High Throughput Kinetic Investigations of Asymmetric Hydrogenations with Microdevices

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Abstract: A high throughput test which is based on a micromachined mixer for molecular gas-liquid reactions was evaluated for the kinetic investigation of the asymmetric hydrogenation of methyl Z-(α)-acetamidocinamate with a rhodium/(*S,S*-BDPPTS) catalyst in an aqueous phase. Up to 214 tests were performed in a short time and with an average inventory of Rh/test as low as 14 μg. Comparisons with traditional batch experiments are provided.

Keywords: asymmetric catalysis; high-throughput screening; homogeneous catalysis; kinetics; microreactors

Asymmetric catalytic hydrogenations is nowadays a mature field in particular due to the pioneering work of H. B. Kagan, W. S. Knowles and R. J. Noyori.[1] However, the gap between the discovery of new chiral catalysts, the basic knowledge of asymmetric induction, e.g., in catalytic hydrogenations, and the industrial use of this reaction is still large. This is mainly due to the molecular diversity of the chiral catalysts (ligands) but also to the lack of knowledge for the prediction of enantiomeric excess under a range of process parameters such as pressure, temperature, concentrations, mixing, etc.

For the chemical engineer or process chemist, this knowledge may be of primary importance for the process design.[2] For the molecular chemist it will be valuable in order to better understand the mechanisms of asymmetric catalysis and to check the results obtained from molecular computations.[3] Many of the answers belong to kinetics and only few researchers aim at the quantitative determination of kinetic models and parameters in asymmetric catalysis.[4] For example, it is well known that many enantioselective catalytic hydrogenations revealed remarkable changes in the ee with pressure.[4d,5] Examples where achiral additives such as surfactants, [6] KBr,[7] or crown ethers,[8] influence the ee were also published. Last but not least, mixing (agitation) may also be detrimental to ees![9] Most of the answers to these observations lie in kinetics simply because selectivity is the result of competition between reactions. Quite often, kinetic studies are not performed because it appears time-consuming, expensive (with respect to the price or availability of most of chiral ligands) and not rewarding.

In a previous report, a new concept to achieve high throughput screening (HTS) of catalysts for liquid-liquid reactions was described.[10] That was based on dynamic sequential operations with a combination of pulse injections and a micromachined mixer. A similar set-up has been further used for synthesis.[11] Some data were also provided to qualitatively indicate the effectiveness of the concept for a gas-liquid asymmetric hydrogenation, albeit at atmospheric pressure.[10] Herein, a more quantitative assessment of the capabilities of this HTS set-up for the kinetic studies of enantioselective hydrogenations is described.

The gas-liquid HTS test reactor must be able to mix the reacting phases with a low to very low inventory of catalytic material while still offering residence time long enough for the reaction to proceed. The principle used is a combination of pulse injections of a mixture the catalyst and the substrate, a micromixer with negligible volume and a tubular reactor (Figure 1). Such a design should offer definitive advantages in terms of catalyst inventory, mass transport, automation, etc. over parallel mini-batch apparatus.[12]

Under operations, the two fluid phases, i.e., aqueous solution and hydrogen, are continuously flowing through the apparatus leading to a stable foam as observed in the tube. For a test, a pulse containing the substrate and the Rh/diphos catalyst dissolved in the water/ethylene glycol/SDS mixture is injected. The composition of this liquid is adjusted to obtained a good quality foam. The reagents are perfectly mixed in the micromixer leading to a reacting segment which travels along the tubular reactor. Collection at the outlet of the reactor, extraction of the organics and analysis afford conversion and ee data. Two parameters are of importance for the operability of the test: The stability of the gas-liquid foam and the size of the reacting segment. It has been found that the foam stability increases with the hydrogen pressure. This ensures a residence time up to 12 minutes at 70 °C without

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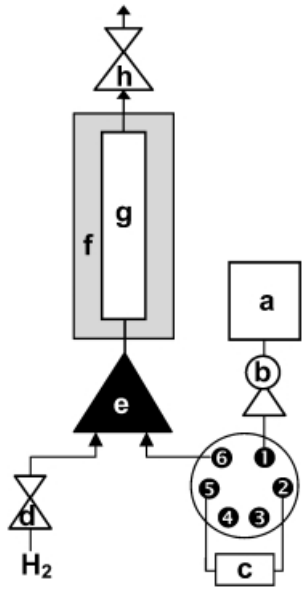
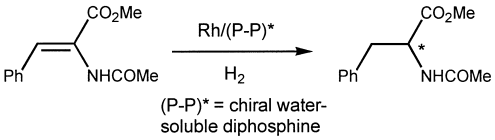


Figure 1. Experimental set-up: **a** water/ethylene glycol/SDS reservoir, **b** high-pressure liquid pumps, **c** catalyst/substrate injection HPLC-type valve equipped with a 200 μL loop, **d** hydrogen supply (5 MPa) and mass flow controller, **e** micro-mixer, **f** heating mantel, **g** tubular glass or quartz reactor (0.4 cm i.d., 80 cm length), **h** back-pressure regulator.

noticeable coalescence of bubbles. Analysis of the residence time distribution reveals some axial dispersion of the segment when the reacting tube is placed vertically, probably due to back-mixing. This was neglected for the reactor/kinetic modelling and can be attenuated by placing the tube horizontally.[13]

In a first experiment, the reproducibility of the test was evaluated. Figure 2 shows the reproducibility achieved for seven tests of asymmetric hydrogenation of methyl Z-(α)-acetamidocinamate (MAC) with an Rh/(*S,S*)-CDBTS water-soluble catalyst [Equation (1) and Figure 2].



(1)

The measured conversion lies in the range 76–94%. This is mostly due to variation of the pressure, which cannot be controlled efficiently with the back-pressure regulator used in this work. However, except for the test no. 6, conversions are in fact between 86 and 94% which is quite good. The enantiomeric excess is very stable, in the range 19.6–20.6% (*S*), in agreement with previous reports.[14]

In a second experiment, the kinetics of the asymmetric hydrogenation of methyl Z-acetamidocinamate (MAC) with an [Rh(*S,S*-BDPPTS)]$^+$ water-soluble catalyst was studied. The chiral diphosphine ligand BDPPTS is the sulfonated counterpart of the well known BDPP diphosphine which is commercially available. Up to 214 experiments were performed in the micro-test to cover a broad range of operating conditions such as temperature (20–70 °C), pressure (0.3–1.1 MPa), rhodium and MAC concentrations. The surfactant SDS has no effect on the rate nor on the ee. Out of the 214 experiments, 44 (20%) were not used since the conversion was $<3\%$. Such low conversions are explained by operating the test under conditions where the catalysis was not fast enough (too short residence time, too low temperature, pressure etc.). This leads to the first conclusion that when investigating unknown (obviously!) kinetics with HTS experiments, some tests will provide uninformative data. In other words, not *all* the experiments will be useful. In fact, a rough knowledge of the reaction conditions will probably drop down the proportion of these uninformative data. The 170 experiments with conversion $> 3\%$ were then fitted with several empirical kinetic models derived from the mechanistic model of Halpern (Scheme 1).[4a]

$$r_{MAC} = -kC_{Rh} \quad \text{(I)}$$

$$r_{MAC} = -kP_{H2}C_{Rh} \quad \text{(II)}$$

$$r_{MAC} = -kC_{MAC}C_{Rh} \quad \text{(III)}$$

$$r_{MAC} = -kP_{H2}C_{MAC}C_{Rh} \quad \text{(IV)}$$

$$r_{MAC} = -\frac{kP_{H2}C_{MAC}C_{Rh}}{1+K_{MAC}C_{MAC}} \quad \text{(V)}$$

$$r_{MAC} = -\frac{kP_{H2}C_{MAC}C_{Rh}}{1+K_{H2}P_{H2}} \quad \text{(VI)}$$

$$r_{MAC} = -\frac{kP_{H2}C_{MAC}C_{Rh}}{1+K_{H2}P_{H2}+K_{MAC}C_{MAC}} \quad \text{(VII)}$$

Scheme 1.

For each model, an iterative fitting process was used in order to reject those experimental data that were not fitted by the model within 3σ (i.e., ±25%). The best statistical model was (IV), depicting a first-order kinetics with respect to the hydrogen pressure, the reagent and the catalyst. The kinetic parameters (k and Ea) are discussed below. With this model, 29 experiments out of the 170 used for the fit (i.e., 17%) were rejected (Figure 3). For the sake of conciseness, the same parameter fitting for the rates of formation of the *R*- and *S*-enantiomers are not displayed but similar features are obtained.

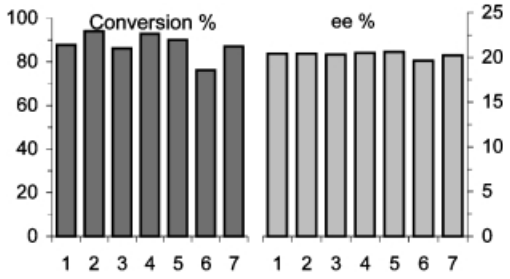


Figure 2. Reproducibility test with an Rh/CBDTS catalyst ([Rh] 0.001 M), [MAC] 0.05 M, 40 °C, 0.3 MPa, reaction time 3.2 min.

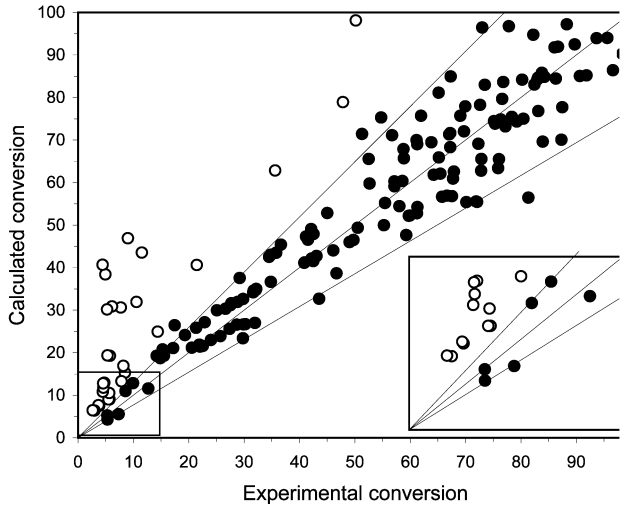


Figure 3. Best parity diagram obtained with model (IV); (o) rejected data, (●) fitted data.

Interestingly, all the rejected data display a computed conversion higher than that measured. This can be interpreted as "bad" tests, i.e., the catalyst was not properly handled (e.g., partial decomposition by air oxidation) which would result in lower activities.

The enantioselectivity was also investigated. Under the quite different operating conditions used in the study, *no significant change* of the ee was noticed. This is well depicted by the ee distribution which reveals that the probability to obtain $40 < ee < 48\%$ is 0.9 (Figure 4).

This is in agreement with the first order kinetics. Thus, ee is just the integrated ratio of the rates of reactions r_R/r_S, i.e., k_R/k_S for first-order reactions, from which ee is deduced easily. Numerical application with $k_R = 6.7$ and $k_S = 2.6$ ($m^3 \cdot kmol^{-1} \cdot MPa^{-1} \cdot min^{-1}$) indeed provides $ee = 44\%$.

Ten control experiments have been performed in a specially design mini-batch reactor (10 cm^3), optimised for low inventory of reacting solution, under the same conditions (liquid phase composition, temperature,...). The kinetic parameters have been computed from the *hydrogen consumption and not from the R and S concentrations* but they should, in theory, give the same results since $r_{H2} = r_{MAC} = -(r_R + r_S)$. Thus, for the same model (IV), the kinetic constant at 323 K is $k_{323} = 9.3$ *vs.* 19.1 ($m^3 \cdot kmol^{-1} \cdot MPa^{-1} \cdot min^{-1}$) and the activation energy is 31 ± 4 *vs.* 40 ± 4 ($kJ \cdot mol^{-1}$) in the micro-test and batch reactors, respectively.

That the values found in the traditional batch reactor are higher than those estimated from the micro-test experiments illustrates the difficulties to carry out experiments with a very low inventory of material. Also, this difference may come from a poor control of the temperature and of the residence time in the micro-test that must be improved. However, the data concerning the enantioselectivity are more in agreement, lying between 40 and 45% (see Figure 4). Finally, the rather bad agreement observed between the traditional and micro-tests, must not hide the advantage of the later (Table 1).

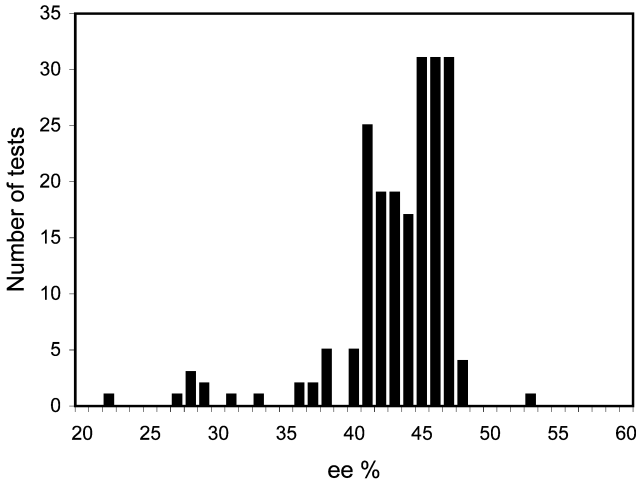


Figure 4. Diagram showing the ee distribution with 90% probability of $40 < ee < 48\%$.

Table 1. Comparison of the batch *vs.* micro-test.

Feature	Batch	Micro
Number of experiments	14	214
Number of significant experiments	11	170
Number of rejected experiments	1	29
% of experiments actually used (%)	71	66
Reaction volume (cm^3)	10	0.2
Amount of aqueous solvent required (cm^3)	140	3000
Average amount of Rh per experiment (μg)	680	14
Average amount of diphos per exp. (μmol)	6.7	0.14
Average TTF[a] (d^{-1})	2	15
Maximum achieved TTF (d^{-1})	3	40[b]
Easy automation (injection, analysis etc.)	No	Yes

[a] TTF is the throughput testing frequency, i.e., the number of experiments per day.

[b] Delay time between injection in the micro-test is only 5 minutes but both the optimised chiral GC analysis (one run per 12 min) and the manual injection limit the test throughput.

In conclusion, despite the fact that this catalytic system Rh/(*S,S*-BDPPTS) displays no pressure or additive (SDS) dependence on ee, the HTS potential of the micro-test is clearly demonstrated. Further research aims at the design of microreactors that should allow more accurate high throughput kinetic investigations with very low inventory of catalytic material.

Experimental Section

Catalyst Preparation

A stock solution of the catalyst was prepared in water: An orange slurry of solid $[Rh(cod)Cl]_2$ (20 mg, 0.11 mmol of Rh) and sulfonated (2*S*,4*S*)-2,4-bis(diphenylphosphino)pentane (BDPPTS) (0.095 g; 2.43 equiv. of phosphorus/kg as analysed by iodide titration, 0.23 mmol of phosphorus) in water (3 cm^3) was stirred at room temperature until all the solid dissolved. The aqueous solution was stored at 4 °C. Ethylene glycol, SDS and water were then added to afford a stock solution of the catalyst having the following features: [Rh] = 0.001 to 0.0001 M, ligand/Rh = 1.07, [SDS] = 0.05 or 0.02 M, ethylene glycol/H_2O = 60/40 vol. For the tests, the substrate MAC was dissolved in the catalyst solution before injection.

G/L Asymmetric Hydrogenation in the Micro-Test

Pulses (200 μL) of aqueous solutions of the catalyst (0.0001 to 0.001 M) and the substrate MAC (0.02 to 0.07 M) were manually injected through the HPLC valve. The yellow-coloured reacting segment was collected (cm^3) at the exit of the back-pressure regulator in a 30 cm^3 flask. The organics were extracted with CH_2Cl_2 (1 cm^3) and analysed by GC. Reaction times (2 – 12 min) are computed from the flow rates: hydrogen 1 to 4 N mL/min, liquid phase 0.3 to 1 mL/min and considering a plug-flow reactor.

G/L Asymmetric Hydrogenation in the Mini-Batch

An aqueous solution (1 cm^3) of the catalyst (0.01 to 0.001 M) was added to a hydrogen saturated solution of the substrate MAC (0.2 to 0.7 mmol) in the aqueous solvent (9 cm^3) without stirring at the reaction temperature. The H_2 pressure was adjusted and the agitation was started.

Analysis

Samples were analysed by gas chromatography on an HP-6890 equipped with a Chirasilval column (25 m, 0.16 μm, d = 0.25 mm, 6.5 cm^3/min He, FID detector, split injection mode, 1 μL, 165 °C 12 min).

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