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The Chemzyme Membrane Reactor in the Fine Chemicals Industry

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Abstract:

Recovery of catalysts from homogeneous reaction mixtures is a major problem in the fine chemicals industry if the amount or the price of catalyst are not negligible. Product purification costs and catalyst costs are the main reasons for attempts to immobilise homogeneous catalyst, on inorganic supports or resins. We present a way to recycle the homogeneous catalyst in situ by binding it to homogeneous, soluble polymers, which can be retained by a membrane reactor system. Different research areas, which are contributing to the system, are discussed, and continuous processes on lab scale are presented.

1. Introduction

Catalysis is frequently a prerequisite for efficiency in organic reactions. Homogeneous asymmetric catalysis has been developed over the last two decades to a very powerful tool, and highly efficient catalysts for enantioselective reduction and oxidation reactions are now available.[1]

However, powerful asymmetric catalysis may be, the available catalysts cover a wide range in terms of activity and stability: The total turnover number (ttn) for a hydrogenation reaction has been optimized for the (*S*)-metolachlor process to >1,000,000, and an initial turnover frequency (tof) of >200,000 h^{-1} is given.[2] However, asymmetric epoxidation reactions frequently suffer from lower turnovers and require higher catalyst load, for example, 0.1−5% (ttn of 20−1000) are required for the Jacobsen salen epoxidation catalyst.[3] Significant issues remain in the field of asymmetric catalysis, especially in the practical, large-scale application of this technology.

A major disadvantage of homogeneous catalysts is the frequently cumbersome catalyst separation from the reaction medium.[4] Therefore, efforts have been made in binding a homogeneous catalyst to an insoluble support/carrier such as an organic resin or an inorganic support. Unfortunately, this immobilisation very often leads to a decrease of activity and selectivity of the heterogeneously bound catalyst. Our aim was to circumvent these problems and maintain the original high activity and selectivity of homogeneous catalysts by connecting them to a soluble support and using ultrafiltration techniques to separate the catalyst.

2. The Chemzyme Membrane Reactor (CMR)

Long before we started to work on homogeneous catalysts in a continuously operating membrane reactors, Degussa and their partners Christian Wandrey and Maria Kula developed the enzyme membrane reactor (EMR) in the early 1980s.[5] The concept is depicted in Figure 1. An enzyme with a molecular weight in a range of 20−200 kD is large enough to be retained behind an ultrafiltration (UF) membrane. In contrast to the enzyme, the product molecules are much smaller and thus are able to pass through the pores of the membrane. This way the enzyme is trapped in the reaction system. Product and unconverted starting material pass through the membrane and can be collected. Due to the cutoff[6] of the membrane the enzyme cannot pass and remains in the reaction vessel. Using this approach, the enzyme is essentially recycled in situ.

In this contribution we want to show the transferability of this concept to homogeneous catalysts. By attaching the catalytically active centre to a soluble polymer support, a situation comparable to that in enzymatic systems should be attained (Figure 2).

Starting materials and converted products are expected to pass through the membrane, as described for the enzyme membrane reactor. The homogeneously soluble polymer-bound catalyst remains in the reactor depending on the cutoff of the membrane.

In this concept, the advantages of homogeneous catalysis, that is, high reaction rate without diffusion limitations and selectivity, especially enantioselectivity, is combined with the advantage of heterogeneous catalysis, that is, the simple recovery of the catalyst. The residence times of product and catalyst are decoupled, which should reduce catalyst costs.

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(1) (a) *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley−VCH: Weinheim, 1998. (b) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Yamamoto, H., Pfaltz, A., Eds.; Springer: Berlin, 1999.

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(6) The cutoff is defined by a substance with a certain molecular weight, leading to 90% retention.

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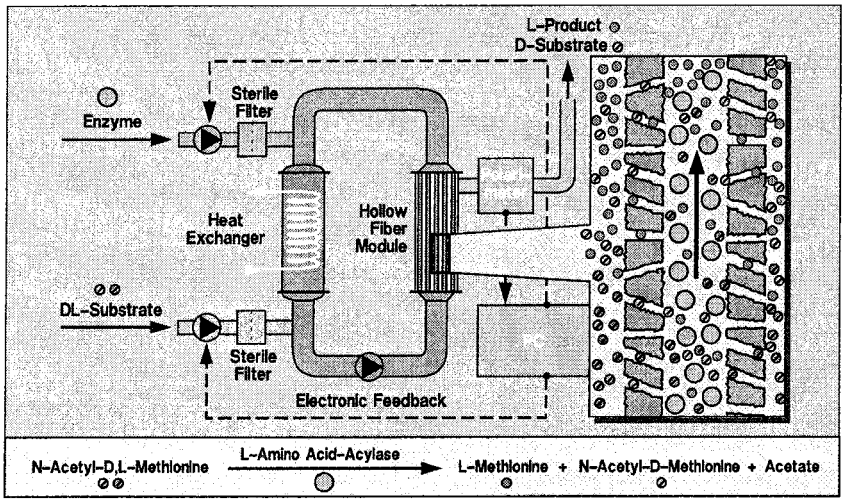

Figure 1. **Acylase process for L-methionine. Degussa-Hüls process for L-methionine, starting form a racemic mixture of *N*-acetyl-D,L-methionine. Only *N*-acetyl-L-methionine is converted by the enzyme into the desired L-amino acid while the enantiomeric *N*-acetyl-D-methionine is left unreacted. The enzyme is retained by the membrane, and only the low-molecular weight reactant and product pass through the membrane.**

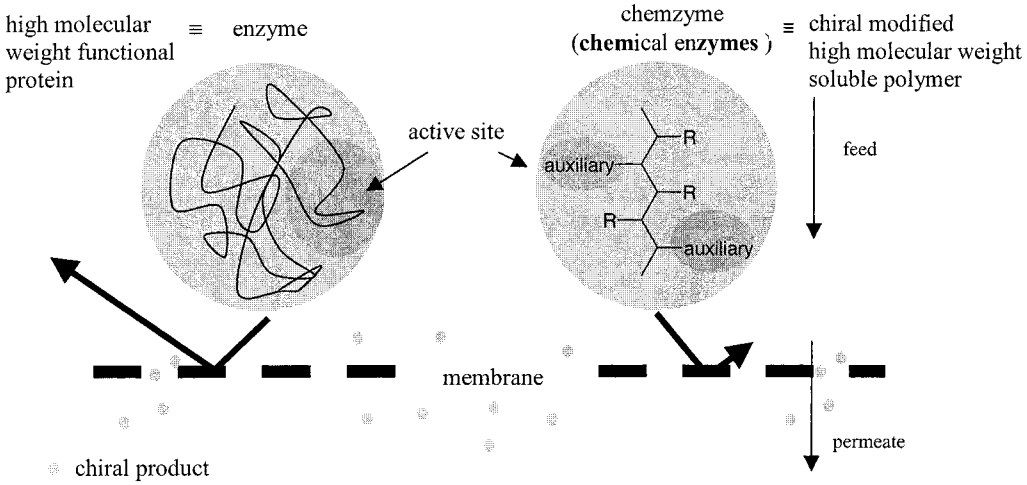

Figure 2. **Comparison between enzymes and molecular weight enlarged homogeneous catalysts.**

3. Catalysis by Molecular Weight-Enlarged Catalysts: Historical Background

Only a few examples of molecular weight-enlarged catalysts are known. There are two major approaches to synthesize molecular weight-enlarged catalysts: using either linear polymers or dendrimers as carriers.

The concept of using homogeneous catalysts bound to soluble polymers had been demonstrated previously: Bayer and Schurig equipped a filtration cell with a membrane for hydrogenation and hydroformylation of mono alkenes.[7] They described the possibility to run the reaction batchwise or, in principle, in a continuous way.

Kragl described a membrane reactor for the catalysed diethylzinc addition.[8] Although the enantiomeric excess was only 50% and the yield was 30% with a residence time of 2.5 h, this reaction demonstrates the first successful operation of a chemzyme membrane reactor (CMR). Our success with the enzyme membrane reactor, which has been used at Degussa since 1980 on a technical scale, prompted us to build on these early results, and we have extended this work since 1996 to a CMR.

In 1997 Felder et al. published a polysiloxane-bound hydroxydiphenylprolinol by describing the synthesis of the enantiomerically pure hydroxydiphenylprolinol and the coupling reaction between this prolinol and the polymer.[9−10] The polymer-bound oxazaborolidine was applied in the reduction of various prochiral ketones by borane and resulted in yields and enantiomeric excesses comparable to results obtained by the use of nonpolymer-bound oxazaborolidines. The continuous reaction was run with optimal conversion and ee for 60 h and obtained total turnover numbers (ttn) up to 560, compared to a ttn between 5 and 20 for monomeric oxazaborolidines.

(7) (a) Bayer, E.; Schurig, V. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 493. (b) Bayer, E.; Schurig, V. *CHEMTECH* **1996**, 212.
(8) Kragl, U.; Dreisbach, C. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 642−644.
(9) (a) Felder, M.; Giffels, G.; Wandrey, C. *Tetrahedron: Asymmetry* **1997**, 1975. (b) German Patent Application DE P: 196 47 982.8, 1996.
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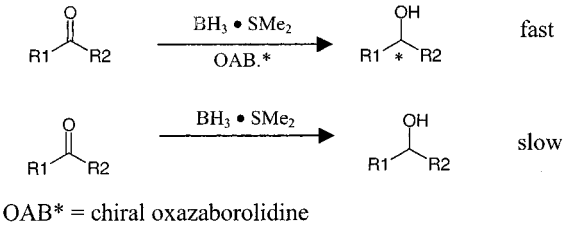


Figure 3. **Catalysed and uncatalyzed reduction of prochiral ketones by borane.**

In addition to efforts connecting homogeneous catalysts to soluble polymers, there are a few reports attaching them to dendrimers.[11−13]

4. Choice of the Reaction

The key success factor of this concept is the choice of an appropriate reaction. This reaction has to meet a few conditions such as (i) a short reaction time—resulting in an high space-time yield (kg/(L·d)), (ii) a stable catalyst system—allowing the reaction to run over a long time and, most importantly, (iii) a highly enantioselective catalyst and reaction.

A suitable reaction for the CMR meeting these demands is the reduction of prochiral ketones by borane in the presence of a chiral oxazaborolidine catalyst (Figure 3).[14] Additionally, no transition metal is involved in the catalysis; this is a clear advantage for pharmaceutical intermediates with stringent requirement for residual heavy metal content.

To run a CMR under optimized conditions, knowledge about the kinetics of the reaction is essential, especially if side reactions are to be suppressed.

The oxazaborolidine-catalysed reaction is a very fast reaction and is frequently complete in less than 1 h. Depending on the substrate, between 1−40 mol % of catalyst is required, and the tof is in a range of 45 h^{-1}. The noncatalyzed side reaction between ketone and borane resulting in a racemic product is much slower and follows different kinetics; first-order kinetics for the noncatalysed reaction was observed at constant borane concentration. For the catalyzed reaction, a Michaelis−Menten-type kinetic was found. According to these results, high enantiomeric excess can be obtained at low reactant concentration,[10b] while the noncatalyzed reaction can be suppressed.

A CMR is ideally suited for such a kinetic between catalyst and uncatalysed reaction, since high local catalyst concentration in the reactor is possible using this in situ catalyst recycle concept, and the catalysed reaction can be heavily favoured over the uncatalysed one.

5. Research Scope

For the successful operation of a chemical membrane reactor an interdisciplinary research effort in the fields of polymer development, auxiliary development, and engineering has to be mustered and requires successful operation of a CMR (Figure 4).

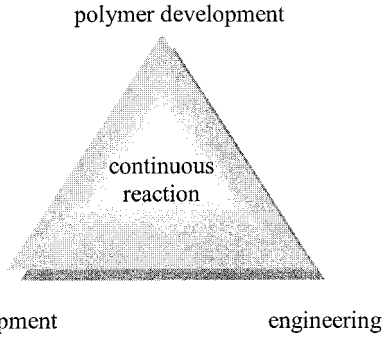
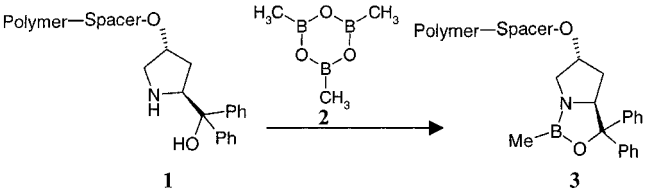


Figure 4. **Important research areas.**



Polymer: methyl-hydrosiloxane-dimethylsiloxane copolymer:

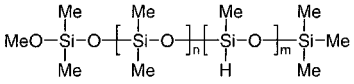


Figure 5. **Oxazaborolidine bound to a polysiloxane.**

6. Auxiliary Development

Intensive auxiliary research is very important for preparing an optimal catalyst. The catalytic performance in terms of selectivity, enantioselectivity, and activity should be sufficient to obtain a good quality product without having to take recourse to multiple and expensive recrystallizations or distillations. Many oxazaborolidine catalysts, especially the one based on the Corey-diphenylprolinol, fulfill this demand.[14−15]

For binding to a polymer the Corey oxazaborolidine has to be modified. Therefore, a functional group should be chosen which is located away from the active site of the auxiliary. Enantiomerically pure hydroxyproline is expected to be an excellent precursor for such an oxazaborolidine.

We decided to start our research from the molecular weight-enlarged catalyst first described by Kragl, where the oxazaborolidine is attached to a polysiloxane.[10] As Kragl used a *B*-H containing oxazaborolidine, the system suffers from moisture sensitivity and we consequently decided to prepare the more stable *B*-Me variant by refluxing the amino alcohol **1** with trimethylboroxine **2** (Figure 5).

A more versatile approach is the copolymerisation of an appropriate amino alcohol-derivatized styrene with unsubstituted styrene (Figure 6). The whole reaction sequence starting from hydroxyprolineester **4** leads to oxazaborolidine−

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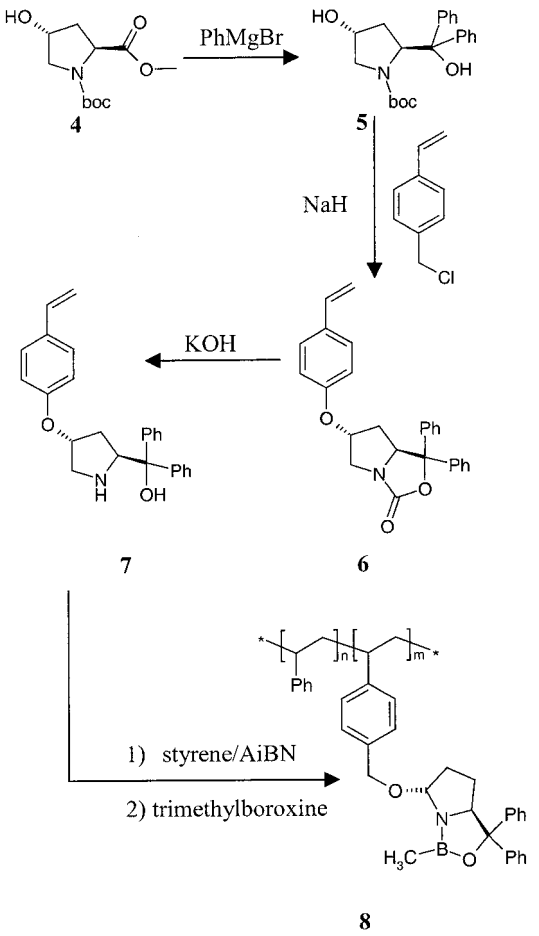

Figure 6. **Oxazaborolidine bound to a polystyrene.**

polystyrene **8** in high yields. By variation of the ratio of styrene and hydroxyprolinol−styrene **7** in the radical copolymerisation step, polymers with different degrees of catalyst loading can be prepared.

7. Polymer Development

The retainability of polymers by membranes depends on the dimensions of the polymer, which correlates with molecular weight and three-dimensional structure for a given polymer. Low molecular weight facilitates the passage of the polymer through the membrane; also, linear polymers pass faster then branched polymers. On the other hand, raising the molecular weight increases the viscosity of a polymer solution. This demonstrates that a narrow molecular weight distribution is crucial for the system.

Three main structures are possible for homogeneously soluble polymers (Figure 7). We decided to focus our work on linear polymers, because they demand fewer synthetic efforts compared to those for starshaped polymers and dendrimers.

For our purpose polystyrene is a useful polymer; it can be prepared easily by radical polymerisation, and the degree of functionality can be adjusted over a wide range by changing the monomer ratio. Another polymer we selected was the methylhydrosiloxane−dimethylsiloxane copolymer. Hydrosilylation allows convenient attachment of an olefin-containing chiral auxiliary to the Si−H groups of the polymer.

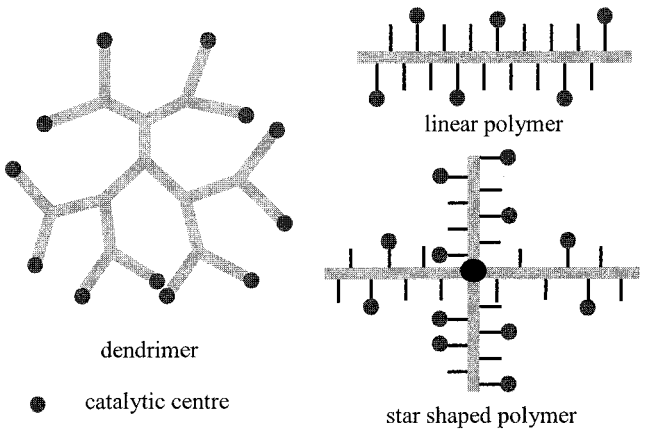

Figure 7. **Possible architecture for polymer-bound homogeneous catalyst.**

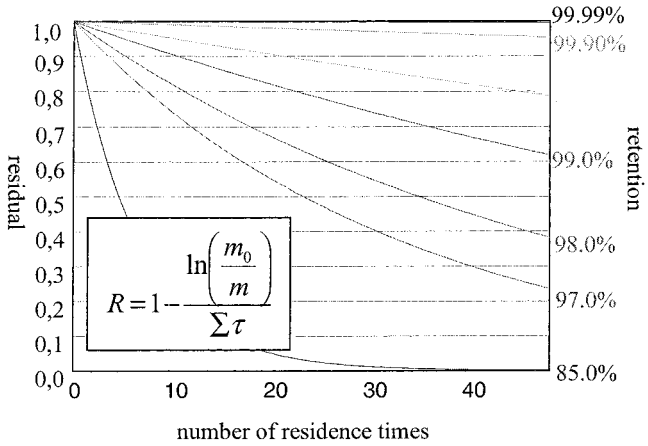

Figure 8. **Residue after 50 residence times, depending on the retention.**

The importance of the retention of a polymer is shown in Figure 8. It indicates that a retention of >99.9% is needed; otherwise the molecular weight-enlarged catalyst will be washed out of the reactor too rapidly. For example, even a retention of 85% for a certain polymer causes the remaining concentration in the reactor to fall below the detection level after 35 residence times. Therefore, high retention of the polymer-bound catalyst is a prerequisite for the successful operation of a CMR.

8. Engineering

To operate a chemical membrane reactor some technical challenges have to be met. A major issue is the solvent stability of membranes. There are basically two types of membranes, inorganic (ceramic) membranes and organic (polymer) membranes. The membranes utilized for enzymatic reactions (polymer membranes) are not sufficiently stable in organic solvents over long times. Apart from solvent stability, the cutoff is another important factor. Better retention of molecular weight-enlarged catalyst at smaller cutoffs have to be balanced against flux by maintaining the pressure at the membrane under these conditions. Fortunately, a wide range of useful membranes are commercially available, so that excellent solutions of this problem are at hand.[16]

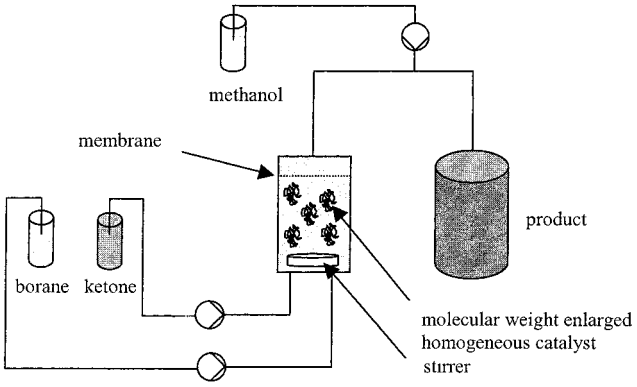

Figure 9. **Setup for continuous reaction.**

In case of borane reduction of ketones, borane and ketone have to be pumped into a stirred reactor, leading to a homogeneous solution with the molecular weight-enlarged soluble catalyst (Figure 9). Under fully optimized reaction conditions, no unreacted ketone will leave the reactor. In the initial optimization it is nevertheless advisable to quench unreacted borane, leaving the reactor to avoid a decrease of enantiomeric excess resulting from uncatalyzed side-reactions between the unconverted prochiral ketone and borane outside the reactor.

9. Continuous Reaction

At this point we have addressed the issues of catalyst preparation and molecular weight enlargement by attaching the catalyst to a polymer as well as the engineering challenges. Our first successful demonstration of the principal used the polysiloxane-bound *B*-Me-oxazaborolidine. Using α-tetralone as a model substrate, we are able to achieve a continuous reaction which ran for 200 residence times at almost quantitative conversion and over 96% enantiomeric excess (Figure 10).[17] This result highlights the importance of catalyst stability; use of the *B*-Me group instead of the *B*-H group of Kragl's catalyst (in both cases, using the polysiloxane backbone) allowed us to improve the lifetime of the catalyst several times.[18]

While we are currently not able to distinguish between catalyst leaching and catalyst disintegration, the observed loss of selectivity is readily explained by assuming that catalyst leaching has reduced the amount of catalyst to below the minimum requirement after 200 residence times.[19]

Table 1: **Comparison between the continuous reactions and the batch experiments**

	polysiloxane-bound catalyst **3**	polystyrene-bound catalyst **9**	original Corey diphenylprolinol catalyst[14]
ttn	321	1374	10
$\Sigma\tau^a$	200	355	1
retention[b]	98.50%	99.94%	
average ee	96.8%	96.8%	>99%[c]

[a] Number of residence times with optimal results (yield/ee). [b] The retention was calculated from the polymer-bound catalyst, which was isolated from the reactor content when the reaction was stopped. [c] In our hands the ee was 97.2%.

According to the starting material concentrations at the point of 200 residence times, a space-time yield of 1.42 kg/(L·d) could be achieved.[17]

An even more impressive performance was possible using the system with polystyrene-bound oxazaborolidine. *It became possible to run the reactor for more than two weeks while maintaining essentially complete conversion (>99%) and high enantioselectivity (96%).* Therefore, a higher retention compared to the polysiloxane-bound oxazaborolidine was achieved (Figure 11). To our knowledge this is the longest run of a continuously operating chemzyme membrane reactor. During this period of time, 1374 turnovers were achieved.

Compared to batch-wise reactions with turnovers of up to 100, this example clearly helps to demonstrate the usefulness of the CMR concept for the preparation of complex products.

The results of the two continuous reactions and a comparison with the original Corey-catalyst are summarized in Table 1. From the results, we can assume that leaching of the catalyst in the first described experiment with catalyst **3** dominates over deactivation of the catalyst. In the second example, retention of catalyst **9** is significantly higher. Deactivation dominates over loss of catalyst by leaching, since an enantioselectivity drop occurs at a point of 70% catalyst residual. In the first experiment, the ee was not effected until the residual dropped down to 5%.

The reason conversion in the first experiment (Figure 10) is still high while ee drops after 200 residence times is the noncatalysed side reaction of borane with tetralone, resulting in racemic product. This side reaction is much slower compared to the catalysed reaction with catalyst **3**, but still fast enough to complete the reaction in a residence time. This is the explanation for the remaining high conversion after 200 residence times. The reason for the drop of conversion in the second experiment is still unclear. Possibly, deactivation products prevent the completion of the reaction per residence time.

The described examples of a successful implementation of the CMR emphasise the absolute necessity for an active, selective, but nevertheless stable, ligand, coupled with high retention of the molecular weight-enlarged catalyst and an

(16) A very good summary about membranes (properties, manufactures) is given in the *European Membrane Guide*: Mulder, M.; Tholen, J.; Maaskat, W. *European Membrane Guide*; Alinea, 1997.

(17) Figure 10 shows the conversion and enantiomeric excess for the reduction of tetralone with borane in the presence of a polysiloxane bound oxazaborolidine in detail. Up to this point of 200 residence times 321 turnovers were obtained. The turnover number was calculated with the simplifying assumption that no catalyst leaching occurred. The reaction was started with 100 mol % of catalyst. After 143 residence times the tetralone concentration was doubled. The tetralone concentration was increased again after 168 residence times to an amount of 25 mol % catalyst, again excluding catalyst loss by leaching or by decomposition of the catalyst.

(18) (a) Wöltinger, J.; Bommarius, A. S.; Drauz, K.; Wandrey, C. DECHEMA-Arbeitsausschüsse "Technische Reaktionen", "Katalyse", und GVC-Fachausschuss "Technische Reaktionsführung"; January 19−20, 1999, Frankfurt. (b) Drauz, K. *ChiraSource U.S.A.*; Philadelphia, PA, November 15−17,1999.

(19) It can be calculated that an amount of 1.2 mol % of catalyst is necessary to run the reduction of tetralone with borane in an optimal way in respect to conversion and enantiomeric excess.

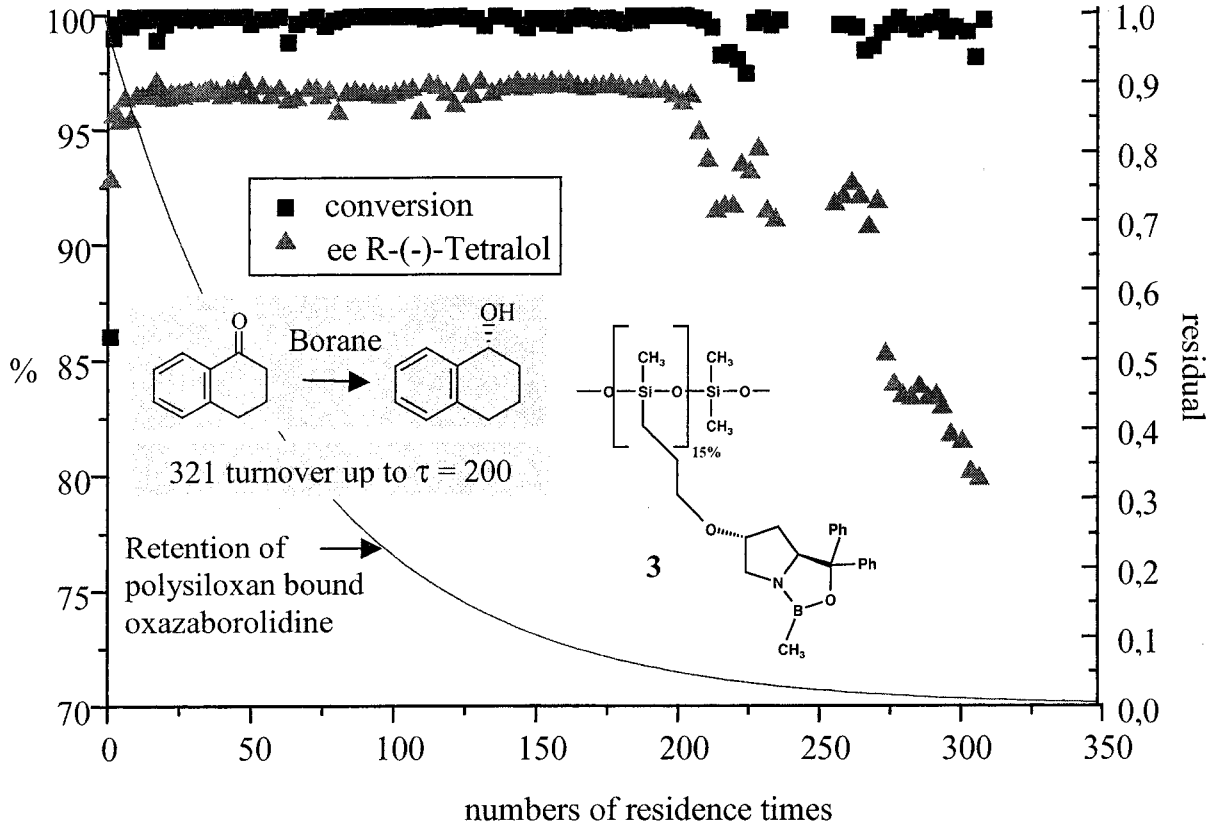

Figure 10. **Continuous reduction of tetralone, applying polysiloxane-bound oxazaborolidine as catalyst.**

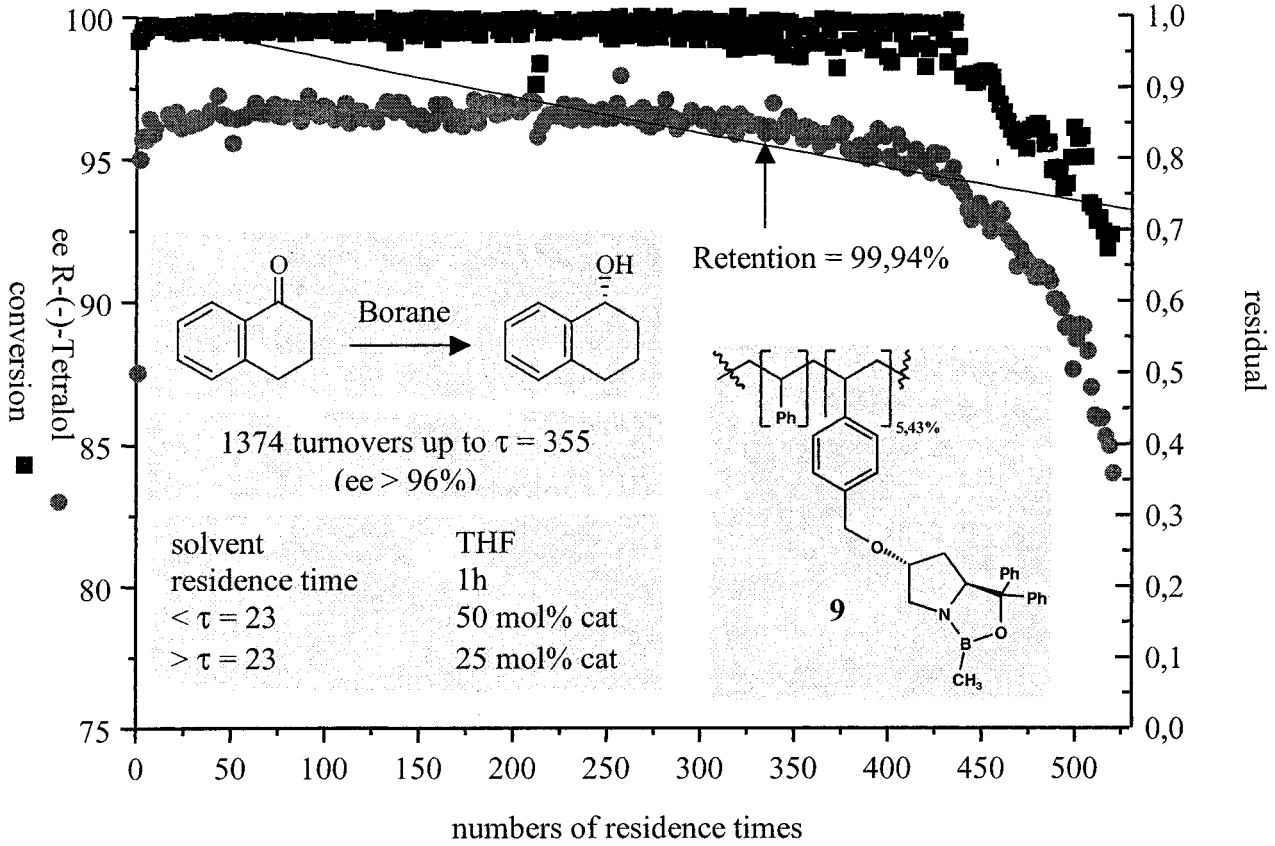

Figure 11. **Continuous reduction of tetralone, applying polystyrene-bound oxazaborolidine as catalyst.**

experimental setup which allows running the reaction under study conditions.

10. Summary

In summary, we have shown that the attachment of a homogeneous catalyst to a soluble polymer and its retention in a membrane reactor allow one to recycle the catalyst in situ, thus solving the catalyst recovery problem while at the same time maintaining high catalyst activity and selectivity. We were able to achieve almost 1400 turnovers in the boranreduction of α-tetralone in the CMR, compared to a batch processes of ∼100 turnovers. The total run of 2 weeks with excellent results (>99% conversion and >96% ee) is, to our knowledge, the best reported and should highlight the potential of this concept. An optimum space-time yield of 1.42 kg/(L·d) was achieved, thus exceeding values of most homogeneously catalysed reactions with other reactor configurations are as well as values for many reactions in an EMR.

11. Experimental Section

Commercially available solvents and reagents were used without further purification. THF was distilled over sodium and benzophenone. Capillary gas chromatography (GC) was performed on a *cyclodex β-I/P*, 50 *3.21 mm i.d. column. NMR spectra were performed on a Bruker 300 MHz.

Prolinolpolysiloxane (1). Prolinolsiloxane **1** was synthesised as described by Felder et al.[9a]

Methyloxazaborolidine−Polysiloxane (3). Prolinolsiloxane **1** (0.85 g, 1 mmol) was dissolved in dry toluene (10 mL) purchased from Aldrich. Trimethylboroxine (100 μL, 0,72 mmol) was added by a syringe. The solution was stirred at room temperature under argon for 1 h. For a further 14 h, the solution was refluxed in a Dean−Stark-condenser equipped with 4 Å molecular sieves. Afterwards, the solvent was evaporated under reduced pressure, and the crude product was dried in high vacuum before use in a continuous reaction.

(2*S*,4*R*)-4-Hydroxy-2-(1-hydroxy-1,1-diphenyl-methyl)-pyrroline-1-carboxylic Acid *tert*-Butylester (5). *trans*-N-Boc-4-hydroxy-L-prolin-methylester **4** (5.01 g, 20.46 mmol) was dissolved in THF (150 mL) and cooled to −78 °C. PhMgBr solution (65.47 mL, 209.5 mmol, 3 M in THF) was added over 3 h. The mixture was allowed to warm to room temperature. The reaction was monitored by TLC. After complete conversion, saturated $NaHCO_3$ (200 mL) and ethyl acetate (200 mL) were added. After phase separation, the aqueous layer was extracted with ethyl acetate three times. The combined organic solutions were dried over Na_2SO_4, and the solvent was evaporated. Further purification occurred by column chromatography (gradient light petroleum/ethyl acetate 3:1 to 1:1) and yielded in 5.89 g (78%) of product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49−7.14 (10 H, m), 5.17 (1 H, dd, J = 7.2, 9.4 Hz), 3.85 (1 H, brs), 3.46 (1 H, d, J = 12.2 Hz), 2.21−1.98 (2 H, m), 1.37 (9 H); IR (film) 3400, 3000, 2950, 1660, 1420, 1165 cm^{-1}.

(6*R*-7a*S*)-1,1-Diphenyl-6-(4-vinylbenzyloxy)-tetrahydro-pyrrolo[1,2-c]oxazol-3-one (6). 5 (1.87 g, 5.08 mmol) was dissolved in DMF (20 mL) at room temperature. Sodiumhydride (280 mg, 11.67 mmol) was added, and the reaction mixture was stirred under nitrogen for 0.5 h. Chloromethylstyrene (859 μL; 6.09 mmol) was added, and the solution was stirred for further 30 min. The solvent was evaporated under vacuum at 50 °C, and the crude product was dissolved in ethyl acetate and extracted with saturated $NaHCO_3$ solution. The aqueous phase was extracted with ethyl acetate three times. The combined organic solutions were dried over Na_2SO_4, and the solvent was evaporated. Further purification occurred by column chromatography (light petroleum: ethyl acetate = 3:1) and 1.405 g (67%) of the title compound was obtained; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60−6.80 (14 H, m), 6.65 (1 H, dd, J = 11.7, 17.3 Hz), 5.69 (1 H, dd, J = 1.6, 17.5 Hz), 5.20 (1 H, dd, J = 5.0, 11.0 Hz), 4.80 (1 H, dd, J = 5.0, 12.5 Hz), 4.10 (1 H, dd, J = 5.0, 10,0 Hz), 4.02−3.92 (1 H, m), 3.26 (1 H, dd, J = 2.5, 12.5 Hz), 1.90−1.74 (2H, m); IR (film) 3080, 2950, 1760, 1490, 1450, 1380, 1360, 1250, 1230, 1090, 760, 700 cm^{-1}; MS (M + H$^+$): *m*/*z* 412.1.

1,1-Diphenyl-1-[(2*S*,4*R*)-4-(4-vinyl-benzyloxy)-pyrrolidin-2-yl]-methanol (7). 6 (1.405 g 3.4 mmol) was dissolved in ethanol (50 mL). Potassium hydroxide (2 g, 35.7 mmol) was added, and the solution was refluxed for 3.75 h. The solution was allowed to cool to room temperature, and the solvent was evaporated. The solid was dissolved in ethyl acetate and extracted with saturated $NaHCO_3$ solution. The aqueous layer was extracted with ethyl acetate three times. The combined organic solutions were dried over Na_2SO_4, and the solvent was evaporated. The crude product was not further purified and used completely for the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56−7.00 (14 H, m), 6.64 (1 H, dd, J = 11.8, 18.6 Hz), 5.67 (1 H, dd, J = 4.3, 18.6 Hz), 5.17 (1 H, dd, J = 6.2, 11.8 Hz), 4.51 (1 H, dd, J = 6.2, 9.3 Hz), 4.36 (2 H, s), 3.98 (1 H, s), 3.06 (2 H, s), 1.79−1.54 (2 H, m), 1.18 (1 H, s); ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 144.9, 138.6, 136.7, 136.5, 128.7, 128.3, 128.0, 127.8, 127.1, 126.6, 126.4, 126.3, 126.0, 125.5, 125.5, 125.4, 114.1, 113.9, 79.5, 70.7, 70.5, 63.4, 52.5, 32.9; IR (film) 3400, 3050, 2900, 2880, 1450, 1095, 990, 800, 750, 700 cm^{-1}; MS (M + H$^+$): *m*/*z* 386.2.

1-[(2*S*,4*R*)-2-(1-Hydroxy-1,1-diphenyl-methyl)-4-(4-vinyl-benzyloxy)-pyrrolidin-1-yl]-2,2-dimethyl-propan-1-one-Styrol Copolymer (8). In cyclohexane (6.4 mL) the crude product **7** (3.4 mmol), styrene (5.9 mL, 51.3 mmol), and AiBN (102.2 mg 0.72 mmol) were dissolved. The solution was degassed by evaporation under stirring and aeration with argon for three times. Afterwards, the mixture was heated to 50 °C for 44 h. The reaction mixture was dropped into methanol, and the polymer was filtered off. Polymer (2.46 g) was obtained. (5.4% functionality); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60−6.10 (117 H, m), 4.60−3.60 (5 H, m), 3.10−2.83 (2 H, brd, J = 19.7), 2.30−0.70 (71 H, m M_N = 22640 g/mol, polydispersity = 2.183 (GPC/calibrated by polystyrene standards).

Methyloxazaborolidine−Polystyrene (9). Prolinolpolystyrene **8** (0.377 g, 0.17 mmol) was dissolved in dry toluene (10 mL) purchased from Aldrich. Trimethylboroxine (36 μL,

0,26 mmol) was added by a syringe. The solution was stirred at room temperature under argon for 1 h. For a further 14 h, the solution was refluxed in a Dean−Stark-condenser, equipped with 4 Å molecular sieves. Afterwards, the solution was used in a continuous reaction without further evaporation of the solvent or purification.

Continuous Reduction Using Methyloxazaborolidine−Polysiloxane (3). The membrane (MPF-50 of Koch Membrane Systems, Düsseldorf, Germany) was placed in a 10 mL polypropylene membrane reactor, and THF was transported through the reactor (10 mL/h). The crude product of methyloxazaborolidine−polysiloxane **3** (1 mmol) was dissolved in 5 mL of THF and pumped into the membrane reactor using Pharmacia P-500 pumps. Afterwards, borane−dimethyl sulfide/THF solution (0.126 mol/L) was pumped through the membrane reactor for 5 h (10 mL/h). The flow was reduced to 8 mL/h, and the tetralone solution (0.5 mol/L in THF) was transferred using another Pharmacia P-500 pump in the reactor (2 mL/h). The borane excess was destroyed by methanol (5 mL/h), and after that the reaction mixture was collected in a fraction collector (Pharmacia Frac 100). After 143 h (equal to residence times) the concentrations were doubled (borane: 0.252 mol/L and tetralone 1 mol/L). After 168 h (equal to 168 residence times) the concentrations of the starting materials were doubled again (borane 0.5 mol/L and tetralone 2 mol/L).

During the whole process the starting materials were kept under argon. It is vital for the process to work completely under moisture exclusion.

Continuous Reduction using Methyloxazaborolidine−Polystyrene (9). For this process the same equipment and process conditions (e.g., residence time) was used as described above for the continuous reduction using methyloxazaborolidine−polysiloxane **3**. The following concentrations of the starting materials were used:

methyloxazaborolidine−polystyrene (0.17 mmol); borane−dimethyl sulfide solution in THF ($\langle\Sigma\tau = 23$: 39.75 mmol/L$\rangle\Sigma\tau = 23$: 79.2 mmol/L), tetralone solution in THF ($\langle\Sigma\tau = 23$: 159 mmol/L$\rangle\Sigma\tau = 23$: 318 mmol/L).

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