Asymmetric Catalytic Hydrogenations of Oximes and Benzylimino Derivatives of Chiral Pyruvamides

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Synopsis. Oximes and benzylimino derivatives of chiral pyruvamides were hydrogenated over palladium hydroxide on charcoal in several solvents. Oximes of pyruvamides containing (*R*)-α-ethylbenzylamine as a chiral source gave (*S*)-alanine in excess (up to 70% e.e.) through the hydrolyses of the hydrogenated products.

In the previous study,[1] oximes of benzoylformamides whose chiral centers were (*S*)-α-methylbenzylamine, were hydrogenated over palladium on charcoal and then hydrolyzed to afford (*S*)-phenylglycine in a low e.e. (5.5%). On the other hand, the catalytic hydrogenations of chiral pyruvamides have given *N*-(*S*)-lactoyl-(*S*)-α-alkylbenzylamine with good asymmetric yields (up to 62%).[2] In the asymmetric catalytic hydrogenations, it was found that α-alkylbenzylamines were useful chiral moieties to stabilize the "chelated intermediates"[3] as shown in Fig. 1. However, asymmetric catalytic hydrogenations of oximes and Schiff bases of pyruvamides whose chiral centers are α-alkylbenzylamines have not been studied.

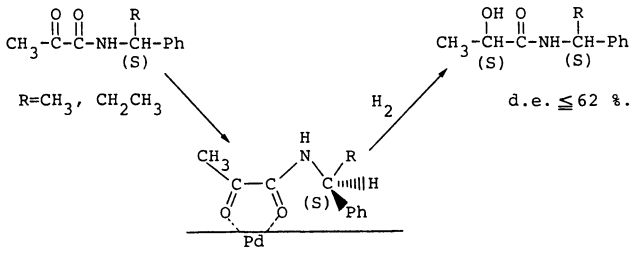
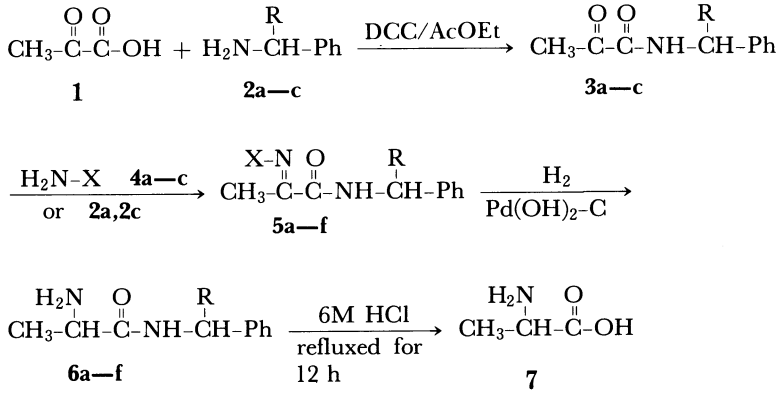


Fig. 1. Possible steric course in the catalytic hydrogenations of chiral pyruvamides **3a**, **b**.[3] d.e.: diastereoisomeric excess.

In this paper, we wish to report on the results of the asymmetric catalytic hydrogenations of oximes **5a—c** and Schiff bases **5d—f** of pyruvamides over palladium hydroxide on charcoal. Substrates **5a—f** were prepared as shown in Scheme 1. The catalytic hydrogenations were carried out in several solvents at 30 °C. After hydrolyses of the hydrogenated products, the chemical yields of alanine were determined by amino acid analyses and the enantiomeric excess (e.e.) were determined by gas chromatographic separation of the derivatized DL-alanine[*N*-(trifluoroacetyl)alanine isopropyl ester].

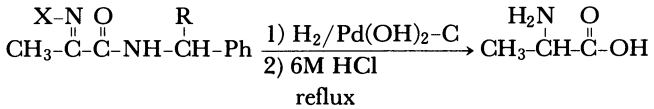
Results and Discussion

The results of the catalytic hydrogenations are shown in Table 1. Substrates **5a**, **b** whose chiral sources were (*S*)-amine and (*R*)-amine, gave (*R*)-alanine and (*S*)-alanine in excess respectively after hydrolyses of hydrogenated products. Substrate **5b** gave higher e.e. (up to 70%) than **5a** gave. Substrate **5c** whose chiral source was (*R*)-amine gave (*S*)-alanine with low e.e. These results suggested that the asymmetric induction was affected by the difference of the bulkiness between H and R groups bonded to the chiral carbon in the substrate molecules. There are two possible steric courses through which oximes **5a** give (*R*)-alanine. Those are steric course A (non-chelation mechanism) and B (chelation mechanism) as shown in Fig. 2.[4] In the first step (A-1) of the steric course A, the carbonyl and the imino groups take s-trans conformation owing to their electrostatic repulsion, and the H and R groups which are bonded to the chiral carbon interpose the NH group. The substrate molecule taking



Scheme 1. **2a**, **3a**: R=Me (*S*); **2b**, **3b**: R=Et (*R*); **2c**, **3c**: R=Me (*R*); **4a**: X=OH; **4b**: X=OCH_2Ph; **4c**: X=CH_2Ph; **5a**: X=OH, R=Me (*S*); **5b**: X=OH, R=Et (*R*); **5c**: X=OCH_2Ph, R=Me (*R*); **5d**: X=CH_2Ph, R=Me (*R*); **5e**: X=—CH(Me)Ph (*S*); R=Me (*R*); **5f**: X=—CH(Me)Ph (*R*), R=Me (*R*).

Table 1. Asymmetric Catalytic Hydrogenations of Oximes and *N*-Benzylimino Derivatives at 30 °C



Substrate	R	X	Confign.[a]	Solvent	Yield of Ala %	e.e. of Ala %	Confign.[b]
5a	Me	OH	*S*	MeOH	52	47	*R*
			S	EtOH	31	34	*R*
			S	Pr^{i}OH	11	36	*R*
			S	AcOEt	42	15	*R*
5b	Et	OH	*R*	MeOH	58	70	*S*
			R	EtOH	21	45	*S*
			R	Pr^{i}OH	19	38	*S*
			R	AcOEt	25	20	*S*
5c	Me	OCH_2Ph	*R*	MeOH	39	15	*S*
5d	Me	OCH_2Ph	*R*	MeOH	61	3.7	*S*
5e		Me (S) -CHPh	*R*	MeOH	57	12	*S*
5f		Me (R) -CHPh	*R*	MeOH	61	0.3	*R*

a) Configuration of chiral amine in the amide moiety. b) Configuration of alanine.

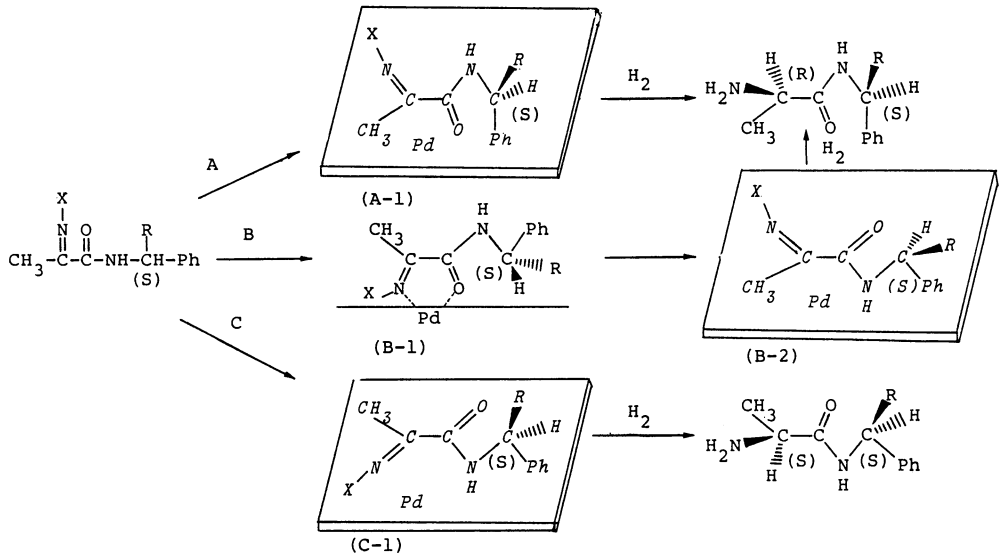


Fig. 2. Possible steric courses in the catalytic hydrogenations of oximes **5a**—**c** and *N*-benzylimino derivatives **5d**, **f**. X=OH, OCH_2Ph, CH_2Ph, CH(Me)Ph.

this conformation could be adsorbed on the palladium surface at the less bulky side of the molecule, and be hydrogenated from the catalyst side to give (*R*)-alanyl-(*S*)-amine. However, the steric course A seemed to contribute little to the asymmetric induction, since A-1 would be unstable due to the steric repulsion between C=O and Ph groups.

On the other hand, the steric course B could explain the stereochemistry of the catalytic hydrogenations. In the first step (B-1), the substrate molecule would stand on the catalyst surface by the carbonyl and oxime groups to form the "chelated intermediate," and the H and R groups interpose the carbonyl group as shown in Fig. 2. In the second step (B-2), the intermediate would be adsorbed at the less bulky side of the substrate on the catalyst, and then hydrogenated from the catalyst side to afford (*R*)-alanyl-(*S*)-amine. The steric course B could explain that the asymmetric induction in the catalytic hydrogenations was caused by the difference of the bulkiness between H and R groups of the asymmetric moiety.

The conformation around the N-C (chiral carbon)

bond of the "chelated intermediate" (B-1) is different from that in Fig. 1, which has been proposed[3] for the hydrogenation of pyruvamides **3a, b**. Since the bond length of α-carbonyl group(-C=O) of **3a, b** is shorter than that of oxime group (-C=N-OH) of **5a, b**, the space between the catalyst and the asymmetric moiety of **5a, b** is smaller than that of **3a, b**. Therefore, the H and R groups would prefer to interpose the amide carbonyl as shown in B-1 in Fig. 2. The low ee of alanine obtained from substrates **5c, d** could also be explained by the steric course B and C. The population of the substrate molecule which passes through the steric course B could be much smaller in the hydrogenations of substrates **5c, d** than **5a, b**, because the OCH_2Ph and CH_2Ph groups in the imino moiety would disturb the formation of the stable "chelated intermediates." And a part of the substrate molecules would pass through the steric course C rather than B, and afford (*S*)-alanine with low ee.

Although substrates **5e, f** have two chiral centers in the amide moiety(*R*) and the imino moiety[(*S*) or (*R*)], these substrates **5e, f** gave alanine with low ee. These low ee could also be explained by the instabilization of the "chelated intermediate" like in substrates **5c, d**.

In this study, the steric course in the catalytic hydrogenations of oximes **5a, c** and *N*-benzylimino derivatives **5d, f** of the chiral pyruvamides could be explained by the chelation mechanism. And a maximum ee (70%) of (*S*)-alanine was obtained in the hydrolysis of the hydrogenated product of substrate **5b** in methanol.

Experimental

The melting points were uncorrected. The 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 Sic Chromatocoda II. 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 hydroxide (10%) on charcoal were prepared by the similar manner in the literature.[5]

Materials. Chiral amines **2a** and **2c** were purchased from Aldrich chemical Co. **2a**. $[\alpha]_D^{20}$ −39.0 (neat), 96% ee[6] **2c**. $[\alpha]_D^{20}$ +39.0 (neat), 96% ee[6] **2b**. $[\alpha]_D^{17}$ +19.0 (neat) 95% ee.[7]

***N*-Pyruvoyl Amines 3a, b.** **3a, b** were prepared by the manner in the literature.[2]

Oximes of *N*-Pyruvoyl Amines 5a—c. Pyruvamides **3a** (1.03 g, 10 mmol) and hydroxylamine hydrochloride (2.08 g, 30 mmol) were dissolved in a mixture of ethanol and pyridine. The solution was refluxed for 3 h. The reaction mixture was evaporated in vacuo to dryness. The residue was redissolved in water (20 ml) and the solution was extracted with three 20 ml portions of ethyl acetate. The ethyl acetate layer was dried with anhydrous magnesium sulfate and was evaporated to give oily product. The oily product was purified with silica-gel column chromatography (benzene-ethyl acetate (5 : 1)) to give 1.13 g **5a** (55%). Mp 51—52 °C ^{1}H NMR ($CDCl_3$) δ=1.85 (3H, d, *J*=7Hz), 2.40 (3H, s), 5.40 (1H, m), 7.20 (1H, br), 7.45 (5H, s), 9.34 (1H, s). IR (KBr) 1530, 1650, 3400 cm^{-1}. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58%. Found: C, 63.82; H, 7.02; N, 13.17%. $[\alpha]_D^{29}$ +24.4 (*c* 1.05, methanol). **5b**. Yield, 37% (oil). ^{1}H NMR ($CDCl_3$) δ=0.90 (3H, t, 7.3 Hz), 1.80 (2H, q, 7.3 Hz), 2.05 (3H, s), 4.90 (1H, q, 7.3 Hz), 7.0—7.1 (1H, br), 7.28 (5H, s). IR (KBr) 1530, 1650, 3400 cm^{-1}. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.71%. Found: C, 64.79; H, 7.42; N, 12.53%. $[\alpha]_D$ −14.7 (*c* 1.01, methanol). **5c**, Yield, 52%. Mp, 70—71 °C. ^{1}H NMR ($CDCl_3$) δ=1.50 (3H, d, 6.8 Hz), 2.05 (3H, s), 4.98—5.28 (1H, m), 5.20 (2H, s), 6.80—7.10 (1H, br), 7.31 (5H, s), 7.34 (5H, s). IR (KBr) 1530, 1650, 3400 cm^{-1}. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.94; H, 6.80; N, 9.45%. Found: C, 72.87; H, 6.83; N, 9.41%. $[\alpha]_D^{20}$ −63.4 (*c* 1.03, methanol).

***N*-(2-Imino-1-oxopropyl) Amines 5d—f.** *N*-Pyruvoylamines **3c, d** (20 mg, 0.1 mmol) and benzylamine (50 μl, 0.46 mmol) were dissolved in dry benzene. The solution was stirred over anhydrous magnesium sulfate (600 mg) for 24 h. After drying agent was filtered off, the resulting filtrate was evaporated to dryness.

Catalytic Hydrogenation of Substrates 5a—f. Substrates **5a—f** (0.1 mmol) were dissolved in 3 ml of methanol, ethanol, 2-propanol, and ethyl acetate, and were hydrogenated over 10% palladium hydroxide on charcoal. After one to seven day's reaction at 30°C, the catalyst was filtered off and the filtrate was evaporated to dryness. The residue was used for hydrolysis without further purification.

Hydrolysis of Hydrogenated Products. The residue obtained by the evaporation of the hydrogenated product was hydrolyzed in 6M HCl (1M=1 mol dm^{-3}) for 12 h.

Determination of Chemical Yield and Enantiomeric Excess of Alanine. Chemical yields of alanine were determined by means of an amino acid analyzer. Enantiomeric excess of alanine was determined by the resolution of derivatized enatiomers of alanine [*N*-(trifluoroacetyl)alanine isopropyl ester) using a gas liquid chromatography equipped with a chiral glass capillary column (Chirasil-Val).[8]

References

1) K. Harada and K. Matsumoto, *J. Org. Chem.*, **32**, 1794 (1967).

2) K. Harada and T. Munegumi, *Bull. Chem. Soc. Jpn.*, **57**, 3203 (1984).

3) K. Harada, Asymmetric Heterogeneous Catalytic Hydrogenation, "Asymmetric Synthesis," ed by J. D. Morrison, Academic Press, New York (1985), Vol. 5, pp. 345—383.

4) T. Munegumi, M. Fujita, T. Maruyama, S. Shiono, M. Takasaki, and K. Harada, *Bull. Chem. Soc. Jpn.*, **60**, 249 (1987).

5) A. Skita and W. A. Meyer, *Ber.*, **45**, 3579 (1912).

6) A. J. Little, J. M. Lean, and F. J. Wilson, *J. Chem. Soc.*, **1940**, 336.

7) W. Theilaker and H. G. Winkler, *Chem. Ber.*, **87**, 691 (1954).

8) H. Frank, G. J. Nicolson, and E. Bayer, *J. Chromatogr.*, **146**, 197 (1978).