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ASYMMETRIC HYDROGENATION OF CHIRAL PYRUVAMIDES[1)]

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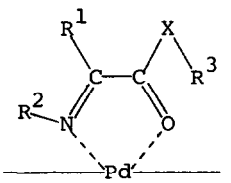
ABSTRACT: Asymmetric catalytic hydrogenations of three kinds of chiral pyruvamides were carried out using palladium on charcoal as a catalyst to give lactamides with diastereomeric ratios ranging from 76:24 to 98:2.

Several studies on asymmetric reduction of α-keto acid derivatives have been performed[2,3)]. However, few examples of asymmetric hydrogenation of chiral α-keto amides have been reported[3)]. In our previous studies on asymmetric amino acid syntheses through hydrogenations of oximes or Schiff bases of α-keto esters or amides, the configurations and the optical yields of products could be interpreted by postulating an intermediate substrate-catalyst complex as illustrated in Fig. 1[4-8)]. On the other hand, Mitsui *et al.* performed hydrogenations of N-[(S)-α-methylbenzyl]benzoylformamide with several kinds of catalysts, resulting in the formation of an (R)-mandelamide[3)]. The configuration of product was also explained by assuming an S-cis conformation of two carbonyl groups in the substrate. The optical yields were 5 -25%.

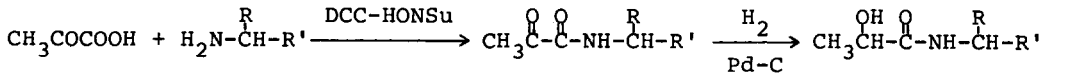
Contrary to the results in the reduction of the benzoylformamide, we found in this study that catalytic hydrogenation of pyruvamides containing (S) chiral centers yielded (S)-lactamides in high optical yields. Elucidation of the steric course in this asymmetric hydrogenation was attempted by employing three kinds of chiral centers as well as by examining the effects of the solvent and the temperature on the optical yield of the reaction.

Thus, N-[(S)-α-methylbenzyl]-, N-[(S)-α-ethylbenzyl]-, and N-[(S)-1-(α-naphthyl)ethyl]pyruvamide (Fig. 2) were prepared by the coupling of the corresponding optically active amines and pyruvic acid with dicyclohexylcarbodiimide in the presence of N-hydroxysuccinimde, followed by purification with Silica gel column chromatography (ethy acetate - n-hexane). All the pyruvamides synthesized here gave satisfactory data on elemental analyses. Each pyruvamide (20mg) was hydrogenated using 5% palladium on charcoal (100mg) as a catalyst in sever-



X = O or NH

Fig. 1. Apostulated substrate-catalyst complex



Ia : R=Me, R'=Ph IIa : R=Me, R'=Ph
Ib : R=Et, R'=Ph IIb : R=Et, R'=Ph
Ic : R=Me, R'=Naph IIc : R=Me, R'=Naph

Fig. 2. A scheme for asymmetric hydrogenation of chiral pyruvamides
Abbreviations ; DCC:dicyclohexylcarbodiimide, Naph:naphthyl
HONSu:N-hydroxysuccinimide.

al kinds of alcohols (3 ml) for 10 - 20 hours at 30 °C. Further, hydrogenation of pyruvamide Ia was carried out at lower temperatures. After hydrogenation, the solvent was removed *in vacuo* and the residue was redissolved in chloroform. Both the reaction yields and the ratios of two diastereomers of the resulting lactamides were determined by the use of gas-liquid chromatography. Table 1. summarizes the analytical conditions and the retention times of the diastereomeric lactamides, whose authentic samples were synthesized by the coupling of the optically active amines and (S)-lactic acid with dicyclohexylcarbodiimide. The gas chromatographic analysis of each sample was repeated three times and the peaks on the chromatogram were integrated with a Hitachi 834-30 chomato-processor. The average values of diastereomeric ratios are shown in Table 2.

All of the pyruvamides of S-configuration afforded (S)-lactic acid amides in high optical yields. The optical yields of the lactamide IIa were in agreement with those of IIb within an experimental error. However, the stereoselectivity of the substrate Ic was obviously higher than those of the others, Ia and Ib. Although hydrogenations in methanol seemed to give higher optical

Table 1. Analytical conditions and the retention times of diastereomeric lactamides in gas chromatography*

Lactamide	Retention time (min)	
	S**	R**
N-[(S)-α-methylbenzyl]lactamide	41	42
N-[(S)-α-ethylbenzyl]lactamide	43	44
N-[(S)-1-(α-naphthyl)ethyl]lactamide	58	59

* A Hitachi 163 gas chromatograph was used under the following operating conditions;
Column: Silicone gum SE52, 3 mm^{ϕ} × 4 m
Temperature program: 2 °C/min from 100 °C
Injection port: 300 °C
N_2 flow rate: 30 - 40 ml/min
Detector: FID.

** Configuration of lactyl moiety in each diastereomeric lactamide.

Table 2. Asymmetric hydrogenation of chiral pyruvamides*(30 °C)

Substrate	Solvent	Diastereomeric ratio (%)	
		S**-S	R**-S
(S)-Ia	MeOH	86	14
	EtOH	84	16
	*iso*PrOH	78	22
	*tert*BuOH	81	19
(S)-Ib	MeOH	89	11
	EtOH	81	19
	*iso*PrOH	76	24
	*tert*BuOH	83	17
(S)-Ic	MeOH	95	5
	EtOH	92	8
	*iso*PrOH	92	8
	*tert*BuOH	88	12

* The chemical yields were 73 - 92% as determined by gas chromatography.
** Configuration of the newly formed chiral center in lactyl moiety.

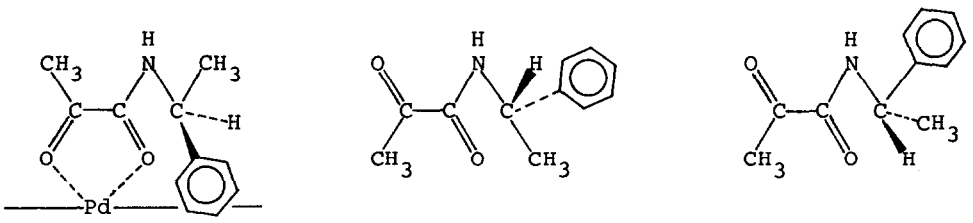
yields than in the other alcohols, the marked solvent effect could not be observed. The temperature dependence of diastereomeric ratio in hydrogenation using substrate Ia in methanol is shown in Table 3. As the temperature lowered, the optical purity of the product increased up to almost 100%.

Taking into account the configuration of the newly formed chiral center in the lactamides as well as the high asymmetric induction of the substrates, model A or B shown in Fig. 3 may possibly be an intermediate of this reaction or a conformation of the substrate. Both the largest (phenyl) and the smallest (hydrogen) group at the chiral center of Ia must be oriented out of the diastereotopic plane to achieve the large degree of asymmetric induction. Model C which is equivalent to Prelog's rule is not suited for explaining the high optical yields. Furthermore, substitution of methyl at the chiral center of Ia by an

Table 3. Temperature dependence in the asymmetric hydrogenation of substrate (S)-Ia in methanol*

Temperature (°C)	Diastereomeric ratio (%)	
	S**-S	R**-S
10	86	14
-10	89	11
-30	98	2

* The chemical yields were 71 - 93% as determined by gas chromatography.
** Configuration of the newly formed chiral center in lactyl moiety.



(A) (B) (C)

Fig. 3. Possible models indicating reaction intermediate or conformation of the substrate in the asymmetric hydrogenation of pyruvamide Ia

ethyl group brought about practically no change in optical yield, however, substitution of phenyl in Ia by a naphthyl group resulted in an increase of asymmetric induction. Models A and B are both consistent with these findings. The conformation in model B, however, could not be preferred due to the deviation of the largest phenyl group out of the molecular plane. Model A, which assumes the adsorption of phenyl or naphthyl group of the substrate on the palladium surface, could support all of the results obtained in this study. This adsorption of the aryl group has been recognized in our previous studies[4-8]. At present, model A seems to be most appropriate for explaining the results. Further, it is worth remarking that a high asymmetric induction was achieved in this hydrogenation, especially at low temperatures. The present study would offer an additional example of a possible substrate-catalyst complex involving two carbonyl groups in an asymmetric catalytic hydrogenation.

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