Journal of Catalysis **210,** 466–470 (2002)
doi:10.1006/jcat.2002.3693

RESEARCH NOTE

Enantioselective Hydrogenation on Palladium

Limitations of Continuous Fixed-Bed Reactor Operation

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Received April 12, 2002; revised May 23, 2002; accepted May 23, 2002

The palladium-catalyzed continuous enantioselective hydrogenation of 4-methoxy-6-methyl-2-pyrone 1 to the corresponding 5,6-dihydropyrone 2 was studied in a fixed-bed reactor. Steady-state enantiodifferentiation was achieved by feeding the chiral modifier (cinchonine). The influence of reaction conditions on the rate and enantiomeric excess (ee) was investigated under differential and integral reactor conditions. Optimization of the enantioselectivity afforded 84.5% ee to (*R*)-2 at 1% conversion and 100% chemoselectivity. The attempt to produce high yield of (*R*)-2 failed since increasing conversion resulted in further hydrogenation of 2 to the tetrahydropyrone derivative 3, and a rapid loss of ee due to hydrogenation of cinchonidine. The poor chemo- and enantioselectivities at higher conversion are attributed to the high Pd/1 and Pd/cinchonine ratios in the fixed-bed reactor. It seems to be a general feature of Pt- and Pd-catalyzed enantioselective hydrogenations that the necessary cinchona alkaloid/reactant ratio is remarkably higher in a continuous reactor than in a slurry reactor.

Key Words: **enantioselective; asymmetric; chiral hydrogenation; continuous fixed-bed reactor; 4-methoxy-4-methyl-2-pyrone; Pd/titania; cinchonine.**

INTRODUCTION

We showed recently that cinchona-modified Pd is the best solid catalyst for the enantioselective hydrogenation of functionalized 2-pyrones (1, 2). Good yields and enantioselectivities were achieved in the partial hydrogenation of six different 2-pyrone derivatives under ambient conditions, using a Pd/TiO_2 catalyst and a cinchona alkaloid (3). At best, 76–80% yield and 90–94% enantiomeric excess (ee) were obtained in the hydrogenation of 4-methoxy-6-methyl-2-pyrone **1** to the corresponding 5,6-dihydropyrone **2** (Scheme 1). Dihydropyrones are important chiral intermediates in the synthesis of biologically active compounds (4–6). Consiglio and coworkers (7, 8) reported a highly efficient homogeneous catalytic method for the hydrogenation of pyrones using a chiral Ru complex catalyst.

The following study is aimed at clarifying the feasibility of the heterogeneous catalytic hydrogenation of **1** in a continuous fixed-bed reactor. Continuous enantioselective hydrogenation of α-ketoesters (9–13), ketopantolactone (9, 14) and 1-phenyl-1,2-propanedione (15) over cinchona-modified Pt/alumina was already demonstrated. As compared to cinchona-modified Pt, some complications arise when using the Pd–cinchona system. First of all, addition of a chiral modifier diminishes the reaction rate on Pd (16–21), while the opposite is observed in the Pt-catalyzed hydrogenation of activated ketones listed earlier. The low reaction rate is particularly disturbing in the hydrogenation of the pseudoaromatic 2-pyrones where good chemoselectivity to the dihydropyrone intermediate is achieved only under very mild conditions (1–3, 22). Besides, Pd is more active than Pt in the hydrogenation of the quinoline ring system of cinchona alkaloids (23). Saturation of the *anchoring moiety* of the modifier results in a weaker adsorption and a loss of the enantiodifferentiating ability (16, 24, 25). To compensate for this effect, a relatively high modifier/reactant ratio is necessary, which further reduces the rate of the target reaction.

In this study we show the striking influence of continuous fixed-bed reactor operation on the enantioselective hydrogenation of **1** over cinchonine-modified Pd/TiO_2. Although an appropriate choice of reaction conditions and continuous feeding of the chiral modifier allow high ee even in a continuous fixed-bed reactor, the good performance of the catalyst is limited to very low conversion.

EXPERIMENTAL

4-Methoxy-6-methyl-2-pyrone **1** was synthesized as described earlier (26) and purified by sublimation in vacuum (140°C, 0.1 mbar), followed by double recrystallization

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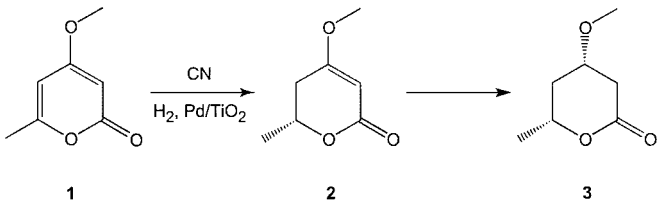
0021-9517/02 $35.00



SCHEME 1. Consecutive hydrogenation of 4-methoxy-6-methyl-2-pyrone (**1**) to 5,6-dihydropyrone (**2**) and tetrahydropyrone (**3**) over cinchonine (CN)-modified Pd/TiO_2.

from hexane. Cinchonine (CN, 99% alkaloid by titration, Fluka) and 2-propanol (99.9%, Backer) were used as received.

A 2.5 wt% Pd/TiO_2 catalyst was prepared as follows. 0.97 g $PdCl_2$ was dissolved in 50 ml water and 2 ml concentrated HCl. 22.31 g TiO_2 (P25, Degussa, 55 $m^2\ g^{-1}$) was added to the solution and the pH was set to 10 by dropping a saturated aqueous Na_2CO_3 solution into the vigorously stirred slurry at room temperature. After centrifugation, the catalyst was washed to neutral and dried at 80°C in vacuum for 24 h. For reduction, the solid was flushed at room temperature for 30 min with 12 ml min^{-1} argon (99.995%), then for 60 min with 20 ml min^{-1} hydrogen (99.999%). The catalyst was stored in air until use (max. 1 week). Metal dispersion was 0.18 as determined by hydrogen chemisorption.

Hydrogenation was carried out in a continuous stainless-steel tubular fixed-bed reactor (10) equipped with electric heating. The hydrogen flow through the 12-mm-inner-diameter reactor tube was kept constant by a two-step expansion valve (PE103, NWA) and measured with a rotameter. Almost all experiments (except under high pressure) were carried out under trickle bed conditions. A quartz wool plug placed at the front end of the catalyst bed served for efficient dispersion of the liquid phase. To warrant proper flow conditions and to avoid significant temperature gradients in the fixed bed the catalyst (0.2-g Pd/TiO_2) was diluted with pure support material (0.8-g TiO_2 P25, Degussa), affording a catalyst bed length (L) of 20 mm. The particle size of the catalyst and the support material (d_p) was 50–120 μm, resulting in the following geometrical ratios of the catalyst bed: L/d_p, 165–400; d_r/d_p, 100–240 (d_r, inner diameter of reactor tube). The reaction temperature was monitored with an adjustable thermocouple inside the catalyst bed. Pressure was kept constant with a controller before the reactor (NWA). The catalyst was re-reduced *in situ* in the reactor in a hydrogen flow for 30 min at room temperature before starting dosing the reaction mixture. Reactant **1** and CN, dissolved in 2-propanol, were continuously fed into the reactor with an HPLC pump (Gilson M305).

Conversion, chemoselectivity and ee were determined by an HP 5890 gas chromatograph and a Chirasil-DEX CB (Chrompack) capillary column. The (S)-enantiomer eluded first. Enantiomeric excess is expressed as ee $(\%) = 100 \times |(R-S)|/(R+S)$. CN always provided ($R$)-**2** in excess. Further hydrogenation to tetrahydropyrone **3** was the only side reaction detected. The turnover frequency (TOF) was calculated from the average reaction rate and the number of surface Pd atoms (Pd_s) contained in the catalyst bed.

Experimental details for the hydrogenation of ethyl pyruvate were described earlier(9).

RESULTS AND DISCUSSION

Optimum in Enantioselectivity under Differential Operating Conditions

First we investigated the stability of the catalyst under continuous operation conditions running long-term experiments of several hours for the hydrogenation of **1** to **2** (Scheme 1). The time-on-stream studies showed steady-state operation after a first initial period of ca. 30 min. The initial transient behavior, characterized by increasing ee and decreasing rate, is attributed to establishment of the chirally modified surface. In the following, the effect of various reaction parameters (CN/**1** ratio, temperature, H_2/**1** ratio, hydrogen pressure, 2-propanol/**1** ratio, total liquid flow rate) on the enantioselectivity (ee) and reaction rate (TOF) was studied on fresh catalyst after the initial stabilization period, i.e., after reaching steady-state. Differential operating conditions were chosen to eliminate the effect of possible gradients of temperature and concentration in the catalyst bed.

A typical feature of enantioselective hydrogenations over Pd is the strong retardation of the reaction by the chiral modifier. Figure 1 illustrates this effect by varying the cinchonine (CN)/**1** molar ratio and keeping constant the mass flow rate of **1** and the solvent (2-propanol). A feasible explanation is that increasing modifier concentration leads

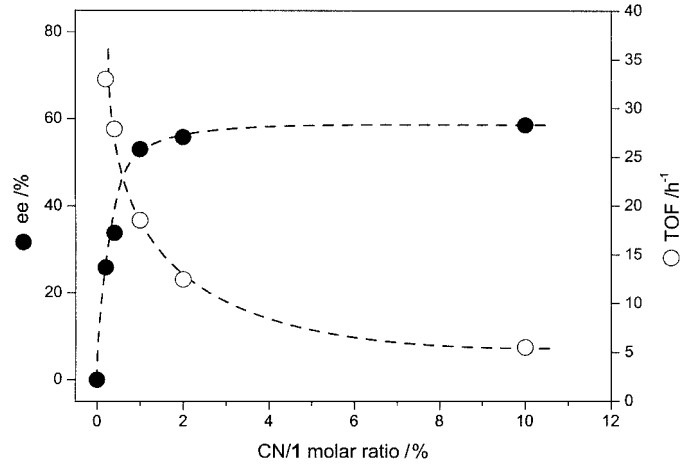


FIG. 1. Influence of CN/**1** molar ratio on the ee and reaction rate (TOF). Conditions: 20°C; 20 bar; total liquid flow rate (reactant + modifier + solvent), 0.3 ml min^{-1}; solvent (2-propanol)/**1** ratio, 150; hydrogen/**1** molar ratio, 10.

to higher coverage on Pd, which enhances the enantioselectivity by hampering the unmodified (*racemic*) reaction. This apparent *chiral poisoning* results in a lower number of active sites available for the adsorption of **1** and hydrogen, thus lowering overall reaction rate. Note that the reaction rate is about 2 to 3 orders of magnitude lower than that generally observed for the enantioselective hydrogenation of ethyl pyruvate and ketopantolactone (9, 10) over Pt/Al_2O_3 modified by cinchonidine.

The influence of temperature was investigated in the range 20–60°C. The best enantioselectivity was achieved at room temperature; increasing temperature enhanced the rate but diminished the enantioselectivity. A drop in ee at higher than room temperature is typical for enantioselective hydrogenations over Pt and Pd (16, 27, 28). The enhanced rate of hydrogenation of the aromatic rings of the modifier with increasing temperature may play a role. Another commonly used explanation is that higher-than-ambient temperature is unfavorable for the adsorption of the modifier. However, it was proposed recently based on a near-edge X-ray absorption fine structure study of quinoline adsorption on Pd(111) (29) that a change in the adsorption geometry of the alkaloid with increasing temperature is unlikely.

The hydrogen/**1** ratio in the range 10–800 mol/mol had no significant influence on the rate and enantioselectivity, probably due to the large excess of hydrogen. Increasing the hydrogen pressure from 5 to 180 bar (at constant molar hydrogen/**1** ratio) resulted in small rate acceleration but the ee dropped to about one-third of the initial value. The detrimental effect of forcing conditions is mainly attributed to the saturation of the aromatic rings of the modifier and a loss of its efficiency (1).

With increasing 2-propanol/**1** molar ratios in the range 100–500 the reaction rate dropped to less than one-half and the enantioselectivity decreased by a few percent. The lower ee at high dilution is astonishing in the light of experiments in the batch reactor where the highest enantioselectivities were achieved by dilution of the reaction mixture with the solvent (3). The explanation is a secondary effect: when keeping the total liquid flow rate and the modifier/**1** ratio at constant values, the modifier concentration decreases with increasing solvent/**1** ratio, which results in lower actual modifier/Pd_s ratios.

The influence of total liquid flow rate on the reaction rate and enantioselectivity is presented in Fig. 2. The fact that the rate decreased with increasing liquid flow rate indicates a complex behavior which cannot be traced to external mass transfer influences. We propose that the key for understanding this unusual behavior is the change in the CN flux to the Pd surface. At low liquid flow rate this flux is low, leading to low CN/Pd_s ratios. Due to the relatively fast hydrogenation of CN on Pd, the low CN flux results in lower ee and higher rate (the rate increases with decreasing modifier/Pd_s ratio). Intraparticle diffusion of the bulky modifier (CN) is assumed to be slow, particularly at low modifier concentration.

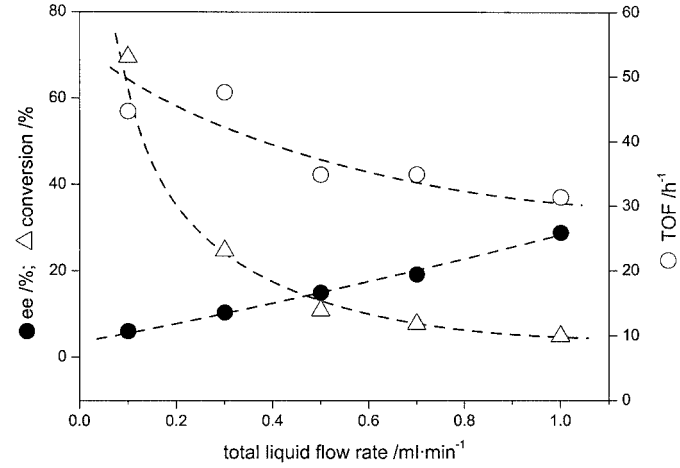


FIG. 2. Influence of total liquid flow rate (reactant + modifier + solvent) on the enantioselectivity (ee), conversion, and reaction rate (TOF) in the hydrogenation of **1**. Conditions: 20°C; 20 bar; CN/**1** molar ratio, 0.2%; solvent (2-propanol)/**1** molar ratio, 150; hydrogen/**1** molar ratio, 10.

Finally, an optimization of the reaction parameters was attempted to obtain the highest enantioselectivity under differential operating conditions. A factorial experimental design (30) afforded 84.5% ee at 1% conversion and the chemoselectivity to **2** was 100%. (Conditions: 20°C, 10 bar pressure, 1 ml min^{-1} total liquid flow rate corresponding to an LHSV of 60 ml g_{cat}^{-1} h^{-1}, CN/**1** molar ratio of 0.1, and solvent/**1** molar ratio of 150.)

Limitations in Achieving High Optical Yields

The parametric sensitivity study indicated that achieving high yield while maintaining a good ee is hampered in the continuous reactor by the counteracting tendencies observed for ee and rate. The difficulties are illustrated in Fig. 3 where the chemo- and enantioselectivities are plotted as a function of conversion. The pronounced scattering of the data points is due to the broad range of reaction conditions applied. For comparison, in the batch reactor further hydrogenation of **2** to **3** was minor up to 90% conversion (Fig. 3, panel a) (22). Similarly, the rapid loss of ee with increasing conversion is typical only for the continuous fixed-bed reactor (Fig. 3, panel b); in batch operation the ee even increased with conversion due to kinetic resolution of the intermediate dihydropyrone **2** (22).

The difference is also striking when the enantioselectivities, achieved in the same continuous reactor in the hydrogenation of **1** and ethyl pyruvate, are compared (Fig. 3, panel b). By increasing the conversion of **1** from 1 to 10% over CN-modified Pd/TiO_2 the ee dropped to less than one-half. In contrast, the ee remained high up to 95% conversion in the hydrogenation of ethyl pyruvate on cinchona-modified Pt/Al_2O_3.

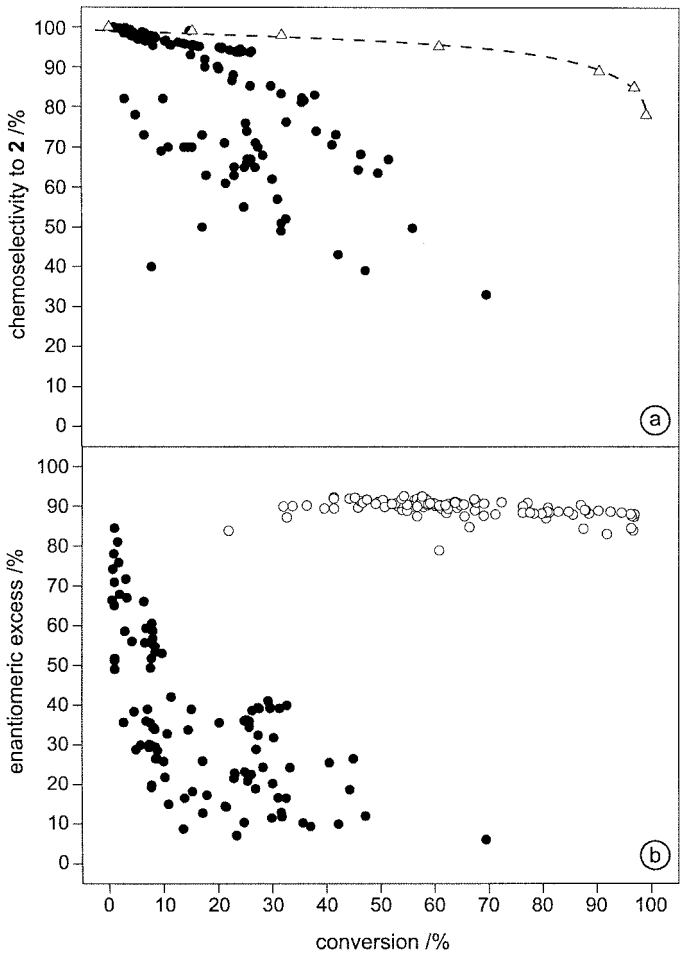


FIG. 3. (a) Influence of conversion on the chemoselectivity in the hydrogenation of **1** to **2** in a continuous fixed-bed reactor (full circles) and batch reactor (open triangles). Conditions in the fixed bed reactor: 10–60°C; 5–180 bar; cinchonine/**1** molar ratio, 0.2–11%; solvent (2-propanol)/**1** molar ratio, 50–1000; hydrogen/**1** molar ratio, 10–800; total liquid flow rate, 0.1–1.6 ml min^{-1}. Conditions in batch reactor: 25°C; 1 bar; cinchonine/**1** molar ratio, 0.95%; solvent (2-propanol)/**1** molar ratio, 1860. (b) Influence of conversion on the enantioselectivity (ee) in the hydrogenation of **1** (full circles) and of ethyl pyruvate (open circles). Conditions for the hydrogenation of **1**: 10–60°C; 5–180 bar; cinchonine/**1** molar ratio, 0.2–11%; solvent (2-propanol)/**1** molar ratio, 50–1000; hydrogen/**1** molar ratio, 10–800; total liquid flow rate, 0.1–1.6 ml min^{-1}. Conditions for the hydrogenation of ethyl pyruvate (EP): 0.1-g 5 wt% Pt/Al_2O_3 (Engelhard 4759); 0.9-g Al_2O_3; 10–60°C; 10–190 bar; CN/EP molar ratio, 0.1–2%; solvent (acetic acid)/EP molar ratio, 0–40; hydrogen/EP molar ratio, 5–100; total liquid flow rate, 0.1–5.2 ml min^{-1}.

A feasible explanation for the rapid loss of chemo- and enantioselectivity with increasing conversion of **1** is the high (actual) Pd_s/**1** and Pd_s/CN ratios in the continuous fixed-bed reactor compared to the corresponding ratios in batch operation. As a consequence, the good chemoselectivity in the partial hydrogenation of the pseudoaromatic **1** to **2** is lost. Note that loss of selectivity to intermediates in consecutive reaction series is common under forcing conditions. We showed earlier that partial hydrogenation of 2-pyrones to the corresponding dihydropyrones is successful on cinchona-modified Pd only under very mild conditions (1).

The possibility for increasing the enantioselectivity in the continuous fixed-bed reactor is limited. The fast hydrogenation of the quinoline rings of CN, leading to a loss of the enantiodifferentiating ability, may be compensated for by increasing the CN concentration in the feed. To obtain the optimum ee of 84.5% at 1% conversion required an already high CN/**1** molar ratio of 0.1. A considerable enhancement of this ratio cannot provide a technically feasible solution for the synthesis of **2**. For comparison, in a batch reactor a CN/**1** molar ratio of 0.02 was sufficient to afford 90% ee at 89% conversion (3).

On the basis of these results we interpret a former observation in the enantioselective hydrogenation of activated ketones on Pt/Al_2O_3 (9). Remarkably higher modifier/reactant ratios were necessary to achieve the best ee in a continuous fixed-bed reactor than in batch operation. For example, in the hydrogenation of ketopantolactone the two values deviated by a factor of 50. The likely explanation is the higher rate of hydrogenation of the modifier in the continuous reactor due to the higher Pt_s/modifier ratio. The loss of efficient modifier had to be compensated by increasing the modifier concentration in the feed. The competing hydrogenation of the quinoline rings of cinchonidine, as an important side reaction on Pt even under ambient conditions, was proved recently by electron-spray ionization mass spectroscopy (31).

CONCLUSIONS

Hydrogenation of 4-methoxy-6-methyl-2-pyrone **1** to the corresponding 5,6-dihydropyrone **2** with the Pd–cinchona system illustrates that in a continuous fixed-bed reactor good enantioselectivity can be achieved only at very low conversion. Producing high yield while maintaining the good ee—a critical requirement for industrial application—is hindered by the high Pd/reactant and Pd/modifier ratios. Hence, a batch (slurry) reactor seems to be the best choice for the heterogeneous catalytic synthesis of chiral dihydropyrones. Most likely, it is a general feature of Pt- and Pd-catalyzed hydrogenation reactions that higher cinchona alkaloid/reactant ratios are necessary to achieve good enantioselectivity in a continuous reactor, compared to the batch reactor.

ACKNOWLEDGMENTS

Helpful discussions with W. R. Huck and financial support by the Swiss National Science Foundation are kindly acknowledged.

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