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New Silica-Immobilized Chiral Amino Alcohol for the Enantioselective Addition of Diethylzinc to Benzaldehyde

**José M. Fraile,[†] José A. Mayoral,*,[†] Jorge Serrano,[†] Miquel A. Pericàs,[‡]
Lluís Solà,[‡] and David Castellnou[‡]**

*Departamento de Química Orgánica, Instituto de Ciencia de Materiales de Aragón,
Facultad de Ciencias, Universidad de Zaragoza-CSIC, E-50009 Zaragoza, Spain, and
Unitat de Recerca en Síntesi Asimètrica, Departament de Química Orgànica,
Universitat de Barcelona, c/Martí i Franquès, 1-11, E-08028 Barcelona, Spain*

mayoral@posta.unizar.es

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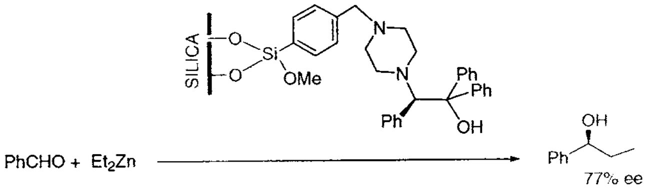
ABSTRACT



A readily available chiral amino alcohol has been immobilized on silica by sol–gel synthesis and grafting. The solid prepared according to the latter method led to the best enantioselectivity (77% ee) described for the asymmetric addition of diethylzinc to benzaldehyde using inorganic solids.

Heterogeneous chiral catalysts[1] are becoming more and more important due to the inherent advantages of handling and separation of the heterogeneous over the homogeneous catalysts and the increasing industrial application of single enantiomers of chiral compounds as pharmaceuticals or agrochemicals. In this context, the addition of dialkylzinc to aldehydes in the presence of a catalytic amount of a chiral β-amino alcohol[2] has been extensively studied using amino alcohols immobilized by covalent bonding to insoluble supports.[1] Since the pioneering work of Frechet,[3] several authors have described excellent results using organic polymers as supports.[4,5] On the contrary, the use of inorganic supports, mainly silica, has been much less investigated and in general with poor results.[6,7] The attempts to improve those results have shown that the type of support, the presence of free silanol groups and the use of BuLi are important factors, but the influence of the amino alcohol has not been so deeply explored.

In this paper, we describe the use of an easily accessible chiral ligand, (*R*)-1,1,2-triphenyl-2-(piperazin-1-yl)ethanol (**1**), for immobilization on silica, following the successful grafting of related amino alcohols on organic polymers.[5] Taking into account that the immobilization on organic

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[†] Universidad de Zaragoza.

[‡] Universitat de Barcelona.

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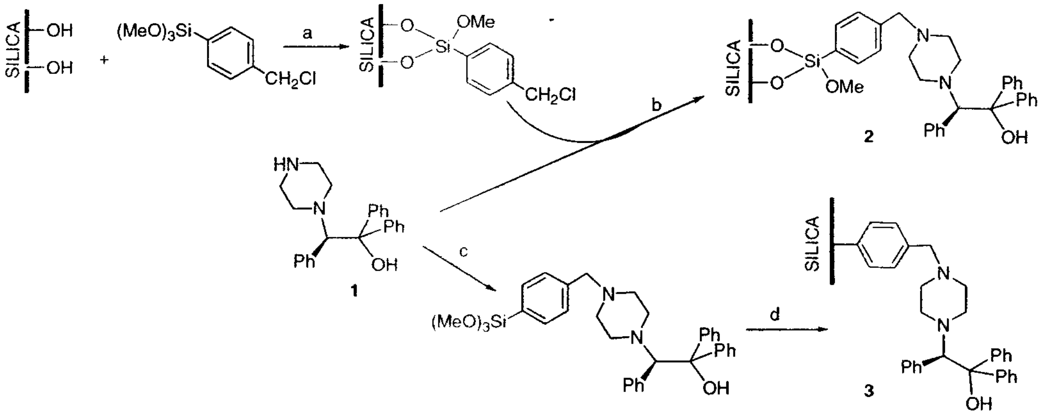
Scheme 1. Immobilization of Amino Alcohol **1** by Grafting and Sol−Gel Synthesis[a]



[a] Reagents and conditions: (a) toluene, reflux (3 h) with azeotropic distillation; (b) Et_3N, toluene, reflux, 20 h; (c) $NaHCO_3$, THF, reflux, 24 h; (d) $Si(OEt)_4$, dodecylamine, EtOH/water, rt, 24 h.

polymers by grafting or copolymerization frequently leads to different results,[8] the grafting onto amorphous silica and the incorporation of the chiral ligand by sol−gel synthesis, a method seldom used to immobilize chiral catalysts, will be compared.[9]

Amino alcohol **1** was obtained by regioselective opening of the enantiomerically pure triphenyloxirane with piperazine.[10] This amino alcohol presents a free nucleophilic position that allows its grafting to a suitable functionalized support obtained by treatment of silica gel (Merck 60) with *p*-chloromethylphenyltrimethoxysilane. On the other hand, reaction of **1** with the same silane leads to a chiral trimethoxysilane able to react with tetraethoxysilane under sol−gel conditions using dodecylamine as base and template[11] to obtain an organic−inorganic hybrid silica with high surface area. The synthesis of the solids is shown in Scheme 1, whereas the properties of the solids are gathered in Table 1.

Table 1. Characterization of the Solids Containing the Chiral Amino Alcohol

solid	S^a ($m^2\ g^{-1}$)	Dp (nm)[a]	content of **1**[b] ($mmol\ g^{-1}$)	C/N ratio
2	387	58	0.48	14.5
3	1045	51	0.20	22.2

[a] Determined by nitrogen adsorption. [b] Calculated from nitrogen analysis.

As can be seen, the solid obtained by sol−gel synthesis (**3**) presents larger surface area than the solid prepared by grafting (**2**), but lower functionalization of amino alcohol. In the solid prepared by grafting (**2**) the C/N ratio is the expected value (15.5−16.5), within the experimental error, whereas in solid **3** the higher content of carbon indicates that part of the ethoxy groups remain on the solid.

The catalytic activity of these solids was tested in the addition of diethylzinc to benzaldehyde (Table 2). The dried solids were poorly active and enantioselective, with the solid prepared by grafting (**2**) being more selective (21% ee) and the one obtained by sol−gel synthesis (**3**) more active (26% yield at −15 °C). It has been described that the free silanol groups of the silica surface are able to promote the reaction.[12] The larger surface area of solid **3**, with the consequent higher number of silanol groups, would be responsible for the higher

Table 2. Results Obtained in the Addition of Diethylzinc to Benzaldehyde Promoted by Solids **2** and **3**[a]

solid	treatment	*t* (h)	*T* (°C)	yield[b] (%)	ee[c] (%)
2	none	24	−15	18	21
2	end-capping[d]	24	−15	20	23
2	BuLi[e]	24	−15	94	73
2	BuLi[e,f]	24	−15	45	69
2	BuLi[e]	96	−25	99	77
3	none	24	−15	26	2
3	end-capping[d]	24	−15	34	4
3	BuLi[e]	24	−15	92	12

[a] Et_2Zn/benzaldehyde/amino alcohol = 3:1:0.06. [b] Determined by GC. [c] Determined by GC with a Cyclodex-B column; (*S*)-1-phenylpropanol is the major isomer. [d] With hexamethyldisilazane in anhydrous toluene under reflux. [e] BuLi/amino alcohol = 1.5. [f] Solid recovered from the previous reaction.

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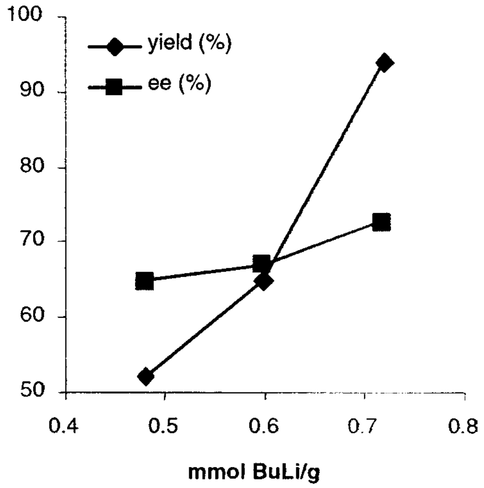

Figure 1. Effect of the variation of BuLi amount on the addition of diethylzinc to benzaldehyde promoted by **2**.

activity but the null enantioselectivity. To prevent this undesired effect, both solids were end-capped with trimethylsilyl groups. However, contrary to expectations, the silanization of the surface has only little effect on both the activity and the enantioselectivity. One possible explanation for this lack of effect is that end-capping modifies mainly the isolated silanol groups,[13] whereas the mechanism of the reaction suggests that it would be better catalyzed by vicinal silanol groups.

A more drastic method to eliminate silanol groups is the treatment of silica with BuLi. It is considered to be a quantitative reaction, since it is used to determine the amount of silanol groups by measurement of the butane evolved in the reaction.[14] In fact this treatment has been described as positive for the behavior of other amino alcohols, immobilized onto mesoporous silicas, in the same addition reaction.[7] In our case, treatment of both solids with BuLi (1.5 equiv with respect to amino alcohol) greatly improves the yield, up to values higher than 90%. However, the behavior of the two types of solids is different when the enantioselectivity is taken into account. Whereas the enantioselectivity remains low with the solid prepared by sol−gel synthesis (**3**) (12% ee), the solid prepared by grafting (**2**) leads to (*S*)-1-phenylpropanol with high enantiomeric excess (73% ee), comparable to the best results described with inorganic supports, namely a derivative of α,α-diphenylprolinol immobilized on the synthetic mesoporous silica SBA-15.[7] The lack of activity in the solution separated in an early stage of the reaction confirmed the heterogeneous character of the catalytically active species. This solid was recovered by filtration and reused under the same conditions, with slightly lower enantioselectivity (69% ee) but significant lower catalytic activity. It is possible to improve the selectivity up to 77% ee with the fresh catalyst by reducing the reaction temperature to −25 °C.

In view of the relevant role played by BuLi, we decided to explore the influence of its amount on the results with solid **2** (Figure 1). As can be seen, a decrease in the amount of BuLi has as a consequence a decrease in both yield and enantioselectivity. However, the effect on the catalytic activity is much more important.

It is not easy to explain the role of BuLi, but it is clear that it favors the reaction in the chiral amino alcohol sites over the silica surface sites. This can be due to two different reasons: (a) the formation of lithium silyloxide species, less active than the analogous zinc species, or (b) the formation of a lithium amino alkoxide species, more active than the analogous zinc derivative. Taking into account that the amount of BuLi used (0.72 mmol/g solid) is not enough to eliminate all the remaining silanol groups present in the range of 3−3.5 mmol/g from the initial value[15] (4.6 mmol/g) and the consumption due to the functionalization with the chiral amino alcohol, perhaps the treatment with BuLi allows the elimination of only one type of silanols, vicinal or isolated, responsible for the nonenantioselective reaction. Regarding the second hypothesis, the role of chiral lithium alkoxide in the stereochemical course of the diethylzinc addition was proposed some years ago,[16] and it has been recently confirmed by theoretical calculations.[17] In fact, important improvements in enantioselectivity have been reported by using the lithium salts of amino alcohols, although this behavior has shown to be highly dependent on the structure of the amino alcohol and even on the amount of catalyst.[18] In our case the treatment with BuLi does not modify the enantioselectivity obtained in solution with amino alcohols of related structure.[19] However, the lack of experimental studies about the relative activity of lithium and zinc species, both on amino alcohol and surface silanol, precludes any conclusive explanation.

In conclusion, the immobilization of the easily available chiral amino alcohol **1** by grafting onto common silica allows results comparable to those obtained with noncommercial inorganic supports. The use of BuLi is necessary to reach high yields and enantioselectivities but its role remains unclear.

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Supporting Information Available: Experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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