

Speeding up heterogeneous catalysis with an improved highly reusable catalyst for the preparation of enantioenriched secondary alcohols



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ABSTRACT

A new catalytic heterogeneous system, very efficient and highly reusable, for the preparation of enantioenriched secondary alcohols through the addition of diethylzinc to benzaldehyde has been developed. This system is based on a chiral bis(hydroxyamide) ligand supported on crosslinked polystyrene. The catalyst has been shown to be very efficient, leading to the corresponding secondary alcohol with an enantiomeric excess of 93% in a time as short as 2 h and using just 4% of the heterogeneous catalyst and just 1.5 equivalents of the organozinc reagent. We have demonstrated that the new catalyst is very stable and can be efficiently recycled with no decrease in yield or enantioselectivity. The presented system has an unquestionable interest for the potential transfer of the reaction to the industry by using catalytic fluidized-bed reactors.

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1. Introduction

Chiral secondary alcohols are key intermediates for the preparation of socio-economically valuable natural and non-natural products with biological activity, including drugs, and new materials with interesting physicochemical properties [1–4]. These intermediates are usually prepared in the industry by asymmetric reduction of ketones, either with chiral boranes or by chiral hydrogenation based on Noyori asymmetric hydrogenation [5–13]. However, the first option produces large amounts of borane waste and the second one requires expensive and non-environmentally friendly metal-ligand combinations. In this sense, the enantioselective addition of organozinc reagents to aldehydes [14–24] offers a very interesting alternative, with the advantages that a new C—C bond is created at the same time and that only a catalytic amount of a more environmentally friendly zinc complex is needed. Because of the relevance of the mentioned reaction, a large effort has been devoted to the development of ligands able to promote the addition enantioselectively. However, the most efficient ligands needed for this reaction are usually synthetically elaborated (and thus very expensive). In addition, because many of them are relatively unstable (most are

amino alcohols), they cannot be recovered from the reaction medium and reused in further reactions. These two facts have hampered the transfer of the reaction to the industry, despite its big interest.

A possible solution for the implementation of this reaction in the industry is the immobilization of chiral ligands or catalysts by covalently anchoring them onto an insoluble polymeric matrix (heterogenization) [20,25–30]. The heterogeneous catalysts offer very interesting advantages for the industry, such as improved operation and control of the industrial process; easy separation of the catalyst after the reaction and possibility of recycling and reusing it, a key issue for sustainability; important savings in solvents, energy and labor time; minimization of catalyst-derived toxic traces in the product (e.g., metals); improved stability and in special cases, improved activity, including selectivity [31–33]. All these advantages help improving the economic and environmental sustainability of the process, therefore being critical to the industry [25–27,34–39].

Among all the possible solid supports, crosslinked polystyrene (PS) is the most commonly used polymer because of its availability, low price, functional group compatibility for the reaction, easy functionalization, and so on [40–47]. In this sense, many efficient homogeneous ligands have been successfully anchored onto PS to provide efficient heterogeneous ligands that could be reused several times [32,48,49]. However, the development of a polymer-supported catalyst is not trivial. In many cases, the catalyst efficiency can be diminished by the polymeric matrix, particularly in that concerning the reaction rate, which is usually negatively affected by the well-known diffusion-rate effect in heterogeneous processes, with the corresponding adverse influence in the process economy [25–27,34,35,40–44].

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Some research groups have made interesting works on designing flow reactors including these heterogeneous catalysts [49,50]. Flow reactors are a very attractive solution for the transfer of asymmetric catalytic reactions to the industry, because they improve mass and heat transfer; entail a significant intensification of the process, making available systems working 24 h a day, 7 days a week; and allow easier optimization through the adjustments of simple parameters such as flow, pressure, and temperature [51–54]. However, they often have a complex design and use: they need a high amount of catalyst, and, moreover, they are subjected to frequent flow obstructions produced by the formation of salts during the reaction or by decomposition of the catalyst. Therefore, this kind of reactors requires highly stable catalysts. These drawbacks of the flow reactors are the reason for their more limited use at industrial scale than the catalytic fluidized-bed reactors, where the solid is suspended in the fluid, with a continuous movement, and thus avoiding flow obstructions [55,56].

Among the various reported ligands for the enantioselective addition of organozinc reagents to aldehydes, chiral hydroxyamides [57] are very attractive, mostly because of two advantages: (1) they can be easily prepared by straightforward coupling reactions (amidation) of cheap starting materials (e.g., hydroxy acids and amines, or acids and amino alcohols), which can be obtained enantiopure from the Chiral Pool and (2) this functional group combination is much more stable than the amino alcohol combination, commonly used for the said reaction. Among all the chiral hydroxyamides, the ones derived from ketopinic acid (e.g., **1** in Fig. 1) must be outlined [58]. These ligands, developed by us from a seminal result early reported by Oppolzer [59–61], have the advantages of easy preparation from commercial (1*S*)-ketopinic acid (an enantiopure starting material derived from renewable natural camphor), high enantioselective efficiency [62], and tunable enantioselectivity reversal [63].

Our group took advantage of the high chemical stability of the amide functional group for the design and development of PS-supported bis(hydroxyamide) **3** (Fig. 1). This heterogeneous ligand was obtained by anchoring bis(hydroxyamide) **2** to a crosslinked PS. Heterogeneous **3** was proven to be a cheap, long-life and highly reusable supported system for the enantioselective addition of organozincs to aldehydes in the absence of titanium (greener organozinc catalysis) at room temperature (energy-saver process) [64]. Unfortunately, a negative effect on the reaction rate was observed when heterogenizing the ligand: the reaction time increased from 1 h for the homogeneous reactions (catalyzed by **1** or by **2**) to 20 h for the heterogeneous reaction (catalyzed by **3**) [64]. We attribute this effect to the low diffusion rates of the substrate and the reactant through the PS chain to reach the catalytic sites. Thus, we thought that this adverse effect could be diminished in new PS-supported bis(hydroxyamides) where the key structure of **2** (indeed, the functional moiety) was located further away from the supporting matrix, thereby enhancing the rate of reactants to reach the catalytic sites (see Fig. 1).

Thus, with regard to our previous work in this area, herein we report an important improvement in the catalytic efficiency (reaction rate enhancement with no loss of enantioselectivity) for PS-supported ketopinic acid-derived bis(hydroxyamides) and the structural factors

controlling it. The catalytic behavior of the designed functional polymers has been investigated for the enantioselective ethylation of benzaldehyde as the test reaction.

2. Experimental

2.1. Materials and instrumentation

Common solvents were dried and distilled by standard procedures. All starting materials and reagents were obtained commercially and used without further purifications. Flash chromatography purifications were performed on silica gel (230–400 mesh ASTM). Melting points were uncorrected. Nuclear Magnetic Resonance (NMR) spectra were recorded at 20 °C and the residual solvent peaks were used as the internal standards. FTIR spectra were obtained using the thin-layer technique. GC analyses were performed at 120 °C in a chromatograph equipped with a capillary silicon-gum (SGL-1) column and a FID and using nitrogen as the mobile phase. Chiral-HPLC analyses were performed at room temperature (r.t.) in a chromatograph equipped with a Chiralpak-IC column and a DAD and using hexane/isopropanol as the mobile phase. Mass spectrometry (MS) and high-resolution mass spectrometry (HRMS) were performed using the electron impact technique. Elemental analyses (C, H and N) were performed by the dynamic flash combustion technique. The nitrogen composition of the functionalized PSs was used to estimate the bis(hydroxyamide) loading (*f*) in the said polymers.

2.2. Preparation of **11**

2.2.1. Synthesis of diazepane **18**

Under argon, anhydrous ammonium formate (2.56 g, 40.6 mmol) and 10% Pd/C (1.67 g, 200 mg/mol) were added to a stirred solution of **17** [65] (3.45 g, 8.1 mmol) in methanol (60 mL), and the resulting mixture was refluxed for 2 h. After cooling down to r.t., the mixture was filtered through a Na₂SO₄ pad to remove the catalyst, and the filtrate submitted to solvent evaporation under reduced pressure. The residue was dissolved in CHCl₃ (60 mL), washed with H₂O (4 × 20 mL) and dried over anhydrous Na₂SO₄. Filtration and solvent evaporation under reduced pressure gave **18** (1.88 g, 92%) as a pale brown viscous oil, which was used in the next step without further purification. ¹H NMR (CDCl₃, 300 MHz), δ: 3.43 (dd, *J* = 6.2, 6.2 Hz, 2H), 3.01 (dd, *J* = 13.7, 5.6 Hz, 2H), 2.82 (m, 4H), 2.65 (dd, *J* = 13.7, 7.5 Hz, 2H), 2.44 (bs, 2H), 1.90 (m, 1H), 0.85 (s, 9H), 0.00 (s, 6H) ppm. ¹³C NMR (CDCl₃, 75 MHz), δ: 64.6, 52.6, 50.6, 44.9, 5.8, 18.1, –5.5 ppm.

2.2.2. Synthesis of bis(ketoamide) **20**

A mixture of **19** (2.58 g, 14.2 mmol), *N*-[3-(dimethylamino)propyl]-*N'*-ethylcarbodiimide hydrochloride (EDC·HCl, 2.73 g, 14.2 mmol), 4-(dimethylamino)pyridine (DMAP, 1.73 g, 14.2 mmol) and **18** (1.73 g, 7.1 mmol) in CH₂Cl₂ (50 mL) was stirred at r.t. for 72 h. Then, CHCl₃ (50 mL) and H₂O (50 mL) were added to the reaction mixture, and the organic layer was separated, washed successively with 10% HCl

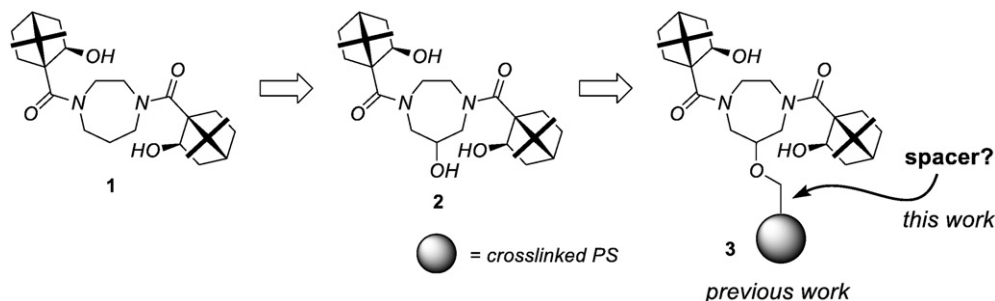


Fig. 1. Development of polystyrene-supported (PS-supported) hydroxyamides for the enantioselective addition of organozincs to aldehydes.

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