trated to 20 mL. Toluene (20 mL) and 5% aqueous acetic acid (20 mL) were added to the concentrate. The phases were well mixed and then separated. The toluene layer was washed with 5% aqueous acetic acid (20 mL). The combined aqueous layers were washed with toluene (10 mL). The aqueous layer was filtered and the insolubles were redissolved by washing the filter with 5% aqueous acetic acid (40 mL). The combined filtrates were concentrated to 40 mL to remove dissolved toluene. The product as the acetate salt crystallized from solution. Water (50 mL) and acetic acid (8.5 mL) were added to the concentrate and the mixture was heated at 45 °C to redissolve the solids. The clear solution was cooled to 20 °C and concentrated ammonium hydroxide (25 mL) was added with stirring at <25 °C. The product precipitated out of solution as a white solid. The slurry was cooled at 5 °C for 1 h. The solid was filtered, washed with water (25 mL), and suction dried: 0.688 g as a crude product (83 wt % by HPLC). The crude solid (500 mg) was suspended in acetonitrile (5 mL) and the mixture was heated at reflux for 45 min. The slurry was cooled to room temperature and then was chilled in an ice bath for 30 min. The solid was filtered, washed with cold acetonitrile (3 mL), and suction dried: 410 mg, 67% overall yield: mp 214-215.5 °C. The ^{1}H NMR spectrum agreed with the spectra of **1a** from the aziridine route.

(5*R*,10*S*,11*R*)-(+)-10,11-Dihydro-5-methyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imin-11-ol (1a). The hydroxylated derivative of MK-0801 was resolved by heating a slurry of **1a** (85.6 g, 0.361 mol) in acetonitrile (856 mL) to reflux. Di-*p*-toluoyl-D-tartaric acid monohydrate (218.9 g, 0.541 mol) in acetonitrile (856 mL) was added, whereupon the amine dissolved. The mixture was allowed to cool to room temperature and the amine–acid salt began to crystallize. A mixture of acetonitrile-ethyl acetate (1:1, 430 mL) was added at room temperature. The resultant slurry was stirred at room temperature for 18 h. The solid was filtered, washed with acetonitrile (1 L), and suction dried (97:3 ratio of (+)/(-) enantiomers, 96% yield of theory). The filtercake (161.7 g) was slurried in acetonitrile (2100 mL) and the slurry was heated at 70–75 °C for 2 h. The mixture was then cooled to room temperature. After a few hours the solid was filtered, washed with acetonitrile (1 L), and vacuum dried (100 g, 65% yield of 27 wt % amine). The salt was partitioned between water (1 L) and isopropyl acetate (500 mL). Concentrated ammonium hydroxide (50 mL) was added until the aqueous phase was basic. Additional isopropyl acetate (500 mL) did not dissolve the crystallized solid. Therefore, the solid was filtered and the two phases of the filtrate were separated. The aqueous layer was washed with isopropyl acetate (500 mL). The combined isopropyl acetate layers were evaporated to dryness under vacuum. The isolated solid was combined with the filtered solid. This mixture was dissolved in 5% aqueous acetic acid (750 mL). The insolubles were filtered and washed with 5% aqueous acetic acid (100 mL). The combined filtrates were made basic with stirring by addition of concentrated ammonium hydroxide (80 mL). The resultant slurry was stirred at room temperature for 30 min. The solid was filtered and washed with water and vacuum dried (25.6 g, 31% yield): mp 217–219 °C; $[\alpha]_D$ +109° (c = 1, methanol) as the maleate salt (prepared from 2-propanol–water, 9:1). Chiral HPLC assay (bis-benzoyl derivative; Pirkle L-phenylglycine covalent; 80:10:1 hexanes/CH_2Cl_2/2-propanol; 1.5 mL/min, 230 nm) gave a >99:1 ratio of the 5*R*,10*S*,11*R*-(+) enantiomer (t_R 8.0 min) to the 5*S*,10*R*,11*S*-(-) enantiomer (t_R 6.1 min). The absolute configuration of (+)-**1a** was established by comparison to the final product **1a** obtained in an alternative synthesis.[5]

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New Solid-Phase Catalysts for Asymmetric Synthesis: Cross-Linked Polymers Containing a Chiral Shiff Base–Zinc Complex

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A cross-linked polystyrene resin containing chiral primary amino alcohol moieties bound through the ether linkage to some of its *p*-methylene-substituted aromatic rings is a useful regenerable chiral auxiliary in the enantioselective catalytic alkylation of aldehydes. The primary amino groups of the chiral amino alcohols react with the aldehydes to form Schiff bases, which catalyze the addition of dialkylzinc to aldehydes leading to optically active secondary alcohols having enantiomeric purity of up to 99%. A series of polymeric amino alcohols were synthesized by two methods involving either attachment of a chiral moiety as a side chain onto a reactive cross-linked polystyrene, or the terpolymerization of a chiral monomer with styrene and a cross-linking agent. New cross-linking agents affording more flexibility to the chiral catalysts were used in the preparation of the chiral polymers and found to provide excellent performance. An interesting extension of the method is its adaptation to a continuous-flow system where diethylzinc and aldehyde are supplied continuously to a column filled with the chiral polymeric catalyst. Large amounts of chiral products and high turnovers may be obtained by this method.

Introduction

Polymers containing main-chain or pendant chirality are finding a number of interesting applications in organic chemistry. While most early work in the application of chiral polymers for asymmetric processes was directed toward materials useful in the chromatographic separation of enantiomers,[1] several reports of the use of polymers as chiral auxiliaries in asymmetric syntheses have appeared. These include polymeric phase-transfer catalysts[2] or chiral polymers used in asymmetric addition[3] or alkylation[4] re-

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Table I. Asymmetric Alkylation of Aldehydes with Dialkylzinc in the Presence of Chiral Amino Alcohols

entry	aldehyde	ZnR_2	amino alcohol[a]	meth[b]	yield, %	temp, °C	time, h	% ee	config
1	PhCHO	$ZnEt_2$	1	A	85–95	0	6	22–73[c]	S
2	PhCHO	$ZnEt_2$	1	B	90	0	6	85	S
3	PhCHO	$ZnEt_2$	1	C	92	0	6	84	S
4	PhCHO	$ZnEt_2$	2	B	88	0	6	51	S
5	PhCHO	$ZnEt_2$	2	C	91	0	6	52	S
6	PhCHO	$ZnEt_2$	3	B	90	0	6	15	S
7	PhCHO	$ZnMe_2$	1	B	82	20	24	89	S
8	BuCHO	$ZnEt_2$	1	B	79	20	30	85	S

[a] The amount of amino alcohol utilized was 0.05 equiv. [b] See the procedure described in the Experimental Section. [c] Reproducible values were not obtained in several runs.

actions. More recently, much activity has been concentrated on polymer-assisted asymmetric reductions.[5] The use of polymers as chiral auxiliaries in asymmetric induction reactions offers interesting possibilities as the chiral polymers may have some unique advantages over their low molecular weight counterparts. For example, the polymers, being insoluble, offer a well-documented purification advantage[6] since separation of the chiral reaction product from the chiral auxiliary only amounts to a filtration; the polymers can also be recycled repeatedly, a definite advantage in view of the generally high cost of chiral reagents or catalysts; and finally, the polymers may provide a unique microenvironment for the reactions, which in favorable cases may result in enhanced stereoselectivities.

In this study, several types of polymers (**6**, **10**, **11**, **12**, **13**) containing a chiral α-amino alcohol were prepared and used as chiral auxiliaries for the catalytic alkylation of aldehydes with dialkylzinc. While all of these polymers have active side chains constituted of the same chiral amino alcohol, they also possess differences in structural features which might have an effect on the enantioselectivity observed during their reaction.

Results and Discussion

Enantioselective Addition of Diethylzinc to Benzaldehyde in the Presence of a Chiral Amino Alcohol. The catalyzed addition of organozinc species to benzaldehyde has now been investigated by a number of research groups using a variety of chiral catalysts.[7-12] We have reported that the successful enantioselective addition of diethylzinc to aldehydes in toluene required the presence of a catalytic amount of polymer-supported chiral amino alcohols.[13] While catalysts such as the Noyori–Fréchet catalysts[7,13,14] and polymer-supported ephedrine[13] gave satisfactory enantioselectivities, other catalysts which contain primary or secondary rather than tertiary amino groups were significantly less effective in this reaction. In a different context,[15-18] we had shown that chiral primary

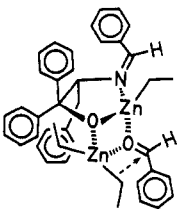
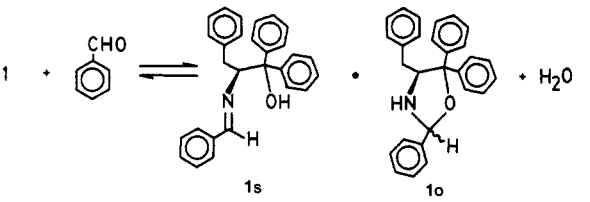
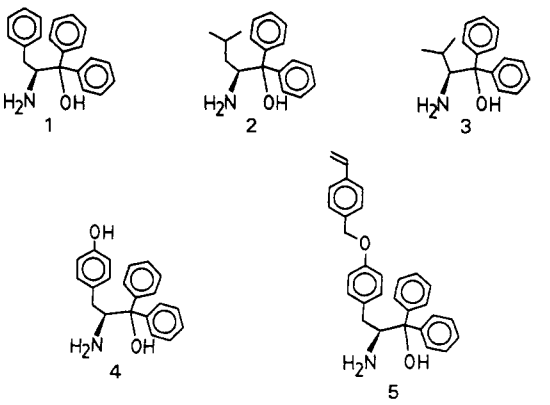


Figure 1.

Scheme I



amino alcohols such as **1** which contained a diphenyl-substituted tertiary alcohol group located α to the primary amino group were very efficient chiral auxiliaries in the asymmetric reduction of ketones and oximes using borane.



Nevertheless, the same amino alcohols did not produce high enantioselectivities in the catalyzed addition of diethylzinc to benzaldehyde. Typically, the selectivities obtained in several reactions run under similar conditions were highly variable from experiment to experiment (Table I, entry 1). During a survey of several reaction conditions, it was found that the order of addition of the reagents was important in this reaction. Method A reported in Table I is the same as that used previously in reactions catalyzed with tertiary amino alcohols.[13] In this method, a toluene

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solution of 1 (5 mol %) is treated successively with a hexane solution of diethylzinc and benzaldehyde. In method B, benzaldehyde is added to a toluene solution of a catalytic amount of 1, and then a hexane solution of diethylzinc is added. As shown in Table I, the results that are obtained through method B always show higher enantioselectivites with reproducible values.

^{1}H NMR measurement on a benzene-d_6 solution of 1 and benzaldehyde show the formation of a mixture of Schiff base **1s** and oxazolidine **1o** (Scheme I). The free amino alcohol 1 disappears completely on standing at room temperature for 3 h in the NMR tube. The ratio of **1s** to **1o** was 2.7:1 as measured by ^{1}H NMR spectroscopy. In method B, **1s** would react with diethylzinc to form a chiral zinc complex. For the asymmetric ethylation of aldehydes using chiral tertiary amino alcohols, the consensus view is that this reaction may well proceed through a six-centered bimetallic transition state as proposed by both Corey et al.[19] and Itsuno et al.[13] The transition state obtained from **1s** that rationalizes the observed sense of asymmetric induction in the benzaldehyde ethylation is shown in Figure 1.

It is tentatively proposed in this type of catalyst that the chirality of the amino alcohol may induce the formation of a new chiral center on the complexed Zn atom during formation of the chiral catalyst. This newly created chiral center would play an important role in the stereoselection. The chiral center of the amino alcohol seems to be located too far from the reaction site to control directly the stereoselection in the transition state, which is illustrated in Figure 1.

The formation of a Schiff base and an oxazolidine is accompanied by the concurrent generation of some water. In method C, the reaction mixture of 1 and benzaldehyde was freeze-dried before its use for asymmetric ethylation to ensure that the presence of a catalytic amount of water did not have any effect on the reaction. These experiments suggested that the presence of a small amount of water adversely affects the reaction (Table I, entries 2–5). Method B was adopted for the polymeric catalysts discussed below because of its greater simplicity.

The structure of the chiral amino alcohols also has a large effect on the enantioselectivity of this reaction. Chiral amino alcohol 1, derived from L-phenylalanine, gave high enantioselectivities while chiral amino alcohol **3** only gave a low % ee even in method B (entry 6).

Preparation of Chiral Polymers Containing Structure 1. The results obtained through the use of chiral amino alcohols (Table I) encouraged us to prepare chiral polymers possessing similar optically active amino alcohol moieties as pendant groups. For this purpose we prepared the two chiral amino alcohols **4** and **5**. Compound **4** can easily be converted into its phenoxide salt, which is then allowed to react with a cross-linked chloromethylated polystyrene resin to give the polymer-supported chiral amino alcohol. Alternatively, the styryl group of **5** can be copolymerized with styrene and some styrenic cross-linking agent to afford directly a chiral polystyrene resin.

The preparation of chiral catalysts by chemical modification of polymers has been used extensively due to the relative simplicity of the method.[20] Therefore, attachment of **4** to partly chloromethylated polystyrene cross-linked with 2% of divinylbenzene (DVB) was performed to prepare chiral polymer **6** as illustrated in Scheme II, eq 1. The chloromethyl group of highly cross-linked polystyrene (**7**) containing 20 mol % of DVB is not suited for this attachment reaction (Scheme II, eq 2) since resin **7** has no swellability in organic solvents and cannot react with the relatively bulky nucleophile: the phenoxide of **4**. A very low degree of functionalization could be obtained in this reaction.

A new cross-linking agent, **8**, containing an oxyethylene chain was developed to replace divinylbenzene in the preparation of a new type of cross-linked chloromethylated polystyrene (**9**) in which the chiral nucleophile would be able to react much more easily, due to the more flexible structure of the cross-linked network and to activation of the nucleophile by coordination of its oxyethylene chain to the metal cation. Indeed, polystyrene resins cross-linked with **8** were found to act as efficient phase-transfer catalysts in Williamson syntheses.[21] Cross-linked polymer **9** swells very well in organic solvents such as toluene or tetrahydrofuran even when the degree of cross-linking is high, and the chloromethyl groups of polymer **9** react readily with **4** to afford chiral polymer **10** with quantitative conversion (Scheme II, eq 3).

Another approach to the synthesis of chiral polymers involves the copolymerization of monomers containing the desired chiral groups with an achiral monomer used as diluent and a cross-linking agent. Optically active monomer **5** was synthesized by coupling of **4** with 4-vinylbenzyl chloride as described previously.[22] Suspension copolymerization of **5** with styrene and DVB afforded the chiral polymer **11** (Scheme II, eq 4). Chiral polymer **11** prepared from **5**, styrene, and DVB in a 1:7:2 molar ratio swelled well in organic solvents such as toluene, benzene, or tetrahydrofuran. For example, a 4-fold volume increase was observed for the dry polymer when suspended in toluene. This unusually high swellability of a highly cross-linked polystyrene resin may be mainly attributable to the bulkiness and polarity of chiral monomer **5**. Chiral monomer **5** was also copolymerized with styrene and cross-linking agent **8** instead of DVB to afford chiral polymer **12**, which also swelled well (4.6-fold increase in volume in toluene) and showed enhanced mechanical stability due to the flexible structure of the cross-linker (Scheme II, eq 5). Soluble linear polymer **13** was also obtained by the solution polymerization method (Scheme II, eq 6) in the absence of a cross-linking agent. All five of the chiral polymers (**6** and **10–13**) contain a common chiral amino alcohol of structure analogous to 1 in their side chains.

When polymer-supported reagents or catalysts are employed in organic synthesis, the polymer bends should be mechanically stable enough to withstand stirring over a long period of time. If the spherical beads are not stable enough, their breakdown during stirring will result in the formation of a fine powder of the insoluble polymer, which drastically hinders their handling in filtration and reduces their ability to be reused repeatedly. This problem is usually only acute for those polymers in which the degree of cross-linking exceeds a few percent. Chiral 20% cross-linked polymers **10** and **12** having a flexible cross-linkage are mechanically much more stable than polymer **11** prepared by using 20% DVB. Magnetic stirring is particularly destructive with highly cross-linked polymer beads; therefore, beads of polymer **11** began to lose their spherical shape after 1 day of magnetic stirring at 200 rpm in toluene; at 350 rpm, almost 50% of the polymer was transformed into a fine powder if stirring was continued

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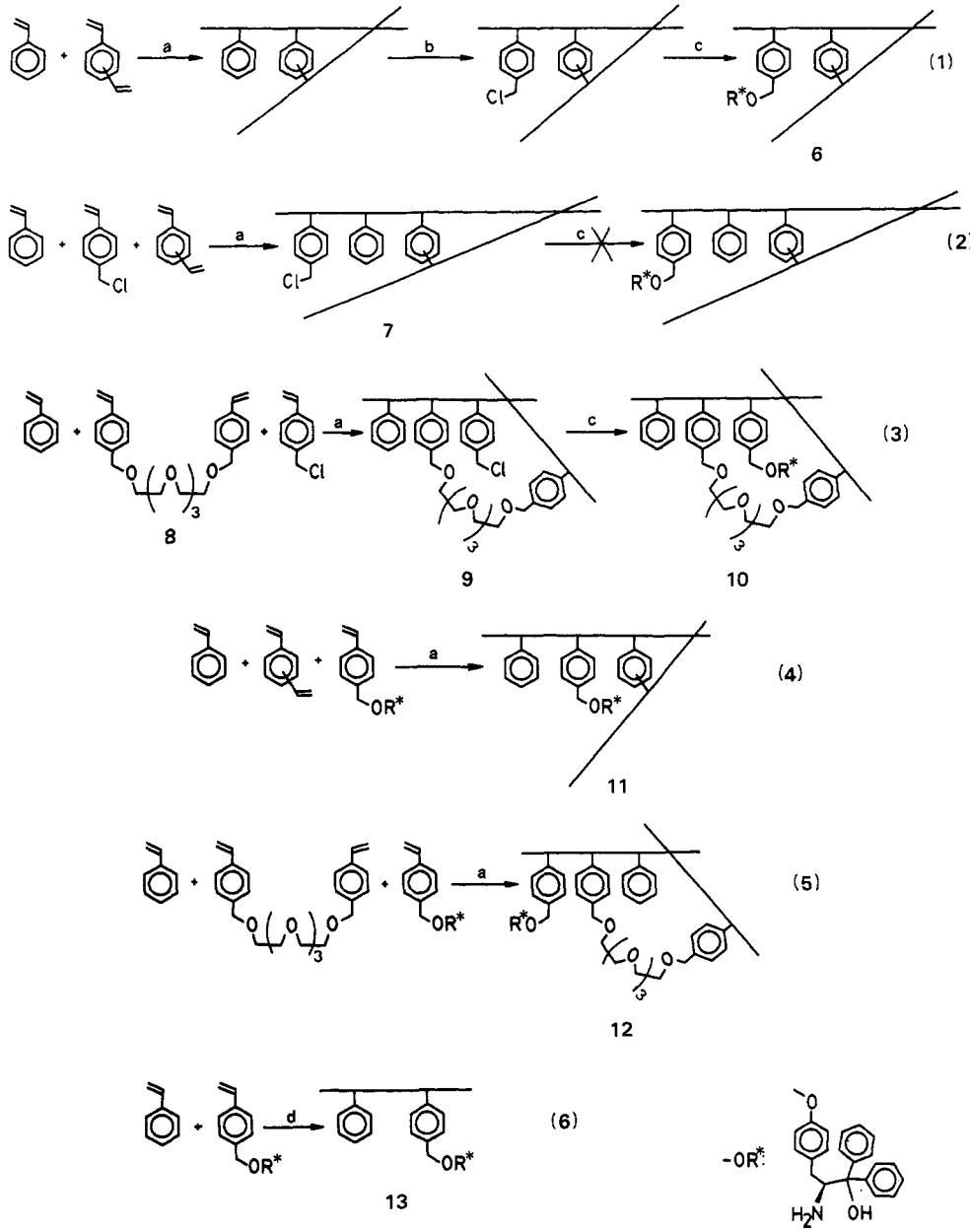
Scheme II[a]



[a] (a) AIBN, benzene, THF, water; (b) $ClCH_2OCH_3$, $SnCl_4$, chloroform; (c) R*OH, NaH, DMF; (d) AIBN, THF.

in toluene for 4 days. In contrast, **10** and **12** kept their original bead form for at least 4 days under the same conditions.

Due to the steric and electronic effects of the aromatic substituent group of the chiral styrenic monomer **5**, its copolymerization with styrene was not expected to afford a completely random copolymer. Therefore, a copolymerization study was carried out to determine the reactivity ratios of the two monomers in free-radical copolymerization. Varying amounts of the two comonomers were used in low conversion copolymerizations, and the composition data were used to calculate reactivity ratios according to the classical expressions.[23] The reactivity ratios calculated were $r_1 = 0.3$ and $r_2 = 1.0$ for monomer **5** and styrene, respectively, which suggests that consecutive incorporation of several units of bulky monomer **5** is not favored in the copolymerization process.

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Asymmetric Ethylation of Aldehydes Using Polymeric Chiral Amino Alcohols. The various chiral polymers (**6** and **10–13**) were tested as catalysts in the ethylation of aldehydes using method B; results are summarized in Table II. In view of the model NMR experiments described above for a mixture of **1** and benzaldehyde, and of the known analogy of reactivity of polymer-supported and free species, it is assumed that polymer-bound Schiff base and oxazolidine are formed upon mixing of the chiral polymer and the aldehyde. Treatment of 4-chlorobenzaldehyde with polymer **11** in toluene likely resulted in the formation of a polymer containing the Schiff base and oxazolidine of 4-chlorobenzaldehyde. This assumption was confirmed by chlorine analysis of the product obtained by addition of 4-chlorobenzaldehyde to polymer **11** isolated after several washings of the polymer with toluene. Analytical data suggests a quantitative reaction.

In the absence of a suitable catalyst, diethylzinc is known to react with benzaldehyde very slowly to give 1-phenyl-

Table II. Asymmetric Ethylation of Benzaldehyde with Diethylzinc in the Presence of Polymeric Chiral Amino Alcohols

entry	polymer	amt of cat., %	solvent[a]	temp, °C	yield, %	% ee	confign
1	**6**	5	T–H	0	95	41	*S*
2	**6**	5	T	0	90	30	*S*
3	**10**	5	T	0	88	49	*S*
4	**11**	5	T–H	0	92	84	*S*
5	**11**[c]	5	T–H	0	96	83	*S*
6	**11**	5	T–H	rt[e]	94	56	*S*
7	**11**	5	T	0	95	70	*S*
8	**11**	5	H	0	91	15	*S*
9[b]	**11**	5	T	0	88–93	10–35[d]	*S*
10	**12**	5	T–H	0	92	85	*S*
11	**12**[c]	5	T–H	0	96	86	*S*
12	**12**	5	T–H	rt	93	79	*S*
13	**12**	10	T–H	0	93	86	*S*
14	**12**	20	T–H	rt	95	75	*S*
15	**12**	5	T	0	90	75	*S*
16	**12**	5	H	0	91	16	*S*
17	**13**	5	T	0	87	77	*S*

[a] T = toluene; H = hexane. [b] Reactions carried out according to method A. [c] Recycled polymer was used. [d] Reproducible values were not obtained in several runs. [e] Room temperature.

Table III. Asymmetric Ethylation of Aldehyde with Diethylzinc in the Presence of Polymeric Chiral Amino Alcohols in Toluene at 0 °C

entry	aldehyde	polymer	yield, %	$[\alpha]_D$, deg (*c*, solvent)	% ee	confign
1	PhCHO	**12**	90	−21.2 (neat)[c]	75	*S*
2	*o*-$MeOC_6H_4CHO$	**12**	83	−11.4 (1.25, toluene)[d]	21	*S*
3	*o*-$EtOC_6H_4CHO$	**12**	94	−27.3 (3.75, toluene)[d]	54	*S*
4	*p*-$MeOC_6H_4CHO$	**12**	83	−10.8 (1.21, toluene)[d]	32	*S*
5	*p*-ClC_6H_4CHO	**6**	78	−14.0 (5.01, C_6H_6)[e]	58	*S*
6	*p*-ClC_6H_4CHO	**10**	91	−14.3 (4.93, C_6H_6)[e]	59	*S*
7	*p*-ClC_6H_4CHO	**11**	93	−21.3 (4.92, C_6H_6)[e]	88	*S*
8	*p*-ClC_6H_4CHO	**12**	95	−23.9 (4.93, C_6H_6)[e]	99	*S*
9[a]	$PhCH_2CH_2CHO$	**12**	90	+2.12 (2.96, C_2H_5OH)[f]	7.9	*S*
10[b]	BuCHO	**12**	84	+4.34 (neat)[g]	65	*S*

[a] Reaction time was 3 days. [b] Reaction time was 5 days at room temperature. [c] $[\alpha]_D$ +28.1° (neat) for (*R*)-1-phenylpropanol: see ref 16. [d] $[\alpha]_D$ +47.0° (*c* 1.2, toluene) for (*R*)-1-(*o*-methoxyphenyl)propanol in 87% ee, $[\alpha]_D$ +46.3° (*c* 1.2, toluene) for (*R*)-1-(*o*-ethoxyphenyl)propanol in 92% ee, $[\alpha]_D$ +20.4° (*c* 1.2, toluene) for (*R*)-1-(*p*-methoxyphenyl)propanol in 61% ee; see ref 14. [e] $[\alpha]_D$ −10.4° (*c* 5, C_6H_6) for (*S*)-1-(*p*-chlorophenyl)propanol in 43% ee: Capillon, J.; Guette, J. *Tetrahedron* **1979**, *35*, 1817. [f] $[\alpha]_D$ +26.8° (*c* 5, C_2H_5OH) for (*S*)-1-phenyl-3-pentanol: Sato, T.; Gotoh, Y.; Wakabayashi, Y.; Fujisawa, T. *Tetrahedron Lett.* **1983**, *24*, 4123. [g] $[\alpha]_D$ +6.68° (neat) for (*S*)-3-heptanol: Pickard, R. H.; Kenyon, J. *J. Chem. Soc.* **1913**, *103*, 1931.

propanol contaminated by benzyl alcohol.[24] As was shown in Table I, chiral amino alcohols accelerate the ethylation of aldehydes to give high yields of chiral ethylated product in 6 h at 0 °C. As slower kinetics are observed when the chiral polymers are substituted for their low molecular weight analogue **1**, it was feared that an increased occurrence of nonstereoselective reactions might be observed. Satisfactory enantioselections obtained for polymers **11**–**13** (Table II) are likely due to a decrease in the conformational mobility between the various alkylation pathways of the polymer-bound intermediates. At room temperature, asymmetric induction using **12** is superior to that obtained using **11** (runs 6 and 12). In contrast, results obtained with chiral polymers **6** and **10** showed a lowering in the enantioselectivity of the reaction. Both of these polymers were prepared by attaching amino alcohol **4** to the chloromethylated polymers. During the chemical modification process, it is possible that some undesired reactions such as N-alkylation might occur since **4** has three different kinds of functionalities including two hydroxy and one amino group, although no evidence of side reactions is seen on IR examination of **11** and **12**. The effect of solvent on stereoselectivity is not negligible. The use of hexane alone results in considerable lowering of the % ee (entries 7 and 16). Toluene, which is a better swelling solvent, affords higher % ee. Best results were obtained by using mixtures of toluene and hexane. The effect of temperature on enantioselectivity is as expected, with better results obtained at 0 °C than at room temperature. Below −50 °C, no product was detected, even after 2 days of reaction. These polymers, being insoluble, can be easily separated from the reaction mixture and recycled after regeneration (entries 5 and 11). Care must be taken in the regeneration step to remove completely a residual deposit of zinc derivatives as these species would interfere with the subsequent enantioselective alkylations. If washing is insufficient, a drastic lowering of the enantioselectivity is observed upon reuse, though the reaction rate suffers no retardation.

We have also prepared soluble copolymers of styrene and **5** and have tested these in the asymmetric ethylation of benzaldehyde. Though the starting polymer **13** is soluble, the reaction mixture turns into a highly viscous solution immediately after addition of diethylzinc, yet the ethylation reaction in toluene at 0 °C still proceeds in 77% ee (entry 17). 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.

The use of chiral amino alcohol **1** or its polymer-bound counterparts (**6** and **10**–**13**) as chiral auxiliaries always results in the predominant formation of the *S* alcohol.

Aldehydes other than benzaldehyde were also tested in this reaction using our polymeric catalysts. When tertiary amino alcohols were used as chiral auxiliaries,[13,25] it has

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Table IV. Asymmetric Ethylation of Benzaldehyde in a Batch System[a]

batch no.	yield, %	% ee	confign
1	72	86	*S*
2	83	87	*S*
3	78	85	*S*
4	81	84	*S*
5	79	85	*S*

[a] Reactions carried out by using polymer **12** in toluene–hexane at 0 °C. Reaction on 10 mmol of benzaldehyde using 5 mol % catalyst.

been reported that an increase of % ee is observed if *o*-alkoxybenzaldehydes are used instead of benzaldehyde. In this study, however, we have observed (Table III) that with our primary amine based catalysts only low % ee's are obtained in the ethylation of *o*-alkoxybenzaldehydes. In contrast, the same primary amine based catalysts afford much higher enantioselectivities, up to 99% ee, in the alkylation of *p*-chlorobenzaldehyde. This is one of the most efficient asymmetric syntheses achieved to date using polymeric catalysts. In the case of aliphatic aldehydes, longer reaction times are required to achieve satisfactory conversions. The relatively low enantioselectivities that are obtained likely result from unavoidable competitive uncatalyzed reactions in solution. All of the alkylations also gave predominantly the products having the *S* configuration.

Asymmetric Ethylation of Aldehydes in a Continuous-Flow System. The use of insoluble polymeric catalysts facilitates greatly the separation of the chiral products which are obtained in solution from the solid catalyst. After removal of the soluble product in solution, the polymeric catalyst should still possess catalytic activity and be reusable many times without requiring regeneration. In a preliminary experiment, we attempted repeated asymmetric ethylations of benzaldehyde in a batch system using a single loading of polymeric catalyst. Introduction and removal of toluene solutions including substrate and chiral product were performed via a syringe needle through rubber septa. As shown in Table IV, the optical yields that were obtained showed reproducible values through five successive runs.

One of the most attractive ways to carry out asymmetric synthesis using polymeric chiral catalysts may be to use a flow system in which the prochiral substrate is converted into a chiral product during its passage through a column filled with the insoluble catalyst[26] since a chiral product can be obtained continuously by this approach. Polymer **11** was chosen to test this concept. Diethylzinc and *p*-chlorobenzaldehyde were added slowly into an ice-cooled jacketed column containing insoluble polymer **11** pretreated with *p*-chlorobenzaldehyde as shown in Figure 2. A solution of the chiral product was eluted continuously in the flask at the bottom of the column. The procedure found to be most effective involves the slow addition of toluene solutions of *p*-chlorobenzaldehyde and diethylzinc in a 1:1.4 molar ratio. A column containing 5 mmol of the polymeric catalyst could produce about 90 mmol of (*S*)-1-(*p*-chlorophenyl)propanol with 94% ee in this continuous-flow system. In a small-scale experiment, 0.7 mmol of the polymeric catalyst also produced 58 mmol of the same product with 92% ee in this system.

Repeated use of the chiral catalyst in either a batch system or a continuous-flow system is realized only when the catalyst is insoluble. Particularly, insoluble polymeric

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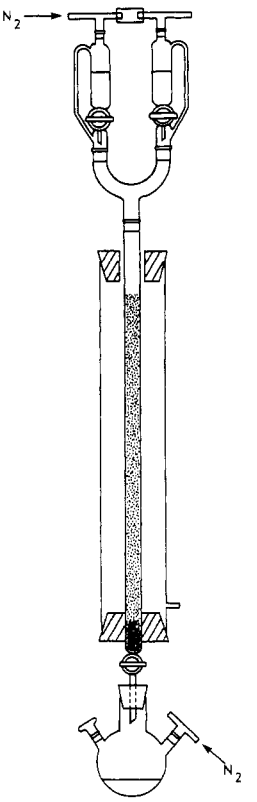

Figure 2.

catalysts seem well suited for the flow system since the swelled polystyrene which holds solvent as well as substrate and reagent offers a satisfactory reaction environment. The continuous-flow system is advantageous as it eliminates the need for stirring, which may cause destruction of the polymeric catalyst during repeated reactions.

Experimental Section

General. Optical rotations were measured on materials isolated by bulb-to-bulb distillation or column chromatography by using a JASCO DIP-140 digital polarimeter with the D line of a sodium lamp. NMR spectra were measured on a JEOL JNM-GX270 spectrometer in $CDCl_3$ solution unless otherwise noted, and the chemical shifts are reported in parts per million from a Me_4Si internal standard. Infrared spectra were recorded on a JASCO A-3 spectrometer. Melting points were determined on a Yanagimoto micro melting point apparatus. Capacities of the polymers determined by gravimetry, elemental analysis, and titrimetry are expressed in millimoles of functional groups per gram of dry resin (mmol/g) or as degree of functionalization (DF). The DF of a polystyrene-based reactive polymer is a measure of the proportion of aromatic styrene rings that carry the desired functionality. For example, DF = 0.30 if 30% of the styrene units are functionalized.

L-Phenylalanine, L-leucine, L-valine, and L-tyrosine were obtained from Kyowa Hakko Co. and used without further purification. All asymmetric alkylations were carried out in dry solvents under nitrogen. Diethylzinc and dimethylzinc were obtained from Toyo Stouffer Chemical Co. Styrene, divinylbenzene, α,α'-azobisisobutyronitrile (AIBN), sodium hydride (NaH), and tetraethylene glycol were obtained from Kanto Chemical Co. 4-Vinylbenzyl chloride (VBC) is a gift from Seimi Chemical Co.

Preparation of Chiral Amino Alcohols. Chiral amino alcohols **1**–**4** were prepared from the corresponding L-amino acids (L-phenylalanine, L-leucine, L-valine, and L-tyrosine) according to the routes described previously.[17]

Chiral monomer **5** was prepared from **4** and 4-vinylbenzyl chloride as described previously.[22]

Preparation of Chiral Polymers. Polymer 6. To a stirred solution of 6.39 g of **4** (20 mmol) in dry *N*-methylpyrrolidone

(NMP) was added 0.48 g (20 mmol) of NaH, and the resulting mixture was stirred until the evolution of hydrogen ceased. To the above reaction mixture was added 2.38 g of the chloromethylated polystyrene (4.2 mequiv of Cl/g), which was prepared from 2% cross-linked polystyrene as described in the literature.[27] The resulting mixture was stirred at room temperature for 45 h under nitrogen. The polymer was then filtered and washed repeatedly with methanol, water, THF–water (1:1), THF, and methanol. After drying in vacuo at 40 °C, 5.2 g of polymer was obtained. Nitrogen analysis indicated a loading of chiral amino alcohol corresponding to 1.92 mmol/g (DF = 0.55) while no chlorine remained on the polymer. IR (KBr): peaks absent at 1265 cm^{-1} for chloride precursor, peak present at 3400 cm^{-1} (br, OH). Anal. Calcd for $(C_8H_8)_{0.43}$·$(C_{30}H_{29}NO_2)_{0.55}$·$(C_{10}H_{10})_{0.02}$: C, 84.30; H, 6.88; N, 2.68. Found: C, 84.51; H, 6.70; N, 2.68.

Polymer 11. To a stirred solution of 1.0 g of poly(vinyl alcohol) in 250 mL of water was added a solution of 8.72 g of **5** (20 mmol), 14.58 g of styrene (0.14 mol), 5.21 g of DVB (40 mmol) and 0.66 g of AIBN in a mixed solvent of benzene (60 mL) and THF (60 mL) at 0 °C. After 1 h of stirring at 0 °C to homogenize the particle size, the temperature was raised to 75 °C and the reaction mixture was stirred vigorously for 32 h at the same temperature. The resulting polymer beads were filtered and washed with water, methanol, THF–methanol, THF, and methanol, respectively. After drying in vacuo at 40 °C, 28.40 g of polymer was obtained. Nitrogen analysis indicated a loading of chiral amino alcohol corresponding to 0.70 mmol/g (DF = 0.10): IR (KBr) 3400 cm^{-1} (OH). Anal. Calcd for $(C_8H_8)_{0.70}$·$(C_{30}H_{29}NO_2)_{0.10}$·$(C_{10}H_{10})_{0.20}$: C, 89.35; H, 7.42; N, 0.98. Found: C, 89.28; H, 7.45; N, 0.99.

Polymer 9. To a solution of 0.25 g of poly(vinyl alcohol) in 62.5 mL of water cooled to 0 °C was added a solution of 0.76 g (5 mmol) of VBC, 4.27 g (10 mmol) of **8**, 3.65 g (35 mmol) of styrene, and 0.16 g of AIBN in 15 mL of benzene and 5 mL of THF. The temperature was raised to 75 °C, and the reaction mixture was stirred for 24 h. After washing and drying as mentioned in the preparation of **11**, 8.25 g of polymer was obtained. Chlorine analysis by titrimetry[28] indicated a loading of chloromethyl group corresponding to 0.58 mmol/g (DF = 0.10): IR (KBr) 1265 (CCl) and 1100 cm^{-1} (COC). Anal. Calcd for $(C_8H_8)_{0.70}$·$(C_9H_9Cl)_{0.10}$·$(C_{26}H_{34}O_5)_{0.20}$: Cl, 2.05. Found: Cl, 2.04.

Polymer 10. Polymer **10** was prepared in 98% yield from 5.17 g (3 mequiv of Cl) of **9**, 1.92 g (6 mmol) of **5**, and 144 mg of NaH in NMP (30 mL) by the same method used in the preparation of **6**. Nitrogen analysis of polymer **10** indicated a loading of amino alcohol corresponding to 0.49 mmol/g (DF = 0.10) while no chlorine remained on the polymer. IR (KBr): peak absent at 1265 cm^{-1} for chloride precursor, peaks present at 3400 and 1100 cm^{-1}. Anal. Calcd for $(C_8H_8)_{0.70}$·$(C_{30}H_{29}NO_2)_{0.10}$·$(C_{26}H_{34}O_5)_{0.20}$: C, 82.15; H, 7.64; N, 0.69. Found: C, 82.20; H, 7.48; N, 0.68.

Polymer 12. Polymer **12** was prepared in 90% yield from 8.72 g of **5** (20 mmol), 14.58 g of styrene (140 mmol), 17.06 g of **8** (40 mmol), and 0.66 g (4 mmol) of AIBN in benzene (60 mL) and THF (40 mL) according to the procedure for the preparation of **11**. Nitrogen analysis of **12** indicated a loading of amino alcohol corresponding to 0.49 mmol/g (DF = 0.10); IR (KBr) spectrum identical with that of **10**. Anal. Calcd for $(C_8H_8)_{0.70}$·$(C_{30}H_{29}NO_2)_{0.10}$·$(C_{26}H_{34}O_5)_{0.20}$: C, 82.15; H, 7.64; N, 0.69. Found: C, 82.10; H, 7.58; N, 0.69.

Preparation of the Cross-Linking Agent 8 Containing Tetraethylene Glycol. A mixture of 3.88 g (20 mmol) of tetraethylene glycol and NaH (1.1 g, 46 mmol) in 40 mL of dry dimethylformamide (DMF) was stirred at room temperature for 1 h. After the addition of a DMF solution of 4-vinylbenzyl chloride (7.05 g, 46 mmol), the mixture was stirred at room temperature for 24 h. Workup was effected by addition of water (20 mL) to the reaction mixture. After removal of DMF by distillation under reduced pressure at 50 °C, the water layer was extracted with ether (3 × 50 mL) and the extract was washed several times with water; the ethereal extracts were dried over $MgSO_4$ and concentrated to afford a product, which was purified by column chromatography using chloroform as eluent to afford a viscous liquid of the pure **8** (6.9 g, 81%): ^1H NMR 3.63 (br, 16 H), 4.52 (s, 4 H), 5.21 (d, 2 H), 5.71 (d, 2 H), 6.67 (dd, 2 H), 7.27 (d, 4 H), 7.36 (d, 4 H); IR (KBr) 1630 (C=C) and 1100 cm^{-1} (COC). Anal. Calcd for $C_{26}H_{34}O_5$: C, 73.21; H, 8.03. Found: C, 73.18; H, 8.05.

Asymmetric Alkylation of Benzaldehyde. (i) Method A. To a toluene solution of 152 mg (0.5 mmol) of **1** was added a 1 M hexane solution of diethylzinc (15 mL, 15 mmol) at 0 °C, and the resulting solution was stirred at 0 °C for 1 h. A toluene solution of 1.06 g (10 mmol) of benzaldehyde was then added dropwise, and the mixture was stirred at 0 °C for 6 h. Workup was effected by addition of water and 1 N HCl. The precipitated hydrochloride of **1** was separated by filtration, and the organic layer of the filtrate was separated. The aqueous layer was then extracted with ether. The combined organic layers were dried on $MgSO_4$ and concentrated to afford the product, which was purified by column chromatography to afford 1-phenylpropanol (1.17 g, 86% yield) with $[\alpha]^{22}_D$ −6.40° (neat), 22% ee based on the maximum reported rotation $[\alpha]^{22}_{D,max}$ 28.1° (neat).[29]

(ii) Method B. A mixture of 1.06 g (10 mmol) of benzaldehyde and 152 mg (0.5 mmol) of **1** was stirred in dry toluene for 15 h under nitrogen atmosphere to form the chiral Schiff base. A hexane solution of diethylzinc (1 M, 15 mL) was added at 0 °C, and the resulting mixture was stirred for 6 h and then quenched by addition of 1 N HCl. After removal of the hydrochloride of **1** by filtration, the usual extractive workup gave 1-phenylpropanol (1.22 g, 90% yield) with $[\alpha]^{22}_D$ −23.89° (neat) for 85% ee.[29]

(iii) Method C. A mixture of 1.0 g of **1** (3.3 mmol) and 0.5 mL of benzaldehyde (4.91 mmol) was stirred at room temperature for 15 h. Freeze-drying of the above mixture gave a white powder of **1s** and **1o**. To a toluene solution of 196 mg (0.5 mmol) of the white powder were added 1.06 g of benzaldehyde (10 mmol) and a 1 M hexane solution of diethylzinc (15 mL, 15 mmol) at 0 °C. After 6 h, the usual extractive workup gave 1-phenylpropanol (1.25 g, 92% yield) with $[\alpha]^{22}_D$ −23.69° (neat) for 84% ee.[29]

Asymmetric Ethylation of Benzaldehyde Using Chiral Polymer 11. A mixture of 1.06 g of benzaldehyde (10 mmol) and 0.71 g of chiral polymer **11** (0.70 mequiv of amino alcohol/g) was stirred in dry toluene (10 mL) for 15 h under a dry nitrogen atmosphere to form the chiral Schiff base. A hexane solution of diethylzinc (1 M, 15 mL) was added at 0 °C, and then the mixture was stirred slowly for 24 h. A 1 N HCl solution was then added dropwise to the reaction mixture at 0 °C, and the chiral polymer was removed by filtration. The polymer was then washed several times with water and ether. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford a product, which was purified by column chromatography (chloroform as eluent), to afford 1-phenylpropanol (1.19 g, 92%). The optical rotation was measured for the sample purified by bulb-to-bulb distillation, $[\alpha]^{22}_D$ −23.63° (neat) for 84% ee.[29]

Asymmetric Ethylation of *p*-Chlorobenzaldehyde in a Continuous-Flow system. A suspension of polymer **11** (5 mmol) in toluene (70 mL) was treated with 3.52 g of *p*-chlorobenzaldehyde (25 mmol) at room temperature for 15 h. The polymer was filtered and washed with dry toluene and resuspended in toluene. A glass column (15 mm × 700 mm) covered by an ice–water jacket (45 mm × 600 mm) was filled with the polymer. Solutions of *p*-chlorobenzaldehyde (0.5 M in toluene) and diethylzinc (0.7 M in toluene) were added dropwise slowly from the dropping funnels fixed on the top of the column as shown in Figure 2. After 200 mL of *p*-chlorobenzaldehyde solution was added to the column, the usual workup of the solution obtained in the receiver flask afforded 15.36 g (90 mmol) of 1-(*p*-chlorophenyl)propanol with $[\alpha]^{22}_D$ −22.81° (*c* 5.585, C_6H_6) for 94% ee.

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