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Application of the continuous Sharpless dihydroxylation[†]

Jens Wöltinger,[a,*] Hans Henniges,[b] Hans-Peter Krimmer,[a] Andreas S. Bommarius[a,‡] and Karlheinz Drauz[a]

[a]*Degussa AG, Business Unit Fine Chemicals, PO Box 1345, D-63403 Hanau, Germany*
[b]*Degussa AG, Business Unit Fine Chemicals, Feldmühlestrasse, D-53859 Niederkassel, Germany*

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Abstract—A continuously run Sharpless dihydroxylation in a membrane reactor gives information on osmate leaching in high molecular weight, homogeneous AD catalysts, allowing conclusions on the leaching of heterogeneous Sharpless catalysts to be drawn. To date, there have been contradictory descriptions of this problem in the literature. © 2001 Elsevier Science Ltd. All rights reserved.

Over the years homogeneous asymmetric synthesis has attracted great interest as a method for constructing homochiral compounds. The disadvantage of this procedure is the complicated separation of the expensive catalysts at the end of the reaction. One option to facilitate the separation and recycling of these catalysts is their combination with a heterogeneous carrier (for instance silica or a resin). Thus, the catalyst can be recovered easily by filtration and re-used repeatedly after its purification. In the technical application of such reactions the separation and recovery of noble metals and ligands from pharmaceutical products are of paramount importance in terms of price and quality.

The Sharpless dihydroxylation (AD) and aminhydroxylation (AA) reactions are of great interest for the synthesis of optically active compounds. By means of these reactions it is possible to create two stereogenic centres from one double bond in a single reaction. Several ligands taking their chiral information from cinchona-alkaloids can be used in these reactions.[1] In general potassium osmate dihydrate is used as a catalyst.

In the past, numerous investigations have been carried out in order to recycle both the valuable ligands and the toxic osmium. Therefore, the ligand was connected either to a heterogeneous carrier[2] or to a soluble polymer.[3] In both cases the ligand was removed by filtration (the homogeneous ligand was first precipitated in a suitable solvent and then filtered) after the reaction for recycling. Here the question of how well the metal is bound to the polymer–ligand complex and if the metal can be efficiently co-recycled needs to be addressed. There is no generally accepted answer, because no standardized protocol is followed during work-up and purification. In the literature contradictory information concerning this matter can be found.[2,3] An interpretation would be substantially more exact, if the catalyst is recycled in situ in a continuous operation.

The continuously run chemzyme membrane reactor (CMR), in which the catalyst attached to homogeneously soluble polymer is retained by a membrane, is a good choice for this task. The low molecular weight products and the unreacted educt can pass the membrane (because of the chosen cut-off) and thus leave the reaction vessel. The educt is continuously dosed into the membrane reactor, while the high molecular weight catalyst is retained in the reaction vessel by the membrane ('in situ recycling').[4]

As a model substrate, homocinnamic acid **1** was transformed to the corresponding diol **2**, which can be used as a core for the construction of HIV protease inhibitors (example in Scheme 1).

For a continuous reaction in a membrane reactor the following demands have to be met:

- The reaction must be as fast and selective as possible, because a continuous process is only efficient under these conditions (problematic of residence times).

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* Corresponding author. Tel.: +49 6181 59 4060; fax: +49 6181 2759; e-mail: jens.woeltinger@degussa.com

[†] Dedicated to Professor Bernhard Lücke for his 65th birthday.

[‡] Present address: School of Chemical Engineering, Georgia Institute of Technology, 315 Ferst Drive, Atlanta, GA 30332-0363, USA.

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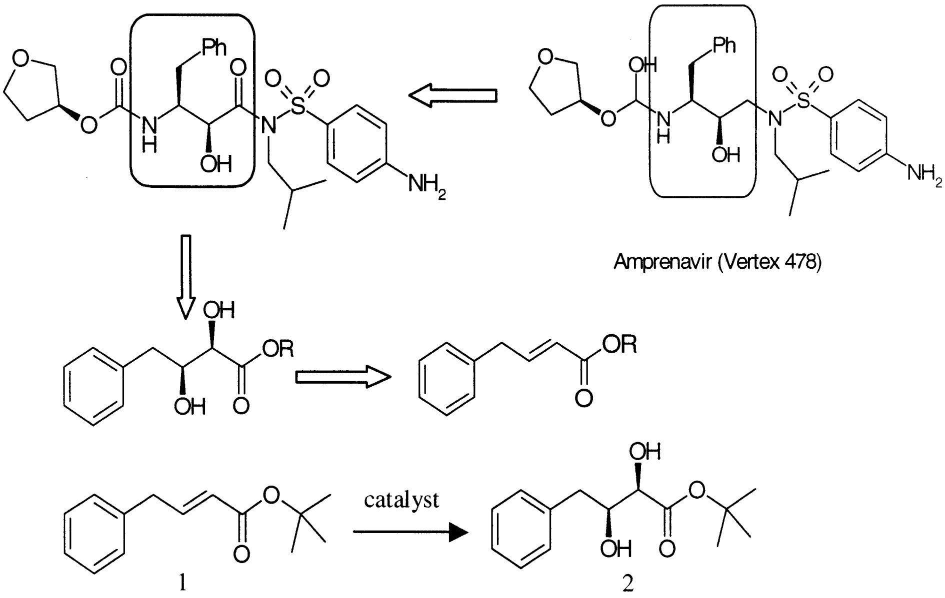


Scheme 1. Homocinnamic ester as a core for the construction of HIV protease inhibitors.

- The chiral ligand must be attached to a polymer and be sufficiently stable in this form, so that it still has the high activity and selectivity of the original ligand after many residence periods.
- The membrane must retain the high molecular weight ligand sufficiently. A desirable level of retention is >99.95%.

Therefore, intensive investigations have to be made and knowledge has to be gained in the fields of:

- homogeneous catalysis,
- synthesis of an appropriate homogeneous polymer, which is resistant to the solvent and can be retained by the membrane and
- reaction techniques, especially the membrane and reactor techniques (reactor, pumps, a.s.o.).

The studies concerning the continuous borane reduction in CMR had excellent requirements.[4a] In contrast to the borane reduction, which is designed for the continuous synthesis of essential pharmacological and agrarian intermediates, running the Sharpless dihydroxylation in the CMR was aimed at obtaining information on the leaching of the unstable metal complexes attached to the high molecular weight catalysts.

In principle, there are two reaction systems for Sharpless dihydroxylation. The first is a mixture of *tert*-butanol and water with potassium hexacyanoferrate as oxidizing agent. The second system is acetone/water (9/1) with NMO as oxidizing compound. We investigated both systems. Herein, we report on the NMO system, although it leads to lower e.e. values than the other system. The NMO system is more easily realized in the CMR than the potassium hexacyanoferrate system and our aim was not to get an ideal e.e. value, but to interpret the problem of osmate leaching.

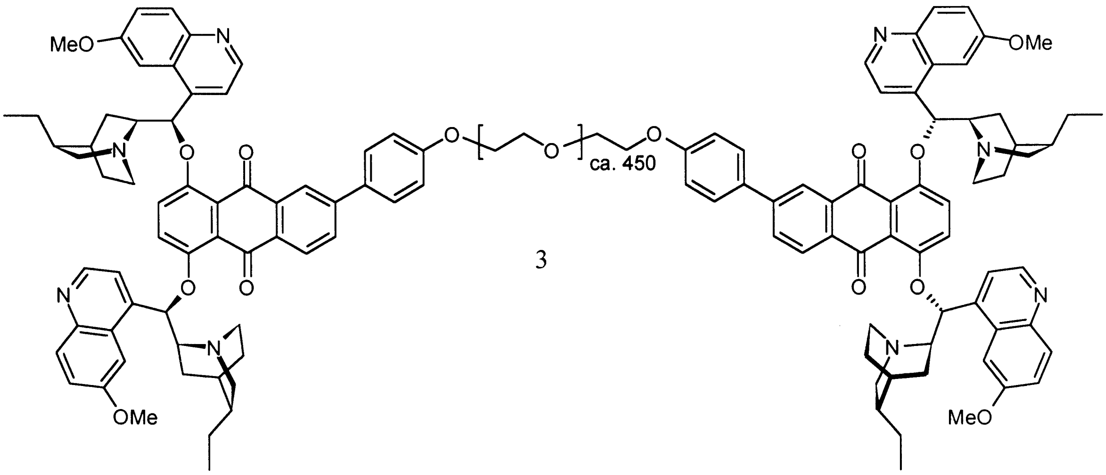
One precondition for a continuous reaction is that it must be complete in a maximum of 2 h. If the reaction time is longer, a continuous reaction process will not make sense and another process should be chosen. A typical Sharpless dihydroxylation takes 6–22 h.[1a] Higher concentrations of osmate and ligand and increasing the reaction temperature from 0°C to room temperature reduced the reaction time to the desired 2 h. No loss of selectivity and activity was detected.[5] Such high concentrations of catalyst can be only used in the membrane reactor.

For these investigations the requisite high molecular weight ligand **3** (Scheme 2) was synthesized analogous to the conditions described by Bolm et al. and applied in the dihydroxylation reaction.[6]

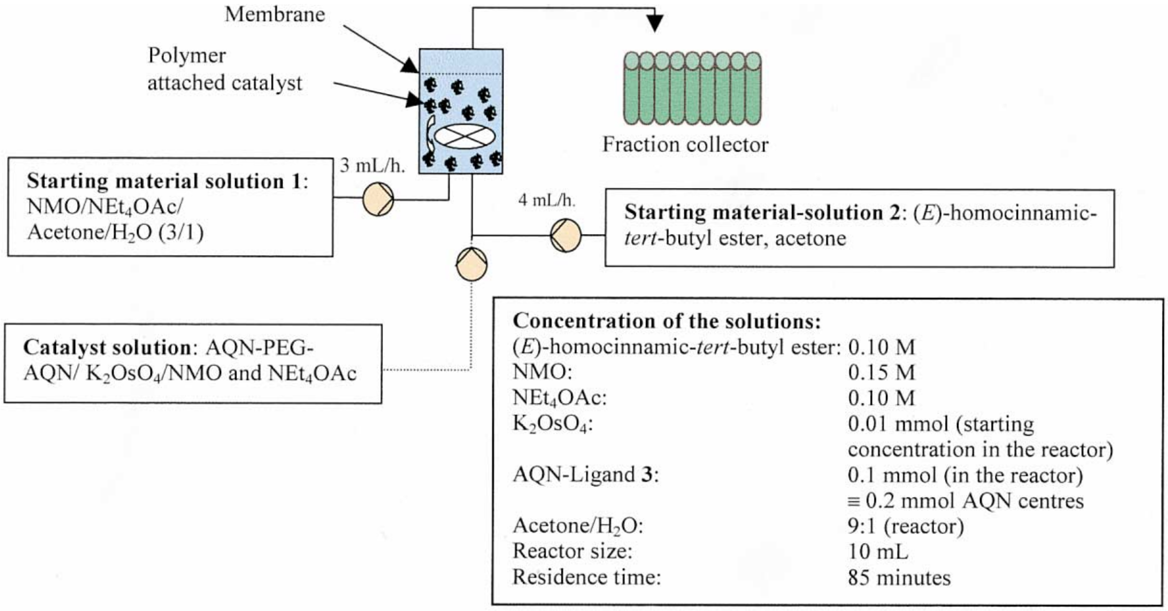
The reactor had a volume of 10 mL and was made of stainless steel. Two pumps delivered the educts into the reactor (see Scheme 3) and the residence time was 85 min. Fractions of the reaction mixture were collected, so that the chronological order of conversion and e.e. could be determined.

In Scheme 4 a plot of the chronological order of the conversion and the e.e. of one CMR experiment is shown. At the beginning, the conversion is ca. 80% and e.e. of ca. 80% can be obtained (which is only a little lower than in the batch experiments). But even at the very beginning of the continuous reaction the conversion drops to only 18% after six residence times. As there is no change in the e.e.s, the deterioration of the conversion can definitely be traced back to a leaching of osmate and not of the ligand.

This conclusion is supported by the fact that continuous dosing of potassium osmate increases the conversion to the starting values. From residence time number 6, 23% of the starting concentration of potassium osmate was added continuously together with the



Scheme 2. Catalyst used in the dihydroxylation of homocinnamic acid–*t*-butylester with a PEG molecular weight of 20.000 g/mol.



Starting material solution 1: NMO/NEt_4OAc/Acetone/H_2O (3/1)

Starting material-solution 2: (*E*)-homocinnamic-*tert*-butyl ester, acetone

Catalyst solution: AQN-PEG-AQN/ K_2OsO_4/NMO and NEt_4OAc

Concentration of the solutions:

(*E*)-homocinnamic-*tert*-butyl ester:	0.10 M
NMO:	0.15 M
NEt_4OAc:	0.10 M
K_2OsO_4:	0.01 mmol (starting concentration in the reactor)
AQN-Ligand **3**:	0.1 mmol (in the reactor) ≡ 0.2 mmol AQN centres
Acetone/H_2O:	9:1 (reactor)
Reactor size:	10 mL
Residence time:	85 minutes

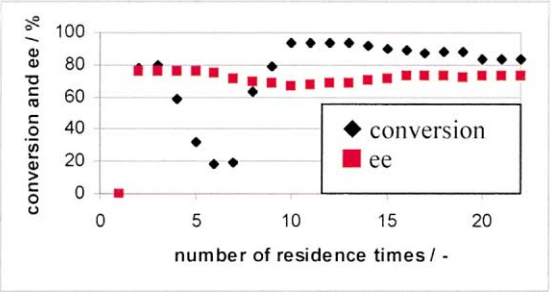
Scheme 3. Set up of the CMR reactor for the continuous Sharpless dihydroxylation. The reaction vessel rinsed the solutions of educt **1** and **2** before dosing in the solution of catalyst. Therefore, the addition of educt **2** was briefly stopped. As soon as the catalyst was in the reactor, the educt solutions **1** and **2** were continuously dosed again.

NMO. The dosage of potassium osmate was not further optimized concerning reaction rate and e.e.

These results clearly show that potassium osmate has a very weak attachment to the ligand and thus effective retention of osmate cannot be achieved. Based on these results it can be assumed that the conditions for heterogeneous dihydroxylation catalysts are comparable to the above described and the recycling of the ligand *including* the osmate complex may not be possible. But, as demonstrated in this reaction, the precious ligands can be recycled in a membrane reactor, which is an important result. Additionally, to our knowledge this is the first reported continuous dihydroxylation reaction.

The retention of the ligand can be influenced by the choice of a polymer with an appropriate chain length, but this does not affect the retention of the metal in a given metal–ligand complex.

In summary, it can be stated that the CMR is suitable not only for continuous synthesis with optimal exploitation of high ligand concentrations due to retention by the membrane,[4] but is also suitable for the explanation of mechanistic questions, as for instance, the metal leaching from a complex or the deactivation of catalysts with time. Thus, the presented experiment gives a hint on the stability of the polymer-enlarged ligand under the reaction conditions. Batch experiments give insufficient information concerning this matter, because the standard process of reaction, precipitation, filtration, washing, and drying cause stress on the catalysts, which can add extra deactivation and leaching to the physical loss of material. These factors are excluded in a continuous process as run in the CMR.



Scheme 4. Chronological order of conversion and e.e. for the continuous Sharpless dihydroxylation reaction. It has to be considered that the e.e. with NMO as oxidising compound is, in general, substantially lower than in the oxidation with $K_3Fe(CN)_6$. In the batch experiment an e.e. of 92% was obtained in the dihydroxylation of homocinnamic *tert*-butyl ester by oxidation with $K_3Fe(CN)_6$ (catalyst not polymer bound), whereas the e.e. was only 80% in the oxidation with NMO (catalyst not polymer bound). τ is equivalent to the number of residence times.

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5. The following conditions have been applied in dihydroxylation: homocinnamic acid–*t*-butylester: 0.1 mmol; NMO: 0.15 mmol; NEt_4OAc: 0.1 mmol; K_2OsO_4: 10^{-4} mmol; $(DHQ)_2AQN$: 0.2 mmol; acetone/water: 9/1.
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