User Guide - Catalytic Oxidations with Os EnCat™ Microencapsulated Osmium Tetroxide Catalysts

General Description:

The addition of osmium tetroxide (OsO_4) to olefins is one of the most reliable and efficient methods for the synthesis 1,2-diols. However, due to its high volatility and toxicity the use of osmium tetroxide is limited and particularly so at large scale. Os EnCat™40 overcomes these issues and offers the benefits of a homogeneous catalyst with the ease of handling of a heterogeneous catalyst.

Key Advantages of Os EnCat™40 Catalyst

Encapsulation of OsO_4 within a porous cross-linked polyurea matrix offers key advantages:

- Easy to handle form of osmium catalyst - *versus* OsO_4
- Non-volatile - *reduced potential of hazardous exposure*
- Facile recovery of catalyst – *simple filtration*
- Low residual osmium levels in final product - *ease of clean-up*
- Potential for catalyst recycle - *sustainability*
- No OsO_4 vapour over catalyst - *increased ease of storage, transport and use*

Os EnCat™40 Properties

Name	Os Metal Content (w/w%)	OsO_4 Loading (mmol/g)	Particle Size Range µm (average)
Os EnCat™ 40	4.8-5.7	0.25-0.30	40-300 (165)

Dihydroxylation Reaction:

In the presence of a co-oxidant, osmium tetroxide catalyses the formation of 1,2-diols from the corresponding olefins.[1] Similarly, catalytic amounts of Os EnCat™ in the presence of stoichiometric quantities of a secondary oxidant successfully converts a variety of alkyl and aryl olefins to their corresponding diols.[2]

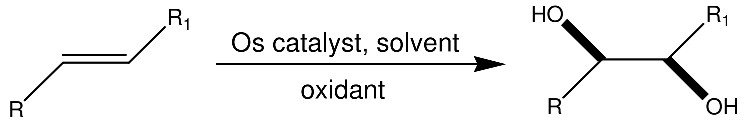
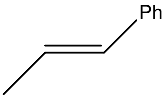
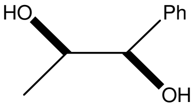
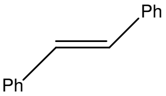
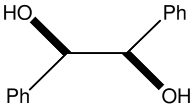
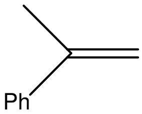
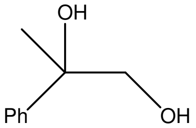
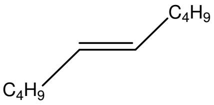
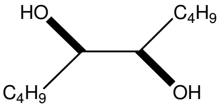
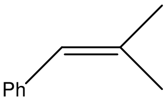
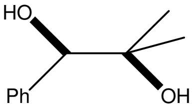
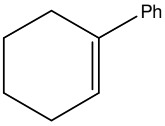
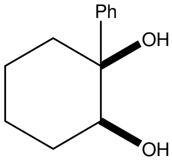
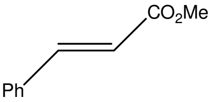
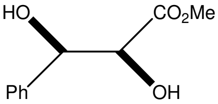
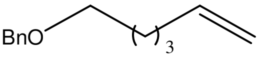
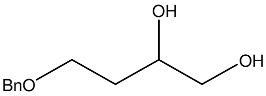


Table 1 summarises some of the substrates that have been successfully converted to their respective diol using Os EnCat™40:

Table 1. Dihydroxylation Reaction of Diverse Olefins using Os EnCat™40

Substrate	Product	Yield[a,b]/ %
		80
		84
		90
		84
		83
		82
		85
		73

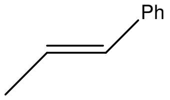
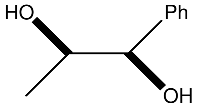
Reagents and conditions: Olefin (1 mmol), NMO (1.5 mmol), Os EnCat™40 (5 mol%), acetone/H_2O (10:1), rt, 12-24 h

[a] based on isolated yields

[b]crude product typically contains osmium levels of 10-40 ppm (ICP measurements)

The utility of Os EnCat™40 has been extended to include asymmetric dihydroxylation (AD) reactions. For example, using Sharpless conditions[3] in the presence of hydroquinidine 1,4-phthalazinediyl $(DHQD)_2$PHAL ligand, stereo selective dihydroxylation of *trans*-β-methyl styrene occurs (Table 2).

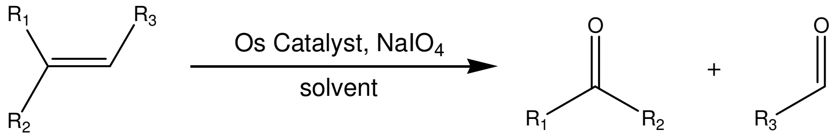
Table 2. Asymmetric Dihydroxylation Reaction of *trans*-β-Methyl styrene

Substrate	Product	Yield/ %	ee/ %
		97	94

Reagents and conditions: Olefin (1 mmol), NMO (1.5 mmol), Os EnCat™40 (5 mol%), $(DHQD)_2PHAL$ 10 mol%, acetone/H_2O (10:1)

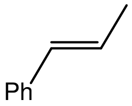
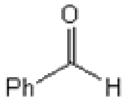
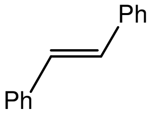
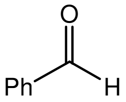
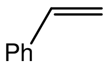
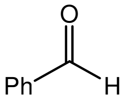
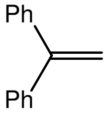
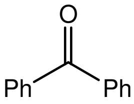
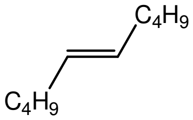
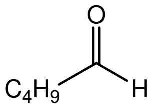
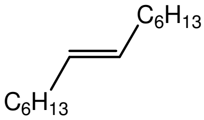
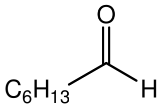
Oxidative Cleavage of Olefins and Glycols:

In the presence of sodium periodate ($NaIO_4$), osmium tetroxide may be used to catalyse the generation of carbonyl compounds from olefins by the oxidative cleavage of the intermediate glycol.[4]



Similarly, Os EnCat™40 has also shown to be an effective catalyst for the oxidative cleavage of olefins producing the respective carbonyl compounds in good yield and under mild reaction conditions. Examples of his reaction are given in Table 3.[2]

Table 3. Oxidative Cleavage of Various Olefins Using Os EnCat™40

Substrate	Product	Yield/ %
		92[a]
		99[a]
		79[a]
		99[a]
		55
		66

Reagents and conditions: Olefin (1 mmol), $NaIO_4$ (3 mmol), Os EnCat™40 (2 mol%), THF/H_2O (2:1), rt, 1-8h

[a] Isolated and identified as the phenyl hydrazone

Solvent Selection:

Due to agglomeration and precipitation of EnCat™ beads at the aqueous/organic interface, reactions using Os EnCat™ are best carried out in monophasic conditions. It has been found that the use of bi-phasic conditions, such as typical Sharpless conditions (*t*-BuOH/H_2O), generally give products in only low yield.[5]

The compatibility of Os EnCat™40 to a number of solvent systems has been screened and Os leaching tested (Table 4). It was found that even after prolonged immersion (>2 months) of the catalyst in various solvents, no Os was detected in any of the solvents (ICP analysis).

Table 4. Solvent Screening of Os EnCat™40

Solvent System	Temperature/ °C	Os in solution after 2 months storage/ ppm
Acetone	Ambient	<5
THF	Ambient	<5
Toluene	Ambient	<5
Acetone/water (10:1)	Ambient	<5
THF/water (2:1)	Ambient	<5
Corn oil	Ambient	<5
Water	Ambient	<5
DMA	Ambient	<5

When using Os EnCat™40 under typical reaction conditions Os leaching is observed (Table 5). A possible mechanism of Os release is by the co-oxidant releasing OsO_4 following oxidation of the intermediate cyclic Os(VI) and Os(IV) species.

Generally, the level of leaching increases with increasing reaction temperature.

Table 5. Solvent Screening of Os EnCat™40 at Elevated Temperatures

Solvent System	Time/ hr	Temperature/ °C	Os in solution/ ppm
Acetone/water/rm[a]	24	Ambient	50
Acetone/water/rm[a]	24	40	55
Acetone/water/rm[a]	24	60	40
THF/water/rm[a]	24	Ambient	<5
THF/water/rm[a]	24	40	25
THF/water/rm[a]	24	60	30

[a] Starting reaction mixture contains: olefin (1 mmol), NMO (1.3 mmol), Os EnCat™40 (5 mol%)

It has been found that acetone/water and THF/water provide the best monophasic solvent systems for catalytic dihydroxylation reactions with Os EnCat™40 giving consistently good yields of product. Regarding biphasic reaction conditions, *t*-BuOH/H_2O is the current system of choice, however, additional considerations, such as the slow addition of olefin to the reaction mixture, need to be brought in.

Use of Co-Oxidant:

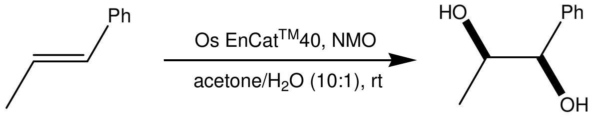
As for standard OsO_4 catalysed dihydroxylation reactions, the use of stoichiometric amounts of a secondary co-oxidant is required to achieve acceptable reaction rates and yields with Os EnCat™40. The latter shows good activity in the presence of NMO (*N*-methylmorpholine *N*-oxide) and also potassium ferricyanide, $K_3[Fe(CN)_6]$. Alternative co-oxidants such as *tert*-butyl hydroperoxide (TBHP) may also be considered.

Recyclability of Os EnCat™40:

Os EnCat™40 functions both as a reservoir of osmium tetroxide and as an effective scavenger of homogeneous, active osmium species. Although some loss of metal takes place during reaction, the relatively low levels potentially allow the catalyst to be re-used many times without significant loss of activity (-studies show that at 2-5 mol% levels, it may take up to 50 recycles to exhaust Os EnCat™40).

Table 6 shows the recycling of Os EnCat™40 in a model dihydroxylation reaction:

Table 6. Recycling of Os EnCat™40 in Dihydroxylation Reaction



Run	Yield[a]/ %
1	77
2	79
3	76
4	73
5	79

Reagents and conditions: Olefin (1 mmol), NMO (1.3 mmol), Os EnCat™40 (5 mol%)

[a] based on isolated yields

Stability, Handling and Storage:

No special storage conditions are deemed necessary and it should be noted that after long-term storage (>12months), Os EnCat™40 catalyst is equally effective in oxidations reactions.

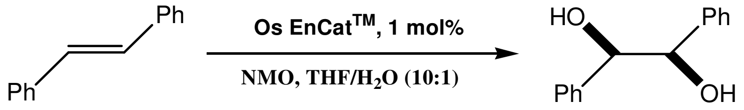
The Os EnCat™40 catalyst is supplied as free-flowing beads and build-up of static charges can make weighing small quantities problematic therefore it is advised that plastic weighing boats, for example, should be avoided where possible. In addition, the beads contain up to 10% (w/w) solvent and care should be taken to avoid contact with sources of ignition during storage and use.

Qualitative tests performed on Os EnCat™40 show no volatile osmium tetroxide vapour emanating from the product after prolonged exposure to corn oil. As such, Os EnCat™40 beads can be handled without the need for high containment facilities such as glove boxes.

Reaction Kinetics:

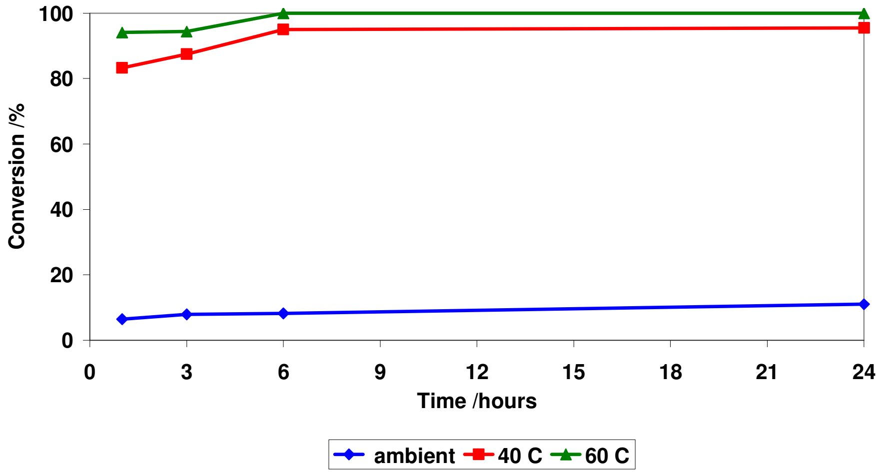
In general reactions with Os EnCat™40 are slower compared to the parent homogeneous catalyst and so heating is recommended to achieve good conversions and rates of reaction.

A kinetic study of a 'standard' Upjohn[6] dihydroxylation reaction was carried out with Os EnCat™40 in a single phase solvent system:



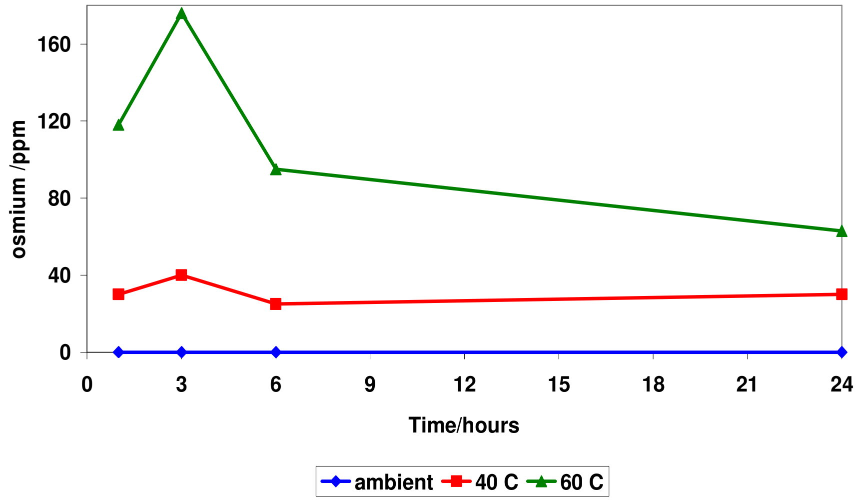
Typically at elevated temperatures conventional homogeneous OsO_4 catalysed reactions suffer diminished diol yields due to over-oxidation of the initial diol product which can further complicate product isolation[6]. However, with Os EnCat™40 the dihydroxylation reactions proceed efficiently at elevated temperatures to give high yield of diol after a few hours reaction.

The graph below show the reaction kinetics of *trans*-stilbene in THF/water at various temperatures (% conversion determined by GC-MS):



At 40°C and 60°C the hydrobenzoin product is obtained in high yield with none of the over oxidised benzaldehyde side-product detected from cleavage of the C=C double bond.

Studies show a direct correlation between reaction rates and the level of Os leached into solution. The Os EnCat™40 appears to act as a reservoir of highly active catalytic species. Analysis of the reaction mixture from the above process indicates that with increasing temperature more Os is leached which subsequently catalyses the dihydroxylation reaction. The following graph shows the leaching profile of the Os EnCat™40 catalyst in the dihydroxylation reaction of *trans*-stilbene at various temperatures (Os content measured by ICP analysis):



Typical levels of Os species in solution are significantly lower compared with standard homogeneous reaction using OsO_4. There is also some evidence to suggest that the Os EnCat™40 beads effectively 'mop-up' some of the Os leached in to the solution at the end of reaction.

In summary, the lower activity of the Os EnCat™40 can be overcome by carrying out reactions at elevated temperatures where reactions proceed with good selectivity to give the required diol product and with relatively low levels of osmium contamination.

Removal of Osmium Contamination

If required, QuadraPure™ metal scavenger resins can be used to remove osmium species from products. For more information on the QuadraPure™ range and applications please write to info@reaxa.com. For R&D quantities of QuadraPure™ please contact: Sigma-Aldrich, www.sigma-aldrich.com.

Experimental Procedures:

General Procedure for Dihydroxylation Reactions using Os EnCat™40:

Os EnCat™40 (5 mol%) was added to a solution of olefin (1 mmol) and *N*-methylmorpholine *N*-oxide (NMO, 1.5 mmol) in acetone/water (10:1, 10 ml) and the reaction mixture stirred for 12-24 hours at room temperature. The mixture was then filtered through a polyethylene frit (20 µm) and the recovered beads washed and filtered with acetone (2 x 10 ml) and water (2 x 10 ml). The filtrate was treated with a saturated solution of sodium metabisulphite (20 ml) and then extracted with ethyl acetate (3 x 20 ml). The combined organic extracts were dried ($MgSO_4$), filtered and then evaporated under reduced pressure followed by purification by flash column chromatography to give the corresponding diol product.

General Procedure for Oxidative Cleavage Reactions Using Os EnCat™40:

Os EnCat™40 (2 mol%) was added to a solution of olefin (1 mmol) and sodium periodate ($NaIO_4$, 3 mmol) in THF/water (2:1, 4.5 ml) and the reaction mixture stirred for 3 hours at room temperature. Dichloromethane (10 ml) was added and water (5 ml) and the mixture then filtered through a polyethylene frit (20 µm), washing with DCM (3 x 10 ml). The filtrate was treated with a saturated solution of sodium metabisulphite (20 ml) and then extracted with DCM (3 x 20 ml). Phenylhydrazine (2.2 mmol) and sodium acetate (0.3 g) was added to the combined organic extracts and the mixture stirred for 1 hour at room temperature. Water (10 ml) was added and the mixture extracted with DCM (3 x 10 ml). Combined organic extracts were dried ($MgSO_4$), evaporated under reduced pressure and purified by flash column chromatography to give the corresponding phenylhydrazone products.

Additional Information

For further technical assistance, regulatory information or commercial enquires please write to info@reaxa.com or call +1 44 161 721 2202.

For R&D quantities of products please contact: Sigma-Aldrich, www.sigma-aldrich.com.
Sigma-Aldrich catalogue number: 65868-5 (Os EnCat, Osmium Tetroxide Microencapsulated, 0.3 mmol Os/g)

Key References:

(1) Schröder M. *Chem. Rev*. **1980**, *80*, 187-213.
(2) Microencapsulation of Osmium Tetroxide in Polyurea. Ley S.V.; Ramarao C.; Smith S.C.; Lee A.L.; Østergaard N.; Shirley I.M. *Org. Lett*., **2003**, *5*, 185-187.
(3) Kolb H.C.; VanNieuwenhze M.S.; Sharpless K.B. *Chem. Rev*., **1994**, *94*, 2483.
(4) Pappo R.; Allen D.S.; Lemieux R.U.; Reider P.J. *J. Am. Chem. Soc*., **2001**, *123*, 10139.
(5) Hentges S.G.; Sharpless K.B. *J. Am. Chem. Soc*., **1980**, *192*, 4269.
(6) Van Rheenen V.; Kelly R.C.; Cha P.Y. *Tetrahedron Lett*., **1976**, 1973.