Asymmetric Catalytic Hydrogenations of Chiral α-Keto Amides

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Asymmetric catalytic hydrogenations of chiral pyruvamides were carried out using palladium on charcoal (Pd-C) as a catalyst to give lactamides with the diastereoisomeric purities (d.p.) of up to 62%. It was found that there was a linear correlation between the d.p. and the dielectric constant of the solvents used in the hydrogenations of chiral pyruvamides. The results were explained by employing the chelation model and the adsorption of the phenyl group in the substrate molecule on the catalyst. The temperature effect on the d.p. of the product was also examined. The catalytic hydrogenations of chiral benzoylformamides were also performed to give low d.p. presumably, the chelation complexes of the substrates could not take a predominant conformation with the catalyst.

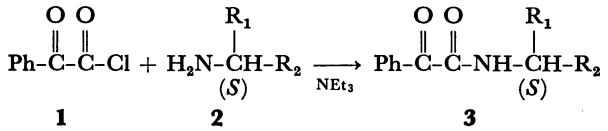
Several studies on the asymmetric catalytic hydrogenations of α-keto acid derivatives have been performed.[1-7] However, a few examples of the asymmetric catalytic hydrogenations of chiral α-keto amides have been reported.[1,7,8] Mitsui and Kanai carried out[1] the hydrogenations of *N*-[(*S*)-α-methylbenzyl]benzoylformamide in ethanol over palladium catalysts. Ojima *et al.* performed[7] the hydrogenations of pyruvamides employing an amino acid ester as the chiral source with palladium on charcoal. In the previous study,[8] we reported the stereochemistry in the catalytic hydrogenations of three pyruvamides whose chiral sources were (*S*)-α-methylbenzylamine, (*S*)-α-ethylbenzylamine, and (*S*)-α-(1-naphthyl)ethylamine. The steric courses in the catalytic hydrogenations could be explained by the formation of a five-membered substrate-catalyst complex-(chelation mechanism[8-17]). It was considered that the complexes were stabilized by the adsorption of the phenyl group in the chiral source, on the catalyst.[8]

In this paper, we wish to describe the stereochemistry on the catalytic hydrogenations of three types of chiral α-keto amides (**3**, **5**, and **10** as shown in Scheme 1—4) over palladium on charcoal using several solvents, in connection with the adsorption of phenyl group on the catalyst. We also would like to correct the analytical data reported in the previous paper,[8] by means of a more accurate analytical method.[17]

In the catalytic hydrogenations of substrates **5** and **10**, it was found that there was a linear correlation between the diastereoisomeric purities(d.p.) of the products and the dielectric constant of the solvents used.

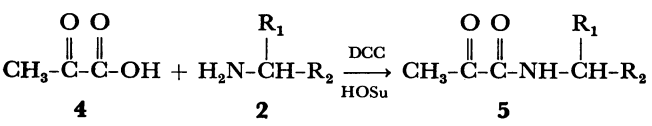
Results and Discussion

Catalytic Hydrogenations of Benzoylformamides **3**. The substrates **3a—c** were prepared as shown in Scheme 1, and were hydrogenated over palladium on charcoal-(Pd-C) at 30 °C in several solvents. The d.p. of the products are listed in Table 1, along with optical purities(o.p.) of mandelic acid obtained through the hydrolyses of the products. The d.p. of the products were determined by the gas chromatographic separation of diastereomeric mandelamides.



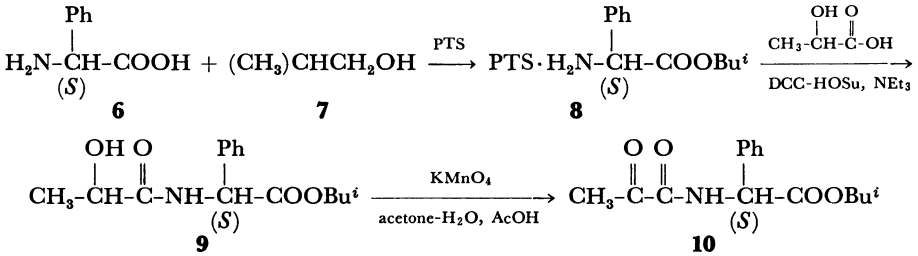
2a: $R_1=CH_3$, $R_2=Ph$ **3a**: $R_1=CH_3$, $R_2=Ph$
2b: $R_1=C_2H_5$, $R_2=Ph$ **3b**: $R_1=C_2H_5$, $R_2=Ph$
2c: $R_1=CH_3$, $R_2=Naph$ **3c**: $R_1=CH_3$, $R_2=Naph$

Scheme 1.



2a : $R_1=CH_3$, $R_2=Ph(S)$ **5a**: $R_1=CH_3$, $R_2=Ph(S)$
2b': $R_1=C_2H_5$, $R_2=Ph(R)$ **5b**: $R_1=C_2H_5$, $R_2=Ph(R)$
2c : $R_1=CH_3$, $R_2=Naph(R)$ **5c** : $R_1=CH_3$, $R_2=Naph(R)$

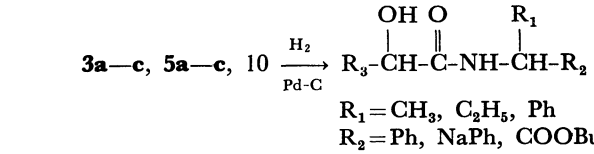
Scheme 2.



PTS: *p*-toluenesulfonic acid. Bu^i: isobutyl.

Scheme 3.

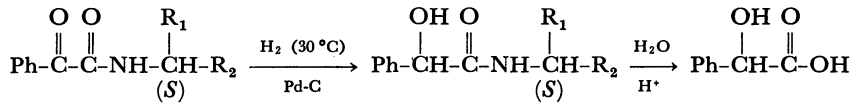
All the hydrogenations of substrate **3a** gave (*R*)-mandelic acid (*S*)-amide [(*R*,*S*)-mandelamide] preferentially. And all the hydrogenations of substrate **3b** gave (*S*)-mandelic acid (*S*)-amide [(*S*,*S*)-mandelamide] preferentially. However, the d.p. of the products were too low (1.3—7.7%) to discuss the steric courses of the catalytic hydrogenations by using these experimental data(Table 1). The reason for the low d.p. could be caused by the adsorption of phenyl group, which attached to the carbonyl carbon, on the catalyst surface, and the adsorbed substrate-catalyst complex could not take a predominant conformation.



Scheme 4.

The catalytic hydrogenations of substrates **3a—b** were carried out in methanol at various temperatures. The temperature effect on d.p. of the products is shown in Table 2. The hydrogenations of substrate **3a** at low temperature mainly gave (*S*,*S*)-mandelamide slightly in excess. The hydrogenation of substrate **3b** at −10 °C

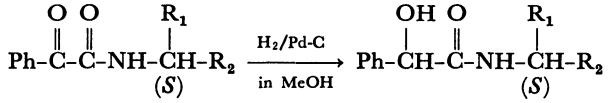
TABLE 1. CATALYTIC HYDROGENATIONS OF SUBSTRATES **3a—c**



R_1	R_2	Confign.[a]	Solvent	Yield/%	$[\alpha]_D^{20}$ [b]	O.p./%[c]	D.p./%[d]	Confign.[e]
CH_3	Ph	*S*	MeOH	59[f] (84)[g]	−3.3	2.2	2.7	*R*
			EtOH	64 (99)	−1.7	1.1	1.3	*R*
			Pr^{i}OH	63 (94)	−1.6	1.1	2.2	*R*
			Bu^{t}OH	60 (100)	−2.2	1.4	2.8	*R*
			C_5H_{11}^{t}OH	67	−2.8	1.8		*R*
			Benzene	61	−1.4	0.9		*R*
C_2H_5	Ph	*S*	MeOH	61 (94)	+4.8	3.2	5.0	*S*
			EtOH	58 (100)	+4.9	3.2	5.4	*S*
			Pr^{i}OH	60 (100)	+4.2	2.8	7.7	*S*
			Bu^{t}OH	66 (98)	+3.7	2.4	7.1	*S*
			C_5H_{11}^{t}OH	59	+5.3	3.5		*S*
			Benzene	63	+8.0	5.3		*S*
			AcOEt	(100)			5.8	*S*
CH_3	Naph	*S*	EtOH	57	−3.9	2.5		*R*
			Benzene	58	0	0		

a) Configuration of the chiral amines. b) c 2.5, H_2O. c) Optical purity of mandelic acid obtained by the hydrolysis. d) Diastereoisomeric purity of mandelamide = $[(R,S)-(S,S)]/[(R,S)+(S,S)]\times 100$ or $[(S,S)-(R,S)]/[(R,S)+(S,S)]\times 100$. e) Configuration of the newly formed chiral center. f) Chemical yield of mandelic acid. g) Chemical yield of mandelamide determined by means of gas chromatography.

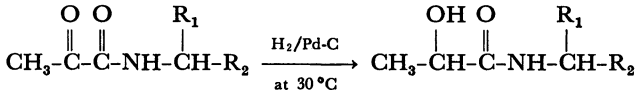
TABLE 2. TEMPERATURE EFFECT ON THE CATALYTIC HYDROGENATIONS OF SUBSTRATES **3a—b**



R_1	R_2	Confign.[a]	Temp[b]/°C	Yield/%	D.p./%[c]	Confign.[d]
CH_3	Ph	*S*	−30	100	≥0	*S*
			−10	100	3.4	*S*
			+10	100	4.5	*S*
			+30	84	2.7	*R*
			+50	82	1.3	*S*
C_2H_5	Ph	*S*	−30	100	7.3	*S*
			−10	100	9.8	*S*
			+10	100	7.0	*S*
			+30	94	5.0	*S*
			+50	82	0.8	*S*

a) Configuration of the chiral amines. b) Temperature of the reaction mixtures during the catalytic hydrogenations. c) Diastereoisomeric purity of mandelamide. d) Configuration of the newly formed chiral center.

TABLE 3. SOLVENT EFFECT ON THE CATALYTIC HYDROGENATIONS OF SUBSTRATES **5a—c**



R_1	R_2	Confign.[a]	Solvent (ε)[b]	Yield/%	D.p./%[c]	Confign.[d]
CH_3	Ph	*S*	MeOH (32.7)	75	59	*S*
		S	EtOH (24.5)	79	55	*S*
		S	Pr^{i}OH (19.9)	72	53	*S*
		S	Bu^{t}OH (12.4)	79	52	*S*
		S	AcOEt (6.0)	72	37	*S*
		S	Benzene (2.0)	56	17	*R*
		S	DMF (36.7)	68	62	*S*
		S	H_2O-MeOH 7 : 3 (46.3)	100	21	*S*
C_2H_5	Ph	*R*	MeOH	76	54	*R*
		R	EtOH	71	46	*R*
		R	Pr^{i}OH	70	35	*R*
		R	Bu^{t}OH	61	29	*R*
		R	AcOEt	69	13	*R*
		R	DMF	71	53	*R*
CH_3	Naph	*R*	MeOH	30	48	*R*
		R	EtOH	18	35	*R*
		R	Pr^{i}OH	24	27	*R*
		R	AcOEt	28	31	*R*

a) Configuration of the chiral amines. b) Dielectric constant of the solvents. c) Diastereoisomeric purity. d) Configuration of the newly formed chiral center.

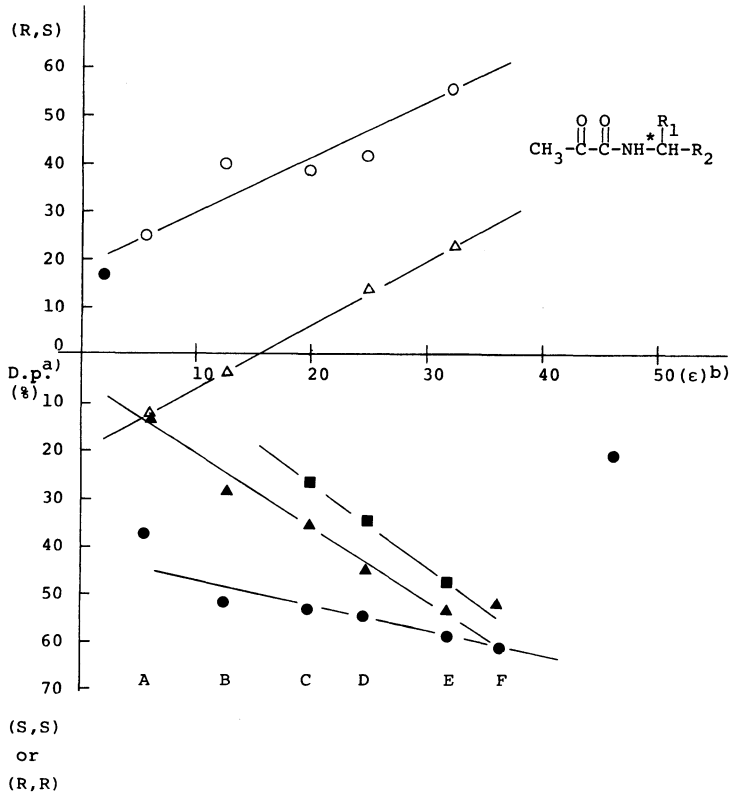


Fig. 1. Solvent effect on the hydrogenations of the substrates **5**, **10**. a) Diastereoisomeric purity of lactamide. b) Dielectric constant. ●: R_1=CH_3, R_2=Ph(S). ▲: R_1=C_2H_5, R_2=Ph(R). :■ R_1=CH_3, R_2=Naph(R). ○: R_1=Ph, R_2=COOBu^t(S). △: R_1=CH_3, R_2=COOBu^t(S). A: Ethyl acetate. B: 2-Methyl-2-propanol. C: 2-Propanol. D: Ethanol. E: Methanol. F: DMF.

gave (*S,S*)-mandelamide in up to 9.8%. However, detailed discussion could not be made on the temperature effect, because the d.p. of mandelamides were so low.

Catalytic Hydrogenations of Substrates ***5a—c.***

This section describes the catalytic hydrogenations of three chiral pyruvamides **5a—c**. (*S*)-α-Methylbenzylamine, (*R*)-α-ethylbenzylamine, (*R*)-1-(1-naphthyl)-ethylamine were used as the chiral sources of pyruvamides.

The substrates were prepared by the coupling of pyruvic acid and the chiral amines with dicyclohexylcarbodiimide (DCC) in the presence of *N*-hydroxysuccinimide (HOSu) as shown in Scheme 2.

The results of the catalytic hydrogenations of substrates **5a—c** at 30 °C in several solvents are listed in Table 3. The d.p. of the products are plotted against the dielectric constants of the solvents used for the hydrogenation as shown in Fig. 1.

Substrate **5a** whose chiral moiety was (*S*)-α-methylbenzyl amine gave *N*-[(*S*)-lactoyl]-(*S*)-amide [(*S,S*)-lactamide] in excess. Substrate **5b** whose chiral moiety was (*R*)-α-ethylbenzylamine and substrate **5c** whose chiral moiety was (*R*)-1-(naphthyl)ethylamine, preferentially gave *N*-[(*R*)-lactoyl]-(*R*)-amide [(*R,R*)-lactamide]. The d.p. of the products in the hydrogenations of substrate **5a** were higher than the results in the hydrogenations of other substrates in all solvents, and the order of the d.p. was as follows: **5a>5b>5c**.

When *N,N*-dimethylformamide (DMF) was used as the solvent, the d.p. of (*S,S*)-lactamide reached to 62%. When benzene was used as the solvent, substrate **5a** gave (*R,S*)-lactamide in excess contrary to the results obtained with alcoholic solvents. Hydrogenation of substrate **5a** in MeOH–H_2O (7:3) gave (*S,S*)-lactamide with 21% d.p.

The linear correlation beween the dielectric constant of the solvents and the d.p. of the products was explained by using the chelation mechanism as shown in Fig. 2. The chelation mechanism involves a two step adsorption of the substrate during the catalytic hydrogenations. In the first step, the substrate molecule forms a five-membered chelated intermediate with the catalyst surface. In the second step, the resulting chelated intermediate is adsorbed on the catalyst from the less bulky side of the substrate and then hydrogenated. The *s-cis* conformation shown in Fig. 2 could be the first stage of the adsorption of the substrate (the chelated intermediate) in the chelation mechanism. The stereochemistry in the catalytic hydrogenation would be determined by the conformation of the first adsorption (the chelated intermediate). The *s-trans* conformation in Fig. 2 shows the mechanism involving one step adsorption on the catalyst. Since the d.p. of the hydrogenation of substrate **5a** was larger than those of **5b** and **5c**, the asymmetric induction would not be caused by the difference of bulkiness between H and alkyl(R_1) groups. Therefore, *s-trans* adsorption state which produces (*S,S*)-lactamide in excess would not affect largely on the asymmetric induction. The steric courses of these reactions could be interpreted by means of three *s-cis* (chelation) adsorption states (conformer A, B, and C)

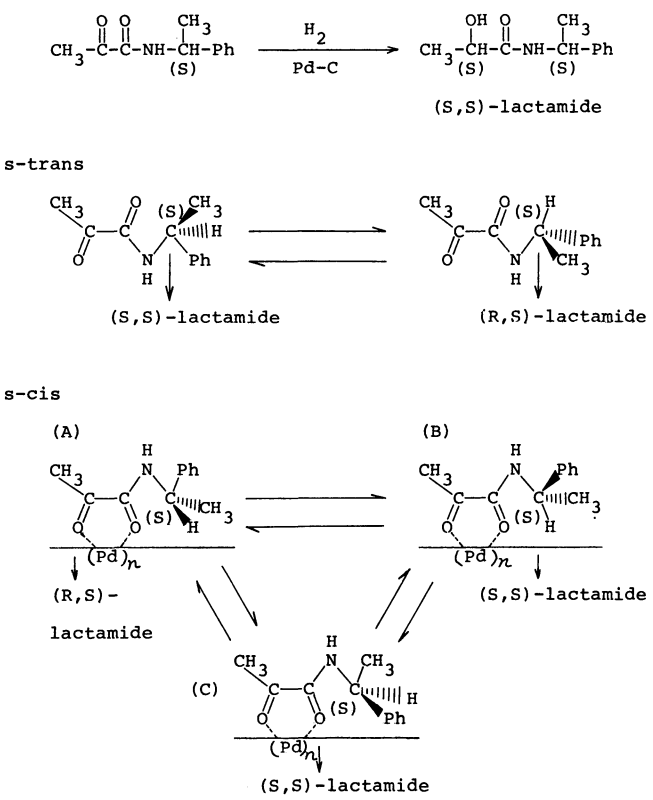


Fig. 2. Possible steric course in the catalytic hydrogenation of substrate **5a**.

in Fig. 2.

Conformer A produces (*R,S*)-lactamide and conformer B and C produces (*S,S*)-lactamide preferentially. Since the hydrogenations of substrate **5a** in the polar solvents gave (*S,S*)-lactamide, the substrate molecule would be hydrogenated mainly through conformer B and C. The decrease of d.p. of (*S,S*)-lactamide with the decrease of dielcectric constant of the solvents could be interpreted by the increase of the proportion of conformer A. In polar solvents, the substrate molecule would tend to take conformer B or C, because of the adsorption of the phenyl group on the catalyst or the phenyl group's escaping from the polar solvent. On the other hand, since the interaction between the phenyl group and the solvent would be stronger in less polar solvents than in polar solvents, the proportion of substrate molecule taking conformation A would increase. Therefore, d.p. of (*S,S*)-lactamide would increase with the increase of the dielectric constant of the solvent used.

The adsorption of the phenyl group on the catalyst could be confirmed by the result obtained by the hydrogenation of substrate **5a** using benzene as a solvent. The hydrogenation of substrate **5a** in benzene gave (*R,S*)-lactamide in excess (17% d.p.) contrary to the results in the hydrogenation in alcoholic solvents [(*S,S*)-lactamide in excess]. Since the phenyl group in the substrate molecule would interact with benzene, the substrate molecule would tend to take conformation A and then be hydrogenated to afford (*R,S*)-lactamide in excess.

The decrease of d.p. in the hydrogenation in

MeOH–H_2O (7:3), which is a very polar solvent system, could not be explained by means of the polarity of the solvent.

It was found that d.p. obtained by the hydrogenations in polar solvents were high (up to 62%) in spite of 1,4-asymmetric induction. These results suggested that the chelated intermediate (conformer B or C) were stable. If the two carbonyl groups were not fixed in *s-cis* conformation by the chelation to the catalyst, these high d.p. of the products would not be obtained.

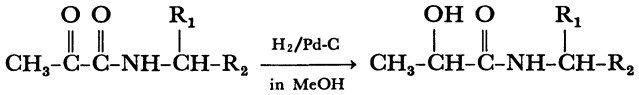
The catalytic hydrogenations of substrates **5a—c** in methanol were carried out at various temperatures. The results of the hydrogenations are listed in Table 4. (*S,S*)-Lactamide was obtained in excess from substrate **5a** at all temperatures. (*R,R*)-Lactamide was obtained in excess from substrate **5b**. However, the temperature effect was rather low on the d.p. of the resulting (*S,S*)-lactamide or (*R,R*)-lactamide.

Catalytic hydrogenations of substrate ***10***. High d.p. in the catalytic hydrogenations of substrates **5a—c** were explained by the chelation of the two carbonyl groups and the adsorption of the phenyl group included in the chiral moiety, on the catalyst. The solvent effect of the catalytic hydrogenations of substrate **10** clarifies the adsorption of the phenyl group, on the catalyst.

Substrate **10** was prepared by oxidation of *N*-lactoyl-(*S*)-phenylglycine ester as shown in Scheme 3. The catalytic hydrogenations were carried out over palladium on charcoal in several solvents. The results of the hydrogenations are listed in Table 5. The hydrogenations of substrate **10** in all solvents gave *N*-[(*R*)-lactoyl]-(*S*)-phenylglycine ester [(*R,S*)-lactamide] in excess. The d.p. of the product [(*R,S*)-lactamide] increased with the increase of the dielectric constant of the solvents. Thus, there was a linear correlation between d.p. and the dielectric constant (Fig. 1).

In the previous paper[15] on the hydrogenations of *N*-pyruvoyl-(*S*)-amino acid esters, we have reported a similar relationship between d.p. and the dielectric

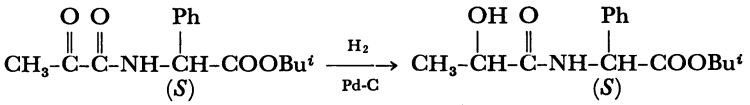
Table 4. Temperature effect on the catalytic hydrogenations of substrates **5a—c**



R_1	R_2	Confign.[a]	Temp/°C[b]	Yield/%	D.p./%[c]	Confign.[d]
CH_3	Ph	*S*	−30	72	61	*S*
		S	−10	79	53	*S*
		S	0	73	58	*S*
		S	+10	72	57	*S*
		S	+30	75	59	*S*
		S	+50	75	58	*S*
C_2H_5	Ph	*R*	−30	72	45	*R*
		R	−10	75	42	*R*
		R	+10	—	42	*R*
		R	+30	76	54	*R*
		R	+50	80	38	*R*
CH_3	Naph	*R*	−30	25	36	*R*
		R	+30	30	48	*R*

a) Configuration of the chiral amines. b) Temperature of the reaction mixtures during the catalytic hydrogenations. c) Diastereoisomeric purity of lactamide. d) Configuration of the newly formed chiral center.

Table 5. Catalytic hydrogenations of substrate **10**



Confign.[a]	Solvent	Temp/°C[b]	Yield/%	D.p./%[c]	Confign.[d]
S	MeOH	+30	100	55	*R*
S	EtOH	+30	100	42	*R*
S	Pr^iOH	+30	83	39	*R*
S	Bu^tOH	+30	100	40	*R*
S	AcOEt	+30	98	25	*R*
S	MeOH	−10	88	42	*R*
S	MeOH	+10	—	49	*R*

a) Configuration of phenylglycine. b) Temperature of the reaction mixtures during the catalytic hydrogenations. c) Diastereoisomeric purity of lactamide. d) Configuration of the newly formed chiral center.

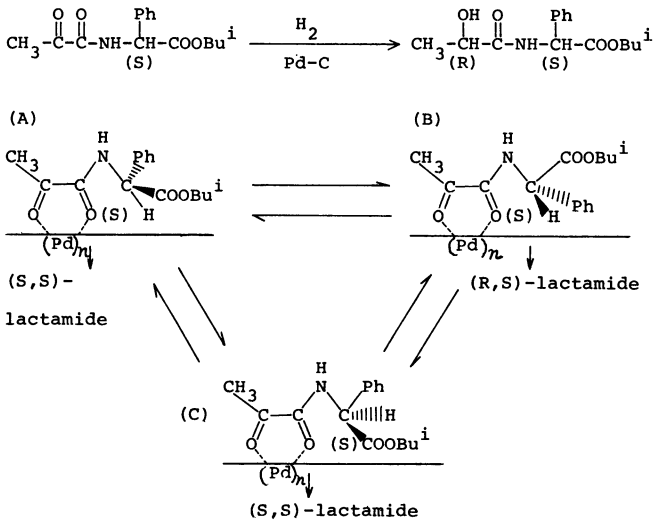


Fig. 3. Possible steric course in the catalytic hydrogenation od substrate **10**.

constant (Fig. 1). The substrates containing (*S*) 2-aminoalkanoic acid isobutyl ester as a chiral source, gave (*R,S*)-lactamide preferentially in polar solvents. And the d.p. of (*R,S*)-lactamide increase with the increase of the dielectric constant of the solvent. However, d.p. in the hydrogenations of substrate **10** were higher (up to 55%) than those in the hydrogenations[15] of other *N*-pyruvoyl-(*S*)-amino acid esters. These results were explained by the adsorption of the phenyl group on the catalyst (Fig. 3). In polar solvents, adsorption of the phenyl group of substrate **10** on the catalyst would be strong as well as substrate **5a**. The affinity between the phenyl group and the catalyst would be weaker with the decrease of the dielectric constant of the solvent. And the affinity between the COOBu^i and the catalyst would be stronger with the decrease of the dielectric constant of the solvents.[15] The proportion of conformer C (Fig. 3) of substrate **10** would increase in less polar solvents.

Therefore, d.p. of (*R,S*)-lactamide obtained from the hydrogenations of substrate **10** were smaller than those of (*S,S*)-lactamide obtained from the hydrogenations of substrate **5a**. (Substrate **5a** does not have an ester group in its chiral moiety.)

In other experiments, the catalytic hydrogenations of substrate **10** in methanol were also carried out at various temperatures. The temperature effect is shown in Table 5. (*R,S*)-Lactamide was preferentially obtained in all temperatures. However, the temperature effect was rather small on the d.p. of the resulting (*R,S*)-lactamide.

Experimental

All the melting points were uncorrected. Optical rotations were measured with a JASCO DIP-181 Digital Polarimeter. All the gas chromatographic analyses were carried out with a Hitachi 163 gas chromatograph, and the peaks on the chromatograms were integrated with a Hitachi 834-30 chromatoprocessor. NMR spectra were measured with a Hitachi R-24 High Resolution NMR spectrometer. IR spectra were measured with a Hitachi 260-50 infrared spectrometer.

Benzoylformyl Chloride[19,20] *1.* A mixture of benzoylformic acid (23.7 g, 158 mmol) and oxalyl chloride (80 g, 630 mmol) was refluxed for 6 h, and the extra oxalyl dichloride was distilled off. The residue was distilled under reduced pressure (68 °C/4 mm Hg (1 mm Hg=133.322 Pa)), and pale yellow liquid was obtained (14.8 g, 56%). IR, 1690 cm^{-1} (C=O), 1780 cm^{-1} (C=O).

Chiral Amines 2a—c. Chiral amine **2a** was purchased from Aldrich Chemical Company, Inc. $[\alpha]_D^{20}$ −39.0° (neat). Chiral amine 2b was obtained by the optical resolution[22] of racemic amine which was prepared by the method reported in the literture.[23] $[\alpha]_D^{20}$ −21.3° (*c* 1.53, benzene). Chiral amine 2c was purchased from Sigma Chemical Company. $[\alpha]_D^{25}$ −59.0° (*c* 1.0, ethanol).

(S)-Phenylglycine 6. $[\alpha]_D^{20}$ +155.6° (*c* 1.0, 1 mol dm^{-3} HCl).

N-[(S)-α-Methylbenzyl]benzoylformamide[1] *3a.* To a cooled dry benzne solution (200 ml) in which benzoylformyl chloride (7.30 g, 43.5 mmol) was dissolved, (*S*)-α-methylbenzylamine (5.27 g, 43.5 mmol) and triethylamine (4.41 g, 43.5 mol) were added dropwise. The reaction mixture was stirred for 2 h at 5—10 °C and 12 h at room temperature. After the reaction, the resulting white precipitate was filtered off and was washed with benzene. The benzene solution was extracted with three 150 ml portions of 1 mol dm^{-3} HCl, saturated $NaCO_3$ aqueous solution and brine respectively. The benzene layer was dried with $MgSO_4$. After drying agent was filtered off, the solution was evaporated *in vacuo*. The oil was purified with silica-gel flash chromatography[24] (eluent; ethyl acetate-hexane (1:9)). The fraction which contained the product were evaporated and the resulting crude white solid was recrystallized from chloroform-hexane. Yield, 7.41 g (67%). Mp, 111—112 °C (lit,[1] 110—111 °C). R_f= 0.28 (silica gel TLC; developing solvent, ethyl acetate-hexane (1:9)). $[\alpha]_D^{25}$ −106° (*c* 1.0, ethanol). NMR (CCl_4): δ=1.5 (3H, *J*=7 Hz), 5.0 (1H, m), 7.25 (9H, m), 8.25 (2H, m). Calcd for $C_{16}H_{15}NO_2$: 75.86; H, 5.96; N, 5.52%. Found: C, 75.86; H, 5.92; N, 5.49%.

N-[(S)-α-Ethylbenzyl]benzoylformamide 3b. To a cooled dry benzene solution (180 ml) in which benzoylformyl chloride (6.17 g, 36.8 mmol) was dissolved, (*S*)-α-ethylbenzylamine (4.98 g, 36.8 mmol) and triethylamine (3.72 g, 36.6 mmol) were added dropwise. The crude product was synthesized and purified by the similar manner in the preparation of 3a. Yield, 5.39 g (55%). Mp, 88.5—89.5 °C. R_f=0.28 (silica gel TLC; developing solvent, ethyl acetate-hexane (1:9)). $[\alpha]_D^{24}$ −107° (*c* 1.0, ethanol). NMR ($CDCl_3$): δ=0.9 (3H, t, *J*=7.5 Hz), 1.9 (2H, q, *J*=7.5 Hz), 4.9 (1H, m), 7.35 (9H, m), 8.3 (2H, m). Calcd for $C_{17}H_{17}NO_2$, C, 76.38; H, 6.41; N, 5.23%. Found: C, 76.31; H, 6.40; N, 5.30%.

N-[(S)-1-(1-Naphthyl)ethyl]benzoylformamide 3c. To a cooled dry benzene solution (30 ml) in which benzoylformyl chloride (1.00 g, 6.00 mmol) was dissolved, (*S*)-1-(1-naphthyl)ethylamine (1.02 g, 6.00 mmol) and triethylamine (0.60 g, 6.00 mmol) were added dropwise. After the reaction, usual treatment was carried out. An oily product was obtained. Yield, 0.92 g (51%). R_f=0.24 (ethyl acetate-hexane (9:1)). $[\alpha]_D^{23.5}$ +0.8° (*c* 1.0, ethanol). $[\alpha]_D^{22.5}$ −46.8° (*c* 1.0, benzene). NMR (CCl_4); δ=1.6 (3H, d, 7 Hz), 5.9 (1H, m), 7.9 (13H, br). Calcd for $C_{20}H_{17}NO_2$: C 79.18; H, 5.64; N, 4.61%. Found: C, 78.04; H, 5.70; N, 4.53%.

Pyruvamides 5a—c. Chiral pyruvamides **5a—c** were prepared by the same manner as shown in the literatures.[8,21]

(S)-Phenylglycine Isobutyl Ester p-*Toluenesulfonate*[10]. (*S*)-Phenylglycine (3.02 g, 20.0 mmol), *p*-toluenesulfonic acid monohydrate (4.19 g, 22.0 mmol), and isobutyl alcohol (20 ml), were mixed in benzene (80 ml). The mixture was

refluxed for 58 h, and the water formed during the esterification was distilled off by the azeotropic method. Crude white product obtained after evaporation of the reaction mixture was recrystallized from ethanol–ether. Yield, 7.95 g (89%). Mp, 180—181 °C. $[\alpha]_D^{25}$ +67.0° (*c* 1.04, ethanol). R_f=0.60 (1-buthanol–acetic acid–water (4:1:2)). Calcd for $C_{19}H_{25}NO_5S$: C, 60.13; H, 6.64; N, 3.69%. Found: C, 60.26; H, 6.68; N, 3.67%.

N-Pyruvoyl-(S)-phenylglycine Isobutyl Ester **10**. To a cooled ethyl acetate solution of **8** (2.26 g, 5.67 mmol), racemic lactic acid (0.50 g, 5.67 mmol), triethylamine (0.57 g, 5.6 mmol), and *N*-hydroxysuccinimide (0.8 g, 6.9 mmol), dicyclohexylcarbodiimide (1.3 g, 6.3 mmol) was added. After the usual treatment of the reaction product, a crude oily product was obtained. The oily product was purified with silica-gel column chromatography (eluent; ethyl acetate–benzene (1:1)). A white solid was obtained by the evaporation of the fraction containing the product. Yield, 1.34 g (85%). This white solid (1.00 g, 3.58 mmol) was dissolved in 30 ml of acetone. To this solution, water (10 ml), acetic acid (1 ml), and $KMnO_4$ (1.0 g) was added under cooling in an ice–water bath. The reaction was carried out for 4 h in an ice–water bath and for 20 h at room temperature. After the reaction was over, MnO_2 was filtered off and the solution was extracted with three 50 ml of portions of benzene. The benzene layer was dried with $MgSO_2$, and then evaporated to afford crude oily product. This was purified with silica-gel column chromatography (benzene–ethyl acetate (19:1)). Yield, 0.28 g (28%). Mp, 63—64 °C. NMR ($CDCl_3$): δ=0.81 (6H, d, J=6 Hz), 1.9 (1H, m), 2.45 (3H, s), 3.92 (2H, d, J=6Hz), 5.49 (1H, d, J=8 Hz), 7.35 (5H, s), 7.85 (1H, br). $[\alpha]_D^{24}$ +114° (*c* 1.1, ethanol). Calcd for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.90; N, 5.05%. Found: C, 64.91; H, 6.91; N, 5.01%.

Hydrogenations of **3a—c** *and Hydrolyses of the Products.* Substrates **3a—c** (500 mg) were dissolved in 10 ml of solvents [methanol (MeOH), ethanol (EtOH), 2-propanol (Pr^iOH), 2-methyl-2-propanol (Bu^tOH), 2-methyl-2-butanol ($C_5H_{11}{}^tOH$), and benzen] and were hydrogenated over 5% palladium on charcoal (purchased from Nippon Engelhald) at 30 °C. After 8—10 h reaction, the catalyst was filtered off, and the reaction mixtures were evaporated *in vacuo* to afford oily products. To these oily products, 20 ml of 6 mol dm^{-3} HCl was added and the mixtures were refluxed for 6 h. After hydrolysis, the reaction mixture was extracted with three 30 ml portions of ether. The ether layer was dried with $MgSO_4$ and the ether layer was evaporated to white solids. Chemical yields were determined by the measurement of the weight of the white solids and the optical purities of mandelic acid were determined by the measurement of the optical rotation.

Hydrogenations of **3a—c** *and Derivatization of the Products for GC Separation.* Substrates **3a—c** (25 mg, 0.10 mmol) were dissolved in 3 ml of solvents [MeOH, EtOH, Pr^iOH, Bu^i, ethyl acetate (AcOEt)] and were hydrogenated over 5% palladium on charcoal at 30 °C. After 8—10 h reaction, the catalyst was filtered off, and the reaction mixtures were evaporated to dryness. The chemical yields of the products were determined by the GC analyses of the residues. A portion of the residue was derivatized to *O*-TFA lactamide by the manner as described in the literature.[18] D. p. was determined by the GC separation of the *O*-TFA derivatives of diastereomeric mandelamides with a chiral stationary phase (Chirasil-Val).[18,25]

Catalyic Hydrogenations of Substrates **5a—c**[9] *and* **10**. Substrates **5a—c** (20 mg, 0.1 mmol) were dissolved in 3 ml of solvents [MeOH, EtOH, Pr^iOH, Bu^tOH, AcOEt, benzene, and *N,N*-dimethylformamide (DMF)], and were hydrogenated at 30 °C over 5% palladium on charcoal (100 mg) for 12—48 h. After the catalyst was filtered off, the reaction mixtures were evaporated to dryness. Both chemical yields[21] and d.p.[18] of the resulting lactamides were determined by the similar manner in the hydrogenations of substrates **3a—c**.

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