

# A Novel Chemoentrapment Approach for Supportless Recycling of a Catalyst: Catalytic Asymmetric Dihydroxylation

Daewon Lee,<sup>a</sup> Honggeun Lee,<sup>a</sup> Seyoung Kim,<sup>a</sup> Chang-Eun Yeom,<sup>a</sup> and B. Moon Kim<sup>a,\*</sup>

<sup>a</sup> School of Chemistry, College of Natural Sciences, Seoul National University, Seoul 151-747, South Korea  
Fax: (+82)-2-872-7505; e-mail: kimbm@snu.ac.kr

Received: September 9, 2005; Revised: March 29, 2006; Accepted: April 6, 2006

**Abstract:** A simple method of recycling a metal catalyst through chemoentrapment in an aqueous layer using ethyl vinyl ether has been developed. Using this new methodology, a highly efficient, filtration-free recycling of osmium for catalytic asymmetric dihydroxylation was accomplished. By means of the formation of a water-soluble  $\text{OsO}_4^{2-}$  using EVE, AD reactions of mono- and disubstituted olefins with 1 mol % of  $\text{OsO}_4$  proceeded for up to 9 cycles without any loss of yields and enantioselectivities.

**Keywords:** asymmetric dihydroxylation; chemoentrapment; ethyl vinyl ether; osmium tetroxide; supportless recycling

Developments in the preparation of enantiomerically pure compounds are becoming increasingly important. Among many methods for the generation of chiral non-racemic compounds, much attention has been focused on catalytic asymmetric transformations and recently remarkable advances have been made in this area.<sup>[1]</sup> Among the many asymmetric reactions, the osmium-catalyzed asymmetric dihydroxylation (AD) of olefins is one of the most efficient reactions for generating enantiomerically enriched vicinal diols.<sup>[2]</sup> However, as in many catalytic asymmetric transformations, the high cost and toxicity of the metal-ligand system have been hurdles against large-scale industrial applications of the AD reaction.<sup>[3]</sup> To address this issue, various heterogeneous support systems have been employed including insoluble inorganic, insoluble organic, and soluble organic materials.<sup>[4,5]</sup> Since the heterogeneous supports have been aimed largely at the recycling of the alkaloid ligand, recovery of the osmium species still remains to be a challenging problem. This appears to be closely related to the low binding affinity of  $\text{OsO}_4$  to the monodentate alkaloid ligand, a must for the catalytic turnover.<sup>[6]</sup> Recently, new, successful examples of immobi-

lization techniques such as microencapsulation of  $\text{OsO}_4$  in a polymer matrix,<sup>[7]</sup> fixation of osmium onto hindered olefins covalently bound on silica or resin supports,<sup>[8]</sup> and use of various ion-exchange supports have been reported.<sup>[9]</sup> Although successful, these approaches require the preparation of the support and feature relatively short repetition cycles. The use of an ionic liquid<sup>[10]</sup> as yet another immobilization medium for the Os-ligand complex enabled recycling of both components for several cycles.

In the search for a new approach for recycling the catalytic system, we focused our attention on the detailed catalytic cycle of AD. In a typical AD reaction employing  $\text{K}_3\text{Fe}(\text{CN})_6$  as a secondary oxidant,  $\text{Os}(\text{VIII})\text{O}_4$ , upon reaction with an olefin, is converted to an osmate ester  $[\text{Os}(\text{VI})]$ , which is hydrolyzed and oxidized to  $\text{Os}(\text{VIII})$  in the aqueous layer with a secondary oxidant. It then migrates back to the organic phase to repeat the catalytic cycle.<sup>[2b]</sup> After consumption of all the olefin, osmium remains as  $\text{Os}(\text{VIII})$  due to the excess of  $\text{K}_3\text{Fe}(\text{CN})_6$ . This  $\text{Os}(\text{VIII})$  can stay as a perosmate anion or neutral  $\text{OsO}_4$  and the majority of the latter would stay in organic layer since it is more soluble in the organic solvent<sup>[11]</sup> and this may be where a major osmium loss occurs when one wants to recycle the catalyst.

To verify this, osmium contents in the aqueous layer were measured with inductively couple plasma (ICP) mass after the AD reaction of styrene under the standard conditions employing  $\text{K}_3\text{Fe}(\text{CN})_6$ .<sup>[12]</sup> After a single AD reaction, only 50 % of the original osmium was found in the aqueous layer, meaning that the other 50 % was extracted into organic layer and when the AD was repeated using the recovered aqueous layer, the reaction yields dropped precipitously at the 3rd run, indicating a significant osmium loss during the extraction process (entry 1, Table 1). To overcome this intrinsic problem, it would be necessary to confine the osmium in the aqueous layer in a form which is soluble only in the aqueous layer.

To chemically trap all the osmium as water-soluble  $\text{Os}(\text{VI})$ , conversion of all the remaining  $\text{Fe}(\text{III})$  to

**Table 1.** Recycling results from consecutive use of aqueous layer in ADs of styrene and Os contents in the aqueous layer.

| Entry | Reducing agent                  | Yield [%] <sup>[a]</sup>                          |                 |                 | Os content in H <sub>2</sub> O [%] <sup>[b]</sup> |      |
|-------|---------------------------------|---------------------------------------------------|-----------------|-----------------|---------------------------------------------------|------|
|       |                                 | 1 <sup>st</sup>                                   | 2 <sup>nd</sup> | 3 <sup>rd</sup> | EA                                                | TBME |
| 1     | none                            | 97                                                | 88              | 55              | 48                                                | 50   |
| 2     | Na <sub>2</sub> SO <sub>3</sub> | 97                                                | 92              | 50              | -                                                 | -    |
| 3     | <b>EVE</b>                      | <b>&gt; 90 % for up to 9 cycles<sup>[c]</sup></b> |                 |                 | 89                                                | 83   |

<sup>[a]</sup> Recycling was performed using the recovered aqueous layer with a new batch of olefin, DHQ<sub>2</sub>PHAL, K<sub>3</sub>Fe(CN)<sub>6</sub> and K<sub>2</sub>CO<sub>3</sub>.

<sup>[b]</sup> Determined with ICP mass after extraction with indicated organic solvent from the first reaction.

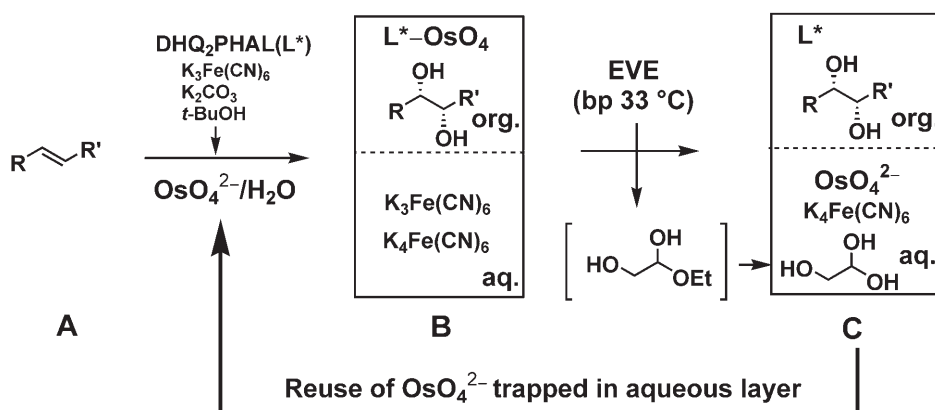
<sup>[c]</sup> For more detailed results, see Table 2.

Fe(II) after the AD reaction would be required. For this purpose, use of an inorganic reductant would be the most straightforward approach. However, when Na<sub>2</sub>SO<sub>3</sub>, a typical inorganic reductant, was employed, reduction of remaining Fe(III) using an exact amount of the inorganic reducing agent was tricky and excess Na<sub>2</sub>SO<sub>3</sub> would be harmful in the next reaction. Even the carefully controlled use of Na<sub>2</sub>SO<sub>3</sub> did not improve the recycling efficiency (entry 2, Table 1).

In this connection, we set the criteria for a successful chemical trapping agent: (a) complete reduction of the secondary oxidant [from Fe(III) to Fe(II)] for the generation of Os(VI) from Os(VIII), and (b) no trace of the reductant in the aqueous layer after reaction. Use of an external olefin after the AD would satisfy the above criteria, however, it will be accompanied by product contamination from the external olefin and its diol product. As a solution to this, ethyl vinyl ether (EVE) was selected as an optimal reducing olefin due to its low boiling point (33 °C) and the generation of a water-soluble dihydroxylated product, glycoacetal, upon dihydroxylation (**B** to **C**, Figure 1).<sup>[13]</sup> If needed, excess EVE can be easily recovered through distillation. Indeed when 40 mol %<sup>[14]</sup> EVE was added to the mixture after completion of the AD reaction, a majority of the osmium (89%) was found in the aqueous layer (entry 3,

Table 1) and dihydroxylation products from EVE were mostly water-soluble, leaving almost no isolable material in the organic layer. ICP mass analysis of the product diol showed 7.5% of Os in the organic compound after the treatment of 40 mol % of EVE.

Encouraged by the above preliminary results, we performed AD reactions of olefins with 1 mol % of OsO<sub>4</sub> in presence of DHQ<sub>2</sub>PHAL (1.5 mol %) and K<sub>3</sub>Fe(CN)<sub>6</sub>/K<sub>2</sub>CO<sub>3</sub> (each 250 mol %) in *t*-BuOH and water and explored the repetition capability using EVE. After each reaction cycle, 40 mol % of EVE was added to the reaction mixture to generate OsO<sub>4</sub><sup>2-</sup>. The Os-containing aqueous layer was almost quantitatively recovered from simple phase separation using ethyl acetate (EA) or *tert*-butyl methyl ether (TBME) as an extracting solvent. Then the recovered aqueous layer was reused for the next reaction with new batches of an olefin, *t*-BuOH, DHQ<sub>2</sub>PHAL, K<sub>3</sub>Fe(CN)<sub>6</sub> and K<sub>2</sub>CO<sub>3</sub>. From the organic layer, DHQ<sub>2</sub>PHAL was also recovered by simple acid/base extraction (> 95% recovery) and AD products were obtained without further purification. As recycling proceeded, cumulative deposition of insoluble K<sub>4</sub>Fe(CN)<sub>6</sub> in the aqueous layer was observed, which eventually interfered with magnetic stirring and decreased reactivity.<sup>[15]</sup> To alleviate the deposition problem, filtration or dilution with an equal volume of

**Figure 1.** Schematic diagram of recycling osmium through OsO<sub>4</sub><sup>2-</sup> using EVE.

**Table 2.** Results of repetitive asymmetric dihydroxylation using chemoentrapment strategy.

| Entry | Olefin                  | Extracting solvent | Yields and 1 <sup>st</sup> | % <i>ees</i> <sup>[a]</sup> (in parenthesis) 2 <sup>nd</sup> | 3 <sup>rd</sup>            | 4 <sup>th</sup>          | 5 <sup>th</sup>          | 6 <sup>th</sup> | 7 <sup>th</sup> | 8 <sup>th</sup>          |
|-------|-------------------------|--------------------|----------------------------|--------------------------------------------------------------|----------------------------|--------------------------|--------------------------|-----------------|-----------------|--------------------------|
| 1     | Styrene                 | EA                 | 97 (96.2)                  | 96 (95.8)                                                    | 91 (95.7)                  | 94 (95.8)                | 93 <sup>[c]</sup> (95.6) | 94 (95.4)       | 94 (95.8)       | 66 (96.6)                |
| 2     | Styrene                 | TBME               | 97 (97.0)                  | 93 (96.8)                                                    | 96 (96.6)                  | 91 (96.5)                | 91 <sup>[c]</sup> (96.3) | 91 (96.9)       | 94 (96.9)       | 92 <sup>[e]</sup> (96.9) |
| 3     | $\alpha$ -Methylstyrene | TBME               | 96 (89.6)                  | 97 (90.7)                                                    | 97 (89.9)                  | 97 <sup>[d]</sup> (90.0) | 97 (90.0)                | 97 (89.8)       | 97 (89.5)       | 96 (89.6)                |
| 4     | <i>trans</i> -Stilbene  | TBME               | 96 (> 99.5)                | 97 (> 99.5)                                                  | 95 <sup>[c]</sup> (> 99.5) | 96 (> 99.5)              | 81 (> 99.5)              | -               | -               | -                        |

<sup>[a]</sup> Determined from HPLC analysis.

<sup>[b]</sup> Reactions were carried out with a molar ratio of olefin/OsO<sub>4</sub>/DHQ<sub>2</sub>PHAL = 1/0.01/0.015 under standard K<sub>3</sub>Fe(CN)<sub>6</sub> conditions at room temperature. Recycling was performed using a new batch of olefin, DHQ<sub>2</sub>PHAL and K<sub>3</sub>Fe(CN)<sub>6</sub>/K<sub>2</sub>CO<sub>3</sub> (each 2.5 mol equivs.).

<sup>[c]</sup> After reaction, insoluble materials were filtered off.

<sup>[d]</sup> After reaction, the aqueous layer was diluted with an equal volume of water.

<sup>[e]</sup> Product of 96.9% ee in 94% yield was obtained at the 9<sup>th</sup> run.

water of the aqueous layer once after 4 or 5 cycles was found to be effective. As shown in Table 2, the AD reaction of styrene with 1 mol% of OsO<sub>4</sub> proceeded for up to seven cycles without any loss of yields in a given reaction time using ethyl acetate as an extracting solvent, however, a decreased yield (66%) was observed in the 8<sup>th</sup> run (entry 1). When the extracting solvent was switched to TBME, the same reaction proceeded for more than 9 cycles (entry 2) presumably due to the lower polarity of TBME. Recycling of  $\alpha$ -methylstyrene, a 1,1-disubstituted olefin, also exhibited almost the same reactivity upon dilution once of the aqueous layer without any filtration (entry 3). ADs of *trans*-stilbene, which is structurally more demanding and thus more sensitive to the osmium content than the other substrates, proceeded for 5 cycles (entry 4) with uniform enantioselectivities. This contrasts with the AD of stilbene in ionic liquid using 1 mol% of OsO<sub>4</sub>, where a yield decrease (70%) and lowered enantioselectivity (98 to 94% ee) were observed at the 4<sup>th</sup> run.<sup>[10b]</sup> The chemoentrapment of osmium using EVE allows for *essentially homogeneous reaction conditions in each recycling experiment*, therefore the highest enantioselectivities were warranted. As can be seen from Table 2, the same levels of enantioselectivity as those of the initial runs were maintained throughout the recycling with all four olefins examined (entries 1–4). Moreover, products were obtained without contamination since the AD product of EVE was accumulated in the aqueous layer. Therefore, in regards to recycling efficiency of the osmium, consistent enantioselectivity, and ease of operation, this chemoentrapment of osmium using EVE offers unique benefits compared to existing osmium immobilization methods including solid supports and ionic liquids.

In summary, we have developed a new chemoentrapment strategy for recycling osmium in catalytic AD reactions using ethyl vinyl ether as a chemical trapping agent. The new strategy allows for an efficient recycling of osmium so that AD reactions of mono- and disubstituted olefins with 1 mol% of OsO<sub>4</sub> proceeded for up to 9 cycles without any loss of yields and enantioselectivities. This new catalyst recycling system is expected to lay the groundwork towards practical applications of AD. The possibility of extending this chemoentrapment strategy to the catalyst recovery of other metal catalytic systems is currently being explored.

## Experimental Section

### Representative Recycling Procedure for ADs of Olefins using EVE

DHQ<sub>2</sub>PHAL (6 mg, 0.008 mmol), K<sub>3</sub>Fe(CN)<sub>6</sub> (411 mg, 1.25 mmol), and K<sub>2</sub>CO<sub>3</sub> (157 mg, 1.25 mmol) were dissolved in *t*-BuOH-H<sub>2</sub>O (each 2 mL). After cooling, an olefin (0.500 mmol) and an aqueous solution of OsO<sub>4</sub> (4 wt%, 0.005 mmol) were added and the mixture was vigorously stirred at room temperature. After completion of the reaction, EVE (20  $\mu$ L, 0.200 mmol) was added and the mixture stirred for 1 h to consume the remaining K<sub>3</sub>Fe(CN)<sub>6</sub>. The reaction mixture was diluted with TBME (4 mL), cooled to 0°C and then allowed to stand for 1 h. The extracted organic layer was washed with 1 N aqueous HCl solution and brine to recover DHQ<sub>2</sub>PHAL. After removal of the solvent and EVE (bp 33°C) under reduced pressure, the desired *cis*-diol was obtained without further purification. Then remaining aqueous layer containing the OsO<sub>4</sub><sup>2-</sup> was reused for the next reaction employing new batches of reactants. When too much solid was deposited in the aqueous layer upon succes-

sive recycling, two different methods were used to alleviate the stirring problem: 1) For entries 1, 2, and 4 in Table 2, the reaction mixture was filtered to remove the insoluble precipitate and the filtered insoluble deposition was washed with *t*-BuOH-H<sub>2</sub>O (2.0 and 0.7 mL, respectively). 2) For entry 3, dilution with water (2 mL) after the 5<sup>th</sup> cycle was performed without filtration and the diluted aqueous layer was used for further recycling experiments. The enantiomeric excesses of the diols were determined from HPLC analysis using chiral columns.

## Acknowledgements

This work was supported by the Korea Research Foundation Grant funded by the Korean Government (MOEHRD) (KRF-2005-041-C00247). D.L., H.L., S.K. and C.-E.Y. thank the BK21 fellowships from the Ministry of Education, Republic of Korea.

## References

- [1] a) *Comprehensive Asymmetric Catalysis*, (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, Vols. 1–3; b) *Catalytic Asymmetric Synthesis*, (Ed.: I. Ojima), VCH, New York, **2000**.
- [2] For reviews, see: a) H. C. Kolb, M. S. Van Nieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483; b) R. A. Johnson, *Catalytic asymmetric dihydroxylation discovery and development*, in: *Catalytic Asymmetric Synthesis*, (Eds.: I. Ojima, K. B. Sharpless), VCH, New York, **2000**, pp. 357–398.
- [3] a) Z.-M. Wang, K. B. Sharpless, *J. Org. Chem.* **1994**, *59*, 8302; b) L. Ahrgren, L. Sutin, *Org. Process Res. Dev.* **1997**, *1*, 425; c) X. Lu, Z. Xu, G. Yang, *Org. Process Res. Dev.* **2000**, *4*, 575.
- [4] For reviews, see: a) C. Bolm, A. Gerlach, *Eur. J. Org. Chem.* **1998**, *21*; b) Q. H. Fan, Y. M. Li, A. S. C. Chan, *Chem. Rev.* **2002**, *102*, 3385; c) C. E. Song, S. G. Lee, *Chem. Rev.* **2002**, *102*, 3495; d) D. E. D. Vos, M. Dams, B. F. Sels, P. A. Jacobs, *Chem. Rev.* **2002**, *102*, 3615.
- [5] Results from this laboratory: H. M. Lee, S. W. Kim, T. Hyeon, B. M. Kim, *Tetrahedron: Asymmetry* **2001**, *12*, 1537.
- [6] H. C. Kolb, P. G. Andersson, K. B. Sharpless, *J. Am. Chem. Soc.* **1994**, *116*, 1278.
- [7] a) S. Kobayashi, M. Endo, S. Nagayama, *J. Am. Chem. Soc.* **1999**, *121*, 11229; b) S. Kobayashi, T. Ishida, R. Akiyama, *Org. Lett.* **2001**, *3*, 2649; c) S. V. Ley, C. Ramarao, A. Lee, N. Østergaard, S. C. Simth, I. M. Shirley, *Org. Lett.* **2003**, *5*, 185; d) T. Ishida, R. Akiyama, S. Kobayashi, *Adv. Synth. Catal.* **2003**, *345*, 576; e) T. Ishida, R. Akiyama, S. Kobayashi, *Adv. Synth. Catal.* **2005**, *347*, 1189.
- [8] a) A. Sevreyns, D. E. De Vos, L. Fiermans, F. Verpoort, P. J. Grobet, P. A. Jacobs, *Angew. Chem. Int. Ed.* **2001**, *40*, 586; b) J. W. Yang, H. Han, E. J. Roh, S. G. Lee, C. E. Song, *Org. Lett.* **2002**, *4*, 4685.
- [9] a) B. M. Choudary, N. S. Chowdari, M. L. Kantam, K. V. Raghavan, *J. Am. Chem. Soc.* **2001**, *123*, 9220; b) B. M. Choudary, N. S. Chowdari, K. Jyothi, M. L. Kantam, *J. Am. Chem. Soc.* **2002**, *124*, 5341.
- [10] a) L. C. Branco, C. A. M. Afonso, *Chem. Commun.* **2002**, 3036; b) C. E. Song, D. Jung, E. J. Roh, S. Lee, D. Y. Chi, *Chem. Commun.* **2002**, 3038; c) L. C. Branco, C. A. M. Afonso, *J. Org. Chem.* **2004**, *69*, 4381.
- [11] For example, solubility of OsO<sub>4</sub> in CCl<sub>4</sub> and water is 3.75 and 0.07 g mL<sup>-1</sup>, respectively: L. H. Anderson, D. M. Yost, *J. Am. Chem. Soc.* **1938**, *60*, 1822.
- [12] a) H. L. Kwong, C. Sorato, Y. Ogino, H. Chen, K. B. Sharpless, *Tetrahedron Lett.* **1990**, *31*, 2999; b) M. Minato, K. Yamamoto, J. Tsuji, *J. Org. Chem.* **1990**, *55*, 766.
- [13] N. A. Milas, S. Sussman, H. S. Mason, *J. Am. Chem. Soc.* **1939**, *61*, 1844.
- [14] In theory, there should be 0.5 equivs. K<sub>3</sub>Fe(CN)<sub>6</sub> remaining after the AD reaction in the reaction mixture, since originally 2.5 equivs. K<sub>3</sub>Fe(CN)<sub>6</sub> were used to ensure excess secondary oxidant. This would require 0.25 equivs. of EVE. We used 0.40 equivs. EVE to ensure to counter this 0.25 equivs. excess of oxidant.
- [15] Efforts to use *N*-methylmorpholine oxide as a secondary oxidant in the EVE-mediated chemoentrainment experiment were unsuccessful. Recycling experiments showed a precipitous drop in yields of AD at the third repetition.