New Enantioselective Reactions catalysed by Cinchonidine-modified Platinum

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The conjugated diketones butane-2,3-dione and hexane-3,4-dione can be hydrogenated enantioselectively over Pt/silica modified by cinchonidine giving enantiomeric excesses in favour of (R)-(−)-3-hydroxybutan-2-one of up to 38% and of (R)-(−)-4-hydroxyhexan-3-one up to 33%.

Few heterogeneous catalysts exhibit enantioselectivity. The two reactions that are well known to proceed with high enantiomeric excess are (i) the hydrogenation of β-ketoesters catalysed by nickel modified by tartaric and similar acids[1] and (ii) the hydrogenation of α-ketoesters catalysed by platinum modified by cinchona alkaloids.[2] The mechanism in these reactions has recently been reviewed.[3] For example, methyl pyruvate is hydrogenated[4] in ethanolic solution (20 ml, 3.8 mol dm^{-3}) over 6.3% Pt/silica to racemic methyl lactate at 293 K and 10 bar pressure at a rate of ca. 50 mmol h^{-1} g$_{cat}$$^{-1}$. Modification of the catalyst by the pre-adsorption of the alkaloid cinchonidine A[4,5] causes the rate under comparable conditions to increase to ca. 1100 mmol h^{-1} g$_{cat}$$^{-1}$. (R)-(+)-Methyl lactate is formed preferentially with an enantiomeric excess of 65–80%; 94% has been reported under specially optimised conditions.[6] Modification of Pt with the near enantiomer cinchonine B imparts comparable enantio-selectivity in favour of (S)-(−)-methyl lactate. This reaction is almost enzymic in its specificity, being virtually confined to Pt as active metal, with the cinchona alkaloids as the only

effective modifiers and (until recently) α-ketoester hydrogen-ation the only reaction showing enantioselectivity. This last mentioned restriction has now been lifted.

Vicinal diketones are hydrogenated enantioselectively by cinchona-modified Pt. Butane-2,3-dione (Aldrich Ltd) is converted to racemic 3-hydroxybutan-2-one over unmodified 6.3% Pt/silica (the standard reference catalyst EUROPT-1
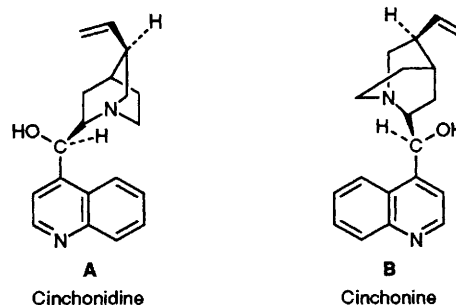

A

Cinchonidine

B

Cinchonine

1054

Table 1 Enantioselective hydrogenations, at 10 bar hydrogen pressure, of butane-2,3-dione **1** and hexane-3,4-dione **2** catalysed by 6.3% Pt/silica (EUROPT-1) modified by cinchonidine.

| Reactant | Solvent | | | Max rate/ mmol h^{-1} g$_{cat}^{-1}$ | Enantio- meric excess (%) |
	Modifica- tion[b]	Reaction	T/K		
1	CH$_2$Cl$_2$	CH$_2$Cl$_2$	268	600	38
1	CH$_2$Cl$_2$	CH$_2$Cl$_2$	273	775	38
1	CH$_2$Cl$_2$	CH$_2$Cl$_2$	293	1650	21
1[a]	CH$_2$Cl$_2$	CH$_2$Cl$_2$	293	1575	−10[c]
1	EtOH	EtOH	263	560	12
1	EtOH	EtOH	293	1650	8
1	MeCOMe	MeCOMe	293	4350	8
1	PhMe	PhMe	293	1825	12
1	CH$_2$Cl$_2$	EtOH	273	1550	23
1	CH$_2$Cl$_2$	EtOH	293	5225	12
1	CH$_2$Cl$_2$	MeCOMe	293	2950	12
2	CH$_2$Cl$_2$	CH$_2$Cl$_2$	293	625	33
2	EtOH	EtOH	293	675	18

[a] Modifier = cinchonine; pressure = 9 bar. [b] Catalyst preparation. [c] (S)-product formed in excess.

prepared by Johnson Matthey and characterised by the EUROCAT group[7–10] in dichloromethane solution (20 ml, 3.8 mol dm^{-3}) at 293 K and 10 bar pressure at 175 mmol h^{-1} g$_{cat}^{-1}$. Modification of the catalyst with cinchonidine (Aldrich Ltd) increased the rate under comparable conditions to 1650 mmol h^{-1} g$_{cat}^{-1}$ and the enantiomeric excess was 21% (50 m Cydex B capillary column, SGE Ltd). Enantiomeric excess was independent of conversion (13–98%), improved as temperature was lowered and depended on the solvent (Table 1). As with methyl pyruvate hydrogenation, modification with cinchonine provided an enantiomeric excess in favour of the (S)-product (entry 4, Table 1). Hydrogenation of hexane-3,4-dione (Aldrich Ltd) to 4-hydroxyhexan-3-one gave higher enantioselectivities under comparable conditions (compare entries 3 and 12, and 6 and 13, Table 1).

The sense of the enantioselectivity in methyl pyruvate hydrogenation and the origin of rate enhancement are both interpreted by a template model[3,4,11] according to which shaped ensembles of Pt atoms remain exposed when the alkaloid forms a non-close-packed adlayer at the Pt surface. The size of the methyl pyruvate molecule matches these shaped Pt ensembles well and a high degree of chirality is thereby induced; butane-2,3-dione on hydrogenation shows a lower chiral selectivity because it is of smaller molecular dimensions and its adsorption shows a correspondingly lower

preference for the configuration which provides the (R)-product on hydrogenation (cinchonidine modification). The higher enantiomeric excess that accompanies the hydrogenation of the larger hexane-3,4-dione is therefore expected.

Enantioselectivity and enhanced rate may also be interpreted in terms of a process involving a 1 : 1 dipolar interaction between adsorbed alkaloid and adsorbed reactant; such a process has been proposed at sites at the edges of metal crystalites where full templating cannot occur.[3] However, there is no reason to expect hexane-3,4-dione to exhibit a higher chiral selectivity than butane-2,3-dione at these sites.

The effect of cinchonidine as modifier is always to enhance the rates of formation of both (S)- and (R)-products but the latter to a greater extent. For example in the fastest reaction recorded in Table 1, (S)-product formation is increased from 88 to nearly 2300 mmol h^{-1} g$_{cat}^{-1}$ and (R)-product formation from 88 to 2925 mmol h^{-1} g$_{cat}^{-1}$. Solvent effect on rate will be discussed elsewhere,[12] but most rapid rates are obtained when the alkaloid is adsorbed onto the Pt from a solvent which is relatively inert towards the Pt surface.

Isolated ketones are not hydrogenated by cinchonidine-modified Pt under these conditions;[12] the presence of an activating function appears to be essential. The search for new chiral reactions at this Pt surface will now concentrate on the use of activated ketones that have molecular dimensions that are best accommodated by the shaped ensembles of Pt atoms as judged by molecular modelling studies.

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