Reactions of aldehydes with diethylzinc catalysed by polymer-supported ephedrine and camphor derivatives: comparisons of enantiomeric excesses achieved with various supports: optimisation of support parameters to enable high enantiomeric excesses to be obtained†

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The reactions of benzaldehyde with diethylzinc catalysed by PS ephedrine or camphor derivatives have been investigated in some depth in order to identify the crucial factors necessary to successfully prepare PS chiral catalysts for such reactions. The most important factor is found to be a favourable interaction of the polymer matrix with the reaction solvent so that the polymer will dissolve or swell to allow the other reactants easy access to the catalytic sites. Accordingly toluene is a better reaction solvent than hexane. The ephedrine-derived catalytic groups reduce the solubility of the linear polymers in toluene and, almost certainly, the swelling properties of the crosslinked polymers. Thus, of the polymers investigated the better linear ones had <*ca.* 1.5 mmol per g of catalyst sites and the better insoluble ones were 1% crosslinked gels with <*ca.* 1.0 mmol per g of catalyst sites. Site–site interactions and microenvironmental effects do not appear to play a major role in these PS reaction systems. For the reaction of benzaldehyde with diethylzinc, using the best linear PS ephedrine derivatives **10f**, **10g** or **11e** affords 1-phenylpropanol (**1**) with 83–88% enantiomeric excesses (ee)s of the (*R*)-enantiomer; using the best linear PS camphor derivative **21** affords the alcohol **1** with a 98% ee of the (*S*)-enantiomer; using the best crosslinked PS ephedrine derivative **12a** affords the alcohol **1** with a 78–81% ee and using the best crosslinked PS camphor derivative **22** affords alcohol **1** with a 97% ee of the (*S*)-enantiomer. These values are close to those obtained using analogues of non-polymeric catalysts under similar reaction conditions.

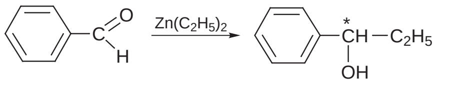
Introduction

Merrifield's method for 'solid phase' peptide synthesis was first described in detail in 1963.[1] During the following two decades polymer-supported (PS) versions of many other synthetic organic reactions were investigated, including innumerable examples of reactions using PS substrates, PS reagents or PS catalysts.[2–8] In this period the fundamental differences between solution reaction systems and PS systems were identified.[9] It is clear that three major factors need to be taken into account when carrying out PS reactions. First, it is necessary to use a combination of support and reaction solvent which allows the soluble reactants to diffuse freely into and out of the support throughout the reaction, thus allowing good site accessibility. Second, depending on the choice of support and the loading and distribution of the PS groups, reactions between supported groups (site–site interactions) may be easier or harder than reactions with, or between, species in solution. Thirdly, microenvironmental effects can accelerate or slow down PS reactions.

Asymmetric organic syntheses achieved using PS chiral catalysts are a particularly attractive type of organic reaction. Thus, the use of the polymer support allows the soluble chiral products to be separated easily from the chiral catalyst and the catalyst to be recovered for possible reuse. This latter feature is especially important if the catalyst moiety is expensive. Furthermore, PS catalysts may be used in automated systems, for example, in flow systems which allow the chiral products to be produced continuously.[10] Because of these various advantages, many attempts have been made to prepare PS versions of the better chiral catalysts, but this is not a trivial exercise and often the percentage enantiomeric excesses (% ees) achieved have been lower in the supported systems.[11] In most cases this is almost certainly because the reaction conditions have not been optimised taking fully into account the three major factors noted above.

In recent years a range of chiral catalysts has been discovered which, in reactions of major synthetic importance, give reaction products with extremely high % ees.[12] Thus, it is now more important than before to be able to successfully prepare PS versions of selected chiral catalysts. To be able to do this rationally we need to know more about how the conditions used in PS reactions influence specific reactions, especially as the % ees obtained in many asymmetric syntheses are extremely sensitive to the reaction conditions. Moreover, in future, combinatorial chemistry techniques will undoubtedly be applied more extensively to optimise PS chiral catalyst design,[13–15] and it will be important to be able to screen such catalysts knowing that the observed differences in performance are due to the different catalytic groups themselves and not to some unidentified polymer effect.

The present paper is concerned with a detailed investigation of the use of PS ephedrine and camphor derivatives as catalysts for the reaction of benzaldehyde with diethylzinc to give 1-phenylpropanol (**1**), [eqn. (1)], and with closely related



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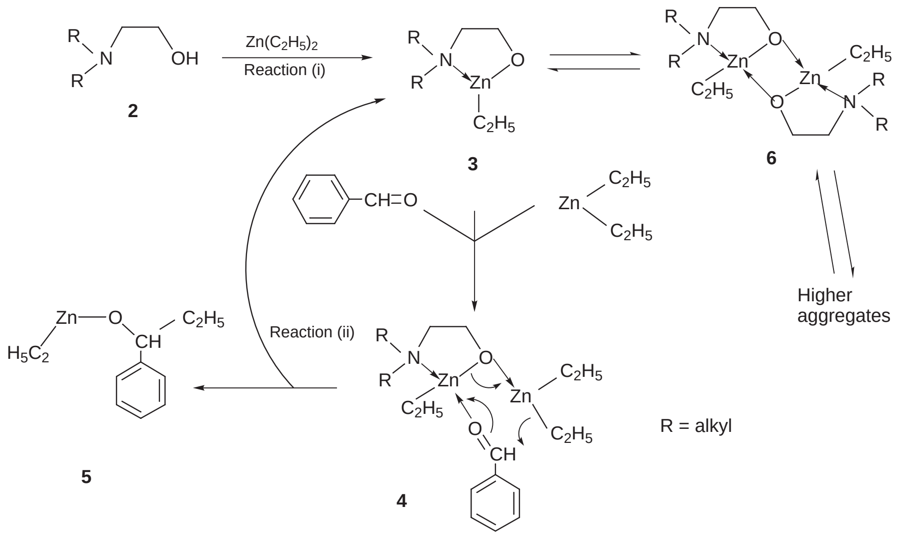
† This project was initiated whilst PH was at the University of Lancaster.

Table 1 Reactions of benzaldehyde with diethylzinc under various conditions[a]

Entry	Added catalyst	Mol% of added catalyst	Reaction conditions T/°C	t/h	Chemical yield[b] (%)	% ee[c]
1	Nil	—	0	48	<1[d]	—
2	Nil	—	20	1	2	—
3	Nil	—	20	24	35[e]	—
4	Nil	—	50	1	14	—
5	Nil	—	75	1	43	—
6	(*R*)-1-Phenylpropanol	5	0	48	22[f]	2[f]
7	Blank beads[g]	—	0	24	14	—
8	Compound **7**	5	20	24	92	81
9	Compound **7**	2	0	70	85	84
10	Compound **7**	2	23	20	88	76

[a] Unless indicated otherwise reactions were carried out using 9.4 mmol of benzaldehyde and 10.4 mmol of diethylzinc in 11.5 ml of toluene with stirring under a dry nitrogen atmosphere. [b] By gas chromatography using an internal standard. [c] Estimated by polarimetry of distilled samples of products. The (*R*)-enantiomer was the major product. [d] The same result was obtained when hexane was used as the reaction solvent. [e] When hexane was used as the solvent the chemical yield was 10%. [f] Allowing for recovered catalyst, the enantiomeric excess was in favour of the (*R*)-alcohol. [g] 200 mg of 2% crosslinked polystyrene beads added.



Scheme 1

reactions. The aims were, first, to investigate a range of linear and crosslinked PS catalysts, with various catalyst loadings and various morphologies, so as to determine how, for this particular catalysed reaction, the choice of support affects the % ee obtained and, second, to thus determine whether the % ees achieved using optimal conditions in the PS reactions can match those achieved using analogous soluble catalysts. PS versions of eqn. (1) and related reactions have been studied before on several previous occasions,[16–24] but little attention has been given to the optimisation of the support. Previous work has been reviewed.[25] Silica gel- and alumina-supported catalysts have also been investigated.[26] Previous work will be discussed below where appropriate. Two recent papers on other types of PS chiral catalyst highlight how crucial the choice of reaction conditions can be.[27,28]

Results and discussion

The mode of action of the catalysts: some relevant observations

The mechanism by which β-amino alcohols (**2**) catalyse the reaction shown in eqn. (1) and related reactions has been discussed by Noyori[29,30] and the accepted mechanism is outlined in Scheme 1. Essentially the β-amino alcohol first reacts with diethylzinc, reaction (i), to generate the true catalyst **3**. The zinc centre in the catalyst **3** behaves as a Lewis acid and binds to a lone pair on the oxygen atom of the carbonyl group, thus activating the latter to nucleophilic attack. A second molecule of diethylzinc binds to a lone pair of the oxygen atom in the catalyst **3**, thus enhancing the nucleophilic properties of the ethyl groups. With both the reactants activated and held in close proximity, see formula **4**, reaction (ii) takes place through a six-membered ring transition state to form the new C–C bond. The product prior to "work up" is the alkoxide **5**. A major feature of the system particularly relevant to the present study is that the catalyst groups **3** tend to reversibly aggregate to give, for example, dimers **6**.[29–31] In the context of PS catalysts such aggregation is important as it would involve site–site interactions and these may be sufficient to serve as crosslinks, so making diffusion within the matrix more difficult.

A second point relevant to the present work is the extent to which the reaction shown in eqn. (1) proceeds in the absence of added catalyst. This is relevant because the product from such a reaction would be racemic. Since data on this topic are scarce, in the present study benzaldehyde was treated with diethylzinc under various conditions. The results are summarised in Table 1. It is evident, entries 1–3, that over a period of 24 h at 0 °C, whether the reaction solvent is toluene or hexane, the chemical yield of alcohol **1** is less than 1%. At 20 °C, however, significant reaction occurs, the yields of 1-phenylpropanol (**1**) after 24 h being 35% when toluene is the reaction solvent and 10% when hexane is the solvent. Raising the temperature further, entries 4 and 5, results in more rapid reactions. These results are consistent with the previous fragmentary literature reports.[16,30,32]

Since the catalysts **3** are alkylzinc alkoxides and the initial reaction products **5** are also compounds of this general type, it was of interest to determine whether the initial product from eqn. (1), *i.e.* the alkoxide **5**, would itself serve as a catalyst. It is evident from the results summarised in Table 1, entries 1 and 6, that the chiral *R*-alkoxide **5**, generated *in situ* from (*R*)-1-phenylpropanol (**1**), is indeed a catalyst for eqn. (1), but that, at 5 mol%, it is not chemically a very effective catalyst. Moreover, it achieves essentially zero asymmetric synthesis. These results are consistent with the brief literature reports on this topic.[33,34] The poor chemical reactivity no doubt results, at least in part, because this sterically uncrowded unchelated alkoxide has a much greater tendency than those alkoxides which are the more successful chiral catalysts to reversibly aggregate to give catalytically inactive species.[30,31] The very poor stereochemical performance is no doubt associated with the lack of the stiff well-organised arrangement that results from the presence of the five-membered chelate ring in the better chiral catalysts. A potential problem when the better chiral catalysts are used for eqn. (1) is, however, that as the alkoxide **5** is the reaction product, even though it is a relatively poor catalyst, this is partly offset by the fact that it is eventually present in *stoichiometric* amounts. Furthermore, it may also interfere by forming mixed aggregates with the chelated alkoxides **3**, so reducing their catalytic efficiency.

It is clear from the various results presented above, therefore, that *in the present work the PS catalysts operate in a competitive situation* and that if the aldehydes and diethylzinc cannot diffuse freely into the polymer supports to reach the catalytic sites, then they will tend to react together anyway, albeit slowly, to give a racemate, and this will lead to a reduction in the overall stereochemical performance of the supported catalysts.

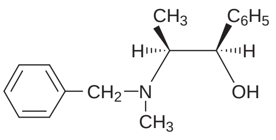
Finally, it is of interest to note, compare Table 1 entries 1 and 7, that blank 2% crosslinked polystyrene beads also catalyse eqn. (1), presumably by absorbing, and thus concentrating, the reactants into the beads. Whether this is also true once the beads are functionalised with the catalyst residues is not clear.

Preparation of linear polymers containing (1*R*,2*S*)-*N*-benzylephedrine residues: the use of these polymers to catalyse eqn. (1)

Initially linear polymers[35] containing (1*R*,2*S*)-*N*-benzylephedrine residues were investigated as catalysts for eqn. (1). Although linear polymers are less easily separated from the final reaction mixtures than crosslinked, and therefore insoluble, polymer beads, providing the linear polymers are soluble in the reaction medium the possible diffusion problems that are encountered with crosslinked polymers are avoided. Thus, information on site–site interactions and on solubilities may be obtained. The latter are of interest as they are closely related to the swelling properties of the corresponding crosslinked polymers.

Polymer synthesis and characterisation. (1*R*,2*S*)-Ephedrine was selected as the starting material for the syntheses of the initial set of catalysts investigated because it is readily available and the use of (1*R*,2*S*)-*N*-benzylephedrine (**7**), or its enantiomer, as catalysts for eqn. (1) typically gives, depending on the reaction conditions, ees of 70–85%.[16,25] There is, therefore, scope for the polymeric systems to give better, as well as poorer, % ees than the non-polymeric systems.

Reaction of (1*R*,2*S*)-ephedrine with a commercial mixture of 3- and 4-vinylbenzyl chloride (mole ratio, 70:30) gave monomers **8** and this mixture was used to prepare a range of linear polymers: see Table 2. Homopolymerisation of monomers **8** in toluene using a free radical initiator gave polymer **9**. Under similar reaction conditions monomers **8** were copolymerised with styrene in various proportions to give copolymers **10a**–**10g**, and with 4-methylstyrene in various proportions to give copolymers **11a**–**11e**. The compositions of the copolymers **10** and **11** were determined by elemental analysis and by ^1H NMR spectroscopy. It is evident from the results summarised in Table 2 that, as expected given the structural and electronic similarities of the polymerisable centres, the compositions of the final copolymers are closely similar to the feed compositions. Molecular weights of the polymers were determined by gel permeation chromatography relative to polystyrene standards. The optical rotations of the various polymers were measured for solutions in chloroform: see Table 2. The specific rotations obtained for the copolymers **10** agree well with those Fréchet *et al.* reported for similar copolymers (different proportions of the monomers) obtained by copolymerising monomers **8** with styrene.[36]



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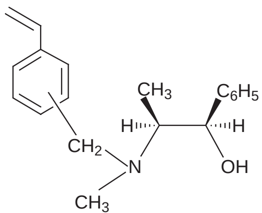

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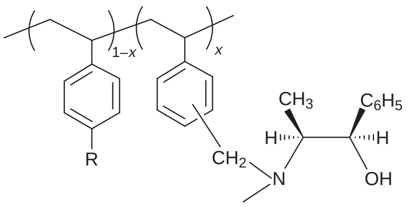


9: *x* = 1.00

10: R = H ; *x* = 0.01–0.66

11: R = CH3; *x* = 0.08–0.52

12: R = H; *x* = 0.06–0.51; prepared from crosslinked polymer beads

Catalyst and solubility properties of the polymers. Initially polymer **9** and the copolymers **10** were used as catalysts for eqn. (1). The reactions were run for 24 hours in toluene at 20 °C using benzaldehyde, diethylzinc and the catalyst in the mole ratios 1.00:1.10:0.05. In each case the final reaction mixture was quenched with methanol, then the polymer was filtered off. The soluble products were extracted from the filtrate and analysed by ^1H NMR spectroscopy. 1-Phenylpropanol (**1**) was the major product in all cases. Benzyl alcohol, evident from a singlet at δ 4.65 ppm, was a minor product ($\leq$9%) in most cases: see Table 3. The presence of benzyl alcohol was confirmed by gas chromatography in comparison with an authentic sample. The alcohol probably arises by reduction of the aldehyde by diethylzinc in the absence of an effective alkylation catalyst.[16,29,37] Distillation of the crude product gave pure 1-phenylpropanol (**1**) and the % ee was then determined by polarimetry. In all cases the (*R*)-enantiomer of alcohol **1** was the major product. The results of these experiments are summarised in Table 3, entries 1 to 8.

It is evident from the results that as the loading of catalytic sites decreases from 3.52 mmol g^{-1} down to 1.32 mmol g^{-1}, the chemical yields and the % ees increase. At and below 1.32 mmol g^{-1} the yields of 1-phenylpropanol (**1**) are essentially quantitative and the % ees plateau at 83%. Use of (1*R*,2*S*)-*N*-benzylephedrine (**7**) as a catalyst in place of the polymers, under otherwise similar reaction conditions, gave 1-phenylpropanol (**1**) in 92% chemical yield and 81% ee: Table 1, entry 8. Thus, the polymeric catalysts **10d**–**10f**, all with a loading of $\leq$1.32 mmol g^{-1}, gave, within experimental error (±1%), the same % ee as the model catalyst **7**.

It is of interest to know why the % ees obtained vary with the loading of catalyst groups. A major reason for using the linear polymers was an attempt to avoid possible diffusion problems

Table 2 Synthesis of linear polymers containing (1*R*,2*S*)-*N*-benzylephedrine residues

Entry	Polymer	Fraction of catalyst monomer		Loading/mmol g^{-1}	$[\alpha]_D^{20}$ /deg cm^2 g^{-1} [a]	Molecular weights of polymers ($\times 10^{-3}$)[b]	
		In feed	In polymer			$\overline{M}$n	$\overline{M}$w
1	**9**	1.00	1.00	3.52	−24.6	2.9	5.1
(a) With styrene as the diluent monomer							
2	**10a**	0.75	0.66	2.98	−23.7	7.8	11.5
3	**10b**	0.50	0.52	2.65	−23.2	6.6	12.5
4	**10c**	0.25	0.28	1.81	−18.0	10.0	19.6
5	**10d**	0.12	0.18	1.32	−14.3	15.9	26.5
6	**10e**	0.06	0.05	0.44	−5.4	5.2	10.1
7	**10f**	0.03	0.03	0.27	−4.6	6.3	15.3
8	**10g**	0.01	0.01	0.09	−2.4	2.9	6.0
(b) With 4-methylstyrene as the diluent monomer							
9	**11a**	0.50	0.52	2.56	−21.2	7.1	13.8
10	**11b**	0.40	0.46	2.38	−18.7	5.6	9.8
11	**11c**	0.30	0.36	2.03	−15.4	5.1	11.6
12	**11d**	0.20	0.17	1.16	−10.3	4.9	9.2
13	**11e**	0.10	0.08	0.61	−6.0	3.3	8.6

[a] In chloroform at 20 °C, concentration 5 g per 100 ml. [b] Determined by gel permeation chromatography. Values relative to polystyrene standards.

Table 3 Use of linear polymers containing (1*R*,2*S*)-*N*-benzylephedrine residues as catalysts for eqn. (1)[a]

Entry	Polymer	Loading of catalyst residues/mmol g^{-1}	Solubility in toluene		Toluene as reaction solvent			Hexane as reaction solvent		
			Starting polymers[b]	Complex[c]	Yield (%) of alcohol **1**	Yield (%) of benzyl alcohol	% ee[d]	Yield (%) of alcohol **1**	Yield (%) of benzyl alcohol	% ee[d]
1	**9**	3.52	I	I	47	9	44	—	—	—
(a) With styrene as the diluent monomer										
2	**10a**	2.98	I	I	56	6	56	—	—	—
3	**10b**	2.65	I	I	66	5	67	—	—	—
4	**10c**	1.81	S	I	80	4	79	—	—	—
5	**10d**	1.32	S	I	95	2	81	—	—	—
6	**10e**	0.44	S	I	98	1	82	—	—	—
7	**10f**	0.27	S	S	100	0	83	—	—	—
8	**10g**	0.09	S	S	100	0	83	—	—	—
(b) With 4-methylstyrene as the diluent monomer										
9	**11a**	2.56	S	I	65	6	69	60	12	20
10	**11b**	2.38	S	I	67	7	74	63	10	37
11	**11c**	2.03	S	I	74	7	76	91	5	54
12	**11d**	1.16	S	I	92	7	81	93	3	63
13	**11e**	0.61	S	I	92	7	86	94	5	65

[a] Reaction carried out for 24 hours at 20 °C with toluene or hexane as the reaction solvent and mole ratios Zn $(C_2H_5)_2$:C_6H_5CHO:catalyst = 1.10:1.00:0.05. The catalysts were prepared using (1*R*,2*S*)-ephedrine and the 1-phenylpropanol produced had the (*R*)-configuration. The % ees were determined by polarimetry. See Experimental section for further details. [b] Solubility in toluene prior to reaction: I = insoluble; S = soluble. All polymers were insoluble in hexane. [c] Complex formed on addition of diethylzinc solution in toluene. [d] Believed to be correct to ±1%.

resulting from insolubility of the catalyst. However, even the starting polymers with the higher loadings, *i.e.* polymer **9** and copolymers **10a** and **10b**, were, unlike unfunctionalised linear polystyrene, insoluble in toluene, presumably due to the presence of the polar β-amino alcohol residues and also the consequent possibility of hydrogen-bonding between the polymer chains. With the less highly loaded polymers that were soluble in toluene, *i.e.* polymers **10c**–**10e**, the addition of the diethylzinc brought about precipitation. This may result (i) from the simple change in the functional moieties from amino alcohol to chelated amino alkoxide, (ii) from crosslinking due to dimerisation of the chelated residues as indicated in formula **6** and/or (iii) from the zinc alkoxide of one moiety complexing with the amine group of a different moiety. Possibilities (ii) and (iii) both involve site–site interactions. It is very difficult to distinguish between these three effects because they are all expected to become more important as the loading increases. The addition of benzaldehyde would be expected to decrease the extent of crosslinking due to reason (ii) but not necessarily to totally remove it. In practice all the reaction systems involving polymer **9** and copolymers **10a**–**10e** remained insoluble on the addition of benzaldehyde, *i.e.* the alkylation reactions took place under heterogeneous conditions. The very lightly loaded polymers **10f** and **10g** are of particular interest because the systems involving these polymers remained soluble throughout the entire reaction process. These homogeneous systems gave the best chemical yields and stereochemical results, though not significantly better than the heterogeneous systems involving polymers **10c**–**10e**. The latter, though insoluble, unlike the more heavily loaded polymers, probably interact sufficiently well with toluene to swell well under the reaction conditions.

Linear polymers **11a**–**11e**, prepared using the readily avail-

Table 4 Reactions of benzaldehyde with diethylzinc catalysed by various crosslinked polymer-supported ephedrines[a]

Entry	Polymer	Starting polymer	Catalyst loading/ mmol g^{-1}	Degree of substitution	Reaction conditions		Toluene as reaction solvent		Hexane as reaction solvent	
					T/°C	t/h	Chem. yield (%)	% ee	Chem. yield (%)	% ee
1	**12a**	1% Crosslinked gel	0.93	0.12	0	70	81	81	81	64
2	**12a**	1% Crosslinked gel	0.93	0.12	22	20	85	78	—	—
3	**12b**	1% Crosslinked gel	1.13	0.15	0	70	77	77	83	62
4	**12b**	1% Crosslinked gel	1.13	0.15	23	20	85	74	81	65
5	**12c**	1% Crosslinked gel	2.30	0.40	0	70	80	74	82	62
6	**12d**	1% Crosslinked gel	2.30	0.40	23	20	86	73	97	65
7	**12d**	2% Crosslinked gel	1.06	0.14	0	70	70	72	—	—
8	**12e**	2% Crosslinked gel	2.62	0.51	0	70	71	69	76	62
9	**12f**	Amberlite XAD-4	0.90	0.11	0	70	59	28	62	39
10	**12g**	Amberlite XAD-4	0.50	0.06	22	22	75	28	70	39
11	**12h**	Polyhipe™	1.51	0.21	0	70	59	42	57	23
12	**13**	Amberlite XAD-4 siloxane graft[b]	0.69	—	20	24	67	36[c]	83	13

[a] Unless indicated otherwise mole ratios $C_6H_5CHO:Zn(C_2H_5):$Catalyst were 1.00 : 1.10 : 0.02. The catalysts were prepared using (1*R*,2*S*)-ephedrine and the 1-phenylpropanol produced had the (*R*)-configuration. The % ee were determined by polarimetry. The % ee are believed to be correct to ±1%. [b] Results reported in reference 22. [c] When 8 mol% of catalyst was used a 65% ee was obtained.

able 4-methylstyrene as the comonomer, were prepared in an attempt to obtain catalyst systems which were soluble in the reaction solvent at higher catalyst loadings than the 0.27 mmol g^{-1} of polymer **10f**. This was partially successful in that all the polymers prepared using 4-methylstyrene, including the 50 : 50 copolymer, were soluble in toluene, but as before the addition of diethylzinc caused precipitation. On the addition of benzaldehyde the reaction systems remained heterogeneous. The trends in chemical yields and % ees as the loadings decreased were similar to those observed with polymer **9** and copolymers **10**: see Table 3. The % ees obtained with the two polymers with ≤1.16 mmol of catalyst sites per gram *i.e.* polymers **11d** and **11e**, gave 1-phenylpropanol (**1**) in % ees equal to or greater than that achieved with the model catalyst **7**.

Hexane has often been used as the reaction solvent to carry out the reaction shown in eqn. (1), or related reactions, with either soluble[18,32] or PS catalysts.[17,18] A series of reactions was, therefore, carried out using linear copolymers **11** in hexane, the other reaction parameters being the same as those described above. All the copolymers **11** were found to be insoluble in hexane and the reaction systems were hetereogeneous throughout. However, chemical yields were comparable to those obtained before and again the % ees obtained increased as the loading decreased. The best % ee, was again obtained with polymer **11e** but now it was only 65%, *i.e.* considerably less than the 86% obtained using toluene as the solvent.

The main conclusion to be drawn from this study of the linear polymers are that in these systems toluene is a better choice of reaction solvent than hexane and that for best results loadings of catalytic groups should be less than *ca.* 1.5 mmol g^{-1}. These trends almost certainly mainly reflect the solubility of the catalysts in the reaction solvent or, when the catalyst systems are insoluble, their ability to swell in the reaction solvent.

Preparation of crosslinked polymers containing (1*R*,2*S*)-*N*-benzylephedrine residues: the use of these polymers as catalysts of eqn. (1)

Attention was next turned to the preparation of crosslinked polymer beads containing catalyst groups and their use as catalysts. As noted above, such polymers, being totally insoluble in all solvents, are much more convenient to use than the linear polymers.

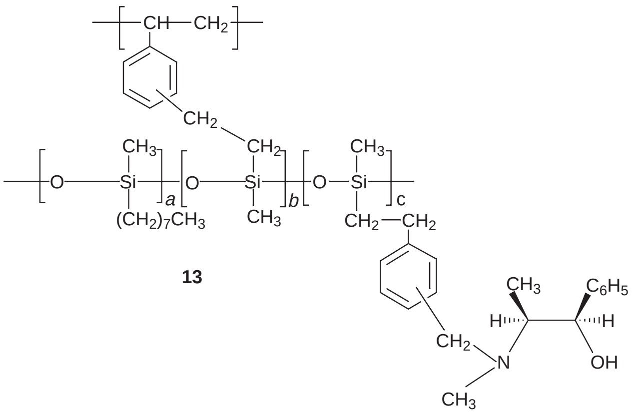
Polymer synthesis. A range of crosslinked polystyrene beads containing (1*R*,2*S*)-*N*-benzylephedrine residues were prepared as detailed below. The loadings achieved are as given in Table 4.

Reaction of three commercial samples of 1% crosslinked gel-type polystyrene beads, containing 1.01, 1.40 and 3.20 mmol g^{-1} of chloromethyl groups respectively, with (1*R*,2*S*)-ephedrine in toluene in the presence of potassium carbonate gave 1% crosslinked beads **12a**–**12c** containing different loadings of (1*R*,2*S*)-*N*-benzylephedrine residues. 2% Crosslinked gel-type polystyrene beads **12d** and **12e** were prepared similarly.

Amberlite XAD-4 is a type of highly crosslinked macroporous polystyrene beads.[38] Chloromethylation of samples of this polymer followed by reaction with (1*R*,2*S*)-ephedrine, using the method outlined above, gave beads **12g** and **12f** with different loadings of (1*R*,2*S*)-*N*-benzylephedrine residues.

Polyhipe™ is an open network of interconnected cells of highly crosslinked macroporous polystyrene.[39] Using the similar procedures to those used with the Amberlite XAD-4 beads, polymer **12h** was prepared.

Amberlite XAD-4 has a significant content of vinyl groups.[38] These arise because in its synthesis relatively large amounts of divinylbenzene are used as the crosslinking agent and in the case of many molecules only one of the vinyl groups takes part in the polymerisation reaction. As reported previously,[22] poly(methylhydrosiloxane) can be grafted to these residual vinyl groups using a platinum-containing catalyst. A portion of the remaining Si–H group can then be reacted similarly with monomer **8** to give catalyst **13**. The results of using polymer **13** as a catalyst are included here simply for comparison with the present results.



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Catalyst properties of polymer beads 12a–12h and 13. The various polymers described in the preceding section were used to catalyse eqn. (1). The reactions were carried out using

Table 5 Reactions of aldehydes with diethylzinc in toluene catalysed by (1*R*,2*S*)-*N*-benzylephedrine **7** or polymer-supported ephedrine **12a**[a]

			Model catalyst **7**		PS-Catalyst **12a**	
Entry	Aldehyde	*T*/°C	Chem. yield (%)[b]	% ee[c]	Chem. yield (%)[b]	% ee[c]
1	Benzaldehyde	0	83	84	81	81
2	Benzaldehyde	23	87	76	85	78
3	2-Methoxybenzaldehyde	0	82	89	88	90
4	2-Methoxybenzaldehyde	23	90	85	91	83
5	4-Chlorobenzaldehyde	0	84	94	83	93
6	4-Chlorobenzaldehyde	23	83	89	84	86

[a] Reactions were carried out in toluene with aldehyde : $Zn(C_2H_5)_2$: catalyst in mole ratios 1.00 : 1.10 : 0.02 for 70 hours at 0 °C or 20 hours at 20 °C. [b] Unless indicated otherwise yield of alcohol is that isolated by bulb-to-bulb distillation. [c] By polarimetry. Believed to be correct to ±1%. See Experimental section for further details.

benzaldehyde, diethylzinc and the catalyst in mole ratios of 1.00 : 1.10 : 0.02 in either toluene or hexane as the reaction solvent at 0 °C or 20–23 °C. At the end of the reaction period the polymer beads were simply filtered off and washed, then the filtrate and washings analysed by gas chromatography using internal standards to determine the yield of 1-phenylpropanol (**1**). These analyses also showed that up to 8% of the benzaldehyde was reduced to benzyl alcohol,[16,29,37] the larger percentages being obtained with the less active catalysts. Removal of the solvent and bulb-to-bulb distillation of the product gave a sample of alcohol **1** pure by ^{1}H NMR spectroscopy. The % ee was determined by polarimetry. The results are summarised in Table 4.

The results obtained with toluene and with hexane as the reaction solvent differed significantly but since the better stereochemical results were obtained using toluene, these results will be discussed first. The lightly crosslinked gel-type polymers proved to be the best supports both in terms of the chemical yields and the % ees. As expected from the results with the linear polymers, the % ees achieved were greater with the less heavily loaded polymers, and the 1% crosslinked polymer, being more easily swollen by the reaction solvent, gave better % ees than the 2% crosslinked polymer. The % ees were also greater at 0 °C than at 23 °C. Thus, the best % ee was obtained under the reaction conditions summarised in Table 4 entry 1 and was 81%. This value is only slightly less than the 84% ee obtained using (1*R*,2*S*)-*N*-benzylephedrine (**7**) under otherwise similar reaction conditions: Table 1 entry 9. The reactions were, however, very slow at 0 °C. Raising the reaction temperature to 23 °C allowed the reaction time for a useful yield to be reduced to 20 h. The ees were then 78% and 76% respectively for the PS catalyst **12a** and the model catalyst **7**.

The results obtained with the catalyst supported on Amberlite XAD-4 or Polyhipe™, especially the % ees, were substantially lower than those obtained using the gel-type supports despite the fact the former had catalyst loadings of ≤1.51 mmol g^{-1}. It may be that with these polymers a substantial fraction of the catalyst sites are present in the more highly crosslinked parts of the support matrix and are, therefore, not readily accessible. It is also possible that many of the catalyst sites are at the inner surfaces of the pores so that the local concentration of catalyst groups is high and this may result in significant site–site interactions. Access to the catalytic groups on the grafted support **13** also appears to be hindered as raising the mol percentage of catalyst from 2% to 8% raised the ee from 36% to 65%.[22] Perhaps the graft substantially blocks the pores.

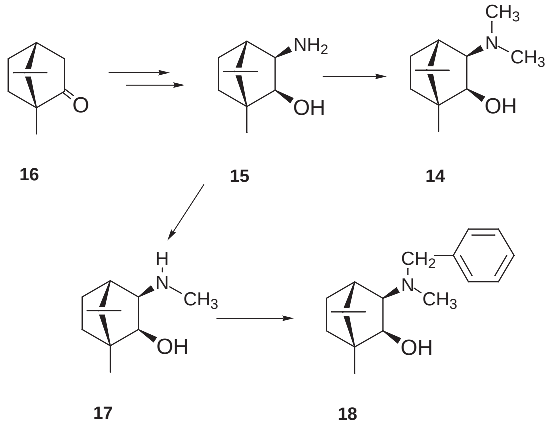
The results obtained with hexane as the solvent showed a different pattern, though the gel-type supports were again the best. The better % ees obtained with these supports were nevertheless significantly lower than those obtained with toluene as the solvent. Surprisingly the % ees obtained at 0 °C were lower than those obtained at 23 °C, and whilst some of the % ees obtained with the macroporous-type supports were poor, they were nevertheless better than those obtained using toluene under similar conditions. The reasons for these latter differences is not clear but is almost certainly related to the fact hexane does not interact as well as toluene with the support matrix.

To confirm that catalyst **12a** in toluene gave stereochemical results very similar to those obtained with (1*R*,2*S*)-*N*-benzylephedrine (**7**) under similar conditions, reactions were also carried out with 2-methoxybenzaldehyde and 4-chlorobenzaldehyde using the aldehyde, diethylzinc and catalyst in the mole ratios 1.00 : 1.10 : 0.02 at 22 °C. The results are summarised in Table 5 together with those for benzaldehyde previously included in Table 4. It is evident that for all three aldehydes, at both 0 °C and 23 °C, the % ee of the PS catalyst **12a** is never more than 4% less than that obtained with model catalyst (**7**) under the same conditions.

Preparation of catalysts containing (+)-3-*exo*-(*N*-benzyl,*N*-methylamino)isoborneol residues: the use of these to catalyse eqn. (1) and related reactions

Having identified suitable conditions for the preparation of successful linear and crosslinked PS ephedrine catalysts, attention was next given to preparing other PS catalysts similarly but starting from a β-amino alcohol which is known to afford higher % ees. Noyori *et al.* have shown that (−)-3-*exo*-(dimethylamino)isoborneol (DAIB) (**14**) is an excellent catalyst for the asymmetric alkylation of aromatic aldehydes using diethylzinc,[40] so this catalyst and various analogues were prepared and studied.

Synthesis of catalysts. The β-amino alcohol **15** was prepared in four steps (see Experimental section) from (1*R*)-camphor (**16**). Reaction of this amino alcohol with aqueous formaldehyde and formic acid gave a sample of DAIB (**14**), and reaction with benzaldehyde to give the imine and alkylation of the imine with methyl iodide gave the secondary amino alcohol **17** (Scheme 2). Reaction of the latter with benzyl chloride gave the



Scheme 2

Table 6 Reactions of aldehydes with diethylzinc catalysed by catalysts **14**, **16** and **20**–**22**[a]

Entry	Aldehyde	Catalyst	Polymer type[b]	Loading/ mmol g^{-1}	Yield of chiral alcohol (%)[c]	% ee[d]
1	Benzaldehyde	**14**	—	—	97	97[e]
2	4-Chlorobenzaldehyde	**14**	—	—	88	92[f]
3	Benzaldehyde	**18**	—	—	90	95[e]
4	4-Chlorobenzaldehyde	**18**	—	—	91	90[f]
5	Benzaldehyde	**20**	L	3.34	89	96[e]
6	Benzaldehyde	**21**	L	2.86	91	98[e]
7	Benzaldehyde	**22**	X	0.64	94	97[f]
8	4-Chlorobenzaldehyde	**22**	X	0.64	94	92[e]

[a] Reactions carried out for 24 hours at 20 °C in toluene using aldehyde, diethylzinc and catalyst in the mole ratios 1.00 : 1.10 : 0.05. [b] L = linear polymer; X = crosslinked polymer. [c] Determined by ^{1}H NMR spectroscopic analysis of extracted organic materials. [d] The predominant enantiomer was the (*S*)-alcohol. [e] Determined by ^{19}F NMR of the Mosher ester derivative:[41] see Experimental section. [f] By polarimetry: see Experimental section.

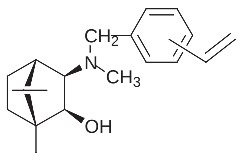
tertiary amino alcohol **18** which is a low molecular weight analogue of the PS catalysts. A similar reaction with the commercial mixture of 3- and 4-vinylbenzyl chlorides gave monomer **19**. The latter was homopolymerised and copolymerised with styrene in the same manner as with the ephedrine-derived analogues, to give homopolymer **20** and the 2 : 1 copolymer **21**. Reaction with 1% crosslinked polystyrene beads containing 0.70 mmol g^{-1} of chloromethyl groups gave crosslinked beads **22** containing 0.64 mmol g^{-1} of catalyst residues.

Catalyst properties of compounds 14 and 18 and polymers 20–22

The various catalysts were used to catalyse eqn. (1) and, in some cases, the analogous reactions using 4-chlorobenzaldehyde. The reactions were carried out in toluene at 20 °C for 24 hours using the aldehyde, diethylzinc and the catalyst in the mole ratios 1.00 : 1.10 : 0.05. The results are summarised in Table 6. Note that with these catalysts the main product is the (*S*)-enantiomer.

The % ees obtained with DAIB (**14**), entries 1 and 2, were slightly lower than those reported by Noyori *et al.*,[40] but this is to be expected because they carried out the reactions at 0 °C. The corresponding results obtained with catalyst **18**, an excellent model for the polymers, were in the case of both aldehydes 5% less than that obtained with DAIB (**14**). Thus, replacement of an *N*-methyl group by a more bulky *N*-benzyl group results in a small fall in the % ee.

The stereochemical results obtained with the two linear polymeric catalysts were excellent, see Table 6 entries 5 and 6, the % ees being very similar to those obtained with the non-polymeric catalysts **14** and **18**. Given the relatively high loadings of the catalyst moieties, ≥2.48 mmol g^{-1}, this is at first surprising. However, unlike the ephedrine-derived polymers of similar loading which showed a relatively poor stereochemical performance, polymers **20** and **21** were soluble in toluene both before and after the addition of diethylzinc. This strongly suggests that in the present reaction system the key factor for success is a polymer support which interacts well, *i.e.* dissolves or swells extensively, with the reaction solvent. It assists in achieving this if the catalytic moieties have a substantial lipophilic character and so interact well with toluene.



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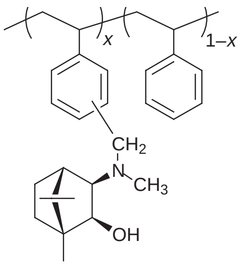

20: *x* = 1.00

21: *x* = 0.66

22: *x* = 0.11; prepared from crosslinked polymer beads

The % ees obtained with the crosslinked polymer beads in reactions with benzaldehyde and 4-chlorobenzaldehyde were also high, see entries 7 and 8, and were slightly higher than those obtained with the model catalyst **18**, compare with entries 3 and 4. The % ee of the product from the reaction summarised in entry 7 was estimated both by polarimetry and by the use of Mosher esters.[41] The % ee obtained with benzaldehyde (97%) using 5% of catalyst at 20 °C is somewhat higher than that (92%) reported previously using 5 mol% of a similar polymer at 0 °C.[16] In the present work a 1% crosslinked polymer with a catalyst loading of 0.64 mmol g^{-1} was used. It is not clear from the brief details given in the literature report[16] just what polymer was used, but it may well have been a 1–2% crosslinked polymer with a catalyst loading of *ca.* 1 mmol g^{-1}.

Conclusions

Many attempts have been made to produce PS versions of the better chiral catalysts for asymmetric organic synthesis, but in many cases the % ees achieved have been less than those achieved using the analogous non-polymeric catalysts.[11] In this paper the reactions of benzaldehyde with diethylzinc catalysed by PS ephedrine or camphor derivatives have been investigated in some depth in an attempt to identify the crucial factors necessary to successfully prepare PS chiral catalysts for such reactions. The most important factor is found to be a favourable interaction of the polymer matrix with the reaction solvent so that the polymer will dissolve or swell to allow the other reactants easy access to the catalytic sites. Accordingly toluene is a better reaction solvent than hexane. The ephedrine-derived catalytic groups themselves reduce the solubility of the linear polymers in toluene and, almost certainly, the swelling properties of the crosslinked polymers. Thus, of the polymers investigated the better linear ones are those with <*ca.* 1.5 mmol per g of catalyst sites and the better insoluble ones are 1% crosslinked gels with <*ca.* 1.0 mmol per g of catalyst sites. At greater loadings and higher percentages of crosslinking a significant fraction of the catalyst sites become inaccessible. The reaction in eqn. (1) which occurs without being under the influence of the intended catalyst **3**, and so achieves low or zero stereoselectivity, makes an important contribution, and the reduction to give benzyl alcohol becomes more significant. Site–site interactions and microenvironmental effects may well be present at the loadings used[9] but they do not appear to play a key role in these PS reaction systems. The reaction of benzaldehyde with diethylzinc using the best linear PS ephedrine derivatives **10f**, **10g** or **11e** affords 1-phenylpropanol (**1**) with 83–86% ee of the (*R*)-enantiomer; using the best linear PS camphor derivative **21** affords the alcohol (**1**) with 98% ee of the (*S*)-enantiomer; using the best crosslinked PS ephedrine derivative **12a** affords the alcohol (**1**) with 78–81% ee of the (*R*)-enantiomer and using the best crosslinked PS camphor derivative **22** gives alcohol **1** with 97% ee of the (*S*)-enantiomer. These values are close to those obtained using analogous non-polymeric catalysts under similar reaction conditions. With other types of reactions and/or using other types of catalyst the most crucial factor(s) for success may well be different.

Experimental

(1*R*,2*S*)-(−)-Ephedrine (99%), (1*R*)-(+)-camphor (99%) and diethylzinc in toluene were obtained from Aldrich. Chloromethylated 1% and 2% crosslinked polystyrene beads were obtained from Kodak. Polyhipe™ was a gift from the National Starch and Chemical Corporation, New Jersey. Other chemicals were obtained from Fluka. Solvents and reagents were dried and purified according to standard procedures. Organic extracts were dried with magnesium sulfate. Samples were dried in a vacuum oven at 1.0 mm Hg.

Infrared spectra were recorded using either a Nicolet MX1 instrument or a Perkin-Elmer 1720 instrument. Solid samples were prepared as potassium bromide discs unless stated otherwise, liquid samples were prepared as thin films between sodium chloride plates. ^{1}H NMR spectra were recorded for solutions in deuterated chloroform on a Varian Gemini 200 MHz NMR spectrometer using TMS as an internal standard. Elemental analyses for chlorine were carried out by Butterworth Laboratories Limited; analyses for nitrogen were made in house on a Carlo Erba model 1106 instrument. Optical rotations were measured using a Perkin-Elmer 141 digital polarimeter, in a cell of path length 10 cm. Gas chromatographic (GC) analyses were carried out using a Pye 204 Chromatograph equipped with a 10% SP1000 stationary phase at 220 °C and a flame-ionisation detector. Molecular weights and polydispersities were determined by gel permeation chromatography (GPC) using a Waters Associates model 502 system equipped with UV and RI detectors. PL gel columns 100 Å and 500 Å were used. The eluant was THF, at a flow rate 1 cm^3 min^{-1}, and data acquisition and analysis was achieved with a Trilab 2000 chromatography data system.

(1*R*,2*S*)-*N*-Benzylephedrine (7)

(1*R*,2*S*)-Ephedrine (43.1 mmol) and benzyl chloride (43.1 mmol) were dissolved in pyridine (20 ml) and stirred at room temperature for 7 days. After reaction, the mixture was quenched with water (20 ml), the product extracted three times with ethyl acetate (60 ml). The extracts were dried and the solvent was then evaporated off. The residue was purified by flash column chromatography using petroleum ether (bp 40–60 °C)–ethyl acetate = 3 : 1 as the eluant. This afforded white crystals (5.21 g, 47% yield), mp 49–51 °C; $[\alpha]_D$ −29.5 (c = 2.35, CHCl$_3$); δ 1.02 (d, 3H, C-CH$_3$), 2.23 (s, 3H, N-CH$_3$), 2.96 (m, 1H, C-2), 3.64 (s, 2H, Ar-CH$_2$), 4.90 (d, 1H, C-1) and 7.22–7.45 ppm (m, 10H, Ar-H). Found C, 80.0; H, 8.4; N, 5.5: $C_{17}H_{21}NO$ requires C, 80.0; H, 8.3; N, 5.5%.

Reactions summarised in Table 1

(a) Entries 1–5. A mixture of benzaldehyde (902 mg, 9.4 mmol) and diethylzinc (9.5 ml of a 1.1 M solution in toluene; 10.4 mmol) in toluene (2.0 ml) was stirred magnetically under an atmosphere of dry nitrogen at the temperatures and for the times given in the Table. The reactions were then quenched by the addition of aqueous hydrochloric acid (6 ml of 1 M) and the organic product extracted into toluene. The extracts were dried and then analysed by GC using durene (1,2,4,5-tetramethylbenzene) as an internal standard.

(b) Entry 6. A mixture of (*R*)-1-phenylpropanol (**1**) (64 mg, 0.47 mmol) and diethylzinc (9.9 ml of a 1.1 M solution in toluene, 10.9 mmol) was stirred at 20 °C under an atmosphere of dry nitrogen for 1 h. A solution of benzaldehyde (902 mg, 9.4 mmol) in toluene (1.6 ml) was added and the mixture stirred at 0 °C for 48 h. The yield of product was estimated as in (a). Bulb-to-bulb distillation (105 °C, 0.5 mm Hg) of the crude product using a Büchi GKR-50 microdistillation apparatus gave 1-phenylpropanol (**1**). The optical rotation, $[\alpha]_D^{20}$ was measured for a 5% solution in chloroform and compared to a value of −45.45 (c 5.15, CHCl$_3$) reported[42] for the pure *S*-enantiomer.

(c) Entry 7. This was carried out as described in (a) above except that 2% crosslinked gel-type beads (200 mg) were added to the reaction mixture.

(d) Entries 8–10. These experiments were carried out as described in (b) above except that catalyst (**7**) (amounts as indicated in Table) was used in place of alcohol **1**.

(1*R*,2*S*)-*N*-(3- and 4-Vinylbenzyl)ephedrines (8)

These were prepared using the procedure described above for compound **7** except that a commercial mixture of 3- and 4-vinylbenzyl chloride (70% the 3-isomer; 30% the 4-isomer) was used. Flash column chromatography with hexane–ethyl acetate 7 : 1 as the eluant gave the desired product as an oil (28.21g, 35% yield). It had $[\alpha]_D$ −36.3 (c = 2.35, CHCl$_3$) (lit.,[36] $[\alpha]_D$ −41.8 (c = 2.35, CHCl$_3$) for the 4-isomer).

Preparation of linear polymers 9, 10 and 11

(a) Typical procedure: polymerisation of monomer (8) to give homopolymer (9). (1*R*,2*S*)-*N*-(3- and 4-Vinylbenzyl)ephedrines (**8**) (17.9 mmol) were dissolved in toluene (10 ml) and azobisisobutyronitrile (0.81 mmol, 4.5 mmol%) was added as the initiator. The solution was degassed thoroughly using three freeze–thaw cycles. The tube was sealed under vacuum and polymerisation achieved by heating at 75 °C for 24 h. The tube was then cooled, the toluene removed by rotary evaporation and the residue dissolved in dichloromethane. The polymer was precipitated twice into petroleum ether bp (60–80 °C). The product was collected and dried in a vacuum oven at 40 °C for 24 h. This gave a pale brown powder (3.58 g). Microanalysis indicated a loading of 3.52 mmol N per g polymer. The molecular weight of the product was determined using GPC: the result is given in Table 2. It had $[\alpha]_D$ −24.6 (c = 2.4, CHCl$_3$); δ (500 MHz) 0.9 (br, 3H, C-CH$_3$), 1.1–2.3 (br, 6H, backbone, N-CH$_3$), 2.8 (br, 1H, C-2), 3.4 (br, 2H, Ar-CH$_2$), 4.8 (br, 1H, C-1) and 6.0–7.4 ppm (br, 9H, Ar-H).

(b). Other polymers were prepared similarly from monomers (**8**) and styrene or 4-methylstyrene. The feedstock compositions and the compositions of the copolymers and the optical rotations were as summarised in Table 2.

Catalytic properties of linear polymers 9–11, 20 and 21

The following procedure is typical of the experiments summarised in Tables 3 and 6 using linear polymers.

Entries 1–8 in Table 1. A mixture of the catalyst (0.24 mmol, 5 mol%) in toluene (5 ml) was cooled down to 0 °C and stirred magnetically. Diethylzinc (5.2 mmol as a 1.1 M solution in toluene) was added and the mixture stirred for an hour before the temperature was raised to 20 °C. Benzaldehyde (4.7 mmol) in toluene (2 ml) was then added and the reaction mixture stirred for 24 hours. At the end of the reaction period the solution was cooled down to 0 °C and quenched with methanol (5 ml) and 1 M hydrochloric acid (5 ml). The precipitated polymer was filtered off. Toluene (20 ml) was added to the filtrate and the organic layer separated. The aqueous layer was extracted with diethyl ether (3 × 15ml), the combined extracts washed with water (5 ml) and finally dried. The organic solvents were carefully evaporated off. The residue was analysed by ^{1}H NMR spectroscopy then purified by bulb-to-bulb distillation (110 °C, 1 mm Hg). The purity of the distillate was confirmed by GC and ^{1}H NMR spectroscopy, then the $[a]_D^{20}$ optical rotation was measured for a solution in chloroform.

Preparation of polymer-supported catalysts 12a–12e

These were prepared from commercial samples of chloromethylated 1% crosslinked polystyrene beads containing 1.01, 1.40, or 3.20 mmol of chlorine per gram. A typical procedure is as follows.

Preparation of polymer 12a. (1*R*,2*S*)-Ephedrine (60.6 mmol), 1% cross-linked chloromethylated polystyrene (20.16 g, 20.2 mmol) of loading 1.01 mmol Cl per g polymer and potassium carbonate (20.3 mmol) were suspended in toluene (125 ml), and the mixture mechanically stirred and heated under reflux for 48 h. At the end of the reaction period, the beads were filtered off and successively washed with methanol, water, tetrahydrofuran, tetrahydrofuran–water (1 : 1), and diethyl ether. Since the beads were to be used as a catalyst they were Soxhlet-extracted with diethyl ether for 48 h before being dried in a vacuum oven at 40 °C for 48 h. This afforded 1% cross-linked polystyrene-supported ephedrine-derived catalyst **12a** (22.15 g), containing, by elemental analysis, 0.93 mmol N per g polymer.

Preparation of polymer-supported catalysts 12f–12h

To remove impurities the commercial Amberlite XAD-4 was Soxhlet-extracted sequentially with water, methanol, THF, hexane and ether for 24 h with each solvent and then dried at 90 °C in the vacuum oven for 2 days. The following preparation of catalyst **12f** is typical. Catalyst **12g** was prepared similarly using half the amount of dimethoxymethane, thionyl chloride and tin chloride. Catalyst **12h** was prepared similarly to polymer **12f** but starting with Polyhipe™.

(a) Chloromethylation of Amberlite XAD-4. In a 1 L, 3-necked, round-bottomed flask equipped with a reflux condenser, stirrer and addition funnel, Amberlite XAD-4 (50 g) was stirred in dichloromethane (500 ml) at 35 °C under a nitrogen atmosphere for 30 minutes. Dimethoxymethane (116 ml) was then added to the suspension over 10 minutes and the mixture stirred for a further 1 h. After cooling to room temperature thionyl chloride (73.6 ml) and stannic chloride (2.8 ml) were added slowly so as to maintain a gentle reflux (*ca.* 1 h). When the addition was complete the temperature was raised to 35 °C and the suspension stirred for a further 18 hours. At the end of the reaction period the suspension was cooled to 20 °C and distilled water (200 ml) was added slowly. The suspension was allowed to stand to allow any excess chloromethyl methyl ether (**CAUTION: SEVERE CARCINOGEN**) to hydrolyse. The polymer was then filtered off and washed successively with water, 2 M hydrochloric acid, water, dichloromethane, THF, THF–water and methanol. The polymer was dried under vacuum at 20 °C overnight. By elemental analysis it contained 1.72 mmol of chlorine per g.

(b) Reaction of chloromethylated Amberlite XAD-4 with (1*R*,2*S*)-ephedrine. This was carried out using the procedure given above for the preparation of polymer **12a**. The final polymer **12f** contained 0.90 mmol of nitrogen per g.

Catalytic properties of crosslinked polymers (12) and (22)

These experiments were carried out similarly to those described above using the linear polymeric catalysts, except that (i) at the end of the reaction period the polymer beads were filtered off prior to treating the filtrate with hydrochloric acid, and (ii) the organic product was analysed by GC. The product from 4-chlorobenzaldehyde distilled at 135 °C/0.1 mmHg and that from 2-methoxybenzaldehyde at 150 °C/0.1 mmHg. The experimental $[a]_D^{20}$ were compared with the literature values of −24.2° (*c* = 5, C_6H_6) for (*S*)-1-(4-chlorophenyl)propanol[43] and of +54.0 (*c* = 1.2, toluene) for (*R*)-1-(2-methoxyphenyl)-propanol.[44]

Synthesis of camphor derivatives

(a) Primary amino alcohol 15. (1*R*)-Camphor **16** was converted into amino alcohol **15** in 4 practical steps essentially as described by Bonner and Thornton.[45] It had mp 188–192 °C (lit.,[45] mp 190–194 °C); $[a]_D$ −6.72 (*c* = 1.4, MeOH) (lit.,[45] $[a]_D$ −1.3° (*c* = 1.43, MeOH); ν_{max} 3393 (O–H, N–H), 2948 (–CH$_2$–, –CH$_3$) and 1107 cm^{-1} (C–O); δ 0.79 and 0.95 (2s, 6H, C-8 and C-9 CH$_3$), 1.06 (s, 3H, C-10 CH$_3$), 1.40–1.85 (m, 4H, C-5 and C-6 CH$_2$) and 3.38 ppm (d, 1H, CHO); CI MS: *m*/*z* 170 (M + H)$^+$.

(b) Tertiary amino alcohol 14. Reaction of amino alcohol **15** with formaldehyde and formic acid as described by Chittenden and Cooper[46] gave amino alcohol **14** as an oil, bp 70 °C/0.1 mm Hg. It had $[a]_D$ −8.0 (*c* = 4.3, EtOH); δ 0.79, (s, 3H, C-8 CH$_3$), 0.98 (s, 3H, C-9 CH$_3$), 1.16 (s, 3H, C-10 CH$_3$) 1.20–1.95 (m, 4H, C-5 and C-6 CH$_2$), 2.25 (s, 6H, N(CH$_3$)$_2$), 3.67 (d, 1H, CHN), 3.81 (d, 1H, C-4) and 4.50 ppm (d, 1H, CHO).

(c) Secondary amino alcohol 17. Primary amino alcohol **15** (66.5 mmol) and benzaldehyde (77.9 mmol) were dissolved in benzene (50 ml). After standing for 24 h the mixture was heated under reflux for 12 h whilst water was removed using a Dean–Stark trap. The benzene was then removed by rotary evaporation and the residue dissolved in dimethylformamide (6 ml). Methyl iodide (80.3 mmol) was added and the mixture allowed to react at 20 °C for 18 hours. Diethyl ether was then added to this mixture until a permanent cloudiness appeared. Cooling caused the precipitation of an orange solid. The solids were collected and heated under reflux with ethanol–water = 1 : 1 (75 ml) for 4 hours after which the aqueous solution was extracted once with chloroform (20 ml) to remove any organic by-product. The aqueous solution was acidified with 1 M hydrochloric acid, then made alkaline with 10% sodium hydroxide and extracted with chloroform (3 × 75 ml). The combined organic extracts were washed with water (50 ml) and dried. Evaporation of the solvents gave amino alcohol **17** as a yellow oil (5.26g, 43% yield). It had $[a]_D$ −12.3 (*c* = 1.5, CHCl$_3$); ν_{max} 3334 (O-H), 2950 (CH$_2$ and CH$_3$) and 1096 cm^{-1} (C–O); δ 0.75 and 0.92 (2s, 6H, C-8 and C-9 CH$_3$), 1.01 (s, 3H, C-10 CH$_3$), 1.10–1.80 (m, 4H, C-5 and C-6 CH$_2$), 2.42 (s, 3H, N-CH$_3$), 2.57 (d, 1H, CHN), 2.91 (d, 1H, C-4) and 3.41 ppm (d, 1H, CHO); CI MS: *m*/*z* 184 (M + H)$^+$.

(d) Tertiary amino alcohol 18. This compound was prepared from secondary amino alcohol **17** using the same procedure as that given above for the synthesis of compound **7** from ephedrine. Compound **18** was obtained as a pale yellow oil (26% yield). It had $[a]_D$ +4.98 (*c* = 1.20, CHCl$_3$); ν_{max} 3338 (O–H), 2957 (CH$_2$ and CH$_3$), 1455 (-C(CH$_3$)$_2$), 1370 (O-H), 740 and 699 cm^{-1} (5 adjacent Ar-H); δ 0.80 and 1.01 (2s, 6H, C-8 and C-9 CH$_3$), 1.13 (s, 3H, C-10 CH$_3$), 1.20–1.90 (m, 4H, C-5 and C-6 CH$_2$), 2.13 (s, 3H, N-CH$_3$), 2.55 (d, 1H, CHN), 3.57 (d, 1H, CHO) and 7.20–7.55 ppm (m, 5H, Ar-H).

(e) Monomers 19. These were prepared from secondary amino alcohol **17** using the same procedure as that given above for the synthesis of monomers **8**. Monomers **19** were obtained as a pale yellow oil (26% yield). The oil had $[a]_D$ −11.75 (*c* = 2.35, CHCl$_3$); δ 0.80 and 1.01 (2s, 6H, C-8 and C-9), 1.14 (s, 3H, C-10), 1.43* (s, 2H, Ar-CH$_2$), 2.15 (s, 3H, N-CH$_3$), 2.55 (d, 1H, CHN), 3.58 (d, 1H, CHO), 5.25* (d, 1H, ABX), 5.75* (d,1H,ABX), 6.72* (d, 1H, ABX) and 7.15–7.45 ppm (m, 4H, Ar-H). (*Smaller peaks were present at these positions due to the presence of the 4-isomer.) Found C, 80.2; H, 9.6; N, 5.1; $C_{20}H_{29}NO$ requires C, 80.2; H, 9.8; N, 4.7%. CI MS: *m*/*z* 300 $(M + H)^+$.

Synthesis of polymer 20

Polymerisation of monomers **19** using the procedure given above for the synthesis of polymer **9** gave polymer **20**. It had $[\alpha]_D$ −9.8 ($c = 2.3$, $CHCl_3$); ν_{max} 3341 (O–H), 1606 (C=C), 1041 (C–O), 820 (2 adjacent Ar-H) and 796 cm^{-1} (3 adjacent Ar-H); δ (500 MHz) 0.7–0.9 (br, 3H,C-8, CH_3) 0.9–1.2 (br, 6H, C-9, C-10 CH_3), 1.2–2.2 (br, 11H, backbone, N-CH_3, C-4, CH, C-5 and C-6 CH_2), 2.3–2.6 (br, 1H, CHN), 3.3–3.7 (br, 2H, Ar- CH_2), 4.2–4.7 (br, 1H, CHO) and 5.9–7.1 ppm (br, 4H, Ar-H). Found C, 80.7; H, 8.7; N, 5.1: $C_{20}H_{29}NO_3$ requires C, 80.2; H, 9.8; N, 4.7%. By GPC it had $M_n = 3300$, $M_w = 5700$.

Synthesis of polymer 21

Copolymerisation of monomers **19** with an equimolar amount of styrene using the procedure given above for the synthesis of polymers **10** gave copolymer **21**. It had $[\alpha]_D$ −8.4 ($c = 2.3$, $CHCl_3$); ν_{max} 3379 (O–H), 1604 (C=C), 1041 (C–O), 820 (2 adjacent Ar-H) and 796 cm^{-1} (3 adjacent Ar-H), 759 and 701 ppm (5 adjacent Ar-H); δ (500 MHz) 0.7–0.9 (br, 3H, C-8, CH_3), 0.9–1.2 (br, 6H, C-9 and C-10 CH_3), 1.2–2.2 (br, 11H, backbone, N-CH_3, C-4, CH, C-5 and C-6, CH_2), 2.3–2.6 (br, 1H, CHN), 3.4–3.7 (br, 2H, Ar-CH_2), 4.2–4.8 (br, 1H, CH0) and 6.0–7.2 ppm (br, 9H, Ar-H). By elemental analysis it contained 2.86 mmol N per g corresponding to a composition of 67% monomers **19** and 33% styrene. By GPC it had $M_n = 3800$, $M_w = 8200$.

Synthesis of polymer 22

This polymer was prepared from 1% crosslinked polystyrene beads (0.70 mmol chlorine per g) and amino alcohol **17** using the procedure described above for the preparation of polymer **12a**. By elemental analysis it contained 0.64 mmol of nitrogen per g.

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