Catalysis Letters Vol. 89, Nos. 3–4, September 2003 (© 2003)

Premodification of Pt/γAl$_2$O$_3$ with cinchonidine for the enantioselective hydrogenation of ethyl pyruvate: effect of premodification conditions on reaction rate and enantioselection

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Received 22 May 2003; accepted 29 May 2003

The premodification of a 5 wt% Pt/γ-Al$_2$O$_3$ catalyst with cinchonidine (0.01 and 0.2 g g$^{-1}_{\mathrm{catalyst}}$) is described and discussed. Premodification is carried out by treating the catalyst with a solution of cinchonidine followed by solvent removal. Catalysts premodified in this way give the same ee and initial rate of reaction for the enantioselective hydrogenation of ethyl pyruvate as those using the standard *in situ* modification procedure. Investigations of different solvents for premodification and reaction (dichloromethane, ethanol) show that it is the solvent used for the reaction that controls the observed enantioselection. Premodified catalysts also display the initial transient behavior typically observed with *in situ* modified catalysts in which the ee increases with conversion in the early part of the reaction. Premodified catalysts show an enhanced rate of reaction when ethanol is used as the reaction solvent compared with *in situ* modified catalysts under the same conditions. Premodification using aerobic conditions gives the best results and premodified catalysts can be stored prior to use for up to a week without loss of catalytic performance.

KEY WORDS: Pt/γAl$_2$O$_3$; premodification/cinchonidine; ethyl pyruvate hydrogenation; enantioselective hydrogenation.

1. Introduction

Heterogeneous asymmetric catalysis has become an increasingly researched topic. A number of approaches have been adopted, which have been reviewed by Davis [1]. In general, the chirality required within the transition state of the reaction, so that enantioselection is achieved, can be supplied by a chiral surface [2,3], by a chiral solvent [4] or by a chiral modifier associated with either an immobilized metal center [5–9] or a metal surface [10,11]. For many studies, it is the latter approach that has been adopted, and of the relatively few systems capable of high levels of enantioselection, the one that has been studied extensively is the asymmetric hydrogenation of α-ketoesters using supported Pt nanoparticles modified with cinchona alkaloids [10–14]. The reaction was first reported in 1979 by Orito *et al.* [15] and is now used as a model reaction of this type of enantioselective reaction.

To date, most reactions have been carried out using an *in situ* modification procedure in which the cinchona alkaloid, catalyst, substrate, and solvent are stirred together at the beginning of the reaction although premodification was used by Orito and coworkers [15] and Wells and Wilkinson [10]. The simplest cinchona alkaloid is cinchonidine, and under reaction conditions in the presence of hydrogen, this is readily converted to its 10,11-dihydro-derivative. During reaction, the cinchona alkaloid adsorbs onto the Pt nanoparticles and D-tracer studies, NEXAFS and ATR-IR spectroscopy have shown that the adsorption is via the interaction of the quinoline moiety [16–18]. The conformation of the cinchonidine in solution has been shown to influence enantioselection and the open 3 configuration is generally associated with the highest enantioselection for the hydrogenation of pyruvate esters [19]. With careful control of reaction conditions, enantiomeric excess (ee) of $>98\%$ has been reported [20] for the formation of *R*-lactates from the reaction of alkyl pyruvate esters.

Apart from the high enantioselection observed with *in situ* modified Pt catalysts, a significant rate enhancement is also observed, and rates of reaction can be enhanced by factors of 2–100 [11]. In a recent study [21], we showed that Pt catalysts could be premodified with cinchona alkaloids and could retain the effects of modification. In this earlier study, achiral hydrogenation using gas-phase reactants were investigated since the main interest in our work, at that time, was the effect of premodification on reaction rate and selectivity. Unfortunately, no rate enhancement was observed with this achiral gas phase hydrogenation. In this paper, we now extend this earlier study to the use of premodified Pt/γAl$_2$O$_3$ catalysts for the enantioselective hydrogenation of ethyl pyruvate in the liquid phase in a high-pressure autoclave. In particular, we demonstrate the conditions required for premodification that lead to high enantioselection, which involve a premodification procedure in which the Pt/γAl$_2$O$_3$ catalyst is treated

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with a solution of the cinchona alkaloid in an air atmosphere under ambient conditions and hence, fortunately, no special precautions are required to achieve highly active and enantioselective premodified catalysts.

2. Experimental

5 wt% Pt/Al_2O_3 was obtained from Johnson Matthey catalysts and was pretreated with hydrogen at 400 °C prior to use. Cinchonidine (Fluka, 98%) was used as received. Ethyl pyruvate (Fluka, > 97%) was purified with great care prior to use. The pyruvate (50 mL) was mixed with CH_2Cl_2 (50 mL) and treated with $KHCO_3$ (0.1 mol l^{-1}, 50 mL). The organic layer was collected and distilled under reduced pressure over $MgSO_4$ to remove CH_2Cl_2. The residue was distilled over anhydrous $CaCl_2$ under vacuum and the purified pyruvate was used immediately. Both the pyruvate esters were confirmed by detailed analysis not to contain any impurities, for example, racemic lactates. CH_2Cl_2 was purified by distillation over anhydrous $CaCl_2$ and stored over 4A molecular sieve. Premodification of the $Pt/\gamma Al_2O_3$ with cinchonidine was carried out using the following procedure. The catalyst (2.0 g) was suspended in the solvent (50 mL) and cinchonidine (20 mg or 400 mg) was added. The mixture was then stirred (2 h, 20 °C) in air (1 bar) with the exclusion of moisture. Alternative premodification atmospheres were investigated by carrying out this process in the autoclave reactor. The solvent was removed by rotary evaporation at 40 °C and the premodified catalyst was dried under vacuum overnight and stored in a desiccator prior to use.

Enantioselective hydrogenations were carried out using a Parr 50 mL stirred autoclave reactor. All experiments were conducted at 20 °C in duplicate. For standard *in situ* modification, the ethyl pyruvate (66 mmol), CH_2Cl_2 solvent (12.5 mL), cinchonidine (2.5 mg) and 5% Pt/Al_2O_3 catalyst (0.25 g) were sealed into the autoclave. The autoclave was purged three times with hydrogen or argon to a pressure of 30 bar to remove residual air. Hydrogen was then admitted to the required reaction pressure (50 bar). At the same time, stirring was commenced (1200 rpm) to start the reaction and the reaction was stopped by stopping the stirring and decreasing the hydrogen pressure, and the product was isolated and analyzed by GC and chiral GC. During the reaction, the rate was monitored by determining the H_2-uptake. For the standard reaction conditions with the premodified catalysts, a similar procedure was adopted but no cinchonidine was added at the reaction stage.

3. Results

5% $Pt/\gamma Al_2O_3$ catalysts premodified in air (1 bar, 20 °C) were prepared with two loadings of cinchonidine (0.01 and 0.20 g g$^{-1}_{\text{catalyst}}$). We have previously described [21] a TPO method that confirms that a significant amount of the cinchonidine is adsorbed on the Pt nanocrystals in these premodified catalysts. Furthermore, analysis of the premodification solution before and after the premodification process confirmed that >99% of the cinchonidine was adsorbed on the 5% $Pt/\gamma Al_2O_3$ catalyst. The two premodified catalysts were investigated for the hydrogenation of ethyl pyruvate under standard reaction conditions and the results are shown in table 1. The ee observed under these conditions are consistent with those expected for a reaction carried out in dichloromethane as solvent [19] and furthermore, as expected, the ee is dependent on the amount of cinchonidine present. Lower loadings of cinchonidine give higher ee and higher initial rates of reaction. These reactions are also compared with the data for an identical reaction using the standard *in situ* modification procedure in which the cinchonidine is added with the reactant at the beginning of the reaction (table 1). Within experimental error, the results obtained from the standard *in situ* modification are identical to those obtained using the new premodification procedures. We consider this to be both a surprising and significant observation. Furthermore, we have found that premodified catalysts can be stored under desiccation for up to a week and still retain their catalytic efficiency.

As the premodified catalysts can be prepared in one solvent and utilized in another, we subsequently investigated this effect using catalysts that were premodified in either dichloromethane or ethanol. Use of ethanol as a solvent is expected to give lower ee for the *R*-ethyl lactate when compared with the reaction in dichloromethane [19]. This is confirmed by an experiment using *in situ* modification for which the ee of *R*-ethyl lactate for the ethanol experiment was 62.5% (table 2), whereas under comparable conditions in dichloromethane an ee >70% is observed. The results (table 2) for the use of a premodified catalyst using either the same or a different solvent than that used for premodification shows that the ee obtained for the

Table 1
Comparison of premodification and *in situ* modification on reaction rate and enantioselectivity[a]

Modification procedure	Cinchonidine g (g$^{-1}_{\text{catalyst}}$)	ee (%)	Initial rate (mmol s^{-1} g$^{-1}_{\text{catalyst}}$)
Premodified[b]	0.01	80.5	0.53
Premodified[b]	0.20	74.5	0.43
In situ modified	0.01	81.0	0.56
In situ modified	0.20	73.0	0.46

[a] Reaction conditions: ethyl pyruvate (33 mmol), CH_2Cl_2 (12.5 mL), 5 wt% Pt/Al_2O_3 (0.25 g), P_{H_2} 50 bar, 20 °C, 1200 rpm. ee recorded at 100% conversion.

[b] Catalyst premodified in CH_2Cl_2 under aerobic conditions, 1 bar pressure.

Table 2
Effect of premodified solvent on initial rate and enantioselectivity[a]

Solvent		Cinchonidine g ($g_{catalyst}^{-1}$)	ee (%)	Initial rate (mmol s^{-1} $g_{catalyst}^{-1}$)
Premodification	Reaction			
CH_2Cl_2	CH_2Cl_2	0.01	72.0	0.47
CH_2Cl_2	CH_2Cl_2	0.20	74.5	0.70
CH_2Cl_2	C_2H_5OH	0.01	68.5	1.02
CH_2Cl_2	C_2H_5OH	0.20	69.0	1.02
–	C_2H_5OH[b]	0.20	62.5	0.68
C_2H_5OH	C_2H_5OH	0.01	66.5	1.12
C_2H_5OH	C_2H_5OH	0.2	69.5	1.20
C_2H_5OH	CH_2Cl_2	0.01	79.0	0.97
C_2H_5OH	CH_2Cl_2	0.2	74.0	0.38

[a] Reaction conditions: ethyl pyruvate (66 mmol), solvent (12.5 mL), 5 wt% Pt/Al_2O_3 (0.25 g), $P_{H_2} = 50$ bar, 20 °C, 1200 rpm, ee recorded at 100% conversion.

[b] *In situ* modification in ethanol solvent.

premodified catalyst is dependent solely on the nature of the solvent used for the hydrogenation reaction. Hence, the positive benefits that might have been expected for the premodification in a solvent known to induce higher enantioselection are not retained when an inferior solvent is utilized. However, the data presented in table 2 do indicate a surprising effect with respect to the initial reaction rate. Premodified catalysts reacted in ethanol demonstrate enhanced initial rates of reaction when compared with *in situ* modified catalysts reacted under the same conditions (figure 1). This effect is observed for catalysts premodified in either dichloromethane or ethanol and subsequently reacted in ethanol. Interestingly, the effect is also observed for the catalyst premodified in ethanol with 0.01 g $g_{catalyst}^{-1}$ cinchonidine and subsequently reacted in dichloromethane (table 2). However, unfortunately, the effect is not observed for the higher loading of cinchonidine investigated.

Following reaction, the premodified catalysts were recovered by filtration and analysis of the solution and catalyst confirmed that >98% of the cinchonidine originally present in the premodified catalyst was retained on the catalyst after use in the autoclave reaction. To investigate if an equilibrium was established between cinchonidine adsorbed on the catalyst surface and that in solution during reaction, a simple flow reactor was used in which the premodified catalyst was treated in flowing dichloromethane at 20 °C together with 1 bar hydrogen. Although not simulating the high-pressure environment of the autoclave reactions, we observed that ca. 25% of the preadsorbed cinchonidine was desorbed during the initial 1 h reaction period. Hence, although in the autoclave reactor >98% of the cinchonidine remains adsorbed at the end of the experiment, it is apparent that a proportion is present in solution during the hydrogenation reaction.

In the preceding experiments, the premodification procedure was conducted in dry air at ambient pressure. We have investigated two additional premodification atmospheres (a) 10 bar air, and (b) 10 bar H_2 both for a 1 h stirring period. Premodification using a dichloromethane solution (0.01 g $g_{catalyst}^{-1}$ cinchonidine) of 5 wt% $Pt/\gamma\text{-}Al_2O_3$ under air and H_2 atmospheres was investigated and the hydrogen uptake curves are shown in figure 2. The initial rate of hydrogen uptake for the catalyst premodified with 10 bar air is slightly higher than that observed for the catalyst premodified with 1 bar air. Both the air-premodified catalysts display significantly higher hydrogen uptakes compared with the H_2-premodified catalysts. The final ee observed for these experiments were 78.5%, 80.5%, and 29.5% for the 10 bar air, 1 bar air, and 10 bar H_2-premodified catalysts, respectively. Overall, it is apparent that the catalyst premodified using the simplest procedure in

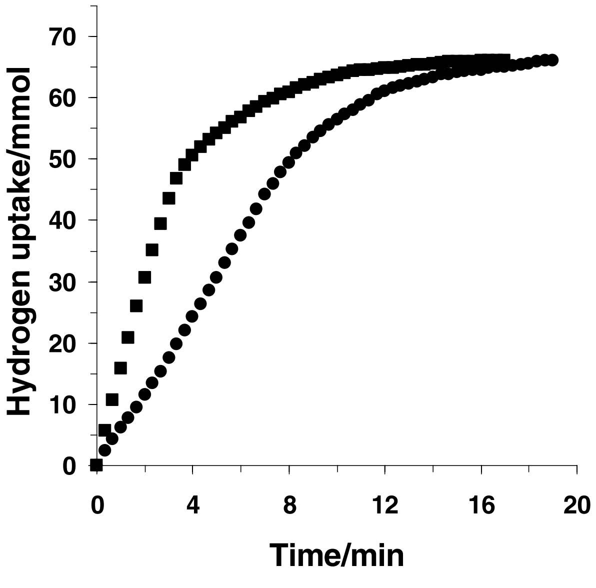

Figure 1. Hydrogen uptake curves: ■ Pt/Al_2O_3 premodified with cinchonidine (0.2 g $g_{catalyst}^{-1}$) in dichloromethane; ● Pt/Al_2O_3 modified *in situ* (0.2 $g_{catalyst}^{-1}$). Reaction conditions: ethyl pyruvate (66 mmol) Pt/Al_2O_3 (0.25 g) ethanol (12.5 mL), $P_{H_2} = 50$ bar, 20 °C, 1200 rpm.

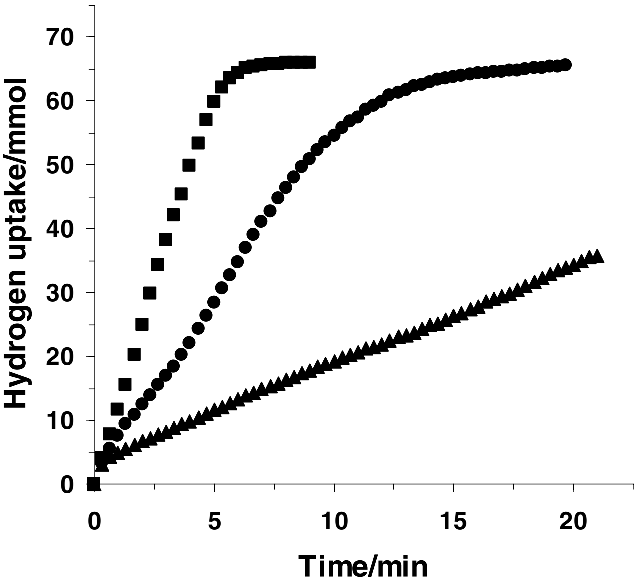

Figure 2. Hydrogen uptake curves for Pt/Al_2O_3 premodified with cinchonidine ($0.01\,gg^{-1}_{catalyst}$) in dichloromethane under ● 1 bar air, ■ 10 bar air, ▲ 10 bar hydrogen. Reaction conditions: ethyl pyruvate (66 mmol) dichloromethane (12.5 mL), Pt/Al_2O_3 (0.25 g), $P_{H_2} =$ 50 bar, 20 °C, 1200 rpm.

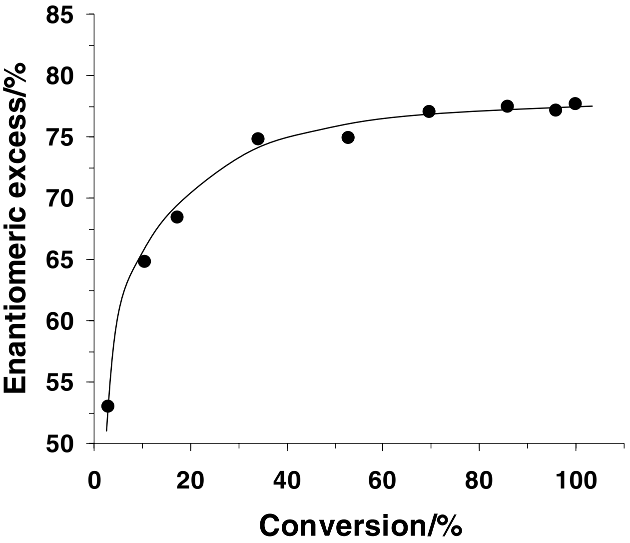

Figure 3. Dependence of ee on ethyl pyruvate conversion for Pt/Al_2O_3 premodified with cinchonidine ($0.01\,g\,g^{-1}_{catalyst}$) in dichloromethane. Reaction conditions: ethyl pyruvate (66 mmol), dichloromethane (12.5 mL), Pt/Al_2O_3 (0.25 g), $P_{H_2} = 50$ bar, 20 °C, 1200 rpm.

the presence of dry air under ambient pressure and temperature gives the best catalytic performance. The loss of enantioselection and lower reaction rate observed with the H_2-premodified catalyst is probably a result of hydrogenation of the cinchonidine during the premodification procedure, although this has not been confirmed.

One intriguing observation with *in situ* modified catalysts has been the observation that the ee of the *R*-ethyl lactate increases significantly with conversion during the early part of the reaction. [22]. This effect has been well studied [22–26] since its initial discovery by Wells and coworkers [26], but the origin of the effect remains unclear [27,28]. We have investigated this effect for the premodified catalysts and have observed that the increase in ee with conversion is still observed for premodified catalysts (figure 3) and is identical in nature to that of *in situ* modified catalysts reacted under identical conditions.

4. Discussion

In this paper, we have shown that Pt/γ-Al_2O_3 catalysts can be effectively premodified with cinchonidine and the premodified catalysts can display identical behavior to that observed with the standard, well utilized, *in situ* modification procedure. Furthermore, we have found that the premodified catalysts can be stored for significant periods without loss of the eventual catalytic performance. Fortunately, the premodification can be carried out in dry air under ambient conditions to obtain the optimal results. This observation has significance for potential spectroscopic investigation of cinchonidine modified surfaces. Most spectroscopic methods cannot be used under the liquid-phase reaction conditions; however, the observation that premodified catalysts are equivalent to *in situ* modified catalysts may provide effective samples for *ex situ* spectroscopic investigation. Nevertheless, we urge caution on this point for two reasons. First, in our experiments we have shown that the premodified catalysts lose ca. 25% of the cinchonidine under simple flow conditions, indicating that there exists a rapid equilibrium between adsorbed and dissolved cinchonidine under the reaction conditions. This desorption/adsorption process could alter the conformation of the adsorbed cinchonidine under reaction conditions. Furthermore, the observation that it is the solvent used for the reaction, rather than that used for the premodification, that controls the observed enantioselection is explained by this desorption/adsorption process, as the conformation of the cinchonidine would be modified by the solvent polarity [19]. Second, the observation that the initial transient behavior is still observed with the premodified catalysts (figure 3) also shows that the nature of the surface of the premodified catalyst may be changing during the initial part of the reaction.

It is apparent that the catalysts modified under hydrogen atmosphere give significantly lower reaction rates and ee when compared to those prepared by premodification under aerobic conditions. It is known that cinchonidine is readily hydrogenated to 10,11-dihydrocinchonidine under normal enantioselective hydrogenation conditions, but 10,11-dihydrocinchonidine is as effective as cinchonidine as a chiral modifier [29]. Hence, the observed decrease in performance cannot be attributed to the formation of 10,11-dihydrocinchonidine. The quinoline ring system of cinchonidine can be hydrogenated, and this is known to decrease its efficiency as a modifier, but this requires considerably higher temperatures and H_2 pressures than those used in our premodification experiments. Hence, we do not consider the effect to be due to modification of the cinchonidine. The enhanced effects due from aerobic premodification may be because of the co-adsorption of oxygen. X-ray photoelectron spectroscopy has confirmed that O_2 and cinchonidine can be co-adsorbed onto a Pt(111) surface from air-saturated solutions of the alkaloid in ethanol [30]. Also a number of previous studies [29,31–33] have found that co-adsorption of oxygen can influence the catalytic performance-supported Pt catalysts for this reaction. The adsorbed surface oxygen species may also play a role in the enhanced rate of reaction observed with ethanol as solvent for the premodified catalysts. Previous X-ray photoelectron studies have shown that adsorbed C_2H_5O species formed from ethanol react in the presence of adsorbed oxygen to form acetate and hydrocarbon species [34]. Hence, ethanol may provide an efficient route to remove adsorbed oxygen species from the surface and this may influence the reaction rate and ee, as acetic acid alters the conformational balance.

In conclusion, we have shown that $Pt/\gamma\text{-}Al_2O_3$ catalysts can be premodified with cinchonidine using a simple aerobic solution procedure, and the premodified catalysts are as effective as the standard reaction procedure using *in situ* modification. Furthermore, the catalysts can be stored for a significant time without loss of catalytic performance and, with care, these premodified catalysts may form the basis of suitable systems that can be used for detailed spectroscopic investigation.

Acknowledgments

We thank the EPSRC for financial support and X.L. thanks the committee of Vice-Chancellors and Principals of the Universities of the United Kingdom for provision of an ORS award.

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