# Effective Homogeneous Hydrogenation of α-Keto Esters Catalysed by Neutral Rhodium(I) Complexes with Phosphine Ligands and Application to the Asymmetric Synthesis of Lactates

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*Summary* The hydrogenation of α-keto esters was found to be catalysed effectively by neutral rhodium(I) complexes with phosphine ligands, and the asymmetric hydrogenation of pyruvates was carried out using the rhodium(I) complexes with chiral diphosphines 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)-butane (diop), and (2*S*,4*S*)-*N*-t-butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine (bppm), in dry benzene or tetrahydrofuran to give optically active lactates (36—76% enantiomeric excess) in nearly quantitative yields.

THE asymmetric hydrogenation of ketones catalysed by cationic rhodium complexes is attracting much interest.[1] However, the optical yields attained in the reaction have been rather low so far for simple prochiral ketones. Recently, Hayashi *et al.* developed a chiral ferrocenyldiphosphine[2] which brought about the effective asymmetric hydrogenation of prochiral ketones when it was employed as a ligand in a rhodium complex, and high optical yields were realized for the hydrogenation of pyruvic acid. Nevertheless, the asymmetric hydrogenation of methyl pyruvate catalysed by the same rhodium catalyst resulted in only 10% asymmetric induction.[3] We have found that neutral

Wilkinson-type catalysts are quite effective for the hydrogenation of α-keto esters although it is known that the corresponding neutral rhodium complexes exhibit only a low catalytic activity towards the hydrogenation of ketones, the Wilkinson catalyst itself, $[(Ph_3P)_3RhCl]$, being completely ineffective.[1f] We report here the effective homogeneous hydrogenation of pyruvate and phenylglyoxylate catalysed by neutral rhodium complexes with phosphine ligand and its application to the asymmetric hydrogenation of pyruvate using a new chiral diphosphine, bppm,[4] as chiral ligand, which gives the corresponding lactates with 66·3—75·8% optical purity in nearly quantitative yields. The results obtained on using diop[5] as chiral ligand are also described.

TABLE 1. Effects of hydrogen pressure on the rate of the hydrogenation of isobutyl pyruvate[a]

| Pressure of hydrogen/atm | Yield (%) of isobutyl lactate[b] $[(Ph_3P)_3RhCl]$ | [(dppb)Rh(S)Cl] |
|---|---|---|
| 1 | 44 | 22 |
| 20 | 98 | 95 |
| 50 | 100 | 100 |

[a] All reactions were carried out with 15 mmol of isobutyl pyruvate and $7·5 \times 10^{-2}$ mmol of the catalyst in 5 ml of dry benzene at 20 °C for 24 h. [b] The yield was estimated by g.l.c. analysis.

As Table 1 shows, the pressure of hydrogen exerts a large influence on the reaction rate, *viz.*, the hydrogenation of methyl, propyl, and isobutyl pyruvate catalysed by $[(Ph_3P)_3RhCl]$ or [(dppb)Rh(S)Cl] [dppb = 1,4-bis(diphenylphosphino)butane; S = solvent], was virtually within 20—30 h under an initial hydrogen pressure of 20—50 atm at ambient temperature, whereas it required 70—100 h under atmospheric pressure of hydrogen. The reaction rate is also markedly dependent upon the structure of the substrate, *e.g.*, the hydrogenation of ethyl phenylglyoxylate was fairly slow and 72 h was necessary to complete the reaction under a hydrogen pressure of 50 atm at 30 °C in tetrahydrofuran (THF). The solvent effects on the rate of the hydrogenation of isobutyl pyruvate are illustrated in the Figure. It is noteworthy that the effects of solvents on the catalytic activities of $[(Ph_3P)_3RhCl]$ and [(dppb)Rh(S)Cl] are considerably different from each other. The difference may principally be due to the *trans* configuration in the active species of the former catalyst and the *cis* configuration in the latter.

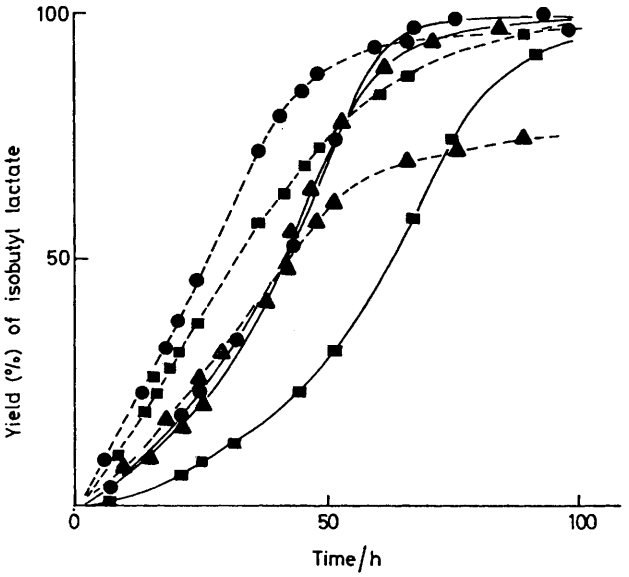


FIGURE. Solvent effects on the rate of the hydrogenation of isobutyl pyruvate (15 mmol) under atmospheric pressure of hydrogen at 20 °C in 5 ml of dry solvent: – – – –, with $[(Ph_3P)_3RhCl]$; ————, with [(dppb)Rh(S)Cl]. ● in $C_6H_6$; ■ in THF; ▲ in $C_6H_6$–MeOH (1:1).

In a typical experiment, the asymmetric hydrogenation of propyl pyruvate (1·95 g) was carried out in dry THF (4 ml) at 20 °C under an initial hydrogen pressure of

TABLE 2. Asymmetric hydrogenation of esters of pyruvic acid[a]

$$MeC(=O)CO_2R \xrightarrow[H_2]{[Rh]^*} MeC^*H(OH)CO_2R$$

| R | Ligand | Solvent[b] | Time /h | Conversion /% | $[\alpha]_D^{18-20}$ (neat) | Optical yield/% [c] |
|---|---|---|---|---|---|---|
| Me | bppm | $C_6H_6$ | 24 | 100 | +5·47 | 66·3 |
| | | THF | 24 | 97 | +5·40 | 65·4 |
| | | MeOH | 90 | 87 | +3·49 | 42·4 |
| | (−)diop | $C_6H_6$ | 24 | 100 | +2·62 | 31·7 |
| | | THF | 20 | 99 | +3·40 | 41·2 |
| | | THF[d] | 20 | 93 | +2·89 | 35·0 |
| | | Monoglyme | 20 | 99 | +3·12 | 37·8 |
| | | MeOH | 90 | 95 | +1·50 | 18·2 |
| Pr$^n$ | bppm | $C_6H_6$ | 24 | 99 | +9·17 | 75·8 |
| | | THF | 24 | 98 | +9·17 | 75·8 |
| | (−)diop | THF | 24 | 100 | +5·07 | 41·9 |
| | | THF[d] | 24 | 91 | +4·85 | 40·1 |
| Bu$^i$ | bppm | $C_6H_6$ | 24 | 100 | +10·70 | 70·7 |
| | | THF | 24 | 100 | +10·76 | 71·1 |
| | (−)diop | THF | 24 | 99 | +5·73 | 37·9 |

[a] All hydrogenations were run with 15 mmol of pyruvate, $3·8 \times 10^{-2}$ mmol of $[Rh(cod)Cl]_2$, and $9·0 \times 10^{-2}$ mmol of diphosphine in 4 ml of solvent at 20 °C under an initial hydrogen pressure of 20 atm. [b] Dry solvent was used unless otherwise noted. [c] Optical yields were calculated on the basis of reported values for the specific rotations of pure enantiomers: (*S*)-methyl lactate; $[\alpha]_D^{20}$ −8·25° (neat) (T. Purdie and J. C. Irvine, *J. Chem. Soc.*, 1899, 483), (*S*)-n-propyl lactate; $[\alpha]_D^{18}$ −12·1° (neat) (E. Wassmer and P. A. Guye, *Chem. Zentralbl.*, 1903, **2**, 1419), (*S*)-i-butyl lactate; $[\alpha]_D^{18}$ −15·1° (neat) (C. E. Wood, J. E. Such, and F. Scarf, *J. Chem. Soc.*, 1926, 1928). [d] 1% water was added.

20 atm in the presence of the rhodium catalyst (0·5 mol%) which was prepared *in situ* from $[Rh(cod)Cl]_2$ (cod = cyclo-octa-1,5-diene) and bppm. The reaction was virtually complete after 24 h (99% yield by g.l.c.). The reaction mixture was then distilled to give (*R*)-(+)-propyl lactate (1·79 g) in 90% yield: $[\alpha]_D^{18}$ + 9·17° (neat).

Similarly, methyl and isobutyl pyruvate were hydrogenated using the rhodium complex with bppm or diop as catalyst. The results (Table 2) show that the optical yield is clearly dependent on the nature of the chiral ligand employed, *i.e.*, bppm is much more effective than diop in the asymmetric induction. The optical yield attained in the case of propyl pyruvate by the use of bppm as chiral ligand (75·8%) is the highest known for the homogeneous asymmetric hydrogenation of keto esters.

The remarkable effect of solvent is also illustrated in Table 2 for the reduction of methyl pyruvate. It should be noted that a dry aprotic solvent, namely, benzene or THF, gives much better results than methanol does in the present system although a protic solvent, *e.g.*, methanol or ethanol, is usually employed[1] for good results in the hydrogenation of ketones catalysed by cationic rhodium complexes; also addition of small quantities of water (1%) to the present system does not increase the rate, but it decreases the extent of asymmetric induction. Therefore, it is strongly suggested that the mechanism of the present reaction is different from that proposed by Schrock and Osborn for reactions catalysed by cationic rhodium complexes.[6]

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