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New Supported β-Amino Alcohols as Efficient Catalysts for the Enantioselective Addition of Diethylzinc to Benzaldehyde under Flow Conditions

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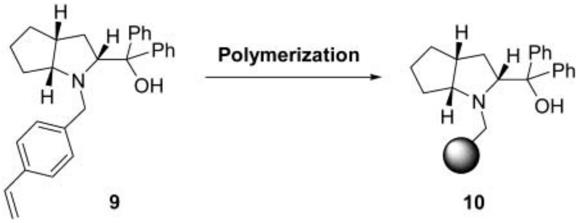
ABSTRACT



Polymeric monoliths 10 containing an amino alcohol moiety derived from an industrial waste material represent one of the best ligands for the enantioselective catalytic addition of $ZnEt_2$ to benzaldehyde (99% ee), being recoverable and usable under flow conditions.

Development of environmentally friendly chemical processes is one of the main challenges for chemical research in this century.[1] In this context, catalysis represents one of the most attractive approaches. Enantioselective synthesis based on transition metal-catalyzed processes is a field of increasing interest in organic chemistry because of their high efficiency for stereoselective synthesis. A great number of those catalysts are needed in pharmaceutical, food, and agricultural industries for the enantioselective synthesis of organic compounds due to their high economical importance in those fields.[2] In the development of chiral catalysts, the use of starting materials of easy accessibility and low cost is highly desirable. Thus, the synthesis of chiral ligands derived from compounds of the so-called chiral pool has been the most useful. An alternative and attractive approach is the use of chiral industrial waste materials. Some of us have been involved, in recent years, in the design of different low-cost and effective chiral ligands using (all-*R*)-2-azabicyclo [3.3.0]-octane-3-carboxylic acid as the starting material, which is a waste material generated in the industrial process of synthesizing the ACE inhibitor Ramipril at Aventis.[3,4] Encouraged by the high catalytic enantioselectivity induced by some of those homogeneous ligands and in the search of more efficient, recoverable, and environmentally friendly catalysts, we decided to investigate the corresponding heterogeneous catalysts derived from **1**. Besides the above-mentioned

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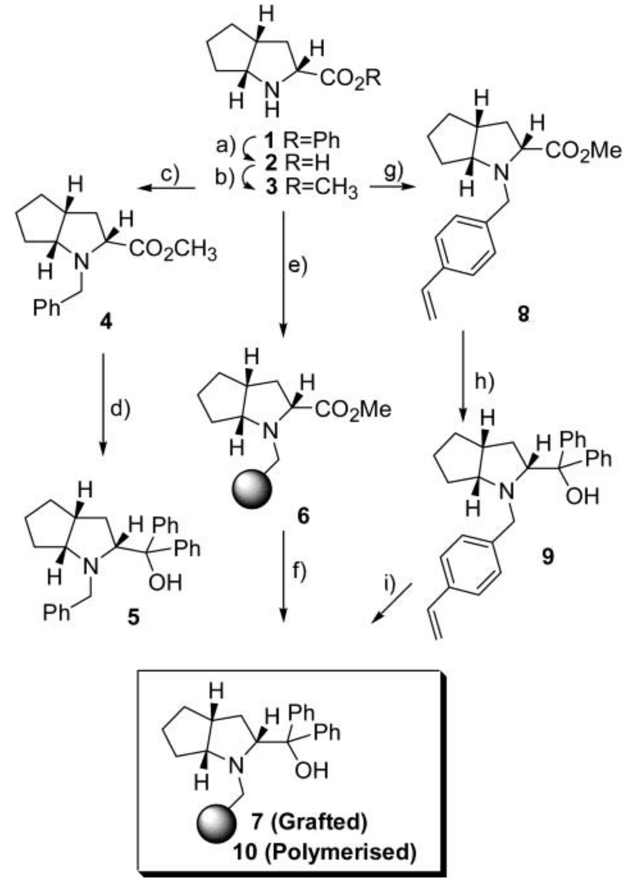
advantages derived from the use of **1** as the starting material, it is important to note that heterogeneous chiral catalysts are, in principle, best suited for industrial applications, in particular due to the possibility of their use in continuous flow systems.[5] In this ideal system, the solution containing the reagents is feed into a reactor in which a chiral heterogeneous catalyst promotes their transformation to the desired chiral products. The need for catalyst separation is suppressed, and the products can be easily isolated just by removing the solvent, increasing the efficiency, and reducing the environmental impact of the whole process.

Enantioselective addition of dialkylzinc to aldehydes in the presence of chiral promoters such as chiral β-amino alcohols has been shown to be a useful method of inducing asymmetric carbon−carbon bond formation.[6,7] Some chiral amino alcohols derived from **1** act as excellent ligands for this enantioselective reaction.[4] Here we report the results obtained for this reaction with both heterogeneous and homogeneous ligands synthesized from **1**. Some of the polymer-supported ligands prepared have shown an optimal behavior in terms of activity, selectivity, and enantioselectivity, being able to act efficiently in flow systems. An increase in selectivity and enantioselectivity has been observed upon immobilization, and those features are maintained for several catalytic cycles.

According to former results and to a preliminary screening on different supported β-amino alcohols derived from **1** as catalysts for the enantioselective addition of diethylzinc to benzaldehyde, we decided to focus our work on the preparation and study of supported catalysts such as **7** and **10**, bearing phenyl groups at the α-position. This diphenyl hydroxymethylene moiety is present in a huge number of asymmetric catalysts and has been termed the “magic group”.[8]

To obtain a better understanding of the behavior of a given heterogeneous catalyst, it is absolutely necessary to evaluate the activity of the homogeneous analogues. It is well-known that results obtained in an enantioselective transformation can dramatically change when going from homogeneous to heterogeneous phases.[9−11] For that reason, the synthesis of the homogeneous catalyst **5** was carried out (see, Scheme 1) as the first step.

Scheme 1[a]



[a] Reagents and conditions: (a) Pd/C. (b) SO$_2$Cl/MeOH. (c) PhCH$_2$Cl (1.2 equiv), 80%. (d) PhMgCl, THF, ref 4a. (e) **3** (3 equiv), Merrifield Resin (1 equiv, loading 1.1 mequiv/g, 1% cross-linking), NaHCO$_3$ (6 equiv), THF, quant. (f) PhMgCl, THF, quant. (g) 4-Chlorovinylbenzene (1.2 equiv), NaHCO$_3$ (2.5 equiv), 18 h, 70 °C, 40% (ref 11b). (h) PhMgX (3 equiv), 75% (ref 15). (i) **9**/DVB/VB/toluene/1-dodecanol, AIBN, 80 °C, 99%.

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On the other hand, the synthesis of the supported chiral auxiliary **7** was initially achieved by the grafting of **3** onto a Merrifield resin (1.1 mmol Cl/g) to obtain **6** and further reaction of this polymer with an excess of phenyl Grignard reagent, using the general methodology developed for the preparation of supported amino alcohols from natural amino acids.[9e−d] A quantitative transformation of polymeric functional groups was achieved as shown by the use of FT-IR and FT-Raman spectroscopy as well as gel-phase ^{13}C NMR.[9a,d,11c]

The catalytic behavior of the soluble ligand **5** was evaluated for the enantioselective addition of $ZnEt_2$ to benzaldehyde (Scheme 2). In a typical procedure, the reaction was carried out at rt in toluene for 24 h with a catalyst concentration of 2−20 mol % relative to the aldehyde. In general, the chemical yields obtained for **12** after fractional distillation ranged from 74 to 88%. Regarding the enantioselectivity, a typical and expected nonlinear relationship was found (entries 1−4, Table 1), enantioselectivities being optimal for catalyst concentrations of 10% or higher.

Scheme 2

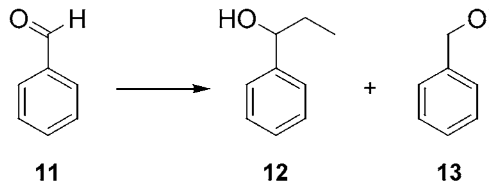

Table 1. $ZnEt_2$ Addition to Benzaldehyde at 25 °C in the Presence of Ligands **5** and **7**

entry	ligand	mol %[b]	yield (%)[c]	ee (%)[d]
1	**5**	2	74	70 (R)
2	**5**	5	74	75 (R)
3	**5**	10	85	87 (R)
4	**5**	20	88	90 (R)
5	**7**	10	83	89 (R)
6	**7**[a]	10	74	80 (R)

[a] Reused catalyst. [b] Percent molar value of the catalyst relative to benzaldehyde. [c] Determined by NMR. [d] Determined by HPLC (Chiralcel OD) or GC.

The heterogeneous ligand **7** was tested for the diethyl zinc reaction using 10 mol % chiral catalyst and conditions similar to those used with the homogeneous catalysts. Good catalytic behavior was observed in terms of yield and enantioselectivity (entry 5, Table 1). The supported catalyst provided an enantioselectivity similar to that obtained with the homogeneous ligand (**5**, 87% ee; **7**, 89% ee). It is worth noting that, in many cases, a decrease of the asymmetric induction has been observed when the immobilization is carried out due to the effects induced by the polymeric matrix.[9] Additionally, the reuse of catalyst **7** was also assayed. As can be seen in entry 6 of Table 1, a slight decrease in the enantioselectivity was observed, 80 vs 89%ee

In some cases chiral-supported catalysts prepared by polymerization have been reported to give better asymmetric inductions than those obtained through grafting.[11] Accordingly, vinylic derivative **9** was prepared in order to obtain the related supported catalyst **10** by polymerization. From the different polymerization techniques, we selected monolithic columns using divinylbenzene and styrene as comonomers for the preparation of **10**.[12] These types of material are the most suitable for the preparation of flow systems due to their porosity properties. The morphology of these macroporous materials, when appropriately tailored, avoids diffusion problems and allows them to act as stable and easily recoverable microreactors.[10,13]

Different polymerization mixtures were evaluated in order to synthesize the polymeric catalyst **10**. A mixture containing 40 wt % monomers (10 mol % **9**/90 mol % DVB; no styrene was used) and 60 wt % toluene-1-dodecanol as the porogenic mixture (10 wt % toluene) provided monoliths with the desired morphology and properties. The monolithic column allowed the design of a flow system (Figure 1) in which the column was attached to a pump and the reaction mixture ($ZnEt_2$ and benzaldehyde) was pumped continuously through the chiral column over a period of 24 h. After this time, the pump was stopped and the reaction was quenched and analyzed. With this experimental setup, an excess of $ZnEt_2$

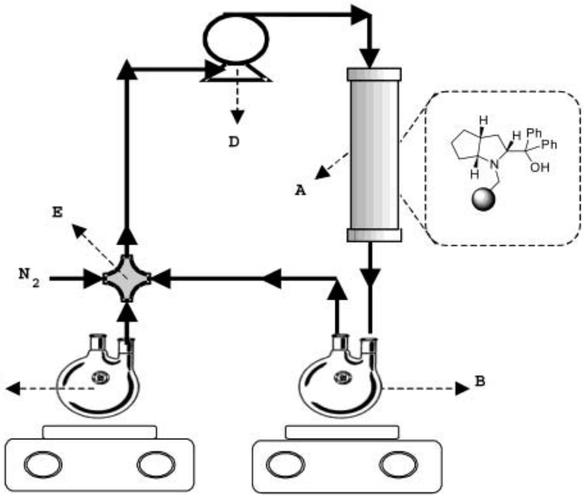

Figure 1. Schematic representation of the flow-bed reactor used in this work. (A) Reactor: macroporous monolithic rod of DVD/**9**. (B) Reservoir 1: Zn_2Et/PhCHO/**12**/**13** in anhydrous toluene. (C) Reservoir 2: toluene (anhydrous solvent to wash the reactor at the end of the reaction). (E) Four-port ways valve. (D) HPLC Gilson pump.

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was used as well as a relatively diluted concentration of the reactants. The final ratio of catalyst/benzaldehyde was approximately 10%. The results showed an excellent catalytic efficiency. A quantitative conversion of benzaldehyde was obtained, along with a selectivity of 85% for the formation of **12** and 99% ee. These figures represent the best enantioselectivities obtained to date for this reaction with a supported catalyst. As a matter of fact, columns of polymer **10** prepared as described above provided significantly better enantioselectivities than those obtained with the homogeneous analogues and with the polymer prepared by grafting. This improvement in the efficiency could be related to the formation of more appropriated chiral cavities during the polymerization process or to the isolation of the catalytic sites provided by the high degree of cross-linking used.[10] On the other hand, the changes on the reaction conditions (concentrations, ratios of catalyst/**11** on the column, etc.) needed for the flow system could also play a role in this context. Finally, we have to consider that the high flow rates provided by the monolithic columns avoid diffusional problems that have been previously reported when using highly cross-linked resins.

Even more interesting results were observed when the catalyst was reused. This catalytic system could be reused for four successive runs, obtaining again very high yields without any loss of its catalytic efficiency, both in terms of selectivity (**12**/**13** ratio) and enantioselectivity ((*R*)-**12**/(*S*)-**12** ratio) (see Figure 2). Similar long-term stability of supported catalysts has been previously reported for monolithic Ti-TADDOLates.[10] These results open the way for the potential application of those catalysts for continuous-flow systems.

Additional work is being carried out with the use of different aldehydes to establish the scope of this reaction, as well as with the use of this catalytic system in other asymmetric transformations. However, the present results clearly show the great potential of the use of functional monoliths derived from industrial chiral waste materials in order to design new, efficient, and environmentally friendly catalysts having exceptional long-term stability.

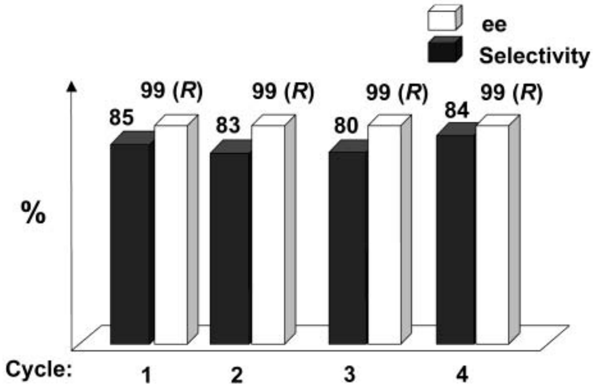

Figure 2. Reuse of the supported catalyst. Each cycle is a 24 h reaction. Cycle 2 after 24 h of **1**. Cycle 3 after 48 h of **1**. Cycle 4 after 2 weeks of **1**. Selectivity is described as the **12/13** ratio, and enantioselectivity (ee) is described as a function of the (*R*)-**12**/(*S*)-**12** ratio.

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

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