CHEMISTRY LETTERS, pp. 495-498, 1979. Published by the Chemical Society of Japan

ASYMMETRIC HYDROGENATION OF α-ACYLAMINOCINNAMIC ACID CATALYZED BY CHIRAL RHODIUM COMPLEXES. REMARKABLE EFFECTS OF HYDROGEN PRESSURE ON STEREOSELECTIVITY

Iwao OJIMA*, Tetsuo KOGURE, and Noriko YODA
Sagami Chemical Research Center, Nishi-Ohnuma 4-4-1, Sagamihara, Kanagawa 229

Remarkable effects of hydrogen pressure on the stereoselectivity were observed in the asymmetric hydrogenation of α-acylaminocinnamic acid and its derivatives catalyzed by chiral rhodium complexes. Effects of added triethylamine on the pressure dependency of stereoselectivity was also studied. Possible mechanisms are proposed.

Homogeneous asymmetric hydrogenation of olefins and carbonyl compounds catalyzed by chiral rhodium complexes has been attracting much interest.[1] However, there have been no systematic studies on the pressure dependency of stereoselectivity in these reactions although each research group seems to choose a certain hydrogen pressure, e.g., 1, 3, 20 and 50 atm, by only taking into account the reaction time and the initial turn over. On the other hand, it has been shown[2] that the addition of a small amount of amine or other bases to the reaction system increases the stereoselectivity, dramatically in some cases, in the asymmetric hydrogenation of olefinic acid, e.g., α-acetamidocinnamic acid. Reasons for this enhancement of stereoselectivity, however, have not been clarified.

We have found that i) hydrogen pressure generally exerts a significant influence in the stereoselectivity of rhodium catalysts bearing chiral diphosphine ligands and ii) the added triethylamine considerably releases the pressure effect. We will describe here the striking effect of hydrogen pressure and added triethylamine on the asymmetric induction in the title reaction, and propose possible mechanisms.

We carried out the asymmetric hydrogenation of (Z)-α-benzamidocinnamic acid (1) using neutral and cationic rhodium complexes with BPPM,[3] (-)DIOP,[4] and DIPAMP[5] under a variety of hydrogen pressures. Results are summarized in Table 1. As Table 1 shows, (R)-N-benzoylphenylalanine is a predominant product under an atmospheric pressure of hydrogen whereas the production of S-isomer is preferred under high pressures such as 50 atm and 100 atm of hydrogen on using BPPM complexes, for example. Namely, the inversion of the preferred configuration of the product takes place only by changing hydrogen pressure.

This phenomenon could be caused by either i) a change in the rate-determining step or ii) an exchange of one mechanism for the other, provided that the reaction proceeds via two competitive mechanisms. According to the mechanism of the hydrogenation catalyzed by a rhodium complex with a cis chelating diphosphine proposed by Halpern et al.,[6] the rate-determining step is suggested to be oxidative addition of molecular hydrogen to the pre-formed rhodium-substrate complex, i.e., step a in Scheme 1. Thus, if the former were the case, a high hydrogen pressure may make the oxidative addition of hydrogen (step a) easy, and the rate determining step may change to the second hydride migration (step c) since no change in stereoselectivity would be expected even when the

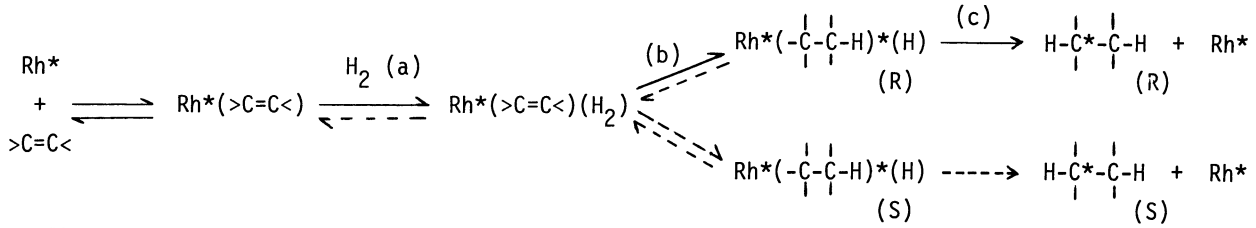
Table 1. Hydrogen pressure dependency of stereoselectivity in the asymmetric hydrogenation of 1[a]

Catalyst[b]	Et_3N/Catalyst	Optical Purity[c] (% e.e.)(Configuration)				
		Pressure of Hydrogen[d]				
		1	5	20	50	100
BPPM-Rh^+	0	83.8(R)	62.3(R)	21.2(R)	4.7(S)	8.4(S)
	2	93.3(R)	83.5(R)	78.7(R)	66.2(R)	64.2(R)
BPPM-Rh^N	0	84.0(R)	67.6(R)	12.9(R)	8.6(S)	14.4(S)
	2	91.8(R)	81.9(R)	75.5(R)	66.6(R)	63.2(R)
(-)DIOP-Rh^+	0	55.2(R)	8.4(R)	0.5(S)	4.9(S)	
	2	--- [e]	41.1(R)	33.1(R)	32.2(R)	
(-)DIOP-Rh^N	0	60.5(R)	38.8(R)	16.5(R)	9.1(R)	
	2	61.8(R)	49.4(R)	48.1(R)	46.8(R)	
DIPAMP-Rh^+	0		63.6(S)		29.9(S)	
	2		88.1(S)		83.8(S)	
DIPAMP-Rh^N	0		85.0(S)		66.2(S)	
	2		88.6(S)		86.7(S)	

[a] All hydrogenations were run with 1.0 mmol of 1, 1.0×10^{-2}mmol (1.0 mol%) of the rhodium catalyst in 12 ml of abs. EtOH at 25°C for 3-15h in a glass reaction vessel with stirring bar. For the experiments at 5-100 atm of H_2, a 100 ml autoclave equipped with the glass vessel was used. Conversion was 100% in each case. [b] Diphosphine-Rh^+ stands for $[(diphosphine)Rh(COD)]^+ClO_4^-$, and diphosphine-$Rh^N$ stands for (diphosphine)Rh(COD)Cl in situ prepared. [c] Optical purities were determined on the basis of the reported maximum rotation: $[\alpha]_{27}^{D}$ -40.3° (c 1.0, MeOH)(see Ref. 11). [d] Initial hydrogen pressure except for 1 atm. [e] Conversion was too low to estimate.

first hydride migration (step b) is the rate determining step. Namely, an isomerization of the coordinating olefinic substrate may occur to facilitate the formation of the other enantiomer, S-isomer in this case.[12] The reaction paths involved in this mechanism are shown in Scheme 1. However, a mechanistic study on the hydrogenation of olefins catalyzed by $(Ph_3P)_3RhCl$ revealed that step c is a fast process while step b is a slow one,[7] and moreover, recent works on the dideuteration of (E)-acylaminocinnamic acid by Kagan's[8a] and Knowles' group[8b] reinforced no equilibrium in step b. Consequently, the first assumption is unlikely in the present reaction.

Scheme 1. Change of rate-determining step[12]

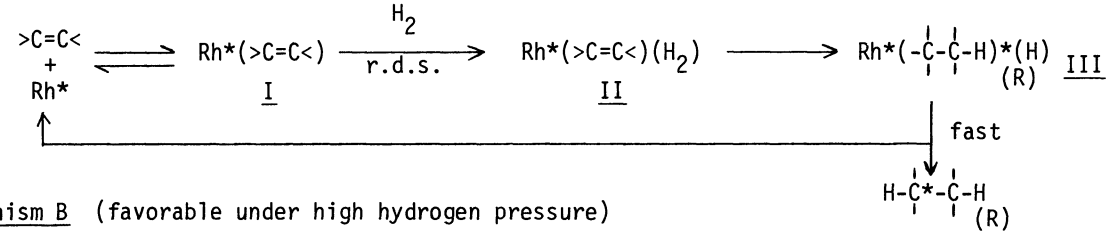


The observed results are well accommodated by taking into account the competitive mechanisms, A and B, shown in Scheme 2. Mechanism A follows the one proposed by Halpern et al.,[3] in which the rate-determining step is the oxidative addition of molecular hydrogen to the intermediate complex I. Mechanism B follows the one which has been widely accepted for the hydrogenation of olefins catalyzed by $(Ph_3P)_3RhCl$.[4] Mechanism A is exclusively operative under 1 atm of hydrogen whereas Mechanism B is getting predominant under high pressures. Namely, it is reasonable to assume that

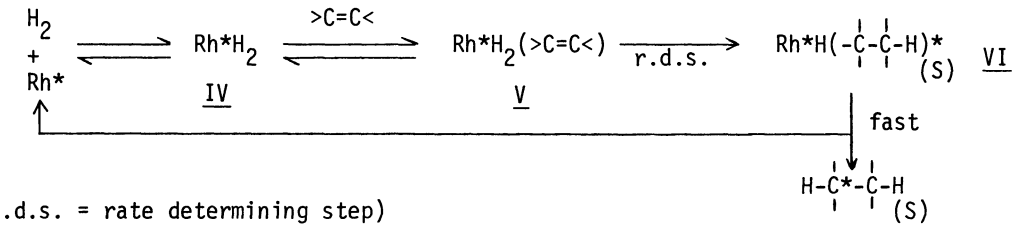
the dihydrido complex IV is stable and is easily formed under higher pressures of hydrogen even though the formation of IV is unfavorable for a complex with chelating diphosphines.[6] As for the stereoselectivity of these mechanisms, Mechanism A should extremely favor the production of R-isomer while Mechanism B should prefer the S-isomer in order to accommodate the results.[12] The CPK model inspection supports the stereochemical requirements in the coordination sphere of the intermediate complexes, II and V, viz., i) in the formation of I the olefinic substrate occupies the coordination site in such a way as to minimize the steric repulsion and gain the attractive interaction,[9] and then molecular hydrogen undergoes oxidative addition keeping the orientation of the substrate to give II, and ii) in the formation of IV hydrogens occupy the most favorable site first, and then the olefinic substrate comes into the coordination sphere to give V, in which the preferable orientation for the substrate may well be opposite to that of II.

Scheme 2. Competitive mechanisms[12]

Mechanism A (favorable under low hydrogen pressure)



Mechanism B (favorable under high hydrogen pressure)



(r.d.s. = rate determining step)

On the other hand, a remarkable effect of added triethylamine on the pressure dependency of the optical yield was observed. As Table 1 shows, the addition of a small amount of triethylamine to the reaction system not only increases the optical yield under the given hydrogen pressure, but also markedly releases the pressure effect on stereoselectivity, i.e., Mechanism B is considerably suppressed by the addition of triethylamine even under a high pressure of hydrogen. The results may imply that the amine generates the carboxylate anion of the substrate, which reacts with the rhodium catalyst to give I much faster than the non-ionized substrate, and as a result, the formation of IV is suppressed. Consequently, the results strongly suggest that the most significant effect of the added amine is to make Mechanism A predominate over Mechanism B although the possibility that the addition of triethylamine improves the stereochemical requirements in the coordination sphere, could not completely be excluded. Thus, there remains a possibility that Mechanism B is operative even under an atmospheric pressure of hydrogen in the absence of triethylamine.

We also investigated the pressure dependency of stereoselectivity using (Z)-α-acetamidocinnamic acid (2), methyl (Z)-α-acetamidocinnamate (3), α-acetamidoacrylic acid (4) and itaconic acid (5) as substrate and BPPM as chiral ligand, and obtained similar results to those described above

although the inversion of configuration was not observed in the case of 2, 3 and 5. Among them, the asymmetric hydrogenation of 3 catalyzed by (BPPM)Rh(COD)Cl in situ prepared, is worth to be mentioned. The reaction gave (R)-N-acetylphenylalanine methyl ester with 95.0% e.e. and 45.5% e.e. under 1 atm and 50 atm of hydrogen, respectively. Thus, it is demonstrated that carboxylic acid moiety is not a requisite for achieving high optical yield on using BPPM although Achiwa discussed a characteristic feature of BPPM ligand on the basis of the fact that a inferior optical yield was obtained in the reaction of 3 under a high hydrogen pressure.[10]

It should be noted that a remarkable effect of the pressure of hydrogen on the stereoselectivity is revealed for the first time, and a new aspect of the effect of added amine is also disclosed. Accordingly, one should be careful about the pressure dependency of optical yield for discussing precisely the stereoselectivity of the given chiral catalyst in the asymmetric hydrogenation.

Acknowledgment: The authors are grateful to Dr. W. S. Knowles of Monsanto Company for his kindly giving them DIPAMP.

References and Notes

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2. a) T. P. Dang and H. B. Kagan, Chem. Comm., 481 (1971); b) A. P. Stoll and R. Süess, Helv. Chim. Acta, 57, 2487 (1974); c) W. S. Knowles, M. J. Sabacky, B. D. Vineyard, D. J. Weinkauff, J. Am. Chem. Soc., 97, 2567 (1975); d) K. Achiwa, J. Am. Chem. Soc., 98, 8265 (1976).
3. BPPM stands for (2S,4S)-N-t-butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine: see Ref. 2d.
4. (-)DIOP stands for (-)-2,3-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane: cf. H. B. Kagan and T. P. Dang, J. Am. Chem. Soc., 94, 6429 (1972).
5. DIPAMP stands for (R,R)-1,2-bis[(o-methoxyphenyl)phenylphosphino]ethane: cf. B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman, and D. J. Weinkauff, J. Am. Chem. Soc., 99, 5946 (1977).
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8. a) C. Detellier, G. Gelbard, and H. B. Kagan, J. Am. Chem. Soc., 100, 7556 (1978); b) K. E. Koenig and W. S. Knowles, ibid., 100, 7561 (1978).
9. cf. I. Ojima and T. Kogure, Chem. Lett., 1145 (1978).
10. Achiwa reported[2d] that S-isomer with low optical purity was obtained in this reaction under 50 atm of hydrogen. However, our careful reinvestigation showed that such an inversion of configuration did not take place. By the way, although Achiwa reported[2d] a dramatic effect of added triethylamine on the optical yield in the asymmetric hydrogenation of (Z)-α-acetamidocinnamic acid catalyzed by a neutral BPPM-rhodium complex, i.e., 30% e.e. without Et_3N ⟶ 83%e.e. with Et_3N in methanol, our careful reinvestigation revealed that such an effect was not observed at all, i.e., 78.7% e.e. in methanol and 83.6% e.e. in ethanol were achieved without Et_3N under 20 atm of hydrogen (91.5% e.e. under 1 atm of hydrogen).
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12. For the results on using DIPAMP, the indicated signs, R and S, should be replaced by S and R, respectively.

(Received February 5, 1979)