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Polymer enlarged oxazaborolidines in a membrane reactor: enhancing effectivity by retention of the homogeneous catalyst

Guido Giffels, Juliane Beliczey, Marcel Felder and Udo Kragl *

Forschungszentrum Jülich GmbH, Institut für Biotechnologie, 52425 Jülich, Germany

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Abstract

Polymer enlarged oxazaborolidines that are homogeneously soluble were used as catalysts for the enantioselective reduction of ketones in a continuously operated membrane reactor equipped with a nanofiltration membrane. The amount of chiral product per mole of catalyst could be enhanced from 10 up to 560 moles (≡0.18 mol% catalyst). The chiral alcohols are obtained in good to excellent *ee* and space–time yield (up to 99% *ee* and 1.4 kg/[$L_{\text{reactor volume}} \times$day)]. © 1998 Elsevier Science Ltd. All rights reserved.

Since the chiral information of the catalyst is multiplied, homogeneous asymmetric catalysis is a valuable method for the synthesis of chiral products.[1] However, up to now only a few processes have made the step from an academically promising method to an application in a larger or even industrial scale. This is due often to the low total turnover numbers (ttn, mole product/mole catalyst) achieved, with the majority of such systems, especially catalysis involving chiral Lewis acids where the ttn rarely exceeds values of 10–50.

Many attempts, therefore, have been made to recycle catalysts. Very often these efforts result in a heterogenisation of the former homogeneous catalyst. Polymer-supported catalysts have been used in many reaction types such as hydrogenations,[2a] nucleophilic additions to carbonyl compounds,[2b] epoxidations,[2c] dihydroxylations,[2d] reductions[3] etc.

The oxazaborolidine catalysed reduction of ketones by borane is a widely used reaction which yields the corresponding chiral alcohols in high enantiomeric excess[4] (Scheme 1). Due to the competing non-catalysed reduction, catalyst concentrations of about 1–20 mol% have to be applied to ensure high enantiomeric excesses. A repetitive use of the valuable chiral amino alcohol ligand after workup is possible, but a simple recycling of the intact catalyst would be even more desirable. Thus, to allow recycling of the catalyst by filtration, the oxazaborolidine moiety was coupled to polystyrene gels.[3] By this means active and enantioselective catalysts were obtained but catalyst ttn could not be increased above values of 20 without a significant loss in enantioselectivity.[3c]

* Corresponding author. Tel.: +49-2461-616772; fax: +49-2461-613870; e-mail: u.kragl@fz-juelich.de

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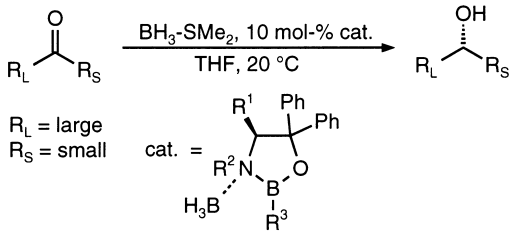
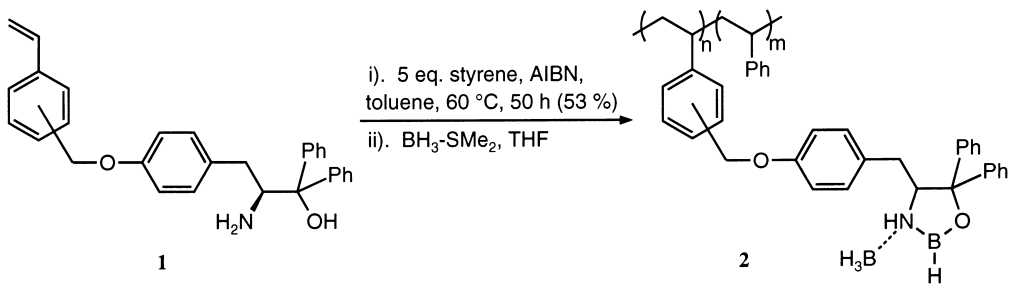


Scheme 1. Oxazaborolidine catalysed reduction of ketones by borane

As we reported recently, the advantages of catalyst retention can be united with the effectiveness of homogeneous catalysis when a *homogeneously soluble* polymer is used instead of the heterogeneous support. The catalyst retention or recovery from the homogeneous solution is achieved by means of an ultra- or nanofiltration membrane. The disadvantages of a heterogenisation resulting from mass transport limitations are avoided. This approach has gained much attention lately as it allows a continuously operated catalysis in a membrane reactor; the reaction products pass through the membrane whereas the polymer enlarged catalyst is retained in the reactor.[5]

We synthesised two types of soluble polymer enlarged oxazaborolidines (Scheme 2). A polymer bound chiral aminoalcohol prepared from monomer **1** (described by Itsuno et al.[6]) was obtained with a functionalisation of 1.18 mmol/$g_{polymer}$ and a molecular weight[7] of 13 800 g/mol. The α,α-diphenyltyrosinol moiety is converted into the active oxazaborolidine **2** in the presence of the reducing agent BH_3.

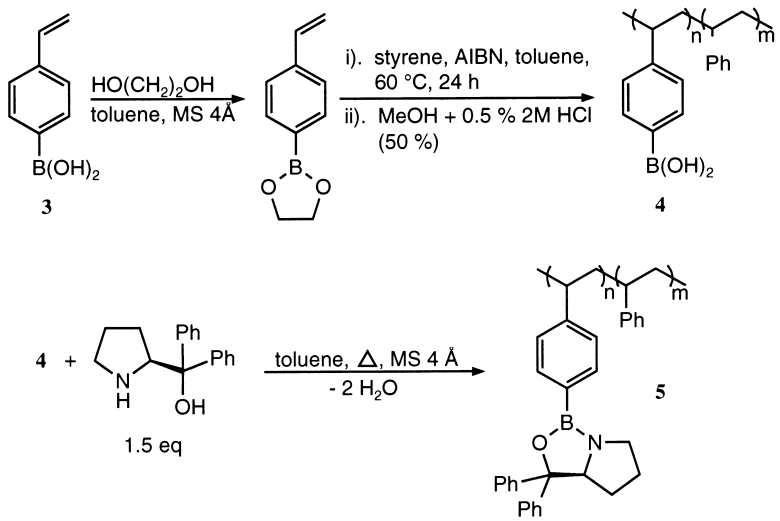


1 **2**

Scheme 2.

Coupling α,α-diphenylprolinol to a soluble polymer containing boronic acids gave another type of polymer enlarged oxazaborolidine **5** bound via the boron atom (Scheme 3). Polymer **4** was prepared by copolymerisation of monomer **3** with styrene as the lithiation of brominated polystyrene followed by addition of $B(OMe)_3$ or BH_3 gives only insoluble products due to crosslinking.[3b] The polymer has a functionalisation of 2.11 mmol/$g_{polymer}$ according to elementary analysis. Oxazaborolidine-formation was achieved by heating a toluene solution[8] of the polymer with an excess of aminoalcohol using a Soxhlet-apparatus containing activated molecular sieve (4 Å). The resulting catalyst solution was used directly for continuous experiments in a membrane reactor since any remaining free ligand is not retained by the membrane and is therefore washed out during the initial phase.

These catalysts were used for the reduction of several ketones in a continuously operated membrane reactor (Table 1). The experimental setup is shown in Scheme 4, in which the membrane reactor itself is a magnetically stirred filtration cell made of polypropylene with a reactor volume of 10 mL. The components of the reactor setup were used as previously described.[5] For polymer retention a solvent stable nanofiltration membrane was applied.[9] The permeating product solution is quenched at the reactor outlet by addition of methanol to avoid a further (racemic) reduction in the absence of the catalyst in the case of incomplete conversion.

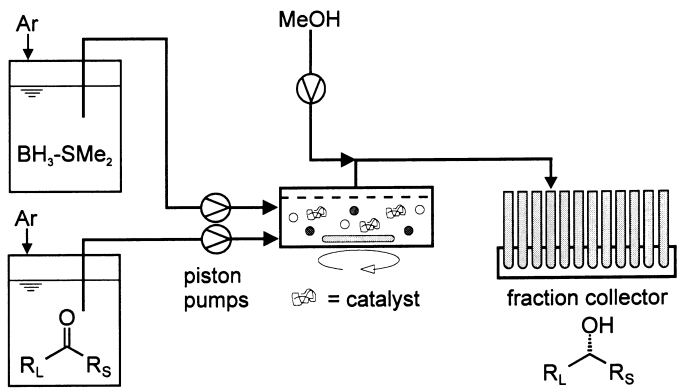


Scheme 3.

Table 1
Continuous reductions of various ketones in the membrane reactor[a]

entry	catalyst (conc.) [mM]	ketone	conc. of educts [mM]	residence time [h]	space-time yield [g/(L×d)]	operating time [h]	*ttn* [-]	*ee*[d] (overall *ee*)[e] [%]
1	**5** (19)	$PhCOCH_3$	100	1	290	25	120	95-90 (93)
2	**5** (40)	tetralone	100	0.33	1067	23	175	99-90 (96)
3	**2** (32)	PhCOEt	200	0.67	967	24	220	84 (84)
4	**2** (35)	$PhCOCH_3$	250[b]	0.5 - 1[c]	1400	65	560	94-90 (91)

[a] All reactions yielded the (*R*)-isomer; the conversion was 95-99 % in every case; [b] BH_3-SMe_2 only 200 mM; [c] the residence time was changed during the experiment; [d] *ee* and conversion were determined by GC or HPLC (entry 2) on a chiral stationary phase[13]; [e] *ee* in the united product solution;



Scheme 4. Experimental setup for the continuous catalysis experiments

Continuous experiments using the membrane reactor afforded higher enantioselectivites than batch experiments in which the ketone was added in one portion. This agrees with data from the literature, according to which a slow addition of the ketone to a solution of the catalyst and the reducing agent results in higher *ee*s.[10] This procedure is widely used but to our knowledge the underlying kinetic behavior has yet not been described in detail. We therefore carried out initial reaction rate measurements with catalyst

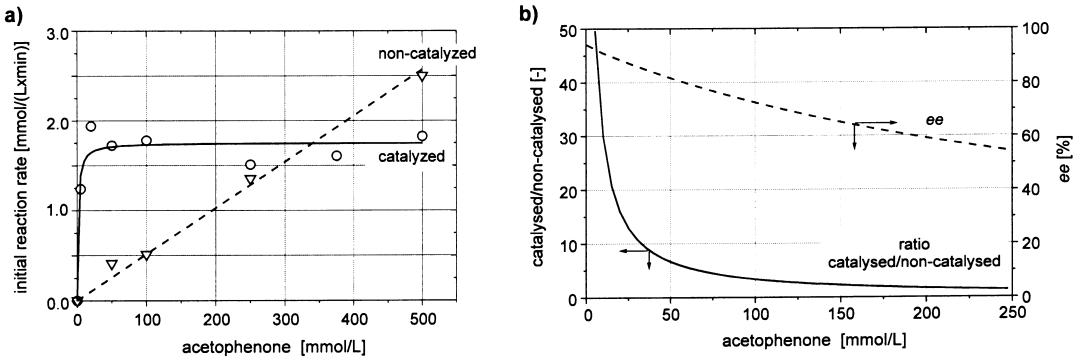


Fig. 1. (a) Initial rate kinetics of oxazaborolidine catalysed reduction as a function of acetophenone concentration; (b) ratio of catalysed and non-catalysed reaction as a function of acetophenone concentration and resulting differential enantioselectivity. Conditions: catalyst **2** 5 mmol/L (4.25 g/L), BH_3–SMe_2 100 mmol/L, THF, 20°C

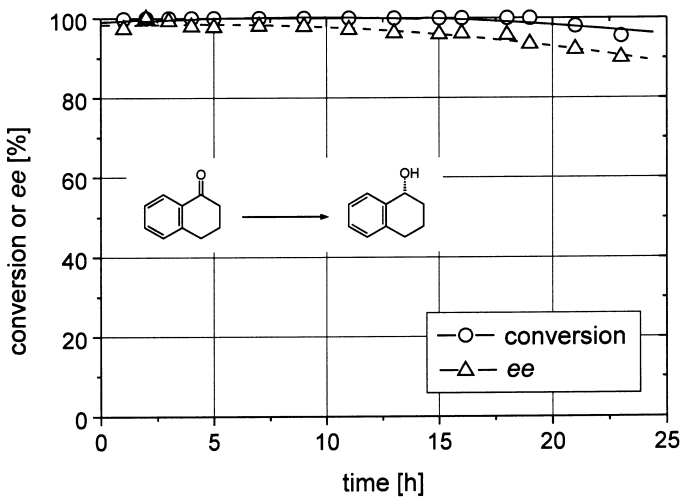


Fig. 2. Continuous reduction of tetralone in the membrane reactor (entry 2, Table 1)

2.[11] The uncatalysed reaction proceeds first order with respect to ketone and borane. In contrast, the catalysed reduction shows Michaelis–Menten type kinetics for the ketone (K_M=2.8 mmol/L) as well as for the borane (K_M=21 mmol/L). The kinetic influence of the ketone concentration on the initial reaction rates is depicted in Fig. 1a. The resulting ratio of catalysed/uncatalysed reaction and the corresponding differential enantioselectivity for the overall reaction are shown in Fig. 1b. It can be seen clearly that the lower the ketone concentration is, the better the resulting *ee*. This is essentially also true for the borane concentration but the effect is far less important due to the higher K_M-value.

The membrane reactor behaves as a continuously stirred tank reactor, which can be operated with high conversion corresponding to a low stationary educt concentration (see Fig. 2). Therefore, the competing uncatalysed reduction yielding the racemate can be suppressed very efficiently.[12]

The results of various experiments are summarized in Table 1, and a typical experiment is shown in Fig. 2. Almost quantitative conversion is reached in all examples. The *ee*s range from 84% (propiophenone) up to >99% for the reduction of α-tetralone. Corresponding with the educt concentrations, excellent space–time yields of up to 1.4 kg/($L_{reactor\ volume}$×day) were reached (entry 4). The catalysts show a slight deactivation under reaction conditions, but beginning with an excess of active catalyst present, this has no significant influence on the reactor performance. The reactor seems to operate under

stable conditions until the concentration of active oxazaborolidine drops below a critical value. This subsequently leads to an observable decrease of conversion as well as enantiomeric excess. Nevertheless the total turnover number of the oxazaborolidines could be enhanced during the operation time up to a value of 560 (!) which would be equivalent to a catalyst concentration of only 0.18 mol% in a batch experiment (entry 4, average *ee* 91%).

In addition to the higher ttn, the workup of the product is simplified because the catalyst is retained by the membrane. As the conversion is almost quantitative, evaporation of the solvent followed by simple distillation afforded the chiral products in high purities (>99%).

In summary it is shown that the use of polymer enlarged oxazaborolidines in a membrane reactor is a very efficient method for producing chiral alcohols with excellent enantioselectivity, space–time yields and much higher total turnover numbers for the catalyst than in batch experiments. These advantages make the use of membrane reactors a very promising technique for homogeneous catalysis in the future. Investigations on other kinds of catalysts are currently in progress.[14] Besides polymer bound catalysts a dendritic enlargement is also gaining more and more attention. The possible application of membrane separation for this kind of catalyst has been announced repeatedly.[15] First experiments revealed that retention rates higher than 98% are possible.

Acknowledgements

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7. M_n according to GPC (polystyrene standard), M_n/M_w=1.6.
8. To obtain a homogeneous solution of the polymer it is necessary to add 0.5% of MeOH to the toluene solution (boroxine opening). The alcohol was than removed by azeotropic distillation, i.e. reduction to half the original volume followed by addition of fresh absolute toluene (3×).
9. Nanofiltration membrane MPF-50 (flat configuration), Koch Membrane Systems, Düsseldorf.
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11. The detailed results of our kinetic investigations comprising a kinetic model which allows predictions of conversions and *ee*s will be published elsewhere.

12. Slow addition of the ketone to the reaction mixture in batch experiments (for example via a syringe pump) also suppresses the uncatalysed reaction down to an almost negligible amount.
13. GC: FS-Cyclodextrine β I/P, 50 m×0.32 mm (Machery & Nagel, Düren, Germany), carrier gas H_2, FID, isothermal with column temperatures between 70 and 135°C adjusted for optimal resolution; HPLC: Chiracel OB (Baker, Griesheim, Germany), heptane:isopropanol=9:1, 0.5 mL/min, UV-detector 220 nm.
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