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A New Approach to Highly Enantioselective Polymeric Chiral Catalysts

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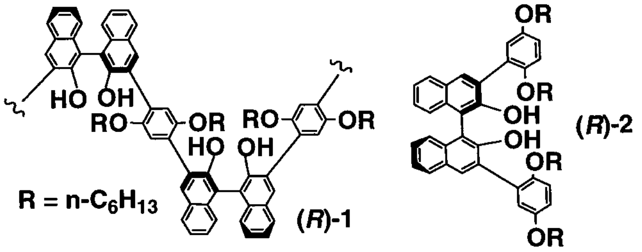
Asymmetric catalysis is one of the most important methods to prepare optically active organic molecules.[1,2] With the growing demand for optically pure drugs, the demand for recoverable and reusable chiral catalysts is also growing because of the expense of the optically active reagents. To facilitate the recovery of the catalysts, monomeric chiral compounds have been anchored to polymer supports to generate either heterogeneous catalysts or soluble macromolecular catalysts.[3,4] The differences of the solubility and the size between the polymers and the small molecules allow the chiral catalysts to be separated conveniently from the reaction system. Using polymeric catalysts also makes it possible to carry out the reactions in flow reactors or flow membrane reactors for continuous production. Although a few good polymeric chiral catalysts have been obtained, this strategy often leads to a significant drop of enantioselectivity after a good monomeric catalyst is attached to a polymer.[3,4] In the traditional polymeric chiral catalysts, the polymer supports such as polystyrene normally have a flexible and sterically irregular achiral structure that produces a microenvironment at the catalytic sites very different from that of the monomeric catalysts. This should be responsible for the observed reduced enantioselectivity in many cases. In addition, because of the flexible and sterically irregular structure, one cannot *systematically* modify the microenvironment of the catalytic sites in these polymers to achieve the desired catalytic properties.

We have carried out a program to use rigid and sterically regular polybinaphthols to develop a new generation of polymeric chiral catalysts for asymmetric catalysis.[5,6] Previously, we have reported the use of polymer (*R*)-**1** for the asymmetric reaction of aldehydes with diethylzinc.[5] This polymer can catalyze the reaction of diethylzinc with aldehydes to give chiral alcohols in over 90% ee for certain substrates. However, the general applicability of (*R*)-**1** was limited because of its lower enantioselectivity for the reactions of *ortho*-substituted benzaldehdyes and aliphatic aldehydes.

To gain further insight into the catalysis carried out by (*R*)-**1**, we have synthesized (*R*)-**2**[7] as the monomeric model compound of (*R*)-**1**. We find that (*R*)-**2** is an extremely general catalyst for the asymmetric reaction of diethylzinc with a broad range of aldehydes.[7] It shows 91−>99% ee's for the reaction of ortho-, meta-, or para-substituted benzaldehydes, linear or branched aliphatic aldehdyes, and aryl- or alkyl-substituted α,*β*-unsaturated aldehydes. We attribute the large enantioselectivity difference between (*R*)-**1** and (*R*)-**2** to their structural differences. In (*R*)-**1**, the two alkoxy oxygens on a phenylene spacer can serve as a dual ligand for both adjacent binaphthyl units. This makes the electronic and steric environment of the catalytic sites in (*R*)-**1** different from that of (*R*)-**2**. On the basis of this analysis, we have designed a new rigid and sterically regular polymeric chiral catalyst in which the steric and electronic environment of the monomeric catalyst is mostly preserved. This strategy has produced the most general polymeric chiral catalyst for the enantioselective reaction of aldehydes with diethylzinc. Herein, this result is reported and the potential application of this strategy is discussed.



(*R*)-**1**

(*R*)-**2**

From the Suzuki coupling[8] of (*R*)-**3**[9] with **4** followed by hydrolysis, chiral polymer (*R*)-**5** is obtained in 90% yield (Scheme 1). This polymer has very good solubility in THF, toluene, and chloroform. Gel permeation chromatography (GPC) analysis of (*R*)-**5** relative to polystyrene standards shows its molecular weight is M_w = 25 800 (PDI = 1.8). The specific optical rotation of this chiral polymer is $[\alpha]_D = -92.9$ (c = 1.01, CH_2Cl_2). (*R*)-**5** gives well-resolved ^{1}H and ^{13}C NMR spectra that are consistent with a well-defined polymer structure. Because the 3,3′-phenylene dialkoxy groups can only serve as ligands for one binaphthyl unit in (*R*)-**5**, the steric and electronic environment of the monomeric catalyst (*R*)-**2** is mostly preserved in the polymer due to the rigidity of the polymer structure.

When (*R*)-**5** is used to catalyze the reaction of aldehydes with diethylzinc, this polymer indeed shows the expected high enantioselectivity for a very broad range of aldehydes. Table 1 summarizes the results for the use of (*R*)-**5**. All of the reactions are carried out in the presence of 5 mol % of (*R*)-**5** in toluene solution at 0 °C unless indicated otherwise. The configuration of the alcohol products is R as determined by comparing their optical rotation values and HPLC or GC data with the literature results.[7,11] The results obtained from the reactions catalyzed by (*R*)-**1**[5] are also included in Table 1 for comparison. As shown in Table 1, (*R*)-**5** exhibits greatly enhanced enantioselectivity over (*R*)-**1**, especially for aliphatic aldehydes and ortho-substituted benzaldehydes. This polymer can be easily recovered by precipitation with methanol, and the recovered (*R*)-**5** shows the same enanti-

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Scheme 1. Synthesis of the Rigid and Sterically Regular Chiral Polymer (*R*)-5

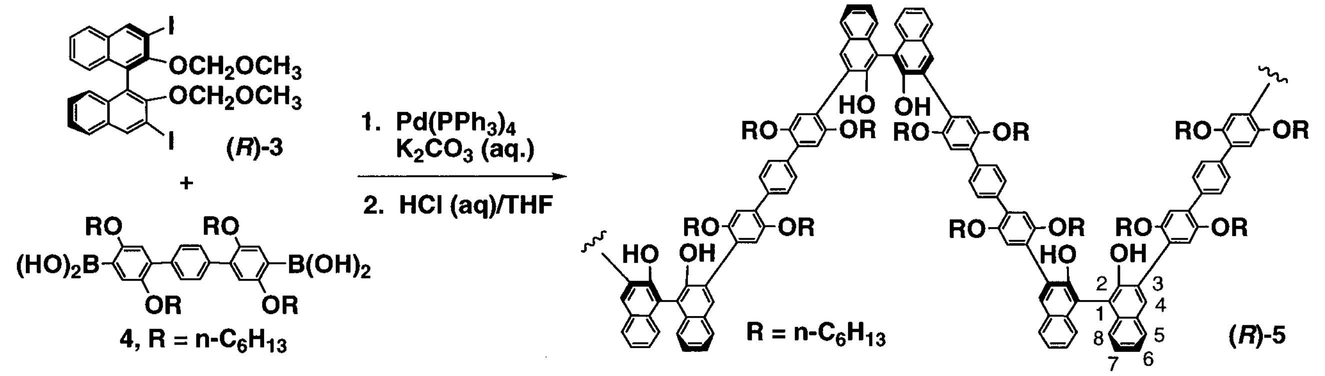
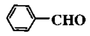
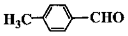
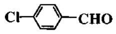
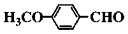
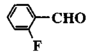
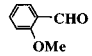
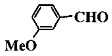
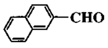
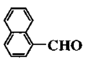
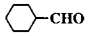
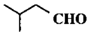
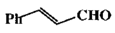
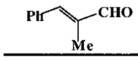


Table 1. Reaction of Aldehydes with Diethylzinc in the Presence of Chiral Polybinaphthyls

Aldehyde	(*R*)-5 Isolated yield (%)	(*R*)-5 *ee* (%)	(*R*)-1 Isolated yield (%)	(*R*)-1 *ee* (%)
	94	98[a]	89	92
	90	98[a,g]	91	92[g]
	90	98[b]	90	93
	94	98[b]	94	93
	89	97[a]	84	88
	88	91[b]	86	35
	90	93[b]	90	59
	93	98[a]	–	–
	95	96[a]	–	–
	93	98[a]	–	–
n-$C_5H_{11}CHO$	71	98[c]	65	74
n-$C_7H_{15}CHO$	85	97[c]	–	–
n-$C_8H_{17}CHO$	88	97[c]	89	74
	81	98[d]	70	83
	65	98[e]	–	–
	93	92[a,f]	86	90
	92	97[a]	–	–

[a] Determined by HPLC-Chiracel OD column. [b] Determined by chiral GC (β-Dex capillary column). [c] Determined by analyzing the acetate derivative of the product on the GC-β-Dex capillary column. [d] Determined by analyzing the propionate derivative of the product on the GC-β-Dex capillary column. [e] Determined by analyzing the Mosher's ester of the product on the GC-β-Dex capillary column. [f] The solvent was a 1:1 mixture of toluene/diethyl ether. [g] The recovered catalyst was used.

oselectivity as the original polymer. Although highly enantioselective polymer-supported amino alcohol catalysts have been developed for the reaction of a few benzaldehyde derivatives with diethylzinc,[10] the best results for the reaction of aliphatic aldehydes using these polymer catalysts are only 69% ee.[11,12] The cross-linked polystyrene-supported chiral α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol–titanium(IV) catalysts can carry out the reaction of diethylzinc with heptyl aldehyde in 92% ee (75% yield) and with cyclohexanecarboxaldehyde in 86% ee (57% yield), but these reactions require the use of a stoichiometric amount of Ti-$(OCHMe_2)_4$ versus the aldehydes.[13] Therefore, (*R*)-**5** is the best polymeric catalyst yet reported for the asymmetric reaction of aldehydes with diethylzinc.

A typical procedure for the use of (*R*)-**5** is described below. Under nitrogen, to a solution of (*R*)-**5** (50 mg, 0.05 mmol) in toluene (4 mL) was added diethylzinc (0.21 mL, 2.0 mmol) at room temperature. After being stirred for 10 min, the solution was cooled to 0 °C and benzaldehyde (0.10 mL, 1.0 mmol) was added. The resulting mixture was stirred for 5 h, and the reaction was monitored by TLC. A 100% conversion of benzaldehyde was observed, and 1 N HCl was added to quench the reaction. The mixture was extracted with Et_2O, and the combined organic layer was washed with brine, $NaHCO_3$, and brine. After evaporation of the solvent, the residue was redissolved in CH_2Cl_2 and precipitated with methanol. The polymer was recovered by filtration and the solution was concentrated under vacuum. The product was purified by flash chromatography on silica gel to give (*R*)-1-phenylpropanol as a colorless oil in 94% yield (128 mg) and 98% ee.

Our earlier discovery of (*R*)-**1** as an enantioselective catalyst is achieved by systematically screening the use of different polymers for the reaction.[5] The design of (*R*)-**5** and the discovery of its high enantioselectivity demonstrate that highly enantioselective polymeric catalysts can be obtained by incorporating good monomeric catalysts into a rigid and sterically regular polymer chain. This new approach may have general applications in the design of enantioselective polymer catalysts from the existing monomeric catalysts. When a monomeric catalyst is introduced into a rigid and sterically regular polymer chain rather than anchored to a flexible and sterically irregular polymer chain as in the traditional polymeric catalysts, the steric and electronic properties of the monomeric catalyst should be mostly maintained because of the rigid and sterically regular polymer structure. The catalytic activity and stereoselectivity of the resulting polymeric catalyst should closely resemble that of the monomer as long as the catalytically active species is not the aggregate of the monomer. The rigidity and stereoregularity the polymer structure also allows a systematic modification of the catalyst when necessary.

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Supporting Information Available: Detailed experimental procedures and characterizations involving (*R*)-**5** and **4** are provided (3 pages).

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