Solvent-free direct enantioselective aldol reaction using polystyrene-supported *N*-sulfonyl-(R_a)-binam-D-prolinamide as a catalyst†

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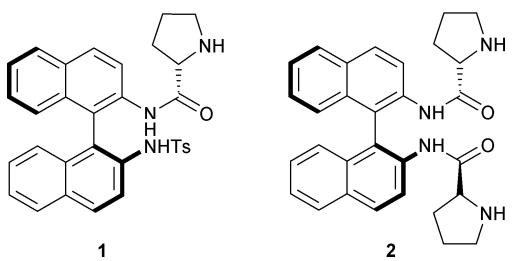
Received 12th February 2010, Accepted 1st July 2010
DOI: 10.1039/c002967j

The immobilization of *N*-sulfonyl-(R_a)-binam-D-prolinamide using polystyrene as a support allows the recovery of an efficient catalytic system for the enantioselective direct aldol reaction between different ketones and aldehydes under solvent-free or aqueous conditions. The polystyrene-supported *N*-sulfonyl-(R_a)-binam-D-prolinamide catalyst in combination with benzoic acid showed similar results to those obtained with unsupported *N*-tosyl-binam-derived prolinamide under similar reaction conditions. The aldol products were obtained at room temperature and using only 2 equivalents of the ketone with high yields, regio-, diastereo- and enantioselectivities. The aldol reaction between aldehydes can also be performed under these reaction conditions with moderate results. The recovered catalyst can be reused up to six times without having a detrimental effect on the achieved results.

Introduction

The direct aldol reaction[1] has been extensively used in industry either in bulk or in fine chemical manufacture and pharmaceutical target production to prepare polyoxygenated architectures from two carbonyl compounds. The application of enantioselective organocatalytic methods[2] to perform this aldol reaction[3] and other C–C or C–heteroatom[4] processes implies advantages over other asymmetric methods. However, in order to obtain high yields, the use of excess of one of the reactants, normally the nucleophile, long reaction times, high catalyst loading and polar solvents are usually needed, with these requirements being a serious drawback for the general application of this procedure. Therefore, more efficient and greener conditions[5] such as the use of solvent-free reaction conditions[6] in asymmetric organocatalytic processes[7] are of great interest.

N-Tosyl-(S_a)-binam-L-prolinamide **1**[8] and bisprolinamides **2**[9] derived from 1,1′-binaphthyl-2,2′-diamine (binam) (Fig. 1), have been used efficiently as organocatalysts in the aldol reaction using different reaction media, including solvent-free reaction conditions.[8,9j,k] While catalyst **2** is easily recoverable and reusable by simple acid–base work-up, more general and efficient catalyst **1** can only be recovered by direct column chromatography from the reaction media.



1 **2**

Fig. 1

Several immobilization strategies, such as the use of different polymers, silica, ionic liquids, or even more sophisticated materials such as dendrimers, nanoparticles or DNA as supports have already been applied to proline and proline-derivatives in order to allow their recyclability as organocatalysts for different organocatalytic processes.[10] Several proline and proline derivatives have been incorporated in insoluble polymeric material and used in the aldol reaction under different conditions. For instance, proline has been directly immobilised through its carboxylic function in a 4-methylbenzhydrylamine resin (MBHA)[11] or in a modified Merrifield resin.[12]

In a similar way, several small peptides have been immobilised in different amine-terminated resins such as PEG-polystyrene resins[13] or Tentagel.[14] Moreover 4-*trans*-aminoproline has been incorporated in different functionalized polystyrene supports,[15] and 4-*trans*-hydroxyproline has been supported through the hydroxy group in poly(ethylene glycol),[16] Merrifield resins[17] and mercaptomethylpolystyrene resins.[18] Generally, for all these polymeric catalysts a high excess of reacting ketone was needed in order to obtain the corresponding aldol products in good yields; sometimes the nucleophilic ketone being the solvent of choice to perform the reaction. The use of such excess of one of the reagents diminished the atom efficiency of the reaction[19] and hampered the use of valuable ketones as starting materials to perform this reaction.

In this paper we describe the immobilization of compound *ent*-**1** in polystyrene and its use as a recoverable catalyst under solvent-free or aqueous conditions for the aldol reaction.

Results and discussion

Synthesis of the grafted polymeric organocatalyst

The use of solvent-free conditions with catalyst **1** permitted the reduction of the excess of the required ketone to only 2

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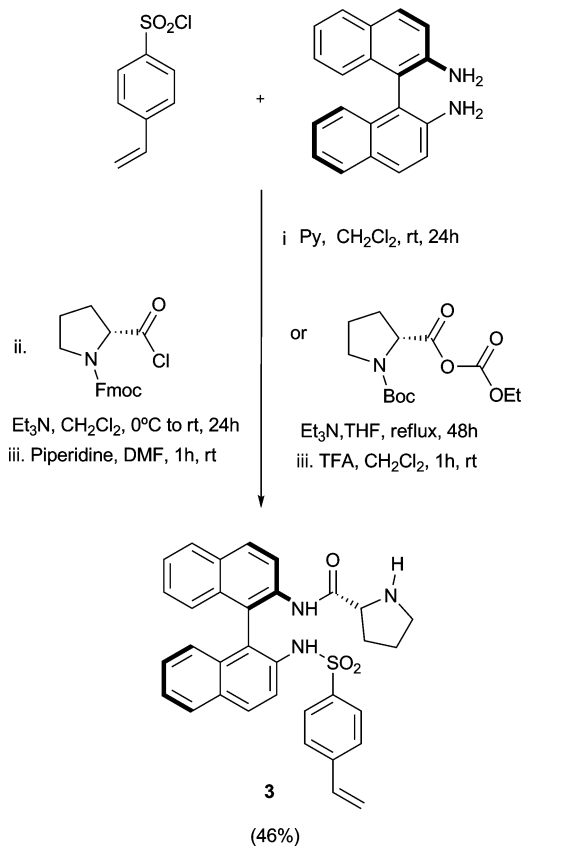
† This paper is dedicated to the memory of Prof. José M. Concellón.

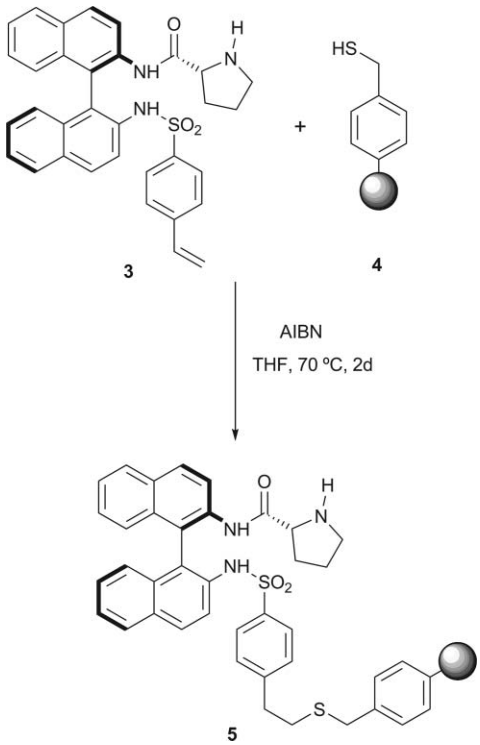
equivalents.[8] Therefore, pursuing a greener process, we were interested in the immobilization of a catalytic system of similar structure and its use in the aldol reaction under solvent-free conditions. Since the functionalization of a polymer *via* a free-radical addition has recently been used as a convenient strategy for grafting chiral subunits to insoluble supports,[18,20] we decided to apply this method to incorporate our catalyst in an insoluble polymeric support. Two synthetic steps were needed for this purpose: (a) the synthesis of a styrylsulfonyl derivative of binam-prolinamide **3** and (b) the thiol-ene coupling (TEC)[21] reaction between a commercially available mercaptomethyl functionalized polystyrene polymer **4** and binam-derivative **3**.

In order to prepare the styryl binam-derivative **3**, commercially available sodium 4-vinylbenzenesulfonate was reacted with thionyl chloride to give the expected sulfonyl chloride derivative,[20] which was trapped with (R_a)-1,1′-binaphthyl-2,2′-diamine (binam, Scheme 1) under a similar procedure to that used for the synthesis of catalyst **1**.[8] The described procedure[20] to perform this reaction used benzene as a solvent, but we decided to use less harmful toluene as the solvent, although the achieved yield was slightly lower.[22] The achieved binam-sulfonyl derivative was subsequently coupled with the *in situ* generated Fmoc-D-Pro chloride followed by deprotection with piperidine affording the styryl binam-derivative **3** in 46% overall yield. Alternatively, the binam-sulfonyl derivative could be coupled with the *in situ* formed mixed anhydride of *N*-Boc-D-Pro and ethyl chloroformate,[23] affording after deprotection with trifluoroacetic acid the styryl derivative **3** with similar results.



Scheme 1 Synthesis of styryl derivative **3**.

Once **3** was prepared, the grafting of the commercially available polystyrene polymer **4** (100–200 mesh, cross-linked with 1% divinylbenzene, 2.5 mmol g^{-1} loading) was accomplished by a radical addition protocol (Scheme 2) giving the expected polymer **5**. After washing the obtained polymer thoroughly several times with methanol and diethyl ether, an incorporation of about 55% of the chiral subunit was achieved (determined by the microanalysis data).

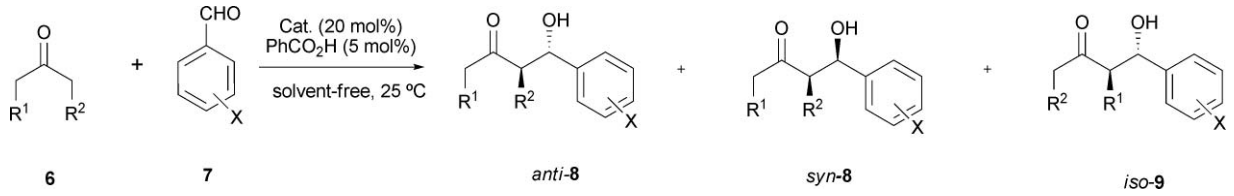


Scheme 2 Synthesis of the grafted polymer **5**.

When using the described procedure for grafting 4-*trans*-hydroxyproline derivative on to mercaptomethyl polystyrene resins,[18] with binam *N*-Boc-protected-D-proline styryl derivative, only 46% monomer incorporation was achieved (determined by microanalysis data).

Catalysis and recycling

The aldol reaction between cyclohexanone and *p*-nitrobenzaldehyde was chosen as a model process to test the catalytic activity of the polymer **5** (Scheme 3 and Table 1). All reactions were carried out in the presence of 20 mol% of polymeric catalyst **5** and 5 mol% of benzoic acid as cocatalyst. Different solvents and temperatures were tested in order to find the best reaction conditions. The reaction failed using polar aprotic solvents even at room temperature and after several days of reaction (Table 1, entries 1–3). However, when the reaction was carried out using a 1/1 mixture of DMF–H_2O, the aldol product **8aa** was obtained after 3 d in high yield, diastereo- and enantioselectivity (Table 1, entry 4). In this case, the formation of a small amount of α,β-unsaturated aldol derivative (less than 4%) was observed.[24] Polar protic solvents such as MeOH and H_2O were then tested as reaction media. Whereas the reaction did not proceed in MeOH, a low conversion was



Scheme 3 Direct asymmetric aldol reaction between ketones and aldehydes under solvent free conditions catalyzed by polymer **5**

Table 1 Optimization of reaction conditions between cyclohexanone and *p*-nitrobenzaldehyde[a]

Entry	Solvent	T°/°C	t (d)	Conv.[b]	Yield (%)[c]	*anti*/*syn*[d]	ee (%)[e]
1	CH_2Cl_2	25	4	NR	—	—	—
2	THF	25	4	NR	—	—	—
3	DMF	25	3	NR	—	—	—
4	DMF–H_2O[f]	25	3	96	88	96/4	78
5	MeOH	25	5	NR	—	—	—
6	H_2O	25	5	32	30	96/4	86
7	None[g]	25	3	98	81	87/13	68
8	none/H_2O[h]	25	1	97	83	95/5	90
9	none/H_2O[h]	10	4	97	90	98/2	82
10	none/H_2O[h]	0	4	NR	—	—	—
11	none/H_2O[hi]	25	9	96	81	93/7	92
12	none/H_2O[j]	25	3	90	77	95/5	90
13	none/H_2O[k]	25	2	90	75	96/4	90
14	none/H_2O[l]	25	3	99	85	91/9	86

[a] Reaction conditions: **6a** (2 equiv.), **7a** (0.1 mmol), benzoic acid (5 mol%) catalyst **5** (20 mol%) and solvent (0.6 mL). [b] Conversion based on the unreacted aldehyde. [c] After purification by column chromatography. [d] Determined by the ^{1}H NMR of the crude product. [e] Determined by chiral-phase HPLC analysis for the *anti* isomer. [f] 1/1 mixture of DMF–H_2O. [g] Solvent-free conditions. [h] 100 μL of H_2O were added to the reaction mixture. [i] Catalyst **5** (10 mol%) and benzoic acid (5 mol%). [j] 200 μL of H_2O were added to the reaction mixture. [k] 50μL of H_2O were added to the reaction mixture. [l] 25 μL of H_2O were added to the reaction mixture.

obtained in H_2O giving the aldol product in high diastereo- and enantioselectivity (Table 1, entries 5 and 6).

Finally, solvent-free conditions were used at room temperature. Under these conditions the reaction took place in a similar yield to that achieved in DMF–H_2O but with lower diastereo- and enantioselectivity (Table 1, compare entries 4 and 7). In order to accelerate the reaction, water (55 equiv.) was added to the reaction mixture,[25] achieving the aldol product in only 1 d, in comparable yields to those previously obtained and with the highest enantioselectivity (Table 1, compare entries 4, 7 and 8). Lowering the temperature to 10 °C increased the reaction time to 4 d but decreased the enantioselectivity probably due to competition with the non-catalyzed reaction (Table 1, entry 9), with the reaction failing at 0 °C (Table 1, entry 10). Under aqueous conditions, the amount of catalyst and co-catalyst were reduced (10 mol% of **5** and 5 mol% benzoic acid) performing the reaction at room temperature. As expected, the reaction time suffered an increase from 1 d to 9 d, but with product **8aa** being achieved with similar yields, diastereo- and enantioselectivities (Table 1, compare entries 8 and 11). Finally, the amount of added water[26] was optimized under the general reaction conditions outlined in entry 8 of Table 1. For the obtained results it could be concluded that increasing the amount of water to 110 equivalents (Table 1, entries 12) or decreasing it to 28 or 14 equivalents (Table 1, entries 13 and 14) led to a slower reaction rate although the yields and selectivities were almost maintained. Recently, the role of water in organocatalyzed aldol reactions has been kinetically studied. While the addition of water increases the catalyst concentration by suppression of the formation of parasitic species, it decreases the relative concentration of some intermediates such as oxazolidinones. Thus, the neat effect in the reaction rate is the sum of these opposing roles, which depends on the different substrates used.[26d]

Under the optimal reaction conditions (Table 1, entry 8), the scope of the reaction was studied varying the ketone and aldehyde (Scheme 3 and Table 2). Different aldehydes were used in the reaction with cyclohexanone giving the expected products in good yields, diastereo- and enantioselectivities. In order to increase the reaction rates, the addition of water (aqueous conditions) was compulsory in all these reactions (Table 2, entries 1–5), with longer reaction times being required for non-activated aldehydes such as benzaldehyde (Table 2, entry 3). Then, several cyclic ketones were used as nucleophiles in the reaction with *p*-nitrobenzaldehyde. As expected cyclopentanone (**6b**) gave the *syn*-**8ba** product as the major isomer (Table 2, entries 6 and 7), the best result being achieved when the reaction was carried out under aqueous conditions at 0 °C (Table 2, entry 6). Surprisingly, 4-tetrahydropyranone (**6c**) gave a better yield in shorter reaction times under solvent-free conditions, with the diastereo- and enantioselectivities achieved being similar for both reactions (Table 2, entries 8 and 9). With other alkyl ketones such as acetone (**6d**) or butanone (**6e**), again the use of aqueous conditions gave high yields (Table 2, entries 10–13). The *iso*-**9ea** product was the major isomer for the case of butanone (Table 2, entry 12). Conversely, the use of functionalizated ketones such as α-methoxyacetone (**6f**) and α-(methylsulfanyl)acetone (**6g**) required the use of dry solvent-free conditions to give the best results. Thus, for α-methoxyacetone, product *anti*-**8fa** was obtained in good yields with lower selectivity (Table 2, entries 14 and 15). In the case of the less reactive α-(methylsulfanyl)acetone, product *iso*-**9ga** was the main isomer but was obtained in low yields (Table 2, entries 16 and 17). Unfortunately, when these conditions were applied to the reaction between less reactive aliphatic aldehydes such as isobutyraldehyde or cinnamaldehyde with acetone or cyclohexanone, the reaction failed. The obtained results were slightly lower in terms of yields, selectivity and optical purity to those obtained under similar reactions conditions with catalyst **1**,[8a] probably due to the longer reaction time required using catalyst **5**, which possibly competes with the background non-catalyzed process.

Polymer **5** was also able to catalyse the aldol reaction between aldehydes **7a** and **7f**, although high catalyst loading (40 mol%) and longer reaction times (10 d) were needed to reach a moderate

Table 2 Reaction between ketones and aldehydes under solvent-free or aqueous conditions catalyzed by polymer **5**[a]

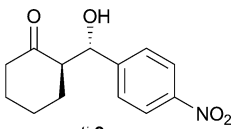
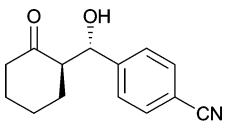
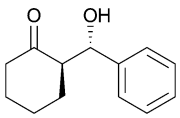
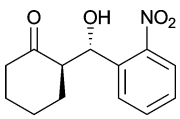
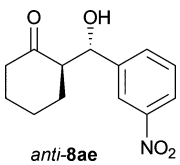
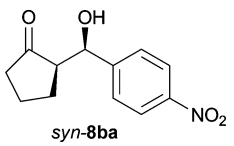
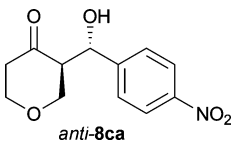
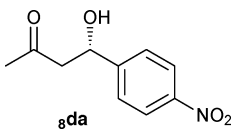
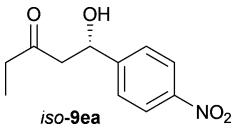
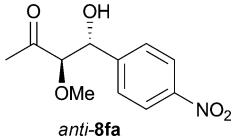
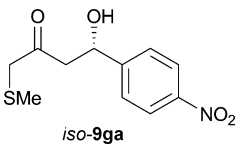
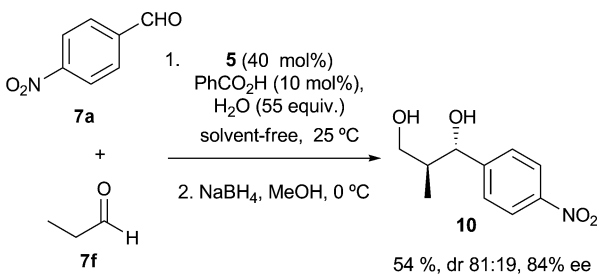
Entry	Product	t (d)	Yield (%)[b]	**8**/**9**[c]	*anti*/*syn*[c]	ee (%)[d]
1[e]	 *anti*-**8aa**	1	83	—	95 : 5	88
2[e]	 *anti*-**8ab**	3	78	—	94 : 6	76
3[e]	 *anti*-**8ac**	8	69	—	94 : 6	86
4[e]	 *anti*-**8ad**	3	81	—	93 : 7	88
5[e]	 *anti*-**8ae**	3	79	—	94 : 6	84
6[e,f]	 *syn*-**8ba**	4	77	—	37 : 63	74
7		3	78	—	37 : 63	56
8[e]	 *anti*-**8ca**	5	52	—	95 : 5	86
9		3	75	—	94 : 6	82
10[e]	 **8da**	3	76	—	—	73
11		5	72	—	—	73
12[e]	 *iso*-**9ea**	3	69	43/57	—	86
13		5	30	37/63	—	84
14[e]	 *anti*-**8fa**	5	20	88/12	80 : 20	80

Table 2 *(Contd.)*

Entry	Product	t (d)	Yield (%)[b]	**8**/**9**[c]	*anti*/*syn*[c]	ee (%)[d]
15		3	82	89/11	83 : 17	88
16[e]	 *iso*-**9ga**	10	20	20/80	—	84
17		8	22	17/83	—	82

[a] Reaction conditions: **6** (2 equiv.), **7** (0.25 mmol), benzoic acid (5 mol%) catalyst (20 mol%), rt. [b] After purification by column chromatography. [c] Determined by the ^{1}H NMR of the crude product. [d] Determined by chiral-phase HPLC analysis for the *anti* isomer. [e] 200 μL of H_2O were added to the reaction mixture. [f] The reaction was carried out at 0 °C.

yield for product **10** (Scheme 4). The use of the polymer under different reaction conditions for the direct aldol intramolecular reaction of 1,5-diketones[8] failed, unfortunately.



Scheme 4 Aldol reaction between *p*-nitrobenzaldehyde and propanal using polymeric catalyst **5**.

Finally, recycling studies were carried out using the model reaction between cyclohexanone and *p*-nitrobenzaldehyde under aqueous conditions (Table 3, Scheme 3). After each cycle the reaction was quenched by filtration and the resin was washed with a 0.5 M solution of NaOH, to remove the benzoic acid occluded in the polymeric matrix. Then, the resin was washed several times either with ethyl acetate, ethanol or acetone and dried under vacuum. The obtained results were consistently high in terms of yields, diastereo- and enantioselectivities even after six reaction cycles.

Table 3 Recycling studies for compound **8aa**[a]

Entry	Cycle	t (d)	Yield (%)[b]	*anti*/*syn*[c]	ee (%)[d]
1	1	1	83	94 : 6	84
2	2	1	80	95 : 5	88
3	3	1	79	95 : 5	88
4	4	1	70	94 : 6	90
5	5	1	69	94 : 6	88
6	6	1	75	93 : 7	84

[a] Reaction conditions: **6a** (2 equiv.), **7a** (0.2 mmol), benzoic acid (5 mol%) catalyst (20 mol%), 200 μL of H_2O, rt. [b] After purification by column chromatography. [c] Determined by the ^{1}H NMR of the crude product. [d] Determined by chiral-phase HPLC analysis for the *anti* isomer.

Conclusions

Polystyrene-supported binam-prolinamide was easily prepared by standard procedures in two steps starting from commercially available mercaptomethyl polystyrene and synthetic styrylsulfonyl binam-derivative using TEC coupling. This polymer has been used in the aldol reaction between several ketones and aldehydes in the presence of benzoic acid under solvent-free or aqueous conditions affording the corresponding aldol product in high yields, regio-, diastereo-, and enantioselectivities. These results are comparable to those obtained under homogeneous conditions using soluble catalyst *N*-tosyl-(S_a)-binam-L-prolinamide **1**. This polymer was also able to catalyse the reaction between aldehydes with moderate results. The recyclability of the polymeric material was confirmed by its recovery by filtration and reused up to six times without detrimental results. Currently, the use of this polymeric material for other organocatalytic processes is under investigation.

Experimental

General

All reactions for the catalyst preparation were carried out under argon. Dry DMF, dry toluene, dry CH_2Cl_2, piperidine and triethylamine and all others reagents were commercially available and used without further purification. Propanal and benzaldehyde were distilled prior to use. Only the structurally most important peaks of the IR spectra (recorded on a Nicolet Impact 400D) are listed. ^{1}H NMR (300 MHz, 400 MHz) and ^{13}C NMR (75 MHz) spectra were obtained on a Bruker AC-300 using $CDCl_3$ as solvent and TMS as internal standard, unless otherwise stated. Optical rotations were measured on a Perkin Elmer 341 polarimeter. HPLC analyses were performed on an Agilent 1100 series equipped with a chiral column (detailed for each compound below), using mixtures of *n*-hexane/isopropyl alcohol (IPA) as mobile phase, at 25 °C. Analytical TLC was performed on Schleicher & Schuell F1400/LS silica gel plates and the spots were visualised under UV light ($\lambda = 254$ nm). For flash chromatography we employed Merck silica gel 60 (0.063–0.2 mm). Elemental analysis was carried out in the Research Technical Services of the University of Alicante.

Synthesis of supported polymeric organocatalyst

Synthesis of (*R*)-*N*-[(*R*)-2′-(4-vinylphenylsulfonamido)-1,1′-binaphthyl-2-yl]pyrrolidine-2-carboxamide 3. To a solution of 4-vinylbenzenesulfonate (1.1 g, 5.3 mmol) in dry toluene (30 mL) were added $SOCl_2$ (2 mL, 27.6 mmol) and a few drops of dry DMF. The resulting solution was refluxed for 15 h and all the volatiles were removed under reduced pressure (0.1 Torr) to yield the corresponding sulfonylchloride derivative. This compound was dissolved in dry CH_2Cl_2 (20 mL) under inert atmosphere and added to a solution of (R_a)-1,1′-binaphthyl-2,2′-diamine (1 g, 3.5 mmol) in 20 mL of dry CH_2Cl_2 and dry pyridine (3.5 mL, 43.44 mmol). The resulting mixture was stirred for 12 h at rt, and then treated with a HCl 5% solution (3 × 15 mL). The organic layer was dried over Na_2SO_4, filtered off and the solvents were removed under reduced pressure (15 Torr). The resulting crude product was purified by column chromatography (hexane–ethyl acetate) to give the (*R*)-*N*-(2′-amino-1,1′-binaphthyl-2-yl)-4-vinylbenzenesulfonamide in 65% yield. Fmoc-D-proline chloride was prepared by slow addition of $SOCl_2$ (1.7 mL, 22 mmol) to a solution of Fmoc-D-proline (0.763 g, 2.2 mmol) dissolved in dry CH_2Cl_2 (15 mL), and subsequent reflux for 1 h and removal of the solvent and excess of the reactants.

To a solution of (*R*)-*N*-(2′-amino-1,1′-binaphthyl-2-yl)-4-vinylbenzenesulfonamide (1.03 g, 2.29 mmol) dissolved in dry CH_2Cl_2 (15 mL) was added a solution of Fmoc-D-proline chloride (1.21 g, 3.4 mmol) in dry CH_2Cl_2 (15 mL) and triethylamine (0.95 mL, 6.8 mmol) at 0 °C. The ice-bath was removed and the reaction was stirred for 24 h at rt. The solvents were removed under reduced pressure (15 Torr) and the resulting solid residue was dissolved in ethyl acetate and washed with brine (3 × 10 mL). The organic layer was dried over Na_2SO_4, filtered and the solvents were removed under reduced pressure (15 Torr). The resulting crude product was dissolved in dry DMF (10 mL) and to this solution at 0 °C, piperidine (7 mL, 70 mmol) was added drop wise. After removal of the ice-bath, the reaction was stirred for 1 h at rt. 20 ml of ethyl acetate were added to the mixture and the resulting solution was washed alternatively with brine and water (5 × 5 mL). The organic layer was dried over Na_2SO_4, filtered and the solvents were removed under reduced pressure (15 Torr). The resulting crude product was purified by column chromatography (hexane–ethyl acetate) to give product **3** (0.876 g, 70%) as a white solid (Found: C, 71.6; H, 5.4; N 7.1; S 5.0. $C_{33}H_{29}N_3O_3S$, requires C, 72.4; H, 5.3; N 7.7; S 5.8). Mp 210–212 °C (EtOAc); HPLC (HPLC Chiralpak AD-H, *n*-hexane/i-PrOH: 80/20, 1.0 mL min^{-1}), R_t = 51.29; R_f 0.28 (EtOAc); $[\alpha]_D$ +111.7 (*c* 1.0 in $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3828, 3369, 3289, 3167, 2965, 2855, 1682, 1592, 1501, 1402, 1313, 1160; δ_H (300 MHz; $CDCl_3$, Me_4Si) 0.66 (1H, m, CH_2), 1.17 (2H, m, CH_2), 1.58 (1H, m, CH_2), 1.73 (1H, m, CH_2), 2.18 (1H, m, CH_2), 3.27 (1H, dd, *J* 4.1, 9.6, CH), 5.42 (1H, d, *J* 10.8, CH_2═), 5.48 (1H, d, *J* 17.6, CH_2═), 6.67 (1H, dd, *J* 10.8, 17.6, ═CH), 6.84 (1H, d, *J* 8.4, ArH), 6.92 (1H, d, *J* 8.4, ArH), 7.17 (2H, m, ArH), 7.31 (2H, d, *J* 8.2, ArH), 7.39 (2H, m, ArH), 7.50 (2H, d, *J* 8.6, ArH), 7.86 (1H, d, *J* 8.2, ArH), 7.93 (1H, d, *J* 8.2, ArH), 8.00 (1H, d, *J* 9.0, ArH), 8.06 (1H, d, *J* 9.2, ArH), 8.21 (1H, d, *J* 9.2, ArH), 8.83 (1H, d, *J* = 9.0, ArH), 9.26 (1H, s, NHCO); δ_C (75 MHz; $CDCl_3$, Me_4Si) 25.2 (CH_2), 30.5 (CH_2), 46.0 (CH_2NH), 60.4 (CH), 116.8 (ArC), 117.9 (CH_2═), 119.1 (ArC), 119.2 (ArC), 120.6 (ArC), 124.0, 125.1, 125.6, 126.4 (ArCH), 127.4 (ArC), 127.45, 127.6, 127.7, 128.1, 128.6, 130.1, 130.5 (ArCH), 130.7, 131.1, 132.1, 133.5 (ArC), 135.0 (CH═), 138.0, 142.0 (ArC), 173.4 (CO).

Alternative synthesis of (*R*)-*N*-[(*R*)-2′-(4-vinylphenylsulfonamido)-1,1′-binaphthyl-2-yl]pyrrolidine-2-carboxamide 3. To a solution of Boc-D-proline (0.215 g, 1 mmol) and triethylamine (0.14 mL, 1.0 mmol) in dry THF (7.5 mL) at 0 °C was drop wise added ethyl chloroformate (0.102 mL, 1 mmol). After stirring the resulting solution for 30 min at 0 °C, a solution of (*R*)-*N*-(2′-amino-1,1′-binaphthyl-2-yl)-4-vinylbenzenesulfonamide (0.45 g, 1.0 mmol) dissolved in dry THF (7.5 mL) was added over 15 min. The ice-bath was removed and the reaction was refluxed for 48 h at rt. The solvents were removed under reduced pressure (15 Torr) and the resulting solid residue was dissolved in dichloromethane

(7.5 mL) and trifluoroacetic acid (2 mL) was added. The resulting mixture was stirred for 1 h. NaOH (3 M) was added to the reaction mixture until pH 7 and the resulting solution was washed with water (3 × 7 mL). The organic layer was dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure (15 Torr). The resulting crude product was purified by column chromatography (hexane–ethyl acetate) to give product **3** (0.380 g, 70%) as a white solid

Synthesis of polystyrene-supported organocatalyst 5. To a suspension of styryl binam-derivative **3** (0.3 g, 0.55 mmol) and mercaptomethyl polystyrene **4** (0.275 g, 0.55 mmol) in dry THF (15 mL) was added AIBN (0.054 g, 0.3 mmol) and the mixture was refluxed for 48 h. After cooling at room temperature, the resin was filtered and washed with MeOH and diethyl ether. The resin was dried under a high vacuum to give 0.350 g of polymer **5**, which corresponds to approximately 55% of monomer incorporation calculated on the basis of elemental analysis and weight difference (Found: C, 78.64; H, 6.74; N, 2.65; $C_{61}H_{57}N_3O_3S_2$ corresponding to 100% of polymer requires C, 77.6; H, 6.1; N, 4.5), IR ν_{max}/cm^1 (KBr) 3079, 3053, 3022, 2970, 2918, 2845, 1687, 1598, 1510, 1494, 1312, 1151.

General procedure for the aldol reaction catalysed by polymer 5 under aqueous conditions. To a mixture of the corresponding aromatic aldehyde (0.1 mmol), catalyst **5** (0.02 mmol, 27 mg) and benzoic acid (0.005 mmol, 0.6 mg) at 25 °C was added the corresponding ketone (0.2 mmol) and H_2O (100 μL). The reaction was stirred until the aldehyde was consumed (monitored by TLC). Then, the mixture was filtered and washed with either EtOAc, EtOH or acetone (3 × 2 mL). The solvents were removed under reduced pressure and the residue was purified by flash chromatography (hexanes/AcOEt) to yield the pure aldol product.

(*R*) - 2 - [(*S*) - Hydroxy(4 - nitrophenyl)methyl]cyclohexanone 8aa[27]. δ_H (300 MHz; $CDCl_3$, Me_4Si) 1.28–1.49 (m, 1H), 1.52–1.73 (m, 3H), 1.79–1.83 (m, 1H), 2.06–2.14 (m, 1H), 2.21–2.31 (m, 1H), 2.33–2.50 (m, 1H), 2.54–2.63 (m, 1H), 3.12 (br s, 1H *syn*), 4.02 (brs, 1H *anti*), 4.88 (d, *J* 8.4, 1H *anti*), 5.46 (s, 1H *syn*), 7.49 (d, *J* 8.7, 2H), 8.19 (d, *J* 8.7, 2H); δ_C (75 MHz; $CDCl_3$, Me_4Si) *anti* 24.6, 27.5, 30.6, 42.6, 57.1, 73.9, 123.5, 127.8, 147.4, 148.3, 214.6; *syn* 24.7, 25.8, 27.7, 42.5, 56.7, 70.0, 123.4, 126.5, 147.5, 149.2, 213.9; HPLC (Chiralcel AD, n-hexane/i-PrOH: 90/10, 0.7 mL min^{-1}), *anti*: R*t* 37.104 (major), R*t* 49.183 (minor), *syn*: R*t* 27.271 (minor), R*t* 33.833 (major).

(*R*) - 2 - [(*S*) - Hydrox4 - (4 - cyanophenyl)methyl]cyclohexanone *anti*-8ab[28]. δ_H (300 MHz; $CDCl_3$, Me_4Si). 1.28–1.49 (m, 1H), 1.52–1.84 (m, 4H), 2.04–2.17 (m, 1H), 2.30–2.47 (m, 1H), 2.50–2.61 (m, 2H), 4.07 (s, 1H), 4.84 (d, 8.4 J = Hz, 1H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.65 (d, *J* 8.3, 2H); δ_C (75 MHz, $CDCl_3$, Me_4Si) 24.6, 27.5, 30.6, 42.6, 57.0, 74.1, 111.6, 118.6, 127.7, 132.2, 146.3, 214.8; HPLC (Chiralcel AD-H, n-hexane/i-PrOH: 95/05, 1.0 ml min^{-1}), *anti*: R*t* 39.774 (major), R*t* 50.913 (minor), *syn*: R*t* 26.595 (major), R*t* 33.786 (minor).

(*R*)-2-[(*S*)-Hydroxy(phenyl)methyl]cyclohexanone *anti*-8ac[28]. δ_H (300 MHz; $CDCl_3$, Me_4Si) 1.27–1.36 (m, 1H), 1.50–1.80 (m, 4H), 2.04–2.12 (m, 1H), 2.30–2.50 (m, 2H), 2.58–2.67 (m, 1H), 4.05 (br s, 1H), 4.78 (d, *J* 8.9, 1H), 7.29–7.37 (m, 5H); δ_C (75 MHz; $CDCl_3$, Me_4Si) 24.7, 27.8, 30.8, 42.6, 57.4, 74.7, 127.0, 127.9, 128.3, 140.8, 215.5; HPLC (Chiralcel ODH, n-hexane/i-PrOH: 95/5, 0.50 mL min^{-1}), *anti*: R*t* 25.358 (minor), R*t* 39.835 (major), *syn* R*t* 19.262 (major), R*t* 21.677 (minor).

(*R*)-2-[(*S*)-Hydroxy(2-nitrophenyl)methyl]cyclohexanone *anti*-8ad[28]. δ_H (300 MHz; $CDCl_3$, Me_4Si) 1.55–1.87 (m, 5H), 2.04–2.17 (m, 1H), 2.28–2.49 (m, 2H), 2.71–2.80 (m, 1H), 4.19 (br s, 1H), 5.45 (d, *J* 7.2, 1H), 7.40–7.46 (m, 1H), 7.61–7.66 (m, 1H), 7.75–7.86 (m, 2H); δ_C (75 MHz; $CDCl_3$, Me_4Si) 24.9, 27.7, 31.0, 42.8, 57.2, 69.7, 124.0, 128.3, 128.9, 133.0, 136.5, 148.6, 214.9; HPLC (Chiralcel AD-H, n-hexane/i-PrOH: 95/5, 0.7 mL min^{-1}), *anti*: R*t* 48.851 (minor), R*t* 51.491 (major), *syn*: R*t* 32.517 (minor), R*t* 35.193 (major).

(*R*)-2-[(*S*)-Hydroxy(3-nitrophenyl)methyl]cyclohexanone *anti*-8ae[28]. δ_H (300 MHz; $CDCl_3$, Me_4Si) 1.37–1.43 (m, 1H), 1.52–1.61 (m, 3H), 1.65–1.70 (m, 1H), 1.81–1.85 (m, 1H), 2.09–2.15 (m, 1H), 2.33–2.41 (m, 1H), 2.48–2.65 (m, 1H), 4.12 (s, 1H), 4.89 (d, *J* = 8.4 Hz, 1H), 7.51–7.55 (m, 1H), 7.67 (d, *J* 7.6, 1H), 8.15–8.21 (m, 2H); δ_C (100 MHz; $CDCl_3$, Me_4Si) 24.6, 27.6, 30.7, 42.6, 57.1, 74.0, 122.0, 122.8, 129.2, 133.1, 143.2, 148.2, 214.8; HPLC (Chiralcel AD-H, n-hexane/i-PrOH: 95/5, 0.7 mL min^{-1}), *anti*: R*t* 52.412 (minor), R*t* 67.849 (major). *syn*: R*t* 40.715 (minor), R*t* 46.446 (major).

(*R*) - 2 - [(*S*) - Hydroxy(4 - nitrophenyl)methyl]cyclopentanone 8ba[27]. δ_H (300 MHz; $CDCl_3$, Me_4Si) 1.72–1.75 (m, 2H), 1.96–2.09 (m, 1H), 2.30–2.74 (m, 2H), 2.74 (d, *J* 4.8, 1H, *syn*), 4.77 (br s, 1H, *anti*), 4.84 (d, *J* 9.1, 1H, *anti*), 5.42 (s, 1H, *syn*), 7.52 (d, *J* 8.4, 2H), 8.21 (d, *J* 8.7, 2H); δ_C (75 MHz; $CDCl_3$, Me_4Si) *syn* 20.2, 22.2, 38.8, 56.0, 70.3, 123.6, 126.3, 147.0, 150.2, 219.6; *anti* 20.2, 26.7, 38.5, 55.0, 74.3, 123.5, 127.3, 147.2, 148.5, 219.7; HPLC (Chiralcel AD-H, n-hexane/*i*-PrOH: 95/5, 1.0 mL min^{-1}), *syn*: R*t* 25.282 (minor), R*t* 35.441 (mayor), *anti*: R*t* 43.471 (mayor), R*t* 45.885 (minor).

(*R*)-3-[(*S*)-Hydroxy(4-nitrophenyl)methyl]dihydro-2*H*-pyran-4(3H)-one 8ca[29]. δ_H (300 MHz; $CDCl_3$, Me_4Si) 2.50–2.57 (m, 1H), 2.63–2.73 (m, 1H), 2.85–2.93 (m, 1H), 3.46 (t, J 9.8, 1H), 3.73–3.81 (m, 2H), 4.16–4.27 (m, 1H), 5.00 (d, J 9.8, 1H, *anti*), 5.54 (d, J 2.9, 1H, *syn*), 7.52 (d, J 8.7, 2H), 8.23 (d, J 8.8, 1H),. δ_C (75 MHz; $CDCl_3$, Me_4Si) 42.7, 57.5, 68.2, 69.7, 71.2, 123.8, 127.4, 147.4, 147.7, 209.1; HPLC (Chiralcel AD-H, n-hexane/i-PrOH: 80/20, 1.0 mL min^{-1}), *anti*: R*t* 18.906 (mayor), R*t* 22.258 (minor), *syn*: R*t* 13.447 (minor), R*t* 15.795 (mayor).

(*S*)-4-Hydroxy-4-(4-nitrophenyl)-butan-2-one 8da[27]. δ_H (300 MHz; $CDCl_3$, Me_4Si). 2.22 (s, 3H), 2.85 (d, *J* 2.9, 2H), 3.59 (d, *J* 3.3, 1H), 5.27 (dd, *J* 2.9, 3.3, 1H), 7.54 (d, *J* 8.8, 2H), 8.21 (d, *J* 8.8, 2H); δ_C (75 MHz, $CDCl_3$, Me_4Si) 30.6, 51.4, 68.8, 123.7, 126.3, 147.3, 149.9, 208.2; HPLC Chiralcel AS-H n-hexane/i-PrOH: 85/15, 1.0 ml min^{-1}: R*t* 45.236 (major), R*t* 32.386 (minor).

(*S*)-1-Hydroxy-1-(4-nitrophenyl)pentan-3-one 9ea[27]. δ_H (300 MHz; $CDCl_3$, Me_4Si). 1.09 (t, *J* 7.3, 3H), 2.48 (q, 2H), 2.82 (d, *J* 4.2, 2H), 3.64 (s, 1H), 5.27 (dt, *J* 3.5, 7.7, 1H), 7.53 (d, *J* 8.6, 2H), 8.21 (d, *J* 9.8, 2H); δ_C (75 MHz, $CDCl_3$, Me_4Si) 7.4, 29.7, 36.8, 50.2, 69.1, 123.7, 126.4, 147.3, 150.1, 211.4. HPLC (Chiralcel AS n-hexane/i-PrOH: 95/05, 0.7 ml min^{-1}), *anti*: R*t*

169.781 (major), R*t* 110.287 (minor), *iso*: R*t* 219.421 (major), R*t* 98.961 (minor)

(3*R*,4*R*)-4-Hydroxy-3-methoxy-4-(4-nitrophenyl)butan-2-one *anti*-8fa[30]. δ_H (300 MHz; $CDCl_3$, Me_4Si) 2.16 (s, 3H), 3.20 (s, 1H), 3.32 (s, 3H), 3.70 (d, *J* 6.2, 1H), 5.02 (d, *J* 6.2, 1H), 7.56 (d, *J* 8.8, 2H), 8.22 (d, *J* 8.8, 2H). δ_C (75 MHz; $CDCl_3$, Me_4Si) 27.5, 59.6, 73.3, 89.6, 123.4, 127.7, 146.7, 147.7, 209.9. HPLC (Chiralpak ODH, n-hexane/i-PrOH: 90/10, 0.8 mL min^{-1}), *anti*: R*t* 16.274 (minor), R*t* 19.208 (mayor); *syn*: R*t* 20.222 (mayor), R*t* 25.535 (minor).

(*S*)-4-Hydroxy-1-(methylthio)-4-(4-nitrophenyl)butan-2-one *iso*-9ga[30]. δ_H (300 MHz; $CDCl_3$, Me_4Si) 2.06 (s, 3H), 3.04–3.07 (m, 2H), 3.19 (s, 2H), 3.50 (d, *J* 3.6, 1H), 5.26–5.31 (m, 1H), 7.57 (d, *J* 8.5, 1H), 8.22 (d, *J* 8.8, 1H). δ_C (75 MHz; $CDCl_3$, Me_4Si) 15.6, 43.3, 48.0, 69.3, 123.7, 126.7, 147.4, 149.8, 204.7. HPLC (Chiralpak ODH, n-hexane/i-PrOH: 88/12, 1.0 mL min^{-1}), R*t* 16.006 (mayor), R*t* 17.103 (minor).

General procedure for the aldol reaction between aldehydes catalysed by polymer 5 under aqueous conditions.

To a mixture of the corresponding aromatic aldehyde (0.1 mmol), catalyst **5** (0.04 mmol, 54 mg) and benzoic acid (0.010 mmol, 1.2 mg) at 25 °C was added the propanal (1.0 mmol, 0.072 mL) and H_2O (100 μL). The reaction was stirred until the aldehyde was consumed (monitored by TLC). Then, the mixture was filtered and washed with EtOAc. The solvents were removed under reduced pressure and the residue was diluted with MeOH (1 mL) then $NaBH_4$ (0.25 mmol, 0.010 g) was added at 0 °C, and the mixture was stirred for 1 h. The resulting residue was purified by flash chromatography (hexanes/AcOEt 4 : 1 to yield the pure product.

(1*R*,2*R*)-2-Methyl-1-(4-nitrophenyl)propane-1,3-diol 10[31]. δ_H (300 MHz; $CDCl_3$, Me_4Si) *anti* 0.78 (d, *J* 7.0, 3H), 2.01–2.06 (m, 1H), 2.74 (br s, 1H), 3.72–3.85 (m, 3H), 4.72 (d, *J* 7.8, 1H *anti*), 7.54 (d, *J* 8.7, 2H), 8.23 (d, *J* 8.7, 2H). (75 MHz; $CDCl_3$, Me_4Si) *anti* 13.6, 41.5, 67.4, 79.3, 123.6, 127.5, 147.4, 150.5. δ_H (300 MHz; $CDCl_3$, Me_4Si) *syn* 0.82(d, *J* 7.2, 3H), 2.01–2.06 (m, 1H), 3.28 (d, *J* 3.6, 1H), 3.67–3.84 (m, 3H), 5.14 (s, 1H), 7.54 (d, *J* 8.7, 2H), 8.23 (d, *J* 8.7, 2H). (75 MHz; $CDCl_3$, Me_4Si) *syn* 9.8, 41.1, 66.6, 75.4, 123.3, 128.3, 147.6, 150.6. HPLC (Chiralpak AD-H, n-hexane/i-PrOH: 96/4, 0.9 mL min^{-1}), *anti*: R*t* 70.698 (minor), R*t* 75.298 (mayor); *syn*: R*t* 63.017 (minor), R*t* 67.671 (mayor).

Acknowledgements

This research was supported by the Ministerio de Ciencia e Innovación (Projects CTQ2007-62771/BQU and Consolider Ingenio 2010 CSD2007-00006), the Generalitat Valenciana (Project PROMETEO/2009/039) and the University of Alicante.

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