High Catalytic Activity of Chiral Amino Alcohol Ligands Anchored to Polystyrene Resins

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Enantiomerically pure (2*S*,3*S*)-2,3-epoxy-3-phenylpropanol (**3**) has been anchored to Merrifield resins with different degrees of cross-linking and functionalization. The resulting epoxy-functionalized resins **4** have been submitted to completely regioselective (C-3 attack) and stereospecific ring-opening with secondary amines [piperidine (**a**), *N*-methylpiperazine (**b**), and *cis*-2,6-dimethylpiperidine (**c**)] in the presence of lithium perchlorate to afford (2*R*,3*R*)-3-(dialkylamino)-2-hydroxy-3-phenylpropoxy resin ethers **5a**−**c**. The progress of these two processes has been monitored by ^{13}C gel-phase NMR spectroscopy. Polymer-supported amino alcohols **5a**−**c** have been evaluated as catalytic ligands in the enantioselective addition of diethylzinc to benzaldehyde, best results being obtained with the *cis*-2,6-dimethylpiperidine containing ligand **5c**. Analogously, (2*R*,3*R*)-3-(*cis*-2,6-dimethylpiperidino)-3-phenyl-1,2-propanediol (**11**) has been anchored to a 2-chlorotrityl chloride resin (Barlos resin) in dichloromethane in the presence of diisopropylethylamine, and the anchoring process has been also monitored by ^{13}C gel-phase NMR spectroscopy. The resulting resin **12** has subsequently been used as a chiral ligand in the catalytic addition at 0 °C of diethylzinc to a family of fourteen representative aromatic and aliphatic aldehydes **8a**−**n**, to afford the corresponding (*S*)-1-substituted 1-propanols **10a**−**n** with a mean enantiomeric excess of 92%.

Introduction

The strategy of attaching a chiral ligand onto a polymer support offers several advantages in catalytic asymmetric synthesis over the use of the same ligand in solution. These advantages include the easy recovery and potential recycling of the chiral catalyst, a highly simplified product purification, and the possibility of carrying out the desired transformation in continuous mode in a flow reactor. According to this, many examples of asymmetric catalysts that employ polymer bound chiral ligands have been reported.[1−5]

Chiral 1,2-amino alcohols have been attached to polymers and subsequently used to catalyze the enantioselective addition of organozinc derivatives to aldehydes in a heterogeneous system[6−19] or even in a continuous reactor.[20] Although some of these heterogeneous catalysts induce the addition of diethylzinc to different aldehydes with notable results, their catalytic activity (turnover number) and enantioselectivity (enantiomeric excess of the resulting alcohols) are consistently lower than those recorded with their homogeneous counterparts. Thus, continuation of efforts in this area, aimed to narrow the gap between the homogeneous and heterogeneous approaches, is fully warranted.

We have recently described the synthesis of a family of enantiomerically pure (1*R*,2*R*)-1-(dialkylamino)-1-phenyl-3-(R-oxy)-2-propanols **1** from a readily available enantiopure building-block.[21] An iterative process, aimed at the fine-tuning of their catalytic properties in the enantioselective addition of diethylzinc to benzaldehyde, allowed the identification of structural features key to high catalytic activity and enantioselectivity. These turned out to be the presence of a bulky protecting group and choice of the dialkylamino substituent as a nitrogen-

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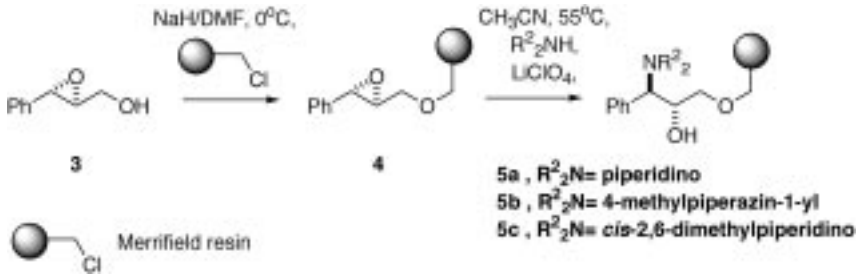
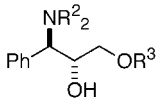
Scheme 1



containing six-membered ring.[21] Compounds **2a**,**b** arose from this process as those possessing the optimal structural features. A subsequent molecular modeling study led to the design and synthesis of ligand **2c** containing the *cis*-2,6-dimethylpiperidino residue,[22] which plays the role of increasing the energy gap (with respect to **2a**) among the diastereomeric transition states leading to the *S* and *R* enantiomers of 1-phenyl-1-propanol. In full agreement with theoretical predictions, ligand **2c** induced high enantioselectivity in the addition of diethylzinc to a broad range of aromatic and aliphatic aldehydes.

With the aim of incorporating the advantages of heterogeneous catalysis onto ligands **2**, we planned anchoring them to polymers possessing a benzylic functionalization through the primary hydroxyl group. As a leading principle, we considered that the polymer body would behave as a very bulky substituent, thus fulfilling the structural requirement for high enantioselectivity we had previously optimized. We report in the present paper the anchoring of ligands **2** to chloromethyl- (Merrifield) and to chloro-(2-chloro)trityl-substituted (Barlos) polymer backbones, and the catalytic properties of the resulting functionalized resins in the enantioselective addition of diethylzinc to aldehydes.



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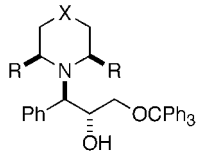

2a (X=CH_2, R=H)
2b (X=NMe, R=H)
2c (X=CH_2, R=Me)

Results and Discussion

Attachment of the (2*R*,3*R*)-3-(Dialkylamino)-2-hydroxy-3-phenylpropoxy Moiety to Merrifield Resins. Our first choice for a polymer backbone was the widely used Merrifield resin (chloromethylated styrene−divinylbenzene copolymer), since the chloromethyl groups contained in its structure provide a convenient means by which to tether the ligand to the solid support. In fact, Leznoff has reported the *O*-linkage of related molecules to such polymers.[23] Moreover, as far as the choice of support is concerned, the Merrifield resin seemed to be appropriate for our purposes, as it forms gels which swell and become highly solvated in organic solvents of intermediate polarity[24,25] such as dichloromethane, dimethylformamide, and toluene. The last one is a suitable solvent to use when testing the catalytic properties of chiral amino alcohols in the enantioselective addition of diethylzinc to aldehydes.

The linkage of the (2*R*,3*R*)-3-(dialkylamino)-2-hydroxy-3-phenylpropoxy moiety to the Merrifield resins was achieved in two steps from enantiopure epoxy alcohol **3**,[26] using as a relay the epoxy-functionalized resin **4**, as indicated in Scheme 1. It is worth noting that this scheme is characterized by a high versatility, since many different ligands **5** are available from a single resin **4** by simple variation of the secondary amine used in the ring-opening process. A range of Merrifield resins with different initial levels of functionalization (1.2−3.5 mmol of active chloride per gram of resin) and cross linkage (1−2% divinylbenzene) was used in order to test the effect of these parameters on the catalytic properties of the final resins.

Epoxy alcohol **3** was first deprotonated with an excess of sodium hydride at 0 °C under nitrogen in DMF, and the resulting alkoxide was allowed to react with the Merrifield resins in DMF at 0 °C under N_2 for 48 h.[27] The progress of the coupling reactions could be efficiently monitored by ^{13}C gel-phase NMR.[28] This simple technique, which can be run on a regular NMR spectrometer and has been widely used in solid-phase synthesis,[29−31] affords a direct measure of the incorporation of ligand into the polymer, thus allowing a fast optimization of reaction conditions. We have represented in Figure 1 the ^{13}C gel-phase NMR spectrum of one of the starting Merrifield resins (2% DVB, $f_o = 3.5$) (a), along with the spectrum recorded at room temperature (b) and at 50 °C (c) of the same resin at the end of the anchoring process. For comparison purposes, the solution ^{13}C NMR spectrum of the closely related monomeric ether **6** has also been included in this figure (d). The chloromethyl carbon

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(27) These reaction conditions (HNa/DMF/0 °C) were analogous to those employed for the model transformation in solution (the reaction of **3** with benzyl chloride), which furnished the corresponding benzyl-protected epoxy alcohol **6** in very high yield.
(28) The final resins gave poor quality gel phase ^1H NMR spectra, rendering this technique unsuccessful in monitoring reaction progress. In addition, the final resins were also studied by magic angle spinning (MAS) NMR; in the resulting spectra, the chain signals were quite broad and overlapped significantly with the resin backbone signals. The results of this study will be reported in due course.
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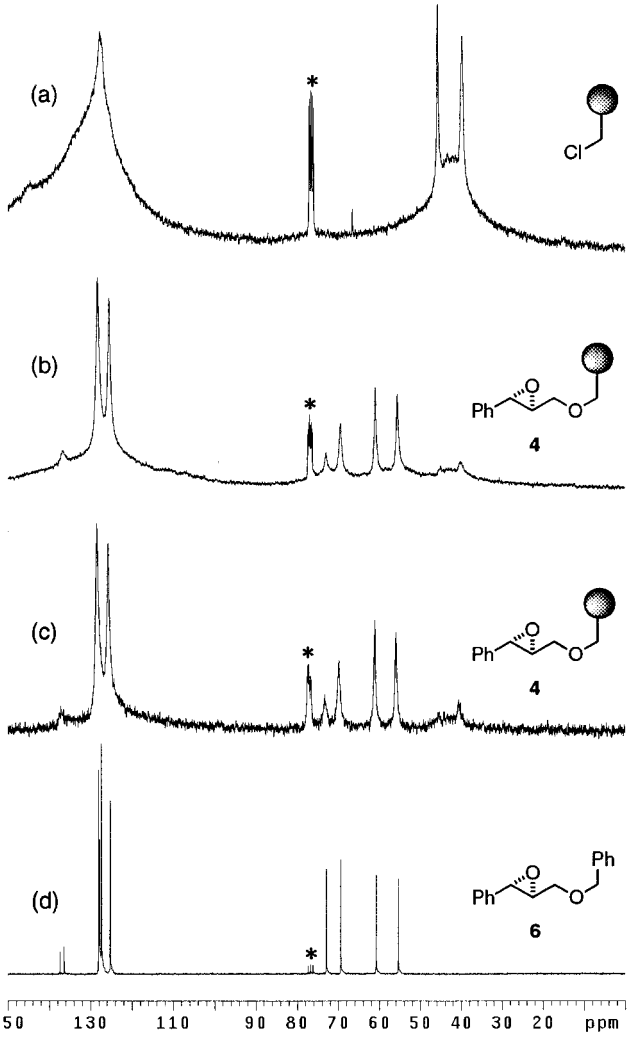
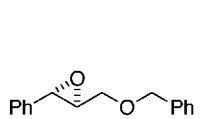


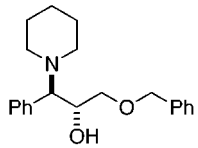
Figure 1. ^{13}C gel-phase NMR spectra of modified polystyrene-2%-*co*-divinylbenzene in $CDCl_3$ at 75.4 MHz (solvent peaks are marked with an asterisk): (a) Merrifield resin: 3.5 mmol of chlorine per gram of resin, 1.5 Hz line broadening, room temperature. (b) Epoxy alcohol bound polymer, 1.5 Hz line broadening, room temperature. (c) Epoxy alcohol bound polymer, 1.5 Hz line broadening, 50 °C. (d) Model compound (**6**) in solution.

signal in the starting resin appears in the ^{13}C gel-phase NMR spectrum at 46.3 ppm.[29] Once the reaction is complete (48 h), this signal has completely disappeared, and four new broad resonances attributed to the 2,3-epoxy-3-phenylpropoxymethyl aliphatic skeleton have appeared at 73.1, 69.7, 60.9, and 55.8 ppm. It is worth pointing out that these chemical shifts are fully coincident with the ones observed in solution for the model compound **6**. The important line broadening (line widths at half-height ranged from 39 to 117 Hz) observed in the gel-phase experiment at room temperature, which can be attributed to chemical shift anisotropy and restricted mobility of the chains,[32] could be partially mitigated by recording the spectrum at 50 °C. Under these conditions, slightly sharper signals (half-height line widths ranged between 35 and 69 Hz) were observed.

The 2,3-epoxy-3-phenylpropoxymethyl functionalized resins **4** were subsequently submitted to ring-opening with a family of six-membered ring cyclic amines: piperidine, *N*-methylpiperazine, and *cis*-2,6-dimethylpiperidine, to afford the functionalized resins **5a**−**c**. The amines employed are those which provided the highest catalytic activity in the original monomeric ligands.[21,22] Crotti's method, which involves the use of a large excess of nucleophile in a 5−10 M solution of lithium perchlorate in acetonitrile (55 °C) and greatly favors attack of nucleophile at the benzylic position, was used for the reactions.[33−38] Under these conditions, the ring-opening of the monomeric benzylated epoxy alcohol **6** proceeds with complete regio- and stereoespecificity, the only isolated product being the one arising from attack at C-3 (**7**).



6



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The ring-opening reaction of the epoxide-functionalized resins with secondary amines was again monitored by ^{13}C NMR gel-phase spectroscopy. In this way, it could be easily established that the reaction takes place by regioselective attack at the benzylic position. Also in this case, the ^{13}C chemical shifts of the (2*R*,3*R*)-3-(dialkylamino)-3-phenyl-2-hydroxypropoxy skeleton in the functionalized polymers were closely similar to those observed in solution for the analogous ligand **7** (Figure 2). In the case of ligand **5a**, for instance, line widths ranged from 14.5 to 206 Hz at room temperature. As line widths are sensitive to the nucleus mobility, it is worth mentioning that the closer the nucleus is to the anchoring point, the broader the corresponding signal. Peaks around 73 ppm (corresponding to CH_2 according to DEPT assignment in the model compound in solution) are the broadest (line width of 206 Hz for two overlapped broad signals), suggesting that they are due to carbons in the neighborhood of the polymer backbone. As expected, peaks at 71.6 ppm (line width 34.1 Hz) and 68.2 ppm (line width 32.3 Hz), which correspond to methine carbons further away from the support, are not as broad. Next, the signals at 51.7 ppm (line width 22 Hz), 26.1 ppm (line width 13.4 Hz) and 24.4 ppm (line width 14.5 Hz) corresponding to the remote piperidine ring, are sharper than those arising from the propoxymethyl chain, thus reflecting that these carbons are further away from the polymer skeleton. Finally, the sharpest signals are those due to the phenyl groups, appearing together with the aromatic hump which can be attributed to the polymer. As can be seen from the examples described above, the relative distance of a carbon from the support (an indication of its mobility)

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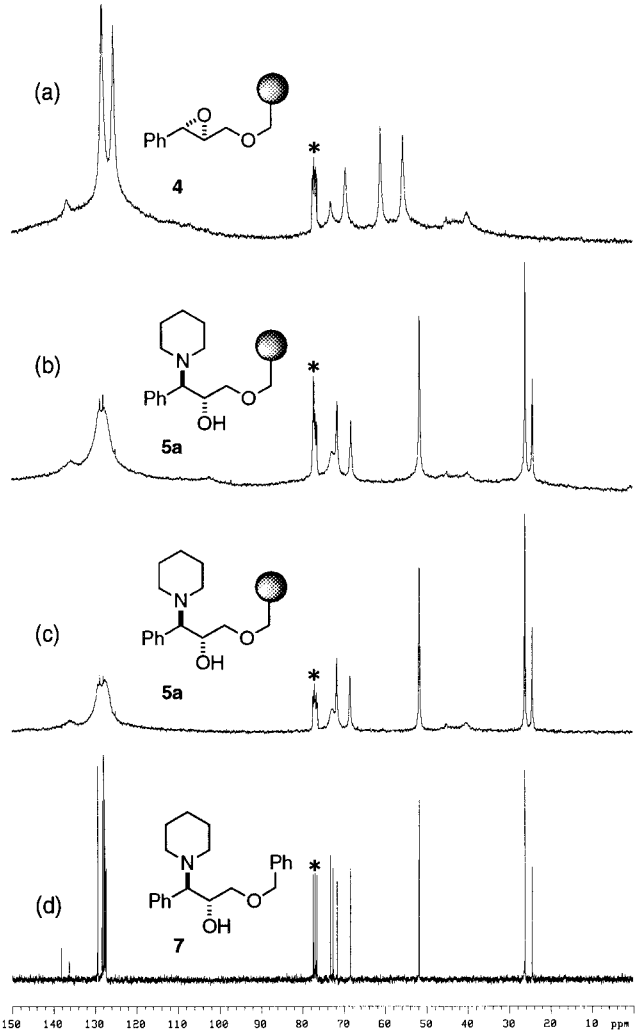


Figure 2. ^{13}C gel-phase NMR spectra of modified polystyrene-2%-*co*-divinylbenzene in $CDCl_3$ at 75.4 MHz (solvent peaks are marked with an asterisk): (a) Starting material in the regioselective ring-opening step, 1.5 Hz line broadening, room temperature. (b) Amino alcohol bound polymer, 1.5 Hz line broadening, room temperature. (c) Amino alcohol bound polymer, 1.5 Hz line broadening, 50 °C. (d) Model compound (**7**) in solution.

is a valuable parameter for peak assignment in ^{13}C gel-phase NMR spectra.

Determination of the level of functionalization of the final resins **5a**−**c** was relatively simple. As neither the starting Merrifield resin nor the intermediate 2,3-epoxy-3-phenylpropoxymethyl-functionalized polymer contain nitrogen atoms, an analytical determination for this element should provide the level of functionalization in the final resins. According to elemental analysis data, the content of amino alcohol units in the final polymers are very close (within experimental error) to the maximum value which can be calculated from the initial ligand substitution level (cf. Table 1). This result indicates that the ring-opening process of epoxides grafted onto the polymer backbone is taking place with high efficiency under Crotti's conditions. This interesting observation, that could be of great value for the preparation of other amino alcohol functionalized resins, is confirmed by ^{13}C gel-phase NMR, since no residual signals corresponding to **4** can be observed in the final products **5**.

Table 1. Ligand Anchorind to Merrifield Resins

starting Merrifield resin		functionalized resins					
		5a		**5b**		**5c**	
DVB (%)	f_o[a]	f[b]	f_{max}[c]	f[d]	f_{max}[c]	f[b]	f_{max}[c]
1	1.2	0.8	1.0	0.9	1.0	1.0	1.0
2	2.3	1.6	1.6	1.6	1.5	1.6	1.5
2	3.5	1.8	2.1	1.7	2.0	1.7	2.0

[a] f_o = mmol Cl/g resin (initial substitution level). [b] f = mmol ligand/g resin (calculated by elemental analysis of nitrogen with the following formula: $f = 0.714\%$ N). [c] f_{max} = maximum ligand substitution level (mmol ligand/g resin), calculated with the following formula:

$$f_{max} = \frac{f_o}{1 + f_o\frac{MW - 35.45}{1000}}$$

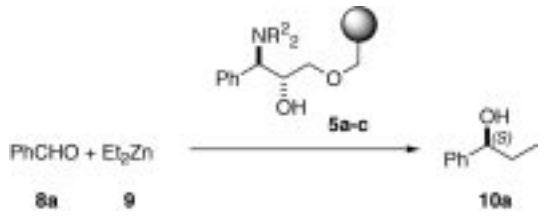
Where f_o is the initial substitution level and MW is the molecular weight of the anchored group. It is implicit in this formula that both the anchoring and ring opening steps are taking place quantitatively. [d] f = mmol ligand/g resin (calculated by elemental analysis of nitrogen with the following formula: $f = 0.357\%$ N).

Table 2. Catalytic Behavior of the Resin-Anchored Ligands 5a−c in the Addition of Et_2Zn to Benzaldehyde[a]

ligand (%DVB; f)	amount (%)[b]	ee of resulting alcohol (%)
5a (1; 0.8)	5	36
5a (2; 1.6)	4	22
5a (2; 1.8)	3	20
5b (1; 0.9)	5	39
5b (2; 1.6)	4	20
5b (2; 1.7)	3	19
5c (1; 1.0)	3	69[c]
5c (2; 1.6)	4	57
5c (2; 1.7)	3	57

[a] All reactions were performed in toluene at room temperature for 24 h using a Et_2Zn/PhCHO molar ratio of 2/1. Conversions were higher than 95% in all cases (determined by GC). [b] Amount of catalyst (% molar with respect to benzaldehyde). [c] Mean of two experiments.

Scheme 2



Catalytic Properties of the Amino Alcohol Substituted Merrifield Resins in the Enantioselective Addition of Diethylzinc to Benzaldehyde. All the modified resins **5a**−**c** which, for a given amino alcohol residue, include different levels of cross-linking and ligand functionalization, were tested in the addition reaction of diethylzinc to benzaldehyde (Scheme 2) to determine how these factors affect the catalytic properties of the resin. The results are summarized in Table 2.

The addition reaction of Et_2Zn to benzaldehyde was studied at room temperature in toluene and using a 3−5% molar amount of ligand as indicated in Table 2. All the substituted resins promoted the enantioselective addition of diethylzinc to benzaldehyde, but with enantioselectivities significantly lower than those observed with the related homogeneous ligands.[21,22] The predominant enantiomer of 1-phenylpropanol (**10a**) formed in the reactions possessed the *S* configuration, in full agreement with the empirical model established by Noyori.[39] Con-

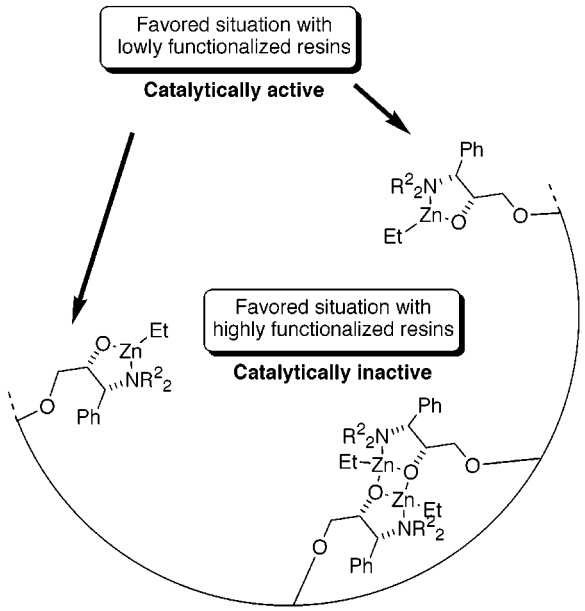
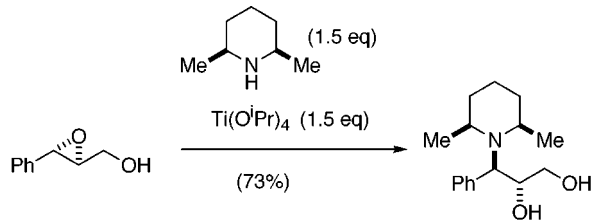


Figure 3.

sistently with the results obtained in solution, for a given level of cross-linking and similar functionalization, the most efficient resin was the one bearing a *cis*-2,6-dimethylpiperidino residue **5c**. In the present case, however, the influence of the dialkylamino moiety on the catalytic activity is much higher than in solution, and the resins containing other amino residues, **5a** and **5b**, provided only mediocre results. An important observation arises when resins containing the same 3-(dialkylamino)-2-hydroxy-3-phenylpropoxy residue, but variable degrees of cross-linking and functionalization, are compared. In all cases, *the best result was obtained with the polymeric ligand arising from chloromethylated polystyrene−1%-co-divinylbenzene with an initial substitution level of 1.2 mmol of chlorine per gram of resin*. For **5c** with these specifications, the addition of diethylzinc to benzaldehyde took place with 69% enantioselectivity. An explanation to this behavior could be as follows: As the amino alcohol residues are increasingly diluted over the polymer backbone, the formation of dimeric zinc alkoxides becomes less favorable (Figure 3). According to the commonly accepted mechanism for the amino alcohol-promoted catalytic addition of Et_2Zn to aldehydes,[40] these dimeric species are catalytically inactive, requiring dissociation as a preliminary step to catalysis.[41] As a consequence, if a ligand for the enantioselective addition of diethylzinc to aldehydes is to be anchored to a solid support, it is advisable to use a low functionalized resin in order to favor a maximal concentration of monomeric zinc alkoxide species and, hence, a maximal catalytic activity.

Preparation and Catalytic Properties of Modified Barlos Resins in the Enantioselective Addition of Diethylzinc to Benzaldehyde. The results obtained

Scheme 3



3 **11**

with the optimal amino alcohol bound Merrifield resin (69% ee with benzaldehyde using **5c**, compared with 95% ee for the same reaction in solution with ligand **2c**), suggested that the polystyrene skeleton was perhaps not behaving as a sufficiently bulky substituent for the primary hydroxy group in our amino diol ligands. This suggestion was based on the consistent observation that in solution, for ligands containing the same amino residue, the induced enantioselectivity increases with the bulk of the R-oxy group. In an attempt to circumvent this difficulty, we considered the possibility of anchoring our amino alcohol optimized ligand to commercial 2-chlorotrityl chloride resin (Barlos resin).[42] This polymer, which is increasingly considered as a convenient support in solid-phase synthesis,[43] possesses essentially the same backbone as the Merrifield resin (polystyrene−1%-*co*-divinylbenzene) except for a 2-chlorotrityl chloride anchor instead of a chloromethyl one. If the 3-amino 1,2-diol **11** could be attached by the primary hydroxyl group to the 2-chlorotrityl anchor, the resulting polymer supported ligand would have a very similar steric and electronic environment in the resin as it has in the structure **2c**. The anchoring reaction of **11** should proceed in a chemoselective way according to literature precedents, as secondary hydroxyl groups react very slowly with trityl halides.[44]

Amino diol **11** was prepared by regio- and stereoselective ring-opening of enantiopure epoxy alcohol **3** by *cis*-2,6-dimethylpiperidine in the presence of titanium tetraisopropoxide (Scheme 3).[21,45,46] The reaction proceeded smoothly at room temperature, amino diol **11** being formed in 73% yield.

Two different reaction conditions were used to attach **11** to the 2-chlorotrityl chloride anchor in the Barlos resin: pyridine in a 1:1 mixture of DMF/CH_2Cl_2,[43] and diisopropylethylamine (DIEA) in CH_2Cl_2.[42] In both cases, an excess of nucleophile (the primary hydroxyl group in **11**) and base are required; Table 3 shows the various reaction conditions tested. The degree of anchoring of **11** in the resulting resins **12** was best established by nitrogen elemental analysis. The highest degree of anchoring (1.2 mmol of ligand per gram of resin, entry III) was achieved with the reaction conditions which involve the use of a large excess of nucleophile and a long reaction time. However, the much milder conditions used in entry II yielded a resin with almost the same degree

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(41) In situations where the dimeric zinc alkoxide predominates, the background, noncatalyzed addition becomes important. In fact, we have seen that the noncatalyzed addition of Et_2Zn (0.56 M) to benzaldehyde (0.22 M) in toluene/hexane (2: 2.5) takes place to a 23% extent at room temperature after 24 h.
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Table 3. Preparation of Functionalized Tritylated Resins Starting from Barlos resin[a]

entry	base/solvent	molar ratio active Cl^- positions:amino diol:base	reactn time (h)	*f* (mmol) ligand/g resin)[b]
I	py/CH_2Cl_2:DMF (1:1)	1:2.2:4.8	96	0.9
II	DIEA/CH_2Cl_2	1:1.4:2.1	24	1.1
III	DIEA/CH_2Cl_2	1:2:3	96	1.2

[a] Polystyrene−1%-*co*-divinylbenzene. Specification of the resin: 1.34 mmol labile Cl/g of resin. [b] Determined by elemental analysis of nitrogen.

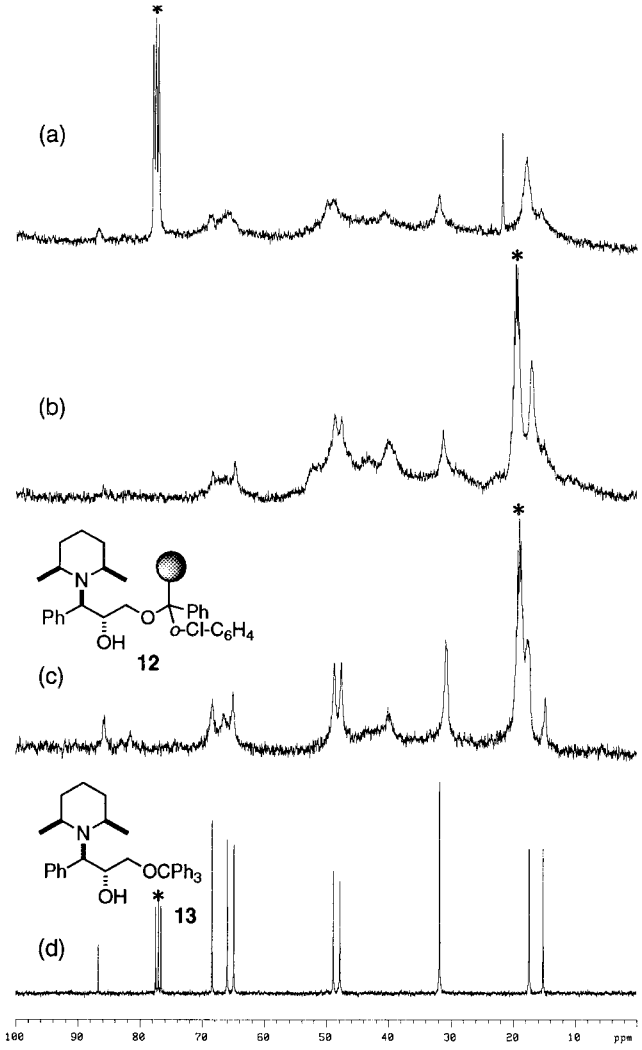


Figure 4. ^{13}C gel-phase NMR spectra of modified Barlos resin (*o*-chlorotritylated polystyrene-1%-*co*-divinylbenzene) at 75.4 MHz (solvent peaks are marked with an asterisk): (a) Modified Barlos resin **12**: $CDCl_3$, 3 Hz line broadening, room temperature. (b) Modified Barlos resin **12**: toluene-d_8, 3 Hz line broadening, room temperature. (c) Modified Barlos resin **12**: toluene-d_8, 3 Hz line broadening, 80 °C. (d) Model compound (**13**) in solution.

of anchoring. On the other hand, the use of pyridine as the base was not as effective in catalyzing the coupling, since even after 4 days the degree of functionalization was lower than that obtained with Hünig's base under the milder conditions in entry II.

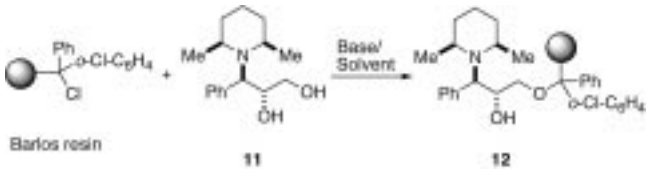
The final resins were characterized by ^{13}C gel-phase NMR spectroscopy. With this technique, the correct number of signals for the aliphatic backbone of the amino alcohol substituent were observed at chemical shifts

Table 4. Catalytic Properties of Functionalized Tritylated Resins in the Amino Alcohol Promoted Addition of Diethylzinc to Benzaldehyde[a]

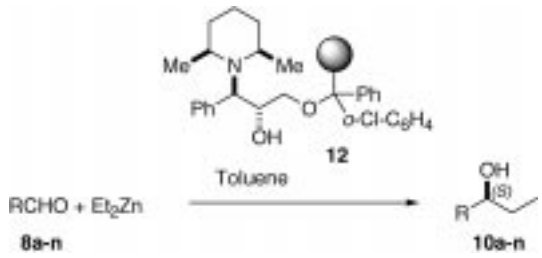
entry	*f* (mmol ligand/ g of resin)	% molar ligand	temp, °C	ee (%)[b]	config[c]
I	0.9	4	rt	79	*S*
II	1.1	5	rt	92	*S*
III	1.1	5	0	93	*S*
IV	1.2	5	0	94	*S*

[a] Resins prepared as described in Table 3. The polymer needs to be stirred smoothly in the appropriate solvent to swell properly prior to use. The resin was left to stir for 24 h in toluene before adding the aldehyde and Et_2Zn in molar ratio of 1:2. Stirring was further continued for 24 h in order to achieve conversions higher than 90% (determined by GC). [b] Enantiomeric excess in the resin promoted addition of diethylzinc to benzaldehyde (determined by GC: β-DEX 120 column). [c] Configuration of the addition product (1-phenylpropanol).

Scheme 4



Scheme 5



coincident with those for the model compound in solution, **13** (Figure 4). Signals in the Barlos modified resins were, however, much broader than those in the modified Merrifield. To increase chain mobility and consequently reduce line widths, the spectrum of this resin was recorded in toluene-d_8 at 80 °C.

Gratifyingly enough, when an amount of functionalized Barlos resin equivalent to 5% mol of amino alcohol units (f = 1.1 mmol ligand per gram of resin, entry II, Table 3) was used to catalytically induce the addition of Et_2Zn to benzaldehyde at room temperature, (*S*)-1-phenylpropanol **10a** of 92% ee was rapidly formed (Scheme 5, R=Ph). The recorded improvement in stereoselectivity was in full agreement with our expectations, as the steric and electronic environment of the anchored amino alcohol in the Barlos resin is very close to that in **2c**. A slight improvement in enantioselectivity (up to 93% ee) could be achieved by simply performing the reaction at 0 °C, and a further improvement (up to 94% ee) was recorded by using the more functionalized resin at 0 °C (entry IV, Table 4). According to these results, ligand **12** is of particular interest as it is placed at the top among the polymer-supported ligands suitable for the enantioselective addition of Et_2Zn to benzaldehyde. In effect, polymer-supported ligands have been reported to induce in this reaction enantioselectivities between 10 and 98%;[6−20] the selectivity displayed by **12** is therefore one of the highest reported in the literature. It is worth noting the small difference in the enantioselectivities recorded with the ligand in solution (97%) and with the immobilized one

Table 5. Catalytic Enantioselective Addition of Et_2Zn to Aldehydes[a] 8a−n Leading to Alcohols 10a−n[b] Mediated by Polymer-Supported Catalyst 12

starting aldehyde	resulting alcohol	conversion[c] (%)	selectivity[d] (%)	enant excess (%)[e] with **12**	enant excess (%)[e] with **2c**
Benzaldehyde (**8a**)	(*S*)-**10a**	99	98	94	97
o-Fluorobenzaldehyde (**8b**)	(*S*)-**10b**	96	96	88	
m-Fluorobenzaldehyde (**8c**)	(*S*)-**10c**	98	96	94	
p-Fluorobenzaldehyde (**8d**)	(*S*)-**10d**	>99	99	95	97
o-Tolualdehyde (**8e**)	(*S*)-**10e**	91	84	91	
m-Tolualdehyde (**8f**)	(*S*)-**10f**	93	94	94	
p-Tolualdehyde (**8g**)	(*S*)-**10g**	93	94	94	97
o-Methoxybenzaldehyde (**8h**)	(*S*)-**10h**	88	92	86	
m-Methoxybenzaldehyde (**8i**)	(*S*)-**10i**	>99	98	94	
p-Methoxybenzaldehyde (**8j**)	(*S*)-**10j**	86	95	94	98
1-Naphthaldehyde (**8k**)	(*S*)-**10k**	86	84	86	90
2-Naphthaldehyde (**8l**)	(*S*)-**10l**	82	75	90	
3-Cyclohexenecarbaldehyde (**8m**)	(*S*)-**10m**	86	90	98	
Isovaleraldehyde (**8n**)	(*S*)-**10n**	99	94	90	90

[a] The resin (1.2 mmol ligand/g resin) was left to stir 24 h in toluene to swell properly. A molar ratio of aldehyde, Et_2Zn and anchored ligand of 1:1.5:0.08 was used for **8b**−**n**. See text for **8a**. The mixture was stirred for 24 h at 0 °C after which it was quenched and analyzed. [b] The *S* enantiomer is preferentially obtained in all the cases. The absolute configuration has been established by comparing the sign of the optical rotation except for **10c**, **10i**, and **10m** in which the *S* configuration has been assumed. [c] Determined by integration of residual starting material in front of all new products in the gas chromatogram of the reaction crude. [d] Determined by integration of the addition products (both enantiomers) in front of other reaction products. [e] By GC using either a *β*-DEX 120 column (for **10a**−**m**) or a α-DEX 120 (for **10n**).

(94%), which suggests that although the ligand is anchored on an insoluble support, the chiral ligand chains possess the required mobility to provide the catalytic sites where the enantioselective reaction takes place. This is remarkable considering that most ligands suffer a significant drop in enantioselectivity when attached to a polymer support. Although the differences in functionalization between the prepared resins are small, the slightly better result (Table 4, entry IV) recorded with the most functionalized resin tends to indicate a different scenario with respect to the situation in Merrifield type resins. Most probably, the simple presence of the bulky trityl substituent is a sufficient condition to prevent the formation of dimeric species with ligands **2c** and **12**.[47]

From a practical point of view, it is worth mentioning that the resin could be simply recovered by quenching the reaction with satd NH_4Cl followed by filtration and reconditioning by washing with 5% aq HCl (to eliminate inorganic residues) and, immediately after the acidic treatment, washing with pH 9 phosphate buffer, water, methanol, and lastly toluene. After careful drying, it was reused, yielding the final alcohol **10a** with no decrease in enantioselectivity.

This highly active new functionalized resin was also studied in the addition of Et_2Zn to a set of 13 representative aldehydes **8b**−**n** including aliphatic ones (cyclic and acyclic), three complete sets of *ortho*-, *meta*-, and *para*-substituted aromatic aldehydes (including both electron-donating and electron-withdrawing substituents), and the naphthaldehydes (1- and 2-substituted). The results of these reactions have been summarized in Table 5, where the results obtained with the closely related homogeneous ligand **2c** have also been included for comparison purposes.

A first point that deserves a comment is the uniformly good performance of the anchored ligand **12** over the range of studied aldehydes. Thus, for the 14 studied aldehydes, the mean enantiomeric excess of the resulting alcohols is 92%, with a standard deviation of only 3.6% ee. Even more importantly, the mean difference in enantiomeric excess of the alcohols obtained with **12** and with its homogeneous counterpart **2c** for a common set of aldehydes is only of 2.6% ee. With respect to individual compounds, very high enantioselectivities were obtained with *para*-substituted benzaldehydes (94−95% ee), irrespective of the electronic nature of the substituent. In any case, and not unexpectedly, the most electron-deficient substrate is also the fastest-reacting one. A completely parallel behavior in reactivity can be found in the *ortho*-substituted benzaldehydes, although the enantioselectivity is slightly lower in this case (86−91% ee). For the less studied *meta*-substituted analogues, in turn, a uniformly high (94% ee) enantioselectivity was observed. For the bulky 1- and 2-naphthaldehydes, a slightly lower enantioselectivity (86−90%) was recorded, as well as for isovaleraldehyde (**8n**). The other aliphatic aldehyde tested (**8m**), however, provided the highest enantioselectivity in the series investigated.

Conclusions

In summary, we have succeeded in attaching (2*S*,3*S*)-2,3-epoxy-3-phenylpropanol to Merrifield resins. This chiral vector has allowed the anchoring of enantiomerically pure amino alcohols through the regio- and stereospecific oxirane ring-opening with secondary amines. From the analytical point of view, ^{13}C gel-phase NMR spectroscopy has proved to be very useful in the characterization of intermediates and final products in the solid phase synthesis. Given the ready availability of this analytical tool and the wide range of nucleophiles capable of reacting with oxiranes, the methodology reported in this paper could be a convenient vehicle for the controlled integration on such resins of many different nucleophile types through an enantiomerically pure handle.

The amino alcohol functionalized Merrifield resins have shown to possess catalytic activity in the enantioselective addition of diethylzinc to benzaldehyde. As observed for related ligands in solution, the *cis*-2,6-dimethylpiperidino fragment imparts to the functionalized resins the optimal catalytic properties and, for all

(47) NMR studies on the relative stability of dimeric zinc alkoxides provide support to this assumption. Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. Unpublished results.

the prepared ligands, the lower the functionalization/reticulation of the ligands, the higher the induced enantioselectivity. This represents a nice confirmation on the monomeric nature of the catalytically active species in this reaction.

In an attempt to further improve the catalytic performance of the resin-immobilized ligands, we have anchored (2*R*,3*R*)-3-(*cis*-2,6-dimethylpiperidino)-3-phenyl-1,2-propanediol to a 2-chlorotrityl chloride (Barlos) resin. The catalytic behavior exhibited by the resulting ligand **12** in the enantioselective addition of diethylzinc to a broad and representative family of aldehydes converts it in the most generally useful heterogeneous ligand for this chemistry ever reported. In light of the exceptional catalytic profile of **12**, we are currently applying this polymeric catalyst to other enantioselective processes catalyzed by amino alcohols.

Experimental Section

General. ^{1}H NMR and ^{13}C NMR spectra in solution were recorded in $CDCl_3$ at 300 and 75.4 MHz, respectively. The NMR gel samples were prepared as follows: the appropriate mass of resin was placed in a 5 mm NMR tube, and the same volume of solvent was added. When the solvent had been absorbed, small additional fractions of solvent were added to obtain a homogeneous gel. The so-prepared samples were allowed to stand for 8−12 h before recording the spectra. ^{13}C gel phase NMR spectra were recorded at 75.4 MHz in $CDCl_3$ or toluene-d_8. Standard conditions were used: 8.7 μs pulse width (the 90° pulse width was 10 μs), acquisition time 1.815 s, 0.2 s delay between pulses, and 1.5 or 3 Hz line broadening). Chemical shifts are quoted relative to solvent signals. Line widths at half-height have been determined using the standard spectrometer software and are given in parentheses. Elemental analyses were carried out by the "Servei d'Anàlisis Elementals del C.S.I.C. de Barcelona". Tungsten(VI) oxide was used in the resin analyses to ensure total combustion of the samples. (2*S*,3*S*)-2,3-Epoxy-3-phenylpropanol, **3**, was prepared according to the procedure described by Sharpless et al.[26] DMF and CH_2Cl_2 were distilled from CaH_2 and stored under N_2. Merrifield resins were commercially available.

Anchoring (2*S*,3*S*)-2,3-Epoxy-3-phenylpropanol to Merrifield Resins. Resin 4 (1% DVB, f_{max} = 1.1)[48] from Chloromethylated Polystyrene (1% DVB, f_o = 1.23). General Procedure. A solution of **3** (660 mg, 4.39 mmol) in DMF (15 mL) was added via cannula to a suspension of sodium hydride (175 mg, ca. 5.83 mmol) in DMF (20 mL) at 0 °C under N_2. The mixture was stirred for 20 min, quickly poured onto a suspension of the Merrifield resin (4.0 g, 4.9 mmol) in DMF (20 mL) at 0 °C, flushed with N_2, and smoothly stirred for 48 h at 0 °C. The functionalized resin was filtered, washed with dimethylformamide (4 × 10 mL) and dichloromethane (4 × 10 mL), and dried under vacuum to constant weight to afford 4.05 g (89% yield) of modified resin **4** (1% DVB, f_{max} = 1.1), which was used in the next step without further purification. ^{13}C gel-phase NMR (75 MHz, $CDCl_3$, 1.5 Hz line broadening) δ 73.2 (22), 69.6 (28), 61.2 (12) and 55.8 (16).[49]

Resin 4 (2% DVB, f_{max} = 1.8)[48] from Chloromethylated Polystyrene (2% DVB, f_o = 2.3). Compound **3** (1.52 g, 10.12 mmol) in DMF (15 mL), sodium hydride (405 mg, ca. 13.5 mmol) in DMF (10 mL), and polymer support (4.0 g, 9.2 mmol) in DMF (20 mL) were treated as described in the general procedure and stirred 24 h at 0 °C. The functionalized resin **4** (2% DVB, f_{max} = 1.8) (4.40 g; 87% yield) was used in the next step without further purification. ^{13}C gel-phase NMR (75 MHz, $CDCl_3$, 1.5 Hz line broadening) δ 73.1 (70), 69.6 (54), 61.0 (37), 55.7 (45).[49]

Resin 4 (2% DVB, f_{max} = 2.5)[48] from Chloromethylated Polystyrene (2% DVB, f_o = 3.5). Compound **3** (1.45 g, 9.65 mmol) in DMF (15 mL), sodium hydride (385 mg, ca. 12.83 mmol) in DMF (8 mL), and polymer support (2.5 g, 8.75 mmol) in DMF (15 mL) were treated as described in the general procedure and stirred 48 h at 0 °C. The functionalized resin **4** (2% DVB, f_{max} = 2.5) (3.21 g; 92% yield) was used in the next step without further purification. ^{13}C gel-phase NMR (75 MHz, $CDCl_3$, 1.5 Hz line broadening) δ 73.0 (117), 69.5 (66), 61.0 (39), 55.6 (51).[49]

Lithium Perchlorate Induced Regioselective Ring-Opening of Polymer Bound Epoxy Ethers by Secondary Amines. Resin 5a (1% DVB; f = 0.8) from Piperidine and 4 (1% DVB, f_{max} = 1.1). General Procedure. Piperidine (1.83 mL, 18.6 mmol) was added via syringe into a mixture of polymer bound epoxy ether **4** (620 mg, 0.67 mmol assuming 100% anchoring) and $LiClO_4$ (1.98 g, 18.6 mmol) in acetonitrile (3 mL) at 55 °C under N_2. After smooth magnetic stirring for 48 h at 55 °C, the functionalized resin was filtered, washed with dimethylformamide (2 × 10 mL), dimethylformamide: water 1:1 (4 × 10 mL), water (4 × 10 mL), methanol (4 × 10 mL), and toluene (4 × 10 mL), and dried under vacuum to constant weight to afford 630 mg (93% yield) of modified resin **5a** (1% DVB; f = 0.8): ^{13}C gel-phase NMR (75 MHz, $CDCl_3$, 1.5 Hz line broadening) δ 73.2 (72), 72.7 (86), 71.7 (14), 68.4 (16), 51.8 (11), 26.3 (7), 24.5 (7 Hz).[49] Anal. Calcd for f_{max}: N, 1.40. Found: N, 1.10.

Resin 5b (1% DVB; f = 0.9) from *N*-methylpiperazine and 4 (1% DVB, f_{max} = 1.1): *N*-Methylpiperazine (2.75 mL, 24.8 mmol), polymer bound epoxy ether **4** (650 mg, 0.70 mmol assuming 100% anchoring), $LiClO_4$ (2.64 g, 24.8 mmol), and acetonitrile (4 mL) were treated as described in the general procedure to afford 705 mg (98% yield) of modified resin **5b** (1% DVB; f = 0.9): ^{13}C gel-phase NMR (75 MHz, $CDCl_3$, 1.5 Hz line broadening) δ 73.2 (87), 72.5 (42), 71.1 (13), 68.2 (11), 55.3 (8), 50.6 (16), 45.8 (13 Hz).[49] Anal. Calcd for f_{max}: N, 2.80. Found: N, 2.42.

Resin 5c (1% DVB; f = 1.0) from *cis*-2,6-dimethylpiperidine and 4 (1% DVB, f_{max} = 1.1): *cis*-2,6-Dimethylpiperidine (2.49 mL, 18.6 mmol), polymer bound epoxy ether **4** (620 mg, 0.67 mmol assuming 100% anchoring), $LiClO_4$ (1.98 g, 18.6 mmol), and acetonitrile (3 mL) were treated as described in the general procedure to afford 660 mg (95% yield) of modified resin **5c** (1% DVB; f = 1.0): ^{13}C gel-phase NMR (75 MHz, $CDCl_3$, 1.5 Hz line broadening) δ 73.1 (55), 68.1 (14), 64.7 (11), 48.7 (27), 47.7 (28), 31.8 (12), 17.3 (14), 15.0 (10 Hz).[49] Anal. Calcd for f_{max}: N, 1.40. Found: N, 1.42.

Resin 5a (2% DVB; f = 1.6) from piperidine and 4 (2% DVB, f_{max} = 1.8): Piperidine (2.44 mL, 24.8 mmol), polymer bound epoxy ether **4** (650 mg, 1.18 mmol assuming 100% anchoring), $LiClO_4$ (2.64 g, 24.8 mmol), and acetonitrile (4 mL) were treated as described in the general procedure to afford 738 mg (98% yield) of modified resin **5a** (2% DVB; f = 1.6): ^{13}C gel-phase NMR (75 MHz, $CDCl_3$, 1.5 Hz line broadening) δ 72.7 (186), 71.6 (26), 68.2 (26), 51.6 (18), 26.1 (11), 24.4 (11 Hz).[49] Anal. Calcd for f_{max}: N, 2.24. Found: N, 2.31.

Resin 5b (2% DVB; f = 1.6) from *N*-methylpiperazine and 4 (2% DVB, f_{max} = 1.8): *N*-Methylpiperazine (2.75 mL, 24.8 mmol), polymer bound epoxy ether **4** (650 mg, 1.18 mmol assuming 100% anchoring), $LiClO_4$ (2.64 g, 24.8 mmol), and acetonitrile (4 mL) were treated as described in the general procedure to afford 760 mg (99% yield) of modified resin **5b** (2% DVB; f = 1.6): ^{13}C gel-phase NMR (75 MHz, $CDCl_3$, 1.5 Hz line broadening) δ 72.8 (107), 72.5 (101), 71.0 (22), 68.0 (24), 55.0 (15), 50.3 (27), 45.6 (29 Hz).[49] Anal. Anal. Calcd for f_{max}: N, 4.20. Found: N, 4.50.

Resin 5c (2% DVB; f = 1.6) from *cis*-2,6-dimethylpiperidine and 4 (2% DVB, f_{max} = 1.8): *cis*-2,6-Dimethylpiperidine (3.3 mL, 24.8 mmol), polymer bound epoxy ether **4** (650 mg, 1.18 mmol assuming 100% anchoring), $LiClO_4$ (2.64 g, 24.8 mmol), and acetonitrile (4 mL) were treated as described in the general procedure to afford 750 mg (96% yield) of modified resin **5c** (2% DVB; f = 1.6): ^{13}C gel-phase NMR (75 MHz,

(48) Maximum functionalization of the resin (mmol 2,3-epoxy-3-phenylpropoxy groups/g resin) calculated with the formula shown in Table 1.

(49) Phenyl group signals are not reported as they significantly overlap with the polymer peaks.

$CDCl_3$, 1.5 Hz line broadening) δ 72.8 (114), 68.0 (29), 64.6 (21), 48.4 (135), 47.7 (115), 31.7 (18), 17.2 (21), 14.9 (20 Hz).[49] Anal. Calcd for f_{max}: N, 2.10. Found: N, 2.18.

Resin 5a (2% DVB; $f = 1.8$) from piperidine and 4 (2% DVB, $f_{max} = 2.5$): Piperidine (3.1 mL, 31.0 mmol), polymer bound epoxy ether **4** (650 mg, 1.62 mmol assuming 100% anchoring), $LiClO_4$ (3.30 g, 31.0 mmol), and acetonitrile (5 mL) were treated as described in the general procedure to afford 714 mg (91% yield) of modified resin **5a** (2% DVB; $f = 1.8$). ^{13}C gel-phase NMR (75 MHz, $CDCl_3$, 1.5 Hz line broadening) δ 72.7 (206), 71.6 (34), 68.2 (32), 51.7 (22), 26.1 (13), 24.4 (14 Hz).[49] Anal. Calcd for f_{max}: N, 2.94. Found: N, 2.53.

Resin 5b (2% DVB; $f = 1.7$) from *N*-methylpiperazine and 4 (2% DVB, $f_{max} = 2.5$): *N*-Methylpiperazine (3.4 mL, 24.8 mmol), polymer bound epoxy ether **4** (650 mg, 1.62 mmol assuming 100% anchoring), $LiClO_4$ (3.30 g, 31.0 mmol), and acetonitrile (5 mL) were treated as described in the general procedure to afford 741 mg (91% yield) of modified resin **5b** (2% DVB; $f = 1.7$). ^{13}C gel-phase NMR (75 MHz, $CDCl_3$, 1.5 Hz line broadening) δ 72.6, 71.3, 68.1, 55.3, 50.6, 45.9, 21.4.[49] Anal. Calcd for f_{max}: N, 5.60. Found: N, 4.74.

Resin 5c (2% DVB; $f = 1.7$) from *cis*-2,6-dimethylpiperidine and 4 (2% DVB, $f_{max} = 2.5$): *cis*-2,6-Dimethylpiperidine (4.1 mL, 18.6 mmol), polymer bound epoxy ether **4** (650 mg, 1.62 mmol assuming 100% anchoring), $LiClO_4$ (3.30 g, 31.0 mmol), and acetonitrile (5 mL) were treated as described in the general procedure to afford 738 mg (88% yield) of modified resin **5c** (2% DVB; $f = 1.7$). ^{13}C gel-phase NMR (75 MHz, $CDCl_3$, 1.5 Hz line broadening) δ 73.2, 68.3, 64.9, 48.8, 48.0, 32.0, 21.5, 17.6, 15.3.[49] Anal. Calcd for f_{max}: N, 2.66. Found: N, 2.36.

Preparation of (2*R*,3*R*)-3-(*cis*-2,6-Dimethylpiperidino)-3-phenyl-1,2-propanediol. *cis*-2,6-Dimethylpiperidine (2.7 mL, 20.0 mmol) and $Ti(O^iPr)_4$ (5.9 mL, 20.0 mmol) were added to a solution of **3** (2.0 g, 13.3 mmol) in CH_2Cl_2 (50 mL) under N_2 at room temperature. After 14 h of stirring at room temperature, a 10% solution of NaOH in brine (25 mL) was added and vigorous stirring continued for a further 24 h. The mixture was filtered through Celite and the residue washed with CH_2Cl_2 (3 × 10 mL). The aqueous solution was extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic extracts dried and concentrated in vacuo. The residual oil was recrystallized from hexane:Et_2O 2:1 to give 2.45 g (73% yield) of **11**: mp 88 °C: $[\alpha]^{23}_D = -16.6$ ($c = 0.9$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.30−7.36 (m, 5H), 4.36 (ddd, 1H, $J = 7.5$, 6.0, and 6.0 Hz), 4.17 (br s, 1H, OH), 4.11 (d, 1H, $J = 7.5$ Hz), 3.46−3.58 (m, 2H), 2.78−2.98 (m, 2H), 2.61 (br s, 1H, OH), 1.23−1.69 (m, 6H), 1.16 (d, 3H, $J = 6.6$ Hz) and 1.15 (d, 3H, $J = 6.6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.8 (C), 129.4 (CH), 128.1 (CH), 127.5 (CH), 68.6 (CH), 66.85 (CH_2), 66.78 (CH), 51.7 (CH), 49.8 (CH), 33.1 (CH_2), 32.9 (CH_2), 20.2 (CH_3), 19.8 (CH_3) and 18.3 (CH_2); IR (KBr) 3401, 3083, 3064, 3021, 2985, 2964, 2933, 2867, 2848, 2821, 2796, 1148, 1115, 1079, 1028, 749, 706 cm^{-1}; MS (EI) *m*/*z* 263 (M^+, 0%), 202 ($M - C_2H_5O_2^+$, 100%). Anal. Calcd for $C_{16}H_{25}NO_2$: C, 72.97; H, 9.57; N, 5.32. Found: C, 73.06; H, 9.53; N, 5.21.

Anchoring of (2*R*,3*R*)-3-(*cis*-2,6-dimethylpiperidino)-3-phenyl-1,2-propanediol to a Barlos Resin (initial substitution level: 1.34 mmol Cl/g).

With diisopropylethylamine (DIEA) as the base: DIEA (345 μL, 1.98 mmol) was added via syringe into a mixture of **11** (350 mg, 1.33 mmol) and the resin (705 mg, 0.94 mmol of active Cl) in CH_2Cl_2 (7 mL) under N_2 at room temperature. After smooth magnetic stirring for 24 h at room temperature, the functionalized resin was filtered, washed with dimethylformamide (2 × 10 mL), dimethylformamide:water 1:1 (4 × 10 mL), water (4 × 10 mL), pH 9 phosphate buffer (4 × 10 mL), water (8 × 10 mL), methanol (4 × 10 mL), and toluene (4 × 10 mL) and dried under vacuum to constant weight to afford 905 mg (99% yield) of **12** (1%, $f = 1.1$). ^{13}C gel-phase NMR (75 MHz, toluene-d_8, 3 Hz line broadening, 80 °C) δ 87.4 (38), 70.1 (50), 68.3 (66), 66.8 (47), 50.4 (43), 49.3 (42), 32.5 (52), 19.2 (200), 16.5 (31).[49] Anal. Calcd for f_{max}: N, 1.40. Found: N, 1.54.

This anchoring step was also studied under more severe conditions: DIEA (775 μL, 4.44 mmol), **11** (780 mg, 3.0 mmol), and resin (1.1 g, 1.47 mmol of active Cl) in CH_2Cl_2 (10 mL) were treated as described above during 48 h. A second fraction of DIEA was added (775 μL, 4.44 mmol) and smooth magnetic stirring continued for 48 h. The resin was purified as described above to afford 1.43 g (99% yield) of **12** (1%, $f = 1.2$). ^{13}C gel-phase NMR set of data was fully coincident with the one described above. Anal. Calcd for f_{max}: N, 1.40. Found: N, 1.64.

With pyridine as the base: Pyridine (585 μL, 7.23 mmol) was added via syringe into a mixture of **11** (865 mg, 3.28 mmol) and the resin (913 mg, 1.22 mmol of active Cl) in CH_2Cl_2 (5.5 mL) and DMF (5.5 mL) under N_2 at room temperature. After smooth magnetic stirring for 72 h at room temperature, the functionalized resin was filtered, washed with dimethylformamide (2 × 10 mL), dimethylformamide:water 1:1 (4 × 10 mL), water (4 × 10 mL), pH 9 phosphate buffer (4 × 10 mL), water (8 × 10 mL), methanol (4 × 10 mL), and toluene (4 × 10 mL), and dried under vacuum to constant weight to afford 977 mg (87% yield) of **12** (1%, $f = 0.9$). ^{13}C gel-phase NMR set of data was fully coincident with the one described above. Anal. Calcd for f_{max}: N, 1.40. Found: N, 1.30.

General Procedure for the Enantioselective Amino Alcohol-Catalyzed Addition of Diethylzinc to Aldehydes. A suspension of the appropriate polymer bound catalyst (3−8% molar as indicated in each case in Tables 2, 4, or 5) in toluene (2 mL) was allowed to stir smoothly under N_2 at room temperature in order to swell the polymer, after which (30 min for a modified Merrifield resin and 24 h for a Barlos one) the aldehyde **8** (1 mmol) was added at room temperature. The mixture was stirred for 20 min and then cooled to the desired temperature if necessary. Diethylzinc (amount indicated in each case in Tables 2, 4, or 5) was added dropwise. The mixture was stirred 24 h under N_2, after which the reaction was quenched by the addition of a saturated NH_4Cl solution (10 mL). The resin was removed by filtration, the aqueous solution was then extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were dried and concentrated in vacuo. The enantiomeric excesses were determined from the crude mixture by GC analyses. Conditions of GC analyses: β-DEX or α-DEX 120 column, 30 m length, 0.25 mm inner diameter, isotherm temperature program, He as carrier gas (2.4 mL/min). For 1-phenylpropanol: β-DEX 120 column, 112 °C, t_R *R* isomer 49.3 min, t_R *S* isomer 52.0 min. For 1-(*o*-tolyl)-propanol: β-DEX 120 column, 120 °C, t_R *R* isomer 59.1 min, t_R *S* isomer 63.8 min. For 1-(*m*-tolyl)propanol: β-DEX 120 column, 120 °C, t_R *R* isomer 52.4 min, t_R *S* isomer 53.8 min. For 1-(*p*-tolyl)propanol: β-DEX 120 column, 120 °C, t_R *R* isomer 50.4 min, t_R *S* isomer 53.3 min. For 1-(2-methoxyphenyl)propanol: β-DEX 120 column, 135 °C, t_R *S* isomer 48.1 min, t_R *R* isomer 54.1 min. For 1-(3-methoxyphenyl)propanol: β-DEX 120 column, 135 °C, t_R *R* isomer 66.2 min, t_R *S* isomer 68.0 min. For 1-(4-methoxyphenyl)propanol: β-DEX 120 column, 135 °C, t_R *R* isomer 68.2 min, t_R *S* isomer 70.4 min. For 1-(2-fluorophenyl)propanol: β-DEX 120 column, 112 °C, t_R *R* isomer 51.0 min, t_R *S* isomer 54.5 min. For 1-(3-fluorophenyl)propanol: β-DEX 120 column, 112 °C, t_R *R* isomer 60.0 min, t_R *S* isomer 63.2 min. For 1-(4-fluorophenyl)-propanol: β-DEX 120 column, 112 °C, t_R *R* isomer 57.3 min, t_R *S* isomer 61.2 min. For 1-(1-naphthyl)propanol: β-DEX 120 column, 160 °C, t_R *S* isomer 98.9 min, t_R *R* isomer 103.2 min. For 1-(2-naphthyl)propanol: β-DEX 120 column, 160 °C, t_R *R* isomer 100.2 min, t_R *S* isomer 102.4 min. For 5-methyl-3-hexanol: α-DEX 120 column, 65 °C, t_R *R* isomer 15.1 min, t_R *S* isomer 15.5 min. For 1-(3-cyclohexenyl)propanol: β-DEX 120 column, 100 °C, t_R *S* isomer 69.8−70.6 min, t_R *R* isomer 74.2−74.4 min.

To establish the absolute configuration of the final compounds, the alcohols were purified by bulb-to-bulb distillation of the crude mixtures. The optical rotation was measured in each case, and its sign was compared with the reported value [*(S)*-1-phenylpropanol,[50] *(S)*-1-(*o*-tolyl)propanol,[51] *(S)*-1-(*m*-

tolyl)propanol,[52] *(S)*-1-(*p*-tolyl)propanol,[53] *(R)*-1-(2-methoxyphenyl)propanol,[54] *(S)*-1-(4-methoxyphenyl)propanol,[53] *(R)*-1-(2-fluorophenyl)propanol,[55] *(R)*-1-(4-fluorophenyl)propanol,[56] *(R)*-1-(1-naphthyl)propanol,[57] *(R)*-1-(2-naphthyl)propanol,[58] and *(S)*-5-methyl-3-hexanol[59]].

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