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Asymmetric Transfer Hydrogenation of Acetophenone with Rhodium(I) Complexes Containing Chiral Diphosphines

Catalysis by transition metal complexes of the reduction of several organic functions using alcohols as hydrogen source has recently been gaining ground as a potentially important reaction (*1–8*). Regioselective reduction (*9, 10*) and a few examples of asymmetric hydrogenation by this system in the presence of Ru (*11, 12*) and Ir (*13, 14*) complexes have been reported. However, a study on the intermediates involved in the catalytic cycle and in the "catalyst activation" in these systems is still lacking. With the aim of obtaining information on the structure of these species and on the various factors influencing the catalytic activity and the optical yields, we have undertaken a study on [Rh(diene)(chiral diphosphine)]$^+$ complexes as catalyst precursors in the asymmetric transfer hydrogenation of acetophenone. The change of the procatalyst during the "activation process" has been followed by ^{31}P NMR and CD spectroscopy.

All manipulations were carried out under an inert atmosphere. Isopropanol and acetophenone were distilled before use. Phosphine ligands were purchased from Strem Chemicals and were used as received. The [Rh(diene)P_2]$^+PF_6^-$ complexes were prepared as previously described (*15*).

The catalyst precursor (4×10^{-5} mol) was dissolved in 50 ml of deaerated isopropanol and the system was refluxed for 15 min. Then aqueous KOH was injected through a serum cap. The activation time started from the addition of the base, in the presence of which the color of the solution turned from yellow–orange to dark brown. Finally, the organic reactant was added.

The reaction was monitored by GLC using a Perkin–Elmer Sigma 3B chromatograph. At the end of the reaction the mixture of alcohol and ketone was recovered by distillation. The optical yields were determined with a Perkin–Elmer 141 polarimeter, using $[\alpha]_D^{21} = -43.5$ (neat) (*16*) for *S*(−)-1-phenylethanol. The enantiomeric excess (e.e.) values were corrected for the unreacted acetophenone. ^{31}P NMR spectra were recorded with a Bruker WP 60 apparatus at 24.28 MHz, using H_3PO_4 as external standard. CD spectra were run on a Jasco J-500A spectropolarimeter.

We have studied the asymmetric hydrogen transfer reaction from isopropanol to acetophenone, to give optically active alcohol

$$MePhC{=}O + Me_2CHOH \rightleftharpoons MePhCHOH + Me_2CO$$

This reaction is catalyzed by rhodium complexes of the type [Rh(diene)P_2]$^+$ (diene = norbornadiene (nbd) or 1,5-cyclooctadiene (cod); P_2 = chelating chiral phosphine: (−)-(2*S*,3*S*)-bis(diphenylphosphino)butane (chiraphos), (+)-(*R*)-bis(1,2-diphenylphosphino)propane (prophos). The presence of small amount of a strong base (KOH) and an appropriate activation of the procatalyst are necessary to achieve catalytic activity; such activation consists in keeping the catalyst precursor for a certain time in refluxing isopropanol and in the presence of the base.

Results obtained in the reduction of acetophenone are reported in Table 1. An inspection of Table 1 clearly shows the influence of the activation time on the optical yields. Using [Rh(diene)(chiraphos)]$^+$ as the catalyst precursor, the e.e. and the topicity (*17*) of the reduction is dependent on the activation time. Changes in the configu-

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TABLE 1

Asymmetric Hydrogen Transfer Reduction of Acetophenone Using Rhodium-Phosphine Compounds as Catalysts[a]

Run	Procatalyst[b]	Activation time[c] (h)	% Conversion (time, h)	Optical yield
1	A	0.0	76 (4)	8.3 R(+)
2	A	0.5	46 (4)	6.6 R(+)
3	A	20	68 (3)	11.6 S(−)
4	B	0.5	60 (3)	9.0 R(+)
5	B	20	60 (5)	11.2 R(+)
6	A_1	0.0	17 (7)	3.0 S(−)
7	A_1	0.5	17 (6)	5.7 R(+)
8	A_1	20	90 (5)	10.0 S(−)
9	B_1	0.5	93 (3)	7.0 R(+)
10	B_1	20	57 (5.5)	13.1 R(+)
11	C	0.0	30 (3)	24.9 R(+)
12	C	20	40 (6)	9.9 S(−)
13	D	0.0	38 (1)	3.9 R(+)
14	D	20	52 (5)	12.2 R(+)

[a] Reaction conditions: Procat. = 8×10^{-4} *M*, React./Cat. = 1000, KOH/Cat. = 8, in 50 ml i-PrOH at reflux.

[b] A, [Rh(nbd)(chiraphos)]$^+$; A_1, [Rh(cod)(chiraphos)]$^+$; B, [Rh(nbd)(prophos)]$^+$; B_1, [Rh(cod)(prophos)]$^+$; C, $[Rh_3(chiraphos)_3(OMe)_2]^+$; D, $[Rh_3(prophos)_3(OMe)_2]^+$.

[c] During activation time the procatalyst was kept in refluxing i-PrOH in the presence of KOH.

ration of the product depending on the experimental conditions were already observed in the reduction of acetophenone catalyzed by Ru–diop complexes (*12, 18*). These results were interpreted on the basis of a change in the mechanism and/or with the formation of different catalytic species.

The cationic rhodium complexes which we used catalyze the hydrogenation of prochiral olefins. Enantiomeric *N*-acylaminoacids are produced with about the same optical purity using *S,S*-chiraphos- or *R*-prophos derivatives. Our systems follow this simple rule only after an activation time of 20 h: as a general trend it appears that the optical yields obtained using rhodium–chiraphos or rhodium–prophos systems in these particular reaction conditions are similar, the topicity with respect to the chiral ligand being the same (compare runs 3,5 and 8,10 in Table 1).

The above-mentioned behavior is no longer followed for shorter activation times, where no regular trends in the configuration of the product mixture are found. Not only this, but substitution of nbd with cod in the procatalyst leads to an inversion of sign in the e.e. for a minor variation in the activation time (runs 1–3 and 6–8, Table 1).

As far as the catalytic activity is concerned, on the contrary, it does not seem to be greatly influenced by changes in the activation time. These results show that during the activation time a pronounced change occurs in the procatalyst to give species of different selectivity even though of rather similar catalytic activity. The reaction mixture was monitored during the activation time by ^{31}P NMR, and spectra are reported in Fig. 1. The starting complex [Rh(nbd)(chiraphos)]$^+$ (Fig. 1a: $\delta = 58$ ppm, $J_{Rh-P} = 153$ Hz) completely reacts in i-PrOH with KOH in a few minutes, to give two species (Fig. 1b), A (doublet at $\delta = 78$ ppm, $J_{Rh-P} = 184$ Hz) and B (doublet at $\delta = 80$ ppm, J_{Rh-P}

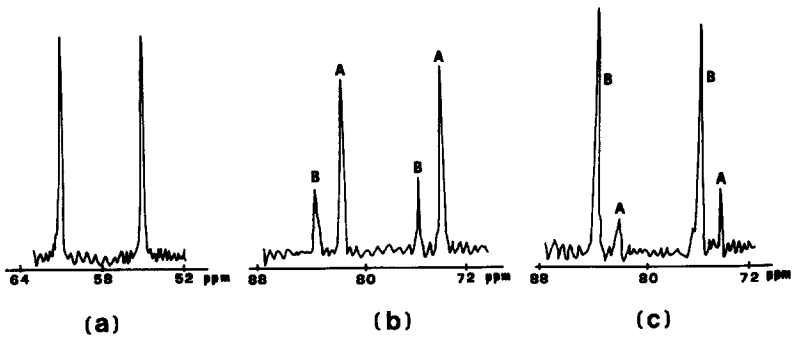


FIG. 1. ^{31}P NMR spectra of [Rh(nbd)(chiraphos)]$^+$ in i-PrOH in the presence of KOH, recorded at various times. (a) [Rh(nbd)(chiraphos)]$^+$, (b) after 5 min, (c) after 5 h.

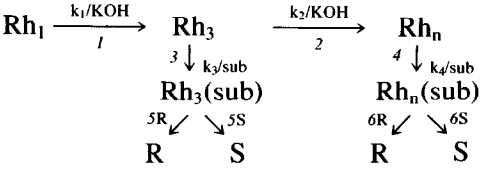
= 194 Hz). Species A slowly turns into species B; after 5 h only a small amount of A is still present (Fig. 1c). [Rh(cod)(chiraphos)]$^+$ shows the same pattern.

It is known (*19*) that when base (OMe^- or sterically hindered amine) is added to a methanolic solution of [Rh(nbd)(diphos)]$^+$ a new species identified as $[Rh_3(diphos)_3(OMe)_2]^+$ forms (^{31}P NMR doublet at δ = 72 ppm, J_{Rh-P} = 201 Hz). The structure of this compound corresponds to a regular triangular array of Rh atoms, each having one bidentate ligand coordinated, and with the P–Rh–P plane perpendicular to the Rh_3 plane. One triply bridging OMe^- ion is symmetrically located on each side of the Rh_3 plane.

We synthesized and isolated the chiraphos and prophos analogs of $[Rh_3(diphos)_3(OMe)_2]^+$ from MeOH and base (if i-PrOH is used in place of MeOH, the resulting compound appears to be unstable and decomposes very rapidly). The ^{31}P NMR spectrum of the chiraphos trimer in CH_2Cl_2 showed a doublet centered at 76 ppm (J_{Rh-P} = 197 Hz). When it was kept for 16 h in refluxing isopropanol in the presence of KOH, the spectrum modified to that of species B (see Fig. 1c).

The trimeric compounds $[Rh_3(P_2)_3(OMe)_2]^+$ (P = chiraphos or prophos) were used as catalysts to reduce acetophenone in isopropanol (runs 11–14, Table 1). In particular runs 11,12 and 13,14 should be compared with runs 2,3 and 4,5 for chiraphos and prophos, respectively. The catalytic activities are not completely comparable probably because of the presence of the methoxy group in the trimer used in runs 11–14. The results support the hypothesis that the main species present after 0.5 h of activation could be the trimeric one (species A in Fig. 1), which is selective toward *R*(+)-1-phenylethanol. Longer times of reaction with KOH lead to a different catalytic species of unknown nuclearity (Rh_n) of high symmetry (species B in Fig. 1), which is selective toward the *S*(−) isomer. We also monitored the activation process via CD, the relative spectra being reported in Fig. 2. These spectra suggest that both [Rh(cod)(chiraphos)]$^+$ and $[Rh_3(chiraphos)_3(OMe)_2]^+$, when left for a long time in refluxing isopropanol and in the presence of KOH, give the same final species (compare spectra 2 and 4 in Fig. 2).

On the basis of the above considerations, we propose the following scheme for the activation process:



where Rh_1 is the catalyst precursor, Rh_3 is the trimer and Rh_n is the final species of unknown nuclearity. Apparently the first step is the formation of Rh_3 species, and the selectivity of the system seems to be determined by the relative rates of reactions 2,3,4,5, and 6. ^{31}P NMR spectra of [Rh(diene)(chiraphos)]$^+$ were recorded also in the presence of acetophenone to verify the existence of a preferential mode of binding of the prochiral ketone to the catalyst. Unfortunately, no conclusions could be drawn from these spectra, though the fast formation of Rh_3 species was observed.

The results of Table 1 can be rationalized in terms of activation energy for paths 5*R*, 5*S* and 6*R*, 6*S*. That is to say, apparently the trimeric species formed at short activation times favors the reduction to R enantiomer for aromatic ketones owing to the lower energy of path $1 \rightarrow 3 \rightarrow 5R$.

By changing the diolefin some unexpected differences can be noted in the catalytic behavior (compare runs 1–3 and 6–8 of Table 1). At longer activation times an Rh_n species is formed and the results are independent of the nature of the coordinated diolefin (runs 3 and 8). At short activation times some differences both in catalytic activity and in selectivity are found. However, as reported above, ^{31}P NMR spectra performed during the activation process did not reveal any significant differ-

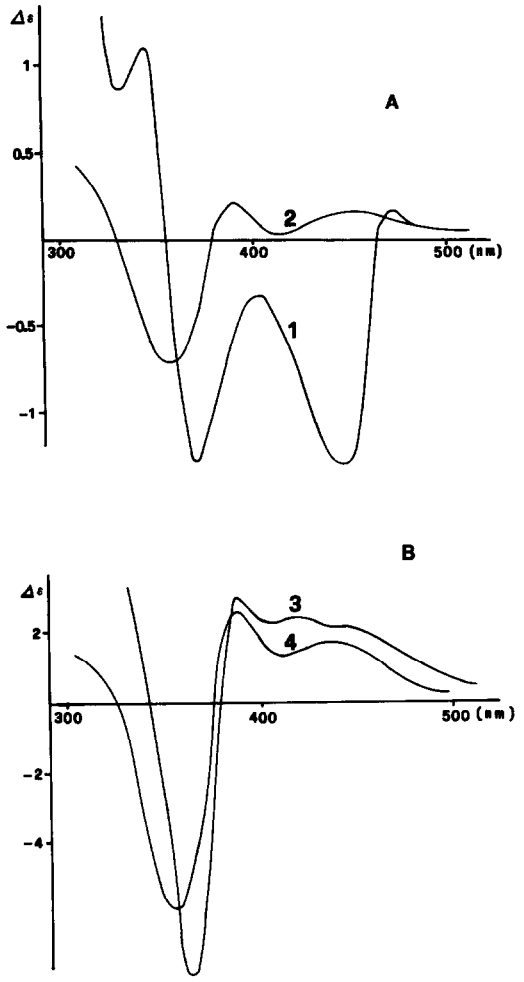


FIG. 2. CD spectra in i-PrOH obtained in various conditions. (A) curve 1, $[Rh(cod)(chiraphos)]^+$; curve 2, $[Rh(cod)(chiraphos)]^+$ after 20 h with KOH. (B) curve 3, $[Rh_3(chiraphos)_3(OMe)_2]^+$; curve 4, $[Rh_3(chiraphos)_3(OMe)_2]^+$ after 20 h with KOH.

ences between the nbd and cod systems. We feel that this apparent discrepancy can be mainly attributed to the different concentrations which must be used in performing the two experiments (^{31}P NMR and catalysis). In fact, in the experimental conditions of Table 1 both the leaving ability of the diolefin (nbd > cod) and the presence of the organic reactant could be of great importance in the activation process.

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