Pergamon

Tetrahedron Letters, Vol. 38, No. 9, pp. 1527-1530, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00129-9

A Soluble Polymer-Bound Approach to the Sharpless Catalytic Asymmetric Dihydroxylation (AD) Reaction: Preparation and Application of a [$(DHQD)_2$PHAL-PEG-OMe] Ligand

Hyunsoo Han and Kim D. Janda*
The Scripps Research Institute
Department of Chemistry and The Skaggs Institute for Chemical Biology
10550 North Torrey Pines Road
La Jolla, CA 92037

Abstract: The synthesis of a soluble polymer-bound $(DHQD)_2$PHAL ligand **1** and its successful application in the catalytic asymmetric dihydroxylation reaction are described. The results highlight that the soluble polymer-bound ligand approach offers all the benefits associated with insoluble supports but with the key advantages of increased reactivity and enantioselectivity inherent with solution-phase methodology. © 1997 Elsevier Science Ltd. All rights reserved.

Since its discovery in 1988,[1] Sharpless' catalytic asymmetric dihydroxylation (AD) of olefins has been continuously refined by both a development of better ligands and improvements in the secondary oxidant/solvent system.[2] In parallel, Sharpless[3] and other groups[4] have investigated immobilization of these expensive ligands onto insoluble polymer supports so as to aid in their recovery. While this strategy provides a simple but elegant way for automating the AD reaction, it has a number of limitations including prolonged reaction times and, more importantly, a reduction in enantioselectivity.

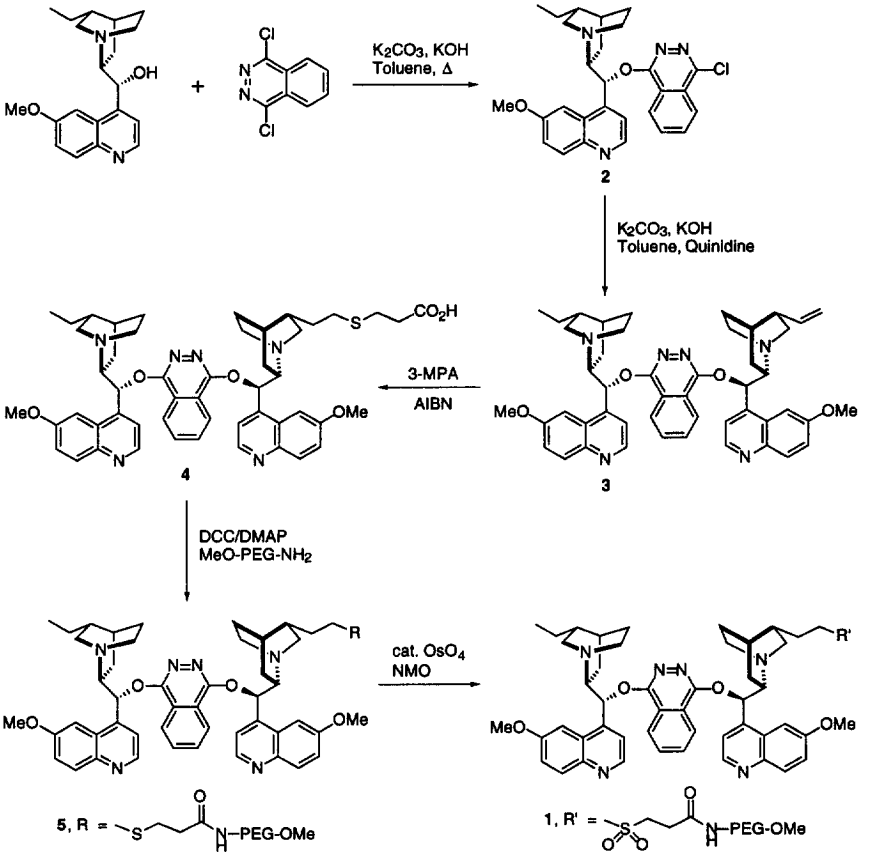
In an effort to circumvent the problems associated with heterogeneous reactions, we recently reported a homogeneous extention to the AD reaction using a soluble polymer, poly(ethylene glycol) mono-methyl ether (MeO-PEG), bound cinchona alkaloid ligand.[5] This liquid-phase methodology[6] provided all of the advantages that an insoluble polymer has to offer, while also being as effective as the free ligand in terms of both reactivity and enantioselectivity. However, in our preliminary report, the ligand utilized was not the most effective in terms of enantioselectivity and reactivity for the solution-phase AD reaction. Therefore in an attempt to improve our liquid-phase approach to the AD reaction we now report the synthesis of a $(DHQD)_2$PHAL ligand bound to MeO-PEG-NH_2 and its successful use in the AD reaction of various olefins.

The five step synthetic route to **1** is outlined in Scheme 1.[7] In the first step, a mixture of dihydroquinidine, 1,4-dichlorophthalazine, KOH, and K_2CO_3 in dry toluene are refluxed, with a concurrent azeotropic removal of water, to give the mono-substituted chlorophthalazine **2** which upon similar transformation with quinidine provided the di-substituted phthalazine **3**.[8] The heating of **3** and 3-mercaptopropionic acid (3-MPA) in the presence of 2,2'-azobisisobutyronitrile (AIBN) in benzene (70 °C) allowed the isolation of **4** as a tan precipitate.[9] The acid **4** was coupled to MeO-PEG-NH_2 in the presence of N,N- dimethylaminopyridine (DMAP) and 1,3-dicyclohexylcarbodiimide (DCC) in methylene chloride (DCM).[10] After the reaction was complete, the insoluble urea side-product was removed by filtration and the pegylated ligand **5** was isolated from the reaction mixture by precipitation following a slow addition of diethyl

ether. The sulfide **5** was oxidized to the desired sulfone **1** by a mixture of OsO_4/*N*-methylmorpholine-*N*-oxide (NMO) [in acetone/water (v/v, 2/1)].[11]

Ligand **1** was completely soluble either in *t*-butanol/water or acetone/water solvent systems allowing the study of homogeneous AD reactions. The AD reaction results of **1** with various olefins are shown in Table 1 and a number of features are noteworthy. First, it is evident that the *t*-Butanol/water solvent produces considerably higher *ees* for all olefins tested consistent with previous reports.[4] Second, in terms of both reaction time and enantioselectivity, ligand **1** accelerated AD reactions are comparable to its free ligand counterpart, strongly suggesting that the MeO-PEG backbone does not adversely alter either asymmetric induction or the rate of formation of the osmium-ligand-olefin ternary complex. Finally, the ligand **1** can be isolated in virtually quantitative yield by precipitation using diethyl ether.[5]

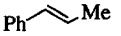
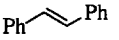
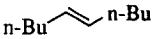
Scheme 1



Combined with our previous report,[5] the present results demonstrate that MeO-PEG bound ligands behave in a similar fashion to unimmoblized ligands in the AD reaction. What makes this finding even more

impressive is that this soluble polymer approach provides the added convenience of ligand recovery and product isolation. We believe that this methodology for ligand/catalyst recovery should be useful and applicable to other catalytic reactions and will be reported in due course.

Table 1. Catalytic Asymmetric Dihydroxylation Reactions using Ligand **1**.[a]

Entry	Olefin	Oxidant	Yield (%)	*ee* (%)
1		NMO	87	72
2		K_3FeCN_6	88	98 (97)[b]
3		NMO	87	91
4		K_3FeCN_6	83	99 (99)[b]
5		NMO	98	94
6		K_3FeCN_6	95	99 (>99)[b]
7		NMO	84	80
8		K_3FeCN_6	80	97 (97)[b]

[a]For NMO system, the molar ratio of olefin/OsO_4/ligand = 1/0.04/0.1, and for K_3FeCN_6 system, the molar ratio was 1/0.005/0.1. For other details, see references 3 and 5. [b]Number in parenthesis represents results for a free ligand $(DHQD)_2PHAL$ from reference 12.

Acknowledgements This work was supported in part by the R. W. Johnson Pharmaceutical Research Institute and The Skaggs Insitute for Chemical Biology at The Scripps Research Insitute.

References and Notes

1. Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.
2. For review, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *116*, 2483. Becker, H.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 448 and references therein.
3. Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett.*. **1990**, *31*, 3003.
4. (a) 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. (g) Petri, A.; Pini, D.; Rapaccini, S.; Salvadori, P. *Chirality* **1995**, *7*, 580. (h) Song, C. E.; Yang, J. W.; Ha, H. J.; Lee S. G. *Tetrahedron: Asymmetry* **1996**, *7*, 645.
5. Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 7632.

6. (a) Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 2539. (b) Han, H.; Janda, K. D. *Methods in Enzymology* **1996**, *267*, 234. (c) Han, H.; Wolfe, M. M.; Brenner, S.; Janda, K. D. *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 6419.

7. **2**: ^{1}NMR (300 MHz, $CDCl_3$) δ 0.91 (t, J = 6.7 Hz, 3H), 1.40-1.70 (m, 6H), 1.77 (m, 1H), 2.12 (m, 1H), 2.65-3.00 (m, 4H), 3.43-3.58 (m, 1H), 3.99 (s, 3H), 7.27 (d, J = 7.0 Hz, 1H), 7.34 (dd, J = 9.3 & 2.8 Hz, 1H), 7.44 (d, J = 4.5 Hz, 1H), 7.62 (d, J = 2.7 Hz, 1H), 7.96 (d, J = 9.2 Hz, 1H), 8.00 (m, 2H), 8.13-8.20 (m, 1H), 8.33-8.42 (m, 1H), 8.64 (d, J =4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.9, 23.5, 25.4, 26.1, 27.1, 37.3, 49.9, 50.9, 55.5, 59.9, 101.7, 118.5, 121.4, 121.8, 122.8, 122.9, 125.3, 127.7, 128.2, 131.6, 133.0, 133.3, 144.0, 144.7, 147.0, 147.2, 150.5, 157.7; HRMS (FAB^+) calcd for [$C_{28}H_{29}ClN_4O_2$ + H^+] = 489.2057, found = 489.2051.
3: ^{1}NMR (300 MHz, $CDCl_3$) δ 0.78 (t, J = 6.7 Hz, 3H), 1.20-1.65 (m, 10H), 1.68 (m, 1H), 1.85-2.30 (m, 3H), 2.55-3.00 (m, 8H), 3.39 (m, 2H), 3.88 (s, 6H), 4.97 (m, 2H), 5.90 (m, 1H), 6.95 (d, J = 6.5 Hz, 1H), 7.01 (d, J = 5.9 Hz, 1H), 7.34 (m, 2H), 7.40 (d, J = 4.6 Hz, 1H), 7.42 (d, J = 4.6 Hz, 1H), 7.52 (d, J = 2.7 Hz, 1H), 7.54 (d, J = 2.6 Hz, 1H), 7.91 (m, 2H), 7.96 (d, J = 9.2 Hz, 1H), 7.97 (d, J = 9.2 Hz, 1H), 8.31 (m, 2H), 8.61 (d, J = 4.5 Hz, 1H), 8.62 (d, J = 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.8, 23.2, 23.4, 25.2, 26.0, 26.2, 26.4, 27.2, 27.7, 37.3, 39.6, 49.4, 49.8, 49.9, 50.8, 55.5, 60.0, 60.2, 76.0, 77.2, 101.9, 102.0, 114.6, 118.2, 118.4, 121.7, 121.8, 122.3, 122.7, 123.0, 127.3, 128.1, 129.0, 131.4, 131.5, 132.0, 132.1, 140.3, 144.6, 144.8, 144.9, 147.3, 156.3, 156.4, 157.5, 157.6; HRMS (FAB^+) calcd for [$C_{48}H_{52}N_6O_4$ + H^+] = 777.4128, found 777.4104.
4: ^{1}NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 6.7 Hz, 3H), 1.25-3.25 (m, 30H), 3.50 (m, 2H), 3.89 (s, 3H), 3.97 (s, 3H), 6.60 (broad s, 1H), 7.30 (m, 3H), 7.44 (t, J = 4.4 Hz, 2H), 7.49 (broad s, 1H), 7.53 (d, J = 2.3, 1H), 7.63 (d, J = 2.4 Hz, 1H), 7.88 (m, 2H), 7.95 (d, J = 9.2 Hz, 1H), 7.96 (d, J = 9.2 Hz, 1H), 8.19 (d, J = 8.1 Hz, 1H), 8.27 (d, J = 7.7 Hz, 1H), 8.59 (d, J = 4.6 Hz, 1H), 8.64 (d, J = 4.5 Hz, 1H); HRMS (FAB^+) calcd for [$C_{51}H_{58}N_6O_6S$ + H^+] = 883.4216, found 883.4242.
5: ^{1}NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 6.7 Hz, 3H), 1.25-2.85 (m, 30H), 3.20-3.75 (PEG peaks), 3.84 (t, J = 6.5 Hz, 2H), 3.88 (s, 6H), 6.59 (broad t, 1H), 6.90 (d, J = 6.6 Hz, 1H), 6.97 (d, J = 5.7Hz, 1H), 7.30 (dd, J = 9.2 & 2.4 Hz, 1H), 7.32 (dd, J = 9.0 & 2.4 Hz, 1H), 7.39 (t, J = 4.6 Hz, 2H), 7.47 (d, J = 2.5 Hz, 1H), 7.51 (d, J = 2.5 Hz, 1H), 7.90 (m, 2H), 7.93 (d, J = 9.0 Hz, 1H), 7.94 (d, J = 9.2 Hz, 1H), 8.28 (m, 2H), 8.59 (d, J = 4.5 Hz, 2H).
1: ^{1}NMR (300 MHz, $CDCl_3$) δ 0.79 (3H), 1.10-3.00 (30H), 3.10-3.80 (PEG peaks), 3.80-4.00 (8H), 6.70 (1H), 6.95 (1H), 7.05 (1H), 7.20-7.45 (7H), 7.50 (1H), 7.80-8.10 (4H), 8.28 (1H), 8.37 (1H), 8.55 (2H). Peak mutiplicity was not further characterized due to line-broadening.

8. (a) Amberg, W.; Bennani, Y. L.; Chadha, R. K.; Crispino, G. A.; Davis, W. D.; Hartung, J.; Jeong, K. S.; Ogino, Y.; Shibata, T.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 844. (b) Lohray, B. B.; Nandanan, E.; Bhushan, V. *Tet. Lett.* **1994**, *35*, 6559.

9. Inagaki, M.; Hiratake, J.; Yamamoto, Y.; Oda, J. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4121.

10. Pillai, V. N. R.; Mutter, M. *J. Org. Chem.* **1980**, *45*, 5364.

11. Kaldor, S. W.; Hammond, M. *Tetrahedron. Lett.* **1991**, *32*, 5043.

12. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M.; Xu, D.; Zhang, X. L. *J. Org. Chem.* **1992**, *57*, 2768.

(*Received in USA* 19 *December* 1996; *revised* 15 *January* 1997; *accepted* 16 *January* 1997)