Effect of gas–liquid mass transfer on enantioselectivity in asymmetric hydrogenations

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Abstract

The enantiomeric excess (ee) in asymmetric hydrogenation may vary with the concentration of hydrogen dissolved in the liquid phase. This concentration is proportional to hydrogen pressure when the reactor operates in chemical regime, but depend on the stirring rate if mass transfer is limiting. For example, decrease of ee from 61 to 51% ee has been observed upon varying the stirring rate from 100 to 2000 rpm. A good characterisation of the reactor used is recommended to quantify the influence of hydrogen on ee.
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1. Introduction

The production of pure enantiomers is a real challenge that asymmetric catalysis has to face. Because the structure of the chiral ligand is the most important component in asymmetric catalysis, research is mainly devoted to the development of new such ligands. However, ee may also depend on the components concentration (reagents or adducts for example) and on the operating conditions (stirring rate, temperature) through the kinetic law. Halpern has demonstrated that enantiomeric excess is not only related to the catalyst properties, but also to kinetic phenomemons. Thus, any reagent, chiral or not, involved in an elementary step occuring before the rate limiting step, and after the coordination of the substrate, can affect the enantiomeric excess [1]. For example, the addition of bromine, lutidine or water during ketones hydrogenation plays a role in the deprotonation of the diastereoisomeric intermediate and induces a change in enantioselectivity [2,3]. In asymmetric hydrogenations, hydrogen is thus also able to influence the enantioselectivity. Hydrogen concentration can indeed appear in the kinetic expression of enantiomeric excess, as explained, for example, by Landis and Halpern [4] in the case of methyl-

Z-acetamidocinnamate catalysed by Rh/DiPAMP. Lots of examples on the role of hydrogen on ee are reported, more in terms of hydrogen pressure than of hydrogen concentration [5]. In the case of γ-geraniol hydrogenation with Ru/(S)-tol-BINAP, ee decreases from 90 down to less than 10% upon increasing hydrogen pressure from 0.05 to 7 bars [6]. Variations of ee are not always so large; in many cases, ee does not vary with hydrogen pressure [7,8]. An increase of ee with hydrogen pressure is also possible [9]. This latter case is the most interesting since a pressure increase would lead to an increase of both rate of reaction (i.e. production) and enantioselectivity.

A confusion is often made between hydrogen concentration and hydrogen pressure. Hydrogen concentration is of course linked to reactor pressure, but it may also depend on the reactor stirring rate, in particular for very fast reactions for which the actual hydrogen concentration is not that at thermodynamic equilibrium (Henry's law). Thus, under the very same hydrogen pressure, the actual hydrogen concentration may take many different values, depending on the reactor stirring rate and the intrinsic rate of the chemical reaction. In the case of geraniol hydrogenation catalysed by Ru/BINAP, Blackmond and co-workers [10] have shown that ee jumps from 21 to 57% at the same pressure, when the stirring rate is increased. Similar observations have been reported in heterogeneous catalysis. In the case of ethyl pyruvate hydrogenation on Pt/Al₂O₃ with a chiral inducer, experiments at constant pressure show that the stirring rate has

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Table 1
List of organometallic materials

	Nomenclature	Supplier
[Rh(COD)$_2$]BF$_4$, catalyst precursor	Bis(1,5-cyclooctadiene)rhodium(I)tetrafluoroborate hydrate	Aldrich
[Rh(*R,R*)–(DiPAMP)(COD)]BF$_4$, catalyst	(*R,R*)-(−)-1,2-Bis[(*o*-methoxy-phenyl)(phenyl)phosphino]ethane(1,5-cyclooctadiene)rhodium(I)tetrafluoroborate	Strem
(*R,R*)-DIOP, ligand	(4*R*,5*R*)-(−)-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane	Strem
(*S,S*)-BPPM, ligand	(−)-(2*S*,4*S*)-2-Diphenylphosphinomethyl-4-diphenylphosphino-1-*t*-butoxycarbonylpyrrolidine	Strem

an influence on enantiomeric excess [11]. A good knowledge of the reactor used to screen the effect of hydrogen pressure on ee is essential and it would be more correct to compare the effect of hydrogen concentration, than that of pressure, to get rid of the reactor characteristics. While these previous reports have qualitatively evidenced the effect of G/L mass transfer on ee, the present work aims at a more quantitative assessment of mass transfer effect. The goal of this publication is two-fold : (i) to convince researchers in the field that the choice of the reactor used to screen chiral ligands is of major importance, (ii) to warn engineers in charge of the scale-up of asymmetric hydrogenations about the complexity of the kinetics laws involved in asymmetric catalysis that may lead to a strong influence of mass transfer on ee. The test reaction used is the asymmetric hydrogenation of methyl-*Z*-acetamidocinnamate (MAC) catalysed by rhodium complexes.

2. Experimental

Methyl-*Z*-acetamidocinnamate was synthesised in the laboratory [12]. Methanol (Fisher Chemicals) was used as a solvent and was deoxygenated under argon before use. The rhodium precursors and diphosphine ligands used in this study are presented in Table 1. Three different reactors were used in this study: a mini-autoclave, a carousel and a microreactor. They have been characterised in terms of gas–liquid mass transfer. A summary is presented in Table 2. The standard experiments have been performed in the mini-autoclave with 10 mL liquid. The standard reaction temperature is 35 °C. In a typical test, 1 mL of catalytic solution (in methanol), 2 mL of reagent solution (in methanol) and 7 mL of methanol are introduced in the reactor under nitrogen leading to final concentration of MAC of 0.1 kmol m^{-3}, and concentration of rhodium of 10^{-4} kmol m^{-3}. Hydrogen is fi-

Table 2
Reactors used

	Mini-autoclave	Carousel	Microcontactor
Supplier	Parr	Radleys	Not available
Liquid volume	10 mL	5 mL	100 μL
$k_L a$ (s^{-1})	up to 4	0.026	2
Reference	Meille et al. [13]	Pestre [12]	Abdallah et al. [14]

nally introduced and stirring is started simultaneously, which determines the beginning of the reaction. Only one analysis is performed at the end of the reaction (above 98% conversion) with a gas chromatograph (Agilent technologies 6890N) equipped with a FID detector and a chiral column (CHIRASIL-VAL from Alltech, length 25 m, layer of thickness 0.16 μm, diameter 0.25 mm). The analysis was performed at 120 °C in 12 min under helium pressure (3.67 bar) and with a split of 1:10.

3. Fundamentals

The kinetics of asymmetric hydrogenation of MAC has been studied in detail by the group of Landis and Halpern [4]. The mechanism is presented in Fig. 1.

The rate law (Eq. (1)) and the kinetic parameters (Table 3) have been determined in the above cited publication

$$r_R = \frac{k_{1R}k_{2R}}{(k_{-1R} + k_{2R}[H_2]_L)}$$

$$\times \frac{[MAC][Rh]_{tot}[H_2]_L}{\left(1 + \frac{k_{1R}[MAC]}{k_{-1R} + k_{2R}[H_2]_L} + \frac{k_{1S}[MAC]}{k_{-1S} + k_{2S}[H_2]_L}\right)} \quad (1)$$

The rate law for the *S* enantiomer is similar and results from exchange of the *R* and *S* indices in Eq. (1). The enantiodifferenciation (thus ee) is governed by the competition between the

$$I + Mac \underset{k_{-1R}}{\overset{k_{1R}}{\rightleftharpoons}} IIR$$

$$I + Mac \underset{k_{-1S}}{\overset{k_{1S}}{\rightleftharpoons}} IIS$$

$$IIR + H_2 \xrightarrow{k_{2R}} I + R$$
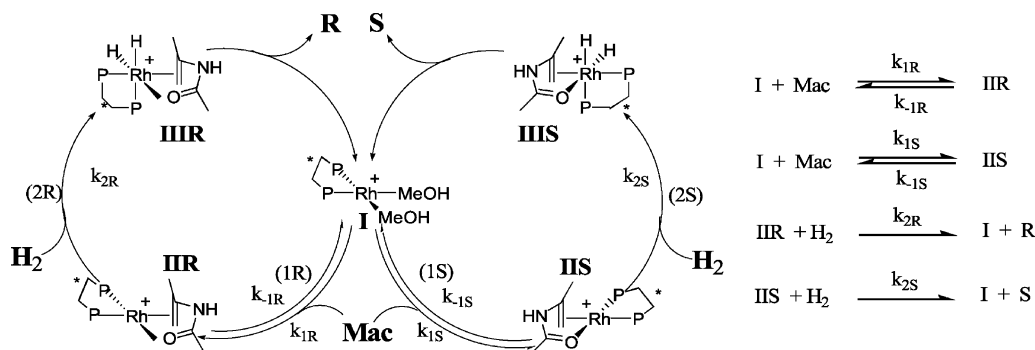
$$IIS + H_2 \xrightarrow{k_{2S}} I + S$$

Fig. 1. Mechanism of MAC hydrogenation according to Landis and Halpern [4]. For the sake of clarity, MAC structure is simplified.

Table 3
Kinetic constants for MAC hydrogenation with [Rh(R,R)–(DiPAMP)(COD)]BF$_4$

T (K)	k_{1R} (m^3 kmol^{-1} s^{-1})	k_{1S} (m^3 kmol^{-1} s^{-1})	k_{-1R} (s^{-1})	k_{-1S} (s^{-1})	k_{2R} (m^3 kmol^{-1} s^{-1})	k_{2S} (m^3 kmol^{-1} s^{-1})
298	5300 ± 400	10600 ± 600	0.15 ± 0.01	3.2 ± 0.2	1.1 ± 0.1	630 ± 50

rate of formation of the R and S enantiomeric products, thus by the ratio expressed by Eq. (2)

$$\frac{r_R}{r_S} = \frac{k_{1R}k_{2R}(k_{-1S} + k_{2S}[H_2]_L)}{k_{1S}k_{2S}(k_{-1R} + k_{2R}[H_2]_L)} \qquad (2)$$

Then ee is a function of hydrogen concentration in the liquid. In a batch reactor under constant pressure with a gas phase composed of hydrogen, the mass balance for the liquid phase is described by the following equations:

$$\frac{d[R]}{dt} = r_R \qquad (3)$$

$$\frac{d[S]}{dt} = r_S \qquad (4)$$

$$\frac{d[MAC]}{dt} = -(r_R + r_S) \qquad (5)$$

$$\frac{d[H_2]_L}{dt} = -(r_R + r_S) + Ek_La\left(\frac{P_{H_2}}{He} - [H_2]_L\right) \qquad (6)$$

In Eq. (6), k_La is the volumetric gas–liquid mass transfer coefficient, E is the enhancement factor, P_{H_2} is the hydrogen pressure in the gas phase, He is the Henry coefficient for hydrogen in the liquid medium and $[H_2]_L$ is the hydrogen concentration in the liquid phase [12]. This equation accounts for the physical transfer of hydrogen from gas phase to the liquid phase that may limit the reaction rate. Under the operating conditions, the reaction occurs mainly in the liquid bulk and then $E = 1$. When the reactor is efficient enough to operate under the so called chemical regime, hence the mass transfer term in Eq. (6) is close to zero and can be neglected.

4. Results and discussion

4.1. Simulations

At a given hydrogen pressure, simulations have been performed, based on the above cited equations, to evaluate the range of deviation of enantiomeric excess due to gas/liquid mass transfer. Fig. 2 shows that when reaching the chemical regime ($[H_2]_L \approx [H_2]_{sat}$), enantiomeric excess reaches a stable value, but this value is the lowest of the graph. For the system studied (hydrogenation of MAC catalysed by [Rh(R,R)–(DiPAMP)(COD)]BF$_4$), the enantiomeric excess decreases drastically when the gas/liquid mass transfer is improved, from 96% to 78%.

Hydrogenation of MAC catalysed by [Rh(R,R)–(DiPAMP)-(COD)]BF$_4$ is the only system for which the kinetics is fully described. Simulations for other real catalytic systems are thus not possible albeit the effect of mass transfer on ee has been proposed on the bases of theoretical work using "virtual" catalysts and a set of hypothetical kinetic constants [15]. The prediction

of the effect of k_La on ee is thus only possible when the kinetic law is known. Moreover, it is very important to take care of the reactor used to screen the catalytic systems.

4.2. Experimental results

In a first set of experiments, the Rh/DIPAMP catalyst was used under the conditions of Halpern's report. The objective was to check the agreement between our experiments with this catalytic system and the published model. In our experiments, the hydrogen concentration in the liquid phase was estimated according to the expression:

$$[H_2]_L = [H_2]_{sat}\left(1 - \frac{\bar{r}}{k_La[H_2]_{sat}}\right) \qquad (7)$$

where $\bar{r}$ is the apparent rate of hydrogen consumption (kmol m^{-3} s^{-1}). Comparison of our experimental results, Halpern experimental results and the simulation performed with Halpern's kinetics is depicted in Fig. 3. Halpern experiments were mainly performed at low hydrogen pressure (≤ 10 bars) and the kinetic parameters are thus more representative of low pressure experiments. Nevertheless, a good agreement between our experiments and Halpern ones is obtained and the model seems to give a good estimation of ee versus hydrogen concentration. In these results, enantiomeric excess varies from 95 down to 65% when hydrogen concentration increases from 0 to 0.12 kmol m^{-3} (corresponding to a pressure range of 0–30 bar in chemical regime). Similar variations are observed experimentally with other ligands, (R,R)-DIOP and (S,S)-BPPM (Fig. 4).

The results obtained with these two ligands demonstrate the importance of studying ee versus hydrogen concentration, and not versus hydrogen pressure. The use of ee versus pressure
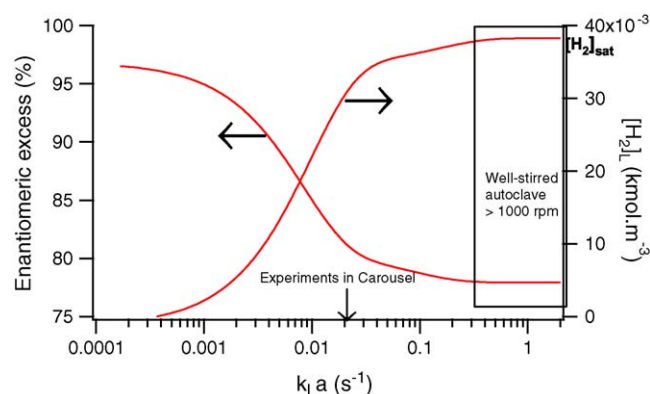

Fig. 2. Simulation of ee and $[H_2]_L$ (at 50% conversion) for MAC hydrogenation with Rh/DIPAMP at 298 K and 10 bar, [Rh] $= 5 \times 10^{-4}$ kmol m^{-3}.
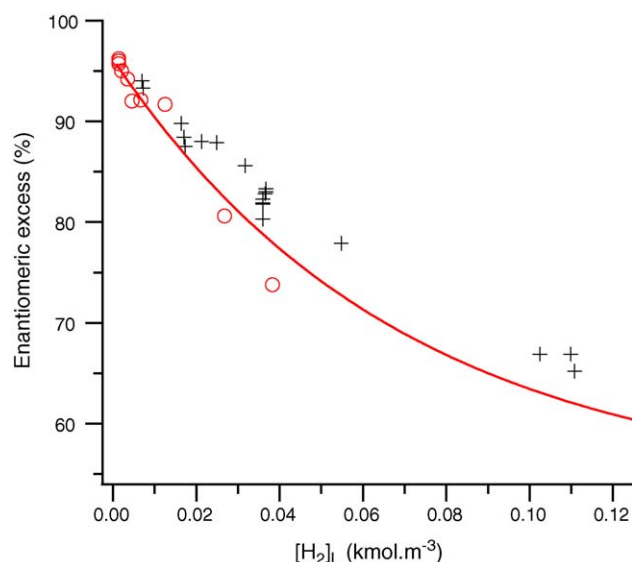
Fig. 3. Enantiomeric excess vs. hydrogen concentration in liquid phase with DIPAMP, experimental results (+), Halpern's results (○) and simulations using Halpern's kinetics (line).

Fig. 5. Enantiomeric excess vs. hydrogen pressure with DIOP, in Parr autoclave.

plot may indeed drive to misleading interpretations (Fig. 5). For example, in a first set of experiments with (R,R)-DIOP, ee is measured at increasing pressures (Fig. 5, plots in the rectangle). A wrong interpretation would consist in stating that ee does not depend on hydrogen pressure or concentration with this ligand. In fact, these data have been obtained at different stirring rates, and thus, even if the pressure is changed, the hydrogen concentration in the liquid remains the same. In a second example (Fig. 5, double rectangle), different values of enantiomeric excess are obtained at the same hydrogen pressure. This is not due to reproducibility problems, but again to mass transfer efficiency. For all these experiments at 10 bar pressure, hydrogen concentration
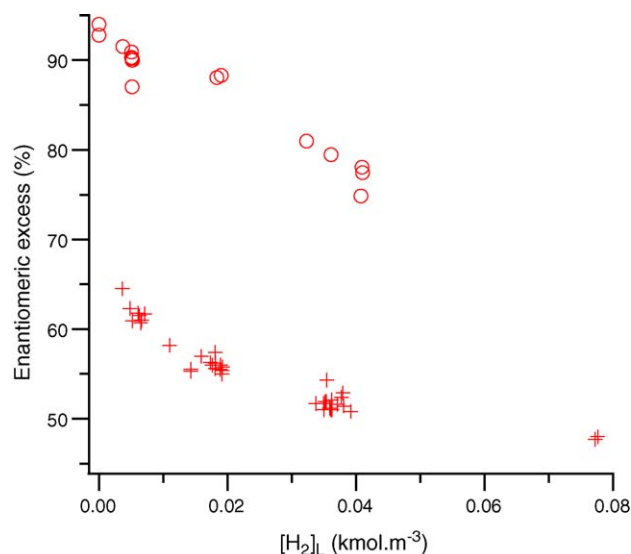
in the liquid varies from 0.02 to 0.04 kmol m^{-3} because some experiments have been obtained with more or less efficient stirring. This phenomenon is representative of what can be observed by different experimentators in different reactors or at different stirring rates, showing again the importance of ploting ee versus hydrogen concentration. The effect of stirring rate is presented in Fig. 6. At a fixed hydrogen pressure, enantiomeric excess and reaction rate strongly depend on the stirring rate. The lowest value of ee (in the range 51.5%) obtained above 3000 rpm corresponds to chemical regime. Note that for the sake of clarity, only the points without catalyst deactivation have been presented. The use of hydrogen concentration instead of hydrogen pressure allows to get rid of the reactor employed and of the stirring rate. Fig. 7 presents the results obtained for (R,R)-DIOP with our three types of reactor: the standard mini-autoclave, the carousel (more or less a Schlenk tube) and the microcontactor. Whatever the reactor used, the trend of ee versus hydrogen concentration is unchanged. The examination of other catalytic systems has allowed to confirm that plotting ee versus hydrogen concentration does not depend on the reactor used.

Fig. 4. Enantiomeric excess vs. hydrogen concentration in liquid phase with DIOP (+) and BPPM (○), in Parr autoclave.

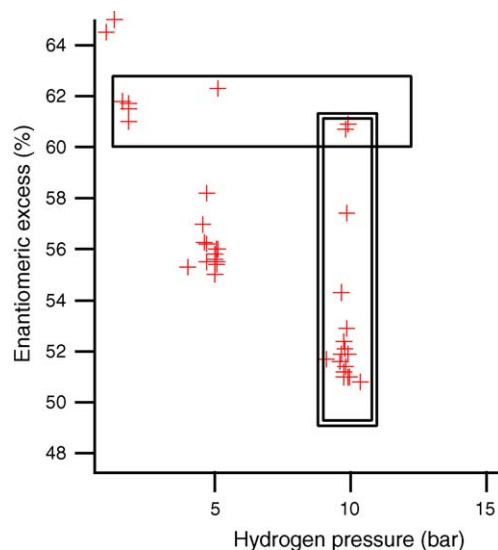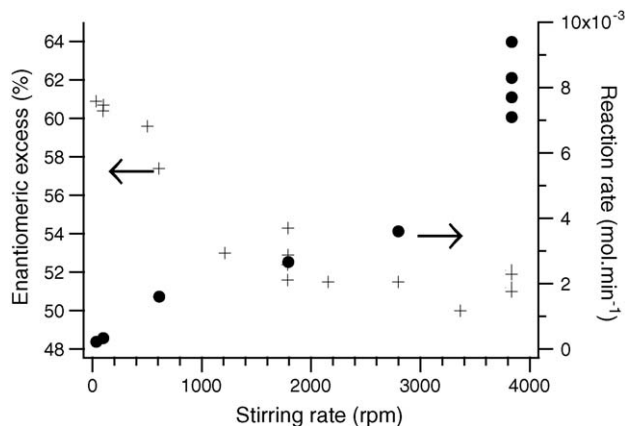Fig. 6. Enantiomeric excess (+) and reaction rate (●) vs. stirring rate with DIOP, in Parr autoclave, for experiments at 10 bar hydrogen pressure.
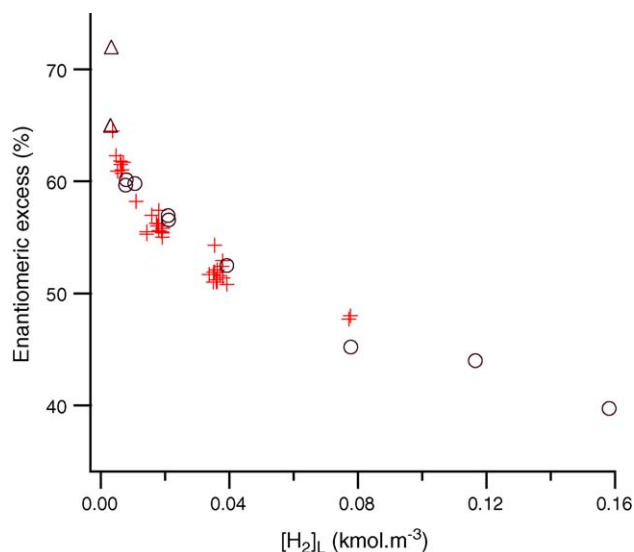
Fig. 7. Enantiomeric excess vs. hydrogen concentration with DIOP in the autoclave (+), in the mesh microcontactor (◯) and in the carousel (△).

5. Conclusion

In this work, the influence of hydrogen concentration, including reactor performances, on enantiomeric excess has been demonstrated for three catalytic systems. The general character of this conclusion for the many existing enantioselective catalysts still remains a question mark. It has also been shown that the comparison of ee according to hydrogen pressure is only possible if chemical regime is reached, providing that the gas/liquid mass transfer coefficient is above $1 \, s^{-1}$. Thus, characterizing hydrogenation reactors in terms of gas/liquid mass transfer is mandatory if comparison of ee with pressure is planned. Further work will consist in: (i) studying the effect of hydrogen concentration for a large variety of catalytic systems, (ii) establishing kinetic laws and determining the elementary steps involved in enantiodifferenciation.

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