  Bull. Chem. Soc. Jpn., 57, 1367—1370 (1984)

Asymmetric Hydrogenation of Schiff Base Prepared from α-Keto Ester with Aliphatic Amino Acid Ester

Kaoru HARADA and Shozo SHIONO

Department of Chemistry, The University of Tsukuba, Sakura-Mura, Niihari, Ibaraki 305

(Received November 29, 1983)

Catalytic hydrogenation of Schiff bases prepared from α-keto esters with amino acid esters was carried out under various conditions. A significant substituent effect of the alkyl group of the ester moiety of amino acid on the stereoselectivity was observed in the hydrogenation of the Schiff bases prepared from methyl pyruvate with (*S*)-alanine ester. Higher asymmetric yields were obtained as the ester residue of amino acid ester became bulkier. A clear temperature effect on the asymmetric hydrogenation was also observed. These results could be explained by the chelation mechanism.

Several studies on the asymmetric hydrogenation of carbon–nitrogen double bonds have been performed.[1–3] In the previous study, hydrogenolytic asymmetric transamination of Schiff bases, prepared from α-keto ester with optically active benzylic amine and optically active aromatic amino acid ester, has been carried out.[4–7] The steric course of the catalytic hydrogenation was explained by the chelation mechanism assuming that the substrate forms a five-membered chelated intermediate with the catalyst and then hydrogenation reaction takes place from the less bulky side of the chelated substrate. The chelation mechanism was supported by the infrared absorption spectrum of ethyl 2-hydroxyimino-3-oxo-3-phenylpropionate on palladium metal which was measured by using the high-sensitivity reflection method.[8] Recently, asymmetric synthesis of amino acid by hydrogenation of the Schiff bases prepared from aliphatic amino acid *t*-butyl esters and methyl pyruvate, followed by oxidative cleavage of carbon–nitrogen single bond was reported by Yamada *et al.*[9] In the present study, the catalytic hydrogenation of Schiff bases prepared from α-keto ester with several aliphatic amino acid esters was carried out in order to examine the steric course of this kind of asymmetric hydrogenation.

Results and Discussion

Schiff bases prepared from α-keto esters with several aliphatic amino acid esters were hydrogenated with 5% palladium on charcoal in several solvents and at various temperatures. The solvents used are methanol, ethanol, 2-propanol, and ethyl acetate, and the reaction temperatures used are in a range −10—+30 °C. The diastereomeric ratio of the resulting iminodicarboxylic acid was determined by gas chromatographic analysis after derivatization of the hydrogenated product to *N*-(trifluoroacetyl)iminodicarboxylic acid diisopropyl ester.

Hydrogenation of the Schiff bases prepared from methyl pyruvate with four kinds of amino acid ester (methyl, ethyl, isopropyl, and *t*-butyl) was carried out in order to examine the substituent effect of the ester group of the chiral moieties on the asymmetric yield. The results were shown in Fig. 1 and Tables 1 and 2. When (*S*)-alanine ester was used as a chiral moiety, (2*S*,2′*S*)-2,2′-iminodipropionic acid was produced dominantly in all cases, and higher asymmetric yield was obtained as the ester group of the amino acid ester became larger as shown in Fig. 1. When (*R*)-2-aminobutyric acid ester was used as a chiral moiety, (*R*)-2-[(*R*)-1-carboxyethylamino]butyric acid was produced dominantly, and similar substituent effect in the ester group of the amino acid ester on the asymmetric yield was observed as shown in Table 2. These results indicate that the asymmetric yield of the newly formed iminodicarboxylic acid depends strongly on the bulkiness of the ester group of the chiral amino acid ester, but depends little on the bulkiness of the alkyl group of the amino acid used as the chiral moiety.

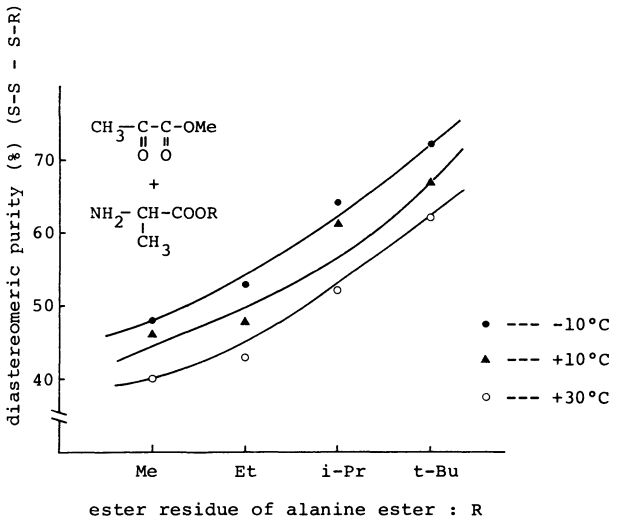

Fig. 1. Substituent effect on the asymmetric yield.

Hydrogenation of the Schiff bases prepared from methyl 2-oxobutyrate with (*S*)-alanine ester was carried out in order to examine the substituent effect of the alkyl group attached to the carbonyl group of the α-keto ester. The results were summarized in Table 3. (*S*)-2-[(*S*)-1-Carboxyethylamino]butyric acid was obtained dominantly in all cases and higher asymmetric yields were obtained as the ester residue of the amino acid ester became bulkier. An interesting result obtained is that lower asymmetric yield was obtained by using methyl 2-oxobutyrate rather than methyl pyruvate.

Hydrogenation of Schiff bases prepared from (*S*)-alanine with ethyl pyruvate instead of methyl pyruvate was carried out. The results were summarized in Table

Table 1. Hydrogenation of Schiff bases prepared from (*S*)-alanine ester and methyl pyruvate

Entry	Ester residue	Solvent	Temp/°C	d.p./%[a,b]	Yield/%[c]
1	Me	MeOH	−10	48	64
2	Me	MeOH	10	46	74
3	Me	MeOH	30	40	46
4	Me	EtOH	10	41	45
5	Me	*i*-PrOH	10	42	65
6	Me	AcOEt	−10	45	66
7	Me	AcOEt	10	38	45
8	Me	AcOEt	30	33	58
9	Et	MeOH	−10	53	59
10	Et	MeOH	10	48	69
11	Et	MeOH	30	43	55
12	Et	EtOH	10	45	45
13	Et	*i*-PrOH	10	48	63
14	Et	AcOEt	10	38	61
15	*i*-Pr	MeOH	−10	64	77
16	*i*-Pr	MeOH	10	61	57
17	*i*-Pr	MeOH	30	52	62
18	*i*-Pr	EtOH	10	58	63
19	*i*-Pr	*i*-PrOH	10	61	51
20	*i*-Pr	AcOEt	10	53	57
21	*t*-Bu	MeOH	−10	72	58
22	*t*-Bu	MeOH	10	67	65
23	*t*-Bu	MeOH	30	62	70

a) Diastereomeric purity. b) The configuration of newly formed chiral center were all S. c) Based on methyl pyruvate.

Table 2. Hydrogenation of Schiff bases prepared from (*R*)-2-aminobutyric acid ester and methyl pyruvate

Entry	Ester residue	Solvent	Temp/°C	d.p./%[a,b]	Yield/%[c]
1	Me	MeOH	−10	52	76
2	Me	MeOH	10	48	83
3	Me	MeOH	30	41	81
4	Me	EtOH	10	40	30
5	Me	*i*-PrOH	10	34	64
6	Me	AcOEt	10	26	39
7	Et	MeOH	10	45	75
8	*i*-Pr	MeOH	10	63	80
9	*t*-Bu	MeOH	10	69	68

a) Diastereomeric purity. b) The configuration of newly formed chiral center were all *R*. c) Based on methyl pyruvate.

4. The results obtained by the use of ethyl pyruvate were almost the same as that obtained by the use of methyl pyruvate.

A Schiff base has two geometric isomers, *E* and *Z*. The major isomer of the substrate Schiff base used in this asymmetric hydrogenation could be the E isomer because the alkoxycarbonyl group of the α-keto esters

Table 3. Hydrogenation of Schiff bases prepared from (*S*)-alanine ester and methyl 2-oxobutyrate

Entry	Ester residue	Solvent	Temp/°C	d.p./%[a,b]	Yield/%[c]
1	Me	MeOH	10	25	42
2	Me	*i*-PrOH	10	23	36
3	Me	AcOEt	10	20	39
4	Et	MeOH	10	32	37
5	*i*-Pr	MeOH	10	43	36

a) Diastereomeric purity. b) The configuration of newly formed chiral center were all *S*. c) Based on methyl 2-oxobutyrate.

Table 4. Hydrogenation of Schiff bases prepared from (*S*)-alanine ester and ethyl pyruvate

Entry	Ester residue	Solvent	Temp/°C	d.p./%[a,b]	Yield/%[c]
1	Me	MeOH	10	46	61
2	Et	MeOH	10	51	73
3	*i*-Pr	MeOH	10	60	53

a) Diastereomeric purity. b) The configuration of newly formed chiral center were all *S*. c) Based on ethyl pyruvate.

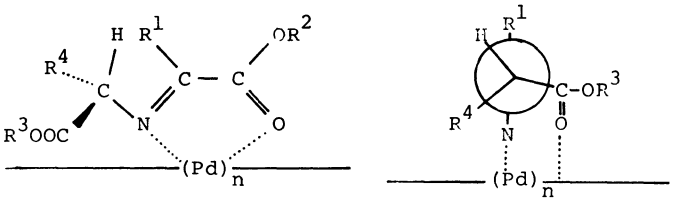

Fig. 2. Palladium–substrate complex.

are much bulkier than methyl or ethyl groups attached to the α-carbon of α-keto esters. If this is the case, the substrate-catalyst complex could be expected to form prior to catalytic hydrogenation as expected by the chelation mechanism. This five-membered chelated intermediate of the Schiff base used in the present study could be depicted as shown in Fig. 2. Considering the steric interaction between the alkyl substituent at the α-carbon of the α-keto ester and amino acid residue and the adsorption of the ester carbonyl oxygen of amino acid ester to catalyst, the conformation of the chiral moiety of the Schiff base with the catalyst could be that as shown in Fig. 2. The existence of the five-membered chelated structure could be supported by the following experimental results listed in Table 1—4 and Fig. 1. 1) The stereoselectivity in the hydrogenation of the Schiff base depends strongly on the bulkiness of the ester group of the amino acid ester. 2) Lower asymmetric yields were obtained by the use of α-keto esters with larger alkyl groups. 3) The use of ethyl pyruvate instead of methyl pyruvate gave practically no effect on the stereoselectivity in the hydrogenation of Schiff base.

Hydrogenation of Schiff base was carried out in several solvents at various temperatures. A clear temperature effect on the stereoselectivity was observed (Tables 1 and 2). Higher asymmetric yields were obtained at

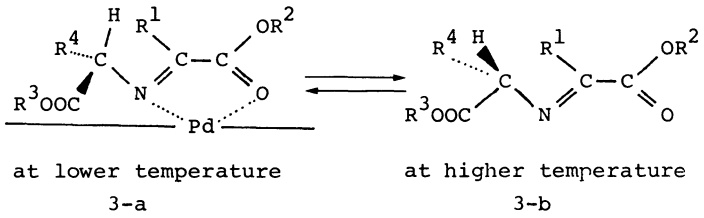

Fig. 3. Conformation of substrate at lower and at higer temperature.

lower temperature than at higher temperature. The Schiff base could form an intermediate chelated complex prior to the hydrogenation at lower temperature. On the other hand, the chelated complex might be liberated from the palladium surface to form a structure as shown in Fig. 3-b at higher temperature. Therefore, the proportion of nonchelated structure increases at higher temperature and this would result in the decrease in the stereoselectivity.

The stereoselectivity in the hydrogenation depends little on the solvent employed. In most cases, higher asymmetric yields were obtained in alcohols than in ethyl acetate. These effects might be explained by a hydrogen bonding between the solvent molecule and the ester group of the amino acid ester in the Schiff base. If the ester group of the amino acid ester in the chelated substrate forms a hydrogen bonding with alcohol, the relative steric bulkiness increases at the diastereomeric face, and this could make the stereoselectivity increase in the alcohols.

The results obtained above are summarized as follows. The stereoselectivity in the hydrogenation depends strongly on the bulkiness of the ester group of the amino acid ester and the alkyl group attached to α-carbon of α-keto ester. The use of bulkier ester group of amino acid ester afforded iminodicarboxylic acid in higher stereoselectivity. Lower asymmetric yields were obtained by the use of methyl 2-oxobutyrate than methyl pyruvate. The hydrogenation at lower temperature afforded iminodicarboxylic acid in higher stereoselectivity.

Considering the overall results, it could be concluded that the hydrogenation of the substrate used in this study proceed via the five-membered chelated intermediate.

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. 5% Palladium on charcoal was purchased from Nippon Engelhald.

General Procedure of Preparation and Hydrogenation of Schiff Base. To a suspension of methyl alaninate hydrochloride (279 mg, 2×10^{-3} mol) in 4 ml of benzene was added a solution of triethylamine (202 mg, 2×10^{-3} mol) in 1 ml of benzene and then a solution of methyl pyruvate (204 mg, 2×10^{-3} mol) in 1 ml of benzene was added to the mixture. After stirring for 1 h at 30 °C, 1 g of anhydrous magnesium sulfate was added to the mixture and the stirring was continued for 22 h at 30 °C. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was dissolved in 6 ml of methanol and the solution was stirred with 50 mg of 5% palladium on charcoal for 9 h at 10 °C under hydrogen atmosphere. Catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was dissolved in 20 ml of 6M-HCl† and the solution was refluxed for 12 h and the hydrolyzate was concentrated *in vacuo*. The residue was dissolved in a small volume of water and charged on a Dowex 50-X8 (H^+ form) column. The column was washed thoroughly with water and then eluted with 2 M-aqueous ammonia. The eluate containing iminodicarboxylic acid was concentrated *in vacuo*. One twentieth of the evaporated residue was treated with 2-propanol saturated with hydrogen chloride gas and then with trifluoroacetic anhydride in order to obtain the derivative of iminodicarboxylic acid for gas chromatographic analysis. Three quarter of the evaporated residue was dissolved in a small volume of water and charged on a column of Dowex 1-X8 (HCOOH form). The column was washed thoroughly with water and then eluted with 2 M-HCOOH. The eluate was concentrated *in vacuo* and obtained iminodicarboxylic acid, yield 178 mg (74%, based on methyl alaninate hydrochloride).

Determination of diastereomeric purity of hydrogenated product. To the residue obtained above was added 1 ml of 2-propanol saturated with hydrogen chloride gas and the mixture was heated for 1 h at 110 °C in a screw capped vial and was concentrated *in vacuo*. To the residue were added 0.5 ml of CH_2Cl_2 and 0.5 ml of trifluoroacetic anhydride and the mixture was heated for 2 h at 110 °C in a screw capped vial. The reaction mixture was concentrated *in vacuo* and the residue was extracted with ethyl acetate. The extract was washed with 10% citric acid, saturated $NaHCO_3$ and dried over magnesium sulfate, and was concentrated *in vacuo*. The residue was dissolved in ethyl acetate and the solution was injected into a gas chromatograph equipped with a glass capillary column (25 m×0.3 mm i.d.) coated with a chiral stationary phase (Chirasil-Val). The column temperature was raised from 80 °C to 180 °C at a rate of 3 °C per minute for the analysis of the diastereomeric ratio of 2,2′-iminodipropionic acid. The column temperature was raised from 80 °C to 180 °C at a rate of 0.25 °C per minute for the analysis of the diastereomeric ratio of 2-(1-carboxyethylamino)-butyric acid.

Authentic iminodicarboxylic acid, (2*S*,2′*S*)- and (2*S*,2′*R*)-2,2′-iminodipropionic acid and (*R*)-2-[(*R*)-1-carboxyethylamino]butyric acid and (*R*)-2-[(*S*)-1-carboxyethylamino]-butyric acid, were derivatized under same conditions. In each analysis of authentic derivatized samples, only a derivatized original diastereomer was detected. These results indicate that the epimerization during the derivatization would be none.

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† 1 M=1 mol dm^{-3}.

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