

Towards more chemically robust polymer-supported chiral catalysts: α,α -diphenyl-L-prolinol based catalysts for the reduction of prochiral ketones with borane

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α,α -Diphenyl-L-prolinol derivatives with *para*-bromo substituents in either one or both of the phenyl rings are easily bound to crosslinked polystyrene beads containing phenylboronic acid residues by Suzuki couplings. By using extended reaction periods boronic acid residues that do not take part in the couplings are simply lost by hydrolysis. The polymer-supported (PS) α,α -diphenyl-L-prolinols were used to catalyse reductions of several prochiral ketones with borane in tetrahydrofuran at 22 °C. The expected secondary alcohols were obtained in high chemical yields and yields were generally in the range 79–97 %. One PS catalyst was recycled 14 times without loss of stereochemical performance.

Introduction

The reduction of prochiral ketones with borane (reaction 1) in the presence of chiral β -amino-alcohols, first introduced by Itsuno *et al.*,¹ has since been developed into a powerful method for asymmetric synthesis.^{2,3} The reductions are actually catalysed by the oxazaborolidines formed *in situ* by reaction of the β -amino-alcohols with borane.² B-Substituted oxazaborolidines can also serve as catalysts and these can be prepared by reacting β -amino-alcohols with boronic acids.² In terms of the percentage enantiomeric excesses (%ees) of the secondary alcohol products, one of the most effective β -amino-alcohols is α,α -diphenyl-L-prolinol **1**.^{4,5} This reacts with borane to give oxazaborolidine **2**, and with boronic acids to give oxazaborolidines **3**.

catalyst recovery, and/or allowing reductions to be achieved in flow systems.^{6,7} In these studies three approaches have been used to bind the catalyst moieties to the polymer support. In one α,α -diphenyl-L-prolinol (**1**) was reacted with beads bearing benzenesulfonyl chloride residues.⁸ The catalyst moieties were then bound *via* the N-atom as part of a sulfonamide link. In a second approach the β -amino-alcohol was reacted with a PS boronic acid.^{9–12} The catalyst moieties were then bound to the support *via* the boron atom of the oxazaborolidine groups. In the third approach, used by Wandrey *et al.* to prepare a soluble polysiloxane for applications in a membrane reaction system,^{13,14} α,α -diphenyl-4-hydroxy-L-prolinol was bound *via* the 4-hydroxyl group. So far, however, the α,α -diphenyl-L-prolinol moiety does not appear to have been bound to a polymer support *via* the phenyl residues, the approach which is the most likely not to result in interference with the catalyst “active site”. The work described in this paper uses this approach. Other PS catalysts used for achieving reaction 1 are PS α,α -diphenyl-L-tyrosinol¹⁵ and certain PS chiral binaphthol derivatives.¹⁶

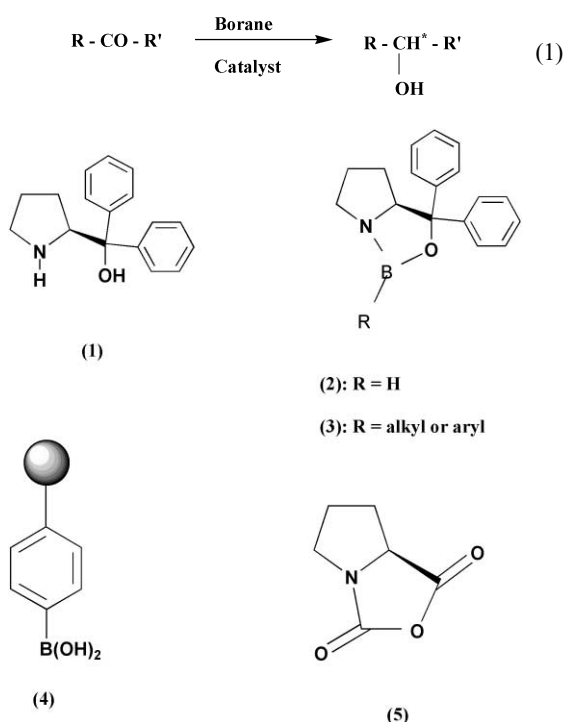
An increasingly important approach to organic synthesis involves the use of appropriate combinations of PS reagents, catalysts and scavengers to prepare organic compounds *in solution*, the PS–RCS approach.^{17,18} This approach has, for example, been used recently to achieve the synthesis of the natural product (+)-plicamine,¹⁹ and for the parallel synthesis of libraries of bicyclo[2.2.2]octanes.²⁰ To aid further progress in this general area there is now a need to develop new and/or improved PS catalysts which, as far as possible, have the following features.

(i) They are easy to prepare with a substantial loading

Ideally they could be prepared by simply linking pre-formed catalyst moieties to supports *via* chemically robust linkages under conditions where the catalyst moieties do not need to carry protecting groups that subsequently need to be removed.

(ii) They are sufficiently physically robust to withstand many reaction cycles

Magnetic stirring generally physically degrades beads. Putting them in a “T-bag” in an apparatus that keeps the beads from the grinding action that takes place between a magnetic stirrer bar and the bottom of the reaction vessel is one possible solution.²¹ Another is to carry out the reaction in a flow system, preferably with the polymer in the form of a monolith.⁷



Various polymer-supported (PS) α,α -diphenyl-L-prolinols, or oxazaborolidine derivatives, have been prepared and studied with the aim of simplifying reaction procedures, facilitating

(iii) They are sufficiently chemically robust to withstand many reaction cycles

Even a small loss of active sites per reaction cycle is significant over many cycles. Ester, acetal or benzyl ether linkages, for example, used to bind the catalyst moieties to the support may not always be sufficiently robust to withstand many reaction cycles. There is also the serious, but so far scarcely investigated,²² question as to the long term stability of the catalyst moieties themselves.

(iv) If the PS catalysts bring about asymmetric synthesis, then they should afford at least the same %ees as the corresponding low-molecular-weight catalysts

To achieve this requires that the reactants in solution have easy access to the catalytic sites, that there are no deleterious interactions between the active sites, that there are no significant microenvironmental effects, and that the “catalytic sites” have not been altered by the method of attachment to the support.^{23,24}

Achieving all these objectives in one system is clearly very demanding. This paper reports progress towards meeting these objectives. It describes the facile synthesis of PS α,α -diphenyl-L-prolinol derivatives where the catalyst moieties are linked to the support through the phenyl rings *via* robust linkages and the use of these catalysts to achieve the asymmetric reduction of various prochiral ketones by borane, reaction 1, through up to 14 reaction cycles with little or no change in the % ee. The better % ees obtained are comparable, or only slightly less, to those obtained using α,α -diphenyl-L-prolinol (**1**). It should be noted that achieving excellent stereochemical results in these reductions is particularly challenging because the PS catalysts have to compete with uncatalysed reductions giving racemic products.¹⁰

Results and discussion

The initial aim of the present project was to prepare bromo derivatives of α,α -diphenyl-L-prolinol. These could then be attached to crosslinked polystyrene beads bearing boronic acid residues **4** by Suzuki reactions. There are several reasons for using the Suzuki reaction here. First, it is very tolerant of functional groups,²⁵ so that it is not necessary to protect the functionalities present in the catalyst moieties. Second, the reaction conditions do not require the use of rigorously dried solvents. Thirdly, the catalyst moieties become attached through very strong links which also serves as small rigid “spacers”.²⁶ Fourthly, by using an extended reaction time the boronic acid residues **4** that do not take part in the Suzuki coupling are simply hydrolysed to leave hydrogen atoms. Thus, *the final product does not have any residues other than the catalyst residues*. This approach to preparing functional polymers has been used previously to prepare polymers with thiophene, phenol, amine or phosphine residues,²⁷ and PS catalysts containing *N*-methyl- α,α -diphenyl-L-prolinol residues which catalyse the reactions of dialkylzincs with aldehydes.²⁸

Synthesis of α,α -diphenyl-L-prolinol (**1**) and bromo derivatives **6** and **7**

α,α -Diphenyl-L-prolinol (**1**) was prepared by the reaction of α -*N*-carbonic anhydride **5** with phenylmagnesium bromide.²⁹ As expected³⁰ this synthesis proceeded without any racemisation problems. Repeating the synthesis but with 4-bromophenylmagnesium bromide as the Grignard reagent³¹ gave α,α -di(4-bromophenyl)-L-prolinol (**6**). To obtain a monobromo derivative, a mixture of phenylmagnesium bromide and 4-bromophenylmagnesium bromide (mol ratio 60 : 40) was reacted with α -*N*-carbonic anhydride **5**. As intended, the product, Product 1, was a mixture of α,α -diphenyl-L-prolinol (**1**) and the epimeric α,α -phenyl-4-bromophenyl-L-prolinols (**7**).

By GC the mol ratio was 77 : 23. No attempt was made to separate out the α,α -diphenyl-L-prolinol (**1**) from the bromo compounds **7**, because only the latter can take part in the Suzuki coupling.

Preparation of PS Catalysts A and B

PS boronic acid **4** was prepared *via* the direct lithiation of 1% crosslinked gel-type polystyrene beads.³² Using this method rather than the more frequently used bromine–lithium exchange ensures the beads contain no bromo residues which might subsequently take part in Suzuki reactions leading to crosslinking. The final beads contained 2.21 mmol g⁻¹ of residue **4**. A suspension of the beads was then reacted with α,α -di(4-bromophenyl)-L-prolinol (**6**) and a mixture of 2 M sodium carbonate, 1,2-dimethoxyethane and tetrakis(triphenylphosphine)palladium[0] at 80–85 °C for 4 days. This afforded PS Catalyst A, see Scheme 1a, that by elemental analysis contained 1.11 mmol g⁻¹ of nitrogen, 0.55 mmol g⁻¹ of bromine and no detectable amount of boron. The former corresponds to a loading of 1.11 mmol g⁻¹ of α,α -diphenyl-L-prolinol residues. Based on the bromine analysis, 50% of these were present as residues **8** and 50% as residues **9**. The ratio of “singly bound” to “doubly bound” residues is consistent with the results of earlier studies.^{33,34}

PS Catalyst B was prepared in order to determine whether having the α,α -diphenyl-L-prolinol residues entirely “singly bound” leads to better stereochemical results. If it does then serious consideration could be given to synthesising pure samples of one or both of the diastereoisomeric monobromo isomers **7**. Reaction of Product 1 with the PS boronic acid **4**, under similar conditions to those used to prepare PS Catalyst A, gave PS Catalyst B: see Scheme 1b. By elemental analysis it contained 0.99 mmol g⁻¹ of nitrogen, but no boron. Thus the loading of “singly bound” α,α -diphenyl-L-prolinol residues **10** was 0.99 mmol g⁻¹.

The use of PS Catalysts A and B to achieve reaction 1

Similarly to our earlier studies,^{9,10} the examples of reaction 1 investigated were carried out for 20 h in THF at 22 °C under nitrogen with a ketone to borane ratio of 1.00 to 0.70. For the reactions using the PS catalysts the reaction vessel was a tube and after an appropriate amount of catalyst had been placed in the tube it was sealed with a septum cap: see Fig. 1. All solutions were then added or removed by syringe. In this way once a reaction was complete the unquenched catalyst in the tube could be stored or could be reused easily. One charge of PS catalyst was used for a series of reactions: see below and Table 1. Each experiment was carried out in duplicate. For each pair of experiments the %ees were essentially the same, *i.e.* within

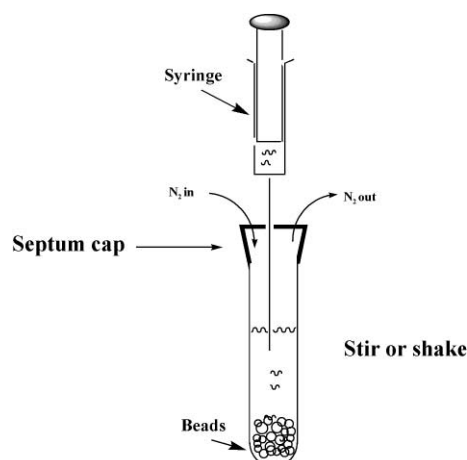
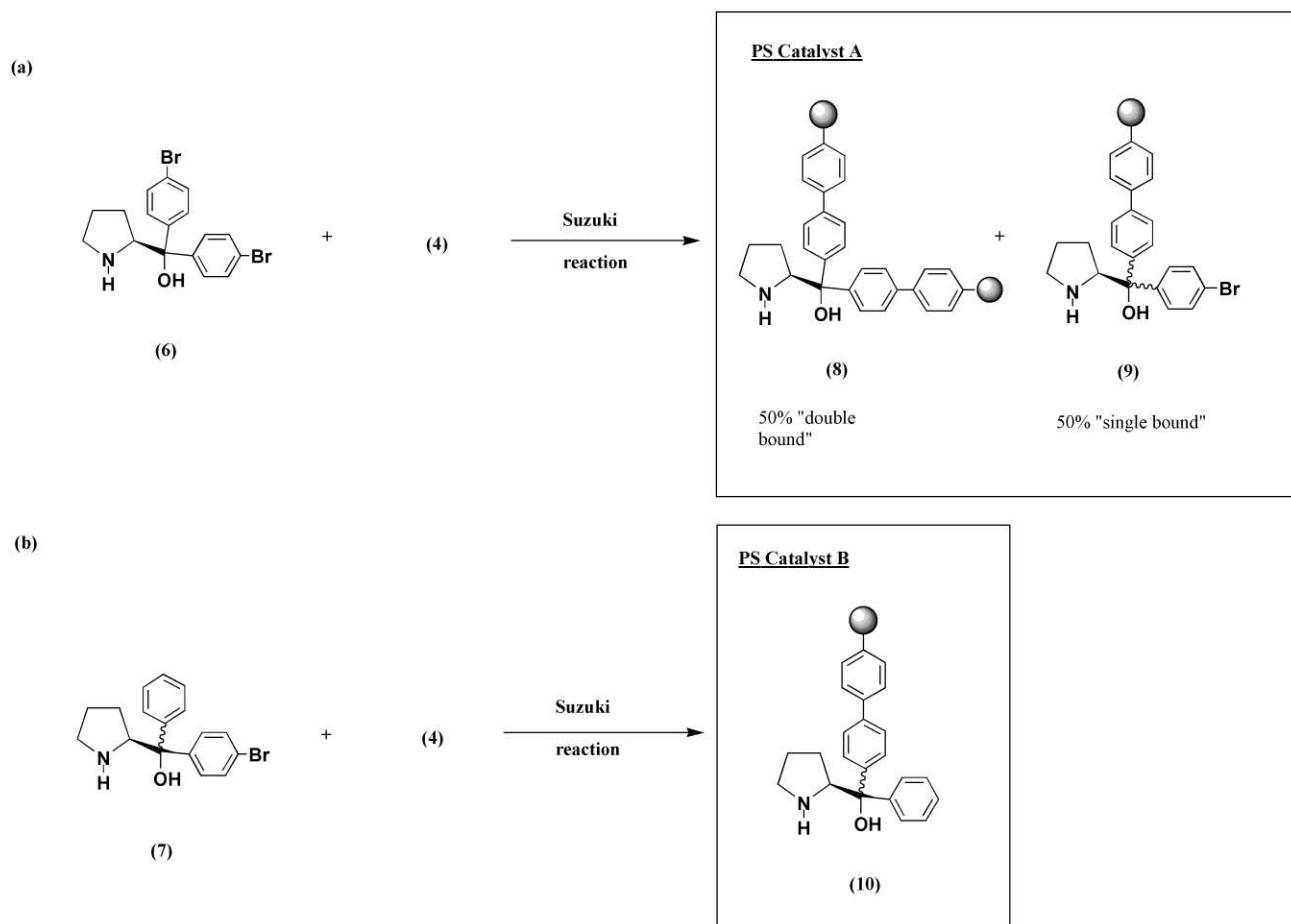


Fig. 1 Reaction vessel arrangement that allowed the PS catalysts to be reused or stored without removal from the tube.

Table 1 Reduction of various prochiral ketones by a borane–dimethyl sulfide complex in the presence of various α,α -diphenyl-L-prolinol^a derivatives

Entry	Ketone	%ee Using:				
		Catalyst A			Catalyst B 30 mol%	α,α -diphenyl-L-prolinol 5 mol%
		10 mol%	20 mol%	30 mol%		
1	Acetophenone	72	88	93	97	99
2	Propiophenone	70	83	87	90	94
3	2-Chloroacetophenone			92		99
4	4-Chloroacetophenone			85	89	92
5	α -Acetonaphthone			54	61	
6	β -Acetonaphthone			84		
7	α -Tetralone			79		80
8	Acetophenone			94 ^b	96 ^c	

^a Reactions carried out in THF at 22 °C using a ketone to borane mol ratio of 1.00 : 0.70. Reactions were carried out in duplicate. The %ees were repeatable within 2%. Chemical yields were >95%. ^b After being used for all the 14 preceding experiments using 30 mol% of Catalyst A. ^c After being used for all the 8 preceding experiments using 30 mol% of Catalyst B.

**Scheme 1** Preparation of PS Catalysts A and B and the catalytic moieties each catalyst contains.

2%. Yields of recovered materials were >95% and of these >95% were the chiral alcohols. As in our previous studies,^{9,10,35} the %ees were determined by GC over a chiral stationary phase.

To determine what mol% of PS Catalyst A was appropriate to use in order that the PS catalyst could compete successfully with the uncatalysed reaction 1 leading to racemate, three tubes were set up for reactions using 10, 20 and 30 mol% of catalyst and they were used for a series of reductions. It is evident from the results summarised in Table 1, entries 1 and 2, that the %ees improved as more catalyst was used. Since 5 mol% of the soluble catalyst **1** is generally sufficient to obtain the optimal %ees, this result suggests that a substantial fraction of the supported catalyst residues, perhaps >80%, are not sufficiently readily accessible for the catalysed reaction to compete successfully with the uncatalysed reaction. Such a high percentage may arise

in part because the “doubly bound” residue **8** correspond to approximately 5% crosslinking in addition to the 1% originally present in the beads. Such a high total percentage crosslinking would seriously reduce the swelling properties of the beads and hence site accessibility.²³

A range of other ketones were then reduced using 30 mol% of PS Catalyst A under the standard conditions: see Table 1, entries 3–7. The %ees ranged from 54%–92%. Various ketones were also reduced using 30 mol% of PS Catalyst B under the standard conditions: see Table 1, entries 1–7. With this catalyst the ees were 3%–7% higher than with PS Catalyst A indicating that it is better to avoid “doubly bound” sites and just have the “singly bound” sites **10**. In most cases the ees were now only 2%–4% less than those obtained with the soluble catalyst **1**. This suggests that binding the α,α -diphenyl-L-prolinol residues

to the support *via* one phenyl group does not significantly interfere with the “active site” of the catalyst moieties.

It was hoped that the PS catalysts would recycle well. The most extensively recycled was a sample of PS Catalyst A. This was used twice for each of the 30 mol% reactions summarised in Table 1, entries 1–7, *i.e.* a total of 14 times. It was then used again at 30 mol% to catalyse the reduction of acetophenone: see Table 1, entry 8. It is evident that the %ee obtained is, within experimental error, the same as in the initial experiment indicating that PS Catalyst A recycles well. Similarly all the experiments carried out in duplicate with PS Catalyst B summarised in entries 1, 2, 4 and 5 were carried out with just one sample of the catalyst, *i.e.* a total of 8 experiments, and on reuse the %ee obtained with acetophenone (see entry 8) was essentially unchanged from the first reduction. This suggests that the catalytic residues are sufficiently chemically stable to withstand many reaction cycles.

After PS Catalyst A had been used for 16 reactions it was recovered and washed (with acid, base and organic solvents) before being used for a further 4 reactions. It was then washed again and analysed. Overall the weight fell to 57% of its original value, an average loss per reaction of <3%. However the nitrogen analysis was essentially the same as for the original catalyst. This suggests that the catalyst groups are firmly bound and that the losses were mainly, if not entirely, due to physical attrition.

Conclusions

PS Catalysts A and B are easily prepared by linking bromo derivatives of α,α -diphenyl-L-prolinol to a polymer support containing boronic acid residues **4** using Suzuki reactions. By using extended reaction times boronic acid residues that do not take part in Suzuki coupling are lost by hydrolysis. In PS Catalyst A half of the prolinol moieties were bound through one phenyl group and half through both phenyl groups, whilst in PS Catalyst B all the prolinol moieties were bound through just one phenyl group. The catalysts were used to achieve reductions of several prochiral ketones with borane in tetrahydrofuran at 22 °C. The expected alcohols were obtained in high chemical yields. The PS catalysts gave good stereochemical results and recycled well. The best %ees were obtained when PS Catalyst B, in which all the catalyst moieties are “singly bound”, was used at 30 mol%. In the four cases where comparisons could be made with the results obtained using 5 mol% of α,α -diphenyl-L-prolinol, the ees obtained with the supported catalyst were only 2%–4% lower than those obtained with the soluble catalyst. PS Catalyst A was shown to suffer physical attrition on repeated use but little or no loss of catalytic sites. Thus, most of the objectives set out above appear to have been met with this catalyst system and the next stage of development is to prepare a specific monobromo isomer of **7** and attach it to a polymer which can be used in a flow system. In such a system the polymer is unlikely to suffer significant mechanical damage on repeated reuse.⁷

Experimental

Organic extracts were dried over magnesium sulfate. Solid samples were dried in a vacuum oven at 1.0 mm of Hg. The THF solution of the borane–dimethyl sulfide complex was purchased from the Aldrich Chemical Company. Infrared spectra were recorded using a Perkin Elmer 1720 instrument: solid samples were measured as potassium bromide discs and liquid samples as thin films between sodium chloride plates. ¹H NMR spectra were recorded for solutions in deuteriated chloroform on a Unity Inova 300 MHz NMR spectrometer using TMS as an internal standard. Electrospray (ES) mass spectra (MS) were obtained using a MicroMass Platform instrument. Chemical ionisation (CI) MS were obtained using a Fisons VG Trio 2000

instrument. Elemental analyses were made in house: for C, H and N analyses a Carlo Erba 1108 Analyser was used: for bromide analyses silver nitrate titrations were carried out using a Metrohm 686 Titroprocessor: for boron analyses a Horizon ICP Elemental Analyser was used. Optical rotations were measured using an Optical Activity Ltd AA-100 Digital Polarimeter with a cell of path length 10 cm and are reported in units of deg cm³ g^{−1} dm^{−1}. GC analyses were carried out using a Carlo Erba 4000 Chromatograph equipped with a flame-ionisation detector and a 25 m capillary column (0.32 mm diameter) packed with WT COT FUS SIL (12 μ particles) supporting the chiral species cyclodextrin- β -2,3,6-M-19.

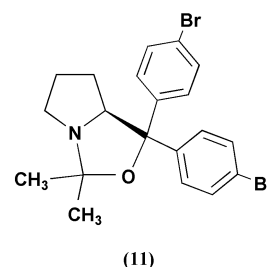
Preparation of α,α -diphenyl-L-prolinol (**1**)

(a) **Preparation of the *N*-carbonic anhydride **5**.** A solution of the *N*-carbonic anhydride **5** in THF was prepared from L-proline (5.76 g, 50 mmol) and bis(trichloromethyl) carbonate (“triphsogene”) (4.95 g, 50 mmol) using the procedure of Daly and Poche.²⁹ The solution was used immediately.

(b) **Reaction of the *N*-carbonic anhydride **5** with phenyl-magnesium bromide.** A Grignard reagent was prepared from bromobenzene (23.55 g, 150 mmol) and magnesium (3.45 g, 150 mmol) in THF and then reacted with the anhydride **5** and the product isolated using the procedures described in detail by Mathre *et al.*³⁰ Recrystallisation of the crude product from hexane gave compound **1** (5.58 g, 44% based on proline) as white crystals mp 78–80 °C (lit.,³⁰ 79–79.5 °C); δ 1.45–1.90 (m; 5H; 2 $\times$ H₃, 2 $\times$ H₄ and NH), 2.85–3.10 (m; 2H; 2 $\times$ H₅), 4.25 (t, *J* = 7.5 MHz; 1H; H₂), 4.55 (br s; 1H; OH), 7.10–7.4 (m; 6H; aromatic protons) and 7.5–7.7 ppm (m; 4H; aromatic protons); [α]_D²⁰ = −53.5 (*c* 0.30, methanol) [lit.,³⁰ −54.3 (*c* 0.26, methanol)].

Preparation of α,α -di(4-bromophenyl)-L-prolinol (**6**)

A Grignard reagent was prepared from 1,4-dibromobenzene (35.40 g, 150 mmol) and magnesium (3.54 g, 154 mmol) in dry THF.³¹ It was reacted with anhydride **5** and the product isolated using the procedure described in detail by Mathre *et al.*³⁰ This gave the crude product **6** (4.75 g, 23% yield based on the proline) as a pale amber gum. This was purified by flash chromatography over silica gel. Elution with acetone–hexane (1 : 1) gave the mixed acetal **11**, mp 44–46 °C; δ 1.16 (s; 3H; CH₃), 1.53–1.65 (m; 2H; 2 $\times$ H₄), 1.69 (s; 3H; CH₃), 1.80–2.15 (m; 2H; 2 $\times$ H₃), 2.81 (m; 2H; 2 $\times$ H₅), 4.54 (dd, *J* = 3.4 and 7.5 Hz; 1H; H₂), 7.21 (m; 2H; aromatic protons), 7.35 (m; 2H; aromatic protons) and 7.46 ppm (m; 2H; aromatic protons). MS (ES) 450, 452 and 454 (intensities 1 : 2 : 1) corresponding to [M + H]⁺ for dibromo products **11** with two ⁷⁹Br, one ⁷⁹Br and one ⁸¹Br, and two ⁸¹Br.



The acetal was decomposed by treatment with a mixture of ether (40 ml), methanol (60 ml) and hydrochloric acid (40 ml, 1 M) at 20 °C. Dilution of the mixture after 72 h and extraction with ether and recovery gave α,α -di(4-bromophenyl)-L-prolinol (**6**) as a white solid, mp 84–85 °C; [α]_D²⁰ = −43.4 (*c* 0.14, chloroform). ν_{max} 3368 (br O–H and N–H), 3083–3028 (aromatic C–H) and 2973–2869 cm^{−1} (aliphatic C–H); δ 1.50–1.85 (m; 5H; 2 $\times$ H₃, 2 $\times$ H₄, NH), 2.92–3.12 (m; 2H; 2 $\times$ H₅), 4.20 (t; *J* = 7.6 Hz; 1H; H₂), 4.40–5.00 (br s; 1H; OH) and 7.20–7.60 ppm (m; 8H; aromatic protons). C₁₇H₁₇Br₂NO requires C, 49.7;

H, 4.2; N, 3.4 and Br, 38.9%. Found C, 50.1; H, 4.3; N, 3.4; and Br, 38.8%.

Preparation of a mixture of α,α -diphenyl-L-prolinol (**1**) and the diastereoisomers of α,α -(4-bromophenyl)phenyl-L-prolinol (**7**)—(Product **1**)

A mixture of Grignard reagents was prepared from bromobenzene (13.24 g, 84.3 mmol), 1,4-dibromobenzene³¹ (13.3 g, 56.2 mmol) and magnesium (3.54 g, 154 mmol) in THF. This was reacted with anhydride **5** using the procedure referred to above. The product was a pale yellow oil (Product **1**) (3.98 g, 32% yield based on the proline). MS (CI) 331 and 333 due to $[M]^+$ for monobromo products **7** with ^{79}Br and ^{81}Br , and 253 due to unbrominated product. By elemental analysis it had 2.8% Br. The NMR spectrum was very similar to that of compounds **1** and **6**. Attempts to achieve crystallization or significant resolution of the diastereoisomers by flash chromatography failed. GC analysis indicated it consisted of compound **1** and the diastereoisomers **7** in the ratio 77 : 12 : 11.

Preparation of crosslinked polystyrene beads containing residues **4**

Polystyrene beads (gel-type; 1% crosslinked; 200–400 mesh) were purchased from Phase Separations Ltd. Direct lithiation of the beads in dry cyclohexane then reaction of the lithiated product with trimethyl borate followed by hydrolysis, as described in detail by Farrall and Fréchet,³² gave beads containing 2.39% B, corresponding to 2.21 mmol g⁻¹ of residues **4**. The infrared spectrum (KBr disc) showed the expected bands at 1380–1310 (B–O) and 1240–620 (B–C) cm⁻¹.

Preparation of PS Catalysts A and B

(a) **PS Catalyst A.** A mixture of polystyrene beads containing boronic acid groups **4** (1.00 g, 2.21 mmol), α,α -di(4-bromophenyl)-L-prolinol (**6**) (1.8 g), 2 M sodium carbonate (2.5 ml, 5.0 mmol) and 1,2-dimethoxyethane (25 ml) was stirred under argon for 15 min. Tetrakis(triphenylphosphine)palladium[0] (248 mg, 0.215 mmol) was added and the mixture stirred and heated at 80–85 °C for 4 days. At the end of this period the beads were filtered off, washed successively on the filter with 1,2-dimethoxyethane (25 ml), 1,2-dimethoxyethane–water (25 ml), and ethyl acetate (30 ml), and dried. The product (1.34 g), PS Catalyst A, had 1.55% N, corresponding to 1.11 mmol g⁻¹ of α,α -diphenyl-L-prolinol residues of both types **8** and **9**, 4.42% Br, and 0.00% of B. The bromine analysis corresponds to 0.55 mmol g⁻¹ of bromine. This indicates that PS Catalyst A contained 0.55 mmol g⁻¹ each of residues **8** and **9**.

(b) **PS Catalyst B.** This catalyst was prepared similarly to PS Catalyst A but using Product **1** (1.8 g) in place of the α,α -di(4-bromophenyl)-L-prolinol (**6**). The product, PS Catalyst B, had 1.38% of N, corresponding to 0.99 mmol g⁻¹ of residues **10**, and 0.0% B.

General procedure for reduction of ketones with borane in the presence of PS catalysts

The following is typical of the procedure used for all the reactions summarised in Table 1 employing 10, 20 or 30 mol% of PS catalyst with respect to the ketones.

Table 1, entry 1, using 30 mol% of catalyst. PS Catalyst A (599 mg, 0.54 mmol) and a small magnetic stirrer bar were placed in a round-bottomed tube (100 mm $\times$ 20 mm) sealed with a septum cap and the tube was mounted in a shaker: see Fig. 1. Nitrogen was passed through the tube *via* syringe needles. Dry THF (3 ml) was syringed into the tube and the mixture was left for 15 min for the beads to swell. A 10 M solution of borane–dimethylsulfide complex in THF (0.18 ml,

1.80 mmol) was then added dropwise, again using a syringe, then the tube was shaken at 22 °C for 18 h. Acetophenone (308 mg, 2.57 mmol) in THF (4.0 ml) was added by syringe over 1 h. It was found helpful to stir the mixture magnetically during this addition. The reaction was allowed to continue for 20 h at 22 °C then the organic layer was syringed off. The beads were washed with THF (4 $\times$ 5.0 ml). The combined organic solutions were added to hydrochloric acid (2.0 ml of 2 M) and distilled water (100 ml). The aqueous solution was extracted with ether (3 $\times$ 5.0 ml), the combined extracts washed with aqueous sodium carbonate (5 ml of 0.5 M) and dried. Evaporation of the solvent gave the crude product as a pale yellow oil (301 mg, 96%). As in previous studies,^{9,10,35} a ¹H NMR spectrum was recorded and a GC run to determine both the %ee and the chemical yield (*i.e.* percentage of ketone in the recovered product converted into the desired alcohol). The GC instrument was equipped with a flame-ionisation detector and a 25m capillary column (0.32 mm diameter) packed with WT COT FUS SIL (12 μ particles) supporting the chiral species cyclodextrin- β -2,3,6-M-19 and it was calibrated using mixtures of enantiomers of known composition.⁹ The PS catalyst in the tube was washed with dry THF (2 $\times$ 5 ml) then used for the next reaction. Each reaction was carried out in duplicate.

Recovery and analysis of PS Catalyst A

As indicated in Table 1, the original charge of PS Catalyst A (599 mg) was used consecutively for 14 reactions without being removed from the reaction tube. In between each reaction it was simply washed with THF (2 $\times$). The duplicate 30 mol% runs of the acetophenone reduction summarised in entry 8 were then carried out. The sample was subsequently removed from the tube and washed successively with THF, THF–2 M HCl, THF–ammonium hydroxide, THF and then methanol and dried. The recovered catalyst (354 mg) was then used for four more reactions before being washed as above. By elemental analysis the recovered catalyst (341 mg) contained 1.54% nitrogen (originally 1.55%) and bromine 3.49% (4.34%).

General procedure for the reduction of ketones with borane in the presence of compound **1**

The following procedure is typical of the reductions summarised in Table 1 using catalyst **1**.

Table 1, entry 1. Catalyst **1** (26 mg, 0.10 mmol, 5 mol%) and a magnetic stirrer bar were placed in a round-bottomed tube (100 mm $\times$ 20 mm). The tube was sealed with a septum cap and nitrogen passed through the tube *via* syringe needles. Dry THF (3 ml) was syringed into the tube. A solution of borane–dimethylsulfide complex in THF (0.18 ml, 10 M, 1.80 mmol) was added dropwise, again using a syringe, then the mixture was stirred at 20 °C for 18 h. Acetophenone (308 mg, 2.57 mmol) in THF (4.0 ml) was added by syringe over 1 h. After 4 h at 22 °C the organic layer was added to hydrochloric acid (2.0 ml of 2 M) and distilled water (100 ml). The product was extracted with ether and analysed as in the experiment with PS Catalyst A described above.

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