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

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ABSTRACT

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

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1. Introduction

Chiral secondary alcohols are key intermediates for the preparation of socio-economically valuable natural and non-natural products with biological activity, including drugs, and new materials with interesting physicochemical properties [1–4]. These intermediates are usually prepared in the industry by asymmetric reduction of ketones, either with chiral boranes or by chiral hydrogenation based on Noyori asymmetric hydrogenation [5–13]. However, the first option produces large amounts of borane waste and the second one requires expensive and non-environmentally friendly metal-ligand combinations. In this sense, the enantioselective addition of organozinc reagents to aldehydes [14–24] offers a very interesting alternative, with the advantages that a new C—C bond is created at the same time and that only a catalytic amount of a more environmentally friendly zinc complex is needed. Because of the relevance of the mentioned reaction, a large effort has been devoted to the development of ligands able to promote the addition enantioselectively. However, the most efficient ligands needed for this reaction are usually synthetically elaborated (and thus very expensive). In addition, because many of them are relatively unstable (most are amino alcohols), they cannot be recovered from the reaction medium and reused in further reactions. These two facts have hampered the transfer of the reaction to the industry, despite its big interest.

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

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

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

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

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

Thus, with regard to our previous work in this area, herein we report an important improvement in the catalytic efficiency (reaction rate enhancement with no loss of enantioselectivity) for PS-supported ketopinic acid-derived bis(hydroxyamides) and the structural factors controlling it. The catalytic behavior of the designed functional polymers has been investigated for the enantioselective ethylation of benzaldehyde as the test reaction.

2. Experimental

2.1. Materials and instrumentation

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

2.2. Preparation of ***11***

2.2.1. Synthesis of diazepane ***18***

Under argon, anhydrous ammonium formate (2.56 g, 40.6 mmol) and 10% Pd/C (1.67 g, 200 mg/mol) were added to a stirred solution of **17** [65] (3.45 g, 8.1 mmol) in methanol (60 mL), and the resulting mixture was refluxed for 2 h. After cooling down to r.t., the mixture was filtered through a Na_2SO_4 pad to remove the catalyst, and the filtrate submitted to solvent evaporation under reduced pressure. The residue was dissolved in $CHCl_3$ (60 mL), washed with H_2O (4 × 20 mL) and dried over anhydrous Na_2SO_4. Filtration and solvent evaporation under reduced pressure gave **18** (1.88 g, 92%) as a pale brown viscous oil, which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 3.43 (dd, J = 6.2, 6.2 Hz, 2H), 3.01 (dd, J = 13.7, 5.6 Hz, 2H), 2.82 (m, 4H), 2.65 (dd, J = 13.7, 7.5 Hz, 2H), 2.44 (bs, 2H), 1.90 (m, 1H), 0.85 (s, 9H), 0.00 (s, 6H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 64.6, 52.6, 50.6, 44.9, 5.8, 18.1, −5.5 ppm.

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

A mixture of **19** (2.58 g, 14.2 mmol), *N*-[3-(dimethylamino)propyl]-*N*′-ethylcarbodiimide hydrochloride (EDC·HCl, 2.73 g, 14.2 mmol), 4-(dimethylamino)pyridine (DMAP, 1.73 g, 14.2 mmol) and **18** (1,73 g, 7.1 mmol) in CH_2Cl_2 (50 mL) was stirred at r.t. for 72 h. Then, $CHCl_3$ (50 mL) and H_2O (50 mL) were added to the reaction mixture, and the organic layer was separated, washed successively with 10% HCl

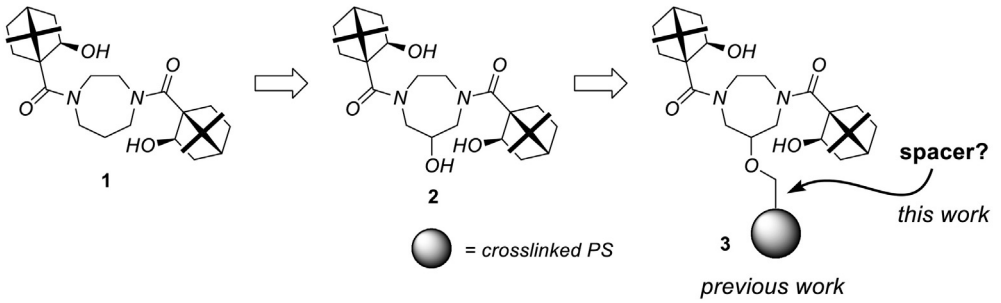


Fig. 1. Development of polystyrene-supported (PS-supported) hydroxyamides for the enantioselective addition of organozincs to aldehydes.

(1 × 50 mL), H_2O (1 × 50 mL), 10% NaOH (1 × 50 mL), H_2O (1 × 50 mL) and brine (1 × 50 mL), and dried over anhydrous Na_2SO_4. Filtration and solvent evaporation under reduced pressure, followed by flash chromatography (silica gel, hexane/ethyl acetate 6/4) gave **20** (3.05 g, 75% yield) as a pale yellow solid. M.p.: 143.7–145.0 °C. $[\alpha]_D^{20}$ +32.1 ($CHCl_3$, c = 0.14 g/100 mL). ^{1}H NMR ($CDCl_3$, 300 MHz, mixture of rotamers), δ: 4.39–3.11 (m, 6H), 2.97–1.61 (m, 16H), 1.41–1.20 (m, 2H), 1.18–0.97 (m, 13H), 0.72 (ms, 9H), −0.11 (s, 6H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, mixture of rotamers), δ: 212.2, 211.6, 169.6, 168.4, 67.5, 63.5, 54.1, 51.0, 50.8, 47.8, 47.0, 46.5, 43.8, 43.7, 43.2, 43.1, 41.4, 28.4, 28.0, 27.5, 26.0, 21.7, 21.6, 21.3, 20.9, 18.3, −5.4, −5.3 ppm. FTIR, υ: 3462.1, 1739.5, 1625.2 cm^{-1}. MS, m/z (%): 572.4 (M^+, 5), 515.3 (100), 487.3 (18), 407.3 (19), 351.2 (84), 275.2 (47), 187.1 (44), 165 (78), 123.1 (34), 95.1 (31). HRMS, m/z: 572.3643 (calcd. for $C_{32}H_{52}N_2O_5Si$: 572.3645).

2.2.3. Synthesis of bis(ketoamide) ***21***

Under argon, a mixture of **20** (2.32 g, 4.0 mmol), 18-crown-6 (1.06 g, 4.0 mmol) and CsF (1.24 g, 8.0 mmol) in acetonitrile (50 mL) was stirred at 50 °C for 18 h. Then, the solvent was evaporated under reduced pressure, and ethyl acetate (20 mL) and water (20 mL) were added. After phase separation, the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with water (3 × 10 mL) and brine (1 × 20 mL) and dried over anhydrous Na_2SO_4. Filtration and solvent evaporation under reduced pressure, followed by flash chromatography (silica gel, CH_2Cl_2/ethyl acetate: 4/6) gave **21** (1.66 g, 90%) as a white solid. M.p.: 179.7–181.9 °C. $[\alpha]_D^{20}$ −5.1 ($CHCl_3$, c = 0.19 g/100 mL). ^{1}H NMR ($CDCl_3$, 300 MHz, mixture of rotamers), δ: 4.60–2.61 (m, 10H), 2.81–1.80 (m, 13H), 1.54–1.40 (m, 2H), 1.26–1.17 (m, 12H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, mixture of rotamers), δ: 212.5, 170.2, 169.4, 67.8, 63.3, 52.3, 51.0, 43.8, 43.2, 43.0, 28.1, 27.2, 21.5, 21.1, 20.9 ppm. FTIR, υ: 3425.2, 1738.2, 1621.3 cm^{-1}.

2.2.4. Synthesis of bis(hydroxyamide) ***11***

Under argon, $NaBH_4$ (0.90 g, 24.1 mmol) was slowly added to a solution of **21** (1.38 g, 3.0 mmol) in methanol (30 mL), and the resulting mixture was refluxed for 24 h. The mixture was then cooled to r.t. and the solvent was evaporated under reduced pressure. Then, $CHCl_3$ (20 mL) and water (20 mL) were added. After phase separation, the aqueous phase was extracted with $CHCl_3$ (3 × 10 mL). The combined organic extracts were washed with water (1 × 10 mL) and brine (1 × 10 mL) and dried over anhydrous Na_2SO_4. Filtration and solvent evaporation under reduced pressure, followed by flash chromatography (silica gel, ethyl acetate) gave **11** (1.29 g, 92% yield) as a white solid. M.p.: 225.4–227.3 °C. $[\alpha]_D^{20}$ + 14.1 (MeOH, c = 0.76 g/100 mL). ^{1}H NMR ($CDCl_3$, 300 MHz, mixture of rotamers), δ: 4.66–3.86 (m, 6H), 3.75–3.03 (m, 6H), 2.99 (m, 2H), 2.33 (m, 1H), 2.00–1.42 (m, 13H), 1.34 (s, 3H), 1.29 (s, 3H), 1.12–0.87 (m, 8H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz mixture of rotamers) δ: 175.0, 173.7, 63.2, 61.7, 60.7, 53.0, 51.0, 50.9, 49.0, 46.5, 46.1, 45.4, 45.1, 42.6, 42.3, 41.3, 30.0, 29.9, 29.7, 27.1, 22.3, 22.2, 22.1 ppm. FTIR, υ: 3330.6, 1603.9 cm^{-1}. MS-ESI, m/z (%): 462 (M, 15). HRMS-ESI: 462.3088 (calcd. for $C_{26}H_{42}N_2O_5$: 462.3094).

2.3. Synthesis of PS-supported bis(hydroxyamide) ***12a***

Under argon, NaH (60% in mineral oil, 29 mg, 0.73 mmol) was slowly added to a mixture of **11** (102 mg, 0.22 mmol), tetrabutylammonium iodide (TBAI, 82 mg, 0.22 mmol) and 18-crown-6 (58 mg, 0.22 mmol) in dry THF (10 mL). The resulting mixture was stirred for 30 min. Then, commercial Merrifield StratoSpheres™ (**27**, chloromethyl-functionalized PS resin, f = 2.0 mmol·g^{-1}, 1% crosslinked with 1,4-divinynilbenzene (DVB), 100–200 mesh, 124 mg, 0.24 mmol) was added, and the mixture was stirred for 3 days. The polymer was filtrated, washed with CH_2Cl_2 (10 mL), water (10 mL) and methanol (10 mL), and dried under vacuum at 50 °C for 4 h to give **12a** (162 mg, 91%) as a white solid. FTIR, υ: 3425.7, 1601.1 cm^{-1}. EA: C 80.21, H 7.64, N 2.35 (bis(hydroxyamide) loading: f = 0.84 mmol·g^{-1}).

2.4. Catalytic tests

2.4.1. General procedure for the heterogeneous enantioselective ethylation of benzaldehyde

Under argon, a suspension of PS **12** (0.04 mmol) in toluene (1 mL) was stirred for 30 min to swell the polymer. Then, diethylzinc (1.5 M in toluene, 1.50 mmol) was slowly added, and the mixture was stirred for 30 min. Then, **22** (1.00 mmol) was slowly added, and the resulting mixture was stirred for 2 h and finally quenched with 3 M HCl (3 mL). The quenched mixture was filtered, the filtrate was extracted using ether (3 × 3 mL), and the obtained organic layers were combined and filtered through celite™. After solvent evaporation under reduced pressure, the obtained residue was dissolved in HPLC-grade hexanes and was analyzed by GC to estimate the yield (**22** conversion) and by chiral HPLC to estimate the enantiomeric excess (*ee*) and absolute configuration for the major enantiomer of **23**.

2.4.2. General procedure for the recycling and reusing of heterogenized chiral ligands by using a fluidized-bed reactor prototype

The reactor shown in Fig. 2, made of a recipient with a porous bottom (filter funnel) capped with a rubber septum and a needle, was used. The recipient was charged with the heterogenized bis(hydroxyamide) (0.08 mmol) and an argon current was passed through the funnel, from bottom to top. Then, toluene (2.0 mL) was added to swell the polymer and the mixture was stirred for 30 min at r.t. Then, diethylzinc (1.5 M, 2 mL, 3.00 mmol) was added and stirred for further 30 min. Finally, benzaldehyde (2.00 mmol) was added and the mixture was stirred for 2 h. The reaction was quenched by inverting the direction of the argon current to separate the catalyst by filtration. The filtrate was poured into a separation funnel and washed with 3 M HCl (3 mL) and the aqueous phase was extracted with ether (3 × 3 mL). The obtained organic layers were combined and filtered through celite™. After solvent evaporation under reduced pressure, the obtained residue was analyzed as described in section 2.4.1. The supported ligand, which remained on the porous bottom of the reactor, was washed with 3 M HCl (3 × 5 mL), water (3 × 5 mL), acetone (3 × 5 mL) and methanol (3 × 5 mL) and dried under vacuum at 50 °C for 4 h to be used in the next catalytic reaction.

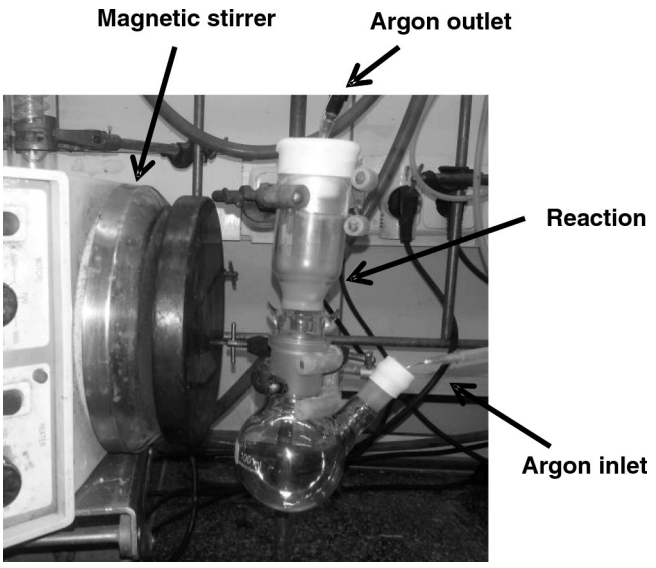


Fig. 2. Experimental set-up for the prototype of fluidized-bed reactor used for the reuse of heterogeneous ligands.

3. Results and discussion

3.1. Synthesis of the ligands

Two initial synthetic strategies (Scheme 1) were considered for the preparation of the desired PS-supported chiral hydroxyamides **10**, having a relatively rigid spacer helping to allocate the ligand far away from the PS matrix. The two strategies were: (1) functionalization of ligand **2** with a spacer before its incorporation into the PS matrix and (2) radical copolymerization of styrene with the ligand, previously functionalized with a spacer having vinylphenyl units (**8**). The second strategy is based on the dendritically crosslinked ligand methodology described by Seebach to prepare porous polymers functionalized with chiral diols [66].

Unfortunately, several attempts to selectively *O*-alkylate (through the diazepane oxygen) **2** with **4** or **7** failed, probably because of the steric hindrance of the central hydroxyl group of **2**. To avoid this problem, hydroxyamide **11** (Fig. 3) was designed as a convenient, more reactive analogue of **2**, having a primary instead of secondary hydroxyl group, while keeping the basic active structure of seminal hydroxyamide **1**. Moreover, the anchoring site is further away from the catalytic site in this new hydroxyamide, that is, the additional methylene group is itself a small spacer between the polymer matrix and the ligand catalytic site. This could have a positive effect on the diffusion problem.

For the preparation of enantiopure **11** (Scheme 2), key diazepane intermediate **18** was obtained in 50% yield according to a patent [65], but with two slight modifications that improved the experimental procedure: (1) the use of chloroform as a solvent in the first step (coupling of **13** and **14**) and (2) the use of ammonium formate/Pd-C for the debenzylation of **17**. Then, *O*-protected diazepane **18** was diacylated with (1*S*)-ketopinic acid (**19**) using EDC/DMAP as the coupling agents, according to the previously optimized procedure to prepare ketopinic-derived bis(hydroxyamides) [62]. The so-obtained **20** was desilylated with CsF to generate **21**, which was finally subjected to selective ketone reduction with $NaBH_4$ to yield **11** with high diastereoselectivity (only the *exo*,*exo*-dihydroxyl diastereomer was detected by ^1H NMR).

Following the initially proposed strategies for the preparation of heterogenized bis(hydroxyamides) from **2**, having a spacer between the ligand and the solid matrix (see Scheme 1), we essayed the selective *O*-alkylation of new ligand **11** with **4** and with **7**. Additionally, we decided to prepare ligand **25** (Scheme 3) as a homogeneous model for the anchoring onto solid matrixes. First, bromobenzyl derivative **24** was obtained by Williamson etherification of **11** with **4**. However, its high reactivity made its purification impossible. On the contrary, ligands **25** and **26** could be easily obtained (by Williamson etherification with corresponding bromobenzyl derivatives), demonstrating the possibility of selective *O*-alkylation of **11** through its central hydroxyl group (see Scheme 3).

The new ligands based on 6-methyl-1,4-diazepane (**11** and its derivatives **25** and **26**) were evaluated in the enantioselective addition to diethylzinc to benzaldehyde (Table 1) to check any possible influence of the central *O*-substitution on the catalytic activity of the ligand. Satisfactorily, ligand **11** provided an enantioselectivity even higher than that of its homologous **2** and very similar to that of **1**, which has no substituents on the diamine moiety. These results support the use of **11** as a useful analogous of **2** for the preparation of functionalized PS. Additionally, the fact that the catalytic activities of **25** and **26** were comparable to the ones displayed by **1** and **11** demonstrates that the central substitution of the diazepane moiety has no negative effect on the catalytic activity of 1,4-diazepane-derived bis(hydroxyamides). Therefore, the heterogeneous catalytic activity should not be negatively influenced

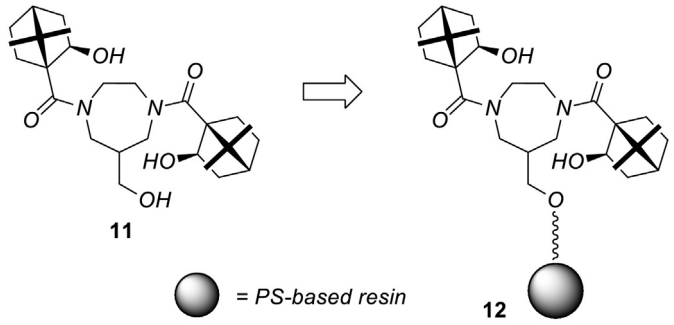
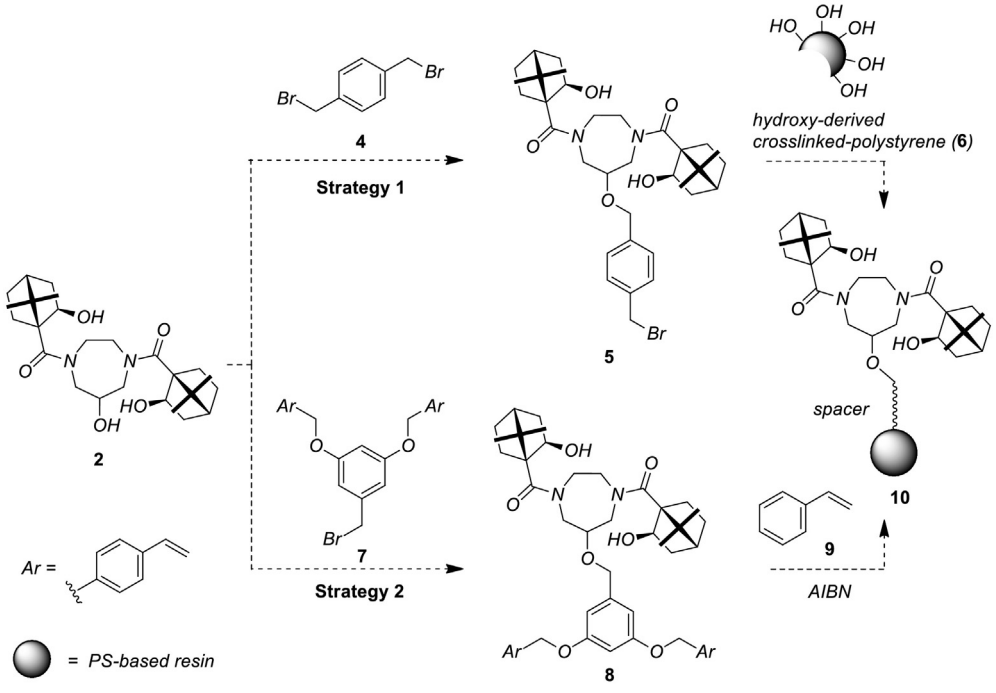
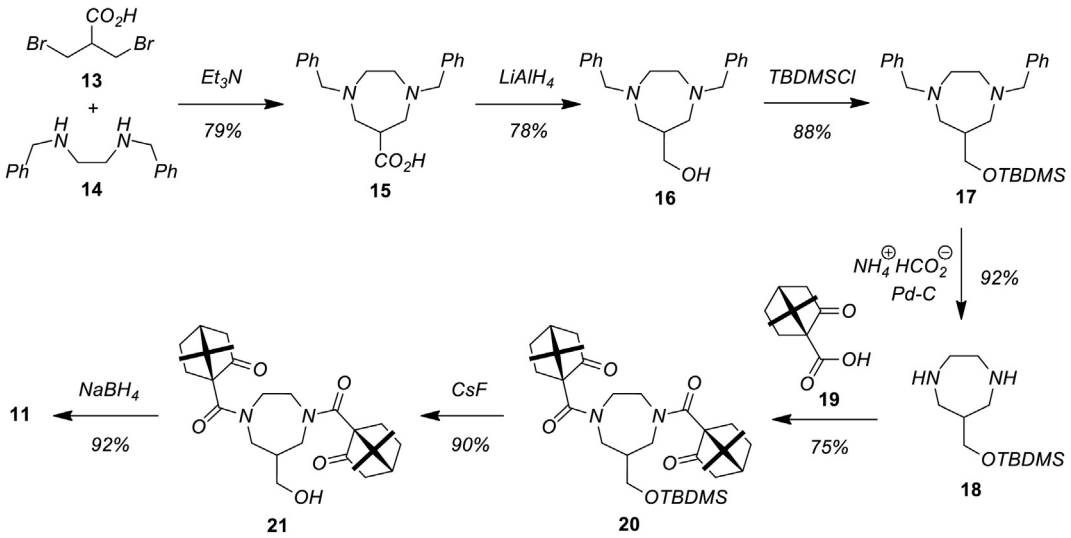


Fig. 3. Proposal of polystyrene-supported (PS-supported) hydroxyamides **12** based on **11**.



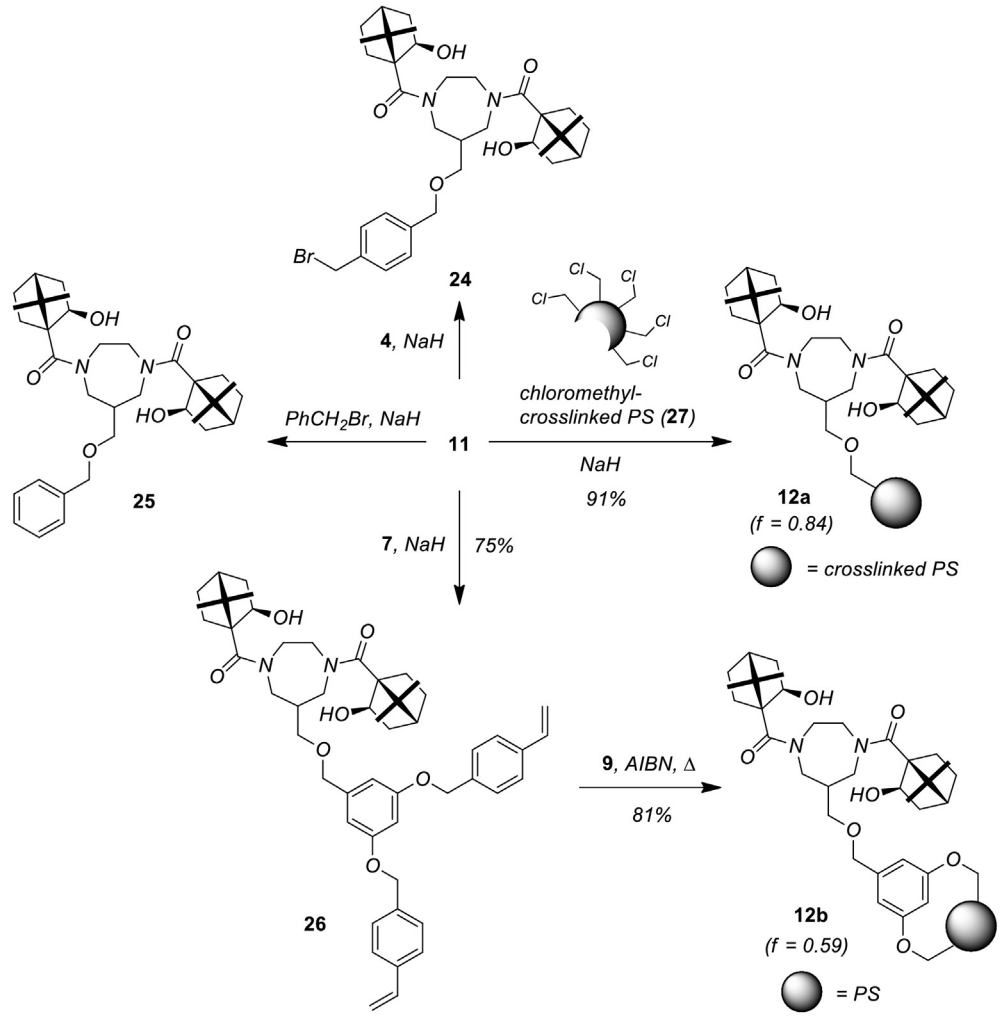
Scheme 1. Initial proposal for polystyrene-supported (PS-supported) chiral hydroxyamides **10**. Synthetic strategies.



Scheme 2. Synthetic route for the preparation of enantiopure **11**.

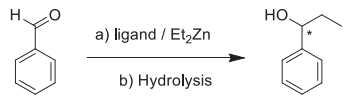
by the methylene-ether group introduced for anchoring the ligand onto the polymeric matrix.

Once we had demonstrated that the new bis(hydroxyamides) **11**, **25**, and **26** are highly efficient homogeneous ligands to promote the enantioselective addition of diethylzinc to benzaldehyde, we proceeded to heterogenize **11**. For this purpose, we followed strategy 2, initially proposed for **2** (see Scheme 1). Thus, the radical copolymerization of **9** and derivative **26**, initiated by the thermal decomposition of AIBN led



Scheme 3. Preparation of **24**, **25** and **26** and related polystyrene-supported (PS-supported) hydroxyamides **12a** and **12b**.

Table 1
Activity of homogeneous chiral hydroxyamides in the enantioselective ethylation of benzaldehyde.[a]

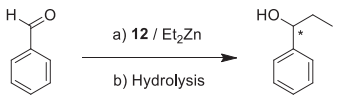


22 23

Ligand	Reaction time (h)	Yield (%)[b]	*ee* (%)[c]
1[d]	1	98	93 (*R*)
2	2	84	87 (*R*)
2	5	99	90 (*R*)
11	1	97	93 (*R*)
25	1	96	92 (*R*)
26	1	94	92 (*R*)

[a] Reaction conditions: **22** (1 mol equiv), ligand (2% mol equiv), Et_2Zn (1 M in hexanes, 1.1 mol equiv.), r.t.
[b] Determined by GC.
[c] Determined by chiral HPLC.
[d] Data from ref. [58].

Table 2
Activity of polystyrene-supported (PS-supported) hydroxyamides **12** in the enantioselective ethylation of benzaldehyde.[a]



22 23

Ligand	*f* (mmol·g^{-1})	Yield (%)[b]	*ee* (%)[c]
12a	0.84	95	93 (*R*)
12b	0.59	38	81 (*R*)
12c	0.25	25	34 (*R*)
12d	0.16	54	31 (*R*)

[a] Reaction conditions: **22** (1 mol equiv), ligand (4% mol equiv), Et_2Zn (1.5 M in toluene, 1.5 mol equiv.), r.t., 2 h.
[b] Determined by GC.
[c] Determined by chiral HPLC

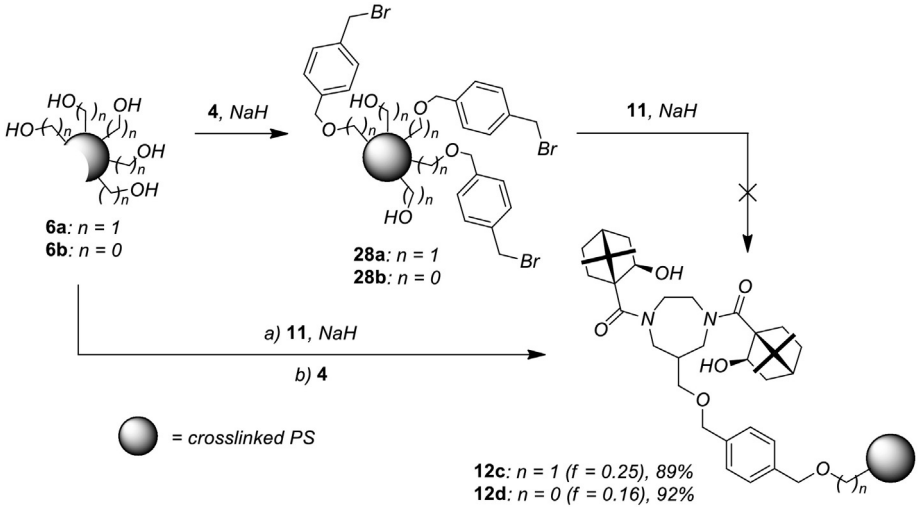
to functionalized polymer **12b** (81% yield, $f = 0.59$ mmol^{-1}·g^{-1}, Scheme 3). Additionally, because the additional methylene group in ligand **11** is a small spacer itself, we prepared heterogeneous **12a** by direct coupling of **11** with commercial Merrifield resin **27** (Scheme 3). Merrifield Stratospheres™ was used for this purpose. The conditions for the anchoring were the ones previously used for preparing heterogeneous **3** (see experimental part) [64], leading to **12a** with 91% yield (ligand loading, $f = 0.84$ mmol^{-1}·g^{-1}).

However, strategy 1 (see Scheme 1) required the functionalization of **11** with **4**, followed by the anchoring of the obtained bromobenzyl derivative onto a hydroxylated PS. However, because of the difficulties encountered for the purification of **24**, we decided to invert the steps in the proposed synthetic route: first, we functionalized commercial hydroxylated PS **6** with **4** and, second, we anchored ligand **11** onto the so-obtained functionalized resin (Scheme 4). As starting material for **6,** we used commercial PSs functionalized with benzyl alcohol (hydroxyl loading, $f = 1.2$ mmol·g^{-1}, **6a**) and commercial PS functionalized with phenol (hydroxyl loading, $f = 1.3$ mmol·g^{-1}, **6b**). Unfortunately, the etherification of **6a** or **6b** with **4** followed by functionalization with **11** did not lead to the anchoring of the ligand, as detected by EA. Next, we tried to carry out a one-pot procedure, mixing together PS **6a** or **6b** with **11** and **4**, without isolating the corresponding intermediate bromomethyl PSs **28** (Scheme 4). In this case, we did obtained PS **12c** and **12d**, with 89% and 92% yield, respectively, albeit with low *f* values (see Table 2).

3.2. Catalytic activity of the heterogenized ligands

Next, we measured the catalytic activity of functionalized PS **12** in the enantioselective ethylation of benzaldehyde. As a preliminary study, we chose a short reaction time, 2 h. The results (Table 2) reveal that PS **12b**, **12c** and **12d** provided low conversions of benzaldehyde in this short time, whereas PS **12a** showed an excellent behavior, both in terms of yield (95%) and *ee* (91%), comparable to that of the homogeneous ligand **11**. The low catalytic activity of **12b** (although with moderate enantioselectivity) can be explained by the methodology used for its preparation (mass copolymerization), thus resulting in a high number of non-accessible catalytic sites. In other words, the effective functionalization (peripheral) of **12b** would be lower than the one determined by EA. The use of higher amounts of the heterogeneous ligand (8% mol equiv.) did not lead to any better results, probably because of the diffusion problems originated from the double amount of polymeric matrix used. With regard to PS **12c** and **12d**, the presence of free hydroxyl groups originating from the starting PS (**6a** or **6b**) can account for the low *ee* obtained. (Note the low catalyst loading reached for **12c** and **12d**).

Next, we ran a kinetic study to evaluate the influence of the structures of the different functionalized polymers **12** on the diffusion phenomenon. Homogeneous **11** was introduced in the study to compare homogeneous and heterogeneous behavior (Fig. 4). PS **12b**, **12c** and **12d** showed slow reaction rates and low conversions in 2 h, as it could be anticipated from the results in Table 2. The reaction did not go to



Scheme 4. Preparation of polystyrene-supported (PS-supported) hydroxyamides **12c** and **12d**.

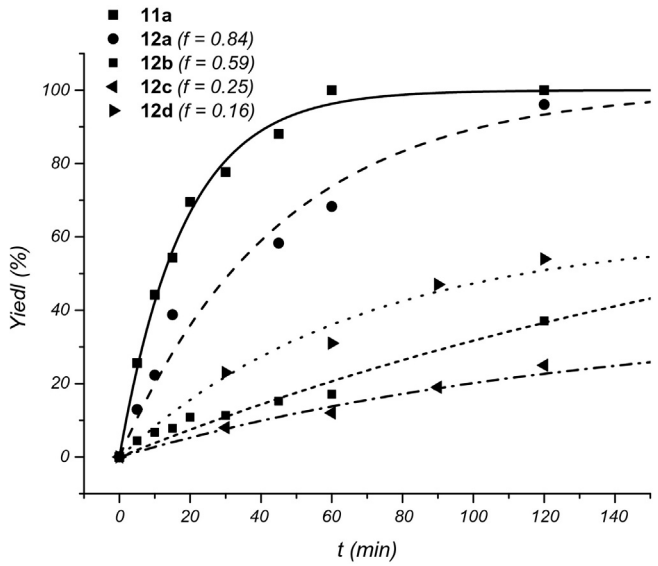


Fig. 4. Kinetic study on the activity of polystyrene-supported (PS-supported) hydroxyamides **12** in comparison with homogeneous **11** in the enantioselective ethylation of benzaldehyde (see Table 2 for reaction conditions).

completion even at long reaction times and the *ee* remained low (less than 40%). However, PS **12a** displayed an excellent behavior, providing almost the same yield and enantioselectivity for the reaction product than that by homogeneous **11** after 2 h. This result confirms the initial hypothesis of introducing a spacer between the polymer matrix and the chiral ligand to minimize the negative effects of diffusion.

Finally, the possibility of recovery and reuse of heterogenized **12a** was studied using the prototype of fluidized-bed reactor designed for reusing **3** [64]. The catalytic reaction was repeated eight times, recovering **12a** after each cycle and reusing it in the next one with no further purification, other than simple washing with some solvents (see Experimental section). As shown in Fig. 5, **12a** had a high stability, which made it to be easily and efficiently recovered, recycled and reused, with constant enantioselectivities (95–97%) and yields (94–97%) in a reaction time of just 2 h.

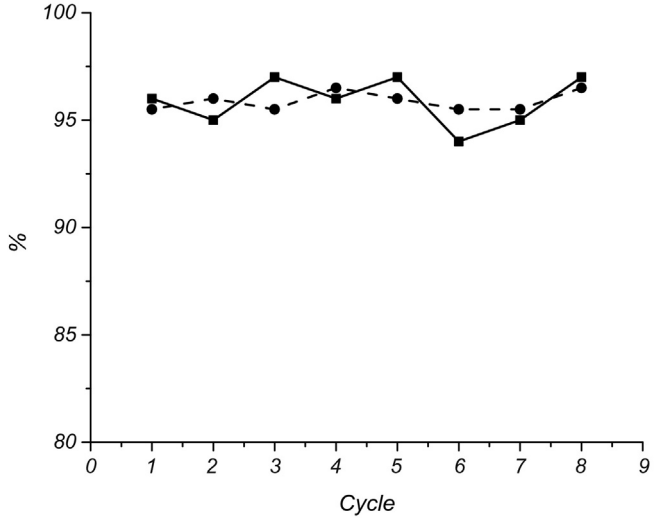


Fig. 5. Enantioselectivity (% *R*, dashed, estimated by chiral HPLC) and yield (bold, estimated by GC) for the formation of **23** catalyzed by **12a** in eight consecutive cycles. (see Table 2 for reaction conditions).

4. Conclusions

The results achieved with heterogenized ligand **12a** confirm the initial hypotheses. First, the stability of the functional group combination hydroxyamide (compared to the commonly used amino alcohol) makes possible the design of an efficient heterogeneous ligand, very stable and therefore highly reusable, which is based on the said functional group combination. Second, the introduction of a spacer between the catalytic site of the ligand and the polymer matrix results in a solution to the diffusion problem encountered by its analogous **3**, leading to a significant increase in the reaction rate (reaction completed in 2 h, instead of 20 h). These results support ligand **12a** as a perfect candidate for the implementation of the enantioselective addition of organozinc reagents to aldehydes in the industry by using catalytic fluidized-bed reactors, which are frequently used in industrial processes. Research on the behavior of this system with other organozinc reagents, different from diethylzinc is under progress. Moreover, this system can be a starting point for the development of other highly reusable systems to be applied in other asymmetric processes involving chiral organozinc catalysts.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.reactfunctpolym.2017.02.008.

References

[1] H.Y. Kim, A.E. Lurain, P. García-García, P.J. Carroll, P.J. Walsh, Highly enantio- and diastereoselective tandem generation of cyclopropyl alcohols with up to four contiguous stereocenters, J. Am. Chem. Soc. 127 (2005) 13138–13139.
[2] B.M. Trost, V.S. Chan, D. Yamamoto, Enantioselective ProPhenol-catalyzed addition of 1,3-diynes to aldehydes to generate synthetically versatile building blocks and diyne natural products, J. Am. Chem. Soc. 132 (2010) 5186–5192.
[3] A.T. Radosevich, V.S. Chan, H.-W. Shih, F.D. Toste, Synthesis of (−)-octalactin a by a strategic vanadium-catalyzed oxidative kinetic resolution, Angew. Chem. Int. Ed. 47 (2008) 3755–3758.
[4] J.D. Armstrong, J.C. McWilliams, Patent No. US 5977371, 1999.
[5] M. Zaidlewicz, M.M. Pakulski, in: J.G. De Vries, G.A. Molander, P.A. Evans (Eds.), Science of Synthesis, Stereoselective Synthesis, 2, Georg Thieme Verlag, Stuttgart, Germany 2011, pp. 59–131.
[6] B.T. Cho, Recent development and improvement for boron hydride-based catalytic asymmetric reduction of unsymmetrical ketones, Chem. Soc. Rev. 38 (2009) 443–452.
[7] H. Shimizu, I. Nagasaki, K. Matsumura, N. Sayo, T. Saito, Developments in asymmetric hydrogenation from an industrial perspective, Acc. Chem. Res. 40 (2007) 1385–1393.
[8] N.B. Johnson, I.C. Lennon, P.H. Moran, J.A. Ramsden, Industrial-scale synthesis and applications of asymmetric hydrogenation catalysts, Acc. Chem. Res. 40 (2007) 1291–1299.
[9] H.-U. Blaser, C. Malan, B. Pugin, F. Spindler, H. Steiner, M. Studer, Selective hydrogenation for fine chemicals: recent trends and new developments, Adv. Synth. Catal. 345 (2003) 103–151.
[10] W. Tang, X. Zhang, New chiral phosphorus ligands for enantioselective hydrogenation, Chem. Rev. 103 (2003) 3029–3070.
[11] S.M. Roberts, G. Poignant, Catalysts for fine chemical synthesis, in: G. Poignant, S.M. Roberts (Eds.), Hydrolysis, Oxidation, and Reduction, 1, John Wiley & Sons, Ltd., Chichester, U.K. 2002, pp. 115–136.
[12] G.-Q. Lin, Y.-M. Li, A.S.C. Chan, Principles and Applications of Asymmetric Synthesis, John Wiley & Sons, Inc., New York, 2002 331–396.
[13] R. Noyori, T. Okhuma, Asymmetric catalysis by architectural and functional molecular engineering: practical chemo- and stereoselective hydrogenation of ketones, Angew. Chem. Int. Ed. 40 (2001) 40–73.
[14] R. Noyori, M. Kitamura, Enantioselective addition of organometallic reagents to carbonyl compounds: chirality transfer, multiplication, and amplification, Angew. Chem. Int. Ed. Eng. 30 (1991) 49–69.
[15] K. Soai, S. Niwa, Enantioselective addition of organozinc reagents to aldehydes, Chem. Rev. 92 (1992) 833–856.
[16] L. Pu, H.-B. Yu, Catalytic asymmetric organozinc additions to carbonyl compounds, Chem. Rev. 102 (2001) 757–824.

[17] L. Pu, Asymmetric alkynylzinc additions to aldehydes and ketones, Tetrahedron 59 (2003) 9873–9886.
[18] B.M. Trost, A.H. Weiss, The enantioselective addition of alkyne nucleophiles to carbonyl groups, Adv. Synth. Catal. 351 (2009) 963–983.
[19] N. Kumagai, M. Shibasaki, in: M. Shibasaki, Y. Yamanoto (Eds.), Multimetallic Catalysis in Organic Chemistry, 2, Wiley-VCH, Weinheim 2004, pp. 43–76.
[20] R. Somanathan, L.Z. Flores-López, R. Montalbo-González, D. Chávez, M. Parra-Hake, G. Aguirre, Enantioselective addition of organozinc to aldehydes and ketones catalyzed by immobilized chiral ligands, Mini-Rev. Org. Chem. 7 (2010) 10–22.
[21] C.M. Binder, B. Singaram, Asymmetric addition of diorganozinc reagents to aldehydes and ketones, Org. Prep. Proced. Int. 43 (2011) 139–208.
[22] L. Pu, Asymmetric functional organozinc additions to aldehydes catalyzed by 1,1′-Bi-2-naphthols (BINOLs), Acc. Chem. Res. 47 (2014) 1523–1535.
[23] M. Funes-Maldonado, B. Sieng, M. Amedjkouh, Enabling asymmetric alkynylation of azaaryl aldehydes with soai autocatalyst, Eur. J. Org. Chem. (2015) 4081–4086.
[24] Z. Szakonyi, Á. Csőr, A. Csámpai, F. Fülöp, Stereoselective synthesis and modelling-driven optimisation of carane-based Aminodiols and 1,3-oxazines as catalysts for the enantioselective addition of diethylzinc to benzaldehyde, Chem. Eur. J. 22 (2016) 7163–7173.
[25] J.A. Gladysz (Ed.), Thematic issue: recoverable catalysts and reagents, Chem. Rev. 102 (2002) 3215–3892.
[26] K. Ding, Y. Uozumi (Eds.), Handbook of Asymmetric Heterogeneous Catalysis, Springer, Weinheim, 2008.
[27] A.F. Trindade, P.M.P. Gois, C.A.M. Afonso, Recyclable stereoselective catalysts, Chem. Rev. 109 (2009) 418–514.
[28] S. Degni, S. Strandman, P. Laari, M. Nuopponen, C.-E. Wilén, H. Tenhu, A. Rosling, New soluble TADDOL-bearing polymers. Preparation and their use as Ti-complex catalysts for enantioselective addition of diethylzinc to benzaldehyde, React. Funct. Polym. 62 (2005) 231–240.
[29] D. Kundu, A.K. Patra, J. Sakamoto, H. Uyama, A palladium-loaded mesoporous polymer monolith as reusable heterogeneous catalyst for cross-coupling reactions, React. Funct. Polym. 79 (2014) 8–13.
[30] T. Srisook, T. Vongsetskul, J. Sucharitakul, P. Chaiyen, P. Tangboriboonrat, Immobilization of 3-hydroxybenzoate 6-hydroxylase onto functionalized electrospun polycaprolactone ultrafine fibers: a novel heterogeneous catalyst, React. Funct. Polym. 82 (2014) 41–46.
[31] L.H. Hsiao, S.Y. Chen, S.J. Huang, S.B. Liu, P.H. Chen, J.C.C. Chan, S. Cheng, Enantioselective addition of diethylzinc to benzaldehyde over mesoporous SBA-15 functionalized with chiral proline derivatives, Appl. Catal. A Gen. 359 (2009) 96–107.
[32] J. Escorihuela, L. González, B. Altava, M.I. Burguete, S.V. Luis, Polymer-supported chiral α-amino amides for the asymmetric addition of diethylzinc to aldehydes: transforming an inactive homogeneous system into an efficient catalyst, Appl. Catal. A Gen. 462 (2013) 23–30.
[33] Y. Dong, Q. Wang, J. Wang, Y. Ma, D. Wang, Z. Wu, M. Abudkremb, M. Zhang, Temperature responsive copolymer as support for metal nanoparticle catalyst: a recyclable catalytic system, React. Funct. Polym. 112 (2017) 60–67.
[34] D.E. De Vos, I.E.J. Vankelecom, P.A. Jacobs (Eds.), Chiral Catalysts Immobilization and Recycling, Wiley-VCH, Weinheim, 2008.
[35] M. Benaglia (Ed.), Recoverable and Recyclable Catalysts, Wiley, Chichester, 2009.
[36] A. Patti, Green Approaches to Asymmetric Catalytic Synthesis (Springer Briefts in Green Chemistry for Sustainability), Springer, London, 2011 97–111.
[37] C. Wiles, P. Watts, Continuous flow reactors: a perspective, Green Chem. 14 (2012) 38–54.
[38] H.U. Blaser, E. Schmidt (Eds.), Asymmetric Catalysis on Industrial Scale, Challegnes, Approaches and Solutions, Wiley-VCH, Darmstadt, 2004.
[39] M. Yoon, R. Srirambalaji, K. Kim, Homochiral metal–organic frameworks for asymmetric heterogeneous catalysis, Chem. Rev. 112 (2012) 1196–1231.
[40] M. Benaglia, A. Puglisi, F. Cozzi, Polymer-supported organic catalysts, Chem. Rev. 103 (2003) 3401–3429.
[41] M.R. Buchmeiser (Ed.), Polymeric Materials in Organic Synthesis and Catalysis, Wiley-CVH, Weinheim, 2003.
[42] S. Bräse, F. Lauterwasser, R.E. Ziegert, Recent advances in asymmetric C-C and C-heteroatom bond forming reactions using polymer-bound catalysts, Adv. Synth. Catal. 345 (2003) 869–929.
[43] P. McHorn, G.H. Hutchings, Heterogeneous enantioselective catalysts: strategies for the immobilisation of homogeneous catalysts, Chem. Soc. Rev. 33 (2004) 108–122.
[44] J. Tulle-Puche, in: F. Albericio, J. Tulle-Puche, F. Albericio (Eds.), The Power of Functional Resins in Organic Chemistry, Wiley-VCH, Weinheim 2008, pp. 3–11.
[45] L. Chen, J. Tang, Q. Zhang, J. Wang, Linear amphiphilic TEMPO-grafted poly(ether sulfone) as polymeric interfacial catalyst: synthesis, self-assembly behavior, and application, React. Funct. Polym. 105 (2016) 134–139.
[46] S.E. Lyubimov, A.A. Vasil'ev, A.A. Korlyukov, M.M. Ilyin, S.A. Pisarev, V.V. Matveev, A.E. Chalykh, S.G. Zlotin, V.A. Davankov, Palladium-containing hypercrosslinked polystyrene as an easy to prepare catalyst for Suzuki reaction in water and organic solvents, React. Funct. Polym. 69 (2009) 755–758.
[47] B. Gao, Y. Li, N. Shi, Oxovanadium (IV) Schiff base complex immobilized on CPS microspheres as heterogeneous catalyst for aerobic selective oxidation of ethyl benzene to acetophenone, React. Funct. Polym. 73 (2013) 1573–1579.
[48] R.J. Kell, P. Hodge, M. Nisar, D. Watson, Towards more chemically robust polymer-supported chiral catalysts for the reactions of aldehydes with dialkylzincs, Bioorg. Med. Chem. Lett. 12 (2002) 1803–1807.
[49] L. Osorio-Planes, C. Rodríguez-Escrich, M.A. Pericàs, Polystyrene-supported (2S)-(−)-3-*exo*-Piperazinoisoborneol: an efficient catalyst for the batch and continuous flow production of enantiopure alcohols, Org. Lett. 14 (2012) 1816–1819.
[50] K.J. Barlow, V. Bernabeu, X. Hao, T.C. Hughes, O.E. Hutt, A. Polyzos, K.A. Turner, G. Moad, Triphenylphosphine-grafted, RAFT-synthesised, porous monoliths as catalysts for Michael addition in flow synthesis, React. Funct. Polym. 96 (2015) 89–96.
[51] C. Rodríguez-Escrich, M.A. Pericàs, Organocatalysis on tap: enantioselective continuous flow processes mediated by solid-supported chiral Organocatalysts, Eur. J. Org. Chem. (2015) 1173–1188.
[52] D. Zhao, K. Ding, Recent advances in asymmetric catalysis in flow, ACS Catal. 3 (2013) 928–944.
[53] S.V. Luis, E. García-Verdugo, S. Itsuno (Eds.), Polymeric Chiral Catalyst Design and Chiral Polymer Synthesis, John Wiley & Sons, Inc., Hoboken, NJ, USA 2011, pp. 125–156.
[54] A.A. Lapkin, in: P.K. Plucinski, S.V. Luis, E. García-Verdugo (Eds.), Chemical Reactions and Processes Under Flow Conditions, RSC Publishing, Cambridge 2009, pp. 1–43.
[55] J.R. Howard, Fluidized Bed Technology: Principles and Applications, Taylor & Francis, New York, 1989.
[56] P. Trambouze, J. Euzen, Chemical Reactors: From Design to Operation, Technip Ed, Paris, 2004.
[57] P. Geoghegan, P. O'Leary, Hydroxyamide-based ligands and their use in the asymmetric catalysis of key organic transformations, ACS Catal. 2 (2012) 573–591.
[58] E.M. Márquez Sánchez-Carnerero, T. de las Casas Engel, B. Lora Maroto, S. de la Moya Cerero, Unexpected efficiency of non-C2-symmetric bis(hydroxyamide)-based zinc-chelate catalysts, Chirality 23 (2011) 523–526.
[59] T. de las Casas Engel, B. Lora Maroto, A. García Martínez, S. de la Moya Cerero, Hydroxyamide-catalyzed enantioselective addition of diethylzinc to benzaldehyde in the absence of titanium, Tetrahedron Asymmetry 19 (2008) 646–650.
[60] T. de las Casas Engel, B. Lora Maroto, A. García Martínez, S. de la Moya Cerero, Hydroxyamides versus amino alcohols in the enantioselective addition of diethylzinc to benzaldehyde, Tetrahedron Asymmetry 19 (2008) 2003–2006.
[61] W. Oppolzer, R.N. Radinov, Enantioselective synthesis of sec-allylalcohols by catalytic asymmetric addition of divinylzinc to aldehydes, Tetrahedron Lett. 29 (1988) 5645–5648.
[62] T. de las Casas Engel, B. Lora Maroto, S. de la Moya Cerero, Ketopinic acid derived bis(hydroxy amides) as cheap, chiral ligands for the enantioselective ethylation of aromatic aldehydes, Eur. J. Org. Chem. (2010) 1717–1727.
[63] E.M. Márquez Sánchez-Carnerero, T. de las Casas Engel, B. Lora Maroto, S. de la Moya Cerero, Dual stereoselection in the addition of diethylzinc to benzaldehyde by using highly structurally close ligands, Chirality 24 (2012) 255–261.
[64] T. de las Casas Engel, E.M. Sánchez-Carnerero, E. Sokolovskaya, C.M. Gallardo-Araya, F. Moreno Jiménez, B. Lora Maroto, S. de la Moya Cerero, Cheap and long-life reusable polymer for asymmetric organozinc catalysis based on camphor-derived hydroxyamides, Chirality 24 (2012) 771–777.
[65] G.D. Cuny, L. Shao, J.R. Hauske, B.M. Aquila, X. Wu, F. Wang, T.D. Bannister, in Heterocyclic analgesic compounds and methods of use thereof, US patent: 6,645,980 B1, 2003.
[66] H. Sellener, C. Faber, P.N. Rheiner, D. Seebach, Immobilization of BINOL by cross-linking copolymerization of styryl derivatives with styrene, and applications in enantioselective Ti and Al Lewis acid mediated additions of Et_2Zn and Me_3SiCN to aldehydes and of diphenyl nitrone to enol ethers, Chem. Eur. J. 6 (2000) 3692–3705.