Catalysis Letters Vol. 100, Nos. 3–4, April 2005 (© 2005)
DOI: 10.1007/s10562-004-3464-3

Continuous stable enantioselective hydrogenation of alkyl pyruvate esters using pre-modified cinchonidine platinum catalysts

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Received 15 July 2004; accepted 5 December 2004

Pre-modification of a 5 wt% $Pt/\gamma\text{-}Al_2O_3$ catalyst with cinchonidine (0.1 g g^{-1} catalyst) leads to a catalyst that give stable enantioselection when using a trickle-bed flow reactor at ambient temperature and pressure. With dichloromethane as solvent sustained enantiomeric excess of >70% for the hydrogenation of ethyl pyruvate to (*R*)-ethyl lactate is observed and this is maintained with very low cinchonidine/catalyst ratios. With dichloromethane the conversion decreases with time an effect we consider to be due to the formation of small amounts of polymer on the catalyst surface. When ethanol is used as solvent the yield of (*R*)-ethyl lactate is stable throughout the test period, although the enantiomeric excess was much lower at ca. 35%.

KEY WORDS: enantioselective hydrogenation; ethyl pyruvate hydrogenation; butadione hydrogenation; $Pt/\gamma\text{-}Al_2O_3$ catalysts.

1. Introduction

Heterogeneous asymmetric catalysis has become an increasingly researched topic and in particular enantioselective hydrogenation remains a very active area of research. A number of approaches have been adopted which have been reviewed by Davis [1,2]. In general the chirality required within the transition state of the reaction to achieve enantioselectivity can be supplied by a chiral surface [2], by a chiral solvent [3] or by a chiral modifier associated with either an immobilised metal centre [4] or a metal surface [5,6]. 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, the asymmetric hydrogenation of α-ketoesters using supported Pt nanoparticles modified with cinchona alkaloids is considered to be a model system [5,6].

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 in an autoclave batch reactor. Although the use a batch reactors is a useful tool to study the chemistry of this complex reaction, industrial operation would prefer the use of a continuous flow reactor. The reasons are two-fold; first it engenders process simplification and intensification, since continuous operation negates the need to remove the catalyst at the end of the reaction, and secondly it avoids a major problem unavoidable in batch operation in that the products remain in contact with the catalysts for very long contact times and this can facilitate by-product formation. Pioneering studies by Baiker and co-workers have shown that continuous flow reactors operating at high pressure can be used [7–9] but that the cinchona modifier has to be continuously fed to sustain the high enantioselection which presents a disadvantage to this improved methodology. We have now successfully addressed this problem and show that using pre-modified catalysts high enantioselection can be sustained using a continuous-flow trickle bed reactor operating at ambient conditions. We have recently shown that pre-modified catalysts can be used with gas phase reactants in a solvent-free continous flow reactor [10]. In this paper we extend this approach to their use in a trickle-bed flow reactor significantly extending both the range of substrates that can be used, as they do not have to be vaporised, and the productivity of the reaction.

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2. Experimental

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. 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.

Pre-modification of the $Pt/\gamma\text{-}Al_2O_3$ with cinchonidine was carried out using the following procedure. About

5 wt% Pt/γ-Al_2O_3 (Johnson Matthey) and was treated with hydrogen (5% H_2/Ar 20 mL min^{-1}) at 400 °C for 2 h prior to use. The catalyst (2.0 g) was suspended in the solvent (dichloromethane, 80 mL) and cinchonidine (200 mg) was added. The mixture was then stirred (1 h, 20 °C) in air (1 bar) with the exclusion of moisture. Analysis of the premodification solution before and after the premodification process confirmed that >99% of the cinchonidine was adsorbed on the 5% Pt/γ-Al_2O_3 catalyst. The solvent was removed by filtration and the premodified catalyst was dried in air overnight and stored in a dessicator prior to use. We have found that catalysts premodified in this way can be stored for several days without loss of catalyst performance.

A glass trickle bed reactor (i.d. 28 mm, length 300 mm) was used with down flow liquid feed (1 mL min^{-1}) and a concurrent H_2 flow (300 mL min^{-1}). The catalyst (0.4 g, 10 μm) was diluted with SiC (Washington Mills, 250 μm) giving a bed depth of 12–13 mm. The reaction temperature was maintained at 25 °C, using a thermostated jacket and the H_2 pressure was 1.25 bar to ensure a steady flow of H_2 through the bed. The liquid contact time was 2 min.

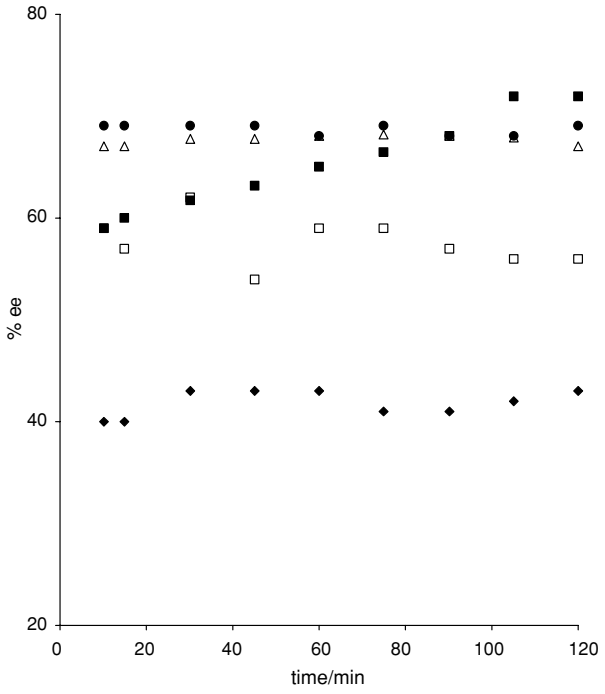

Figure 1. Effect on e.e of pretreatment of the pre-modified catalyst with dichloromethane and H_2 prior to the start of the ethyl pyruvate reaction at 25 °C. ◆ 0 h, ■ 0.5 h, △ 1 h, ● 2 h, □ 3 h.

3. Results and discussion

A series of enantioselective hydrogenations were carried out using a continuous flow trickle bed reactor. All experiments were conducted at 25 °C with H_2 (1.25 bar) in duplicate. The cinchonidine pre-modified 5% Pt/γ-Al_2O_3 catalysts were investigated for ethyl pyruvate hydrogenation and the results are shown in figure 1. If the flow of ethyl pyruvate (25 mmol L^{-1} in dichloromethane) was started immediately the H_2 flow was established a stable e.e. was observed but it was disappointedly low, ca. 40%. However, surprisingly we have found that if the addition of ethyl pyruvate to the feed is delayed then improved stable enantioselection is observed (figure 1). Even if the start of the flow of ethyl pyruvate is delayed for 30 min significant improvements are observed, although the best results, with e.e. >70% are observed when dichloromethane is flowed over the catalyst for 1–2 h in the presence of H_2 prior to the introduction of ethyl pyruvate. The e.e. observed under these mild flow conditions is similar to that observed with dichloromethane as solvent in batch autoclaves at higher pressures[a]. During this initial period two things occur. First, the cinchonidine is rapidly hydrogenated to 10,11-dihydrocinchonidine, but under these conditions this is a rapid process. We have found that the hydrogenation of the modifier does not influence the enantioselection markedly (table 1) when the reactions are carried out at high pressure in anautoclave, and so we do consider this effect to be significant in our studies. Secondly, excess cinchonidine is removed from the catalyst (figure 2) and this is rapid at the start of the process when ca. 20% of the cinchonidine is removed during the first hour of this treatment, following which there is a very slow loss of cinchonidine up to ca. 4 h. However, after this time, loss of cinchonidine is negligible and the remaining modifier remains adsorbed. It is apparent that the excess cinchonidine, when starting with cinchonidine: catalyst weight ratio of 0.1, impedes the attainment of high e.e. in this reaction. Interestingly, we have found that sustained e.e. for this reaction can be achieved with an initial cinchonidine amounts that are considerably lower than those used initially and similar results can be achieved with cinchonidine: catalyst weight ratios of 0.02, but below this level much lower enantioselection is observed (figures 3 and 4). Lower initial amounts of the modifier also improve the stability of the catalyst.

The initial solvent treatment also improves the activity of the pre-modified catalysts (figure 5) although

Table 1
Comparison of enantiomeric excess and initial rate for the enantioselective hydrogenation of ethyl pyruvate using cinchonidine and 10,11-dihydrocinchonidine as chiral modifiers[a]

Modifier	Enantiomeric excess %	Initial rate mmol g^{-1} min^{-1}
Cinchonidine	71.5	42
10,11-Dihydrocinchonidine	75.5	46

[a]12.5 mL dichloromethane, 66 mmol ethyl pyruvate, 0.25 g 5% Pt/Al_2O_3, modifier 50 mg, 50 bar H_2 (autoclave), stirring 1200 rpm, 100% conversion, $T = 20 \pm 2$ °C.

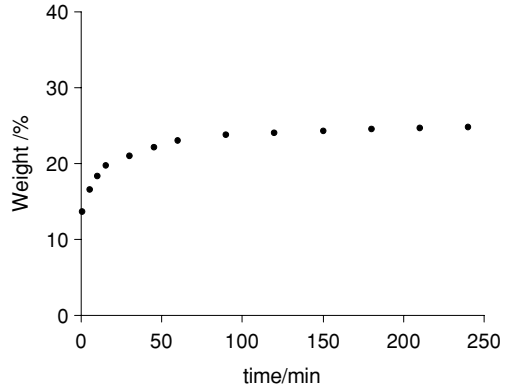

Figure 2. Loss of cinchonidine from the pre-modified catalyst in dichloromethane in the presence of H_2 monitored using UV-spectroscopy.

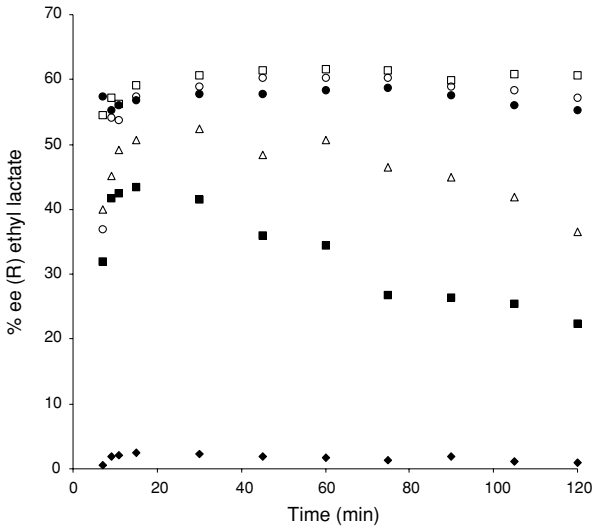

Figure 3. The effect of varying the amount of cinchonidine used in the pre-modification of 5% Pt/Al_2O_3 on the enantioselective excess for the hydrogenation of ethyl pyruvate Key : ◆ 1 mg, ■ 5 mg, △ 10 mg, ○ 20 mg, □ 30 mg, ● 50 mg, (cinchonidine/0.5 g catalyst).

all give lower conversion than the corresponding catalyst prepared without the addition of cinchonidine. This presents an interesting difference with reactions carried out in a batch reactor, typically at higher pressure [5,6], where cinchonidine addition leads to a significant enhancement in the conversion of the alkyl pyruvate ester, clearly this is not observed when these catalysts are operated in the continuous feed mode under mild conditions. Indeed, we also observed this effect in our previous study using gas phase reactants [10]. We consider this effect to be due to the formation of polymers on the surface of the catalyst, although it should be noted the mass the amount of polymer is very limited as the carbon mass balance is always close to 100%. It should be noted that under these mild reaction conditions all the catalysts lose activity with time, even the non-modified, cinchonidine free, catalyst. In the absence of the initial substrate free period the pre-modified catalyst rapidly deactivates but the activity is considerably improved when the catalyst is pre-treated in H_2 and dichloromethane for 1 h (figure 5). Most surprisingly, we have found that with ethanol as solvent can give stable conversion throughout the timescale of the experiment (figure 4) although the ee is still stable it is markedly lower, as expected for this solvent, ca. 35% [11]. Interestingly, under these mild flow conditions addition of acetic acid (0.05%) to the dichloromethane solvent leads to a rapid loss of both enantioselection and

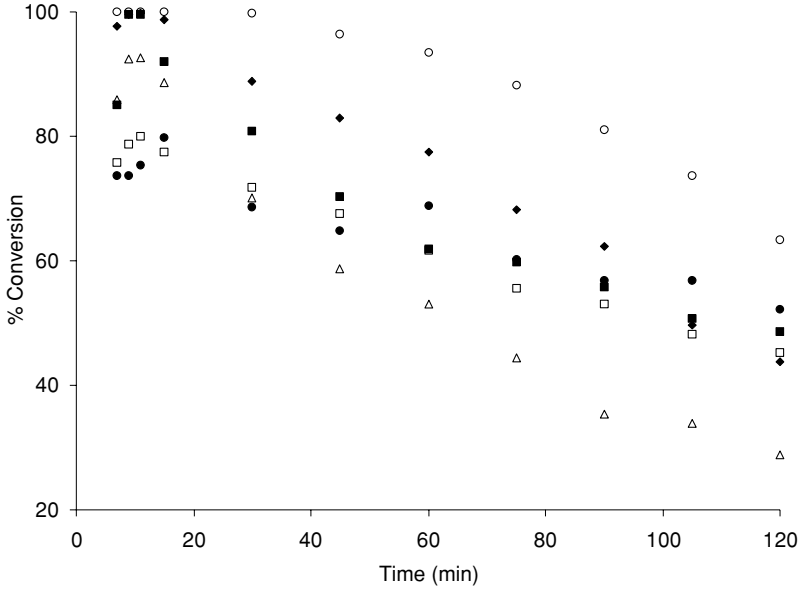

Figure 4. The effect of varying the amount of cinchonidine used in the pre-modification of 5% Pt/Al_2O_3 on the conversion for the hydrogenation of ethyl pyruvate Key : ◆1 mg, ■5 mg, △10 mg, ○ 20 mg, □ 30 mg, ● 50 mg, (cinchonidine/0.5 g catalyst).

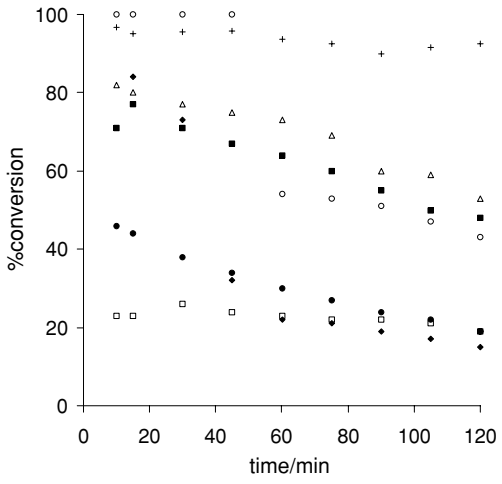

Figure 5. Effect on ethyl pyruvate conversion of the pre-treatment of the pre-modified catalyst with dichloromethane and H_2 prior to the start of ethyl pyruvate reaction at 25 °C. ◆ 0 h, ■ 0.5 h, △ 1 h, ● 2 h, □ 3 h, + 0.5 h ethanol as solvent, ○ no cinchonidine reference catalyst giving racemic hydrogenation.

conversion under our conditions. This is again in contrast to reaction in a batch reactor at higher pressure where reactions in the presence of acetic acid give the highest e.e. [5,6] and this is attributed to the modification of the conformation of the cinchonidine [11]. We have also carried out similar experiments for methyl pyruvate and obtained sustained enantioselection. Hence, we consider the pre-modification procedure presents an easy way in which enantioselective catalysts can be prepared, and furthermore, these catalysts can give stable sustained enantioselection when used in a continuous flow trickle bed reactor operating under mild conditions.

Acknowledgment

We thank the EPSRC for financial support.

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