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Title: Polymer-supported chiral  $\alpha$ -amino amides for the asymmetric addition of diethylzinc to aldehydes: Transforming an inactive homogeneous system into an efficient catalyst



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1	Polymer-supported chiral $\alpha$ -amino amides for the asymmetric addition
2	of diethylzinc to aldehydes: Transforming an inactive homogeneous
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13	Abstract
14	A series of polymer-supported $\alpha$ -amino amides derived from natural amino acids have
15	been easily synthesized and fully characterized. Their chiral Zn (II) complexes
16	catalyzed the enantioselective addition of diethylzinc to aldehydes to form chiral
17	secondary alcohols in high yields and enantioselectivities up to 95% were obtained. The
18	results showed that the immobilization of this chiral ligand onto a polymeric matrix
19	transforms the inactive homogeneous system into an efficient catalyst. Moreover, the
20	supported catalyst could be re-used at least five times without any significant loss of
21	catalytic activity.
22	
23	Keywords: asymmetric catalysis, polymer-supported catalysts, diethylzinc, N-
24	containing ligands, enantioselective addition
25	

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#### 25 1. Introduction

26 The use of polymer-supported catalysts in asymmetric reactions is a vigorously pursued 27 area of research.[1-4] Besides simplification of separation and recycling, immobilized 28 catalysts offer additional benefits including easier handling of toxic reagents, improved 29 stability of labile systems in the polymeric matrix and convenient operation in 30 continuous flow reactors, making the catalytic processes more environmentally friendly 31 and industrially applicable.[5] Thus, the industrial applications of even expensive and 32 complex chiral catalysts can be achieved in an economical and environmentally benign 33 way. Carbon-carbon bond formation is the essence of organic synthesis and provides the 34 foundation for generating more complicated organic compounds from the simpler ones. 35 In this regard, the enantioselective organozinc addition to aldehydes is of long standing 36 research interest as the resulting optically active sec-alcohols are important building 37 blocks, [6] and has become a benchmark reaction in enantioselective catalysis. [7-8] This 38 process is efficiently catalyzed by homogeneous catalysts derived from a variety of 39 chiral ligands such as amino alcohols (N, O ligands), [9-11] diamines (N, N 40 ligands),[12-13] or diols (O, O ligands).[14-15]. Some drawbacks of the homogeneous 41 catalytic systems are the difficulties involved in separation of catalyst from the reaction 42 media, purification of the products and the reuse of the catalyst, normally requiring 43 tedious procedures. Thus, it is not surprising that, since the seminal work by Soai, Itsuno and Frechet, [16-17] different research groups have been involved in the 44 45 preparation of polymer-supported chiral ligands, being able to efficiently mediate this 46 transformation.[18-23] Most efforts are directed towards the preparation of supported 47 systems being able to act in a comparable way to that of the homogeneous counterparts 48 by reducing the potential interferences of the polymeric matrix.[24-27] This has been 49 based on the consideration that the micro heterogeneities provided by the presence of 50 the matrix produce a reduction in the performance of the polymer-supported system. An 51 alternative approach is to take advantage of the properties of the polymeric matrix and 52 the immobilization process to develop supported catalytic systems with higher activities 53 and selectivities than their homogeneous counterparts.[28-30]

54

From the several families of chiral ligands used in asymmetric catalysis, nitrogencontaining ligands have received an important attention over the last years.[31] In this regard, simple  $\alpha$ -amino amides **1** and bis(amino amides) **2**, having an amino group and an easily ionisable N-H amide subunit, can be compared to amino alcohols and

59 structures of this class have been recently reported as good ligands for different 60 enantioselective transformations, such as, the Ru (II)-catalyzed asymmetric transfer 61 hydrogenation of acetophenone, [32-33] or the conjugate addition of dialkylzinc to 62 chalcones,[34] Zn(II) complexes of related bis(amino amide) ligands 2 (Figure 1) gave 63 high enantioselectivities in the addition of dialkylzinc reagents to aromatic 64 aldehydes[35] and their corresponding Cu (I) complexes were effective for the cypropoparation reaction.[36] Recently, we have shown that Ni (II) complexes of 65 66 amino amides are able to efficiently catalyze the addition of dialkylzincs to aldehydes, 67 achieving an excellent dual stereocontrol just by a proper adjustment of the 68 stoichiometry of those Ni complexes.[37-39] Taking this into account, we consider the 69 preparation of the corresponding polymer-supported systems derived from 1, as 70 heterogeneous catalyst offer many advantages over the homogeneous systems.

71

72 Thus, herein we report, in connection with our previous work in this area how a non-73 active homogenous system can be transformed, upon immobilization onto a 74 polystyrene-divinylbenzene polymer, into an active, highly selective and 75 enantioselective catalytic system. The catalytic behaviour of the corresponding 76 polymer-supported  $\alpha$ -amino amides has been investigated for the enantioselective 77 addition of dialkylzinc compounds to aldehydes.

78

#### 79 **2. Experimental**

#### 80 2.1. Materials

81 All reagents were used as received, without any further purification. All samples were 82 vacuum-dried at 60 °C for 24 h before making any spectroscopic measurements to remove most of the adsorbed water. Raman spectra were acquired on a JASCO NRS-83 3100 dispersive spectrometer under the following conditions: 785 nm laser with a single 84 monochromator, grating 600 lines mm<sup>-1</sup>, slit 0.2 mm, resolution 12.75 cm<sup>-1</sup>, with a 85 center wavenumber of 1200 cm<sup>-1</sup>, a laser power of 90.1 mW, and ten accumulations of 5 86 87 s each. FTIR spectra were recorded on a JASCO 4000 spectrometer equipped with a 88 PIKE ATR MIRacle. Elemental analyses were performed on an Elemental Carlo Erba 89 1108 apparatus. DSC curves were obtained at 10 K/min under nitrogen atmosphere. 90 Thermal analyses were carried out using a TG-STDA Mettler Toledo model 91 TGA/SDTA851e/LF/1600 analyzer under a flow of N<sub>2</sub>. The temperature range for TGA was 30-400 °C at 10 °C min<sup>-1</sup>. TEM and XDS experiments were carried out with a JEOL 92

93 2100 instrument. Access to the above equipment was provided by the SCIC (Servei

94 Central d'Instrumentació Científica) of the Universidad Jaume I.

95

#### 96 **2.2. Catalysts preparation and characterization.**

97 Synthesis of resins 4a-k. To a suspension of chloromethylated resin 3 (1 mmol) in dry 98 DMF (10 mL), sodium phthalimide (2.5 mmol in DMF) was slowly added and reaction 99 mixture was stirred at 50-60 °C for 18 h. The resulting resin was filtered and washed 100 with DMF ( $3 \times 10 \text{ mL}$ ), methanol, ( $3 \times 10 \text{ mL}$ ) water ( $3 \times 10 \text{ mL}$ ) and methanol ( $3 \times 10 \text{ mL}$ ) 101 and vacuum dried at 50°C overnight to give polymer 4. The NBP test was applied with 102 negative results to a sample of the polymer. [40] FT-IR (KBr) v<sub>max</sub> 3031, 2921, 1718, 1602, 1492, 1452, 1027, 696 cm<sup>-1</sup>; FT-Raman  $v_{max}$  2953, 1770, 1640, 1451, 1170, 1019 103 cm<sup>-1</sup>: Elemental analysis (in parentheses theoretical results for a quantitative 104 transformation) for 4a, 1.20% N (1.22% N); 4b, 1.40% N (1.41% N); 4c, 1.88% N 105 (1.95% N); 4d, 2.26% N (2.29% N); 4e, 2.58% N (2.74% N); 4f, 2.79% N (2.98% N); 106 107 4g, 1.24% N (1.27% N); 4h, 2.08% N (2.15% N); 4i, 2.50% N (2.61% N); 4j, 2.78% N 108 (2.95% N); 4k, 3.34% N (3.42% N).

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Synthesis of resins 5a-k. To a suspension of resin 4 (1 mmol) in ethanol (10 mL), a 110 solution of hydrazine (2.5 mmol in ethanol) was added dropwise under an inert 111 atmosphere and refluxed. The resulting resin was filtered and washed with ethanol 112 113 (3×10 mL), diluted KOH solution (3×10 mL), water (3×10 mL) and methanol (3×10 mL) and vacuum dried at 50 °C overnight to give polymer 5. FT-IR (KBr) v<sub>max</sub> 3374, 114 3022, 2921, 1603, 1493, 1452, 1028, 697, 532 cm<sup>-1</sup>; FT-Raman v<sub>max</sub> 2956, 1170, 1636, 115 1451, 1179, 1014 cm<sup>-1</sup>; Elemental analysis (in parentheses theoretical results for a 116 117 quantitative transformation) for 5a, 1.31% N (1.38% N); 5b, 1.50 % N (1.61% N); 5c, 2.26% N (2.38% N); 5d, 2.79% N (2.90% N); 5e, 3.50% N (3.67% N); 5f, 4.01% N 118 119 (4.13% N); 5g, 1.38% N (1.43% N); 5h, 2.55% N (2.69% N); 5i, 3.32% N (3.44% N); 120 5j, 3.91% N (4.06% N); 5k, 4.89% N (5.02% N).

121

Synthesis of resins 6a-k. To a suspension of resin 5a (1 mmol) in dry THF (5 mL), a solution of Cbz-(*S*)-2-amino-N-benzyl-3-phenylpropanamide (2.3 mmol in THF) was added dropwise under an inert atmosphere. The reaction mixture was stirred at 50-60 °C for 12 h. The resulting resin was filtered and washed with THF ( $3 \times 10$  mL), methanol ( $3 \times 10$  mL), water ( $3 \times 10$  mL) and methanol ( $3 \times 10$  mL) and vacuum dried at 50°C

overnight to give polymer 6a. <sup>13</sup>C RMN (75 MHZ, gel phase, CDCl<sub>3</sub>) δ: 42.6, 50.3, 127 61.2, 68.8 ppm; FT-IR (KBr) v<sub>max</sub> 3412, 3032, 2925, 1716, 1671, 1605, 1493, 1452, 128 1027, 697 cm<sup>-1</sup>; FT-Raman  $v_{max}$  2954, 1770, 1639, 1451, 1172, 1033 cm<sup>-1</sup>; Elemental 129 130 analysis (in parentheses theoretical results for a quantitative transformation) for **6a**, 2.11% N (2.16% N); 6b, 2.31% N; (2.44% N) 6c, 3.12% N (3.22% N); 6d, 3.44% N 131 (3.67% N); **6e**, 4.11% N (4.22% N); **6f**, 4.40% N (4.51% N); **6g**, 2.11% N (2.23% N); 132 133 **6h**, 3.32% N (3.50% N); **6i**, 3.98% N (4.07% N); **6j**, 4.31% N (4.47% N); **6k**, 4.93% N 134 (5.00% N).

135

Synthesis of resins 7a-k. To a suspension of resin 6a (1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL), a 136 137 solution of HBr/AcOH (33%) was slowly added and the mixture was stirred at rt during 138 18 h. The resulting resin was filtered and washed with diethylether  $(3 \times 10 \text{ mL})$ , 139 methanol ( $3 \times 10$  mL), water ( $3 \times 10$  mL), diluted KOH solution ( $3 \times 10$  mL), methanol  $(3 \times 10 \text{ mL})$  and CH<sub>2</sub>Cl<sub>2</sub>  $(3 \times 10 \text{ mL})$  and vacuum dried at 50 °C overnight to give 140 polymer 7a. <sup>13</sup>C RMN (75 MHz, gel phase, CDCl<sub>3</sub>) δ: 42.1, 51.3, 61.6 ppm; FT-IR 141 (KBr) v<sub>max</sub> 34180, 3020, 2923, 1674, 1602, 1492, 1455, 1274, 696 cm<sup>-1</sup>; FT-Raman v<sub>max</sub> 142 2952, 1639, 1454, 1174, 1029 cm<sup>-1</sup>: Elemental analysis (in parentheses theoretical 143 144 results for a quantitative transformation) for 7a, 2.23% N (2.41% N); 7b, 2.64% N (2.76% N); 7c, 3.59% N (3.80% N); 7d, 4.38% N (4.45% N); 7e, 5.14% N (5.30% N); 145 13f, 5.58% N (5.76% N); 7g, 2.38% N (2.49% N); 7h, 4.05% N (4.20% N); 7i, 4.88% N 146 147 (5.06% N); 7j, 5.48% N (5.69% N); 7k, 6.36% N (6.57% N).

148

#### 149 Synthesis of the Zn complex derived from 7a.

To a toluene suspension of resin **7a** 2.2 equivalents of  $Et_2Zn$  (1.1 M in toluene) were slowly added under inert atmosphere at 0 °C during 30 minutes. After washing with dry toluene and drying with a stream of N<sub>2</sub>, the resulting zinc complex was isolated and kept under inert atmosphere. FT-IR  $v_{max}$ : 3023, 2923, 1662, 1594, 1488, 1446, 1025, 751, 696 cm<sup>-1</sup>.

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#### 156 **2.3. Catalytic tests**

General Procedure for the Asymmetric Addition of Diethylzinc to Aldehydes
Catalyzed by PS Catalysts. To a stirred suspension of the polymer-supported catalyst
(10 mol %) in toluene (1 mL) was added a solution of aldehyde in hexanes under argon,
and the stirring was continued at r.t. for 30 min. After the addition of diethylzinc (1.1 M

161 in toluene) at 0°C, the reaction mixture was stirred at r.t. for a further 36 h, and was then 162 quenched with 1 M HCl (4 mL). The resulting mixture was filtered and the filtrate was 163 extracted with  $CH_2Cl_2$  (3×10 mL). The combined organic layers were dried with 164 anhydrous MgSO<sub>4</sub> and concentrated under reduced pressure. Purification of the residue 165 by flash chromatography (PE/AcOEt 15:1) afforded the desired alcohol. The enantiomeric excess and the absolute configuration of the resulting alcohols were 166 167 determined by HPLC and optical rotation. The catalyst was collected by filtration, washed with dry  $CH_2Cl_2$ , vacuum dried and used for a new run. For regeneration, the 168 169 polymer was stirred with 1 M HCl-THF (1:2 mL) for 1 h, and then washed successively 170 with CH<sub>2</sub>Cl<sub>2</sub> (3×15 mL), THF (2×15 mL) and MeOH (2×15 mL). After vacuum dried at 171 50 °C for 5 h, the resin could be reused in the successive catalytic reactions. A typical 172 analysis of the reaction products separated reveals (R)- and (S)-1-phenyl-1-propanol 173 (12), and a small amount of benzyl alcohol (13), as the side-product. The selectivity was calculated by the following equation based on the <sup>1</sup>H NMR peak areas: 174

175 Selectivity = 
$$\frac{12}{12 + 13} \times 100$$

176

177 Conditions for the Analysis of Chiral Secondary Alcohols. Chiral Capillary GC 178 column VF-5 ms; 30 m × 0.25 mm, 0.25  $\mu$ m. Carrier Gas: H<sub>2</sub> (5 mL·min<sup>-1</sup>). Inyector 179 230 °C, Detector (FID) 300 °C, oven 60-130 °C, 10 °C min<sup>-1</sup>. Chiral HPLC: Chiralcel 180 OD columm; 254 nm UV detector. The racemic alcohols products were obtained by 181 addition of Et<sub>2</sub>Zn and Me<sub>2</sub>Zn to aldehydes. The conditions of analysis and retention 182 times of the *R* and *S* isomers have been reported elsewhere.[42-43]

183

#### 184 3. Results and discussion

#### 185 **3.1. Synthesis of polymer-supported chiral α-amino amides**

186 Considering the advantages of immobilized catalysts in asymmetric synthetic reactions, 187 we considered to anchor  $\alpha$ -amino amide ligands onto a polystyrene-divinylbenzene resin. Initial attempts of synthesizing polymer-supported chiral  $\alpha$ -amino amides were 188 189 carried out by direct reaction of ligand 1 with commercial Merrifield resins with a low level of crosslinking (gel-type chloromethylated PS-DVB, 1% DVB), but the analysis of 190 191 the resulting functionalized polymers suggested that polyalkylation of the amine groups 192 was taking place, as inferred from elemental analysis data. In order to avoid this 193 problem, an alternative grafting methodology was designed (Figure 1). For this strategy,

194 both, gel-type commercially available Merrifield resins and monolithic macroporous 195 chloromethylated resins were used as the starting polymers 3. In the case of macroporous polymers, monolithic resins were prepared by polymerization of a mixture 196 197 of styrene (8), divinylbenzene (9) and chloromethylstyrene (10) under radical conditions 198 (Supplementary Material), using AIBN as the initiator and toluene/dodecanol as the 199 porogenic mixture, following previously described procedures.[44-45] Under the 200 studied conditions, polymerizations proceed in general in quantitative yields obtaining 201 polymers with crosslinking degrees of 1 and 2% for gel-type resins (see Table 1) and 20 202 % for the monoliths.

203

204 205 FIGURE 1

As shown in Figure 1, treatment of polymers **3** with potassium phtalimide in DMF at 50 206 °C gave resins 4 with quantitative yields.[46-47] The reaction was easily monitored 207 208 using FT-IR and FT-Raman spectroscopy.[48] Thus, FT-IR spectra showed the appearance of new bands at 1717 cm<sup>-1</sup>, for the phthalimide moiety, as well as the 209 complete disappearance of the C-Cl band at 1265 cm<sup>-1</sup>, which was even clearer in the 210 FT-Raman spectra. Complete substitution of the chloride was also confirmed by 211 elemental analysis and by the NBP test, which showed negative results.[40] The NBP 212 213 test is able to easily determine the presence of reactive chloride groups and was found to 214 be very important to characterize this step. After, phtalimide treatment, reaction of 215 resins 4 with hydrazine hydrate in refluxing ethanol overnight provided the 216 transformation of phthalimide groups into amine groups, affording resins 5, whose IR spectra showed the absence of bands at 1717 cm<sup>-1</sup>. The conversion of the aminomethyl 217 resins 5 into functionalized polymers 6 was carried out by reaction with N-Cbz-L-218 phenylalanine in THF. The resulting resins 6 displayed IR bands at 1671 and 1716 cm<sup>-1</sup>, 219 220 corresponding to the Cbz-N-protected amino amide moiety, showing the effective 221 immobilization of the ligand onto the polymeric support. Final deprotection of the 222 amine groups was obtained by overnight treatment with 33% HBr/HOAc in CH<sub>2</sub>Cl<sub>2</sub> to 223 afford the desired amino amide polymers 7, following a similar protocol to that used for 224 the preparation of related compounds in solution.[49-53] These functionalized resins showed the complete absence of the Cbz band at 1716 cm<sup>-1</sup> in their IR spectra. By using 225 this methodology, functionalized resins with final loadings ranging from 0.80 to 2.27 226 227 mmol/g, according to the elemental analyses, were obtained. (Table 1) These values are

in good agreement, within the experimental error, with the values expected for aquantitative transformation from 3.

230

231 <sup>13</sup>C gel-phase NMR spectroscopy could also be applied to monitor those synthetic transformations and to characterize the final polymers in the case of low crosslinked (1-232 2%) gel-type resins.[54-55] The <sup>13</sup>C gel-phase NMR spectrum reveals several broad and 233 intense peaks around 40 and 130 ppm corresponding to the C atoms of the PS-DVB 234 235 resin. The appearance new peaks of aliphatic carbons at 42.1, 51.3 and 61.6 ppm 236 indicates the successful anchoring of the  $\alpha$ -amino amide on the polymeric matrix (see 237 Supplementary material). Likewise, these polymers were characterized by DSC and 238 TGA, showing thermal stabilities over 210 °C (see Supplementary Material). Similar 239 behavior was observed for the catalytic complex.

- 240
- 241 242

#### TABLE 1

In general, for the synthesis of the different polymer-supported chiral  $\alpha$ -amino amides, very good yields could be achieved for all the considered transformations. This is clearly illustrated by the data shown in Table 1, which shows the values obtained for conversion and loading for the final polymer-supported ligands from the corresponding elemental analysis data.

248

#### 249 **3.2.** Catalytic activity in the asymmetric addition of diethylzinc to aldehydes

The catalytic efficiency of the functionalized polymers 7 was tested for the addition of 250 251  $Et_2Zn$  to benzaldehyde leading to the formation of 1-phenyl-propanol. This benchmark 252 reaction is a commonly used method for synthesizing chiral secondary alcohols, which 253 are useful intermediates for the preparation of biologically active compounds and are 254 often components of natural products. Although previous studies in solution with ligand 255 1 and related compounds had shown that an efficient enantioselective catalysis of the 256 addition of Et<sub>2</sub>Zn to benzaldehyde required the previous formation of their Ni (II) 257 complexes, [37] preliminary experiments were carried out with resin 7a (10 % molar), 258 1.0 equivalent of benzaldehyde (1.1 M in toluene) and 2.2 equivalents of Et<sub>2</sub>Zn (1.1 M 259 in toluene) at 0 °C. Rather surprisingly, (see Table 2, entry 1) after 18 h, (S)-1-260 phenylpropanol was obtained in 87% yield, with 91% ee. After 36 h, the yield was 261 raised to 94% and the enantioselectivity slightly increased up to 92%. When compared

to the results for the homogeneous system (see entry 12, Table 3), this represents one of
the more dramatic positive effects of the polymeric backbone up to now reported for
polymer-supported reagents or catalysts.

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266

267

#### FIGURE 2

268 The "*in situ*" formation of the catalyst during the addition reaction was supported by 269 experimental ATR-FTIR studies in inert atmosphere. Thus, the zinc complex was 270 prepared by treatment of the resin 7a with 2.2 equivalents of  $Et_2Zn$  (1.1 M in toluene) at 271 0 °C during 30 minutes under inert atmosphere, subsequent washing with dry toluene 272 and drying by a stream of N<sub>2</sub>. As shown in Figure 2, the vibrational band observed for 7a at 1672 cm<sup>-1</sup>, assigned to the C=O stretching, is shifted to lower wavenumbers (1594 273 cm<sup>-1</sup>) indicating the participation of the deprotonated amide group in the coordination to 274 275 the zinc atom, as observed in related systems.[56-59] Additionally, transmission 276 electron microscopy (TEM) and energy dispersive X-ray spectroscopy (EDS) were used 277 to characterize the catalytic zinc complex and results confirmed the presence of this 278 metal in the polymeric matrix (see Supplementary Material). As illustrated by the inlet in Figure 2, TEM images and EDX (Supplementary Material) also confirm the presence 279 of zinc in the polymeric matrix. No changes occur after the reaction if the sample is 280 281 handled with care, under an inert atmosphere. In the presence of humidity, the catalytic complex is destroyed as revealed by the appearance of the C=O band at 1674 cm<sup>-1</sup> (see 282 Supplementary Material). Under those circumstances, zinc oxide seems to be formed. 283

284

285

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# Initially, a screening of solvents was carried out under identical conditions to study the solvent effect. Positive results were also obtained using other solvents such as THF, CH<sub>2</sub>Cl<sub>2</sub> or hexane, although the enantioselectivities obtained were significantly lower

TABLE 2

288 solvent effect. Positive results were also obtained using other solvents such as THF, 289 CH<sub>2</sub>Cl<sub>2</sub> or hexane, although the enantioselectivities obtained were significantly lower (see Table 2). Lowering the reaction temperature for the addition to -20 °C, resulted in a 290 291 slight increase of enantioselectivity (93% ee) but at the expenses of an important 292 decrease in the reaction rate. Next, in order to determine the optimal amount of the 293 ligand needed for the addition of diethylzinc to benzaldehyde, several experiments using 294 variable quantities of functionalized resin 7a were carried out. In these studies, the 295 concentrations of benzaldehyde and diethylzinc were kept constant at 0.5 and 1.1 mM,

296 respectively, and the reaction was conducted at 0 °C in toluene. Decreasing the catalyst 297 loading to 5% reduced slightly the enantioselectivity to 90% ee, maintaining the 298 conversion. Most likely, this indicates that for this catalyst loading the uncatalyzed 299 reaction starts to provide a significant contribution to the process. This is confirmed 300 when a further decrease in catalyst loading (3 and 1%) is studied (see Supplementary 301 Material), as, in this case, also the conversion is reduced for the same reaction time. The 302 selectivity also decreases, as reducing the rate of the process increases the relative 303 importance of the alternative reaction of aldehyde reduction. Thus, optimal conditions 304 seems to correspond to the use of 5 molar % of functionalized resin in toluene at 0 °C 305 for 36 h.

306

307

308

#### TABLE 3

The different resins 7, containing variable levels of cross-linking and ligand 309 310 functionalization, were then assayed for this benchmark reaction. The results are 311 summarized in Table 3. The reaction was studied at 0 °C in toluene, using a 5% molar 312 amount of the supported catalyst for 36 hours. All of them promoted the enantioselective addition of diethylzinc to benzaldehyde, with enantioselectivities from 313 314 moderate to high and in good yields. The predominant enantiomer of 1-phenyl-1propanol formed in the reactions possessed the S configuration, which suggest the 315 316 prevalence of the mechanistic model established by Noyori and coworkers for the amino 317 alcohol mediated reaction.[60-61]

318

319

320

#### FIGURE 3

321 A similar mechanism can be proposed for the polymer-supported  $\alpha$ -amino amides, as shown in Figure 3. After elimination of an ethane molecule from diethylzinc, the zinc 322 323 atom can be coordinated by the amide and amine sites to form a five-membered 324 intermediate, involving deprotonation of amide, as inferred from IR spectra. This zinc 325 complex coordinates to benzaldehyde through the zinc atom activating the carbonyl 326 group. Interaction with a second diethylzinc molecule, provides the product forming complex, facilitating the ethyl migration to benzaldehyde via a tricyclic transition state. 327 328 Based on this model, the product forming complex is regenerated upon reaction with 329 diethylzinc and benzaldehyde, after elimination of a stable dialkylzinc alkoxyde and

330 completing the catalytic cycle. The stereochemistry of the alkoxyde product is 331 kinetically determined by the relative energy of the two most stable diastereomeric 332 transition states, namely *anti-trans* and *anti-cis*, which favour the formation of the (S)-333 and (R)-product, respectively. In this case, an energy difference of 2.8 kcal/mol is 334 calculated between the two transition states (Supplementary Material) using DFT 335 calculations with the Spartan 10 software package.[62] Thus, calculations predict a high 336 enantioselectivity with the S stereoisomer being the main product, which is consistent 337 with the experimental results.

338

339 The dramatic effect on activity observed upon immobilization could be related with the 340 formation of inactive aggregated species for the homogeneous system.[63-64] As a matter of fact, formation of some colloidal particles is observed after some time, 341 342 although complete precipitation does not take place. To get further information in this 343 regard, several solvents where tested using **1** as ligand. Again, no activity was observed 344 in hexane, THF and CH<sub>3</sub>CN. Previous formation of the Zn complex by treatment by 345  $Zn(OAc)_2$  provided some activity but without any enantioselectivity. Although the 346 reaction rate and enantioselectivity of immobilized catalysts are sometimes lower than those of the homogeneous system, [29] mainly because the chiral selective sites may be 347 348 more hindered when anchored onto the solid supports, this steric hindrance, associated 349 with the rigidity of the polymeric matrix, can also avoid the formation of such 350 aggregated systems (Supplementary Material). This is confirmed by the results shown 351 in Table 3 that show how the enantioselectivity decreases when the functionalization 352 degrees are increased. Rather interestingly, monolithic resins always give place to 353 significantly lower enantioselectivities (see entries 7-11). This suggests that the 354 polymerization of the monomeric mixture, under the conditions used, does not provide a 355 uniform distribution of the chloromethyl functional groups through the polymer, and 356 accordingly of the catalytic sites, probably concentrated on the accessible surfaces. This 357 decreases the efficiency of the pseudodilution effect required to achieve a higher 358 enantioselectivity.[65]

359

A kinetic study was performed under the optimized conditions (catalyst **7b**, toluene, 0 C) and Figure 4 displays the conversion of benzaldehyde and product yields as a function of the reaction time. The graph also includes the variation of selectivity and enantioselectivity during the reaction period considered. The concentration of

benzaldehyde decreases with time while that of the main product (1-phenyl-1-propanol)
increases almost linearly during the first reaction period of ca. 10 h. Then, the
conversion slows down and the product yield approaches a plateau after a period of ca.
20 h. In comparison, the yield of the minor 1-phenyl-1-methanol by-product increases
during the initial reaction period but slows down after 10 h. The addition was essentially
complete after 30 h. In this way, the selectivity slightly increases with time, while the
enantioselectivity remains essentially constant.

371 372

373

FIGURE 4

374 The general applicability of resin **7b** was tested on a variety of aldehydes, including 375 aromatic and aliphatic aldehydes, under the optimized reaction conditions (catalyst 7b) (10% mol) in toluene at 0 °C, 36 h.). The desired sec-alcohols were obtained in high 376 377 conversions and some results are gathered in Table 4. For the aromatic aldehydes 378 studied, the products were isolated in excellent yields (83-90%) and enantioselectivities 379 (86-95%). In all cases, the (S)-enantiomer of the addition product was obtained as the 380 major isomer. The substitution on the aromatic ring in aromatic aldehydes has an 381 appreciable effect on the enantioselectivity. Thus, the presence of a strong electronreleasing group (methoxy) in para gives place to the higher yields and 382 383 enantioselectivities (see entry 2 in Table 4), whiles the presence of an electron-384 withdrawing group, such as chlorine, reduces both yield and enantioselectivity (entry 4, 385 Table 4). The aliphatic aldehydes tested were also ethylated with a high degree of 386 enantioselectivity (73 and 80%, entries 7 and 8). This is noteworthy, as this process is, 387 in general, less efficient with most of the homogeneous and heterogeneous systems 388 studied.[66-68] When the enantioselective addition of dimethylzinc to aldehydes was 389 investigated (entries 9-11), good to excellent enantioselectivities could be achieved for 390 various aromatic aldehydes. It was also found that this catalyst was efficient for the 391 addition of dimethylzinc to aliphatic aldehydes (entry 11), although with lower conversions and enantioselectivity. 392

393

- 394
- 395

Finally, the potential reuse of the resin **7b**, using a 5 % catalyst loading, was examined for the enantioselective addition of  $Et_2Zn$  to benzaldehyde. After 36 h of reaction, the

TABLE 4

398 resin was filtered, washed with CH<sub>2</sub>Cl<sub>2</sub> and vacuum dried. The resulting resin was 399 directly used for a new catalytic cycle at 0 °C. The results in Figure 5 show that the 400 resin could be used for five consecutive runs to afford (S)-1-phenyl-1-propanol in 401 excellent yields (87-90%) with only a minor drop in enantioselectivity (from 91 to 402 87%). Both yield and enantioselectivity dropped significantly (to 70 and 62 403 respectively) for the sixth run, most likely for a non-appropriate washing. Nevertheless, 404 a thorough washing protocol including the use of 1 M HCl, allowed to regenerate the 405 resin that could be used for a 7th cycle with similar results to those obtained in the 406 initial series of experiments. These results indicate that the polymer-supported  $\alpha$ -amino 407 amides are stable during the reaction and can be easily regenerated and reused after 408 filtration and washing with acid. It is important to note that although TON values for 409 each batch reaction using catalysts like 7b are clearly lower than those using the 410 corresponding Ni complexes, the easy reuse of this supported system clearly compensates for this and the TON values attained after 5 reuses (TON  $\sim$  100) are fully 411 comparable with those reported for the Ni complexes.[38] 412

413

414

#### FIGURE 5

415

#### 416 **4. Conclusions**

417 In summary, the results here presented clearly demonstrate the immobilization of a catalytic system onto a polymeric matrix can be accompanied by a dramatic increase in 418 the observed enantioselectivity. Most likely this can be associated with the reduced 419 420 formation of aggregates taking place in the supported system due to the pseudodilution effect. The resulting polymer-supported  $\alpha$ -amino amide is highly effective for the 421 catalysis of the addition of dialkylzinc reagents to a variety of aldehydes, including 422 423 some aliphatic aldehydes. The polymer supported system can be used for at least 5 cycles without an appreciable loss of its efficiency, and, more importantly, can be easily 424 425 regenerated to achieve essentially, the same results than the original system.

426

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430

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546	LIST OF FIGURE AND TABLE CAPTIONS
547	
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549	of PS-amino amides.
550	Figure 2. Partial ATR-FTIR spectra for 7b (blue), Zn complex for 7b (blue) and TEM
551	images of the zinc-supported catalyst (inlet).
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553	benzaldehyde catalyzed by polymer-supported $\alpha$ -amino amides.
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560	
561	Table 1. Loadings for the different polymers 7.
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563	different solvents.
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- Figure 1. Structures of  $\alpha$ -amino amide 1 and bis(amino amide) 2 ligands and synthesis 568
- of PS-amino amides 569
- 570



- 574 Figure 2. Partial ATR-FTIR spectra for 7b (green), Zn complex for 7b (blue) and TEM
- 575 images of the zinc-supported catalyst (inlet).



#### СС A.

Figure 3. Possible mechanism of enantioselective addition of diethylzinc to benzaldehyde catalyzed by polymer-supported  $\alpha$ -amino amides. 



584

Figure 4. Conversion of benzaldehyde (11) and relative yields for 1-phenyl-1-propanol
(12) and benzyl alcohol (13) as a function of time, using the catalyst 7b at 0°C in
toluene. Evolution of selectivity (red line) and enantioselectivity (blue dotted line) is
also given.



592 Figure 5. Reuse of the polymer supported catalyst 7b. Reaction conditions: toluene,

593 0°C, 36 h, 5 % catalyst loading.

594



595 596

597

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597

**Table 1.** Loadings for the different polymers **7**.

599

Entury	Resin	Crosslinking Loading		Loading	
Entry		degree (%)	Found <sup>[a]</sup>	Calculated <sup>[b]</sup>	1 lelu (70)
1	7a <sup>[d]</sup>	1	0.80	0.86	93
2	7b <sup>[d]</sup>	1	0.94	0.99	95
3	7c <sup>[d]</sup>	2	1.28	1.36	94
4	7d <sup>[d]</sup>	1	1.56	1.59	98
5	7e <sup>[d]</sup>	2	1.84	1.89	97
6	7f <sup>[d]</sup>	1	1.99	2.06	97
7	7g <sup>[e]</sup>	20	0.85	0.89	96
8	7h <sup>[e]</sup>	20	1.45	1.50	97
9	7i <sup>[e]</sup>	20	1.74	1.81	96
10	7j <sup>[e]</sup>	20	1.96	2.03	97
11	7k <sup>[e]</sup>	20	2.27	2.35	97

600

[a] Calculated by N elemental analysis (mmol functional group/g resin). [b] Based on a quantitative
conversion for all the steps in Scheme 1 (mmol functional group/g resin). [c] Calculated as
(loading<sub>found</sub>/loading<sub>calculated</sub>) × 100. [d] Gel type [e] Monolith.

604

606 **Table 2.** Enantioselective Addition of  $Et_2Zn$  to Benzaldehyde Catalyzed by resins **7a** in

- 607 different solvents.<sup>[a]</sup>
- 608

Entry	Solvent	T (°C)	Time	Conversion (%) <sup>[b]</sup>	Selectivity (%) <sup>[b]</sup>	ee (%) <sup>[c]</sup>
1	Toluene	0	18	91	99	91 ( <i>S</i> )
2	Toluene	0	36	99	99	92 ( <i>S</i> )
3	Hexane	0	36	95	92	51 (S)
4	CH <sub>3</sub> CN	0	36	96	89	55 (S)
5	$CH_2Cl_2$	0	36	90	91	61 ( <i>S</i> )
6	THF	0	36	92	85	32 ( <i>S</i> )
7	Toluene	25	36	97	86	71 ( <i>S</i> )
8	Toluene	-20	36	58	99	93 ( <i>S</i> )

609

610 [a] Reaction conditions: Benzaldehyde (1 equiv), Et<sub>2</sub>Zn (2.2 equiv), and catalyst 7a (10% mol), 36 h. [b]

611 Determined by <sup>1</sup>H NMR. [c] Determined by chiral HPLC (Chiralcel OD) or GC; the major enantiomer is
 612 indicated in parenthesis.

613

#### 614

Table 3. Enantioselective Addition of Et<sub>2</sub>Zn to Benzaldehyde Catalyzed by resins 7a-f
 .<sup>[a]</sup>

617

Entry	Catalyst	Conversion (%) <sup>[b]</sup>	Selectivity (%) <sup>[b]</sup>	ee (%) <sup>[c]</sup>
1	7a <sup>[d]</sup>	88	98	92 ( <i>S</i> )
2	7 <b>b</b> <sup>[d]</sup>	92	99	92 ( <i>S</i> )
3	7c <sup>[d]</sup>	95	97	87 ( <i>S</i> )
4	$\mathbf{7d}^{[d]}$	99	95	87 ( <i>S</i> )
5	7e <sup>[d]</sup>	99	96	84 ( <i>S</i> )
6	<b>7f</b> <sup>[d]</sup>	99	96	82 (S)
7	7g <sup>[e]</sup>	99	91	62 (S)
8	<b>7h</b> <sup>[e]</sup>	99	92	62 ( <i>S</i> )
9	7i <sup>[e]</sup>	98	89	55 (S)
10	7j <sup>[e]</sup>	99	91	52 (S)
11	7 <b>k</b> <sup>[e]</sup>	99	89	48 ( <i>S</i> )
12	1			

618

 $[a] Reaction \ conditions: \ Benzaldehyde \ (1 \ equiv), \ Et_2Zn \ (2.2 \ equiv), \ and \ catalyst \ (10\% \ mol) \ in \ toluene \ at$ 

620 0 °C, 36 h. [b] Determined by <sup>1</sup>H NMR. [c] Determined by chiral HPLC (Chiralcel OD); the major

621 enantiomer is indicated in parenthesis. [d] Gel type [e] Monolith.

#### 622

#### 623 **Table 4.** Enantioselective Addition of R<sub>2</sub>Zn to Aldehydes Catalyzed by resin **7b**.<sup>[a]</sup>

624

Entry	Aldehyde	R	Conversion (%) <sup>[b]</sup>	Selectivity (%) <sup>[b]</sup>	ee (%) <sup>[c]</sup>
1	Benzaldehyde	Et	91	99	92 ( <i>S</i> )
2	4-Methoxybenzaldehyde	Et	97	98	95 ( <i>S</i> )
3	4-Methylybenzaldehyde	Et	89	99	89 ( <i>S</i> )
4	4-Chlorobenzaldehyde	Et	88	98	86 ( <i>S</i> )
5	1-Naphtaldehyde	Et	87	99	88 (S)
6	2-Naphtaldehyde	Et	88	99	90 ( <i>S</i> )
7	3-Phenylpropionaldehyde	Et	85	97	73 ( <i>S</i> )
8	Hexanal	Et	65	95	80 ( <i>S</i> )
9	Benzaldehyde	Me	87	98	75 ( <i>S</i> )
10	4-Methoxybenzaldehyde	Me	86	97	77 ( <i>S</i> )
11	Hexanal	Me	69	94	67 ( <i>S</i> )

625

626 [a] Reaction conditions: Aldehyde (1 equiv), Et<sub>2</sub>Zn (2.2 equiv), and catalyst **7b** (10% mol) in toluene at 0

627 °C, 36 h. [b] Determined by <sup>1</sup>H NMR. [c] Determined by chiral HPLC (Chiralcel OD) or GC; the major

628 enantiomer is indicated in parenthesis.

- 629 Highlights
- 630 Immobilization of catalytic  $\alpha$ -amino amide system onto a polymeric matrix
- 631 Increase in the enantioselectivity due to the pseudodilution effect.
- 632 Supported catalyst are effective for the addition of dialkylzinc reagents to aldehydes
- 633 The supported system can be used for 5 cycles without lost of its efficiency
- 634



