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A Polymer-Bound Oxazaborolidine Catalyst: Enantioselective Borane Reductions of Ketones

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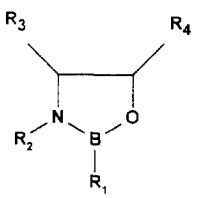
Abstract : A polymer-bound oxazaborolidine catalyst has been prepared and used in the enantioselective borane reduction of two model ketones. The catalyst is derived from (S)-a,a-diphenyl-2-pyrrolidinemethanol and poly-*p*-styrene boronic acid (1 % cross-linked). After reduction of acetophenone, the reaction mixture was quenched and the polymer-bound catalyst was recovered by simple filtration. Subsequent use of this catalyst "as is" for a second reduction of acetophenone was investigated and only a marginal loss in selectivity was observed. The selectivity began to diminish during a third and subsequent reductions. The preparation and use of such a polymer-bound catalyst are described.

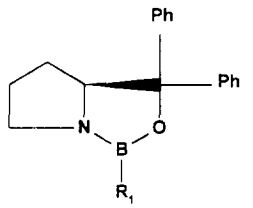
Introduction

Oxazaborolidines (ie. **1** and **2**) are well known catalysts for the efficient asymmetric borane reduction of prochiral ketones to the corresponding enantiomerically enriched alcohols. Numerous publications[4] describe optimization, variations, mechanistic proposals, as well as applications in total synthesis. Several review articles exist[5] concerning this methodology. Much of the published research effort in this field has been from various industrial research groups[6] which indicates that this is an example of a powerful research method that has promise for being adapted into a technically feasible industrial process.



1

Oxazaborolidines (general formula)



2

(S)-α,α-Diphenyl-2-pyrrolidinemethanol Derived Oxazaborolidines

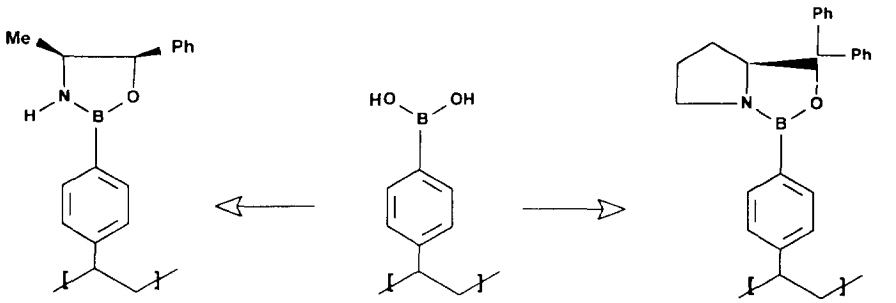
Indeed, one attractive feature from an industrial point of view is that recovery of the expensive ligand and eventual regeneration of the catalyst is possible. However, the procedure is lengthy and recovery is not complete.[7] If the catalyst remained intact after a "safe" quench and was insoluble (ie. polymer-bound), it could be easily separated from the product thus avoiding lengthy recovery and purification. Such a catalyst would offer a great advantage over the monomer version in that it could be recovered by simple filtration and

then reused. In addition, because of this inherent stability, the catalyst could be stored[8] over long periods of time without degradation. A true test of intact recovery and stable storage would be the performance of this recovered or stored catalyst in subsequent reduction reactions. In order for all this to be possible, the catalyst must be more stable than those already described in the literature. This report describes our attempt to develop such an optimal catalyst by preparing a polymer-bound oxazaborolidine.

We are not the first to work towards a polymer-bound oxazaborolidine catalyst. Itsuno and co-workers have published[9] a number of papers describing their preparation of several ligands covalently bounded to various polymer supports and the subsequent generation of oxazaborolidine catalysts for the reduction of ketones, imines, and oximes. In the case of borane catalyzed reductions of ketones, the active catalyst is actually the B-H oxazaborolidine formed in-situ from the polymer-bound ligand and a source of BH_3. More ketone and BH_3 were added leading to an enantioselective reduction. They eventually used apparatus allowing for "batch systems" and a "flow reactor". In this sense the chiral ligand was easily recovered by filtration and reused without a loss in selectivity. While very attractive, this approach did not satisfy our requirements for an optimal catalyst because it is the ligand and not the catalyst that can be recovered intact. While less relevant to our goal it should be mentioned that other authors[10] have prepared similar catalysts for the enantioselective addition of diethylzinc to aldehydes. Towards the end of our efforts in the laboratory and during the revision of this manuscript, Caze and co-workers published[11] their results describing enantioselective reductions of prochiral ketones catalyzed by polymer-supported oxazaborolidines bound via the boron atom. Their approach and results are closely related[12] to ours.

Our goal of developing an optimal catalyst with potential for industrial use resulted in the decision to bind the polymer via the boron atom, more specifically, we set out to prepare a catalyst whereby the boronic acid partner would be poly-*p*-styrene boronic acid (**7**).[13] Because we wanted to develop a catalyst for industrial application, we were concerned about simplicity of recovery, scale-up, reproducibility and safety. The most challenging aspect for us was safety, which meant initial destruction of any active hydride before filtering. The idea of this approach was that such a catalyst, even though it contained the oxazaborolidine moiety, would be stable to quenching and could perhaps be recovered intact. This approach appeared to be risky while the usefulness depended on this unknown stability of the oxazaborolidine moiety when bound to a polymer. If the catalyst proved to be sufficiently stable and our goals were achieved, then we would really have an industrially useful catalyst offering advantages over the monomer catalyst. This is in fact what Caze and co-workers achieved to some extent using (1*R*,2*S*)-(-)-norephedrine as the chiral ligand to prepare the catalyst **3**. We used (S)-α,α-diphenyl-2-pyrrolidinemethanol with similar success to prepare **4**.[1] In contrast to other polymer-bound oxazaborolidine catalysts, **3** and **4** were prepared with the intent of recovering not only of the ligand but the intact catalyst (**Scheme 1**).

It seemed important that for the polymer catalyst to be effective, there needed to be similarities to the monomer especially with respect to the active site responsible for selectivity. This is in fact the case of the boronic acid polymer derived catalysts. An additional advantage would be easy access to a variety of



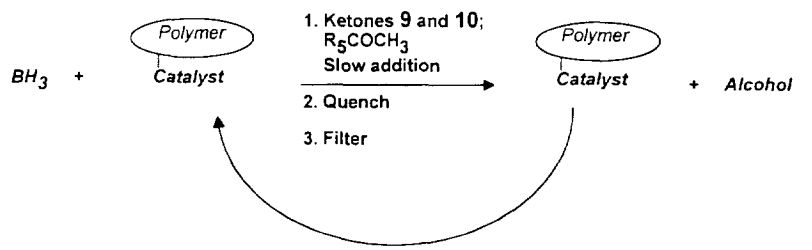
3
Caze's Boron-Polymer Bound Oxazaborolidine Catalyst

7

4
Our Boron-Polymer Bound Oxazaborolidine Catalyst

catalysts which could be prepared simply by varying the chiral amino acid partner used in the formation of the catalyst. In the event that hydrolysis occurs during recovery or if there is a significant decrease in catalytic activity and selectivity, then there would be no advantage compared to the monomer catalyst. We therefore had to answer 4 questions: could we prepare the catalyst; would such a catalyst have sufficient catalytic activity; would the selectivity of the reduction remain high; could we recover the catalyst intact and use it in subsequent reductions with minimal losses in selectivity. This paper describes our successful efforts to prepare and apply such a catalyst for the enantioselective borane reductions of two model ketones. While the recovery and reuse of the catalysts for a second reduction with only almost no loss in selectivity appears to be feasible, a third reduction without significant selectivity loss has not yet been achieved and is currently under investigation.

Scheme 1 The Polymer-Bound Catalyst Applied to Borane Reduction of Ketones



Results and Discussion

Preparation of the Polymer-Bound Catalyst

Starting with polystyrene as our polymer support of choice, we initially carried out experiments using the 2 % cross-linked variety. In our hands complete functionalization of the bromo-derivative **5** with 2 % cross-linkage was never achieved (see **Table 1**). In addition to this problem, subsequent reactions were better and more reproducible when 1 % cross-linked was used and therefore only such experiments will be

described here in this paper. Two types of 1 % cross-linked polystyrene, 200-400 mesh and 80 mesh, were used to prepare the polymeric catalysts.

Preparation of the polymeric boronic acid (**Scheme 2**) : The synthesis of the poly-*p*-styrene boronic acid (7) from polystyrene via *p*-bromo-polystyrene (**5**) has already been described in the literature.[13] The polymeric boronic acid was analyzed by microanalysis for boron and bromine heteroatom. **Table 1** shows the influence of the degree of cross-linking and degree of functionalization on the conversion of the bromopolystyrene **5** into the boronic acid 7.

Scheme 2. Preparation of the Polymeric Boronic Acid 7.[13]

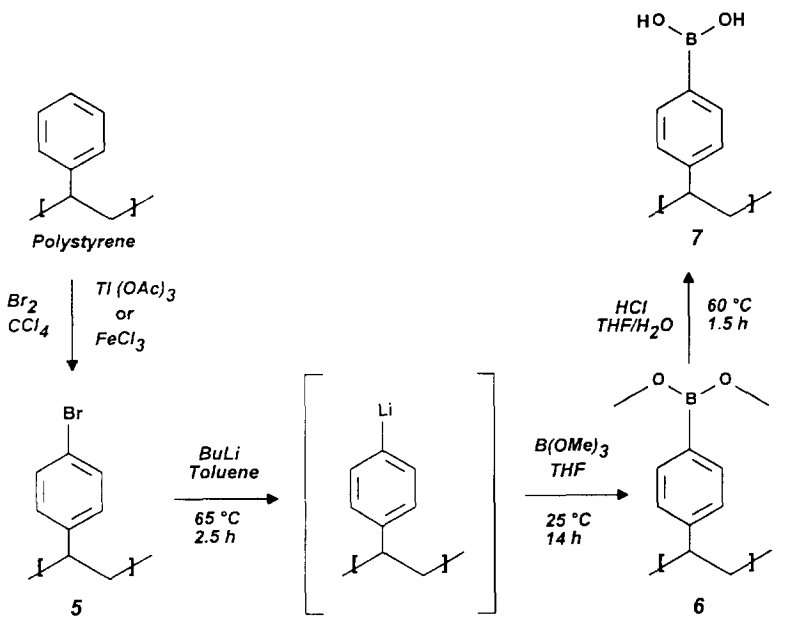


Table 1. Effect of cross-linking/functionalization of the bromopolystyrene on the formation of 7

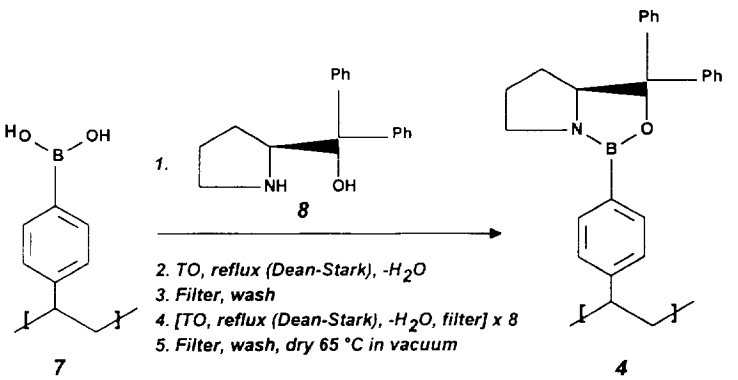
Degree of cross-linking (%)	Degree of functionalization (%)	Conversion of the Br[a] (%)	Remaining Br (%)[a]
1	10	79	1
1	41	60	1
2	8	43	49
2	68	20[b]	43
20	33	1	95

[a]Percentage of conversion and of remaining bromine were calculated from the boron and bromine microanalysis. Total amount of the conversion and of remaining bromine was never equal to 100% because of partial hydrolysis of the lithium derivative.
[b]Lithiation carried out over 6 h instead of 2.5 h.

We subsequently decided to utilize the 40 % functionalized (about 3 mmoles Br/g) bromopolystyrene (**5**) instead of the 10 % variety in order to have a catalyst with sufficient functionalization and thus avoiding the need for large mass quantities of the polymeric catalyst for the subsequent reductions. We also showed that it is possible to prepare the boronic acid in a one-pot procedure thus avoiding the filtration of the lithiate which we determined to be somewhat of a safety problem.[14] The boronic ester (**6**) was then hydrolyzed in an acidic solution using THF instead of dioxane as solvent. Under these conditions, the conversion was slightly reduced from 60% (B: 2.04 mmoles/g) to 50 % (B: 1.57 mmoles/g). The use of 200-400 or 80 mesh grade did not make any difference in the preparation of the polymeric boronic acid **7**.

Preparation of the polymer-bound oxazaborolidine catalyst (**Scheme 3**): The polymer-bound oxazaborolidine catalyst **4** (200-400 mesh) was prepared from the boronic acid **7** and 1.5 equivalents of (S)-diphenylprolinol **8**[15] at reflux in toluene for 48 h with a dean-stark trap to remove water. The polymer-catalyst was then washed three times with toluene and finally with hexane. The catalyst **4** was analyzed by microanalysis content of nitrogen (1.14 mmoles N/g), oxygen (2.72 mmoles O/g), and boron (1.48 mmoles/g). Nitrogen content corresponded to the amount of ligand **8** ((S)-diphenylprolinol) introduced into the polymer. After 72 h of reaction, the content of nitrogen was not higher. Unfortunately, when the polymeric catalyst was suspended in solvents (THF, toluene), a loss of the ligand was observed by tlc. Moreover infrared spectrum of the catalyst showed two absorptions corresponding to O-H and N-H bonds. For these reasons, the polymeric catalyst **4** was heated several times at reflux in fresh toluene for 1 h, each time followed by filtration. After about eight filtrations, no more ligand was removed.[16] The catalyst was dried at 65 °C under vacuum for 48 h and re-suspended few days later in toluene without loss of ligand. In contrast to the monomer, the polymeric catalyst is stable and can be kept without precautions.

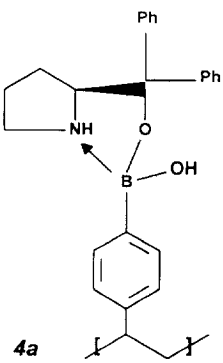
Scheme 3. Preparation of the Polymer-Bound Oxazaborolidine Catalyst **4**.



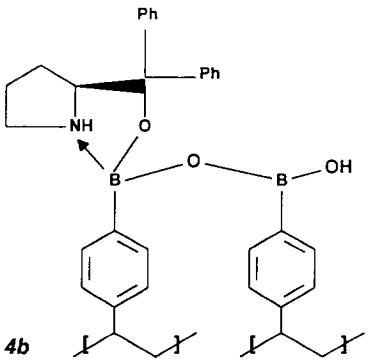
It is possible that before the washing in toluene at reflux, the free ligand finds itself encapsulated in the resin and somehow complexed with the functionalized polymer. At the end, the nitrogen content was only 0.47 mmoles N/g (a loss of 59 %). 30 % of the boronic acid **7** was thus converted into the

oxazaborolidine and at the end the polymer was functionalized to an extent of 8 % with the oxazaborolidine moiety. For the formation of the catalyst, the addition of p-toluenesulphonic acid as catalyst, the use of molecular sieves at room temperature to remove water or the use of xylene instead of toluene to increase temperature did not give better results. Steric hindrance can perhaps explain this low functionalization with the oxazaborolidine group. Starting from the polymeric boronic acid 80 mesh, the formation of the catalyst was better. After 24 h at reflux in toluene with 1.2 equivalents of ligand and after eight washings with fresh toluene at reflux for an hour, the nitrogen content was 0.78 mmoles N/g. This result was unexpected because the size of the particles in the 80 mesh polystyrene are bigger and interaction surface with reagent is thus lower.

The washed polymeric catalyst showed always an absorption corresponding to N-H bond even if it has been reduced. To explain this, opened forms of the type **4a** or **4b** may also be present with compound **4**. To confirm this hypothesis, solid ^{11}B-NMR was carried out.[17] According to literature,[6a] it is possible to distinguish between a complexed and a non complexed boron. When the polystyrene is replaced by a methyl group, the chemical shift of the non complexed boron is 34.3 ppm whereas the opened monomer forms corresponding to **4a** and **4b** gave a peak at 8.9 or 7.8 ppm. In our case, ^{11}B spectrum exhibits at least two peaks, one with a large quadrapolar interaction giving rise to a broad signal from 30 to 6 ppm which could correspond to the non complexed boron of the remaining boronic acid **6**, the oxazaborolidine catalyst **4** and the half opened form **4a**. The second peak at about 0 ppm could be two peaks but with small quadrapolar interactions corresponding to the complexed boron of structure **4a** and **4b**. The catalyst, numbered as **4**, is likely to contain these structures.



4a



4b

Enantioselectivity in the Reduction of Ketones Using the Polymer-Bound Oxazaborolidine Catalyst

The polymeric catalyst **4** was tested using two ketones, acetophenone **9** and the cyclohexylmethyl ketone **10**. For all the reductions, borane ("BH_3") was added to a 10 mol % suspension of the catalyst **4** in THF (**Table 2**). The suspension was heated to 40 °C[18] and the ketone was added slowly during 3-4 h (**Scheme 1**). At the end of the addition, the reaction was complete. After the hydrolysis with methanol, the reaction

mixture was filtered and the polymer washed three times with THF and finally with hexane. No loss of the ligand was observed by tlc, which was confirmed by the nitrogen microanalysis of the catalyst. No further purification of the alcohol was done before determination of the enantiopurity. The chemical purity of the crude alcohol was determined by HPLC (>98 %) for (*R*)-1-phenylethanol (**11**) and by GC (>97 %) for (*R*)-1-cyclohexylethanol (**12**).

Different complexes of borane (THF, 1,4-oxathiane, and dimethylsulfide) were tried (**Table 2**). When BH_3-THF complex was used, 1.2 equivalents were needed for complete reaction. Otherwise, 0.6 equivalents of borane were enough for complete reactions. There was not much difference in terms of the selectivity (93 % - 95 % ee) for the reduction of acetophenone but for the reduction of cyclohexylmethyl ketone, borane-dimethylsulfide or borane-1,4-oxathiane complex gave better results (81-83% ee) than borane-THF (62-67 % ee). It has been mentioned in the literature that more consistent results are obtained with neat borane-dimethylsulfide complex instead of the borane-THF. The enantioselectivities achieved using the polymeric catalyst **4** are compared to borane-phenyl oxazaborolidine **2** (**Table 2**). Such good results were not expected, especially for the reduction of cyclohexylmethyl ketone **9** which reacts faster than acetophenone **10** with borane in the absence of catalyst. This probably explains why the enantioselectivity was lower for the reduction of this ketone. It is perhaps somewhat surprising that the enantioselectivities obtained using the polymer-bound catalyst were comparable with those obtained using the monomer catalysts. The ketone must first diffuse into the polymer before complexation can take place and could therefore increase the chance of uncatalysed reduction.

Table 2. Enantioselectivity in the reduction of two ketones **9** and **10** by "BH_3" and the catalyst **4**. Two entries are included for comparison with the monomer catalyst **2** (R_1=Ph).

Catalyst[a]	R_1	*Ketone*	R_S	*"BH_3"*	ee(%)[b]
2	Ph	**9**	Ph	1,4-Oxathiane (0.6 eq)	97
4	Polystyrene[c]	**9**	Ph	THF (1.2 eq)	95
4	Polystyrene[c]	**9**	Ph	1,4-Oxathiane (0.6 eq)	94
4	Polystyrene[c]	**9**	Ph	SMe_2 (0.6 eq)	93
4	Polystyrene[d]	**9**	Ph	SMe_2 (0.6 eq)	98
2	Ph	**10**	C_6H_{11}	1,4-Oxathiane (0.6 eq)	80
4	Polystyrene[c]	**10**	C_6H_{11}	THF (1.2 eq)	62
4	Polystyrene[c]	**10**	C_6H_{11}	SMe_2 (0.6 eq)	81
4	Polystyrene[d]	**10**	C_6H_{11}	THF (1.2 eq)	67
4	Polystyrene[d]	**10**	C_6H_{11}	SMe_2 (0.6 eq)	83
4	Polystyrene[d]	**10**	C_6H_{11}	1,4-Oxathiane (0.6 eq)	82

[a] % mol catalyst used was always 10 %; [b] ee was determined on the crude reaction products; [c] 200-400 mesh; [d] 80 mesh

Recycling of the Catalyst

The recycling of the catalyst was tested by the reduction of acetophenone **9** using BH_3-dimethylsulfide and catalyst **4** derived from polystyrene with 200-400 and 80 mesh (**Table 3**). The second reduction was performed ("without regeneration") with lower but still high enantioselectivity. The difference between the first and the second reduction was only from 1 to 4 % ee. The catalyst was analyzed by microanalysis of boron, oxygen and nitrogen atoms. In most cases, the boron and oxygen content increased from 15 to 30% after the reduction and the nitrogen content was nearly constant. Perhaps, after the hydrolysis with methanol, trimethylboronate was formed which would be difficult to removed from the polymeric matrix. Unfortunately, the enantioselectivity during a 3rd reduction diminished to ca 70-78 %. We are currently trying to improve this approach by modifying the "quench" and recovery procedure in order to favor an intact recovery of the catalyst so that further reductions will be possible with no selectivity loss.

Table 3. Reuse of the polymeric catalyst for a second reduction of acetophenone.

Polystyrene (mesh)	Catalyst B; N contents (mmoles/g)	1st reduction[a] ee (%)	2nd reduction[a] without regeneration[b] ee (%)	2nd reduction[a] with regeneration[b] ee (%)
200-400	0.69; 0.46	96	93	94
200-400	1.76; 0.48	95	90	91.5
80	1.11; 0.78	98	96	97

[a] Reductions were performed with borane-dimethylsulfide complex at 40°C (see *Experimental* section); [b] After the first reduction, the catalyst was separated into two parts. The first part, "without regeneration", was directly used for a second reduction. The second part was regenerated by first washing with toluene at reflux to eliminate the alcohol encapsulated in the polymeric matrix, filtering, then refluxing in fresh toluene with a dean-stark trap to remove all the volatile solvent such as methanol used for the quenching of the reaction of reduction.

CONCLUSION

This paper describes the preparation of a polymer-bound oxazaborolidine catalyst and its performance for the borane reduction of two prochiral ketones. Enantioselectivities were similar to those obtained using the monomer catalyst. The polymer-bound catalyst has the advantage of being more stable and may be therefore handled without any special precautions. The catalyst, recovered by filtration, was successfully used a second time with almost no loss in selectivity for the reduction of acetophenone. While this appears promising, a third reduction without a loss of selectivity was not achieved. We believe that the ultimate potential of such a catalyst is great and therefore more effort will be directed towards avoiding this loss in selectivity.

EXPERIMENTAL

Polystyrene resin (1% divinylbenzene; 200-400 mesh) was purchased from Fluka and polystyrene (1% divinylbenzene; 80 mesh) was purchased from Parolit Company. All the solvents were analytic grade and were used without further purification. Infrared spectra were recorded on a BRUKER IPS-66 spectrometer using potassium bromide pellets. ^{11}B solid NMR was recorded on a bruker ASX 500 spectrometer. ^{11}B chemical shifts are reported in ppm from an external reference of boron trifluoride etherate (0.0 ppm). Elemental analysis were performed at Sandoz Laboratories. Purity of the alcohol **11** was determined by HPLC on a HEWLETT PACKARD 1050 using a lichrospher 100 RP-18 5µ (250 x 4 mm) column with a Uv

detection at 210 nm. 20 µL of a solution of alcohol **11** (10 mL) in a mixture of acetonitrile/water, 5/15 (20 mL), was injected. The mobile phase was a mixture of phase A and B (A: 4.5 g of trimethylammonium hydroxide in 900 mL of water and 100 mL of acetonitrile with the pH adjusted to 4.7 with concentrated H_3PO_4; B: 4.5 g of trimethylammonium hydroxide in 400 mL of water and 600 mL of acetonitrile with the pH adjusted to 4.7 with concentrated H_3PO_4. For 2 min, the mobile phase was 30% of B then increased to 70% of B during the next 15 min (flow rate was 1.5 mL/min at 40° C). Purity of the alcohol **12** was determined by GC on a Perkin-Elmer 8700 using a DB 1 (30 x 0.32 mm) column. 1 µL of a solution of alcohol **12**, 0.1 % in dichloromethane was injected at 50 °C and temperature of the column was increased to 180 °C with a gradient of 10° C/min. Determination of the enantiomeric excess was done by chiral HPLC analysis. *For (R)-1-phenyl ethanol* **11**: analysis was carried out on the free alcohol using a Chiracel OD (DAICEL, 250 x 4.6 mm) column with Uv detection at 210 nm (flow rate was 0.5 mL/min at 40 °C). The mobile phase was 2.5 % isopropanol in n-hexane. The column was rinsed in between injections with 40 % isopropanol in n-hexane during 35 min. The racemic alcohol as well as the pure antipode were tested under the same conditions as a control and the pure antipodes showed no sign of epimerization. *Analysis for (R)-1-cyclohexyl ethanol* **12**: the crude reaction product was converted to the phenylisocyanate ester for analysis. Column conditions were as described above with Uv detection at 235 nm and the column temperature of 25 °C. The mobile phase was 10% isopropanol in n-hexane.

Bromopolystyrene 5 Bromopolystyrene **5** was prepared as described in the literature[13] from the polystyrene 1 % cross-linked (80 mesh or 200-400 mesh) and 0.46 equivalents of bromine in the presence of 2.7 % of $FeCl_3$ used as catalyst. Microanalysis: Br 24.9 % (3.12 mmoles/g).

Polymeric boronic acid 7 In a dried flask under argon, bromopolystyrene **5** (3.12 mmoles Br/g; 80 mesh) (20 g; 62.4 mmoles of Br) was suspended in 300 mL of toluene. The reaction mixture was stirred for 30 min and a solution of 1.6 M of butyllithium in hexane (105.3 mL; 168.5 mmoles) was added dropwise. After complete addition, the mixture was heated to 65 °C for 2.5 h, then cooled to room temperature. The trimethylborate (26.9 mL; 237.12 mmoles) was added and the mixture stirred overnight at room temperature. The resin was filtered and washed with THF. After addition of 200 mL of THF, 17 mL of water and 52 mL of concentrated HCl, the mixture was heated at 60° C for 1.5 h. The resin was collected on a filter and washed repeatedly with THF/H_2O (3/1), THF, acetone, and methanol. After drying 60° C under vacuum, the polymeric boronic acid **7** was recovered as a pale yellow powder. The infrared spectrum included two large absorptions at 3550 (O-H) and 1317 (B-O) cm^{-1} Microanalysis: B 1.7 % (1.57 mmoles/g); O 4.2 % (1.63 mmoles/g); B 0.9 % (0.11 mmoles/g).

Polymer-bound oxazaborolidine catalyst 4 In an apparatus equipped with a Dean-Stark trap, the polymeric boronic acid **7** (20.3 mmoles B/g; 200-400 mesh) (10 g; 20.3 mmoles of B) was suspended in 250 mL of toluene and (S)-α,α-diphenyl-2-pyrrolidinemethanol[8] **8** (7.71 g; 30.5 mmoles) was added. The mixture was stirred for 48 h at reflux and a few drops of water were removed. The mixture was cooled to room temperature and the polymer was filtered, washed three times with toluene and resuspended in 200 mL of fresh toluene. It was then heated to reflux for 1 h and filtered. This last operation was repeated (8 to 10 times) until all the free ligand **8** ((S)-α,α-diphenyl-2-pyrrolidinemethanol) was completely removed (detection by GC). After the last filtration, the catalyst **4** was rinsed with toluene and finally hexane. It was dried at 65 °C under vacuum. The infrared spectrum included two small absorptions at 3540 (O-H), 3300 (N-H) and a large one at 1339 (B-O and B-N) cm^{-1}; ^{11}B solid NMR (500 MHz) δ 0.0; 2.5; 14.5; 19.3; Microanalysis: B 1.7 % (1.57 mmoles/g); O 3.55 % (2.22 mmoles/g) N 0.66 % (0.47 mmoles/g).

General procedure for reduction of ketones In a dried flask under nitrogen, the catalyst **4** was suspended (0.46 mmoles N/g; 200-400 mesh) (3 g; 1.38 mmoles of N) in 25 mL of THF. The 10.1 M borane-SMe_2 complex (0.82 mL; 8.28 mmoles) was added and the mixture was heated to 40° C. A solution of ketone **9** or **10** (13.8 mmoles) in 10 mL of THF was added slowly over 3-4 h so that ketone did not accumulate in the reaction flask. At the end of the addition, the reaction was complete. The mixture was cooled to room temperature and was hydrolysed with 2 mL of MeOH. The catalyst was filtered and rinsed with THF. It was then washed three times in 20 mL of fresh toluene at reflux for 1 h to remove completely the alcohol encapsulated in the resin and dried at 65 °C under vacuum. To the organic phase was added oxone (2.8 g; 4.55 mmoles) to oxidize the foul smelling dimethyl sulfide and the mixture was stirred for 20 min. The crude product was extracted with ethyl acetate and washed with a saturated solution of NaCl. It was dried on $MgSO_4$ and the solvent was evaporated. The purity of the alcohols **11** and **12** were respectively determined by HPLC (> 95 %) or by GC (> 93 %). The enantiopurity of alcohols (Preparation of phenylisocyanate derivative for HPLC analysis: 5 mg of the crude reaction product was dissolved in 150 mL of CH_2Cl_2 and mixed with 150 mL of phenylisocyanate. This mixture was heated at 60 °C for 30 min in a closed pressure stable vial. The solvent was removed by a stream of N_2 and the residue was dissolved in 10 % isopropanol in n-hexane to give a final volume of 10 mL.) **11** and **12** was respectively 93 % and 83 % ee. The infrared spectrum of the catalyst was unchanged. Microanalysis: N 0.53 % (0.38 mmoles/g).

Regeneration of the catalyst 4 for a second reduction The recovered catalyst **4** (0.53 mmoles N/g) (3 g; 1.59 mmoles of N) was suspended in 30 mL of toluene and heated to reflux for 1 h. By Tlc, traces of alcohol were detected in the liquid phase, perhaps product trapped in the polymeric matrix. The catalyst was filtered and the same operation was repeated three times to remove completely the alcohol. The catalyst was resuspended in 40 mL of fresh toluene and refluxed for 5 h with a dean-stark trap to remove volatile solvents. Fresh toluene was added and solvent was distilled until about 100 mL of solvent was recovered. The catalyst was filtered washed with toluene then hexane and finally dried at 65 °C under vacuum for at least 48 h. The infrared spectrum of the catalyst was identical to that recorded before the regeneration. Microanalysis: N 0.64 % (0.46 mmoles/g)

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1 Presented as a poster at two conferences: 1. *Sipsy's Symposium on Asymmetric Catalysis* (Paris, June 22-23, 1995); 2. *The Fifth French-American Chemical Society Meeting* (Bordeaux, June 25-29, 1995).

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7 Under normal conditions, the catalyst is hydrolyzed to the free amine. Recovery of the ligand then requires subsequent acidification, separation of the product, liberation of the non-protonated ligand and final purification of the free amine by recrystallization. From this purified material the catalyst may be regenerated using the described conditions.

8 Originally it was described that the catalyst is best kept as a concentrated toluene solution under inert atmosphere and used as a stock solution when needed. Such solutions are relatively stable

over a short period of time but would probably not be a solution for long-term storage. To avoid this problem of storage, researchers at Merck (*see Ref. 6e*) prepared a oxazaborolidine-borane complex (OAB-BH_3), which is a crystalline, free flowing solid and remarkably stable over long periods of time. It was reported that samples stored even over a two year period continued to catalyze with high enantioselectivity.

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12 Several points of difference: While it was mentioned that recovery and re-use of the catalyst in subsequent reductions is possible with only little or no loss of performance, there is no specific experimental data for this recovery and reuse procedure. It was simply described that the catalyst and product were separated by removing the organic phase with a syringe and then subjecting it to dilute hydrochloric acid. In contrast to this we first quenched the reaction (methanol or acetone) to insure the complete destruction of BH_3 (a potential safety hazard) and we subsequently filtered to separate the product from the polymer-catalyst. The manner in which one quenches (with what and how long) has certainly an influence on whether or not the catalyst remains intact and this crucial point is currently receiving our attention. We were concerned with whether or not the catalyst was altered after the filtration and we therefore analyzed carefully the catalyst after such filtrations before continuing with a second reduction. While Caze clearly showed that the catalyst retained its prior performance, there is no mention of such analysis that would help determine the quality of the catalyst. Lacking such analysis it would not be possible to know if 10, 20, or 30 mol % catalyst was actually present in the subsequent reductions. In addition, we took advantage of our own published results[19] describing the observation that higher selectivities were obtained at temperatures higher than room temperature. As a result, using only 10 % mol catalyst, we were able to obtain identical selectivities as reported for monomer. Another point of difference is that we employed the well known experimental detail of adding the ketone very slowly to the catalyst and borane source.

13 Poly-*p*-boronic acid 7: Farrall, M. J.; Fréchet, J. M. J. *J. Org. Chem.* **1976**, *41*, 3877-3882.

14 Significant warming was observed during filtration and washing of the lithiate.

15 Prepared in the same manner as the monomer which is well described: *see Ref. 6b*

16 Final washing of the formed catalyst was about 8 times before no more loss of ligand.

17 B-NMR was carried out by Dr. S. Steuernagel (Bruker GMBH), 76287 Rheinstetten Silberstreifen, Germany.

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