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Chiral fixed bed reactor for stereoselective heterogeneous catalysis: modification, regeneration, and multiple product syntheses

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Abstract

A chiral fixed bed reactor (CFBR) was used for continuous enantioselective hydrogenations of ethyl pyruvate (EP) and ethyl benzoylformate (EB) on cinchonidine (Cind) and cinchonine (Cin) modified Pt/Al_2O_3. The reactions were carried out with ethanol (EtOH) as solvent at 0 and 20 °C, under a typical feed hydrogen mole fraction of $x_{H_2} \approx 0.007$ and total pressures of 60–200 bar. Due to the configuration used, the feeds of reactants as well as total pressure could be varied independently. In addition, the analytical method used was different from the commonly used method. HPLC with tandem UV–vis/circular dichroism were used to assess conversion and selectivity. The primary findings concerning the chemistry and reaction engineering include the following: (i) the method of contacting ethyl pyruvate is important (EP was cold stored and contacted with ethanol immediately prior to reaction to minimize hemiketal formation); (ii) 0 °C provides a more stable hydrogenation than 20 °C; (iii) e.e. is independent of system pressure; (iv) effective demodification and subsequent remodification in the CFBR is possible, thereby allowing regeneration of the catalytic system where activity and enantioselectivity are maintained; and (v) multiple product syntheses can be achieved using the same Pt/Al_2O_3 catalyst with multiple substrates and multiple modifiers. These results demonstrate the technological feasibility of using one-and-the-same supported-metal packed bed for many diverse syntheses of chiral products.

Keywords: Heterogeneous catalysis; Enantioselective hydrogenation; CFBR; Reduction; Remodification; Regeneration; De-modification; HPLC-CD

1. Introduction

The enantioselective hydrogenation of α-ketoesters over supported platinum is by far the most well-studied heterogeneous catalyzed stereoselective system [1]. Various types of supported platinum have been prepared [2–4], numerous natural and synthetic chiral modifiers particularly from the cinchona alkaloid group have been tested [5–7], and a host of substrates have been used [8–10]. The kinetics of the reaction have been studied [11,12], and a simple ligand-accelerated two-site mechanism involving racemic and enantioselective sites has been shown to be capable of modeling both the rate and enantiomeric excess (e.e. or optical yield) [13]. The exact origin of the enantioselectivity, particularly with respect to the interaction between substrate and modifier, appears complex and has been the focus of many studies [14–17].

The most serious complications associated with these reactions appear to be substrate purity [18], interaction/reaction between substrates and solvents [19], temperature dependence of the reaction (high temperatures lead to desorption of modifier and hence more racemic sites) [14,20], and perhaps most importantly degradation of the chiral modifier [21]. The last item arises primarily from hydrogenation of the aromatic rings, which are needed to ensure adsorption on the platinum surface. Due to the extraordinarily high reaction rates of this ligand-accelerated reaction in well-stirred tanks, gas–liquid, liquid–solid, and intraparticle transport problems arise, and these can lead to a pronounced decrease in enantiomeric excess [22–24]. This effect arises from the different hydrogen mole fraction dependencies of the racemic and enantioselective catalytic cycles.

Typically, the enantioselective hydrogenation of α-ketoesters has been performed on a batch scale—as is common for many fine chemical and pharmaceutical syntheses performed in the liquid phase, particularly stereoselective syntheses. Such a configuration exacerbates some of the com-

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plications mentioned previously. Indeed, the most serious is the degradation of the chiral modifier leading to lower product selectivity as a function of time. Since the initial conditions fix the accessible region of composition space, adequate modification of the metal crystallites cannot be ensured at later reaction times.

Continuous enantioselective hydrogenation using a fixed bed reactor has been demonstrated [20,25–27]. In principle, such a configuration allows maintenance of surface modification throughout the reaction period, thereby alleviating the primary complication associated with the present class of reactions. However, the potential utility of a chiral fixed bed reactor (CFBR) extends considerably beyond this advantage. Since stereoselective syntheses are normally performed to obtain only small/modest amounts of chiral products, and since a particular supported metal catalyst can be used in a variety of syntheses, a specific fixed bed could be used (in principle) for semicontinuous multiple product syntheses. This idea is somewhat similar in spirit to a multipurpose batch plant, with the very important and notable exception that *all* the reactions are performed in the same reactor on the same supported catalyst.

The present contribution examines the technological considerations needed to achieve multiple product stereoselective heterogeneous catalytic syntheses using one-and-the-same catalyst packed reactor. These considerations include the following:

(i) taking full advantage of the special contacting pattern available;
(ii) identifying protocols for in situ catalyst regeneration (thereby avoiding/delaying return of the catalyst to the manufacturer);
(iii) demonstrating the use of multiple substrates with multiple chiral modifiers to achieve multiple product syntheses.

Proof of concept opens a wide range of new opportunities for bench scale, pilot plant, and even production syntheses. Clearly, such opportunities are not necessarily limited to the cinchona-alkaloid/α-ketoester/supported platinum systems—which are the test reactions considered here.

2. Experimental

2.1. Materials

Ethyl pyruvate (Merck, 98%) was distilled under vacuum (bp 45 °C) and stored at 0 °C. Ethanol was used as the solvent and was obtained from Merck. Before use, ethanol and the HPLC mobile phase, water, and acetonitrile (Mallinckrodt, 99.9%) were filtered using a 0.45-μm, 47-mm nylon filter membrane. Ethyl benzoylformate (Aldrich, 95%), cinchonidine (Fluka, 98%), cinchonine (Fluka, 99%), *R*-ethyl lactate (Fluka, 99%), *S*-ethyl lactate (Fluka, 99%), *R*-ethyl mandelate (Aldrich, 99%), *S*-ethyl mandelate (Aldrich, 99%), and hydrogen (Soxal, 99.9995%) were used as received. Ethyl benzoylformate and alkaloid modifier were dissolved in filtered ethanol before use in the catalytic experiments. The containers of freshly prepared solutions were kept at room temperature and connected to the quaternary pump for catalytic experiments. In contrast, during the catalytic hydrogenation experiments the container with distilled ethyl pyruvate was kept at 0 °C in an ice/water bath. *The ethyl pyruvate was not in solution with ethanol while stored.* The containers with reagents for catalytic experiments were not bubbled under flowing helium. References for *R*-, *S*-ethyl lactate and *R*-, *S*-ethyl mandelate were prepared in ethanol for analytical measurements.

The Pt/alumina catalyst (Engelhard 4759) was prereduced at 400 °C for 2 h in 30 ml min^{-1} flowing hydrogen and then kept at room temperature for continuous use for a maximum of 6 months. The particle size distributions, platinum loadings as a function of particle size, and texture parameters as a function of particle size for Engelhard 4759 are known [22].

2.2. Apparatus

The experimental configuration for continuous enantioselective hydrogenation carried out in fixed bed reactor is quite different from that in a batch reactor. A schematic structure of the whole continuous reaction setup is given in Fig. 1.

The enantioselective hydrogenation of α-ketoesters (ethyl pyruvate and ethyl benzoylformate) on cinchona-modified platinum/Al_2O_3 catalyst was performed in a fixed bed reactor. An HPLC column cartridge (2.1-mm i.d., 50-mm length) was used as the reactor. This empty cartridge was packed with Pt catalyst ($\sim$ 0.2 g). Another cartridge of exactly the same size was used as a premixer. This premixer was packed with inert glass beads to ensure good mixing of reagents prior to passage through the reactor. The premixer and the fixed bed reactor were connected to an HPLC system (HP1100, Agilent Technologies) in series (in a similar manner as a guard column and separation column).

Substrates, cinchona modifier/ethanol, and ethanol were pumped into the reactor via different solvent channels by an HPLC quaternary pump (G1311A). A vapor–liquid equilibrium concentration of dissolved hydrogen in ethanol was prepared in a 1.0-L stainless steel autoclave (Model TBC100SS, Godo Engineering, Korea). Dissolved hydrogen was introduced into the CFBR by a high-pressure liquid metering pump (Model B-100-S-2-CE, Eldex Lab. Inc, USA). Reaction temperature control was achieved by the thermostated compartment (G1316A) of the HPLC system or by immersion in a refrigerated bath for low-temperature experiments (Model 9005, PolyScience, US). Deionised water and isopropyl alcohol (AR grade, JT baker) were used as the solution in the refrigerant bath. System pressure was achieved and adjusted by a back-pressure regulator (Model 26-1762-24, 50–6000 psi, Tescom, USA). Product collec-

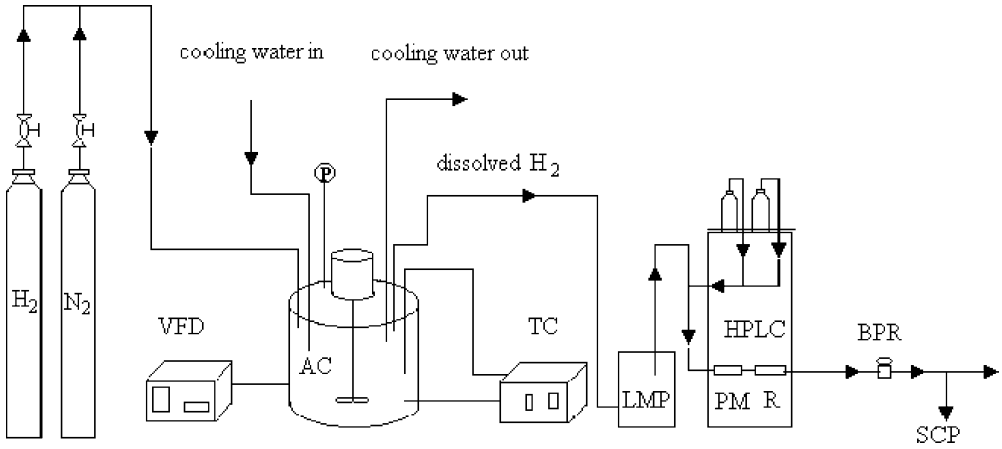


Fig. 1. Schematic diagram of fixed bed reactor and associated apparatus. VFD, variable frequency drives; AC, autoclave; TC, temperature controller; LMP, liquid metering pump; HPLC, HPLC setup; PM, premixer; R, reactor; BPR, back-pressure regulator; SCP, sample collecting point.

tion was performed by sampling behind the back-pressure regulator using 4-ml amber vials.

2.3. Reaction procedure

Prior to reaction runs, gas leakage tests using nitrogen followed by hydrogen were carried out, which is necessary in view of the dangers associated with hydrogenation at high pressures. The system was found to be safe and leak-free. After the system leakage test, hydrogen was introduced into the autoclave, which was maintained at 40 bar during the whole reaction. A minimum of 40 min was needed for hydrogen to dissolve and reach its vapor–liquid equilibrium in ethanol. Dissolved hydrogen was then fed into the reactor at a flow rate of 0.55 ml min^{-1} during the whole reaction. Simultaneously, different combinations of solvent, substrate (substrate/solvent), and modifier/solvent were pumped into the CFBR. The compositions depended on the specific experimental reaction protocol used. Total flow rate in the reactor was adjusted to maintain 0.65 ml min^{-1}. Therefore, the same hourly space velocity was used in all experiments. System pressure was typically maintained at 60 bar. The first sample for each new series of reactions was taken 30 min after the reaction was initiated (flow started through CFBR). The other samples were taken at regular intervals of 20 min. Three different types of reaction procedures were applied.

Stereoselective hydrogenation procedure. Reaction was carried out at 0 °C. The total flow rate of substrate and modifier/ethanol was maintained at 0.1 ml min^{-1}. For ethyl pyruvate, the substrate flow rate was maintained at 0.16 mmol min^{-1}. The modifier concentration (expressed as modifier/substrate (mol/mol) in this contribution) in the liquid phase was maintained at 175 ppm. For ethyl benzoylformate, substrate flow rate was 0.0027 mmol min^{-1} and modifier concentration (expressed as modifier/substrate (mol/mol) in this contribution) in the liquid phase was maintained at 0.01.

Racemic hydrogenation procedure. Reaction was carried out at 0 °C. The total flow rate of substrate and ethanol was kept at 0.1 ml min^{-1}. Flow rate of ethyl pyruvate and ethyl benzoylformate was kept at 0.16 and 0.0027 mmol min^{-1}, respectively. No modifier was fed in.

CFBR cleaning procedure. Cleaning (demodification) of the platinum catalyst was carried out at 50 °C. Flow rate of ethanol was set to 0.1 ml min^{-1}. Neither substrate nor modifier was fed in.

In this work different batches of ethyl pyruvate were used, resulting in minor differences in the e.e. values. The platinum catalyst was pre-reduced and then kept at room temperature for a maximum use of 6 months. Due to the above reasons, some fluctuations in the experimental e.e. values were observed from one set of data to another. However, within each set of experiments, the reagent feedstreams/reaction conditions were constant.

The three primary procedures outlined above were used extensively. Any variations to the above-mentioned protocols will be noted in the appropriate part of Section 3.

2.4. Analytical measurements

GC is the commonly used analytical method for studying the conversion and stereoselectivity of ethyl pyruvate to ethyl lactate reaction. Often, either derivertisation followed by separation on a chiral capillary column (Chirasil-(L)-Val) [21], or direct separation on a chiral column (Chiralsil-Dex CB), has been used [25]. This method has been quite useful since it affords relatively rapid and reproducible results, particularly on e.e. However, such methods have some shortcomings if other information is desired, i.e., quantification of hemiketal formation or alkaloid distribution. Indeed, the higher temperatures needed in GC will badly affect the former and the latter will not elute.

In this contribution, a different approach was taken. Since an HPLC column adequate for separating all species and

stereoisomers in the reaction products could not be obtained, circular dichroism spectra were employed as well. The reaction mixtures were analyzed by an HPLC-CD method. This procedure required two separate experimental measurements.

In the first procedure, a second HPLC setup (HP1100, Agilent technologies), consisting of a quaternary pump with degasser (G1311A), an autosampler (G1313A), a thermostated column compartment (G1316A), and a diode array detector (G1315A), was used for analytical measurement. The reaction mixture sample was separated on a nonchiral high-performance liquid chromatography stationary phase, using an Eclipse XDB-C8 column. This column is capable of giving very good separation of the products (both enantiomers together) from unreacted reagent and any residual modifier or reacted modifier (namely, hydrogenated modifier). The mobile phase of the chromatographic separation was acetonitrile and water (70/30, v/v), 0.5 ml min^{-1}. The elution of the solutes was measured at a wavelength of 230 nm using the diode array detector. The HPLC separation provided information on conversion/yield.

In the second procedure, the circular dichroism spectra were measured on a spectropolarimeter (J-810, Jasco Corporation, Japan) using a 0.1-mm pathlength CaF_2 cell in the range 200–400 nm. The instrument was calibrated with a standard solution of ammonium d-10-camphorsulfonate. Scanning speed, sensitivities, band width, and data pitch were selected to give optimum signal-to-noise ratios. Enantiomeric excess was determined by circular dichroism spectroscopy, and the actual concentration of each enantiomer was back-calculated from the HPLC plus CD measurements.

The use of a UV diode array as the detector for HPLC and the use of CD in the UV region are entirely appropriate for analytical studies of the present system. Indeed, all the substrates, products, and modifiers have rather strong absorbance in the UV due to the pi–pi* or n–pi* transitions. Further, all the stereoisomers of the products and modifiers have chiral centers in close proximity to a UV-sensitive group. Therefore, strong CD signals arise. The modifiers, namely, cinchonidine and cinchonine, have a number of chiral centers (typically denoted as C_3, C_4, C_8, and C_9) [28–30]. Each of the four products, namely, *R*-, *S*-ethyl lactate and *R*-, *S*-ethyl mandelate, has one chiral center—its alcohol group—generated from the prochiral carbonyl group in the substrates.

One final analytical remark is necessary. The substrate and the solvent are nonchiral molecules and theoretically should not have circular dichroism. However, high substrate concentration sometimes introduces severe noise to the circular dichroism spectra. In this case, the CD spectra have to be further treated by spline filtering as will be mentioned in Section 2.5. High substrate concentration causes a shift in the circular dichroism spectra of the modifier if the latter is also at a high concentration as stated by Margitfalvi [31]. The amount of modifier used in the present contribution is extremely small; thus, the observed changes in the modifier CD spectra are negligible.

2.5. Methodology

Usually, enantiomers are impossible to differentiate in all respects but one, their interaction with circularly polarized light. Circular dichroism spectroscopy (CD) is one of the most useful techniques employed for distinguishing enantiomers. For CD spectra, the ellipticity θ (mdeg) is proportional to the product of path length l (dm), concentration c (g/ml), and specific ellipticity $[\theta]$ as shown in Eq. (1):

$$\theta = lc[\theta]. \tag{1}$$

The UV-CD method and the HPLC-CD method have been used to simultaneously determine enantiomeric excess (e.e.) and concentration of each enantiomer in our previous research [32]. Because some unknown nonchiral complexes appeared during the current catalytic reactions, the curve fitting of the UV part of the reaction spectra failed [32]. Therefore, only the HPLC-CD method is applied to the current experimental reaction data.

A brief summary of the HPLC-CD method is stated below. First, all of the noisy experimental CD spectra should be filtered by a cubic smoothing spline. Second, estimated pure enantiomer spectra A_R^{est} and A_S^{est} are prepared by subtracting a proper solvent reference A_{sol} from the mixture (enantiomer plus solvent) spectra A_R^{mix} and A_S^{mix}. It is known that pure *R* and *S* enantiomers have identical UV spectra and mirror-image CD spectra. Therefore, the minimization problem can be constructed by Eq. (2),

$$\begin{aligned}\textbf{Min}\quad & f_1 = \sum_i \left(A_{R,i}^{\mathrm{est,\,CD}} + A_{S,i}^{\mathrm{est,\,CD}}\right) \\ & \quad + \lambda \sum_i \left(A_{R,i}^{\mathrm{est,\,UV}} - A_{S,i}^{\mathrm{est,\,UV}}\right) \\ \text{w.r.t.}\quad & y_R \quad \text{and} \quad y_S \\ & A_R^{\mathrm{est}} = A_R^{\mathrm{mix}} - y_R A_{\mathrm{sol}}, \quad A_S^{\mathrm{est}} = A_S^{\mathrm{mix}} - y_S A_{\mathrm{sol}},\end{aligned} \tag{2}$$

where λ is the weight for balancing the contribution of UV and CD part. Once the minimum of the objective function is reached, the optimal subtraction factors y_R and y_S are achieved. Consequently, pure *R* and *S* enantiomer spectra are obtained.

After that, specific ellipticity ($[A_R^{\mathrm{ref}}]$ and $[A_S^{\mathrm{ref}}]$) of enantiomers can be generated by Eqs. (3) and (4),

$$\left[A_R^{\mathrm{ref}}\right] = \frac{A_R^{\mathrm{ref}}}{l \times c_R^{\mathrm{mix}}}, \tag{3}$$

$$\left[A_S^{\mathrm{ref}}\right] = \frac{A_S^{\mathrm{ref}}}{l \times c_S^{\mathrm{mix}}}, \tag{4}$$

where A_R^{ref} and A_S^{ref} are pure enantiomer spectra obtained by Eq. (1). c_R^{mix} is the concentration of *R*-ethyl lactate when

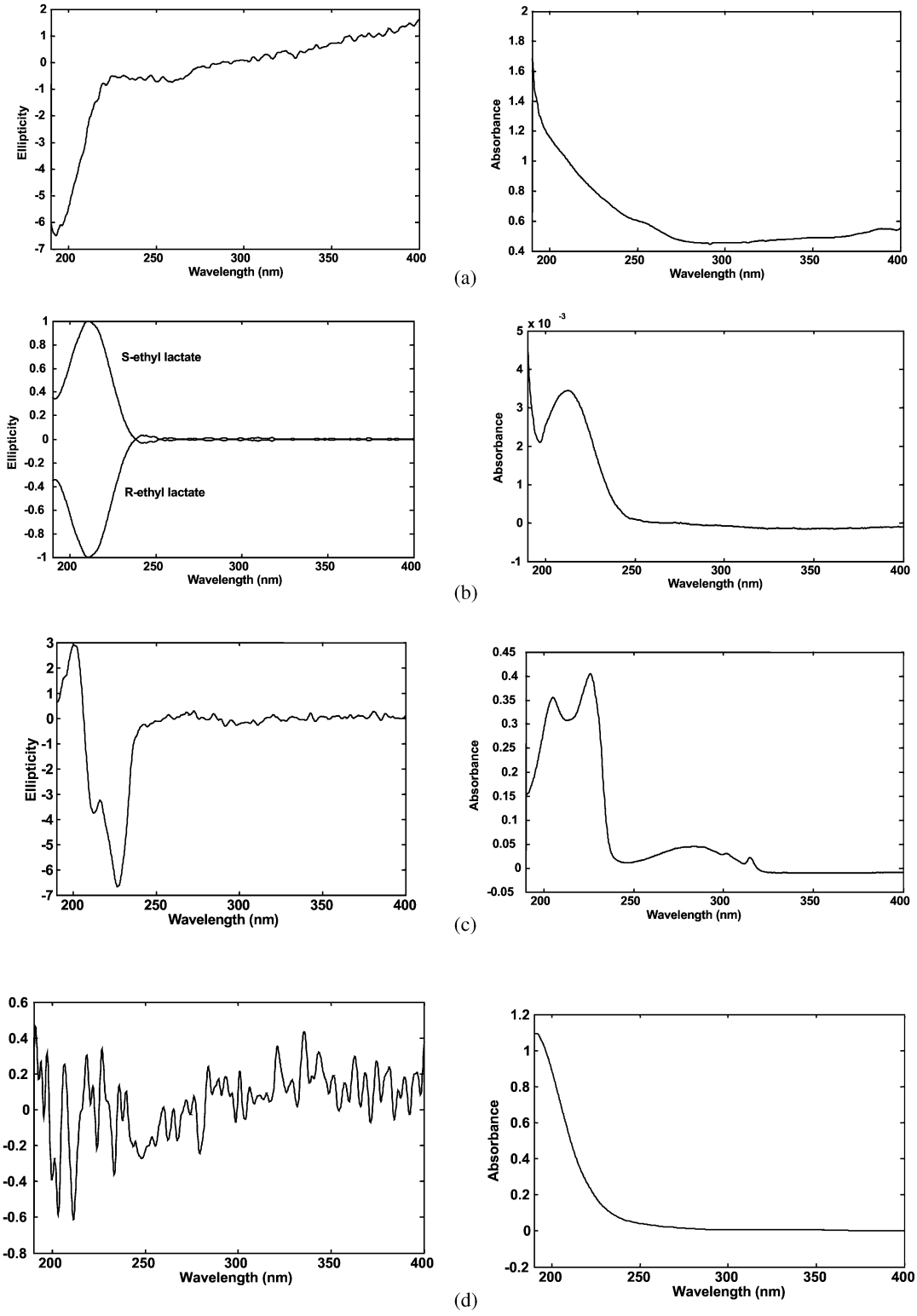


Fig. 2. Reference spectra of ethyl pyruvate/(*R*, *S*)-ethyl lactate/cinchonidine/ethanol system: (a) ethanol plus cell spectrum; (b) pure *R*- and *S*-ethyl lactate spectra; (c) pure cinchonidine spectrum; (d) pure ethyl pyruvate spectrum.

R-ethyl lactate is dissolved in ethanol. c_S^{mix} is the concentration of *S*-ethyl lactate. Furthermore, other pure component reference spectra are generated by subtracting a proper solvent reference from their corresponding mixture spectra. All of the reference spectra used in this study are shown in Fig. 2.

Third, the HPLC-CD method employs the CD spectra with the total concentrations of *R* plus *S* enantiomers pro-

vided by HPLC using a nonchiral stationary phase. A least-square fit is applied to curve fit the experimental CD spectra as shown in Eq. (5),

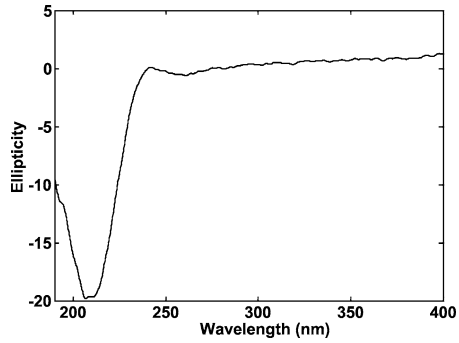
$$\begin{aligned}
&\textbf{Min} \quad f_2 = \sum_{v=1}^{L} \left(A_{\mathrm{v}}^{\mathrm{est}} - A_v^{\mathrm{exp}}\right)^2,\\
&\text{w.r.t.} \quad x_R \quad \text{and} \quad x_i, \quad i = 1, 2, \ldots, n-2,\\
&\qquad A^{\mathrm{est}} = \sum_{i=1}^{n-2} x_i A_i^{\mathrm{ref}} + x_R\left[A_R^{\mathrm{ref}}\right] + x_S\left[A_S^{\mathrm{ref}}\right],\\
&\qquad x_S = l(c_R + c_S) - x_R, \qquad (5)
\end{aligned}$$

where L is the length of the CD spectral data and $[A_R^{\mathrm{ref}}]$ and $[A_S^{\mathrm{ref}}]$ are specific ellipticities of enantiomers. The total concentration of enantiomers $(c_R + c_S)$ is given by HPLC. Once an optimal subtraction factor x_R is obtained, enantiomeric excess can be calculated by Eq. (6),

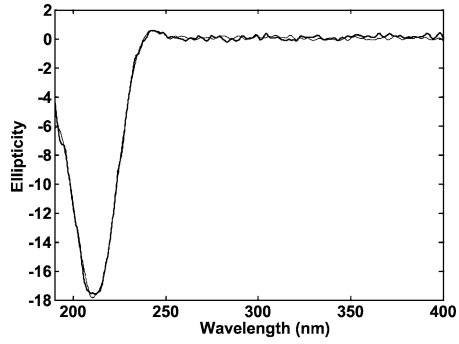
$$\text{e.e.} = \frac{c_R - c_S}{c_R + c_S} \times 100\%, \qquad (6)$$

where c_R and c_S are the concentrations of enantiomers. The quantity e.e. is $+100\%$ for a sample of the pure R enantiomer and -100% for a sample of the pure S enantiomer [33,34].

After application of the HPLC-CD method to this experimental reaction system, all of the experimental CD spectra are curve-fitted very well. As shown in Figs. 3a and 3b, an experimental CD spectrum and its curve-fitted spectrum by the HPLC-CD method are plotted.



(a)



(b)

Fig. 3. An experimental CD spectrum and its curve-fitted spectrum for catalytic enantioselective hydrogenation of ethyl pyruvate on Pt/cinchonidine. (a) Experimental CD spectrum; (b) the CD spectrum (solid) after subtraction of ethanol plus cell, pure cinchonidine and pure ethyl pyruvate, and its curve-fitted CD spectrum (dashed).

3. Results

3.1. Important precatalytic considerations for CFBR

The contacting pattern for the reagents is one of the primary differentiating characteristics between the CFBR and the conventional batch operation for stereoselective synthesis. This difference in contacting pattern opens up a number of possibilities. The primary preliminary consideration needed for the use of a CFBR for the present system is the mode of contacting the substrate with solvent due to the known substrate–solvent interaction.

A number of side reactions involving the rather reactive α-ketoesters have been identified by Margitfalvi et al. [15, 35,36]. In alcoholic solvents, they found that hemiketals could be formed between substrate and solvent. Our present HPLC studies provide further support for this kind of interaction and the temperature dependence of the interaction between ethyl pyruvate and ethanol.

Three groups (a, b, c) of samples were prepared. Each group consists of two samples. For each group, the first sample was analyzed by HPLC (separation condition as indicated in Section 2) immediately after sample preparation. The second sample of each group was analyzed after the sample was exposed to 20, 0, and $-20\,^{\circ}$C, respectively, for 20 h. Chromatograms of the different groups are shown in Fig. 4. HPLC results show that there was ethyl pyruvate–ethanol complex, namely, hemiketal, formed after exposure of the solution to 20 °C for 20 h. The formation of hemiketal was suppressed considerably when the temperature was decreased to 0 °C. Further suppression occurred when the temperature was $-20\,^{\circ}$C. The results indicate that the solution of ethyl pyruvate dissolved in ethanol is very sensitive to temperature and interaction time.

The products of the side reaction can alter the intrinsic kinetics of the enantioselective hydrogenation. To minimize this kind of side reaction, all the catalytic reactions in this contribution were carried out under standard reaction conditions. Two features of this "standard condition" are highlighted as follows: (i) Ethyl pyruvate was kept at 0 °C using an ice/water bath and (ii) substrate and ethanol were fed into the system via different HPLC channels. In this way the contacting time for ethyl pyruvate and ethanol was very short. It is obvious that quick mixing and then immediate use of the reactants at lower temperature is the best way to operate the fixed bed reactor.

3.2. R-ethyl lactate synthesis—the ethyl pyruvate/cinchonidine system

Generally, good enantiomeric excess ($\sim 75\%$) was achieved in the CFBR when the *stereoselective hydrogenation*

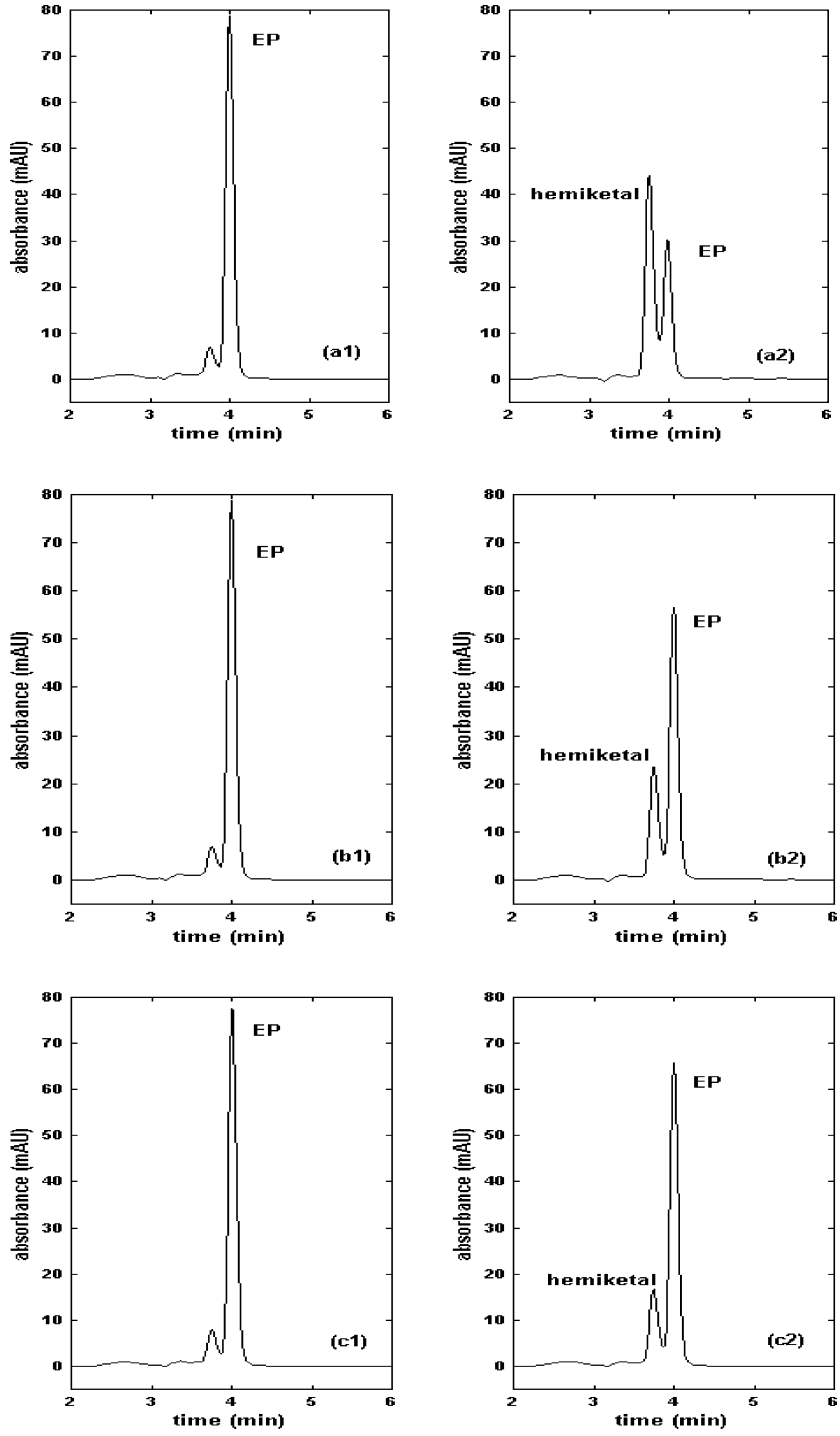


Fig. 4. Substrate–solvent interaction for noncatalytic reaction. Sample concentration EP/EtOH = 0.005 (v/v). (a1), (b1), (c1): Samples analyzed immediately after preparation. (a2), (b2), (c2): Samples analyzed after the sample was exposed to 20, 0, and −20 °C, respectively, for 20 h.

procedure mentioned in Section 2 was employed. In this procedure, the hydrogen used in the enantioselective hydrogenation of ethyl pyruvate was thoroughly dissolved in the liquid phase prior to the mixing of all reagents and subsequent flow into the CFBR. Before addressing the main aims of this work, good operating conditions for two important system parameters, namely, modifier concentration and system pressure, were first investigated. A proper choice of these parameters was needed prior to investigation of catalytic stability, etc.

3.2.1. Variation of enantiomeric excess with modifier concentration

Two sets of experiments were performed to examine the influence of modifier (cinchonidine) concentration on enan-

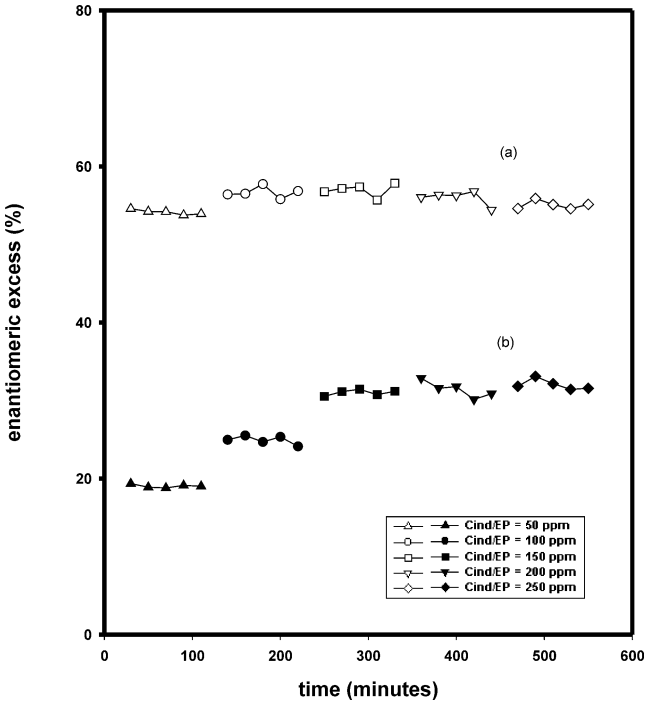


Fig. 5. Variation of enantiomeric excess with cinchonidine concentration (50–250 ppm). Ethyl pyruvate with cinchonidine-modified Pt/Al_2O_3 at (a) 0 °C, open symbols; (b) 20 °C, filled symbols.

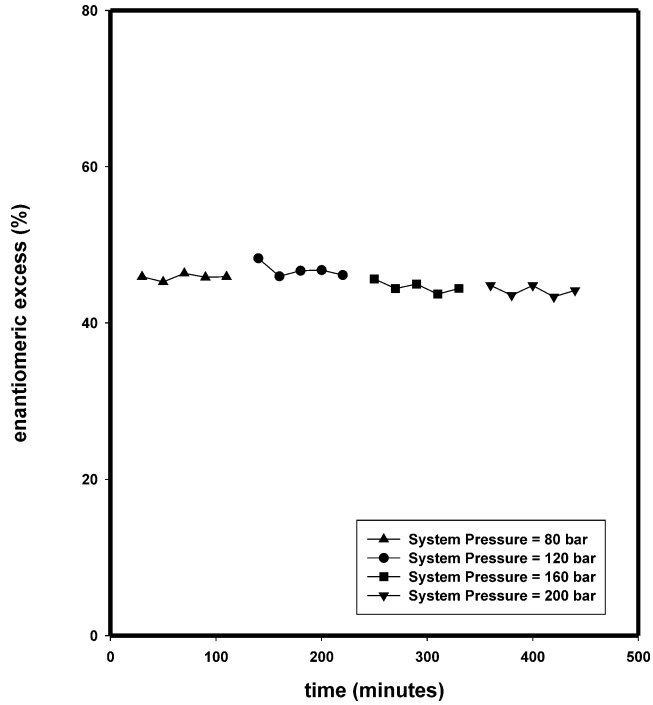


Fig. 6. Variation of enantiomeric excess with system pressure (80–200 bar). Ethyl pyruvate with cinchonidine-modified Pt/Al_2O_3 at 0 °C.

tioselectivity. The substrate used was ethyl pyruvate. The two sets of experiments were carried out following the stereoselective hydrogenation procedure except that different cinchonidine concentrations were applied and the reaction temperature of the second set was 20 °C. Fig. 5 shows the dependence of enantiomeric excess on cinchonidine feed concentration in the CFBR.

The open symbols on curve (a) and filled symbols on curve (b) show the effect of modifier concentration on enantiomeric excess at 0 and 20 °C, respectively. Because of the constant flow rate of ethyl pyruvate, the different molar ratios of cinchonidine to ethyl pyruvate correspond to different cinchonidine concentrations.

Several features of the dependence of enantiomeric excess on cinchonidine concentration are noteworthy. First, in each series of experiments, after a relatively short 30-min period, the value of enantiomeric excess becomes constant, which essentially means that a steady state for the stereoselective reaction was achieved. Second, the reaction carried out at 0 °C provides much higher values of enantiomeric excess than that performed at 20 °C, implying that enantiomeric excess is very sensitive to temperature. It is also worthy to note that optimal modifier operation range is strongly dependent on temperature. Curve (a) shows that good enantiomeric excess could be achieved over the whole range of 50–250 ppm, whereas curve (b) shows that a good operation range is 150–250 ppm. These different activity patterns observed indicate that catalyst saturation by adsorbed modifier and/or transformation of the modifier is strongly dependent on temperature. The two curves also suggest that continuous addition of modifier at a 150 ppm molar ratio or more results in an active and stable stereoselective system which exhibits little or no deactivation.

3.2.2. Variation of enantiomeric excess with system pressure

One set of experiments was carried out as described in the stereoselective hydrogenation procedure except that different system pressures were employed. In contrast to a batch reactor, total system pressure and hydrogen mole fraction were independently adjustable parameters in this CFBR because of the use of a back-pressure regulator. The enantiomeric excess as a function of time and system pressure at constant dissolved hydrogen mole fraction feed is shown in Fig. 6.

At 0 °C, there is no significant variance in the value of enantiomeric excess over the entire high-pressure range. This result indicates that system pressure has little or no effect on the enantioselective hydrogenation carried out in the CFBR. It suggests that enantioselective catalytic reaction might be operated in a quite broad range of system pressure without leading to significant variation of the enantiomeric excess. It also suggests that the volumes of activation for the rate-limiting steps for *both* the enantioselective and racemic cycles are small.

3.2.3. Preliminary experiment on stereoselective catalytic system stability

For most practical purposes, catalyst activity and stability during long time hydrogenation is crucial for meaningful stereoselective catalytic syntheses. As the results in Figs. 5

and 6 indicate, enantioselective hydrogenations can be stable for hours at a time. However, as pointed out in Section 1, substrate purity can be a complication. This problem is exemplified by the following catalyst stability test, where another batch of substrate was used, and the enantioselective heterogeneous hydrogenation of ethyl pyruvate on cinchonidine modified Pt catalyst was carried out (stereoselective hydrogenation procedure) continuously for 15 h. Here, sample collection was performed every 3 h, which is somewhat different than the standard procedure. The experimental results are shown in Fig. 7. Solid symbols on curve (a) refer to the value of enantiomeric excess at different reaction times. Open symbols on curve (b) represent ethyl lactate produced during the hydrogenation. Obviously, during the long time hydrogenation shown here using another batch of EP, there are slight drops in both enantiomeric excess and product formed.

These declines in e.e. and rate are probably related to some change in substrate purity, resulting in either physical (polymeric coverage) blockage of a particular type of reaction site (enantiomeric or hydrogen activation) and/or chemical transformation or poisoning of sites. However, for the present development, the exact mechanism of such deactivation is actually of secondary importance. The primary issue is that deactivation can unexpectedly take place. Therefore, effective protocols for catalyst regeneration are necessary and crucial for continuously/semicontinuous operation of stereoselective catalytic reaction in a fixed bed reactor.

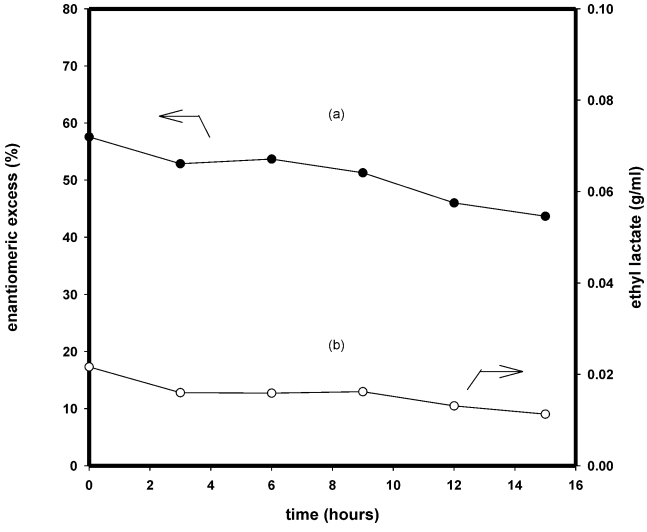


Fig. 7. Stereoselective catalytic system stability. Ethyl pyruvate with cinchonidine modified Pt/Al_2O_3 (stereoselective hydrogenation procedure). Filled symbols, enantiomeric excess; open symbols, ethyl lactate concentration.

3.2.4. Demodification, reduction, and remodification of catalyst

Given the above result, it can be expected that long time reaction will generally lead to catalyst deactivation and this will result in poor enantiomeric excess and lower conversions. Effective protocol for reduction and regeneration is needed to reactivate the catalyst. Again, the hydrogenation of ethyl pyruvate on Pt (cinchonidine) catalyst was used as the test reaction and carried out in our CFBR. Experiments were performed to identify procedures for efficient demodification, reduction, and remodification. In other words, these combined steps constitute a *regeneration* of the active system.

One long semicontinuous series of experiments consisting of five individual parts was performed. The semicontinuous series of steps involved one cleaning step and four kinetic reactions. The four kinetic reactions can be further regarded as two cycles. Both cycles are carried out in a similar manner; that is, racemic hydrogenation of ethyl pyruvate on Pt (*racemic hydrogenation procedure*) was followed by enantioselective hydrogenation on cinchonidine modified Pt (stereoselective hydrogenation procedure). The exact duration and reaction conditions are shown in Table 1.

Enantiomeric excess and ethyl lactate production as a function of reaction time are shown in Fig. 8. Filled symbols refer to enantiomeric excess and open symbols represent ethyl lactate produced during the whole procedure. Normal triangles and inverted triangles in Fig. 8 refer to Racem-I and -II. Circle and diamond symbols represent Stereo-I and -II. Between these two cycles is the catalyst regeneration experiment (*CFBR cleaning procedure*) carried out with only hydrogen/ethanol and carrier ethanol.

Fresh catalyst was loaded into the reactor and then used during the first catalytic reaction period and no modification was done. Consequently, this step resulted in racemic hydrogenation. For Racem-I, fluctuation of the e.e. value from −4% to 2% is seen in Fig. 8. This result is consistent with a reasonable error range for the measurement of racemic product formation (see Analytical measurements section).

Table 1
Specific reaction conditions of catalyst demodification, reduction, and remodification for the ethyl pyruvate/cinchonidine system

Reaction type	Time sequ. (min)	Flow rate ($ml\,min^{-1}$)				Temperature (°C)
		EP	Cind/EtOH (3.5×10^{-7} $mol\,ml^{-1}$)	EtOH	H_2/EtOH	
Racem-I	0–110	0.018	–	0.082	0.55	0
Stereo-I	110–220	0.018	0.082	–	0.55	0
Clean	220–330	–	–	0.10	0.55	50
Racem-II	330–440	0.018	–	0.082	0.55	0
Stereo-II	440–550	0.018	0.082	–	0.55	0

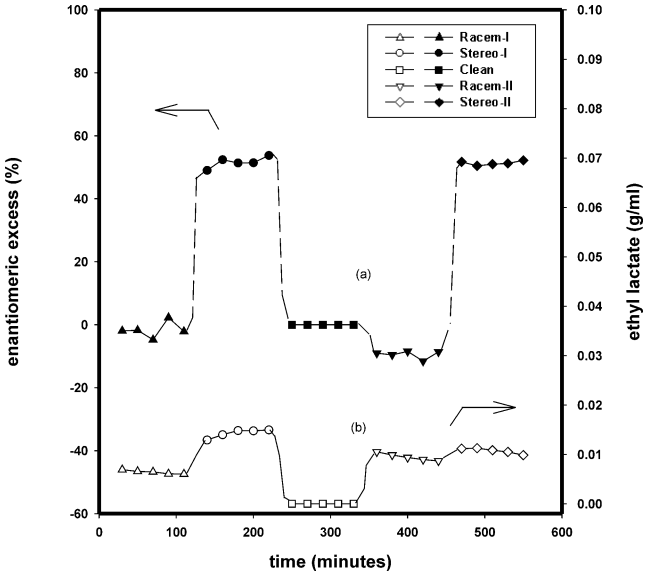


Fig. 8. Demodification, reduction, and remodification of catalyst. Ethyl pyruvate with cinchonidine modified Pt/Al_2O_3 under specific reaction conditions: Racem-I and -II, racemic hydrogenation procedure; Stereo-I and -II, stereoselective hydrogenation procedure; Clean, CFBR cleaning procedure. Experimental parameters, see Table 1.

Stereo-I was then performed with cinchonidine as modifier. Upon addition of cinchonidine, the Pt catalyst was gradually modified in a manner appropriate for the production of the *R*-product (average 52% enantiomeric excess). This is a modification procedure. In this sense the packed bed becomes a chiral fixed bed reactor (CFBR). The active catalyst in the CFBR is thus composed of both unmodified Pt and modified Pt, giving rise to both racemic and enantioselective cycles, and hence the observed enantioselectivity.

After the first cycle was finished, Clean was performed with only hydrogen/ethanol fed in. This procedure was carried out with no substrate feed; thus, no product was formed. The residual product concentration was unobservable and the enantiomeric excess was set to zero. The square symbols in Fig. 8 simply represent this nonproduct situation. At the relatively high temperature of 50 °C used during this procedure, and under flow conditions, the modifier previously adsorbed on the Pt surface is probably flushed out of the system with the carrier ethanol. The period was in fact used to regenerate a relatively clean and reactivated catalyst surface by hydrogenation/desorption of the modifier and rereduction of any oxidized platinum.

Racem-II in the second cycle was performed at similar reaction conditions as Racem-I with the primary exception that the Pt catalyst is now regenerated and not fresh. This procedure can actually serve as an important test of the previous Clean step. An efficient cleaning procedure will result in truly racemic reaction product during the Racem-II period, similar to the observed results in Racem-I. The observed average enantiomeric excess was ca. −9%, deviating slightly from the results obtained from Racem-I. This e.e. is outside the error range of our analytical method and is therefore real.

The −9% enantiomeric excess indicates that the *S*-product was preferentially formed by some residual surface modification. This nonzero e.e. was probably caused by the impurities in the modifier, a change in conformation/adsorption mode, or some high molecular weight chiral residue left over after reaction. Regarding the first possible reason, it is known that the modifier has a nonnegligible level of impurities (quinine ($\leqslant 2\%$) and quinidine ($\leqslant 8\%$)). Quinine used as chiral auxiliary usually gives the *R*-product in a manner similar to cinchonidine, whereas quinidine provides *S*-product [37]. Since the enantiomeric pairs of cinchonidine/cinchonine and quinine/quinidine arise from two functionally distinct parent cinchona alkaloids, these pairs will have distinctly different surface adsorption equilibrium constants. A larger equilibrium adsorption constant for quinidine than for cinchonidine, and/or a slower desorption rate, is perhaps the simplest rationalization for the observed change in sign for the enantiomeric excess.

Although the above seems to be the most likely explanation, another possible reason might be attributed to a conformation change of cinchonidine [38] at low concentrations, or an adsorption mode change [14], at extraordinarily low surface coverage. In any event, the experimental data suggests that the amount of cinchonidine left on the Pt catalyst was extremely small. The clean procedure certainly gives rise to a CFBR with much lower loading of chiral alkaloids, and the new catalyst surface may be quite suitable for further remodification and *R*-product formation.

The diamond symbols in Fig. 8 refer to the results of Stereo-II carried out in the period immediately following Racem-II. An average of 51% enantiomeric excess was achieved, which is in excellent agreement with the results obtained in Stereo-I. The regenerated catalyst exhibits almost the same stereoselectivity as the fresh catalyst, implying that remodification can be successfully carried out. It is not necessary to refill the reactor with fresh catalyst pretreated at 400 °C under a flow of H_2.

3.3. Alternating enantiomer syntheses—ethyl pyruvate/cinchonidine/cinchonine system

Stereoselective hydrogenations of ethyl pyruvate on Pt modified with different cinchona modifier, namely, the enantiomeric pairs of cinchonidine and cinchonine, were performed. Catalyst demodification, reduction, and remodification protocols as described in the previous section were applied in this semicontinuous, two-enantiomer-product synthetic strategy. Detailed reaction conditions are shown in Table 2.

Solid symbols in curve (a) and open symbols in curve (b) in Fig. 9 refer to enantiomeric excess and ethyl lactate formed as a function of reaction time. Two cycles consisting of four kinetic reactions and one regeneration procedure were carried out. The sequence of steps was Racem-I → Stereo-I → Clean → Racem-II → Stereo-II. Addition of *cinchonidine* was performed in Stereo-I, resulting

Table 2
Specific reaction conditions for alternating enantiomer syntheses in CFBR for the ethyl pyruvate/cinconidine/cinchonine system

Reaction type	Time sequ. (min)	Flow rate ($ml\,min^{-1}$)					Temperature (°C)
		EP	Cind/EtOH (3.5×10^{-7} mol ml^{-1})	Cin/EtOH (3.5×10^{-7} mol ml^{-1})	EtOH	H_2/EtOH	
Racem-I	0–110	0.018	–	–	0.082	0.55	0
Stereo-I	110–220	0.018	0.082	–	–	0.55	0
Clean	220–330	–	–	–	0.1	0.55	50
Racem-II	330–440	0.018	–	–	0.082	0.55	0
Stereo-II	440–550	0.018	–	0.082	–	0.55	0

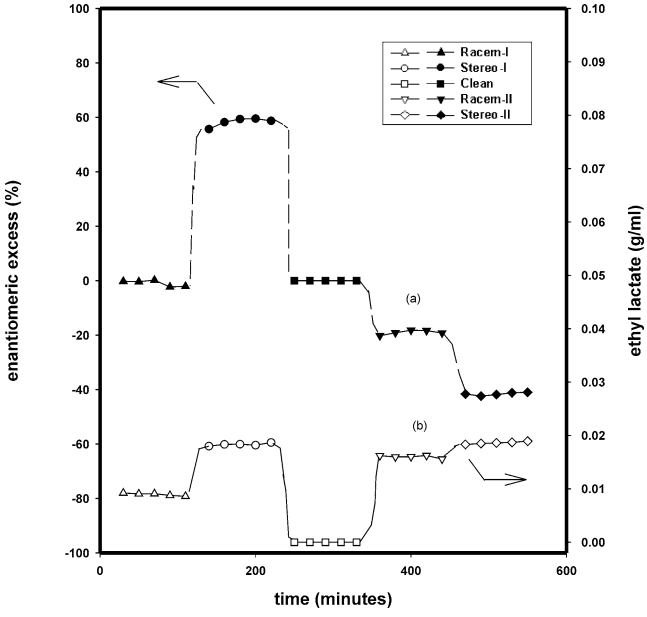


Fig. 9. Alternating enantiomer syntheses in CFBR. Ethyl pyruvate/cinconidine/cinchonine system under specific reaction conditions: Racem-I and -II, racemic hydrogenation procedure; Stereo-I and -II, stereoselective hydrogenation procedure; Clean, CFBR cleaning procedure. Experimental parameters, see Table 2.

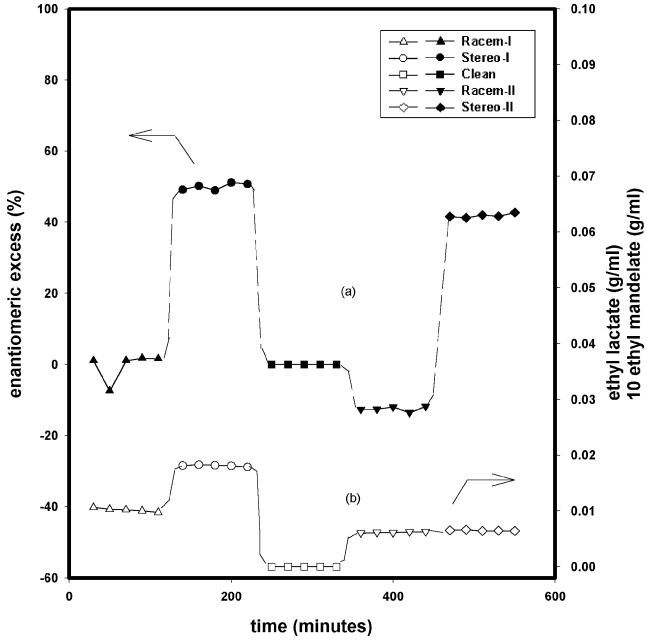


Fig. 10. Multiple stereo-product syntheses in CFBR. Ethyl pyruvate/ethyl benzoylformate/cinchonidine system under specific reaction conditions: Racem-I and -II, racemic hydrogenation procedure; Stereo-I and -II, stereoselective hydrogenation procedure; Clean, CFBR cleaning procedure. Experimental parameters, see Table 3.

in ca. 58% enantiomeric excess. The cleaning procedure was then performed for catalyst demodification and reduction. The observed average enantiomeric excess of Racem-II was ca. −19%, deviating from the results obtained from Racem-I. In Stereo-II, *cinchonine* was used as an auxiliary instead of cinchonidine. With the addition of cinchonine, the Pt catalyst was gradually remodified in a manner to generate *S*-product, resulting in the expected inversion of the enantiomeric excess (∼ 41%). The lower value of the enantiomeric excess in Stereo-II compared with that of Stereo-I indicates that cinchonine offers slightly lower stereoselectivity than that of cinchonidine. Cinchonine is known to give lower e.e. when investigated in a batch reactor system [39].

The product formation represented by the concentration of ethyl lactate is shown in curve (b). With the addition of cinchonidine or cinchonine, there is a rate enhancement as well as enantioselectivity. Results obtained for the CFBR are consistent with that achieved in batch reactors. In stereoreaction II, although cinchonine provides lower enantioselectivity than cinchonidine, the reaction rate enhancement upon addition of cinchonidine and cinchonine is almost the same.

3.4. Multiple stereo-product syntheses—ethyl pyruvate/ethyl benzoylformate/cinchonidine system

Sequential stereoselective hydrogenations of different substrates, namely, ethyl pyruvate and ethyl benzoylformate, were carried out in the CFBR with the purpose of achieving multiple end-product syntheses. The reaction conditions are shown in Table 3.

A reaction procedure similar to *alternating enantiomer syntheses* was performed. The difference is that, in the second cycle of the present experiment, ethyl benzoylformate was fed into the reactor as substrate.

The enantiomeric excess and product formed as a function of reaction time are shown in Fig. 10. Inverted triangles refer to the racemic reaction product in Racem-II. Diamond

Table 3
Specific reaction conditions for multiple stereo-product syntheses in CFBR for the ethyl pyruvate/ethyl benzoylformate/cinchonidine system

Reaction type	Time sequ. (min)	Flow rate ($ml\,min^{-1}$)					Temperature (°C)
		EP	EB/EtOH ($0.1555\ mol\,ml^{-1}$)	Cind/EtOH ($3.5 \times 10^{-7}\ mol\,ml^{-1}$)	EtOH	H_2/EtOH	
Racem-I	0–110	0.018	–	–	0.082	0.55	0
Stereo-I	110–220	0.018	–	0.082	–	0.55	0
Clean	220–330	–	–	–	0.1	0.55	50
Racem-II	330–440	–	0.018	–	0.082	0.55	0
Stereo-II	440–550	–	0.018	0.082	–	0.55	0

symbols represent the stereoselective hydrogenation results in Stereo-II. The primary features of Fig. 10 are as follows:

(i) Ethyl mandelate was formed when ethyl benzoylformate was fed instead of ethyl pyruvate. Stereoisomers of two chemically different products were synthesized in one-and-the-same fixed bed.
(ii) *S*-ethyl mandelate was formed in excess of *R*-ethyl mandelate ($\sim$ 12% e.e.) in Racem-II.
(iii) With the addition of cinchonidine, *R*-ethyl mandelate formation was dominated in the stereoselective reaction, resulting in ca. 42% enantiomeric excess.

The reaction conditions used and the results obtained using ethyl pyruvate (Racem-I and Stereo-I) are quite different from those obtained using ethyl benzoylformate (Racem-II and Stereo-II). First, conversion of ethyl benzoylformate was almost 100% in Racem-II and Stereo-II, resulting in approximately the same ethyl mandelate concentration in the second cycle. Second, the amount of substrate in Stereo-II was much lower than that in Stereo-I, and the cinchonidine concentration in liquid phase in the Stereo-II was much higher than that in Stereo-I.

The first observation is consistent with the ability of ethyl benzoylformate to displace the more weakly adsorbed solvent, resulting in a high hydrogenation rate. The second observation, of a higher modifier/substrate ratio for the ethyl benzoylformate system, is again consistent with a strong interaction of substrate and Pt catalyst. The aromatic ring of ethyl benzoylformate probably results in a higher adsorption equilibrium, making itself adsorb strongly on the surface of platinum via the π system. This reduces the amount of modifier adsorbed because of surface coverage competition.

4. Discussion

The precatalytic EP/ethanol experiments show that the kinetics of hemiketal formation, in the absence of catalytic reaction conditions Fig. 4, are rather slow (half-life of many hours). To increase interexperiment catalytic reproducibility, we chose to use initial feed conditions which were essentially constant. Therefore, cold storage of EP and immediate and on-line premixing with ethanol prior to reaction was part of our experimental protocol. This helps to avoid issues concerning the time-dependent development of hemiketal prior to catalytic experimental runs.

The cinchonidine loading experiments (Fig. 5) clearly indicate the advantages of lower temperatures. Very low cinchonidine loadings of 50 ppm resulted in good e.e. at 0 °C. At 20 °C, maximum e.e. was not reached until ca. 150 ppm. The maximal e.e. of 75% observed in the cinchonidine experiments is somewhat lower than the maximal e.e. typically found using platinum (Engelhard 4759) in ethanol in a batch reactor (ca. 80%).

This lower e.e. is easily traced to the rather low dissolved hydrogen concentrations combined with the integral reactor used. In the present experimental configuration, the feed mole fraction of hydrogen was 0.007. This corresponds to an effective partial pressure of ca. 34 bar. However, based on the conversion of EP, the average effective mole fraction of hydrogen is only 0.006. Such a low value for the hydrogen mole fraction will result in lower e.e.'s due to the known hydrogen dependencies of the racemic and enantioselective catalytic cycles. Furthermore, the bulk liquid–solid mass transfer will be less effective in a CFBR than in a well-stirred batch reactor [22], especially for the limiting reagent hydrogen.

The cinchonidine level needed for maximum e.e. in the present study (50–150 ppm) is noticeably lower than that reported by others [25]. Previously, 200–2000 ppm was reported as an optimal cinchonidine loading. Since the same catalyst was used in both studies, the reasons for the difference certainly include the lower temperature used here, but may also include the higher catalyst loading used in Ref. [25]. The most obvious difference between the present reactor system and that used in Ref. [25] is that the latter was a three-phase reactor (at least initially), wherein gaseous hydrogen was introduced to the fixed bed. Partial wetting of catalyst surfaces, in other types of three-phase reactors, i.e., trickle beds, is known to lead to anomalous results with some types of catalytic systems [40].

As emphasized already, in the CFBR, hydrogen mole fraction and total pressure effects can be separated. A negligible change in e.e. was observed in the pressure interval 80–200 bar (Fig. 6). Therefore, the volumes of activation for the rate-limiting steps for both the enantioselective and the racemic cycles must be relatively small. Otherwise, a change in e.e. would be observed. It is known that redox reactions and other electro-constricted transition states have

a large absolute activation volume change [41]. Although the present pressure interval is somewhat modest (120 bar), the results do suggest that whatever the mechanisms of the rate-determining steps are, they might not involve a redox reaction or other electro-constriction event.

In almost all experimental series presented in this contribution, catalyst stability was very good. This is clearly seen in Figs. 5 and 6. However, the ethyl pyruvate substrate is known to be problematic, and indeed one series of experiments, namely, Fig. 7, shows this. Catalyst system stability in this latter figure is not nearly as good as in Figs. 5 and 6. The half-life in rate was ca. 15 h. This provides a driving force for the development of regeneration protocol.

The results of Fig. 8 were crucial. They show that the catalyst surface can be regenerated to a state with considerably lower stereoselectivity (almost resembling their initial condition). Furthermore, the surface can be remodified to regenerate a state resembling the initial cycle of stereoselective hydrogenation. The mean values of the enantiomeric excess in Stereo-I and -II were ca. 52% and 51% and the mean rates were ca. 0.012 and 0.011 g/ml. There is no doubt that the present regeneration protocol was effective.

It should be noted, however, that the ligand-accelerated rate increase of the stereoselective reaction over the racemic reaction is not as dramatic in the CFBR as in a well-stirred tank reactor. The most direct explanation is that (i) the enantioselective reaction is first order and the racemic reaction is zero order in the composition regimes studied, and (ii) the reactions are *almost* diffusion controlled in well-stirred tanks [22]. Taken together, an exacerbation of mass transfer effects will occur in the packed bed (significantly lower bulk liquid to solid transport), the reaction will be mass transfer controlled and a lower rate should be observed.

The advantage of the present CFBR over a batchwise synthesis approach is most clearly demonstrated by comparison with more conventional catalyst recycle experiments. It has been shown elsewhere [42] that the rate of enantioselective hydrogenation of EP over cinchonidine/Pt (Engelhard 4759) declines ca. 20–25% for each recycle, although e.e. is maintained.

The use of two different modifiers in a semicontinuous protocol is shown in Fig. 9. Indeed, the switch in modifier from cinchonidine to cinchonine changed the product formed (from *R* to *S*). In addition, the rate of Stereo-II was not compromised. It was equal to or greater than that exhibited by Stereo-I.

The primary aim of the present study, namely, multiple product syntheses, is fully realized in Fig. 10. Here, two different substrates were each stereoselectively hydrogenated, in a sequential manner, to two different end products, respectively. Reasonable e.e.'s were obtained in each part of the semicontinuous experimental run.

Taken together, the above-mentioned protocols suggest that more efficient use of precious metal catalyst may be provided by semicontinuous CFBR operations. The catalyst, better protected from oxidation and other adverse effects compared to batch recycle, can be used repeatedly. One large preparative packed column of supported precious metal could be used, with low activity loss, for a variety of syntheses.

Finally, the observations of a nonzero e.e., in fact an inversion in the sign of e.e., after cleaning (Racemic-II Fig. 8, Racemic-II Fig. 9, and Racemic-II Fig. 10) is worth mentioning again. The cleaning process was not perfect, and the exact reason for this observation is currently unclear. As mentioned in the results, it could be due to chiral impurities having different adsorption characteristics, adsorption mode or conformation changes, or even chiral residues left on the surface. Obviously, more extensive investigations are needed to provide a better explanation for the observed reversal of enantioselectivity and therefore provide enough information for further understanding of the mechanism involved. The small increase in the rates observed in Racemic-II (which actually exhibited a low nonzero e.e.) over Racemic-I (for Figs. 8 and 9) are consistent with a modest ligand-accelerated rate increase in the presence of increased bulkliquid to surface mass transfer control in the CBFR configuration.

5. Conclusion

The basic elements of protocol for multiproduct semicontinuous stereoselective heterogeneous catalysis in a CFBR have been tested. Modification and stereoselective hydrogenation can be carried out, followed by demodification/reduction and then remodification. Repeated stereoselective hydrogenations can be performed. The set of cleaning operations (demodification/reduction) together with remodification can be considered as complete regeneration of the system. Semicontinuous stereoselective heterogeneous catalysis in a CFBR may provide a convenient synthetic methodology for bench-scale, pilot-plant, and even production-scale multiple product syntheses.

Acknowledgments

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