benzene, 4:1) and hydroxylamine **26** (429 mg, 77%), mp 218–220 °C dec. The analytical specimen, mp 224–226 °C dec, was obtained as pale pink crystals by crystallization from benzene–hexane: IR 3580 cm^{-1}; NMR δ 1.10 (s, 9), 2.38 (s, 6), 6.76–7.46 (m, 11). Anal. Calcd for $C_{26}H_{27}NO$: C, 84.50; H, 7.37; N, 3.97. Found: C, 84.20; H, 7.40; N, 3.73. A Grignard reaction involving chloride **23** failed, even when activated Mg was used.

2-[9,10-Dihydro-9,10-dimethyl-9,10[1′,2′]-benzenoanthracenyl] *tert*-Butyl Nitroxide (27). A 45-mg sample of **26** was oxidized with $K_3Fe(CN)_6$ as above to afford 44 mg of **27**. Preparative TLC and elution with CH_2Cl_2 gave 36 mg (80%) of pure **27** as an orange-red powder, mp 123–125 °C dec: ESR, see text; NMR (after phenylhydrazine[27] addition) δ 1.10 (s, 9), 2.38 (s, 6) and aromatic proton absorption. Anal. Calcd for $C_{26}H_{26}NO$: C, 84.74; H, 7.12; N, 3.80. Found: 84.54; H, 7.12; N, 3.52.

Vesicle Experiments. Multilamellar vesicles were prepared according to the general procedure of Bangham and Johnson.[38] The following procedure is representative. To a solution of dimyristoylphosphatidylcholine (45 mg) in 3 mL of $CHCl_3$ was added 3.78 mL (0.378 mg) of a CH_2Cl_2 stock solution of nitroxide **1** (0.10 mg/mL). The solvent was removed under a stream of nitrogen, leaving a thin film that was dried under vacuum (0.05 mm). Then phosphate buffer (2.25 mL, 0.1 M, pH 7.4) was added and the mixture was vortexed for 7 min at 32 °C. A 0.2-mL aliquot was transferred to an ESR tube, nitrogen as bubbled through the solution for 5 min, and then the spectrum was recorded (Figure 2A). In separate experiments, vesicles containing either nitroxide **3** or nitroxide endoperoxides **18** or **20** were similarly prepared and the ESR spectra recorded. In one series of experiments an isotropic ESR spectrum of each nitroxide was obtained after the addition of two volumes of MeOH to the respective ESR tubes. In another series of experiments the ESR tubes containing either nitroxide **1** or **3** in the bilayer of the vesicles and methylene blue (final concentration, 1 mg/4.5 mL) in the aqueous phase were irradiated at 32 °C open to the atmosphere with a 150-W sunlamp. At appropriate intervals the tubes were removed from the light source, two volumes of MeOH were added, nitrogen was bubbled through the solution, and the isotropic ESR spectrum was recorded in order to follow the progression of the reaction with singlet oxygen.

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Registry No. **1**, 97634-94-1; **2**, 103438-60-4; **3**, 103438-61-5; **4**, 103438-62-6; **5**, 131-09-9; **6**, 572-83-8; **7**, 56971-01-8; **8**, 103438-63-7; **9**, 97634-97-4; **10** (R = CH_3, X = Br), 103456-61-7; **10** (R = H, X = Cl), 103438-77-3; **11**, 43217-24-9; **12**, 103438-64-8; **13**, 103438-65-9; **14**, 103438-66-0; **15**, 43217-28-3; **16**, 103438-67-1; **17**, 103438-68-2; **18**, 97634-95-2; **19**, 103438-69-3; **19** (*N*-hydroxy), 103438-78-4; **20**, 103438-70-6; **21**, 103438-71-7; **22**, 15254-40-7; **23**, 103438-72-8; **24**, 103438-73-9; **25**, 97634-96-3; **26**, 103438-74-0; **27**, 103438-75-1; 2-methyl-2-nitrosopropane, 917-95-3; 9-bromoanthracene, 1564-64-3; anthranilic acid, 118-92-3; maleic anhydride, 108-31-6; 1-methyl-4-(2-carboxyethyl)naphthalene, 76673-34-2; 3-(1,4-epidoxy-4-methyl-1,4-dihydro-1-naphthyl)propionic acid, 76673-35-3; 2-chloro-9,10-dihydro-9,10-diphenyl-9,10-epidioxyanthracene, 103438-76-2.

Polymer-Assisted Asymmetric Reactions. 4. Polymer-Bound Ephedrine, Its Use and Limitations in Supported $LiAlH_4$ Reductions†

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A cross-linked polystyrene resin containing (1*R*,2*S*)-(−)-ephedrine moieties bound through nitrogen to some of its *p*-methylene-substituted aromatic rings is a useful regenerable chiral auxiliary in the enantioselective reduction of acetophenone by the chiral polymer-bound complexes of lithium aluminum hydride and an added achiral phenol. Evidence is presented to explain the capacity-dependent behavior of the polymer in the formation of chiral complexes and its effect on the enantioselectivity of the reduction of acetophenone. At high capacities, both unbound achiral and multiply bound chiral complexes are formed while numerous chiral ligands appear to be inaccessible to the hydride; under such conditions the enantioselectivity of the reaction is poor. In contrast, at low capacities corresponding to 8–10% substitution of the styrene repeating units, the polymer-bound chiral moieties can act independently from one another and are fully accessible to the hydride. The reduction then proceeds with a high enantioselectivity, comparable to that of similar small chiral molecules. This mechanism is consistent with and explains the phenomena observed with other polymer-supported hydride reagents.

Introduction

The use of polymers containing chiral groups in asymmetric processes has received increasing attention over the past few years following the notable success which has been achieved in the area of the chromatographic separation of enantiomers.[1,2] Extensive efforts have also been devoted to the development of polymer-supported chiral moieties containing quaternary ammonium or phosphonium salts for use as catalysts in simple asymmetric phase transfer catalyzed reactions.[3] The latter application has only met with limited success in most cases due to the lack of intimate contact between the chiral moiety and the reaction loci. More successful approaches have involved reactions[4]

† Dedicated to Professor Dr. Georg Manecke on his 70th birthday.

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catalyzed by poly(amino acids) or polymer-bound alkaloids.

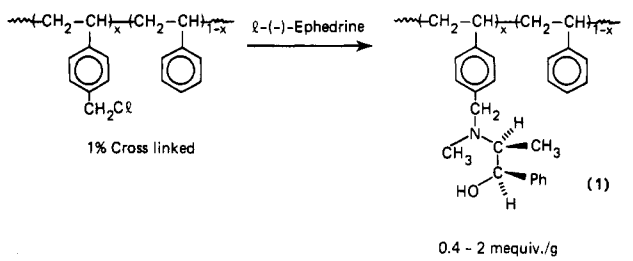
Another approach to the use of polymers in asymmetric induction reactions involves their application as chiral auxiliaries[5] in processes where the chiral site becomes temporarily attached to an achiral molecule thereby controlling the approach of an external reagent and favoring an enantioselective reaction. As the chiral auxiliary is liberated unchanged during or at the end of the reaction, it appears to be particularly advantageous to attach it to an insoluble polymer, thereby facilitating its recovery, purification, and reuse. This "purification advantage" has been the main asset of polymer-assisted reactions since their development by Merrifield[6] in the early 1960's.

However, numerous studies have since shown that, in some instances, other advantages which we shall gather loosely under the term "polymer effect" have resulted from attachment of reactive species to polymer backbones. This polymer effect has resulted in reactivities of bound species which sometimes differ significantly from those of their unbound counterparts.[7-9] In general, the observed differences may result from changes in the polarity of the microenvironment at the site of the reaction, separation or clustering of the reactive groups, and other electronic or steric effects. In the case of polymer-supported asymmetric reactions,[10] such polymer effects would be desirable if they could contribute to the enhancement of the stereoselectivity of the reaction. Earlier work in this area[11,12] has suggested that, at least in the case of the methylation of cyclohexanone imines derived from polymer-supported chiral amines, a polymer effect resulting in increased stereoselectivity and the ability to carry out the reaction at room temperature rather than at low temperature was observed. This effect is likely due to a decrease in the conformational mobility of the polymer-bound intermediates in the key step of the reactions which, in turn, favor one of the possible alkylation pathways.[12]

The enantioselective hydride reduction of prochiral ketones is one of the most extensively studied chiral transformations[13] and, as such, it is interesting for a comparative study of the effect of free and polymer-bound chiral auxiliaries on the enantioselectivity of the reaction.

In most cases, the reaction is carried out using a reagent such as $LiAlH_4$ (LAH) partly modified by reaction with an optically active alcohol or amine used as chiral auxiliary. Notable successes have been accomplished by using chiral auxiliaries such as binaphtol,[14] *N*-methylephedrine,[15] Darvon alcohol,[16] chiral pyrrolidine derivatives,[17] and

Scheme I



1,2-amino diols,[18] while other attempts at using polymer-bound species[19-22] will be discussed herein.

This study is focused on the use of a polymer-bound analogue of *N*-benzylephedrine in the partial deactivation of LAH for the stereoselective reduction of acetophenone. The ephedrine derivative is chosen for its ready availability and the fact that reduction only proceeds in moderate optical yield in the case of the unbound moiety, thereby allowing for the observation of any eventual polymer effect on the enantioselectivity.

Results and Discussions

The insoluble polymer-bound *N*-methylstyryl analogue 1 of *N*-metylephedrine is prepared most conveniently by chemical modification of crosslinked chloromethylated polystyrene (Scheme I).

Although, several procedures are effective, best results leading to quantitative displacement of chloride from the polymer are obtained by using a 3-fold excess of (-)-ephedrine in DMF at 85 °C. In contrast, reactions carried out in Me_2SO lead to some oxidation of the polymer while the use of other solvents or of smaller amounts of ephedrine in the presence of acid acceptors generally lead to incomplete replacement of chloride.[23]

The final degree of functionalization (DF) of polymer 1 is determined solely by the initial degree of functionalization of the chloromethylated resin and, in our preliminary experiments, we chose to work with polymers in which 28–35% of the aromatic rings of the styrene repeating units carried the ephedrine moiety (x = DF = 0.28 to 0.35 in structure 1). This relatively high DF was thought to be desirable to reduce the amount of polymer and solvent used in each experiment.

In a typical experiment, the chiral reducing agent 3 is prepared as shown in Scheme II by successive treatment of a solution of lithium aluminium hydride (LAH) with 2 molar equiv of 3,5-dimethylphenol and, after a period of equilibration, 1 molar equiv of the solid polymer. This approach is analogous to that used by Vigneron et al.[15] and others in work with *N*-methylephedrine–LAH or other similar complexes; ideally it would afford after equilibra-

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(23) Care must be taken to avoid both quaternization of the polymer-bound ephedrine moieties and hydrolysis of the starting chloromethylated polymer to the corresponding hydroxymethyl polymer as these species would interfere with the enantioselective reduction.

Scheme II

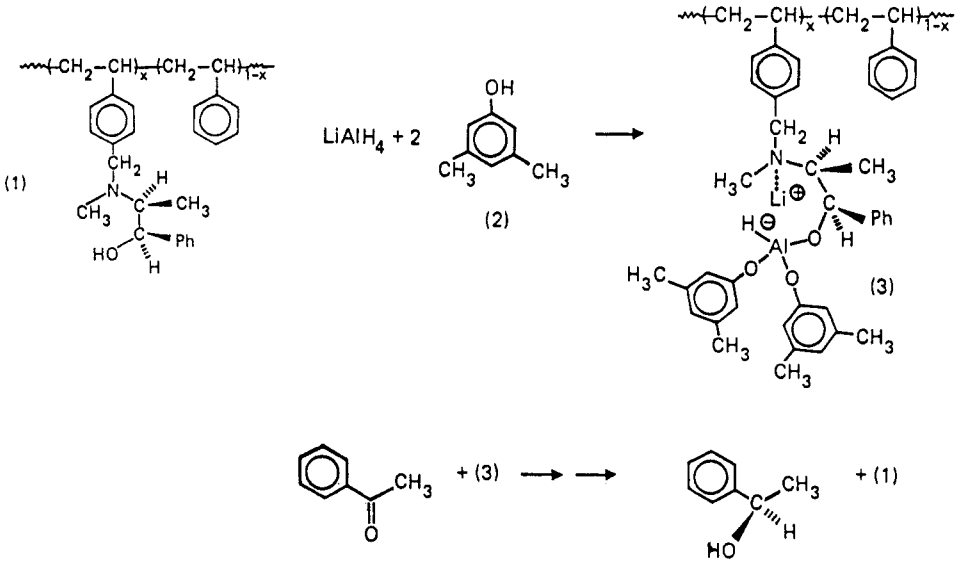

Table I. Reduction[a] of Acetophenone with Highly Loaded Polymer-Bound Hydride Reagent

no.	molar ratio LAH/Ⓟ/ROH	solvent	T, °C	reaction cycle[c]	procedure[d]	yield, %	ee, %
1	1:1:2	ether	−78	1	A	85	6.6
2	1:1:2	THF	−78	1	A	50	18.3
3	1:1:2	ether	−15	1	A	90.5	19.1
4	1:1:2	ether	−15	2	A	91	21.5
5	1:1:2[b]	ether	−15	1	A	60	5
6	1:1:2	THF	−15	1	A	84.5	20.1
7	1:1:2	ether	0	1	A	78	10.8
8	1:1:2	THF	0	1	A	87.5	6.7
9	1:1:2	ether	−15	1	B	47.5	36.5
10	1:1:2	ether	−15	2	B	44	43
11	1:1:2[b]	ether	−15	1	B	37	16.5
12	1:1:2[b]	ether	0	1	B	43	10
13	1:2:2	ether	−15	1	A	84	32.6
14	1:2:2	ether	−15	2	A	62	39
15	1:2:2	ether	−15	1	B	31	40

[a] Reactions with 1.25:1 ratio of LAH/acetophenone using 1% cross-linked gel-type polymer-bound ephedrine with a capacity of 1.81 mmol/g. [b] Macroporous Amberlite XE-305 resin, capacity 2.1 mmol/g. [c] Freshly prepared polymer used in cycle 1, regenerated polymer used in cycle 2. [d] Procedure A, normal addition; procedure B, filtration of soluble phase and washing of polymer prior to addition of acetophenone (see Experimental Section).

tion a chiral reducing complex such as **3** Scheme I, with a single hydride functionality remaining in a chiral environment.[24] Reduction of a prochiral ketone (Scheme II) such as acetophenone would be expected to proceed through the preferential formation of an intermediate such as **4** in which Ⓟ represents the partially parasubstituted polystyrene backbone, thereby resulting in an enantioselective reduction.

Unfortunately, the results obtained in this reaction were extremely disappointing at first, as shown in Table I, as polymer **1** seems incapable of affording high enantioselectivities. Unlike the similar reaction with miniature analogues where ether appear to be a better solvent than THF, reductions with polymer **1** appears to be essentially unaffected by a change of solvent from ether to tetrahydrofuran.

In principle, THF should be a better medium than ether for this reaction due to its ability to better swell the polymer, in practice, however, this swelling causes numerous technical difficulties[26] and most of this study was carried out in anhydrous ether. Contrary to what would have been expected from model studies, the enantioselectivity of the reaction with polymer **1** is not inversely related to temperature as is often the case,[14] better results being obtained at −15 °C rather than −78 °C, especially in the case of reactions involving ether as the reaction medium.

These observations and comparisons with miniature analogues[27] suggest that it is an inherent property of the polymer itself, rather than of the bound ligand, that is

(24) It is recognized that complexes of $LiAlH_4$ with alcohols tend to undergo disproportionation,[14,25] though several design or procedural approaches[14,18] have been used to reduce the number of active species present in the reaction mixture.

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(26) The 1% cross-linked polymer swells to up to 10 times its original volume when immersed in THF making the reaction unwieldly and difficult to stir and workup. In contrast, very little swelling is observed in ether.

(27) Similar reductions of acetophenone with *N*-methylephedrine complexes are reported to proceed in 79–83% yield[15] while our own model experiments with *N*-benzylephedrine and 2 equiv of 3,5-dimethylphenol in ether at −15 °C afforded (*R*)-1-phenylethanol in 80–85% ee.

(28) Liu et al.[19] made their $[\alpha]_D$ measurements in benzene, yet calculated optical yields using a maximum value of $[\alpha]_D$ for pure 1-phenylethanol obtained for a neat measurement. The optical rotation of 1-phenylethanol in benzene is significantly higher that of the neat compound reported in ref 31. Depending on concentration, optical rotations reported in benzene are approximately 18–20% higher than those for neat 1-phenylethanol.

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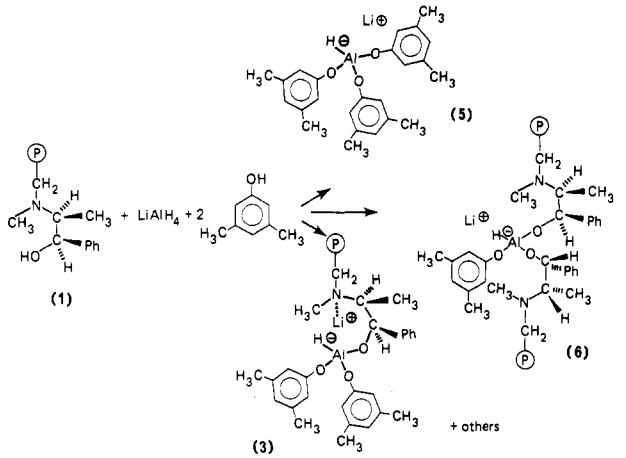
Scheme III



responsible for the loss in enantioselectivity. Of particular concern is the possibility that reduced swelling may affect the accessibility of the reactive sites within a polymer bead.

To verify this hypothesis, a series of experiments was carried out using a different procedure (B in Table I) whereby the polymer was filtered and washed, after formation of the chiral polymer-bound complex and equilibration, to remove any reducing agent which might not have become bound to the polymer. As can be seen in Table I (entries 9 and 10) the use of this procedure resulted in a sharp increase in the stereoselectivity of the reaction with a concurrent lowering of the chemical yield due to the loss of some unbound reducing species in the filtrate during the washing of the polymer. Analysis of the soluble material washed from the polymer confirmed that it consisted of various complexes with reducing properties.

Clearly, reducing complex **3** is not the only species formed in the reaction of $LiAlH_4$ with 3,5-dimethylphenol and polymer **1**. Scheme III shows two of the other three trialkoxyaluminium hydride complexes, **5** and **6**, which could be formed in addition to **3**, similarly a great variety of mono or dialkoxyaluminium hydride complexes not shown in Scheme III can be formed and all, as well as uncomplexed $LiAlH_4$, can participate in the reaction. It is quite conceivable that some of these complexes might actually be better than **3** in their enantioselectivities. For example, the results shown in entries 13 and 14 of Table I might be interpreted as suggesting that complexes involving more than one unit of the chiral moiety would indeed provide better results than those involving only one chiral polymer unit, although, as will be seen below, other explanations are possible.

The improvements obtained by using procedure B, Table I, confirm that soluble achiral species such as **5** and others are formed and are eliminated, at least partly, by the filtration–washing procedure. This disturbing finding indicates that only a fraction of the hydroxyl groups of polymer **1** seems to be able to participate in formation of the reducing complex. Acid-base considerations are irrelevant in this context since excess hydride is provided both with respect to alcoholic and phenolic groups; there remains only the possibility of lack of accessibility of groups within the polymer bead and/or the possibility of site interactions within the polymer beads.

A solution to the problem of accessibility which has been suggested by some is to use macroporous resins[5] instead of the cross-linked gels chosen for most of this study. As can be seen in entries 5, 11, and 12 of Table I the use of a macroporous bead does not lead to any improvement in enantioselectivity, on the contrary lower ee's are obtained. In addition, the use of a macroporous resin complicates reaction processing as the beads tend to fracture into fine particles when stirred and these are very difficult to filter.

Table II. Influence of Polymer Capacity on Enantioselectivity[a]

capacity, mmol/g	DF	yield, %	ee, %
2.1	0.35	86	5.5
1.9	0.30	89	14.1
1.8	0.27	90	19.5
0.7	0.09	97	78.8

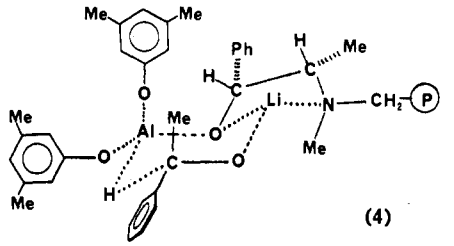
[a] All reactions using 0.8 molar equiv of acetophenone with 1% cross-linked polymer in ether at −15 °C with a molar ratio LAH/polymer/ROH 1:1:2 and using once recycled polymer in procedure A.

Table III. Reduction of Acetophenone with Lightly Loaded Polymer-Bound Hydride Reagent[a]

no.	molar ratio LAH/Ⓟ/ROH	solvent	T, °C	reaction cycle	yield, %	ee, %
1	1:1:2	ether	−15	1	93	75.5
2	1:1:2	ether	−15	2	97	78.8
3	1:1:2	ether	−15	5	94	78.5
4	1:1:2	ether	0	1	98	71.4
5	1:1:2	THF	−15	1	70	29.1
6	1:1.1:2	ether	−15	2	70	67.2
7	1:1.15:2	ether	−15	2	65	59.8
8	1:1.15:1.85	ether	−15	2	88	60.6
9	1:2:2	ether	−15	2	0	0

[a] Reductions of acetophenone with 1% cross-linked polymer having DF = 0.09.

The results shown in Table II, whereby a dramatic increase in optical yield results from a decrease in polymer capacity, suggest that site–site interactions may in fact be responsible for the lack of accessibility of highly loaded resins. As the DF of the polymer is reduced from 0.35 to 0.09 the optical yield increases from 5% to almost 80%. Such a large increase, which brings the enantioselectivity of the reaction to a level equivalent to that obtained by Vigneron et al.[15] with similar *N*-methylephedrine complexes, suggests that with the lightly loaded polymers, equilibration of the final complex responsible for the reduction is more uniform and produces species which likely resemble **3** and **4** in the key steps of the overall process. In addition, the results given in Table III confirm that all the groups in polymer **1** with DF 0.09 are fully accessible and point toward the formation of complexes having structure **3** and intermediates such as **4** when the proper stoichiometry is maintained in a medium which can be fully penetrated by all reagents.



Thus, while both high chemical yield and high enantioselectivity are observed with a 1:1:2 molar ratio LAH/chiral polymer/achiral phenol, the use of a 1:2:2 ratio (entry 9 Table III) leads to the complete neutralization of LAH and no reduction whatsoever is observed. Indeed this result confirms the accessibility of all sites of **1** to the hydride reagent and is in sharp contrast to the results reported in Table I (entries 13–15) where high reduction yields were obtained despite the presence of excess ligands which would have been expected to deactivate fully LAH had all the reactive sites of the polymer been available.

Similarly, Table III shows that an increase in the amount of chiral ligand, which forces the interactions of several sites of the polymer, causes a decrease in both chemical and optical yields (entries 6 and 7). Finally, if the molar ratio of the chiral and achiral alcoholic components is adjusted (entry 8) to form complexes with an average of one remaining hydride but with some units incorporating more than one chiral ligand, the chemical yield is high while the optical yield is depressed with respect to the standard reaction (entry 2).

We have confirmed the ability of the polymer-bound ephedrine 1 to be recycled and reused through dozens of separate experiments; typical results are shown in the first three entries of Table III. It is generally observed that the first reaction cycle affords a slightly lower enantioselectivity than subsequent cycles. As analytical monitoring of the polymer shows no remaining chloromethyl groups in 1 prior to the first reaction and no apparent change in either nitrogen content or infrared spectrum after one or more uses, it can only be assumed that this enhancement of the polymer is due to very minor changes in composition or structural arrangement within the polymer beads. Indeed, a freshly prepared polymer subjected to rapid treatment with LAH then washed with acid and base affords results comparable to those of a recycled polymer.

Although THF is a far better swelling agent than ether, its use with lightly loaded polymer 1 free from site interactions results in a lowering of the optical yield when compared to the same reaction in ether; this is also the case in the model reaction with *N*-methylephedrine.[15,32] This is likely due to the better solvating properties of THF itself which competes effectively with the polymer's nitrogen ligand in the complexation of the lithium cation and therefore disrupts the selective formation of an intermediate such as 4.

At this juncture, it is useful to compare the results we have obtained in over 100 experiments with polymer 1 to those reported by others for similar reductions using polymer-bound LAH complexes. If one considers the data reported by Liu, Kondo, and Takemoto,[19] after downward correction[28] of all reported optical yields, these results can be interpreted and explained by using the conceptual model we have developed with polymer 1. In their work,[19] a polymer-supported bornanediol is used as a chiral auxiliary in the asymmetric reduction of acetophenone with LAH partly neutralized by addition of an equivalent of methanol. The use of bornanediol, which can form a bidentate complex with LAH, minimizes the number of reactive hydride species that can be present in the mixture, yet this does not preclude the formation of fully deactivated aluminium complexes if two neighboring chiral sites combine to a single LAH molecule. Thus, Liu et al. generally report ee's which are significantly lower for a cross-linked polymer with DF 0.31 than for the soluble miniature model compound, and they also notice a further decrease in optical yield as the percent cross-linking is increased and therefore the accessibility of the reactive sites is decreased. In addition, with a highly loaded polymer and in the absence of added chiral component, no enantioselectivity is obtained,[19] perhaps due to the favored formation of fully deactivated 2:1 complexes of the polymer-supported bornanediol with LAH and a lack of accessibility of reactive sites within the beads.

Similarly, the extremely low enantioselectivities reported by Suda et al.[20] for their polymer-based chiral dihydroxybiphenyl–LAH complexes is probably due to extensive site interactions in the high-capacity polymer they chose to use. Again, the formation of a bidentate complex with LAH, though decreasing the number of active complexes which can possibly be formed, does not prevent interaction of sites which, in this case again, results in significant amounts of soluble achiral reducing agent being present in the reaction mixture, thus lowering the enantioselectivity of the reaction.

Similar explanations may be proposed to explain the poor enantioselectivities we observed in our prior work with other polymer-supported amino alcohols and polyols.[21]

Both Liu et al.[19] and Suda et al.[20] report that chiral ligands linked to soluble polymers perform better than cross-linked polymers with similar structures. We have also prepared soluble copolymers of styrene and *N*-(*p*-methylstyryl)-(1*R*,2*S*)-ephedrine and have tested these in the asymmetric LAH reduction of acetophenone. Though the polymers are soluble, they precipitate immediately when added to a 1:2 complex of LAH and 3,5-dimethylphenol; yet the reduction proceeds in 20% ee using a polymer with a capacity of 3.55 mmol/g (DF = 1.0),[33] increasing to 32% and 45% ee with polymers having capacities of 2.66 and 0.86 mmol/g, respectively (DF = 0.52 and 0.11). The relatively better performance of the soluble high-capacity polymers as compared to their cross-linked analogues is likely due to the increased accessibility of the reaction sites. Though precipitation occurs immediately, presumably due to cross-linking through LAH, it is expected that a larger number of ephedrine moieties in the polymer chain are exposed and participate to the hydride complex than is the case with the more difficulty accessible chiral ligands of the highly loaded cross-linked bead polymers.

With the lower capacity polymer, the observed enantioselectivity is less than with a comparable cross-linked material (45% vs. 79% ee), perhaps due to the unavoidable formation of cross-links through LAH and to the fact a number of the chiral groups may not participate in complex formation once the polymer has precipitated. Overall, handling of the soluble polymer is much more difficult than that of its cross-linked analogue, and small processing losses are harder to avoid making quantitative recovery of the soluble polymer almost impossible to achieve.

In conclusion, it can be said that though this work confirms that polymer-bound chiral auxiliaries may have a place in polymer-supported asymmetric reactions which they facilitate through the classical "Merrifield" purification advantage, their use cannot be realisitically contemplated in applications where site–site interactions can potentially interfere as is the case in reductions with LAH complexes. This work demonstrates clearly that better approaches, where additional benefits may result from the use of a polymer, are those where a single well-defined intermediate is involved. In asymmetric reductions, this may mean the use of chiral polymer-bound boranes[22,29] rather than of LAH complexes.

Experimental Section

General. Optical rotations were measured on material isolated by preparative thin-layer or column chromatography using a Perkin-Elmer Model 241 digital polarimeter with the D-line of a sodium lamp. Care was taken to ensure that the material was

(32) Vigneron et al.[15] report obtaining on optical yield of 80.2% with *N*-methylephedrine complexes in ether vs. only 23.5% in THF under the same reaction conditions.

(33) This polymer is prepared by free radical homopolymerization of *N*-(*p*-methylstyryl)-(1*R*,2*S*)-ephedrine. Lower capacity soluble copolymers we obtained by copolymerization with styrene after it was determined that the two monomers form a random copolymer. Denaide, F. V.; Lecavalier, P.; Fréchet, J. M. J., manuscript in preparation.

not contaminated with any acetophenone since the optical rotation of 1-phenylethanol is very sensitive[16,31] to both the presence of impurities and changes in solvent. Optical rotations were measured by using neat compound,[31] cyclopentane solutions,[16] or in some cases chloroform solutions. In the latter case, a calibration curve was used since the values of rotations in chloroform, benzene, etc. are significantly higher than the corresponding values for neat compound or cyclopentane solutions. NMR spectra were measured on Varian CFT-80 or XL-300 spectrometers in $CDCl_3$ solutions unless otherwise noted, the chemical shifts are reported in parts per million from Me_4Si internal standard. Infrared spectra were recorded on a Nicolet 10 DX FT-IR spectrometer. The 1% cross-linked polymer used in this work was obtained from Bio-Rad laboratories (Bio-Beads SX-1); the polymer was washed before use as described earlier.[30] Capacities of the polymers determined by gravimetry and elemental analysis are expressed in millimoles of functional groups per gram of dry resin (mmol/g) or as degrees of functionalization DF. The DF of a polystyrene-based reactive polymer is a measure of the proportion of aromatic styrene rings which carry the desired functionality. For example if 30% of the styrene units are functionalized DF = 0.30.

(1*R*,2*S*)-(−)-Ephedrine was obtained from Sigma Chemical Co. and used without further purification. All asymmetric reductions were carried out in dry solvents under argon. In most cases, ethereal solutions of $LiAlH_4$ (Aldrich) were used after titration. All yields are reported for isolated materials.

Preparation of Chloromethylated Polystyrene. 1% cross-linked polystyrene (Bio-Beads SX1, Bio-Rad Laboratories) is chloromethylated as described previously[6,30] to yield the chloromethylated polymer with loading which varies with reaction conditions. Polymers with DF 0.08 to 0.35 were used in the experiments reported below.

Preparation of the Polymer-Bound Ephedrine. A mixture of 10.00 g of chloromethylated polystyrene (2.36 mmol of Cl/g) and 11.7 g (70.8 mmol) of *l*-(−)-ephedrine in 80 mL of dimethylformamide is stirred at 85 °C for 4 days. The polymer is then filtered and washed repeatedly with ethanol, water, THF–water (1:1) until no chloride ion is found in the wash liquid, THF, and ethanol. After drying in vacuo at 40°, 13.01 g of polymer are obtained. Nitrogen analysis indicates a loading of ephedrine corresponding to 1.81 mmol/g while no chlorine remains on the polymer.

Other polymers with varying loadings were also prepared by a similar procedure using the quantitative displacement of chloride from appropriately functionalized chloromethylated resins.

Asymmetric Reduction of Acetophenone. (i) Procedure A. To a stirred solution of lithium aluminium hydride (1.25 mmol) and anhydrous ether (5 mL) is added dropwise an ethereal (5 mL) solution of 3,5-dimethylphenol (2.50 mmol) over a period of 30 min under argon atmosphere. After the mixture is stirred 1 h at room temperature, the mixture is cooled to 0 °C and stirred while the solid polymer-bound ephedrine (once used sample, 1.710 g or 1.25 mmol) is added slowly with a screw-type powder addition funnel over a period of 1 h. Stirring is continued 2 h at 0 °C to afford the desired ethereal suspension which is then cooled to −15 °C and a solution of acetophenone (1.00 mmol) in ether (2 mL) is added over a 2-h period and the whole is stirred for an additional hour at −15 °C. Workup is effected by addition of 0.1 M NaOH (5 mL) to the cooled reaction mixture which, after 15 min of stirring, is allowed to reach room temperature while the mixture is neutralized with 1 M HCl. The polymer is then washed several times with water and ether; the ethereal extracts are dried over $MgSO_4$ and concentrated to afford a product which is purified by preparative TLC (ethyl acetate–hexane 1:3) to afford the pure 1-phenylethanol (0.1164 g, 97%) with $[\alpha]^{20}_D$ + 34° (*c* 7, cyclopentane) for ee 78.8%.

(ii) Procedure B. The procedure is identical with procedure A above except that the polymer-bound reducing agent is filtered and washed twice with anhydrous ether under argon atmosphere at 0 °C and then resuspended in cooled ether prior to the addition of acetophenone.

Regeneration of the Polymer. The used polymer (10 g) is stirred overnight in a 4:1 mixture of dioxane–3 M HCl (100 mL). After filtration and thorough washing with water and 4:1 dioxane–water, the polymer is suspended in a 4:1 mixture of dioxane–2 M NaOH (100 mL) and the suspension is stirred overnight. After filtration, the polymer is washed repeatedly with water, 4:1 dioxane–water, and ethanol. After drying in vacuo nitrogen analysis shows no loss of chiral ligand.

Preparation of (1*R*,2*S*)-*N*-Benzyl-(−)-ephedrine. To a solution of 12.06 g (73.0 mmol) of 1-ephedrine in 20.0 mL of dry pyridine is added 9.24 g (80.3 mmol) of freshly distilled benzyl chloride. After the mixture was stirred for 72 h at room temperature, 20.0 mL of H_2O is added and the mixture is extracted 3 times with ethyl acetate, dried over $MgSO_4$, and evaporated to afford 11.84 g of crude product. After chromatography (9:1 hexane–ethyl acetate) (1*R*,2*S*)-*N*-benzyl-(−)-ephedrine is obtained in 60% yield. ^1H NMR: 0.97 (d, 2 H), 2.17 (s, 3 H), 2.90 (m, 1 H), 3.23 (s, br, OH), 3.53 (s, 2 H), 4.80 (d, H), 7.23 (d, 10 H Ar). ^{13}C NMR: 9.732 (q), 38.653 (q), 59.158 (t), 63.479 (d), 73.465 (d), 126.136–142.295 (Ar). Anal. Calcd (C, H, N): 79.96, 8.29, 5.48. Found: 79.84, 8.46, 5.59. MS: *m/e* 256 (M + 1, chemical ionization, ether) 148 ($C_{10}H_{14}N^+$), 91 ($C_7H_7^+$). IR (cm^{-1}): 3112 (OH), 1025 (C–O stretch).

Reduction of Acetophenone Using *N*-Benzyl-*l*-ephedrine. To 2.51 mL of lithium aluminium hydride (LAH) 1.0 M in ether diluted with 5.0 mL of anhydrous ether under argon is added 0.6423 g (2.51 mmol) of *N*-benzylephedrine dissolved in 4.0 mL of ether over 1 h. The mixture is stirred for 30 min and 0.6129 g (5.02 mmol) of 3,5-dimethylphenol dissolved in 4.0 mL of ether is added over a period of 30 min. The homogeneous mixture is stirred at room temperature for 2 h after which the temperature is lowered to −15 °C and 0.2513 g (2.09 mmol) of acetophenone in 1.5 mL of ether is added slowly over a period of 2 h. The reaction is continued at −15 °C for another hour, then 6 M HCl is added to hydrolyze and dissolve the Al salts (acidic pH). The alcohol is extracted 3 times with ether and the combined organic phases are backwashed once with water, dried over $MgSO_4$, and evaporated. The crude product is separated on TLC plates by using a 4:1 mixture of hexane and ethyl acetate to yield 0.2190 g (86%) of isolated alcohol, $[\alpha]_D$ +36.8° (*c* 7.260, cyclopentane), (max $[\alpha]_D$ −43.1° (*c* 7.19, cyclopentane).[21]

Reduction of Acetophenone Using a Soluble Polymer-Bound Ephedrine. To 1.75 mL of LAH 1.0 M in ether diluted with 5.0 mL of anhydrous ether under argon is added 0.4274 g (3.50 mmol) of 3,5-dimethylphenol in 4.0 mL of ether over 30 min. 0.6682 g (1.75 mequiv) of polymer-bound ephedrine dissolved in 15.0 mL of ether is added to the mixture over a period of 1 h. Upon addition of the polymer solution a precipitate is immediately formed. The heterogeneous solution is stirred at room temperature for 2 h after which the temperature is lowered to −15 °C and 0.1512 g (1.26 mmol) of acetophenone in 1.5 mL of ether is added slowly over 2 h. After it was stirred for another hour at −15 °C, the mixture is hydrolyzed with 6 M HCl. The polymer is filtered and rinsed with water and then ether, and the alcohol is isolated as described above to yield 0.1099 g of alcohol (71%) with optical rotation $[\alpha]_D$ +13.9° (*c* 7.144, cyclopentane).

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