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Catalytic Asymmetric Dihydroxylation Using Phenoxyethoxymethyl-polystyrene (PEM)-Based Novel Microencapsulated Osmium Tetroxide (PEM-MC OsO_4)

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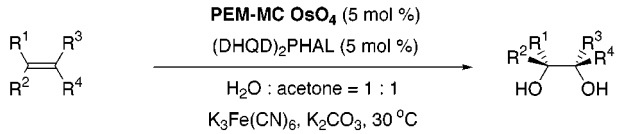
ABSTRACT



A phenoxyethoxymethyl-polystyrene (PEM)-based novel polymer-supported osmium catalyst has been developed. The catalyst was readily prepared from PEM polymer based on a microencapsulation technique, and asymmetric dihydroxylation of olefins has been successfully performed using $(DHQD)_2PHAL$ as a chiral ligand and $K_3Fe(CN)_6$ as a cooxidant in H_2O/acetone. The catalyst was recovered quantitativery by simple filtration and reused without loss of activity several times.

Osmium-catalyzed dihydroxylation of olefins is one of the most efficient methods for the preparation of vicinal diols.[1] In particular, the catalytic asymmetric dihydroxylation of olefins using a catalytic amount of osmium tetroxide in the presence of chiral ligands allows access to a wide variety of enantiomerically pure vicinal diols.[2] In 1992, Sharpless et al. reported a catalytic system based on biscinchona alkaloids such as 1,4-bis(9-*O*-dihydroquinidinyl)phthalazine ($(DHQD)_2$-PHAL), which has received a great deal of interest due to the broad scope of substances available and the high enantioselectivities attained.[3] Although a number of processes have gained wide acceptance of this asymmetric dihydroxylation that could be applied to the synthesis of pharmaceuticals, fine chemicals, etc.,[4] few fruitful industrial applications have been accomplished, probably because osmium tetroxide is highly toxic, expensive, volatile, and cannot be recovered. To address this issue, several groups have investigated immobilization of chiral ligands onto soluble and insoluble polymers.[5] However, complete recovery and reuse of the osmium were not accomplished.[6] In 1998, we reported microencapsulated osmium tetroxide based on polystyrene (PS-MC OsO_4) as a polymer-supported catalyst, which first achieved complete recovery and reuse of the osmium component in achiral oxidations.[7a] Microencapsulation is a new method for immobilizing catalysts onto polymers on the basis of physical envelopment by the polymers and electron interactions between the π electrons of the benzene rings of the polystyrene-based polymers and vacant orbitals of catalysts.[8] Furthermore, we have modified the polymer support and achieved catalytic asymmetric dihydroxylation using poly(acrylonitrile-*co*-butadiene-*co*-styrene) (ABS)-MC OsO_4, biscinchona alkaloids as a ligand, and *N*-methylmorpholine *N*-oxide as a cooxidant.[7b]

However, this reaction requires a slow addition of olefins and hence incurs some problems such as a tedious procedure and the difficulty of using insoluble substances. In this paper, we report recoverable and reusable osmium-catalyzed asymmetric dihydroxylation of olefins without the slow addition

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(2) Review: (a) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547. (b) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*, 2nd ed; Ojima, I., Ed.; VCH: Weinheim, 2000, pp 357−398.
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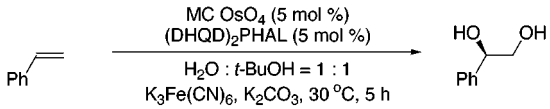
of olefins using microencapsulated osmium tetroxide derived from a novel polymer support.

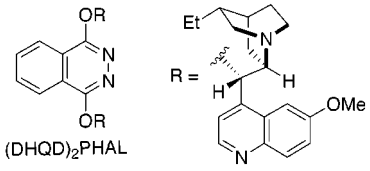
In our initial studies, we intended to apply ABS-MC OsO_4 to the asymmetric dihydroxylation under two-phase conditions with potassium hexacyanoferrate ($K_3Fe(CN)_6$) as a cooxidant (Table 1). In the presence of ABS-MC OsO_4 and

Table 1. Study of Several Polymers



		yield (%) (ee (%), recovery (%))		
entry	MC OsO_4	1st	2nd	3rd
1	ABS[a]	81 (94, 88)	83 (94, 74)	84 (93, 74)
2	PS[b]	4 (−, 97)		
3	AS[c]	5 (−, 99)		

[a] ABS = poly(acryronitrile-*co*-butadinen-*co*-styrene). [b] PS = polystyrene. [c] AS = poly(acrylonitrile-*co*-styrene).



(DHQD)$_2$PHAL (5 mol % each), styrene was treated with $K_3Fe(CN)_6$ (2.0 equiv) and potassium carbonate (2.0 equiv) in H_2O/*t*-BuOH (1:1) for 5 h, and the desired diol was obtained in 84% yield with 84% ee. The recovered catalyst was reused three times, and no loss of activity was observed, although the recovery was diminished (Table 1). We also examined other polymer supports such as polystyrene (PS) and poly(acrylonitrile-*co*-styrene) (AS). However, these polymers were not effective under these reaction conditions.

We then took ^{1}H NMR spectra of ABS-MC OsO_4 using a swollen-resin magic angle spinning (SR-MAS) NMR technique.[9] It was revealed that the ABS polymer had an olefin moiety derived from the butadiene monomer and that osmium tetroxide reacted with this olefin moiety in microencapsulation (Figure 1). We assumed that the diol moiety of

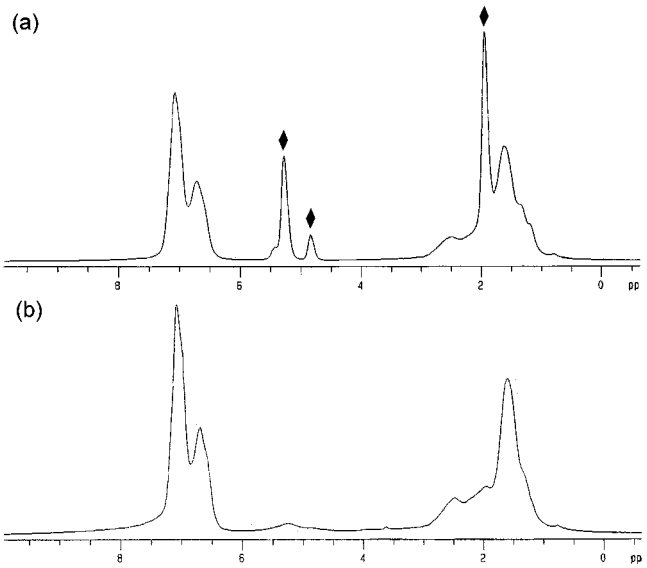


Figure 1. ^{1}H Swollen-resin magic angle spinning (SR-MAS) NMR spectra of (a) ABS polymer; (b) ABS-MC OsO_4 ($CDCl_3$). (♦) Butadiene moiety.

the polymer support was very effective in two-phase dihydroxylation, probably as a result of the hydrophilic property of the cooxidant. However, ABS-MC OsO_4 could not be recovered, presumably because this polymer was too hydrophilic and a part of the polymer was dissolved in the H_2O/*t*-BuOH solution. On the other hand, PS and AS are lipophilic and were difficult to react with the cooxidant.

On the basis of these experiments and consideration, we designed phenoxyethoxymethyl-polystyrene (PEM-polysty-

(4) (−)-Ovalicin: (a) Corey, E. J.; Dittami, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 256−257. (b) Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am. Chem. Soc.* **1994**, *116*, 12109−12114. Vancomycin: (c) Evans, D. A.; Wood, M. R.; Trotter, B. W.; Richardson, T. I.; Barrow, J. C.; Katz, J. L. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2700−2704. (d) Evans, D. A.; Dinsmore, C. J.; Watson, P. S.; Wood, M. R.; Richardson, T. I.; Trotter, B. W.; Katz, J. L. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2704−2708. (e) Nicolaou, K. C.; Natarajan, S.; Li, H.; Jain, N. F.; Hughes, R.; Solomon, M. E.; Ramanjulu, J. M.; Boddy, C. N. C.; Takayanagi, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2708−2714. (f) Nicolaou, K. C.; Jain, N. F.; Natarajan, S.; Hughes, R.; Solomon, M. E.; Li, H.; Ramanjulu, J. M.; Takayanagi, M.; Koumbis, A. E.; Bando, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 2714−2716. (g) Nicolaou, K. C.; Takayanagi, M.; Jain, N. F.; Natarajan, S.; Koumbis, A. E.; Bando, T.; Ramanjulu, J. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2717−2719. Fluvirucin B_1: (h) Houri, A. F.; Xu, Z.; Cogan, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 2943−2944. (i) Xu, Z.; Johannes, C. W.; Salman, S. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 10926−10927. (j) Xu, Z.; Johannes, C. W.; La, D. S.; Hofilena, G. E.; Hoveyda, A. H. *Tetrahedron* **1998**, *53*, 16377−16390. (k) Lindstroem, U. M.; Somfai, P. *Tetrahedron Lett.* **1998**, *39*, 7173−7176. Acetogenins: (l) Trost, B. M.; Calkins, T. L.; Bochet, C. G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2632−2635. (m) Hoye, T. R.; Tan, L. *Tetrahedron Lett.* **1995**, *36*, 1981−1984. (n) Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1993**, *115*, 4891−4892. Paclitaxel: (o) Wang, Z.-M.; Kolb, H. C.; Sharpless, K. B. *J. Org. Chem.* **1994**, *59*, 5104−5105. Zaragonic acids: (p) Nicolaou, K. C.; Yue, E. W.; La Greca, S.; Nadin, A.; Yang, Z.; Leresche, J. E.; Tsuri, T.; Naniwa, Y.; De Riccardis, F. *Chem. Eur. J.* **1995**, *1*, 467−494. (q) Carreira, E. M.; Du Bios, J. *J. Am. Chem. Soc.* **1994**, *116*, 10825−10826. (r) Carreira, E. M.; Du Bios, J. *J. Am. Chem. Soc.* **1995**, *117*, 8106−8125.

(5) Review: (a) Salvadori, P.; Pini, D.; Petri, A. *Synlett* **1999**, 1181−1190. (b) Bolm, C.; Gerlach, A. *Eur. J. Org. Chem.* **1998**, *21*, 21−27.

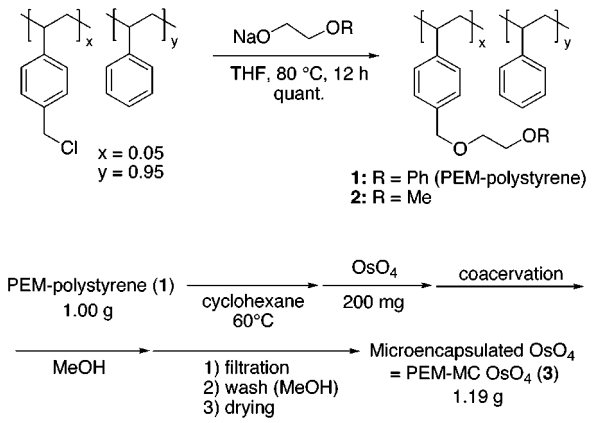
(6) Recently, osmium tetroxide was immobilized onto a silica-anchored tetrasubstituted olefin. Sevrens, A.; De Vos, D. E.; Fiermans, l.; Verpoort, F.; Grobet, P. J.; Jacobs, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 586−589.

(7) (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.

(8) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1998**, *120*, 2985−2986.

(9) The usefulness of the SR-MAS NMR technique for structure determination of resins directly without cleavage from polymer supports has been demonstrated through the development of several useful reactions using cross-linked polystyrene-based resins in the solid-phase in our laboratories. (a) Kobayashi, S.; Akiyama, R.; Furuta, T.; Moriwaki, M. *Mol. Online* **1998**, *2*, 35−39. (b) Kobayashi, S.; Aoki, Y. *Tetrahedron Lett.* **1998**, *39*, 7345−7348. (c) Kobayashi, S.; Akiyama, R. *Tetrahedron Lett.* **1998**, *39*, 9211−9214. (d) Kobayashi, S.; Furuta, T.; Sugita, K.; Okitsu, O.; Oyamada, H. *Tetrahedron Lett.* **1999**, *40*, 1341−1344. (e) Aoki, Y.; Kobayashi, S. *J. Comb. Chem.* **1999**, *1*, 371−372. (f) Okitsu, O.; Oyamada, H.; Furuta, T.; Kobayashi, S. *Heterocycles* **2000**, *52*, 1143−1162. (g) Kobayashi, S.; Akiyama, R.; Kitagawa, H. *J. Comb. Chem.* **2000**, *2*, 438−440.

Scheme 1. Synthesis of PEM-MC OsO_4 (**3**)



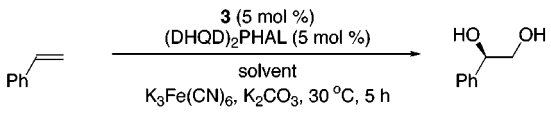
rene, **1**) shown in Scheme 1. This polymer was readily prepared from chloromethyl-polystyrene by etherification. Preparation of a new type of microencapsulated osmium tetroxide (PEM-MC OsO_4, **3**) was performed according to a standard method (Scheme 1).[10]

PEM-MC OsO_4 (**3**) thus prepared was first tested in asymmetric oxidation of styrene using $(DHQD)_2PHAL$ in H_2O/alcohol solutions (Table 2, entries 1−3). Although the desired products were obtained in good yields in the first run, activity of the catalyst decreased significantly in the second and third runs. In H_2O/THF, the results were similar to those in H_2O/alcohol (entry 4). On the other hand, in H_2O/acetone, moderate chemical yields, good enantiomeric excesses, and high recovery of the catalyst were obtained (entry 5). Use of polymer **2** instead of **1** was not effective (entry 5 vs 6). It seemed that the phenyl ether moiety of **1** was required for good recovery. It is noted that the osmium catalyst **3** was recovered quantitatively[11] by simple filtration and that no leaching of the osmium from **3** occurred.[12]

To increase the chemical yields, we examined separate addition of the cooxidant and the base, because it was observed that the desired reaction stopped halfway. When $K_3Fe(CN)_6$ (2.0 equiv) and potassium carbonate (2.0 equiv) were added at first and they were added again after 3 h, the best result was obtained (entry 7).

This system was applied to other olefins, and the results are summarized in Table 3.[13] In most cases, the desired diols were obtained in good yields with high enantiomeric excesses. It is noteworthy that a wide variety of olefins are applicable in this system and that the catalyst was recovered quantitatively by simple filtration.

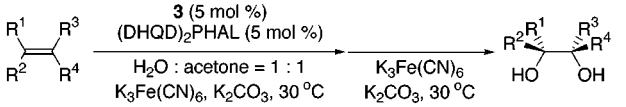
Table 2. Effect of Linkers and Solvents

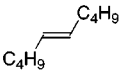
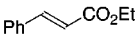


		yield (%) (ee (%), recovery (%))		
entry	solvent[a]	1st	2nd	3rd
1	A	77 (94, 94)	37 (80, 86)	NR (−, 84)
2[b]	A	93 (93, 93)	34 (90, 90)	3 (−, 83)
3	B	65 (92, 86)	4 (−, 82)	
4	C	80 (80, 74)	trace (−, 61)	
5	D	35 (77, quant)	56 (79, quant)	53 (79, quant)
6[b]	D	44 (76, quant)	49 (78, 94)	60 (78, 90)
7[c]	D	85 (78, quant)	66 (78, quant)	84 (78, quant)

[a] A, H_2O/*t*-BuOH (1:1); B, H_2O/*i*-PrOH (1:1); C, H_2O/THF (1:1); D, H_2O/acetone (1:1). [b] Polymer **2** was used instead of **1**. [c] Cooxidant (2.0 equiv) and base (2.0 equiv) were added at first and then again after 3 h.

Table 3. Asymmetric Dihydroxylation of Olefin Using PEM-MC OsO_4 (**3**)



entry	olefin	time (h)	yield (%)	*ee* (%)
1		3+2	85 (80)[a]	78 (−82)[a]
2		3+2	86	94
3		3+2	85	76
4		5+4	85	95
5		3+2	41	91
6[b]		3+2+2+2[c]	66	>99
7[b]		3+2	51	>99

[a] $(DHQ)_2PHAL$ (5 mol %) was used instead of $(DHQD)_2PHAL$. [b] Methanesulfonamide (1.0 equiv) was added. [c] One equivalent each of $K_3Fe(CN)_6$ and K_2CO_3 was added four times.

(10) Compound **1** (1.00 g) was dissolved in cyclohexane (20 mL) at 60 °C, and to this solution was added osmium tetroxide (OsO_4, 0.200 g) as a core (OsO_4 was dissolved). The mixture was stirred for 1 h at this temperature and then slowly cooled to 0 °C. Coaservates (phase separation) were found to envelop the core dispersed in the medium, and MeOH (30 mL) was added to harden the capsule walls. The mixture was stood at room temperature for 12 h, and the catalyst capsules were then washed with MeOH several times. PEM-MC OsO_4 (**3**, 1.19 g) was obtained after drying at room temperature for 24 h. Unencapsulated OsO_4 was recovered from the washings. This is a standard procedure for the preparation of microcapsules. Donbrow, M. *Microcapsules and Nanoparticles in Medicine and Pharmacy*; CRC Press: Boca Raton, FL, 1992. For details on microencapsulated catalysts, see refs 7 and 8.

(11) Determined by weight and fluorescence X-ray analysis.

(12) Confirmed by fluorescence X-ray analysis.

(13) **Typical Experimental Procedure for the Catalytic Asymmetric Dihydroxylation of Olefins.** PEM-MC OsO_4 (43.7 mg, 5 mol %), $(DHQD)_2PHAL$ (21.5 mg, 5 mol %), $K_3Fe(CN)_6$ (362.2 mg, 1.1 mmol), and K_2CO_3 (152.0 mg, 1.1 mmol) were combined in H_2O/acetone (1:1, 3.5 mL), and the heterogeneous slurry was stirred vigorously at 30 °C for 1 h. To this mixture was then added an olefin (0.55 mmol). After the mixture stirred for 2 h, $K_3Fe(CN)_6$ (362.2 mg, 1.1 mmol) and K_2CO_3 (152.0 mg, 1.1 mmol) were added again, and the mixture was further stirred for 2 h. Methanol (10 mL) was then added, and the mixture was stirred for 10 min. PEM-MC OsO_4 was separated by filtration and reused (reuse data are shown in Table 2, entry 7). The crude product was purified by chromatography on silica gel to afford the desired *cis*-diol. The optical purity of the product was determined by HPLC analysis.

In summary, we have developed phenoxyethoxymethylpolystyrene (PEM)-based novel polymer-supported osmium catalyst. The catalyst was readily prepared from PEM (new polymer) by means of a microencapsulation technique, and asymmetric dihydroxylation of olefins has been successfully performed using $(DHQD)_2PHAL$ as a chiral ligand and $K_3Fe(CN)_6$ as a cooxidant in H_2O/acetone. This reaction process does not require a slow addition of olefins, and the catalyst was recovered quantitatively by simple filtration and reused without loss of activity. As a result of the simple procedure, use of a recoverable and reusable catalyst, and lack of leaching of the osmium catalysts, this reaction is suitable for the synthesis of optically active diols on an industrial scale.

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