

Silica Gel-Supported *Cinchona* Alkaloid-OsO₄ Complex for Catalytic Heterogeneous Asymmetric Dihydroxylation of Olefins by H₂O₂ using a Titanium Silicalite-Based Coupled Catalytic System

Boyapati M. Choudary,* Naidu S. Chowdari, Karangula Jyothi, Sateesh Madhi, Mannepilli L. Kantam

Inorganic and Physical Chemistry Divisions, Indian Institute of Chemical Technology, Hyderabad 500 007, India
Fax: (+91) 40-7160921, e-mail: choudary@iict.ap.nic.in

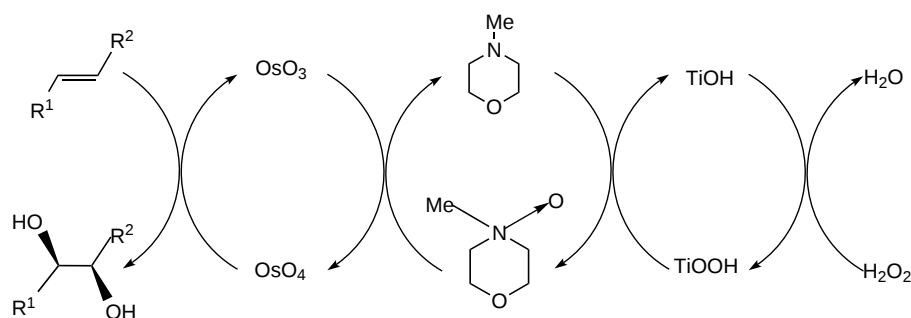
Received: March 11, 2002; Accepted: April 29, 2002

Abstract: A triple catalytic system designed for asymmetric dihydroxylation of olefins, composed of NMM and two divergent heterogeneous catalysts, titanium silicalite and silica gel-supported 1,4-bis(9-*O*-dihydroquinidiny)phthalazine [SGS-(DHQD)₂ PHAL]-OsO₄ complex relays the transport of two electrons from olefin to H₂O₂ used as a terminal oxidant to provide chiral diols with good yields and high enantiomeric excesses in a single pot.

Keywords: asymmetric synthesis; diols; immobilization; olefins; osmium; oxidation

Osmium-catalyzed asymmetric dihydroxylation (AD) of olefins provides one of the most elegant methods for the preparation of chiral vicinal diols, the key intermediates for many biologically active compounds.^[1] Heterogenization of the chiral ligands on various polymers^[2] and silica gel^[3] is undertaken in order to effect the easy recovery of the expensive ligands and to some extent OsO₄ after the reaction for reuse. Recently, osmium is immobilized on various supports based on microencapsulation^[4] and ion-exchange techniques^[5] to achieve complete recovery of osmium. Various cooxidants such as *N*-methylmorpholine *N*-oxide (NMO),^[6] potassium ferricyanide,^[7] and molecular oxygen^[8] are employed to reoxidize the osmium in AD reactions. However, each of these oxidants has its own disadvantages. For example, employing three molar equivalents of potassium ferricyanide per mole of the olefin in AD leaves a large amount of solid waste as effluent to render the process incompatible to the environment and possibly uneconomical for large-scale operations, while molecular oxygen gives lower ee's and yields. The use of NMO-based dihydroxylations is thus rejuvenated due to the easy adaptability for large-scale operations.^[6d, e] However, the use of expensive NMO in stoichiometric

amounts and the cumbersome procedures practiced for the recovery of the by-product, *N*-methylmorpholine and its reoxidation to NMO in separate units accrue additional costs to the process. The biomimetic approach to realize multi-step reactions, composed of multi-component systems in a single-pot synthesis, is an attractive strategy to achieve the ideal organic synthesis in terms of conservation of energy, abatement of pollutants, lowering the inventory of equipment and processing time.^[9] An interesting development was made by Backvall et al. in realizing a more highly economical process by using H₂O₂, the terminal oxidant, in molar equivalents and NMM in catalytic amounts to continuously generate NMO *in situ* via oxidation of the latter using biomimetic flavin as the electron transfer mediator in the multi-component catalytic system for AD reactions of olefins.^[10] However, the flavin is unstable and cannot be reused in the dihydroxylation process. Recently, we demonstrated the reoxidation of NMM to facilitate continuous *in situ* production of NMO to sustain the Os(VI)/Os(VIII) catalytic cycle induced by a reusable bifunctional heterogeneous catalyst composed of osmium and tungsten oxides on a single matrix using H₂O₂ as the terminal oxidant.^[11] In continuation of our interest on cost effective methodologies, we report here a divergent approach using a triple catalytic system composed of NMM and two heterogeneous catalysts in which titanium silicalite (TS-1) acts as electron transfer mediator (ETM) to perform oxidation of NMM used in catalytic amounts with hydrogen peroxide to provide *in situ* NMO continuously for AD of olefins, which is catalyzed by another heterogeneous catalyst, silica gel-supported *Cinchona* alkaloid [SGS-(DHQD)₂ PHAL]-OsO₄ for the first time (Scheme 1). The triple redox catalytic system devised to perform oxidation of TS-1, NMM, and Os(VI) using molar quantities of H₂O₂, a cheaper terminal oxidant, offers chiral diols in a single pot to make the process more economical. Incidentally, this forms the first report of TS-1-catalyzed oxidation of tertiary amines for SGS-



Scheme 1. The catalytic cycle in the osmium-catalyzed dihydroxylation using H_2O_2 as the terminal oxidant.

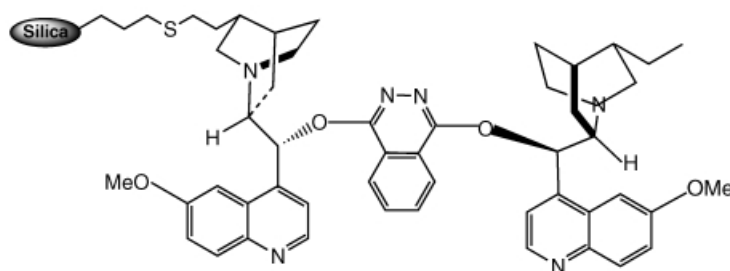


Figure 1. SGS-(DHQD) $_2$ PHAL.

(DHQD) $_2$ PHAL- OsO_4 -catalyzed AD reaction with H_2O_2 .

The silica gel-anchored bis-*Cinchona* alkaloid was prepared by adopting the modifications to the reported procedure.^[3b] The reaction of 4-(9-*O*-dihydroquinidinyldiethylphthalazine with mercaptopropyl-silica gel in the presence of AIBN as the radical initiator in chloroform gave SGS-(DHQD) $_2$ PHAL (Figure 1). The elemental analysis results confirmed the incorporation of 15.34 wt % of monomeric alkaloid on the silica gel. The BET surfaces of silica gel and silica-anchored alkaloid were found to be 249 and 152 $\text{m}^2 \text{g}^{-1}$, respectively. The reduction in the surface area after anchoring is due to the presence of the chiral ligand on the surface of silica gel.

Recently, titanium silicalite (TS-1) with MFI topology^[13] was found to possess very good redox properties in catalyzing oxidation reactions. TS-1 with H_2O_2 oxidant serves as a reusable catalyst and is easily separable by simple filtration.

The *in situ* generated SGS-(DHQD) $_2$ PHAL- OsO_4 complex, TS-1, and NMM employed in catalytic amounts in the AD reaction of methyl cinnamate using H_2O_2 as oxidant in H_2O -*t*-BuOH afforded the corresponding diol in excellent yield and ee (Table 1, Entry 1).

In an effort to widen the scope and application of the triple catalytic system, various substrates were subjected for AD under similar conditions. The results are summarized in Table 1. SGS-(DHQD) $_2$ PHAL- OsO_4 exhibited equivalent activity and ee compared with that of homogeneous analogue, (DHQD) $_2$ PHAL- OsO_4 .^[6]

Table 1. Asymmetric dihydroxylation of olefins using SGS-(DHQD) $_2$ PHAL- OsO_4 /NMM/TS-1/ H_2O_2 .^[a]

entry	olefin	yield (%)	ee (%)
1		94	98
2		91	99
3		75	99
4		55	93
5		90	91
6 ^[b]		72	89

^[a] All the chiral diols were well characterized by NMR, MS and IR. The ee is measured by HPLC analysis (see ref. 5a). For entry 3 the results are without slow addition of olefin.

^[b] Olefin and H_2O_2 were added slowly over a period of 20 h.

Slow addition of the olefin to the reaction mixture is warranted, except in the case of *trans*-stilbene, to keep the availability of the olefin at a bare minimum level to achieve higher ee. For example, with slow addition of styrene, the corresponding diol was obtained with 93% ee as against 76% ee when charged in one portion at the beginning of the reaction. These observations are in agreement with earlier findings.^[6a] In the case of cinnamates we achieved excellent ee's (Entry 1; 98% and Entry 2; 99%) as against the reported 88% ee.^[6c] The improved ee's are attributed to the slow addition of the olefin and oxidant. Various olefins ranging from mono- to trisubstituted, activated to simple were subjected to the dihydroxylation. In most cases, the desired diols were formed in higher yields and ee's similar to those obtained under homogeneous catalysis. The trisubstituted olefin was also dihydroxylated to the corresponding diol with higher ee in the presence of tetraethylammonium acetate (TEAA) additive and an increase of the addition time for olefin and H₂O₂ from 12 to 20 h (Entry 6). This phenomenon substantiates that the hydrolysis of osmate ester, a pronounced slow process in the case of trisubstituted olefins, was accelerated with the addition of the additive to afford higher ee.^[6a] Thus, higher ee's in the AD reaction are possible using H₂O₂ as oxidant catalyzed by SGS-(DHQD)₂PHAL-OsO₄. H₂O₂ serves as a better oxidant if slow addition of the oxidant and olefin is administered to minimize the secondary cycle, which is considered to lower the ee. H₂O₂ is believed to be the most economical and environmentally acceptable oxidant in industry, since the only by-product is water.

The recovered SGS-(DHQD)₂PHAL-OsO₄/TS-1 was reused successfully in AD, albeit after replenishment of ~30% osmium source in the form of K₂OsO₄ · 2 H₂O which was leached during the reaction (Table 2). When the catalyst was reused as such without further addition of osmium in the AD reaction, the activity was

decreased, while the ee remained the same (Run 4). With extended reaction time (20 h) the yield is improved. In this heterogeneous system, excellent ee has been achieved with an equimolar ratio of ligand to osmium, in contrast to the homogeneous reaction where an excess of the expensive chiral ligand to osmium is required.^[1,6,10] This indicates that the binding ability of the present heterogeneous osmium catalyst is greater than that of the homogenous analogue.^[3b]

It is a highly attractive proposition to apply TS-1 catalyzed *N*-oxidation to the recycling of NMM to NMO in the SGS-(DHQD)₂PHAL-OsO₄-catalyzed AD reaction, which provides reoxidation of Os(VI). The mechanism of the triple catalytic H₂O₂ oxidation is depicted in Scheme 1. The oxidation involves a transport of two electrons from the olefin to hydrogen peroxide mediated by a cascade of electron transfer reactions. The Os(VIII) directly dihydroxylates the olefin and the Os(VI) formed is efficiently reoxidized by NMO. The recycling of NMM to NMO is, in turn, effected by the titanium hydroperoxo species and the TS-1 is reoxidized by H₂O₂. The highly controlled kinetic reactions effect the dihydroxylation selectively. For example, the olefin is coordinated to Os(VIII), the *N*-oxide to Os(VI), NMM to titanium hydroperoxo species and finally hydrogen peroxide to TS-1 to relay the transport of electrons effectively and selectively. It is very remarkable that the triple catalytic system composed of two divergent heterogeneous systems helps to relay the transport of electrons through interaction with H₂O₂, NMM, NMO and olefin very effectively to open a new era in the catalysis.

In summary, the SGS-(DHQD)₂PHAL-OsO₄/NMM/TS-1/H₂O₂ system has been successfully employed for heterogeneous AD of olefins to afford the chiral diols with higher yields and ee's. Coupling of the AD reaction with the *in situ* *N*-oxidation in a single pot indeed reduces the unit operation, energy and the amount of NMM used in place of NMO by 50%. The possible large-scale synthesis of diols employing the heterogeneous catalyst H₂O₂ as an oxidant directed to minimize the solid waste effluent is also addressed. The use of the cheaper H₂O₂-NMM system in place of the relatively expensive NMO is a better option to offer a cost-effective process. The simple procedure, easy recovery and reusable catalytic systems are expected to contribute to the development of benign chemical processes and products.

Experimental Section

Preparation of SGS-(DHQD)₂PHAL

Silica gel (200 mesh; 4 g) was treated with 18 mL of 3-mercaptopropyltrimethoxysilane in 22 mL of anhydrous 1:1 pyridine/toluene. The slurry was heated at 90 °C for 24 h. After

Table 2. Reuse of catalyst in the AD of methyl cinnamate.^[a]

Run	Time [h]	Yield [%]	ee [%]
1	12	94	98
2	12	91	98
3	12	92	96
4 ^[b]	12	69 (90) ^[c]	97

^[a] Runs 2 and 3 were carried out using recovered catalyst with addition of 0.3 mol % K₂OsO₄ · 2 H₂O.

^[b] Reaction was carried out using the recovered catalyst from run 3.

^[c] Yield obtained after 20 h.

filtration, the solid was washed with toluene followed by Soxhlet extraction with toluene, then dried under vacuum for 1 h to give 3-mercaptopropyl-silica gel containing 3.38% S, corresponding to 1.05 mmol of S per gram.

This derivatized silica gel (2 g) was suspended in chloroform and refluxed with 4-(9-*O*-dihydroquinidiny1)-1-(9-*O*-quinidiny1)phthalazine (0.781 g, 1 mmol) and AIBN (55 mg) as radical initiator for 48 h. The solid was filtered followed by washing with methanol, Soxhlet extraction with toluene and drying under vacuum for 1 h to give SGS-(DHQD)₂PHAL (1.66 wt % of N, corresponding to 0.197 mmol of alkaloid per gram).

Typical Procedure for Asymmetric Dihydroxylation of Olefins using SGS-(DHQD)₂PHAL-OsO₄/NMM/TS-1 with H₂O₂

SGS-(DHQD)₂PHAL (50 mg, 0.01 mmol), K₂OsO₄ · 2 H₂O (3.68 mg, 0.01 mmol), NMM (50 mg, 0.5 mmol), TEAA (522 mg, 2 mmol), TS-1 (20 mg, 0.038 mmol of Ti/g, Si/Ti: 32) in *t*-BuOH-H₂O (3:1, 5 mL) were stirred at room temperature for 20 min. To this mixture were added an olefin (1 mmol) and H₂O₂ (169 µL, 30% aqueous, 1.5 mmol) over a period of 12 h using separate syringe pumps. After the addition was complete, the reaction mixture was stirred for another 1 h and the catalyst was filtered and washed with ethyl acetate. The solvent was removed and the crude material was chromatographed on silica gel to afford the corresponding *cis*-diol.

Acknowledgements

N. S. C. and S. M. thank the Council of Scientific and Industrial Research, India, for the award of senior research fellowship.

References

- [1] a) H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, 94, 2483; b) I. E. Markó, J. S. Svendsen, in *Comprehensive Asymmetric Catalysis*, Vol. II: (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, pp. 723; c) R. A. Johnson, K. B. Sharpless, in *Catalytic Asymmetric Synthesis*, 2nd edn., (Ed.: I. Ojima), VCH, Weinheim, **2000**, pp. 357.
- [2] a) B. M. Kim, K. B. Sharpless, *Tetrahedron Lett.* **1990**, 31, 3003; b) D. Pini, A. Petri, A. Nardi, C. Rosini, P. Salvadori, *Tetrahedron Lett.* **1991**, 32, 5175; c) B. B. Lohray, E. Nandanan, V. Bhushan, *Tetrahedron Asymmetry* **1996**, 7, 645; d) H. Han, K. D. Janda, *Tetrahedron Lett.* **1997**, 38, 1527; e) H. Han, K. D. Janda, *Angew. Chem. Int. Edn. Engl.* **1997**, 36, 1731; f) C. Bolm, A. Gerlach, *Eur. J. Org. Chem.* **1998**, 1, 21; g) P. Salvadori, D. Pini, A. Petri, *Synlett* **1999**, 1181.
- [3] a) B. B. Lohray, E. Nandanan, V. Bhushan, *Tetrahedron Asymmetry* **1996**, 7, 2805; b) C. E. Song, J. W. Yang, H. -J. Ha, *Tetrahedron Asymmetry* **1997**, 8, 841; c) C. Bolm, A. Maischak, A. Gerlach, *Chem. Commun.* **1997**, 2353; d) C. Bolm, A. Maischak, *Synlett* **2001**, 93; e) I. Motorina, C. M. Crudden, *Org. Lett.* **2001**, 3, 2325.
- [4] a) S. Nagayama, M. Endo, S. Kobayashi, *J. Org. Chem.* **1998**, 63, 6094; b) S. Kobayashi, M. Endo, S. Nagayama, *J. Am. Chem. Soc.* **1999**, 121, 11229; c) S. Kobayashi, T. Ishida, R. Akiyama, *Org. Lett.* **2001**, 3, 2649.
- [5] B. M. Choudary, N. S. Chowdari, M. L. Kantam, K. V. Raghavan, *J. Am. Chem. Soc.* **2001**, 123, 9220.
- [6] a) J. S. M. Wai, I. E. Markó, J. S. Svendsen, M. G. Finn, E. N. Jacobsen, K. B. Sharpless, *J. Am. Chem. Soc.* **1989**, 111, 1123; b) H. C. Kolb, K. B. Sharpless, *J. Org. Chem.* **1994**, 59, 5104; c) Z.-M. Wang, K. B. Sharpless, *J. Org. Chem.* **1994**, 59, 8302; d) L. Ahrgren, L. Sutin, *Org. Process Res. Dev.* **1997**, 1, 425; e) X. Lu, Z. Xu, G. Yang, *Org. Process Res. Dev.* **2000**, 4, 575.
- [7] a) K. B. Sharpless, W. Amberg, M. Beller, H. Chen, J. Hartung, Y. Kawanami, D. Lubben, E. Manoury, Y. Ogino, T. Shibata, T. Ukita, *J. Org. Chem.* **1991**, 56, 4585; b) H. Becker, K. B. Sharpless, *Angew. Chem. Int. Edn. Engl.* **1996**, 35, 448.
- [8] a) C. Dobler, G. Mehlretter, M. Beller, *Angew. Chem. Int. Ed.* **1999**, 38, 3026; b) C. Dobler, G. Mehlretter, U. Sundermeier, M. Beller, *J. Am. Chem. Soc.* **2000**, 122, 10289.
- [9] a) C. A. Roessner, A. Scott, *Chem. Biol.* **1996**, 3, 325; b) A. Domling, I. Ugi, *Angew. Chem. Int. Ed. Engl.* **1993**, 32, 563; c) P. A. Wender, S. T. Handy, D. L. Wright, *Chem. Ind.* **1997**, 766; d) N. Jeon, S. D. Seo, J. Y. Shin, *J. Am. Chem. Soc.* **2000**, 122, 10220; e) D. J. Kopecky, S. D. Rychnovsky, *J. Am. Chem. Soc.* **2001**, 123, 8420; f) Y. Guindon, K. Houde, M. Prevost, B. Cardinal-David, S. K. Landry, B. Daoust, M. Bencheqroun, B. Guerin, *J. Am. Chem. Soc.* **2001**, 123, 8496; g) S. Yamasaki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, 123, 1256; h) R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, *Eur. J. Org. Chem.* **2001**, 1045; i) H. -B. Yu, Q. -S. Hu, L. Pu, *J. Am. Chem. Soc.* **2000**, 122, 6500.
- [10] a) K. Bergstad, S. Y. Jonsson, J.-E. Bäckvall, *J. Am. Chem. Soc.* **1999**, 121, 10424; b) S. Y. Jonsson, K. Farnegardh, J.-E. Bäckvall, *J. Am. Chem. Soc.* **2001**, 123, 1365; c) A. H. Ell, S. Y. Jonsson, A. Borje, H. Adolfsson, J.-E. Bäckvall, *Tetrahedron Lett.* **2001**, 42, 2569.
- [11] B. M. Choudary, N. S. Chowdari, S. Madhi, M. L. Kantam, *Angew. Chem. Int. Edn.* **2001**, 40, 4619.
- [12] a) A. Thangaraj, S. Sivasankar, P. Ratnasamy, *J. Catal.* **1991**, 131, 394; b) D. R. C. Huybrechts, L. De Bruycker, P. A. Jacobs, *Nature* **1990**, 345, 240.