Pergamon

Tetrahedron 56 (2000) 1693–1699

TETRAHEDRON

Microgel-supported Oxazaborolidines: Novel Catalysts for Enantioselective Reductions

C. Schunicht, A. Biffis and G. Wulff*

Institute of Organic Chemistry and Macromolecular Chemistry, Heinrich-Heine University Duesseldorf, D-40225 Duesseldorf, Germany

Received 3 January 2000; accepted 25 January 2000

Abstract—Microgel-bound oxazaborolidines have been prepared and used as catalysts in the enantioselective reduction of prochiral ketones. The preparation of these soluble, crosslinked polymer molecules was accomplished by solution polymerisation. The approach involved the preparation of microgels bearing free boronic acid functionalities and their subsequent conversion to oxazaborolidines. The selectivities of these supported catalysts are in most cases comparable to those achieved with low molecular weight analogues. The advantage of the application of microgel-bound catalysts is their good solubility together with low viscosity of the solution. Reagents of this type can easily be removed by ultrafiltration and the process can be performed in a continuous mode in a membrane reactor. © 2000 Published by Elsevier Science Ltd. All rights reserved.

Introduction

The interest in chiral boron-containing heterocycles as enantioselective catalysts has been significantly increased during the last ten years.[1–7] Following the pioneering work of Yamamoto[4] with acyloxyboranes as catalysts for asymmetric reductions and C–C bond formations, as well as the success of the borane reduction of prochiral ketones, catalysed by chiral oxazaborolidines (CBS reduction),[1,2] quite a number of heterocyclic compounds containing boron have been investigated. At present, chiral oxazaborolidines appear to be the most versatile catalysts of this kind, having been successfully employed in the CBS reduction as well as in a plethora of other reactions of synthetic interest.[3,5–7] In particular, the CBS reduction has paved the way to the development of novel synthetic strategies for the asymmetric synthesis of important compound classes such as prostaglandins or aminoacids, as well as for the preparation of industrially relevant pharmaceuticals and natural compounds.[5,6]

The main disadvantage of the application of oxazaborolidines for asymmetric reductions is the relatively large amount of catalyst which is required to achieve high selectivity. At least 1 mol% is needed in the CBS reduction, and for most of the other reactions the substrate-to-catalyst ratios are even lower.[3,6] Under these conditions, the efficiency of catalyst recovery and recycling becomes a critical feature for the economical viability of an industrial process based on such compounds. Since the oxazaborolidine ring is generally unstable under the workup conditions of the reaction mixture, a practical means of separating the catalyst before workup has to be devised; an obvious solution to this problem consists of binding the oxazaborolidine to a heterogeneous support. In the last few years extensive investigations have been conducted on the use of oxazaborolidines bound to insoluble polymers.[6,8] Following this approach, some researchers succeeded in preparing heterogenised CBS catalysts which closely approached the selectivities obtained with the soluble analogues.[8b,c] Unfortunately, this was possible only by using gel-type polymer supports with a very low degree of crosslinking (1–2%), for which the mechanical properties under the reaction conditions are very poor. With increasing degree of crosslinking, diffusional limitations inside the polymer support slow down the rate of the catalysed reduction so that the direct, non-selective borane reduction becomes competitive, causing a marked decrease in the overall selectivity. These findings suggest that the application of *soluble* polymer supports should bring a decisive advantage. Such materials can in principle be conveniently separated from the reaction mixture through precipitation, ultracentrifugation or ultrafiltration, whereby the use of membrane reactors[9] allows for the application of the catalyst in a continuous mode. In this respect, recent results from Kragl and coworkers with CBS catalysts supported on linear polymers appear very encouraging.[10]

We present in this paper an approach making use of *microgels*[11]—intramolecularly crosslinked polymer molecules that build stable solutions in suitable solvents—as carriers of the catalytic functionalities. In comparison to linear polymers, microgels offer the advantage of a very low solution viscosity, which simplifies the handling of the

Keywords: microgels; oxazaborolidines; borane; enantioselective reduction.
* Corresponding author. Tel.: +49-211-8114760; fax: +49-211-8114788; e-mail: wulffg@uni-duesseldorf.de

0040–4020/00/$ - see front matter
PII: S0040-4020(00)00072-7

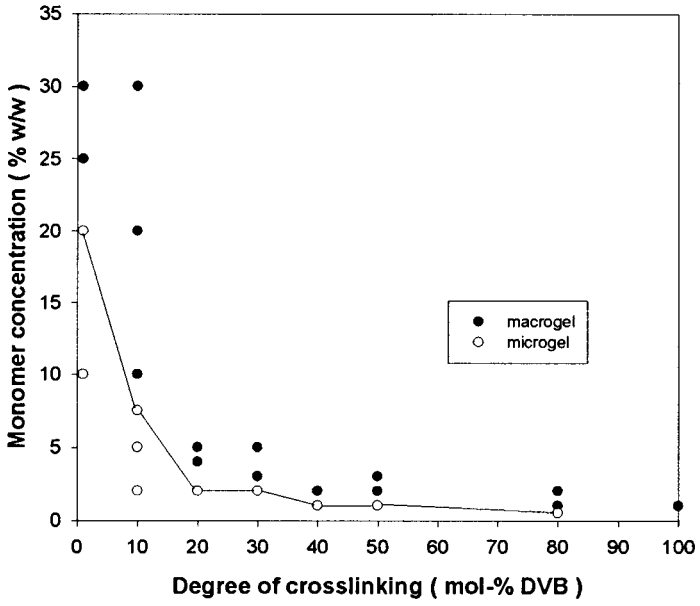

Figure 1. Dependence of the critical monomer concentration (C_m) on the degree of crosslinking.

reaction mixture. Furthermore, the microgel morphology can be tuned by variation of the degree of crosslinking, which in turn exerts an influence on the reactivity of the bound functional groups through size-exclusion or micro-environmental effects.[12,13]

Results and Discussion

Microgels can be prepared using virtually all the known polymerisation procedures. We chose radical solution polymerisation[14] which is probably the simplest available method in microgel synthesis. It does not make use of surfactants; the stabilisation of the growing microgels towards macrogelation is accomplished on the basis of the osmotic repulsion forces generated by the interactions of the polymer chains attached to the microgels—namely through steric stabilisation.[15] To achieve this, it is necessary to polymerise in very diluted solutions with the monomer concentration below a critical value (critical monomer concentration, C_m). Under these conditions, the microgels which are produced in the course of the polymerisation do not react intermolecularly to build an insoluble polymer network (macrogel), but intramolecularly to yield a stable solution. The value of the C_m is dependent on the type of monomer, the degree of crosslinking, the solvent and the polymerisation conditions. We started our investigation by determining C_m in THF under standard polymerisation conditions (64°C, 4 days) for styrene–divinylbenzene (DVB) microgels of different degree of crosslinking (Fig. 1). We found that C_m decreased continuously with increasing amount of crosslinking, as expected from the steric stabilisation theory. However, excessive lowering of the degree of crosslinking also caused a significant decrease in the polymerisation yields. We found an optimal value for obtaining high microgel yields in relatively concentrated solutions at about 5–10 mol% of crosslinker.

Using the polymerisation conditions listed above, we turned to the synthesis of microgel-bound 1,3,2-oxazaborolidines (Fig. 2). Two different approaches can be used. The most direct method consisted of preparing the microgels by copolymerisation of styryl-functionalised oxazoborolidines with styrene and DVB,[16] but surprisingly this method gave low selectivities in reductions. We therefore turned to a second method which consisted of preparing microgels containing boronic acid moieties followed by the synthesis of the oxazaborolidine ring in a second step by a polymer-analogous reaction with chiral aminoalcohols. The advantage of this strategy is the flexibility of the approach: in this

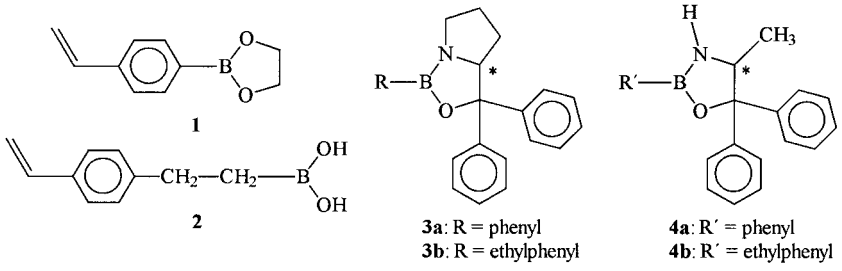

Figure 2.

Table 1. Synthesis of polymer-bound oxazaborolidenes (for polymerisation conditions, see Experimental)

Microgel	Functional monomer[a]	Crosslinking degree and agent	Aminoalcohol[b]	Reaction yield (%)[c]	Content of catalyst groups (mmol/g)
M1	**1**	5% DVB	DPA	52	0.68
M2 (a)	**1**	10% DVB	DPA	68	0.84
M2 (b)	**1**	10% DVB	DPP	60	0.74
M3	**1**	2% EDMA	DPA	70	0.90
M4 (a)	**1**	5% EDMA	DPA	37	0.50
M4 (b)	**1**	5% EDMA	DPP	57	0.72
M5 (a)	**1**	10% EDMA	DPA	57	0.71
M5 (b)	**1**	10% EDMA	DPP	41	0.52
M6	**1**	30% EDMA	DPA	43	0.48
M7	**2**	5% DVB	DPA	18	0.25
M8 (a)	**2**	5% EDMA	DPA	21	0.29
M8 (b)	**2**	5% EDMA	DPP	24	0.32

[a] The content of **1** or **2** in the polymerisation mixture was 17 mol%.
[b] DPA: (*S*)-α,α-diphenylalaninol; DPP: (*S*)-α,α-diphenylprolinol.
[c] Based on the initial content of **1** or **2**.

way different aminoalcohols can be bound to aliquots of the same microgel backbone, allowing a better comparison of the selectivity of different chiral modifiers.

The microgel synthesis was accomplished by the copolymerisation of the boronic acids **1** or **2** with different comonomers. Because of the higher polarity, the *p*-styrylboronic acid was used as its ethylene glycol ester **1**. After copolymerisation, the ester functions were hydrolysed with water. The microgels were isolated by precipitation.

To investigate the influence of the polymer backbone on catalyst performance, we prepared styrene–divinylbenzene (DVB) based microgels as well as ethylene dimethacrylate (EDMA) and methyl methacrylate (MMA) based microgels. The polymerisation conditions for EDMA based polymers could be kept the same as for the polymers based on DVB, as EDMA microgels in THF exhibit an even higher C_m than DVB microgels. The molecular weights of the microgels were determined by membrane osmometry. We found a strong dependence on the percentage of crosslinker in the monomer mixture. Molecular weights range from 8.2×10^4 g mol^{-1} for the low crosslinked microgel M1 to 3.2×10^5 g mol^{-1} for the higher crosslinked microgel M6. The intrinsic viscosities $[\eta]$ of the prepared microgels in THF are found to lie between 8 and 15 ml g^{-1}. These are remarkably low values when compared to solutions of analogous linear polymers, which show an intrinsic viscosity of 70–100 ml g^{-1}. The low viscosity of microgel solutions allows higher concentrations of catalyst and a much better processability (e.g. ease of ultrafiltration) in comparison to the linear polymer analogues.

It is known that all microgels possess a certain amount of pendant vinyl groups stemming from the only partially reacted crosslinker.[11a] In principle the presence of such vinyl groups can have a deleterious effect on the yield and the enantioselectivity of the CBS-reduction, since the borane reagent can hydroborate the residual vinyl groups and this part would therefore be lost for the ketone reduction. Moreover, it has been reported that hydroboration of the residual vinyl groups can cause a change in the solubility of the microgels, which precipitate from the reaction solution.[11a,17] The amount of the pendant vinyl groups was initially assessed by considering the intensity of the related IR absorption band at 1635 cm^{-1}, but a more accurate quantification can be obtained by a procedure involving the titration of the acetic acid generated by the reaction of the vinyl groups with mercury(II)-acetate.[18] However, because of the disturbing influence of boronic acid moieties only unfunctionalised microgels could be used for this determination.

The number of residual vinyl groups is expected to increase with increasing amount of crosslinker. Accordingly, in the case of our microgels, which contain only small amounts of the crosslinking agent, the number of unreacted vinyl groups turned out to be rather low. For an unfunctionalised microgel based on styrene and DVB with a crosslinker content of 10 mol%, this amount was 0.1 mmol g^{-1}. For a comparable microgel based on MMA and EDMA, the amount of vinyl groups was hardly detectable.

We were able to show that this small amount of vinyl groups has no effect on the results of the CBS-reduction. For this, we treated a microgel sample containing pendant boronic acid moieties with the reagent diimine. By using this selective reducing agent we nearly quantitatively reduced the vinyl groups throughout the microgel particles without affecting the boronic acid moieties. In a direct comparison with the original, untreated microgel still possessing vinyl groups we found no difference in the catalytic performance in the CBS-reduction. Thus, we decided to use all other microgels without previous reduction of the vinyl groups.

For catalyst preparation, the microgels were condensed with the aminoalcohols (*S*)-α,α-diphenylprolinol (DPP) or (*S*)-α,α-diphenylalaninol (DPA) to afford the polymer-bound oxazaborolidines. Analogous structures as depicted in **3** and **4** were obtained, in this case immobilized at a polymer. Relevant data for the microgel-supported catalysts are reported in Table 1. The catalysts were employed in the enantioselective borane reduction of acetophenone or α-tetralone, with borane–dimethylsulfide complex as the reducing agent. The catalyst amount was 10 mol% in all cases. The results are listed in Table 2. Free oxazaborolidine catalysts were also tested under the same conditions for comparison (Table 2, **3a**–**4b**). We found that the monomeric

Table 2. CBS reductions with microgel-bound catalysts (M1–M8) and reference catalysts (**3a**, **3b**, **4a**, **4b**) (for reduction conditions, see Experimental)

Catalyst[a]	Aminoalcohol [b]	Substrate	Enantiomeric excess[c] (%) [configuration]
M1	DPA	Acetophenone	91 [*R*]
M2 (a)	DPA	Acetophenone	90 [*R*]
M2 (b)	DPP	Acetophenone	87 [*R*]
M2 (b)	DPP	α-Tetralone	89 [*R*]
M3	DPA	Acetophenone	93 [*R*]
M4 (a)	DPA	Acetophenone	93 [*R]*
M4 (a)	DPA	α-Tetralone	93 [*R]*
M4 (b)	DPP	Acetophenone	92 [*R*]
M4 (b)	DPP	α-Tetralone	94 [*R*]
M5 (a)	DPA	Acetophenone	93 [*R*]
M5 (a)	DPA	α-Tetralone	93 [*R*]
M5 (b)	DPP	Acetophenone	93 [*R*]
M6	DPA	Acetophenone	84 [*R*]
M7	DPA	Acetophenone	83 [*R*]
M8 (a)	DPA	Acetophenone	90 [*R*]
M8 (a)	DPA	α-Tetralone	85 [*R*]
M8 (b)	DPP	Acetophenone	89 [*R*]
3a	DPP	Acetophenone	98 [*R*]
3a	DPP	α-Tetralone	97 [*R*]
3b	DPP	Acetophenone	97 [*R*]
3b	DPP	α-Tetralone	97 [*R*]
4a	DPA	Acetophenone	93 [*R*]
4a	DPA	α-Tetralone	94 [*R*]
4b	DPA	Acetophenone	93 [*R*]
4b	DPA	α-Tetralone	93 [*R*]

[a] Catalyst see Table 1.
[b] Aminoalcohol bound to the boronic acid at the polymer: DPA, (*S*)-α,α-diphenylalaninol; DPP, (*S*)-α,α-diphenylprolinol.
[c] Determined by HPLC; isolated yield in all cases >95%.

catalyst **4a** and **4b** derived from (*S*)-α,α-diphenylalaninol exhibit excellent selectivity combined with low cost, although the use of this aminoalcohol is rather uncommon in the CBS reduction.

By using microgels based on monomer **1**, high enantioselectivities were achieved in all cases. With EDMA as the crosslinking agent, selectivities were sometimes comparable to the values for the new monomeric CBS catalyst **4a** and close to those for the widely used monomeric catalyst **3a**[19] (Table 2). The better performance of the EDMA crosslinked polymers in comparison to the styrene-based analogues may be due to the higher flexibility of the methacrylate-based microgel network.

The selectivities obtained by the use of microgel catalysts based on monomer **2** were satisfying as well but on a lower level compared to the use of monomer **1**. This result is somewhat surprising, because CBS reductions with the related unbound catalysts **3b** and **4b** gave excellent selectivities comparable to those achieved with the free catalysts **3a**, **4a**, respectively (Table 2). Apparently, the higher flexibility of the boronic acid moiety has a disturbing influence when it is bound to a polymer backbone. The reason for this probably lies in the possible side reaction of boronic acid moieties to form the corresponding anhydrides. As a result, the accessibility of the catalyst sites inside of the microgels would be reduced because of the higher degree of crosslinking. In addition, the formation of boronic acid anhydrides could explain the significantly lower yield of polymer-bound aminoalcohol (Table 1).

Table 3. Consecutive reduction series with a microgel-bound catalyst (microgel M3) (substrate: acetophenone, for reduction conditions: see Experimental)

Entry	Enantiomeric excess[a] (%) [configuration]
1	93 [*R*]
2	93 [*R*]
3	93 [*R*]
4	92–93 [*R*]

[a] Determined by HPLC; isolated yield in each case >95%.

These initial findings prompted us to test the microgel catalysts in consecutive reduction series. The reductions were run in a stirred ultrafiltration reactor with microgel M3 as catalyst and acetophenone as the substrate. After each reduction, the microgel solution was purified by repeated concentration by membrane filtration and dilution with fresh solvent and directly recycled without isolation. Separation and recycling of the catalyst was possible for at least three times in addition to the first reduction with no or only a slight decrease in the enantiomeric excess (Table 3).

These results demonstrate the applicability of microgels as supports for oxazaborolidine catalysts. In particular, the simple preparation by solution polymerisation and the low intrinsic viscosity of the microgels are remarkable advantages. Consequently, microgels seem to be suitable candidates as soluble supports for anchoring other catalytic groups as well, thus providing a practical means of catalyst recovery while maintaining optimal accessibility of the functional groups. Especially, the application in a continuous mode in a membrane reactor seems to be rather promising. In this case the low viscosity is a particular advantage over the use of supported linear polymers.

Experimental

General

Melting points were determined on a Büchi 510 melting point apparatus. Elemental analyses were performed at the Institute of Pharmaceutical Chemistry, University of Duesseldorf. ^{1}H NMR (300 MHz) spectra were recorded on a Varian VXR 300 spectrometer. IR spectra were taken on a Perkin–Elmer 1420 spectrophotometer. Optical rotations were measured on a Perkin–Elmer 241 MC polarimeter. Ultrafiltration was done in Schleicher & Schuell SC 300 and Millipore XFUF 04701 stirring cells, using Celfa CMF-DY-040 ultrafiltration membranes (molecular weight cut off: 40 000 Dalton). Solution viscosity measurements were performed at 25°C in THF with a micro-Ubbelohde viscosimeter (Schott); the flow times were determined for three microgel concentrations between 0.05 and 0.02 g/ml. Microgel molecular weights were determined on a Knauer A0330 membrane osmometer equipped with a Celfa CMF-DY-040 ultrafiltration membrane; the osmotic pressure was determined in THF at 25°C for four microgel

concentrations ranging between 0.02 and 0.002 g/ml. Chiral HPLC analysis was accomplished with a Daicel Chiralcel OD column (mobile phase: hexane–*i*-propanol 95:5; flow rate: 1 ml/min) with UV detection at 256 nm.

All solvents employed were dried and distilled if necessary by standard procedures before use. THF was distilled over calcium hydride, dried over sodium wire and redistilled immediately before use under an argon atmosphere. Acetophenone and α-tetralone were dried over calcium hydride and distilled immediately before use under an argon atmosphere. Borane–dimethylsulfide complex (2 M in THF, Aldrich) was used as received. *tert*-Butyl-peroxy-2-ethylhexanoate (Luperox 26-R®) was a gift from Elf Atochem and was used as received. Commercially available monomers were dried over calcium hydride before use and purified by distillation at reduced pressure under a nitrogen atmosphere. Pure *p*-divinylbenzene (*p*-DVB),[20] (*S*)-1,1-diphenyl-2-aminopropanol (DPA),[21] (*S*)-1,1-diphenyl-2-pyrrolidinemethanol (DPP),[19] ethylene glycol O-[(4-vinylphenyl)-boronate] **1**,[22] triphenylboroxine and 2-(4-vinylphenyl)-ethyl boronic acid **2**[23] were prepared according to literature procedures.

(S)-2,5,5-Triphenyl-1H,3H-pyrrolo[1,2-c]-[1,3,2]oxazaborolidine (3a). 2.0 g (7.9 mmol) DPP and 0.823 g (2.6 mmol) triphenylboroxine were heated in 50 ml toluene under an argon atmosphere. The water formed was removed by azeotropic distillation using a Dean–Stark trap filled with molecular sieves (4 Å). After 16 h, the solvent was evaporated and the residue was purified by bulb-to-bulb distillation. The product was stored under an argon atmosphere. Yield: 95% (lit.[19] 98% without distillation); bp 175°C (0.1 mbar); ^{1}H NMR ($CDCl_3$): δ (ppm): 7.97–7.93 (m, 2H) 7.63–7.55 (m, 2H) 7.48–7.17 (m, 11H) 4.60 (dd, 1H, ^3J=5.77, 9.67 Hz) 3.63–3.55 (m, 1H) 3.40–3.32 (m, 1H) 1.95–1.68 (m, 3H) 1.0–0.85 (m, 1H); IR (KBr) (cm^{-1}): 3040(s), 3005(s), 2955(m), 2860(s), 1595(s), 1440(s)

(S)-2,5,5-Triphenyl-4-methyl-[1,3,2]oxazaborolidine (4a). This catalyst was prepared from (DPA) and triphenylboroxine following the method described for catalyst **3a**. Yield: 97%; bp 160°C (0.1 mbar); ^{1}H NMR ($CDCl_3$): δ (ppm): 7.82–7.13 (m, 15H) 4.57–4.54 (m, 1H) 3.80 (s, 1H) 0.88 (d, 3H, ^3J=6.35 Hz); IR (KBr) (cm^{-1}): 3400(m), 3220(m), 3020(s), 3005(s), 2960(m), 1595(s), 1440(s), 1015(s), 700(s); elemental analysis: calc. for $C_{21}H_{20}BNO$: C 80.53, H 6.44, N 4.47; found: C 80.17, H 6.43 N 4.39

Tri-(2-phenylethyl)-boroxine. The Grignard reagent solution prepared from 8.5 g (0.35 mol) magnesium and 50 g (0.27 mol) 2-phenylethyl bromide in 150 ml THF was cooled to 0°C and added to a cooled solution of 62 g (0.27 mol) tri-*n*-butylborate in 150 ml THF at −78°C. The mixture was allowed to warm to room temperature overnight and was hydrolysed with a saturated aqueous solution of NH_4Cl. After the addition of 100 ml diethyl ether, the organic phase was isolated and the aqueous phase was extracted twice with 150 ml of diethylether. After the evaporation of the solvent, the butanol was evaporated azeotropically under addition of water. The remaining solid was dried, solved in 150 ml toluene and condensed to the corresponding boroxine by heating under an argon atmosphere. The water formed was removed by azeotropic distillation using a Dean–Stark trap filled with molecular sieves (4 Å). After 8 h, the solvent was evaporated and the residue was purified by bulb-to-bulb distillation. The product was stored under an argon atmosphere. Yield: 55%; bp: 180°C (0,05 mbar); ^{1}H NMR ($CDCL_3$): δ (ppm): 1.30 (t, 6H, ^3J=7,98 Hz) 2.78 (t, 6H, ^3J=7,97 Hz) 7.12–7.32 (m, 15H); IR (KBr) (cm^{-1}): 3200(m), 3040(m), 3005(s), 2920(s), 1595(m), 1450(s), 1330(s); MS (EI): found 396 (M^+), (CI): found 414 (MNH_4^+) calc. 396,22; elemental analysis: calc. for $C_{24}H_{27}B_3O_3$: C 72.81, H 6.87; found: C 73.00, H 7.08

(S)-2-(2-phenylethyl)-5,5-diphenyl-1H,3H-pyrrolo[1,2-c]-[1,3,2]oxazaborolidine (3b). This catalyst was prepared from DPP and tri-(2-phenylethyl)-boroxine following the method described for catalyst **3a**. The product is a colorless liquid, which crystallizes upon standing and can be stored under an argon atmosphere. Yield: 95%; bp 175°C (0.055 mbar); ^{1}H NMR ($CDCl_3$): δ (ppm): 7.52–7.12 (m, 15H) 4.32 (dd, 1H, ^3J=5.77, 9.89 Hz) 3.30–3.21 (m, 1H) 3.02–2.94 (m, 1H) 2.89 (t, 2H, ^3J=7.96 Hz) 1.76–1.52 (m, 3H) 1.28 (t, 2H, ^3J=7.97 Hz) 0.80–0.66 (m, 1H); MS (EI): found 367 (M^+), calc. 367.21; elemental analysis: calc. for $C_{25}H_{26}BNO$: C 81.70, H 7.14, N 3.81; found: C 81.34, H 7.24, N 3.63.

(S)-2-(2-phenylethyl)-5,5-diphenyl-4-methyl-[1,3,2]oxazaborolidine (4b). This catalyst was prepared from DPA and tri-(2-phenylethyl)-boroxine following the method described for catalyst **3b**. Yield: 93%; bp 160°C (0.055 mbar); ^{1}H NMR ($CDCl_3$): δ (ppm): 7.62–7.16 (m, 15H) 4.42–4.36 (q, 1H, ^3J=6.28 Hz) 3.35 (s, 1H) 2.81 (t, 2H, ^3J=8.17 Hz) 1.27 (t, 2H, ^3J=8.18 Hz) 0.77 (d, 3H, ^3J=6.38 Hz); MS (EI): found 341 (M^+), calc. 341.20; elemental analysis: calc. for $C_{23}H_{24}BNO$: C 80.95, H 7.09, N 4.10; found: C 80.66, H 7.26, N 4.01.

Polymerisation procedures

Unfunctionalised microgels: For the determination of the critical monomer concentration (C_m), styrene and *p*-DVB were weighed into flasks in the desired proportions. 3% w/w azobis(isobutyronitrile) (AIBN) was added as initiator; the mixture was diluted with the required amount of THF to achieve a specific monomer concentration and nitrogen was bubbled for some minutes through the solutions to remove atmospheric oxygen. The flasks were subsequently sealed and placed in an oven at 63°C for four days, after which they were checked for gelation. The highest monomer concentration which could be employed with a given monomer mixture without sample gelation was taken as the critical monomer concentration (C_m).

Some unfunctionalised microgels were isolated after polymerisation for the determination of the pendant vinyl groups. For this, the microgel solutions were concentrated to about 1/10 of their volume, added dropwise with efficient stirring to about five times their volume of petroleum ether, filtered off and vacuum dried to constant weight.

Microgel-bound oxazaborolidenes: A mixture of commercial (DVB) (5–10 mol%; crosslinker content: 80%), styrene

and monomer **1** or **2** (17 mol%) was prepared in a round-bottomed flask; 3% (w/w) *tert*-butyl-peroxy-2-ethylhexanoate was added and the resulting mixture was diluted with THF to reach a monomer concentration [M] of 5% (w/w). The solution was degassed three times through freeze–thaw cycles and polymerised at 64°C for four days.

Functionalised microgels based on the comonomers MMA and EDMA were also prepared by this procedure. After polymerisation, the microgel solutions were concentrated to about 1/10 of their volume and, when monomer **1** was used, treated with a small amount of water for ester cleavage. After 15 min, the solutions were added dropwise with efficient stirring to about five times their volume of a mixture of water–MeOH (1:1 w/w) containing a small amount of sodium chloride. The precipitated microgels were filtered off and dissolved again in THF. Traces of water were removed with sodium sulfate. The microgels were then precipitated from petroleum ether, filtered off and vacuum dried to constant weight.

For the conversion of the free boronic acid moieties to oxazaborolidines, the boronic acids were condensed with the aminoalcohols DPA or DPP. The precipitated microgel was dissolved in THF containing a small amount of water. 1.5 equiv. of the aminoalcohol of choice were added and the solution was heated under an argon atmosphere. The water formed was removed by azeotropic distillation using a Dean–Stark trap filled with molecular sieves (4 Å). After 48 h, the microgel solution was purified by membrane filtration in an ultrafiltration stirring cell by repeated concentration and dilution with fresh solvent and stored under an argon atmosphere.

Microgel characterisation

Catalyst content: A sample of purified microgel solution was evaporated to dryness at room temperature. The residue was vacuum-dried in an oven at 50°C to constant weight. The catalyst content in the microgel was determined by nitrogen analysis of the residue.

Determination of the pendant vinyl groups by oxymercuration:[18] 200 mg of precipitated microgel were treated with 5 ml of a solution of 150 ml dry methanol, 2.5 g mercury(II)-acetate and 3 drops of acetic acid. After stirring for 20 h, 0.25 g sodium bromide and 8 drops of a solution of 1% phenolphthaleine in MeOH were dissolved in the suspension. The mixture was cooled to 0°C and titrated with 0.025 M NaOH in MeOH. The amount of NaOH solution used was corrected for the amount needed for the titration of the pure mercury(II)-acetate solution. Another 200 mg of the same microgel were similarly treated with 5 ml of a solution of 150 ml dry methanol and 3 drops of acetic acid and titrated following the procedure given above. Again, this blank value was corrected for the amount of NaOH needed for the titration of the pure solution. From the difference between the two results, the amount of pendant vinyl groups in the microgel sample was calculated.

Reduction of the pendant vinyl groups with diimine: Diimine was generated in situ by acid decomposition of potassium azodicarboxylate, prepared following the method of Hamersma and Snyder.[24] To a microgel solution in THF containing 1 equiv. of pendant vinyl groups, 20 equiv. of potassium azodicarboxylate were added. 40 equiv. acetic acid in THF (40% w/w) were added dropwise to this mixture over 2 days. After complete addition, the microgel was isolated by precipitation in water/MeOH (50% w/w). (*Caution:* this reaction can produce hydrazine. Hydrazine is toxic and may cause cancer.)

Catalytic tests

General reduction method for low molecular weight catalysts: In a dried flask, 10 mmol of the borane–dimethylsulfide complex were added to a solution of 1 mmol of catalyst **1b** or **2b** in 30 ml dry THF under an argon atmosphere. After 30 min, 10 mmol of the ketone (acetophenone or α-tetralone) dissolved in 3 ml dry THF were added continuously at room temperature during 30 min. The reaction mixture was stirred for further 12 h, after which it was quenched with MeOH and concentrated in vacuo. The product was isolated by bulb-to-bulb distillation; the enantiomeric excess was determined by HPLC.

General reduction method for microgel-bound catalysts: A dried flask was charged with an amount of microgel solution in THF corresponding to 1 g microgel. The solution was diluted with dry THF so that a concentration of 1 g microgel in 45 ml solvent resulted. The further procedure followed the one employed for the low molecular weight catalysts; the catalyst amount was maintained at 10 mol%.

Consecutive reduction series with a microgel-bound catalyst: The reductions were performed under an argon atmosphere in an ultrafiltration stirring cell with acetophenone as the substrate. The procedure for each reduction followed the one previously described. After each reaction, the microgel solution was purified by repeated concentration by membrane filtration and dilution with fresh solvent, after which the new catalytic run was started. The filtered product solution was quenched immediately with MeOH and the ketone was isolated as described above.

Acknowledgements

This research was supported by the ‘Bundesministerium für Bildung, Wissenschaft, Forschung und Technologie’, Bonn, (reference number 03D0029C6) and by ‘Fonds der Chemischen Industrie’. A fruitful cooperation with Prof. H. G. Schmalz, University of Cologne, is gratefully acknowledged.

References

1. Hirao, A.; Itsuno, S.; Nakahama, S.; Yamazaki, N. *J. Chem. Soc. Chem. Comm.* **1981**, 315.
2. Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.
3. Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1475.
4. Maruoka, K.; Yamamoto, H. *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: Weinheim, 1993.

5. Deloux, L.; Screbnik, M. *Chem. Rev.* **1993**, *93*, 763.
6. Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1987.
7. (a) Shimizu, M.; Kamei, M.; Fujisawa, T. *Tetrahedron Lett.* **1995**, *36*, 8607. (b) Ostendorf, M.; Romagnoli, R.; Pereiro, I. C.; Roos, E. C.; Moolenaar, M. J.; Nico Speckamp, W.; Hiemstra, H. *Tetrahedron: Asymmetry* **1997**, *8*, 1773. (c) Kinugasa, M.; Harada, T.; Oku, A. *J. Org. Chem.* **1996**, *61*, 6772. (d) Kiyooka, S.; Hena, M. A. *Tetrahedron: Asymmetry* **1996**, *7*, 2181.
8. (a) Itsuno, S.; Nakano, M.; Ito, K.; Hirao, A.; Owa, M.; Kanda, N.; Nakahama, S. *J. Chem. Soc. Perkin Trans. 1* **1985**, 2615. (b) Caze, C.; El Moualij, N.; Hodge, P.; Lock, C. J.; Ma, J. *J. Chem. Soc. Perkin Trans. 1* **1995**, 345. (c) Franot, C.; Stone, G. B.; Engeli, P.; Spöndlin, S.; Waldvogel, E. *Tetrahedron: Asymmetry* **1995**, *6*, 2755.
9. See for example Prazeres, D. M. F.; Cabral, J. M. S. *Enzyme Microb. Technol.* **1994**, *16*, 738.
10. Giffels, G.; Beliczey, J.; Felder, M.; Kragl, U. *Tetrahedron: Asymmetry* **1998**, *9*, 691.
11. For recent reviews, see (a) Funke, W.; Okay, O.; Joos-Müller, B. *Adv. Polym. Sci.* **1998**, *136*, 139. (b) Antonietti, M. *Macromol. Symp.* **1995**, *92*, 1995.
12. (a) Stacey, K. A.; Weatherhead, R. H.; Williams, A. *Makromol. Chem.* **1980**, *181*, 2517. (b) Stacey, K. A.; Weatherhead, R. H.; Williams, A. *Makromol. Chem.* **1980**, *181*, 2529.
13. Ford, W. T.; Lee, J.-J.; Yu, H.; Ackerson, B. J.; Davis, K. A. *Macromol. Symp.* **1995**, *92*, 333.
14. Graham, N. B., UK Patent GB2090264b, 1984; Graham, N. B.; Mao, J.; Urquhart, A. *Angew. Makromol. Chem.* **1996**, *240*, 113; Graham, N. B.; Cameron, A. *Pure Appl. Chem.* **1998**, *70*, 1271.
15. *Dispersion Polymerisation in Organic Media*, Barrett, K. E. J. Ed.; Wiley: New York, 1975.
16. Schunicht, C. PhD Thesis, University of Duesseldorf, 1999.
17. Seitz, U. *Makromol. Chem.* **1977**, *178*, 1689.
18. (a) Gyenes, I. *Titrationen in nichtwäßrigen Medien*; Ferdinand Enke Verlag; 1970, p. 592. (b) Kaess, S. PhD Thesis, University of Duesseldorf, 1988.
19. Mathre, D. J.; Jones, T. K.; Xavier, L. C.; Blacklock, T. J.; Reamer, R. A.; Mohan, J. J.; Turner Jones, E. T.; Hoogsteen, K.; Baum, M. W.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 751.
20. (a) Campbell, T. W.; McDonald, R. N. *J. Org. Chem.* **1959**, *24*, 1246. (b) Wulff, G.; Akelah, A. *Makromol. Chem.* **1979**, *179*, 2647.
21. Dammast, F.; Reißig, H.-U. *Chem. Ber.* **1993**, *126*, 2449.
22. Wulff, G.; Hohn, J. *Macromolecules* **1982**, *15*, 1255.
23. Wulff, G.; Sarhan, A.; Gimpel, J.; Lohmar, E. *Chem. Ber.* **1974**, *107*, 3364.
24. Hamersma, J. W.; Snyder, E. I. *J. Org. Chem.* **1965**, *30*, 3985.