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Chiral oxazaborolidines bound via the boron atom to polymers prepared using 2-vinylthiophene: polymer-supported catalysts for the enantioselective reduction of prochiral ketones by borane

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Polymer-supported chiral oxazaborolidines bound to the polymer via the boron atom, have been prepared from a series of crosslinked polymers synthesized using 2-vinylthiophene. The polymer-supported oxazaborolidines were used to catalyse the reduction of prochiral ketones using the borane–dimethyl sulfide complex, a reduction which also occurs in the absence of catalyst to give racemic products. Using the catalysts in this competitive situation together with measurement of the enantiomeric excesses (*ees*) obtained provides a sensitive way of comparing the performances of the various polymer supports. Best results were obtained using lightly crosslinked polymers prepared using approximately equimolar amounts of 2-vinylthiophene and styrene. However, the *ees* obtained using even these catalysts were significantly smaller than those obtained using the non-polymeric analogue of the catalysts. This is most probably due to diffusion barriers limiting the access of the ketone and/or the borane to the catalytic sites on the polymers.

(Keywords: oxazaborolidines; 2-vinylthiophene; enantioselective reduction)

INTRODUCTION

In recent years there has been great interest in polymers containing functional groups[1–3] which, for example, allow the polymers to be used as catalysts or reagents in organic reactions[1,2] or as metal ion extractants[4]. Most commonly the polymers are derivatives of crosslinked polystyrenes and the required functional groups are introduced by the chemical modification of an appropriate preformed crosslinked polystyrene. Three chemical modification procedures have been widely used: (1) chloromethylation of the crosslinked polystyrene[5–8] followed by reaction with an appropriate nucleophile[9,10]; (2) an appropriate electrophilic aromatic substitution reaction[11,12]; and (3), if the electrophile is not sufficiently reactive to be used in the second approach, metallation of the crosslinked polystyrene followed by reaction with the appropriate electrophile[13–18]. Organolithium derivatives are the most commonly used in the last approach[13–16], though organomagnesium[17], organomercury[18] and organothallium[18] derivatives have also been studied. The direct lithiation of crosslinked polystyrenes on treatment with a substantial excess of n-butyllithium results in up to ca. 25% of the phenyl residues reacting[13,14]. Up to 100% can be lithiated if the polystyrene is first brominated and then the bromination product treated with a substantial excess of n-butyllithium to achieve a bromide–lithium exchange[13,15]. These lithiation procedures are not only expensive in that they use large excesses of n-butyllithium, but we also find that both procedures tend to give erratic results[19]. The latter may in part be due to the fact that organolithiums generally oligomerize reversibly, the extent of oligomerization being a function of the particular organolithium, the solvent, the concentration and the possible presence of other species, for example lithium bromide, which may permit other organolithium complexes to form[20]. With the lithiated polymers oligomerization is a form of crosslinking. The latter will both restrict the extent of oligomerization itself and will also result in reduced access to the functional groups inside the crosslinked polymer beads.

Compared with benzene, thiophene is easily lithiated. Thus thiophene reacts rapidly and cleanly at room temperature with an equimolar amount of n-butyllithium to give 2-thienyllithium in essentially quantitative yield[21]. This prompted us previously to prepare and study the lithiation of (1) linear poly(2-vinylthiophene)[22], (2) a copolymer of 2-vinylthiophene and divinylbenzene[23] and (3) various copolymers of 2-vinylthiophene, styrene and divinylbenzene[23]. To take our investigation of this

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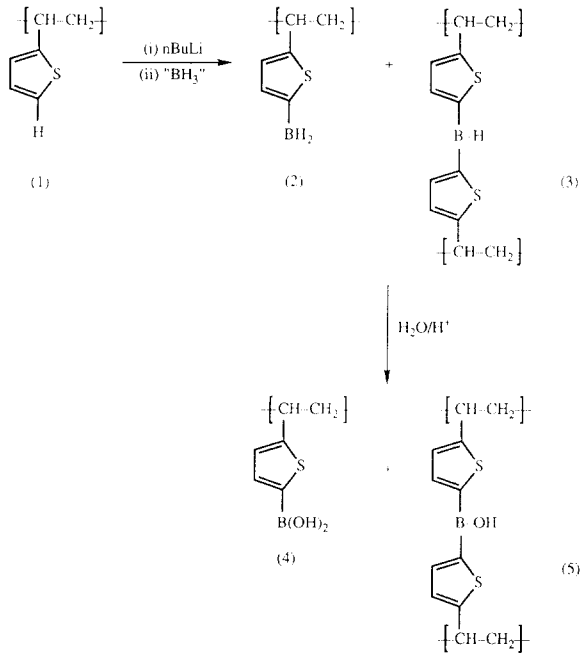
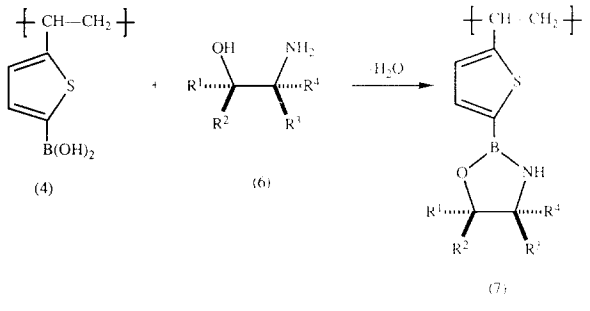
general approach a stage further, we have now prepared, via the lithiation of various 2-vinylthiophene–styrene–divinylbenzene copolymers, and other reactions shown in *Schemes 1* and *2*, some polymer-supported (PS) chiral oxazaborolidines **7**. *Scheme 3* shows the reactions used



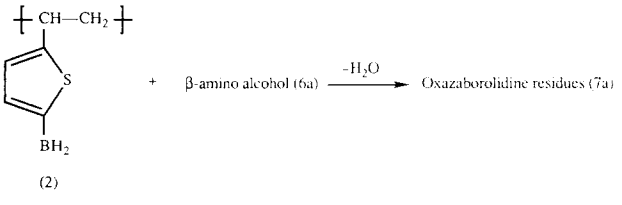
Scheme 1

Reaction 1

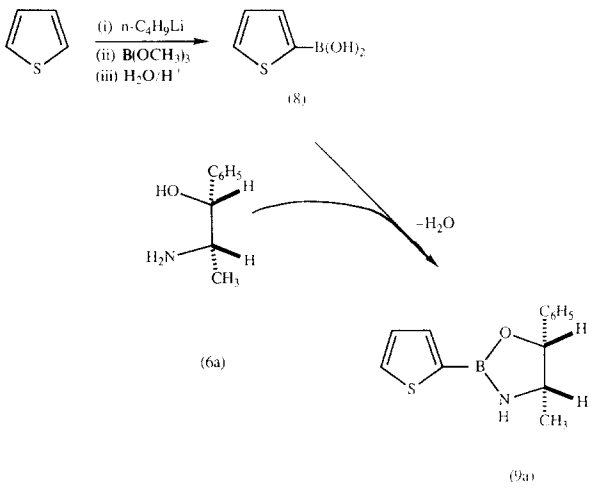


	R^1	R^2	R^3	R^4
(a)	H	C_6H_5	CH_3	H
(b)	H	H	CH_3	H
(c)	CH_3	H	H	H
(d)	H	H	$CH(CH_3)_2$	H
(e)	H	C_6H_5	CH_2OCH_3	H
(f)	C_6H_5	H	H	CH_3

Reaction 2



Scheme 2



Scheme 3

to prepare the non-polymeric analogues. The various catalysts were then used to catalyse the borane reduction of several prochiral ketones (see reaction 3). The results of this study are now presented in this paper.

The use of PS chiral catalysts to achieve asymmetric synthesis promises to become a major area of development in the future which is of particular interest to the pharmaceutical industry[24]. Interest can be expected to increase as the enantiomeric excesses (*ees*) achieved increase and the range of reactions which give high *ees* increases.

EXPERIMENTAL

Acetophenone and propiophenone were distilled under reduced pressure from calcium hydride. (1*R*,2*S*)-(−)-Norephedrine **6a** and (1*S*,2*R*)-(+)-norephedrine **6f** were both >99% pure. Borane in tetrahydrofuran (THF) and the borane–dimethyl sulfide complex in THF solution were purchased from Aldrich and used as received. THF was distilled from sodium prior to use. All reactions were carried out under dry nitrogen.

Gel permeation chromatography (g.p.c.) was carried out using a Waters μ-Styragel 4 column with THF as the eluent. Surface area measurements were made using a Quantasorb chromatography instrument, the values for the surface area being estimated using the standard BET method. Pore volumes were measured using a Carlo–Erba 800 instrument; this instrument utilizes mercury porosimetry.

Optical rotations were measured in a 0.25 dm cell on a Polartronic (Haensh–Schmidt) polarimeter using the sodium D line. Gas–liquid chromatography (g.l.c.) was performed on a Chrompak CP9000 instrument (injection temperature 250°C, flame ionization detector temperature 260°C, column temperature 115°C) using a WCOT Fus sil column (50 m × 0.25 mm) containing CP cyclodextrin-β-2,3,6-M-19. The ratios of (*R*)- and (*S*)-alcohols were determined by their peak areas. Nuclear magnetic resonance (n.m.r.) spectra were obtained on a Gemini 200 (200 MHz) instrument for solutions in $CDCl_3$. Infra-red (i.r.) spectra were measured on either a Perkin–Elmer 882 or a Perkin–Elmer 1710 instrument.

Synthesis of polymer supports

2-Vinylthiophene (2VT) was synthesized by the method of Emerson and Patrick[25]. The properties of the various supports are summarized in *Table 1*.

Linear polymer ***10.*** 2VT was homopolymerized using the procedure described before[22]. By g.p.c. the product had, relative to polystyrene standards, $\bar{M}_n = 24\,700$ and $\bar{M}_w = 39\,600$.

Linear polymer ***11.*** A solution of 2VT (10.35 g, 94 mmol), styrene (10.87 g, 103 mmol) and azobisisobutyronitrile (0.77 g, 4.7 mmol) in toluene (70 ml) was degassed by three freeze–thaw cycles. The vessel was then sealed and heated in an oil bath at 95°C. After 14 h the reaction mixture was cooled and the solvent removed under reduced pressure. The crude product was dissolved in chloroform and reprecipitated into methanol. This gave a white powder (8.61 g, 40%). It had a sulfur content of 18.1%, corresponding to a thiophene content of 61 mol%. By g.p.c. relative to polystyrene standards the product had $\bar{M}_n = 19\,000$ and $\bar{M}_w = 35\,500$.

Crosslinked polymers ***12–16.*** These were prepared by suspension polymerizations using the procedure given before[23]. The molar ratios of the monomers used were as given in *Table 1*. The loadings of thiophene residues, as estimated by elemental analysis for sulfur, are also given in *Table 1*.

Macromoporous crosslinked polymer ***17.*** This was prepared by the method of Guyot *et al.*[26] with heptane (50 mol%) as the porogen. The molar ratios of the monomers used were as given in *Table 1*. The surface area of the beads was 236 $m^2 g^{-1}$ and the pore volume was 0.88 ml g^{-1}.

Introduction of boronic acid residues ***4***

The properties of the various polymer-supported boronic acids are summarized in *Table 1*.

Into polymer ***10.*** The procedure given previously involving lithiation, treatment with borane in THF and then aqueous acid was used[22]. The product **18** had i.r. peaks (ν_{max}) at 3470 (O–H) and 1335 cm^{-1} (B–O). By elemental analysis for boron the loading of boronic acid residues was 2.2 mmol g^{-1}. The product was insoluble in all solvents tried.

Into polymer ***11.*** A solution of the polymer (500 mg, 2.8 mmol of thienyl units) in THF (5 ml) was added over 15 min to a stirred solution of n-butyllithium (1.5 ml of a 2.06 M solution in hexane, 3.1 mmol) in THF (10 ml) under nitrogen. The resulting mixture was stirred at 30–40°C for 30 min. The mixture was cooled to 20°C, borane in THF (3.5 ml of a 1 M solution, 3.5 mmol) was added dropwise and after the addition was complete the mixture was stirred for 14 h. Dilute hydrochloric acid (20 ml of 1 N) was added and the resulting tan precipitate filtered off. The precipitate was suspended in water at 50°C for 2 h and then collected. It was also suspended in ether at 20°C for 2 h and then collected. The tan solid was dried *in vacuo*. The final product **19** (283 mg) had i.r. peaks (ν_{max}) at 3480 and 1340 cm^{-1} and a boron content of 1.3%, corresponding to a boronic acid content of 1.3 mmol g^{-1}. It was insoluble in all solvents tried.

Into polymer ***14.*** The polymer (10.0 g, 46 mmol of thienyl units) was allowed to swell in toluene (80 ml) for 50 min before n-butyllithium (44 ml of a 2.5 M solution in THF, 110 mmol) was added to the stirred mixture. The mixture was stirred for 2 h at 40°C and 2 h at 20°C. The dark red polymer was allowed to settle and the solvent was removed using a syringe. The polymer was washed with THF (3 × 10 ml) using a syringe, then suspended in THF (80 ml). Borane–dimethyl sulfide complex (11 ml of a 10.1 M solution in THF, 110 mmol) was added and the reaction mixture was stirred at 20°C for 4 h before removal of the solvent under reduced pressure. The residue was stirred with 1 N hydrochloric acid (50 ml) for 2 h. It was then collected and washed in a Soxhlet apparatus first with water, then with THF. After drying *in vacuo* the polymer **22** (10.5 g) had i.r. peaks (ν_{max}) at

Table 1 Preparation of unfunctionalized polymer supports and the introduction of thienylboronic acid residues **4** into these supports

	Preparation of unfunctionalized supports						Introduction of boronic acid residues **4**		
Entry	Polymer support number	Degree of crosslinking[a] (%)	Polymer type[b]	2VT content (%) In feedstock	2VT content (%) In polymer[c]	Loading of thiophene residues **1** in polymer[c] (mmol g^{-1})	Loading of boronic acid residues[d] (mmol g^{-1})	Yield (%)	Designation of final polymer
1	**10**	0	L	100	100	9.1	2.2	27	**18**
1	**11**	0	L	48	61	5.6	1.3	25	**19**
3	**12**	1	G	40	46	4.2	2.0	52	**20**
4	**13**	2	G	10	13	1.2	0.8	69	**21**
5	**14**	2	G	44	51	4.6	2.1	50	**22**
6	**15**	2	G	60	73	6.7	4.0	72	**23**
7	**16**	5	G	49	53	4.8	0.6	13	**24**
8	**17**	40	M	10	15	1.4	0.9	67	**25**

[a] Percentage of divinylbenzene in the feedstock (after allowance for the ethylstyrenes present in the commercial material)
[b] L = linear; G = crosslinked gel; M = crosslinked macroporous
[c] By elemental analyses for sulfur
[d] By elemental analyses for boron

3475 and 1342 cm^{-1} and a boron content of 2.1%, corresponding to a boronic acid content of 2.1 mmol g^{-1}.

Into polymers 12, 13 and 15–17. These reactions were carried out as for polymer **14** above. The results are summarized in *Table 1*. The macroporous product **25** from polymer **17** had a surface area of 404 $m^2 g^{-1}$ and a pore volume of 1.94 ml g^{-1}.

Preparation of polymer-supported oxazaborolidines from linear polymers 10 and 11

The following procedure is typical. The results obtained starting with polymer **10** are given in *Table 2*, entry 1.

From linear polymer 11. Borane in THF (3.5 ml of a 1 M solution) was added dropwise with stirring to a suspension of the lithiated polymer (prepared from 300 mg of unfunctionalized polymer as above) in THF (15 ml). After 2 h a solution of (1*S*,2*R*)-(+)-norephedrine **6f** (529 mg, 3.5 mmol) in THF (5 ml) was added and the reaction mixture was stirred at 20°C for 16 h. The polymer **27** was then filtered off, washed with THF and dried (330 mg). It had a boron content of 1.8% and a nitrogen content of 2.5%, corresponding to 1.8 mmol g^{-1} of oxazaborolidine residues **7f**. The product was stored in a desiccator.

Preparation of polymer-supported oxazaborolidines from crosslinked polymers 12–17

These experiments are summarized in *Table 2*, entries 3–16. The following experiment is typical.

Entry 6. Toluene (40 ml) was added to a flask containing the polymer **23** (8.0 g, 32 mmol of boronic acid) and (1*R*,2*S*)-(−)-norephedrine **6a** (5.74 g, 38 mmol) and the flask was fitted with a Dean–Stark trap containing 4A molecular sieves. The polymer was allowed to swell for 1 h and then the mixture was heated under reflux for 24 h. The reaction was allowed to cool and the polymer was filtered off and purified by Soxhlet extraction first with toluene, then with THF, before drying *in vacuo*. The product **31** was obtained as a white powder (9.4 g). It had a boron content of 3.0% and a nitrogen content of 3.0%, corresponding to 2.12 mmol g^{-1} of oxazaborolidine residues **7a** and 0.91 mmol g^{-1} of unreacted boronic acid. The product was stored in a desiccator.

Asymmetric reductions of ketones catalysed by polymer-supported oxazaborolidines 7

The following is the general procedure used for the reductions summarized in *Tables 3–5*.

A mixture of the polymer-supported catalyst (0.33–3.3 mmol depending on the particular experiment; see the appropriate table) and THF (15.5 ml) was stirred for 1 h at 20°C prior to the addition of the borane–dimethyl sulfide complex (5.5 ml of a 2.0 M solution in THF, 11.1 mmol). After 30 min a solution of the ketone (11.1 mmol) in THF (2 ml) was added dropwise over 5 min. The mixture was stirred at 20°C for 24 h. Using a syringe, the reaction solvent was removed and the polymer beads were washed several times with THF. The combined organic solutions were quenched with 2 N hydrochloric acid (100 ml) and the reaction product was extracted with ethyl acetate (3 × 25 ml). The combined extracts were washed with saturated aqueous sodium chloride (2 × 10 ml), dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was distilled bulb to bulb at 5 mmHg and 100°C. The purity of the product was determined by ^1H n.m.r. spectroscopy.

Table 2 Synthesis of polymer-supported oxazaborolidines by reactions 1 and 2

Entry	Starting polymer	β-Amino alcohol used	Synthetic method[a]	Yield[b] (%)	Composition of polymeric product: Boronic acid residues (mmol g^{-1})	Composition of polymeric product: Oxazaborolidine residues (mmol g^{-1})	Designation of polymeric catalyst
1	**10**	**6f**	A	32[c]		2.00	**26**
2	**11**	**6f**	A	45[c]		1.80	**27**
3	**20**	**6a**	B	72	0.48	1.23	**28**
4	**21**	**6a**	B	49	0.35	0.34	**29**
5	**22**	**6a**	B	51	0.91	0.95	**30**
6	**23**	**6a**	B	70	0.91	2.12	**31**
7	**24**	**6a**	B	13	0.54	0.08	**32**
8	**25**	**6a**	B	50	0.43	0.43	**33**
9	**21**	**6b**	B	52	0.38	0.41	**34**
10	**21**	**6c**	B	53	0.37	0.42	**35**
11	**21**	**6d**	B	41	0.46	0.32	**36**
12	**21**	**6e**	B	50	0.38	0.38	**37**
13	**25**	**6b**	B	50	0.44	0.44	**38**
14	**25**	**6c**	B	51	0.43	0.45	**39**
15	**25**	**6d**	B	49	0.45	0.43	**40**
16	**25**	**6e**	B	50	0.42	0.42	**41**

[a] A = synthesis achieved using reaction 2; B = synthesis achieved using reaction 1
[b] Unless indicated otherwise, the percentage yield given is for reaction 2 only
[c] Percentage yield given is the overall yield for the introduction of the oxazaborolidine moieties into the previously unfunctionalized support

Optical rotations were determined for solutions in dichloromethane or chloroform and compared with the following literature values. For (*S*)-1-phenylethanol, $[\alpha]_D^{23} = -52.5°$ ($c = 2.27$, CH_2Cl_2)[27], and for (*R*)-1-phenylpropanol, $[\alpha]_D^{23} = +45.45°$ ($c = 5.15$, $CHCl_3$)[27]. Typical g.l.c. retention times for (*R*)- and (*S*)-1-phenylethanol were 26.7 and 28.3 min, respectively, while for (*R*)- and (*S*)-1-phenylpropanol they were 30.8 and 32.0 min, respectively.

Preparation of 2-thienylboronic acid ***8***

Thiophene (10 ml, 125 mmol) in THF (50 ml) was added dropwise to a solution of n-butyllithium (50 ml of a 2.5 M solution in hexane, 125 mmol) in THF (100 ml) at 0°C. The reaction was allowed to warm to room temperature and stirred for 1 h. Trimethyl borate (14.2 ml, 125 mmol) in THF (50 ml) was added dropwise with cooling in an ethanol–solid CO_2 bath. The resulting mixture was then stirred for 48 h at room temperature before quenching with dilute sulfuric acid. The THF was removed under reduced pressure and the mixture was extracted with ether (3 × 30 ml). The extracts were washed with saturated aqueous sodium chloride and the solvent was removed under reduced pressure. The residue was filtered through a pad of flash silica (benzene as eluent), and the product was recrystallized from water to give 2-thienylboronic acid **8** as colourless needles (5.23 g, 34%), melting point 129–130°C (from benzene) (literature value[28,29] 133–134°C).

Preparation of oxazaborolidine ***9a***

A 50 ml flask was charged with (1*R*,2*S*)-(−)-norephedrine **6a** (500 mg, 3.3 mmol), 2-thienylboronic acid **8** (640 mg, 5 mmol) and toluene (25 ml). The flask was fitted with a Dean–Stark trap containing 4A molecular sieves. The reaction mixture was stirred and heated under reflux for 3.5 h. After allowing the mixture to cool, the solvent was removed under reduced pressure. The crude product was distilled bulb to bulb (250°C, 0.1 mbar) to give **9a** as a colourless, glassy solid (200 mg, 25%) with a ν_{max} of 3486 cm^{-1} (N–H). The ^1H n.m.r. δ values (ppm) were 0.75 (3H, d, $J = 6.6$ Hz, CH_3), 3.8 (1H, br s, NH), 4.12 (1H, q, $J = 8.2$ and 6.6 Hz), 5.68 (1H, d, $J = 8.2$ Hz), 7.4 (6H, m, ArH) and 7.7 (2H, m, ArH). The relevant *m/e* values were 243 (M^+, 60.5%) and 228 (M^+–NH, 100%). For M^+ we found 243.0882; $C_{18}H_{14}NBOS$ requires 243.0889.

General procedure for the asymmetric reduction of ketones catalysed by oxazaborolidine ***9a***

The borane–dimethyl sulfide complex (7.4 ml of a 1 M solution in THF, 7.4 mmol) was added dropwise over 10 min to a stirred solution of compound **9a** (140 mg, 0.57 mmol). After 30 min a solution of propiophenone (0.76 ml, 5.7 mmol) in THF (10 ml) was added over 5 min at 22°C. After 20 min the reaction mixture was cooled in an ice–water bath and then quenched with 2 N hydrochloric acid (10 ml). The mixture was extracted with chloroform (3 × 10 ml) and the combined extracts were washed with water and dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude alcohol was purified by bulb to bulb distillation (100°C, 0.5 mbar). The purity of the product was checked by ^1H n.m.r. spectroscopy and the *ee* was estimated from the optical rotation as above.

RESULTS AND DISCUSSION

Synthesis of unfunctionalized polymer supports

All the polymer supports used in the present project were prepared by free radical polymerizations using 2-vinylthiophene (2VT). Here, 2VT was synthesized from thiophene, acetaldehyde and hydrogen chloride by the method of Emerson and Patrick[25]. Two linear polymers were prepared. One, polymer **10**, was a homopolymer of 2VT. The other, polymer **11**, was an approximately 50:50 copolymer of 2VT and styrene. Five gel-type crosslinked polymers **12**–**16** were prepared by suspension copolymerizations. These supports differed in the extent of crosslinking and/or the content of 2VT. One macroporous copolymer, polymer **17**, was prepared by carrying out a suspension polymerization in the presence of heptane as a porogen. As expected[23], all the copolymers contained slightly greater proportions of 2VT than the feedstocks. The polymerization results are summarized in *Table 1*.

Functionalization of polymer supports

Introduction of boronic acid moieties ***4***. Thienylboronic acid moieties **4** were introduced into all the polymer supports using the reaction sequence outlined in *Scheme 1*, i.e. by reaction first with a modest excess of n-butyllithium, then with borane and finally with hydrochloric acid[23]. The results are summarized in *Table 1*.

To obtain evidence as to the site of lithiation, the soluble linear polymer **11** was treated with n-butyllithium and then D_2O. The ^1H n.m.r. spectrum of the polymer produced indicated that under the present conditions (i.e. modest excesses of n-butyllithium and relatively short reaction times) only the thienyl groups lithiate. This experiment and an analogous one with the homopolymer **10** confirmed[22] that >95%, if not all, of the lithiation takes place at the free α-positions of the thienyl moieties **1**. The crosslinked polymers almost certainly reacted similarly.

It had been hoped to use the linear polymers in n.m.r. spectral studies which would have monitored examples of the other chemical modifications carried out. However, during the introduction of boronic acid residues **4** the polymers became insoluble, almost certainly due to crosslinking as a consequence of the formation of a small amount of the diarylborane moieties **3** during the treatment of the lithiated polymer with borane[18]. In the subsequent treatment with aqueous acid these would become diarylborinic acid moieties **5**.

The overal yields for the introduction of boronic acid moieties **4** were greatest (50–72%) for the lightly crosslinked polymers **12**–**15** and the macroporous polymer **17**. The yields for the linear polymers **10** and **11** and the 5% crosslinked gel-type polymer **16** were significantly lower. These results are not surprising. For gel-type polymers, accessibility decreases with crosslinking; macroporous polymers are designed to make a substantial fraction of the aryl residues readily accessible; and the 'linear' polymers, as noted above, were almost certainly crosslinked.

Introduction of oxazaborolidine residues ***7a***–***7f***. Oxazaborolidine residues were introduced into the crosslinked

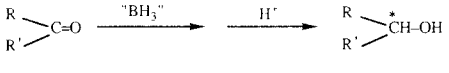
polymers using reaction 1 in *Scheme 2*. Thus, in each case the boronic acid containing polymer and the appropriate β-amino alcohol were heated together in toluene at reflux temperature for 24 h whilst the water was removed. The results are summarized in *Table 2*. The various β-amino alcohols used were chosen because of their ready availability. With (1*R*,2*S*)-(−)-norephedrine **6a** the reactions proceeded in yields of 49–72% with the lightly crosslinked polymers and with the macroporous polymer. The 5% crosslinked polymer again gave an inferior result.

Attempts to prepare linear polymers containing oxazaborolidine residues were made using reaction 2 in *Scheme 2*, but, as with the preparation of the boronic acid containing polymers, the products, though containing the desired oxazaborolidine residues **7f**, were insoluble in all solvents tried.

Asymmetric reductions using the polymer-supported oxazaborolidines 7

The reaction selected for study using the various PS oxazaborolidines as catalysts was the reduction of prochiral ketones by the borane–dimethyl sulfide complex (see reaction 3). In most instances the reductions studied were those of acetophenone (R=C_6H_5 and R′=CH_3) and/or propiophenone (R=C_6H_5 and R′=C_2H_5). Reaction 3 was selected because the reaction proceeds quite rapidly in the absence of added catalyst to give the racemic alcohol. A typical reaction is substantially complete within ca. 5 h at ambient temperatures[30,31]. Because of this background reaction the PS catalysts operate in a competitive situation, and if, for example, access to the catalytic sites in the polymer beads is significantly restricted by diffusion and/or the supported groups interfacing with each other in any way, then the background reaction will play a significant part in the reduction. This will result in a decrease in the enantiomeric excesses (*ees*) obtained. This is, therefore, a powerful way to compare the performances of a range of polymer supports.

Reaction 3



The various reductions were carried out using equimolar amounts of ketone and the borane–dimethyl sulfide complex. Each reduction was carried out using ca. 1 g of the ketone and the chiral alcohols produced were isolated using bulb to bulb distillation. The chemical yields given in *Tables 3–5* are for the isolated products. The actual amounts of alcohols formed would, therefore, be somewhat higher. In view of the small scale of the reactions, which makes the efficiency of the isolation procedure relatively modest, the quoted chemical yields canot be usefully compared too closely. The quoted *ees* were determined by measurement of the optical rotations of the isolated alcohols. In most cases they were also determined by gas–liquid chromatography using a chiral stationary phase. Within experimental error (±1% *ee*) the results from the two methods were the same.

In order to identify suitable reaction conditions for the reductions, a series of experiments were carried out using the gel-type catalyst **30** in different solvents, at different temperatures and with different molar percentages of catalyst. The results are summarized in *Table 3*. Several conclusions can be drawn from these results.

1. The best of the solvents tried was THF, though toluene was only marginally inferior. Accordingly, THF was used as the reaction solvent in all subsequent experiments.
2. In the reduction of acetophenone, as the reaction temperature was progressively increased from −25 to 45°C the *ee* obtained at first increased, levelled out at 20–24°C, then decreased. Clearly, at least two effects are operating, one which increases the *ee* as the temperature is raised and one that decreases the *ee*. The latter is a common trend in asymmetric synthesis: raising the temperature simply decreases reaction selectivity. It is not actually clear why the *ee* should increase with temperature, but it is almost certainly a result of the polymer mobility and swelling increasing with temperature, hence making the catalytic sites more accessible to the other reactants. In view of these results all subsequent reactions were carried out at 20–24°C.
3. The *ee* obtained from the reduction of acetophenone increased as the molar percentage of catalyst increased, but only up to 30 mol%. Similar trends were also obtained with catalyst **29** in the reduction of propiophenone and in some other experiments using both ketones, summarized in *Table 4*, which used 10 and 30 mol% of catalyst. Presumably, 30 mol% of catalyst is required to ensure that sufficient catalytic sites are accessible on the polymer for essentially all the reduction to take place under the control of the PS catalyst. Similar effects have been observed before using both polymeric[30,31] and non-polymeric[32] catalysts.

A range of catalysed reductions were carried out using the other PS catalysts which had been prepared. The catalysts were used at 10 and/or 30 mol% in THF at 20°C. The results are summarized in *Table 4*. Several conclusions can be drawn from the results.

1. Of the catalysts prepared from the 2% crosslinked polymers, the better ones were catalysts **30** and **31**. These were prepared from the polymers with 51 and 73% of 2VT units and they respectively contained 0.95 and 2.12 mmol g^{-1} of catalytic groups (compare entries 6 and 7 with 5 in *Table 4*). It is difficult to determine which is the more important effect – the percentage of 2VT in the polymers or the loading of catalytic groups. Since the results obtained with 0.95 and 2.12 mmol g^{-1} of catalytic groups are similar (entries 6 and 7), it is probably the former effect which is the more important. This is not surprising as in our earlier work[23] with crosslinked polymers prepared using 2VT and styrene, the extents of lithiation and the absorptions of both benzene and THF were very sensitive to polymer composition and were optimal with crosslinked polymers that incorporated approximately equal amounts of 2VT and styrene. A similar effect may exist with the present catalysts.
2. Comparison of entries 5 and 8 and of entries 3, 6 and 7 indicates that increasing the extent of crosslinking of gel-type polymers from 1 to 2 to 5% decreases the *ees* obtained, especially in the last case. This is to be

Table 3 Various reductions catalysed by polymers **29** and **30**

Entry	Polymer	Reaction solvent	Reaction temperature (°C)	Amount of catalyst (mol%)	Reduction of acetophenone		Reduction of propiophenone	
					Chemical yield[a] (%)	*ee*[b] (%)	Chemical yield[a] (%)	*ee*[b] (%)
1	**30**	THF	20	30	81	61	79	56
2	**30**	Toluene	20	30	75	53	78	50
3	**30**	Dioxane	20	30	28	9	30	5
4	**30**	THF	−25	30	22	7		
5	**30**	THF	0	30	55	52		
6	**30**	THF	24	30	83	61		
7	**30**	THF	30	30	89	59		
8	**30**	THF	45	30	85	32		
9	**30**	THF	20	10			>95[c]	31
10	**30**	THF	20	40			>95[c]	54
11	**30**	THF	20	50			>95[c]	55
12	**29**	THF	20	10			32	26
13	**29**	THF	20	30			45	46
14	**29**	THF	20	40			>95[c]	47
15	**29**	THF	20	50			>95[c]	49

[a] Reactions carried out for 24 h using equimolar amounts of ketone and borane–dimethyl sulfide complex. Yields quoted are of isolated products
[b] Determined by optical rotation of isolated product. All reactions produced predominantly the (*R*)-alcohol
[c] By g.l.c. analysis

Table 4 Reductions of acetophenone and propiophenone using various catalysts[a]

Entry	Catalyst	Starting copolymer	Degree of crosslinking (%)	Loading of oxazaborolidine residues (mmol g^{-1})	Amount of catalyst (mol%)	Reduction of acetophenone		Reduction of propiophenone	
						Chemical yield[b] (%)	*ee*[c] (%)	Chemical yield[b] (%)	*ee*[c] (%)
1	**26**	**10**	0	2.00	5			92	26[d]
2	**27**	**11**	0	1.80	5			57	18[d]
3	**28**	**20**	1	1.23	30			88	61
4	**29**	**21**	2	0.34	10	46	21	33	26
5	**29**	**21**	2	0.34	30	56	48	45	46
6	**30**	**22**	2	0.95	30	81	61	79	56
7	**31**	**23**	2	2.12	30	79	60	62	53
8	**32**	**24**	5	0.28	30			35	12
9	**33**	**25**	40	0.43	10			>95[e]	26
10	**34**	**21**	2	0.41	10	>95[e]	11	58	13
11	**34**	**21**	2	0.41	30	41	27	53	27
12	**35**	**21**	2	0.42	10	55	8[d]	48	9[d]
13	**35**	**21**	2	0.42	30	58	33[d]	54	38[d]
14	**36**	**21**	2	0.32	10	42	11	44	8
15	**36**	**21**	2	0.32	30	48	43	46	36
16	**37**	**21**	2	0.38	10	47	9	36	7
17	**37**	**21**	2	0.38	30	48	20	41	18
18	**38**	**25**	40	0.44	10			>95[e]	11
19	**39**	**25**	40	0.45	10			>95[e]	4[d]
20	**40**	**25**	40	0.43	10			>95[e]	8
21	**41**	**25**	40	0.42	10			>95[e]	5

[a] All reactions carried out in THF at 20–24°C for 24 h using equimolar amounts of ketone and borane–dimethyl sulfide complex
[b] Yield of isolated product
[c] Determined by optical rotation on isolated product. Unless indicated otherwise, the predominant alcohol was the (*R*)-enantiomer
[d] Predominant alcohol was the (*S*)-enantiomer
[e] By g.l.c. analysis

expected as increasing the crosslinking reduces the swelling of the polymers and hence the accessibility of the catalytic sites.

3. Comparison of entries 4 and 9 suggests that the macroporous PS catalyst **33** behaves comparably to the otherwise similar 2% crosslinked gel-type polymer **29**, i.e. the macroporous polymer is one of the better supports.

4. Extrapolation of the results presented in *Table 3*, entries 1 and 9–11 suggest that when polymer **30** is used at 5 mol% it would give *ees* from the reduction of propiophenone of ca. 15–20%. The linear polymer **27** (*Table 4*, entry 2), which had a similar monomer composition to polymer **30**, gave a similar *ee*, suggesting that the previously linear polymers were probably ca. 1–2% crosslinked.
5. Comparison of the results obtained with catalysts **29** and **34–37** and with catalysts **33** and **38–41** indicates that in the present work the most successful catalysts, i.e. those which produced the greatest *ees*, were those prepared using (1*R*,2*S*)-(−)-norephedrine **6a** as the β-amino alcohol. These results also indicate that the gel-type PS catalysts are slightly superior to the macroporous PS catalysts. All the PS catalysts which had the substituents on the top face of the molecule, as presented in **7a–7e**, gave predominantly the (*R*)-alcohols, while those with substituents on the bottom face gave predominantly the (*S*)-alcohols. These results are as expected[32]. It should be stressed here that the object of the present work was to compare supports, not to obtain very high *ees* by optimizing the β-amino alcohol used.

One of the better catalysts, polymer **30**, was used to catalyse the reduction of a range of prochiral ketones. The results are presented in *Table 5*. The reductions of aryl alkyl ketones afforded *ees* of 56–65%, whereas the dialkyl ketones afforded *ees* of only 24 and 30%. This trend is expected[32]. The catalyst from the reduction of propiophenone was reused successfully three times. The *ees* were successively 61, 58, 63 and 60%.

Comparisons with asymmetric reductions using other catalysts

It is of interest to compare the better PS catalysts with their non-polymeric analogue, viz. oxazaborolidine **9a**. The latter was prepared using a method analogous to that used to prepare the polymeric catalysts. When compound **9a** was used as a catalyst at 30 mol% in THF at 20°C, acetophenone gave (*R*)-1-phenylethanol in 81% *ee* and propiophenone gave (*R*)-1-phenylpropanol in 72% *ee*. These *ees* are significantly higher than those obtained using the PS **30**, viz. 20 and 16% higher, respectively. There are probably two main reasons for the differences. The first is that the PS catalysts contain thienylboronic acid residues **4** in amounts comparable with the amounts of the catalytic residues, and it is known from non-polymeric studies that the presence of boronic acids can result in reduced *ees*[32]. The second, and more likely, reason is that despite attempts to optimize the PS catalysts, it is probable that diffusion barriers still remain. These barriers appear to be a particular problem with crosslinked polymers prepared using 2VT. Thus, as noted before[23], the reactivity and swelling properties of gel-type crosslinked polymers prepared using 2VT and styrene are very sensitive to the proportions of these monomers in the polymer and are optimal when the monomers are incorporated in approximately equimolar amounts. Moreover, PS chiral oxazaborolidines bound to 2% crosslinked polystyrenes perform almost as well as the corresponding non-polymeric analogues, despite the presence of phenylboronic acid residues in the polymers[30,31].

Table 5 Asymmetric reduction of various ketones using polymer-supported oxazaborolidine **30**[a]

Substrate	Alcohol produced: Chemical yield[b] (%)	Optical yield[c] (%)	Configuration of major enantiomer
Acetophenone	81	61	(*R*)[d]
Propiophenone	79	56	(*R*)[d]
p-Methoxypropiophenone	35	62	(*R*)[d]
2-Chloroacetophenone	85	65	(*R*)[d]
Butan-2-one	43	24	(*R*)[e]
Pentan-2-one	40	30	(*R*)[e]

[a] All reactions used equimolar amounts of ketone and borane–dimethyl sulfide complex and 30 mol% of catalyst in THF at 23°C
[b] Yield of isolated alcohol
[c] By g.l.c. analysis using a chiral stationary phase
[d] Major enantiomer identified by g.l.c. analysis using authentic samples of both enantiomers
[e] Assignment of major enantiomer made simply by analogy with literature results[33,34]

CONCLUSIONS

PS chiral oxazaborolidines **7** bound to the polymer via the boron atom have been prepared from a range of polymer supports synthesized using 2VT plus, in most cases, styrene and divinylbenzene. The PS oxazaborolidines **7** were used to catalyse the reduction of prochiral ketones with the borane–dimethyl sulfide complex, a reaction that also proceeds without added catalyst. Using the PS catalysts in this competitive situation together with measurement of the *ees* obtained provides a sensitive way of comparing the performances of the various supports.

Best results were obtained using lightly crosslinked polymers prepared from approximately equal amounts of 2VT and styrene. However, even these PS catalysts afforded stereochemial results which were significantly inferior to those obtained using the non-polymeric analogue **9a**. This is probably partly due to the fact that the PS catalysts contain some free boronic acid residues **4** and partly because even the best supports still present significant diffusion barriers which the soluble reactants need to cross to gain access to the supported catalyst groups. The latter is probably the more important limitation. This suggests that crosslinked supports prepared using 2VT, though they are functionalized via lithiation more easily than the analogous crosslinked polystyrenes, present significant diffusional barriers to non-polymeric reactants which will limit their applicability.

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