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A general route for the preparation of polymer-supported *N*-tosyl aminoalcohols and their use as chiral auxiliaries

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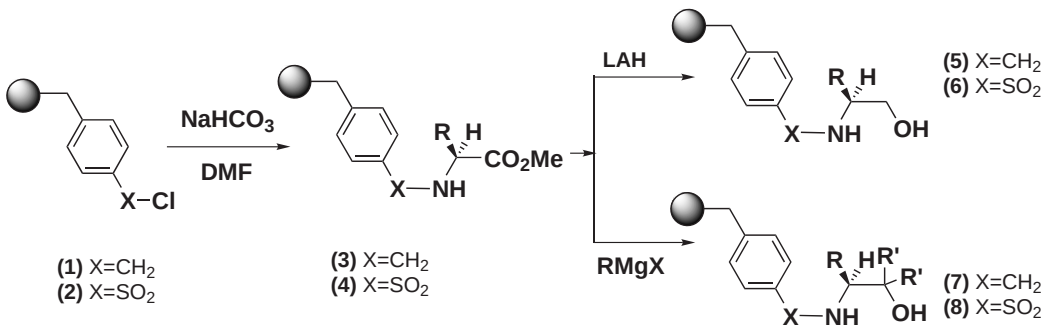
Abstract—Resin-supported chiral aminoalcohols bound to polymeric network via a sulfonamide link are prepared very efficiently from polymeric *N*-tosylamides of aminoacid esters. Preliminary results show that those compounds can be used as useful chiral auxiliaries. The presence of the sulfonyl group plays an important role in determining the properties of the resulting supported reagents. © 2001 Elsevier Science Ltd. All rights reserved.

Development of polymer-supported enantioselective catalysts and reagents is one of the most practical applications of functional polymers.[1] For this purpose, chloromethylated Merrifield resins continue to be mainly used when the ligand is introduced by grafting. A large number of other linkers have been described in recent years, mainly for solid phase peptide and combinatorial synthesis.[2] Nevertheless, most of those linkers are unsuitable in the field of enantioselective catalysis because of their lability or by the interference of the additional functional groups that can be present.[3] Chlorosulfonated resins seem to be a simple and accessible alternative to chloromethylated resins as a starting material for the preparation of different functional polymers even if they have been much less used.[4]

Recently, we have shown how solid phase parallel synthesis approaches starting from Merrifield resins (**1**, $X=CH_2$) can be very useful for the preparation of a variety of supported aminoalcohols.[3] According to those results and to the interest of sulfonyl amines and aminoalcohols as chiral auxiliaries in different homogeneous processes,[5,6] we have considered the application of this approach starting from chlorosulfonated polymers. In order to accomplish this target, two main points need to be addressed: how much the presence of the sulfonamide moiety can affect the ability to carry out efficiently the synthetic transformations shown in the Scheme 1, and how much it influences the final properties of the resulting chiral auxiliaries.

The first step in Scheme 1, the incorporation of the aminoester moiety, appears to be one of the most critical steps. To succeed in the further transformations, it was necessary to obtain a quantitative conversion of the chlorosulfonyl groups in **2** into the sulfonamide



Scheme 1.

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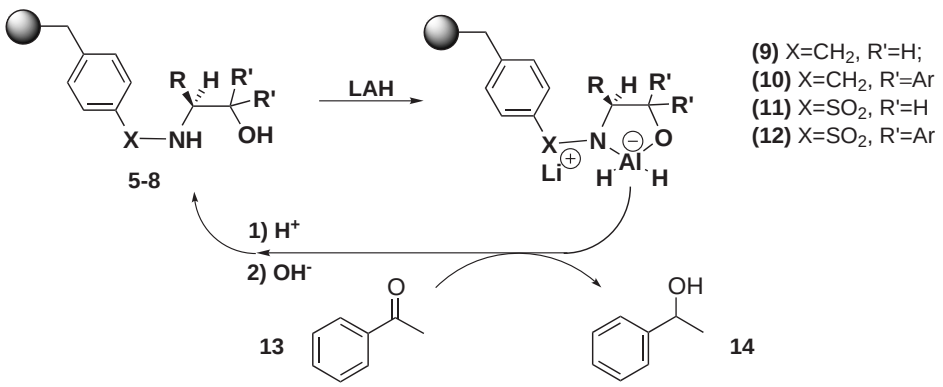
fragments in **4**. The presence of minor amounts of chlorosulfonyl or sulfonic groups greatly affected the whole process. In this respect, the presence of even a small band at 1125 cm^{-1} in the FT-Raman spectrum, which is present in sulfonic resins, was always accompanied by a drastic decrease in the synthetic efficiency of further steps. This precluded the use of highly loaded polymers such as those derived from commercial ion exchange sulfonic resins. Best results were obtained using chorosulfonated resins with loadings of ca. 2 mmol g^{-1} $((C_8H_8)_{0.73}(C_8H_7SO_2Cl)_{0.26}(C_{10}H_{11})_{0.01}$, DF = 0.26, 26% of the aromatic groups of PS-1% DVB being substituted). These were obtained by a carefully controlled chlorosulfonation at 40°C.[6a]

An efficient conversion of resins **2** into aminoesters **4** could be carried out only under very mild conditions (rt, 48 h), using the hydrochloride of the corresponding aminoesters in DMF and Et_3N as the base. Elemental analysis showed the expected values for N and S for a quantitative transformation. The FT-IR spectra showed the disappearance of the S-Cl band at 1374 cm^{-1} and the presence of the C=O band at 1730 cm^{-1}. The FT-Raman spectra showed a complete absence of the band at 1125 cm^{-1}. In this way, resins **4** containing *N*-sulfonyl derivatives of valine, leucine and phenylalanine were prepared with loadings of ca. 1.6 mmol g^{-1} (DF = 0.26). Gel-phase ^{13}C NMR spectra could be obtained in most instances for those resins.[7] Thus, for resin **4** derived from valine, the NMR spectrum showed the presence of sharp peaks at ca. 17, 30, 52 and 61 ppm, in good agreement with calculated values.

Treatment of supported esters **4** with an excess of LAH gave polymeric aminoalcohols **6** whilst addition of organomagnesium reagents gave supported α,α-disubstituted aminoalcohols **8** (THF, reflux, 24 h). Quantitative transformation of the ester groups was shown by the complete disappearance of the band at ca. 1730 cm^{-1} in the FT-IR spectra and the methyl ester peak at 52 ppm in the ^{13}C NMR spectra. Elemental analyses gave the expected results for resins with loadings of 1.3–1.7 mmol g^{-1}.

Preliminary studies of functionalized polymers **6** and **8** as chiral auxiliaries were carried out for the enantioselective reduction of acetophenone (Scheme 2), a benchmark reaction that has been studied in detail with different homogeneous and supported aminoalcohols, including resins **5** and **7**.[4,8] Initial results have shown that supported species can afford better enantioselectivities than homogenous analogs (compare the first and last entries in Table 1). Important differences between resins **6** and **8** and polymers **5** and **7** can be detected. Thus, for auxiliaries **5** and **7** derived from a Merrifield polymer, it has been observed that appreciable enantioselectivities were only obtained for aminoalcohols **7** containing bulky aryl substituents at the α position.[4b] The situation, however, is different for resins functionalized with *N*-tosyl aminoalcohols. In this case, moderate selectivities were obtained with the polymer **6** derived from valine and having no substituents at the α position. As a matter of fact the enantioselectivities were lower for reagent **12** (R ≠ H). On the other hand, best results were obtained for resins **6** and **8** derived from valine, whilst phenylalanine derivatives were best suited when supported *N*-alkyl aminoalcohols (**5** and **7**) were used. These resins can be reused after a washing cycle. In general, a decrease in activity is observed with reuse, but the selectivity is maintained or even increased. This seems to reflect the presence of non-chiral sites in the polymer, where the reagent can be weakly bound, that can be blocked with use.

Those differences in behavior cannot be ascribed to the increased acidity of the N–H bonds in **6** and **8**. The evolution of 2 mol/mol of H_2 upon reaction of **5**–**8** with LAH evidences the formation, in all cases, of the cyclic structures **9**–**12**. According to this, the general mechanism proposed for supported ephedrine derivatives would not apply here.[8a] In general, it is considered that the Li cation acts as a Lewis acid cooperating to locate the carbonyl group of the substrate in close proximity to the aluminum atom for the hydride transfer. Preliminary calculations suggest that the high charge densities on the oxygens of the sulfonyl group can provide a way to locate the cation in this region in close proximity to the side chain of the aminoacid but far away from the substituents at the α position. In the absence of the sulfonyl group, the situation is opposite and the lithium would be located close to the oxygen of the aminoalcohol moiety, being much more influenced by the groups in the α position. Accordingly, the sulfonyl group here



Scheme 2.

Table 1. Results obtained in the reduction of **13** with different polymer-bound reagents

X	R	R′	Cycle[a]	Yield (%)[b]	ee (%)
SO_2	$(CH_3)_2CH$-	H	1	85	28
SO_2	$(CH_3)_2CH$-	H	2	50	31
SO_2	$(CH_3)_2CH$-	H	3	30	43
CH_2[c]	$(CH_3)_2CH$-	H	2	100	2
SO_2	$(CH_3)_2CHCH_2$-	H	2	100	5
SO_2	$PhCH_2$-	H	2	100	7
SO_2	$(CH_3)_2CH$-	Ph	2	33	27
SO_2	$(CH_3)_2CHCH_2$-	Ph	2	89	5
SO_2	$PhCH_2$-	Ph	2	100	7
CH_2[c]	$PhCH_2$-	Ph	2	100	42
	N-Tosylvalinol[d]	H	–	100	3

[a] Number of times the same resin has been used.
[b] After 15 h at −70°C.
[c] From Ref. 4b.
[d] Used as an homogeneous analogue of resin **6** (R = $(CH_3)_2CH$-).

plays a very important role as has been observed in other catalytic and non-catalytic systems containing related moieties.[5a,b]

In conclusion, the present approach has been of interest for the preparation of novel supported chiral auxiliaries. Further work is in progress in order to understand better the mechanism of the processes considered here and to optimize the procedures and structures to be used as well as to study the application of those auxiliaries for other processes.

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