Juliá–Colonna Asymmetric Epoxidation in a Continuously Operated Chemzyme Membrane Reactor

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Abstract: Two novel soluble polymer-bound oligo-L-leucines **2** and **5**, which can be retained by a membrane reactor system, have been prepared and used as catalysts for the continuously operated asymmetric epoxidation of chalcone. The optimized batch reaction conditions yield epoxychalcone in high enantioselectivities (up to 94%) and conversions (over 99%) after 15 minutes.

Key words: enantioselective epoxidation, homogeneous catalysis, *trans*-chalcone epoxides, continuously-operated CMR, oligo(L-leucine)s

Epoxides are widely used compounds in organic synthesis.[1] For this reason several approaches to effect enantioselective epoxidation have been made.[2] Among the well-developed methods, the Juliá–Colonna epoxidation, which utilizes chiral polyamino acids (in particular poly-L-leucine) as heterogeneous catalysts, has emerged as the first reliable method for the asymmetric epoxidation of electron-deficient olefins, exhibiting exceptionally high chiral induction for chalcone.[3]

Degussa and their partners from the University of Liverpool have worked intensively on the improvement of heterogeneous Juliá–Colonna oxidation. A noteworthy modification includes the introduction of percarbonate in dimethoxyethane as a cheap oxidant/solvent system for the use in some polyamino acid-catalysed epoxidations.[4]

The poly-L-leucine catalyst remained insoluble under all the reaction conditions applied. The first homogeneous version of the Juliá–Colonna epoxidation of *trans*-chalcone was reported recently.[5] However, the conversion observed was only 39% after 1 hour and 80% after 24 hours with an ee of 95–98%.

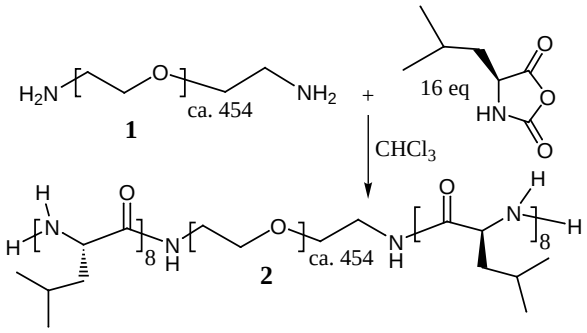
Since the chiral information has to be transferred from the catalyst to the olefinic substrate, homogeneous asymmetric catalysis is a more attractive method for the synthesis of chiral epoxides. However, up to now, no process has made the step from an academically promising method to an application on larger scale.

The interest of Degussa in developing methods for asymmetric synthesis in a chemzyme membrane reactor[6] promoted further investigation of the homogeneous enantioselective epoxidation of α,β-unsaturated ketones.

We reasoned that the preparation of polymer enlarged oligo(L-leucine)s which were soluble in common organic solvents and large enough to be retained in a membrane reactor could allow us to develop a continuously operated asymmetric epoxidation of *trans*-chalcone.

There are two major approaches to synthesize homogeneously soluble polymer-enlarged catalysts, that is using either linear polymers or dendrimers as carriers.

We have focused our work on linear polymers, because they demand less synthetic effort. Thus, we prepared two types of soluble polymer enlarged oligo(L-leucine)s **2** and **5** (Scheme 1, Scheme 2). The approach to catalyst **2** involved the co-polycondensation of 1 equivalent of commercially available *O,O*-bis(2-aminoethyl)-polyethyleneglycol 20000 **1** with 16 equivalents of L-leucine-*N*-carboxyanhydride in $CHCl_3$.[7]



Scheme 1 Synthesis of homogeneously soluble oligo(L-leucine) **2**.

We found that the resulting polyethyleneglycol-supported oligo(L-leucine) **2** can act as an efficient homogeneous chiral catalyst in the epoxidation of *trans*-chalcone **6** employing the urea hydrogen peroxide addition compound as the oxidant. The optically active epoxy ketone **7** (Table 1) was obtained in high enantioselectivity of 94% at a conversion over 99% after 15 minutes.

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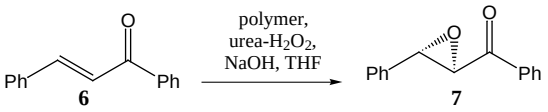
Table 1 Asymmetric Epoxidation of Chalcone **6**[8] with Soluble Polymers **2** and **5**

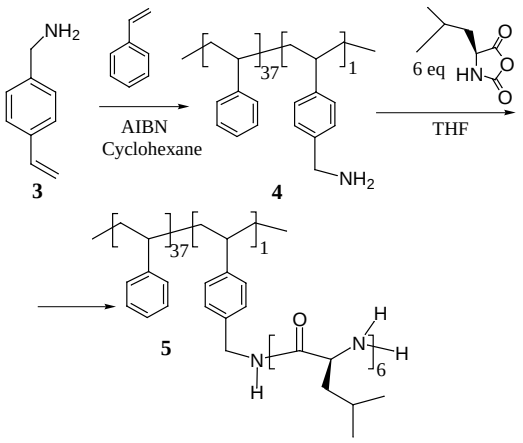


Polymer	Mol% of active centers in the polymer	t (min)	Conversion[a] (%)	ee (%)[b]
no	–	60	1.8	–
2	32	15	> 99	94
2	16	30	> 99	89
5	25	60	83	95
5	100	60	92	97

[a] Determined by HPLC (RP-18).
[b] Determined by HPLC chiralcel-OD column.

Epoxidation of chalcone **6** was carried out at room temperature employing a saturated solution of urea–H_2O_2 in THF as the oxidizing agent.[8] It was confirmed that epoxidation does not occur in the absence of catalyst, thus dismissing the possibility of background reactions (Table 1).

Another polymer selected for reacting with L-Leu-NCA was the first homogeneous version of styrene/aminomethyl styrene-copolymer **4**, which was synthesized by radical co-polymerisation of styrene with *p*-vinylbenzylamine **3**[9] (Scheme 2). Soluble (in THF, CH_2Cl_2) chiral copolymer **5** was prepared by the reaction of 1 equivalent of aminomethyl polystyrene **4** with 6 equivalents of L-Leu-NCA in THF.[10]



Scheme 2 Synthesis of homogeneously soluble oligo(L-leucine) **5**.

5 Was used for promoting the homogeneous asymmetric Juliá–Colonna epoxidation. We obtained epoxide **7** with an ee of up to 97% (92% conversion after 60 min) (Table 1).

The remarkable enantiomeric excesses and conversions we observed in the batch reactions showed the potential for the new catalysts **2** and **5** to be used as chiral inducers in a continuously operated chemzyme membrane reactor. The experimental set-up is depicted in Figure 1; the membrane reactor itself is a magnetically stirred filtration cell with a volume of 10 millilitres.

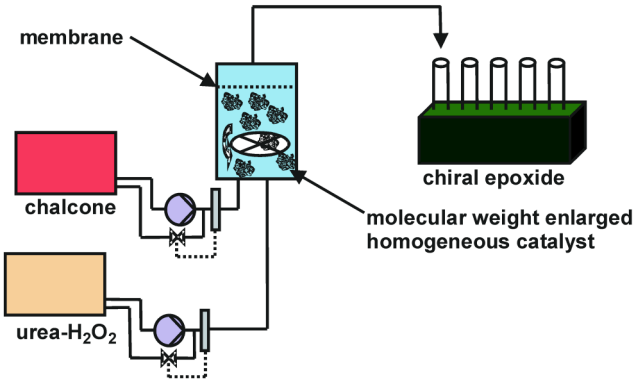


Figure 1 Setup for continuous epoxidation reaction.

Catalyst retention was achieved by means of a nanofiltration membrane. The epoxide and unconverted chalcone pass through the membrane whereas the polymer-enlarged catalyst is retained in the reactor.

Thus the advantages of catalyst retention can be united with the effectiveness of homogeneous catalysis when a soluble polymer is used instead of heterogeneous support.

In this concept, high reaction rate and selectivity are combined with simple catalyst recovery. The residence times of product and catalyst are decoupled, reducing catalyst costs.[6]

Thus, both catalysts were tested for a number of residence times in a chemzyme membrane reactor.[11] Figure 2 shows the conversion-time-curves for these two experiments. In the first experiment with catalyst **2**, conversions of up to 86% and ee of up to 90–95% were observed until a residence time of 25 was reached (Figure 2). The addition of freshly prepared urea–H_2O_2 solution after residence time 45 leads to a significant increase in conversion as well as enantiomeric excess. The reason for the drop of enantioselectivity of catalyst **2** under the reaction conditions is still under investigation.

While the conversion of chalcone in the second experiment with catalyst **5** (Figure 2) dropped significantly to 47% after 28 residence times, little loss of selectivity was observed (still over 90% ee). The reactor was operated until the concentration of active oligo(L-leucine) **2** or **5** dropped below a critical value (at residence time 50). Since the retention of polymer **5** is comparable (and even higher) with that of polymer **2** (Table 2), we can assume that deactivation of catalyst **5** dominates over its leaching through the membrane.

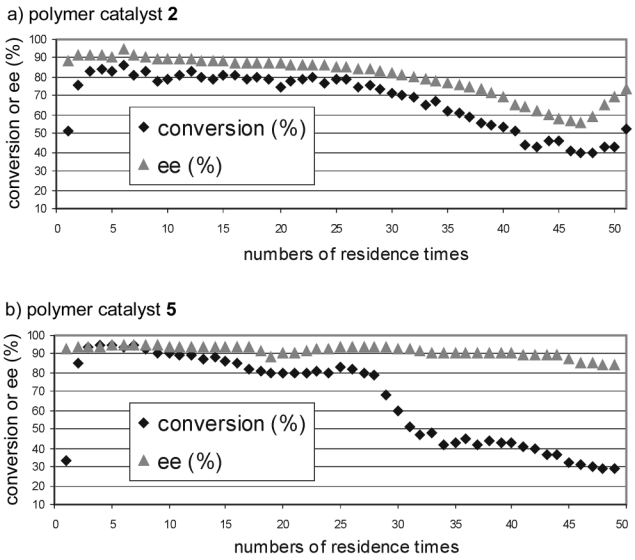


Figure 2 Conversion plots of the continuous reactions using catalysts **2** and **5**.

Table 2 Summary of the Two Continuous Reactions

	PEG-bound Catalyst **2**	Aminomethyl Polystyrene-Bound Catalyst **5**
Retention of catalyst[a]	98.87%	98.99%
Average conversion	69.3%	80.0%
Average ee	80.6 %	91.5%

[a] Retention was calculated by isolation of the polymer from the reactor after the reaction was stopped.

It is interesting to note that the epoxidation reaction in the membrane reactor, catalyzed by polymer **5**, reduces the time required for 92–94% conversion of chalcone from 60 minutes to 30 minutes (Table 1). This reaction showed ee of up to 90–95% throughout the 50 residence times.

The polymer catalysts **2** and **5** that have been employed in the continuous reactions were recovered and reused for batch asymmetric epoxidation reactions. No decrease in ee (up to 97%) and conversion (around 85% after 60 min) was observed.

In conclusion, we have prepared two novel polymer-supported oligo(L-leucine)s that are soluble in organic solvents and we have effected the first enantioselective synthesis of epoxy chalcone in a continuously-operated chemzyme membrane reactor. It is shown that the catalyst retention in the reactor solves catalyst recovery problems and provides a simple reaction procedure associated with high catalyst activity and selectivity.

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Dedicated to Professor Dr. Dr. h.c. L. F. Tietze on the occasion of his 60th birthday.

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(7) To a stirred solution of *O*,*O*-bis(2-aminoethyl)-polyethylenglycol 20000 **1** (3.05 g, 0.152 mmol, 1 equiv) in $CHCl_3$ (60 mL) was added a solution of L-leucine-*N*-carboxyanhydride (384 mg, 2.44 mmol, 16 equiv) in $CHCl_3$ (27 mL). The reaction mixture was stirred under nitrogen at r.t. for 20 h. After solvent evaporation under vacuum, addition of diethyl ether caused precipitation of a white solid (3.3 g).

(8) **Asymmetric epoxidation of *trans*-chalcone (batch reaction)**. The following procedure is representative of these reactions. To a stirred solution of polymer **2** (3.89×10^{-3} mmol; 32 mol% of active centers) in THF (0.5 mL) was added NaOH (0.065 mmol) and chalcone (0.024 mmol). Stirring at r.t. was continued for 20 min before the addition, (over 15 min) of a sat. solution of urea–H_2O_2 (0.213 mmol, 98% pure from Aldrich) in THF (1.5 mL; prepared using an ultrasound bath over 45 min followed by filtration).

(9) (a) 4-vinylbenzylamine (0.80 g, 6.08 mmol; prepared according to the literature, see ref.[9b]), styrene (12.7 g, 13.9 mL; 122 mmol) and AIBN (119 mg, 0.72 mmol) were dissolved in cyclohexane (15 mL). The solution was degassed three times by evaporation (with stirring) and repressurizing with N_2, followed by heating at 50 °C for 90 h. The reaction mixture was cooled to r.t., dropped into methanol (600 mL), and the polymer **4** (11 g) was filtered off. (b) Zhou, W.-J.; Kurth, M. J.; Hsieh, Y.-L.; Krochta, J. M. *Macromolecules* **1999**, *32*, 5507.

(10) To a solution of styrene/aminomethyl styrene copolymer **4** (3.51 g, 0.88 mmol, 1 equiv) in THF (115 mL) was added a solution of L-leucine-*N*-carboxyanhydride (829 mg, 5.28 mmol, 6 equiv) in THF (60 mL). The reaction mixture was stirred under nitrogen at r.t. for 20 h, then concentrated to ca. 20 mL and dropped into methanol (400 mL); 3.5 g of polymer was filtered off.

(11) (a) **Continuous epoxidation of *trans*-chalcone using catalyst 2.** The nanofiltration membrane (MPF-50 of Koch Membrane Systems, Düsseldorf, Germany. The cutoff is defined by a substance with a certain molecular weight, leading to 99.8% retention) was placed in a 10 mL

chemzyme membrane reactor (CMR), and THF was transported through the reactor (20 mL/h). The mixture of polymer catalyst **2** (0.089 mmol of active centers), dissolved in of THF (6 mL), and NaOH (0.775 mmol) was stirred at r.t. for 20 min. The solution was filtered, and the filtrate was pumped into the membrane reactor using a Pharmacia P-500 pump. Afterwards, a sat. solution of urea–H_2O_2 (1.4×10^{-4} mol/L) was pumped through the membrane reactor with a flow rate of 7 mL/h. At the same time a solution of chalcone (48 mmol/L in THF) (which was previously stirred with NaOH (0.052 mol) at r.t. for 30 min and then filtered) was pumped in the reactor (13 mL/h) using another Pharmacia P-500 pump. The product and unconverted chalcone were collected in a fraction collector (Pharmacia Frac 100) with a residence time of 30 min. (b) **Continuous epoxidation of *trans*-chalcone using catalyst 5.** The same equipment and conditions were used as described above. The following concentration of polymer **5** was used: 0.190 mmol of active centers.