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Polymer-supported L-prolinol-based catalysts for the enantioselective addition of dialkylzinc reagents to *N*-(diphenylphosphinyl)imines

Raquel Almansa, Juan F. Collados, David Guijarro *, Miguel Yus *

Departamento de Química Orgánica, Facultad de Ciencias and Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain

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Dedicated to the memory of Professor Balbino Mancheño Magán

ABSTRACT

L-Prolinol-based ligands anchored to Merrifield or Wang-type resins have been shown to form efficient catalysts for the enantioselective addition of dialkylzinc reagents to *N*-(diphenylphosphinyl)imines. The enantioselectivity achieved with the polymeric catalyst (ee up to 88%) is slightly lower than the one obtained with the homogeneous ligand *N*-benzyl-L-prolinol, but the polymer-supported ligand presents the advantage of its recyclability: it can be recovered and used in up to six consecutive catalytic cycles with only a slight decrease in the enantiomeric excess. The phosphinamides obtained as addition products can be transformed into the corresponding enantiomerically enriched α-branched primary amines under mild acidic conditions.

1. Introduction

The enantioselective addition of dialkylzinc reagents to *N*-(diphenylphosphinyl)imines is one of the most reliable methods for the asymmetric synthesis of amines.[1,2] Chiral phosphinamides that are obtained as the addition products can be easily transformed into the corresponding primary amines by simple acidic treatment without any loss of enantiomeric purity.[3] Dialkylzinc reagents[4] are very interesting nucleophiles since they tolerate several functional groups,[5] allowing the preparation of polyfunctionalised organic compounds. However, the reaction of *N*-phosphinylimines with dialkylzincs is very slow and low yields of the addition products are obtained over long reaction times unless an additive is used to facilitate the reaction.[6–12] β-Aminoalcohols are among the most efficient promoters for these addition reactions. A variety of them have been shown to induce excellent enantioselectivities, but, in most cases, the use of a stoichiometric amount of the aminoalcohol ligand is necessary.[6] A few years ago, we found out that *N*-benzyl-L-prolinol was a very efficient ligand for the addition of dialkylzinc reagents to *N*-(diphenylphosphinyl)imines, obtaining ee's in up to 94% with 0.5 equiv of the aminoalcohol.[13] However, the amount of ligand used was still relatively high and we thought that the productivity of the catalyst could be increased if it could be easily recovered and reused several times. Moreover, reuse of the catalyst would reduce the amount of waste material and make the process more environmentally friendly, with potential applications in the chemical industry. One interesting way to achieve the recovery of the catalyst is the use of ligands immobilized on solid supports. There are several examples in the literature of addition reactions of dialkylzinc reagents to aldehydes[14] and imines[6b,15] promoted by supported aminoalcohols. The most popular supports that have been used are polymers,[14,15a,b,d] although other supports have proved to be efficient, such as dendrimers,[14c–e,15c,e–g] silica gel,[14c–e] molecular sieves[14c] and zirconium phosphates.[14d] The immobilization of the chiral ligand onto an insoluble polymeric chain, such as polystyrene, is still one of the best options, since it allows the recovery of the ligand by simple filtration. In a continuation of our studies on the addition of dialkylzinc reagents to *N*-(diphenylphosphinyl)imines, we have developed L-prolinol-based ligands anchored to Merrifield or Wang-type resins and herein we report the results of our research activities.

2. Results and discussion

Since *N*-benzyl-L-prolinol has been shown to efficiently catalyse the addition of dialkylzincs to *N*-(diphenylphosphinyl)imines,[13] we decided to prepare several polymers bearing the prolinol framework bonded to the polymeric chain through the benzylic substituent on the nitrogen atom. The supported aminoalcohols were synthesised from L-prolinol and commercially available Merrifield or Wang-type resins, both containing benzylic halide moieties that could be used as electrophiles to benzylate the nitrogen atom of L-prolinol. The commercial polymers and L-prolinol were stirred in DMF at room temperature for 90 h (Scheme 1). By using Merrifield resins with different chloride contents and changing the aminoalcohol load, polymers **1a–f** with different levels of prolinol incorporation were obtained (Table 1, entries 1–6). In order to study the effect on the enantioselectivity of the presence of a linker

* Corresponding authors. Fax: +34 965903549.
E-mail addresses: dguijarro@ua.es (D. Guijarro), yus@ua.es (M. Yus).

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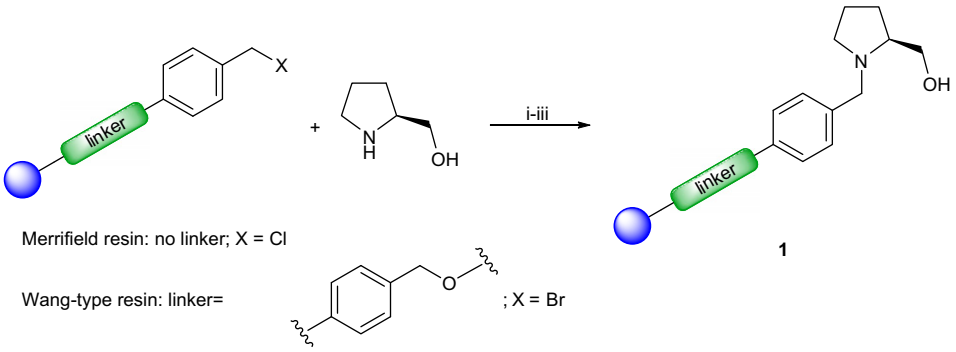
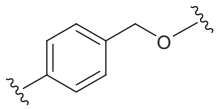


Scheme 1. Reagents and conditions: (i) DMF, 25 °C, 90 h; (ii) filtration; (iii) successive washing with DMF, EtOH, THF, THF/H_2O (1:1), MeOH, acetone and Et_2O.

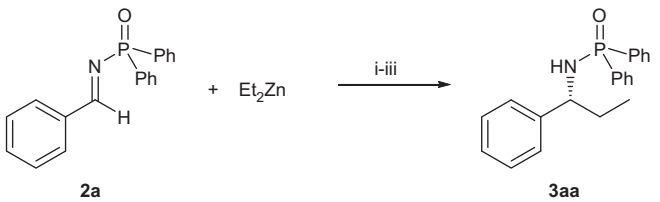
separating the polymeric chain from the prolinol moiety, Wang-type resin **1g** was also prepared (Table 1, entry 7). In all cases, the amount of aminoalcohol present in the polymeric ligands was calculated by determining the nitrogen content of the polymers by elemental analysis.

Table 1
Preparation of the polymer-supported prolinols

Entry	Commercial resin			Polymeric ligand	
	Linker	X	mmol X/g	No.	mmol Prolinol/g[a]
1	—	Cl	1.0	**1a**	0.61
2	—	Cl	4.3	**1b**	0.87
3	—	Cl	1.5	**1c**	0.93
4	—	Cl	1.5	**1d**	1.09
5	—	Cl	1.7	**1e**	1.48
6	—	Cl	4.3	**1f**	3.10
7		Br	0.5-1.5	**1g**	1.00

[a] Determined by elemental analysis of nitrogen.

Polymeric ligands **1** were evaluated as promoters of the addition of diethylzinc to *N*-(diphenylphosphinyl)benzaldimine **2a** as a model reaction (Scheme 2) and the results were compared with those previously obtained with *N*-benzyl-L-prolinol as a homogeneous ligand.[13] Diethylzinc (6 equiv) was added dropwise to a suspension of the polymeric ligand **1** (1 equiv) in a solution of imine **2a** in toluene at room temperature over ca. 10 min. After stirring for 2 days at the same temperature, the liquid phase was separated from the polymer by syringe and the solution was hydrolysed, to afford, after work-up, the expected phosphinamide **3aa** in the yields and ee's indicated in Table 2.



Scheme 2. Reagents and conditions: (i) polymeric ligand **1** (1 equiv), toluene, 25 °C, 2 days; (ii) separation; (iii) NH_4Cl (aq).

We found that polymeric ligands **1a** and **1b** gave slightly lower ee's than those obtained with the homogeneous ligand (compare entries 1–3 in Table 2). However, the enantioselectivity decreased with the other ligands derived from Merrifield resins, **1c–f** (Table 2, entries 4–7). According to these results, it seems that a low prolinol incorporation in the polymeric catalyst leads to higher enantioselectivities. Ligand **1g**, derived from a Wang-type resin, gave an ee of 70%, which was only slightly higher than the ee achieved with the Merrifield-type ligand **1d** with similar prolinol content (compare entries 5 and 8 in Table 2). Therefore, it seems that the possible beneficial effect of having a linker between the polymeric support and the prolinol moiety is not very pronounced in this case.

Table 2
Enantioselective addition of diethylzinc to imine **2a** in the presence of supported prolinols **1**[a]

Entry	Ligand	Product **3aa**	
		Yield[b] (%)	ee[c] (%)
1[d]	*N*-Benzyl-L-prolinol	79	92
2	**1a**	84	82
3	**1b**	71	84
4	**1c**	72	52
5	**1d**	84	62
6	**1e**	78	74
7	**1f**	62	50
8	**1g**	80	70

[a] All reactions were performed by the dropwise addition of diethylzinc (6 equiv) over ca. 10 min to a stirred suspension of the polymeric ligand **1** (1 equiv) in a solution of imine **2a** (0.25 mmol) in anhydrous toluene (3.5 mL) under argon at room temperature and stirring was continued for 2 days.
[b] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting imine **2a**. Isolated compound **3aa** was always ⩾95% pure (300 MHz ^1H NMR).
[c] Enantiomeric excess determined by HPLC using a ChiralCel OD-H column. The (*R*)-enantiomer was the major one in all cases.
[d] Results previously reported by us.[13b]

Next, we performed a recyclability study with the two ligands that gave the highest enantioselectivities, **1a** and **1b**. When the addition reaction of diethylzinc to imine **2a** was complete, stirring was stopped and the polymer was allowed to settle at the bottom of the flask, after which the liquid layer was separated with the aid of a syringe. The polymeric ligand was then washed three times with anhydrous toluene under argon and then used directly as a promoter of the next addition reaction. The results obtained with both ligands in the different cycles are collected in Table 3 and represented in Figure 1. In all the reactions, a small amount of by-product resulting from the reduction of imine **2a** was also observed; however, this could be separated from the desired addition product by column chromatography. We assume that the reduction process took place via a β-hydride transfer from diethylzinc to the imine carbon atom.

Both ligands gave yields in the range of 60–80% in all the cycles. However, ligand **1a** showed a much better recyclability than ligand **1b**. As can be seen in Fig. 1, the ee obtained with ligand **1b** decreased considerably in the third cycle, whereas in the reactions promoted by ligand **1a**, the ee value remained practically constant during the first five cycles, decreased slightly in the sixth cycle and

Table 3
Recyclability study performed with ligands **1a** and **1b**. Yields and ee's obtained for the addition of diethylzinc to imine **2a**[a].

Cycle	Ligand **1a**		Ligand **1b**	
	Yield[b] (%)	ee[c] (%)	Yield[b] (%)	ee[c] (%)
1	77	82	60	84
2	74	78	67	72
3	74	78	58	50
4	73	78	66	52
5	68	76	68	46
6	74	70	58	38
7	61	56	—	—
8	68	50	—	—
9	74	42	—	—

[a] All reactions were performed by the dropwise addition of diethylzinc (6 equiv) over ca. 10 min to a stirred suspension of polymeric ligand **1** (1 equiv) in a solution of imine **2a** (0.25 mmol) in anhydrous toluene (3.5 mL) under argon at room temperature and stirring was continued for 2 days. After completion of the reaction, the polymeric ligand was separated from the liquid layer, washed three times with anhydrous toluene and used directly in the next cycle.
[b] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting imine **2a**. Isolated compound **3aa** was always ⩾95% pure (300 MHz ^{1}H NMR).
[c] Enantiomeric excess determined by HPLC using a ChiralCel OD-H column. The (*R*)-enantiomer was the major one in all cases.

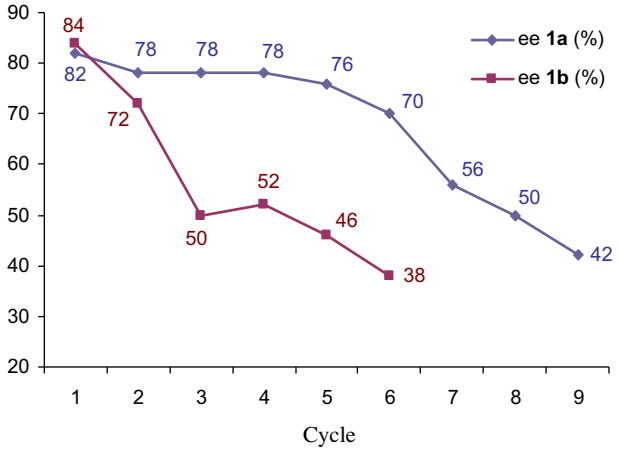


Figure 1. Enantiomeric excesses obtained in the addition of diethylzinc to imine **2a** promoted by recovered ligands **1a** and **1b**.

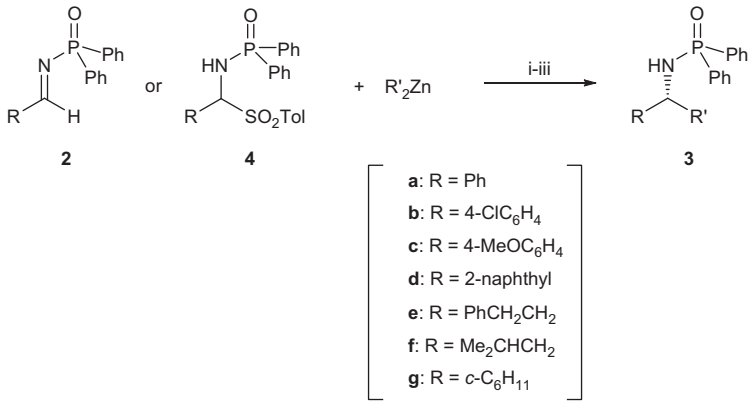
then started to greatly decrease from the seventh cycle. The decrease in catalytic activity of these ligands with the number of cycles could be due to the degradation of the polymeric chain after prolonged stirring.[14c] Although a stoichiometric amount of the polymeric ligand **1a** was used, the fact that it could be quantitatively recovered by a simple separation procedure and reused in five more cycles without a significant loss of chiral induction improves its catalytic efficiency.

Once we had established that **1a** was the ligand of choice, we decided to investigate the scope of this reaction by testing some other dialkylzinc reagents and imines (Scheme 3 and Table 4). As stated above, the addition of diethylzinc to imine **2a** gave product **3aa** in 84% yield and 80% ee (Table 4, entry 1). With the idea of reducing the reaction time and increasing the yield, this reaction was repeated with heating in a microwave reactor at 50°C (70 W, 0.8 bar) for 1 h,[16] which improved the yield to 95%, but caused the ee to decrease to 62% (Table 4, entry 2). As previously reported,[3,6c] dimethylzinc turned out to be much less reactive than diethylzinc and no addition product was formed after stirring the reaction for 2 days at room temperature. The addition of diisopropylzinc to imine **2a** gave product **3ab** in good yield and enantioselectivity (Table 4, entry 4). Dibutylzinc was as efficient as diethylzinc, and afforded the addition product **3ac** in 80% yield and 86% ee (Table 4, entry 6). We also tried to prepare compounds **3aa–ac** by the reaction of the corresponding dialkylzinc reagent

Table 4
Enantioselective addition of dialkylzinc reagents to in situ generated *N*-(diphenylphosphinyl)imines **2** in the presence of polymeric ligand **1a**[a]. Preparation of compounds **3**.

Entry	Substrate	R'_2Zn		Product		
		R′	Equiv	No.	Yield[b] (%)	ee[c] (%)
1	**2a**	Et	6	**3aa**	84	82
2[d]	**2a**	Et	6	**3aa**	95	62
3	**4a**	Et	6	**3aa**	86	84
4	**2a**	*i*-Pr	6	**3ab**	77	76
5	**4a**	*i*-Pr	6	**3ab**	88	64
6	**2a**	*n*-Bu	6	**3ac**	80	86
7	**4a**	*n*-Bu	6	**3ac**	82	64
8	**4b**	Et	6	**3b**	99	78
9	**4c**	Et	6	**3c**	61	88
10	**4d**	Et	6	**3d**	84	74
11	**4e**	Et	8	**3e**	82	30
12	**4f**	Et	6	**3f**	92	32
13	**4g**	Et	6	**3g**	80	56

[a] All reactions were performed by the dropwise addition of diethylzinc (6 equiv) over ca. 10 min to a stirred suspension of the polymeric ligand **1a** (1 equiv) and substrate **2** or **4** (0.25 mmol) in anhydrous toluene (3.5 mL) under argon at room temperature and stirring was continued for 2 days.
[b] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the substrate **2** or **4**. All isolated compounds **3** were ⩾95% pure (300 MHz ^{1}H NMR).
[c] Enantiomeric excess determined by HPLC using a ChiralCel OD-H column or a Chiralpak AD column. The (*R*)-enantiomer was the major one in all cases.
[d] Reaction performed under microwave irradiation at 50 °C (70 W, 0.8 bar) for 1 h.



Scheme 3. Reagents and conditions: (i) polymeric ligand **1a** (1 equiv), toluene, 25 °C, 2 days; (ii) separation; (iii) NH_4Cl (aq).

with the sulfinic acid adduct **4a** (Scheme 3). In these reactions, imine **2a** is generated in situ and then undergoes the addition of the dialkylzinc reagent.[17] This procedure gave slightly higher yields for all products **3aa**–**ac**. However, variable results were obtained with regard to the enantioselectivity: a small improvement was observed for the ethylation product **3aa**, whereas lower ee's were obtained for compounds **3ab**–**ac** (compare entry 1 with 3, entry 4 with 5 and entry 6 with 7 in Table 4).

Next, the addition of diethylzinc to several aromatic and aliphatic imines **2b**–**g** was attempted. However, when we tried to prepare these imines by literature procedures,[18] we obtained them in very small amounts and we could not purify them either by column chromatography on deactivated silica gel or by recrystallization. Fortunately, imines **2b–g** could be generated in situ from their corresponding sulfinic acid adducts **4b**–**g** (Scheme 3). All imines derived from aromatic aldehydes gave very good ee's, irrespective of the electronic nature of the substituents on the aromatic ring (Table 4, entries 8–10). It is worth noting that the addition of dibutylzinc to benzaldimine **2a** and the reaction of diethylzinc with adduct **4c**, with a methoxy group at the *para* position of the benzene ring, afforded products **3ac** (86% ee) and **3c** (88% ee), respectively, with ee values that were very similar to the ones obtained when *N*-benzyl-L-prolinol was used as a homogeneous ligand to catalyse the same reactions (90% and 92% ee, respectively).[13b] For the rest of the examples of aromatic imines (Table 4, entries 3, 4, 8 and 10), an average loss of ee of 13% was observed in comparison with the reactions catalysed by the homogeneous ligand. However, the polymeric ligand **1a** was less efficient in promoting the enantioselective addition of diethylzinc to the in situ generated aliphatic imines **2e**–**g**: although the isolated yields were very good in all cases, only moderate ee values were observed in the addition products **3e**–**g** (30-56%, Table 4, entries 11–13).

As described above, ligand **1a** is an efficient and recyclable catalyst for the addition of dialkylzinc reagents to *N*-(diphenylphosphinyl)aldimines. Since the phosphinyl group can be easily removed from the addition products under acidic conditions,[3] this methodology represents an interesting procedure for synthesizing α-branched primary amines with high enantiomeric purities. It is worth noting that D-prolinol is also commercially available and could be used to prepare other polymeric ligands with enantiomeric aminoalcohol moieties, which would provide the opportunity of preparing the enantiomers of the final amine products.

3. Conclusions

In conclusion, we have reported that *N*-benzyl-L-prolinol anchored to a polymeric support is an efficient promoter for the addition of dialkylzinc reagents to *N*-(diphenylphosphinyl)imines. By the appropriate choice of the prolinol content, a polymeric ligand was prepared that could be recovered and used in up to six consecutive cycles without a significant loss of enantioselectivity. The enantiomeric excesses achieved with the supported catalyst were slightly lower than those obtained with *N*-benzyl-L-prolinol as an homogeneous ligand, but the former has the advantage of its recyclability. This methodology is very useful for the preparation of enantiomerically enriched protected amines from aromatic *N*-(diphenylphosphinyl)imines, but is less effective when imines bearing aliphatic substituents are used as substrates.

4. Experimental

4.1. General

For general experimental information, see reference.[11] Imine **2a** was prepared according to a literature procedure.[9h,18] Adducts **4** were prepared by reaction of the corresponding aldehydes with *P*,*P*-diphenylphosphinic amide and *p*-toluenesulfinic acid following a literature procedure.[17] Commercially available L-prolinol (Aldrich, 97%), Merrifield resins (Aldrich, 1 mmol Cl/g; Aldrich, 1.5 mmol Cl/g; Fluka, 1.7 mmol Cl/g; Aldrich, 4.3 mmol Cl/g), Wang-type resin (Aldrich, 0.5–1.5 mmol Br/g), solutions of Et_2Zn (Aldrich, 1.1 M in hexanes), $(i\text{-Pr})_2Zn$ (Aldrich, 1.0 M in toluene) and $(n\text{-Bu})_2Zn$ (Acros, 1.0 M in heptane) were used as received. Anhydrous toluene (Scharlau, 99.9%, $H_2O \leqslant 0.017\%$) was used as a solvent in all of the addition reactions. HPLC analyses were performed at 25°C on a JASCO apparatus, equipped with a PU-2089 Plus pump, a MD-2010 Plus detector and an AS-2059 Plus automatic injector. Elemental analyses were performed by the Technical Services of the University of Alicante.

4.2. Preparation of the polymeric ligands 1. General procedure

L-Prolinol (1.0 mL, 10.5 mmol) was added to a suspension of the Merrifield or Wang-type resin (2.5 mmol of Cl) in DMF (25 mL) and the mixture was stirred for 90 h at room temperature. Next, the solid was filtered and washed successively with DMF, EtOH, THF, THF/H_2O (1:1), MeOH, acetone and Et_2O, then dried under vacuum for several hours until no loss of weight was observed. The number of millimoles of prolinol per gram of the polymeric ligand was calculated by determining the nitrogen content of the polymer by elemental analysis; the following results were obtained: **1a** (0.86% N, 0.61 mmol prolinol/g), **1b** (1.22% N, 0.87 mmol prolinol/g), **1c** (1.30% N, 0.93 mmol prolinol/g), **1d** (1.52% N, 1.09 mmol prolinol/g), **1e** (2.08% N, 1.48 mmol prolinol/g), **1f** (4.33% N, 3.10 mmol prolinol/g) and **1g** (1.42% N, 1.00 mmol prolinol/g).

4.3. Recyclability study performed with polymeric ligands 1a and 1b

A suspension of imine **2a** (0.25 mmol) and ligand **1a** or **1b** (0.25 mmol of N) in anhydrous toluene (3.5 mL) under argon was prepared in a centrifuge tube. Next, diethylzinc (1.5 mmol, 1.4 mL of a 1.0 M solution in toluene) was added dropwise over ca. 10 min to that stirred suspension at room temperature. After stirring for two days at the same temperature, the tube was centrifuged and the liquid layer was carefully extracted with a syringe trying to avoid the extraction of the solid particles. Anhydrous toluene (3.0 mL) was then added to the solid, after which the mixture was stirred for 5 min, the tube was again centrifuged and the liquid phase was extracted with a syringe. This washing process was performed three times. The combined organic layers were hydrolysed with an aqueous saturated solution of NH_4Cl (10 mL) and work-up was performed as described in Section 4.4.

Solid imine **2a** (0.25 mmol) was quickly added to the centrifuge tube containing the polymeric ligand **1a** or **1b** from the previous reaction and an inert atmosphere was created inside the tube by carrying out several vacuum-argon cycles. Anhydrous toluene (3.5 mL) was added to the solid mixture and then diethylzinc (1.5 mmol, 1.4 mL of a 1.0 M solution in toluene) was added dropwise over ca. 10 min to the stirred resulting suspension at room temperature and the reaction was stirred for two days at the same temperature. Following this procedure, ligands **1a** and **1b** were used in 9 and 6 consecutive reactions, respectively.

4.4. Addition of dialkylzinc reagents to imines 2 catalysed by ligand 1a. Preparation of compounds 3. General procedure

The dialkylzinc reagent (1.5 mmol) was added dropwise over ca. 10 min to a stirred suspension of imine **2a** or adduct **4** (0.25 mmol) and ligand **1a** (0.25 mmol of N) in anhydrous toluene (3.5 mL) un-

der argon at room temperature. After stirring for two days, the polymer was allowed to settle to the bottom of the flask and the liquid layer was carefully extracted with a syringe while trying to avoid extraction of the solid particles (if necessary, the mixture was centrifuged before removing the liquid phase). Next, anhydrous toluene (3.0 mL) was added to the solid, the mixture was stirred for 5 min, the polymer was again allowed to settle and the liquid phase was extracted with a syringe. This washing process was performed three times. The combined organic layers were hydrolysed with an aqueous saturated solution of NH_4Cl (10 mL). Water (5 mL) was then added and the mixture was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine (10 mL), and then dried ($MgSO_4$). After filtration and evaporation of the solvents, the crude residue was purified by column chromatography (silica gel, hexane/ethyl acetate), to give products **3** in the yields and enantiomeric excesses indicated in Table 4. Compounds **3aa**,[3] **3ab**,[13b] **3ac**,[11] **3b**,[3] **3c**,[6k] **3d**,[13b] **3e**,[17] **3f**[17] and **3g**[17] were characterised by comparison of their physical and spectroscopic data with the values reported in the literature. These products were analysed by HPLC on a ChiralCel OD-H column using a 254 nm UV detector, 10% *i*-PrOH in hexane as eluent and a flow rate of 1.0 mL/min or on a Chiralpak AD column using a 254 nm UV detector, 20% *i*-PrOH in hexane as eluent and a flow rate of 1.0 mL/min. The retention times were: 8.6 (*R*) and 12.3 (*S*) for **3aa** (OD-H column), 8.6 (*R*) and 10.3 (*S*) for **3ab** (OD-H column), 6.8 (*R*) and 12.8 (*S*) for **3ac** (OD-H column), 11.9 (*R*) and 14.1 (*S*) for **3b** (AD column), 12.9 (*R*) and 16.0 (*S*) for **3c** (AD column), 10.4 (*R*) and 14.7 (*S*) for **3d** (AD column), 22.0 (*R*) and 30.7 (*S*) for **3e** (AD column), 7.5 (*S*) and 10.7 (*R*) for **3f** (AD column), 7.1 (*S*) and 8.9 (*R*) for **3g** (AD column). The absolute configuration of the major enantiomer of **3aa** was determined by its hydrolysis[3] and comparison of the specific rotation of the free amine obtained with the reported data.[3] The absolute configuration of the major enantiomer of **3ab**–**ac** was tentatively assigned according to the order of elution of the two enantiomers in the HPLC analysis by analogy to the product **3aa**. For addition products **3b**–**d**, the absolute configuration of the major enantiomer was tentatively assigned according to the HPLC data described in the literature for similar compounds under the same conditions.[17] The retention times of the two enantiomers of compounds **3e**–**g** have already been described.[17]

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