Soluble Polymer-Bound Ligand-Accelerated Catalysis: Asymmetric Dihydroxylation

Hyunsoo Han and Kim D. Janda*

The Scripps Research Institute
Departments of Molecular Biology and Chemistry and
The Skaggs Institute of Chemical Biology
10550 North Torrey Pines Road
La Jolla, California 92037

Received March 12, 1996

Insoluble polymer-reagents and catalysts have achieved wide recognition and acclaim.[1] However, as successful as insoluble reagent and catalyst supports have been there are limitations associated with such species.[2] An alternative to insoluble polymer-bound reagents or catalysts is soluble polymer bound ligands, reagents, or catalyst supports,[3] the difference being that reactions are carried out homogeneously and separation of the homopolymer from reaction products can be achieved by taking advantage of the properties of the polymer chain. We have been interested in applying soluble polymers in the arena of combinatorial synthesis. As such we recently introduced what we term "liquid phase combinatorial synthesis" or LPCS.[4] The cornerstone of LPCS is a linear homopolymer [polyethylene glycol monomethyl ether (MeO-PEG)] which serves a dual role as both a terminal protecting group and a solublizing agent for any compound(s) synthesized on the support. Using this approach, we have synthesized combinatorial peptide, small molecule,[4] and peptidomimetic libraries.[5]

The ligand-accelerated catalytic (LAC) asymmetric dihydroxylation (AD) of olefins based on cinchona alkaloid ligands was described by Sharpless in 1988;[6] since this seminal report, the AD reaction has been further developed to include application to a wider range of olefins, improved enantiomeric efficiency, and overall simplicity of operation.[7] From the standpoint of cost, ligand and/or metal recovery and recycling are of prime interest because the cinchona alkaloid ligand and osmium tetroxide are the most expensive components of the procedure. In this regard, several groups have reported the catalytic asymmetric dihydoxylation of olefins using insoluble polymer bound cinchona alkaloid-ligands.[8] While it was hoped that this methodology would provide convenience and improve the economics of the process, it was deemed less than satisfactory because of increased reaction times, highly variable yields, and lower enantioselectivity[9] than had previously been obtained with its solution phase counterpart.

The problems associated with LAC in which the ligand is localized by attachment to an insoluble polymer can be understood by considering the basic tenet upon which this concept is based.[10] By definition, the LAC phenomenon requires that the addition of a ligand increases the reaction rate of an already existing catalytic transformation. Both the ligand-accelerated and the nonaccelerated reactions operate in solution simultaneously and in competition with each other. Obviously, if the ligand does not have equivalent access to all the reaction compartments where the substrate, metal oxidant, and olefin reside, the most fundamental requirement for a successful ligand accelerated catalysis scenario is not met. For the present case, this means that the chiral ligand resides only in the insoluble phase, while the OsO_4 and olefin are in solution and free to react anywhere. In this situation the optimal LAC conditions can probably never be achieved even when using a large excess of the insoluble polymer-bound ligand.[9]

In an effort to circumvent the problems observed with insoluble supports and LAC, yet provide the economical and physical advantages (product isolation and reagent recovery) that a polymeric support can offer, we have investigated the potential of applying the soluble homopolymer MeO-PEG as a suitable scaffold for the AD reaction. We report here the synthesis of polyethylene glycol monomethyl ether bound cinchona alkaloid ligands (Figure 1) and their successful use in the LAC asymmetric dihydoxylation reaction of various olefins.

The synthesis of the MeO-PEG-bound dihydroquinidine ligands is depicted in Scheme 1. The commercially available hydroquinidine **5** was acylated using glutaric anhydride and 4-*N*,*N*′-dimethylaminopyridine (DMAP) to provide carboxylic acid **6**. This reaction, though simple, provides the linking unit necessary for attachment to the homopolymer MeO-PEG or any other amino or alcohol group. The coupling of acid **6** to polyethylene glycol monomethyl ether and ethyl alcohol in the presence of dicyclohexylcarbodiimide and DMAP produced the homopolymer **2** and its simple diester homologue **3**, respectively.

The chiral homopolymer **2** was the archetype used to examine and compare all of the AD reactions investigated. The structural similarity of **2** to the insoluble acrylonitrile ligand **1** allowed for a direct comparison between soluble and insoluble supports to be made,[8a] while contrasting the reactivity of ligands **2**, **3**, and **4** in the AD reaction would delineate any effect that the polyethylene glycol backbone may have on asymmetric induction. In addition, to standardize the comparisons between our soluble ligand support and the insoluble ligand support, we used the same conditions as reported for the **1**-AD catalytic reaction.[8a]

The MeO-PEG-supported catalyst **2** is completely soluble in an acetone−water mixture (v/v = 10/1); thus the catalytic reaction is completely homogeneous. Of greater note is that the reaction is complete within the same time frame as that of its solution counterpart with no decrease of yields or enantioselectivity (Table 1). For this methodology to be useful, product isolation,

* To whom correspondence should be addressed.

(1) (a) Pittman, C. U. *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon Press: Oxford, 1982. (b) Mathur, N. C.; Narang, C. K. Williams, R. E. *Polymers as Aids in Organic Chemistry*; Academic Press: New York, 1980. (c) Frechet, J. M. J. *Tetrahedron* **1981**, *37*, 663. (d) *Syntheses and Separations Using Functionalized Polymers*; Sherrington, D. C., Hodge, P., Eds.; Wiley: New York, 1988. (e) Bergbreiter, D. E.; Blanton, J. R.; Chandran, R.; Hein, M. D.; Huang, K.-J.; Treadwell, D. R.; Walker, S. A. *J. Polym. Sci., Polym. Chem. Ed.* **1989**, *27*, 4205.

(2) Barany, G.; Merrifield, R. B. In *The Peptides*, Gross, E., Meienhofer, J., Eds.; Academic Press: New York, 1979; Vol. 2, p 1.

(3) (a) Bayer, E.; Schurig, V. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 493. (b) Bayer, E.; Schurig, V. *CHEMTECH* **1976**, *6*, 212. (c) Bergbreiter, D. E. *ACS Symposium Series* **1986**, *308*, 17. (d) Bergbreiter, D. E.; Chandran, R. *J. Am. Chem. Soc.* **1987**, *109*, 174. (e) Bergbreiter, D. E. *CHEMTECH* **1987**, *17*, 686. (f) Phelps, J. C.; Bergbreiter, D. E. *Tetrahedron Lett.* **1989**, *30*, 3915. (g) Bergbreiter, D. E.; Walker, S. A. *J. Org. Chem.* **1989**, *54*, 2726. (i) Bergbreiter, D. E.; Morvant, M.; Chen, B. *Tetrahedron Lett.* **1991**, *32*, 2731. (j) Doyle, M. P.; Eismont, M. Y.; Bergbreiter, D. E.; Gray, H. N. *J. Org. Chem.* **1992**, *57*, 6103. (k) Bergbreiter, D. E.; Zhang, L.; Mariagnanam, V. M. *J. Am. Chem. Soc.* **1993**, *115*, 9295.

(4) Han, H.; Wolfe, M. M.; Brenner, S.; Janda, K. D. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 6419.

(5) Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 2539.

(6) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.

(7) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *116*, 2483.

(8) (a) Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett.* **1990**, *31*, 3003. (b) Pini, D.; Petri, A.; Nardi, A.; Rosini, C.; Salvadori, P. *Tetrahedron Lett.* **1991**, *32*, 5175. (c) Lohray, B. B.; Thomas, A.; Chihari, P.; Ahuja, J. R.; Dhal, P. K. *Tetrahedron Lett.* **1992**, *33*, 5453. (d) Pini, D.; Petri, A.; Salvadori, P. *Tetrahedron: Asymmetry* **1993**, *4*, 2351. (e) Lohray, B. B.; Nandanan, E.; Bhushan, V. *Tetrahedron Lett.* **1994**, *35*, 6559. (f) Pini, D.; Petri, A.; Salvadori, P. *Tetrahedron* **1994**, *50*, 11321. (g) Pini, D.; Petri, A.; Salvadori, P. *Tetrahedron Lett.* **1995**, *36*, 1549. (h) Sung, E. C.; Roh, E. J.; Lee, S.-G.; Kim, I. O. *Tetrahedron: Asymmetry* **1995**, *6*, 2687.

(9) A recent report by Salvadori and co-workers describes an insoluble support that provides improved enantioselectivity. However, their system still required long reaction times (24 h) and excess of polymeric ligand. Furthermore, reaction yields were lower than observed under homogeneous reaction conditions. Petri, A.; Pini, D.; Rapaccini, S.; Salvadori, P. *Chirality* **1995**, *7*, 580.

(10) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1059.

S0002-7863(96)00809-8 CCC: $12.00

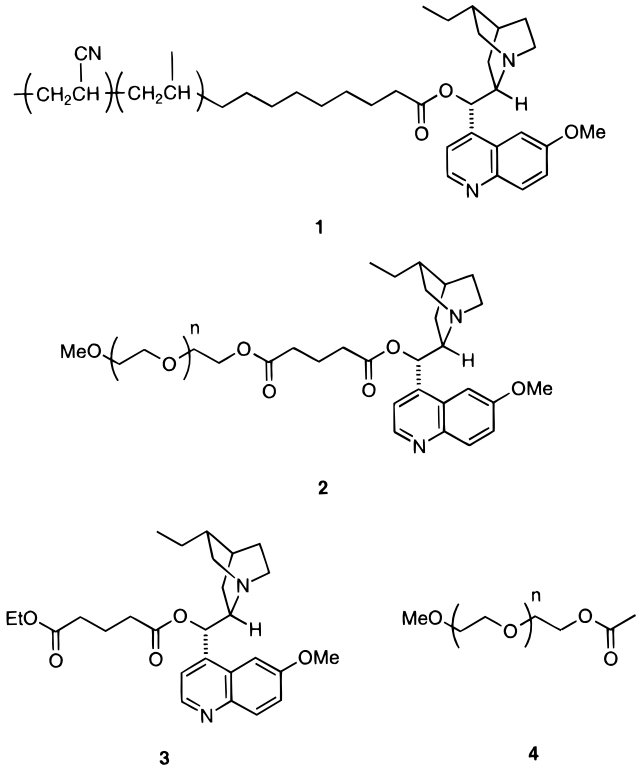
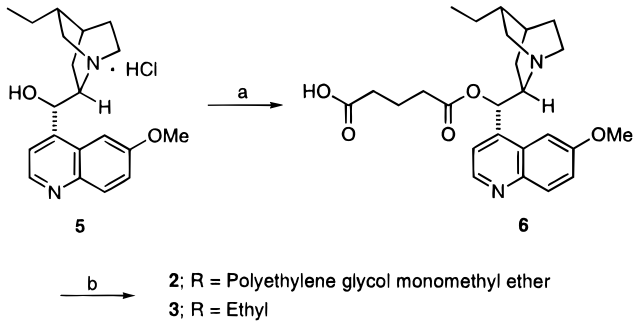


Figure 1. Various asymmetric dihydroxylation ligands.

Scheme 1[a]

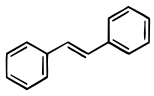
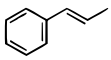
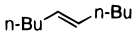


[a] (a) TEA, DMAP, glutaric anhydride (60%); (b) DCC, DMAP, ROH (95%).

separation, and recovery of the polymer bound ligand must be straightforward and reliable. Upon completion of the AD reaction, the entire mixture was diluted with methylene chloride, dried (anhydrous sodium sulfate), and filtered. Diethyl ether was added to the resulting mixture in order to precipitate MeO-PEG-bound ligand (typically, the MeO-PEG-bound ligand was recovered in >98% yield). The filtrate contained the dihydroxylated product.

The asymmetric dihydroxylation of a variety olefins by ligands **1**−**4** is shown in Table 1. Immediately evident is the fact that MeO-PEG-bound ligand **2** is more efficient than the insoluble polymer bound ligand **1**, both in its enantioselectivity and reactivity (entries 1 and 2, Table 1). What is more, the polymer-bound ligand **2** is easily recovered in near quantitative fashion and recycled several times with no loss of reaction yield or enantioselectivity (entry 3, Table 1). With all four olefins tested, MeO-PEG-bound ligand **2** was as effective as free ligand **3** (compare entries 2 and 4, entries 6 and 7, entries 8 and 9, and entries 10 and 11). These findings strongly suggest that the MeO-PEG backbone does not influence or affect the observed asymmetric induction (entry 5). Furthermore, these findings provide direct support for our notion that for successful polymer-bound LAC all components involved in the reaction must be able to interact freely with each other in solution.

Table 1. Comparison of Catalytic Asymmetric Dihydroxylations Using Ligands 1−4[a]

Entry	Ligand	Olefin	Reaction Time	Yield (%)	ee (%)
1	**1**		48 h	87	82[b]
2	**2**		5 h	89	88
3	**2**[c]		5 h	87	87
4	**3**		5 h	89	88
5	**4**		5 h	5	0
6	**2**		5 h[d]	80	60
7	**3**		5 h[d]	80	60
8	**2**		5 h[d]	80	84
9	**3**		5 h[d]	80	85
10	**2**		10 h[d]	62	42
11	**3**		10 h[d]	65	43

[a] See 8a and references contained within for experimental details. General conditions employed, *N*-methylmorpholine-*N*-oxide and acetone/water (10/1, v/v) were used as the solvent system. [b] Results from ref 8a. [c] Entry two (2) was recycled a total of five times, the average yield and ee for these five runs is listed here. [d] Slow addition time for the olefin.

In summary, we have demonstrated how a chiral ligand can be integrated into a soluble polymeric species so that LAC can operate in an unhindered manner on a polymer support. The soluble polymer-bound ligand provides all the advantages that an insoluble support can offer, while also being as effective as a free ligand both in reactivity and selectivity. This new soluble polymer bound-ligand system should be applicable to other classes of AD ligands[11] for improved enantioselectivity[7] as well as other enantioselective catalytic processes.[12] We believe the MeO-PEG polymer will not only be useful to the research chemist but also for effecting the separation of catalyst from product in homogeneous industrial applications.[13] Finally because of its desirable physical properties, this and other ligand accelerated catalysts that are incorporated within liquid phase supports may find use in automated high through-put synthetic efforts.[14]

Acknowledgment. We thank Professor K. B. Sharpless for his helpful suggestions and critical reading of the manuscript. This work was supported in part by The R. W. Johnson Pharmaceutical Research Institute, The Scripps Research Institute, The Skaggs Institute of Chemical Biology, and the A. P. Sloan Foundation.

Supporting Information Available: Synthetic details and spectral data for compounds **2**, **3**, and **6** and the general procedure for the asymmetric dihdroxylation reaction (4 pages). See any current masthead page for ordering and Internet access instructions.

JA9608095

(11) The $(DHQD)_2$-PHAL ligand has been appended to MeO-PEG; this new liquid phase ligand provides significantly greater enantioselectivity (Han, H.; Janda, K. D. Unpublished results).

(12) (a) Takaya, H.; Ohta, T.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Inoue, S.; Kasahara, I.; Nayori, R. *J. Am. Chem. Soc.* **1987**, *109*, 1596. (b) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801. (c) Lowenthal, R. E.; Masasmune, S. *Tetrahedron Lett.* **1991**, *32*, 7373. (d) Li, Z.; Cosner, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326. (e) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D.M. *J. Am. Chem. Soc.* **1993**, *115*, 5328. (f) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: Weinheim, 1993; pp 103−158. (g) Jacobsen, E. N. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: Weinheim, 1993; pp 159−202. (h) Li, G; Chang, H.-T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 451.

(13) (a) Steckhan, E.; Herrmann, S.; Ruppert, R.; Thommes, J.; Wandrey, C. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 388. (b) Herrmann, W. A.; Kohlpaintner, C. W. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1524. (c) Bergbreiter, D. E.; Zhang, L.; Mariagnanam, V. M. *J. Am. Chem. Soc.* **1993**, *115*, 9295. (d) Horvath, I. T.; Rabai, J. *Science* **1994**, *266*, 72.

(14) (a) Frisbee, A. R.; Nantz, M. H.; Kramer, G. W.; Fuchs, P. L. *J. Am. Chem. Soc.* **1984**, *106*, 7143. (b) Sabadosa, G. J.; Fuchs, P. L.; Kramer, G. W. *Lab. Rob. Automation* **1989**, *1*, 265. (c) Dewitt, S. H.; Czarnik, A. W. *Current Opin. Biotech.* **1995**, *6*, 640.