether, and the aqueous solution was made alkaline with K_2CO_3, then extracted with ether. The ethereal extracts were washed with satd. NaCl, and dried over anhyd. Na_2SO_4. Filtration and evaporation *in vacuo* gave a yellow oil. Quantitative analysis of the crude **15a** by GLC (column A, 95°C; internal standard, naphthalene (t_R, 9.4 min)) showed that 0.72 g of **15a** (t_R, 6.8 min) had been prepared in 37% yield based on **9a** (62.5% from **11b**). The crude oil was distilled under reduced pressure to give pure (*S*)-(+)-**15a** (0.48 g) as a colorless oil, bp 83—86°C (15 mmHg), $[\alpha]_D^{15}$ +22.7° (*c*=4.35, EtOH). Infrared (IR) and NMR spectra were identical with those of an authentic sample.

Benzoyl chloride (0.52 g, 3.7 mmol) was added to a stirred, cold suspension of **15a** (0.25 g, 1.85 mmol) in 5 ml of 10% NaOH. The mixture was stirred at 0°C for 2 h, then extracted with ethyl acetate. The organic extracts were washed with 10% HCl and satd. NaCl, then dried over anhyd. Na_2SO_4. Filtration and evaporation *in vacuo* gave crystals, which were purified by silica gel column chromatography (ether–hexane, 1: 1) to afford the benzoate of (*S*)-(+)-**15a** (0.38 g, 86%) as colorless crystals, $[\alpha]_D^{25}$ +45.1° (*c*=1, MeOH). Spectral (IR and NMR) and chromatographic (thin layer chromatography (TLC)) properties were identical with those of an authentic sample.

Asymmetric Syntheses of (*S*)-(−)-α-Phenethylamine ((*S*)-(−)-15b)——Reaction procedure for asymmetric synthesis of (*S*)-(−)-**15b** from (*S*)-phenylalanine ethyl ester and acetophenone (**9b**) (Table II, run 2) is described as an example. A benzene solution (60 ml) of acetophenone (1.44 g, 12 mmol) and (*S*)-phenylalanine ethyl ester (2.34 g, 12.1 mmol) was refluxed under azeotropic conditions for 72 h, then was concentrated *in vacuo* to give an oily residue. Hydrogenation was carried out in 35 ml of ethanol using 0.7 g of 5% palladium on charcoal at room temperature for 16 h (initial pressure, 60 kg/cm²). The crude product was purified by silica gel column chromatography (ether–hexane, 1: 1) to afford **11f** (0.7 g, 20%) as a colorless oil. NMR (in $CDCl_3$): 1.15 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 1.3 (3H, d, *J*=7 Hz, $C_6H_5CHC\underline{H}_3$), 1.85 (1H, s, NH), 2.8 (2H, d, *J*=7 Hz, $C_6H_5CH_2$), 3.3 (1H, $C\underline{H}COOEt$), 3.7 (1H, q, *J*=7 Hz, $C\underline{H}CH_3$), 4.05 (2H, q, *J*=6 Hz, $C\underline{H}_2CH_3$), 7.1 (10H, s, $C_6H_5\times2$). IR ν_{max}^{film} cm^{-1}: 1740. GLC analysis (column A, 200°C) of this oil showed two peaks (t_R, 8 min (major peak) and 9.1 min (minor peak)). A solution of **11f** (0.7 g, 2.35 mmol) in 2.5 ml of ether was treated with a solution of *tert*-butyl hypochlorite (0.27 g, 2.5 mmol) in 1.5 ml of ether at 0°C. The mixture was stirred at 0° for 0.5 h, then a solution of sodium ethoxide (prepared from 0.078 g of sodium (0.0034 gram atom) and 2.5 ml of ethanol) was added. The mixture was stirred at 40°C for 1 h, then the solvent was evaporated off *in vacuo*. Hydrolysis with 5% sulfuric acid and usual work-up gave crude **15b**. Quantitative analysis of the crude **15b** by GLC (column A, 95°C; internal standard, 1,2,4,5-tetramethylbenzene (t_R, 6.4 min)) showed that 0.19 g of **15b** (t_R, 4 min) had been prepared in 13% yield from **9b** (65% from **11f**). The crude oil was distilled under reduced pressure to give (*S*)-(−)-**14b** (0.11 g) as a colorless oil, bp 65—68°C (15 mmHg), $[\alpha]_D^{20}$ −15.5° (*c*=1, EtOH). The benzoate was prepared in 93% yield by the usual method,

$[\alpha]_D^{20}$ −29° (c=0.8, benzene). IR and NMR spectra were identical with those of an authentic sample.

Reduction of Schiff Bases with Sodium Borohydride——Reaction procedure for reduction of the Schiff base prepared from (*S*)-valine ethyl ester and phenylacetone (**9a**) (Table IV, run 3) is described as an example. A mixture of phenylacetone (0.925 g, 6.9 mmol) and (*S*)-valine ethyl ester (1.0 g, 6.9 mmol) in 30 ml of benzene was refluxed for 48 h under azeotropic conditions. The solvent was evaporated off *in vacuo* and the residue was dissolved in 40 ml of ethanol, then sodium borohydride (0.26 g, 6.9 mmol) was added under ice-cooling. The mixture was stirred for 3 h in an ice bath, then the solvent was removed *in vacuo*. After the addition of 10 ml of 2% NaOH, the aqueous solution was extracted with ether and the ethereal extracts were washed with satd. NaCl. Drying (Na_2SO_4) and evaporation gave an oily residue, which was purified by silica gel column chromatography (ether/hexane, 1: 3) to afford **11c** (0.68 g, 38%) as a colorless oil. NMR (in $CDCl_3$): 0.85 (6H, d, J=7 Hz, $(CH_3)_2CH$), 0.95 (3H, d, J=6 Hz, $CHCH_3$), 1.25 (3H, t, J=7 Hz, CH_2CH_3), 1.65 (1H, s, NH), 1.6—2.9 (4H, m, other protons), 3.0 (1H, d, J=7 Hz, CHCOOEt), 4.15 (2H, q, J=7 Hz, CH_2CH_3), 7.18 (5H, m, C_6H_5). IR ν_{max}^{film} cm^{-1}: 1740. GLC analysis (column A, 170°C) of this oil showed two peaks (t_R, 18 min (minor peak) and 21 min (major peak)).

Physical Data of 11——**11a**: NMR (in $CDCl_3$): 0.95 (3H, d, J=6 Hz, $CHCH_3$), 1.1 (3H, t, J=7 Hz, CH_2CH_3), 1.6 (1H, s, NH), 2.2—2.7 (3H, m, $C_6H_5CH_2CHCH_3$), 2.66 (2H, d, J=7 Hz, $C_6H_5CH_2CHCOOEt$), 3.4 (1H, t, J=7 Hz, CHCOOEt), 4.0 (2H, q, J=7 Hz, CH_2CH_3), 7.15 (10H, m, $C_6H_5\times2$). **11d**: NMR (in $CDCl_3$): 0.95 (3H, d, J=6 Hz, $CHCH_3$), 1.2 (6H, m, $CH_2CH_3\times2$), 1.88 (1H, s, NH), 2.35—3.0 (5H, m, other protons), 3.65 (1H, t, J=6 Hz, CHCOOEt), 4.1 (4H, m, $CH_2CH_3\times2$), 7.15 (5H, m, C_6H_5). **11e**: NMR (in $CDCl_3$): 0.98 (3H, d, J=6 Hz, $CHCH_3$), 1.24 (6H, m, $CH_2CH_3\times2$), 1.76 (1H, s, NH), 1.7—2.8 (5H, m, other protons), 3.3 (1H, t, J=6 Hz, CHCOOEt), 4.1 (4H, m, $CH_2CH_3\times2$), 7.2 (5H, m, C_6H_5). **11g**: NMR (in $CDCl_3$): 1.2—1.5 (9H, m, $CH_3CHCOOCH_2CH_3$, $C_6H_5CHCH_3$), 2.0 (1H, s, NH), 3.05 (1H, q, J=7 Hz, CHCOOEt), 3.7 (1H, q, J=6 Hz, C_6H_5CH, 4.15 (2H, q, J=7 Hz, CH_2CH_3), 7.2 (5H, s, C_6H_5). GLC: column A, 200°C, t_R, 12.1 min (major peak) and 14 min (minor peak). **11h**: NMR (in $CDCl_3$): 0.8—1.4 (12H, m, $(CH_3)_2CH$, CH_2CH_3, $CHCH_3$), 1.6—2.2 (2H, NH, $(CH_3)_2CH$), 2.75, 3.05 (1H, two d, J=6 Hz, CHCOOEt), 3.6 (1H, q, J=6 Hz, C_6H_5CH), 4.15 (2H, q, J=7 Hz, CH_2CH_3), 7.15 (5H, s, C_6H_5). GLC: column B, 170°C, t_R, 10.6 min (major peak) and 12.2 min (minor peak). **11i**: NMR (in $CDCl_3$): 1.1—1.4 (9H, m, $CH_2CH_3\times2$, $CHCH_3$), 2.1 (1H, s, NH), 2.6 (2H, d, J=6 Hz, CH_2COOEt), 3.3 (1H, t, J=6 Hz, CHCOOEt), 3.8—4.3 (5H, m, $CH_2CH_3\times2$, C_6H_5CH), 7.2 (5H, s, C_6H_5). GLC: column B, 200°C, t_R, 16.4 min (major peak) and 18.4 min (minor peak). **11j**: NMR (in $CDCl_3$): 0.9 (6H, d, J=7 Hz, $(CH_3)_2CH$), 1.3 (3H, d, J=6 Hz, $CHCH_3$), 1.6—2.2 (2H, NH, $(CH_3)_2CH$), 2.75, 3.05 (1H, two d, CHCOOEt), 3.5 (1H, s, $CHCH_3$), 3.65 (3H, s, $COOCH_3$), 7.2 (5H, s, C_6H_5). GLC: column B, 170°C, t_R, 10 min (major peak) and 11.5 min (minor peak). **11k**: NMR (in $CDCl_3$): 0.9 (6H, d, J=7 Hz, $(CH_3)_2CH$), 1.3 (3H, d, J=6 Hz, $C_6H_5CHCH_3$), 1.45 (9H, s, $(CH_3)_3$), 1.6—2.2 (2H, NH, $(CH_3)_2CH$), 2.6, 2.9 (1H, two d, J=6 Hz, $CHCOO(CH_3)_3$), 3.6 (1H, q, J=6 Hz, $CHCH_3$), 7.2 (5H, s, C_6H_5). GLC: column B, 170°C, t_R, 10.1 min (major peak) and 11.9 min (minor peak). **11l**: NMR (in $CDCl_3$): 0.7—1.0 (9H, m, $(CH_3)_2CH$, $CHCH_3$), 1.4 (9H, s, $(CH_3)_3$), 1.6—2.2 (2H, NH, $(CH_3)_2CH$), 2.0—2.8 (3H, m, CH_2CH), 2.9 (1H, d, J=6 Hz, $CHCOO(CH_3)_3$), 7.2 (5H, s, C_6H_5). GLC: column B, 170°C, t_R, 18 min (minor peak) and 21 min (major peak).

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