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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

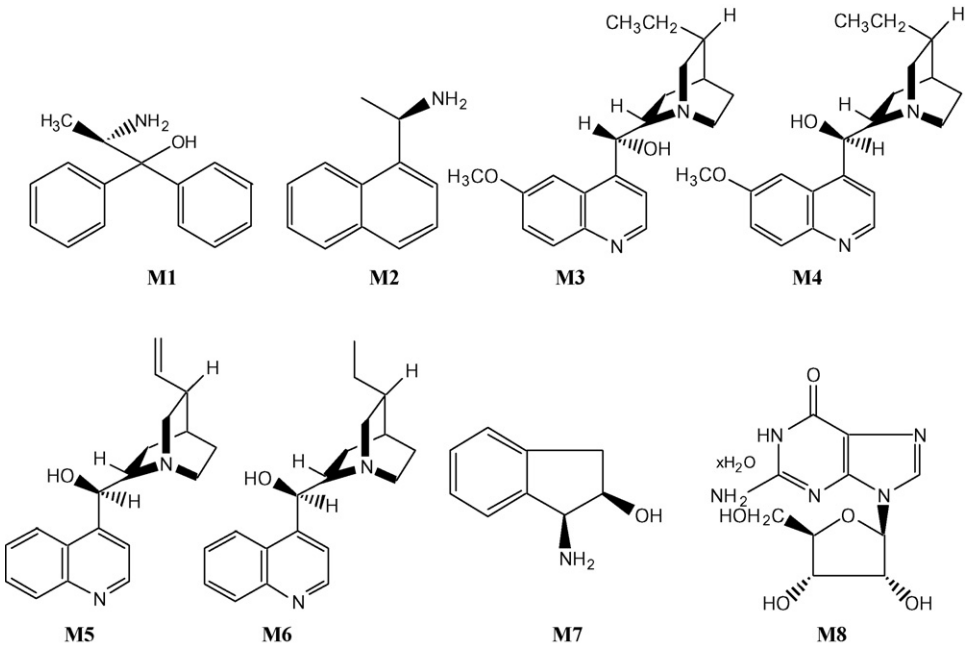

Fig. 1. Chiral modifiers tested for the asymmetric hydrogenation of ethyl pyruvate.