Journal of Macromolecular Science, Part A
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597274

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To cite this Article Stille, J. K.(1984) 'Polymer-Supported Chiral Catalysts in Asymmetric Synthesis', Journal of Macromolecular Science, Part A, 21: 13, 1689 — 1693
To link to this Article: DOI: 10.1080/00222338408082084
URL: http://dx.doi.org/10.1080/00222338408082084

J. MACROMOL. SCI.–CHEM., A21(13 & 14), pp. 1689-1693 (1984)

Polymer-Supported Chiral Catalysts in Asymmetric Synthesis

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INTRODUCTION

By far the best method of synthesis of chiral organic compounds from prochiral substrates is through the use of chiral catalysts or enzymes. This approach has several advantages, the most important of which is that either the enzyme is naturally occurring or the catalyst can be easily generated from a naturally occurring chiral material. If resolution needs to be accomplished, it is carried out with small amounts of catalyst rather than with large quantities of product. Thus from a catalytic amount of chiral material large quantities of one enantiomeric product can be generated.

Homogeneous catalysis is a very effective method of running an asymmetric synthesis because it can be carried out under very mild reaction conditions, taking advantage of the differences in the energies of activation leading to the two enantiomers [1-4]. A very practical limit to carrying out homogeneously catalyzed reactions in the liquid phase is the difficulty in separating the product from the catalyst or in removing the product continuously. In these reactions the expensive transition metal and chiral ligand are not readily recovered.

To overcome the difficulty of separating product and catalyst, homogeneous catalysts have been attached to a variety of heterogeneous supports, including cross-linked polymers [5]. By doing this, the catalyst retains the selectivity characteristic of homoge-

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neous catalysts and still functions under mild reaction conditions, but essentially acquires the property of insolubility. Most of synthetic polymer supports to which homogeneous catalysts have been attached are polystyrenes, and these polymer-attached catalysts have been prepared by connecting the catalyst to an already formed polystyrene bead. This approach has resulted in the generation of many poor catalysts. In particular, when the catalyst construction is carried out by attachment of the active site to a preformed polymer, without consideration of the requirements of the reaction, low catalyst activity and low enantiomeric excesses in asymmetric synthesis generally result.

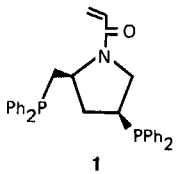
One of the most challenging problems, therefore, is to design an effective polymer-supported catalyst. Not only is the choice of the ligand for the transition metal important but also the type of polymer matrix and the way in which the catalyst is attached to the polymer is critical. Our approach, the synthesis of a ligand-bearing monomer, followed by copolymerization with a second monomer and finally exchange of the transition metal onto the ligand sites, has several advantages. First, the optical purity of the ligand on the monomer can be assured. Second, the concentration of the ligand-bearing monomer on the polymer can be controlled. Third, depending on the comonomer, and thus the reactivity ratios of the two monomers, isolation of the ligand-bearing monomer can be assured. Fourth, the nature of the polymer backbone, polar or nonpolar, can be varied, depending on the selection of comonomer. Fifth, varying degrees of cross-linking may be introduced.

RESULTS AND DISCUSSION

A number of phosphine-containing monomers have been synthesized and copolymerized with suitable comonomers and cross-linking monomers to provide polymers containing the chiral phosphine sites to which the transition metal was bound [6-9]. In most cases, both enantiomers of the chiral phosphine monomer have been synthesized, allowing the asymmetric synthesis of either enantiomeric product. In addition, at present, it is nearly impossible to predict which enantiomer will be produced in a catalytic reaction from a given chiral phosphine.

Our initial studies were concerned with the synthesis of the appropriate polymer-supported catalyst for the hydrogenation of olefins, particularly α-N-acylaminoacrylic acid derivatives, that give S-amino acids [10-16]. The use of a Wilkinson-type rhodium catalyst could be designed to give high optical yields (~90%ee) of amino acids. The key requirement for these catalysts was that the polymer be compatible with the polar reaction solvent necessary to obtain solutions of the substrate. Thus the polymer bearing the chiral phosphine ligand was constructed mainly of a hydrophilic comonomer such as hydroxyethyl methacrylate, so that the cross-linked polymer would swell in ethanol.

One of the more useful monomers in the asymmetric hydrogenation reactions was N-acryloyl-(2S,4S)-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl] pyrrolidine (1) derived from the naturally occurring L-hydroxyproline [14]. Hydrogenation of (Z)-N-acetyl-α-aminocinnamic with a catalyst prepared from a copolymer of 1, hydroxyethyl acrylate and ethylene dimethacrylate, onto which rhodium had been exchanged (3), gave (R)-N-acetyl phenylalanine in 90% enantiomeric excess. Unfortunately, the catalyst derived from the naturally occurring hydroxyproline gave the unnatural amino acid. Consequently, its enantiomer the 2R,4R isomer (2) was synthesized [14], the catalyst which produced the naturally occurring amino acid. The catalysts were easily recovered after the reaction by simple filtration, and the catalyst could be reused with no loss in optical yield and little loss in rate.



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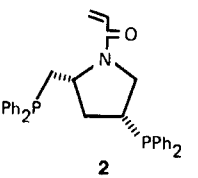

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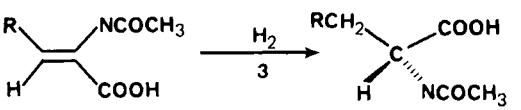

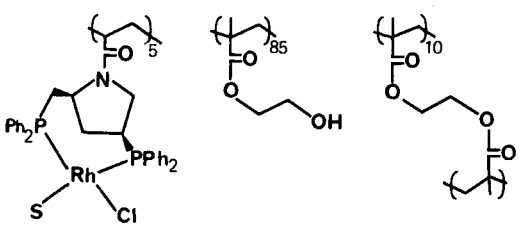

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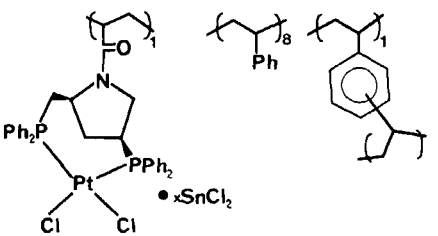
Most of the transition metal-catalyzed asymmetric organic syntheses via polymer attached optically active phosphine ligands have been asymmetric hydrogenations. Only a few asymmetric hydroformylations have been carried out by polymer-attached chiral catalysts, and generally low enantiomeric excesses were obtained [17]. We were able to effect an asymmetric hydroformylation with a DIOP-rhodium catalyst

bound to polystyrene beads, but the enantiomeric excess obtained from styrene was lower (~11%ee) than the enantiomeric excess obtained from the analogous homogeneous catalyst (~30%ee).

This type of asymmetric synthesis in which a carbon-carbon bond formation generates the chiral center is a valuable transformation for the synthesis of chiral molecules. The enantiomeric excesses achieved, however, are high enough to be useful as an asymmetric synthesis [1-4]. More recently, high optical yields in hydroformylation have been realized utilizing catalysts prepared from dibenzophosphole DIOP $PtCl_2$-$SnCl_2$ [18]. In order to test the asymmetric hydroformylation reaction with the platinum-tin catalyst, we prepared an insoluble copolymer of 1, styrene, and divinylbenzene by a suspension polymerization to obtain 60 μm beads onto which platinum was exchanged [19]. The resulting catalyst (4) was used for the hydroformylation of styrene.



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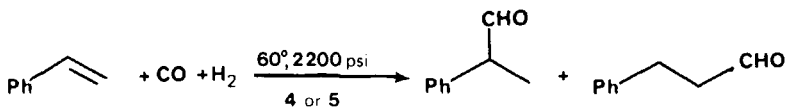
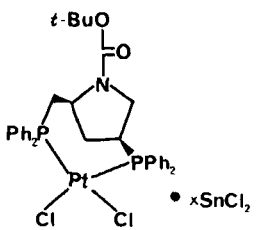
The hydroformylation reaction of styrene was carried out at 60°C, 2200 psi (H_2/CO = 1) to yield both 2-phenylpropanal and 3-phenylpropanal in a 1:2 ratio. Optical yields as high as ~75%ee could be achieved. This optical yield compares favorably with the analogous homogeneous catalyst (5), from which an 80%ee could be obtained.





5

The polymer catalyst (4) could be filtered and reused, with no loss in optical yield. This represents the highest entiomeric excess achieved to date in a hydroformylation reaction with a polymer-supported chiral catalyst.

ACKNOWLEDGMENT

This research was supported by a grant DMR from the National Science Foundation.

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