

Asymmetric Catalytic Hydrogenations of *N*-Pyruvoyl-(*S*)-proline Esters

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Asymmetric catalytic hydrogenations of the entitled compounds were carried out over palladium on charcoal in various solvents to afford *N*-[(*S*)-lactoyl]-(*S*)-proline esters with a d.e. (=diastereoisomeric excess) of up to 59%. The stereochemistry of the catalytic hydrogenation was explained by the "chelation mechanism." And the effects of temperature and bulkiness of the ester groups on the asymmetric induction were also described.

Many studies on homogeneous asymmetric reactions have been reported^{1,2)} and the stereochemical models of those asymmetric inductions have been proposed. Prelog's model³⁾ and Cram's model⁴⁾ are typical examples. However, there are few general stereochemical models to explain the mechanism of the asymmetric induction in the heterogeneous hydrogenations. A hypothesis which explains the

stereochemistry of the heterogeneous catalytic hydrogenations of α -keto acid derivatives was proposed.⁵⁾ We speculated a five-membered cyclic intermediate with the palladium catalyst as shown in Fig. 1. Many experimental results have supported the hypothesis which was named "chelation mechanism"^{5,6)} as a general model for asymmetric induction in the heterogeneous catalytic hydrogenations of α -keto acid derivatives.

In the previous papers,^{6–8)} the steric courses of asymmetric catalytic hydrogenations of several chiral pyruvamides over palladium on charcoal have been explained by the "chelation mechanism."^{5,6)} Of these asymmetric catalytic hydrogenations, the pyruvamides which contain amino acid esters as chiral sources gave low asymmetric yields [diastereoisomeric excess (d.e.) < 24%].⁸⁾ Those low asymmetric yields seemed to be caused by the free rotation around the N–C bond between the amide nitrogen and chiral carbon (Fig. 1). Thus, there would be several possible "chelation intermediates" which took different conformations, and a mixture of these conformers was catalytically hydrogenated to afford lower d.e.

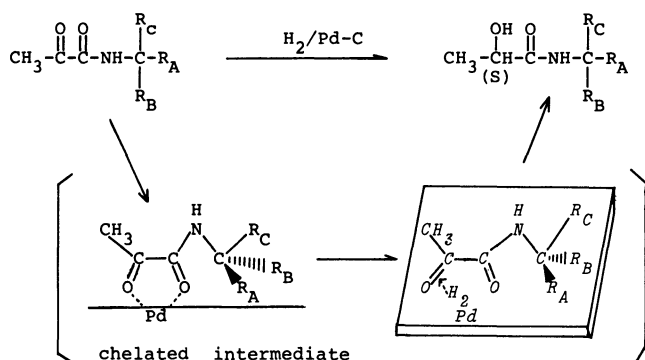
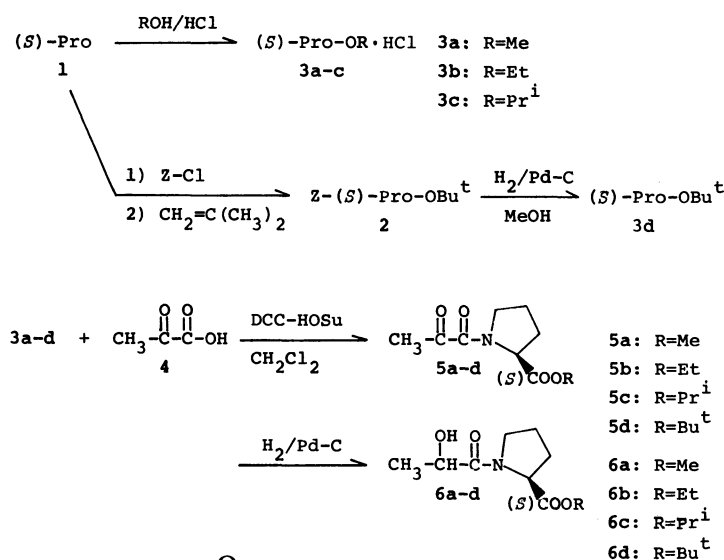


Fig. 1. Chelation mechanism in the catalytic hydrogenations of pyruvamides. R_A is bulkier than R_B .



Scheme 1. Z: $\text{C}_6\text{H}_5\text{CH}_2\text{O}-\text{C}(=\text{O})-$, Bu^t : $(\text{CH}_3)_3\text{C}-$, DCC: dicyclohexylcarbodiimide, HOSu: *N*-hydroxysuccinimide.

In this paper, we wish to report the catalytic hydrogenations of pyruvamides having the N-C bond which does not rotate. We chose *N*-pyruvoyl-(*S*)-proline esters (methyl=Me, ethyl=Et, isopropyl=Prⁱ, *t*-butyl=Bu^t) as the substrates for the asymmetric catalytic hydrogenations. The *N*-pyruvoyl-(*S*)-proline esters^{9,10} were prepared by the manner as shown in Scheme 1. Substrates **5a–d** were hydrogenated in various solvents (methanol=MeOH, ethanol=EtOH, isopropyl alcohol=PrⁱOH, *t*-butyl alcohol=Bu^tOH, ethyl acetate=AcOEt, and tetrahydrofuran=THF) at 30 °C over palladium on charcoal. The hydrogenations in MeOH, EtOH, PrⁱOH were carried out at different temperatures (–30, –10, +10, +30, 50 °C). The diastereomeric mixtures of the hydrogenation products [*N*-lactoyl-(*S*)-proline esters] were separated to each diastereomer by a gas chromatography equipped with a chiral glass capillary column (Chirasil-Val).¹¹ Those diastereomers were identified by comparing the retention times with those of the authentic lactamides which were prepared separately from (*S*)-lactic acid [or (*R,S*)-lactic acid] and corresponding proline esters with dicyclohexylcarbodiimide as described in the literature.¹²

Results and Discussion

Substrates **5a–d** were hydrogenated over 5% palladium on charcoal to give diastereomeric mixtures of lactamides **6a–d** using various solvents at 30 °C as shown in Scheme 1. The results of the catalytic hydrogenations are shown in Table 1. All the catalytic hydrogenations of substrates **5a–d** gave *N*-[(*S*)-lactoyl]-(*S*)-proline esters [(*S,S*)-lactamides] in excess over *N*-[(*R*)-lactoyl]-(*S*)-proline esters [(*R,S*)-lactamides].

Table 1. Solvent Effect on the Catalytic Hydrogenations of Substrates **5a–d** at 30 °C

$\text{CH}_3-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{C}-\text{N} \begin{array}{c} \diagup \\ \text{COOR} \end{array} \xrightarrow{\text{H}_2/\text{Pd-C}} \text{CH}_3-\overset{\text{OH}}{\underset{\text{O}}{\text{C}}}-\text{C}-\text{N} \begin{array}{c} \diagup \\ \text{COOR} \end{array}$					
R	Confign. ^{a)}	Solvent(ε) ^{b)}	Chemical Yield/%	d.e. ^{c)} %	Confign. ^{d)}
Me	<i>S</i>	MeOH(33)	100	56	<i>S</i>
	<i>S</i>	EtOH(25)	99	50	<i>S</i>
	<i>S</i>	Pr ⁱ OH(20)	80	49	<i>S</i>
	<i>S</i>	Bu ^t OH(12)	49	51	<i>S</i>
	<i>S</i>	THF(8)	5	49	<i>S</i>
	<i>S</i>	AcOEt(6)	6	48	<i>S</i>
Et	<i>S</i>	MeOH	100	58	<i>S</i>
	<i>S</i>	EtOH	71	56	<i>S</i>
	<i>S</i>	Pr ⁱ OH	75	50	<i>S</i>
	<i>S</i>	Bu ^t OH	18	51	<i>S</i>
	<i>S</i>	THF	6	55	<i>S</i>
	<i>S</i>	AcOEt	11	52	<i>S</i>
Pr ⁱ	<i>S</i>	MeOH	98	57	<i>S</i>
	<i>S</i>	EtOH	85	51	<i>S</i>
	<i>S</i>	Pr ⁱ OH	92	49	<i>S</i>
	<i>S</i>	Bu ^t OH	89	47	<i>S</i>
	<i>S</i>	THF	75	48	<i>S</i>
	<i>S</i>	AcOEt	76	45	<i>S</i>
Bu ^t	<i>S</i>	MeOH	93	51	<i>S</i>
	<i>S</i>	EtOH	86	48	<i>S</i>
	<i>S</i>	Pr ⁱ OH	68	42	<i>S</i>
	<i>S</i>	Bu ^t OH	89	41	<i>S</i>
	<i>S</i>	THF	15	43	<i>S</i>
	<i>S</i>	AcOEt	16	39	<i>S</i>

a) Configuration of the chiral source. b) Dielectric constant of solvents. c) Diastereoisomeric excess = $[(S,S) - (R,S)] / [(S,S) + (R,S)] \times 100$ (%). d) Configuration of the newly formed chiral moiety.

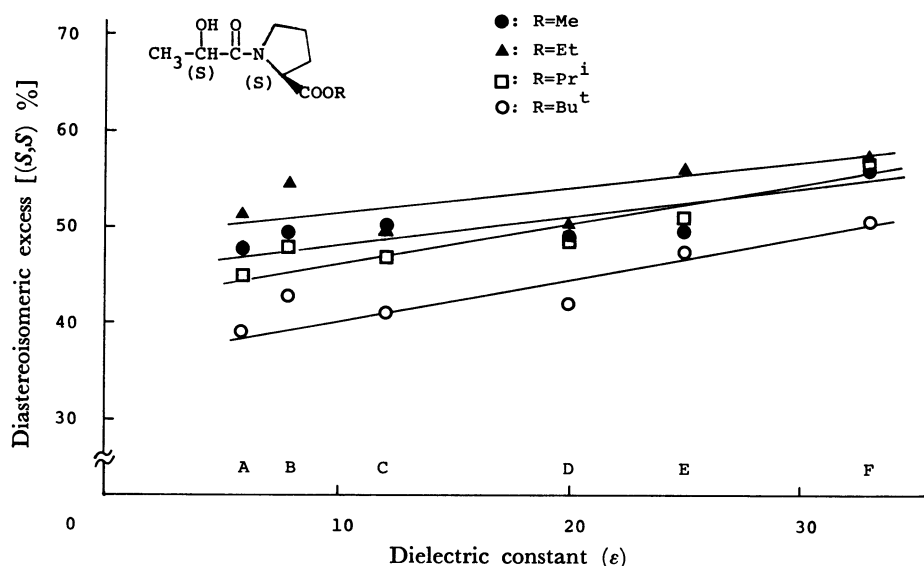


Fig. 2. Solvent effect on d.e. of hydrogenation products.

Solvent: A, AcOEt; B, THF; C, Bu^tOH; D, PrⁱOH; E, EtOH; F, MeOH.

The values of the d.e. of the asymmetric catalytic hydrogenations in Table 1 were plotted against the dielectric constants of the solvents used for the hydrogenations in Fig. 2. In most cases, the d.e. of the hydrogenation products were slightly higher in the solvents with higher dielectric constants than in the solvents with lower dielectric constants. The values of the d.e. were plotted against the bulkiness of R ($\text{Me} < \text{Et} < \text{Pr}^i < \text{Bu}^t$) as shown in Fig. 3. Substrate **5b** gave higher d.e. than **5a**. Substrate **5c** gave slightly lower d.e. than **5b**. Substrate **5d** gave the lowest d.e. In all solvents used, substrates **5a–d** gave (*S,S*)-lactamide in excess over (*R,S*)-lactamide with rather higher d.e. (up to 58%) than *N*-pyruvoyl-(*S*)-amino acid esters used in the previous study.⁸ These results suggested that the fixation of the *N*-C bond gave stable conformers to make the d.e. of the resulting (*S,S*)-lactamide higher.

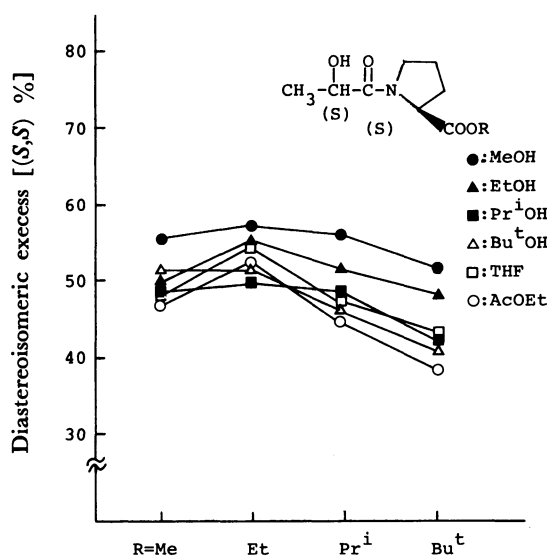


Fig. 3. Effect of bulkiness of substituent group on d.e.

There are two possible steric courses (A and B) through which substrates give (*S,S*)-lactamides in excess in the catalytic hydrogenations (Fig. 4). In the first step (A-1) of the steric course A, the two carbonyl groups take a *s-trans* conformation owing to their electrostatic repulsion, and the amide bond formed by pyruvic acid and proline ester moieties take a *cis*¹³ conformation as shown in Fig. 4. The substrate molecule taking this conformation would be adsorbed on the palladium surface at the less bulky side of the molecule and be hydrogenated from the catalyst side to give (*S,S*)-lactamide. Thus, in the steric course A, the substrate molecule would be hydrogenated through one step adsorption on the palladium surface and then be hydrogenated. However, this steric course A seemed to contribute little to the asymmetric induction, because A-1 would be unstable due to the steric repulsion between $\text{CH}_3\text{C}=\text{O}$ and COOR group binding to the chiral center.

The steric course B which is the "chelation mechanism" could explain the stereochemistry of the catalytic hydrogenations as follows. In the first step (B-1), the substrate molecule would stand on the catalyst surface by the two carbonyl oxygens which take a *s-cis* conformation, and the amide bond would be *trans*¹³ as shown in Fig. 4. This is the "chelated intermediate." In the second step (B-2), the intermediate would then be adsorbed at the less bulky side of the substrate on the catalyst. And the substrate molecule would be hydrogenated from the catalyst side to give (*S,S*)-lactamide in excess. Thus, in the steric course B, the "chelated intermediate" would be formed first between the substrate molecule and the palladium catalyst and then hydrogenated. Thus, the steric course B could explain the experimental results that (*S,S*)-lactamide was obtained in excess over (*R,S*)-lactamide with the fairly high d.e. (39–59%).

However, while the d.e. of the hydrogenation products would increase with the increase of the

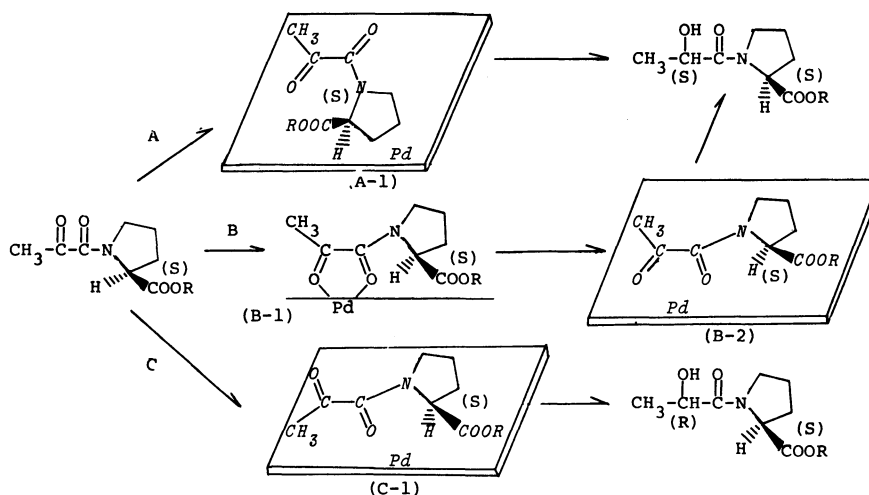


Fig. 4. Possible steric courses in the hydrogenations of substrates **5a–d**.

bulkiness of the ester moiety, acturely the d.e. decreased a little in the hydrogenations of substrates **5c,d** ($R=Pr^i$, Bu^i) as shown in Fig. 3. This could be due to the larger steric repulsion between the ester moiety of substrate **5c** or **5d** and the catalyst surface. Thus, the steric repulsion would inhibit the formation of the "chelated intermediate." And the molecular model of these substrate supported this possibility. Therefore, as the R group becomes larger, the proportion of the substrate molecule which takes other conformation as C-1 on the catalyst increased to give (*R,S*)-lactamide. And the d.e. of (*S,S*)-lactamide in the hydrogenation of substrates **5c,d** might slightly decrease.

The hydrogenations of substrates **5a—d** were performed in MeOH, EtOH, and Pr^iOH at various

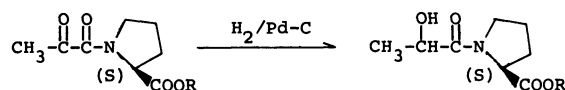
temperatures. The results of these hydrogenations are shown in Table 2. Substrates **5a—c** gave similar d.e. at each temperature in each solvent. Substrate **5d** gave slightly higher d.e. at lower temperatures. The d.e. from **5d** reached to 59% (*S,S*) at $-30^\circ C$.

From the experimental results described above, we could conclude that the asymmetric induction of substrates **5a—d** would be explained by the chelation mechanism. And these experimental results might be useful to speculate the steric course of other heterogeneous asymmetric hydrogenation reactions.

Experimental

The melting points were uncorrected. Optical rotations were measured with a Jasco DIP-181 Digital polarimeter.

Table 2. Temperature Effect on the Catalytic Hydrogenations of Substrates **5a—d**



R	Confign. ^{a)}	Solvent	Temperature °C	Chemical Yield/%	d.e. ^{b)} %	Confign. ^{c)}
Me	<i>S</i>	MeOH	-30	85	45	<i>S</i>
	<i>S</i>	MeOH	$+10$	100	56	<i>S</i>
	<i>S</i>	EtOH	-10	88	51	<i>S</i>
	<i>S</i>	EtOH	$+30$	99	50	<i>S</i>
	<i>S</i>	Pr^iOH	-30	50	49	<i>S</i>
	<i>S</i>	Pr^iOH	$+10$	87	50	<i>S</i>
	<i>S</i>	Pr^iOH	$+30$	80	49	<i>S</i>
Et	<i>S</i>	MeOH	-10	84	51	<i>S</i>
	<i>S</i>	MeOH	$+30$	100	58	<i>S</i>
	<i>S</i>	EtOH	-30	46	42	<i>S</i>
	<i>S</i>	EtOH	$+10$	70	55	<i>S</i>
	<i>S</i>	EtOH	$+50$	70	47	<i>S</i>
	<i>S</i>	Pr^iOH	-10	97	52	<i>S</i>
	<i>S</i>	Pr^iOH	$+30$	75	50	<i>S</i>
Pr^i	<i>S</i>	MeOH	-30	97	34	<i>S</i>
	<i>S</i>	MeOH	$+10$	100	47	<i>S</i>
	<i>S</i>	EtOH	-30	100	42	<i>S</i>
	<i>S</i>	EtOH	$+10$	100	44	<i>S</i>
	<i>S</i>	EtOH	$+50$	99	46	<i>S</i>
	<i>S</i>	Pr^iOH	-30	93	41	<i>S</i>
	<i>S</i>	Pr^iOH	$+30$	92	49	<i>S</i>
	<i>S</i>	Pr^iOH	$+50$	73	34	<i>S</i>
Bu^i	<i>S</i>	MeOH	-30	94	58	<i>S</i>
	<i>S</i>	MeOH	-10	100	53	<i>S</i>
	<i>S</i>	MeOH	$+30$	93	51	<i>S</i>
	<i>S</i>	EtOH	-30	94	59	<i>S</i>
	<i>S</i>	EtOH	$+10$	100	48	<i>S</i>
	<i>S</i>	EtOH	$+50$	60	45	<i>S</i>
	<i>S</i>	Pr^iOH	-30	71	50	<i>S</i>
	<i>S</i>	Pr^iOH	-10	78	45	<i>S</i>
	<i>S</i>	Pr^iOH	$+30$	68	42	<i>S</i>

a) Configuration of the chiral sources. b) Diastereoisomeric excess. c) Configuration of the newly formed chiral moiety.

The gas chromatographic analyses were carried out with a Hitachi 163 gas chromatograph, and the peaks on the chromatograms were integrated with a Shimadzu C-R3A Chromatopac. NMR spectra were measured with a Hitachi R-24 High Resolution NMR spectrometer. IR spectra were measured with a Hitachi 260-50 infrared spectrometer. Palladium on charcoal(5%) was purchased from Nippon Engelhard.

Materials. *N*-Benzyloxycarbonyl-(*S*)-proline *t*-Butyl Ester (**2**):^{14,15} The compound **2** was prepared from *N*-benzyloxycarbonyl-(*S*)-proline (Mp 73.5–74.5 °C [α]_D²⁰ –38.0° (*c* 1.09, MeOH)) and isobutene in dichloromethane in the presence of H₂SO₄. Yield, 93%. Mp 40–41 °C. [α]_D²⁴ –45.3° (*c* 1.00, AcOEt).

(*S*)-Proline Methyl, Ethyl, and Isopropyl Ester Hydrochloride (3a–c): These compounds **3a–c** were prepared by the esterification of **1** with HCl in the corresponding alcohols (MeOH, EtOH, and *Pr*OH).

(*S*)-Proline *t*-Butyl Ester (3d): *N*-Benzyloxycarbonyl-(*S*)-proline *t*-butyl ester **2** (2.08 g, 6.8 mmol) was hydrogenated in ethyl acetate in the presence of 5% palladium on charcoal. After the catalyst was removed off, the filtrate was evaporated in vacuo to give an oily product. This oil was redissolved in ethyl acetate and was used for preparation of **5d**.

***N*-Pyruvoyl-(*S*)-proline Methyl Ester (5a):**⁹ (*S*)-Proline methyl ester hydrochloride (**3a**) (3.03 g, 20 mmol) was liberated with triethylamine (1.76 g, 20 mmol) and was coupled with pyruvic acid (**4**) by using dicyclohexyl-carbodiimide (4.54 g, 22 mmol) in ethyl acetate in the presence of *N*-hydroxysuccinimide (2.76 g, 24 mmol). The reaction was carried out for two hours at 0 °C and for 24 h at room temperature. After usual work-up, an oily crude product was obtained and was purified with silica-gel column chromatography (eluting solvent: benzene–ethyl acetate (12:1)) to give 1.29 g oil (32%). [α]_D¹⁵ –76.5° (*c* 1.25, EtOH). ¹H NMR (CCl₄) δ =1.50–2.50 (4H, br), 2.35 (3H, d), 3.64 (3H, s), 3.50 (2H, t), 4.75 (1H, br). IR: 1630, 1700, 1730 cm^{–1}. Found: C, 54.65; H, 6.83; N, 6.76%. Calcd for C₉H₁₃NO₄: C, 54.26; H, 6.57; N, 6.73%.

***N*-Pyruvoyl-(*S*)-proline Esters 5b–d.**⁹ Substrates **5b–d** were prepared by the similar method to prepare **5a**. The physical data are shown as follows: **5b**. [α]_D¹⁷ –75.5° (*c* 1.22, EtOH). ¹H NMR (CCl₄) δ =1.25 (3H, t), 1.50–2.50 (4H, br), 2.30 (3H, d), 3.60 (2H, br), 4.05 (2H, br), 4.70 (1H, br). IR, 1630, 1710, 1730 cm^{–1}. Found: C, 56.02; H, 7.13; N, 6.47%. Calcd for C₁₀H₁₃NO₄: C, 56.32; H, 7.09; N, 6.56%. **5c**. [α]_D¹⁷ –65.5° (*c* 1.08, EtOH). ¹H NMR (CDCl₃) δ =1.15–1.30 (6H, dd), 1.80–2.25 (4H, br), 2.32–2.38 (3H, d), 3.40–3.90 (2H, br), 4.20–4.50 (1H, br). IR, 1620, 1700, 1710 cm^{–1}. Found: C, 57.88; H, 7.60; N, 6.22%. Calcd for C₁₂H₁₉NO₄: C, 58.13; H, 7.54; N, 6.16%. **5d**. [α]_D¹⁷ –71.4° (*c* 1.07, AcOEt). ¹H NMR (CDCl₃) δ =1.44 (9H, s), 2.07 (4H, br), 2.40 (3H, d), 3.50–3.83 (2H, br), 4.60–4.83 (1H, br). IR, 1640, 1720–1740 cm^{–1}. Found: C, 59.81; H, 8.11; N, 6.08%. Calcd for C₁₃H₂₁NO₄: C, 59.73; H, 7.93; N, 5.80%.

Catalytic Hydrogenations of Substrates 5a–d. Substrates **5a–d** (0.10 mmol) were dissolved in 5 ml solvents (MeOH,

EtOH, *Pr*OH, BuOH, THF, and AcOEt) in the presence of 20 mg of 5% palladium on charcoal and were hydrogenated at 30 °C. After 2–7 d hydrogenations, the catalyst was filtered off and the filtrate was evaporated in vacuo to give an oily product. Chemical yields and d.e. (=diastereoisomeric excess) of the hydrogenation products were determined by using gas liquid chromatography. Catalytic hydrogenations of **5a–d** at some different temperatures (–30, –10, +10, and +50 °C) were also carried out by the same manner.

***N*-Lactoyl-(*S*)-Proline Ester 6a–d.** Authentic *N*-lactoyl-(*S*)-proline esters were prepared from (*S*)-lactic acid[or (*R,S*)-lactic acid] and the corresponding (*S*)-proline esters as described in the literature.¹²

Gas Liquid Chromatographic Analyses. All the diastereomer mixture of the hydrogenation products were not derivatized and directly separated to each diastereomer by using a Hitachi gas chromatograph with a fused glass capillary column (Chirasil-Val¹⁰ 25 m×0.25 mm I.D.) which was purchased from Alltech Associates, Inc. Applied Science Labs. IL 60015 U.S.A. Carrier gas was helium. The column temperature during the analyses was 170 °C (constant). Flame thermionic detector was used for these analyses.

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