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Novel Polymer-Supported Chiral Catalysts for the Asymmetric Addition of Diethylzinc to Aldehydes

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Newly synthesized polymer-supported chiral amino alcohol catalysts 5a and 5b have been proved to be effective for the enantioselective addition of diethylzinc to aldehydes, affording the corresponding *sec*-alcohols in moderate enantiomeric excesses with good to excellent yields. The recycled catalyst could be reused in the same reaction without significant deterioration in performance.

Key words polymer-supported; amino alcohol; diethylzinc; aldehyde; enantioseletivity

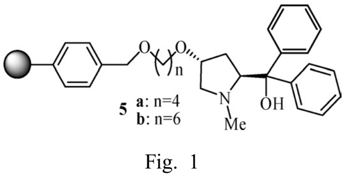
Polymer-supported catalysis in asymmetric reactions has emerged as a vigourously pursued area of research in recent years,[1—3] owing to its prevailing advantages over homogenous systems. Besides simplification of seperation and recycling, immoblized catalysts offer desirable benefits including easier handling of toxic reagents, improved stability in polymer matrix and convenient operation in continuous flow reactors. Thus, the industrial applications of even expensive and complex chiral catalysts can be achieved in an economical and enviromentally benign way.

Inspired by the pioneering work of Itsuno[4] and Soai,[5] various PS chiral amino alcohols[4—16] have been developed as catalysts in asymmetric transformations. In particular, the enantioselective organozinc addition to aldehydes is of long standing research interest due to affording optically active *sec*-alcohols as important building blocks for the synthesis of many natural products and biologically active compounds. Among numerous ligands developed[17—38] so far, (*S*)-diphenyl(1-methyl-pyrrolidin-2-yl)methanol[21] is most distinguished for its strong potential in enantioselectivity. However, the separation and recovery of the catalyst from reaction mixture remains problematic in large-scale production.

(2*S*,4*R*)-4-Hydroxy-1-methylazolan-2-yl-diphenylmethanol (**4**), a readily available analogue of (*S*)-diphenyl(1-methylpyrrolidin-2-yl)methanol, provides a convenient site for attachment to various supports such as mesoporous silica[39] and soluble macromoleculars[40] *etc.* with least disturbance to the accessibility of the catalytic center. To the best of our knowledge, polymer-supported catalysts generated by attaching the 4-hydroxyl group of **4** to Merrifield resin with a long methylene spacer are rarely studied in asymmetric reactions. Herein, we wish to report the preparation of a new class of PS-supported chiral amino alcohols **5a**—**b** (Fig. 1) and their use as catalysts for the enantioselective addition of diethylzinc to aldehydes.

The preparation of the PS-supported catalysts **5a**—**b** is shown in Chart 1. (2*S*,4*R*)-4-Hydroxy-1-methylazolan-2-yl-diphenylmethanol (**4**) was prepared from commercially available *trans*-4-hydroxy-L-proline in four steps following the reported procedures.[39] Alkylation of diols with Merrifield resin **1** (1% DVB; 100—200 mesh; chlorine content 1.0 mmol/g) in the presence of 60% NaH in DMF at 65 °C afforded the desired polymer **2a** and **2b** respectively, which upon treatment of refluxing $SOCl_2$ were converted into polymer **3a** and **3b**. The chiral amino alcohol **4** was subjected to alkylation by treatment of **3a** and **3b** with NaH in DMF at 65 °C to yield the PS-bounded catalysts **5a** and **5b** with a loading of amino alcohol moiety 0.66 mmol/g and 0.42 mmol/g, respectively, according to elemental analysis (C, H, N).

The efficiency of these new catalysts **5a** and **5b** was examined in the addition of diethylzinc to benzaldehyde. Initially, the reaction was performed in hexane with 10 mol% polymer-supported chiral amino alcohol **5a**. As can be seen from Table 1, the addition of diethylzinc to benzaldehyde afforded (*S*)-1-phenylpropanol in 91% yield with 63% ee (entry 2). Lowering the reaction temperature to 0 °C resulted in a slight decrease in the reactivity (entry 4). When reaction temperature continued to be lowered to −10 °C, the reactivity and enantiomeric excess were obviously decreased (entry 5). It's worth noting that there was no significant increase in chemical yield and enantioselectivity when the catalyst amount was increased to 20 mol% (entry 6). The solvent effect was then investigated. It was found that the nature of the solvent was revealed to have a remarkable effect upon the enantioselectivity and chemical yield. When changing the solvent from hexane to toluene, the similar chemical yield and enantioselectivity were obtained (entry 7). THF showed moderate ee value (entry 8). CCl_4 and $CHCl_3$ gave very poor chemical



5 a: n=4 b: n=6

Fig. 1

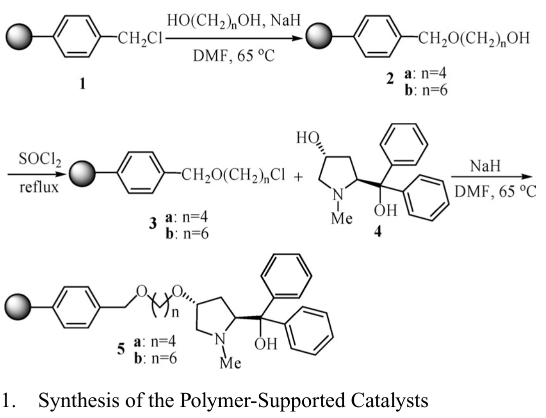


Chart 1. Synthesis of the Polymer-Supported Catalysts

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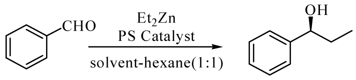
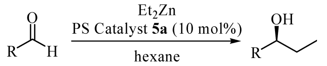
Table 1. Enantioselective Addition of Diethylzinc to Benzaldehyde Catalyzed by **5a**—**b**



Entry	Catalyst (mol%)	Et_2Zn (eq)	Solvent	*T* (°C)	Time (h)	Yield (%)[a]	Ee (%)[b]	Config.[c]
1	**5a**, 10	1.5	Hexane	r.t.	36	67	42	*S*
2	**5a**, 10	3	Hexane	r.t.	36	91	63	*S*
3	**5a**, 10	5	Hexane	r.t.	24	78	45	*S*
4	**5a**, 10	3	Hexane	0	48	89	53	*S*
5	**5a**, 10	3	Hexane	−10	60	75	44	*S*
6	**5a**, 20	3	Hexane	r.t.	24	93	60	*S*
7	**5a**, 10	3	Toluene	r.t.	36	92	61	*S*
8	**5a**, 10	3	THF	r.t.	36	83	52	*S*
9	**5a**, 10	3	CCl_4	r.t.	48	32	28	*S*
10	**5a**, 10	3	$CHCl_3$	r.t.	48	45	39	*S*
11	**5b**, 10	3	Hexane	r.t.	36	85	57	*S*

a) Yields of isolated pure products. *b*) Determined by HPLC using a chiral OD column. *c*) Absolute configurations were assigned by comparison of absolute optical rotation in the literature.

Table 2. Enantioselective Addition of Diethylzinc to Various Aldehydes Catalyzed by **5a**[a]



Entry	Aldehyde	Yield (%)[b]	Ee (%)[c]	Config.[d]
1	*p*-$OMeC_6H_4CHO$	96	73	*S*
2	*p*-MeC_6H_4CHO	93	70	*S*
3	*m*-MeC_6H_4CHO	95	63	*S*
4	*p*-FC_6H_4CHO	92	65	*S*
5	*o*-FC_6H_4CHO	90	62	*S*
6[e]	*p*-ClC_6H_4CHO	89	54	*S*
7	*o*-ClC_6H_4CHO	82	50	*S*
8[e]	*p*-BrC_6H_4CHO	93	73	*S*
9	*o*-OHC_6H_4CHO	56	11	*S*
10[e]	*p*-$NO_2C_6H_4CHO$	—[f]	—	—
11	Cyclohexanecarbaldehyde	58	42	*S*

a) All substrates were reacted with 3 eq Et_2Zn in hexane in the presence of 10 mol% **5a** at r.t. for 36 h. *b*) Yields of isolated pure products. *c*) Determined by HPLC using a chiral OD column. *d*) Absolute configurations were assigned by comparison of absolute optical rotation in the literature. *e*) Toluene–hexane (1 : 1) was used as co-solvent. *f*) A mixture of (4-aminophenyl)methanol (41%), unreative aldehyde (34%) and unidentified compounds (25%) was detected.

yield and enantioselectivity (entries 9 and 10). Under the optimized conditions, catalyst **5b** was also tested in the same reaction, and was found similarly effective as **5a** (entry 11).

The optimized reaction protocol was then used in the addition of diethylzinc to a variety of aldehydes. In all cases, the reactions were performed in the presence of 10 mol% **5a** in hexane at r.t. for 36 h and the results are summarized in Table 2. Unfortunately, we found that the chemical yield and enantioselectivity were largely dependent on the structure of the aldehydes. Most substituted aromatic aldehydes were effective substrates for this addition and gave the corresponding products in high chemical yields and moderate ees (entries 1—8). However, only chemical yield of 53% and enantiomeric excess of 11% was observed for the addition of diethylzinc to salicylic aldehyde (entry 9). Interestingly, with *p*-nitrobenzaldehyde as substrate the reaction was unsuccessful and no desired product was detected (entry 10). It is noteworthy that the reaction was also tested with cyclohexanecarbaldehyde, and a drop in the chemical yield (58%) and the ee value (42%) was observed (entry 11).

Table 3. The Recycling of the PS-Supported Catalyst **5a** in the Enantioselective Addition of Diethylzinc to Benzaldehyde

Entry	Run	Yield (%)[a]	Ee (%)[b]
1	1	89	61
2	2	93	64
3	3	90	60
4	4	88	57
5	5	85	55

a) Yields of isolated pure products. *b*) Determined by HPLC using a chiral OD column.

The catalytic recyclability was assessed by the consecutive addition of diethylzinc to benzaldehyde using the same batch of polymer-supported catalyst **5a** for five consecutive runs. As shown in Table 3, no loss of catalytic activity was observed in three successive cycles in terms of chemical yield and enantioselectivity (entries 1—3). In the forth and fifith cylce, there was a slight deterioration in catalytic activity (entries 4 and 5).

In conclusion, two new polymer-supported chiral amino alcohols have been synthesized and applied as catalysts to promote enantioselective addition of diethylzinc to aldehydes. Good to excellent yields and moderate enantioselectivities were accomplished in the ethylation of most aromatic aldehydes with diethylzinc at room temperature. The polymer-supported catalyst **5a** was fully recyclable without diminishing the catalytic effectiveness. Further studies are in progress in our laboratory with the aim of expending applications of these inexpensive chiral catalysts to other enantioselective catalytic processes.

Experimental

General Experimental Procedures All solvents were distilled by standard methods prior to use. The addition reactions were carried out under argon and monitored by GC-MS on a Agilent GC-MS spectrometer. Optical rotations were recorded on a JASCO P-1020 polarimeter. The ee was determined by HPLC using a DAICEL CHIRALCEL OD-H column (0.46 cmϕ×25 cm) with hexane–*i*-PrOH as the eluent.[37,41] HPLC was conducted on a Waters 1515 Isocratic HPLC pump and a Waters 2487 Dual λ Absorbance UV detector (254 nm). Elemental analyses (C, H, N) were performed on a Vario El III analyzer.

Preparation of the Polymer-Supported Catalysts 5a—b To a stirred solution of butane-1,4-diol (4.05 g, 45 mmol) in DMF (30 ml) was added

60% NaH (0.6 g, 15 mmol) at 0 °C. Stirring was continued at the same temperature for 30 min. Merrifield resin (5 g, 1% DVB; chlorine content 1.0 mmol/g; 100—200 mesh) was then added to the mixture. The reaction mixture was stirred at 65 °C for a further 48 h and was then quenched with H_2O (20 ml) at 0 °C. The polymer was collected by filtration and was washed successively with H_2O (3×20 ml), THF (3×20 ml) and MeOH (2×20 ml) and vacuum dried at 50 °C for 5 h to give polymer **2a** (5.24 g).

A mixture of polymer **2a** (4 g) and $SOCl_2$ (30 ml, 0.41 mol) was stirred under reflux for 40 h. Then the excess $SOCl_2$ was removed by filtration and the polymer was washed successively with H_2O (3×20 ml), THF (3×20 ml) and MeOH (2×20 ml) and vacuum dried to give polymer **3a** (4.09 g).

To a stirred solution of (2*S*,4*R*)-4-hydroxymethylazolan-2-yl-di-phenylmethanol (**4**) (2.04 g, 72 mmol; optical purity >99.6%) in DMF (15 ml) was added 60% NaH (0.096 g, 2.4 mmol) at 0 °C. Stirring was continued at the same temperature for 30 min. Polymer **3a** (1.0 g) was added and the reaction mixture was stirred at 65 °C for an additional 48 h. The reaction was quenched with H_2O (10 ml) at 0 °C. The polymer was collected by filtration and was washed successively with H_2O (3×10 ml), THF (3×10 ml) and MeOH (2×10 ml) and vacuum dried to afford the catalyst **5a** (1.18 g). The loading of amino alcohol moiety of **5a** was determined to be 0.66 mmol/g (*Anal.* Calcd: N, 1.39. Found: N, 0.92) by elemental analysis (C, H, N).

Catalyst **5b** (1.12 g) was prepared according to the same procedure described above. The loading of amino alcohol moiety of **5b** was determined to be 0.42 mmol/g (*Anal.* Calcd: N, 1.39. Found: N, 0.59) by elemental analysis (C, H, N).

General Procedure for the Asymmetric Addition of Diethylzinc to Aldehydes Catalyzed by 5a—b To a stirred suspension of the PS catalyst (0.04 mmol, 10 mol%) in hexane (1 ml) was added a solution of aldehyde (0.4 mmol) in hexane (0.2 ml) under argon, and stirring was continued at r.t. for 30 min. After the addition of diethylzinc (1.0 M in hexane, 1.2 ml, 1.2 mmol) at 0 °C, the reaction mixture was stirred at r.t. for a further 36 h, and was then quenched with 1 N HCl (4 ml). The resulting mixture was filtered and the filtrate was extracted with CH_2Cl_2 (4×10 ml). The combined organic layers were dried with anhyd. $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash chromatography (PE/AcOEt 15 : 1) afforded the desired alcohol. The enantiomeric excess and absolute configuration of the resulting alcohols were determined by HPLC and optical rotation.

The catalyst was collected by filtration and stirred with 1 N HCl–THF (1 : 2, 6 ml) for 1 h, and then washed successively with H_2O (3×5 ml), 1 N NaOH (3×5 ml), H_2O (3×5 ml) , THF (2×5 ml) and MeOH (2×5 ml). After vacuum dried at 50 °C for 5 h, the catalyst could be reused in the successive reactions.

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