Highly Effective Soluble Polymer-Supported Catalysts for Asymmetric Hydrogenation

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Homogeneous asymmetric catalysis is one of the most important developments in modern chemistry over the past three decades. Many chiral catalysts are known to exhibit high activities and enantioselectivities.[1] However, a major problem associated with most homogeneous catalyst systems is the separation and recycling of the expensive chiral catalyst. A possible solution to this problem is to "heterogenize" a homogeneous catalyst, either by anchoring the catalyst on a solid support or by using a liquid−liquid two-phase system. Over the past two decades, the studies of insoluble polymer-supported catalysts have attracted much attention.[2,3] Unfortunately, despite the advantage of easy separation, the use of insoluble polymer-supported catalysts suffered from lowered catalytic activity and stereoselectivity due to the restriction of the polymer matrix which resulted in limited mobility and accessibility of the active sites. The leaching of the noble metal catalyst from the polymer support was also a significant problem. Recently, some progress on using polymer-supported heterogeneous catalysts has been made in the areas such as asymmetric dihydroxylation,[4] epoxidation,[5] and hydrogenation.[6] However, the significant decline of catalytic activity and/or enantioselectivity of the catalysts was still the major obstacle of this approach. Thus the development of a novel polymeric catalyst with high activity and enantioselectivity without leaching of catalytic species is highly desirable. For this purpose, we have designed and developed a highly effective polymer-supported chiral catalyst by using the concept of "one-phase catalysis and two-phase separation". This class of catalysts combines the advantages of homogeneous and heterogeneous catalysis: high catalytic activity and stereoselectivity with easy separation and convenient recycle of the polymer-supported catalyst from the reaction mixture. Because of the possible positive influence of the polymer support on the rate and/or stereoselectivity of the catalyst, the successful use of soluble polymer as chiral catalyst support may open up a new area for active research. Recently, cinchona alkaloid-type ligands were anchored on soluble poly(ethylene glycol) and showed similar catalytic activity and selectivity as compared to the corresponding free catalysts in the osmium-catalyzed asymmetric dihydroxylation of unfunctional olefins.[7,8] This finding was highly interesting, even though the separation of the polymer-supported ligands from the reaction
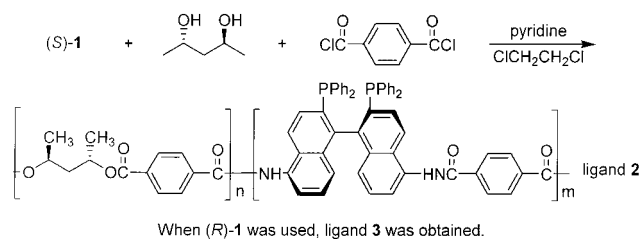

Figure 1. The synthesis of chiral polyester-supported BINAP ligands.

mixture through the manipulation of several different solvents including diethyl ether was still inconvenient. A disadvantage of the use of poly(ethylene glycol) support was that it limited the binding site of the ligand to the terminals of the polymer and consequently limited the possible interactions of the polymer support with the catalyst. In this study, we developed a new type of polymer-supported catalysts which offered better rate of reaction than the corresponding monomeric homogeneous catalyst while retaining the high stereoselectivity. This new approach also offered opportunities for the study of polymer−catalyst interaction in the supported chiral phosphine-containing catalysts.[9]

In choosing a model ligand for this study, we noticed that among all the known chiral phosphine ligands which had been studied for asymmetric catalysis, BINAP was probably the most versatile and effective.[10] Both rhodium and ruthenium BINAP complexes have been extensively studied and several commercial processes based on these catalysts have been developed.[11] An innovative attempt to immobilize this class of catalysts was the use of "supported aqueous-phase catalysis" in which the sulfonated form of the complex was dissolved in a thin ethylene glycol film that was adhered to a high-surface-area hydrophilic support.[12] However, the system was restricted in the choice of possible substrates and solvents, and the supported catalyst showed lower catalytic activity in comparison to the corresponding "free" catalyst. Recently, Vankelecom and co-workers[13] reported another approach to immobilized BINAP complexes via the occlusion of the catalyst in a poly(dimethylsiloxane) membrane. The system, however, was also restricted in the choice of possible substrates and showed lower enantioselectivity and activity. In this paper, we report the first example of the soluble polymer-supported chiral phosphine-containing catalyst, which showed higher activity than the corresponding "free" catalyst while retaining the high stereoselectivity.

Since BINAP itself cannot be easily attached to a polymer support, 5,5′-diamino-BINAP (**1**)[14] was used for this study. Polymer-supported BINAP ligands (**2** or **3**) were synthesized by the polycondesation of (*S*)-**1** or (*R*)-**1**, terephthaloyl chloride, and (2*S*,4*S*)-pentanediol in the presence of pyridine in 1,2-dichloroethane (Figure 1). A model compound of small molecule **4** (5,5′-dibenzamido-BINAP) was also synthesized by reacting (*S*)-**1** with benzoyl chloride in the presence of pyridine in dichloromethane for the purpose of comparison. The chiral polyester-supported BINAP ligands (**2** or **3**) were soluble in common nonprotic organic solvents such as toluene, THF, and dichrolomethane, but quantitatively precipitated upon the addition of methanol. The ligands were characterized by ^{1}H and ^{31}P NMR. The molecular weights of the polyester-supported ligands (**2** or **3**) were determined by

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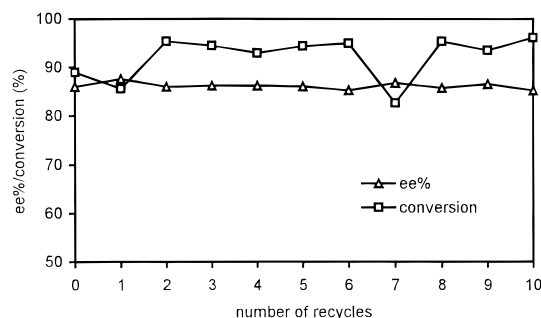
Figure 2. A plot of conversion and ee values vs the number of recycles in the asymmetric hydrogenation of **5** catalyzed by polyester-supported Ru(BINAP).

gel permeation chromatography (GPC). The detailed experimental data are summarized in the Supporting Information. BINAP attached to polymer support by copolymerization provided several key advantages: (1) facile control of the incorporation of BINAP in the polymer chains and (2) easy adjustment of the nature of the polymer matrix (configuration of chiral center on the polymer chain, rigidity, polarity, etc.) by using suitable comonomers, which offered an opportunity to study the "polymer effect" and to fine-tune the catalyst.

We chose the asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)acrylic acid (**5**) as the model reaction. This choice was
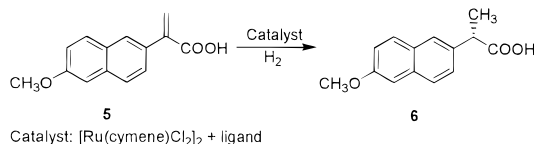
based on the fact that Ru(BINAP)-type catalysts were effective in the asymmetric hydrogenation of 2-arylacrylic acids and the reduced products represented an important class of antiinflammatory drugs. The product (naproxen) in this particular reaction is a high-value antiinflammatory drug with annual sales of $600 million. The catalyst, which was conveniently prepared in situ from polyester-supported BINAP ligand (**1**) and [Ru(cymene)-Cl$_2$]$_2$ in a methanol−toluene (2:3, v/v) mixed solvent system, was completely homogeneous. The hydrogenation of **5** with a substrate/catalyst molar ratio of 200 and under 69.0 kg cm^{-2} H$_2$ pressure at room temperature gave 95.5% conversion and 87.7% ee in 4 h. When the methanol−toluene (9:1, v/v) solvent system was used, the same reaction under otherwise identical conditions gave only 37.5% conversion and 80.5% ee in 60 h. The profound solvent effect was due to the insolubility of the polyester-supported catalysts in the solvent system with a high level of methanol. These results are consistent with the rationale of designing soluble polymer-supported chiral catalysts.

The different solubility of the chiral polyester-supported BINAP ligands in different types of solvents provided a convenient and reliable method for the separation and recovery of the polymeric catalysts. Upon completion of the catalytic hydrogenation, methanol was added to the reaction mixture and the catalyst was quantitatively precipitated, filtered, and reused. The filtrate contained the hydrogenation product, and the Ru content in the filtrate was found to be below 16 ppb according to atomic absorption measurement (detection limit). In repeated experiments, the polyester-supported catalyst was found to maintain the same activity and enantioselectivity after more than 10 recycles (Figure 2).

The positive influence of the polymer support on the catalyst is another potential advantage of the soluble polymer-supported catalyst and is of high scientific and practical interest. For comparison, ligand **4** was synthesized as a homogeneous monomeric analogue of the polymer-supported ligand. The results of the comparison study are shown in Figure 3, which clearly revealed the positive influence of the support on catalytic activity.
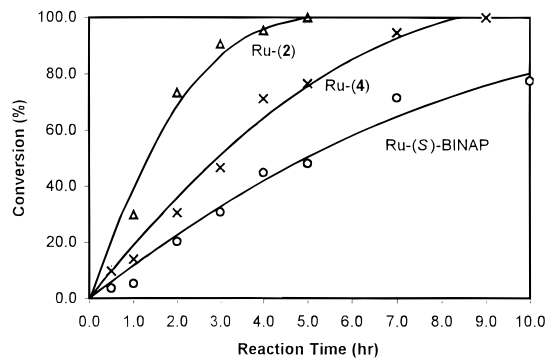

Figure 3. The comparison of the rates of hydrogenation catalyzed by Ru-(**2**), Ru-(**4**), and Ru-(*S*)-BINAP.

Table 1. Studies of the Polymer Effect on the Asymmetric Hydrogenation of 5[a]

entry	catalyst (prepared in situ)	time, h	conv, %[b]	ee, %[b]
1	**3** + [Ru(cymene)Cl$_2$]$_2$	18	100	92.9 (*R*)
2	**2** + [Ru(cymene)Cl$_2$]$_2$	12	97.4	93.6 (*S*)
3[c]	**2** + [Ru(cymene)Cl$_2$]$_2$	12	100	93.3 (*S*)
4	**4** + [Ru(cymene)Cl$_2$]$_2$	36	99.8	93.5 (*S*)
5	(*S*)-BINAP + [Ru(cymene)Cl$_2$]$_2$	48	94.7	93.5 (*S*)
6	**2** + [Ru(cymene)Cl$_2$]$_2$	4	95.4	87.7 (*S*)
7	**4** + [Ru(cymene)Cl$_2$]$_2$	4	64.2	89.2 (*S*)
8	(*S*)-BINAP + [Ru(cymene)Cl$_2$]$_2$	4	56.5	88.7 (*S*)

[a] The hydrogenation was carried out in 0.026 M **5** in methanol−toluene (2:3, v/v) solution (except for entry 3) under the following conditions: Sub./Cat. = 200 (mol/mol); NEt$_3$/Sub. = 1:1 (mol/mol); H$_2$ = 110 kg/cm^2 except for entries 6−8 (69 kg/cm^2). reaction temperature = 1−2 °C except for entries 6−8 (room temperature). [b] Determined by HPLC analysis using a SUMICHIRAL OA-2500 column. [c] Methanol/toluene = 1:3, v/v; other conditions were identical to those listed in footnote *a*.

The polyester-supported catalyst was found to be substantially more active as compared to the corresponding monomeric catalyst. This effect was probably due to the cooperation of the polyester backbone and the BINAP ligand, in which the polyester chains serve as large substituents on the BINAP ligand. The steric effect of these large substituents affected the dihedral angle of the binaphthyl rings in the Ru(BINAP) complex, which consequently gave faster rate of reaction. Similar acceleration effects have been observed in the asymmetric hydrogenation of unsaturated carboxylic acids catalyzed by Ru(II) catalysts containing H$_8$-BINAP[15] or bis-steroidal phosphine,[16] which possessed a larger steric hindrance than that of BINAP. It was also observed that while the rate of hydrogenation was faster with the polymer-supported catalyst the high ee of the product was maintained (Table 1).

In conclusion, we have developed a new, highly efficient polymer-supported chiral catalyst that showed higher catalytic activity as compared to the free corresponding catalysts. This study opens up a new frontier for the development of highly effective and easily separated chiral catalysts. We believe this new technique will have the potential not only for laboratory-scale research but also for industrial applications.

Supporting Information Available: Experimental details for the characterization of the modified BINAP ligands, the synthesis of polyester-supported ligands **2** and **3**, and procedures for the hydrogenation and recycling of catalysts (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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