

In Defense of the Catalytic Asymmetric Cis Dihydroxylation of Olefins Utilizing Insoluble Polymeric Ligands

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A recent report¹ dealing with the catalytic asymmetric dihydroxylation² of olefins using soluble polymer-bound (SPB) ligands prompts this paper as a sequel to our work³ using insoluble polymer-bound (IPB) Cinchona alkaloid ligands. We provide evidence that suggests that the IPB ligands are competitive with the SPB systems and offer potential for significant industrial application.

For an easier comparison between the homogeneous and heterogeneous processes, we synthesized^{3c} the functional monomer **1a** containing the 4-chlorobenzoate group (CLB) (Figure 1), used also by Sharpless as chiral ligand in the homogeneous phase reaction.⁴

Monomer **1a** was copolymerized^{3c} with ethyleneglycol dimethacrylate and hydroxyethyl methacrylate, providing polymer **poly-1a** (Scheme 1), which was continuously extracted in a Soxhlet device to remove any trace of monomer and soluble material.

The insoluble fraction of the polymer was used in the cis dihydroxylation reaction in the heterogeneous phase following the experimental procedure adopted for the homogeneous process:^{5a} K₃Fe(CN)₆:K₂CO₃ 1:1 in 'BuOH:H₂O 1:1 as cooxidant, 0.5–1% of OsO₄, and 10–25% of **poly-1a**, calculated from the incorporated alkaloid, which is exactly the same catalytic amount of polymeric ligand used by Sharpless^{5b} and by Janda.¹ We chose styrene, an extensively used molecule both in homogeneous and heterogeneous processes, as a suitable substrate to show differences in terms of enantioselectivity and reactivity. (*R*)-(-)-1-Phenyl-1,2-ethanediol was obtained after 20 h in 75% isolated yield and an enantiomeric excess (ee) of 65% (entry 1, Table 1).

The effect recycling the catalyst had on the yield and the ee of the reaction was next examined. The polymeric chiral catalytic precursor was quantitatively recovered at the end of the reaction by filtration, avoiding any chemical or chromatographic separation from the reaction products, necessary when the chiral catalyst is soluble in the reaction medium. Some OsO₄ was lost to the mother liquor as well as the methanol used to wash the resin. Therefore, a small amount (0.2% of OsO₄) was added to completely regenerate the reaction conditions. The above procedure was repeated 5 times, and the results obtained are shown in Figure 2, where the plots of the percentages of

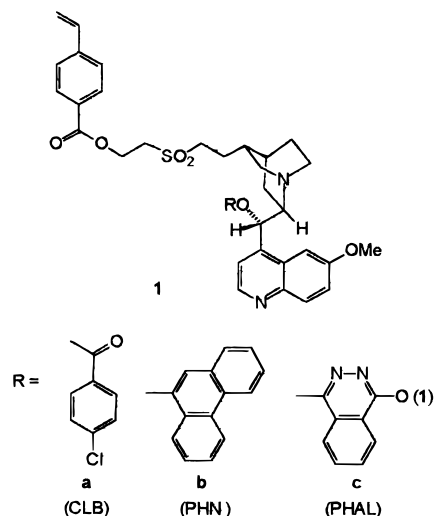


Figure 1. Functional monomer **1**, containing different Cinchona alkaloid derivatives.

Scheme 1

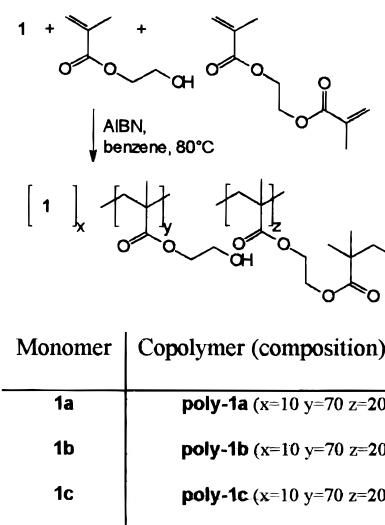


Table 1. Heterogeneous Catalytic Asymmetric Dihydroxylation^a of Olefins Using Different Cinchona Alkaloid Derived Insoluble Ligands

entry	olefin	polymer	yield ^b	e.e. ^c
1		poly-1a	75	65 (73)
2		poly-1b	84	68 (74)
3		poly-1c	86	91 (97)
4		poly-1c	88	94 (94)
5		poly-1c	85	97 (99)
6		poly-1c	90	>99 (>99)

^a The asymmetric dihydroxylation reactions were run for 20 h at 0 °C using as secondary oxidant K₃Fe(CN)₆ in 'BuOH:H₂O 1:1. ^b Isolated yield by column chromatography. ^c The ee values were determined by HPLC analysis of the diols.^{3c} In parentheses, the ee values obtained by the reaction in the homogeneous phase, using as chiral catalytic ligands the 4-chlorobenzoate ester,⁴ the 9-O-phenanthryl ether⁵ and the phthalazine ether⁹ of dihydroquinidine.

pure recovered diol and ee vs the number of recycles of the catalyst are reported.

The extent of dihydroxylation of styrene as well as the ee values were also investigated by direct analysis of the reaction

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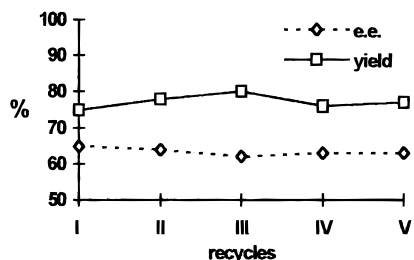


Figure 2. Plot of yields and ee values vs recycles of polymer **poly-1a** catalyzed dihydroxylation of styrene.

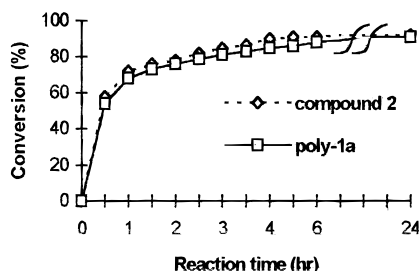
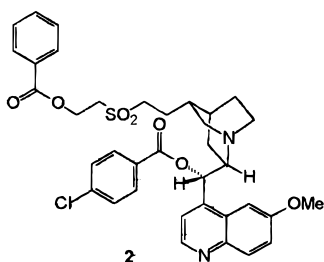


Figure 3. Conversion vs time curve of polymer **poly-1a** and soluble model compound **2** catalyzed dihydroxylation of styrene.

mixture using HPLC on a chiral DAICEL column, coupled with UV and CD detectors. The diol enantiomers, chemical impurities, and unreacted styrene were easily and directly monitored without any isolation of the products. In Figure 3 the conversion vs time plot of the reaction catalyzed by insoluble **poly-1a** is reported together with that for the reaction in the presence of **2**, a soluble model compound of the monomeric unit.



It is evident that the dihydroxylation rate in the presence of **poly-1a** is very similar to that with the soluble analog **2** and the conversion is over 80% within a few hours, for both the homogeneous and the heterogeneous ligands. In our previous work, we have adopted the standard time reported for the homogeneous reaction^{5a,6} (20–24 h) in order to compare different polymeric systems or cooxidants. We have already reported^{3b} that by using a cross-linked polystyrene polymer and *N*-methylmorpholine *N*-oxide (NMO) as cooxidant, high dihydroxylation yields can be obtained in shorter reaction times (max

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7 h), without the slow addition of the olefin. When NMO was used as cooxidant, lower^{3c} enantioselectivity was observed. The slow addition of the olefin (20–24 h in many cases) to the reaction mixture⁷ resulted in some improvement; however, ee values were lower than those obtained by using $K_3Fe(CN)_6$, an effect which is presumably the manifestation of the “second cycle” problem observed by Sharpless.⁸

As far as the enantioselectivity is concerned, the ee extent, determined periodically by HPLC on chiral stationary phase, was practically constant in the presence of **poly-1a** and comparable to that obtained with homogeneous ligands employing the soluble model compound **2**. When **poly-1b** and **poly-1c** are used,^{3d,e} synthesized from monomers **1b** and **1c** having different substituents in the alkaloidic moiety, the diol was obtained with ee of 68% and 91%, respectively (Table 1, entries 2 and 3). A similar trend has been observed for the reaction using homogeneous ligands.² In fact, Sharpless has demonstrated that replacing the CLB group used in the original catalytic procedure with phenanthryl ether⁶ (PHN) or a phthalazine derivative⁹ (PHAL) led to a considerable increase in the enantioselectivity of the reaction. As seen in Table 1, a number of olefins having different structures gave products with useful ee values.

Taking into account the results obtained, some closing remarks can be drawn. The polyhydroxy methacrylic backbone offers a favorable microenvironment to the chiral catalytic sites confirming that once an appropriate support compatible with the reaction medium is found, the reactivity with soluble or insoluble ligands is very similar. This concept is illustrated by the curves in Figure 3. It is also evident that insoluble polymers **poly-1(a–c)** show the following attractive features: (i) short reaction times, without slow addition of the olefin; (ii) easy recovery of the catalyst by simple filtration and the ability to be recycled repeatedly without significant loss of reactivity or enantioselectivity; (iii) a high extent of enantioselectivity. In addition this polymeric system is very flexible, since the connecting site to the polymeric chain leaves the hydroxyl group of the alkaloidic moiety (R = H, Figure 1) accessible for the modification, which plays a fundamental role in the asymmetric dihydroxylation process.¹⁰

In conclusion, the results obtained in the present investigation demonstrate that reliable insoluble polymeric ligands can be designed for the *cis* dihydroxylation of olefins. These ligands retain the advantages of their soluble monomer counterparts in terms of activity, enantioselectivity, and allowable reaction conditions. Furthermore, the ease of handling and ability to recycle make these polymer-bound ligands ideal for both large and small scale synthesis.

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