Diastereoselective Catalytic Hydrogenation of N^{α}-Pyruvoyl-(*S*)-prolinamide

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Synopsis. Catalytic hydrogenation of N^{α}-pyruvoyl-(*S*)-prolinamide over palladium on charcoal in several solvents resulted in the formation of N^{α}-[(*S*)-lactoyl]-(*S*)-prolinamide in good d.e. up to 77%. Usefulness of *N*-isopropyl-(*S*)-prolinamide as an asymmetric moiety is described in the catalytic hydrogenation.

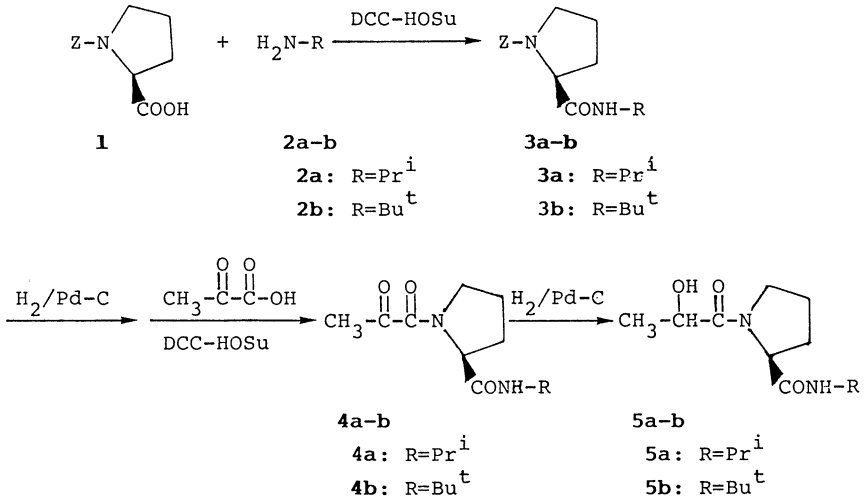
Asymmetric induction in heterogeneous catalytic hydrogenation is a classical but still interesting field[1] because of its simplicity and clean procedure for the preparation of various kinds of asymmetric compounds. However, the mechanism of the asymmetric induction using heterogeneous catalyst has not been well clarified[1] except for the hydrogenation of α-keto acid derivatives.[2,3] In the previous papers,[2-5] the steric courses of the heterogeneous catalytic hydrogenations of chiral derivatives of α-keto acid have been explained by the 'chelation mechanism'[2,3] which is based on a possible five-membered cyclic intermediate[2,3] between hetero atoms of the substrate and the catalytic surface. Of these α-keto acid derivatives, *N*-pyruvoyl-(*S*)-amino acid (Ala, Val, and Leu) esters gave *N*-[(*S*)-lactoyl]-(*S*)-amino acid esters in low d.e. (<24%)[4] through the catalytic hydrogenation. On the other hand, the *N*-pyruvoyl-(*S*)-proline esters, in which the N-C bond between the chiral carbon and the nitrogen does not rotate, gave higher d.e. (<59%),[5] and the steric course was explained by the 'chelation mechanism'.[2,3]

In the present study, (*S*)-prolinamides which are considered to be more rigid in structure than the corresponding esters were used as the chiral source in order to improve d.e. in the diastereoselective catalytic hydrogenation. *N*-isopropyl-N^{α}-pyruvoyl-(*S*)-prolinamide (**4a**) and *N*-*t*-butyl-N^{α}-pyruvoyl-(*S*)-prolinamide (**4b**) were prepared by condensation of pyruvic acid with the corresponding (*S*)-prolinamide as shown in Scheme 1. Substrates **4a—b** were hydrogenated in several solvents over palladium on charcoal to give diastereomeric mixtures **5a—b**.

Results and Discussion

The results of the catalytic hydrogenation are summarized in Table 1. The d.e. (54—76%) in the catalytic hydrogenation of **4a** at 30 °C were higher than those (34—47%) of **4b** in all solvents used. The d.e. values in the catalytic hydrogenation of **4a—b** were higher in polar solvents than those in less polar solvents. And the hydrogenation of substrate **4a** in methanol at −10 °C gave the highest d.e. (77%). The d.e. (34—47%) of the products derived from **4b** were similar to those (39—51%)[2] of *N*-pyruvoyl-(*S*)-proline *t*-butyl ester and a little lower than those (45—57%)[2] of *N*-pyruvoyl-(*S*)-proline isopropyl ester. On the other hand, the d.e. (54—76%) of the hydrogenated products of substrate **4a** were about 20% higher than those (45—57%) of *N*-pyruvoyl-(*S*)-proline isopropyl ester. These results indicate that (*S*)-proline isopropyl amide is a more effective chiral moiety than the other (*S*)-proline derivatives.

Effects of *N*-isopropyl-(*S*)-prolinamide moiety on the asymmetric induction could be summarized as follows. Substrate **4a** is expected to be adsorbed on



Scheme 1. Preparation and hydrogenation of N^{α}-Pyruvoyl-(*S*)-prolinamides (**4a—b**).

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Table 1. Diastereoselective Catalytic Hydrogenation of N^{α}-pyruvoyl-(*S*)-prolinamides(**4a-b**)

Substrate	Solvent	Temp °C	R.t.[a] h	Yield %	d.e.[b] %	Confign.[c]
4a	MeOH	30	64	100	76	S
	EtOH	30	64	83	64	S
	i-PrOH	30	64	75	54	S
	t-BuOH	30	64	79	54	S
	THF	30	70	76	66	S
	AcOEt	30	70	76	55	S
	i-PrOH	0	72	100	45	S
	MeOH	−10	105	100	77	S
	EtOH	−10	105	100	63	S
	MeOH	−30	168	100	65	S
	EtOH	−30	168	100	69	S
4b	MeOH	30	117	100	47	S
	EtOH	30	117	90	46	S
	i-PrOH	30	117	81	34	S
	t-BuOH	30	117	70	38	S
	THF	30	120	38	42	S
	AcOEt	30	120	64	38	S
	MeOH	10	87	100	48	S
	EtOH	10	87	100	40	S
	EtOH	−10	172	74	42	S
	MeOH	−30	138	100	50	S

a) Reaction time for catalytic hydrogenation. b) Diastereomeric excess. c) Configuration of the newly formed asymmetric moiety.

the catalyst surface to form the 'chelated intermediate'[5] as shown in Fig. 1. And the chelated intermediate could be adsorbed on the catalyst at the less bulky side to be hydrogenated. However, substrate **4b** is not easy to form the chelated intermidiate, due to the steric hindrance of the bulky *t*-butyl carbamoyl group. The molecular models of these compounds supported this possibility. Thus it is assumed that the higher asymmetric induction is not always caused by the bulkiness of the carbamoyl group. Substrate **4a** having less bulky carbamoyl group than **4b** gave higher d.e. (ca. 30%) than **4b** did. And also substrate **4a** gave higher d.e. compared with *N*-pyruvoyl-(*S*)-proline isopropyl ester. These results show that the carbamoyl moiety(-CONH-Pr^{i}) **4a** is more effective in yielding asymmetric induction than the ester moiety-(-COO-Pr^{i}). However, the bulkiness of the amide moiety seems to be similar to that of the ester moiety. The effectiveness of the amide moiety could be referred to the rigidity and or the adsorption[7] of amide.

The *N*-isopropyl-(*S*)-prolinamide moiety in the catalytic hydrogenation was found to be an useful chiral source and the asymmetric moiety could be applied in other diastereoselective catalytic hydrogenation.

Experimental

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

***N*$^{\alpha}$-Benzyloxycarbonyl-(*S*)-prolinamides (3a—b).** *N*$^{\alpha}$-Benzyl-oxycarbonyl-(*S*)-prolinamides were prepared by the coupling between *N*-benzyloxycarbonyl-(*S*)-proline (**1**) (mp 73.5—74.5 °C) and corresponding amines[isopropylamine (**2a**), *t*-butylamine (**2b**)] in the presence of dicyclohexylcarbodiimide (DCC) and *N*-hydroxysuccinimide (HOSu). **3a**: Yield, 85%, mp 123—5 °C, $[\alpha]_D^{24}$ −49.3 (*c* 1.0, ethyl acetate). **3b**: Yield, 90%, mp 84—85 °C, $[\alpha]_D^{24}$ −43.5 (*c* 1.0, ethyl acetate).

***N*-isopropyl-*N*$^{\alpha}$-pyruvoyl-(*S*)-proliamide (4a).** *N*-Isopropyl-*N*$^{\alpha}$-benzyloxycarbonyl-(*S*)-prolinamide (**3a**) (2.62 g, 9.0 mmol) was hydrogenolyzed in methanol in the presence of 5% palladium on charcoal and the filtered reaction mixture was evaporated to give an oily product. The oily product was redissolved in dichloromethane and was coupled with pyruvic acid (0.79 g, 9.0 mmol) in the presence of DCC and HOSu at 0 °C for 2 h and at room temperature for 24 h. After usual work-up, the resulted crude oily product was purified with silica-gel column chromatog-

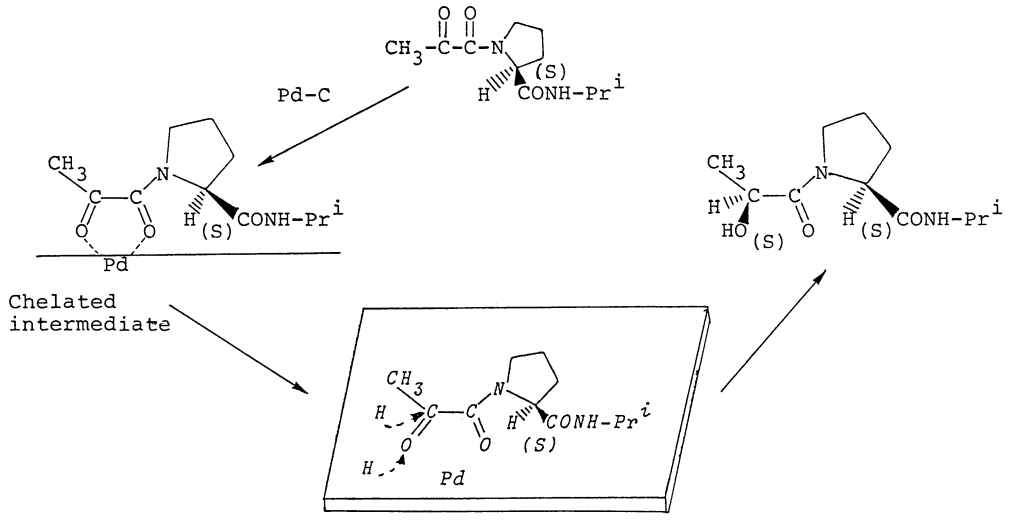

Fig. 1. Chelation mechanism in the catalytic hydrogenation of N^{α}-pyruvoyl-(*S*)-prolinamide.

raphy (eluant: chloroform-methanol (40-1)). Yield, 2.0 g (38%), mp 58—60 °C. $[\alpha]_D^{17}$ −85.6 (*c* 1.1, ethyl acetate). NMR ($CDCl_3$) δ=1.06—1.30 (6H, d), 180—2.30 (4H, br), 2.40—2.50 (3H, d), 3.60—4.13 (3H, br), 4.50—4.70 (1H, br), 6.70 (1H, br). IR (KBr): 3250, 3040, 1700, 1680—1600 cm^{-1}. Anal., Calcd for $C_{11}H_{18}N_2O_3$: C, 58.38; H, 8.01; N, 12.38%. Found: C, 58.15; H, 8.02; N, 12.33%.

***N*-*t*-Butyl-N^{α}-pyruvoyl-(*S*)-prolinamide (4b).** *N*-*t*-Butyl-N^{α}-pyruvoyl-(*S*)-prolinamide was prepared from *N*-*t*-butyl-N^{α}-benzyloxycarbonyl-(*S*)-prolinamide (2.07 g, 6.8 mmol) by the similar method to **4a**. Yield, 0.58 g (43%), mp 102—103 °C. $[\alpha]_D^{24}$ −43.5 (*c* 1.0, ethyl acetate). NMR (DCl_3) δ=1.33 (9H, s), 1.96—2.00 (3H, d), 2.71—2.78 (2H, q), 3.18—3.25 (1H, br), 152—1.82 (4H, br). IR (KBr): 3300, 3040, 1720, 1680, 1620 cm^{-1}. Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.97; H, 8.38; N, 5.80%. Found: C, 59.81; H, 8.11; N, 6.08%.

N^{α}-[(*S*)-Lactoyl]-(*S*)-prolinamides (5a—b). N^{α}-[(*S*)-Lactoyl]-(*S*)-prolinamide were prepared by the coupling between (*S*)-lactic acid and the corresponding (*S*)-prolinamide in the presence of DCC and HOSu. **5a**. Yield, 61% (oil). $[\alpha]_D^{15}$ −117.1 (*c* 0.95, ethyl acetate). NMR ($CDCl_3$) δ=1.06—1.30 (6H, m), 1.40 (2H, s), 1.82—2.46 (4H, br), 3.42—3.76 (3H, br), 3.86—4.73 (4H, m), 6.86 (1H, br). IR (NaCl): 3380, 3250, 3040, 1720, 1680—1600 cm^{-1}. Calcd for $C_{11}H_{20}N_2O_3$: C, 57.83; H, 8.83; N, 12.27%. Found: C, 57.19; H, 8.95; N, 11.78%. **5b**. Yield, 53% (oil). $[\alpha]_D^{20}$ −109.3 (*c* 1.01, ethyl acetate). NMR ($CDCl_3$) δ=1.33 (9H, s), 2.03 (4H, s), 2.77 (3H, d), 3.53 (2H, br), 4.16 (2H, br), 4.83 (1H, br), 6.80 (1H, br). IR (NaCl): 3380, 3250, 3040, 1720, 1660—1600 cm^{-1}. Anal., Calcd for $C_{12}H_{22}N_2O_3$: C, 59.48; H, 9.15; N, 11.56%. Found: C, 57.81; H 9.14; N, 10.65%.

Catalytic Hydrogenation of Substrates 4a—b. Substrates **4a—b** (0.10 mmol) were dissolved in 5 ml solvents (MeOH, EtOH, Pr^iOH, Bu^tOH, THF, and AcOEt) in the presence of 20 mg of 5% palladium on charcoal and were hydrogenated at 30 °C. After hydrogenation, the catalyst was filtered off and the filtrate was evaporated in vacuo to give an oily product. Chemical yields and d.e. (=diastereomeric excess) of the products were determined by using gas liquid chromatography. Catalytic hydrogenation of substrates **4a—b** at some different temperatures (10, 0, −10, −30 °C) was also carried out by the same manner.

Gas Chromatographic analysis. All diastereomeric mixtures of the hydrogenated products were directly separated to each diastereomer by using a Hitachi gas chromatograph with a fused glass capillary column (Chirasil-Val, 25 m×0.25 mm I.D.) which was purchased from Alltech Associates, Inc., Applied Science Labs., IL 60015, U.S.A., carrier gas: helium. The column temperature during the analyses was 170 °C (constant). Flame thermoionic detector was used for the analyses.

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7) Similar effect of amide was observed in the catalytic hydrogenations of the Schiff base prepared from methyl pyruvate and (*S*)-Ala-NH-Pr^i. The Schiff base derived from (*S*)-Ala-NH-Pr^i gave higher d.e. (65%) by catalytic hydrogenation at 30 °C in MeOH than that from (*S*)-Ala-OPr^i. The results might be explained by stronger adsorption of nitrogen of the amide moiety. See S. Shiono, Doctral Thesis, University of Tsukuba (1985).