

# Immobilized Osmium Catalyst for Asymmetric Dihydroxylation of Olefins

**Moumita Roy**

Department of Chemistry, Ramsaday College, Amta, Howrah, West Bengal, India

Corresponding Author's Email: moumitaroy.iict@gmail.com

## ABSTRACT

Chiral vicinal diol units are important intermediates in different natural products and drugs. Among various synthetic routes available in the literature, osmium-catalyzed Sharpless asymmetric dihydroxylation (AD) of alkenes is the most popular method among organic synthetic communities to afford diversified enantiomerically enriched 1, 2-diols. However, the high cost of osmium and chiral ligands, as well as the high toxicity of osmium, can contaminate target products, limiting the application of AD reactions in large-scale processes. Heterogeneous catalysts have an added advantage over homogeneous catalysts due to easy recovery and recyclability, which are beneficial in terms of economic, and environmental concerns. In this direction, various research groups from different parts of the world have worked to overcome the demerits of the homogeneous osmium catalysts by immobilizing the active catalytic center onto heterogeneous support, and have achieved very good success. This review discusses recent work on supported osmium catalysts for AD reactions, highlighting their benefits and drawbacks. It serves as a useful guide for the continued development of improved catalytic systems.

**Keywords:** Asymmetric Dihydroxylation; Chiral Vicinal Diols; Osmium; Heterogeneous; Catalyst

## Introduction

Catalytic asymmetric reactions by transition metals are of immense importance to synthesize enantiomerically pure molecules. Several advantages of such strategies include their economic benefit, potential environmental friendliness, and simplicity of purification (Lapuh, Mazeh & Besset, 2020; Cabré, Verdaguer & Riera, 2022; Fu, Chen & Nishihara, 2021). The fascinating transition metal complex catalysts, visualized to mimic enzymes in many complicated asymmetric reactions have been realized with high success. Unlike with enzymes, the synthesis of either of the desired antipodes of the chiral molecule using transition metal complexes, unlike with enzymes, forms a significant advancement (Leenders *et al.*, 2015). In addition to this, the metal complexes have a widened scope of applicability that includes a large variety of reactions with a broader substrate choice. It is due to this distinct presentation of their features that these catalysts are ideal for making organic molecules. Hydrogenation catalysts (Knowles & Sabacky, 1968; Miyashita *et al.*, 1980) and oxidation catalysts (Kolbe, VanNieuwenhze & Sharpless, 1994; Wail *et al.*, 1989; Wang & Sharpless, 1994; Lu, Xu & Yang, 2000; Zhang *et al.*, 1990; Jacobsen *et al.*, 1991) are some

of the synthetic asymmetric catalysts, which compete with enzymes that have long been considered monopolists in terms of enantioselectivity.

Chiral vicinal diol units are important intermediates in different natural products and also in drugs e.g. Bicalutamide, Diltiazem hydrochloride, and Taxol. Asymmetric cis-dihydroxylation of olefins using osmium compounds is highly significant in this direction (Mushtaq *et al.*, 2023). The first catalytic version, one of the cornerstones for fine organic synthesis, i.e. AD of alkenes is a well-established method for the synthesis of various enantiomerically pure vicinal diols (Willingh, 2021). The importance of the process lies in the utilization of cinchona alkaloid-based chiral ligands, which opened an alternative path to allow the catalytic use of toxic and volatile osmium (Schroder, 1980; Bolm & Gerlach, 1997; Bolm & Gerlach, 1998). However, the large-scale application of homogeneous catalytic systems faced challenges due to the prohibitive cost of osmium, and chiral ligands. In addition, there is always a probability of contamination of the target product with toxic osmium.

Therefore, there is an urgent need to replace soluble catalysts with heterogeneous catalysts that are recyclable and easily separated from the reaction mixture with little to no effluent emissions. Hence, the future and well-being of mankind largely depend on the development of science and technology, especially in the field of catalysis, which is related to the fight against environmental pollution, and the conservation of natural resources and energy.

Initial attempts were made to immobilize the ligand on a heterogeneous support, e.g., polymer, silica gel and subsequent heterogenization of Os via complexation with ligands but with very limited success or no success in terms of recovery and re-use of the precious Os. This was explained due to the equilibrium between anchored osmium tetroxide and soluble osmium tetroxide during the reaction (Han & Janda, 1996; Bolm & Gerlach, 1998; Kim & Sharpless, 1990; Bolm, Hildebrand, & Muniz, 2000). The microencapsulation technique (Nagayama, Endo & Kobayashi, 1998; Nagayama, Endo & Kobayashi, 1998; Kobayashi, Ishida & Akiyama, 2001; Ishida, Akiyama & Kobayashi, 2003) first adopted by Kobayashi *et al.* addressed the issue and opened up a new direction towards supported osmium catalysts. Different types of materials, such as polymers, silica-based materials, ion exchangers, ionic liquids, etc. were explored.

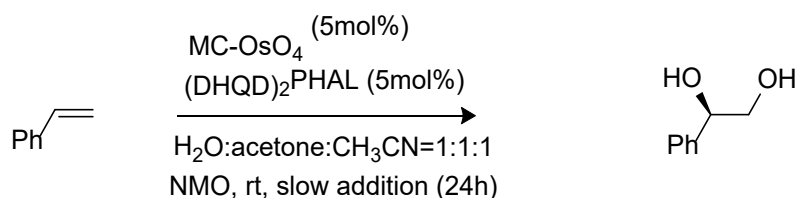
Developing good reoxidation systems for Os (VI) is also highly desirable. Numerous reoxidation systems were evolved, of which the two maximums generally used are based totally on NMO (N-methylmorpholine-N-oxide) (Knowles & Sabacky, 1968) and potassium ferricyanide (Minata, Yamamoto & Tsuji, 1990; Sharpless *et al.*, 1991). Using ferricyanide in AD reactions has certain drawbacks that encompass managing huge amounts of salts (1.4 g/mmol alkene) and effluent disposal, which makes ferricyanide oxidant no longer a real desire for large-scale utility. Of late, the NMO-based hydroxylations are revigorated due to the simplicity of the unit operation. *N-methylmorpholine* (NMM) formed as a byproduct from the reduction of NMO is easy to remove and recycle after oxidation to NMO in an attempt to further add value.

## Literature Review

### Immobilized Osmium Catalyst on Polymeric Support

Microencapsulation of OsO<sub>4</sub> in polymer capsules *via* the interaction of pi (π) electrons from polystyrene benzene rings with empty d-orbitals of osmium provides a recyclable and reusable osmium catalyst for AD reactions (Nagayama, Endo & Kobayashi, 1998; Kobayashi, Nagayama & Endo, 1998; Kobayashi, Ishida & Akiyama, 2001; Ishida, Akiyama & Kobayashi, 2003). This initial attempt with polystyrene microencapsulated catalyst (PS-MC Os) (Nagayama, Endo & Kobayashi, 1998) afforded low yields, selectivity as well as recovery of the catalyst. Later on, they introduced acrylonitrile-butadiene-polystyrene encapsulated osmium catalyst (ABS-MC Os) (Nagayama, Endo & Kobayashi, 1998), and poly[4-(phenoxyethoxymethyl)styrene-co-styrene] microencapsulated osmium (PEM-MC Os) (Kobayashi, Ishida & Akiyama, 2001) which showed improved activity (Table-1).

**Table 1: AD Reaction of Styrene by Microencapsulated Osmium Catalysts (MC-OsO<sub>4</sub>)**

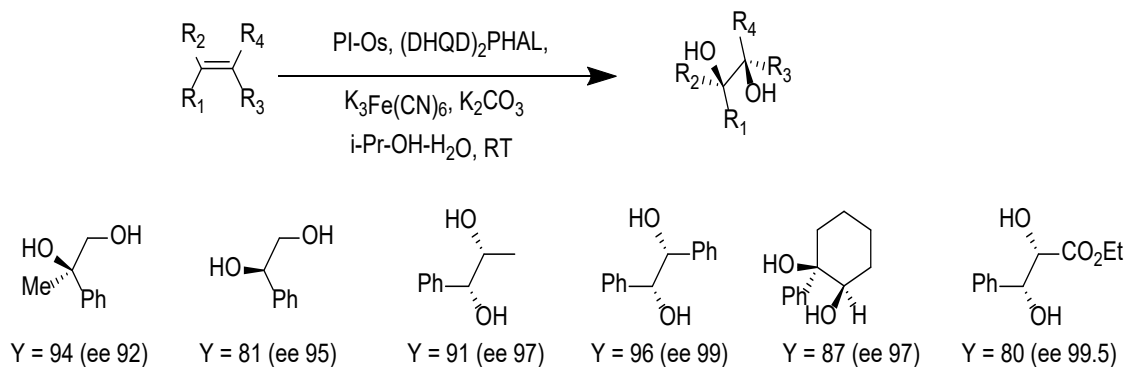


Entry	MC-OsO <sub>4</sub>	Yield (%), (ee (%), recovery (%))		
		1 <sup>st</sup> run	2 <sup>nd</sup> run	3 <sup>rd</sup> run
1.	PS	4 (-, 97)	-	-
2.	PEM	85 (78, 100)	66 (78, 100)	84 (78, 100)
3.	ABS	81 (94, 88)	83 (94, 74)	84 (94, 74)

\*PS: Polystyrene; PEM: Poly[4-(phenoxyethoxymethyl)styrene-co-styrene]; ABS: Acrylonitrile-butadiene-polystyrene

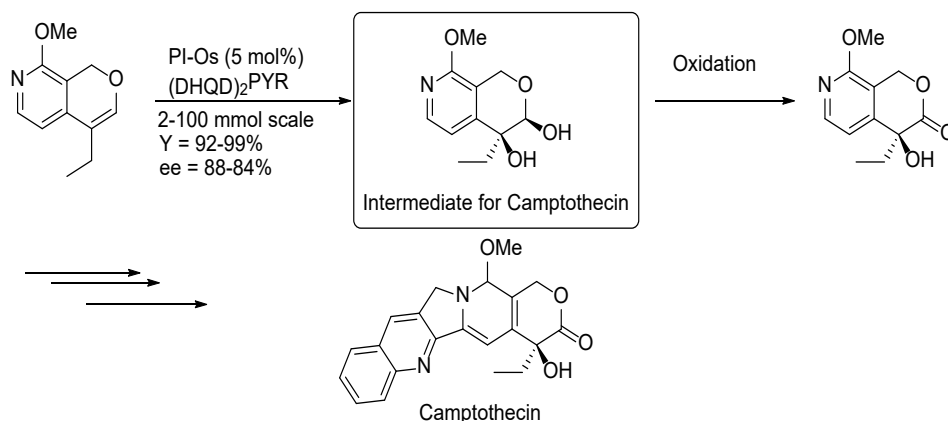
The same group further reported the development of air-stable, nonvolatile and less toxic “polymer-incarcerated osmium (PI Os) catalysts” (Ryo *et al.*, 2012) for AD reactions. The catalysts were prepared using microencapsulation followed by cross-linking so that they became insoluble in common organic solvents. Acute toxicity assays showed these catalysts were benign. XAFS analysis of the catalyst revealed the reduction of Os (VIII) to Os (IV) during catalyst preparation.

The catalyst produced excellent yield as well as enantioselectivity for different olefins with very low leaching of Os (Figure 1).



**Figure 1: AD of Alkenes Using PI Os Catalyst**

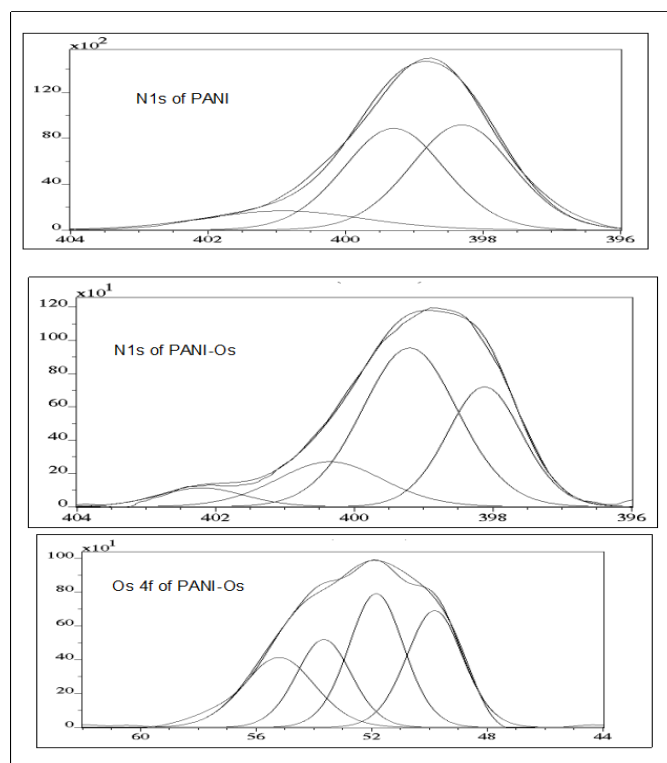
PI Os found its relevance in the high-yielding and enantiomerically enriched scale-up synthesis of an important intermediate of Camptothecin which is a known anti-cancer drug (Figure 2).



**Figure 2: Synthesis of Camptothecin Intermediate Using PI-Os Catalyst**

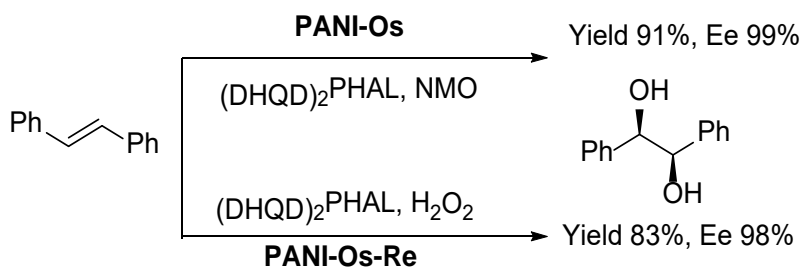
Polyaniline (PANI), which is prepared from readily available commodity chemicals like aniline, is extensively studied as a conducting polymer for applications in the fields of electronics and optics. PANI has excellent environmental stability and attractive redox properties. In addition, PANI exhibited modular doping levels through acid and de-doping through base, inertness and insolubility in aqueous and common non-aqueous (organic) solvents. Such characteristics are paramount for qualification as support in heterogeneous catalysis.

By exploiting modular redox behavior of polyaniline, a simplified and convenient protocol for the immobilization of osmium onto polyaniline was developed by Choudary *et al.* (2006). The catalyst was well characterized by different instrumental techniques namely FTIR, XPS, UV-VIS-DRS, and EDAX. The FT-IR spectrum of PANI-Os showed the presence of the Os-O bond. UV-Visspectrum of the catalyst also supported the same. XPS analysis of PANI-Os revealed the presence of Os (IV) and Os (II) oxidation states (Figure 3).



**Figure 3: XPS Spectrum of PANI-Os**

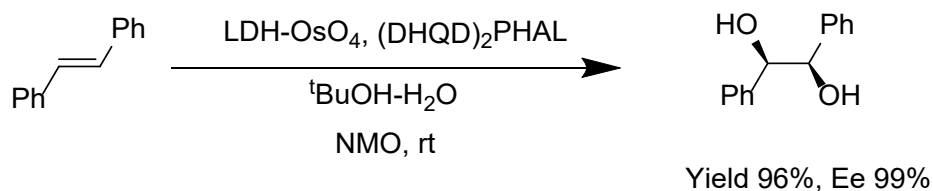
When this polyaniline-anchored osmium catalyst was used in the AD of alkenes, it exhibited very good reusability up to 5 cycles. They have prepared one bi-functional PANI-Os-Re catalyst which can utilize  $\text{H}_2\text{O}_2$  in place of NMO as the co-oxidant (Figure 4).



**Figure 4: PANI-Os and PANI-Os-Re Catalyzed Dihydroxylation of Trans-stilbene Ion-exchanger-supported Osmium Catalysts**

Choudary and co-workers contributed a lot (Choudary *et al.*, 2001; Choudary *et al.*, 2001; Choudary *et al.*, 2002; Choudary *et al.*, 2004) to asymmetric dihydroxylation catalyzed by ion-exchanger osmium catalysts. In their first paper (Choudary *et al.*, 2001a) they explored layered double hydroxides of Mg and Al (LDH), chemically functionalized silica, and polymeric resin as support material for osmium in catalytic AD of alkenes.  $\text{OsO}_4^{2-}$  is swapped with LDH-Cl to afford LDH- $\text{OsO}_4$ . Similarly, the  $\text{OsO}_4^{2-}$  is also anchored onto quaternary ammonium groups of silica and organic resin to obtain  $\text{SiO}_2\text{-OsO}_4$  and resin- $\text{OsO}_4$ . All of these catalysts were studied using FTIR, and UV-DRS, which indicated that most of the osmate was

unaffected during the exchange process. SEM-EDX was used to evaluate the osmium content and it was observed that LDH-OsO<sub>4</sub> had the maximum osmium content. All the catalysts were explored for the Sharpless AD of *trans*-stilbene and afforded excellent yield and enantioselectivity (Figure 5).



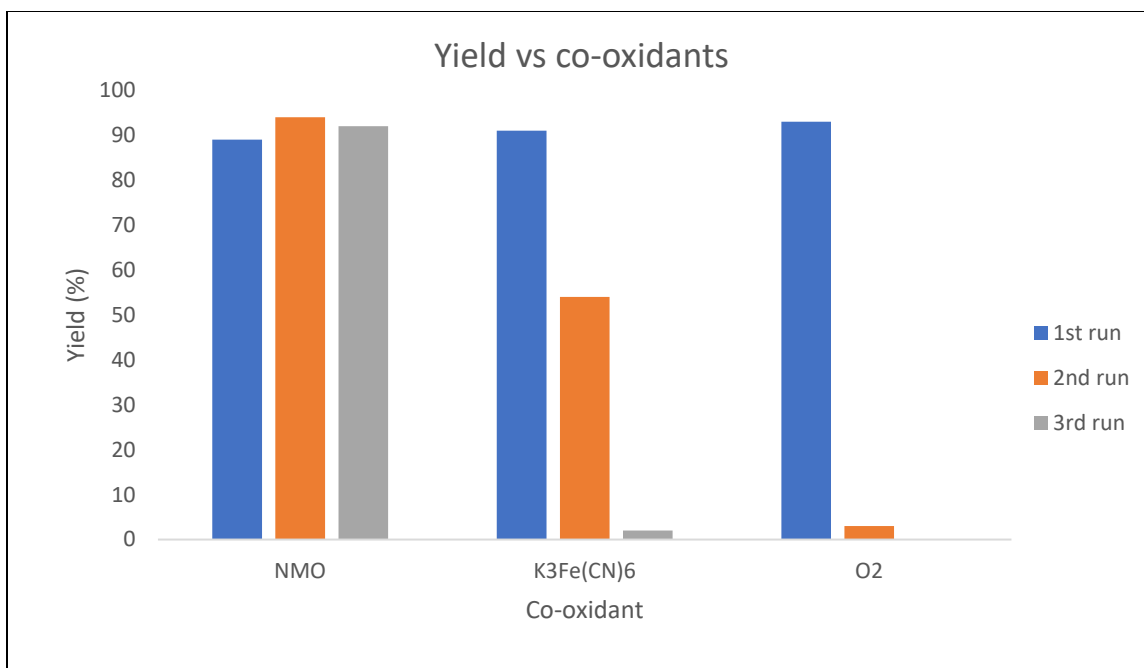
**Figure 5: AD of *Trans*-stilbene Using LDH-OsO<sub>4</sub>**

To check the catalytic efficacy, LDH-OsO<sub>4</sub> is further used in the dihydroxylation of other alkenes (Table 2).

**Table 2: AD of Alkenescatalyzed by LDH-OsO<sub>4</sub>**

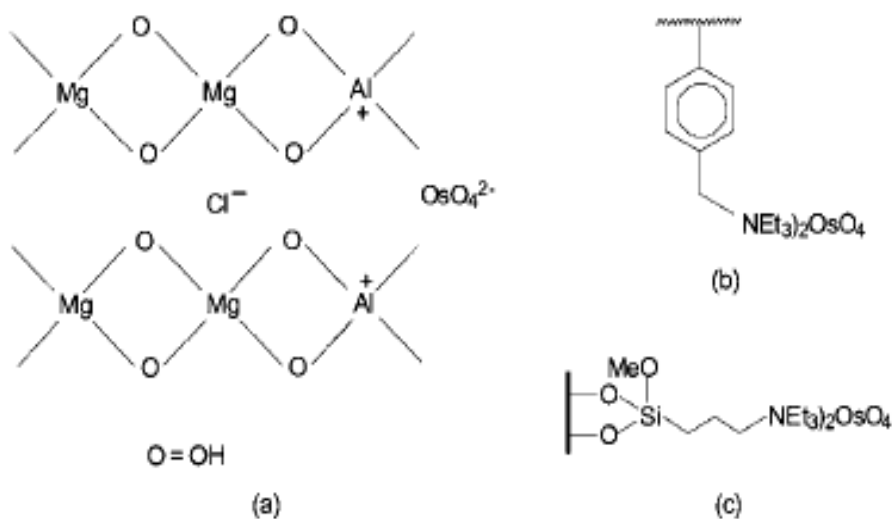
Entry	Substrate	Yield (%)	Ee(%)
1.		89	90
2.		96	97
3.		94	95
4.		90	82
5.		94	77
6.		92	91

Catalysts were almost quantitatively separated by filtration and reused with retention of catalytic activity over a number of cycles. In their follow-up article (Choudary *et al*, 2002), they published a detailed study on the use of various co-oxidants to understand the scope, limitations, and activity of the catalyst. The combination of NMO and LDH-OsO<sub>4</sub> exhibited excellent activity over a number of cycles whereas when K<sub>3</sub>Fe(CN)<sub>6</sub> and O<sub>2</sub> were utilized as co-oxidants, the catalyst lost its activity after the first use only (Figure 6).

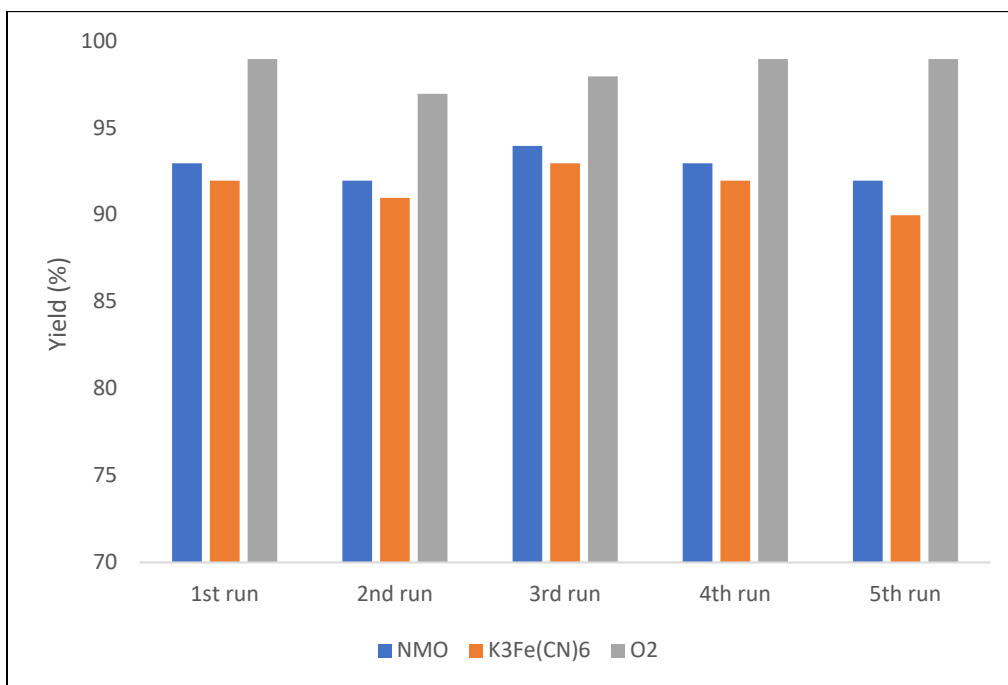


**Figure 6: Schematic Presentation of Effect of Different Co-oxidants in the Dihydroxylation of  $\alpha$ -methylstyrene Using LDH-OsO<sub>4</sub>**

As envisaged that leaching of osmate from LDH-OsO<sub>4</sub> in the presence of K<sub>3</sub>Fe(CN)<sub>6</sub> and O<sub>2</sub> was the main cause of the deactivation of the catalyst, they designed polymeric resin and chemically modified silica-supported osmium catalysts (Figure 7) which showed far better activity in AD of alkenes in presence of Fe(CN)<sub>6</sub><sup>3-</sup> and oxygen co-oxidants. Resin-OsO<sub>4</sub> showed very high reusability with NMO, K<sub>3</sub>Fe(CN)<sub>6</sub>, and O<sub>2</sub> (Figure 8).



**Figure 7: Schematic Presentation of Different Supported Osmium Catalysts**



**Figure 8: Reusability of Resin-OsO<sub>4</sub> Catalyzed Dihydroxylation of  $\alpha$ -methylstyrene Using Various Co-oxidants**

The same group has further reported a trifunctional catalyst to achieve multistep reactions in one pot. A trifunctional LDH-PdOsW catalyst was prepared by exchanging  $\text{PdCl}_4^{2-}$ ,  $\text{OsO}_4^{2-}$  and  $\text{WO}_4^{2-}$  from  $\text{Na}_2\text{PdCl}_4$  and  $\text{K}_2\text{OsO}_4$  and  $\text{Na}_2\text{WO}_4$  respectively, onto chloride-saturated LDH. The catalyst was characterized using various instrumental techniques, such as X-ray photoelectron spectroscopy which showed the oxidation state of the catalytically active metals such as Pd, Os, and W. XRD data categorically identified the edge alignment of the  $\text{PdCl}_4^{2-}$ ,  $\text{OsO}_4^{2-}$  and  $\text{WO}_4^{2-}$ . Tandem Heck, AD, and N-oxidation afforded the desired diol with excellent yield and enantioselectivity (Figure 9 & Table 3).



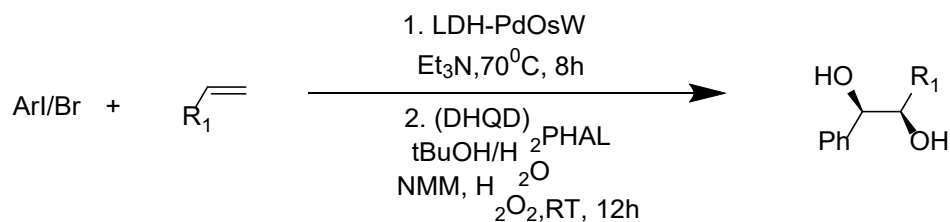
**Figure 9: Proposed Reaction Sequences Involving LDH-PdOsW**

This novel technique allowed low-priced bulk chemicals for the in-situ preparation of chiral diols. Cheaper  $\text{H}_2\text{O}_2$  is used to oxidize NMM to NMO which completes the catalytic cycle to



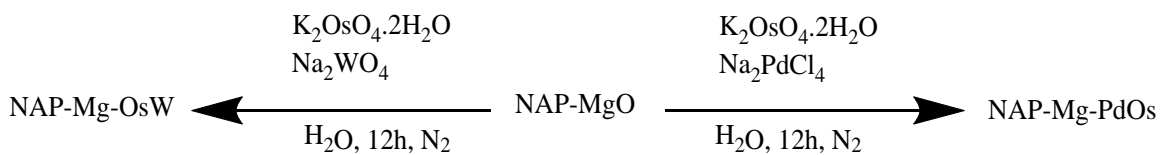
produce the end product i.e., substituted optically pure diols. As per the authors, controlled addition of H<sub>2</sub>O<sub>2</sub> promotes hydrolysis of osmium mono-glycolate ester and eventually higher ee was achieved. Catalyst was recovered almost quantitatively via filtration and repeated use for five times showed only 3% yield loss but ee remained 99%.

**Table 3: LDH-PdOsW Catalyzed Heck-AD Reactions**



Sl. No.	Haloarene	Alkene	Di-ol product	Yield (%)	ee (%)
1.	PhI			85	99
2.				93	99
3.	PhBr			90	99
4.	PhI			90	47


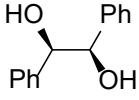
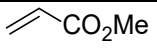
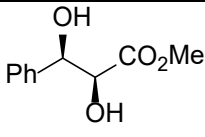
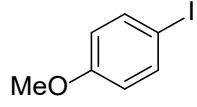
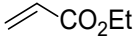
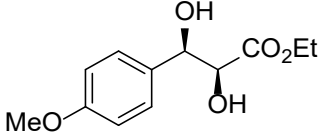
Choudary *et al.* (2004) reported nanocrystalline magnesium oxide (NAP-MgO) supported bifunctional catalysts to promote one-pot sequential Heck and AD reactions to afford diversified optically active diols. Nanocrystalline metal oxides have interesting properties as support materials because they have many surface sites, such as crystal corners, edges, ion vacancies, etc., which improve surface reactivity. NAP-Mg-PdOs and NAP-Mg-OsW catalysts were obtained by treating NAP-MgO with an aqueous solution of Na<sub>2</sub>PdCl<sub>4</sub>, K<sub>2</sub>OsO<sub>4</sub>, and Na<sub>2</sub>WO<sub>4</sub> (Figure 10).



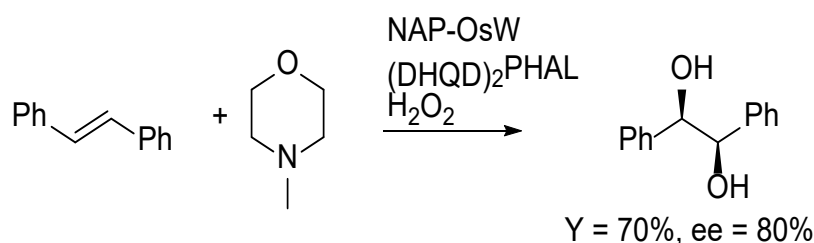
**Figure 10: Synthesis of NAP-Immobilized bi-functional Catalysts**

Using NAP-PdOs in the one-pot Heck followed by dihydroxylation starting from aryl iodides and alkenes, diversified diols were obtained in the same reaction vessel (Table 4). Similarly, NAP-OsW was utilized in the concomitant dihydroxylation and N-oxidation (Figure 11).

**Table 4: Tandem Heck-AD reaction using NAP-PdOs**

Entry	Aryl halide	Olefin	Product	Yield%/ee%
1	PhI			80/85
2	PhI			85/73
3				82/78

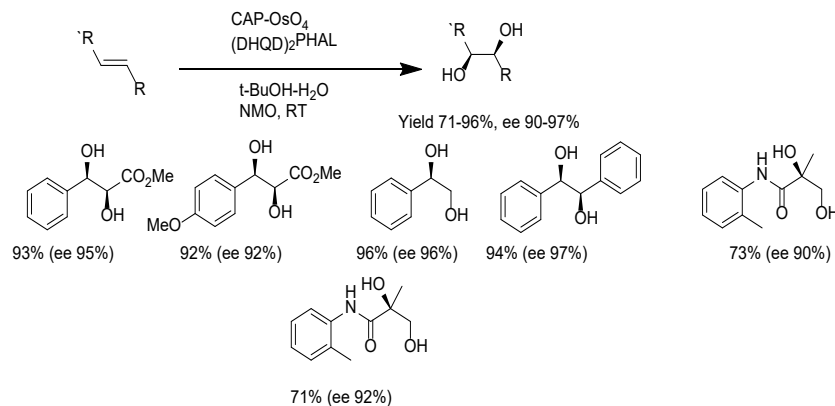
Reaction condition: NAP-PdOs (3 mol %), aryl halide (1 mmol), olefin (1 mmol) and Et<sub>3</sub>N (1.3 mmol) in CH<sub>3</sub>CN (2 mL) were stirred at 70 °C for 12 – 16 h. After completion of the Heck coupling, the heating was stopped and NMO (1.3 mmol) and (DHQD)<sub>2</sub> PHAL (7.8 mg, 0.01 mmo) in t-BuOH-H<sub>2</sub>O (5 : 1, 6 mL) were added under stirring



**Figure 11: One Pot N-oxidation and AD Using NAP-OsW**

Dehury and Hariharakrishnan, (2007) reported a recyclable “osmate-exchanged chloroapatite (CAP-OsO<sub>4</sub>) catalyst” for AD reaction of alkenes. Weakly amphoteric apatites can act as supports for diversified ions *i.e.*, cations and anions as they can be easily placed into the apatite framework owing to its high propensity for ion exchange. CAP-OsO<sub>4</sub> was prepared by exchanging OsO<sub>4</sub><sup>2-</sup> onto chloroapatite. The catalyst was explored in AD reactions on a variety of alkenes containing diversified functional groups e.g. α,β-unsaturated carbonyls, amides, carbonyls, and esters. A good to moderate yield of product was obtained along with high

optical purity. The catalyst was recovered and reused for multiple times without a noticeable drop in activity. Osmium leaching from the reaction mixture was also tested and found to be nominal.


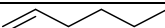


**Figure 12: CAP-OsO<sub>4</sub> Catalyzed AD Reaction**

Shilpa, Manna and Rana (2015) reported a bioinspired nanoparticle assembly route to obtain a highly effective immobilized osmium catalyst for the AD reactions. Biomaterials have gained immense significance in organic synthesis due to the control achieved over the reaction can be used to develop new routes to functional materials. Thus Poly (allylamine) hydrochloride (PAH) and colloidal silica were used to get a microsphere structure to provide the required textural property and stability to hold osmium securely. Different analytical methods such as DLS, SEM, TEM, EDX, FTIR, UV-Vis, XPS are used to characterize the catalyst thoroughly. The SEM images depicted spherical morphology and TEM analysis showed the formation of silica nanoparticles. XPS analysis revealed the presence of hexavalent osmium. FTIR analysis showed an effective interaction between osmate and PAH. The scope of the catalytic system was studied for AD reaction utilizing NMO as a co-oxidant (Table 5). The efficiency of the catalyst is explained by the advantage of the encapsulation of the catalytic center by polyamines leading to increased activity and the structural stability provided by the inorganic material.

**Table 5: Synthesis of Chiral Diols Using Microsphere Encapsulated Os Catalyst**

Entry	Alkene	Conversion of alkene (%)	Yield of diols (%)	Ee (%)
1.		99	94	98
2		99	96	98
3		99	99	>99

4		99	98	96
5		99	97	99

Reaction condition: Alkene (0.2 mmol), NMO (1.3 equiv.), Os@MS prepared using PAH (0.118 mol-% of Os w.r.t. olefin), CH<sub>3</sub>COCH<sub>3</sub>/H<sub>2</sub>O (12:1 v/v, 0.6 mL), room temp. (DHQD)<sub>2</sub>PHAL (0.01 equiv.) was used as the ligand and olefin was added slowly within a reaction period of 8 h.

### Ionic Liquid-modified Osmium Catalysts

Ionic liquid-mediated organic transformations draw attention due to their easy recovery and environmental concern. Qiu *et al.*, (2011) reported “1-methyl-3-(trimethoxysilyl) propylimidazolium chloride (MTMSPIm<sup>+</sup>Cl<sup>-</sup>)” ionic liquid modified bimodal mesoporous silica (FBMMs) to anchor osmium and the chiral ligand for the AD reaction. To prepare the catalyst, FBMMs were stirred with the acetonitrile/water solution of ((QN)<sub>2</sub>PHAL) and K<sub>2</sub>Os(OH)<sub>4</sub>.2H<sub>2</sub>O. Immobilization of the ionic liquid on to the mesoporous silica established through analysis by FTIR and pore sizes of the catalyst were calculated using nitrogen adsorption and desorption studies. XRD revealed the reduction in the mesostructure after the introduction of OsO<sub>4</sub>-(QN)<sub>2</sub>PHAL. Catalytic efficacy was demonstrated in the AD reaction of trans-stilbene. It showed good retention of chiral efficiency over five recycles but product formation dropped significantly e.g. yield loss over six cycles: 99% to 25%. This is attributed to the leaching of the osmium metal as well as the chiral ligand from the catalyst matrix.

### Conclusion

This review elucidates the importance and evolution of the supported osmium catalysts for the synthesis of syn diols which are the important building block for numerous biologically relevant organic molecules. Supported catalysts exhibited good to excellent recyclability which further reduces the cost of the goods as well as metal effluent. This is expected to serve as a guiding tool for further development in this field of osmium catalysis.

### Acknowledgement

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