PAPER

Dual stereocontrolled alkylation of aldehydes with polystyrene-supported nickel complexes derived from α-amino amides†

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Nickel(II) complexes derived from α-amino amide ligands anchored to gel-type and monolithic polymers act as efficient catalysts for the enantioselective addition of dialkylzinc reagents to aldehydes. Similar to the analogous homogeneous systems, dual stereocontrol in addition products can be achieved by controlling the stoichiometry of the immobilized nickel complex. Aromatic and aliphatic aldehydes were alkylated in good yields with enantioselectivities comparable to those obtained with the homogeneous analogues. These polymer-supported catalysts offer significant advantages as no metal leaching is observed and they can be easily recovered from the reaction mixture by simple filtration and reused for subsequent experiments with consistent catalytic activity.

Introduction

Asymmetric catalysis constitutes one of the most important areas in organic chemistry and thousands of chiral ligands and their transition metal complexes have been reported in the past several decades for different enantioselective reactions.[1] However, only a few examples have evolved into industrial processes due to their high cost and the limitations related to the required work-up.[2] Additionally, sometimes the final product contains high levels of metal contamination derived from catalyst decomplexation or degradation during the workup, which can become a serious drawback if the metal is toxic, especially for application in pharmaceutical and food industries. Therefore, in order to facilitate the separation of the chiral catalysts from the reaction mixture, different methods for anchoring homogeneous catalysts onto solid supports have been developed in the last years.[3] This immobilization facilitates the separation of the catalyst from reagents and products, simplifies the recovery of the often expensive or toxic catalysts,[4] and its reuse, and potentially allows the adaptation of the immobilized catalysts to continuous flow type processes, making the catalytic processes industrially applicable.[5] Moreover, the reuse of the catalyst would reduce the amount of waste material generated and make the process more environmentally friendly, providing attractive their potential application in the chemical industry.[6] The immobilization of the chiral ligand onto an insoluble polymeric chain is still one of the best options. Polystyrene matrices are often selected, because of their well-known properties, their easy functionalization and their excellent mechanical and chemical stability.

Carbon–carbon bond formation is the essence of organic synthesis and provides the foundation for generating complex organic compounds from simple starting materials. In this regard, the enantioselective organozinc addition to aldehydes is of long standing research interest, as the resulting optically active *sec*-alcohols are important building blocks,[7] and has become a benchmark reaction in asymmetric catalysis.[8] Several examples of polymer-supported chiral catalysts that have been applied for the addition of dialkylzinc reagents to aldehydes can be found in the literature, in particular involving chiral amino alcohol structures as the ligand fragments (Fig. 1).[9]

From the different families of chiral ligands used in asymmetric catalysis, nitrogen-containing ligands have received
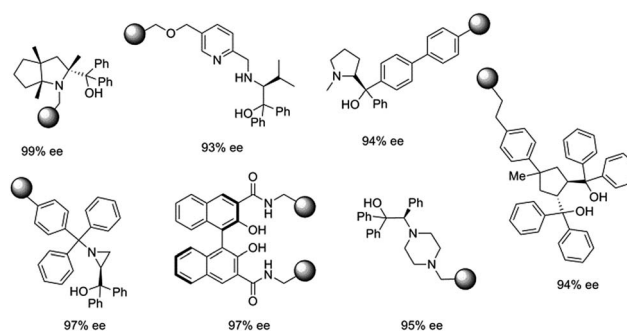
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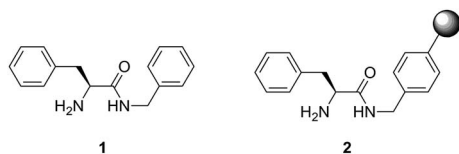
Fig. 1 Polystyrene-supported catalyst for the enantioselective addition of dialkylzinc reagents to aldehydes.

Fig. 2 Structures of α-amino amide **1** and polymer-supported α-amino amide ligand **2**.

important attention over the last years.[10] In this regard, simple α-amino amides **1**, having an amino group and an easily ionisable N–H amide subunit, can be compared to amino alcohols and structures of this class have been recently reported as good ligands for different transformations, such as the Ru(II)-catalyzed asymmetric transfer hydrogenation of acetophenone,[11] epoxidation of chromenes[12] and the conjugate addition of dialkylzinc to chalcones.[13] In previous contributions from our group, Ni(II) complexes of amino amides were shown to be able to efficiently catalyse the addition of dialkylzincs to aldehydes, achieving an excellent dual stereocontrol just by a proper adjustment of the stoichiometry of those Ni complexes.[14] In this regard, we showed that 1 : 1 Ni : ligand complexes provided the *S* enantiomer for the addition product (up to 97% ee) while the 1 : 2 Ni complexes afforded the *R* enantiomer (up to 95% ee). Both catalytic systems were demonstrated to be very active, the corresponding 1 : 1 complexes providing faster reactions than their related 1 : 2 complexes.

Recently, it has been shown that the Zn complexes of this kind of homogenous ligands (**1**), which are inactive for the considered reaction, can be transformed, upon immobilization of the ligand onto a polystyrene–divinylbenzene polymer (**2**), into an active, highly selective and enantioselective catalytic system (Fig. 2).[15]

In the past years, the possibility of obtaining both enantiomers using a single chiral source by changing the reaction conditions has received special attention.[16] This dual stereocontrol can be achieved in different ways, such as using different metals coordinated to the chiral ligand, by modification of the solvent system or by introducing structural features that modify the catalytic mechanism or the structure of the catalytic site. Although, most examples focus on homogeneous systems, a few examples have been reported using immobilized catalysts.[17]

Herein, as a continuation of our catalytic studies with polymer-supported α-amino amides, we report the preparation and study of novel heterogeneous chiral Ni(II) complexes derived from α-amino amides supported on Merrifield resins. Supported complexes with 1 : 1 and 1 : 2 stoichiometries have been prepared, and their application in the enantioselective addition of dialkylzinc reagents to aldehydes has allowed an efficient dual stereocontrol in the catalytic reactions. Besides, they provide additional features as green catalysts.

Experimental

Materials

All reagents were used as received, without any further purification. All samples were vacuum-dried at 60 °C for 24 h before

making any spectroscopic measurements to remove most of the adsorbed water. Raman spectra were acquired on a JASCO NRS-3100 dispersive spectrometer under the following conditions: 785 nm laser with a single monochromator, grating 600 lines per mm, slit 0.2 mm, resolution 12.75 cm^{-1}, with a center wavenumber of 1200 cm^{-1}, a laser power of 90.1 mW, and ten accumulations of 5 s each. FTIR spectra were recorded on a JASCO 4000 spectrometer equipped with a PIKE ATR MIRacle. Elemental analyses were performed on an Elemental Carlo Erba 1108 apparatus. DSC curves were obtained at 10 K min^{-1} under nitrogen atmosphere. Diffuse reflectance UV-Visible (DR UV-Vis) spectra were recorded on a Shimadzu UV-2450 spectrometer equipped with an integrating sphere unit (ISR-2200). Thermal analyses were carried out using a TG-STDA Mettler Toledo model TGA/SDTA851e/LF/1600 analyzer under a flow of N$_2$. The temperature range for TGA was 30–400 °C at 10 °C min^{-1}. TEM and XDS experiments were carried out with a JEOL 2100 instrument. Access to the above equipment was provided by the SCIC (Servei Central d'Instrumentació Científica) of the Universidad Jaume I.

Synthesis of resins 2

The general synthesis and characterization of α-amino amide functionalized resins **2** has been described elsewhere in our previous work.[15]

General procedure for the preparation of nickel complexes with 1 : 1 metal : ligand stoichiometry (3)

A solution of nickel(II) acetate (1 equiv.) in methanol was added to a suspension of **2** (1.2 equiv.) in methanol. After stirring the mixture for 20 min at room temperature, KOH (3 equiv.) in CH$_2$Cl$_2$: methanol (1 : 1) was added and the solution was refluxed overnight. The resulting resin was filtered and washed with diethylether (3 × 10 mL), methanol (3 × 10 mL), water (3 × 10 mL), a diluted KOH solution (3 × 10 mL), methanol (3 × 10 mL) and CH$_2$Cl$_2$ (3 × 10 mL) and vacuum dried at 50 °C overnight to give the polymer-supported nickel complex **3**. IR: ν_{max} = 3023, 2921, 2848, 1663, 1600, 1499, 1442, 752, 690 cm^{-1}; elemental analysis (N, theoretical values given in parentheses) for **3a**, 1.70% N (1.93% N); **3b**, 1.82% N (2.15% N); **3c**, 2.58% N (2.94% N); **3d**, 3.01% N (3.15% N); **3e**, 3.22% N (3.35% N); **3f**, 1.67% N (1.90% N); **3g**, 2.55% N (2.71% N); **3h**, 2.76% N (2.94% N); **3i**, 3.08% N (3.23% N).

General procedure for the preparation of nickel complexes with 1 : 2 metal : ligand stoichiometry (4)

A solution of α-amino amide **1** (1 equiv.) in methanol was added to a suspension of **3** (1 equiv.) in CH$_2$Cl$_2$: methanol (1 : 1). After stirring the mixture for 20 min at room temperature, KOH (3 equiv.) in CH$_2$Cl$_2$: methanol (1 : 1) was added and the solution was refluxed overnight. The resulting resin was filtered and washed with diethylether (3 × 10 mL), methanol (3 × 10 mL), water (3 × 10 mL), a diluted KOH solution (3 × 10 mL), methanol (3 × 10 mL) and CH$_2$Cl$_2$ (3 × 10 mL) and vacuum dried at 50 °C overnight to give the polymer-supported nickel complex **4**. IR: ν_{max} = 3028, 2921, 2845, 1668, 1601, 1500, 1444, 754,

692 cm^{-1}; elemental analysis (N, theoretical values given in parentheses) for **4a**, 3.12% N (3.31% N); **4b**, 3.61% N (3.83% N); **4c**, 4.88% N (5.04% N); **4d**, 5.19% N (5.33% N); **4e**, 4.79% N (5.02% N); **4f**, 3.18% N (3.43% N); **4g**, 4.34% N (4.70% N); **4h**, 4.68% N (5.02% N); **4i**, 5.12% N (5.44% N).

General procedure for the asymmetric addition of diethylzinc to aldehydes catalysed by Polystyrene-Supported (PS) catalysts

To a stirred suspension of the polymer-supported catalyst (10 mol%) in toluene (1 mL) was added a solution of diethylzinc (1.1 M in toluene) at 0 °C, and the stirring was continued at 0 °C for 10 min. Next, an aldehyde solution in toluene was slowly added under an argon atmosphere. After the addition was complete, the reaction mixture was stirred at 0 °C during 36 h, and was then quenched with 1 M HCl (4 mL). The resulting mixture was filtered and the filtrate was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic layers were dried with anhydrous MgSO$_4$ and concentrated under reduced pressure. Purification of the residue by flash chromatography (PE/AcOEt 15 : 1) afforded the desired alcohol. Conversions and selectivities were determined by ^{1}H NMR before column purification. The enantiomeric excess and the absolute configuration of the resulting alcohols were determined by HPLC and optical rotation. The catalyst was collected by filtration, washed with dry CH$_2$Cl$_2$, vacuum dried and used for a new run. For regeneration, the polymer was stirred with 1 M HCl–THF (1 : 2 mL) for 1 h, and then washed successively with CH$_2$Cl$_2$ (3 × 15 mL), THF (2 × 15 mL) and MeOH (2 × 15 mL). After vacuum dried at 50 °C for 5 h, the resin could be reused in the successive catalytic reactions. When performing the recycling studies, the catalyst was separated by filtration, under a N$_2$ atmosphere, before quenching and washed with CH$_2$Cl$_2$, being quantitatively reused as such for subsequent runs.

### Conditions for the analysis of chiral secondary alcohols

Chiral Capillary GC column VF-5 ms; 30 m × 0.25 mm, 0.25 μm. Carrier gas : H$_2$ (5 mL min^{-1}). Injector 230 °C, detector (FID) 300 °C, oven 60–130 °C, 10 °C min^{-1}. Chiral HPLC : Chiralcel OD columm; 254 nm UV detector. The racemic alcohols products were obtained by addition of Et$_2$Zn and Me$_2$Zn to aldehydes. The conditions of analysis and retention times of the *R* and *S* isomers are described in the ESI.†

Results and discussion

Catalyst preparation and characterization

Taking into consideration our previous results showing the excellent reactivity and enantioselectivity obtained in the addition of organozinc reagents to aldehydes displayed by polymer-supported chiral amino amides (**2**),[14] as well as the ability of the Ni(ii) complexes of homogeneous amides **1** to achieve a dual stereocontrol for this reaction through different metal : ligand stoichiometries,[15] we envisaged the potential of the related nickel complexes as green catalyst systems for the addition of organozinc reagents to aldehydes with efficient dual stereocontrol. In this regard, the approach shown in Scheme 1 was
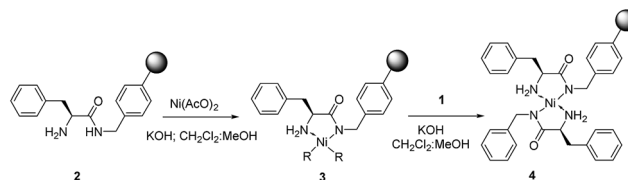
Scheme 1 Synthesis of polymer-supported Ni(ii) complexes with 1 : 1 and 1 : 2 metal : ligand stoichiometries.

considered for the preparation of the corresponding supported Ni(ii) complexes with 1 : 1 and 1 : 2 stoichiometries. The preparation of the 1 : 1 complex follows a strategy very similar to that used for the preparation of the catalytic zinc complexes, but involved the preparation and isolation of the metal complex prior to its application in the catalytic process. For the preparation of the 1 : 2 complex, however, a different approach was used involving the incorporation of a second non-supported ligand moiety to the preformed 1 : 1 supported complex.

According to previous studies in the field of polymer-supported catalysts, the morphology and loading of the polymeric support can have a significant influence on the nature of the complexes formed and on the final catalytic results. Thus, a detailed study of this aspect was required in this case for a proper understanding of the experimental results.[18] For this purpose, both, gel-type commercially available Merrifield resins (for the preparation of catalysts **3a–e** and **4a–e**) and monolithic macroporous resins (for the preparation of catalysts **3f–i** and **4f–i**) were used as the starting polymers. They provided polymer supported amino amides **2** with different loadings as shown in Table 2. Monolithic chloromethylated resins with appropriate properties, in particular regarding morphology and porosity, were previously prepared by polymerization of a mixture of styrene, divinylbenzene and chloromethylstyrene under radical conditions following reported procedures.[19] Under the studied conditions, polymerizations proceed, in general, in quantitative yields. The crosslinking degrees for the polymers used in this work were 1% for gel-type resins and 20% for the monoliths.

Treatment of these chloromethylated polymers with potassium phthalimide and subsequent reaction with hydrazine hydrate provided the corresponding aminomethyl polystyrene resins in high yields. The complete conversion of the chloromethyl groups into amine groups was assessed by means of FTIR, Raman spectroscopy, and the 4-(4-nitrobenzyl)pyridine (NBP) test.[20] The conversion of the aminomethyl resins into amino amide functionalized polymers was carried out by reaction with *N*-Cbz-(*S*)-phenylalanine succinimide ester and final deprotection of the amine groups with 33% HBr/HOAc treatment, following a similar protocol to that used for the preparation of related compounds in solution.[14,15,21] The final functionalized resins showed the complete absence of the Cbz band at 1716 cm^{-1} in their IR spectra.

Thus, by using this methodology, two different families of functionalized PS–DVB resins, with final loadings ranging from 0.8 to 2.0 mmol g^{-1}, according to their elemental analysis, were obtained. The first group (**2a–e**) were microporous resins (1% crosslinked, 0.8 to 2.0 mmol g^{-1}); whereas the second (**2f–i**)
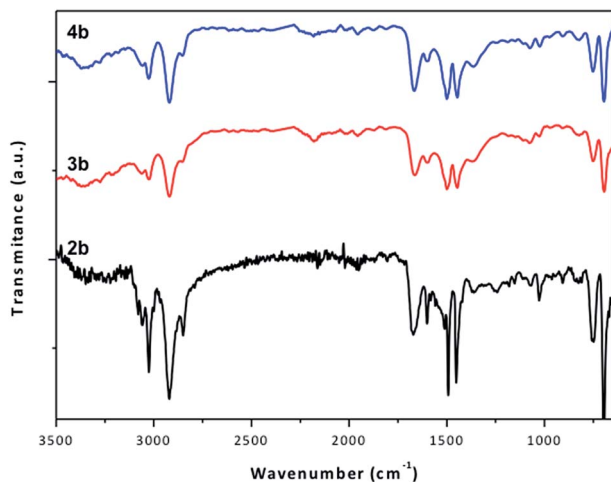
Fig. 3 FTIR spectra for polymers **2b**, **3b** and **4b**; **3b** and **4b** prepared from **2b** containing 1 mmol of α-amino amide per g of resin.

consisted of macroporous resins (20% crosslinked, 0.9 to 2.0 mmol g^{-1}). In general, for the synthesis of the different polymer-supported chiral α-amino amides, excellent yields could be achieved for all the considered transformations.

Next, polymer-supported nickel complexes with 1 : 1 and 1 : 2 metal : ligand stoichiometries, namely resins **3** and **4**, respectively were prepared (Scheme 1). The formation of the corresponding 1 : 1 active complexes (**3**) was carried out in methanol containing KOH and was accompanied by deprotonation of the amide (NH) group. In all cases, the vibrational band corresponding to the C=O stretching (Fig. 3), was shifted to lower wavenumbers (from 1670 to 1553 cm^{-1}) indicating the participation of the deprotonated amide group in the coordination to the nickel atom, as observed in related systems.[22] As nickel(II) acetate in basic methanol is used for the preparation of these complexes, the R groups in **3** can be either acetate or methoxy groups or solvent molecules. Addition of an additional equivalent of the homogeneous ligand **1** to the supported 1 : 1 complexes **3** afforded the corresponding heterogeneized 1 : 2 complexes **4**.

In addition, transmission electron microscopy (TEM) of these immobilized catalysts was carried out to characterize the catalytic complexes. As inferred from the TEM images (Fig. 4), PS–Ni catalysts (**3b** and **4b**) showed a uniform distribution of the metal species in the polymeric matrix. Energy-dispersive X-ray analyses (EDX analysis) of the metallic complexes **3b** and **4b** confirmed the presence of the metal complexes in the polymeric matrix as shown in Fig. S4 and S5 (ESI†).

The functionalized resins were also characterized by UV-Vis spectroscopy in the diffuse reflectance mode (DR UV-Vis) to elucidate the coordination environment of the metallic cation in the polymeric network. Some of the recorded spectra are displayed in Fig. 5. As it can be seen, the spectra showed the bands mainly associated with the d–d transitions of Ni^{2+} (d^8). In the case of the catalysts derived from **2b**, the UV-Vis spectrum for **3b** displayed two peaks at 390 nm and at 640 nm, which corresponds to Ni^{2+} in octahedral coordination and are
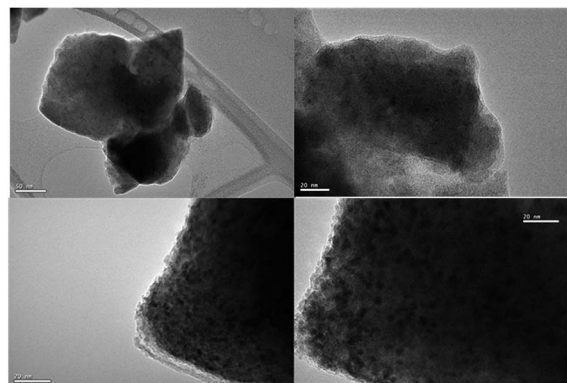

Fig. 4 TEM images of the PS–Ni catalyst **3b**.

assigned to two spin-allowed transitions $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ and $^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$.[23] According to this, additional solvent molecules must be coordinated to the metal center to provide this octahedral coordination sphere. For the 1 : 2 immobilized Ni(II) complex (**4b**), the UV-Vis spectra displayed a band at 440 nm, assigned to the LMCT transitions ($^1A_{1g} \rightarrow {}^3A_{2g}$), which clearly revealed the existence of a complex with square planar geometry.

Finally, the thermal stability of the complexes was investigated using TGA–DTA at a heating rate of 10 °C min^{-1} in air over a temperature range of 50–500 °C. The TGA curves for the polymer-supported ligand **2b** and the corresponding metal complexes **3b** and **4b** are shown in Fig. 6. It can be seen that the presence of the Ni(II) complexes is accompanied by a slight increase in the thermal stability of the polymers **3b** and **4b** as compared with **2b**. A similar effect is reflected in the DTA curves.

Catalysis with immobilized nickel complexes

The catalytic efficiency of the functionalized resins **3** and **4** was initially tested for the asymmetric addition of Et$_2$Zn to benzaldehyde (**5**) leading to the formation of 1-phenylpropanol (**6**), as the model reaction (Scheme 2) and the results were compared
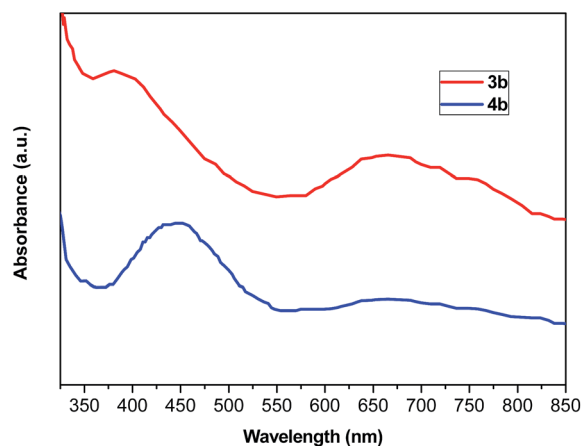

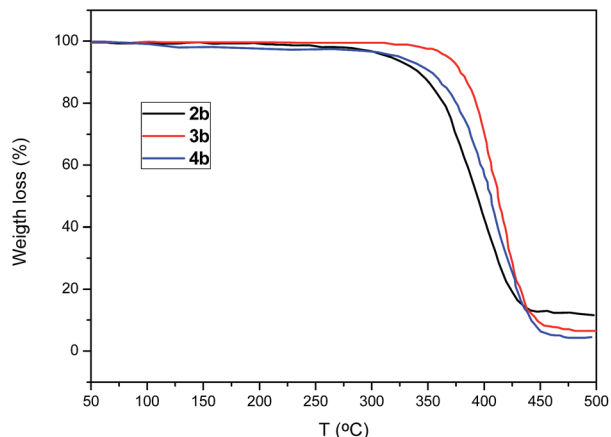Fig. 5 DR-UV-Vis spectra for PS–Ni catalysts **3b** and **4b**.

Fig. 6 Thermal analysis of the polymeric ligand **2b**, and the polymeric complexes **3b** and **4b**.

Scheme 2 Asymmetric addition of Et$_2$Zn to benzaldehyde.

with those previously obtained with the homogeneous systems.[14a,14b]

Catalysts **3b** and **4b** were used for the optimization studies. For the initial study, diethylzinc (1.2 equiv.) was added dropwise to a suspension of the polymeric catalyst (5 mol%) at 0 °C over *ca.* 10 min, and then a solution of benzaldehyde (1 equiv.) was slowly added. After stirring for 36 h at the same temperature, the liquid phase was separated from the polymer by simple filtration and the solution was quenched (1 M HCl), to afford, after the corresponding work-up, the expected chiral secondary alcohol.

The solvent is known to influence the activity and the enantioselectivity of a catalytic reaction.[24] Therefore, various solvents frequently used for this type of reaction were screened. The results, gathered in Table 1 for the supported catalysts **3b** and **4b**, showed a remarkable effect of the solvent on the enantioselectivity and the yield. Non-coordinating solvents such as hexane and toluene gave higher enantioselectivities than coordinating solvents such as THF (entries 1 and 2 *vs.* entry 4). Interestingly, when changing the solvent from hexane to toluene (entries 1 and 2), the enantioselectivity significantly increased from 44 to 64% for **3b** and the yield was almost quantitative. In the case of **4b** the change from hexane to toluene produced a clear improvement in the yield, but the enantioselectivity was less affected, as excellent enantioselectivities were observed in both cases (up to 91% for toluene). In the case of CH$_2$Cl$_2$ and CH$_3$CN (entries 3 and 5), yields were around 90% for **3b**, but significantly lower enantioselectivities were observed. Similar trends were observed for **4b**, although these solvent effects were less pronounced. Since toluene gave the best yield and enantioselectivity for both supported catalysts, this solvent was selected for the rest of the study.

As previously reported for the related homogeneous catalysts, the immobilized 1 : 1 complex afforded (*S*)-1-phenylpropanol as the major enantiomer whilst the complex prepared with a 1 : 2 metal : ligand ratio produced (*R*)-1-phenylpropanol as the predominant product. Thus, an effective chirality switching is achieved with this simple ligand just by adjusting
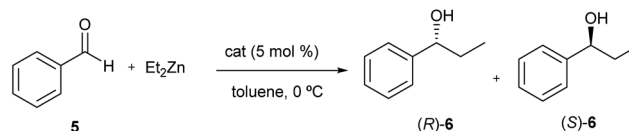
the stoichiometry of the corresponding Ni complexes (1 : 1 or 1 : 2 metal : ligand ratio).

The effect of the temperature on the reaction was then investigated. It must be noted that the addition of dialkylzinc to aldehydes usually reaches a maximum ee value at a certain temperature, which is called the isoinversion temperature.[25] As described above, initial experiments were carried out at 0 °C. A further decrease in the reaction temperature to −25 °C did not provide a significant variation of the enantioselectivity, but, on the contrary much lower reaction rates were observed (entry 6, Table 1). On the other hand, when the reaction was carried out at room temperature, the enantioselectivity decreased to 59% in the case of **3b**. A similar trend was observed when performing the addition reaction in the presence of the PS-catalyst **4b**. According to the former results, all subsequent reactions were carried out in toluene at 0 °C.

In order to determine the optimal amount of the polymer-supported catalyst, experiments using variable quantities of resins **3b** and **4b** were also carried out. In these studies, the concentrations of benzaldehyde and diethylzinc were kept constant at 1.0 and 1.2 mM, respectively, and the reaction was conducted at 0 °C in toluene. When the reaction was carried out using a 1 mol% loading of catalyst **3b** lower yields (below 90%) and ee (below 50%) were observed (ESI†). When the loading of the catalyst was increased to 3 mol%, the yield and ee slightly increased. Optimum results, in terms of yield and enantioselectivity were achieved when 5 mol% of **3b** were used. A further increase of the catalyst to 10 mol% did not significantly improve the results. Similar trends were observed when using resin **4b**. Thus, for all subsequent reactions, loadings of the functionalized resins were kept at 5 mol%. Most likely, this indicates that for low catalyst loadings, for which an important reduction in the rate of the catalysed reaction takes place, the non-catalysed addition starts to provide a relatively significant contribution to

Table 1 Solvent effects on the addition of Et$_2$Zn to benzaldehyde[a]

Entry	Solvent	Catalyst **3b**		Catalyst **4b**	
		Yield[b] (%)	ee[c] (%)	Yield[b] (%)	ee[c] (%)
1	Hexane	74	44 (*S*)	75	88 (*R*)
2	Toluene	91	64 (*S*)	98	91 (*R*)
3	CH$_2$Cl$_2$	87	57 (*S*)	71	83 (*R*)
4	THF	48	27 (*S*)	72	67 (*R*)
5	CH$_3$CN	89	52 (*S*)	87	72 (*R*)
6	Toluene[d]	69	65 (*S*)	70	92 (*R*)

[a] Performed at 0 °C using polymeric catalysts **3b** or **4b** (5 mol%). [b] Isolated yield after column chromatography. [c] Determined by HPLC (Chiralcel OD). [d] Performed at −25 °C.
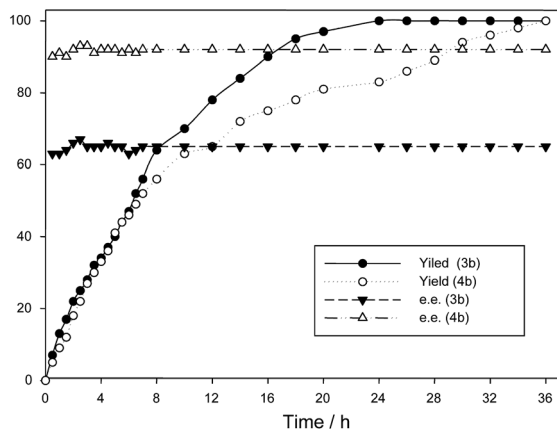
Fig. 7 Kinetic analysis of the reaction of benzaldehyde with Et$_2$Zn using catalysts **3b** and **4b** at 0 °C in toluene. Selectivity > 99%.

the process. In the same way, the selectivity also decreases for low catalyst loadings, as the non-catalysed side reaction leading to the formation of benzyl alcohol also increases.

Finally, a kinetic study was performed under the optimized conditions (5 mol% catalyst, toluene, 0 °C) and the yield, conversion and selectivity (>99%) of the formed product was determined by performing ^{1}H NMR spectroscopy on periodically collected samples (ESI†). The corresponding ee values were determined by chiral HPLC. As shown in Fig. 7, the formation of 1-phenylpropanol increased almost linearly during the first reaction period of 8 h. Then, the conversion slowed down and the product yield reached a plateau at a period of 24 and 34 h, for the 1 : 1 and the 1 : 2 polymer-supported nickel complexes, respectively. In comparison with the homogeneous systems, longer reaction times were required to complete the studied reaction, being the catalyst **3b** slightly more active than **4b**.

From results shown in Table 1 and Fig. 7, it is clear that enantioselectivities obtained from catalyst **4b** are always significantly higher than those observed with catalyst **3b**, which represents a remarkable deviation from the behaviour observed with the related homogeneous catalysts. In the latter case, when comparing to the homogeneous system, a 33% decrease in

enanatioselectivity was observed for the 1 : 1 supported catalyst. However, for 1 : 2 complexes, enantioselectivities were similar to those obtained with the homogeneous analogue. This suggests that the uniform formation of 1 : 2 complexes is easily achieved in the heterogeneous catalyst **4b**, while the formation of these 1 : 2 complexes cannot be completely avoided when the preparation of the corresponding polymer-supported 1 : 1 Ni complexes is attempted.

Taking this into consideration, the morphology and loading of the polymers could have a key influence on the catalytic properties of the resulting supported Ni complexes, in particular in the case of catalysts **3**. Accordingly, after achieving optimum reaction parameters, the effect of the resin morphology and loading was studied. For this, the asymmetric addition of diethylzinc to benzaldehyde was assayed using several gel-type and monolithic polymer-supported catalysts with different crosslinking degrees and loadings. The results obtained are presented in Table 2. As can be seen in this table, catalysts **3a–e** derived from gel-type resins with low crosslinking degrees gave better results in terms of enantioselectivity than the monolithic analogues **3f–i**. However, yields were not significantly affected in most cases. This seems surprising as gel-type resins with low crosslinking degrees provide a higher degree of flexibility to the polymeric chains, and accordingly to the functional sites, which could favor the formation of the more stable 1 : 2 complexes. Thus, the observed results suggest that, in the case of the monoliths, the polymerization of the monomeric mixture, under the described conditions, does not provide a uniform distribution of the functional groups through the polymer, thus the catalytic sites are not concentrated on the accessible surfaces. On the other hand, no significant differences were observed for PS-catalysts **4a–i**, which suggests that formation of 1 : 2 complexes involves one covalently polymer-linked ligand unit and a second non-polymeric ligand fragment, as depicted in Scheme 1. This is more favourable than formation of 1 : 2 intrapolymeric complexes involving two covalently supported ligand moieties.

To further investigate the scope of the catalytic systems, the addition of diethylzinc to a wide variety of aldehydes was

Table 2 Effect of resin morphology on the addition of Et$_2$Zn to benzaldehyde^a

Entry	Resin	Crosslinking degree (%)	Loading found^b	Catalyst **3b**		Catalyst **4b**	
				Yield^c (%)	ee^d (%)	Yield^c (%)	ee^d (%)
1	a^e	1	0.8	95	61 (S)	94	90 (R)
2	b^e	1	1.0	91	64 (S)	98	91 (R)
3	c^e	1	1.6	94	62 (S)	98	89 (R)
4	d^e	1	1.8	92	58 (S)	98	88 (R)
5	e^e	1	2.0	94	60 (S)	98	90 (R)
6	f^f	20	0.9	95	55 (S)	98	90 (R)
7	g^f	20	1.5	87	40 (S)	98	89 (R)
8	h^f	20	1.7	85	35 (S)	98	90 (R)
9	i^f	20	2.0	90	32 (S)	98	89 (R)

^{a} Performed at 0 °C using polymeric catalysts **3b** or **4b** (5 mol%). ^{b} Loading of α-amino amide groups in resins **2** calculated by N elemental analysis (mmol functional group per g resin). ^{c} Isolated yield after column chromatography. ^{d} Gel type. ^{e} Determined by by HPLC (Chiralcel OD). ^{f} Monolith.

Table 3 Enantioselective addition of diethylzinc to aldehydes in the presence of polymer-supported Ni(II) complexes[a]

Entry	RCHO (R)	Catalyst 3b		Catalyst 4b	
		Yield[b] (%)	ee[c] (%)	Yield[b] (%)	ee[c] (%)
1	C_6H_5	91	64 (S)	98	91 (R)
2	p-$CH_3OC_6H_4$	95	69 (S)	98	94 (R)
3	p-$CH_3C_6H_4$	90	59 (S)	89	88 (R)
4	p-ClC_6H_4	91	56 (S)	86	82 (R)
5	o-$CH_3OC_6H_4$	76	51 (S)	82	86 (R)
6	m-$CH_3OC_6H_4$	94	52 (S)	98	94 (R)
7	2-Naphtyl	88	53 (S)	89	84 (R)
8	Cyclohexyl	84	52 (S)	89	77 (R)
9	n-C_5H_{11}	59	44 (S)	87	76 (R)

[a] All reactions were performed using polymeric catalysts 3b or 4b (5 mol%) at 0 °C. [b] Isolated yield after column chromatography. [c] Determined by HPLC (Chiralcel OD).

examined and several trends emerged from these experiments (Table 3). In general, using both catalysts 3b and 4b good yields were obtained (>75%), although in all cases better enantioselectivities were obtained when catalyst 4b was used. The presence of electron-donating or electron-withdrawing substituents on the aromatic ring is also compatible with these reaction conditions, although, in general, aromatic aldehydes with electron-donating groups were ethylated with higher enantioselectivities. When catalyst 4b was used, aromatic substrates including 2-naphthaldehyde, benzaldehyde, 4-methoxybenzaldehyde and 4-chlorobenzaldehyde reacted with diethylzinc to afford the corresponding (R)-alcohol in 82–94% ee. The observed substituent effect was most pronounced at the *ortho* position, most likely due to the increased steric effects that these groups exert in this position. Interestingly, aliphatic aldehydes were also ethylated, although the enantioselectivity, and in some cases the yields were reduced in comparison with aromatic aldehydes (entries 8 and 9).

Enantioselective addition of dimethylzinc to aldehydes has attracted much less attention than diethylzinc additions because of its lower reactivity.[26] However, the development of an efficient method for the asymmetric addition of dimethylzinc is still a highly desirable goal in asymmetric catalysis. The related process for the addition of dimethylzinc to aldehydes was then evaluated with the same supported catalysts. Thus, in the presence of 5 mol% of the Ni(II) catalyst 4b, the reaction with benzaldehyde was complete after 24 h at 0 °C with a 91% ee. At 25 °C the reaction afforded the desired product in 83% yield with 81% ee. At room temperature, a further increase in the catalyst loading to 10 mol% did not benefit the enantioselectivity and the yield of the product was maintained. Thus, 5 mol% of catalyst loading and 0 °C was selected as the best reaction conditions in toluene.

In the asymmetric addition of dimethylzinc to aldehydes the supported catalysts 3b and 4b gave moderate to excellent yields (Table 4). The enantioselectivities were moderate when catalyst 3b was used, affording the major (S) enantiomer. While much higher ee values were obtained when the catalyst 4b was used to

give the major (R) enantiomer. Thus, with 4b, aromatic aldehydes gave excellent yields and ee values, especially for aldehydes with strong electron-donating groups, with enantioselectivities reaching up to 92% (entry 2). On the contrary, the presence of an electron-withdrawing group seems to produce a decrease in the ee value (78% for Cl, entry 4). Even bulky aromatic aldehydes, such as 2-naphthaldehyde, afforded good enantioselectivies (82%, entry 5). Also, aliphatic aldehydes (entries 6 and 7) provided good results when catalyst 4b was used, although the corresponding enantiomeric excesses were somewhat lower than those for aromatic aldehydes. As previously reported by different authors, the steric bulk around the chiral carbon atom or the nitrogen atom in chiral β-amino alcohol ligands generally enhances the enantioselectivity of the Et_2Zn addition to benzaldehyde.[27] Accordingly, the polymer-supported 1 : 1 and 1 : 2 nickel complexes prepared from α-amino amides derived from different amino acids were assayed as catalysts in the asymmetric addition of diethylzinc to benzaldehyde under the optimized reaction conditions (5 mol% catalyst, 0 °C, toluene, 36 h). According to the above considered results, the polymeric support used in this case was identical to the one employed in the case of the catalysts 3b and 4b. The main results obtained are gathered in Table 5 and confirms the expected trends. All polymer-supported catalysts provided the chiral alcohol with yields higher than 90%. Again, better ee

Table 4 Enantioselective addition of dimethylzinc to aldehydes in the presence of polymer-supported Ni(II) complexes[a]

Entry	RCHO (R)	Catalyst 3b		Catalyst 4b	
		Yield[b] (%)	ee[c] (%)	Yield[b] (%)	ee[c] (%)
1	C_6H_5	86	62 (S)	85	91 (R)
2	p-$CH_3OC_6H_4$	84	58 (S)	97	92 (R)
3	p-$CH_3C_6H_4$	87	60 (S)	84	83 (R)
4	p-ClC_6H_4	92	67 (S)	85	78 (R)
5	2-Naphtyl	86	51 (S)	88	82 (R)
6	n-C_5H_{11}	60	33 (S)	74	72 (R)
7	Cyclohexyl	63	32 (S)	71	67 (R)

[a] Performed at 0 °C using polymeric catalysts 3b or 4b (5 mol%). [b] Isolated yield after column chromatography. [c] Determined by GC.

Table 5 Effect of the amino acid side chain in the addition of diethylzinc to benzaldehyde[a]

Entry	Amino acid	1 : 1 Catalyst		1 : 2 Catalyst	
		Yield[b] (%)	ee[c] (%)	Yield[b] (%)	ee[c] (%)
1	Phe	95	65 (S)	96	91 (R)
2	Val	94	51 (S)	95	61 (R)
3	Leu	94	33 (S)	92	79 (R)
4	Ala	91	29 (S)	93	59 (R)
5	PhGly	90	68 (S)	91	92 (R)

[a] Performed at 0 °C using polymeric catalysts derived from different amino acids related to 3b or 4b (5 mol%). [b] Isolated yield after column chromatography. [c] Determined by HPLC (Chiralcel OD).
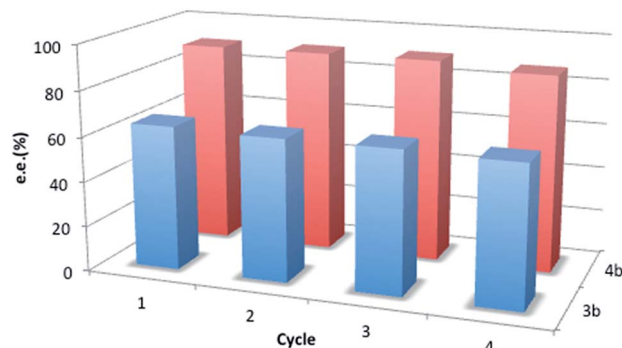
Fig. 8 Reuse of polymer supported catalysts **3b** and **4b**.

values were obtained when 1 : 2 metal : ligand catalysts were used to give the (*R*)-alcohol as the major enantiomer. Catalysts containing ligands derived from phenylalanine and phenylglycine provided the highest ee values for the ethylation of benzaldehyde (91–92% ee). The enantioselectivity observed for catalysts derived from ligands containing aliphatic side chains was significantly affected by the presence of α and β-branching. In this regard, the enantioselectivity was higher for the Val derivative than for the Leu derivative for the corresponding 1 : 1 complexes, while the reverse was observed for the 1 : 2 complexes. As expected, the Ala derivatives, having the less sterically demanding side chain gave lower enantioselectivities.

One of the purposes for designing heterogeneous catalysts is to reuse the catalyst in subsequent reactions. Thus, the potential reuse of the functionalized resins was examined for the enantioselective addition of Et$_2$Zn to benzaldehyde. After completion of the reaction as monitored by TLC analysis, the catalyst was separated by filtration under N$_2$ atmosphere and washed with dry CH$_2$Cl$_2$. Importantly, the presence of neither metal nor ligand was detected in the solution, indicating that no leaching had occurred. The results in Fig. 8 show that the polymer-supported catalysts **3b** and **4b** could be used for four consecutive runs to afford the corresponding chiral secondary alcohol in excellent yields (89–94%) and essentially maintaining the same enantioselectivity. It is important to note that although TON values for each batch reaction using polymer-supported nickel catalysts are clearly lower than those using the corresponding homogeneous Ni complexes, the easy reuse of the supported system was clearly demonstrated. The TON values attained after 4 reuses are comparable with those reported for the Ni complexes.

Conclusions

In summary, our present work shows that nickel(II) complexes derived from α-amino amide ligands anchored to polymeric supports act as efficient catalysts for the addition of dialkylzinc reagents to aldehydes. Both 1 : 1 and 1 : 2 metal : ligand supported complexes have been obtained and assayed. Thus, by the appropriate control of the Ni(II) complex stoichiometry, a dual stereocontrol can be achieved and good yields and moderate-high enantioselectivities can be obtained for the alkylation of

aromatic and aliphatic aldehydes. The preparation of 1 : 2 complexes, obtained by reaction of the supported 1 : 1 complexes with an additional equivalent of the homogeneous ligand, illustrates the potential of this novel approach, in which the metal is anchored first and then a chiral ligand is bound from the solution to metal. The results obtained clearly demonstrate the capacity of these heterogeneous catalysts for the production of both enantiomers, which may be produced by fully green catalytic processes. Although the enantiomeric excesses were slightly lower than those obtained with homogeneous catalysts in the case of 1 : 1 complexes, the enantioselectivity was identical in the case of 1 : 2 complexes, and both heterogeneous systems (1 : 1 and 1 : 2 metal : ligand complexes) had the advantage of their simple and efficient recyclability. Further investigation on the applications of these nickel complexes for other asymmetric reactions as well as the use in continuous flow systems is ongoing in our laboratory.

Acknowledgements

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