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Asymmetric Hydroformylation of Styrene. The Effects of the Reaction Conditions on the Stereoselectivity

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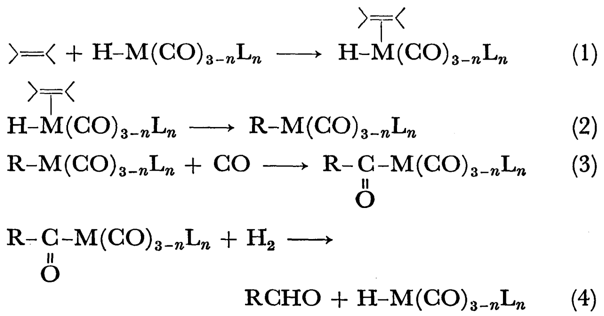
The effects of the reaction conditions on the asymmetric hydroformylation of styrene with rhodium catalysts have been studied. The $[\alpha]_D$ value and the configuration of the product, hydratropaaldehyde, were much affected by the phosphine/rhodium ratios, the reaction temperatures (20—110 °C), and the partial pressures of carbon monoxide and hydrogen (10—100 atm). The results were mainly explained in terms of the structures of the catalysts and the skeletal isomerization of acyl complexes. The predominant species of the catalysts and the participation of a π-benzyl-type intermediate were also discussed.

Recently, catalytic asymmetric syntheses with chiral phosphine transition-metal complexes have attracted much interest, and several papers on the asymmetric hydroformylation of olefins with chiral phosphine rhodium complexes have been published.1–4) However, there has been no example of an investigation of the effects of the reaction conditions on the asymmetric hydroformylation. The hydroformylation reaction is believed to proceed *via* the π-olefin, alkyl, and acyl complexes:



$$\rangle\!=\!\langle + \text{H-M(CO)}_{3-n}\text{L}_n \longrightarrow \text{H-}\overset{\rangle=\langle}{\text{M}}\text{(CO)}_{3-n}\text{L}_n \tag{1}$$

$$\text{H-}\overset{\rangle=\langle}{\text{M}}\text{(CO)}_{3-n}\text{L}_n \longrightarrow \text{R-M(CO)}_{3-n}\text{L}_n \tag{2}$$

$$\text{R-M(CO)}_{3-n}\text{L}_n + \text{CO} \longrightarrow \text{R-}\underset{\text{O}}{\underset{\|}{\text{C}}}\text{-M(CO)}_{3-n}\text{L}_n \tag{3}$$

$$\text{R-}\underset{\text{O}}{\underset{\|}{\text{C}}}\text{-M(CO)}_{3-n}\text{L}_n + \text{H}_2 \longrightarrow \text{RCHO} + \text{H-M(CO)}_{3-n}\text{L}_n \tag{4}$$

where L is carbon monoxide or a phosphorus ligand and M is cobalt or rhodium. Great effects on the reaction rate and the distribution of the products (the straight/branched ratio) are brought about by changing the reaction conditions, the structure of the active species and the reaction mechanisms have been discussed on the basis of these results.5)

In this paper, the authors will describe the effects of the reaction conditions (the reaction temperatures, the phosphine/rhodium ratios, and the partial pressures of carbon monoxide and hydrogen) on the asymmetric hydroformylation of styrene with chiral phosphine rhodium complexes.

Experimental

Benzene was refluxed over lithium aluminum hydride, distilled under argon, and stored over calcium hydride. Styrene was distilled at a reduced pressure of argon and was stored with *p*-*tert*-butylcatechol as a radical inhibitor in a refrigerator. Neomenthyldiphenylphosphine6) and (*R*)-benzylmethylphenylphosphine7) were prepared according to the methods of the literature.

The glpc analysis was carried out on a Shimadzu model GC-3B apparatus equipped with a stainless steel column ($3\ \text{mm}^{\phi} \times 3$ m) packed with diethylene glycol adipate polyester on chromosorb. The optical rotations were measured neat on a JASCO model DIP-180 automatic polarimeter.

Reaction Procedure. An autoclave (100 ml) made of stainless steel (SUS-32) and equipped with a magnetic stirrer was used. Ten ml of benzene, 10 ml of styrene, 3.1 mg of μ,μ'-dichlorotetracarbonyldirhodium, and a desired amount of a chiral phosphine were placed into the autoclave under a slow stream of argon. After the autoclave has been purged with 20 atm of hydrogen several times, hydrogen and carbon monoxide were introduced at certain pressures, after which the mixture was heated up to the desired temperature. The reaction temperature was regulated automatically within a variation of ±1 °C. After having been agitated for a certain time, the autoclave was discharged and an aliquot of the reaction mixture was analyzed by gas chromatography. The optically-active hydratropaaldehyde produced was isolated by the distillation of the reaction mixture, and then the optical rotation was measured.

Reduction of Hydratropaaldehyde. The configuration and the maximum rotation of hydratropaaldehyde are unknown. Therefore, the aldehyde was transformed into 2-phenyl-1-propanol, whose configuration and maximum rotation are known. To a suspension of lithium aluminum hydride (2.19 g) in ether (120 ml), an ether solution (20 ml) of hydratropaaldehyde (5.4 g, $[\alpha]_D$ +1.28°) was added, drop by drop, at 0 °C, and then the mixture was refluxed for 2 hr. The resultant solution was hydrolyzed with 3 M H_2SO_4 (60 ml), and the aqueous layer was extracted three times with 30 ml portions of ether. The combined organic layer was washed with water, dried over magnesium sulfate, and distilled to give 4.7 g of 2-phenyl-1-propanol; bp 63.0—64.2 °C/0.6 mmHg, $[\alpha]_D$ −0.120° (neat). As the maximum rotation of (*S*)-2-phenyl-1-propanol is $[\alpha]_D$ −15.16° (neat),8) that of (*S*)-hydratropaaldehyde is estimated to be $[\alpha]_D$ +160° (neat) if the reduction of the aldehyde proceeds without racemization. However, since such a racemization has been noted,2) the authors will use not the "optical yield" but the $[\alpha]_D$ value in this text.

Results and Discussion

The effects of the reaction conditions (the reaction temperatures, the partial pressures of hydrogen and carbon monoxide, and the phosphine/rhodium ratios) on the $[\alpha]_D$ value of the product were examined; some typical results are summarized in Tables 1 and 2. Under the conditions used, styrene was converted into hydratropaaldehyde and hydrocinnamaldehyde. The former was always the main product, and no other by-products were detected by gas chromatography.

The Effects of the Phosphine/Rhodium Ratio. The

Table 1. ASYMMETRIC HYDROFORMYLATION OF STYRENE CATALYZED BY (*R*)-BENZYLMETHYLPHENYLPHOSPHINE–RHODIUM COMPLEXES[a]

Exp. No.	Reaction conditions					Yield[d] (%)	Iso-%[e]	$[\alpha]_D$ (neat)
	Temp. (°C)	Partial pressure,[b] (atm) CO	H_2	P/Rh[c]	Time (hr)			
1	75	70	70	1	8	41.8	89.7	+0.07
2	75	70	70	8	21	36.0	94.9	+60.2
3	110	70	70	4	6	15.8	78.5	+41.6
4	90	70	70	4	8	26.7	89.2	+46.0
5	60	70	70	4	72	18.5	98.0	+67.4
6	110	10	50	2	2	29.6	68.6	+11.0
7	110	70	50	2	2	96.5	88.6	+27.0
8	110	100	50	2	2	90.5	85.1	+18.7
9	90	30	70	4	8	22.9	89.9	+45.6
10	110	15	50	3	6	37.5	85.3	+29.2
11	110	70	50	3	5	53.0	90.4	+38.3
12	110	100	50	3	2	~100	86.9	+21.8
13	110	50	10	2	3	22.0	65.4	+9.6
14	110	50	95	2	1.5	96.1	89.5	+29.3
15	110	50	10	3	7	22.6	87.6	+26.4
16	110	50	100	3	2	86.8	91.3	+37.6
17	90	70	30	4	23	38.6	89.2	+43.6

a) Styrene: 10 ml, benzene (solvent): 10 ml, $[Rh(CO)_2Cl]_2$: 3.1 mg. b) Initial pressure. c) Phosphine/rhodium ratio. d) Total yield of hydratropaaldehyde and hydrocinnamaldehyde based on the amount of styrene used. e) 100 × Hydratropaaldehyde/(hydratropaaldehyde + hydrocinnamaldehyde).

Table 2. ASYMMETRIC HYDROFORMYLATION OF STYRENE CATALYZED BY NEOMENTHYLDIPHENYLPHOSPHINE–RHODIUM COMPLEXES[a]

Exp. No.	Reaction conditions			Yield[c] (%)	Iso-%[d]	$[\alpha]_D$ (neat)
	Temp. (°C)	P/Rh[b]	Time (hr)			
18	75	2	12	67.5	89.3	+1.28
19	75	50	6.5	68.1	93.1	−1.61
20	100	2	2	96.1	70.8	+0.67
21	20	2	216	42.1	96.7	−4.61

a) Styrene: 10 ml, benzene (solvent): 10 ml, $[Rh(CO)_2Cl]_2$: 3.1 mg, initial partial pressure of carbon monoxide and hydrogen: 70 atm, respectively. b) Phosphine/rhodium ratio. c) Total yield of hydratropaaldehyde and hydrocinnamaldehyde based on the amount of styrene used. d) 100 × Hydratropaaldehyde/(hydratropaaldehyde + hydrocinnamaldehyde).

effects of the phosphine/rhodium ratio on the $[\alpha]_D$ value and the percentage of hydratropaaldehyde were examined under the conditions, initial partial pressure of hydrogen and carbon monoxide of 70 atm and at 75 °C. Two kinds of chiral phosphines were used: (*R*)-benzylmethylphenylphosphine and neomenthyldiphenylphosphine (nmdpp). The former has an asymmetric center on phosphorus, while the latter has three asymmetric centers on the alkyl group. The results are illustrated in Figs. 1 and 2.

In the case of (*R*)-benzylmethylphenylphosphine, when the phosphine/rhodium ratio was 1 the stereochemical control was not so effective, so the $[\alpha]_D$ value was nearly zero. However, an increase in the ratio resulted in a larger stereoselectivity, and the $[\alpha]_D$ value amounted to +50.8° at the 2: 1 ratio. Then it approached asymptotically to a limit with an increase in the ratio (4: 1 and 8: 1). These results suggest an equilibrium among active species which is affected by both the phosphine/rhodium ratio and the partial pressure of carbon monoxide, which will be discussed later:

$$HRh(CO)_3 \xrightleftharpoons[CO,\ -P^*]{P^*,\ -CO} HRh(CO)_2P^* \xrightleftharpoons[CO,\ -P^*]{P^*,\ -CO} HRh(CO)P_2^* \quad (5)$$

where P* is a chiral phosphine. $HRh(CO)_3$ may be predominant at the 1: 1 ratio, and in principle, the

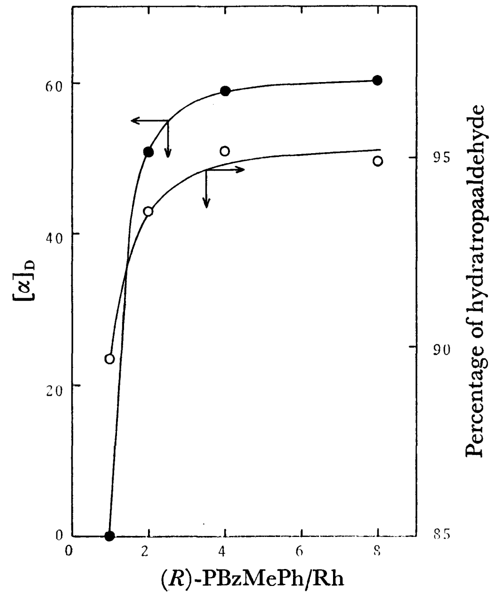


Fig. 1. Effects of (*R*)-benzylmethylphenylphosphine/rhodium ratios on the $[\alpha]_D$ value and the percentage of hydratropaaldehyde. ($P_{CO} = P_{H_2} = 70$ atm, 75 °C)

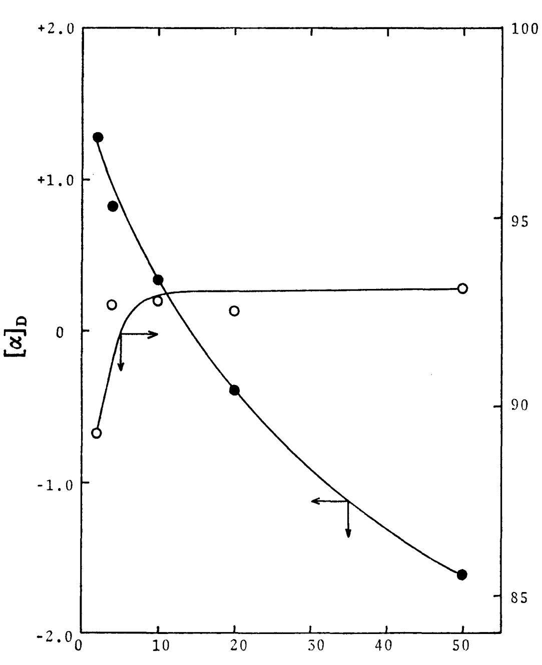


Fig. 2. Effects of neomenthyldiphenylphosphine/rhodium ratios on the $[\alpha]_D$ value and the percentage of hydratropaaldehyde. ($P_{CO}=P_{H_2}=70$ atm, 75 °C)

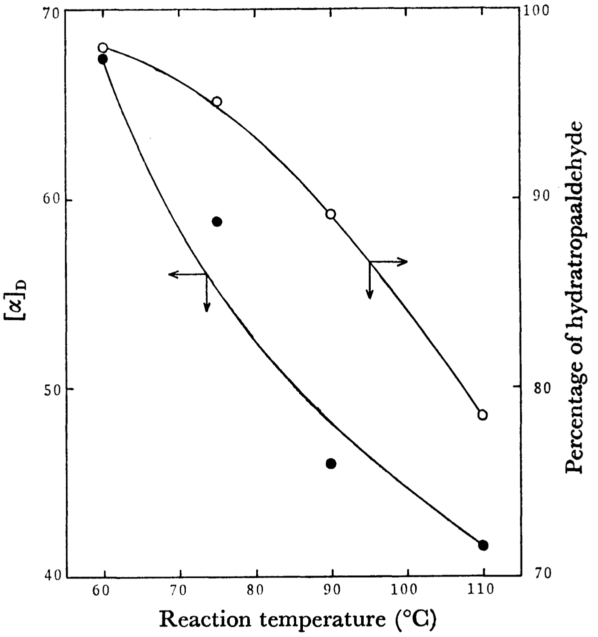


Fig. 3. Effects of reaction temperatures on the $[\alpha]_D$ value and the percentage of hydratropaaldehyde. ($P_{CO}=P_{H_2}=70$ atm, (R)-benzylmethylphenylphosphine /rhodium=4)

hydroformylation proceeds without any asymmetric induction. Therefore HRh(CO)$_2$P* may be the dominant species at larger ratios, and it may be alternated with HRh(CO)P$_2$* when the ratio becomes much larger. With catalytic activities, there may be no drastic differences among the species, judging from the results shown in Table 1. Therefore, it can be concluded that Equilibrium (5) is responsible for the relationship between the phosphine/rhodium ratio and the $[\alpha]_D$ value.[9]

As Fig. 2 shows, when nmdpp was used the effect on the $[\alpha]_D$ value was very different from that in the case of (R)-benzylmethylphenylphosphine. Thus, the $[\alpha]_D$ value decreased monotonously from +1.28° to −1.61° when the phosphine/rhodium ratio increased gradually from 2: 1 to 50: 1. The configuration of hydratropaaldehyde was reversed from S to R at a ratio around 14: 1. These results clearly suggest the participation of the equilibrium mentioned above. It seems reasonable that, when the phosphine/rhodium ratio is smaller, HRh(CO)$_2$P*, which may be responsible for the formation of S-aldehyde, is predominant, and that HRh(CO)P$_2$*, responsible for the formation of R-aldehyde, may take the place of HRh(CO)$_2$P* at larger ratios.

The difference in the behavior of the $[\alpha]_D$ value between these two phosphines may be attributed to the differences in their structures and coordination abilities.

On the other hand, the percentage of hydratropaaldehyde was slightly increased with an increase in the ratio both in the case of (R)-benzylmethylphenylphosphine and in that of nmdpp.

The Effect of the Reaction Temperature. The relationships between the reaction temperature and the $[\alpha]_D$ value, and the percentage of hydratropaaldehyde respectively, were examined under the conditions of a phosphine/rhodium ratio of 4: 1 for (R)-benzylmethylphenylphosphine, or one of 2: 1 for nmdpp, and with initial partial pressures of carbon monoxide and hydrogen of 70 atm. The results are illustrated in Figs. 3 and 4.

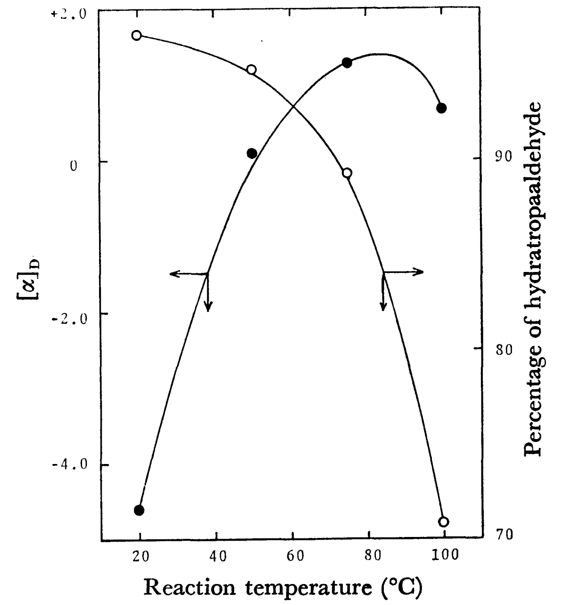


Fig. 4. Effects of reaction temperatures on the $[\alpha]_D$ value and the percentage of hydratropaaldehyde. ($P_{CO}=P_{H_2}=70$ atm, neomenthyldiphenylphosphine/ rhodium=2)

As Fig. 3 shows, when (R)-benzylmethylphenylphosphine was used as a chiral ligand, the $[\alpha]_D$ value of hydratropaaldehyde increased almost proportionally with a decrease in the reaction temperature. The $[\alpha]_D$

value reached +67° at 60 °C.* In considering the effect of the reaction temperature on the $[\alpha]_D$ value, two factors may be mainly taken into account: the reaction rate and the stability of the conformations of the reaction intermediates. Lowering the reaction temperature made the overall reaction slow down (see Tables 1 and 2). Though the real mechanism of the asymmetric induction is not clear, the reactions involving the diastereomeric key intermediate, which decides the configuration of the product, may also become slower, and so the stereoselection may be effective. About the second factor, the conformation and configuration of catalytically-active species and reaction intermediates may be more stable at lower temperatures. This means that the chiral environment at the reaction site is fixed and that the epimerization of the intermediates (the racemization of the alkyl or acyl group of the intermediates) does not occur easily. This factor, therefore, may result in a high $[\alpha]_D$ value.

In the case of nmdpp, a different type of relationship was observed. When the reaction temperature was lowered from 100 to 75 °C, the $[\alpha]_D$ value increased by a factor of about 2. This dependency is analogous to that in the case of (*R*)-benzylmethylphenylphosphine. However, the $[\alpha]_D$ value decreased when the temperature lowered further (50 and 20 °C). Thus, it was +1.28° at 75 °C, nearly zero at 50 °C, and −4.61° at 20 °C with a change in the configuration of hydratropaaldehyde from *S* to *R*. These facts clearly imply that the mode of the stereochemical control is delicately altered by changing the reaction temperature. The phosphine coordinated to rhodium can rotate around the coordination bond axis, and several metastable conformations of the catalytically-active species are possible. Therefore, the unexpected phenomenon may be attributed to this type of conformational alternation in the catalyst molecule. This conformational factor may be rather important with nmdpp, for neomenthyl group has three asymmetric carbons. On the other hand, as has been described above, the phosphine/rhodium ratio affects the $[\alpha]_D$ value and the configuration; these results have been discussed from the standpoint of the number of the phosphine coordinated to rhodium. The effect of the reaction temperature can be partly explained on the basis of this consideration. Lowering the reaction temperature has the same effect on the $[\alpha]_D$ value as the increase in the phosphine/rhodium ratio. Therefore, it is likely that the number of the phosphine on the rhodium is larger at lower temperatures. The unexpected phenomenon of the effect of the reaction temperature may also be attributed to this factor.

As is shown in both Figs. 3 and 4, the percentage of hydratropaaldehyde gradually decreases as the reaction temperature becomes higher. Previous work[10)] in this laboratory has demonstrated that α-phenylpropionyltetracarbonylcobalt, which is formed by the reaction of hydridotetracarbonylcobalt with styrene under a carbon monoxide atmosphere, easily undergoes a skeletal isomerization to give the β-isomer, and that this type of isomerization is accelerated by elevating the reaction temperature. Under the conditions of the asymmetric hydroformylation;

$$PhCH(CH_3)CORh(CO)_{3-n}P_n^* \longrightarrow PhCH_2CH_2CORh(CO)_{3-n}P_n^* \quad (6)$$

an analogous isomerization seems to occur; therefore the percentage of hydratropaaldehyde decreases with an increase in the reaction temperature.

The Effect of the Partial Pressure of Carbon Monoxide. The effects of the partial pressures of carbon monoxide on the $[\alpha]_D$ value and the percentage of hydratropaaldehyde were examined by the use of (*R*)-benzylmethylphenylphosphine under the following

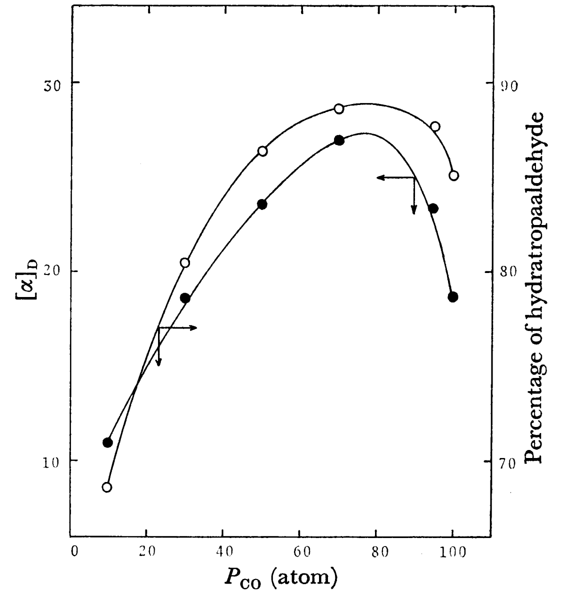


Fig. 5. Effects of partial pressures of carbon monoxide on the $[\alpha]_D$ value and the percentage of hydratropaaldehyde. (P_{H_2}=50 atm, 110 °C, (*R*)-benzylmethylphenylphosphine/rhodium=2)

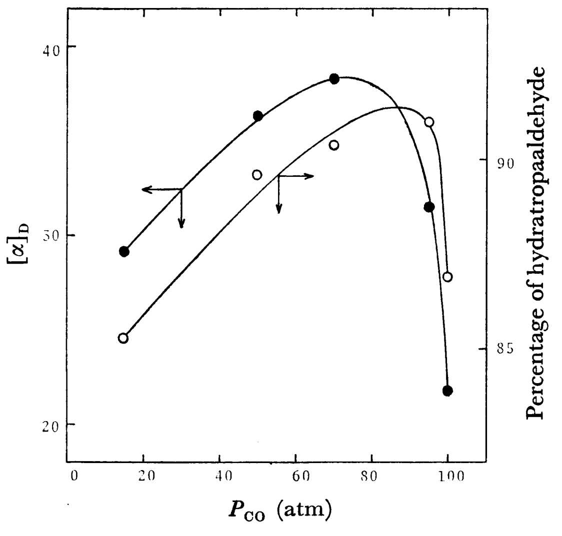


Fig. 6. Effects of partial pressures of carbon monoxide on the $[\alpha]_D$ value and the percentage of hydratropaaldehyde. (P_{H_2}=50 atm, 110 °C, (*R*)-benzylmethylphenylphosphine/rhodium=3)

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* Taking the optical purity of the phosphine (76.6%) into consideration, this optical rotation indicates a 52% optical yield.

conditions; 110 °C, an initial partial pressure of hydrogen of 50 atm, and a phosphine/rhodium ratio of 2: 1 or 3: 1. The results are illustrated in Figs. 5 and 6.

As Figs. 5 and 6 show, the $[\alpha]_D$ value and the percentage of hydratropaaldehyde at first increased monotonously to a maximum, and then decreased with an increase in the partial pressure of carbon monoxide, when the other reaction conditions were fixed. These relations may be partly explained by the equilibrium of the active species. As the partial pressure of carbon monoxide increases, the Equilibrium (5) is shifted to the left; this shift brings about a decrease in the $[\alpha]_D$ value and the percentage of hydratropaaldehyde, as has been described in connection with the effect of the phosphine/rhodium ratio. The tendency of the right-hand half of the curves in Figs. 5 and 6 to decrease may be attributed to this factor. However, the left-hand half can not be explained clearly.

In contrast with the results shown in Figs. 5 and 6, the change in the partial pressure of carbon monoxide did not result in any appreciable effect at the phosphine/rhodium ratio 4: 1 (see Exps. No. 4 and 9 in Table 1). The (5) equilibrium seems to lie very far to the right at larger ratios; therefore, the equilibrium is not profoundly affected by changing the partial pressure of carbon monoxide in the range examined.

The Effect of the Partial Pressure of Hydrogen. The effects of the initial partial pressure of hydrogen were also examined; the results are shown in Figs. 7 and 8. As Figs. 7 and 8 show, the $[\alpha]_D$ value and the percentage of hydratropaaldehyde increased monotonously as the partial pressure increased, when the phosphine/rhodium ratio, the partial pressure of carbon monoxide, and the temperature were fixed at 2: 1 or 3: 1, 50 atm, and 110 °C respectively.

As has been described above, the effect of the partial pressure of carbon monoxide was much larger at a phosphine/rhodium ratio of 3: 1 or 2: 1 than that at the 4: 1 ratio. This observation is also applicable to the present case. At the 4: 1 ratio, no significant effect of the partial pressure of hydrogen was observed (see Exps. No. 4 and 17 in Table 1).

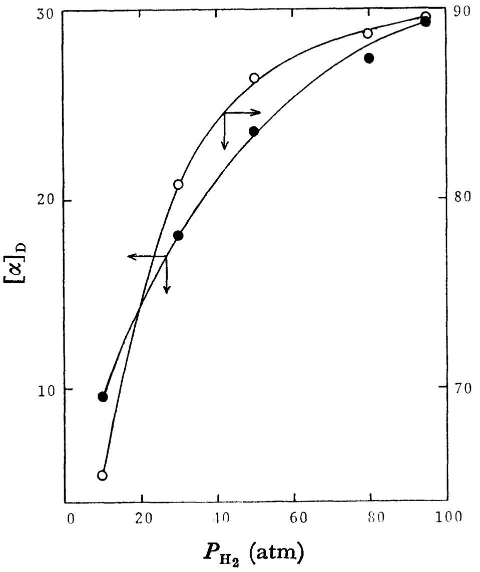


Fig. 7. Effects of partial pressures of hydrogen on the $[\alpha]_D$ value and the percentage of hydratropaaldehyde. (P_{CO}=50 atm, 110 °C, (*R*)-benzylmethylphenylphosphine/rhodium=2)

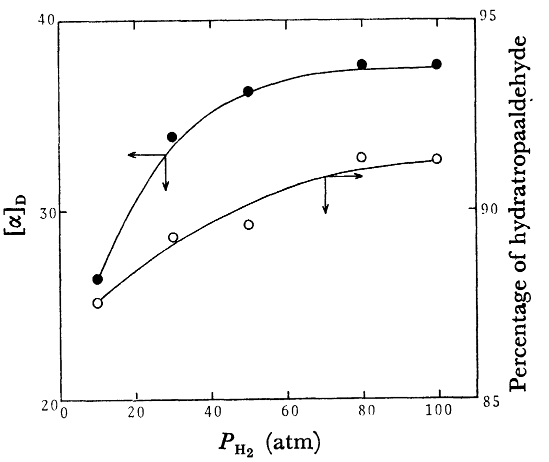
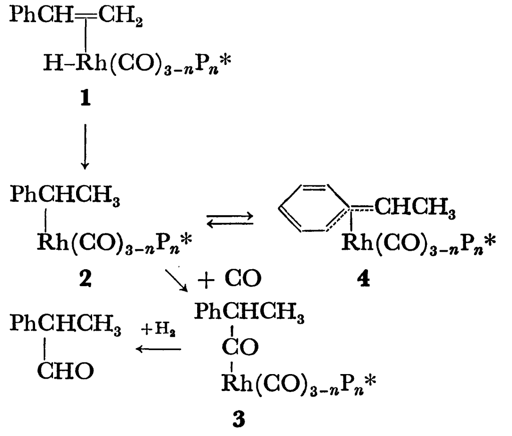


Fig. 8. Effects of partial pressures of hydrogen on the $[\alpha]_D$ value and the percentage of hydratropaaldehyde. (P_{CO}=50 atm, 110 °C, (*R*)-benzylmethylphenylphosphine/rhodium=3)

General Discussion. As has been mentioned above, the $[\alpha]_D$ value and the percentage of hydratropaaldehyde show a fairly good parallelism in Figs. 5—8. This parallelism seems to indicate that the $[\alpha]_D$ value is also dependent on the route through which the hydratropaaldehyde is formed. According to the generally-accepted mechanism of hydroformylation, hydratropaaldehyde is thought to be formed *via* a styrene–rhodium π-complex (**1**), an α-phenethyl–rhodium complex (**2**), and an α-phenylpropionyl–rhodium complex (**3**) as intermediates. However, styrene shows behavior different from that of simple olefins in hydroformylation. With simple 1-olefins, the formylation mainly occurs on a terminal carbon to give a straight-chain aldehyde as a major product.[5] On the other hand, with styrene the inner carbon is predominantly formylated to give hydratropaaldehyde, a branched-chain aldehyde. Furthermore, with simple olefins an incremental addition of phosphine causes an increase in the percentage of the straight-chain aldehyde and a decrease in that of the branched-chain one, while with styrene an increase in the phosphine/rhodium ratio brings about an increase in the percentage of hydra-



tropaaldehyde. These facts show that styrene has a marked tendency to be formylated on the inner carbon. From these considerations, an alternative route which contains a π-benzyl-type complex (**4**) as an intermediate may reasonably be suggested. This is supported by the fact that a π-benzyl-rhodium complex is formed in the reaction of benzyl chloride and Rh(I) complexes ($RhClL(PPh_3)_2$, L; CO or PPh_3).11) This hypothesis of a participation of the π-benzyl-type complex is not only consistent with the fact that styrene is mainly formylated on the inner carbon, but is also reasonable in view of the stereoselectivity. Thus, in the asymmetric hydroformylation of olefins such as styrene derivatives, simple olefins, and unsaturated ethers, the stereoselectivity is highest in styrene, while that of the other olefins is far lower.12) The π-benzyl-type complex of styrene will construct a rigid conformation of the diastereomeric intermediate to make the asymmetric induction more effective. This is probably the reason why styrene shows a larger stereoselectivity than the other olefins examined in the asymmetric hydroformylation.

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