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# MCM-41 anchored cinchona alkaloid for catalytic asymmetric dihydroxylation of olefins: a clean protocol for chiral diols using molecular oxygen

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MCM-41 anchored 1,4-bis(9-*O*-quininyl)phthalazine (MCM-$(QN)_2$PHAL)-$OsO_4$, is prepared for the first time and used in the heterogeneous asymmetric dihydroxylation of olefins to afford diols with good to excellent enantiomeric excesses in the presence of *N*-methylmorpholine *N*-oxide, $K_3Fe(CN)_6$ or molecular oxygen as cooxidants.

**KEY WORDS:** asymmetric synthesis; dihydroxylation; immobilization; olefins; oxygen; osmium.

## 1. Introduction

Osmium-catalyzed asymmetric dihydroxylation (AD) of olefins provides one of the most elegant methods for the preparation of chiral vicinal diols [1,2]. Although the reactions could be applied to the synthesis of pharmaceuticals, fine chemicals, etc., the high cost and toxicity of osmium catalysts restrict its use in industry. Heterogenization of the ligands on various polymers [3,4] and silica gel [5] is undertaken in order to effect the easy recovery of the entire ligand and large portion of $OsO_4$ after the reaction for reuse. Recently osmium has been immobilized on various supports based on microencapsulation [6] and ion-exchange techniques [7] to achieve complete recovery of osmium. However, none of these methods provides complete recovery of both osmium as well as chiral ligand. Therefore, the development of new heterogeneous osmium catalysts to achieve complete recovery is highly desirable. Moreover, the major disadvantage of these heterogenized systems is the use of potassium ferricyanide as cooxidant in large amounts, which renders the process incompatible with the environment and uneconomical [3,5]. The inorganic supports are proved to be efficient in terms of mechanical and thermal stability over polymer supports. In this regard we designed a highly ordered mesoporous MCM-41 anchored cinchona alkaloid–$OsO_4$ complex to execute the AD reaction using more economical oxidants such as NMO and molecular oxygen. We report here the preparation of MCM-41 anchored cinchona alkaloid for the first time for use in the AD reaction after subsequent *in situ* complexation with $OsO_4$ using various cooxidants such as *N*-methylmorpholine *N*-oxide (NMO) or molecular oxygen and compared with $K_3Fe(CN)_6$ in a heterogeneous way. Incidentally, this forms the first report using molecular oxygen mediated heterogeneous catalyst and with improved enantiomeric excesses (ee) using NMO for asymmetric dihydroxylation.

## 2. Experimental

### 2.1. *Immobilization of monomer* **1** *on MCM-41*

MCM-41 was prepared according to the earlier procedure [8] and capped MCM-41 (4 g) by treating MCM-41 with $Ph_2SiCl_2$ [8d]. Then, the capped MCM-41 was treated with 18 ml of 3-mercaptopropyl trimethoxysilane in 22 ml of anhydrous 1 : 1 pyridine/toluene. The slurry was heated at 90 °C for 24 h. After filtration, the solid was washed with toluene followed by Soxhlet extraction with methanol and dried under vacuum for 1 h to give 3-mercaptopropyl MCM-41 **2** (scheme 1) containing 3.38% S, corresponding to 1.05 mmol of S per gram. This derivatized MCM-41 **2** (2 g) was suspended in chloroform and refluxed with 1,4-bis(9-*O*-quininyl)phthalazine (0.779 g) and AIBN (55 mg) as radical initiator for 48 h. The solid was filtered followed by washing with methanol, Soxhlet extraction and drying under vacuum for 1 h to give **3** (7.5 wt% of N).

### 2.2. *Asymmetric dihydroxylation of olefins using MCM-41 anchored bis-cinchona alkaloid* **3**

*Using NMO as the cooxidant:* MCM-$(QN)_2$PHAL **3** (50 mg, 1 mol%), $K_2OsO_4 \cdot 2H_2O$ (1.8 mg, 1 mol%), and *N*-methylmorpholine *N*-oxide (NMO, 0.65 mmol) were

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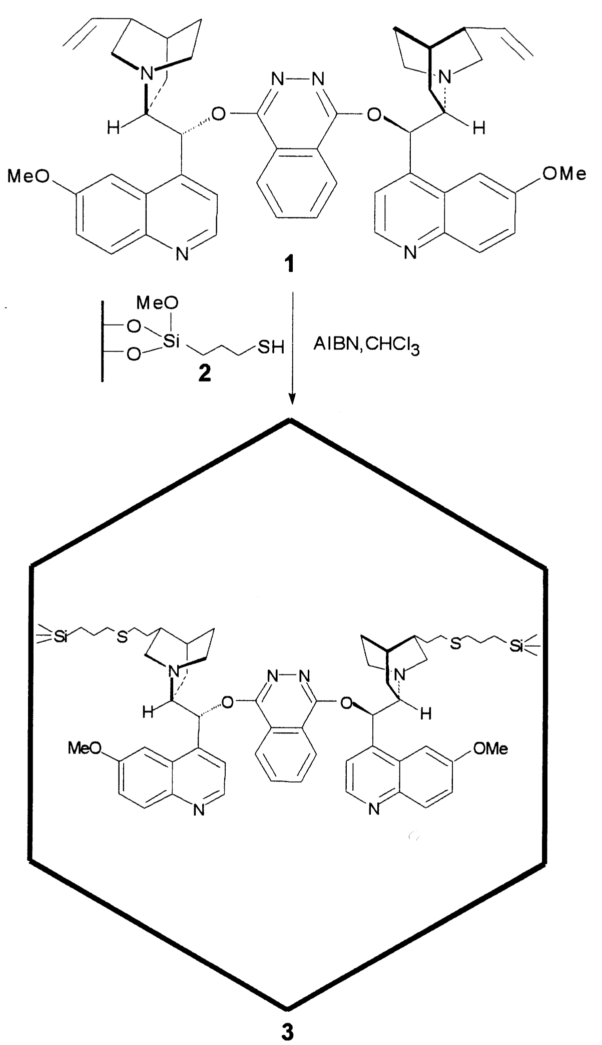


Scheme 1. Depiction of the cinchona alkaloid bound inside the hexagonal pores of MCM-41.

taken in a round-bottomed flask containing $^t$BuOH–water (1 : 1, 5 ml) and stirred at room temperature. To this mixture was added an olefin (0.5 mmol) slowly over a period of 24 h. After completion of the reaction, the catalyst was filtered and washed with ethyl acetate. After removing the solvent, the crude material was chromatographed on silica gel to afford the corresponding *cis*-diol.

*Using $K_3Fe(CN)_6$ as the cooxidant:* MCM-(QN)$_2$PHAL **3** (50 mg, 1 mol%), $K_2OsO_4 \cdot 2H_2O$ (1.8 mg, 1 mol%), $K_3Fe(CN)_6$ (1.5 mmol) and $K_2CO_3$ (1.5 mmol) were taken in a round-bottomed flask containing $^t$BuOH–water (1 : 1, 5 ml). To this mixture, was added an olefin (0.5 mmol) and stirred at room temperature for 16–24 h. After completion of the reaction, the catalyst was filtered and washed with ethyl acetate. After removing the solvent, the crude material was chromatographed on silica gel to afford the corresponding *cis*-diol.

*Using molecular oxygen as the cooxidant:* MCM-(QN)$_2$PHAL **3** (50 mg, 1 mol%) and $K_2OsO_4 \cdot 2H_2O$ (1.8 mg, 1 mol%) in a round-bottomed flask containing aqueous buffer solution (6 ml, pH 10.4) and $^t$BuOH (3 ml) were stirred at 1 bar $O_2$ and 50 °C in an oil bath. After 10 min, an olefin (0.5 mmol) was added in one portion and the reaction mixture was stirred vigorously with a magnetic stirring bar. After completion of the reaction (16–24 h as monitored by TLC), the catalyst was filtered and washed with ethyl acetate. After removing the solvent, the crude material was chromatographed on silica gel to afford the corresponding *cis*-diol.

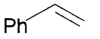
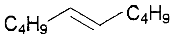
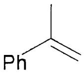
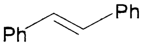
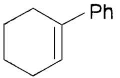
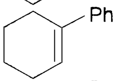
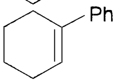
## 3. Results and discussion

### 3.1. Characterization of the catalyst

The mesoporous solid MCM-41 [8] contains silanol (SiOH) groups both on the external and internal surface, which could be suitably derivatized to anchor a chiral catalyst. The external surface of MCM-41 was capped by treatment with an appropriate amount of $Ph_2SiCl_2$ [8d]. The capping of the external surface ensures that the alkaloid, a ligand for AD, is bound to the internal surface of MCM-41 on subsequent reaction. The capped MCM-41 was treated with 3-mercaptopropyl trimethoxysilane to yield a material with internal mercaptopropyl tether [8e]. The MCM-41 anchored bis-cinchona alkaloid **3** was prepared by the reaction of chiral monomer **1** with mercaptopropyl MCM-41 **2** in the presence of AIBN as the radical initiator in chloroform (scheme 1) [5a]. Due to the large pore size (40 Å) of MCM-41, the alkaloid can be tethered inside the hexagonal pores. We have characterized the incorporation of an organic moiety by IR and $^{13}$C NMR. The IR spectrum of **2** shows a vibration band at 2575 cm$^{-1}$ assigned to the SH group. The presence of a mercaptopropyl group is also indicated by $^{13}$C NMR of **2** which shows peaks at $\delta$ 11 ($C_3$) and 27 ($C_1$, $C_2$). The nitrogen analysis of **3** confirmed incorporation of 7.5 wt% of monomeric alkaloid **1**. The IR and $^{13}$C NMR spectra of **3** indicate that there is no perceptible shift of peaks upon the anchoring process. It is significant to note that the alkaloid moiety on MCM-41 is bound by a covalent bond, as the alkaloid could not be extracted during the Soxhlet extraction. The X-ray powder diffraction patterns of the initial MCM-41 and the MCM-(QN)$_2$PHAL reveal that the mesoporous structure is preserved during the anchoring of the alkaloid. The BET surface area of MCM-41, mercaptopropyl MCM-41 and MCM-QN)$_2$PHAL is found to be 920, 667 and 309 m$^2$ g$^{-1}$, respectively. The reduction in the surface area after anchoring of the spacer and ligand substantiates the presence of the respective organic moieties in the MCM-41.

In an effort to understand the scope and application of immobilized catalyst, various cooxidants were screened. The heterogeneous AD of olefins using MCM-(QN)$_2$PHAL **3** was performed under standard conditions in $H_2O$-$^t$BuOH using NMO [9], $K_3Fe(CN)_6$ [10] and molecular oxygen [11] as cooxidants and the results are

Table 1
Asymmetric dihydroxylation of olefins using MCM-41 anchored bis-cinchona alkaloid **3**[a]

| Entry | Olefin | Cooxidant | | | | | |
|---|---|---|---|---|---|---|---|
| | | NMO | | $K_3Fe(CN)_6$ | | $O_2$ | |
| | | Yield (%) | ee (%) | Yield (%) | ee (%) | Yield (%) | ee (%) |
| 1 |  | 92 | 95 | 88 | 96 | 42[g] | 88 |
| 2 |  | 95 | 68[b] | 92 | 92[c] | 97 | 84 |
| 3 |  | 94 | 91 | 90 | 94 | 99 | 79 |
| 4[d] |  | 96 | 99 | 95 | 99 | 15[g] | 90 |
| 5 |  | 92 | 88[b] | 90 | 94[c] | 78 | 83 |
| 6[e] |  | 65 | 87[b] | 63 | 92[c] | 60 | 83 |
| 7[f] |  | 93 | 86[b] | 86 | 93[c] | 80 | 82 |

[a] Isolated yields. All reactions were carried out with 1 mol% of osmium and 1 mol% of immobilized ligand **3** for 12–24 h. In the case of NMO as cooxidant, olefin was added slowly over a period of 24 h. Enantiomeric excess determined by HPLC analysis using chiral columns.

[b] Two equivalents of TEAA.

[c] One equivalent of $CH_3SO_2NH_2$.

[d] An excess of 5 ml of $^t$BuOH was employed.

[e] Reaction was carried out using recovered catalyst from entry 5 without further addition of $K_2OsO_4 \cdot 2H_2O$.

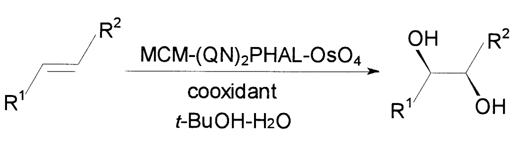
[f] Reaction was carried out using recovered catalyst from entry 5 with addition of 0.3 mol% $K_2OsO_4 \cdot 2H_2O$.

[g] Benzaldehyde and benzoic acid are observed as over-oxidized products.

summarized in table 1. NMO serves as a better cooxidant provided slow addition of the olefin is administered to minimize the secondary cycle, which is responsible for lower ee [9a]. Molecular oxygen is believed to be most economical and environmentally acceptable oxidant in the industry. All these reactions using **3** exhibited comparable reaction rates and ee with those of homogeneous analogue $(DHQ)_2PHAL$ [10]. We have conducted the experiments using other solvents such as acetone and acetonitrile, and identical activity is observed. As the $^t$BuOH solvent gave more superior ee than the other solvents, we used the $^t$BuOH solvent for all the experiments. We have conducted the experiment with oxygen under neutral pH and the product formation is not found. When we used the buffer at pH 10.4 the diols are obtained in good yield. In the case of NMO and $K_3Fe(CN)_6$ the diol is obtained without using any buffer. The use of buffer in NMO and $K_3Fe(CN)_6$ experiments also resulted in faster reaction.

Slow addition of olefin is warranted in the case of NMO cooxidant to keep the availability of the olefin at a bare minimum level in order to achieve higher ee. For example, with slow addition of styrene, the corresponding diol is obtained with 95% ee as against 75% ee when charged in one portion at the beginning of the reaction. These results are in agreement with earlier observations [9]. Various olefins ranging from mono- to tri-substituted, activated to simple, are subjected to the dihydroxylations. In most cases, the desired diols are formed in higher yields, albeit with almost similar ee compared with that obtained in the homogeneous catalysis. Even the trisubstituted olefin could be dihydroxylated to the corresponding diol with higher yield and ee in the presence of tetraethyl ammonium acetate (TEAA) or $CH_3SO_2NH_2$ additive (entry 5). This phenomenon substantiates that the hydrolysis of osmate ester to give diol, a pronounced slow process specifically in the case of trisubstituted olefin, is accelerated by the addition of TEAA or $CH_3SO_2NH_2$ additives. These are in conformity with earlier observations [9a,10]. Thus, the higher ee in the AD reaction is realized using NMO as cooxidant catalyzed by MCM-$(QN)_2$PHAL-$OsO_4$ (scheme 2).

When the recovered MCM-41 anchored alkaloid–$OsO_4$ complex was reused as such without further addition of osmium in the AD reaction, there was a drop in activity, while ee remained the same (entry 6). The loss of activity on reuse is attributed to the leaching of the osmium into solution in the preceding cycle during



Scheme 2.

the reaction. However, when the recovered catalyst from the fresh cycle was reused after replenishing with ~30% osmium source in the form of $K_2OsO_4 \cdot 2H_2O$, the activity in the AD reaction was restored (entry 7). Since amine ligands coordinate to osmium under equilibrium conditions, the recovery of the osmium using supported ligands is generally difficult. Therefore the leaching of osmium is usually found in the polymer- and silica-ligated systems. In this heterogeneous system, excellent ee have been achieved with 1 : 1 ratio of ligand to osmium, in contrast to the homogeneous reaction where excess of expensive chiral ligand to osmium is usually required to give optimum ee [9]. These results provide evidence that the binding ability of the present heterogeneous catalyst is greater than the homogeneous analogue [5].

Finally, the molecular oxygen served as a better cooxidant for aliphatic olefins as well as aromatic olefins with no $\alpha$ hydrogen atom. However, the lower yields of the diol in the case of aromatic olefins possessing $\alpha$ hydrogen atom (entries 1 and 4) using molecular oxygen is attributed to the over-oxidation of the benzylic position, while the lower ee with molecular oxygen compared with that with $K_3Fe(CN)_6$ and NMO cooxidants is ascribed to the higher reaction temperatures employed in the former system (table 1). Over-oxidized products such as aldehydes and acids are obtained as side products when oxygen is used as oxidant.

In summary, the MCM-41 anchored bis-cinchona alkaloid–$OsO_4$ complex has been successfully employed for asymmetric dihydroxylation of olefins to afford chiral diols with higher yields and ee. The possible large-scale synthesis of diols employing the heterogeneous catalyst using NMO or molecular oxygen as cooxidant directed to minimize the solid waste effluent is addressed. The simple procedure, easy recovery and reusable catalytic systems are expected to contribute to the development of benign chemical processes and products.

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