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Application of nanofiltration to re-use the sharpless asymmetric dihydroxylation catalytic system

Frederico Castelo Ferreira,[a,b,*] Luís C. Branco,[c,d] Kaushal Kishor Verma,[a] João G. Crespo[a,*] and Carlos A. M. Afonso[c,*]

[a]*REQUIMTE, Departamento de Química, Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, 2829-516 Caparica, Portugal*
[b]*Imperial College London, Department of Chemical Engineering and Chemical Technology, South Kensington Campus SW7 2AZ, UK*
[c]*CQFM, Instituto Superior Técnico, Complexo-1, Universidade Técnica de Lisboa, 1049-001 Lisboa, Portugal*
[d]*Department of Chemistry, University of Cambridge, Cambridge CB2 IEW, UK*

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Abstract—In this paper, successive batch steps of an osmium-catalyzed asymmetric dihydroxylation reaction using Sharpless conditions and nanofiltration of post-reaction mixture were coupled, allowing us to enhance the cumulative catalyst turn over number to about 3.7 times over six cycles. The nanofiltration step provides for isolation of the chiral product, whereas the catalytic system (osmium and chiral ligand) is re-used in the following batch cycle. In this work the osmium average rejection through the selected nanofiltration membrane, Starmem™120, was 83%; this result may indicate the existence of free osmium in solution and implies residual product osmium contamination at an average value of 1.5 mg Os/g-product. Effective application of this methodology to the model reaction requires improvement of catalyst rejection, which calls for an effective complexation of osmium by the ligand. Nevertheless, the enantioselectivity of the reaction was maintained constant over the six cycles at a value of 69%.

1. Introduction

The Sharpless catalytic asymmetric dihydroxylation (AD) of olefins is a key reaction for the synthesis of chiral 1,2-diols. High reaction yields and high product enantioselectivities have been reported for a broad range of olefins in water/organic solvent (1:1) mixtures, with *tert*-butanol, acetone or methyl *tert*-butyl ether as the organic solvent. The AD catalytic system is composed of the osmium catalyst (OsO_4 or $K_2OsO_2(OH)_4$ salt) and a dimeric ligand based on a *cinchona* alkaloid (dihydroquinidine, DHQD or dihydroquinine, DHQ) with groups of the type phathalazine (PHAL), pyrimidine (PYR) or indoline (IND).[1,2] Industrial applications of the AD reaction have been restricted either by the toxicity and volatility of the osmium species or by the high costs of the chiral ligands employed. Therefore, the scientific community has looked into several strategies for immobilization of this catalytic system aiming at retaining and re-using it over several reaction cycles.[3] Among such immobilization techniques there are studies on microencapsulation with polystyrene polymers or polyurea microcapsules;[4] ion exchangers;[5] anchoring tetrasubstituted olefins in silica,[6] in polyethylene glycol matrixes or in Amberlite containing residual vinyl groups;[7] use of gold colloids or nanocrystalline magnesium oxide;[8] and more recently use of an aqueous sucrose solution.[9] However in the mentioned studies, either the amount of osmium catalyst added was significantly higher than that usually employed (1–5 mol % vs 0.2–0.5 mol %) or the addition of chiral ligand after each cycle was required. Additionally, the immobilization of chiral ligands onto soluble and insoluble polymers requires long synthesis of each chiral ligand and its application leads to reduction of enantioselectivity. Moreover, osmium leaching was observed and therefore effective recovery and re-use of the catalyst was not possible.[10] Combination of ionic liquids as alternative media with product extraction using an organic solvent (diethyl ether or *n*-hexane)[11] or supercritical CO_2[12] has also been described; in these studies the catalytic system was recycled over 14 or six reaction–extraction cycles, respectively.

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[*] Corresponding authors. E-mail addresses: fcf@dq.fct.unl.pt; jgc@dq.fct.unl.pt; carlosafonso@ist.utl.pt

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2. Results and discussion

Herein, we propose to process the post-AD reaction solution by nanofiltration in order to isolate the product in the permeate and retain the catalytic system (osmium and chiral ligand) into the retentate, allowing for re-use of the catalytic system into successive reaction–nanofiltration (R–NF) cycles (Fig. 1). This process aims at improving cumulative catalyst turnover number (TON) as the catalyst, loaded only in the first cycle, is re-used over successive R–NF cycles. The post-reaction mixture is directly processed by nanofiltration, without the need for catalyst heterogenization and consequent losses of catalytic activity and selectivity. Additionally, the nanofiltration process should provide for a neat isolation of the product, potentially free or with lower levels of metal contamination. Therefore, in an optimum scenario, the nanofiltration membrane would be able to completely retain the catalytic system and allow complete permeation of the product. Process feasibility depends also upon an acceptable solvent flux through the membrane, where the solvent is the reaction medium, and also on low losses of catalytic activity over the process.

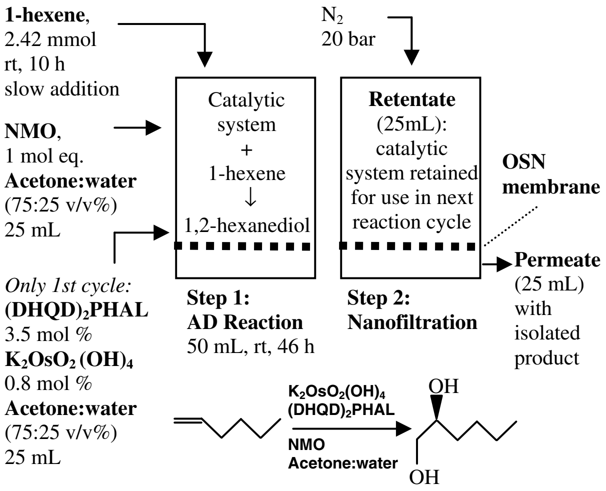

Figure 1. Schematic diagram of the reaction–nanofiltration process.

Nanofiltration membranes had been initially applied for solute separations in water medium,[13] but several nanofiltration membranes stable in a range of organic solvents have been developed over recent years. Examples of organic solvent nanofiltration (OSN) membranes commercially available are the Starmem™[14a] and MPS series,[14b] respectively, from W. R. Grace and Co and Koch; additional OSN membranes are supplied by SolSep BV.[14c] OSN has been previously applied to recover and re-use homogeneous transition metal catalysts[15] in several reactions such as the Pd-catalyzed allylic substitution,[16] Heck reaction[17] and Suzuki couplings[18] and asymmetric hydrogenations.[19,20] Initially, the success of these applications required catalyst enlargement, but later, as OSN membrane selectivity was improved, catalyst modification became dispensable. For the reactions mentioned it was reported that the metal catalysts have been re-used in successive reaction cycles and catalyst TON improved. As this methodology is applied here for the first time to the Sharpless catalytic asymmetric dihydroxylation of olefins, the limitations and challenges are identified.

2.1. Selection of model system and experimental conditions

In this study, we selected the $K_2OsO_2(OH)_4$ salt (M_w 368 g mol^{-1}) and the chiral ligand $(DHQD)_2PHAL$ (M_w 779 g mol^{-1}) as a catalytic system and the asymmetric dihydroxylation of 1-hexene into 1,2-hexanediol (M_w 118 g mol^{-1}) as a model reaction. Table 1 shows the reaction yields and enantiomeric excesses (ee's) for our model reaction obtained at several molar ligand/osmium (L/Os) molar ratios in *tert*-butanol/water (50:50 v/v %). No significant effect on the reaction yield was observed for the range of L/Os tested, but a significant improvement in ee was obtained. Therefore an initial L/Os molar ratio of 4.4 was used in the first reaction–nanofiltration (R–NF) cycle in order to maximize enantioselectivity. This higher L/Os molar ratio may also contribute to reduce the existence of free osmium (M_w 190 g mol^{-1}) species that are able to permeate throughout the membrane.

Table 1. Reaction yield and enantiomeric excess of model reaction for different L/Os molar ratios

L/Os (mol mol^{-1})	ee (%)	Reaction yield (%)
1	70	89
2	83	85
4	97	89

From the commercially available OSN membranes, Starmem™120 has the lowest molecular weight cut off (MWCO), 200 g mol^{-1}, therefore it was selected for the nanofiltration step in order to maximize catalyst rejection. Since the product has a molecular weight considerably bellow membrane MWCO, it is expected that there will be a reasonable permeation of this through the membrane.

The flux of mixtures of *tert*-butanol/water (50:50 v %) through Starmem™120 membrane proved to be considerably low (1.2 L m^{-2} h^{-1} at 30 bar). Therefore, for this study, acetone/water mixtures were selected as the reaction media; AD reactions in this media have been previously reported.[1] The solvent mixture fluxes through out Starmem™120 at the pressure of 20 bar and the reaction yields and ee obtained for different acetone:water mixtures: 100%, 90:10 v/v %, 75:25 v/v % and 50:50 v/v % are presented in Figure 2.[21] The solvent flux decreases with increase in water content, whereas the reaction performance increases with water content. Based on a trade off between reaction and nanofiltration performance, a solvent composition of acetone/water 75:25 v/v % was selected as the reaction medium.

$K_3Fe(CN)_6$ and *N*-methylmorpholine-*N*-oxide (NMO) are possible co-oxidants successfully tested for the AD reaction. NMO is fully soluble in the selected reaction media and it was employed at 1 mol equiv as a co-oxidant in this study. NMO has a molecular weight (M_w 135 g mol^{-1})

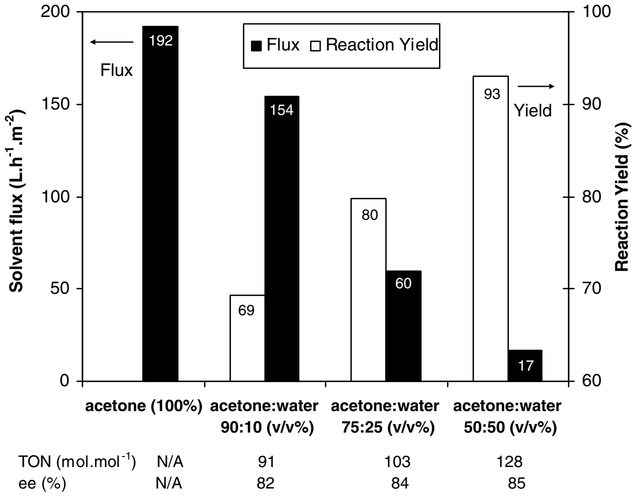

Figure 2. Solvent fluxes through Starmem™120 at an applied pressure of 20 bar and reaction yields and ee's for reaction in several acetone/water mixtures under the same conditions of the R–NF cycles.

below the membrane MWCO, which implies that once the post-reaction is processed by nanofiltration, its reduced form will end up in the permeate. The model substrate (1-hexene) was added over 10 h to 50 mL of reaction medium volume, which in the first cycle represents a 0.8 mol % of catalyst to substrate. Details of the experimental conditions for each of the six R–NF cycles are shown in Figure 1 and Table 2. At the end of each reaction, a pressure of 20 bar was applied using pressurized nitrogen until 25 mL of permeate solution was collected. The product was then isolated from the permeate solution, and its yield and ee were quantified.[22] After filtration, 25 mL of fresh acetone/water 75:25 v % solution and fresh co-oxidant were added to the retentate, and a new reaction was initiated with a slow addition of substrate.

2.2. The reaction nanofiltration cycles

The process yields and ee obtained in each R–NF cycle are presented in Table 2. An average ee of (69 ± 2)% was obtained for the six cycles with an average process yield of (44 ± 2)%. The catalytic system is added only into the first cycle. Therefore, as the product is isolated in the permeate, a significant increase in the cumulative catalyst TON$_{(i)}$ is observed.[23]

Table 2. Process yields, ee and cumulative TON$_{(i)}$ for six successive R–NF cycles[a]

Cycle	Process yield[26] (%)	ee (%)	TON$_{(i)}$[23] (mol mol^{-1})	Os in permeate[24] (%)	Osmium rejection[27] (%)
1	43	71	56	7.4	81.5
2	39	66	107	4.9	86.2
3	49	69	166	4.0	87.4
4	44	70	222	5.1	82.5
5	43	65	275	5.2	79.7
6	47	70	334	3.9	83.2

[a] Reaction conditions are shown in Figure 1. A total of 46 h reaction time was selected in order to ensure that reaction was completed prior to filtration.

Notice that data in Tables 1 and 2 resulted from experiments performed at different reaction conditions and, therefore, they are not directly comparable. In particular, the study for selection of L/Os molar ratio (Table 1) used the *tert*-butanol/water 50:50% solvent mixture as a reaction media, but the R–NF cycles (Table 2) were carried out in acetone/water 75:25%, a reaction media more suitable for this membrane application. Therefore, the ee values obtained for the six cycles (69%) are quite acceptable, in spite of being significantly lower than the ones reported in Table 1 (89%, for L/Os = 4 mol mol^{-1}). More importantly, the ee value does not decrease with successive cycles, showing that there is no loss of catalytic enantioselectivity.

Usually reaction performance is reported in terms of reaction yields,[25] which accounts for all the 1,2-hexanediol obtained at the end of the reaction (Table 1 and Fig. 2). The process yield[26] reported in Table 2 only accounts for the product isolated in the permeate stream which, under the experimental conditions employed, was half of the reaction volume solution. The process yields obtained over the six cycles, and the consequent increase in TON, indicate that it is possible to use the proposed methodology to re-use the AD catalytic system. Since some product is carried out between cycles in the retentate solution, it should be expected that there is an increase in the product concentration and in the process yield along the R–NF cycles.

Osmium was quantified in the post-reaction solutions before and after nanofiltration. From the 18.5 μmol of osmium initially added, only 14.8 μmol was measured in the first post-reaction solution. This quantification was performed previously to any nanofiltration processing; therefore the 3.7 μmol of osmium losses cannot be attributed to osmium permeation through the membrane. This loss results from segregation and/or adsorption of osmium in the experimental apparatus/membrane surface, which is not accounted by analysis of the liquid solution.

Osmium losses based on the feed solution were calculated for each cycle as the difference between the osmium initially added (18.5 μmol) and the dissolved osmium measured in the post-reaction solution to be processed by nanofiltrations (Fig. 3). Once the initial 3.7 μmol of osmium loss is taken into account, 80% of the cumulative losses are due to permeation of osmium through the membrane and 20% from further losses due to segregation and/or adsorption of osmium.

Over the six cycles, 30.5% of the initially added osmium left the system throughout the permeate stream. Notice that an initial 0.8 mol % of catalyst to osmium was targeted. However the first cycle was performed at a value of 0.6 mol %, which decreased until there was a value 0.4 mol % in the last cycle. An average osmium rejection[27] of 83% was measured for the six cycles (Table 2). This rejection value implies the existence of free osmium species. An average osmium concentration of (7.1 ± 1.8) ppm was measured in the permeate stream representing an osmium contamination of the product of (1.5 ± 0.4) mg Os/g product. Improvements on osmium rejections may be achieved

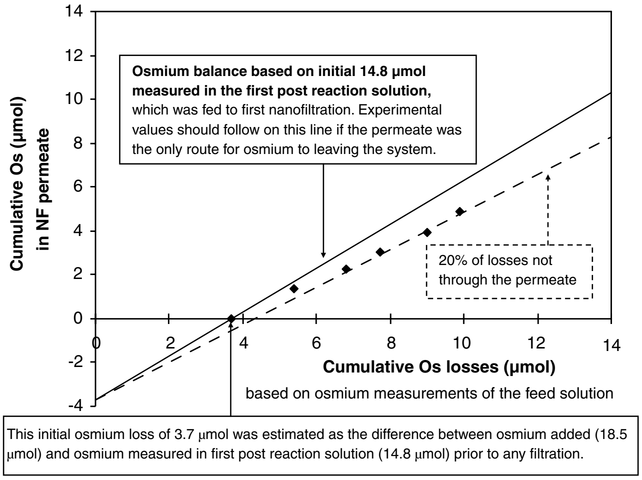

Figure 3. Osmium rejections and cumulative osmium in permeate against cumulative osmium losses (measured as differences in osmium add into the 1st cycle and osmium in each post-reaction solution).

either by using higher molecular osmium species,[28] which are not commercially available, or by introducing electrical charges through membrane surface modification; this approach would contribute an additional membrane rejection of the osmium salt, but not of the neutral product.

3. Conclusions

The present study illustrates a methodology in which nanofiltration is applied for re-use of the catalytic system into successive AD reactions. The results are encouraging with respect to conservation of enantioselectivity over re-use of this catalytic system and improvement of respective TON. However, estimations of osmium losses through the membrane and consequent product contamination by osmium should be taken into consideration. Since a membrane of a quite low MWCO (200 g mol^{-1}) was already employed, further improvement of osmium rejection requires different approaches such as the use of larger osmium species, and/or improvement of rejection based on electrostatic interactions with the membrane surface rather than size exclusion only.

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21. The membrane was previously preconditioned by filtration of 200 mL of acetone at 20 bar to remove the preservative oil and obtain constant solvent fluxes.
22. Permeate solutions were extracted with dichloromethane (3 × 25 mL) and the obtained solution dried ($MgSO_4$), evaporated using vacuo and purified by flash chromatography

using diethyl ether. (*R*)-1,2-hexanediol was isolated as a colourless oil. Ee was determined by gas chromatography using Beta-Dex 120 column from Supelco (30 m × 0.25 mm) [carrier gas flux of 0.9 mL/min, temperatures: oven, 102 °C; injector, 270 °C; detector, 270 °C].

23. $\mathrm{TON}_{(i)}\ (\mathrm{mol\ mol}^{-1}) = \dfrac{\sum_{i=\text{1st-cycle}}^{n\text{-cycle}} \text{diol in permeate}_i\ (\text{mol})}{\text{catalyst added in 1st cycle (Os mol)}}$.
24. $\text{Osmium in permeate}\ (\%) = \frac{\text{Permeate (mL)} \times \text{Osmium in permeate (mM)}}{\text{Osmium added } (\mu\text{mol})} \times 100$.
25. $\text{Reaction yield}\ (\%) = \frac{\text{diol produced (mol)}}{\text{substrate added (mol)}} \times 100$.
26. $\text{Process yield}\ (\%) = \frac{\text{diol in permeate (mol)}}{\text{substrate added (mol)}} \times 100$.
27. $\text{Rej}\ (\%) = \left(1 - \frac{[\text{Solute}]_{\text{Permeate}}}{[\text{Solute}]_{\text{Feed}}}\right) \times 100$; In this study, the solute is either osmium or diol.
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