Osmium Tetroxide–$(QN)_2$PHAL–Sugar: a New Recyclable Catalyst System for Asymmetric Dihydroxylation of Olefins

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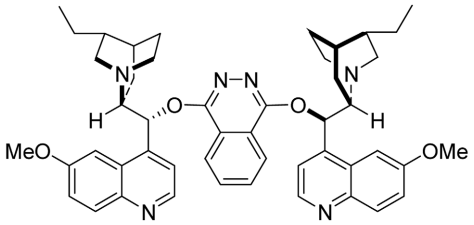
The international chemistry community is under increasing pressure to change current working practices and to find greener alternatives because of the increasingly stringent environmental regulations. This means that chemical manufacturers need to develop more environmentally sustainable processes that produce less waste and avoid, as much as possible, the use of toxic and/or hazardous reagents.

The Sharpless Os-catalyzed asymmetric dihydroxylation (AD) of olefins is undoubtedly one of the most efficient methods of synthesizing chiral vicinal diols.[1] Although this reaction offers a number of processes that can be applied to the synthesis of chiral drugs, natural products and fine chemicals, etc., the cost, toxicity and contamination of products with osmium restricts its use in industry. Therefore, a great deal of effort have been directed at immobilizing the catalyst system, *e.g.* covalent attachment[2] of an alkaloid ligand to a soluble or insoluble support or immobilizing the osmium catalyst itself by the microencapsulation of OsO_4 in a polymer matrix,[3] using an ion-exchange technique[4] or by the osmylation[5] of macroporous resins bearing residual vinyl groups such as Amberlite XAD-4. However, most examples of supported catalysts exhibit inferior catalytic properties to their homogeneous counterparts (1 mol% of osmium is usually needed to complete the reaction, whereas in homogeneous case 0.1-0.2 mol% of osmium is enough to complete most of the reactions) and require additional synthetic steps for their preparation that raises catalyst costs. Quite recently, an ionic liquid[6] and poly(ethylene glycol)[7] have been used as reaction media as well as immobilizing agents for the catalyst in AD reactions. However, it has yet to be authenticated whether the use of ionic liquids and polyethylene glycol provides cheap and green processes. Therefore, it would still be highly desirable to develop a simpler, cheaper and greener immobilization method for recycling the catalytic components (osmium and chiral ligand).

We disclose here for the first time that an aqueous solution of ordinary white sugar (sucrose) can be used as a cheap and new immobilization medium for the recovery of OsO_4/chiral ligand in the Os-catalyzed asymmetric dihydroxylation of olefins. This method requires neither the additional modification of ligand nor a high loading of osmium (0.1 mol% of osmium is enough to complete the reactions).

In order to investigate the effect of an sucrose on catalysis as well as the recyclability of both catalytic components, the AD reactions of *trans*-stilbene, styrene and methyl *trans*-cinnamate were initially carried out using 0.1 mol% of OsO_4 and the well-known ligand, 1,4-bis(9-O-dihydroquininyl-)-phthalazine [$(DHQ)_2$PHAL], under standard Upjohn conditions[8] (*N*-methylmorpholine-*N*-oxide (NMO) as a cooxidant) in the presence of sucrose at 20 °C. As shown in Table 1, the results obtained in the presence of the sucrose were comparable to those achieved without sucrose. In particular, when *trans*-stilbene was added in one portion, the reaction was completed within 2 h, affording the desired diol in excellent yield (92%) and ee (>99%) (entry 2 in Table 1). Encouraged by this result, the following catalyst recycling experiment was next performed (entry 3 in Table 1): After completing the reaction of entry 2, all the volatiles were removed under reduced pressure and the chiral diol produced was extracted with pre-cooled (0 °C) diethyl ether from the residue. The residue was then subjected to the next run with a new batch of the olefin and NMO without any addition of osmium or the chiral ligand. However, the further re-use of the recovered sucrose phase resulted in a decrease in the yield and ee (66%, 93% ee after 24 h, entry 3 in Table 1) of the product, which was caused by the leaching of catalyst during the extraction with ether. The leaching of the catalytic components during extraction can be ascribed to some solubility of $(DHQ)_2$PHAL in ether. Because the complex formation of OsO_4 and an alkaloid ligand is expected to be reversible, the lowering of the chiral ligand concentration by the leaching during the extraction might result in more OsO_4 leaching to the ether phase.

Recently, it was reported by us[6a] that the use of a highly polar alkaloid ligand such as the compound **1**, generated in situ from $(QN)_2$PHAL[9] during the AD reaction (Fig. 1) could minimize Os leaching because such polar ligands can be strongly immobilized in a polar immobilization medium (*e.g.* ionic liquid). Quite recently, Sheldon *et al.* confirmed this by determining the distribution of $(DHQ)_2$PHAL or **1** between Et_2O and ionic liquid using HPLC.[10] According to the HPLC analysis, *ca.* 75% of the $(DHQ)_2$PHAL was extracted into the ether phase, while only 0.6% of the



(DHQ)$_2$PHAL

Table 1. Asymmetric dihydroxylation of olefins using (DHQ)$_2$-PHAL in the sugar[a]

Entry	Olefin	Time (h)	Yield (%)[b]	Ee (%)[c]	Abs. Config.
1	*trans*-Stilbene	13	93	>99	*S*,*S*
2[d]	*trans*-Stilbene	***2***	***92***	***>99***	*S*,*S*
3[d,e]	*trans*-Stilbene	***24***	***66***	***93***	*S*,*S*
4	Styrene	16	92	82	S
5	Methyl *trans*-cinnamate	16	91	>99	2*R*,3*S*

[a]Unless indicated otherwise, all the reactions were carried out on a 3 mmol reaction scale of olefin using 0.1 mol% of OsO_4, 2.5 mol% of (DHQ)$_2$PHAL, 3.3 mmol of NMO and 1 g of sucrose in acetone-H_2O (v/v = 10 : 1, 30 mL) at 20 °C the olefins were added using a syringe pumpe for 12 h. [b]Isolated yield. [c]Determined by chiral HPLC. [d]The olefin was added in one portion and the reaction was carried out in acetone-H_2O (v/v = 10 : 1, 4.5 mL). [e]The reaction was carried out with the recovered sugar phase obtained from the reaction in entry 2 without further addition of OsO_4 and (DHQ)$_2$PHAL.

Table 2. AD reactions of *trans*-stilbene using 0.1 mol% of OsO_4 and (QN)$_2$PHAL in the presence of sucrose[a]

Time, Yield, ee			
Run 1	Run 2	Run 3	Run 4
16 h, 92%, 99% ee	21 h, 89%, 99% ee	27 h, 87%, 99% ee	48 h, 82%, 81% ee

[a]The recycle experiments were carried out on a 3 mmol reaction scale of olefin using 0.1 mol% of OsO_4, 2.5 mol% of (QN)$_2$PHAL, 3.3 mmol of NMO and 1 g of sucrose in acetone-H_2O (v/v = 10 : 1, 30 mL) at 20 °C. *trans*-Stilbene was added using a syringe pump for 12-48 h. From the second run, the reaction was carried out with the sugar phase recovered from the first run without further OsO_4 and (QN)$_2$PHAL addition.

tetrahydroxylated ligand **1** was present in the ether phase after extraction.[10] Therefore, we next examined the recyclability of Os and ligand in aqueous sugar solution using the (QN)$_2$PHAL ligand. As shown in Table 2, the use of (QN)$_2$PHAL instead of (DHQ)$_2$PHAL afforded the same yields and ees, but resulted in drastic improvement in the recyclability of both catalytic components. The recovered sugar phase containing the osmium and compound **1** could be recycled four times (Table 2), affording 3500 of total turnover number (TON). To the best of our knowledge, this is the highest total TON value ever reported under Upjohn conditions. An explanation for this improvement in the

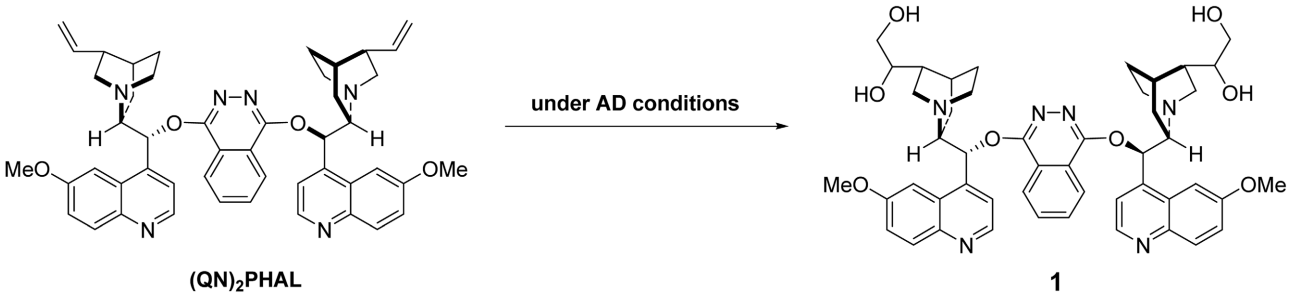


Figure 1. In situ generation of **1** from (QN)$_2$PHAL during AD reactions.

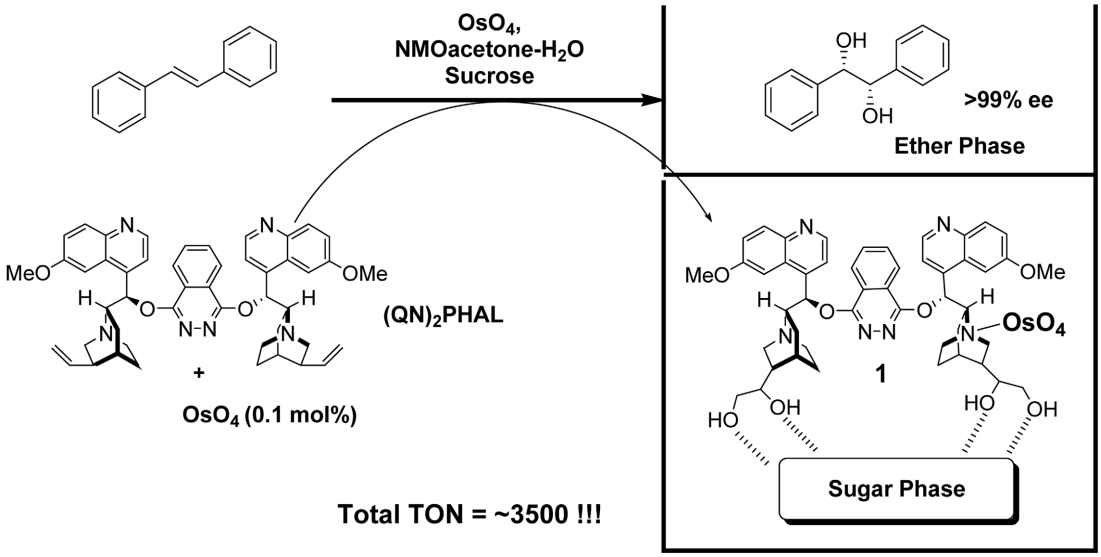


Figure 2.

Table 3. Asymmetric dihydroxylation of olefins in the presence of sucrose[a]

Entry	Substrate	Time/ h	Yield (%)[b]	Ee[c] (%)	Abs. Config.
1	Styrene	16	93	80	S
2	α-Methylstyrene	16	94	69	S
3	Methyl *trans*-cinnamate	16	92	>99	2*R*,3*S*
4	Methyl *p*-methoxy- *trans*-cinnamate	16	92	>99	2*R*,3*S*

[a]All the reactions were carried out on a 3 mmol reaction scale of olefin using 0.1 mol% of OsO_4, 2.5 mol% of $(QN)_2PHAL$, 3.3 mmol of NMO and 1 g of sucrose in acetone-H_2O (v/v = 10 : 1, 30 mL) at 20 °C. Olefins were added by a syringe pump for 13-15 h. [b]Isolated yield. [c]Determined by chiral HPLC.

catalyst recyclability is that, as expected, the double bonds present in the $(QN)_2PHAL$ ligand undergo dihydroxylation to produce the highly polar tetrahydroxylated analogue **1** which cannot be not extracted from the sugar phase by diethyl ether, resulting in minimizing Os-leaching (Fig. 2). However, there was still a decrease in activity upon reuse, owing to partial extraction of the Os catalyst into the organic phase. According to ICP analysis, *ca.* 11-13% of Os used initially was leached into the product phase after first run.

In order to substantiate these results and check the versatility, other olefins were subjected to asymmetric dihydroxylation, and the results are summarized in Table 3. In all cases, the desired diols were obtained in yields and enantioselectivities similar to those obtained under the homogeneous conditions.

In summary, this work demonstrates that the combination of an aqueous solution of sugar and highly polar alkaloid ligand such as compound **1** generated *in situ* from $(QN)_2PHAL$ during the reaction provided a highly simple and efficient approach to the recycling of both catalytic components (OsO_4 and the chiral alkaloid ligand) for AD reactions. This method requires neither the additional modification of a ligand nor a osmium high loading. 0.1 mol% of osmium was enough to complete most reactions. However, there was still a decrease in activity upon reuse, owing to partial extraction of the Os catalyst into the organic phase. Tuning the polarity of the ligand to minimize leaching of the catalyst into the organic phase and optimization of reaction conditions are currently underway.

Experimental Section

General. The NMR spectra were recorded on a Varian Unity Inova 300 MHz spectrometer. HPLC (High Performance Liquid Chromatography) for the determination of enantiomeric purity was performed by Varian Prostar 321 UV/VIS apparatus and Chiral OJ or OD-H purchased from Daiecel Chemical Industries. Ion conductive plasma spectroscopy (ICP) data were collected on a ICP-AES JY2000S. Column chromatography was performed using Kieselgel 60 (230-400 mesh) and TLC was carried out using glass sheets pre-coated with silica gel $60F_{254}$ purchased from Merck.

OsO_4 was purchased from Next Chimica, South Africa. All of olefins, $(DHQ)_2PHAL$, NMO were purchased from Aldrich. All other solvents and chemicals were obtained from commercial sources, and were used without further purification. The chiral ligand $(QN)_2PHAL$ was synthesized according to our literature procedure.[9]

Representative Procedure for Asymmetric Dihydroxylation in Sugar. A 50 mL flask was charged with acetone-H_2O (10 : 1, v/v, 10 mL), $(QN)_2PHAL$ (57 mg, 0.075 mmol), OsO_4 (0.072 mL of 1.0 wt% of aqueous solution, 0.003 mmol, 0.1 mol%), sugar (1 g). After stirring for 1 h, *N*-methylmorpholine-*N*-oxide (NMO, 387 mg, 3.3 mmol, 1.1 equiv) was added. Subsequently, *trans*-stilbene (541 mg, 3 mmol) dissolved in acetone-H_2O (10 : 1, v/v, 20 mL) was then added by a syringe pump for 12 h and the reaction mixture was stirred at 20 °C until the reaction was completed. Following evaporation of all the volatiles the chiral diol produced was extracted with pre-cooled (0 °C) ether (3 × 20 mL) from the residue. The residue containing sugar was recycled to the next run. The ether phase was evaporated and the crude product was purified by flash column chromatography on silica (EtOAc/hexane 1 : 2) to give pure 1,2-diphenyl-1,2-ethanediol as a white solid.

In the recycling experiment, 10 mL of acetone-H_2O (10 : 1, v/v), and 387 mg (3.3 mmol) of NMO were added to the recovered sugar phase from the above experiment. After stirring for 5 min, *trans*-stilbene (541 mg, 3 mmol) dissolved in acetone-H_2O (10 : 1, v/v, 20 mL) was added by a syringe pump for 16-48 h and worked up as described above.

Characterization of Products. The following compounds are known compounds, and their NMR spectra are in accordance with those reported in the literature. The enantiomeric excess of the diols was determined by HPLC analysis with chiral stationary phases.

1,2-Diphenyl-1,2-ethanediol: HPLC (Chiralcel OJ, *i*-PrOH/hexane (v/v = 10 : 90), flow rate 1.0 mL min^{-1}): t_R = 14.8 min (*S*,*S*-isomer), t_R = 17.8 min (*R*,*R*-isomer).

1-Phenyl-1,2-ethanediol: HPLC (Chiralcel OD-H, *i*-PrOH/hexane (v/v = 5 : 95), flow rate 0.5 mL min^{-1}): t_R = 31.5 min (*R*-isomer), t_R = 34.7 min (*S*-isomer).

2-Phenyl-1,2-propanediol: HPLC (Chiralcel OJ, *i*-PrOH/hexane (v/v = 10 : 90), flow rate 1.0 mL min^{-1}): t_R = 10.5 min (*R*,*R*-isomer), t_R = 14.5 min (*S*,*S*-isomer).

Methyl 2,3-dihydroxy-3-phenylpropionate: HPLC (Chiralcel OJ, *i*-PrOH/hexane (v/v = 20 : 80), flow rate 1.0 mL min^{-1}): t_R = 11.0 min (2*R*,3*S*-isomer), t_R = 14.5 min (2*S*,3*R*-isomer).

Methyl 2,3-dihydroxy-3-(4-methoxyphenyl)propionate: HPLC (Chiralcel OJ, *i*-PrOH/hexane (v/v = 15 : 85), flow rate 0.5 mL min^{-1}): t_R = 54.4 (2*R*,3*S*-isomer), t_R = 65.8 (2*S*,3*R*-isomer).

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