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Asymmetric hydrogenation in a membrane reactor: recycling of the chiral catalyst by using a retainable micellar system

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Abstract

A micellar enlarged Rh-(2*S*,4*S*)-*N*-*tert*-butoxycarbonyl-4-diphenylphosphino-2-diphenyl-phosphino-methyl-pyrrolidine (BPPM) catalyst was used for the enantioselective hydrogenation of α-amino acid precursors in a membrane reactor, equipped with an ultrafiltration membrane. The chiral α-amino acid derivatives were obtained with good enantioselectivity and space–time yields. The catalyst, embedded in micelles, obtained from triblock copolymers as surfactants, was retained and reused several times without loss of activity and enantioselectivity. Only a minimal leaching of the catalyst components was found.

Keywords: Asymmetric hydrogenation; Rhodium complex; Amphiphiles; Membrane reactor

1. Introduction

Within the last decades the asymmetric hydrogenation of amino acid precursors became a very effective method for synthesis of the corresponding enantiomerically enriched amino acid derivatives [1]. Traditionally, organic solvents were used, but with the development of water-soluble ligands aqueous two-phase systems became important in the transition metal complex catalysed hydrogenation [2]. Oehme et al. [3] discovered that the enantioselectivity and activity of chiral rhodium catalysts increases on addition of micelle forming amphiphiles originally in water-insoluble systems, which became a convenient alternative in colloidal aqueous dispersions [4].

Another goal in the field of asymmetric catalysis is an easy separation of catalyst and product and the recycling of the catalyst. Often, heterogenisation of the homogenous catalyst on a solid support is used in order to use conventional filtration [5,14]. For the work presented here the soluble catalyst is recovered using ultrafiltration membranes. Contrary to a heterogeneous support these systems normally do not have mass transport limitations [6].

We used triblock copolymers as surfactants for the hydrogenation in aqueous micellar media [7,8]. The advantage of these amphiphiles is their molecular weight (often more than 5000 g mol^{-1}) allowing their recovery using ultrafiltration membranes. The application of these compounds for micellar enhanced ultrafiltration for water purification has been reported recently [9]. In a similar way micelles containing the embedded Rh-complex catalyst can be recovered in membrane reactor equipped with an ultrafiltration

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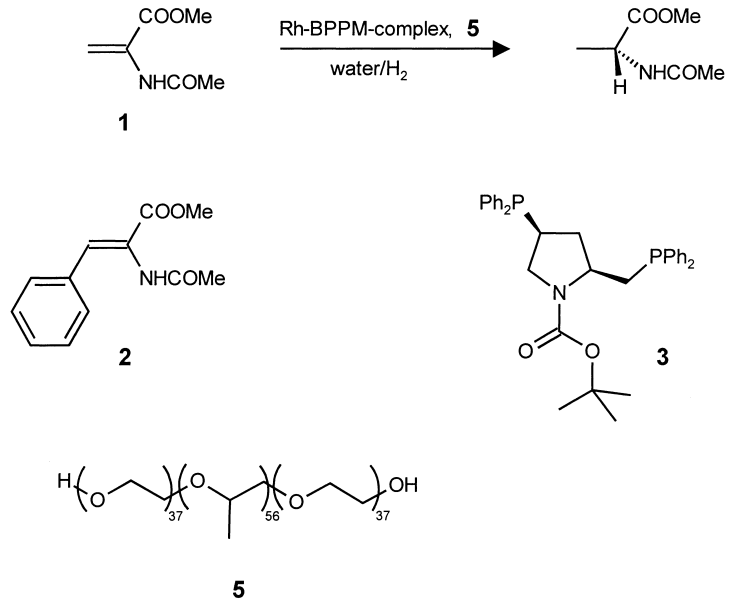

Scheme 1.

membrane and reused in a new reaction cycle. This is a further example of the membrane reactor technology for recovery of homogeneous soluble catalysts [10–12], this time involving a gas phase.

As a model reaction, the asymmetric hydrogenation of α-acetamidoacrylic acid methyl ester (**1**) and (*Z*)-α-acetamidocinnamic acid methyl ester (**2**) was investigated. As chiral ligand (2*S*,4*S*)-*N*-*tert*-butoxycarbonyl-4-diphenylphosphino-2-diphenyl-phosphinomethyl-pyrrolidine (BPPM) (**3**) was used which formed the active catalyst together with $[Rh(cod)_2][BF_4]$ (**4**). The triblock copolymer P105 (**5**) gave the best results in hydrogenation experiments. By Oehme and co-workers other substrates yielding, e.g. phophono- and phosphino-amino acid derivatives have been hydrogenated as well [13] (Scheme 1).

2. Experimental

2.1. Chemicals

BPPM was obtained from Merck, Darmstadt; *N*-acetamidoacrylic acid methyl ester was from Aldrich Steinheim. (*Z*)-α-acetamidocinnamic acid methyl ester and $[Rh(cod)_2][BF_4]$ were synthesised according to published methods [4]. All other chemicals were obtained from Fluka, Neu-Ulm. Argon and hydrogen (both 99.99999%) were obtained from Messer Griesheim, Krefeld, Germany.

The triblock copolymer P105, molecular weight 6500 g mol^{-1} was a gift from the company Erbslöh, Krefeld, Germany.

For retention experiments, a stirred ultrafiltration cell was used, equipped with different membranes (ultrafiltration and nanofiltration membranes from several suppliers, membrane diameter 63 mm) as described elsewhere [6]. This cell has been commercialised recently by Jülich Fine Chemicals, Jülich, Germany (www.juelich-chemicals.de).

Solutions of known concentrations of substrate, catalyst and catalyst in micellar media (amphiphile P105), respectively were pumped into the reactor. Water was then pumped through the reactor at a flow of 10 ml min^{-1} resulting in a pressure between 6 and 15 bar. Fractions from the reactor outlet and samples from the vessel itself were taken. Concentrations were either determined by measuring the UV-absorption photometrically at 245 nm (compound **2**) or 345 nm (Rh-complex **3**/**4** with/without triplock copolymer **5**).

Educt **1** was measured by weighting after evaporation of the solvent. The retention R was calculated by using Eqs. (1) and (2) and observed values for total filtration time t, residence time τ, retentate concentration c_{Ret}, permeate concentration c_{Per} and given value of the start concentration c_0.

$$c_{\mathrm{Ret}} = c_0 \mathrm{e}^{-(1-R)t/\tau} \quad (1)$$

$$R = 1 - \frac{c_{\mathrm{Per}}}{c_{\mathrm{Ret}}} \quad (2)$$

To ensure formation of micelles the concentration of **5** was well above the critical micellar concentration, which was estimated to be $4.6\,\mathrm{g\,l^{-1}}$. For the hydrogenation reaction requiring a gas phase a stirred filtration cell SR 75 from Schleicher and Schuell, Einbeck, Germany, 47 mm membrane diameter was used allowing recovery of the catalyst in repetitive batch experiments. This cell is made from glass, teflon and stainless steel. A catalyst solution containing 4 mg (0.01 mmol, $0.67\,\mathrm{mmol\,l^{-1}}$) $[\mathrm{Rh(cod)_2}][\mathrm{BF_4}]$, 7 mg (0.01 mmol, $0.67\,\mathrm{mmol\,l^{-1}}$) BPPM and 650 mg (0.1 mmol, $6.7\,\mathrm{mmol\,l^{-1}}$) P105 in 15 ml de-aerated water (vacuum, introduction of Ar and storage under Ar) was placed in the argon filled membrane reactor equipped with the ultrafiltration membrane YC05 (Amicon/Millipore, Eschborn, Germany). Substrate **1** 143 mg (1 mmol, $67\,\mathrm{mmol\,l^{-1}}$) was added and the reactor was tightly closed. The argon in the membrane reactor was replaced by hydrogen at atmospheric pressure and the hydrogenation started by stirring. Samples with a volume of 100 μl were taken at fixed times through a silicon septum to follow the progress of the reaction. The samples were extracted with the same volume of chloroform. The organic phase was separated and ee as well as conversion were determined by gas chromatography. Conditions: GC Chrompack 438A, capillary column Chirasil-Val (Macherey-Nagel, Düren, Germany), 25 m × 0.25 i.d., carrier gas H_2, temperature programme 80 → 104°C with $4^\circ\mathrm{C\,min^{-1}}$.

After every reaction cycle the hydrogen supply was closed and the remaining hydrogen was flushed out by argon to stop the reaction. After 5 min the septum was exchanged for a steel seal, the argon pressure was increased to 5–6 bar and the reactor outlet was opened. In the case of the larger reaction volume (45 ml) 30 ml filtrate were collected, in the case of the smaller volume (15 ml) 10 ml. Then the outlet was closed and the steel seal was opened slowly to release the pressure. New substrate (143 mg, 1 mmol) and water (30 ml or 10 ml) were added and the reactor was closed with a new septum. After replacing the argon by hydrogen and starting the stirrer a new reaction cycle was performed.

For determination of the leaching of the catalyst and ligand samples were analysed for phosphorus and rhodium using elementary analysis.

3. Results and discussion

3.1. Retention measurements

Several commercially available membranes from different suppliers were tested with respect to their retention for substrates **1** or **2**, catalyst components **3** and **4** and amphiphile **5**. An aqueous solution of these compounds was filtered through the reactor and the retention was determined. Very high retention for the catalyst and low retention for the substrate and products (after hydrogenation), respectively were needed, allowing an effective recovery of the catalyst. The membrane YC05, an ultrafiltration membrane consisting of regenerated cellulose from AMICON, was found as most suitable. The results are shown in Table 1 and Fig. 1, respectively. Although, there is a substantial retention for the substrate, it can be seen that it is washed out very easily. For the Rh-BPPM complex a retention of 0.95 is found, which would mean a loss of 40% of the active catalyst after 10 replacements of the reaction solution. For the amphiphile as well as for the Rh-BPPM complex in micellar media retention rates >0.99 are found allowing the recovery of the micellar embedded catalyst with almost no loss.

Table 1
Retention rates of substrates and catalysts for the membrane YC05

Compound	Molecular weight ($\mathrm{g\,mol^{-1}}$)	Retention
1	143	0.26
2	219	0.28
Rh-BPPM-complex (**3**, **4**)	962	0.950
5	6500	0.993
5 and Rh-BPPM-complex (**3**, **4**) (micelle)	Not known (>7462)	0.991

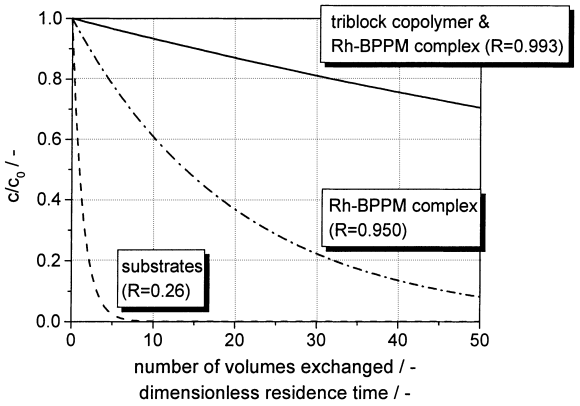

Fig. 1. Retention of substrates and catalysts for the membrane YC05.

3.2. Asymmetric hydrogenation in the membrane reactor

By variation of different reaction conditions like stirrer speed, hydrogen pressure, substrate concentration and reaction volume optimum conditions for repetetive batch experiments in the membrane reactor were established. Enhancement of the stirrer speed and increasing hydrogen pressure led to a higher reaction velocity, but lower enantioselectivity. For the latter, a low stationary and constant hydrogen pressure in the solution would be advantageous, preferably controlled by an online-measurement. A smaller reaction volume and high substrate concentrations gave good reaction velocity, conversion and enantiomeric excess. Therefore, the reaction conditions as given in the legends for Figs. 2 and 3 were chosen for the repetitive batch experiments. Some preliminary kinetic studies suggest a Michaelis–Menten analog saturation kinetics when the concentration of the substrate is varied.

Fig. 2 gives the results for the recovery of the active catalyst by ultrafiltration. From the similarity of the time course for the different runs it can be deduced that there is no loss of volumetric activity, neither by deactivation of the catalyst nor by a loss through the membrane. In a control experiment by exchange of the complete mixture above the membrane against fresh substrate solution without catalyst it could be confirmed that there is no adsorption of the catalyst on the membrane. The conversion has been limited to 50% by purpose due to two reasons: (i) to concentrate on the initial phase of the reaction where a deactivation or loss of active catalyst can be detected more easily; (ii) to shorten the overall reaction time in order to minimise the danger of catalyst deactivation by other reasons such as oxygen uptake. The main purpose of this study was to show that it is possible to recover a micellar chiral Rh-complex catalyst by membrane filtration. Additionally, some data shown need some explanations: (i) only 90% of product solution can be removed by a single filtration step without washing. Therefore, the runs following the first run start with an ‘apparent’ conversion of 10%; (ii) during run 3 some analytical problems occurred resulting in some-

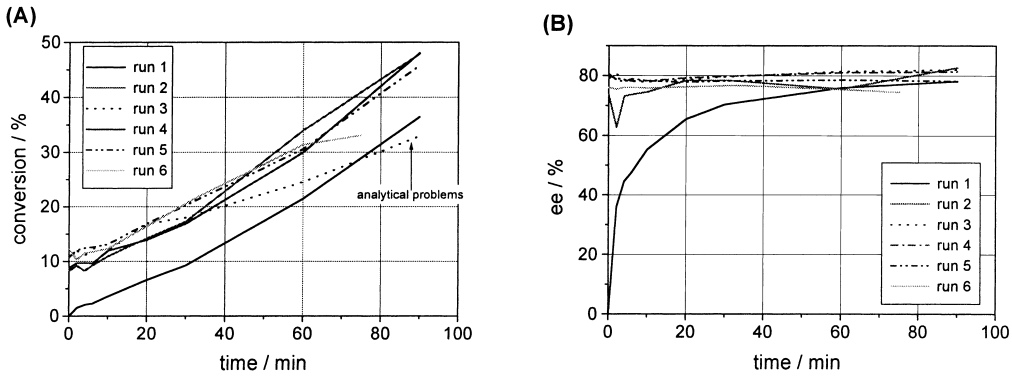

Fig. 2. Conversion (A) and enantiomeric excess (B) for six consecutive hydrogenation batches of substrate **1** with recovery of the active catalyst by membrane filtration. Conditions: stirrer speed 1100 rpm, H_2 pressure 1 bar, 25°C, reaction volume 45 ml, substrate to catalyst ratio 100, filtration time 3 h.

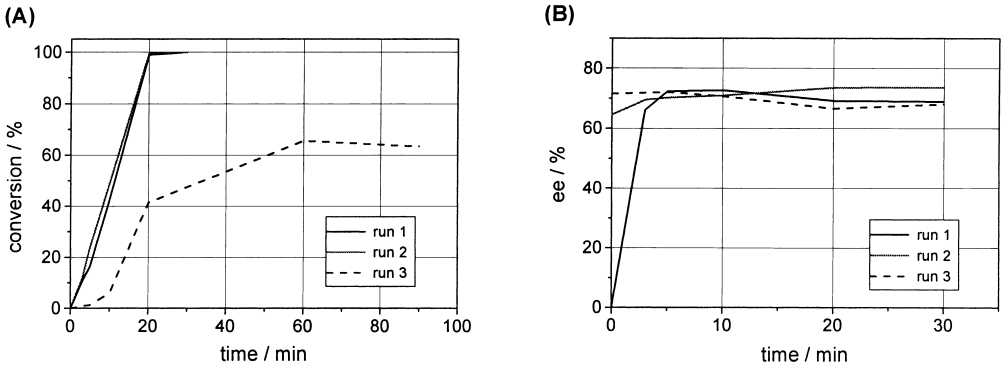

Fig. 3. Conversion (A) and enantiomeric excess (B) for three consecutive hydrogenation batches of substrate **1** with recovery of the active catalyst by membrane filtration. Conditions: stirrer speed 1100 rpm, H_2 pressure 1 bar, 25°C, reaction volume 15 ml, substrate to catalyst ratio 300, filtration time 1.5 h.

what lower values for the conversion measured; (iii) during run 1 the active catalyst is formed increasing the enantioselectivity after a lag time. For the following runs the active catalyst was already present. The enantioselectivity in the membrane reactor is somewhat lower as reported before [3]. This might be due to the different reactor geometry. By the repeated use of the catalyst its total turnover number [1] could be enhanced almost two-fold up to 194. The space–time yield is 18.6 g l^{-1} per day. [2]

In a second set of experiments the substrate to catalyst ratio was raised to 300 and the reaction volume was reduced to 15 ml in order to improve the hydrogen delivery into the solution. As can be seen in Fig. 3 after a short reaction time complete conversion was reached for the first two runs. But for the third run the reaction stopped after 50% conversion. In all three experiments a good enantiomeric excess was obtained. The reason for the rapid decrease in activity in the third run is not yet clear. A more thorough technique to keep away oxygen traces could increase the number of runs but the conversion and enantioselectivity still was declining. For this special substrate **1** a polymerisation due to the higher educt concentration is possible. This was supported by an increasing viscosity of the solution during the consecutive experiments. As further investigations aim at hydrogenation to obtain more interesting products such as phophono- and phosphino-amino acid derivatives as mentioned before, this was not followed up further. Nevertheless, caused by the short reaction time, higher substrate concentration and reduced filtration time due to the smaller volume the space–time yield was increased to 348 g l^{-1} per day and the turnover number to 795.

3.3. Adsorption and leaching

As mentioned before there was no adsorption of the catalyst on the membrane. However, all continuously operated processes or repetitive batch processes suffer from the problem of leaching of catalysts or ligands, especially when there is no covalent attachment of the catalyst but only formation of a complex. Only a very small leaching of the catalyst was found. Rhodium and phosphorus, as a measure for the diphosphine ligand, were measured in the permeate and retentate. As can seen from Fig. 4 there was almost no leaching for the phosphine ligand, whereas for the metal there was a small leaching. From the data a retention of 0.99 was calculated for rhodium, which was in good agreement with the initial retention measurements. Certainly the causes for this different leaching are the hydrophobicity of the ligand, which is embedded into the

[1] The total turnover number (ttn) is defined as mol product formed/mol of catalyst used.

[2] For calculation of the space–time yield 0.5 h for disassembling/assembling the reactor were considered besides the reaction and filtration time.

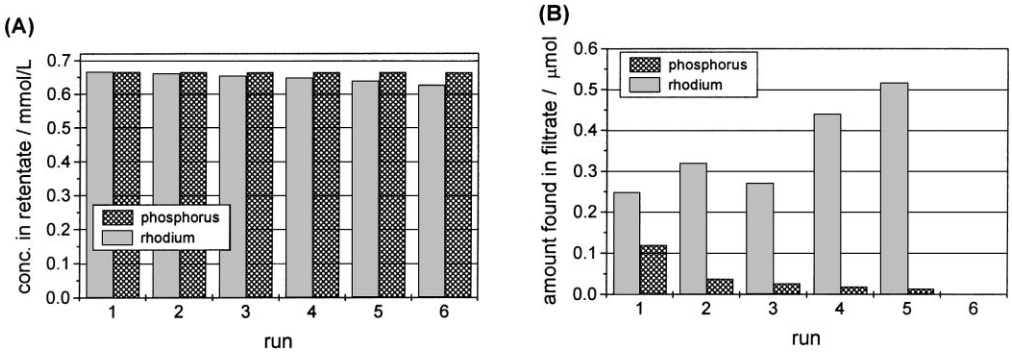

Fig. 4. Concentrations of the ligand and rhodium in the retentate (A) and the filtrate (B).

micellar structure. The retention of the hydrophilic ionic rhodium on the contrary is determined by the complex stability between the metal and the phosphine ligand.

4. Conclusions

It could be shown, that micellar enlarged catalysts can be retained by an ultrafiltration membrane in a membrane reactor. The recycled catalyst can be reused without a loss of activity. A big advantage is the simple preparation of the retainable catalyst, which is obtained just by mixing of the triblock copolymer with the pre-catalyst in water. No complicated and costly heterogenisation steps are necessary. Due to the hydrophobic properties of the amphiphile and the ligand the latter is effectively retained in the micellar structure behind the membrane, whereas for the hydrophilic metal ion a higher leaching is observed. Further studies will demonstrate the feasibility of this approach for the conversion of more interesting substrates for asymmetric hydrogenation.

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