Asymmetric synthesis of 1-phenylpropanol using polymer-supported chiral catalysts in simple bench-top flow systems†

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Reactions of aldehydes with diethylzinc catalysed by PS ephedrine or PS camphor derivatives in bench-top flow systems have been investigated. This type of reaction system allows the PS chiral catalysts to be conveniently used for extended periods. When the PS camphor derivative **3** was used in a flow system to catalyse the reaction of benzaldehyde with diethylzinc [Reaction (1)], 1-phenylpropanol **1** was initially obtained in a chemical yield of > 95% and an ee of > 94%, but after *ca.* 275 h in use the chemical yields had dropped to 50–60% and the ee to 81–84%. The deterioration in performance appears to be due to the gradual chemical degradation of the catalyst sites. It is suggested that this results from oxidation of the 3-*exo*-hydroxy group of the catalyst moiety. Thus, when, in future, PS catalysts are to be repeatedly recycled then it will not only be necessary to use a physically robust polymer, but it will also be necessary to select catalytic groups which do not chemically degrade significantly during the extended reaction periods. High % ee could be obtained in certain flow systems. Thus, under optimum conditions the use of both PS ephedrine and PS camphor derivatives as catalysts for Reaction (1) gave 1-phenylpropanol **1** in 97–99% ee. The result with the PS ephedrine derivative is surprising because when (1*R*,2*S*)-*N*-benzylephedrine **5** is used in batch systems under typical reaction conditions it affords (*R*)-alcohol **1** in only *ca.* 81% ee. The increase in the ee probably arises because the flow system produces the effect of a high mol% of catalyst and/or of diethylzinc and/or because the initial alkoxide reaction product, which acts as a catalyst and gives product with a very low % ee, is continuously removed from the reaction system. This result indicates that catalyst species can be formed from the PS ephedrine derivatives and from (1*R*,2*S*)-*N*-benzylephedrine **5** which produce very high enantioselectivities but which are not normally present in sufficient amounts to dominate the reaction system.

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 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] and it became clear that three major factors need to be taken into account when carrying out PS reactions. These are: (i) site accessibility, (ii) possible site–site interactions, and (iii) possible microenvironmental effects.

Asymmetric organic syntheses achieved using PS chiral catalysts are a very attractive type of organic reaction. Thus, since the PS catalyst is easily filtered off at the end of the reaction, the soluble chiral reaction products are easily freed of the chiral catalyst and the latter is easily recovered for possible reuse. This latter feature is especially important if the catalyst moiety is expensive. Because of these advantages, many attempts have been made to prepare PS versions of the better chiral catalysts, but this is not a trivial exercise and in many cases the percentage enantiomeric excesses (% ees) achieved have been lower in the supported systems.[10]
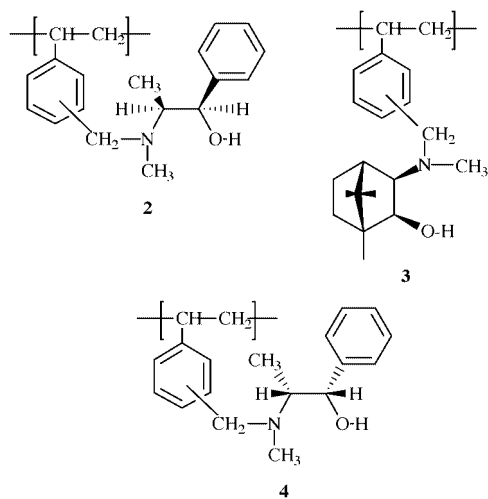
The present paper is concerned with the use of PS ephedrine or PS camphor derivatives in bench-top flow systems to catalyse the reaction of benzaldehyde with diethylzinc to give 1-phenylpropanol **1**: Reaction (1). This is a particularly interesting reaction to study in PS systems because the reaction occurs slowly in the absence of added catalyst to give racemic **1**. The PS chiral
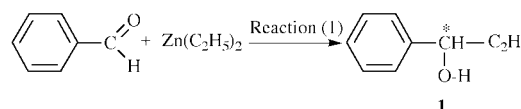
catalysts are, therefore, operating in a competitive situation which makes it particularly difficult to obtain % ees as high as those obtained in simple solution systems. PS versions of Reaction (1) and related reactions have been studied before on several occasions,[11–21] and the earlier work has been reviewed.[22] Recently we sought to identify the best combination of support type, loading of catalyst groups and reaction solvent for Reaction (1) and to do this prepared a range of linear and crosslinked polymers (28 polymers) containing residues **2** or **3**, and used them in toluene or hexane as catalysts for Reaction (1).[17,21] With the crosslinked polymers, which are more convenient to use than linear polymers,[23] the highest % ees were obtained with lightly crosslinked gel-type polystyrene beads containing < *ca.* 1.0 mmol g^{-1} of catalyst residues used in combination with toluene as the reaction solvent.[21] Thus, using 2 mol% of 1% crosslinked polystyrene beads with 0.93 mmol g^{-1} of residues **2** (Catalyst A) in toluene at 0 °C, (*R*)-1-phenylpropanol **1** was obtained in 81% ee, and using 5 mol% of 1% crosslinked polystyrene beads with 0.64 mmol g^{-1} of residues **3** (Catalyst B) in toluene at 20 °C, (*S*)-1-phenylpropanol **1** was obtained in 97% ee. These % ee are within 3% of those obtained with analogous low-molecular-weight (LMW) catalysts under similar reaction conditions. Similar results were obtained with other aromatic aldehydes.[21]

The present work extends our earlier studies to the use of PS catalysts, including Catalysts A and B, in simple bench-top flow reactors. There were two major objectives. First, to investigate how long the PS catalysts could perform satisfactorily. It is

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Table 1 Properties of polymer supported Catalysts 'A' to 'D'

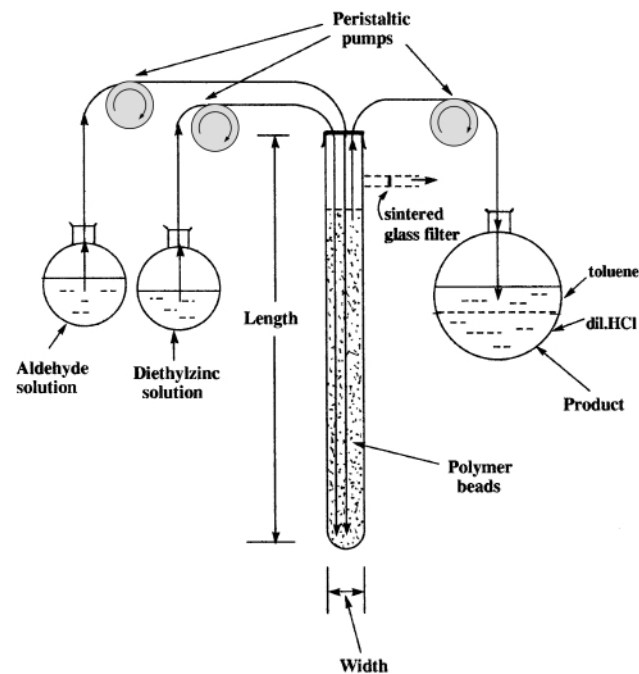| Catalyst designation	Percentage crosslinking	Catalyst residues	Loading of catalyst residues (mmol g^{-1})	Uptake of toluene (w/w)
A	1	2	0.93	3.5
B	1	3	0.64	3.2
C	1	4	1.11	2.9
D	0.2	2	1.78	7.1

Fig. 1 General arrangement of the flow system. The whole system was continuously flushed with dry nitrogen. For clarity the system used to achieve this is not shown. In the Mark I apparatus the flow tube was 22 cm long × 1.9 cm wide with a volume of ~60 ml: the final solution was removed through the indicated side arm equipped with a filter. In the Mark II apparatus the tube was 90 cm × 1.4 cm giving a volume of ~150 ml: the final solution was removed through the indicated side arm. In the Mark III apparatus the tube was 60 cm × 1.4 cm giving a volume of ~100 ml: there was no side arm and the final solution was pumped out as shown.

often reported that PS species can be recycled but, if they are reused at all, it is rarely more than 3 or 4 times. Monitoring their long term performance in a flow system avoids the problems of the physical attrition of the polymer beads on reuse and the tedium of repeatedly carrying out the same reaction. The second objective of the present work was to investigate in some detail the stereochemical performance of some PS chiral catalysts in simple flow systems. Previous studies in which PS reactions have been carried out by passing solutions of LMW reactants through beds or columns of a PS reactant include (i) the use of columns of PS substrates in 'solid phase' peptide synthesis,[24,25] (ii) the use of columns of PS reagents as in oxidations of penicillins using a PS peroxy acid,[26] and of quinols using a PS periodate,[27] and (iii) the use of columns of PS catalysts such as PS phosphonium salts to catalyse the reaction of 1-bromooctane with potassium iodide,[28,29] and PS flavin analogues to catalyse the oxidation of dihydronicotinamides.[30] In the field of asymmetric synthesis columns of a PS α,α-diphenyl-L-tyrosinol have been used to catalyse the reduction of prochiral ketones and oximes by borane,[31] and columns of a PS chiral Schiff base–zinc complex have been used to catalyse the reaction of 4-chlorobenzaldehyde with diethylzinc.[15] Reaction (1) has been catalysed by a PS Ti-TADDOLate (TADDOL = α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol) trapped in a 'tea bag'[32] which was then immobilized in a reactor,[33] and by α,α-diphenyl-N-alkyl-L-prolinol groups bound to soluble *linear* polymers in membrane reactors.[18,34] Previous work will be considered below where relevant.

Results and discussion

Polymer-supported catalysts

The properties of the various PS catalysts used in the present project are summarised in Table 1. The preparations of Catalysts A and B, which contain residues **2** and **3** respectively, have been described before.[21] Catalyst C was prepared by (i) copolymerising styrene with 1 mol% of a commercial mixture of *m*- and *p*-divinylbenzenes (mol ratio: 70:30) in a suspension system, (ii) chloromethylating the crosslinked beads so obtained, and (iii) reacting the chloromethylated product with (1*S*,2*R*)-ephedrine. Thus, Catalyst C contained residues **4**. Catalyst D was prepared similarly but the copolymerisation used only 0.2% of divinylbenzenes and the chloromethylated beads were reacted with (1*R*,2*S*)-ephedrine. Thus, Catalyst D contained residues **2**.

Flow apparatus

Reactions (1) were carried out by placing the catalyst beads in a round-bottomed tube sealed at the top with a septum cap.

Using peristaltic pumps solutions of the aldehyde in toluene and diethylzinc in toluene were pumped through long syringe needles to the bottom of the bead bed. The reactants slowly passed up through the bed and were removed at the top of the column and quenched in dilute hydrochloric acid. The final apparatus, the Mark III version, is shown in Fig. 1. Initially reactions were carried out in shorter wider tubes, the Mark I apparatus, but a significant fraction of the solutions flowing through the system appeared to pass between the wall of the tube and the catalyst bed. This was less of a problem with the longer thinner tubes used in the Mark II and III apparatuses. Also initially, with the Mark I and II apparatuses, the final reaction solution was removed at the top of the tube by passage through a short side arm equipped with a glass sinter to retain any beads which were carried to the exit. It was found, however, that such beads could easily be retained simply by pumping the final solution from the top of the column through a syringe needle. This not only simplified the apparatus to that shown in Fig. 1, but it also allowed the point at which the product was collected from the column to be easily adjusted. This allowed the amount of solution containing no catalyst beads (the beads tended to float) to be minimised. It should be noted that most of the earlier work using flow systems referred to in the Introduction simply used gravity-driven feed and flow arrangements.

The use of flow tubes of the type shown in Fig. 1 has several

Table 2 Reactions carried out in flow tubes using PS-ephedrine Catalysts 'A', 'C' and 'D'[a]

Entry	Reaction set up[b]	Catalyst	Weight of catalyst/g	Diethylzinc solution[a]		Benzaldehyde solution[a]		Yield (%) of alcohol **1**	Yield (%) of benzyl alcohol	% ee[c]	Configuration of major product
				Concentration/ mol L^{-1}	Flow/ ml h^{-1}	Concentration/ mol L^{-1}	Flow/ ml h^{-1}				
1	I	C	8.1	0.50	10	0.20	10	69	4	72	S
2	I	C	8.1	0.50	0.5	0.20	0.5	85	3	79	S
3	II	A	11.0	0.50	10	0.20	10	81	3	81	R
4	II	D	10.9	0.50	10	0.25	10	97	3	91	R
5	II	D	10.9	0.50	10	0.20	10	98	2	98	R
6	II	D	10.9	0.50	10	0.20[d]	10[d]	96[c]	—	97[d]	R[d]

[a] Toluene was used as the solvent throughout. All reactions carried out for 12 h at 20 °C under nitrogen. Unless otherwise indicated the substrate was benzaldehyde. [b] See Fig. 1 and text for a description of the Mark I apparatus and the Mark II apparatus. [c] Determined by polarimetry. [d] Reaction carried out with 4-chlorobenzaldehyde.

attractive features.[35] Thus, (i) chiral products can potentially be produced continuously, (ii) there is virtually no physical damage to the polymer beads in contrast to that that can happen easily in, for example, magnetically stirred batch systems where the beads can be ground between the stirrer and the bottom of the flask, (iii) at the end of a reaction period the syringe needles could if it was wanted be withdrawn and the sealed tube stored until it is next required; meanwhile the rest of the apparatus could be used with a different tube and another reaction, and (iv) potentially the whole procedure could be automated and controlled by a small computer.

Catalysis of Reaction (1)

The procedure used for all the flow reaction runs was to separately and continuously pump toluene solutions of the aldehyde and diethylzinc through the bed of catalyst beads at 20 °C either for 12 or 18 h. The product was then collected and the yield of chiral alcohol, in most cases 1-phenylpropanol **1**, determined by gas chromatography. The crude product was fractionally distilled and the % ee determined by polarimetry and, in some cases, also by gas chromatography over a chiral stationary phase.

Catalysis by Catalysts 'A', 'C' and 'D': i.e. by PS ephedrine derivatives. To gain experience in the operation of the flow tubes, experiments were first carried out using the PS ephedrine derivatives. These catalysts are more readily accessible than the PS camphor derivative, the preparation of which includes a 5-stage synthesis from camphor of the appropriate compound for linking to the chloromethylated polystyrene beads.[21]

Initially reactions were carried out using beads containing catalytic groups **2** or **4**, each derived from an enantiomer of ephedrine, and the reactants were pumped through the bed of beads for 12 h. These experiments are summarised in Table 2. In the first two experiments Catalyst C, prepared from 1% crosslinked beads, was used in the Mark I apparatus: see Fig. 1. In the first run, entry 1, the reactant concentrations and flow rates were set so that 2.0 mmol of benzaldehyde per h passed into the tube and the diethylzinc to aldehyde ratio was 2.5:1. The chemical yield was 69% and the ee was 72%. In an attempt to improve on these values a second run was carried out, see entry 2, using a greatly reduced flow rate. Both values improved, the chemical yield was 85% and the ee was 79%, but for the modest improvement in the results the flow rate was unacceptably slow. In another attempt to improve the results, and for the reasons given in the previous section, the Mark II apparatus was used, i.e. the reaction tube was changed from a short wide one to a longer thinner one. Using Catalyst A, which was very similar to Catalyst C except that the catalyst residues **4** were the opposite enantiomer to those in Catalyst A, the first experiment was repeated: see entry 3. Whilst maintaining a flow rate of 2.00 mmol of benzaldehyde per h, the chemical yield and ee were now 81%. When used in a batch procedure at 23 °C and with a

diethylzinc to aldehyde ratio of 1.10:1.00 this same catalyst afforded the (R)-alcohol **1** in 78%ee.[21] Thus, under these conditions the batch and flow procedures produced comparable stereochemical results.

In the previous study[21] it had been found that 1% crosslinked beads produced somewhat better results than 2% crosslinked beads. This prompted the synthesis of Catalyst D where the beads were only 0.2% crosslinked. Whilst such extremely lightly crosslinked beads would normally be too fragile to be practically useful, it was anticipated that they might nevertheless be satisfactory under the very gentle conditions prevailing in the flow apparatus and, indeed, this proved to be the case. Although the loading of catalyst residues (1.78 mmol g^{-1}) is substantially greater than that (<1.0 mmol g^{-1}) previously found to be optimal, it was expected that it would nevertheless prove to be satisfactory because these beads swell in toluene about twice as much as the previous beads: see swelling data in Table 1. Several reaction runs (which are not reported in Table 2) were carried out to find satisfactory concentrations and flow rates for use with Catalyst D. The conditions summarised in entry 4 proved to be satisfactory and to give repeatable results. With an input of 2.6 mmol of benzaldehyde per h and a diethylzinc to aldehyde ratio of 1.9:1.0 the chemical yield was almost quantitative and the (R)-alcohol **1** was obtained in 91% ee, a significantly better value than before. Slowing the aldehyde flow rate a little, which not only has the effect of increasing the residence time in the column but also raises the diethylzinc to aldehyde ratio to 2.5:1.0, maintained the high chemical yield and now afforded the (R)-alcohol **1** in 98% ee: see entry 5. The same conditions used with 4-chlorobenzaldehyde gave a 97% ee of the corresponding alcohol: see entry 6.

The question arises as to why such high % ees were obtained. Compared with the conditions extant in batch reactions, the soluble reactants in the flow system may in effect encounter relatively high mol%s of catalyst. Also the amount of the excess of diethylzinc may affect the stereochemical course of the reaction. This prompted a series of batch experiments in which Reaction (1) was catalysed by (1R,2S)-N-benzylephedrine **5**,
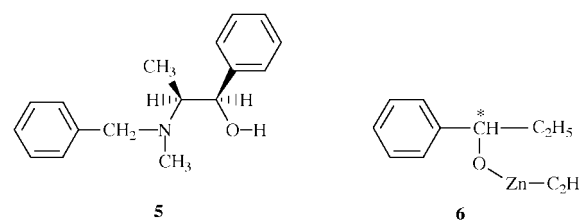
which is an excellent LMW model for Catalysts A, C and D, in toluene at 20 °C using different mol%s of catalyst and different excesses of diethylzinc. It is evident from the results, summarised in Table 3, that both factors have a major effect, especially

the latter, and that in combination they can raise the ee up to 98%. Such factors may, therefore, explain the results obtained with the flow reactor. The effect of the excess of diethylzinc in raising the % ees of similar reactions using other ephedrine-derived catalysts has been noted before.[36] A third factor, that may also assist with the flow reactor, is that the alkoxide **6**, *i.e.* the initial product of Reaction (1), is continuously removed from the system. This alkoxide is a poor chemical catalyst and its use produces very poor % ees,[21] but in batch reactions it is, of course, present in up to stoichiometric amounts.

Finally, it is interesting to note that (1*R*,2*S*)-*N*-benzylephedrine **5** is actually capable of giving very high % ee. This indicates that compound **5** can form a catalyst species that is as highly enantioselective as many of those derived from more sophisticated and expensive catalysts such as, for example, α,α-diphenyl-*N*-methyl-L-prolinol.[37] It also suggests that when **5** is used under the reaction conditions more commonly used with such catalysts, for example, benzaldehyde, diethylzinc and the catalyst in the mole ratios 1.00 : 1.10 : 0.02, there is simply insufficient of this catalytic species present and/or it is not sufficiently kinetically active to dominate the reaction system.

Catalysis by Catalyst 'B', *i.e.* by the PS camphor derivative.
Having identified a satisfactory flow tube procedure using the readily accessible PS ephedrine derivatives as catalysts, attention was now turned to using a potentially better catalyst, Catalyst B, in the flow system for an extended period. The catalytic moiety **3** present in these beads is of a type that generally produces better stereochemical results than the ephedrine

Table 3 Reactions of benzaldehyde with diethylzinc catalysed by (1*R*,2*S*)-*N*-benzylephedrine **5** under various conditions[a]

Entry	Mol% of catalyst	Mol of diethylzinc[b]	Yield (%) of alcohol **1**[c]	Yield (%) of benzyl alcohol[c]	% ee[d]
1	2	1.10	76	5	70
2	5	1.10	86	7	79
3	10	1.10	91	3	88
4	5	1.50	86	4	85
5	5	2.00	89	4	96
6	5	4.00	96	4	98

[a] All reactions carried out in toluene for 24 h at 20 °C. [b] Moles of diethylzinc per mol of benzaldehyde. [c] By gas chromatography. [d] By polarimetry and by gas chromatography over a chiral column.

derivatives.[22] All the experiments were carried out in the Mark III apparatus using toluene as the reaction solvent at 20 °C. The aldehyde and diethylzinc solutions were 0.2 and 0.5 M respectively. Both solutions were pumped into the reactor at a rate of 6 ml h⁻¹. A run lasted 16–18 h. Diethylzinc is pyrophoric, so, for safety reasons, at the end of a run the pumps were stopped overnight. The next run was started simply by switching on the pumps again. In total the system was run for *ca.* 275 h over a 16 day period.

Several aspects of the flow system merit comment. Thus, the 10.3 g of Catalyst B used swelled in toluene to a volume of *ca.* 33 ml. The beads were not compressed in use and the total volume of the bead bed was *ca.* 70 ml, so approximately half the bed volume was occupied by beads and approximately half was interstices. Given the volume of solution in the column, both inside and outside the beads, and the rate at which the reactants were pumped into the column, it can be simply calculated that the average residence time was *ca.* 5–6 h, corresponding to *ca.* 3–4 bed volume changes per run. About 3 g of alcohol **1**, or other alcohol, was produced per run.

The results obtained from selected runs are summarised in Table 4. Benzaldehyde was used as the substrate in most of these runs. In the first six runs using this substrate the yield of 1-phenylpropanol **1** was generally > 95% and the ee was > 94% in favour of the *S*-enantiomer. The formation of benzyl alcohol was a minor side reaction. Thus, under the conditions used, the initial flow results and the previously reported[21] batch results with Catalyst B were similar. However, for the later runs the chemical yields had fallen to *ca.* 50–60% whilst the ee had fallen to *ca.* 81–84%. Thus, over approximately 275 h of use the catalyst performance had decreased, corresponding on average to losses of *ca.* 2.5% chemical yield and *ca.* 1.0% ee per run. These losses may seem small but given the long period it would be desirable for a flow system to operate they are significant losses. The results suggest that in batch reactions, that typically have reaction times of *ca.* 20 h,[21] Catalyst B would give satisfactory results on approximately the first six occasions it was used.

Runs 8–10 were carried out using different aldehyde substrates. The results were consistent with those obtained with benzaldehyde.

In order to confirm the loss of catalyst performance, after the sixteenth run the polymer beads were recovered from the column, washed thoroughly, and dried. Based on elemental analyses for nitrogen the beads now had 0.57 mmol of catalytic group **4** per g compared with the original 0.64 mmol g⁻¹. However, the difference in these small values is well within experimental error. The beads were then used in batch reactions of

Table 4 Reactions carried out in flow tube using PS-Catalyst 'B'[a]

Entry	Run	Aldehyde	Yield (%) of benzyl alcohol[b]	Yield (%) of chiral alcohol[b]	% ee[c]
1	1	Benzaldehyde	5	95	97[d]
2	4	Benzaldehyde	3	97	97
3	6	Benzaldehyde	2	81	94
4	7	Benzaldehyde	3	97	86
5	8	4-Chlorobenzaldehyde	13[e]	76	92[d]
6	9	2-Methoxybenzaldehyde	4	64	76[d]
7	10	Cyclohexanecarbaldehyde	—	67	70
8	12	Benzaldehyde	2	59	87
9	14	Benzaldehyde	2	50	84
10	15	Benzaldehyde	2	60	81
11	16	Benzaldehyde	2	54	81

[a] Reactions were carried out using 10.3 g of Catalyst B in the Mark III apparatus with toluene as the reaction solvent at 20 °C. The aldehyde solution was 0.2 M and the flow rate 6 ml h⁻¹. The diethylzinc solution was 0.5 M and the flow rate was 6 ml h⁻¹. A 'run' lasted 16–18 h. [b] Estimated by GC. [c] Estimated from the optical rotation of the appropriate fraction of the distilled product. See reference 21 for [a]$_D^{20}$ values used. All products had the *S*-configuration. [d] Also estimated from ¹H NMR spectra of Mosher esters.[40] The values by the two methods agreed to ±1%. [e] 4-Chlorobenzyl alcohol.

Table 5 Comparison of results obtained with 'fresh' and 'recovered' Catalyst 'B'[a]

|	With 'fresh' Catalyst B[b]		With 'recovered' Catalyst B[c]	
Aldehyde	Yield (%)	% ee[d]	Yield (%)	% ee[d]
Benzaldehyde	94	97	75[e]	50
4-Chlorobenzaldehyde	94	92	77[f]	68

[a] Reactions carried out for 24 h at 20 °C in toluene using aldehyde, diethylzinc and catalyst mol ratios of 1.00:1.10:0.05. [b] Data from reference 21. [c] Chemical yields and % ee of 1-phenylpropanol and 1-(4-chlorophenyl)propanol determined as with products of the flow reactions. [d] By polarimetry. See reference 21 for literature $[a]_D$ of homochiral alcohols. [e] Benzyl alcohol was obtained in 4% yield. [f] 4- Chlorobenzyl alcohol was obtained in 8% yield.

the type reported previously.[21] The results, summarised in Table 5, show significant decreases in both the chemical yields and the % ees and thus confirm the earlier results.

It is not clear why the PS Catalyst B loses performance. The elemental analysis results indicate that the catalyst groups are not detached from the beads. They are, therefore, presumably slowly transformed into residues which are at best inferior catalysts. It is evident that the catalysed reactions of aldehydes with diethylzinc, including Reaction (1), are accompanied by a side reaction in which the aldehyde is reduced into the corresponding alcohol. Thus, in the present work benzaldehyde gives up to 5% of benzyl alcohol. It is believed that the reducing agent is diethylzinc:[11,21] see Reaction (2). Careful analysis of the product formed from the reaction of benzaldehyde with diethylzinc catalysed by (1R,2S)-N-benzylephedrine 5 in toluene at 20 °C for 24 h indicated the presence of at least one further side reaction. Thus, GC-MS analysis indicated that in addition to 1-phenylpropanol 1 (83% yield) and benzyl alcohol
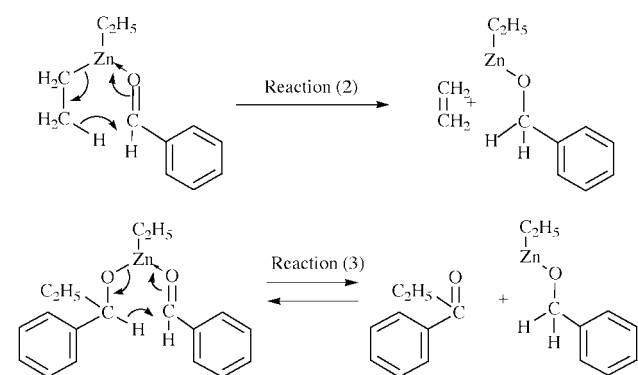
(7% yield), the product contained propiophenone (2%). The presence of the latter clearly indicates that alcohol groups can, if only to a small extent, be oxidized under the reaction conditions. Consistent with this, allowing the alkoxide formed by treating (1R)-phenylpropan-1-ol with an equimolar amount of diethylzinc to react with an equimolar amount of benzaldehyde in toluene for 24 h at 20 °C gave propiophenone (10% yield) and benzyl alcohol (7%). We suggest that this is due to the occurrence of an Oppenauer-type oxidation involving a zinc alkoxide rather than an aluminium alkoxide: see Reaction (3). If Reaction (4) (Scheme 1), which is analogous to Reaction (3), occurred with the catalyst residues 3 the β-amino alcohol would be transformed into a β-amino ketone and the catalytic properties lost. Since, however, the infrared spectrum of the recovered beads did not show a clear carbonyl band, the ketone may be reduced by a reverse reaction, (c.f. the Meerwein–Ponndorf–Verley reduction) to give both the exo- and endo-alcohols: see Scheme 1. The former would be the original catalyst but the latter would probably be a much less effective catalyst. We
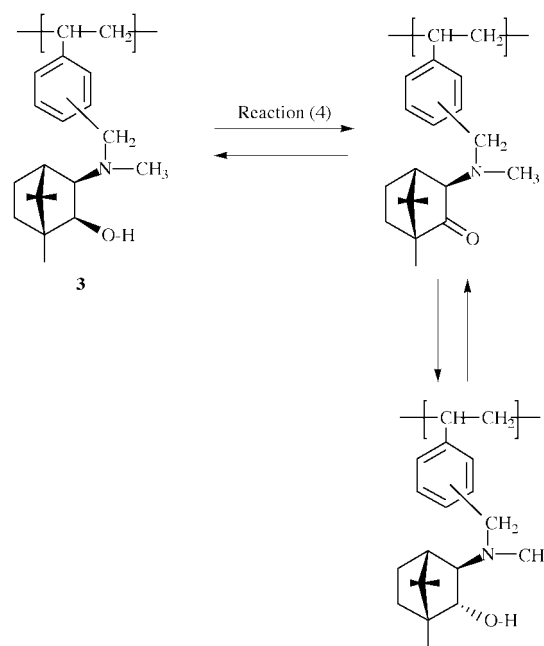
Scheme 1

suggest that it is the occurrence of one or more of these various side reactions that explains the decrease in the catalyst performance. If so, it will be noted that such a loss of activity would not occur if a tertiary alcohol group, rather than a secondary alcohol, was present in the catalyst. An alternative explanation is that side reactions cause further crosslinking of the polymer beads, so hindering access to the catalytic sites. This seems unlikely as the swelling properties of the beads did not noticeably change during use.

Conclusions

Reactions of aldehydes with diethylzinc in toluene catalysed by PS ephedrine or PS camphor derivatives in bench-top flow systems have been investigated. One aim was to investigate the extended use of such PS chiral catalysts without the tedium of repeatedly carrying out batch reactions and without the problem of the physical attrition of the polymer beads. When used initially to catalyse Reaction (1) in the flow system, the PS camphor derivative 3 afforded a chemical yield of >95% and an ee of >94%. After the catalyst had been used for ca. 275 h, the chemical yields dropped to 50–60% and the ee to 81–84%. The results suggest that this catalyst could be re-used successfully in batch reactions approximately 6 times. The deterioration in performance is apparently due to the gradual chemical degradation of the catalyst sites, possibly as a result of an Oppenauer-type oxidation of the 3-exo-hydroxy group of the catalyst moiety, i.e. the conversion of the β-tertiary-amino alcohol into a β-tertiary-amino ketone: Reaction (4). Thus, in future, if PS chiral catalysts are to be repeatedly recycled, it will not only be necessary to use polymer beads that are resistant to physical attrition, but it will also be neccessary to select catalytic groups whose stereochemical performance decreases by <1% per run. This probably requires <1% of chemical degradation per run. In general, for most chiral catalysts used in asymmetric syntheses, whether polymeric or non-polymeric, such information is simply not available.

A second aim was to determine if high % ee could be obtained using a flow system. Use of both PS ephedrine and PS camphor derivatives under optimum conditions in the flow apparatus to catalyse Reaction (1) gave 1-phenylpropanol 1 in 97–99% ee. That the former catalyst should achieve this is surprising because when (1R,2S)-N-benzylephedrine 5 is used in batch systems under typical reaction conditions it only affords

alcohol **1** in *ca.* 81% ee.[21] The increase probably arises because the flow system produces the effect of a high mol% of catalyst and/or of diethylzinc and/or because the reaction product, which acts as a catalyst and gives very low % ee, is continuously removed from the reaction system. This result indicates that catalyst species can be formed from the PS ephedrine derivatives and from (1*R*,2*S*)-*N*-benzylephedrine **5** which produce very high enantioselectivities but which are not normally present in sufficient amounts to dominate the reaction system.

When 4-chlorobenzaldehyde was used as the substrate, the % ee obtained with PS ephedrine Catalyst D was 97% and with the PS camphor derivative Catalyst B 92%. These values are very similar to that of 94% obtained previously using a PS chiral Schiff-base catalyst.[15]

Unlike in the present flow system, the use of a *linear* polymer containing α,α-diphenyl-*N*-alkyl-L-prolinol residues as a catalyst for Reaction (1) in a membrane reactor produced very surprising results.[18,34] Thus, with benzaldehyde as the substrate not only the ee depended strongly on the diethylzinc : benzaldehyde ratio but also the dominant configuration of the product. Thus, an excess of diethylzinc results in an ee of up to 80% of (*S*)-1-phenylpropanol whereas an excess of benzaldehyde yields (*R*)-1-phenylpropanol in up to 50% ee. It is not at all clear why this reversal in enantioselectivity occurs.

The use of PS Ti-TADDOLates in 'tea bags' to carry out Reaction (1) has been studied previously in considerable detail.[32,33] The catalyst was re-used 20 times. Initially the ee of (*S*)-1-phenylpropanol **1** was 90%. After 20 cycles it had fallen to 76%, an average drop of 0.7% per cycle. It is not clear whether the loss of catalyst performance in this system is due to physical attrition, catalyst site degradation, both of these effects or some other effect.

Overall the results obtained with the flow systems discussed here suggest that with further development, it will be possible to have 'permanently assembled' septum-sealed tubes containing PS chiral catalysts which, when required, can have syringe needles inserted to carry out the desired reactions and that after use the needles will be withdrawn and the tube returned to storage. This approach is, however, more likely to be developed initially with a reaction that is more rapid than the present ones.

Experimental

Organic extracts were dried with magnesium sulfate. Samples were dried in a vacuum oven at 1.0 mmHg. Infrared spectra were recorded using either a Nicolet MX1 instrument or a Perkin-Elmer 1720 instrument: solid samples were prepared as potassium bromide discs and, unless stated otherwise, liquid samples were prepared as thin films between sodium chloride plates. Unless indicated otherwise, ^{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. For the quantitative analysis of mixtures, ^{1}H and ^{19}F NMR spectra were recorded using a Varian Unity 500 (500 MHz) machine. The ^{19}F NMR spectra were referenced to CFCl$_3$ ($\delta = 0$). 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 131 digital polarimeter, in a cell of path length 10 cm and are given in units of 10^{-1} deg cm^2 g^{-1}. Gas chromatographic (GC) analyses were carried out using a Pye 204 Chromatograph equipped with a 10% SP 1000 stationary phase at 200 °C and a flame-ionisation detector. GC-mass spectrometry analyses were carried out using a Kratos Concept 1S machine. This incorporated a Carlo Erba GC unit with helium carrier gas.

Suspension polymerisations

(a) 1% Crosslinked polystyrene beads. The stabiliser was removed from styrene and from commercial divinylbenzene (55% w/w divinylbenzenes in ethylstyrene) by washing samples with aqueous sodium hydroxide (10%; 2 × an equal volume) and then water (3 × an equal volume). Benzoyl peroxide was purified by precipitation into methanol from chloroform solution. Polyvinyl alcohol (85–89% hydrolysed, $M_w = 70\ 000$; 0.5 g) was dissolved in water (500 ml) and the solution placed in the polymerisation vessel.[38] The solution was heated up to reaction temperature (80 °C) and stirred at 600 rpm under a blanket of nitrogen. A mixture of benzoyl peroxide (0.50 g), styrene (49.0 ml) and divinylbenzene (1.0 ml) was added to the reaction flask. The resulting suspension was mechanically stirred (600 rpm) at 80 °C under a nitrogen blanket for 6 hours. The reaction mixture was then cooled and the polymer beads collected by filtration. The beads were washed exhaustively on the filter with boiling water and then with methanol, dichloromethane, THF and finally Soxhlet extracted with methanol. The product was dried at 30 °C under vacuum (yield 34.5 g, 76%) and sieved. The fraction 125–212 μ, *i.e.* 70–120 mesh, was collected (52% yield overall) and used for the chemical modification.

(b) 0.2% Crosslinked polystyrene beads. The method outlined above was followed, with adjustment of the styrene to divinylbenzene ratio. However, the suspension stabilisers used were poly(vinylpyrrolidone) (5.0 g; $M_w = 44\ 000$) and calcium phosphate (re-precipitated; 2.5 g). Yield, of 70–120 mesh beads, 40%.

Solvent uptake of polymers

The swelling properties of crosslinked polymers were estimated as follows.

An accurately weighed sample of polymer (*ca.* 0.2 g) was placed in an accurately weighed clean dry glass tube fitted with a sintered glass filter. The tube was filled with the swelling solvent and left for 30 minutes. The sample and tube were then removed from the solvent, and the excess solvent removed by vacuum filtration. The sample and tube were weighed and the amount of solvent absorbed by the polymer calculated. The 1% crosslinked polystyrene beads prepared above absorbed 5.4 times their weight of toluene. The 0.2% crosslinked beads absorbed 11.6 times their own weight of toluene.

Chloromethylation of polystyrene beads

(a) Chloromethylation of 1% crosslinked polystyrene beads. The 1% crosslinked polystyrene beads prepared above (50.1 g) were chloromethylated using dimethoxymethane, thionyl chloride and stannic chloride with dichloromethane as the solvent using the literature procedure.[21] The yield was 54.7 g. Found by elemental analysis Cl, 5.00% corresponding to a loading of 1.41 mmol g^{-1}. The beads absorbed 3.5 times their own weight of toluene.

(b) Chloromethylation of 0.2% crosslinked polystyrene beads. The 0.2% crosslinked polystyrene beads prepared above (5.04 g) were suspended in carbon tetrachloride (150 ml) in a round-bottomed flask (250 ml) fitted with a rubber septum and magnetic stirrer, and the mixture was cooled in an ice bath. Chloromethyl methyl ether (8.5 ml) (**CAUTION:** *chloromethyl ether is highly carcinogenic*) was added *via* a syringe. The suspension was allowed to warm up slowly to 20 °C and stirring was continued for a further 24 h. The resulting polymer was collected by filtration in a well-ventilated fume hood and washed successively on the filter with 50% aqueous dioxane, 50% 1 M hydrochloric acid–dioxane, water, dioxane and methanol. The polymer was then transferred to a Soxhlet extraction thimble and extracted for 24 h with methanol. Finally the polymer was dried under vacuum at 30 °C. The yield was 5.45 g. By elemental analysis it had Cl, 4.97%, correspond-

ing to loading of 1.40 mmol g^{-1}. The beads absorbed 8.4 times their own weight of toluene.

Preparation of polymer-supported catalysts

Catalysts A and B were available from a previous study.[21] The beads were 100–200 mesh.

Catalysts C and D were prepared by reacting the chloromethylated polystyrene beads whose preparations are described above with (1S,2R)- or (1R,2S)-ephedrine as appropriate using the procedure given previously for the preparation of Catalyst A.[21] Catalyst C had, by elemental analysis, N 1.55% corresponding to 1.11 mmol g^{-1} of residues **4**. Catalyst D had N 1.71% corresponding to 1.22 mmol g^{-1} of residues **2**. The beads were 70–120 mesh.

Continuous flow apparatus and general details of the reaction procedure

The general arrangement of the various flow apparatuses is shown in Fig. 1. The flow tubes were made in house from commercial Quickfit ™B14 joints and standard Pyrex glass tubing by the departmental glassblower. In the Mark I and II apparatuses the glass sinters in the sidearms were of No. 3 porosity. The dimensions of the tubes were as given in the caption to Fig. 1.

The setting up of the Mark III apparatus is typical. Thus, the PS catalyst B (10.3 g), pre-swollen in toluene (50 ml), was transferred into the flow tube with the aid of a glass powder funnel. The tube was then sealed with a standard 'B14' rubber septum and placed in a water bath held at 20 °C by a Techne TU16A Tempunit® Thermoregulator. Hypodermic needles (19G, 24 in) (purchased from Aldrich) were inserted through the septum so as to reach to the bottom of the tube. Initially, to allow the bed to settle, toluene was pumped through the tube by two Watson-Marlow 503U peristaltic pumps equipped with 501RL and 303D/A pumpheads (these were subsequently used for the diethylzinc and aldehyde reservoirs respectively) using Viton® (0.8 mm ID) tubing. The reagent reservoirs were standard round-bottomed flasks (each 500 ml; B24 joints) equipped with 'B24' rubber septa. The final reaction solution was extracted from the reactor using another hypodermic needle (18G, 10 in) placed ∼0.5 cm above the bead bed and a Watson-Marlow 501U peristaltic pump equipped with a 501RL pumphead and Viton® tubing (1.6 mm ID). The receiver was a round-bottomed flask (500 ml; B24 joint), equipped with a rubber septum, containing a stirred mixture of toluene and 1 M aqueous hydrochloric acid. Flow rates for each pump were determined at each control setting by measuring the volume of toluene pumped in a given period of time. Since *diethylzinc is pyrophoric* at all times the column, reservoirs and the receiver were kept under a dry nitrogen atmosphere. This was achieved by having a series of gas lines, branching from one source, with the nitrogen introduced into the various pieces of the apparatus *via* small syringe needles inserted through the rubber septa. The system was vented *via* a similar set of needles and gas lines.

Typical reaction procedure; run 1 in Table 4

A solution of freshly distilled benzaldehyde (8.5 g) in dry toluene (400 ml) was placed in one reagent reservoir. Diethylzinc (20.5 ml, 24.7 g), purchased as the neat liquid from Aldrich, was transferred *via* hypodermic syringes (**GREAT CARE:** *diethylzinc is pyrophoric!*) into dry toluene (400 ml) in the second reservoir. Both reactant solutions were then pumped, each at a rate of 6 ml h^{-1}, into the flow tube for 17 h at 20 °C. At the end of this period the pumps were simply switched off and the toluene layer collected from the receiver, washed with water (3 × equal volume) and dried. The solvent was then carefully removed using a rotary evaporator. The crude product (2.9 g) was analysed by GC and by ^{1}H NMR spectroscopy as described

before.[21] This indicated that the chemical yield of 1-phenylpropanol was 95% and that benzyl alcohol was formed in 5% yield. Toluene was also present. The crude 1-phenylpropanol was purified by bulb-to-bulb fractional distillation in a Kügelrohr apparatus. The major fraction (1.4 g) collected at 105 °C/0.1 mmHg was pure by GC and ^{1}H NMR spectroscopy. This fraction had $[a]_D^{20}$ +42.7 (c = 5.0, CHCl$_3$) (lit,[39] $[a]_D^{20}$ +45.45 (c = 5.15, CHCl$_3$) for the R-enantiomer) corresponding to an ee of 94%. In the present case, in addition the Mosher esters[40] were prepared and the % ee determined by ^{1}H and by ^{19}F NMR spectroscopy. The R- and S-enantiomers had signals at δ 5.91 and 5.83 ppm respectively in the ^{1}H NMR spectrum and at δ −72.88 and −73.20 ppm respectively in the ^{19}F NMR spectrum in a ratio corresponding to an ee of 96%.

For the subsequent run the reagent reservoirs were simply recharged and the pumps restarted. In some cases in addition to determining the % ee by polarimetry, it was also determined by GC analysis using a capillary column at 115 °C packed with WT COT Fus Sil possessing the chiral species cyclodextrin-β-2,3,6-M-19.[21] With 1-phenylpropanol, for example, the R- and S-enantiomers eluted after 35.5 and 36.8 minutes respectively.

Recovery of catalyst 'B' from flow apparatus: re-use in batch reactions

After the 16th run summarised in Table 4, entry 11, the polymer beads were quenched with methanol and transferred to a Buchner filter. They were washed successively with methanol, 1 M hydrochloric acid-methanol (1:1), water, 10% triethylamine in methanol, THF–methanol (1:1), THF, diethyl ether and dried (10.2 g). The beads had an infrared spectrum indistinguishable from the original: for example, there was no clear carbonyl band. By elemental analysis they contained 0.57 mmol of N per g.

The recovered beads were used to catalyse batch reactions following the previously described procedures.[21] These reactions and the results obtained are summarised in Table 5.

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