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The synthesis of supported proline-derived ligands and their application in asymmetric diethylzinc addition to aldehydes

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Abstract

Attachment of the proline-derived ligand **5** to two types of polymers, i.e. aminomethylated polystyrene resin and respectively MeO-PEG, was achieved via a succinyl linkage from the 4-hydroxy group. Both of the supported ligands (**7** and **8**) were proved to be highly active with good enantioselectivity (up to 90% ee) for the catalyzed asymmetric diethylzinc addition to aldehydes. The insoluble polymer-supported catalyst could be easily recovered and was reusable for several consecutive catalytic runs without significant loss in enantioselectivity.

Keywords: Supported proline-derived ligand; Asymmetric diethylzinc addition; Aldehydes

1. Introduction

The enantioselective addition of dialkylzinc to aldehydes in the presence of a catalytic amount of a chiral β-aminoalcohol ligand was one of the most attractive chemical methods to obtain optically active secondary alcohols, which are useful building blocks for the construction of many optically and biologically active compounds [1–4]. However, in order for these reactions to be successfully exploited in large-scale applications, the chiral ligands have to be readily available or easily recycled. In recent years, researchers have focused on the immobilization of a chiral ligand by anchoring it onto a polymeric support [5–12]. Polymer-supported catalysts have inherent operational and economical advantages: facilitating the separation from reaction mixtures, the possibility of reutilizing the usually expensive catalyst for successive reactions and hence the development of environmentally safe processes for the production of fine chemicals.

Although the methodology of attaching a chiral ligand onto a polymer has been proved to be useful and practical, there are still some shortcomings such as lengthy synthetic route to the modified ligands and lower catalytic activity and enantioselectivity compared to those recorded for their paternal counterparts. Thus, continuous efforts in this area have been devoted in order to devise economic ways to obtain the supported catalysts and narrow the efficiency gap between the supported and paternal catalysis approaches.

Pyrrolidinylmethanol derivatives, which are readily attainable from proline [2,13], have been shown to be an effective chiral ligand for enantioselective addition of dialkylzinc to aldehydes. Considerable work has been done for the development of polymer-supported version of pyrrolidinylmethanol derivatives leading to different degree of success in terms of enantioselectivity and reusability for the enantioselective addition of diethylzinc to aldehydes [12,14–18]. Among these strategies, anchoring the ligand from the 4-position via an ether bond was considered to have high enantioselectivity due to the releasing of the restriction of the polymer matrix to the ligand [14,17]. However, the ethereal linkage was either constructed with difficultly or instable for tolerating the following acidic work-up procedure. For example, Ellman has first developed supported ligands of this class with tetrahydropyranyl as linker that provide high enantioselectivities (89% ee) for diethylzinc addition to benzaldehyde, but the reutilization of the catalyst was not documented [14].

In this paper, we wish to report the preparation of the proline-derived ligand **5** and attachment to two different kinds of polymers (insoluble aminomethylated polystyrene resin and soluble MeO-PEG) using succinyl as the linker. The catalytic activities of the supported ligands were investigated in the enantioselective addition of diethylzinc to aldehydes.

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2. Experimental

2.1. General experimental procedures

Melting points were determined with an Electrothermal-Engineering-LTD-9026 and are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were acquired on a JEOL 400 MHz spectrometer with TMS as internal standard. FT-IR spectra were performed on AVATAR360. Elemental analyses were performed on Perkin-Elmer 240-C. Optical rotation value was measured on a Perkin-Elmer 341MC polarimeter. Enantiomeric excesses were determined on chiral GC with a Supelco β-Dex 120 (60 m × 0.25 mm) column, or on chiral HPLC with a chiralcel OD-H column. The reactions were monitored by thin layer chromatography coated with silica gel.

All solvents were purified and dried by standard procedures and kept over a suitable drying agent prior to use. Diethylzinc (1 M solution in hexane) was purchased from Acros and used as received. The aldehydes were obtained from Acros or previously synthesized and purified by distillation or recrystallization prior to use. All catalytic asymmetric addition reactions were carried out under nitrogen atmosphere.

2.2. Synthesis of ligands

2.2.1. N-Ethyl carbamate-(4R)-(tetrahydro-2H-pyran-2-yloxy)-(S)-proline methyl ester (3)

The compound **2** (prepared from *trans*-4-hydroxy-L-proline (**1**) according to literature [19]) (6.5 g, 30 mmol), 3,4-dihydro-2*H*-pyran (3.0 g, 36 mmol) and catalytic amount of 4-methylbenzenesulfonic acid were dissolved in CH_2Cl_2 (60 mL) at room temperature. The resulting solution was stirred at room temperature for 2 h. Ether (50 mL) was added to the mixture after half of the solvent was removed by evaporation. The mixture was washed sequentially with aqueous solution of saturated aq. Na_2CO_3/brine/H_2O (2/2/3) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the oily product **3**, which was used directly for the next step without further purification. Yield: 8.8 g (98%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.64–4.63 (m, 1H), 4.44–4.41 (m, 2H), 4.16–4.13 (m, 2H), 3.85–3.71 (m, 5H), 3.62–3.53 (m, 2H), 2.42–2.31 (m, 1H), 2.07–2.05 (m, 1H), 1.80–1.78 (m, 1H), 1.70–1.69 (m, 1H), 1.59–1.53 (m, 4H), 1.27–1.20 (m, 3H).

2.2.2. (2S,4R)-N-(Ethyl carbamate)-2-(diphenylhydroxymethyl)-4-hydroxypyrrolidine (4)

The phenylmagnesium bromide Grignard reagent was prepared from 3.6 g of magnesium turnings and 22.0 g of bromobenzene in dry THF as usual. The compound **3** (8.4 g, 28 mmol) in 50 mL THF was added dropwise under nitrogen atmosphere at 0 °C. The reaction was further stirred for 4 h at 0 °C. The reaction was quenched with saturated ammonium chloride solution. The liquid was collected leaving behind a white precipitate which was extracted with ethyl acetate (3× 30 mL). Evaporation of the solvent of the combined organic extracts afforded yellow oils, which were dissolved in THF (20 mL). Acetic acid (40 mL) and H_2O (10 mL) were added to the mixture. The reaction mixture was stirred at 44 °C for 18 h. After removal of most of the solvent by evaporation, water was added to the mixture, and the aqueous phase was extracted with ethyl acetate (3× 80 mL). The organic extracts were combined and washed sequentially with 10% aq. $NaHCO_3$ and brine, and then dried over anhydrous $MgSO_4$. After filtration, the organic solvent was concentrated under vacuum to afford **4** as a yellow solid. The product was purified by recrystallization from hot ethyl acetate/petroleum ether. Yield: 8.1 g (85%).

mp: 169–170 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.37–7.30 (m, 10H), 5.11–5.08 (m, 1H), 4.08–3.90 (m, 3H), 3.56–3.53 (m, 1H), 3.00 (br, 1H), 2.18–2.05 (m, 2H), 1.76 (br, 1H), 1.17–1.15 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 157.71, 145.47, 143.29, 128.04, 127.76, 127.50, 81.58, 69.79, 64.47, 62.13, 56.17, 39.26, 14.58. IR (KBr): 3420, 2995, 2904, 1681, 1417, 1200, 1109, 703 cm^{-1}. Elemental Analysis Found: C, 70.08; H, 6.65; N, 4.12. Calad: C, 70.36; H, 6.79; N, 4.10.

2.2.3. (3R,5S)-5-(Hydroxydiphenylmethyl)-1-methylpyrrolidin-3-ol (5)

To a cooled (0 °C) suspension of $LiAlH_4$ (2.3 g, 60 mL) in freshly distilled THF (40 mL) was added dropwise a THF (10 mL) solution of compound **4** (6.8 g, 20 mmol). Upon completion of addition of **4**, the reaction mixture was gently warmed to reflux, and the suspension was stirred until the reaction was complete, as indicated by TLC (4 h). The reaction was quenched with 5N aqueous NaOH (10 mL), stirred for 5 min at room temperature. Neutral Al_2O_3 (16 g) was added to the mixture and stirred for another 5 min. The reaction mixture was filtered, and concentrated *in vacuo* to afford **5** as a white solid. Yield: 5.7 g (100%).

mp: 118–119 °C. $[\alpha]_D^{20}$ +1.03 (c 2, $CHCl_3$) (lit. [20] $[\alpha]_D^{20}$ 0.8 ± 0.3 (c 2, $CHCl_3$)). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.66–7.14 (m, 10H), 4.28–4.26 (m, 1H), 4.00 (t, J = 7.8 Hz, 1H), 3.38–3.35 (m, 1H), 2.52–2.51 (m, 1H), 1.92 (s, 3 H), 1.88–1.75 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 147.92, 146.18, 128.16, 126.38, 125.60, 125.38, 76.58, 71.16, 70.45, 65.99, 44.05, 39.24. IR (KBr): 3369, 2948, 2807, 1492, 1448, 1316, 1087, 1015, 760, 706 cm^{-1}. Elemental Analysis Found: C, 76.23; H, 7.54; N, 4.92. Calad: C, 76.29; H, 7.47; N, 4.94.

2.2.4. 4-((3R,5S)-5-(Hydroxydiphenylmethyl)-1-methylpyrrolidin-3-yloxy)-4-oxobutanoic acid (6)

A mixture of compound **5** (2.84 g, 10 mmol), succinic anhydride (1.00 g, 10 mmol) and DMAP (1.34 g, 11 mmol) in dry CH_2Cl_2 (60 mL) was stirred at 35 °C until the reaction was complete, as indicated by TLC (24 h). The reaction mixture was used directly for the next step of the immobilization on the polymer.

2.2.5. The aminomethylated polystyrene resin supported ligand 7

The mixture described in Section 2.2.4 was added to the suspension of aminomethylated polystyrene resin (1.07 mmol/g,

8.0 g, 8.56 mmol) in anhydrous DMF (30 mL) under nitrogen. 1-Hydroxybenzotriazole (2.31 g, 17.1 mmol), DIC (2.15 g, 17.1 mmol) and Pr^i_2NEt (1.12 g, 8.6 mmol) were added to the suspension. The resulting mixture was stirred at room temperature for 36 h under nitrogen. The polymer was filtered, rinsed sequentially with methanol, CH_2Cl_2 and acetone and dried at 50 °C *in vacuo* to yield the product as light yellow beads.

IR (KBr): 3410, 3024, 2920, 1736, 1676, 1492, 1450, 1156, 1024, 756, 697 cm^{-1}. Elemental Analysis Found: C, 83.76; H, 7.04; N, 2.20. Calad: N, 2.13.

Conversion: 100%. Loading: 0.76 mmol/g.

2.2.6. The MeO-PEG supported ligand **8**

The mixture described in Section 2.2.4 was added to the solution of MeO-PEG-OH ($M_w = 2000$) (19.6 g, 9.8 mmol, 0.98 equiv.) in anhydrous CH_2Cl_2 (50 mL) under nitrogen. DMAP (1.2 g, 10 mmol) and DCC (6.2 g, 30 mmol) were then added to the mixture. The resulting mixture was stirred at room temperature for 24 h under nitrogen. The mixture was filtered, and the filtrate was concentrated *in vacuo* to about 20 mL. Et_2O (1 L) was added into the solution and the mixture was stirred under 0 °C for 0.5 h. The resulting precipitate was filtered off and washed with cold *i*-PrOH (100 mL) and Et_2O (300 mL), to give 21.5 g of the supported ligand **8** as white solid (93% isolated yield).

^{1}H NMR (400 MHz, DMSO-d_6, δ): 7.69–7.26 (m, 10H), 5.05 (br, 1H), 4.68 (br, 1H), 4.25 (t, $J = 4.8$ Hz, 2H), 3.98 (t, $J = 7.8$ Hz, 1H), 3.69–3.55 (m, 179H), 3.38 (s, 3H), 2.65–2.61 (m, 4H), 2.05–1.94 (m, 5H). IR (KBr): 2886, 1736, 1467, 1360, 1343, 1280, 1109, 1061, 963, 843 cm^{-1}. Elemental Analysis Found: C, 56.10, H, 8.25, N, 0.60; Calad: N, 0.59. Conversion: 100%. Loading: 0.42 mmol/g.

2.3. General procedure for asymmetric addition of diethylzinc to aldehydes

2.3.1. Asymmetric addition of diethylzinc to aldehydes using aminomethylated polystyrene resin supported ligand **7**

To a suspension of the supported ligand **7** (required amount for 0.15 mmol methylated amino alcohol) in anhydrous toluene (5 mL) under nitrogen at 0 °C, diethylzinc (1.0 M solution in hexane, 1.4 mL) was added and stirred for 0.5 h. Aldehyde (1 mmol) was added and the mixture was stirred at room temperature for 12 h. The reaction mixture was quenched by 1 M HCl, diluted with ethyl acetate (20 mL) and filtered. The filtrate was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the crude product was passed through a short silica column to afford the *sec*-alcohol. The ee values were determined by chiral GC or chiral HPLC.

2.3.2. General procedure for the restoration of aminomethylated polystyrene resin supported ligand **7**

After one catalytic cycle, the aminomethylated polystyrene resin supported ligand was washed sequentially with 1 M HCl (30 mL), H_2O (15 mL), MeOH (15 mL), and CH_2Cl_2 (15 mL), and dried under vacuum at 50 °C for 6 h. The supported ligand could be employed for the next catalytic cycle.

2.3.3. Asymmetric addition of diethylzinc to aldehydes using MeO-PEG supported ligand **8**

To a solution of the supported ligand **8** (required amount for 0.15 mmol methylated amino alcohol) in anhydrous toluene (5 mL) under nitrogen at 0 °C, diethylzinc (1.0 M solution in hexane, 1.4 mL) was added and stirred for 0.5 h. Aldehyde (1 mmol) was added and the mixture was stirred at room temperature for 12 h. After removal of the most solvent under vacuum, the mixture was cooled to 0 °C and cold Et_2O (40 mL) was added. The precipitated polymeric catalyst was collected by filtration for re-use in the next run. The filtrate was washed with 1 M HCl (10 mL) and brine and dried over anhydrous Na_2SO_4. After removal of the solvent the crude product was passed through a short silica column to afford the *sec*-alcohol. The ee values were determined by chiral GC or chiral HPLC.

The absolute configuration of the product was determined by comparison of retention time with literature data [21,22]. For 1-(2,6-dichlorophenyl)propan-1-ol and 1-(2,3-dimethoxyphenyl)propan-1-ol, the absolute configuration was assumed to be *S*.

(*S*)-1-Phenylpropan-1-ol [21]: the ee was determined by chiral GC [Supelco β-Dex 120 (60 m × 0.25 mm) column; carrier gas: nitrogen, 3 atm; injection temperature: 220 °C; detection temperature: 250 °C]. Column temperature: 100–130 °C, 1 °C/min, hold for 30 min; retention times: 43.7 min (minor *R*-enantiomer), 44.6 min (major *S*-enantiomer). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.37–7.33 (m, 4H), 7.26 (t, $J = 6.8$ Hz, 1H), 4.58–4.55 (m, 1H), 1.90 (br, 1H), 1.79–1.71 (m, 2H), 0.90 (t, $J = 7.4$ Hz, 3H).

(*S*)-1-*p*-Tolylpropan-1-ol [21]: the ee was determined by chiral GC with a Supelco β-Dex 120 column; column temperature: 130–170 °C, 1 °C/min, hold for 30 min; retention times: 52.6 min (minor *R*-enantiomer), 53.4 min (major *S*-enantiomer). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.20–7.13 (m, 4H), 4.55–4.52 (m, 1H), 2.31 (s, 3H), 1.92 (br, 1H), 1.79–1.72 (m, 2H), 0.89 (t, $J = 7.4$ Hz, 3H).

(*S*)-1-(4-Methoxyphenyl)propan-1-ol [21]: the ee was determined by chiral GC with a Supelco β-Dex 120 column. Column temperature: 160–185 °C, 1 °C/min, hold for 50 min; retention times: 53.4 min (minor *R*-enantiomer), 53.9 min (major *S*-enantiomer). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.24 (d, $J = 8.7$ Hz, 2H), 6.86 (d, $J = 8.2$ Hz, 2H), 4.53–4.49 (m, 1H), 3.78 (s, 3H), 2.02 (br, 1H), 1.80–1.70 (m, 2H), 0.88 (t, $J = 7.3$ Hz, 3H).

(*S*)-1-(2-Chlorophenyl)propan-1-ol [21]: the ee was determined by chiral GC with a Supelco β-Dex 120 column. Column temperature: 160–190 °C, 1 °C/min, hold for 30 min; retention times: 43.4 min (minor *R*-enantiomer), 43.9 min (major *S*-enantiomer). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.54 (d, $J = 7.6$ Hz, 1H), 7.31–7.18 (m, 3H), 5.08–5.06 (m, 1H), 2.04 (br, 1H), 1.82–1.73 (m, 2H), 0.99 (t, $J = 7.6$ Hz, 3H).

(*S*)-1-(4-Chlorophenyl)propan-1-ol [21]: the ee was determined by chiral GC with a Supelco β-Dex 120 column. Column temperature: 160–190 °C, 1 °C/min, hold for 30 min; retention times: 46.0 min (minor *R*-enantiomer), 46.4 min (major *S*-enantiomer). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.29–7.23 (m, 4H), 4.56–4.53 (m, 1H), 2.08 (br, 1H), 1.77–1.69 (m, 2H), 0.88 (t, $J = 7.4$ Hz, 3H).

(*S*)-1-(2,6-Dichlorophenyl)propan-1-ol: the ee was determined by chiral GC with Supelco β-Dex 120 column. Column temperature: 140–185 °C, 1 °C/min, hold for 30 min; retention times: 60.8 min (minor *R*-enantiomer), 61.3 min (major *S*-enantiomer); ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.31–7.19 (m, 3H), 5.26–5.25 (m, 1H), 2.08 (br, 1H), 1.99–1.88 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H).

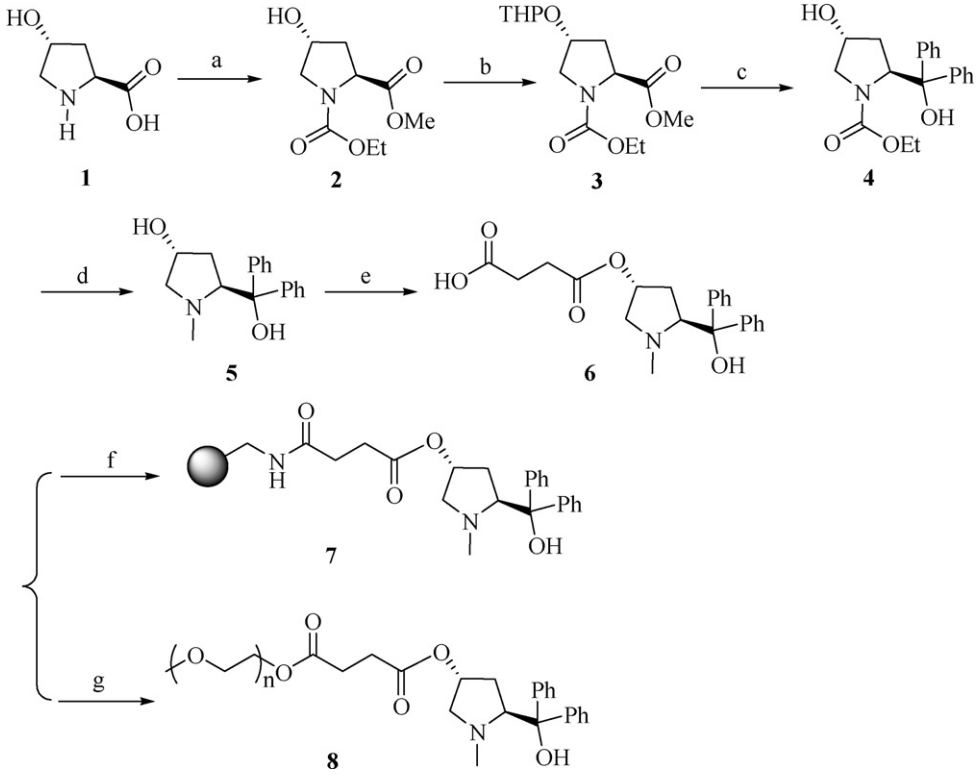
(*S*)-1-(2,3-Dimethoxyphenyl)propan-1-ol: the ee was determined by chiral HPLC with Chiralcel-OD-H column. Retention times: 14.8 min (major *S*-enantiomer), 16.0 min (minor *R*-enantiomer). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.04–6.84 (m, 3H), 4.85–4.82 (m, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 1.79–1.77 (m, 2H), 0.95 (t, J = 7.8 Hz, 3H).

(*S*)-1-(Naphthalen-1-yl)propan-1-ol [21]: the ee was determined by chiral GC with a Supelco β-Dex 120 column. Column temperature: 190–210 °C, 1 °C/min, hold for 30 min, and then 210–220 °C, 1 °C/min, hold for 30 min; retention times: 69.3 min (major *S*-enantiomer), 69.8 min (minor *R*-enantiomer). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.09 (d, J = 7.4 Hz, 1H), 7.86–7.75 (m, 2H), 7.61 (d, J = 7.3 Hz, 1H), 7.50–7.45 (m, 3H), 5.26–5.25 (m, 1H), 2.08 (br, 1H), 1.99–1.88 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H).

(*S*)-(*E*)-1-Phenylpent-1-en-3-ol [22]: the ee was determined by chiral HPLC with Chiralcel OD-H column. Retention times: 12.8 min (minor *R*-enantiomer), 19.0 min (major *S*-enantiomer). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.39–7.24 (m, 5H), 6.57 (d, J = 16.0 Hz, 1H), 6.24–6.18 (m, 1H), 4.21–4.19 (m, 1H), 1.67–1.63 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H).

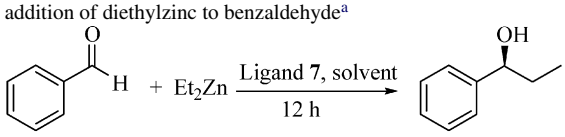
3. Results and discussion

The synthetic procedure for the polymer-supported proline-derived ligand **7** or **8** using *trans*-4-hydroxy-L-proline (**1**) as starting material is shown in Scheme 1. The reaction of compound **2**, synthesized from *trans*-4-hydroxy-L-proline (**1**) by a literature procedure [19], with commercially available 3,4-dihydro-2*H*-pyran yielded compound **3**. Treatment of compound **3** using phenylmagnesium bromide furnished the tertiary alcohol **4**. After deprotection of the THP group with a mild acidic catalysis, the carbamate group was converted to the corresponding methylamine through reduction with lithium aluminium hydride yielding our key intermediate (3*R*,5*S*)-5-(hydroxydiphenylmethyl)-1-methylpyrrolidin-3-ol (**5**) in 85% yield. The reaction **5** with succinic anhydride led to the formation of *N*-methylated amino alcohol **6** bearing a carboxyl functional group at the 4 position of the pyrrolidine moiety quantitatively. Without any further treatment, the resultant mixture containing the amino alcohol **6** could be used for the next attachment. Thus, reaction of **6** with the insoluble polymer (commercially available aminomethylated polystyrene resin, 1.07 mmol NH_2/g resin, 1% DVB) afforded the supported ligand **7**. The coupling condition was mild and the coupling efficiency was determined to be nearly quantitative with a loading of 0.76 mmol/g by nitrogen element analysis. The FT-IR spectrum (KBr) of resin-immobilized ligand **7** revealed new absorptions at 1735 cm^{-1} and 1676 cm^{-1}, indicating that the expected transformation of polymeric functional groups had occurred. Next, the soluble polymer-supported



Scheme 1. *Reagents and condition*. (a) Ethyl chlorformate, K_2CO_3, methanol, 89% yield. (b) 3,4-Dihydro-2*H*-pyran, TsOH, CH_2Cl_2, 98% yield. (c) (1) PhMgBr, THF; (2) AcOH, THF, H_2O, 44 °C, 85% yield. (d) $LiAlH_4$, THF, 100% yield. (e) Succinic anhydride, DMAP, CH_2Cl_2. The mixture was used directly for the next step. (f) Aminomethylated polystyrene resin, DIC, HOBt, Pr^i_2NEt, DMF/CH_2Cl_2, rt, 100% yield. (g) MeO-PEG (M_w = 2000), DMAP, DCC, CH_2Cl_2, rt, 100% conversion.

Table 1
The catalytic behavior of the polymer-supported ligand **7** for the asymmetric addition of diethylzinc to benzaldehyde[a]



Entry	Ligand **7** (mol%)	Solvent	Temperature (°C)	Yield (%)[b]	ee (%)[c]
1	5	Toluene	25	47	60
2	10	Toluene	25	86	62
3	**15**	**Toluene**	**25**	**92**	**68**
4	20	Toluene	25	91	68
5	15	CH_2Cl_2	25	36	41
6	15	Hexane	25	55	35
7	15	Toluene/CH_2Cl_2 (1:1)	25	41	50
8	15	Toluene	0	57	67
9	15	Toluene	40	87	59

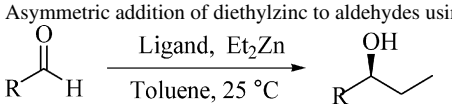
[a] Unless otherwise stated, the reaction was carried out using 1 mmol of benzaldehyde in 7 mL of solvent; PhCHO/Et_2Zn = 1:1.4; Et_2Zn (1 M solution in hexane); reaction time (not optimized): 12 h.
[b] Isolated yield.
[c] Determined by chiral GC.

chiral ligand **8** was synthesized quantitatively from the reaction of MeO-PEG-OH (M_w = 2000) with compound **6** under similar conditions. The loading of the immobilized ligand **8** was determined to be 0.42 mmol/g by nitrogen element analysis and ^1H NMR. The FT-IR spectrum (KBr) revealed a stronger absorption at 1735 cm^{-1}, also confirming the desired conversion.

With the polymer-supported ligands **7** and **8** in hand, the catalytic behavior of the insoluble polymer-supported ligand **7** was firstly evaluated for the asymmetric addition of $ZnEt_2$ to benzaldehyde (Table 1). The ligand **7** was found to be highly effective, yet the activities and enantioselectivities varied greatly with the employed amount of the ligand. The optimal amount of catalyst was 15 mol% of ligand **7** (Table 1, entry 3). A profound solvent effect was observed in the optimization study, and toluene was found to be superior to other common organic solvents (Table 1, entries 3, 5–7). Although the aminomethylated polystyrene resin swelled well in CH_2Cl_2, it was proved not to be an appropriate choice for the reaction (Table 1, entry 5) due to low yield. For reaction temperature optimization, the reactions were performed in toluene with 15 mol% of **7** at three temperatures between 0 and + 40 °C (Table 1, entries 3, 8, 9). The optimal temperature for the addition was 25 °C (Table 1, entry 3). This may be the best condition upon a balance between the polymer swelling and diminishing the side reaction.

In general, the addition reaction was carried out at 25 °C for 12 h in a molar ratio of aldehyde:ligand:diethylzinc (1 M solution in hexane) = 1:0.15:1.4. Under this standard condition, a number of substituted benzaldehydes were investigated toward this asymmetric addition with diethylzinc in the presence of 15 mol% ligand **7**. As shown in Table 2, the catalyst provided moderate to good enantioselectivity (in the range of 34–71% ee) in addition to high chemical yields. For example, it gave optically active (*S*)-1-phenyl-1-propanol with 68% ee and 92% yield (Table 2, entry 2). The electronic nature of the substitution on the phenyl ring seems to have an appreciable effect

Table 2
Asymmetric addition of diethylzinc to aldehydes using supported ligands[a]



Entry	R	Ligand	Yield (%)[b]	ee (%)[c]
1	Ph	**1**	94	91
2	Ph	**7**	92	68
3	Ph	**8**	94	90
4	4-MeC_6H_4	**7**	57	63
5	4-MeC_6H_4	**8**	68	87
6	4-$MeOC_6H_4$	**7**	89	34
7	4-$MeOC_6H_4$	**8**	95	42
8	2-ClC_6H_4	**7**	88	64
9	2-ClC_6H_4	**8**	94	85
10	4-ClC_6H_4	**7**	81	71
11	4-ClC_6H_4	**8**	93	90
12	2,6-$Cl_2C_6H_3$	**7**	31	63
13	2,6-$Cl_2C_6H_3$	**8**	44	76
14	2,3-$(MeO)_2C_6H_3$	**7**	71	52
15	2,3-$(MeO)_2C_6H_3$	**8**	89	81
16	1-Nap	**7**	76	56
17	1-Nap	**8**	90	88
18	(*E*)-PhCH = CH	**7**	93	62
19	(*E*)-PhCH = CH	**8**	96	77

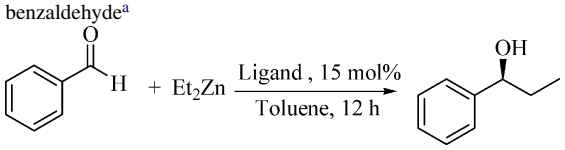
[a] Unless otherwise stated, the reaction was carried out at 25 °C using 1 mmol of aldehyde in 7 mL of toluene; aldehyde/Et_2Zn/ligand = 1:1.4:0.15 (mole); Et_2Zn (1 M solution in hexane); reaction time (not optimized): 12 h.
[b] Isolated yield.
[c] Determined by chiral GC or chiral HPLC.

on the enantioselectivity. Thus, from 4-methoxybenzaldehyde bearing a strong electron-releasing substituent (methoxy) on the *p*-position high chemical yield but low enantioselectivity were achieved (Table 2, entry 6). On the other hand, 4-chlorobenzaldehyde having an electron-withdrawing chlorine substituent on the *p*-position position could offer a high enantioselectivity (71% ee) (Table 2, entry 10).

Next, the soluble polymer-supported chiral ligand **8** was evaluated for the reaction and the results are listed Table 2 for a comparison to the use of **7**. From Table 2, all the aldehydes tested provided higher chemical yield and higher enantioselectivity with **8** than those obtained using its heterogeneous counterpart **7**. Taking the reaction of benzaldehyde as an example, while 68% ee was obtained using the insoluble polymer-supported chiral ligand **7**, a high enantioselectivity of 90% ee by employing **8** was achieved (Table 2, entry 3 versus entry 2). Comparable results were observed for the reaction of 4-chlorobenzaldehyde (Table 2, entry 11 versus entry 10). The difference in ee's from using **8** and **7** as supported chiral ligands for other aldehydes such as 2-ClC_6H_4CHO, 2,3-$(MeO)_2C_6H_3CHO$, and 1-NapCHO was also obvious (Table 2, entries 9 versus 8, 15 versus 14, 17 versus 16). These may be accounted for by the insoluble polystyrene skeleton which behaves as a restricted bulky substituent and hence limited mobility and accessibility of the active sites.

A most significant feature of polymer-supported catalysts is their easy recovery and reuse. As a final test on the performance of the supported ligands **7** and **8**, the possibility of their recovery and reuse was evaluated. After the reaction was quenched with 1 M HCl, the insoluble polymer-supported ligand **7** was

Table 3
Reusability of supported ligands for the asymmetric addition of diethylzinc to benzaldehyde[a]



Entry	Ligand	Run	Yield (%)[b]	ee (%)[c]
1	**7**	1	92	68
2	**7**	2	91	65
3	**7**	3	91	60
4	**7**	4	63	35
5	**8**	1	94	90
6	**8**	2	17	78

[a] Unless otherwise stated, the reaction was carried out at 25 °C using 1 mmol of benzaldehyde in 7 mL of toluene; benzaldehyde/Et_2Zn/ligand = 1:1.4:0.15 (mole); Et_2Zn (1 M solution in hexane); reaction time (not optimized): 12 h.
[b] Isolated yield.
[c] Determined by chiral GC.

recovered quantitatively from the reaction mixture by filtration, and the alcohol product was isolated from the mixture following the usual workup. Gratifyingly, ligand **7** could be reused for at least three cycles with essentially similar activity, and the enantioselectivity dropped feebly, plausibly due to the influence of moisture in the reaction mixture and work-up procedure (as shown in Table 3). At the fourth run, both the activity and enantioselectivity dropped sharply, maybe due to a significant decomposition of the catalyst (Table 3, entry 4). In the study of the soluble polymer-supported ligand **8**, most solvent and volatiles were removed after the reaction was completed. Then, cold ether was added to the mixture and the catalyst was quantitatively precipitated and recovered via filtration. Although the MeO-PEG supported ligand **8** can afford higher activity and better enantioselectivity than ligand **7**, its reuse was not satisfactory (Table 3, entries 5 and 6).

4. Conclusion

In summary, we presented in this paper the aminomethylated polystyrene resin supported proline-derived ligand **7** (insoluble) and the MeO-PEG supported proline-derived ligand **8** (soluble). The ligands were easily to prepare and exceptionally practical to use. The catalyzed asymmetric diethylzinc addition to a series of aldehydes has been successfully performed at 15 mol% ligand dosage with high enantioselectivity up to 90% ee for the diethylzinc addition with 4-chlorobenzaldehyde. The different behaviors of asymmetric addition of diethylzinc to aldehydes with the insoluble and soluble polymer-supported ligands were also noted. Particularly, the insoluble polymer-supported catalyst could be recovered easily and the recycled catalysts were shown to maintain their efficiency in three consecutive runs. The use of these recoverable polymer-supported proline-derived ligands in other transformations is in progress.

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