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# Osmylated macroporous resins: safe, highly efficient and recyclable catalysts for asymmetric aminohydroxylation of olefins†

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**Osmylated macroporous resins displayed excellent catalytic performances in the asymmetric aminohydroxylation of olefins and, moreover, these resins were easily recovered and reused without any significant decrease in catalytic efficiencies.**

Today, because of 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 osmium-catalysed aminohydroxylation (AA) of olefins provide one of the most elegant methods for the synthesis of chiral aminoalcohols in enantiomerically enriched form.[1] Although this reaction offers a number of processes that could be applied to the synthesis of chiral drugs, natural products, fine chemicals, *etc*., the high cost of osmium and the chiral alkaloid ligands as well as the high toxicity and volatility of osmium component has made their large-scale industrial applications with these reagents difficult. Another serious problem of homogeneous Os-catalysed reactions is that toxic osmium metal can exist as an impurity in the prepared products which will be a deathblow especially to drug intermediates.[2] Thus, it would be highly desirable to develop the immobilised catalyst system that could be readily separated from the reaction mixture and provide the possibility of reuse of catalyst. Surprisingly, in spite of the importance of this issue, only a few attempts to solve the above-mentioned problems have been made.[3–5] Several years ago, we first reported heterogeneous asymmetric aminohydroxylation of olefins using silica-supported bis-cinchona alkaloid.[3] After our report, another example of a cinchona alkaloid immobilised onto polymer supports came from Nandana[4] and Salvadori.[5] Although using our silica-supported bis-cinchona alkaloid, up to > 99% ee was achieved in the AAs of *trans*-cinnamate derivatives, this type of attempt to immobilise osmium on solid-supported alkaloid ligands failed due to severe osmium leaching. Very recently, Choudary and his coworkers employed their $K_2OsO_4{\cdot}2H_2O$ anchored by the ion exchange method onto layered double hydroxides (LDH) for the AAs of olefins.[6] Although it was reported that LDH–$OsO_4$ was used for three cycles in AA of *trans*-stilbene (*ca*. 60% ee per each cycle), the activity of catalyst decreased drastically upon reuse. On the other hand, the microencapsulated osmium tetroxide in a polymer matrix developed by Kobayashi[7] might be used as a recyclable catalyst for asymmetric aminohydroxylation of olefins. However, it has been known that the activity of this polymeric osmium tetroxide is too low and thus the amount (5 mol%) of this catalyst needed to achieve reasonable reaction rate is too large compared to that (0.2–1 mol%) needed in homogeneous AD reactions.

In searching for the more efficient and practical immobilisation method for $OsO_4$, we have very recently found that $OsO_4$ can be simply immobilised by osmylation onto the resins bearing residual vinyl groups such as Amberlite XAD-4, XAD-7 and XAD-16, *etc*. (Fig. 1).[8] According to XPS (X-ray Photoelectron Spectroscopy) analysis of the osmylated resins, osmium exists in forms of Os(VI) monoglycolate and Os(IV) bisglycolate.[8] These osmylated resins are air-stable, nonvolatile and thus much easier to handle than their homogeneous counterpart ($OsO_4$). Moreover, the resin-bound $OsO_4$ exhibited excellent catalytic performances in asymmetric dihydroxylation of olefins, and could be easily recovered by simple filtration and reused for consecutive reactions without any significant loss of catalytic efficiency. These results encouraged us to examine the efficiency of our osmylated resins in the AA reactions. We report here our preliminary findings.

The AA reactions of olefins using the osmylated macroporous resins (XAD-4-$OsO_4$ and XAD-16-$OsO_4$, ~ 0.36 mmol Os per gram resin) were carried out with AcNHBr–LiOH as the oxidant/nitrogen source under the same reaction conditions adopted for the analogous homogeneous process.† The results are summarised in Table 1. The data show that all reactions employing the osmylated resins gave excellent ees ( > 99% ee for all *trans*-cinnamate derivatives). Moreover, in the case of cinnamate derivatives, the chemical yields obtained in this study were significantly higher than those[9] achieved in homogeneous conditions (entries 1 and 2 in Table 1).

The efficiency with which the osmylated resin can be recycled has also been examined. For these experiments, osmylated resins are loaded onto a commercially available small cylindrical container with mesh wall (MicroKan™), in order to minimise grinding of osmylated resin through stirring during the reaction. The dark-coloured Amberlite XAD-4-Os complex was recovered by simple filtration after each reaction, which is not possible in a homogeneous process. The alkaloid ligand was also almost quantitatively recovered by simple acid–base extraction. The AA reactions were repeated with these recovered resins without any further addition of osmium. As shown in Table 2, the recovered catalyst could be used for three times without any significant loss of yields and enantioselectivity. However, leaching of $OsO_4$ into solution has been found, causing increased turnover time upon reuse.[10]

On the basis of all these results it can be assumed that osmium anchored to resins is highly exposed to the oxidant, and once

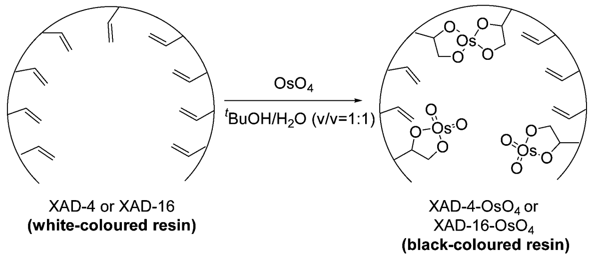

**Fig. 1** Osmylated macroporous resins.

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† Electronic supplementary information (ESI) available: experimental procedure. See http://www.rsc.org/suppdata/cc/b3/b303022a/

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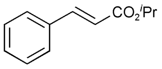
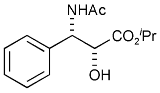
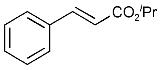
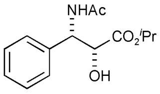
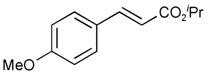
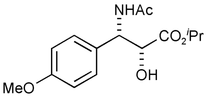
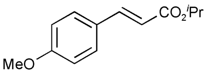
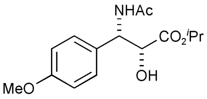
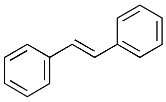
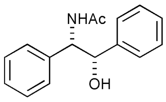
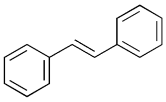
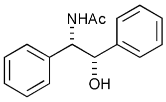
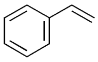
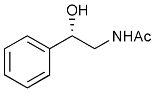
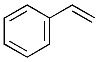
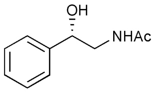
**Table 1** Acetamide-based asymmetric aminohydroxylation of various olefins using Amberlite XAD-4 or XAD-16·Os complexes[a]

| Entry | Resin-Os | Substrate | Product | Time/h | Regio-selectivity[b] | ee (%)[c] | Yield (%)[d] |
|---|---|---|---|---|---|---|---|
| 1 | XAD-4 |  |  | 5 | > 20 : 1 | > 99 | 93 |
|  | XAD-16 |  |  | 5 | > 20 : 1 | > 99 | 90 |
| 2 | XAD-4 |  |  | 5 | > 20 : 1 | > 99 | 83 |
|  | XAD-16 |  |  | 5 | > 20 : 1 | > 99 | 80 |
| 3[e] | XAD-4 |  |  | 24 | — | 88 | 48 |
|  | XAD-16 |  |  | 24 | — | 90 | 41 |
| 4[f] | XAD-4 |  |  | 4 | 5.6 : 1 | 84 | 39 |
|  | XAD-16 |  |  | 4 | 5.2 : 1 | 84 | 40 |

[a] All reactions were performed on a 1 mmol scale using 4 mol% of Amberlite XAD-4·$OsO_4$ or Amberlite XAD-16·$OsO_4$, 5 mol% of $(DHQ)_2PHAL$, AcNHBr (1.1 mmol) and LiOH (1.02 mmol) in $^t$BuOH–$H_2O$ (v/v = 1 : 1) at 4 °C. [b] Determined by $^1H$ NMR spectroscopy. [c] Determined by chiral HPLC. See ref. 9. [d] Isolated yield. [e] KOH as base and $^i$PrOH–$H_2O$ (v/v = 1 : 1) as the solvent was used. [f] $CH_3CN$–$H_2O$ (v/v = 1 : 1) was used as the solvent.

**Table 2** Acetamide-based asymmetric aminohydroxylation of isopropyl *trans*-cinnamate with recycled Amberlite XAD-4·$OsO_4$ complex[a]

| Run | Time/h | Yield (%)[b] | ee (%)[c] |
|---|---|---|---|
| 1 | 6 | 91 | > 99 |
| 2 | 15 | 86 | > 99 |
| 3 | 24 | 79 | > 99 |

[a] All reactions were performed on a 1 mmol scale using 4 mol% of Amberlite XAD-4·$OsO_4$, 5 mol% of $(DHQ)_2PHAL$, AcNHBr (1.1 mmol) and LiOH (1.02 mmol) in $^t$BuOH–$H_2O$ (v/v = 1:1) at 4 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis. See ref. 9.

oxidised, it became free to react with other more readily accessible alkenes and ligands in solution. After the oxidant and starting alkenes are consumed the residual osmium may form new bonds with less accessible resin-bound vinyl groups.

In summary, an efficient, economical and eco-friend Os-catalysed asymmetric aminohydroxylation of olefins has been developed by using osmylated macroporous resins. The reactions proceeded with excellent enantioselectivity ( > 99% ee for all *trans*-cinnamate derivatives) and regioselectivity. After reaction, the resins could be quantitatively recovered from the reaction mixture by simple filtration. And the recovered catalyst could also be reused for consecutive reactions without any significant loss of catalytic efficiencies. To the best of our knowledge, our result is the most successful work reported until now on the osmium-mediated asymmetric aminohydroxylation of olefins. Optimisation studies on reaction conditions, especially to minimise osmium leaching, are currently in progress.

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