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# ASYMMETRIC TRANSFER HYDROGENATION OF KETONES CATALYZED BY PHOSPHINE-RHODIUM(I) AND -IRIDIUM(I) COMPLEXES

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## Summary

The asymmetric hydrogen transfer from propan-2-ol to prochiral ketones is effectively catalyzed by diphosphine complexes of iridium and rhodium. The influence of the reaction conditions on the activity and selectivity of the catalysts has been investigated.

## Introduction

The hydrogenation reaction of unsaturated substrates catalyzed by transition metal complexes has received much attention over the years. Catalysts containing optically active ligands (essentially phosphines) have been widely used with success in reductions, with high optical yields, of many prochiral organic substrates, most frequently aminoacid precursors. Several reviews are available [1–5]. The use of alcohols or other organic compounds as a source of hydrogen is currently receiving increasing attention, and with transition metal complexes as catalysts several organic functions have been reduced by such hydrogen transfers, e.g. carbon–carbon double bonds [6–9], ketones (to alcohols) [10–12] and imines (to amines) [13].

Regioselective reduction has also been successfully carried out by transfer hydrogenation. For instance $\alpha$, $\beta$-unsaturated aldehydes have been reduced to the corresponding unsaturated alcohols in the presence of an iridium catalyst [14], and more recently non conjugated unsaturated ketones have also been reduced to the corresponding unsaturated alcohols by phosphine-rhodium and -iridium systems [15].

Asymmetric transfer hydrogenation catalyzed by transition metal compounds containing coordinated chiral ligands or carried out in chiral solvents has received

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little attention, and only a few examples have been reported. Prochiral unsaturated esters and acids were reduced by hydrogen transfer using $[Ru_2Cl_4(\pm)(diop)_3]$ in various alcohols [16], with a maximum optical yield of 26.4%. Ketones were reduced with $[H_4Ru_4(CO)_8((-)\text{-diop})]$ as catalyst [17], but optical yields did not reach 10%.

Enantioselective reduction of ketones by hydrogen transfer was achieved using cationic iridium complexes of the type $[Ir(1,5\text{-cyclooctadiene})(chel)]^+$, where chel is an optically active Schiff base [18]. Recently we reported the reduction of ketones by the same method with iridium complexes containing chiral diphosphines as catalysts which gave an optical yield of 30% [19]. A study of the intermediates involved in the catalytic cycle and in the "catalyst activation" by rhodium complexes in these systems has been reported recently [20]. We describe here the catalytic reduction of prochiral ketones in different solvents, with rhodium(I) and iridium(I) complexes containing chiral phosphines as ligands. The influence of the activation time on the optical yield is also considered.

## Results and discussion

We studied the asymmetric hydrogen transfer reaction from propan-2-ol to various prochiral ketones, to give optically active alcohols

$$R^1R^2C{=}O + Me_2CHOH \rightleftharpoons R^1R^2CHOH + Me_2CO$$

This reaction is catalyzed by complexes of the type $[M(diene)P_2]^+$ (M = Rh or Ir; diene = norbornadiene (nbd) or 1,5-cyclooctadiene (cod); $P_2$ = chiral diphosphines: (−)-(2*S*,3*S*)-bis(diphenylphosphino)butane (chiraphos), (+)-(*R*)-bis(1,2-diphenylphosphino)propane (prophos), (+)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (diop)).

Results obtained with a variety of substrates are reported in Table 1 for rhodium complexes and Tables 2 and 3 for iridium. The presence of a small amount of the strong base KOH and appropriate activation of the procatalysts are necessary to achieve catalytic activity. The method of activation depends on the metal used; in the case of rhodium it involves keeping the catalyst precursor for a certain time in refluxing propan-2-ol in the presence of base whereas when iridium is used, the procatalyst must be kept at reflux in propan-2-ol for some time (denoted by $T_1$) before KOH is added and the resulting solution is refluxed for a further time (denoted by $T_2$). During time $T_1$ the deep red solution becomes yellow as a result of a reaction of $[Ir(cod)P_2]^+$ with propan-2-ol; from this solution we isolated a yellow compound which could not be characterized. However, its $^1H$ NMR spectrum showed signals which can be attributed to bridging hydrides at −7 ppm and terminal hydrides at −20 ppm. Consistently the IR spectrum in Nujol mull shows a band at 2175 $cm^{-1}$ attributable to $\nu$(Ir–H). The $^{31}P$ NMR spectrum shows broad signals which could be indicative of a non rigidity of the molecule. These features suggest that the species is analogous to a hydrido complex prepared by Crabtree et al. [21], which was also converted by treatment with KOH into the catalytically active system.

Some features of Tables 1 and 2 merit discussion. The most interesting is the influence of the activation time on the catalytic activity and optical yield. With both rhodium and iridium complexes the optical yield and even the topicity [22] of the reduction depend on the activation time in the case of substrates having at least one

TABLE 1

ASYMMETRIC HYDROGEN TRANSFER REDUCTION OF PROCHIRAL KETONES USING PHOSPHINERHODIUM COMPOUNDS AS CATALYST PRECURSORS[a]

| Run | Procatalyst[b] | Substrate | Act. time[c] (h) | Conversion (%) (time (h)) | Optical yield (%) |
|---|---|---|---|---|---|
| 1 | A | PhCOEt | 0.5 | 59 (4) | 34.3 (*R*)(+) |
| 2 | A | | 20 | 58 (4) | 1.4 (*S*)(−) |
| 3 | B | | 0.5 | 54 (4) | 11.6 (*R*)(+) |
| 4 | B | | 20 | 61 (6) | 22.3 (*R*)(+) |
| 5 | A | $PhCOPr^n$ | 0.5 | 53 (5.5) | 6.7 (*R*)(+) |
| 6 | A | | 20 | 46 (5.5) | 15.3 (*S*)(−) |
| 7 | A | MeCOEt | 0.5 | 70 (4) | 3.1 (*S*)(+) |
| 8 | A | | 20 | 88 (6) | 3.4 (*S*)(+) |
| 9 | B | | 0.5 | 80 (1) | 1.2(*R*)(−) |
| 10 | A | MeCOHx[d] | 0.5 | 41 (3) | 8.5 (*S*)(+) |
| 11 | A | | 20 | 93 (6) | 6.0 (*S*)(+) |
| 12 | B | | 0.5 | 87 (3) | 4.7 (*R*)(−) |
| 13 | B | | 20 | 95 (3) | 4.5 (*R*)(−) |
| 14 | A | $MeCOPr^i$ | 0.5 | 60 (3) | 4.6 (*S*)(+) |
| 15 | B | | 0.5 | 78 (1) | 2.8 (*R*)(−) |
| 16 | A | $MeCOBu^t$ | 0.5 | 41 (8) | 9.4 (*R*)(−) |
| 17 | B | | 0.5 | 38 (7) | 3.4 (*S*)(+) |
| 18 | A | $MeCOCH_2Ph$ | 0.5 | 33 (7.5) | 6.9 (*S*)(+) |
| 19 | A | | 20 | 86 (4) | 12.9 (*S*)(+) |
| 20 | A | PhCOMe[e] | 0.5 | 46 (4) | 6.6 (*R*)(+) |
| 21 | A | | 20 | 68 (3) | 11.6 (*S*)(−) |
| 22 | B | | 0.5 | 60 (3) | 9.0 (*R*)(+) |
| 23 | B | | 20 | 60 (5) | 11.2 (*R*)(+) |
| 24 | C | | 0.5 | 61 (5) | 1.5 (*S*)(−) |
| 25 | C | | 20 | 21 (6) | 0.4 (*S*)(−) |

[a] Reaction conditions: [Procat] $8\times10^{-4}$ *M*, Sub/Cat 1000, KOH/Cat 8, in 50 ml of i-PrOH at 82°C. [b] A: [Rh(nbd)(chiraphos)]$^+$; B. [Rh(nbd)(prophos)]$^+$; C: [Rh(nbd)(diop)]$^+$. [c] During the activation time the procatalyst is kept in refluxing i-PrOH in the presence of KOH. [d] Hx = hexyl. [e] Data from ref. 20.

aromatic ring directly bonded to the carbonyl group. In all other cases (aliphatic ketones, ketones where the phenyl group is not directly bonded to the carbonyl group or in prophos containing complexes) no such change of topicity is observed. Changes in the configuration of the product have been interpreted in the case of rhodium complexes in terms of the formation of species such as $[Rh_3(P_2)_3(OR)_2]^+$ which could have a different selectivity [20].

As mentioned above, the procatalyst $[Ir(cod)P_2]^+$ reacts during the activation time in propan-2-ol to give an iridium compound which further reacts in the presence of KOH. All these reactions markedly influence the selectivity, which is thus greatly affected by a change in the activation time.

The catalytic activity, in contrast does not seem to be greatly influenced by changes in the activation time or in the ketone. In the hydrogenation of ketones catalyzed by transition metal complexes both reaction rates and optical yields are usually lower for aliphatic than for aromatic ketones [17,23]. This was timed in our experiments only for the optical yields, and the reaction rates are sometimes even higher for aliphatic ketones (see Table 1). It is possible that an interaction between the aromatic ring of ketones and those of the chiral ligands is mainly responsible for

TABLE 2

ASYMMETRIC HYDROGEN TRANSFER REDUCTION OF $PhCOCH_3$ WITH PHOSPHINEIRIDIUM COMPOUNDS AS CATALYST PRECURSORS [a]

| Run | Procatalyst [b] | Act. time [c] (h) | | Conversion (%) (h) | Optical yield (%) |
|---|---|---|---|---|---|
| | | $T_1$ | $T_2$ | | |
| 1 | A | 0.25 | 0.5 | 36 (51) | 13 (*S*)(−) |
| 2 | A | 2 | 0.5 | 48 (30) | 28 (*S*)(−) |
| 3 | A | 7 | 0 | 27 (24) | 24 (*S*)(−) |
| 4 | A | 7 | 0.5 | 41 (22) | 12 (*S*)(−) |
| 5 | A | 7 | 3 | 36 (21) | 4 (*S*)(−) |
| 6 | A | 7 | 15 | 42 (9) | 11 (*R*)(+) |
| 7 | B | 0.25 | 0.5 | 91 (32) | 4 (*S*)(−) |
| 8 | B | 1.5 | 0.5 | 67 (6.5) | 30 (*S*)(−) |
| 9 | B | 15 | 0.5 | 58 (9) | 26 (*S*)(−) |
| 10 | B | 15 | 1.5 | 60 (6.5) | 39 (*S*)(−) |
| 11 [d] | B | 15 | 3 | 68 (2.5) | 51.5 (*S*)(−) |
| 12 | B | 15 | 5.5 | 71 (2.5) | 58 (*S*)(−) |

[a] Reaction conditions: [Procat] $8\times10^{-4}$ *M*, Sub/Cat 535, KOH/Cat 8, in 50 ml of i-PrOH at 82°C. [b] A: $[Ir(cod)(chiraphos)]^+$; B: $[Ir(cod)(prophos)]^+$. [c] A or B are kept at 82°C in i-PrOH for $T_1$ and in the presence of KOH for $T_2$. [d] KOH/Cat 16.

TABLE 3

OPTICAL YIELDS OBTAINED IN REDUCTIONS OF KETONES USING $[Ir(cod)P_2]^+$ AS PROCATALYST

| Substrate | $P_2$ | | |
|---|---|---|---|
| | chiraphos [a] | prophos [b] | diop [c] |
| PhCOMe | 24 (*S*)(−)<br>11 (*R*)(+) [d] | 58 (*S*)(−) | 14 (*S*)(−) |
| PhCOEt | 19 (*R*)(+) | 66 (*S*)(−) | |
| $PhCOPr^n$ | | 56 (*S*)(−) | |
| $PhCOPr^i$ | | 51 (*S*)(−) | |
| MeCOHx | 6 (*S*)(+) | 17 (*S*)(+) | |

[a] Methods of activation used: Run 3 of Table 2. [b] Run 12 of Table 2. [c] $T_1 = T_2 = 0.5$ h. [d] Run 6 of Table 2.

the enantiotopic face discriminating complexation of the carbonyl group to the rhodium atom which is necessary for asymmetric induction. A different type of interaction of the carbonyl group with the metal atom could also operate, and it has been suggested that ketones may be *n*- or $\pi$-coordinated depending on the oxidation state of rhodium [24].

Stronger interaction should lead to higher yields. Hydrogenation of aminoalkyl aryl ketones using the rhodium-diop catalyst gives enantioselectivities of up to 95% [25]. High e.e. values achieved with these ketones are thought to be due to the simultaneous coordination of nitrogen and oxygen atoms of the substrates to the central atom, which would lead to a more rigid structure of the intermediate. A similar effect is responsible for the high optical yield achieved in the hydrogenation of *N*-acylaminocinnamic acid derivatives [26].

## Experimental

*Chemicals*

Propan-2-ol and sec-butanol were distilled over CaO before use and stored under an inert atmosphere. Benzene was distilled over sodium wire before use. Phosphine ligands were purchased from Strem Chemicals and used as received.

*Complexes*

$[M(diene)Cl]_2$ and $[M(diene)P_2]^+$ (M = Rh, Ir; diene = norbornadiene (nbd) or 1,5-cyclooctadiene (cod); $P_2$ = bidentate phosphine) were prepared by published procedures [27–30]. $[Ir(cod)P_2]^+$ ($P_2$ = chiraphos or prophos) were prepared by adding stoichiometric amount of the ligand to a suspension of $[Ir(cod)(py)_2]^+$ [31] in an oxygen-free 2/1 $CH_3OH/H_2O$ mixture.

*Procedure*

All the reactions were carried out in refluxing propan-2-ol under a stream of $N_2$ with magnetic stirring. The equipment consisted of a 100 ml three-necked round bottom flask fitted with a condensor and a gas inlet and outlet. The catalyst was activated as follows:

*(a) Rhodium complexes.* The catalyst precursor, $[Rh(diene)P_2]^+$ ($4 \times 10^{-5}$ mol) was dissolved in 50 ml of deaerated propan-2-ol, the system was brought to reflux and kept at 82°C for 15 min, then aqueous KOH was injected through a serum cap. In the presence of the base the colour of the solution turned from yellow-orange to dark brown. Finally the substrate was carefully added from a dropping funnel thermostated at 60°C.

*(b) Iridium complexes.* A solution of the catalyst precursor, $[Ir(diene)P_2]^+$ ($4 \times 10^{-5}$ mol), in 50 ml of deaerated propan-2-ol was refluxed for time $T_1$ (Table 2), during which the solution turned from dark to yellow. Aqueous KOH was then injected through a serum cap and the solution refluxed for time $T_2$ (Table 2).

The reactions were monitored by GLC, using a Perkin–Elmer Sigma 3B chromatograph, equipped with a thermal conductivity detector, helium as carrier gas and a Carbowax 20M column. At the end of the reaction, the solvent was evaporated off and the residual mixture (alcohol and ketone) distilled at reduced pressure. The composition of the distillate was determined by GLC.

The optical yields were determined by optical rotation measurements with a Perkin–Elmer 141 polarimeter, using the following values for the optically pure alcohols: (*S*)(−)-1-phenylethanol $[\alpha]_D^{21}$ −43.5° (neat) [32], (*S*)(−)-1-phenylpropanol $[\alpha]_D^{22}$ −28.1° (neat) [33], (*R*)(+)-1-phenylbutanol $[\alpha]_D^{20}$ +43.6° (*c* 4.8 in $C_6H_6$) [33], (*S*)(+)-sec-butanol $[\alpha]_D^{20}$ 13.8° (neat) [34], (*S*)(+)-2-octanol $[\alpha]_D^{25}$ +10.2° (neat) [35], (*S*)(+)-methylisopropylcarbinol $[\alpha]_D^{25}$ +5.3° (neat) [36], (*S*)(+)-methyl-t-butylcarbinol $[\alpha]_D^{25}$ +8.1° (neat) [37], (*R*)(−)-methylbenzylcarbinol $[\alpha]_D$ −20.2° (*c* 5 in ether) [34].

The e.e. values were corrected for the unreacted ketone, and in the case of acetophenone and propiophenone, a calibration curve obtained by plotting the optical rotation of alcohol/ketone mixtures of the same optical purity against the alcohol/ketone ratio were used to determine the correct $[\alpha]_{Dmax}$ values.

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