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# A polymer-enlarged homogeneously soluble oxazaborolidine catalyst for the asymmetric reduction of ketones by borane

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***Abstract:*** A polymer-enlarged homogeneously soluble oxazaborolidine catalyst has been prepared and used in the enantioselective borane reduction of ketones. The catalyst is derived from (2*S*,4*R*)-α,α-diphenyl-2-[(4-allyloxy)-*N*-benzyloxycarbonyl]-pyrrolidinemethanol **3** and a methyl hydrosiloxane–dimethylsiloxane copolymer **4** (15% functionalized). Enantioselective reduction of prochiral ketones to the corresponding chiral alcohols proceeds with enantiomeric excesses up to 98%. The catalyst can be retained by a nanofiltration membrane and thus could be recovered after reaction or used in a continuously operated membrane reactor. © 1997 Elsevier Science Ltd

The enantioselective reduction of prochiral ketones leading to the corresponding optically active secondary alcohols is a topic of current interest.[1] One of the more successful methods has been based on the use of chiral 1,3,2-oxazaborolidines as catalysts. This method was developed by Itsuno et al.[2] and then improved by Corey[3] and co-workers (CBS reduction[3a]). Over the past decade, numerous examples describing the application of this method have been reported by several groups.[4] Some of these catalysts have been extensively studied with great success, however the development of cost-effective catalysts that exhibit high reactivity and enantioselectivity is still a challenging target in asymmetric synthesis. One approach to reduce the product-specific catalyst costs is to use the chiral catalyst repeatedly. In order to avoid lengthy recovery and purification several polymer-bound heterogeneous oxazaborolidine catalysts have been prepared.[5]

Our interest in developing methods for continuous asymmetric synthesis in a membrane reactor[6] led us to investigate the enantioselective reduction of prochiral ketons by borane. For this application it was crucial to prepare a homogeneously soluble polymer-enlarged catalyst. Here we describe our attempt to develop a novel catalyst by preparing a polymer-enlarged homogeneously soluble oxazaborolidine **6a** by a sequence of reactions shown in Scheme 1.

The synthesis of *N*-Cbz-protected amino alcohol **3** was achieved by established methods converting enantiomerically pure *trans*-4-hydroxy-L-proline into the corresponding *N*-Cbz-protected methyl ester **1** which subsequently was reacted with allyl bromide and silver oxide to give **2**[7] in an overall yield of 65%. Reaction of compound **2** with phenylmagnesium bromide in tetrahydrofuran (THF) provided the *N*-Cbz-protected amino alcohol **3** in 54% yield. Compound **3** was subjected to platinium-catalyzed hydrosilylation with polymer **4**[8] affording, after deprotection, polymer-enlarged amino alcohol **5**.

Chiral oxazaborolidines **6a** and **6b** were easily prepared by the reaction of the corresponding amino alcohol with $BH_3 \cdot SMe_2$ complex according to the procedure reported by Corey et al.[9] The polymer-enlarged catalyst **6a** prepared here was examined for its enantioselectivity in the reduction of prochiral ketones **7–9** with borane (Table 1). Catalyst **6b** was synthesized as a model compound in order to test the influence of the new stereogenic center at the pyrrolidine ring on the enantioselectivity of the reduction. As shown in Table 1 (entry 2), the reached enantioselectivity (98% ee) is in the same range as with the unsubstituted oxazaborolidine.[10]

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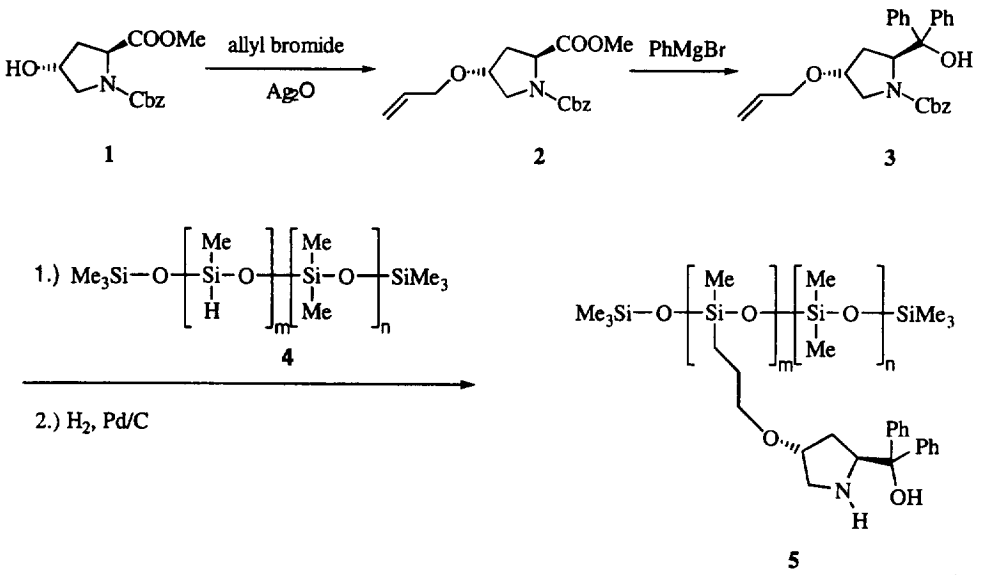


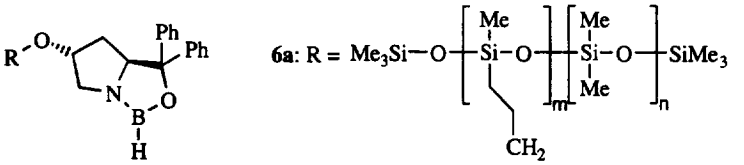

**Scheme 1.**

**Table 1.** Enantioselective reduction of various ketones using 10 mol% of **6a** or **6b** in THF

| entry | catalyst | ketone | Yield (%)[a] | ee (%)[b] | config.[c] |
|---|---|---|---|---|---|
| 1 | **6a** | $PhCOCH_3$ (**7**) | 86 | 97 | R[11a] |
| 2 | **6b** | $PhCOCH_3$ (**7**) | 89 | 98 | R[11a] |
| 2 | **6a** | $PhCOCH_2CH_3$ (**8**) | 88 | 89 | R[11b] |
| 3 | **6a** | $PhCOCH_2Cl$ (**9**) | 83 | 94 | S[11c] |

a. Isolated yield after purification. b. Determined by chiral HPLC analysis (Daicel Chiralcel ODH).

c. The absolute configuration was determined on base of the sign of the specific rotation[11].




**6b**: R = $CH_2Ph$

Reduction of acetophenone **7** was carried out at r.t. by using **6a** (10 mol% of acetophenone) as a solution in THF and $BH_3 \cdot SMe_2$ complex as reducing agent (1 eq. of acetophenone) to give (*R*)-phenylethanol of 97% ee (Table 1, entry 1).[12] In a similar manner, reduction of other prochiral ketones gave the corresponding alcohols in good to excellent selectivity.

It is noteworthy that the observed enantiomeric excesses (up to 97%) are as high as in analogous reactions with non polymer-enlarged chiral oxazaborolidine catalysts. These results show the potential of **6a** as chiral inductor for the use in a continuously operated membrane reactor. Next a limited study was conducted on the retention of **6a** by nanofiltration. We found that **6a** could be retained and thus can be used in a continuously operated membrane reactor. The aim of a continuous process in a

membrane reactor is to decouple the residence time of catalyst and reactants in order to achieve high total turnover numbers (TTNs) for the catalyst.

In summary, we have developed a new, homogeneously soluble polymer-enlarged oxazaborolidine catalyst for the enantioselective borane reduction of prochiral ketones. Alternatively it should be possible to couple the hydroxyproline derived catalyst precursor **3** also to a dendrimer to achieve the high molecular weight, that is required for the retention by a nanofiltration membrane. Studies aimed to improve the use of this catalyst for continuous asymmetric reduction in a membrane reactor are currently under investigation.

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12. **Experimental procedure using oxazaborolidines 6a or 6b**: A solution af **6a** (0.1 ml, 1.0 M in THF, 10 mol%) was added to the reaction flask containing 5 ml of dry THF. To the solution at r.t. was added $BH_3 \cdot SMe_2$ complex (0.12 ml, 1.0 mmol) followed by a solution of 1.0 mmol of the ketone in 1 ml of anhydrous THF. After the addition, the mixture was stirred for 30 min at r.t. The reaction was then quenched with 5 ml of MeOH. Normal workup provided the crude product which could be further purified by either flash chromatography on silica gel or distillation under reduced pressure.

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