# PRIORITY COMMUNICATION

# Continuous Enantioselective Hydrogenation of Activated Ketones

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**Heterogeneous enantioselective hydrogenation of activated ketones in a fixed-bed reactor was achieved by continuous feeding of minute amounts of chiral modifier to the reactant stream. The potential of this concept is illustrated using the hydrogenation of ketopantolactone and ethyl pyruvate over Pt/alumina modified by cinchonidine. Production rates and enantiomeric excesses (ee) achieved without optimization at room temperature and 40 bar were 94 mmol/$g_{cat} \cdot$ h and 83.4% ee for ketopantolactone, and 23 mmol/$g_{cat} \cdot$ h and 89.9% ee for ethyl pyruvate. Transient measurements by stopping of the cinchonidine flux indicate that continuous feeding of the modifier in ppm concentration is essential.**

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## INTRODUCTION

Synthesis of complex chiral molecules in optically pure form is a demanding task which requires new efficient catalytic technologies. Enantioselective hydrogenation of ketopantolactone to (*R*)-pantolactone is a good example for the "green chemistry" approach. (*R*)-Pantolactone is a key intermediate in the synthesis of pantothenic acid (1), a member of the vitamin B family and constituent of coenzyme A. Chemoselectivity of the hydrogenation reaction is excellent, usually 100% with both homogeneous and heterogeneous catalysts. The highest enantiomeric excess (ee) of 98.7% has been achieved with a homogeneous Rh(I) catalyst containing chiral diphosphine and achiral trifluoroacetato ligands (2). The reaction runs at ambient conditions but requires a rather high concentration of the expensive catalyst (catalyst/substrate: 0.5 mol%). We have shown recently (3, 4) that cinchonidine (CD)-modified Pt/alumina can afford 91.6% ee to (*R*)-pantolactone at 70 bar, using only 8.8 ppm CD related to the substrate (Scheme 1). The extremely low CD concentration required for the batch process inspired us to explore the possibility of continuous operation.

From a technological point of view continuous operation in a fixed-bed reactor is the most attractive solution which can remarkably enhance productivity, due to eliminating of time required for charging, discharging, and cleaning. Other important advantages of the fixed-bed reactor are the avoidance of catalyst separation and abrasion problems. To our knowledge, no report has appeared yet on a successful continuous asymmetric hydrogenation reaction. An early attempt has been made for methyl pyruvate hydrogenation in Wells' laboratory (5) with the aim of estimating the adsorption strength of cinchona alkaloid on Pt. The catalyst was chirally modified but CD was not fed, and experiments resulted in marginal conversions of about 7% and enantioselectivities below 80%.

Here we report a new continuous high-pressure procedure for asymmetric hydrogenation of activated ketones (6). The study paves the way to the industrial production of (*R*)-pantolactone. For proof of a more general applicability of the concept, some experiments were also made with ethyl pyruvate as reactant (Scheme 1).

## METHODS

Ketopantolactone (KPL, dihydro-4,4-dimethyl-2,3-furanedione, F. Hoffmann-La Roche AG) was dried by azeotropic distillation with toluene (>99.7%, Riedel-de Haën). Ethyl pyruvate (Aldrich) was freshly distilled before use. Cinchonidine (CD, >98%, Fluka) was used as received. The catalyst (5 wt% Pt/Al$_2$O$_3$, Engelhard 4759) was pretreated before use in a fixed-bed reactor by flushing with 12 ml min$^{-1}$ N$_2$ (99.995%) at 400°C for 30 min, followed by a reductive treatment in H$_2$ (99.999%) for 90 min at the same temperature. After cooling to room temperature in H$_2$, the catalyst was immediately transferred to the reactor and held under nitrogen. Platinum dispersion after heat treatment was 0.27 (3).

Hydrogenation was carried out in a 38 ml inconel tubular reactor (inner diameter: 12 mm), equipped with either an electric heating or a cooling jacket. Generally, 1 g catalyst with a particle size of 50–100 $\mu$m was used, resulting in a bed length of ca. 15 mm. The reaction temperature was monitored by an adjustable thermocouple inside the catalyst bed. The solution containing reactant, CD, and toluene was

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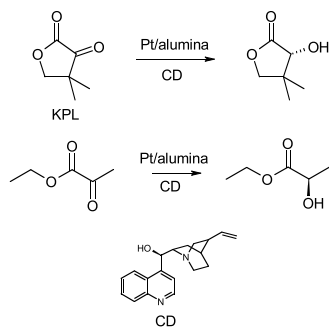
**SCHEME 1**

continuously fed into the reactor by an HPLC-pump (Gilson M305). The hydrogen flow was kept constant by a two step expansion valve (NWA PE103) and monitored by a rotameter. Constant pressure was maintained by a pressure controller (NWA).

Conversion and ee were determined by an HP 5890A gas chromatograph with a chiral capillary column (WCOT Fused Silica 25 m × 0.25 mm, coating CP Chiralsil-Dex CB, Chrompack). Enantioselectivity is expressed as ee (%) = $R$ (%) − $S$ (%). Reaction rate was calculated as moles of product formed per unit amount of catalyst in unit time (productivity), or TOF related to the number of surface Pt sites, under the following conditions:

KPL: 40 bar, 20°C, 5 ml · min$^{-1}$ liquid flow rate, 0.39 mmol · min$^{-1}$ substrate, molar ratio CD/substrate = 2800 ppm, time-on-stream: 30 min;

ethyl pyruvate: 40 bar, 20°C, 2.5 ml · min$^{-1}$ liquid flow rate, 0.38 mmol · min$^{-1}$ substrate, molar ratio CD/substrate = 3750 ppm, time-on-stream: 30 min.

## RESULTS AND DISCUSSION

Development of an efficient continuous hydrogenation process in a fixed-bed reactor included the study of the influence of several reaction parameters. Concentration of the chiral modifier CD in the feed was one of the most influential parameters. Contrary to an earlier attempt on continuous operation of a slurry reactor (5), it was found to be crucial to feed CD continuously to the reactor. Transient experiments with stopping of the CD flux (Fig. 1) revealed that steady state operation necessitates one to maintain a low but constant CD concentration in the feed. Conversion was 100% during the whole experiment. The drop in ee in the region where only KPL and hydrogen were fed can be attributed to washing out of CD from the Pt surface by the flowing fluid (5). Another important reason for the observed effect may be the partial hydrogenation of the quinoline ring system of CD under high pressure conditions which lowers the adsorption strength and the efficiency of the chiral modifier (7). This point has been addressed in a recent study of $\alpha$-ketoester hydrogenation over cinchona-modified Pt (8).

In Fig. 1 there is a clearly observable initial transient period after starting feeding the toluenic solution of KPL and CD. A transient period in ee lasting at least 15 min was always observed after starting the experiments by feeding the substrate and modifier, or changing the feed composition. Transient experiments revealed that the length of the initial transient period depended strongly on the condition which caused the transient behavior, i.e., whether the flow of substrate, modifier, or both of them was stopped for a certain time period.

Similar initial transient behavior has been described for the enantioselective hydrogenation of various reactants over cinchonidine-modified Pt and Pd in batch reactors (9). The sometimes considerable variation in ee was proposed to be due to competitive adsorption of hydrogen, substrate, modifier, and solvent and to the possible removal of surface impurities. The influence of hydrogen pressure in the range 20–190 bar confirms this proposal (Fig. 2). High hydrogen pressure in the system, which corresponds to high initial hydrogen concentration on the Pt surface, prolongs considerably the transient period. Apparently, the higher the surface hydrogen concentration before starting the liquid feed, the longer the time required for approaching the steady state surface concentrations of other reaction components by competitive adsorption. Note that the ee data in the figures are cumulative (integral) values; variations in incremental (differential) ee are even larger.

A study of a longer period (6 h) of time-on-stream revealed that after an initial stabilization period the ee slowly decreased. For example, at 40 bar and 17°C between 2 and 6 h time-on-stream the ee declined from 81.3 to 78.4%. Note that a decline in ee is also observed in batch runs when the catalyst is reused, which indicates that the phenomenon is not due to continuous operation. The minor loss in efficiency of the Pt-CD system is attributed to the formation and accumulation of traces of nonvolatile byproduct(s) which could not be detected by GC analysis of the effluent.
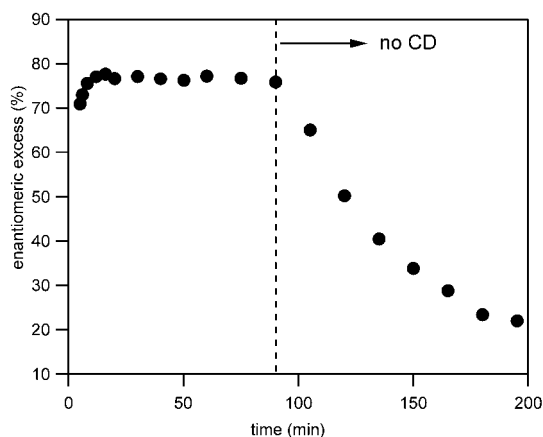


**FIG. 1.** Enantioselective hydrogenation of KPL in a continuous fixed-bed reactor. Transient experiment where CD flux was stopped after 90 min. Conditions: $1.95 \times 10^{-4}$ mol · min$^{-1}$ KPL, $1.1 \times 10^{-6}$ mol · min$^{-1}$ CD, 5 ml · min$^{-1}$ total liquid flow, 18°C, 1 g catalyst; conversion: 100%.

No product other than pantolactone could be recognized in any experiment. For estimating the role of possible impurities we have to keep in mind that the optimum in modifier/reactant ratio found in a batch reactor (4) is orders of magnitude lower than the usual impurity level of substrate and solvent. Even traces of impurities, barely detectable by chromatography, can adsorb strongly on the Pt surface and disturb the enantio-differentiating process.

Figure 2 also indicates that after approaching steady state conditions the hydrogen pressure had only minor influence on the enantioselectivity. Between 20 and 190 bar the ee varied in a range less than 5% (time-on-stream: 30 min). The highest selectivity was achieved at 40 bar (not shown). Under similar conditions (40 bar, 20°C, 0.39 mmol/min KPL, 1.1 $\mu$mol/min CD, 5 ml/min total flow, 0.2 g catalyst, 80% conversion) the KPL production rate was very high, 94 mmol/$g_{cat} \cdot$ h, corresponding to an average TOF of 1420 h$^{-1}$. Similar pressure dependence was found in a batch reactor: pressures higher than 20 bar had only minor effect on the ee (3).

Bigger differences in the behavior of the two reactor types were observed when comparing the role of modifier/substrate molar ratio (Fig. 3). The range of highest selectivity in the slurry reactor was 4–40 ppm, while—at least under the conditions used—the best ee in the fixed-bed reactor was achieved in the range 200–2000 ppm. It is not clear yet whether this remarkable difference is typical. Optimization of reaction conditions is likely to lower the required modifier/substrate ratio in the continuous system. The highest ee to (R)-pantolactone (83.4%) was measured at 40 bar and 17°C, using a CD/KPL = 2800 ppm molar ratio.

For exploring the general applicability of continuous operation, the enantioselective hydrogenation of ethyl pyruvate was also examined in the fixed-bed reactor (Fig. 3c). High ee up to 89.9% ee was achieved, but the reaction was considerably slower (ethyl lactate production rate 23 mmol/$g_{cat} \cdot$ h; average TOF = 370 h$^{-1}$) than the hydrogenation of KPL (see above).
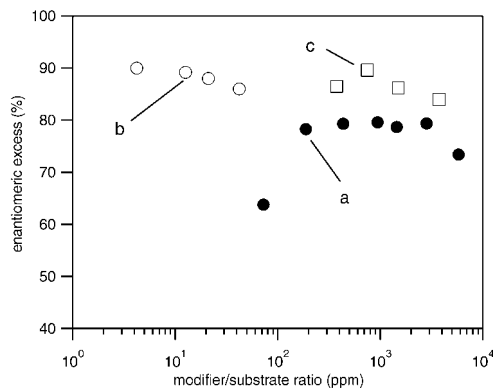


**FIG. 3.** Influence of modifier/substrate ratio on the enantiomeric excess in KPL and EP hydrogenation carried out in continuous fixed-bed and batch reactors; conversion: always 100%. Conditions: (a) continuous reactor, $3.9 \times 10^{-4}$ mol $\cdot$ min$^{-1}$ KPL, 5 ml $\cdot$ min$^{-1}$ total liquid flow, 40 bar hydrogen, 17°C, 1 g catalyst, time-on-stream: 30 min; (b) mechanically stirred batch reactor, 32 mmol KPL, 105 mg catalyst, 51 ml toluene, 70 bar hydrogen, −5°C [10]; (c) continuous reactor, $3.8 \times 10^{-4}$ mol $\cdot$ min$^{-1}$ ethyl pyruvate, 2.5 ml $\cdot$ min$^{-1}$ total liquid flow, 40 bar hydrogen, 23°C, 1 g catalyst, time-on-stream: 30 min.

## CONCLUSIONS

Continuous feeding of trace amounts of the chiral modifier has been shown to provide the opportunity to carry out enantioselective hydrogenation of activated ketones in a fixed-bed reactor. The process belongs to the class of clean technologies: the chemoselectivity is practically 100% and separation of the minute amount of modifier is in many cases not necessary. The concept should be applicable to other catalytic systems based on chirally modified metal hydrogenation catalysts and may open the door to a more efficient screening of potential chiral modifiers.

## ACKNOWLEDGMENT

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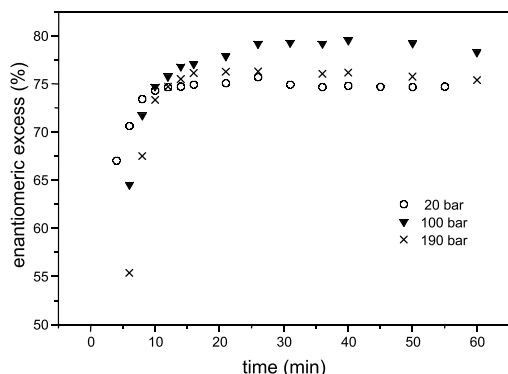


**FIG. 2.** Initial transient period in the hydrogenation of KPL in a continuous fixed-bed reactor at various pressures. Conditions: $3.9 \times 10^{-4}$ mol $\cdot$ min$^{-1}$ KPL, $1.1 \times 10^{-6}$ mol $\cdot$ min$^{-1}$ CD, 5 ml $\cdot$ min$^{-1}$ total liquid flow, 17°C, 1 g catalyst; conversion: 100%.