Preparation and Optimization of Polymer-Supported and Amino Alcohol Based Enantioselective Reagents and Catalysts

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Preparation and Optimization of Polymer-Supported and Amino Alcohol Based Enantioselective Reagents and Catalysts

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The preparation of small focused libraries of supported catalysts and reagents represents an intermediate approach lying between combinatorial and single-compound methodologies. In this case, the potential structural variations can be selected according to previous studies in solution, to limit, to a reasonable extent, the number of components of the library. In our case, we have applied this strategy to the optimization of the structure of supported chiral amino alcohols for their use in catalytic processes (addition of $ZnEt_2$ to benzaldehyde) as well as in noncatalytic reactions (lithium aluminum hydride reduction of acetophenone). This approach allows taking into consideration simultaneously both the structural variations on the chiral unit and the role of the support.

Introduction

Many efforts have been directed in recent years to the development of novel polymer-supported reagents and catalysts for application in organic chemistry.[1−3] The clear practical advantages that those systems can provide in terms of their easier separation from the reaction mixture and the possibility of their reuse or recycling justify the efforts needed in many cases for the preparation of efficient polymeric reagents and catalysts. Within this field, synthesis of supported chiral auxiliaries for stoichiometric and/or catalytic enantioselective organic transformations represents one of the most important goals. It is also one of the most difficult ones according to the large effects that even small changes in the structure or microenvironment can have on enantioselectivity.

To prepare the functionalized resins containing chiral fragments needed for that purpose, different strategies can be considered. Probably the most general approach, and the first to be developed, is the one for which the structure of a given chiral catalyst displaying high activities and enantioselectivities in solution is selected as an ideal candidate for being anchored onto a Merrifield's or similar resin very often. Very often, unfortunately, the activity and/or selectivity shown by the supported analogue do not achieve the expected values and a new homogeneous candidate needs to be selected. This is related, in many cases, with the structural modifications needed for the grafting process or with the microenvironment effects induced by the polymeric matrix.[4,5] This is a "one by one" strategy that follows a trial-and-error methodology because the effects of the support cannot be easily predicted.

On the other hand, a different approach can be based on combinatorial methodologies.[2,6] In this case, after selection of the general structure to be considered, a large library of supported species is prepared and evaluated for the reaction of interest. For the building of this library, as many diversity points as possible, including those related with the support, need to be considered. This can be denominated as a "many at the same time" strategy. Ideally this is a very powerful tool but has some limitations where the development of enantioselective reagents and catalysts is concerned. First, it requires the use of complex and expensive instrumentation. Second, even if progress is being made in this direction, it is not easy to devise general methodologies that would allow for a really high throughput analysis of the efficiency in terms of enantioselectivity.[6]

The single-compound approach is to be selected when a specific, very well-known, and defined structure is the target. In contrast, combinatorial methodologies are appropriate when much less is known on the effects of structural modifications on the efficiency of our system. In the field of enantioselective reagents and catalysts, however, a large number of studies have been made in solution for many systems. This allows for the preparation of small focused libraries where the potential structural variations can be selected from solution data, to limit, to a reasonable extent, the components of the library. This represents an intermediate approach ("several at the same time") lying between combinatorial and single-compound methodologies. Using this strategy, both the role of the structural modifications and that of the support can be considered simultaneously.

Here we present our studies on the application of this parallel approach to the optimization of the structure of chiral amino alcohols for stoichiometric [lithium aluminum hydride (LAH) reduction of acetophenone (**2**)] and catalytic (addition of $ZnEt_2$ to benzaldehyde) processes.

Results and Discussion

Chiral β-amino alcohols, which can be easily prepared from natural or synthetic enantiopure amino acids, have been used as chiral ligands or auxiliaries for a large

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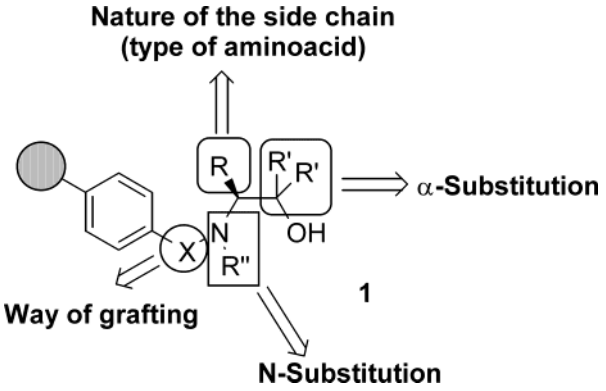
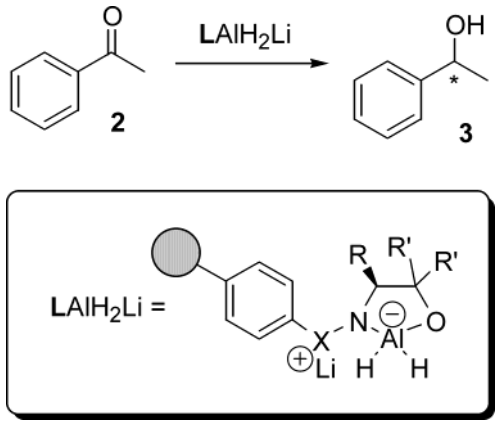
Chart 1



Scheme 1. Enantioselective Reduction of 2 in the Presence of Chiral LAH Derivatives



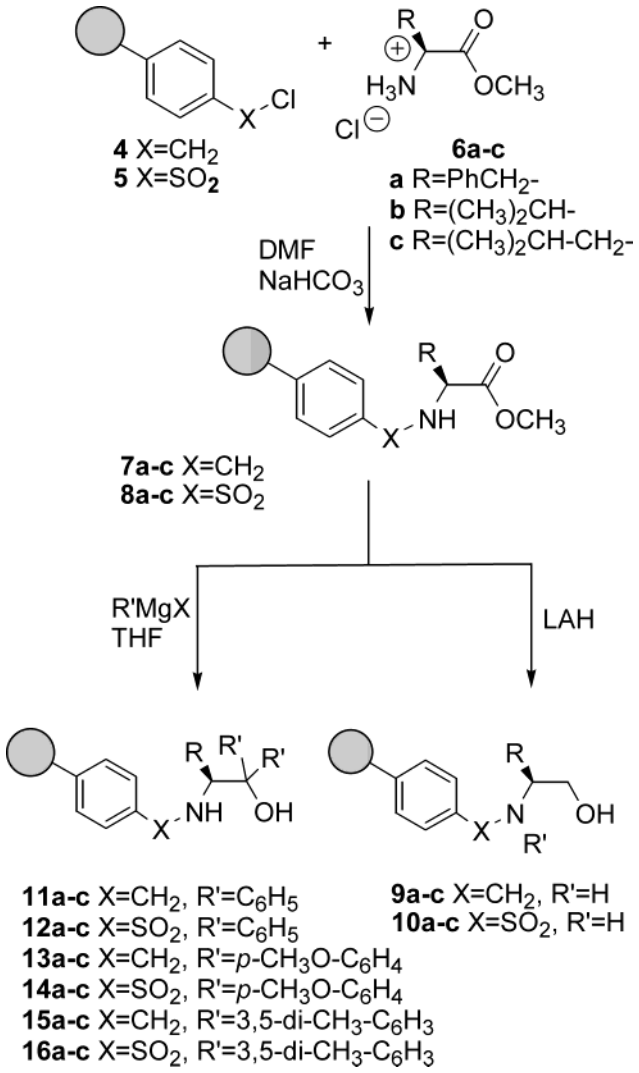
number of processes, and different examples of the use of the corresponding polymer-supported analogues have been reported.[3,7,8]

Even for the most simple cases, the structures of supported amino alcohols (see Chart 1) contain a number of diversity points that need to be considered in order to prepare the corresponding library. In particular, structural modifications can be achieved through changes in the nature of the side chain of the amino acid (R in Chart 1), the α,α-substitution (R′ in Chart 1), the N-substitution (R″ in Chart 1), or the way in which the functional moiety is anchored to the polymer (X).

The first example to be discussed is a simple, well-studied, noncatalytic process, the enantioselective reduction of **2** to phenylethanol (**3**) by LAH in the presence of a stoichiometric amount (relative to LAH) of a chiral amino alcohol (see Scheme 1).[9] The small library of supported amino alcohols was prepared as depicted in Scheme 2.[10]

The first step is the anchoring of an amino acid methyl ester (**6a**−**c**) onto a functionalized polystyrene (PS)−divinylbenzene (DVB) copolymer (**4** and **5**) to give a supported common intermediate (**7** and **8**) from which the amino alcohols containing different α,α substituents could be efficiently prepared, either by reaction with LAH (**9** and **10**) or with the corresponding Grignard derivative (**12**−**16**). According to the most general protocol, a commercial Merrifield resin [**4**; X = CH_2, 1 mmol/g, degree of functionalization (DF) = 0.11, 1% DVB] was selected as one of the starting resins. In this case, intermediate **7** as well as final amino alcohols **9**, **11**, **13**, and **15** could be obtained in quantitative yields in all cases using standard synthetic procedures. A

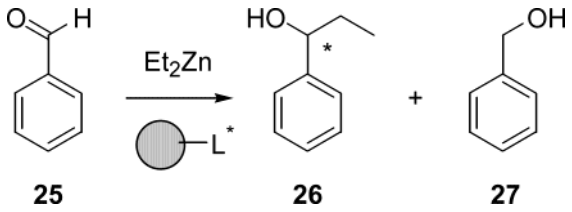
Scheme 2. General Synthetic Procedure for the Preparation of Polymer-Supported Amino Alcohols Used for the LAH Enantioselective Reduction of 2



chlorosulfonated polymer (**5**; X = SO_2) was selected as the second starting polymer in the search for a linker that could strongly modify the nature of both the properties of the amino alcohol moiety (i.e., the acidity of the resulting N−H bond) and those of the polymeric matrix to which it was bound.[11] In this case, however, a very careful control of all synthetic steps was required in order to obtain a quantitative transformation of the functional groups of the polymer into the desired amino alcohol moieties (**10**, **12**, **14**, and **16**). Very disappointing results were obtained starting from commercial sulfonic or chlorosulfonic polymers or with resins prepared in our laboratory containing high loading degrees. For those cases, it was observed that a variable amount of functional sites were converted, during the first step (**5** → **8**), into sulfonic functionalities that strongly affected the subsequent transformations, leading to low conversions. Finally, good results were obtained with a chlorosulfonated resin containing ca. 2 mmol of functional sites/g (DF ∼ 0.26) prepared from PS−DVB (1% cross-linked) using the method reported by Itsuno and co-workers.[12]

One of the advantages of this parallel approach is the possibility of working with amounts of polymer, for each synthetic step, large enough to allow for a full set of

Scheme 3. Enantioselective $ZnEt_2$ Addition to Benzaldehyde



analytical techniques to guarantee that the desired transformation had taken place as expected. Those analytical techniques include standard Fourier transform infrared, Fourier transform-Raman, elemental analysis, and gel-phase ^{13}C NMR spectroscopy, which are easily available and do not require the special techniques (single-bead analysis) developed for combinatorial methodologies, where only very minor amounts of material (often a single bead) are amenable to analysis.[2,5a,13]

Taking into account previous studies under homogeneous conditions, three different amino acid derivatives were considered: those derived from phenylalanine, containing an aromatic side chain (**6a**; R = $PhCH_2$), and those derived from valine [**6b**; R = $(CH_3)_2CH-$] and leucine [**6c**; R = $(CH_3)_2CH_2CH-$], containing bulky aliphatic side chains.[9b] As the α,α substituents, three different aromatic systems with different electronic properties and steric requirements were selected (**11**−**16**) along with polymers **9** and **10**, which contained only hydrogen atoms at the α position.

When the small library of 24 polymers, **9**−**16**, was evaluated for the benchmark reaction shown in Scheme 1, some general trends were obtained, as can be observed in the results shown in Figure 1.

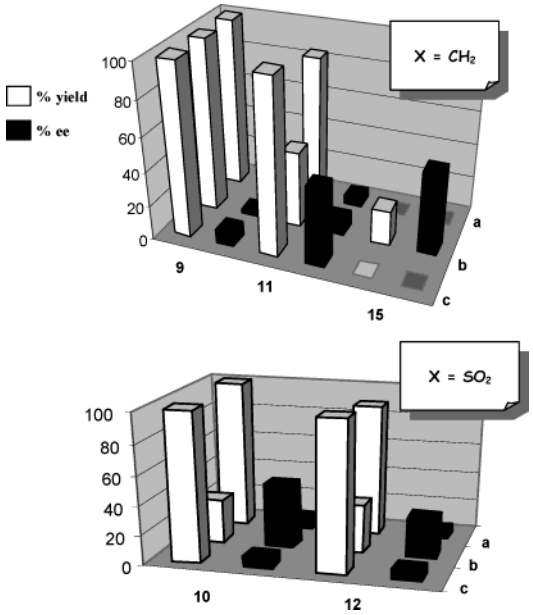


Figure 1. Results obtained for the LAH reduction of **2** in the presence of resins **9**−**16**.[19]

The presence of very bulky substituents is often reflected in a lower activity, as had been previously observed in other related systems.[5b] In this context, lower yields were always found with valine derivatives. When the enantioselectivity of the process is considered, only moderate enantioselectivities could be achieved within this library of supported amino alcohols. Nevertheless, some dramatic differences between polymers derived from **4** and those derived from **5** were detected. Thus, for resins anchored to the polymeric backbone through the *N*-methylene bridge (**9**, **11**, **13**, and **15**), the

Scheme 4. General Synthetic Procedure for the Preparation of Polymer-Supported Amino Alcohols Used for the $ZnEt_2$ Addition to Benzaldehyde

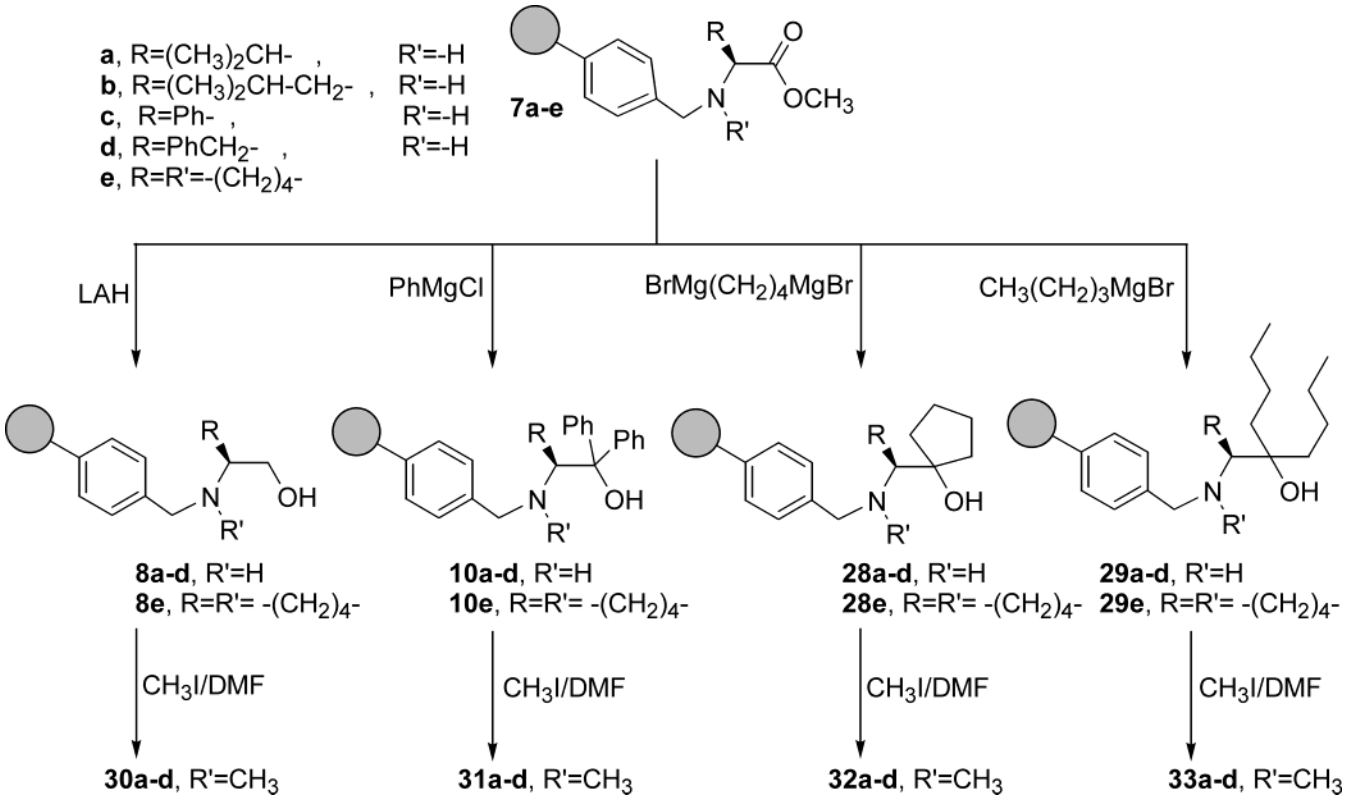
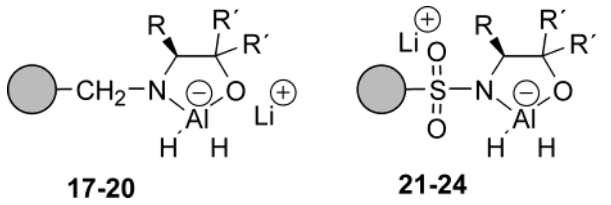


Chart 2



best selectivities were obtained for systems containing bulky substituents at the α position [**11a**, R = $PhCH_2$−, R′ = Ph; **15b**, R = $(CH_3)_2CH$−, R′ = 3,5-$(CH_3)_2C_6H_3$−]. A very different situation was found for resins **10**, **12**, **14**, and **16** containing a sulfonamide linker. In this case, the best enantioselectivities were observed for the valine derivative containing no substituents at the α,α position [**10b**, R = $(CH_3)_2CH$−, R′ = H].

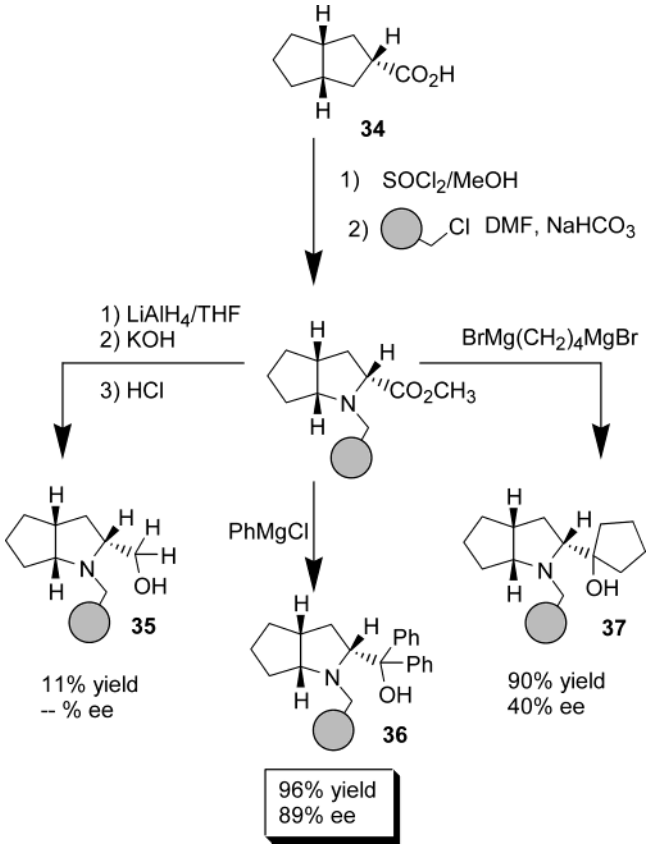
The different acidities of the N−H groups in both cases cannot be considered as responsible for those changes. In both cases, analytical data suggest that cyclic aluminum complexes such as those considered in **17**−**24** (Chart 2) are formed.[12c] Taking into account that the Li^+ cation plays a central role in those systems, acting as a Lewis acid that helps to locate the carbonyl moiety, preliminary electronic density studies suggest that in complexes **17**−**20** the lithium cation should be preferentially coordinated by the oxygen atom of the amino alcohol, a situation similar to that considered for ephedrine derivatives and related systems.[9a] In this case, the presence of bulky α,α substituents would favor the location of the coordinated carbonyl subunit in the vicinity of the side chain, increasing the asymmetric induction. In the case of **21**−**24**, the higher electron density is located on the sulfonamide group, favoring the location of the Li^+ cation (and the carbonylic component) close to it. In this case, an increase in the size of α,α substituents could disfavor the location of the ketone in the proximity of the stereogenic center.[10c]

The second example is concerned with a well-known benchmark reaction, as is the addition of $ZnEt_2$ to benzaldehyde (Scheme 3) catalyzed in the presence of amino alcohols.[7,8] The general strategy was similar to the one considered before, but in this case α,α substituents were selected as shown in Scheme 4 for polymers **8**, **10**, and **28**−**33**.[15]

In this case, besides the α,α-diphenyl-substituted derivatives (**10**), which represent the most common structural feature studied for those compounds, we selected some aliphatic α,α substituents such as the butyl groups in amino alcohols **28** or the butylenic fragment of **29**. This kind of aliphatic α,α substituent had not been previously studied in supported species but had shown to afford good activities and enantioselectivies in solution for this benchmark reaction.[15] Along with those α,α-substituted amino alcohols, the unhindered derivatives **8** were also prepared. In this case, proline [**6e**; R = −$(CH_2)_4$−] and phenylglycine (**6d**; R = Ph) methyl esters were also used as starting materials.[14]

When resins **8**, **10**, **28**, and **29** were evaluated for the Et_2Zn addition to benzaldehyde, the best results in terms of yield (conversion of **25**), selectivity (formation of **26** over **27**), and enantioselectivity [(*R*)-**26** as the major isomer] were obtained for proline derivatives, in particular with the one containing a cyclopentylidene ring in the α position. Thus, for **9e** an 83% yield of **26** (45% ee) was obtained, while a 78% yield (10% ee) was observed for **10e**. This is in good agreement with the

Scheme 5. General Procedure for the Preparation of Polymer-Supported Amino Alcohols Derived from 34[a]



[a] Yields and ee values refer to the use of **35**−**37** for the $ZnEt_2$ addition to benzaldehyde.

fact that proline derivatives have been the most studied supported amino alcohol ligands for this reaction.[8]

Different potential structural modifications were then evaluated in order to design and generate a second family of polymeric amino alcohols. Such variations included the size of the ring in the α position, the formation of oxaazaborolidines, the preparation of Ni^{2+} or Cu^{2+} complexes, and the N-alkylation, in particular N-methylation.[8,16] Preliminary results suggested that N-methylation was the most effective way for improving the efficiency of ligands **8**, **10**, **28**, and **29**. Accordingly, a second family of supported amino alcohols **30**−**33** was easily prepared from **8**, **10**, **28**, and **29**. Analysis of the results obtained with this second library allowed us to observe that N-methylation always produced better yields and selectivities. On the other hand, bulky α,α substituents always produced more efficient chiral ligands for this reaction. Finally, the best results were obtained when aliphatic substituents were present at the α,α position. The results were very much dependent on the nature of the side chain of the starting amino acid (R). Thus, the best results were observed for the leucine derivative **33b** (91% yield, 74% ee) having butyl substituents and for the valine derivative **32a** containing an α-cyclopentylidene ring (86% yield, 80% ee).

The efficiency of those supported ligands is within the range observed for other related systems, but the former results seem to suggest that simple amino alcohol structures do not easily allow one to obtain the high enantioselectivities (>90%) obtained for other polymer-supported amino alcohols having more elaborate struc-

tures.[8,12,16] Taking this into account, a similar parallel approach was considered starting from the non-natural bicyclic amino acid (all *R*)-2-azabicyclo[3.3.0]octane-3-carboxylic acid (**34**) whose derivatives had been previously studied in solution.[17]

The results are gathered in Scheme 5 and clearly reveal that optimum results can be achieved with resin **36** containing two phenyl α,α substituents. Further improvement was obtained, in this case, through modification of the nature of the polymeric matrix.[4,5c,e,12,18,20]

Conclusions

In summary, the preparation of small, focused libraries represents a simple and efficient method to prepare and optimize polymer-supported chiral ligands to be used as auxiliaries for the preparation of enantioselective catalysts and reagents. In the same way, the results obtained with those libraries allow us to analyze and rationalize trends in structure−activity relationships for supported systems. On the other hand, this simple approach does not neglect the effects that the support, the polymeric matrix, can have on the final results. From the data obtained to date, it seems clear that for any of the two processes under study there is not a single structural parameter that could be considered as responsible for the enantioselectivities observed. On the contrary, it is the conjunction of the different structural factors (R, R′, and R″), including the attachment to the polymeric network, that determines the stereochemical outcome of the reaction. This highlights the usefulness of the present approach for the development and study of polymeric reagents and catalysts.

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(19) General procedure for the enantioselective reduction of acetophenone: The polymer-bound amino alcohols were suspended in dry tetrahydrofuran (THF). The mixture was stirred, under an argon atmosphere at 0 °C, and a 1 M solution of $LiAlH_4$ in THF (1 equiv) was then added. Stirring at 0 °C was continued for 1 h and then at room temperature for 2 h. After this time, the temperature was lowered to −70 °C and the corresponding amount of acetophenone (0.8 equiv) was introduced. The mixture was stirred at −70 °C for 15 h, and then a 1 M solution of NaOH was added. When the suspension reached room temperature, it was carefully neutralized with 1 M HCl, and the mixture was filtered. The solution was extracted with Et_2O, and the organic phase was dried and evaporated. The crude product was weighed and analyzed by NMR in the absence and presence of $Eu(hfc)_3$, and the $[\alpha]^{20}_D$ values were measured by polarimetry in CH_2Cl_2.

(20) General procedure for the addition of $ZnEt_2$ to benzaldehyde: The corresponding polymer-supported amino alcohol (0.5 mmol) was suspended in dry toluene (10 mL), under an argon atmosphere at −40 °C, and a 1.1 M solution of Et_2Zn in toluene (10 mL, 11 mmol) was added dropwise. The mixture was stirred

at this temperature for 30 min, and then benzaldehyde (0.54 g, 5 mmol) in dry toluene (20 mL) was added at room temperature. Stirring was continued for 24 h, and then the reaction was quenched at 0 °C by the addition of a 2 M solution of HCl (60 mL). The mixture was extracted with diethyl ether, and the organic phase was washed with a saturated solution of $NaHCO_3$, dried, and vacuum evaporated. Yields and selectivities were obtained from ^1H NMR ($CDCl_3$) using the following signals (δ): benzaldehyde (9.9, s, 1H); 1-phenyl-1-propanol (4.45, t, 1H); benzyl alcohol (4.65, s, 2H). The enantiomeric excess was determined by the use of high-performance liquid chromatography (Chiralcel OD) using a mixture of *n*-hexane−*i*-propanol (97:3) as the eluent (1 mL/min), (*R*)-1-phenyl-1-propanol (room temperature, 10.48 min), and (*S*)-1-phenyl-1-propanol (room temperature, 12.64 min).

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