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The potential of membrane reactors in the asymmetric opening of *meso*-anhydrides

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Abstract—A polymer attached cinchona-alkaloid was investigated in the asymmetric opening of *meso*-anhydrides. Variation of reaction parameters reduced the reaction time to 1 hour, which is very important for a continuous reaction. It turned out that due to product inhibition of the catalyst the conversion and enantiomeric excess decreased rapidly during a continuous reaction. In a repetitive batch system, it was possible to run the reaction over 18 cycles with a conversion of >99%. The ee value decreased to 60% over the first 7 runs and was stable at this value for the last 11 runs.

meso-Anhydrides are versatile compounds for natural product synthesis or for the preparation of active pharmaceutical ingredients because of the potential for desymmetrization.[1] Both resulting functional groups (ester and acid) can be transformed selectively, e.g. to β-amino acids.[2] A very encouraging approach to chiral mono-esters is the ring opening catalyzed by chiral amines. Cinchona alkaloids are the preferred catalysts employed.[3] This reaction suffers from very low reaction temperatures, long reaction times and high catalyst consumption in order to achieve high enantioselectivities.[4] For an industrial application short reaction times are essential to obtain a high space-time-yield and low catalyst consumption is required for economical reasons.

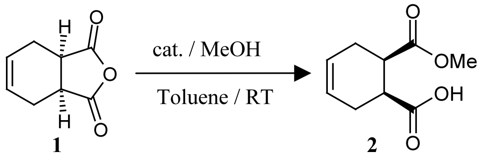
To run the reaction in a short reaction time and at ambient temperature a high catalyst concentration would be necessary. Therefore the ease and efficiency of catalyst recycling is vital for the whole process.

Membrane reactors are the perfect set-up for reactions which require high catalyst concentrations.[5] Due to the in situ recycling of catalysts the catalyst consumption per kg product is decreased compared with a single batch.

Besides a high retention of the polymer attached catalyst, which has to be soluble in the reaction solvent in order to maintain the advantage of homogeneous catalysis, a short reaction time is the key for a efficient continuous process.

We chose *cis*-4-cyclohexene-1,2-dicarboxylic anhydride **1** as a model substrate (Scheme 1). The commercially available $(DHQD)_2$-AQN-ligand was employed as catalyst: the reaction time was reduced from 60 h to 15 min and the temperature could be raised from −20°C to room temperature by using 100 mol% of catalyst and 10 equiv. of methanol. Under these conditions an enantiomeric excess of 90% of **2** was obtained.

To synthesize a suitable polymer-attached catalyst we started with the hydroxy-AQN-ligand **4** which was synthesized according to a literature procedure.[6] In contrast to the polymer-attached AQN-ligand used in the Sharpless-dihydroxylation, the AQN-ligand **4** was attached to a linear polystyrene (Scheme 2). The polystyrene **3** was prepared by radical polymerization of styrene and *p*-chlorovinylstyrene in cyclohexane with AIBN as radical initiator. The main reason for the choice of this polymer is its good solubility in the



Scheme 1. *cis*-4-Cyclohexene-1,2-dicarboxylic anhydride **1** was employed as a model substrate for the asymmetric opening of *meso*-anhydrides.

Keywords: chemzyme-membrane-reactor; continuous reaction; repetitive batch; asymmetric opening of anhydrides.

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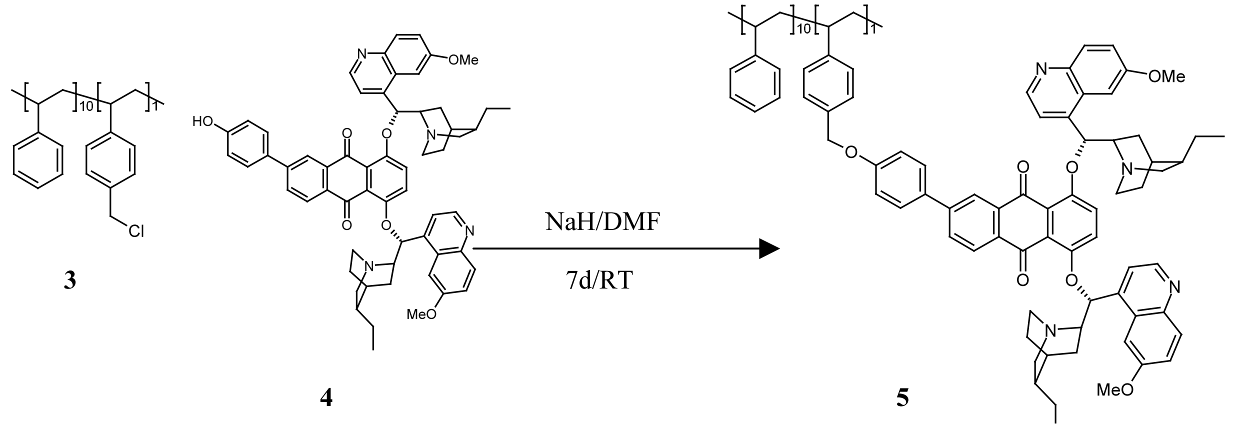


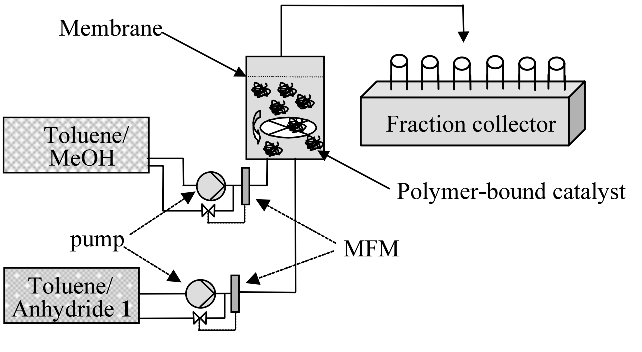
Scheme 2. Preparation of the polymer-bound catalyst.

required solvent (toluene) and the ease of modification of the chain length of the polymer in the radical polymerization.

Using the polymer-attached catalyst **5** full conversion was reached in 1 hour at room temperature. This is a longer reaction time compared with the original $(DHQD)_2$-AQN ligand, where the reaction was complete within 15 minutes under the same reaction conditions, however the selectivity could be maintained. For the continuous reaction we chose a reaction set-up, which we adapted from our previous work (Scheme 3).[5,7]

In Fig. 1 the conversion and ee values of the continuous reaction are illustrated. The intense decline of both ee value and conversion is not caused by leaching of the catalyst, even though the catalyst retention is poor at 95.4%. Batch experiments showed that the amount of catalyst remaining within the reactor after 20 runs is enough for high conversion within 1 hour. A further continuous experiment supported this result, because an increase of methanol from 10 to 20 equiv. raised the conversion from 60% to 90% after 20 residence times and a further methanol increase to 30 equiv. showed a conversion of 95%, which could be maintained for over 30 residence times. In both cases the ee was almost unaffected and remained at a level of 50%. Furthermore, the decline of the ee value cannot be explained by catalyst leaching, since the uncatalyzed reaction between anhydride **1** and 10 equiv. of methanol resulting in racemic product is slow (12% conversion after 24 hours). Batch experiments were conducted to investigate the decline in reaction rate. The opening of anhydride **1** was complete within 15 minutes in the presence of 1 equiv. of product while 4 hours were required in the presence of 8 equiv. of product. This indicates product inhibition could be one reason for the rapid decline of conversion in the continuous reaction.

If product inhibition is responsible for the decline of both ee and conversion, a continuous reaction is not favored because of the high product concentration inside the reactor. A repetitive batch reaction set-up is much more suitable since the complete reaction volume is changed after completion of the reaction and high values of conversion and ee should be achieved. The system used for the repetitive batch reaction is shown in Scheme 4.



Scheme 3. Reaction set-up for the continuous reaction. 30 min was selected as residence time. A 10 mL stainless steel reactor was chosen together with a flow of 5 mL per pump. The flow was controlled by mass flow meters (MFM). 0.25 mmol anhydride **1** in 5 mL toluene, 2.5 mM MeOH in 5 mL toluene and 1.0 mmol catalyst **3** were set as concentrations.

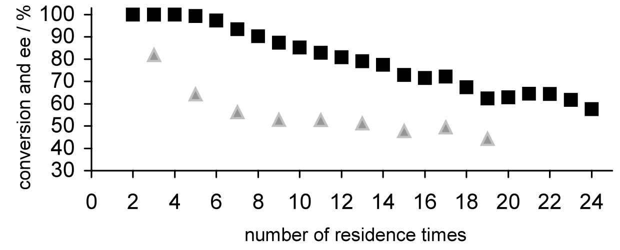
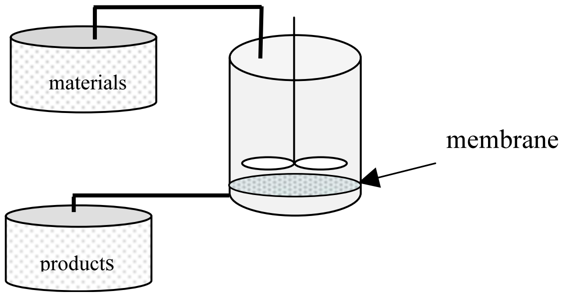


Figure 1. Conversion (■) and ee (▲) values of the continuous ring-opening of anhydride **1**.

In Fig. 2 the ee value and conversion trends for two repetitive batch cycles, each of 18 single runs, are given. The reactor was charged with the polymer-bound AQN-catalyst **5** and solvent, containing the low molecular weight compounds, methanol and anhydride **1**. After completion of the reaction, the catalyst **5** was separated from the low molecular weight compounds by pressing the liquid through the membrane. Catalyst



Scheme 4. Set-up for the repetitive batch reaction. The reaction was performed in 10 mL toluene. 0.25 mmol anhydride **4**, 2.5 mmol methanol and 0.25 mmol catalyst **3** were used in the reaction.

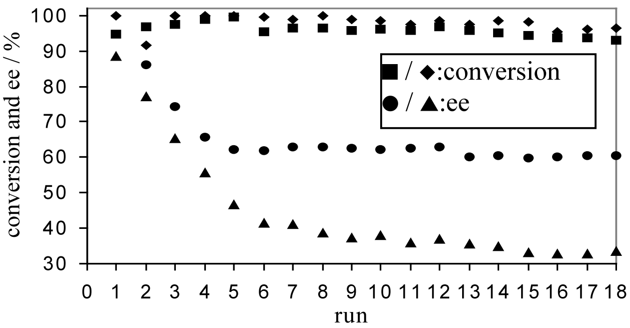


Figure 2. Conversions and ee values for two repetitive batch reactions have been illustrated. Repetitive batch 1 (■ and ▲) without washing procedure between two runs and repetitive batch 2 (◆ and ●) with washing procedure between two runs. Conversion and ee values have been determined by HPLC.

5 was retained by the membrane. For the next run the filtration cell was refilled with fresh anhydride, methanol and solvent. This procedure was repeated for 18 runs.

As shown in Fig. 2 the conversion remains at over 90% for 18 cycles. That is a significant improvement compared with the continuous experiment, but the ee values remained low (40% ee after six runs).

To improve the selectivity, the catalyst solution between two runs was washed twice with toluene containing 10 equiv. methanol based on the amount of anhydride at the start of the reaction, and twice with pure toluene. By employing this slightly different work-up procedure an improvement in the enantioselectivity to 60% was observed.

As shown in Fig. 2 a further improvement in conversion was obtained. However the increase in the enantioselectivity was more spectacular. The values of the enantioselectivity dropped from almost 90% to 60%, but stayed at this level from runs 5 to 18. NMR studies of the recovered and washed catalyst showed that 2 molecules of product were attached per AQN-ligand. This indicated that the acid attached to the catalyst is responsible for the decrease in selectivity. Enhancement of the washing procedure between two runs should result in a reconstitution of the original catalyst and high conversion and enantioselectivity for each run should be possible.

The principle of catalyst recovery by using a polymer attached homogeneous catalyst has been introduced in the asymmetric opening of *meso*-anhydrides. By using the set-up of a repetitive batch system, the ease of recovery and reuse of this type of catalyst has been demonstrated. The drawbacks of this reaction in terms of high catalyst concentration can be compensated for by using membrane reactor technology. On running the asymmetric opening with the original $(DHQD)_2$-AQN ligand, 100 mol% of catalyst was needed to complete the reaction within 15 minutes at room temperature to obtain high selectivity. Calculating the catalyst employed in a repetitive batch system with 18 cycles 5.6 mol% of catalyst was required for one single batch and this amount would decrease even further with each further run.

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