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Continuous enantioselective hydrogenation in fixed-bed reactor: towards process intensification

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Abstract

The platinum-catalyzed enantioselective hydrogenation of ethyl pyruvate (EP) has been studied in a continuous fixed-bed reactor working under trickle bed conditions. The alumina-supported platinum catalyst was chirally modified by continuous dosing of small amounts of cinchonidine (CD) to the reactor feed containing EP and hydrogen dissolved in acetic acid. A parametric sensitivity study, including CD/EP ratio, hydrogen pressure, temperature, solvent/EP ratio and total liquid feed rate indicated significant dependence of reaction rate and enantiomeric excess (ee) on these parameters. Optimization using the Box Wilson method with hydrogenation rate as objective function and ee $> 90\%$ as boundary condition afforded a site–time–yield, expressed as average turnover frequency (TOF), of $84\,000\,\mathrm{h}^{-1}$. The space–time–yield was found to be approximately one order of magnitude higher than that achieved in a batch reactor (autoclave) under otherwise similar conditions. These findings indicate that the continuous fixed-bed reactor operation may provide an interesting opportunity for process intensification of this type of asymmetric catalytic hydrogenations.

Keywords: Enantioselective; Asymmetric; Hydrogenation; Platinum; Cinchonidine; Ethyl pyruvate; Fixed-bed reactor; Process intensification

1. Introduction

Among the various methods applied for the production of pure enantiomers [1], catalysis is unique in the sense that with a small amount of chiral catalyst a large quantity of a chiral product can be synthesized. The vast majority of catalytically prepared compounds are synthesized by homogeneous catalytic routes in batch reactors. Heterogeneous catalytic processes have so far not found significant application in the field of asymmetric catalysis, which is not surprising in view of the limited number of efficient heterogeneous catalytic systems known today [2]. From a technical point of view, heterogeneous catalytic processes possess several inherent advantages connected with separation, regeneration, reuse and handling of the catalysts. Furthermore, heterogeneous catalysis is more suitable for the development of continuous processes.

In a previous study [3,4], we have shown for the first time the feasibility of continuous enantioselective hydrogenations of activated ketones in a fixed-bed reactor. Ketopantolactone and ethyl pyruvate (EP) were hydrogenated over Pt/alumina modified by cinchonidine (CD) affording 83 and 90% enantiomeric excess (ee) respectively. Continuous feeding of minute amounts of the modifier proved to be sufficient to maintain the enantiodifferentiation. More recently, Toukoniitty et al. [5] used the same concept for the continuous enantioselective hydrogenation of 1-phenyl-1,2-propanedione.

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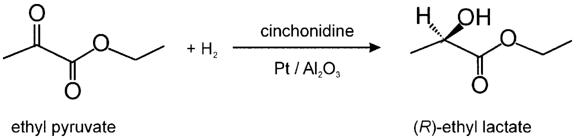

Scheme 1. Continuous asymmetric hydrogenation of EP over platinum modified by CD. Note that the modifier is continuously added in small amount to the reactor feed containing EP, acetic acid (solvent) and hydrogen.

The objective of the present study was to gain some information about the parametric sensitivity of such complex three-phase reactor systems and to explore their potential for process intensification. For this purpose we have chosen the best studied model reaction, the enantioselective hydrogenation of EP (Scheme 1).

2. Experimental

One gram of 1:9 mixture of commercially available 5 wt.% Pt/alumina (Engelhard 4759) and pure alumina (>98%; Fluka) was prereduced in flowing hydrogen for 90 min at 400 °C. The catalyst was then cooled to room temperature under hydrogen, flushed with argon and transferred to the fixed-bed reactor immediately. Pt dispersion after heat treatment was 0.27 as determined by TEM. Solvent (acetic acid, 99.8%; Fluka) and modifier (CD, >98%; Fluka) were used as received, whereas EP (>97%; Fluka) was purified by distillation.

All experiments were carried out in a 12 mm inner diameter tubular stainless steel fixed-bed reactor (Fig. 1a) working 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.

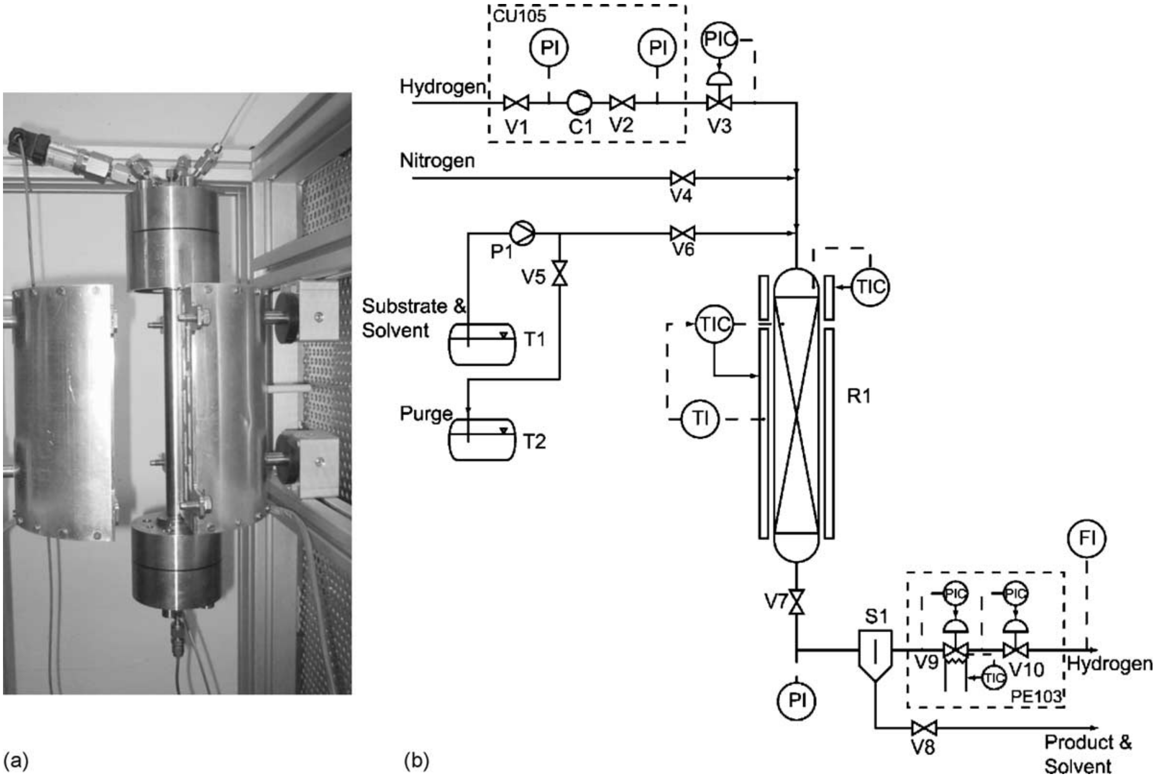

Fig. 1. (a) Photograph of the 12 mm inner diameter tubular high pressure reactor with heating jacket. (b) Flowsheet of continuous hydrogenation apparatus. CU105: compression unit (NWA, New Ways of Analytics, Germany), PE103: two step expansion valve (NWA), V: valve, C: compressor, P: HPLC pump (Gilson M305), T: tank, R: reactor, S: high pressure separator, PI: pressure indicator, PIC: pressure controller with indicator, TIC: temperature controller with indicator, TI: temperature indicator, FI: flow indicator (rotameter, Vögtlin, Switzerland).

In order to warrant proper flow conditions and to avoid significant temperature gradients in the fixed-bed the catalyst was diluted with pure support material in the ratio mentioned above, affording a catalyst bed length (L) of ca. 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 temperature in the catalyst bed was monitored with a movable thermocouple positioned axially in the catalyst bed.

Depending on the reaction conditions the reactor was heated electrically or cooled by a cooling jacket. Liquid and solved components (solvent, substrate and modifier) were fed by an HPLC pump (Gilson M305, Fig. 1b, P1) into the reactor. Hydrogen pressure was adjusted before the reactor (Fig. 1b, V3), whereas the hydrogen flow was regulated after the reactor by an expansion unit (Fig. 1b, NWA, PE103) and measured by a rotameter. Samples were taken on-line from the high pressure separator (Fig. 1b, S1).

Conversion and ee were determined using an HP 5890 gas chromatograph and a Chirasil-DEX CB (Chrompack) capillary column. Here, ee is expressed as $ee\,(\%) = 100 \times |R - S|/(R + S)$. Site–time–yields expressed as average turnover frequencies (TOFs) were derived from the average hydrogenation rate and the accessible platinum contained in the catalyst bed.

3. Results and discussion

In a first step, an extensive parameter study was carried out to find significant first-order influences on enantioselectivity and rate of the hydrogenation of EP. In the field of examined parameters: modifier/substrate ratio, reaction temperature, hydrogen pressure, solvent/substrate ratio and total liquid flow rate revealed significant influence on rate and/or ee.

Fig. 2 depicts the influence of the modifier/substrate (CD/EP) ratio on the rate, expressed as TOF, and the ee. Increasing modifier (CD) concentration lowered the activity (TOF) by about 50% over the observed region, whereas ee remained almost constant. This effect can be explained by the increased coverage of the platinum surface by modifier at higher CD/EP ratio and the resulting loss of free active sites on the catalyst. Recent in situ ATR-infrared studies [6,7] of CD adsorption on platinum uncovered that with increasing surface coverage the adsorption mode changed from nearly parallel π-bonded adsorption via the aromatic quinoline ring to CD bound by the nitrogen lone pair

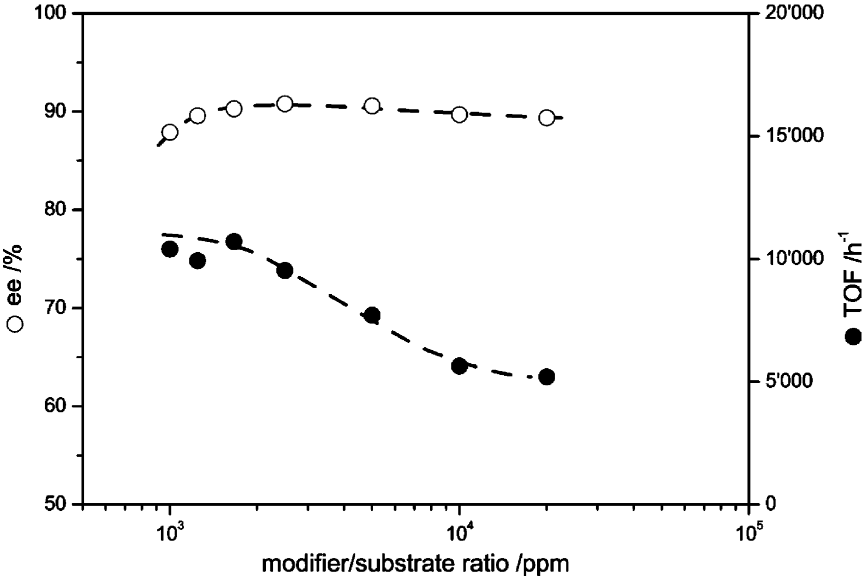

Fig. 2. Influence of modifier/substrate (CD/EP) ratio on ee and activity, expressed as average TOF. Conditions: 20 °C, 150 bar, total liquid flow (substrate, modifier, solvent): 1 ml min^{-1}, hydrogen/substrate ratio: 10 mol/mol, solvent/substrate ratio: 10 mol/mol.

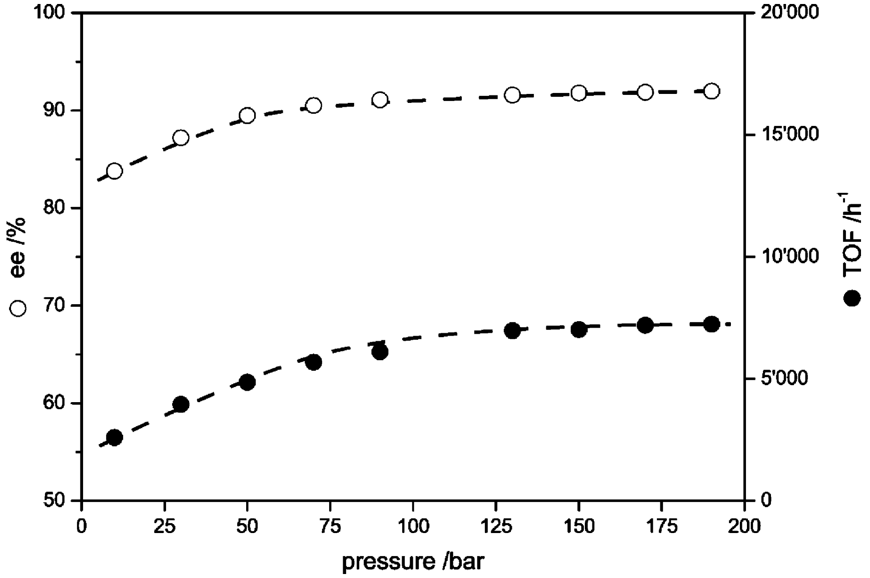

Fig. 3. Influence of pressure on ee and TOF. Conditions: 20 °C, total liquid flow (substrate, modifier, solvent): 1 ml min^{-1}, hydrogen/substrate ratio: 10 mol/mol, modifier/substrate ratio: 1000 ppm mol/mol, solvent/substrate ratio: 10 mol/mol.

of the quinoline ring. According to model suggestion [8,9] the latter adsorption mode is not considered to contribute to the enantiodifferentiating catalytic process, but to blocking of free surface sites, which could explain the decrease of rate at higher modifier concentration.

Activity and ee significantly increased by raising hydrogen pressure reaching a plateau above 100 bar (Fig. 3). This behavior is in accord with that observed earlier in batch reactor investigations, where pressures above 100 bar were found to offer only marginal benefit concerning reaction rate and ee [10]. The plateau formation at higher pressure can be understood on the basis of a Langmuir–Hinshelwood mechanism in which the surface reaction between EP and hydrogen controls. However, at high hydrogen pressure a possible influence of competing quinoline ring hydrogenation, which disables proper anchoring of the CD [11], cannot be ruled out.

Interestingly, increasing temperature from 15 to 60 °C did not afford higher rate, and the ee decreased at temperatures higher than 40 °C (Fig. 4). Increased reaction temperatures are supposed to cause a change of the adsorption mode of the modifier from π-bonded parallel adsorption via the quinoline moiety to nitrogen lone pair bound species [12]. The slower racemic reaction, favored at higher temperature, seems to compensate for the general rate enhancing effect of temperature.

Further crucial parameters for the performance of the reaction system are the solvent/substrate (acetic acid/EP) ratio and the total liquid flow rate. More concentrated reaction mixtures and the associated higher substrate coverage on the catalyst surface afforded highest TOF but slightly diminished enantioselectivities (Fig. 5). Dilution with solvent caused the rate to decrease strongly, as expected.

Fig. 6 shows the influence of the total liquid flow rate (solvent, EP, modifier) on the activity and ee. TOF continuously increased with higher total liquid flow rate, whereas ee changed comparatively little. This behavior could originate from two different phenomena which occur at low flow rate. At low flow rate the CD flux to the active platinum sites may be insufficient to maintain the necessary CD coverage. Furthermore, external mass transfer influences are supposed to become significant. As concern intraparticle diffusion influences, they should not depend on the flow rate. Previous studies in a batch reactor did not indicate prominent influence of intraparticle mass transfer with particles smaller than 100 μm under similar conditions [13]. The region where the TOF leveled off

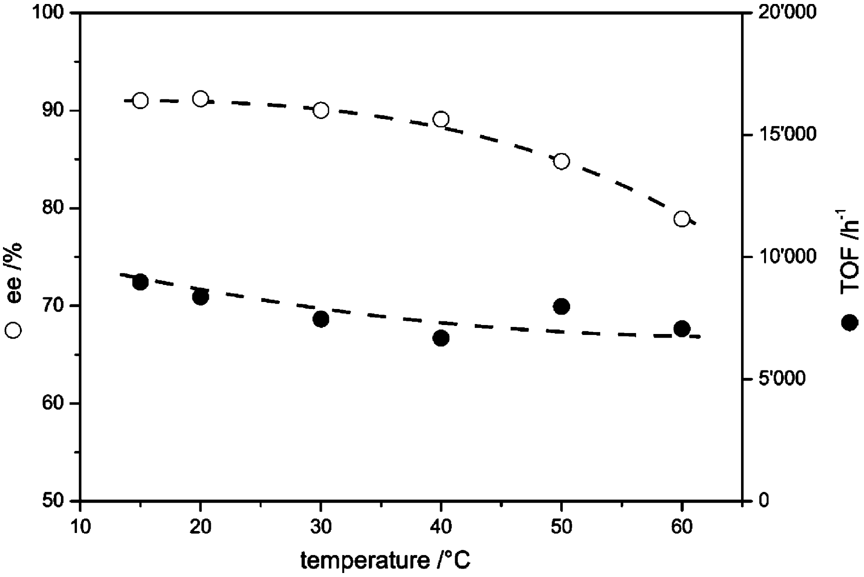

Fig. 4. Influence of temperature on ee and TOF. Conditions: 150 bar, total liquid flow (substrate, modifier, solvent): 1 ml min^{-1}, hydrogen/substrate ratio: 10 mol/mol, modifier/substrate ratio: 1000 ppm mol/mol, solvent/substrate ratio: 10 mol/mol.

was at around 4.3 ml min^{-1}. Interestingly, both parameters, solvent/substrate ratio and total liquid flow rate, show a change in TOF by an order of magnitude over the investigated parameter ranges, whereas the ee remains almost constant except at low solvent/substrate ratio and total liquid flow.

A fractional factorial 2^{5-2}-experimental design was applied resulting in a second-order linear model,

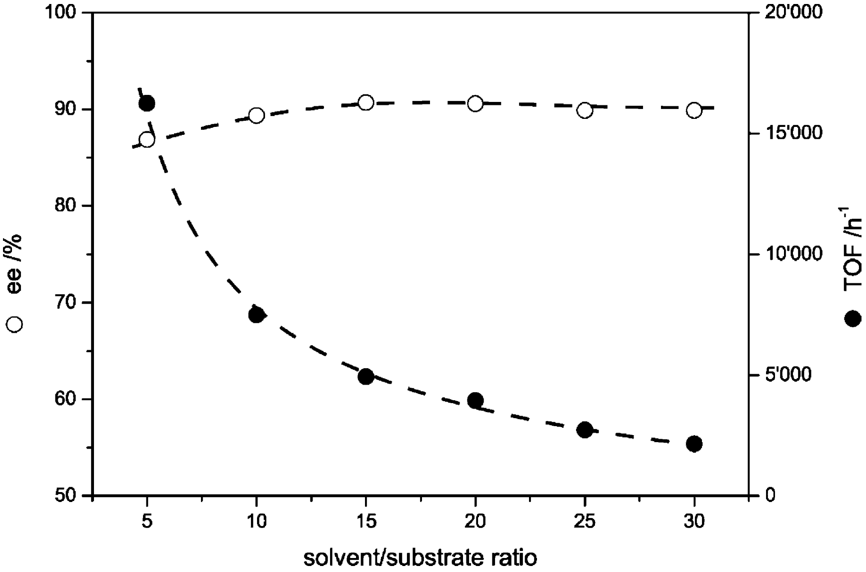

Fig. 5. Influence of solvent/substrate ratio on ee and TOF. Conditions: 20 °C, 150 bar, total liquid flow (substrate, modifier, solvent): 1 ml min^{-1}, hydrogen/substrate ratio: 10 mol/mol, modifier/substrate ratio: 1000 ppm mol/mol.

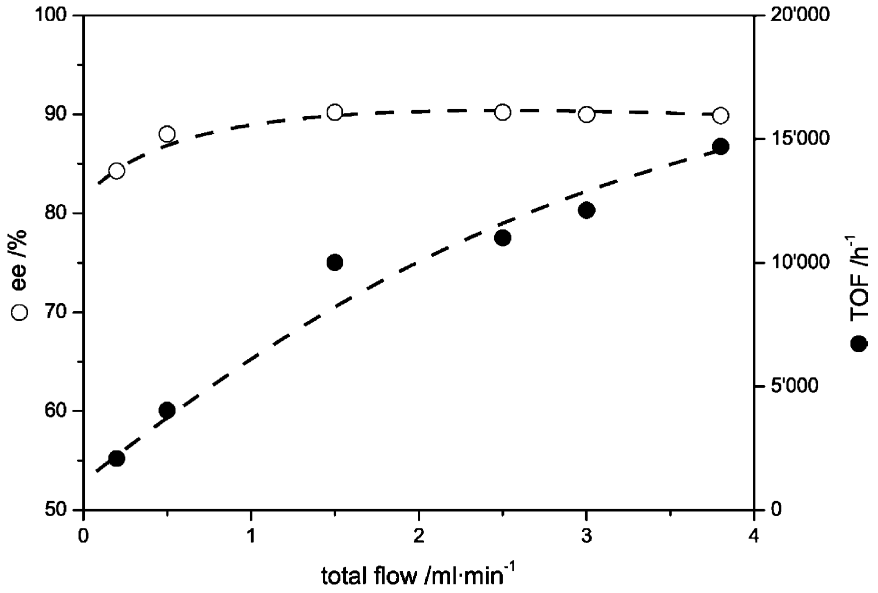

Fig. 6. Influence of total liquid flow (substrate, modifier solvent) on ee and TOF. Conditions: 20 °C, 150 bar, hydrogen/substrate ratio: 10 mol/mol, modifier/substrate ratio: 1000 ppm mol/mol, solvent/substrate ratio: 10 mol/mol.

which was optimized by Box Wilson's (steepest ascent) method [14] with TOF as objective function and ee $>$ 90% as boundary condition. The parameters affording the highest TOF with an enantioselectivity of more than 90% were: modifier/substrate ratio, 1870 ppm; solvent/substrate ratio, 4.15 mol/mol; hydrogen/substrate ratio, 10 mol/mol; temperature, 28 °C; liquid flow rate, 4.3 ml min^{-1}; and hydrogen pressure 145 bar. These conditions afforded a site–time–yield, i.e. an average TOF of 84 000 h^{-1} which corresponds to an average production rate of 1.94 mol min^{-1} g_{Pt}^{-1}. In order to assess the process intensification we may compare the space–time–yield in the fixed-bed reactor with that achieved in the batch reactor under similar conditions. Taking values from the literature for the batch reactor performance [8,13,15,16], we find a range of 0.06–0.33 mol min^{-1} l^{-1} which is about an order of magnitude less than the space–time–yield achieved in the fixed-bed reactor (4.3 mol min^{-1} l^{-1}). The reason for this behavior can be traced to the much higher density of active platinum sites per reactor volume in the fixed-bed reactor (3.1 mol Pt/m^3) compared to the batch reactor (ca. 0.15 mol Pt/m^3).

This work demonstrates that the continuous operation in a fixed-bed reactor may bare an interesting potential for process intensification in enantioselective heterogeneous hydrogenation on chirally modified metals. However, this potential can be exploited, only when the reaction rate is sufficiently fast, as in the case of α-ketoester hydrogenation on cinchona-modified platinum. It is shown elsewhere [17] that continuous fixed-bed operation is not suitable for the enantioselective hydrogenation of substituted 2-pyrones [18] over cinchona-modified palladium due to counteracting effects of modifier concentration on rate and enantioselectivity. Sufficiently high ee could only be achieved at relatively high modifier concentration, which in turn afford low reaction rates due to the decelerating effect of high modifier concentration (high modifier surface coverage) typical for the palladium–cinchona system. Thus, several criteria have to be fulfilled in order to make beneficial use of continuous fixed-bed reactor operation in enantioselective heterogeneous hydrogenations over chirally modified metal catalysts.

4. Conclusions

The continuous platinum-catalyzed enantioselective hydrogenation, based on admixing a small quantity of chiral modifier to the reactant feed, is shown to provide an interesting opportunity for the intensification of the performance of such catalytic systems. The process intensification has been demonstrated for the enantioselective hydrogenation of EP on an alumina-supported platinum catalyst for which much higher production rates could be achieved with the continuous fixed-bed reactor, compared to operation in the batch reactor. The process intensification is attributed to the much higher density of active platinum sites per reactor volume in the fixed-bed reactor compared to the batch slurry reactor. Extension of the continuous operation to the enantioselective hydrogenation of several other substrates is presently pursued in our laboratory [17,19].

Acknowledgements

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