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Micro-structured reactors as a tool for chiral modifier screening in gas–liquid–solid asymmetric hydrogenations

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Abstract

A continuous micro-structured reactor equipped with a perforated (5 μm) membrane is used for the investigation of the gas–liquid–solid asymmetric hydrogenation of ethylpyruvate on a Pt/γ-Al_2O_3 catalyst modified with chiral inductors under high hydrogen pressure (45 bar). Up to eight chiral inductors have been evaluated, the best enantioselectivity (63%) being obtained with cinchonidine. The very low reaction volume (100 μl) offers short operating time. Solvent effect, deactivation studies and the effect of modifier leaching are also reported.

Keywords: High throughput screening; Micro-reactor; Heterogeneous catalysis; Ligand library; Asymmetric hydrogenation; Ethylpyruvate; Chiral modifiers

1. Introduction

Synthesizing chiral molecules in pure enantiomeric form requires the use of appropriate asymmetric catalytic systems. The *a priori* prediction of the suitable system for a chosen reaction is still not obvious and the experimental screening of catalysts is thus necessary. In the case of three-phase asymmetric hydrogenations, the asymmetric catalytic system is generally composed of a traditional hydrogenation catalyst, Pt/Al_2O_3, and a chiral inductor that adsorbs on the Pt surface, leading to chiral catalytic sites [1]. This reaction has been studied for years and many catalyst modifiers are known for their potential to induce enantioselectivity [2–4]. Cinchonidine and other cinchona alkaloids are the most frequently employed modifiers. Enantioselectivities up to 90% are observed, depending on the operating conditions (solvent, pressure, temperature, concentration of substrate and modifier). The screening is usually performed in an autoclave where the test of each catalytic system requires a new experiment with fresh substrate, catalyst and solvent [5], even when the tests are performed in parallel, thanks to screening test platforms [6,7]. In our laboratory, we are interested in developing new tools for rapid screening of catalytic systems with simplified and/or easy to robotize procedures for the charging, discharging, cleaning and filtration steps. Standard continuous reactors like packed-beds can fulfil some of these requirements. Thus, reports have been published describing packed-bed reactors containing 25 mg to 1 g of catalyst for continuous G/L/S enantioselective hydrogenations but they were not centred on catalyst screening [8–12]. Considering overall criteria such as inventory of expensive catalysts and/or chiral ligands, operability, short response time, mass and heat transfer efficiency and fluid flow control, catalyst screening using micro-structured reactors rather than mini-packed-bed reactors would be more attractive.

The advantages provided by micro-structured reactors for the screening of homogeneous chiral catalysts have been published [13,14]. The methodology used for homogeneous catalyst screening can also be applied to chiral modifier screening. It consists in sequential injections of the reactants and catalysts through the micro-reactor, generating successive collected fractions allowing to evaluate and classify the different catalysts. For the purpose of the present study concerning gas–liquid–solid (G/L/S) operation, the target reaction is the asymmetric hydrogenation of ethyl pyruvate on Pt/Al_2O_3 and the reactor used is a G/L/S micro-structured contactor already described [15]. The objective is to demonstrate the concept of sequentially (i) adsorb a chiral inductor; (ii) perform a reaction; (iii) desorb the chiral inductor, without demounting the reactor.

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2. Experimental

2.1. Chemicals and catalyst

Ethyl pyruvate (Aldrich, 98%) was used as received. It is stored at 0 °C before use. The solvents: toluene, ethanol, methanol and methylcyclohexane (Fisher Chemicals) were used as received. The chiral modifiers tested are represented in Fig. 1. M1: (*S*)-(−)-2-Amino-1,1-diphenyl-1-propanol (Aldrich, 99%), M2: (*R*)-(+)-alpha-(1-naphtyl)ethylamine (Aldrich, 99%), M3: Hydroquinidine (Aldrich, 99%), M4: Hydroquinine (Aldrich, 99%), M5: Cinchonidine, M7: (1*S*,2*R*)-*cis*-1-amino-2-indanol (Aldrich, 99%) and M8: Guanosine hydrate (Aldrich, 99%) were used as received. Dihydrocinchonidine (M6) was prepared by hydrogenation of cinchonidine in a hydrochloric acid solution (1 mol/L) with Pd/C (5 wt.%) as catalyst [4]. The product was recrystallised in a mixture of toluene and methanol. Stock solutions of the ligands and substrate were kept at room temperature during an experiment.

The Pt/alumina catalyst was deposited on a glass insert whose design is specific to the micro-reactor used [15]. A γ-Al_2O_3 layer of about 20 microns thick is first deposited on the glass insert and further impregnated with a solution of platinum acetylacetonate in toluene [16]. After calcination and subsequent reduction of the platinum, a catalytic layer on the glass insert (ca. 3.5 wt.% Pt/Al_2O_3) is obtained with a catalytic bed volume of 25.10^{-9} m^3 (apparent density of γ-Al_2O_3 = 1).

2.2. Apparatus

The hydrogenation reactions were performed in a gas/liquid/solid film contactor which consists of two cavities separated by a micro-structured nickel mesh. A detailed description has been published [17]. The micro-structured contactor used for gas/liquid operation was designed, fabricated and first used in a joint effort [15,18]. The upper and lower cavities are filled respectively with the gas phase and the liquid phase. The solid catalyst, deposited on the top of the bottom glass insert has no contact with the gas phase but is in direct contact with the liquid. This micro-contactor was characterised for gas/liquid mass transfer and displayed a high volumetric G/L mass transfer coefficient (1–2 s^{-1}) which ensures a chemical regime for the investigated reactions [17]. A schematic representation of the whole reaction set-up is given in Fig. 2.

The solution was pumped from reservoir A into the reactor through an HPLC pump (Shimadzu LC 10 AT-VP) (B). A gas flow meter (C) was used for the hydrogen flow regulation. An injection valve (D) equipped with a loop (100 μl) was used for the injection of substrate or ligands in the micro-structured reactor (E) described above. The pressure regulation was achieved by means of needle valves (F) used as a back pressure regulators and fitted at both the gas and liquid outlets. A four-port connexion valve (G) was used for the batch mode thus allowing long contact times. Samples were collected for chemical analysis using 2 ml vials.

2.3. Screening protocol

The screening protocol consists of three steps: (1) adsorption of the chiral inductor to be evaluated on the solid catalyst surface; (2) reaction; (3) desorption of the ligand and cleaning of the catalyst. This cycle can be repeated for the screening of several inductors and/or under different operating conditions. Thus, the overall test procedure in sequential mode is: (1) stabilization of the reactor under the operating pressure and temperature at a constant flow rate of liquid ($1.67.10^{-9}$ m^3 s^{-1}) and gas (20 sccm h^{-1}); (2) introduction of the ligand

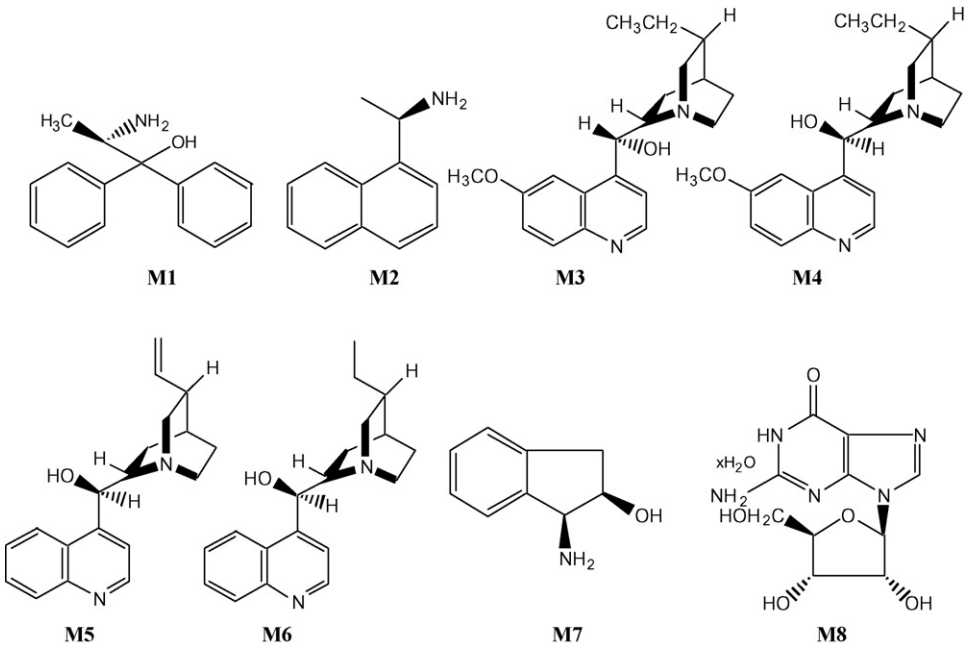

Fig. 1. Chiral modifiers tested for the asymmetric hydrogenation of ethyl pyruvate.

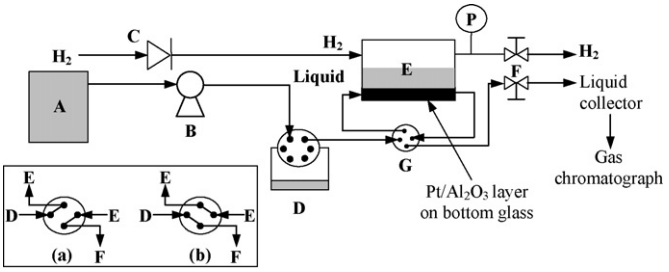

Fig. 2. Liquid tank (A); HPLC pump (B); gas flow meter (C); injection valve equipped with a loop (100 μl) (D); micro-reactor (E); needle valves (F); four-port connection valve (G); P pressure sensor. Cartoon: position of valve G for continuous mode (a) and batch mode (b).

(10 × 100 μL pulses) using the injection valve D (Fig. 2); (3) injection of the substrate (pure ethyl pyruvate, 100 μl) using the injection valve D; (4) sample collection during 10 min; (5) washing with methanol during 30 min for desorption of the modifier; (6) rinsing for 30 min with the solvent used to carry out the tests. Other feeding procedures for modifiers such as (i) continuous feeding, (ii) continuous co-feeding and (iv) *ex situ* adsorption using the so called ''pre-modification'' technique have also been evaluated for the continuous experiments [19]. The catalyst, deposited on the bottom glass insert of the reactor, can be regenerated *ex situ* (400 °C, calcination 3 h, hydrogenation 3 h) when a decrease in the activity is noticed.

2.4. Adsorption studies

For the ''pre-modification'' tests, i.e. for the experiments with pre-loaded chiral modifier, and for the isotherm determination, a well-stirred flat-bottom isothermal batch reactor is used. A solution containing the solvent and the modifier is placed in the reactor equipped with a circulation loop fitted with a pump and a UV detector (Jasco). The residence time in the loop is about 10 s. Then, the catalytic glass insert of the micro-reactor is immerged in the solution under nitrogen. On-line UV monitoring (315 nm) of the solution shows a decrease of the modifier concentration. The adsorption is considered as completed when no further decrease is observed.

2.5. Chemical analysis

The analysis of the reaction mixture is carried out with a gas chromatograph (6890N Agilent Technologies), equipped with a chiral column (Chirasilval Alltech, 25 m, 0.16 μm, 0.25 mm) and a FID detector. The method is as follows: 40 °C (3 min), then 15 K/min until 200 °C and finally 2 min at 200 °C. The pressure of helium used is 3 bar with a split ratio of 1:100.

3. Results and discussion

3.1. Screening protocol for modifier adsorption

As depicted above, the screening protocol consists of three steps: (1) adsorption of the chiral inductor; (2) reaction; (3) cleaning. Several published procedures for adsorption of the modifier are available. The perfect control of such procedure is of importance since enantioselectivity-saturation-type dependence as a function of modifier concentration is frequently observed for α-ketoesters [1a]. However, they are difficult to adapt to the screening set-up described in this work. In published batch experiments, the quantity of modifier (L^*) and of platinum are set to a molar ratio L^*/Pt in the range of 1–3 [4]. Despite the low solubility of most chiral modifiers in toluene (e.g. 1 g/L; 3.4 mmol/L for cinchonidine), such ratio are readily achieved in batch reactors since the catalyst concentration is very low, typically in the range 0.2–5 g/L [4], i.e. 0.04–1.3 $\mathrm{mmol_{Pt}/L}$, thus for very low solid hold-up (typically $< 1\%$). Because of both the high solid hold-up (25%) in the micro-structured reactor and the low solubility of modifiers in toluene, a special protocol has been designed to feed enough chiral inductor into the liquid cavity. For this step, the injection valve D equipped with the 100 μl injection loop was used, which can lead to a maximum molar modifier/Pt ratio of ca. 0.07 for one single injection of a saturated solution of the modifier to be screened. Thus to vary the modifier/Pt ratio, successive injection of 100 μl pulses have been used. Of course, the important criteria for comparison with the published (batch) experiments is not the global L^*/Pt ratio but rather the L^*_{ad}/Pt in which L^*_{ad} stands for adsorbed chiral modifier. In a first approximation considering Pt/Al_2O_3 catalysts, the concentration of L^*_{ad} (mmol g^{-1}_{cata}) can be determined from the adsorption isotherm (Fig. 3). The experimental data have been fitted with a Langmuir model:

$$[L^*_{ad}] = \frac{a[L^*]_{liq}}{1 + a[L^*]_{liq}} [L^*_{ad}]_{max} \quad (\mathrm{mmol\ g^{-1}_{cata}}) \tag{1}$$

where a (L $\mathrm{mmol^{-1}}$) is the Langmuir type adsorption constant, $[L^*]_{liq}$ (mmol $\mathrm{L^{-1}}$) the modifier concentration in the liquid phase and $[L^*_{ad}]_{max}$ (mmol g^{-1}_{cata}) is the saturation concentration of the modifier on the catalyst. The values of a and $[L^*_{ad}]_{max}$ are 0.023 ± 0.003 (L $\mathrm{mmol^{-1}}$) and 0.175 ± 0.015 (mmol g^{-1}_{cata}), respectively, in toluene. From the isotherm, assuming similar numerical values, a L^*_{ad}/Pt ratio of 0.6 for dihydrocinchonidine has been computed, under the conditions used for a published

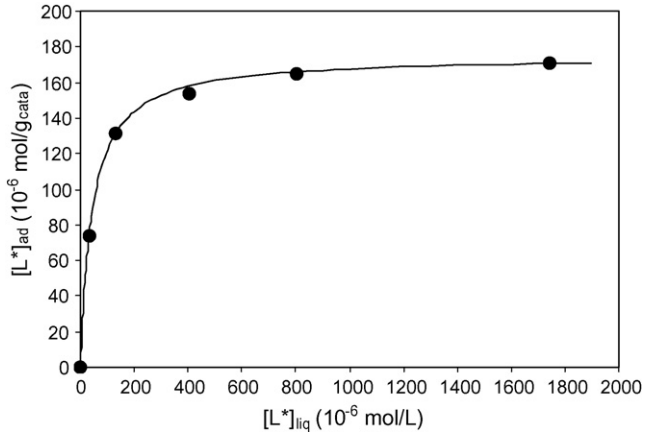

Fig. 3. Adsorption isotherm (25 °C) of cinchonidine in toluene corresponding to the reaction conditions.

quantitative study [4]. This value corresponds to the saturation of the isotherm. In order to reach such level of adsorbed chiral modifier, a procedure has been set where a total volume of 1 mL of a saturated solution of cinchonidine (see above) was injected using 10 pulses of 100 μL each (see Section 2).

Preliminary experiments for the cleaning step were based on a very recent report about the role of ethanol as a solvent for chiral modifier desorption from the surface of catalysts [11]. It has been found that only cinchonidine and dihydrocinchonidine can be completely removed using ethanol. On the contrary, methanol was able to ensure the complete desorption of all chiral modifiers used in this study. That was further checked by performing the hydrogenation of ethyl pyruvate which should lead to a racemic mixture of *R*- and *S*-ethyl lactate ($|ee| < 2\%$).

3.2. Screening results

One advantage of our set-up is the facility to change the operating conditions (solvent, temperature, pressure, etc.) within a very short period of time (less than 10 min) and without the need to filtrate the catalyst (fixed bed). The screened parameters are the nature and the concentration of the modifiers and the reaction solvent.

Table 1 summarizes the conversion and the enantioselectivity obtained with the different modifiers employed. These results show that the best enantioselectivity is obtained with cinchonidine (M5).

However, the ee obtained remain very low compared with published data in batch reactors where ee reaches 90% under the same operating conditions. Such a difference between batch and continuous reactors has already been described. In a recent report, it was proposed to account for lower ee's by the poor G/L mass transfer capabilities of the continuous reactor compared to the well-stirred tank batch reactor [20]. The characterization of G/L mass transfer in our mesh micro-contactor seems not to favour this hypothesis [17]. Rather, the ''reactor'' effect may simply be due to different concentrations of chiral modifier in the liquid phase for these two types of reactors, which in turn will result in different concentrations at the surface of the catalyst.

Table 1
Screening of the eight ligands for the hydrogenation of the ethyl pyruvate at 21 °C in toluene

Ligands		P_{H2} (Bar)	Conversion (%)	ee (%)
M1	(*S*)-(−)-2-Amino-1,1-diphenyl-1-propanol	27	32	16
M2	(*R*)-(+)-α-(1-naphtyl)ethylamine	33	42	2
M3	Hydroquinidine	26	25	−13
M4	Hydroquinine	25	33	31
M5	Cinchonidine	21	21	63
M6	Dihydrocinchonidine	28	38	52
M7	(1*S*,2*R*)-*cis*-1-amino-2-indanol	25	50	5
M8	Guanosine	36	24	15

Another important parameter is the nature of solvent which has a great influence on the activity, enantioselectivity and on the rate of desorption of the chiral modifier from the surface of catalyst [21]. For example, acetic acid which generally promotes the enantioselectivity could not be used in this study because of the chemical compatibility with the nickel mesh. Three solvents, ethanol, toluene and methylcyclohexane were evaluated for two chiral inductors, hydroquinidine (M3) and dihydrocinchonidine (M6) (Fig. 4). As expected, both the enantioselectivity and the conversion were found to be solvent sensitive. Note that in both cases, the test performed after the cleaning procedure with methanol and without added chiral inductors, reveal a good conversion but a negligible enantiomeric excess. This demonstrates the efficiency of methanol for the desorption and ensure no cross-contamination between the tests.

3.3. Leaching of the modifier

A continuous operation was achieved to check the possible evolution of enantiomeric excess and conversion with time-on-stream. The modifier chosen for this demonstration is that

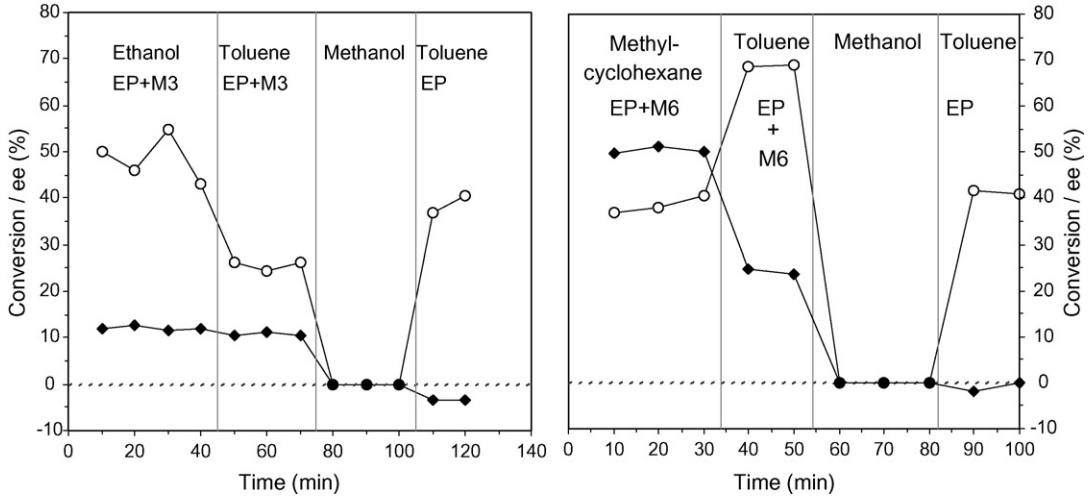

Fig. 4. Influence of the solvent on the time-on-stream evolution of enantiomeric excess (◆) and conversion (○) for several solvents and for ligand hydroquinidine M3 (left) and dihydrocinchonidine M6 (right). Conditions: 21 °C, pulse injection of EP, residence time 1 min, pressure 25 bar.

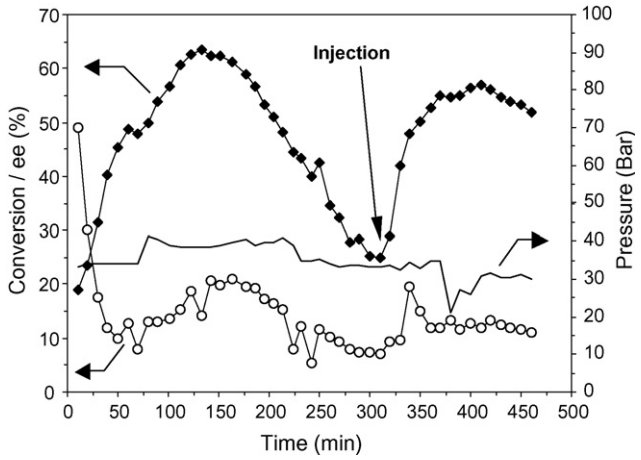

Fig. 5. Time-on-stream evolution of enantiomeric excess (◆), conversion (○) and pressure (−) for ligand M5. Conditions: 21 °C, [EP] 1.3 mol/L, residence time 1 min, pressure 25 bar.

which gives the best enantioselectivity in the screening tests (cinchonidine, M5). After a stabilisation time, a maximum ee (65%) is reached at ca. 150 min which is followed by a steep decrease down to 25% at ca. 300 min. A concomitant decrease of the activity of the catalyst is also evidenced (Fig. 5).

At ca. 300 min, an injection of the ligand M5 (3×100 μl) stabilizes the ee during ca. 1 h, from 330 to 400 min. This experiment demonstrates the possibility for compensating the desorption of the cinchonidine by injections of the chiral modifier without stopping the test.

Another mean to keep a high enantioselectivity is the continuous co-feeding of the chiral modifier with the substrate in the inlet liquid flow (Fig. 6). However, a decrease in the activity and the enantioselectivity with time is also observed, likely due to the desorption of the ligand. Note that the rate of decrease of the enantioselectivity is lower than in the absence of co-feeding (Fig. 5).

Because the ligand concentration in the inlet liquid flow (3.1×10^{-6} mol/L) corresponds to the saturation of the isotherm (see Fig. 3), the decrease of both the ee and activity

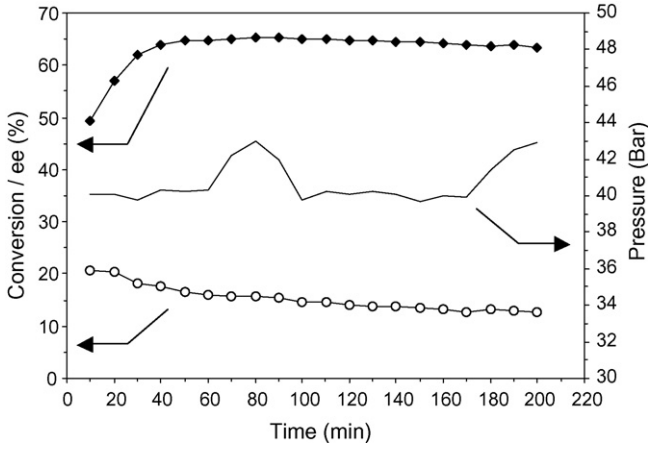

Fig. 6. Time-on-stream evolution of enantiomeric excess (◆), conversion (○) and pressure (−) with continuous feeding of ligand M5. Other conditions: toluene, 21 °C, [EP] 1.1 mol/L, [M5] 0.0031 mol/L, residence time 1 min.

observed during this experiment cannot be ascribed to the desorption of the chiral modifier. Thus the mechanism proposed for the sequential injection of the chiral modifier (i.e. without co-feeding) to explain the results shown in Fig. 5 cannot operate here. Considering the two sites mechanism generally found in the literature [4], it is proposed in this work that the rate of deactivation of the more active enantioselective sites is higher than that of the non-enantioselective (racemic) sites.

4. Conclusion

The reported results are, to the best of our knowledge, the first demonstration of the use of a gas–liquid–solid high pressure micro-structured reactor (up to 45 bar) for screening applications and deactivation studies [22]. The facility to change various parameters and operating conditions (temperature, residence time, substrate and modifier concentrations, solvents, etc.) without the cumbersome filtration of the catalyst is a real practical advantage. The results have allowed to propose that enantioselectivity can be strongly decreased by selective deactivation. Furthermore, the first quantitative data on the adsorption isotherm of the very popular cinchonidine chiral modifier are presented. The combination of the adsorption isotherm and of pulse experiments provides an explanation for the lower enantioselectivities generally obtained in continuous reactors (ca. 65%) compared to batch results (>85%).

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