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Enantioselective Hydrogenation

III. Methyl Pyruvate Hydrogenation Catalyzed by Alkaloid-Modified Iridium

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Enantioselective hydrogenation of methyl pyruvate, MeCOCOOMe to methyl lactate, MeCH(OH)COOMe, is catalyzed in solution at room temperature by supported iridium catalysts modified with cinchona alkaloids. Modification with cinchonidine or quinine yields R-lactate in excess, whereas modification with cinchonine or quinidine favors S-lactate formation. Ir/SiO_2 catalysts (20%) calcined at 393 to 573 K and reduced at 523 to 593 K were highly active for racemic hydrogenation in the absence of a modifier (rates typically 1.8 mol h^{-1} g_{cat}^{-1}) and were comparably active when modified with cinchonidine but gave an enantiomeric excess of about 30%. Use of higher calcination or reduction temperatures led to substantially inferior activity and selectivity. The high rates recorded for both racemic and enantioselective reactions are dependent on the catalysts being activated before use by a procedure involving exposure of the catalyst to air after the initial reduction. Use of a Cl-free precursor gave an Ir/SiO_2 catalyst (20%) of superior activity but inferior enantioselectivity. Ir/$CaCO_3$ (5%) was more active for racemic hydrogenation than for enantioselective hydrogenation, but provided the highest value of the enantiomeric excess 39%. Kinetics of reaction are reported. Exchange of H for D in 10,11-dihydrocinchonidine at room temperature over Ir/$CaCO_3$ occurred in the quinoline moiety but not in the quinuclidine ring system, indicating that the alkaloid was adsorbed to the Ir surface via the interaction of its π-electron system. For both silica-supported and calcium carbonate-supported Ir, the presence of chloride ion in the catalyst was advantageous for the achievement of enantioselectivity.

INTRODUCTION

Heterogeneous catalysts play an important role in industrial chemical processes in general but their development as agents for asymmetric synthesis, which is of rapidly growing importance in the pharmaceutical, agrochemical, and fine chemicals industries, is in its infancy. Hydrogenation of a prochiral precursor over conventional metal catalysts yields a racemic product; however, in a few cases the presence of a chiral substance at the catalyst surface serves to direct the reaction so that one enantiomer is formed preferentially. Of the many systems investigated only two have been the subject of detailed mechanistic investigation, namely Ni-catalyzed β-ketoester hydrogenation and Pt-catalyzed α-ketoester hydrogenation (1–5). The latter has its origins in the work of Lipkin and Stewart (6) and of Orito *et al.* (7) and has been studied recently in this laboratory and by Blaser and co-workers (8–16). Modification of supported Pt catalysts by the alkaloids cinchonidine or quinine causes the hydrogenation of methyl pyruvate, MeCOCOOMe, to methyl lactate, MeCH(OH)COOMe, to exhibit chiral selectivity in favor of R-lactate; enantiomeric excesses of 90% have been obtained (7, 15). Catalyst modification by the near enantiomeric alkaloids cinchonine and quinidine results in an excess of S-lactate. A mechanism has been proposed which correctly predicts the sense of the observed enantioselectivity and which interprets the enhanced rates that always attend this enantioselective hydrogenation over Pt (4, 16).

This reaction is almost enzymic in its specificity: it is virtually restricted to cinchona alkaloids as modifiers and to α-ketoester hydrogenation. Few experimental difficulties attend the catalysis of this reaction by Pt, provided the metal particle size is not too small (17), but attempts to use the other Group 8 metals frequently, indeed normally, fail. Blaser and co-workers have reported optical yields of 20 to 30% in ethyl pyruvate hydrogenation over modified Rh/Al_2O_3 at 75 bar pressure (13) but experiments in this laboratory at 10 bar pressure with a comparable catalyst have so far failed to register enantioselectivities greater than 4%. However, we have for the first time obtained reproducible enantioselectivities over a va-

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riety of supported alkaloid-modified iridium catalysts, which are the subject of this paper.

EXPERIMENTAL

Catalysts

Ir/Al_2O_3 catalyst. Preliminary studies were conducted with 5% Ir/Al_2O_3, total surface area 120 $m^2\ g^{-1}$ and metal surface area 14.4 $m^2\ g^{-1}$ (Johnson Matthey research sample).

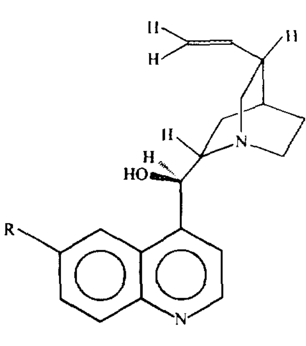
Ir/SiO_2 catalysts. Ir/SiO_2-1 (7%) (catalyst 1) was prepared by impregnation at room temperature of Cab-O-Sil silica (ca. 190 $m^2\ g^{-1}$) with a solution of chloroiridic acid ($H_2IrCl_6 \cdot 6H_2O$, assayed at 39.16% Ir, Johnson Matthey) in 4 wt% HCl. Excess solvent was removed under evacuation. The precursor was dried at 393 K for 18 h and calcined and samples were reduced at temperatures indicated later in the text.

Several batches of 20% Ir/SiO_2 were prepared by a similar method, by use of either a standard solution containing 10.15 mg ml^{-1} of Ir in 4 wt% HCl (Aldrich) as the iridium source, or an equivalent solution of $H_2IrCl_6 \cdot 6H_2O$. These materials are referred to as Ir/SiO_2-2 (catalyst 2).

Ir/SiO_2-3 (20%) (catalyst 3) was prepared similarly from a chloride-free precursor using a solution containing 9.98% Ir in nitric acid as the iridium source (Johnson Matthey).

$Ir/CaCO_3$ catalysts. Two batches of 5% iridium supported on calcium carbonate were supplied by Johnson Matthey ($Ir/CaCO_3$-4 (catalyst 4) and $Ir/CaCO_3$-5 (catalyst 5)); total surface area was ca. 10 $m^2\ g^{-1}$ and metal area ca. 4.5 $m^2\ g^{-1}$. These catalysts had chloride contents of 0.24 and 0.81%, respectively.

Materials



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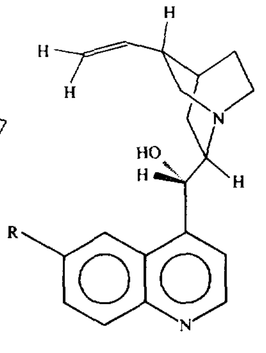

B

Methyl pyruvate (Fluka), cinchonidine (structure (A) above, R = H, Aldrich), quinine ((A), R = OMe, Ventron), cinchonine (structure (B), R = H, Hopkin and Williams), quinidine ((B), R = OMe, BDH), quinine-*N*-oxide (Alfred Bader), and EtOD (Sigma) were used as received, as were the solvents ethanol (AnalaR), dodecanol, toluene (AnalaR), and dichloromethane. 10,11-Dihydrocinchonidine was prepared by the partial hydrogenation of cinchonidine as described previously (9).

Procedures

A fresh sample of catalyst was used for each reaction. Typically, 0.10 g catalyst was pumped under high vacuum before reduction under 760 Torr hydrogen for 0.5 h (reduction temperatures: 5% Ir/Al_2O_3, 393 K; 20% Ir/SiO_2, see Tables 1 and 2; 5% $Ir/CaCO_3$, 593 K). The catalyst was then evacuated and modification was achieved by injection of a 5-ml aliquot of alkaloid solution (0.2 g alkaloid dissolved in 40 ml of the reaction solvent) through a septum onto the catalyst. The thoroughly wetted catalyst was transferred to an open beaker

TABLE 1

Initial Rates, R_i, and Values of the Enantiomeric Excess, ee, Obtained in Methyl Pyruvate Hydrogenation at 10 Bar Pressure and 298 K in Ethanol over Ir/SiO_2-1 and Ir/SiO_2-2 Catalysts Prepared from Chloride-Containing Precursors

	Preparation conditions				
Catalyst	$T_{calcination}$ (K)	$T_{reduction}$ (K)	Modifier[a]	R_i (mmol $h^{-1}\ g^{-1}$)	ee (%)
2	393	523	None[b]	60	0
2	393	523	None[c]	700	0
2	393	523	None[d]	1430	0
2	393	523	CD	1560	31
2	573	523	None[c]	680	0
2	573	523	CD	1400	33
2	773	523	CD	380	20
2	873	523	CD	310	11
2	1023	523	CD	210	7[e]
2	573	573	None[c]	470	0
2	573	573	None[d]	1760	0
2	573	573	CD	1780	13
2	773	473	CD	40	5
2	773	523	CD	380	20
2	773	683	CD	270	8
2	773	823	CD	230	3
1	393	523	CD	670	19
1	573	523	CD	630	14
1	773	523	CD	70	3

Note. Conversions were typically 90%.

[a] CD = cinchonidine, catalyst modification involved stirring in air.

[b] Catalyst activation by procedure 3 (anaerobic conditions), conversion <10%.

[c] Catalyst activation by procedure 2 (without stirring in air), conversions were typically 35%.

[d] Catalyst activation by procedure 1 (with stirring in air).

[e] Optical yield by polarimetry.

TABLE 2

Initial Rates, R_i, and Values of the Enantiomeric Excess, ee, Obtained in Methyl Pyruvate Hydrogenation at 10 Bar Pressure and 298 K in Ethanol over Ir/SiO_2-3 Catalysts Prepared from a Chloride-Free Precursor

Catalyst preparation conditions				
$T_{calcination}$ (K)	$T_{reduction}$ (K)	Modifier[a]	R_i (mmol h^{-1} g^{-1})	ee (%)
393	523	None[b]	920	0
393	523	None[c]	1970	0
393	523	CD	1790	15
393	593	None[c]	2120	0
393	593	CD	2010	15
573	523	CD	1170	11
773	523	CD	830	12

Note. Conversions were typically 90%.

[a] CD = cinchonidine, catalyst modification involved stirring in air.

[b] Catalyst activation by procedure 2 (without stirring in air), conversions were typically 35%.

[c] Catalyst activation by procedure 1 (with stirring in air).

and the remaining 35 ml of modifier solution was added. The slurry was stirred in air for 1 h, after which the catalyst was separated from the solution (which contained excess alkaloid) and transferred to the high-pressure reactor. This procedure is the same as that described previously for the modification of supported Pt catalysts in our studies and is based on the procedures originally reported by Orito *et al.* (7–9). For examination of racemic hydrogenation (in which no modifier was used) either exactly the same procedure was adopted (procedure 1) or the step in which the catalyst was stirred in air for 1 h was omitted (procedure 2) or the reaction was conducted anaerobically (procedure 3), in which case the reduced catalyst was stirred in solvent under a hydrogen atmosphere (760 Torr) in the autoclave for 1 h. In procedure 3 solvent and freshly distilled methyl pyruvate were subjected to three freeze–thaw cycles to remove dissolved gases.

Two high-pressure reactors were used, a Fischer Porter glass reactor and a Büchi glass autoclave. Standard reaction conditions were adopted, under which 10 ml of methyl pyruvate (113 mmol) was hydrogenated to methyl lactate under 10 bar hydrogen pressure at 293 K or other appropriate temperature. Solvent volumes were 20 ml (Fischer Porter) or 50 ml (Büchi). Each reactor was fitted with a computer-operated hydrogen admission system which maintained hydrogen pressure at 10 bar; the data systems recorded hydrogen uptake as a function of time and provided the value of the initial reaction rate, R_i in units of mmol h^{-1} (g catalyst)$^{-1}$. Since closely similar values of R_i, ±2%, were obtained whether or not methyl pyruvate was freshly distilled before use, our practice was to use the ester as received. No acceleratory period was observed (as was the case over Pt (8)) and hence, initial rates were determined over the first few minutes of reaction.

Experiments over 5% $Ir/CaCO_3$ were analyzed exactly as described previously (8, 9), conversion being determined by glc, and the enantiomeric excess of the distilled product was assessed by polarimetry and expressed as optical yield. Experiments over Ir/SiO_2 were analyzed by chiral glc (column: Cydex B, 50 m, SGE Ltd.) so that conversion and enantiomeric excess were determined simultaneously. The agreement between these two methods of analysis for the determination of enantioselectivity was demonstrated in Part II (9). Optical yield and enantiomeric excess are defined as %|(R-lactate − S-lactate)/(R-lactate + S-lactate)|.

Deuterium Tracer Study

Evidence for the mode of adsorption of alkaloid on 5% $Ir/CaCO_3$ was obtained by examination of H/D exchange between 10,11-dihydrocinchonidine and C_2H_5OD at room temperature. (Dihydrocinchonidine was studied, in preference to cinchonidine in order to preclude complications that might have arisen as a result of adsorption via the vinyl group.) $Ir/CaCO_3$-4 (0.10 g) was reduced in 760 Torr deuterium, but otherwise pretreatment was as described above. Dihydrocinchonidine (0.1 g) in 10 ml C_2H_5OD was injected into the reduction vessel at 293 K; the solution and catalyst were stirred for 18 h at 293 K, after which the alkaloid was recovered and analyzed by ^1H NMR and by mass spectrometry. The experiment was repeated with an exchange time of 9 days.

Nomenclature

In this paper the term racemic hydrogenation is used only to describe those reactions conducted over catalysts in the absence of a modifier. The term enantioselective hydrogenation refers to reaction conducted over modified catalysts.

RESULTS

Preliminary experiments with unmodified 5% Ir/Al_2O_3, activated using procedure 2, gave modest racemic hydrogenation rates, R_i, (typically 185 mmol h^{-1} g^{-1}) in ethanol under 10 bar pressure at 293 K. The same catalyst, when modified by cinchonidine, gave enhanced enantioselective hydrogenation rates with low optical yields (2% optical yield at a rate of 425 mmol h^{-1} g^{-1}). A higher optical yield of 5% was obtained after the catalyst had been sintered in flowing hydrogen at 1223 K for 4 h, cooled, passivated in CO_2 at 323 K, rereduced, and used under standard conditions. This preliminary study was encouraging

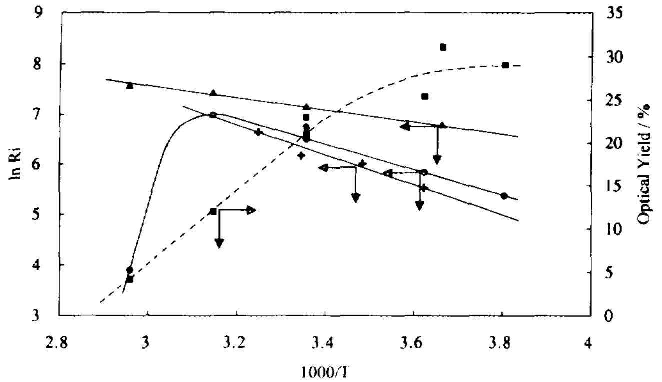

FIG. 1. Dependence of initial rate, R_i (mmol h^{-1} g^{-1}), on temperature for racemic hydrogenation over Ir/SiO_2-2 (crosses) and Ir/$CaCO_3$-1 (triangles) activated by procedure 2. Variation of initial rate (circles) and optical yield (squares) with temperature over cinchonidine-modified Ir/$CaCO_3$-1.

because it represented the first observation of Ir-catalyzed enantioselective hydrogenation. Enantioselectivity appeared to be favored by a larger Ir particle size.

Further work was carried out using Ir/SiO_2-1, -2, and -3 and Ir/$CaCO_3$-4 and -5. Investigation of the racemic reaction showed that initial reaction rate was very sensitive to previous exposure of the catalyst to oxygen (Tables 1 and 2). Thus, catalysts prepared by procedure 3 (careful exclusion of oxygen) proceeded slowly; preparation by procedure 2 (use of air-saturated solvent and reactant, but no stirring in air) gave fast reaction (450 to 950 mmol h^{-1} g^{-1}) and procedure 1 (stirring in air for 1 h) enhanced the rate by a further factor of 2 to 4. In this respect Ir behaves differently from Pt, for which procedure 3 gives an almost inactive catalyst, and procedures 2 and 1 give catalysts of low but equal activity, typically 50 mmol h^{-1} g^{-1}. An apparent activation energy of 24 ± 2 kJ mol^{-1} (277 to 308 K) was recorded for racemic hydrogenation over unmodified Ir/SiO_2-2 calcined at 393 or 573 K, reduced at 523 K, and activated by procedure 2 (Fig. 1).

Samples of Ir/SiO_2-2 were prepared using a variety of calcination and reduction conditions, activated by procedure 1, modified by cinchonidine, and examined under our standard reaction conditions (see Experimental). Performances are recorded in Table 1. For a constant calcination temperature of 773 K the optimum reduction temperature was 523 K giving an enantiomeric excess of 20%. Calcination at 393 and 573 K with reduction at 523 K and subsequent modification resulted in enantioselective catalysts displaying fast initial rates, ≥1400 mmol h^{-1} g^{-1}, and giving enantiomeric excesses of 32 ± 1%. Catalysts calcined at 873 K and above showed much-reduced activities and enantioselectivities. Similar rates of reaction were observed for both alkaloid-modified and unmodified catalysts, which contrasts with the enhanced rates previously observed over modified Pt/SiO_2 (8, 9).

Similarly, the rates and enantiomeric excesses obtained over 7% Ir/SiO_2-1 (catalyst 1) decreased with increasing calcination temperature, with a drastic fall after 573 K (Table 1). The decrease in activity upon calcination of this catalyst at 773 K was much greater than that of 20% Ir/SiO_2-2.

Comparable features were observed using an equivalent silica-supported iridium catalyst Ir/SiO_2-3 prepared from a chloride-free precursor (Table 2). This modified catalyst displayed optimal activity, within the more limited range of conditions studied, when calcined at 393 K, reduced at 593 K, and activated by procedure 1. Both the initial rate and the enantiomeric excess decreased when higher calcination temperatures were used. The rate of racemic hydrogenation was faster over this catalyst (1970 mmol h^{-1} g^{-1}) than over the equivalent catalyst prepared using chloroiridic acid (1430 mmol h^{-1} g^{-1}, Table 1). Lower enantiomeric excesses were achieved over the chloride-free catalyst.

Ir/$CaCO_3$ (5%) gave very fast racemic hydrogenation rates of 1930 and 2550 mmol h^{-1} g^{-1} in ethanol (Table 3); the apparent activation energy was 11 ± 2 kJ mol^{-1} over the range 263 to 338 K (Fig. 1). Optical yields of 39% were obtained with cinchonidine-modified Ir/$CaCO_3$-5 at

TABLE 3

Initial Rates, R_i, and Optical Yields, OY, in Methyl Pyruvate Hydrogenation at 10 Bar Pressure and 298 K over 5% Ir/$CaCO_3$

Catalyst[a]	Modifier[b]	Solvent	R_i (mmol h^{-1} g^{-1})	Conversion (%)	OY (%)
4	None[c]	Ethanol	1270	80	0
4	None[d]	Ethanol	1930	76	0
4	CD	Ethanol	895	81	23
4[e]	CD	Ethanol	300	84	31
4	Q	Ethanol	525	76	17
4	C	Ethanol	675	67	9[f]
4	QD	Ethanol	370	51	6[f]
4	CD	Dodecanol	270	73	13
4	CD	Toluene	110	12	14
4	CD	Dichloromethane	[g]	8	5
5	None[c]	Ethanol	1680	80	0
5	None[d]	Ethanol	2550	76	0
5	CD	Ethanol	1680	90	39
5[e]	CD	Ethanol	660	90	39

[a] Chloride content: catalyst 4 = 0.24%, catalyst 5 = 0.81%.

[b] CD = cinchonidine; C = cinchonine; QD = quinidine; Q = quinine.

[c] Catalyst activation by procedure 2 (without stirring in air).

[d] Catalyst activation by procedure 1 (with air stirring).

[e] Reaction at 273 K.

[f] S-methyl lactate in excess.

[g] Not determined.

273 and 298 K and 31% over $Ir/CaCO_3$-4 at 273 K. Selective formation of S-lactate occurred when cinchonine and quinidine were used as modifiers (Table 3). Orders for the enantioselective reaction by the initial rate method at 298 K were zero in pyruvate (initial concentration varied from 0.7 to 3.8 mol $liter^{-1}$, hydrogen pressure = 10 bar) and the first in hydrogen (pressure varied from 4.1 to 10.0 bar, initial pyruvate concentration = 1.9 mol $liter^{-1}$). The effects of temperature on initial rate and optical yield are shown in Fig. 1; the apparent activation energy was 22 ± 2 kJ mol^{-1} (263 to 295 K). The rate collapsed above 318 K and the optical yield showed a gradual decline as the reaction temperature was increased.

Rates and enantioselectivities were solvent dependent, each falling in the sequence ethanol > dodecanol > toluene > dichloromethane. By contrast, dichloromethane was a good solvent for the Pt-catalyzed reaction (14).

It is possible that the alkaloid modifier might be oxidized to the *N*-oxide in air-saturated ethanolic solution and that adsorbed alkaloid–*N*-oxide might be an effective modifier. To test this hypothesis, Ir/SiO_2-1 was modified with quinine–*N*-oxide (11 mg) under anaerobic conditions; the catalyst was ineffective. Reaction commenced at an initial rate of 30 mmol h^{-1} g^{-1} and ceased at ca. 8% conversion. It was concluded that this alkaloid–*N*-oxide was not an effective modifier, and the formation of such compounds in solution, if it occurs, is not beneficial.

Optical yields over $Ir/CaCO_3$-4 modified by 10,11-dihydrocinchonidine were closely similar to those obtained with cinchonidine as modifier. Exchange of H for D in dihydrocinchonidine under the conditions described under Experimental occurred as shown in Fig. 2. Exchange at the hydroxyl group occurred rapidly, and at the 2-, 6-, and 8-positions in the quinoline moiety more slowly. No exchange occurred in the quinuclidine moiety, and no hydrogenation or hydrogenolysis products were detected by either NMR or mass spectrometry.

DISCUSSION

This investigation establishes that supported iridium catalysts are very active materials for α-ketoester hydrogenation and can be modified with cinchona alkaloids to facilitate enantioselective hydrogenation. These Ir-catalyzed reactions exhibit some similarities and some differences by comparison with the well-studied Pt-catalyzed reactions. The reactions are similar in that modification by adsorption of cinchonidine or quinine onto each metal induces enantioselectivity in favor of the R-isomer, whereas modification by cinchonine or quinidine provides an excess of the S-product. Furthermore, enantioselectivity is lost over both metals at temperatures above ca. 320 K. An important difference between the Ir- and Pt-catalyzed reactions relates to the relative magnitudes of the racemic reaction rate (R_i, no alkaloid present) and enantioselective reaction rate (R_i, alkaloid present). Ir catalysts activated by procedure 1 provided rapid racemic reaction under standard reaction conditions (1430 to 1760 mmol h^{-1} g^{-1} over Ir/SiO_2 (Table 1), 1970 to 2120 mmol h^{-1} g^{-1} over Ir/SiO_2-3 (Table 2), 1930 mmol h^{-1} g^{-1} over $Ir/CaCO_3$-4, and 2550 mmol h^{-1} g^{-1} over $Ir/CaCO_3$-5 (Table 3)); these values compare with 50 mmol h^{-1} g^{-1} over 6.3% Pt/SiO_2 (EUROPT-1). For racemic hydrogenation, apparent activation energies of 24 kJ mol^{-1} and 11 kJ mol^{-1} are observed when iridium is supported on silica and calcium carbonate, respectively; these values are lower than that of ca. 30 kJ mol^{-1} obtained for silica-supported platinum (for comparability, all catalysts were activated by procedure 2).

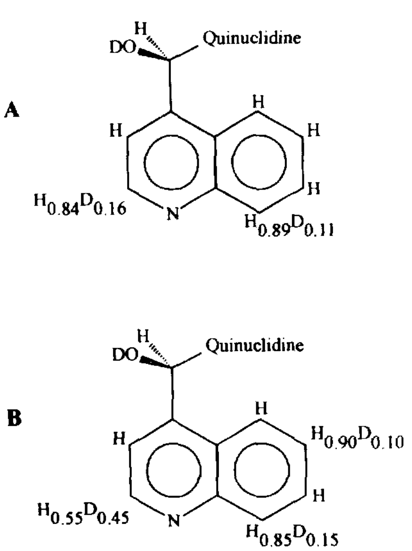

FIG. 2. Exchange of H for D in 10,11-dihydrocinchonidine in the presence of 5% $Ir/CaCO_3$ after (A) 18 h and (B) 9 days. The location and extent of exchange around the quinoline ring is indicated; no exchange was detected at other positions or within the quinuclidine moiety.

Following the modification procedure in which the reduced catalyst is stirred in a solution of alkaloid (17 m*M*) in appropriate solvent (ethanol), the catalyst is capable of enantioselective hydrogenation. Adsorption of alkaloid onto silica-supported Ir catalysts induces enantioselectivity, with little variation of the reaction rate. The change in reaction rate is significantly less pronounced than that observed over Pt/SiO_2 catalysts, for which typically a 30-fold rate enhancement is observed. Although the rates of enantioselective reactions over silica-supported Ir and Pt are comparable and typically 1500 mmol h^{-1} g^{-1}, the enantiomeric excesses recorded over Ir (up to 39%) are poorer than those over Pt (up to 90%), probably because of the rapidity of any racemic reaction that occurred over Ir surface not effectively modified by the alkaloid. Enantioselective hydrogenation over both

Pt and Ir is zero order in ester and first order in hydrogen, with similar forms of the hydrogen uptake against time curves and optical yields that are almost independent of conversion (8). The apparent activation energy for enantioselective hydrogenation over $Ir/CaCO_3$ (22 kJ mol^{-1}) is lower than that over Pt/SiO_2 (42 kJ mol^{-1}). Only limited efforts have been made to optimize the Ir system by variation of metal particle morphology and calcination and reduction temperatures; no attempt has been made to optimize modifier or reactant concentrations, reactor pressure, or the condition of the catalyst by desorption of adsorbed hydrogen before modification, all of which were found to improve the performance of Pt catalysts (9, 12).

The variation of catalyst activity following calcination and reduction at a series of temperatures has been studied for silica-supported Ir catalysts. Within the range of temperatures studied, optimal catalyst performance is observed following calcination between 393 and 573 K and subsequent reduction typically at 523 K. Catalyst performance was more sensitive to reduction temperature than to calcination temperature. The greater dependence of catalyst performance upon reduction conditions, rather than calcination conditions, for alumina-supported platinum catalysts has been reported by Wehrli *et al.* (18). Diminished enantiomeric excesses were obtained when iridium catalysts were either reduced at or below 473 K, possibly as a result of incomplete reduction of the precursor, or reduced at temperatures above 593 K, perhaps as a result of sintering or of morphological changes to the metal particles. Calcination at 773, 873, and 1023 K provided catalysts displaying progressively poorer activities and enatioselectivities. At these temperatures sintering of the Ir oxide particles and, following reduction, formation of roughened Ir metal particles may be expected (19–21). High resolution transmission electron microscopy showed that the size distribution of the Ir particles in Ir/SiO_2-2 prepared by calcination at 393 K was centered at ca. 1.7 nm, and this catalyst provided an enantiomeric excess of 31% (Table 1). Calcination at 773 K gave Ir-containing particles having irregular shaped features that had the appearance of large faceted platelets, indicating that calcination had substantially sintered the iridium-containing phase. Schmidt and co-workers, using XPS and TEM, have demonstrated that Ir particles are totally oxidized to IrO_2 upon heating in O_2 at 773 K; the expanded oxide phase grows out as protrusions from the particle and subsequent reduction at or below 673 K results in very rough and cracked metallic particles (21).

Analogous features were observed for the 7% Ir/SiO_2 catalyst (Table 1). Comparison with the information for 20% Ir/SiO_2 shows that the rate of reaction increased with Ir loading as expected. Transmission electron micrographs indicated that this catalyst had a mean Ir particle size centred at ca. 1.6 nm when calcined at 393 K. Calcination at 573 and 773 K, respectively, caused significant particle migration and sintering, thus forming fewer large particles having poorer catalytic activity.

By contrast, the 6.3% Pt/SiO_2 (EUROPT-1) produced a fast enantioselective reaction (typically 1200 mmol h^{-1} g^{-1}) with high optical yield, typically 75%, and this was achieved at the surface of Pt particles having a narrow size range centered at 1.8 nm (22). The effect of sintering EUROPT-1 at 1273 K was to move the Pt particle size distribution so that it was now centered at 4.0 nm and optical yield improved by 4% (23). Gao and Schmidt have shown that silica-supported Pt exhibits no morphological or phase changes upon heating in O_2 at 773 K; however, heating in H_2 at 873 K produces predominantly cube-shaped particles exposing mostly (100) planes (20). Wehrli *et al.* found that large platinum particles produced by long-term sintering of alumina-supported platinum catalysts in air displayed only slightly altered optical yields (12).

The poor optical yield, 2%, obtained over unsintered 5% Ir/Al_2O_3 indicates that very small Ir particles accommodate alkaloid, methyl pyruvate, and hydrogen less efficiently. This accords with our experience using a 0.6% Pt/silica catalyst with a majority of the active phase present as clusters typically of 0.7 nm, which also showed very little activity for enantioselective hydrogenation, presumably because the Pt particles were too small to allow the adjacent adsorption of both alkaloid and methyl pyruvate (17). Sintering Ir/Al_2O_3 at 1223 K served to increase the Ir particle size distribution so that it was centered at ca. 1.1 nm, and improved enantioselectivities were observed. Burkhardt and Schmidt sintered Ir/SiO_2 in hydrogen at 1073 K for 4 h; TEM micrographs which were obtained demonstrated that the resultant metal particles had smooth faceted surfaces (21).

The results clearly demonstrate the beneficial effect of oxygen during the activation procedure, irrespective of the presence of alkaloid. Stirring reduced catalyst with solvent (ethanol) in air for 1 h (procedure 1) resulted in very active catalysts, capable of methyl pyruvate hydrogenation at initial rates greater than 1400 mmol h^{-1} g^{-1}. Reducing air exposure by omitting the air activation step (procedure 2) diminishes activity indicating that there is sufficient dissolved oxygen in the solvents to activate the catalyst. Complete exclusion of oxygen (procedure 3), following catalyst reduction in the autoclave with use of distilled and degassed solvents, resulted in a very low reaction rate (R_i = 60 mmol h^{-1} g^{-1}, reaction stopped at $<10\%$ conversion). Similar features have been observed using EUROPT-1 under anaerobic conditions (9, 16).

The mechanism whereby exposure to oxygen induces activation is unclear. Any requirement for the participation of bulk iridium oxide can be discounted because the use of high calcination temperatures and low reduction temperatures led to poor activity. It is more likely that O-containing species adsorbed on iridium metal play a role since oxygen is more effective when the solvent can be easily oxidized (ethanol, dodecanol) than when it is oxidation resistant (dichloromethane). Although this study has shown that Pt and Ir sometimes show different chemistry in this catalytic reaction, nevertheless, we note that XPS studies of the adsorption of 10,11-dihydrocinchonidine from air-saturated ethanolic solution onto Pt(111) results in the formation of O-containing adsorbate(s) in addition to the alkaloid, and that the adsorption of air-saturated ethanolic solution onto Pt(111) provides a range of adsorbed species including acetate-like species (16, 24). Clearly there is a complex chemistry involving O-containing intermediates at the surfaces of Ir and Pt during both racemic and enantioselective pyruvate hydrogenation that merits further study.

Adsorption of the cinchona alkaloids with the aromatic function parallel to the metal surface is a necessary prerequisite for the induction of enantioselectivity as envisaged in the mechanism previously proposed (4, 8). Such adsorption geometry also permits the establishment of the H-bonding interaction between the N atom of the quinuclidine system and the hydroxyl group of the half-hydrogenated state Me(C*)(OH)COOMe which we propose to be responsible for the enhanced rate over Pt (4, 10). H/D exchange in the alkaloid modifier, under favorable conditions, may provide information concerning its mode of adsorption. The observed exchange at the 2-, 6-, and 8-positions in the quinoline-ring system of the dihydrocinchonidine establishes that the molecule adsorbes on iridium by interaction of the aromatic system with the metal surface, and the pattern of exchange suggests that the quinoline ring system may be adsorbed approximately parallel to the surface. Such a conclusion would indicate that the adsorbed state is similar to that at the Pt surface, where a comparable experiment produced exchange at all six positions (4, 25). The less extensive exchange over Ir may simply indicate that the adsorbed alkaloid is less reactive toward adsorbed deuterium, or that the concentration of adsorbed D derived from dissociative adsorption of C_2H_5OD is lower, or that the alkaloid forms other adsorbed states that do not undergo exchange. No choice between these alternatives can be made.

The slower rates of enantioselective reaction over quinine- and quinidine-modified $Ir/CaCO_3$, by comparison with those observed over cinchonidine- and cinchonine-modified catalysts, respectively (Table 3), accords with experience over Pt and is attributable at least in part to the smaller numbers of quinine and quinidine molecules that can be accommodated per unit area of surface, and hence to the smaller numbers of enantioselective sites that are thereby created.

Rates and enantioselectivities were affected by the presence of chloride ion. Comparison of Tables 1 and 2 shows that Cl-containing Ir/SiO_2 gave lower rates and higher enantioselectivities (under comparable conditions) than Cl-free Ir/SiO_2. Transmission electron microscopy indicated that the Cl-free catalyst calcined at 393 K displayed a mean Ir particle size centered at ca. 1.5 nm, similar to that of the Cl-containing catalyst. Furthermore, samples of Ir/SiO_2-2 which were calcined at 573 and 773 K, washed with ammonium carbonate to remove chloride, reduced at 523 K, and modified, showed enhanced activity (by 20%) and lower enantioselectivities (up to one third). Thus, chloride ion is to be regarded as a favorable promoter for silica-supported Ir. The situation was somewhat different when calcium carbonate was used as support; Table 3 shows that $Ir/CaCO_3$ with the higher chloride content (catalyst 5) gave the higher enantioselectivity, as expected, but also the higher activity, contrary to expectation. For the Pt-catalyzed reaction, Wehrli *et al.* report that Pt/alumina prepared from chloride-containing precursors gave higher optical yields than comparable catalysts prepared from chloride-free precursors (18). The favorable promoter action of chloride ion may therefore be general and of importance in the optimization of the design of enantioselective catalysts.

CONCLUSIONS

Iridium is highly active for the hydrogenation of the α-keto group in methyl pyruvate, giving R-methyl lactate with an enantiomeric excess of up to 39% when the metal surface is modified by the adsorption of cinchonidine. Enantioselectivity is dependent on the calcination and reduction temperatures used in catalyst preparation, which suggests the importance of iridium particle morphology. Exposure of the catalyst and the solvent to air during the modification procedure is required to activate the catalysts. Reaction rate is enhanced by the presence of carbonate ions and enantioselectivity benefits from the presence of chloride ions. These iridium catalysts differ from supported platinum in that they provide faster racemic hydrogenation and little rate enhancement in the presence of alkaloid, which limits their performance as enantioselective catalysts.

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