# Osmylated Macroporous Cinchona Alkaloid Resins: Highly Efficient and Recyclable Catalysts for Asymmetric Dihydroxylation of Olefins†

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A simple method for simultaneous recovery and reuse of $OsO_4$ and alkaloid ligand in the asymmetric dihydroxylation of olefins has been developed by using macroporous alkaloid resins bearing residual vinyl groups.

**Key Words :** Asymmetric dihydroxylation, Macroporous alkaloid resins, Recycling of osmium and ligand

## Introduction

Today, due to increasingly stringent environmental and social regulations, the international chemistry community is under increasing pressure to change current working practices and to find greener and safer alternatives, *i.e.* chemical manufacturers should develop such processes that produce less waste and avoid, as much as possible, the use of toxic and/or hazardous reagents.

The Sharpless Os-catalyzed asymmetric dihydroxylation (AD) of olefins provides one of the most elegant methods of synthesizing chiral vicinal diols.[1] Although the AD reaction offers a number of processes that could be applied to the synthesis of chiral drugs, natural products and fine chemicals, the high cost of osmium and the chiral ligands as well as the high toxicity and volatility of the osmium component have made large-scale industrial applications with these reagents difficult. In order to overcome the above-mentioned problems, several attempts to immobilize this catalytic system have been made.[2-4] Early attempts to immobilize $OsO_4$ on solid-supported alkaloid ligands failed due to severe osmium leaching.[2] Recently, alternative methods of immobilizing the osmium catalyst by microencapsulation of $OsO_4$ in a polymer matrix[3] and using an ion-exchange technique[4] have been reported. Although recycle experiments using this type of immobilized osmium catalysts have been successfully performed for several times, higher loading (1-5 mol%) of immobilized osmium catalyst was generally required than that needed in homogeneous reactions. Thus, there is still a demand driven by economic and environmental considerations, to develop a more efficient and simple immobilization method for recovery and reuse of both catalytic components.

In searching for a more efficient heterogeneous catalytic system for AD reactions, we recently found that $OsO_4$ could be simply immobilized onto resins such as Amberlite XAD-4 or XAD-7 bearing residual vinyl groups (Figure 1).[5] The resulting osmylated resins were air-stable, nonvolatile and much easier to handle than their homogeneous counterpart ($OsO_4$). Moreover, the resin-bound $OsO_4$ exhibited excellent catalytic activity in the asymmetric dihydroxylation of olefins, and was easily recovered and reused in consecutive reactions without any decrease in product yield. Although this approach is highly efficient for recycling of the osmium component, the extra acid-base work-up procedure is needed to recover the alkaloid ligand, which makes the process (especially on a large scale) very tedious. Thus, it would be desirable to develop an immobilization method for simultaneous recovery and reuse of both catalytic components (osmium and alkaloid ligand).

We now report here that the macroporous cinchona alkaloid resin **1** bearing residual vinyl groups (Figure 2)

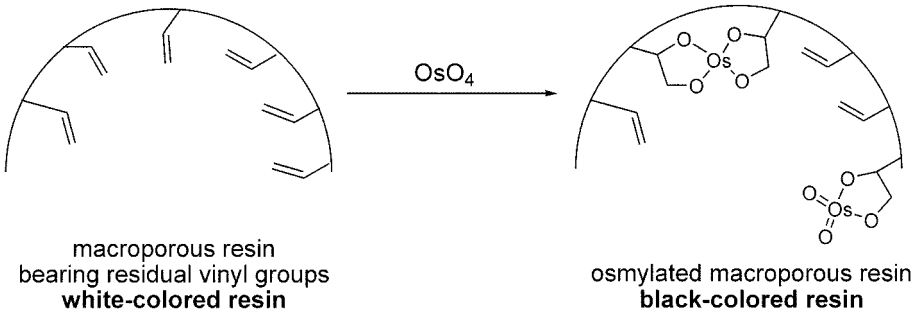


**Figure 1**.

†Dedicated to Professor Yong Hae Kim for his distinguished achievements in organic chemistry.
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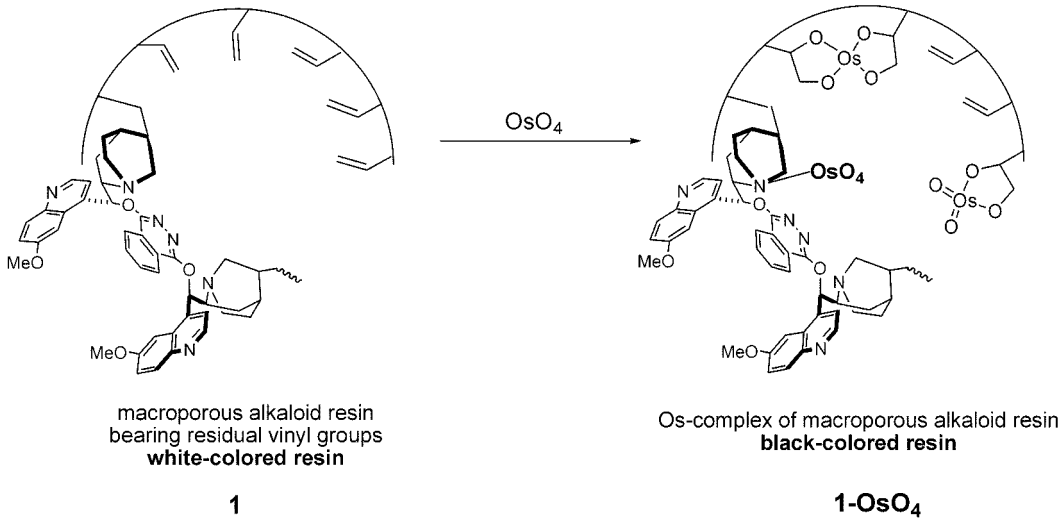



**Figure 2**.

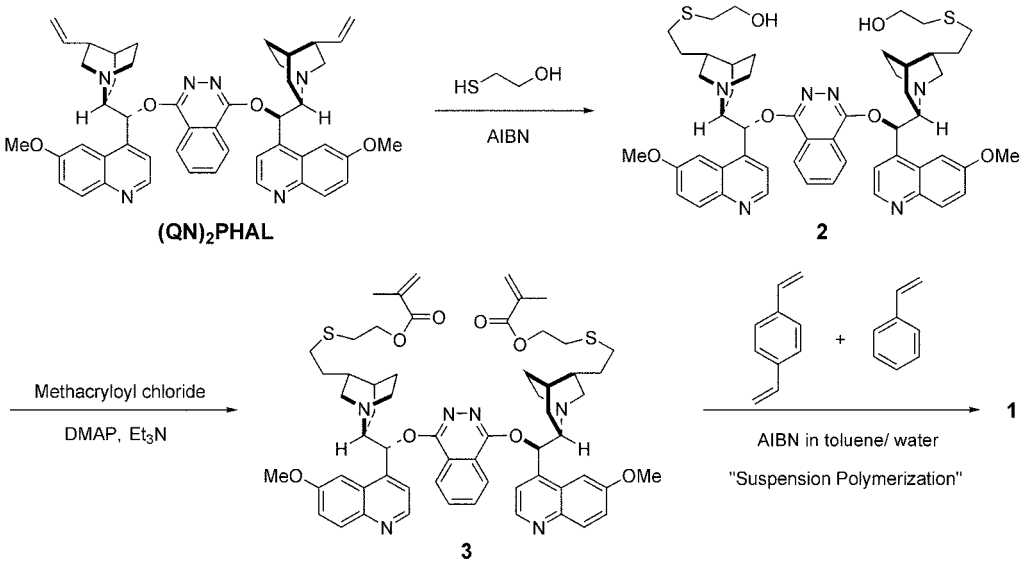
exhibited excellent degree of activity and enantioselectivity (up to 99% ee) in heterogeneous Os-catalyzed asymmetric dihydroxylation reactions. Moreover, both catalytic components (*i.e.*, Os-complex of **1**) could be simultaneously recovered by simple filtration and reused several times without any significant loss of catalytic efficiency.

## Results and Discussion

The macroporous alkaloid resin **1** was synthesized by the route depicted in Scheme 1. Radical reaction of $(QN)_2PHAL$[6] with 2-mercaptoethanol in the presence of AIBN, followed by the reaction of the resulting functionalized $(QN)_2PHAL$ **2** and methacryloyl chloride in the presence of $Et_3N$ and DMAP afforded the monomeric alkaloid moiety **3**. The monomeric moiety **3** was then copolymerized with styrene and divinylbenzene in the presence of AIBN under the typical suspension polymerization conditions, under which 50 mol% of divinylbenzene was used to increase the content of residual vinyl groups. The resulting macroporous alkaloid resin **1** was then continuously extracted in a Soxhlet device with THF for 48 h to remove unreacted alkaloid monomer **3**. Nitrogen analysis of **1** indicated that 0.35 mmol/g of the monomeric moiety were incorporated. The content of active vinyl groups in the resin **1** was also determined by mercury acetate titration method (0.62 mmol/g of active vinyl groups).

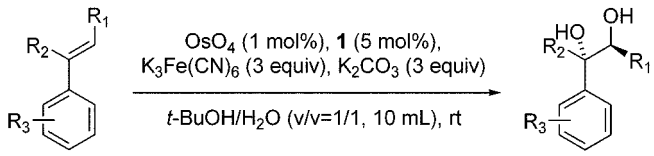
To investigate catalytic performance of the macroporous alkaloid resin **1**, the ADs of various olefins were carried out under the standard $K_3Fe(CN)_6$ conditions.[7] As shown in Table 1, in all cases, the desired diols were obtained in similar yields and enantioselectivities to those obtained in the homogeneous conditions.

Encouraged by these promising results, we next examined the recyclability of both catalytic components. After each reaction, the black colored Os-complex of alkaloid resin **1**




**Scheme 1**

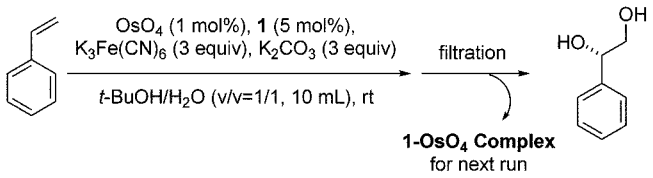
**Table 1**. Asymmetric dihydroxylation of olefins using polymer-supported ligand/$OsO_4$ complex[a]




| Entry | Olefins | Time (h) | Yield (%)[b] | Ee (%)[c] |
|---|---|---|---|---|
| 1 | Styrene | 1 | 92 | 90 |
| 2 | α-Methylstyrene | 3 | 90 | 82 |
| 3 | 1-Phenylcyclohexane | 4.5 | 85 | 90 |
| 4 | *trans*-Stilbene | 12 | 90 | 99 |
| 5 | Methyl *trans*-cinnamate | 5 | 91 | 99 |
| 6 | Methyl *trans*-(4-methoxy) cinnamate | 7 | 92 | 99 |

[a]All reactions were carried out on 1 mmol reaction scale of olefins using 1 mol% of $OsO_4$, 5 mol% of alkaloid resin **1**, 3 equiv of $K_3Fe(CN)_6$ and 3 equiv of $K_2CO_3$ in the *t*-BuOH/$H_2O$ (v/v = 1/1, 10 mL) at rt. [b]Isolation yield. [c]Determined by chiral HPLC.

**Table 2**. Asymmetric dihydroxylation of styrene with recycled Os-complex of the macroporous alkaloid resin **1**[a]




| | 1st run | 2nd run | 3rd run | 4th run | 5th run |
|---|---|---|---|---|---|
| Time (h) | 2.5 | 2.5 | 5 | 12 | 24 |
| Yield (%)[b] | 92 | 88 | 86 | 81 | 80 |
| % Ee[c] | 90 | 90 | 90 | 90 | 90 |

[a]Recycle experiments were carried out on 1 mmol reaction scale of olefins using 1 mol% of $OsO_4$, 5 mol% of alkaloid resin **1**, 3 equiv of $K_3Fe(CN)_6$ and 3 equiv of $K_2CO_3$ in the *t*-BuOH/$H_2O$ (v/v = 1/1, 10 mL) at rt. After the first run, the recovered Os-complex of alkaloid ligand **1** was successively subjected to further catalytic reactions without any addition of Os-sources. [b]Isolation yield. [c]Determined by chiral HPLC.

was recovered by simple filtration, and the recovered resin was successively subjected to further catalytic reactions without any addition of Os-sources. As shown in Table 2, the recovered catalyst could be recycled for five times without any significant loss of yields and enantioselectivities. All these results indicated that osmium anchored to alkaloid resins was highly exposed to the oxidant, and once oxidized, it became free to react with other more readily accessible alkenes in solution. After starting alkenes are consumed, the residual $OsO_4$ may form new bonds with less accessible resin-bound vinyl groups. However, according to the ICP-analysis of the filtrate after each run, leaching of ca. 8-10% of Os into solution has been found, causing increased turnover time upon reuse.

In summary, we have developed a simple method for simultaneous recovery and reuse of $OsO_4$ and alkaloid ligand by using macroporous alkaloid resins **1** bearing residual vinyl groups. The macroporous alkaloid resins **1** exhibited excellent degree of activity and enantioselectivity (up to 99% ee) in Os-catalyzed asymmetric dihydroxylation reactions. Moreover, both catalytic components could be simultaneously recovered by simple filtration and reused several times without any significant loss of catalytic efficiency. Optimization studies on process conditions are currently in progress.

## Experimental Section

**General.** Chromatographic purification of products was carried out by flash chromatography using Merck silica gel 60 (230-400 mesh). Thin layer chromatography was carried out on Merck silica gel 60F plates. $^1$H NMR (300 MHz) spectra were recorded on a Brucker-Spectrospin 300 spectrometer using TMS as an internal standard. HPLC (High Performance Liquid Chromatography) analysis was performed by Agilent 1100 interfaced to a HP 71 series computer workstation. Osmium concentration was analyzed by ICP-AES (Jobin Yvon-2000). $OsO_4$ was purchased from Next Chimica, South Africa. Methyl *trans*-(4-methoxy)cinnamate was prepared by esterification of *trans*-(4-methoxy)cinnamic acid, while the other olefins were purchased from Aldrich. All other solvents and chemicals were obtained from commercial sources, and were used without further purification.

**Preparation of $(QN)_2PHAL$.**[6] To a 500 mL three-necked round bottom flask attached with a Dean-Stark condenser, quinine (26.40 g, 81.4 mmol), 1,4-dichlorophthalazine (8.10 g, 40.7 mmol) and potassium carbonate (16.87 g, 122.1 mmol) were dissolved and suspended in dry toluene (300 mL). After the two-hour reflux under nitrogen, potassium hydroxide (6.85 g, 122.1 mmol) pellets were added and the reaction mixture refluxed (with azeotropic removal of water) for an additional 12 h. The orange-colored reaction mixture was cooled to room temperature, mixed with water (100 mL), and then extracted with ethyl acetate. The organic layer was washed with water and brine and dried at reduced pressure to remove the solvent. To the residue was mixed diethyl ether and stirred. While stirring, white solid of 1,4-bis(9-*O*-quininyl)phthalazine was precipitated. After the precipitate was filtered, washed with $Et_2O$ and dried at reduced pressure, 23.7 g (30.6 mmol, 75% yield) of product was obtained.

m.p. 159-160 °C; $[\alpha]_D^{23}$ +348.4 (*c* 1.08, MeOH); $^1$H NMR (300 MHz; $CDCl_3$) $\delta$ 8.65 (d, *J* = 4.7 Hz, 2H), 8.31 (m, 2H), 7.99 (d, *J* = 10.0 Hz, 2H), 7.94 (m, 2H), 7.58 (d, *J* = 2.7 Hz, 2H), 7.44 (d, *J* = 5.3 Hz, 2H), 7.38 (d, *J* = 2.7 Hz, 1H), 7.35 (d, *J* = 2.7 Hz, 1H), 7.02 (d, *J* = 6.0 Hz, 2H), 5.83 (m, 2H), 4.99 (t, *J* = 10.0 Hz, 4H), 3.92 (s, 6H), 3.50 (m, 2H), 3.12 (m, 2H), 3.06 (d, *J* = 11.7 Hz, 1H), 3.01 (d, *J* = 11.0 Hz, 1H), 2.58 (m, 2H), 2.25 (bs, 2H), 1.82 (m, 12H), 1.49 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 157.91, 156.65, 147.64, 144.97, 144.91, 142.19, 132.55, 131.79, 127.43, 123.01, 122.67, 122.09, 118.67, 114.53, 102.09, 76.36, 60.30, 56.87, 55.77, 42.75, 39.97, 27.97, 27.79, 23.88; Anal. Calcd for $C_{48}H_{50}N_6O_4$: C, 74.39; H, 6.50; N, 10.84. Found: C, 74.3; H,

6.69; N, 10.5; HRMS (FAB) calcd for $C_{48}H_{51}N_6O_4$ ($M^+$) 775.3972, found 775.3973.

**Preparation of monomer 3.** $(QN)_2PHAL$ (10.0 g, 12.9 mmol), AIBN (1.0 g, 6.0 mmol) and 2-mercaptoethanol (10 mL, 139 mmol, 10.8 equiv) are dissolved in $CHCl_3$ (150 mL) under $N_2$ and was refluxed for 48 h and the resulting solution was acidified by HCl (2 N, 20 mL) and the water phase was separated. The separated aqueous layer was treated with NaOH pellet until the solution became basic and extracted with $CHCl_3$ (100 mL). After removing the solvent, the crude product was purified by chromatography on silica gel to give the **2** (7.17 g, 59%) as a white-yellow.

The functionalized $(QN)_2PHAL$ **2** (100 mg, 0.11 mmol), triethylamine (0.06 mL, 0.43 mmol), dimethylaminopyridine (0.1 mg, 0.0043 mmol, 2 mol%) were dissolved in $CHCl_3$ (5 mL) under nitrogen atmosphere with stirring, and 2-methacryloyl chloride (0.03 mL, 0.32 mmol) was added slowly at 0 °C, then stirred at rt for 24 h. The resulting solution was washed with a 10% aqueous solution of $NaHCO_3$ and dried. Purification by column chromatography provided the desired monomer **3**.

$^1$H NMR (300 MHz; $CDCl_3$) $\delta$ 8.62 (d, $J$ = 4.5 Hz, 2H), 8.30-8.34 (m, 2H), 7.95-7.98 (m, 4H), 7.57 (bs, 2H), 7.40 (d, $J$ = 4.5 Hz, 2H), 7.35 (dd, $J$ = 9.3, 2.1 Hz, 2H), 7.08 (bs, 2H), 6.06 (bs, 2H), 5.53 (bs, 2H), 4.24 (t, $J$ = 7.0 Hz, 4H), 3.90 (s, 6H), 3.46 (bs, 2H), 3.0-3.2 (m, 4H), 2.3-2.8 (m, 10H), 1.4-1.9 (m, 24H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 167.04, 157.85, 156.20, 147.16, 144.56, 144.15, 135.95, 132.43, 131.43, 127.04, 125.79, 122.69, 122.35, 121.99, 118.16, 101.81, 63.57, 59.75, 57.70, 55.81, 42.56, 34.49, 34.38, 30.43, 30.20, 27.94, 25.51, 24.61, 22.99, 18.19; HRMS (FAB) calcd for $C_{60}H_{70}N_6O_8S_2Na$ ($M^+$+Na) 1089.4594, found 1089.4574.

**Preparation of macroporous alkaloid resin 1.** Acacia (0.53 g) with $H_2O$ (240 mL) was stirred at 40 °C for 30 min to dissolve the acacia completely. To this solution, styrene (5.2 g, 49.9 mmol), divinylbenzene (7.2 g, 55.4 mmol), monomer **3** (5.91 g, 5.54 mmol), AIBN (0.11 g, 0.67 mmol) and toluene (70 mL) were added, and the resulting solution was stirred for 40 min at 40 °C and additionally stirred for 8 h at 80 °C. The produced resin **1** was filtered and washed thoroughly with $H_2O$ and methanol. The macroporous alkaloid resins **1** were then transferred to a Soxhlet thimble and extracted for 24 h using acetone to remove the unreacted alkaloid monomer **3**. Finally the resin **1** were dried under vacuum to produce a nearly quantitative yield of dry beads. Nitrogen analysis of **1** indicated that 0.35 mmol/g of the monomeric moiety were incorporated. The content of active vinyl groups in the resin **1** was also determined by mercury acetate titration (0.62 mmol/g of active vinyl groups): Elemental Analysis of **1**: C, 83.2; H, 7.4; N, 3.0.

**Analysis of the active vinyl group.** The macroporous alkaloid resin (**1**, 349 mg) was added into the aqueous mercury (II) acetate (0.05 M, 10 mL) and stirred for 1 h and additionally stirred for 10 min with NaCl (100 mg) and 3 drops of phenolphthalein solution was added and the resulting solution was titrated with NaOH (0.01 M, 22.2 mL) to show the vinyl contents (0.62 mmol/g).

**Typical procedure for AD reaction of olefins.** A mixture of macroporous alkaloid resin (**1**, 143 mg, 5 mol%), $OsO_4$ (0.24 mL of 1 wt% of aqueous solution, 1 mol%), $K_3Fe(CN)_6$ (988 mg, 3.0 mmol), $K_2CO_3$ (415 mg, 3.0 mmol) and styrene (162 mg, 1.0 mmol) in *t*-BuOH-$H_2O$ (v/v = 1:1, 10 mL) was stirred at room temperature. After completion of the reaction, the resin-catalyst was filtered and subsequently washed with *t*-BuOH-$H_2O$ (v/v = 1:1). Saturated aqueous sodium sulfite was added to the filtrate and the mixture was stirred for an additional hour. Organic product was extracted with ethyl acetate. After removing the solvent, the crude product was purified by chromatography on silica gel with EtOAc/hexane (1:1) to afford *cis*-diol. The recovered resins were reused for successive reactions without any addition of osmium source.

**Charaterization of products.** The following compounds are known compounds, and their NMR spectra are in accordance with those reported in the literature. The enantiomeric excess of the diols was determined by HPLC analysis with chiral stationary phases.

*1-Phenyl-1,2-ethanediol*. HPLC (Daicel Chiralcel OD-H, *i*-PrOH/hexane (v/v = 5:95), flow rate 0.5 mL min$^{-1}$): $t_R$ = 31.6 min (*R*-isomer), $t_R$ = 34.8 min (*S*-isomer).

*1-Phenyl-1,2-propanediol*. HPLC (Daicel Chiralcel OD, *i*-PrOH/hexane (v/v = 4.5:95.5), flow rate 0.75 mL min$^{-1}$): $t_R$ = 20.8 min (*R*,*R*-isomer), $t_R$ = 22.0 min (*S*,*S*-isomer).

*1-Phenyl-1,2-cyclohexanediol*. HPLC (Daicel Chiralcel OJ, *i*-PrOH/hexane (v/v = 8:92), flow rate 1.0 mL min$^{-1}$): $t_R$ = 11.2 (*S*,*S*-isomer), $t_R$ = 14.6 (*R*,*R*-isomer).

*1,2-Diphenyl-1,2-ethanediol*. HPLC (Chiralcel OJ, *i*-PrOH/hexane (v/v = 10:90), flow rate 1.0 mL min$^{-1}$): $t_R$ = 14.8 min (*S*,*S*-isomer), $t_R$ = 17.8 min (*R*,*R*-isomer).

*Methyl 2,3-dihydroxy-3-phenylpropionate*. HPLC (Daicel Chiralcel OJ, *i*-PrOH/hexane (v/v = 20:80), flow rate 1.0 mL min$^{-1}$): $t_R$ = 11.0 min (2*R*,3*S*-isomer), $t_R$ = 14.3 min (2*S*,3*R*-isomer).

*Methyl 2,3-dihydroxy-3-(4-methoxyphenyl)propionate*. HPLC (Daicel Chiralcel OJ, *i*-PrOH/hexane (v/v = 15:85), flow rate 0.5 mL min$^{-1}$): $t_R$ = 54.4 min (2*R*,3*S*-isomer), $t_R$ = 65.8 min (2*S*,3*R*-isomer).

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## References

1. For reviews: (a) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483-2547. (b) Beller, M.; Sharpless, K. B. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B.; Herrmann, W. A., Eds.; VCH: 1996; Vol. 2, pp 1009-1024. (c) Markó, I. E.; Svendsen, J. S. *Dihydroxylation of Carbon-Carbon Double Bonds* in *Comprehensive Asymmetric Catalysis II*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer Verlag: Berlin, 1999; Vol. 2, pp 713-787. (d) Johnson, R. A.; Sharpless, K. B. *Catalytic Asymmetric Dihydroxylation-Discovery and Development* in *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: 2000; pp 357-398. (e) Bolm, C.; Hildebrand, J. P.; Muniz, K. *Recent Advances in Asymmetric Dihydroxylation and Aminohydroxylation* in *Catalytic Asymmetric*

*Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: 2000; pp 399-428.
2. Reviews for solid-supported alkaloid ligands: For reviews: (a) Song, C. E.; Lee, S.-g. *Chem. Rev.* **2002**, *102*, 3495-3524. (b) Salvadori, P.; Pini, D.; Petri, A.; Mandoli, A. In *Chiral Catalyst Immobilization and Recycling*; De Vos, D. E. Vankelecom, I. F. J. Jacobs, P. A., Eds.; Wiley-VCH: 2000; pp 235-246. (c) Salvadori, P.; Pini, D.; Petri, A. *Synlett* **1999**, 1181-1190. (d) Bolm, C.; Gerlach, A. *Eur. J. Org. Chem*. **1998**, 21-27.
3. (a) Nagayama, S.; Endo, M.; Kobayashi, S. *J. Org. Chem*. **1998**, *63*, 6094-6095. (b) Kobayashi, S.; Endo, M.; Nagayama, S. *J. Am. Chem. Soc*. **1999**, *121*, 11229-11230. (c) Kobayashi, S.; Ishida, T.; Akiyama, R. *Org. Lett*. **2001**, *3*, 2649-2652.
4. (a) Choudary, B. M.; Chowdari, N. S.; Kantam, M. L.; Raghavan, K. V. *J. Am. Chem. Soc*. **2001**, *123*, 9220-9221. (b) Choudary, B. M.; Chowdari, N. S.; Jyothi, K.; Kantam, M. L. *J. Am. Chem. Soc*. **2002**, *124*, 5341-5349.
5. (a) Yang, J. W.; Han, H.; Roh, E. J.; Lee, S.-g.; Song, C. E. *Org. Lett*. **2002**, *4*, 4685; (b) Jo, C. H.; Han, S.-H.; Yang, J. W.; Roh, E. J.; Shin, U.-S.; Song, C. E. *Chem. Commun*. **2003**, 1312-1313.
6. Song, C. E.; Yang, J. W.; Ha, H. J.; Lee, S.-g. *Tetrahedron: Asymmetry* **1996**, *7*, 645-648.
7. (a) Kwong, H.-L.; Sorato, C.; Ogino, Y.; Chen, H.; Sharpless, K. B. *Tetrahedron Lett*. **1990**, *31*, 2999. (b) Minato, M.; Yamamoto, K.; Tsuji, J. *J. Org. Chem*. **1990**, *55*, 766-768.