Cheap and Long-Life Reusable Polymer for Asymmetric Organozinc Catalysis Based on Camphor-Derived Hydroxyamides

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ABSTRACT Polystyrene grafted with a chiral zinc-complexing camphor-derived *N,N*-disubstituted hydroxyamide is proposed as a new type of functional polymer of high reusability for the development of sustainable organozinc-catalyzed asymmetric reactions. The main goal of this new functional polymer is the ease of the hydroxyamide-moiety preparation (cheap chiral ligand obtained straightforwardly from an enantiopure starting material coming from the chiral pool), as well as its chemical robustness when compared with other related zinc-complexing functional groups. The latter allows the polymer to be active after multiple applications, without significant loss of its catalytic activity. This fact is exemplified by the design and preparation of a polymer functionalized with a bis(hydroxyamide) proved previously as active in the homogeneous enantioselective addition of diethylzinc to aldehydes. The result is a cheap functional polymer with a very high reusability (the enantioselectivity and chemical yield are maintained practically constant after 20 applications). Additionally, a methodology for the multicycle use of these functional polymers is presented. *Chirality 00:000 –000, 2012.* © 2012 Wiley Periodicals, Inc.

KEY WORDS: asymmetric catalysis; diethylzinc reaction; sustainable chemistry; ketopinic acid; hydroxyamides

INTRODUCTION

Chiral organometallic catalysts based on zinc have found broad application in asymmetric organic synthesis.[1–13] In some cases, these catalysts could be efficiently recycled from the reaction media and reused several times in new reactions.[14–20] This possibility is very interesting for sustainable organozinc-catalyzed processes, especially when they must be performed at the industrial multikilogram level. Supporting the chiral-ligand moiety in a polymeric solid matrix (i.e., polystyrene (PS)) is usually the best option for designing reusable functional polymers that can be recovered by simple filtration.[21–25] However, the development of a heterogeneous supported catalyst is not trivial, and in many cases, the catalytic activity can be negatively affected by the supporting matrix.[14–25] Moreover, it is well known that the successive recovering–recycling–reusing cycles used to decrease the catalyst activity,[14–25] which can be overridden by enhancing the chemical robustness of the active ligand in some cases.[26]

One of the most studied asymmetric reactions promoted by organozinc catalysts is the enantioselective addition of organometallic reagents (mainly organozinc ones) to aldehydes.[1–3,5–7,11–13] In this line, many recyclable catalysts based in the immobilization of the most successful homogeneous ligands (i.e., β-amino alcohols) have been described for this valuable asymmetric C-C bond-forming reaction.[14–19] This strategy (ligand heterogenization) has also given good results for the development of interesting continuous-flow reactors, which can be also used in multiple applications.[27] Despite this huge effort, the higher numbers of consecutive applications of a heterogenized ligand, without significant loss of activity, have been reported for titanium catalysts instead of zinc ones,[14–19] probably because of a higher chemical robustness of the chiral ligands involved in such titanium catalysts. Thus, Seebach has reported some heterogeneous BINOL- and TADDOL-based titanium catalysts, which can be recycled and reused in, at least, 20 consecutive applications without any significant loss of activity.[28–30]

In a previous paper, we have described that the piperazine-based bis(hydroxyamide) **1**, a robust and cheap chiral ligand straightforwardly obtained from renewable camphor-derived (1*S*)-ketopinic acid (sustainable ligand),[31] is able to promote the enantioselective ethylation of benzaldehyde in the absence of titanium by formation of a C_2-symmetric zinc-chelate catalyst.[32] Recently, we have discovered that analogue 1,4-diazepane-based **2** also promotes efficiently the same reaction, although through a non-C_2-symmetric zinc-chelate catalyst.[33] The latter is highly interesting because it opens the way to the design of active immobilized ligands based of those bis(hydroxyamides), which irremissibly will generate non-C_2-symmetric zinc-chelate catalytic centers because of the covalent joint of the active ligand structure to the

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supporting matrix. This observation prompted us to investigate the use of the robust and cheap hydroxyamides of the type of **2** for the development of new long-life recyclable functional polymers for the catalyzed enantioselective addition of organozinc reagents to aldehydes, as a starting model for other organozinc-catalyzed asymmetric reactions.

EXPERIMENTAL

Materials and Methods

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). Melting points (m.p.) are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded at 20 °C, and the residual solvent peaks were used as internal standards. Fourier transform infrared (FTIR) spectra were obtained using the thin-layer technique. Gas chromatography (GC) analyses were realized at 120 °C in a chromatograph equipped with a capillary silicon-gum (SGL-1) column, a flame ionization detector and using nitrogen as mobile phase. Chiral high-performance liquid chromatography (HPLC) analyses were realized at room temperature (r.t.) in a chromatograph equipped with a Chiralpak-IC or Chiralpak-IA column and a diode array detector and using hexane/isopropanol as mobile phase. Mass spectra (MS) were recorded using the electrospray ionization (ESI) technique. high resolution mass spectra (HRMS) were obtained by the ESI-Fourier transform mass spectrometry (FTMS) technique. Elemental analyses (C, H, and N) were performed by the dynamic flash combustion technique.

Synthesis of Chiral Hydroxyamide Ligands

1,4-diazepan-6-ol. The preparation of key 1,4-diazepan-6-ol is based on a procedure reported previously by Saari *et al.* via 1,4-bis(*p*-toluenesulfonyl)-1,4-diazepan-6-ol as key intermediate.[34] We have optimized the preparation of such key bis(*p*-toluenesulfonyl) intermediate as follows: *N,N*-ethylenebis (*p*-toluenesulfonamide)[34] (12.23 g, 36 mmol) was dissolved in 350 ml of absolute ethanol, and a solution of KOH (5.60 g, 100 mmol) in 50 ml of absolute ethanol was added. The mixture was refluxed for 5 min with formation of a white precipitate. Then, a solution of 2,3-dibromopropan-1-ol (7.85 g, 36 mmol) in 50 ml of ethanol was added, and the reaction mixture refluxed for 7 h. The warm mixture was filtered, and the solvent evaporated under vacuum. The resulting residue was recrystallized from methanol to give 11.31 g (74% yield) of 1,4-bis(*p*-toluenesulfonyl)-1,4-diazepan-6-ol. The spectral data match up with those described previously in the bibliographic reference.[34]

1,4-bis{[(1*S*,2*R*)-7,7-dimethyl-2-hydroxynorborn-1-yl]carbonyl}-1,4-diazepan-6-ol (4). First step. In a round-bottom flask provided with a magnetic stirrer, (1*S*)-ketopinic acid (1.27 g, 7.0 mmol), *N*-[3-(dimethylamino)propyl]-*N*-ethylcarbodiimide hydrochloride (EDC·HCl, 1.53 g, 8.0 mmol), 4-(dimethylamino)pyridine (DMAP, 1.95 g, 16.0 mmol), and 1,4-diazepan-6-ol dihydrobromide (0.97 g, 3.5 mmol) were suspended in CH_2Cl_2 (50 ml) and stirred at room temperature for 72 h. Then, $CHCl_3$ (50 ml) and H_2O (50 ml) were added. The organic layer was separated, washed successively with 10% HCl (1 × 50 ml), H_2O (1 × 50 ml), 10% NaOH (2 × 50 ml), H_2O (1 × 50 ml), and brine (1 × 50 ml), and dried over anhydrous $MgSO_4$. The mixture was filtered and the solvent evaporated under reduced pressure. 1,4-Bis{[(1*S*)-7,7-dimethyl-2-oxonorborn-1-yl]carbonyl}-1,4-diazepan-6-ol (1.17 g, 73% yield) was isolated as a white solid and used for the next step without further purification. M.p.: 225–226 °C; $[\alpha]_D^{20}$ +0.6 (*c* 0.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) (as a mixture of rotamers): δ = 4.75–2.95 (m, 10H), 2.51 (d, *J* = 18.4 Hz, 2H), 2.40–1.83 (m, 8H), 1.89 (d, *J* = 18.4 Hz, 2H), 1.54–1.38 (m, 2H), 1.30–1.11 ppm (several s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) (as a mixture of rotamers, major signals are given): δ = 212.7 (CO), 170.7 (N-CO), 67.8 (CH-OH), 67.5 (C), 54.7 (CH_2), 51.9 (CH_2), 50.8 (C), 43.63 (CH_2), 43.59 (CH_2), 43.1 (CH), 43.0 (CH), 27.9 (CH_2), 27.6 (CH_2), 27.1 (CH_2), 27.0 (CH_2), 21.26 (CH_3), 21.12 (CH_3), 20.9 (CH_3), 20.7 ppm (CH_3); FTIR: ν = 3404 (w), 1738 (s), 1622 (s); MS (ESI-neg): *m/z* (%): 443 (64), 479 (100); HRMS (ESI-neg-FTMS): *m/z*: calculated for $C_{25}H_{35}N_2O_5$: 443.2546; found: 443.2609.

Second step. A two-neck round-bottom flask provided with a magnetic stirrer and a water condenser was charged with 1,4-bis{[(1*S*)-7,7-dimethyl-2-oxonorborn-1-yl]carbonyl}-1,4-diazepan-6-ol (0.89 g, 2.0 mmol), $NaBH_4$ (0.61 g, 16.0 mmol), and methanol (50 ml). The mixture was refluxed for 24 h under argon. Then, the mixture was cooled down and concentrated under reduced pressure. The residue was diluted with ethyl acetate (50 ml), and water (50 ml) was added. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 25 ml). The combined organic layers were dried over anhydrous $MgSO_4$. The mixture was filtered and the solvent evaporated under reduced pressure. The crude was purified by flash column chromatography (ethyl acetate) to obtain **4** (0.81 g, 90% yield) as a white solid. M.p.: decomposes at 220 °C; $[\alpha]_D^{20}$ −219.2 (*c* 0.75, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) (as a mixture of 1:1 rotamers): δ = 5.77–5.16 (br s, 2H), 4.70 (dd, *J* = 15.0, 3.7 Hz, 1H), 4.50 (ddd, *J* = 12.0, 12.0, 6.3 Hz, 1H), 4.40 (dd, *J* = 14.3, 6.3 Hz, 1H), 4.35–4.29 (m, 2H), 4.18 (br s, 1H), 4.13 (dd, *J* = 8.3, 3.7 Hz, 1H), 3.28 (br s, 1H), 3.21 (dd, *J* = 12.0, 5.4 Hz, 1H), 3.10 (d, *J* = 15.0 Hz, 1H), 3.06–2.99 (m, 1H), 2.87 (ddd, *J* = 14.3, 12.0, 5.4 Hz, 1H), 1.99–1.91 (m, 2H), 1.89–1.81 (m, 2H), 1.81–1.65 (m, 4H), 1.64–1.48 (m, 4H), 1.40 (s, 3H), 1.38 (s, 3H), 1.18–1.01 (m, 2H), 1.07 (s, 3H), 0.97 ppm (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) (as a 1:1mixture of inseparable amidic rotamers): δ = 178.7 (CO), 175.4 (CO), 77.5 (CH-OH), 76.6 (CH-OH), 71.5 (CH-OH), 61.6 (C), 61.4 (C), 54.3 (CH_2), 50.7 (C), 50.3 (C), 48.7 (CH_2), 47.4 (CH_2), 46.3 (CH_2), 44.9 (CH), 44.8 (CH), 41.3 (CH_2), 40.0 (CH_2), 29.0 (CH_2), 26.9 (CH_2), 26.7 (CH_2), 22.2 (CH_3), 21.9 (CH_3), 21.6 (CH_3), 21.5 ppm (CH_3); FTIR: ν = 3397 (w), 1607 (s); MS (ESI): *m/z* (%): 447 (61), 493 (100); HRMS (ESI-FTMS): *m/z*: calculated for $C_{25}H_{39}N_2O_5$: 447.2865; found: 447.2869.

6-(benzyloxy)-1,4-bis{[(1*S*,2*R*)-7,7-dimethyl-2-hydroxynorborn-1-yl]carbonyl}-1,4-diazepane (7). Into a round-bottom flask provided with a magnetic stirrer, charged with **4** (95 mg, 0.21 mmol), tetrabutylamonium iodide (TBAI, 78 mg, 0.21 mmol), and 18-crown-6 (56 mg, 0.21 mmol) in dry tetrahydrofuran (THF) (5 ml) under argon, NaH (9 mg, 0.23 mmol, 60% in mineral oil) was added. The mixture was stirred for 15 min, and then, benzyl bromide (39 mg, 0.23 mmol) was added. After stirring the reaction mixture at r.t. for 18 h, water (15 ml) and ethyl acetate (15 ml) were added. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 15 ml). The combined organic layers were washed with brine (1 × 15 ml) and dried over anhydrous $MgSO_4$. The crude was purified by flash column chromatography (ethyl acetate) to obtain **7** (90 mg, 79%) as a white solid. M.p.: 98–99 °C; $[\alpha]_D^{20}$ −131.0 (*c* 0.155, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) (as a mixture of inseparable amidic rotamers): δ = 7.55–7.21 (m, 5H), 5.05–2.03 (m, 15H), 2.02–1.17 (m, 18H), 1.16–0.87 ppm (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) (as a mixture of inseparable amidic rotamers; only major signals are dated): δ = 173.8 (N-CO), 172.8 (N-CO), 138.6 (C_{Ar}), 136.9 (C_{Ar}), 129.0 (CH_{Ar}), 128.2 (CH_{Ar}), 128.0 (CH_{Ar}), 77.8 (CH-O), 76.3 (CH-O), 74.9 (CH-O), 72.9 (CH-O), 71.6 (CH_2-O), 71.3 (CH_2-O), 61.2 (C), 59.9 (C), 54.3 (CH_2), 53.6 (CH_2), 50.5 (C), 50.4 (C), 48.1 (CH_2), 46.3 (CH_2), 45.2 (CH_2), 44.9 (CH), 44.7 (CH), 42.6 (CH_2), 41.9 (CH_2), 40.8 (CH_2), 40.3 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 26.8 (CH_2), 22.0 (CH_3), 21.8 (CH_3), 21.7 ppm (CH_3); FTIR: ν = 3454 (w), 1618 (s); MS (ESI): *m/z* (%): 539 (4), 561 (100); HRMS (ESI-FTMS): *m/z*: calculated for $C_{32}H_{47}N_2O_5$: 539.3479; found: 539.3477.

SYNTHESIS OF HYDROXYAMIDE-GRAFTED POLYMERS 6

Synthesis of 6b (Typical Procedure). Into a round-bottom flask provided with a magnetic stirrer, charged with **4** (0.50 g, 1.1 mmol), TBAI (0.41 g, 1.1 mmol), and 18-crown-6 (0.29 g, 1.1 mmol) in THF (50 ml) under argon, NaH (0.05 g, 1.2 mmol, 60% in mineral oil) was added. The

mixture was stirred for 15 min and then Merrifield StratoSpheres™ (4-(chloromethyl)polystyrene, $f^{\circ} = 2.0\,\text{mmol g}^{-1}$, 1% cross-linked with 1,4-divinylbenzene, 100–200 mesh, **5b**) (0.56 g, 1.1 mmol) was added. After stirring at r.t. for 6 days, the solvent was eliminated by filtration, and the filtrate was washed with CH_2Cl_2 (50 ml), water (50 ml), and methanol (50 ml); **6b** (0.72 g) was isolated as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$, gel phase): $\delta = 7.06$ (m, 15H), 6.56 (m, 10H), 4.99–2.45 (m, 11H), 2.36–0.32 ppm (m, 35H); ^{13}C NMR (175 MHz, $CDCl_3$, gel phase): $\delta = 173.6$, 145.7, 128.1, 71.9, 61.5, 53.5, 50.7, 48.3, 44.9, 40.5, 29.7, 27.1, 22.0 ppm. Elemental analysis: found (%): C 80.13, H 7.77, N 2.41 ($f = 0.86\,\text{mmol g}^{-1}$).

Synthesis of 6a. By following the same procedure used for the synthesis of **6b**, **4** (0.10 g, 0.22 mmol) was reacted with Merrifield resin (4-(chloromethyl)polystyrene, $f^{\circ} = 1.5$–$2.0\,\text{mmol g}^{-1}$, 1% cross-linked with 1,4-divinylbenzene, 100–200 mesh, **5a**) (0.15 g, 0.22–0.30 mmol); **6a** (0.20 g) was isolated as a white solid. Elemental analysis: found (%): C 79.05, H 7.62, N 2.28 ($f = 0.82\,\text{mmol g}^{-1}$).

Synthesis of 6c. Following the same procedure used for the synthesis of **6b**, **4** (0.10 g, 0.22 mmol) was reacted with Wang chlorinated resin ([4-(chloromethyl)phenoxymethyl] polystyrene, $f^{\circ} = 0.5$–$1.0\,\text{mmol g}^{-1}$, 1% cross-linked with 1,4-divinylbenzene, 100–200 mesh, **5c**) (0.45 g, 0.22–0.44 mmol); **6c** (0.41 g) was isolated as a white solid. Elemental analysis: found (%): C 81.83, H 7.13, N 0.92 ($f = 0.33\,\text{mmol g}^{-1}$).

ENANTIOSELECTIVE ETHYLATION OF ALDEHYDES

General Procedure for The Homogeneous Enantioselective Ethylation of Aldehydes

Into an argon-purged 10-ml round-bottom flask provided with a magnetic stirrer and a septum and containing the ligand (0.02 mmol), diethylzinc solution (1.0 M in hexanes, 1.10 mmol) was added at room temperature. The mixture was stirred at r.t. for 5 min. After that, the corresponding aldehyde (1.0 mmol) was added and the reaction mixture stirred at r.t. for 1 h. Then, the reaction was quenched by the addition of aqueous HCl (3 M, 3 ml). The resulting mixture was extracted with ether (3×3 ml). The combined organic layers were submitted to celite filtration and solvent evaporation. The obtained residue was dissolved in HPLC-grade hexanes and submitted to analysis by GC and chiral HPLC.

General Procedure for The Multicycle Heterogeneous Enantioselective Ethylation of Benzaldehyde

Into the reaction vessel shown in Figure 1, with an argon flow, provided with a magnetic stirrer and containing **6b** (0.08 mmol), toluene (2 ml) was added. The argon flow was passed continuously through the reaction mixture from below the fritted disc to keep the reaction mixture from falling through the disc to the flask. The polymer was swollen by stirring for 0.5 h. Then, diethylzinc solution (1.5 M in toluene, 3.0 mmol) was added at room temperature. The mixture was stirred at r.t. for 5 min. After that, benzaldehyde (2.0 mmol) was added and the reaction mixture was stirred at r.t. for 20 h. Once the reaction was finished, the argon flow was interrupted and the reaction mixture filtered under vacuum. The obtained filtrated solution was quenched by the addition of aqueous HCl (3 M, 3 ml), and the obtained layers separated. The aqueous layer was extracted with ether (3×3 ml) and the combined organic layers submitted to celite filtration and solvent evaporation under vacuum. The obtained residue was dissolved in HPLC-grade hexanes and submitted to analysis by GC and chiral HPLC.

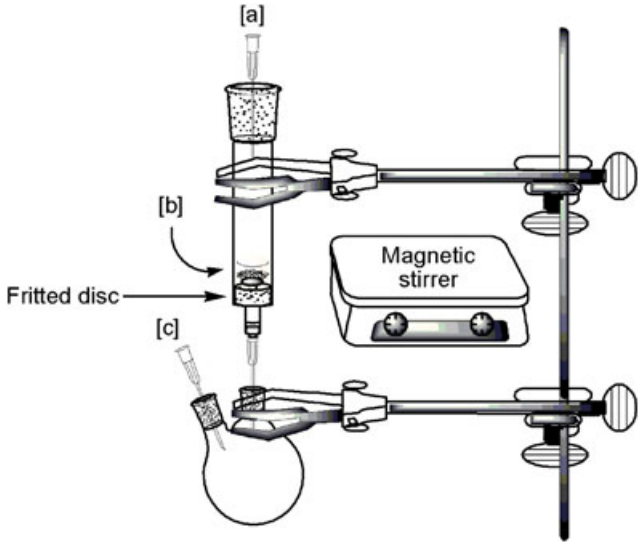


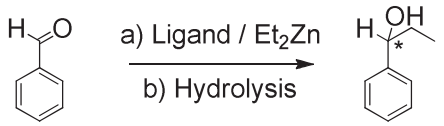
Fig. 1. Reaction vessel for the multicycle process. Reaction: [**a**] Ar outlet, [**b**] reacting mixture, [**c**] Ar inlet. Work up: [**a**] Air inlet, [**b**] heterogeneous mixture to be filtered, or functional polymer to be washed or dried, [**c**] outlet connected to the vacuum system.

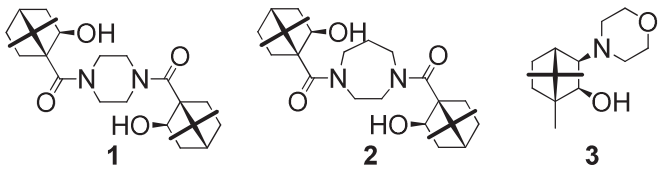
The used polymer kept in the reaction vessel was then recycled for the next reaction by washing with aqueous HCl (3 M, 3×5 ml), water (3×5 ml), acetone (3×5 ml), and methanol (3×5 ml), and final drying under vacuum.

RESULTS AND DISCUSSION

Although the activity of ligand **2** in enantioselective ethylation of benzaldehyde has been recently reported by us,[33] the selection of this ligand, as key moiety for the construction of the desired long-life reusable polymer, makes necessary a comparison study of such activity in relation with the activity of other well-known homogeneous ligands, which have been also used in reusable polymers. Thus, we investigated the efficiency of **2**[33] in comparison with 3-*exo*-(morpholino)isoborneol (**3**), a known very active amino-alcohol ligand developed by Nugent.[35] As a test reaction, we chose the ethylation of benzaldehyde, which was performed with a low catalyst loading (0.5% mol eq) and a short reaction time (0.5 h) for detecting efficiency differences (Table 1). Ligand **1**,[32] the first-generation analogue of **2**, was also submitted to this study to detect possible efficiency differences when compared with **1**. We used the E (defined as E = TOF·*ee*, TOF being the turnover frequency) as a convenient one for measuring the efficiency of the tested ligands. This parameter is interesting to our purpose because it weights not only enantioselectivity (*ee*) but also reaction rate (TOF). On the basis of E, the efficiency of hydroxyamide **2** proved to be 0.72 times the efficiency of amino alcohol **3** (Table 1, relative-E column), which is very high, taking into account the structural differences of the functional groups involved in both ligands (note the higher zinc-chelating character of an amine group when compared with an amide one). Additionally, **2** was probed to be more efficient than **1** (see Table 1), as it was expected because of the higher conformational flexibility of **2** when compared with **1**.[33]

TABLE 1. Ligand efficiency in enantioselective ethylation of benzaldehyde[a]





1 **2** **3**

Ligand	Yield (%)[b]	*ee* (%)[c]	TOF(h^{-1})	E	Relative E
1	50	88 (*R*)	200	17600	0.49
2	71	92 (*R*)	284	26182	0.72
3	98	92 (*R*)	392	36064	1.00

[a]Benzaldehyde, 1 mol eq; Ligand, 0.5% mol eq; Et_2Zn (1 M in hexanes), 1.1 mol eq; T, real time; *t*, 0.5 h.
[b]Determined by gas chromatography.
[c]Determined by chiral high-performance liquid chromatography.

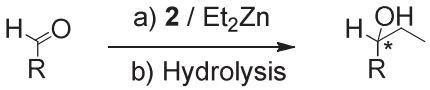
Once the good efficiency of hydroxyamide **2** is established, we tested its versatility for the ethylation of a small battery of representative aldehydes (Table 2). As shown in Table 2, ligand **2** was able to produce the asymmetric ethylation of aliphatic and aromatic aldehydes with different substitution patterns.

Once the election of **2** is supported as key moiety for designing the desired recyclable (easily filterable) functional polymers, we proceeded to obtain such polymers. For this purpose, we decided to graft **2** onto polystyrene (PS), on the basis of the known good swollen properties of this polymer by the action of several organic solvents used in organozinc reactions (i.e., toluene). The polymer swelling factor is a key parameter in catalyst heterogenization because a good swelling factor reduces the undesired diffusion effect produced by the heterogenization.[30] For grafting **2** onto PS, we prepared **4** as a conveniently functionalized analogue of **2**. This ligand could be easily and selectively linked to different chloromethylated PS (**5**), by a Williamson reaction involving its less-hindered central hydroxyl group, to generate **6** (Scheme 1). Moreover, the central location of such reacting hydroxyl group of **4**, as well as its remote disposition from the catalytic region (zinc-dialkoxide complex),[32,33] makes it possible to keep the basic structural characteristics of the homogeneous parent ligand **2** after the immobilization (tail-tied-ligand strategy).[36]

Ligand **4** was straightforwardly obtained from (1*S*)-ketopinic acid and 1,4-diazepan-6-ol following the two-step synthetic strategy we described previously for the preparation of its analogue **2**,[33] using 1,4-diazepan-6-ol[34,37] instead of 1,4-diazepan. The preparation of starting 1,4-diazepan-6-ol was optimized as previously commented in the Experimental section.

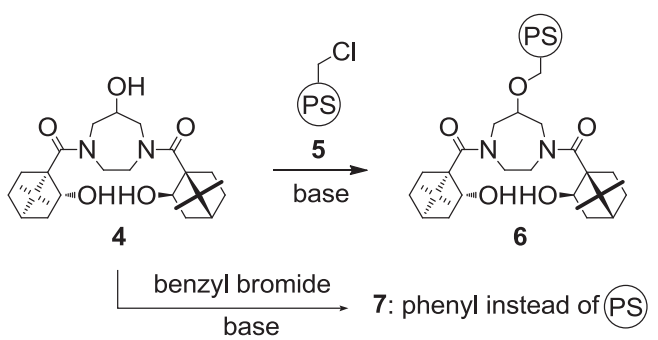
Before preparing **6**, the effect of the benzyloxyl linkers on the catalytic activity of the hydroxyamide-based centers was tested. For this purpose, we prepared ligand **7**, as a homogenous model of **6**, to be compared with its non-benzyloxylated analogue **2**. The preparation of **7** was also realized from **4** via a Williamson reaction as shown in Scheme 1. As expected, the etherification was highly selective, involving only the central less-hindered hydroxyl group of **4**, and other possible ethers being undetected. Benzaldehyde ethylation was used as a test reaction for the comparison study between **2** and **7**. Gratifyingly, the measured activity of **7** (97% yield and 93% *ee*, by using 2% mol eq of ligand, 1.1 mol eq of Et_2Zn, r.t. and 1 h of

TABLE 2. Activity of homogeneous ligand 2 in enantioselective ethylation of aldehydes[a]



Aldehyde	Yield (%)[b]	*ee* (%)[c]
benzaldehyde	98[d]	93[d]
2-chlorobenzaldehyde	91	92
4-chlorobenzaldehyde	94	93
2-methylbenzaldehyde	83	92
4-methylbenzaldehyde	81	92
2-methoxybenzaldehyde	97	92
hexanal[f]	95	74[f]
cyclohexanecarbaldehyde[f]	89	80[f]

[a]Aldehyde (RCHO), 1.0 mol eq; **2**, 2% mol eq; Et_2Zn (1 M in hexanes): 1.1 mol eq; *T*, real time; *t*, 1 h.
[b]Determined by gas chromatography.
[c]Determined by chiral high-performance liquid chromatography (major enantiomer: *R* in all cases).
[d]Data from Ref. 11.
[e]**2**, 5% mol eq; *t*, 2 h.
[f]Analysis of the corresponding alcohol benzoates.



Scheme 1. Preparation of functionalized polymers **6** based on (polystyrene) PS and homogeneous benzoyloxylated analogue **7**.

reaction) resulted practically identical to the activity of **2** under the same conditions.[33]

The preparation of hydroxyamide-grafted polymers of the type of **6** was optimized to improve the level of ligand loading (f) in relation with the polymer activity (Table 3). As starting chloromethylated PS **5**, we used a Merrifield resin with a chlorine loading (f°) of 1.5–2.0 mmol g^{-1} (**5a**), Merrifield StratoSpheres™ with f° = 2.0 mmol g^{-1} (**5b**), and a Wang resin with f° = 0.5–1.0 mmol g^{-1} (**5c**).

A moderate **4** loading (f) in polymer **6**, obtained by using a stoichiometric amount of sodium hydride for the grafting reaction, was enough to reach a good activity (see entries 3 and 12 of Table 3). A higher ligand loading, achieved by rising the grafting time, improved the polymer activity (cf., entries 4 and 3). On the other hand, higher loadings, obtained by using an excess of sodium hydride, diminished noticeably the activity of the corresponding **6** (cf., entries 2 and 3). This fact can be explained by a loss of highly active catalytic moieties involving the key bis(hydroxyamide)-chelated zinc-dialkoxyde structure[32,33] because of an extra grafting of some ligand moieties onto the polymer by more than one hydroxyl function. Therefore, the use of a stoichiometric amount of base for the Williamson grafting reaction is a key parameter for achieving a good highly loaded active polymer.

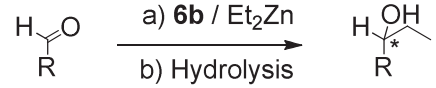
Optimization of the asymmetric-reaction conditions was carried out for the highest-loaded polymer **6a** (f = 0.82 mmol g^{-1}) (Table 3, entries 4–9). The highest chemical yield and enantioselectivity were reached when 1.5 mol eq of diethylzinc and 4% mol eq of supported ligand were used (entry 8). The optimization was followed by a study on the influence of the polymeric matrix on both ligand grafting and catalytic activity (entries 8, 10, and 12). This study lets us choose grafted polymer **6b** (f = 0.72 mmol g^{-1}) as the most privileged (entry 10). Finally, a higher ligand loading in **6b** (f = 0.86 g mol^{-1}), which optimizes the mass of polymer to be used in the asymmetric reaction, was achieved by increasing the grafting time (cf., entries 11 and 10).

To validate the heterogenization of ligand **2** as polymer **6b**, we proceeded to realize a comparison study on the scope of both in enantioselective ethylation of aldehydes. Satisfyingly, no noticeable differences between **2** and **6b**, beyond the logical reaction rate decreasing for the grafted polymer, were found (cf., Table 4 and 2).

Once **6b** was confirmed as a functional polymer based on a chemically robust chiral hydroxyamide, we proceeded to test its stability in an asymmetric multicycle process. The chosen test reaction was the ethylation of benzaldehyde. In each cycle, the reaction was finalized by standard acid quenching (diluted HCl) and the functional polymer recovered by simple filtration (see Experimental section).

Thus, the optimized polymer **6b**, with a ligand loading of 0.86 mmol g^{-1}, was employed in 20 consecutive enantioselective additions of diethylzinc to benzaldehyde (Fig. 2). The

TABLE 4. Activity of 6b in enantioselective ethylation of aldehydes[a]



Aldehyde	Yield (%)[b]	*ee* (%)[c]
benzaldehyde	97	93
2-chlorobenzaldehyde	91	92
4-chlorobenzaldehyde	82	90
2-methylbenzaldehyde	81	90
4-methylbenzaldehyde	82	89
2-methoxybenzaldehyde	92	84
hexanal	96	76[d]
cyclohexanecarbaldehyde	92	76[d]

[a]Aldehyde (RCHO), 1.0 mol eq; **6b** (f = 0.86 mmol g^{-1}), 4% mol eq; Et_2Zn (1.5 M in toluene), 1.5 mol eq; T: room temperature; t, 20 h.
[b]Determined by gas chromatography.
[c]Determined by chiral high-performance liquid chromatography (major enantiomer: R in all cases).
[d]Determined by analysis of the corresponding alcohol benzoates.

TABLE 3. Optimization of 6 preparation in function of its activity in enantioselective ethylation of benzaldehyde (see reaction in Table 1, ligand = 6)

	6 preparation[a]				Benzaldehyde ethylation[b]			
Entry	Starting **5**	NaH (mol eq)	t (d)	f (mmol g^{-1})[c]	**6** typology (% mol eq)	Et_2Zn (mol eq)	Yield (%)[d]	*ee* (%)[e]
1[f]	**5a**	3.0	6	0.20	**6a** (2)	1.1	18	63
2	**5a**	3.0	3	0.69	**6a** (2)	1.1	23	57
3	**5a**	1.1	2	0.44	**6a** (2)	1.1	83	93
4	**5a**	1.1	4	0.82	**6a** (2)	1.1	95	90
5	**5a**	1.1	4	0.82	**6a** (1)	1.1	82	87
6	**5a**	1.1	4	0.82	**6a** (4)	1.1	95	90
7	**5a**	1.1	4	0.82	**6a** (8)	1.1	85	90
8	**5a**	1.1	4	0.82	**6a** (4)	1.5	97	93
9	**5a**	1.1	4	0.82	**6a** (4)	2.0	97	92
10	**5b**	1.1	4	0.72	**6b** (4)	1.5	97	94
11	**5b**	1.1	6	0.86	**6b** (4)	1.5	97	93
12	**5c**	1.1	4	0.33	**6c** (4)	1.5	97	90

[a]**4**, 1.0 mol eq; **5**, 1.0 mol eq (for calculating the amount of **5a** and **5c**, the lowest value of the f° interval was considered); tetrabutylammonium iodide (TBAI), 1.0 mol eq; 18-Crown-6, 1.0 mol eq; solvent, tetrahydrofuran; T, room temperature.
[b]1.5 M Et_2Zn in toluene. T, room temperature; t, 20 h.
[c]Determined by elemental analysis.
[d]Determined by gas chromatography.
[e]Determined by chiral high-performance liquid chromatography (major enantiomer: R in all cases).
[f]Without adding TBAI/18-crown-6.

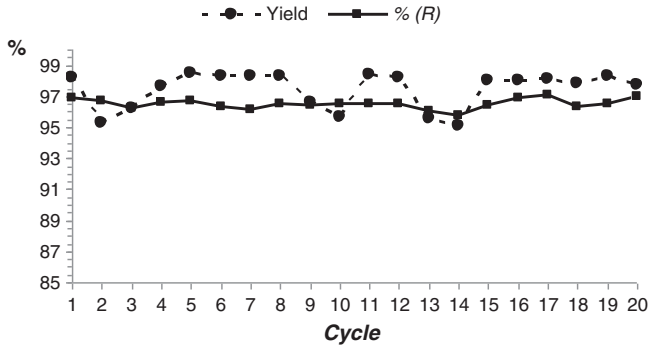


Fig. 2. Enantioselectivities and chemical yields in the formation of (*R*)-1-phenylpropan-1-ol by using **6b** in 20 consecutive catalytic cycles under optimized reaction conditions (Table 3, entry 11).

obtained results show the high stability of these hydroxyamide-grafted polymers because **6b** could be easily recovered, recycled, and reused in, at least, 20 sequential applications with practically constant both enantioselectivity (96–97% of *R* isomer) and chemical yield (95–98%). This high reproducibility is similar to the ones achieved for certain titanium catalysts in the same reaction,[28–30] which is especially noticeable by taking into account the acidic treatment used for the reaction quenching in our case, and as it was expected by us on the basis of the chemical robustness of the used hydroxyamide ligands toward such treatment.

CONCLUSIONS

We have demonstrated the success of using a robust and cheap chiral hydroxyamide derived from camphor for the design of a long-life reusable polymer for the enantioselective addition of organozinc reagent to aldehyde in the absence of additional metals (organozinc catalysis). Although the recorded enantioselectivities are somewhat lower than those achieved with standard catalysts, the hydroxyamide-supported polymeric system demonstrated a remarkable recyclability, allowing 20 consecutive uses (more cycles were not tested), including 20 consecutive catalyst quenching and polymer washing and drying, which is not the common case in most of the recyclable organozinc-based catalysts. Therefore, it is worthwhile to investigate this strategy in other asymmetric reactions involving zinc catalysts, as well as the use of dendritically cross-linked polymers[28–30] or nanosized matrixes[38–40] to reduce the observed negative diffusion effect on the reaction rates.

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