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Polymer-Supported BINOL Ligand for the Titanium-Catalyzed Diethylzinc Addition to Aldehydes: A Remarkable Positive Influence of the Support on the Enantioselectivity of the Catalyst

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A new polymer-supported BINOL (1,1′-Bi-2-naphthol) was synthesized by coupling of aminomethyl polystyrene resin and (*S*)-2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxylic acid. This new ligand was found to be more enantioselective for the asymmetric addition of diethylzinc to aldehydes than its “free” analog [Ti(BINOL)^{i}PrO$_2$]. A range of 57−99% ee's as well as 78−97% yields was obtained, and the electronic properties of the enantioselectivity were also observed.

The methodology of attaching a chiral ligand onto a polymer has been widely applied to the development of new polymer-supported catalysts for asymmetric catalytic reactions.[1] This strategy often afforded several advantages over the use of homogeneous catalysts in asymmetric synthesis: (1) the ease of separation of the catalyst from the reaction system and (2) convenient operation in flow reactors or flow membrane reactors for continuous production.[2] Unfortunately, previous studies often showed significant decrease of catalytic activity and/or enantioselectivity for the supported catalysts as compared to their homogeneous counterparts[3] except for a few examples.[4] From both fundamental and practical standpoints, it is of high interest to explore the potential positive influence of the polymer support on the supported chiral catalysts. In this paper, we wish to report a new class of polymer-supported chiral catalyst that showed significantly higher enantioselectivity than its homogeneous counterpart.

1,1′-Bi-2-naphthol (BINOL) has been extensively studied as a chiral auxiliary in asymmetric synthesis.[5] While the BINOL ligand can be attached to a solid support via the linkage at several sites of the naphthyl rings, we are particularly interested in the attachment at the 3,3′-positions. The proximity of these positions to the catalyst center offered excellent opportunities for the study of the influence of the polymer support on the resulting catalyst. The 3,3′-functionalized (supported) BINOL **4** was synthesized according to Scheme 1. 2,2′-Dihydroxy-1,1′-binaphthyl-3,3′-dicarboxylic acid **3**[6] was synthesized in two steps in 54% yield from (*S*)-BINOL. This acid was further coupled with aminomethylated polystyrene[7] to give the desired ligand **4** with a loading of 0.38 mmol/g using DCC/HOBt (1-hydroxybenzotriazole hydrate) as coupling reagent.[8] The presence of the expected supported BINOL anchored to two polymer links is evidenced by the presence of −CONH− functionality at 1626 cm^{-1} and the disappearance of peaks of COOH at 1660, 3058 cm^{-1} in the FT-IR spectra.

The polymer-supported ligand **4** was found to be highly effective in the titanium-catalyzed alkylation of aldehydes with diethylzinc. A profound solvent effect was observed in the initial study, and dichloromethane (DCM) was found to be superior to other common organic solvents. The enantioselectivities also varied significantly when different levels of ligands were used. The optimum amount of ligand is 20 mol %. The Ti-**4** catalyst was also found to be highly effective for the asymmetric addition of diethylzinc to other aryl aldehydes. In most cases, the polymer-supported catalyst was found to be substantially more enantioselective than its “free” analogue [Ti(BINOL)(O^{i}Pr)$_2$].[9] The detailed experimental results are shown in Table 1.

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(7) The aminomethylated polystyrene (poly(4-vinyl benzylamine, 1% DVB, active −NH$_2$ group: 1.0 mmol/g) with its HCl salt was purchased from Hecheng Science & Technology Development Co., Nankai University, and was treated with Et$_3$N before use.

(8) The loading of **4** was determined by microanalysis, which is in good agreement with the value calculated by mass increase of the polymer.

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Scheme 1

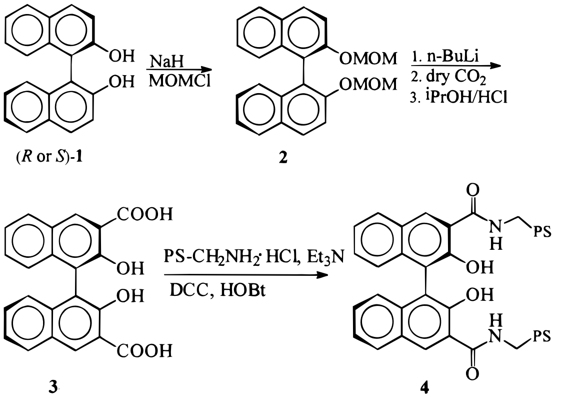

Table 1. Reaction of Aldehydes with Diethylzinc Catalyzed by Chiral Polymer-Supported Ti−BINOL Complex[a]

run	R/RCHO	time (h)	yield[b] (%)	ee[c] (%)
1	Ph	24	93	97 (91.9)[d]
2	2-ClPh	25	92	91 (68.6)
3	3-ClPh	24	89	94 (88.2)
4	4-ClPh	30	88	92 (88.1)
5	2-MeOPh	24	92	89
6	3-MeOPh	28	78	92 (94.0)
7	4-MeOPh	48	90	83 (79.0)
8	3-NO$_2$Ph	54	88	99 (70.0)
9	4-NO$_2$Ph	48	90	96
10	4-N(Me)$_2$Ph	18	97	57
11	3,4-(MeO)$_2$Ph	24	93	95
12	Piperonyl	30	89	65
13	1-Br-2-Nap[e]	28	95	95
14	(*E*)-PhCH═CH	28	97	93
15	2-Nap	48	89	94
16	2-MeO-1-Nap	24	87	99
17	Isopropyl	72	65	78[f]
18	Undecyl	72	52	65[f]
19	CH$_3$CH═CH	60	61	88[f]

[a] Aldehyde: Ti(O^{i}Pr)$_4$/Et$_2$Zn/**4** = 1:1.8:4:0.2; all the reactions were carried out at 0 °C. [b] Isolated yields. [c] Determined by HPLC with Daicel Chiracel OD column. [d] Data in brackets were the results from a study using BINOL ligand. See refs 9 and 5a. [e] Nap: naphthyl. [f] The ee was measured by analyzing the benzoate derivative of the alcohol by HPLC with Daicel Chiracel OD column.

Interestingly, with this polymer-supported catalyst, similar results were obtained for the substrates with identical substituents at the ortho, meta, or para position of the aromatic aldehydes (entries 2−4, 5−7, and 8−9). However, the 3,4-dimethoxybenzaldehyde and the structurally similar piperonal gave very different results (entries 11 and 12). It was reported that electronic properties had a remarkable effect on the enantioselectivity, and the substituents bearing electron-withdrawing groups in the para position of aryl aldehydes afforded higher enantioselectivity than those with electron-donating groups.[10] This might explain the low enantioselectivity of the diethylzinc addition to 4-(dimethylamino)benzaldehyde (Hammett constant $\sigma_p = -0.83$ for $-N(CH_3)_2$) (entry 10). Most of the polymer-supported amino alcohols could only give 8−65% ee for the reaction of aliphatic aldehydes with Et$_2$Zn.[11] This polymer-supported BINOL, however, provided slight higher ee's for the α-branched aliphatic and aliphatic aldehydes (runs 17 and 18). Good enantioselectivity was also achieved for the α,β-unsaturated aliphatic aldehydes (runs 14 and 19). Compared with the addition of aromatic aldehydes with Et$_2$Zn, the aliphatic aldehydes took a much longer time as well as lower yields.

To learn more about the influence of the polymer on the enantioselectivity, we also studied the reaction of Et$_2$Zn with benzaldehyde using a homogeneous BINOL derivative **5** having a CONHCH$_2$C$_6$H$_5$ group at the 3,3′-positions of BINOL. The Ti-**5** catalyst provided a faster reaction (12 h at 0 °C) but lower enantioselectivity (63% ee, 87% yield) than Ti-**4** (97% ee).

A Typical Experimental Procedure. A suspension of **4** (50 mg, 0.38 mmol/g) in DCM was allowed to stir under Ar at room temperature for 12 h to swell the resin. Ti(O^{i}Pr)$_4$ (60 μL, 0.175 mmol) was added, followed by a solution of Et$_2$Zn (0.38 mL of 1 M solution in DCM, 0.38 mmol). After 20 min, benzaldehyde (10 μL, 0.096 mmol) was added dropwise at 0 °C, and the reaction was allowed to proceed for a period of time, at the end of which the cool solution of NH$_4$Cl was introduced to quench the reaction. The polymer was removed by filtration. The alcohol was isolated by flash chromatography (silica gel) after extraction with an organic solvent and the ee value was determined by HPLC with a chiral OD column.

In summary, we have synthesized a useful and highly effective polymer-supported BINOL ligand and tested its capability in the enantioselective addition of diethylzinc to aldehydes. The present results showed that the polymer-supported catalyst was substantially more enantioselective than its homogeneous analogue. The key feature of the new catalyst may be due to the increased steric influence by the support on the catalyst. This finding opens a new frontier of development for the improvement of polymer-supported catalysts. A systematic modification of the new catalyst is in progress.

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Supporting Information Available: Detailed experimental procedures and characterizations involving **2**−**5** and the resulting alcohols.

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