

PII: S0957-4166(97)00192-4

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

Marcel Felder, Guido Giffels and Christian Wandrey *

Forschungszentrum Jülich GmbH, Institut für Biotechnologie, Leo-Brandt-Straße, D-52425 Jülich, Germany

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 $(2S,4R)-\alpha,\alpha$ -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 Corey³ 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 reactor⁶ 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 polymerenlarged 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

^{*} Corresponding author. Email: c.wandrey@kfa-juelich.de



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 ^{ila}
2	6b	PhCOCH ₃	(7)	89	98	R ^{ila}
2	6a	PhCOCH ₂ CH ₃	(8)	88	89	R ^{11b}
3	6a	PhCOCH ₂ Cl	(9)	83	94	Slic

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 rotation¹¹.





Reduction of acetophenone 7 was carried out at r.t. by using **6a** (10 mol% of acetophenone) as a solution in THF and BH₃·SMe₂ 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.

Acknowledgements

We thank J. Allgaier for fruitful discussions and H. Offermann for her skillful help and enthusiasm. We are grateful to Degussa AG for providing us *trans*-4-hydroxy-L-proline.

References

- 1. V. K. Singh, Synthesis 1992, 605.
- 2. (a) A. Hirao, S. Itsuno, S. Nakahama, N. Yamazaki, J. Chem. Soc., Chem. Commun. 1981, 315.
 (b) S. Itsuno, K. Ito, A. Hirao, S. Nakahama, N. Yamazaki, *ibid.* 1983, 469. (c) S. Itsuno, K. Ito, J. Org. Chem. 1984, 49, 555.
- 3. (a) E. J. Corey, K. R. Bakshi. S. Shibata, J. Am. Chem. Soc. 1987, 109, 5551. (b) E. J. Corey, G. A. Reichard, Tetrahedron Lett. 1989, 30, 5207. (c) E. J. Corey, J. O. Link, *ibid.* 1992, 33, 3431. (d) E. J. Corey, C. J. Helal, *ibid.* 1995, 36, 9153. (e) C. J. Helal, P. A. Magriotis, E. J. Corey, J. Am. Chem. Soc. 1996, 118, 10938.
- (a) S. Wallbaum, J. Martens, *Tetrahedron: Asymmetry* 1992, *3*, 1475. (b) L. Deloux, M. Srebnik, *Chem. Rev.* 1993, *93*, 763. (c) D. J. Mathre, S. A. Thompson, A. W. Douglas, K. Hoogsteen, J. D. Carroll, E. G. Corley, E. J. J. Grabowski, *J. Org. Chem.* 1993, *58*, 2880. (d) M. P. Deninno, R. J. Perner, H. E. Morton, S. DiDomenico, *ibid.* 1992, *57*, 7115. (e) J. Bach, R. Berenguer, J. Gracia, T. Loscertales, J. Vilarrasa, *ibid.* 1996, *61*, 9021. (f) G. J. Quallich, J. F. Blake, T. W. Woodall, *J. Am. Chem. Soc.* 1994, *116*, 8516.
- (a) S. Itsuno, Y. Sakurai, K. Shimizu, K. Ito, J. Chem. Soc., Perkin Trans. I. 1990, 1859. (b) S. Itsuno, K. Ito, A. Hirao, S. Nakahama, *ibid*. 1984, 2887. (c) C. Caze, N. El Moualij, P. Hodge, C. J. Lock, J. Ma, *ibid*. 1995, 345. (d) C. Franot, G. B. Stone, P. Engeli, C. Spöndlin, E. Waldvogel, *Tetrahedron: Asymmetry* 1995, 6, 2755.
- 6. (a) German Patent Application. DE P: 196 47 892.8, 1996. (b) U. Kragl, C. Dreisbach, C. Wandrey Applied Homogeneous Catalysis with Organometallic Compounds; VCH: Weinheim, 1996; pp. 832-843.
- 7. S. Mori, T. Ohno, H. Harada, T. Aoyama, T, Shioiri, Tetrahedron 1991, 47, 5051.
- Methyl hydrosiloxane-dimethylsiloxane copolymer (15% functionalized) was purchased from ABCR GmbH & Co., D-76151 Karlsruhe, Germany.
- 9. E. J. Corey, S. Shibata, P. K. Bakshi, J. Org. Chem. 1987, 53, 2861.
- 10. E. J. Corey, S. Shibata, P. K. Bakshi, C.-P. Chen, V. K. Singh, J. Am. Chem. Soc. 1987, 109, 7925.
- (a) R. Huisgen, C. Rüchardt, *Liebigs Ann. Chem.* 1956, 601, 21. (b) H. Kwart, D. P. Hoster, J. Org. Chem. 1967, 32, 1867. (c) J. W. Hartgerink, L. C. J. Van der Lean, J. B. F. N. Engberts, T. J. de Boer, *Tetrahedron* 1971, 27, 4323.
- 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 BH₃·SMe₂ 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.

(Received in UK 21 April 1997)