Small Libraries of Polymer-Supported Amino Alcohols: An Application to the Enantioselective Reduction of Acetophenone by LAH

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Keywords: Amino alcohols / Polymers / Enantioselective reagents / Catalysis / Merrifield resins

Starting from simple amino acid esters and Merrifield resins, a small library of polymer-bound chiral-β-amino alcohols can be prepared. By reaction with $LiALH_4$ the corresponding chiral reducing agents are obtained, having structural variations at both the α and β positions. All supported reagents are able to reduce acetophenone to 1-phenylethanol. Enantioselectivity is observed when the steric hindrance in the chiral fragment is increased. Best results are obtained for the supported derivative of α,α-diphenyl phenylalaninol.

Introduction

Recent advances in combinatorial chemistry have produced an increased interest in the general area of polymer-supported organic chemistry.[1−3] Many of the efforts in this area have been directed towards the preparation of large libraries of potentially bioactive compounds. However, some attempts have also been made to prepare libraries of compounds having applications as enantioselective catalysts.[4] Preparation of resins modified with chiral auxiliaries as enantioselective reagents or catalysts and for chiral separations has been for years one of the main targets in the field of functional polymers.[5−7] There are two alternative strategies for the preparation of such materials: chemical modification of preformed polymers and polymerization of functionalized monomers. Several examples have been reported showing that, under some circumstances, polymer-bound reagents or catalysts prepared by polymerization can give better enantioselectivities.[8] However, the grafting strategy continues to be used the most because of the better knowledge of the preformed polymeric structure and the increased availability of starting materials and synthetic procedures.

Accordingly, the first step for the preparation of polymer-supported enantioselective reagents or catalysts is, usually, the analysis of a homogeneous process of interest and the selection of a chiral auxiliary which is active for that process. An appropriately functionalized derivative is then grafted to a polymer and the selected reaction is again studied under heterogeneous conditions. Nevertheless, very often, the activity or selectivity observed for the homogeneous system is changed when the supported auxiliary is used. In a number of cases lower enantioselectivities are observed. In this respect, one should always consider the role played by the structural modifications produced on the auxiliary upon anchoring, as well as the influence of the polymeric backbone itself.[5−7,9]

However, if the concepts and techniques developed for combinatorial chemistry and parallel synthesis are taken into account, a more efficient approach can be considered in some instances. This strategy involves the preparation of small resin-bound libraries starting from the grafting of simple chiral compounds. The resulting polymers are then assayed for the process of interest.[4,9,10]

Amino alcohols represent a very simple class of chiral auxiliaries.[11] Several examples of the preparation and use of polymer-bound amino alcohols have been described,[7−9,12,13] and Ellman has reported a solid-phase route for the preparation of 2-pyrrolidinemethanol ligands.[4a] Amino alcohols represent some of the most interesting chiral auxiliaries used for the LAH enantioselective reduction of ketones, and some recent results show the interest in developing novel structures for this target. Accordingly we have tested the above-mentioned solid-phase synthesis strategy for the preparation of a small library of supported amino alcohols and its application to the study of the benchmark LAH enantioselective reduction of acetophenone,[14] a reaction that has been studied in detail with supported ephedrine as the chiral auxiliary.[13]

Results and Discussion

The preparation of the polymers containing chiral amino alcohol moieties was carried out very efficiently as shown in the Scheme 1.[15] Reaction of Merrifield's resins **1** with amino acid methyl esters **2** afforded polymers **3**. LAH reduction of the ester group gave resins **4** whilst addition of organomagnesium reagents allowed us to obtain α,α-disubstituted supported amino alcohols **5**−**7**. Quantitative transformation of polymeric functional groups was achieved in all cases. Thus, starting from chloromethylated resins containing 1 mmol Cl/g (DF = 0.11, 1% crosslinked), resin-

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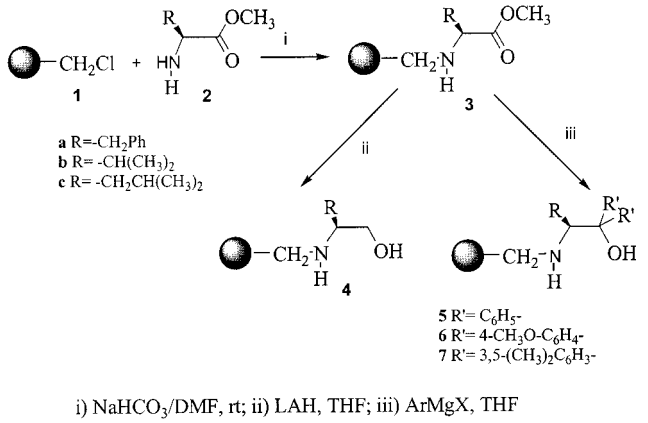
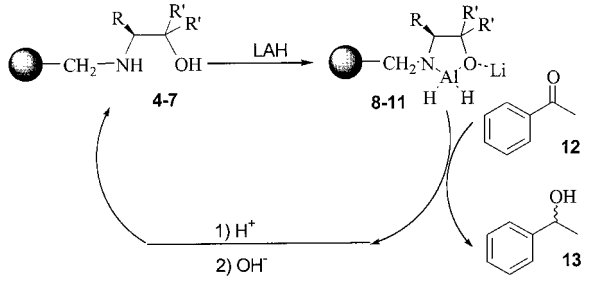
bound amino alcohols **4−7** were prepared having functionalization degrees of ca. 0.8−0.9 mmol/g (DF = 0.11).



Scheme 1. Synthetic route for the preparation of supported amino alcohols

The functionalized polymers **4−7** were used as chiral auxiliaries for the enantioselective reduction of acetophenone, a benchmark reaction that has been studied in detail with a variety of homogeneous and heterogeneous reagents.[13][14] The global process is shown in the Scheme 2. The first step is the formation of the resin-bound reducing agent **8−11** by reaction of the polymeric amino alcohol with a THF solution of $LiAlH_4$. The formation of both O−Al and N-Al bonds, as shown in the cyclic structures **8−11**, is evidenced by the evolution of two mols/mol of H_2 upon reaction. The heterogeneous chiral reagent is then used for the reduction of the prochiral ketone **12**. The solution containing the resulting 1-phenylethanol **13** and the unchanged acetophenone **12** was then analyzed by NMR spectroscopy to check the chemical yield of the reaction; the remaining ketone was then separated off by column chromatography and the composition of the enantiomeric mixture of alcohol **13** was determined by polarimetry and by NMR spectroscopy with $Eu(hcf)_3$ as a chiral auxiliary.



Scheme 2. Reduction of acetophenone using **4−7** as chiral auxiliaries

Initially, a complete set of experiments was performed in order to find the best conditions both for the formation of the polymeric reductive agent and the reaction itself. Some results are gathered in Table 1 for the use of the resin-bound α,α-disubstituted amino alcohol **5a** (R = CH_2Ph, R′ = C_6H_5).

First, it can be seen that the addition of an excess of $LiAlH_4$ for the preparation of the polymeric reducing agent **9a** is not necessary (compare entries 1 and 2 with entries 3 and 4). It should be noted, however, that a slight excess of the heterogeneous reductant over the ketone was always used (**12**/**9a** ratio ≈ 0.8) in order to ensure better chemical yields, as is usual for this kind of reaction. The resin-bound reagent is best prepared at temperatures close to room temperature to improve the binding to the polymer through the O−Al bond formation. Nevertheless, long reaction times at room temperature for this step are unfavorable as lower chemical yields are then obtained (compare, for example, entries 3 and 4). The slower reaction can be ascribed to the formation of less reactive species in which several O−Al bonds are formed by reaction with additional alcohol groups or with residual water molecules.

When the second step is considered, it can be observed that relatively long reaction times are needed to achieve reasonable chemical yields. Better enantioselectivities are always obtained at lower temperatures (see entry 4). Similar trends have been shown to be general for related systems. According to the former results, other reductions were all carried out under the same experimental conditions (entry 4, Table 1). The most significant results are summarized in Table 2.

The use of polymeric reagents **8**, derived from amino alcohols **4** unsubstituted at the α position, afforded the quantitative reduction of ketone **12** to alcohol **13**, but very low *ee* values were observed (entries 1−3 in Table 2). An increase in the steric hindrance in the proximity of the reactive site by substitution of the α-hydrogen atoms by phenyl groups is reflected, in most instances, in an increase in the *ee* observed (entries 4, 7 and 10, in Table 2). As indicated in Scheme 2, the polymers resulting after the reduction can be easily reused after a complete washing cycle of acidic and basic conditions. The use of those recycled polymers, after treatment with LAH, gave, in general, slightly lower yields, but higher enantioselectivities. Similar trends are often observed when polymer-supported reagents are used, and this can be related to the presence of very weakly bound reactive sites that are blocked or modified after the first use.[5][13] Physical modification of the polymeric beads has also to be considered.[6]

The results gathered in Table 2 clearly show that amino alcohols derived from phenylalanine **9a** are the most effective chiral auxiliaries for the process under consideration. This is not easy to rationalize, as, in principle, isopropyl groups seem to be more sterically demanding. Nevertheless, it has to be taken into account that the aromatic moiety of the R group in compound **9a** can provide additional interactions with the aromatic residues of the polymeric backbone. These interactions could be of importance to fix a favored conformation for the complex with **12** and therefore for the corresponding transition state.

A modification of the nature of the aryl group at the α-position of the amino alcohol fragment also affects the re-

Table 1. Results obtained in the reduction of **12** by **9a** using different conditions for the preparation of **9a** and for the reduction step

Entry	LAH/Polymer ratio	Conditions[c] [*T* (°C), *t* (h)]	Ketone/Polymer ratio	Conditions[d] [*T* (°C), *t* (h)]	Yield%[b]	*ee* %
1	excess[a]	1) 0°C, 1 h 2) room temp., 15h	0.8	1) −30°C, 4 h 2) room temp., 15h	10	13
2	excess[a]	−15°C, 3h	0.8	1) −30°C, 4 h 2) room temp., 15h	50	6
3	1	1) 0°C, 1 h 2) room temp., 15h	0.8	1) −30°C, 4 h 2) room temp., 15h	20	10
4	1	1) 0°C, 1 h 2) room temp., 2h	0.8	−70°C, 15h	100	18

[a] An excess of $LiAlH_4$ solution over that needed to reduce the amino alcohol groups present in the polymer was added and the resulting resin was then exhaustively washed with THF (under anhydrous conditions) to wash out the remaining $LiAlH_4$. − [b] Estimated from NMR spectroscopy. − [c] For the preparation of **9a**. − [d] For the reduction step.

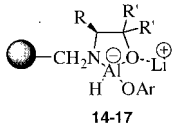
Table 2. Results obtained in the reduction of **12** with different polymer-bound reducing reagents

Entry	Resin-Bound Reagent	R	R′	Cycles[a]	Yield(%)[b]	*ee* (%)
1	**8a**	$-CH_2Ph$	H	1	100	8
2	**8b**	$-CH(CH_3)_2$	H	1	100	2
3	**8c**	$-CH_2CH(CH_3)_2$	H	1	100	–
4	**9a**	$-CH_2Ph$	$-C_6H_5$	1	100	18
5	**9a**	$-CH_2Ph$	$-C_6H_5$	2	100	42
6	**9a**	$-CH_2Ph$	$-C_6H_5$	3	90	45
7	**9b**	$-CH(CH_3)_2$	$-C_6H_5$	1	97	5
8	**9b**	$-CH(CH_3)_2$	$-C_6H_5$	2	100	5
9	**9b**	$-CH(CH_3)_2$	$-C_6H_5$	3	44	8
10	**9c**	$-CH_2CH(CH_3)_2$	$-C_6H_5$	1	100	2
11	**9c**	$-CH_2CH(CH_3)_2$	$-C_6H_5$	2	85	5
12	**9c**	$-CH_2CH(CH_3)_2$	$-C_6H_5$	3	75	5
13	**11b**	$-CH(CH_3)_2$	$3,5\text{-}(CH_3)_2C_6H_3$	1	26	19
14	**11b**	$-CH(CH_3)_2$	$3,5\text{-}(CH_3)_2C_6H_3$	2	20	47
15	**11b**	$-CH(CH_3)_2$	$3,5\text{-}(CH_3)_2C_6H_3$	3	40	31

[a] Refers to the number of times the same resin has been used. − [b] Estimated from NMR spctroscopy.

sults obtained. In this respect, the replacement of the phenyl α-substituents in **9** (R′= C_6H_5) by the 4-methoxyphenyl group (**10**, R′ = $4\text{-}CH_3OC_6H_4$) did not produce significant differences in the reduction of **12**. The change of the α-phenyl groups by 3,5-dimethylphenyl groups results in more important differences, as is to be expected from the large steric hindrance provided by this fragment. Higher enantioselectivities were found when the polymeric reagents **11** [R′ = $3,5\text{-}(CH_3)_2C_6H_3$] were used instead of **9** or **10**. The differences were more important for those amino alcohols giving rise to lower *ee* values with the smaller α-substituents, as is illustrated in entries 13−15 for the valine derivative **11b** [R=$CH_2(CH_3)_2$, R′ = $3,5\text{-}(CH_3)_2C_6H_3$]. The change, however, was much less important for the corresponding phenylalanine derivative **11a**. On the other hand, these results are accompanied by an important decrease in the chemical yields obtained in the same reaction time.

In a further attempt to increase the enantioselectivities obtained for the transformation of **12** to **13**, the addition of a bulky alcohol, such as 3,5-dimethylphenol, to resins **8−11** was considered. The formation of the new RO−Al bond in **14−17** provides a way of increasing the steric hindrance in the vicinity of the reaction site and could increase the selectivity of the reaction. In the case of supported ephedrine derivatives, the addition of such phenolic groups has been reported to favor the formation of a transition state in which a clear differentiation of both faces of the carbonyl groups occurs.[13] In our case, however, the reactivity of the polymeric species **14−17** was always very low and, accordingly, this modification of the process was not considered further.



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Conclusions

In conclusion, the preparation of small libraries of polymer-bound chiral compounds represents a very useful approach for the development of novel enantioselective reagents or catalysts. In our case, a library of resin-bound chiral amino alcohols can easily be prepared from very simple amino acid derivatives and chloromethylated polymers. The utility of this approach is clearly revealed by its application to the preparation of polymeric LAH reagents for the enantioselective reduction of acetophenone. The whole set of data shows that, for fragments bound to the matrix through N-benzyl groups, the preparation of enantioselective reagents requires the presence of bulky substituents at the α position [C_6H_5- or $3,5\text{-}(CH_3)_2C_6H_3$-]. The best results up to now have been obtained for the polymeric amino al-

cohol **9a** (R=$PhCH_2$, R′=Ph) for which a reasonable reactivity is observed along with an appreciable enantioselectivity. The polymeric backbone itself seems to play an important role in determining this result. It is clear that more work is needed in order to further modify the structures of the chiral auxiliaries and to improve the enantioselectivities observed, but the present results illustrate the usefulness of this approach for the development of novel polymer-supported reagents and catalysts.

Experimental Section

Commercial polystyrene-divinylbenzene copolymers were purchased from Fluka and washed with a series or organic solvents (MeOH, acetone and CH_2Cl_2) and vacuum-dried to constant weight before use. IR spectra of KBr pellets of the polymers were recorded on a Perkin−Elmer 2000 FT-IR spectrophotometer. Raman spectra were obtained on the Raman accessory for the same instrument. Quantitative elemental analyses were performed in duplicate on a Carlo Erba EA1108 CHNS-O instrument.

General Procedure for the Preparation of Polymer-Supported Amino Esters 3: A chloromethylated resin (1 mmol Cl/g, 1% DVB, 2 g, 2 mmol) was added, under an argon atmosphere, to a solution containing a mixture of the L-amino acid methyl ester hydrochloride (6 mmol) and anhydrous $NaHCO_3$ (12 mmol) in dry DMF (50 mL). After stirring at 65°C for 24 h, the resin was filtered and washed with DMF, MeOH, H_2O, MeOH and CH_2Cl_2 and vacuum-dried to give polymers **3** showing a quantitative transformation of the chloromethyl groups (IR: 1260 cm^{-1}) (DF = 0.11, 0.88−0.92 mmol/g).

General Procedure for the Preparation of Polymer-Supported Amino Alcohols 4: Polymers **3** (0.5 g, ca 0.45 mmol) were treated with an excess of $LiAlH_4$ (ca. 50 mg, ≈ 1.35 mmol) in dry THF (30 mL) at room temperature for 48 h, under an argon atmosphere. The polymer was then filtered, washed with THF, dilute HCl, H_2O, MeOH, and CH_2Cl_2 and vacuum-dried to give resins **4** showing a quantitative transformation of the ester groups (IR: 1730−1735 cm^{-1}) (DF = 0.11, 0.9−0.94 mmol/g)

General Procedure for the Preparation of Polymer-Supported Amino Alcohols 5−7: Polymers **3** (0.5 g, ca. 0.45 mmol) were suspended in dry THF (30 mL) and treated with an excess of a solution of the arylmagnesium halide (3.7 mmol) in THF. The mixture was heated at reflux for 24 h under an argon atmosphere and the polymer was filtered, washed with THF, dilute HCl, H_2O, MeOH and CH_2Cl_2 and vacuum-dried to give resins **5−7** showing quantitative transformation of the ester groups (IR: 1730−1735 cm^{-1}) (DF = 0.11, 0.79−0.82 mmol/g).

General Procedure for the Reduction of Acetophenone: The polymer-bound amino alcohols (3 g, 2.37−2.82 mmol) were suspended in dry THF (20 mL). The mixture was stirred under an argon atmosphere at 0°C and a 1M solution of $LiAlH_4$ in THF (2.37−2.82 mmol) 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 appropriate amount of acetophenone (1.9−2.25 mmol) was introduced. The mixture was stirred at −70°C for 15 h and then a 1M solution of NaOH (10 mL) was added. When the suspension reached room temperature, it was carefully neutralized with 1M HCl and the mixture was filtered. The solution was extracted with Et_2O and the organic phase was dried over anhydrous $MgSO_4$. The solvent was evaporated and, when reduction was not complete (as shown by TLC and NMR spectroscopy), the crude product was purified by column chromatography. The $[\alpha]_D^{20}$ values measured by polarimetry in CH_2Cl_2 and the NMR spectra in the presence of $Eu(hfc)_3$ allowed us to estimate the *ee* values. A very good agreement was obtained with both techniques.

Acknowledgments

Financial support has been provided by CICYT and BANCAIXA (projects MAT96−1053 and P1B97−10).

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Received February 2, 1999
[O99071]