Asymmetric Hydrogenations of *N*-Pyruvoyl-(*S*)-amino Acid Esters

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N-[(*R*)-Lactoyl]-(*S*)-amino acid isobutyl esters were obtained with a diastereoisomeric purity up to 34%, through the catalytic hydrogenations of *N*-pyruvoyl-(*S*)-amino acid (alanine, valine, and leucine) isobutyl esters over palladium on charcoal. It was found that a linear correlation exists between the dielectric constant of the solvent and the diastereoisomeric purity of the product obtained by catalytic hydrogenation. The ratio of *N*-[(*S*)-lactoyl]-(*S*)-amino acid isobutyl ester to *N*-[(*R*)-lactoyl]-(*S*)-amino acid isobutyl ester increased with the decrease of the dielectric constant of the solvent. This solvent effect could be explained by the chelation mechanism. The temperature effect on the asymmetric catalytic hydrogenation was also studied.

Although many studies on the asymmetric hydrogenations of α-keto acid derivatives have been reported, only a few reports appeared on those of α-keto acid amide.[1-3] An asymmetric catalytic hydrogenation of *N*-[(*S*)-α-methylbenzyl]benzoylformamide was carried out over palladium on charcoal(Pd–C) by Mitsui and Kanai, and the hydrolysis of the product gave (*R*)-mandelic acid (o.p.=5—25%).[1] Recently, Ojima *et al.* performed hydrogenation of pyruvamide employing an amino acid as the chiral source with Pd–C or rodium phosphine complexes.[2] Through the hydrogenation using Pd–C, *N*-[(*S*)-lactoyl]-(*S*)-amino acid ester was obtained with a diastereomeric purity of 15%. We have previously reported[3] the catalytic hydrogenation of pyruvamides, in which the chiral sources were (*S*)-α-methylbenzylamine, (*S*)-α-ethylbenzylamine, and (*S*)-1-(1-naphthyl)ethylamine, using Pd–C (Fig. 1). The steric course of the hydrogenation was explained[3] in terms of the assumption (which is called the chelation mechanism[4-10]) of the five-membered chelated intermediate shown in Fig. 1. According to the mechanism, the substrate forms a chelated intermediate first, which is then hydrogenated from the less bulky side of the molecule. From the large asymmetric yield (>53%) and the absolute configuration of the formed lactoyl moiety, it was suggested that the aromatic group in the chiral source of the substrate would be adsorbed on the catalyst surface.[3]

In this paper, the solvent and the temperature effects in asymmetric catalytic hydrogenations are studied using *N*-pyruvoyl-(*S*)-amino acid(alanine, valine, and leucine) esters as substrates which contain no aromatic groups.

The substrates **3a**—**c** were prepared by condensation of pyruvic acid with amino acid isobutyl esters **2a**—**c** by dicyclohexylcarbodiimide in the presence of *N*-hydroxysuccinimide (DCC–HOSu method) (Fig. 2). The hydrogenations of the substrates **3a**—**c** were carried out over Pd–C under atmospheric pressure in the following solvents: methanol, ethanol, 2-propanol, 2-methyl-2-propanol, and ethyl acetate. The diastereoisomeric purity and the yield of product was determined by gas chromatographic analysis.

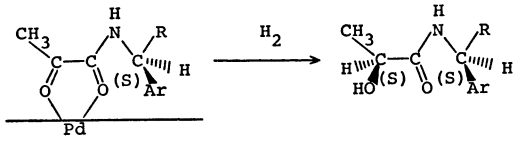

Fig. 1. Chelation mechanism of hydrogenation of chiral pyruvamide.

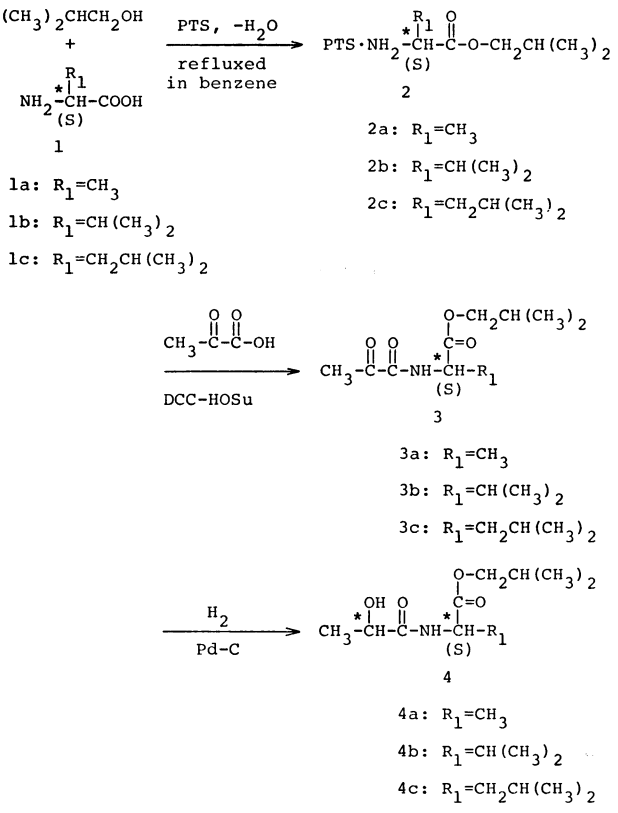

Fig. 2. Asymmetric catalytic hydrogenation of *N*-pyruvoyl-(*S*)-amino acid isobutyl ester. PTS: *p*-Toluenesulfonic acid. **4a**—**c**: Diastereomer mixture.

Experimental

All the gas chromatographic analyses were carried out with a Hitachi 163 chromatograph, and the peaks on the chromatogram were integrated with a Hitachi 834-30 chromatogrocessor. Optical rotations were measured with a JASCO DIP-181 Digital Polarimeter. All the melting points were uncorrected. 5% Palladim on charcoal was purchased from Nippon Engelhald.

(S)-Amino Acid Isobutyl Ester p-*Toluenesulfonate* ***2a—c.*** The amino acid esters **2a**—**c** were prepared by usual azeotropic method.[4,6] **2a**: Yield, 76%; mp, 118—120 °C (lit,[6] 120—121 °C); $[\alpha]_D^{21}$ −0.79 (*c* 1.0, ethanol) (lit,[6] $[\alpha]_D$

Table 1. Elementary analyses of the substrates

Substrate	Yield %	Optical rotation (ethanol)		Elementary analysis C(%)	H(%)	N(%)
3a	18 (oil)	$[\alpha]_D^{26}$ −36° (*c* 1.2)	Found	55.61	7.95	6.68
			Calcd ($C_{10}H_{17}NO_4$)	55.80	7.96	6.50
3b	15 (oil)	$[\alpha]_D^{26}$ −16° (*c* 1.3)	Found	58.78	8.64	5.88
			Calcd ($C_{12}H_{21}NO_4$)	59.23	8.70	5.75
3c	15 (oil)	$[\alpha]_D^{26}$ −35° (*c* 1.6)	Found	60.64	9.00	5.78
			Calcd ($C_{13}H_{23}NO_4$)	60.67	9.00	5.44

Table 2. Retention times of lactamides

Lactamide	Retention time/min $S^{a)}$-*S*	$R^{a)}$-*S*	Separation factor
4a	37.5	38.3	1.021
4b	43.7	45.2	1.034
4c	46.7	47.5	1.017

Conditions of gas chromatography: stainless steel column (4 m×3 mm I.D.) with 80/100 mesh Chromosorb W AW DMCS coated with 5% SE-52; carrier gas, nitrogen at a flow rate of 39 ml/min; temperature, from 100 °C to 250 °C (2 °C/min); the temperature of the injection port, 300 °C. a) Configuration of the lactoyl moiety.

−1.1, ethanol). **2b**: Yield, 84%; mp, 144—145 °C; $[\alpha]_D^{21}$ +9.8 (*c* 1.0, ethanol). **2c**: Yield, 88%; mp, 137—138 (lit,[6] 137—138 °C); $[\alpha]_D^{21}$ +9.7 (*c* 1.0, ethanol) (lit,[6] $[\alpha]_D$ +10.3, ethanol).

N-Pyruvoyl-(S)-amino Acid Isobutyl Ester ***3a—c.*** The amino acid esters **2a—c** were liberated by triethylamine, and coupled with pyruvic acid by means of DCC-HOSu method[3,11]. The oily products obtained were purified by usual flash chromatography[12] (eluting solvents: ethyl acetate-hexane (1:10)). Yields, optical rotations, and elementary analyses of the substrates are listed in Table 1.

Hydrogenations of substrates ***3a—c.*** Substrates **3a—c** (20 mg, 0.1 mmol) were dissolved in 3 ml of the solvent (methanol, ethanol, 2-propanol, 2-methyl-2-panol, and ethyl acetate), and was hydrogenated at 30 °C over 5% palladium on charcoal (100 mg) for 40—72 h. The substrates were almost quantitatively converted to the corresponding diastereomeric lactamides. In separate experiments, hydrogenations of substrates **3a—c** were carried out in methanol at 10, −10, and −30 °C. Both the chemical yield and ratio of the two diastereomers of the resulting *N*-lactoyl-(*S*)-amino acid isobutyl esters were determined by use of gas-liquid chromatography.

Gas Chromatographic Analysis. After filtration of the catalyst from the reaction mixture, the solvent was removed *in vacuo*, and the residue was redissolved in chloroform. The solution was injected into the gas chromatograph ten seconds after injection of 3 μl of a pyridine solution of *N*-trimethylsilylimidazole (TMS-Im) (TMS-Im/pyridine= 2).[11,13] The analytical conditions and the retention times of the diastereomers of the products are summerized in Table 2. The peaks due to the diastereomers were identified by comparing their retention times with those of authentic samples,[13] which were prepared by coupling of the amino acid ester and (*S*)-lactic acid with DCC.

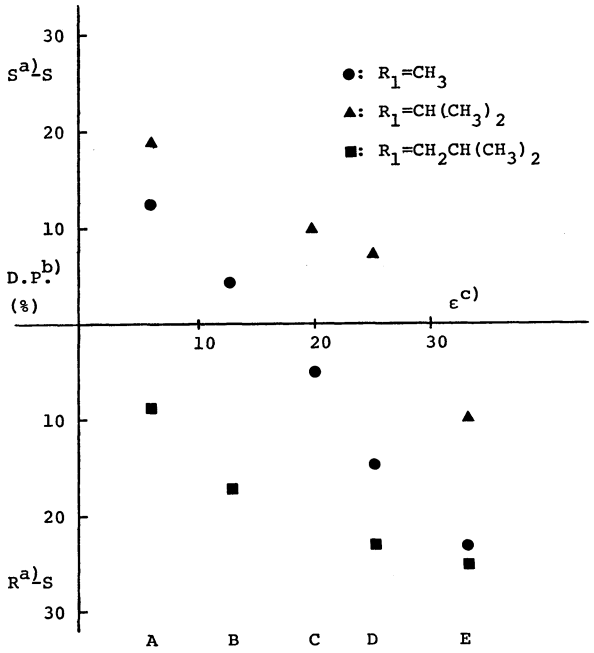

Fig. 3. Solvent effect in the hydrogenation of the substrates. a) Configuration of the newly formed chiral moiety. b) Diastereoisomeric purity. c) Dielectric constant. A: Ethyl acetate. B: 2-Methyl-2-propanol. C: 2-Propanol. D: Ethanol. E: Methanol.

Results and Discussion

Solvent Effect. The results of the catalytic hydrogenations using several solvents summerized in Fig. 3. The diastereoisomeric purities of the lactamides obtained through the hydrogenation of the substrates are plotted against the dielectric constants of the solvents used. When methanol was used as the solvents, all the substrates **3a—c** gave *N*-[(*R*)-lactaoyl]-(*S*)-amino acid esters ((*R*,*S*)-lactamide) in excess. The ratio of *N*-[(*S*)-lactoyl]-(*S*)-amino acid esters((*S*,*S*)-lactamide) to (*R*,*S*)-lactamide increased gradually with the decrease of the dielectric constant of the solvent. However, when the solvents having smaller dielectric constant were used, (*S*,*S*)-lactamide was the major product

TABLE 3. TEMPERATURE EFFECT IN THE HYDROGENATION OF THE SUBSTRATES

R_1	Confign.[a]	Solvent	Temperature °C	Yield %	D.p[b] %	Confign.[c]
CH_3	*S*	Methanol	10		34	*R*
			−10	69	26	*R*
			−30	69	30	*R*
$CH(CH_3)_2$	*S*	Methanol	10		18	*R*
			−10	50	19	*R*
			−30	22	21	*R*
$CH_2CH(CH_3)_2$	*S*	Methanol	10		29	*R*
			−10	53	27	*R*
			−30	39	26	*R*

a) Configuration of amino acid. b) Diastereoisomeric purity. c) Configuration of the newly formed chiral moiety.

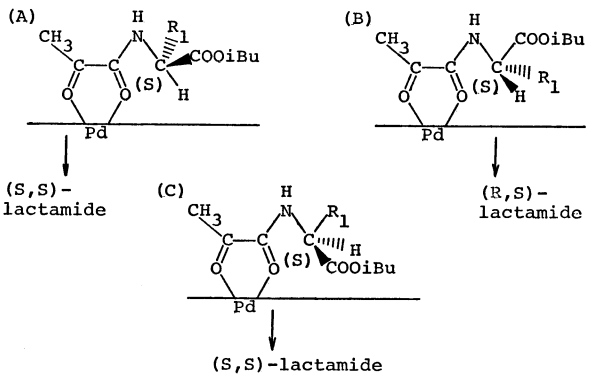

Fig. 4. Steric course of hydrogenation of *N*-pyruvoyl-(*S*)-amino acid isobutyl ester.

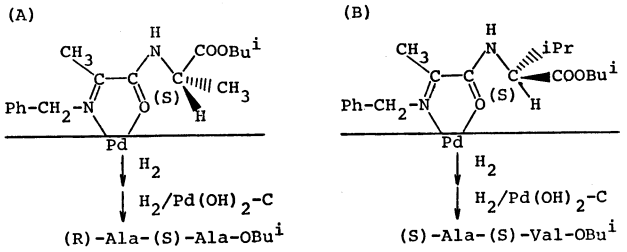

Fig. 5. Hydrogenation of Schiff base of *N*-pyruvoyl-(*S*)-amino acid isobutyl ester[4,6].

in the hydrogenations of substrates **3a**—**b**. In the hydrogenation of **3c**, (*R,S*)-lactamide was formed in excess in all solvents.

The linear correlation (Fig. 3) between the dielectric constant of the solvent and the diastereoisomeric purity could be explained by the interaction of the two carbonyl groups in the substrates with the catalyst. It may be considered that substrates **3a**—**c** were hydrogenated after forming a five-membered chelated intermediate[3-10] as shown in Fig. 4.

In order to discuss the steric course of the hydrogenations of substrates **3a**—**c** in detail, the conformation of the asymmetric moiety in the substrates must also be taken into account. It was found previously that the bulkiness of the substituted group of the asymmetric source has a large effect on the asymmetric yield in the hydrogenations of Schiff bases of α-keto acid amides[4,6] (Fig. 5). The change of the conformation of the newly formed asymmetric center mainly depends on the size of the R_1 group (Fig. 5A and B).

The conformation of the asymmetric source in substrates **3a**—**c** could affect the diastereoisomeric purities of the products, as in the Schiff bases[4,6] in Fig. 5. Although the steric course in the hydrogenation of the Schiff bases has been explained[4,6] by considering the two conformer (A and B) shown in Fig. 5, in fact the chelated intermediate does not necessarily have to be a single conformer. This assumption was applied to the hydrogenations of substrates **3a**—**c**, and it could be possible to consider that the chelated intermediate in the hydrogenation of the substrate was a mixture of three conformer A, B, and C in Fig. 4.

Since the interaction between the COOBu^i group in the molecule and the catalyst is weak in a polar solvent, the substrate is hydrogenated after formation of conformer A and B. However, in a less polar solvent, the interaction between the COOBu^i group with the catalyst is stronger than that in a polar solvent and the substrate is hydrogenated after formation of conformer C. Conformer B was hydrogenated to form (*R,S*)-lactamide in excess, and conformer A and C gave (*S,S*)-lactamide in excess. Thus, with the decrease of the dielectric constant of the solvent, the ratio of (*S,S*)-lactamide over (*R,S*)-lactamide would increase. The observed diastereoisomeric purity of the product could be interpreted by the combined asymmetric induction of the hydrogenation of conformer A—C.

Temperature Effect. The catalytic hydrogenations of substrates **3a**—**c** in methanol were also carried out at various temperatures. The temperature effect is shown in Table 3. (*R,S*)-Lactamide was obtained with a diastereoisomeric purity of up to 34% at 10 °C. However, the temperature effect was rather small on the diastereoisomeric purities of the resulting (*R,S*)-lactamide.

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