

DOI: 10.1002/adsc.200800269

# Sharpless Asymmetric Dihydroxylation of Olefins in Water-Surfactant Media with Recycling of the Catalytic System by Membrane Nanofiltration


Luis C. Branco,<sup>a,\*</sup> Frederico Castelo Ferreira,<sup>b,c</sup> José L. Santos,<sup>c</sup> João G. Crespo,<sup>c,\*</sup> and Carlos A. M. Afonso<sup>a,\*</sup>

<sup>a</sup> CQFM Centro de Química-Física Molecular and IN – Institute of Nanoscience and Nanotechnology, Instituto Superior Técnico, Complexo-1, Av. Rovisco Pais, 1049-001 Lisboa, Portugal  
Fax: (+351)-21-846-4455; e-mail: lbranco@dq.fct.unl.pt, carlosafonso@ist.utl.pt

<sup>b</sup> ICEMS, Departamento de Engenharia Química e Biológica, Instituto Superior Técnico, Complexo-1, Av. Rovisco Pais, 1049-001 Lisboa, Portugal

<sup>c</sup> REQUIMTE, Departamento de Química, Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, 2829-516 Caparica, Portugal  
E-mail: jgc@dq.fct.unl.pt

Received: May 2, 2008; Published online: August 21, 2008

 Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/adsc.200800269>.

**Abstract:** This paper presents a new and more sustainable alternative approach for the Sharpless catalytic asymmetric dihydroxylation (AD) of olefins using a water/surfactant system as reaction media. The AD reaction was performed using several cationic and anionic surfactants allowing yields and enantiomeric excesses higher or comparable with the conventional systems (using organic mixtures). The use of this water/surfactant medium offers the additional advantage of performing the reactions without the need of a slow addition of olefins. Asymmetric dihydroxylation of 1-hexene in a 1.5 mM sodium cholate aqueous solution, using *N*-methylmorpholine *N*-oxide (NMO) as co-oxidant was selected as model

system to evaluate the feasibility of recycling the Sharpless catalytic system by nanofiltration. The reaction media was processed by nanofiltration, the product was isolated in the permeate, whereas the catalytic system and surfactant were retained by the membrane and recycled through six successive reactions, improving the catalyst turn-over number. The experimental results were compared with the ones calculated on the basis of mass balances, membrane rejections to product and reaction yields.

**Keywords:** aqueous media; nanofiltration; olefins; osmium; Sharpless asymmetric dihydroxylation reaction

## Introduction

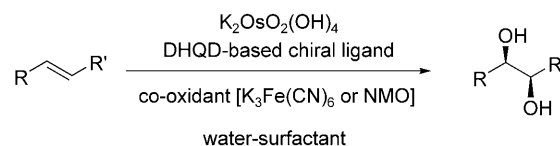
The Sharpless catalytic asymmetric dihydroxylation (AD) of olefins is a powerful methodology for the preparation of chiral 1,2-diols from a broad range of olefins, in which high reaction yields and product enantioselectivities are achieved.<sup>[1]</sup> A water/*tert*-butanol (1:1, v/v) mixture has been described as the best medium for the AD reaction, where high enantioselectivity is achieved as simultaneous solubilization and effective interaction between the catalytic system and the substrate are ensured. Industrial applications of these experimental protocols have been limited, mainly because the high toxicity and volatility of osmium species, which can contaminate the final

product, but as well due to the high cost of osmium and chiral ligands.<sup>[2,3]</sup> In order to address these challenges, several approaches have been described for osmium catalyst immobilization, including microencapsulation techniques<sup>[4]</sup> with polystyrene polymers or polyurea microcapsules;<sup>[5]</sup> ion exchangers;<sup>[6]</sup> anchoring tetrasubstituted olefins in silica,<sup>[7]</sup> in polyethylene glycol matrixes or in Amberlite containing residual vinyl groups;<sup>[8]</sup> use of gold colloids or nanocrystalline magnesium oxide<sup>[9]</sup> and more recently using an aqueous solution of sucrose.<sup>[10]</sup> Recycling experiments have been successfully performed until a maximum of six cycles. However in these studies, either the amount of osmium catalyst added was significantly higher than the ones usually employed (1–5 mol% vs.

0.2–0.5 mol%<sup>[2]</sup>) or addition of chiral ligand after each cycle was required to maintain the catalyst performance. On the other hand, the immobilization of chiral ligands onto soluble and insoluble polymers requires long synthesis of each chiral ligand and its application leads to a reduction of enantioselectivities. Moreover, osmium leaching was observed and thus recovery and re-use of the catalyst was not completely possible.<sup>[11]</sup>

The use of ionic liquids as alternative co-solvents<sup>[12]</sup> or solvents<sup>[13]</sup> for the AD reactions was proposed as a methodology to recycle and re-use the AD catalytic system (osmium/chiral ligand) by extraction the post-reaction solution with an organic solvent or supercritical CO<sub>2</sub> (scCO<sub>2</sub>). Modifications of AD reactions in ionic liquid media also included: replacing the co-oxidants K<sub>3</sub>Fe(CN)<sub>6</sub> or *N*-methylmorpholine *N*-oxide (NMO) by H<sub>2</sub>O<sub>2</sub>; to use flavin as an alternative catalytic system;<sup>[14]</sup> to include VO(acac)<sub>2</sub> or MeReO<sub>3</sub> as co-catalysts;<sup>[15]</sup> and a latest approach proposed by us, in which chiral ionic liquids are used as an alternative chiral promoter without need of the Sharpless chiral ligand.<sup>[16]</sup>

Recently, we explored the possibility to perform the AD reaction using a conventional water-organic solvent system in combination with nanofiltration, in which we demonstrated the possibility to reuse the catalytic system. Additionally, we identified some limitations of this combined process, namely the occurrence of moderate enantioselectivity for the best solvent system (water/acetone 75:25) required for the nanofiltration process and also osmium contamination in the permeate product of 3.4 to 7.4%.<sup>[17]</sup> Herein, we present a new and greener alternative process for AD reaction using water/surfactant as reaction media, K<sub>2</sub>OsO<sub>2</sub>(OH)<sub>4</sub>/(DHQD)<sub>2</sub>PHAL as AD catalytic system and K<sub>3</sub>Fe(CN)<sub>6</sub> or NMO as co-oxidant (Figure 1). Besides hydroquinidine 1,4-phthalazinediyl diether, (DHQD)<sub>2</sub>PHAL, hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether [(DHQD)<sub>2</sub>PYR] were also tested as chiral ligand in this study. Additionally, we use a membrane nanofiltration process to recycle and re-use the AD catalytic system (osmium catalyst/chiral ligand) as well as the surfactants selected.



**Figure 1.** Reaction scheme for asymmetric dihydroxylation of olefins in water/surfactant media.

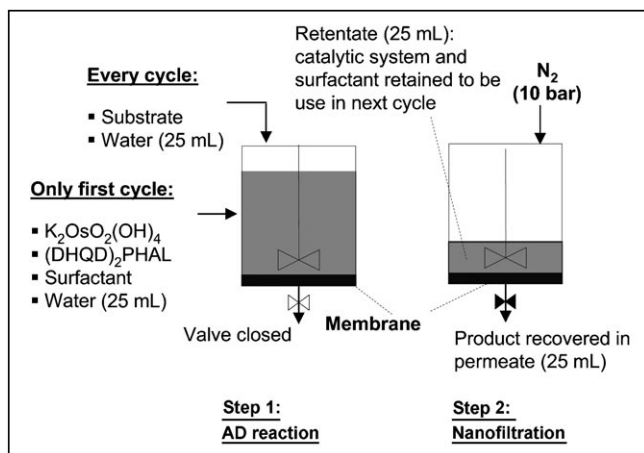
The use of water as an alternative medium for organic transformations has attracted a great interest in the chemistry community.<sup>[18]</sup> Replacing traditional organic solvents by water offers environmental and economical advantages, because in comparison with organic solvents, water is a benign, non-toxic, safe, environmental friendly and cheap medium. However, most organic compounds and organometallic catalysts are insoluble in water. This drawback may be overcome by using surfactants, which solubilize the organic components or form colloidal dispersions within an aqueous medium, allowing substrates and catalysts to combine and react to form the products.<sup>[19]</sup> The efficient use of water/surfactant systems (micellar media) has been described in several organic reactions such as Friedel–Crafts, Diels–Alder, aldol, Mukaiyama–aldol, Pauson–Khand, Mannich, allylation, arylation, Michael and asymmetric hydrogenation reactions. In the case of the AD reaction we selected a range of commercial cationic and anionic surfactants as presented in Table 1.

Nanofiltration membranes had been initially applied for solute separations in aqueous medium.<sup>[20]</sup> Further developments of suitable solvent-stable membranes allowed the use of nanofiltration to separate organometallic catalysts from reaction products when dissolved in homogeneous conventional organic solvents.<sup>[21]</sup> Several of these studies<sup>[22]</sup> show that expensive metal catalysts can be recycled into successive reaction cycles, so improving the catalyst turn-over, without the need of traditional heterogenization and consequent losses of catalytic activity and selectivity. The key challenging aspects identified for the organic solvent nanofiltration studies were the possible losses of catalytic activity and the level of metal contamination.

**Table 1.** Structures of screened surfactants.

Surfactant Name	Short name	Molecular formula	MW (g·mol <sup>-1</sup> )
methyltrioctylammonium chloride	[Aliquat] [Cl]	[CH <sub>3</sub> (CH <sub>2</sub> ) <sub>6</sub> CH <sub>2</sub> ] <sub>3</sub> NCH <sub>3</sub> Cl	404.2
octyltrimethylammonium bromide	[C <sub>8</sub> TMA] [Br]	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>6</sub> N(CH <sub>3</sub> ) <sub>3</sub> Br	252.2
decyltrimethylammonium bromide	[C <sub>10</sub> TMA] [Br]	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>9</sub> N(CH <sub>3</sub> ) <sub>3</sub> Br	280.3
dodecyltrimethylammonium bromide	[C <sub>12</sub> TMA] [Br]	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>11</sub> N(CH <sub>3</sub> ) <sub>3</sub> Br	308.3
tetradecyltrimethylammonium bromide	[C <sub>14</sub> TMA] [Br]	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>13</sub> N(CH <sub>3</sub> ) <sub>3</sub> Br	336.4
hexadecyltrimethylammonium bromide	[C <sub>16</sub> TMA] [Br]	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>15</sub> N(CH <sub>3</sub> ) <sub>3</sub> Br	364.5
1-dodecanesulfonic acid sodium salt (SDS)	[Na][C <sub>12</sub> SO <sub>3</sub> ]	C <sub>12</sub> H <sub>25</sub> SO <sub>3</sub>	272.4
sodium cholate	[Na] [cholate]	C <sub>24</sub> H <sub>39</sub> NaO <sub>5</sub>	430.6
3-[(3-cholamidopropyl)-dimethylammonio] 1-propanesulfonate	CHAPS	C <sub>32</sub> H <sub>58</sub> N <sub>2</sub> O <sub>7</sub> S	614.9

tion of the product in the permeate stream. Stabilization of the catalyst in the retentate was attempted by the use of ionic liquids as co-solvents.<sup>[23]</sup> This work follows a similar approach, but for an aqueous/surfactant medium. The nanofiltration membrane retains the surfactant and the catalytic system, composed of an osmium salt and chiral ligand, which are then recycled into several successive reaction-nanofiltration (R-NF) cycles. Fresh substrate and co-oxidant are added in each new reaction cycle as shown in Figure 2.



**Figure 2.** Scheme of nanofiltration-reaction successive cycles. The following species were added only in the first cycle: **Osmium (Os)**,  $K_2OsO_2(OH)_4$ , (8.2 mg, 22  $\mu$ mol); **Ligand (L)**,  $(DHQD)_2PHAL$ , (75.1 mg, 96  $\mu$ mol); **Surfactant**,  $[Na][cholate]$ , (32.5 mg, 75  $\mu$ mol). Added every cycle: **Substrate (S)**, 1-hexene, (0.3 mL, 2.42 mmol); **Co-oxidant (NMO)**, (0.5 g, 3.75 mmol). Molar ratios  $L/Os=4.3$ ,  $S/Os=109$ . Reaction progressed over 40 h at room temperature.

## Results and Discussion

### Selection of Surfactant for AD Reaction in Water/Surfactant Media

Five alkyltrimethylammonium (TMA) bromide salts ( $[C_nTMA][Br]$ ) and a methyltrioctylammonium chloride salt ( $[Aliquat][Cl]$ ) were selected as examples of cationic surfactants, sodium dodecyl sulfate ( $[Na][C_{12}SO_3]$ ) and sodium cholate ( $[Na][cholate]$ ) as anionic surfactants; and 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate (CHAPS) as zwitterionic surfactant. The surfactants selected for this study are shown in Table 1. The critical micellar concentration (CMC) of the surfactants tested ranges from values below 1 mM for the trimethyl (TMA) quaternary ammonium bromide salts<sup>[24a]</sup> to values high as 12–13 mM for sodium cholate.<sup>[24b]</sup> On the other hand  $[Na][C_{12}SO_3]$  (SDS)<sup>[24c]</sup> and CHAPS<sup>[24d]</sup>

have intermediate CMC values at about 4 and 6–10 mM, respectively; notice however that the indicative literature CMC values may change in the presence of the solutes involved on the reaction.

Initially, we studied the effect of different water/surfactant media on the AD reaction using 1-hexene as model substrate, an osmium salt/chiral ligand ( $K_2OsO_2(OH)_4/(DHQD)_2PHAL$ ) as catalytic system and  $K_3Fe(CN)_6$  as inorganic co-oxidant or NMO as organic co-oxidant. Each surfactant was tested for two different concentrations (0.1 and 0.01 M), except in the cases of  $[C_8TMA][Br]$  and  $[C_{14}TMA][Br]$ , which were only tested at the lower surfactant concentration. The reaction yields ( $Y_{react}$ )<sup>[25]</sup> and enantiomeric excesses (*ees*) obtained are presented in Table 2. The specific yield<sup>[26]</sup> was also defined in an attempted to capture in a single parameter both yield and enantioselectivity and the corresponding values are shown in Figure 3.

When NMO was used as co-oxidant, all experiments were performed by adding the olefin at once (normal addition) to the reaction mixture. Normally, the use of NMO as organic co-oxidant requires a slow addition of the substrate to prevent the occurrence of the second catalytic cycle,<sup>[1,2]</sup> which would lead to low enantioselectivity. Recently, we described the possibility to avoid this slow addition protocol just by using specific ionic liquids as unique reaction medium.<sup>[13]</sup> Here, we also showed that several surfactants can be used in order to achieve high *ees* without the need of a slow addition of the olefin (Table 2, entries 1–3 and 6, 7, providing *ees* higher than 87% for experiments using 0.1 M of surfactant).

The CMC of the cationic surfactants  $[C_nTMA][Br]$  are lower than any of the surfactant concentrations employed (0.1 and 0.01 M); nevertheless the higher concentration of these cationic surfactants provides for either superior specific yields (when NMO is used as co-oxidant with any of these surfactants) or negligible effects {when  $K_3Fe(CN)_6$  was used as co-oxidant together with the  $[C_{10}TMA][Br]$  and  $[C_{16}TMA][Br]$ }.

The five combinations of surfactants type/surfactant concentration at which we observed that the higher yields and *ees* were obtained for (*R*)-hexanediol are marked with an arrow on Figure 3A and Figure 3B, respectively, for reactions using  $K_3Fe(CN)_6$  and NMO as co-oxidant. The five reaction conditions were selected to test the AD reaction of seven representative olefins for each of the co-oxidants.

$[C_{12}TMA][Br]$  at 0.1 M and  $[C_{16}TMA][Br]$  at 0.01 M were selected as cationic surfactants for further substrate testing using  $K_3Fe(CN)_6$  as co-oxidant (Figure 3A); whereas the use of an higher  $[C_{12}TMA][Br]$  concentration provides for an higher (*R*)-hexanediol production, no significant positive effect was observed between the two  $[C_{16}TMA][Br]$  concentrations.  $[C_{10}TMA][Br]$  at 0.1 M and  $[C_{14}TMA][Br]$  at 0.01 M

**Table 2.** Asymmetric dihydroxylation of 1-hexene using different surfactants at 0.1 and 0.01 M,  $K_2OsO_2(OH)_4$ /(DHQD)<sub>2</sub>PHAL as a catalytic system and  $K_3Fe(CN)_6$  or NMO as co-oxidants.<sup>[a]</sup>

Entry	Surfactant	[Surfactant] (M)	$K_3Fe(CN)_6$		NMO	
			$Y_{\text{react}}^{[b]}$ [%]	$ee^{[c]}$ [%]	$Y_{\text{react}}^{[b]}$ [%]	$ee^{[c]}$ [%]
1	[Na] [C <sub>12</sub> SO <sub>3</sub> ]	0.1	63	98	76	98
		0.01	80	92	85	87
2	[Na] [cholate]	0.1	47	74	43	95
		0.01	91	96	91	95
3	CHAPS	0.1	61	99	88	97
		0.01	80	94	64	70
4	[Aliquat] [Cl]	0.1	88	63	26	65
		0.01	59	75	28	82
5	[C <sub>8</sub> TMA] [Br]	0.1	–	–	–	–
		0.01	76	99	57	60
6	[C <sub>10</sub> TMA] [Br]	0.1	65	85	73	99
		0.01	70	85	56	81
7	[C <sub>12</sub> TMA] [Br]	0.1	93	98	76	89
		0.01	69	94	69	64
8	[C <sub>14</sub> TMA] [Br]	0.1	–	–	–	–
		0.01	54	74	99	89
9	[C <sub>16</sub> TMA] [Br]	0.1	98	95	94	67
		0.01	96	93	61	77

<sup>[a]</sup> All reactions were carried out using 1-hexene (0.5 mmol),  $K_2OsO_2(OH)_4$  (0.5 mol%), chiral ligand (DHQD)<sub>2</sub>PHAL, (1.0 mol%), co-oxidant  $K_3Fe(CN)_6$  (3.0 mol equiv.),  $K_2CO_3$  (3.0 mol equiv.) or NMO (1.0 mol equiv.), surfactant (0.1 or 0.01 M), water (1.5 mL) at room temperature, 48 h [substrate concentration of 340 mM, L/Os=2.0 mol·mol<sup>-1</sup>, S/Os=187 mol·mol<sup>-1</sup>, NMO/S=1.5 mol·mol<sup>-1</sup>].

<sup>[b]</sup> Reaction yield ( $Y_{\text{react}}$ ):  $Y_{\text{react}} (\%) = \frac{\text{diol produced (mol)}}{\text{olefin/substrate added (mol)}} \times 100$ .

<sup>[c]</sup> Absolute configuration of the diol is (*R*).

were selected as cationic surfactants for testing further substrates using NMO as co-oxidant (Figure 3B). Experiments which were carried out using [C<sub>n</sub>TMA][Br] (*n* = 10, 12) in the higher cationic surfactant concentration (0.1 M) gave similar specific yields (73–78%). From the cationic surfactants tested, [C<sub>10</sub>TMA][Br] and [C<sub>14</sub>TMA][Br] provided, respectively, the highest *ees* (*ee* 99%, Table 2, entry 6) and yield (99%, Table 2, entry 8).

The yields obtained using [Aliquat][Cl] were quite low and no further tests were performed using this surfactant. Contrarily to [C<sub>n</sub>TMA][Br] salts, [Aliquat][Cl] is a viscous liquid at room temperature and almost insoluble in water. These properties may explain its lower efficiency in AD reactions.

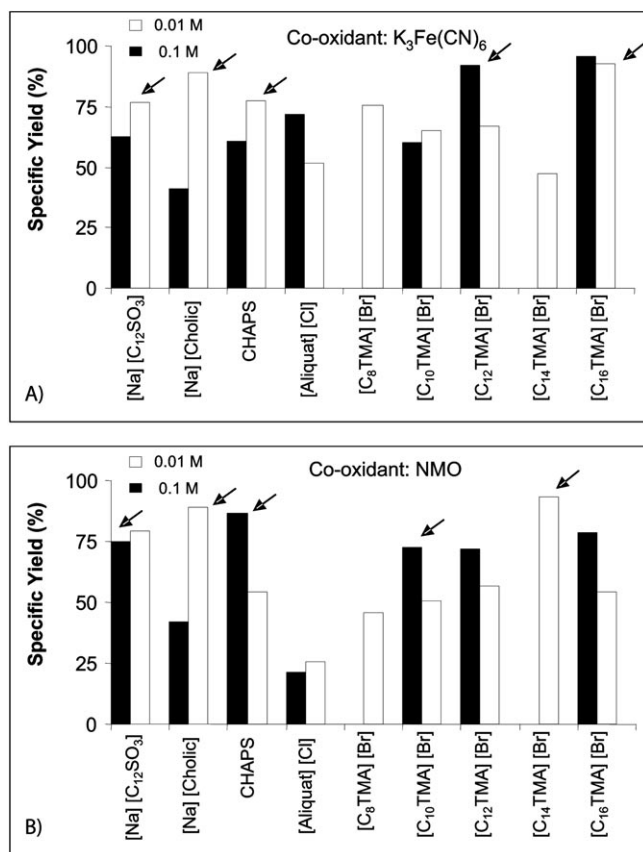
The results obtained using five different [C<sub>n</sub>TMA][Br] salts with *n* = 8, 10, 12, 14 and 16 at surfactant concentration of 0.01 M, allow an evaluation of the effect of surfactant alkyl chain size vs. reaction performance. For the series in which the NMO was used as co-oxidant, (*R*)-hexanediol production increases with alkyl chain length and the opposite effect is observed when  $K_3Fe(CN)_6$  is used as co-oxidant. However, for both co-oxidant series, the use of [C<sub>16</sub>TMA][Br] as surfactant resulted in yield performances against these trends.

The two anionic surfactants tested [Na][C<sub>12</sub>SO<sub>3</sub>] and [Na][cholate] seem to provide for (*R*)-hexanediol

in higher yields for the lower surfactant concentration (Table 2, entries 1 and 2) for both co-oxidants, in particular for sodium cholate. The anionic surfactant concentrations used for further substrate testing are indicated in Figure 3. The effect of zwitterionic surfactant concentration (CHAPS) on reaction yield depends of the co-oxidant selected; therefore 0.1 M or 0.01 M of CHAPS was selected for further testing using NMO or  $K_3Fe(CN)_6$  as co-oxidant, respectively. Notice that for the anionic and zwitterionic surfactants the lower concentration used is in the range of the respective CMCs. One should keep in mind that the use of specific yield as only selection criteria can be biased towards enantioselectivity. For example, higher specific yields were found for 0.01 M surfactant concentrations in the case of [Na][C<sub>12</sub>SO<sub>3</sub>] with NMO or CHAPS with  $K_3Fe(CN)_6$ , however for the same cases a superior *ee* of 98 or 99% (against 87 or 94%) can be obtained using surfactant concentrations of 0.1 M (Table 2).

The best five selected surfactants and concentrations were also tested for the chiral ligands (DHQD)<sub>2</sub>PYR and (DHQD)<sub>2</sub>PHAL using 1-hexene as substrate model (Table 3). (DHQD)<sub>2</sub>PYR seems to provide a superior performance reaction when NMO is used as co-oxidant together with most of the selected surfactants and also when  $K_3Fe(CN)_6$  is used in combination with the anionic surfactants.





**Figure 3.** Asymmetric dihydroxylation of 1-hexene using different surfactants at 0.1 and 0.01 M,  $K_2OsO_2(OH)_4$ /(DHQD) $_2$ PHAL as a catalytic system and  $K_3Fe(CN)_6$  or NMO as co-oxidants at a 1.5-mL scale.

### Feasibility of AD Reaction in Water/Surfactant Media for Several Olefins

Seven different representative olefins (containing aliphatic and aromatic units) were selected as representative substrates: 1-hexene, *trans*-5-decene, 1-methylcyclohexene, styrene,  $\alpha$ -methylstyrene, *trans*-stilbene and methyl *trans*-cinnamate. Reaction yields, specific yields and *ees* obtained in each of the optimized water/surfactant systems are listed in Table 4 and Table 5, using  $K_3Fe(CN)_6$  and NMO as co-oxidant, respectively. Substrates are presented by decreasing order of lipophilicity, according with the respective olefin's  $\log P^{[27]}$  (octanol-water partition coefficient).

As a general rule, cationic surfactants increase the rate of reactions between a neutral substrate and an anion, like in basic hydrolysis and nucleophilic substitution reactions.<sup>[18]</sup> The same behavior is observed in deacylations, decarboxylations, intramolecular nucleophilic anionic cyclizations, and *cis*- to *trans*- isomerizations.

Anionic surfactants increase the rate of bimolecular reactions with positively charged reactive counterions, e.g., metal-ligand substitution reactions and acid-catalyzed reactions. Conversely, they tend to inhibit bimolecular reactions of neutral substrates with anionic nucleophiles because they repel the reactive anions and keep them away from the micellar solubilized substrate<sup>[18a,i,19]</sup>.

Some considerations can be drawn based on the results showed in Table 4 and Table 5. 1) In the case of cationic surfactants the best results ( $Y_{\text{react}}$  and *ees*) were achieved for methyl *trans*-cinnamate and 1-hexene using  $K_3Fe(CN)_6$  (Table 4) and styrene and 1-methylcyclohexene using NMO (Table 5). 2) [Na]-

**Table 3.** Asymmetric dihydroxylation of 1-hexene using different chiral ligands: (DHQD) $_2$ PHAL and (DHQD) $_2$ PYR.<sup>[a]</sup>

Co-oxidant	Surfactant	$Y_{\text{react}}$ [%] <sup>[b]</sup>		<i>ee</i> [%] <sup>[c]</sup>		Specific Yield [%] <sup>[d]</sup>	
		PHAL	PYR	PHAL	PYR	PHAL	PYR
$K_3Fe(CN)_6$	[Na] [C <sub>12</sub> SO <sub>3</sub> ] 0.01 M	80	95	92	90	77	90
	[Na] [cholate] 0.01 M	91	96	96	99	89	96
	CHAPS 0.01 M	80	70	94	93	78	68
	[C <sub>12</sub> TMA] [Br] 0.1 M	93	66	98	67	92	55
	[C <sub>16</sub> TMA] [Br] 0.01 M	96	73	93	99	93	73
NMO	[Na] [C <sub>12</sub> SO <sub>3</sub> ] 0.1 M	76	96	98	97	75	95
	[Na] [cholate] 0.01 M	91	85	95	94	89	82
	CHAPS 0.1 M	88	95	97	99	87	95
	[C <sub>10</sub> TMA] [Br] 0.1 M	73	96	99	97	73	95
	[C <sub>14</sub> TMA] [Br] 0.01 M	99	97	89	99	94	97

<sup>[a]</sup> All reactions were carried out using 1-hexene (0.5 mmol),  $K_2OsO_2(OH)_4$  (0.5 mol%), chiral ligand (DHQD) $_2$ PHAL or (DHQD) $_2$ PYR, (1.0 mol%), co-oxidant  $K_3Fe(CN)_6$  (3.0 mol eq.),  $K_2CO_3$  (3.0 mol equiv.) or NMO (1.0 mol equiv.), surfactant (0.1 or 0.01 M), water (1.5 mL) at room temperature, 48 h. [substrate concentration of 340 mM, L/Os=2.0 mol·mol<sup>-1</sup>, S/Os=187 mol·mol<sup>-1</sup>, NMO/S=1.5 mol·mol<sup>-1</sup>].

<sup>[b]</sup> Reaction yield ( $Y_{\text{react}}$ ):  $Y_{\text{react}} (\%) = \frac{\text{diol produced (mol)}}{\text{olefin/substrate added (mol)}} \times 100$ .

<sup>[c]</sup> Absolute configuration of the diol is (*R*).

<sup>[d]</sup> R-Y = specific yield (%) =  $\frac{\text{diol (mol)}}{\text{substrate added (mol)}} \times 100 = \frac{Y_{\text{react}} (\%)}{2} (1 + \frac{ee (\%)}{100})$ .

**Table 4.** Asymmetric dihydroxylation of olefins in surfactant/aqueous media using  $K_3Fe(CN)_6$  as co-oxidant.<sup>[a]</sup>

Co-oxidant: $K_3Fe(CN)_6$	[Na] [C <sub>12</sub> SO <sub>3</sub> ] 0.01M	[Na] [cholate] 0.01M	CHAPS 0.01M	[C <sub>12</sub> TMA] [Br] 0.1 M	[C <sub>16</sub> TMA] [Br] 0.01M										
Log P	$Y_{react}^{[b]}$ [%]	$ee^{[c]}$ [%]	Specific Yield <sup>[d]</sup> [%]	$Y_{react}$ [%]	$ee$ [%]	Specific Yield [%]	$Y_{react}$ [%]	$ee$ [%]	Specific Yield [%]	$Y_{react}$ [%]	$ee$ [%]	Specific Yield [%]			
<i>trans</i> -5-decene	5.04	87	96	85	89	94	86	92	94	99	84	91	77	87	72
<i>trans</i> -stilbene	4.52	99	96	97	98	75	86	96	95	83	94	81	92	94	89
1-methylcyclohexene	3.51	98	98	97	97	86	90	78	99	84	97	83	88	86	82
$\alpha$ -methylstyrene	3.44	82	91	78	93	97	92	95	98	91	88	86	83	72	71
1-hexene	3.15	80	92	77	91	96	89	80	94	93	98	92	96	93	93
styrene	2.89	92	85	85	87	98	86	82	97	87	98	86	98	96	96
methyl cinnamate	2.34	65	94	63	93	72	80	89	92	93	97	92	95	90	90

<sup>[a]</sup> All reactions were carried out using 1-hexene (0.5 mmol),  $K_2OsO_2(OH)_4$  (0.5 mol%), chiral ligand (DHQD)<sub>2</sub>PHAL, 1.0 mol%), co-oxidant  $K_3Fe(CN)_6$  (3.0 mol equiv.),  $K_2CO_3$  (3.0 mol equiv.) or NMO (1.0 mol equiv.), surfactant (0.1 or 0.01M), water (1.5 mL) at room temperature, 48 h [substrate concentration of 340 mM, L/Os=2.0 mol·mol<sup>-1</sup>, S/Os=187 mol·mol<sup>-1</sup>, NMO/S=1.5 mol·mol<sup>-1</sup>].

<sup>[b]</sup> Reaction yield ( $Y_{react}$ ):  $Y_{react} (\%) = \frac{\text{diol produced (mol)}}{\text{olefin/substrate added (mol)}} \times 100$ .

<sup>[c]</sup> Absolute configuration of the diol is (R).

<sup>[d]</sup> R-Y = specific yield (%) =  $\frac{Y_{react} (\%)}{\text{substrate added (mol)}} \times 100 = \frac{Y_{react} (\%)}{2} (1 + \frac{ee (\%) }{100})$ .

**Table 5.** Asymmetric dihydroxylation of olefins in surfactant aqueous media using NMO as co-oxidant.<sup>[a]</sup>

Co-oxidant: NMO	[Na] [C <sub>12</sub> SO <sub>3</sub> ] 0.1M	[Na] [cholate] 0.01M	CHAPS 0.1M	[C <sub>10</sub> TMA] [Br] 0.1M	[C <sub>14</sub> TMA] [Br] 0.01M										
Log P	$Y_{react}^{[b]}$ [%]	$ee^{[c]}$ [%]	Specific Yield <sup>[d]</sup> [%]	$Y_{react}$ [%]	$ee$ [%]	Specific Yield [%]	$Y_{react}$ [%]	$ee$ [%]	Specific Yield [%]	$Y_{react}$ [%]	$ee$ [%]	Specific Yield [%]			
<i>trans</i> -5-decene	5.04	92	95	90	91	90	86	95	90	95	96	93	98	83	90
<i>trans</i> -stilbene	4.52	87	94	84	95	95	93	85	76	80	78	71	81	77	72
1-methylcyclohexene	3.51	86	99	86	91	96	89	88	95	94	99	94	91	92	87
$\alpha$ -methylstyrene	3.44	95	99	95	89	98	88	88	73	99	96	97	91	75	80
1-hexene	3.15	76	98	75	91	95	89	88	97	73	99	73	99	89	94
styrene	2.89	88	84	81	89	97	88	88	98	97	99	97	95	98	94
methyl cinnamate	2.34	65	71	56	60	80	54	73	98	79	73	68	75	76	66

<sup>[a]</sup> All reactions were carried out using 1-hexene (0.5 mmol),  $K_2OsO_2(OH)_4$  (0.5 mol%), chiral ligand (DHQD)<sub>2</sub>PHAL, 1.0 mol%), co-oxidant  $K_3Fe(CN)_6$  (3.0 mol equiv.),  $K_2CO_3$  (3.0 mol equiv.) or NMO (1.0 mol equiv.), surfactant (0.1 or 0.01M), water (1.5 mL) at room temperature, 48 h. [substrate concentration of 340 mM, L/Os=2.0 mol·mol<sup>-1</sup>, S/Os=187 mol·mol<sup>-1</sup>, NMO/S=1.5 mol·mol<sup>-1</sup>].

<sup>[b]</sup> Reaction yield ( $Y_{react}$ ):  $Y_{react} (\%) = \frac{\text{diol produced (mol)}}{\text{olefin/substrate added (mol)}} \times 100$ .

<sup>[c]</sup> Absolute configuration of the diol is (R).

<sup>[d]</sup> R-Y = specific yield (%) =  $\frac{Y_{react} (\%)}{\text{substrate added (mol)}} \times 100 = \frac{Y_{react} (\%)}{2} (1 + \frac{ee (\%) }{100})$ .

[cholate] as anionic surfactant presents a high efficiency for all the olefins tested, except in the case of *trans*-stilbene [ $K_3Fe(CN)_6$ ] and methyl *trans*-cinnamate (NMO). 3) CHAPS as zwitterionic surfactant allowed high enantioselectivities for all the substrates in both co-oxidants, except for methylstyrene and *trans*-stilbene using NMO as co-oxidant. 4) Similar or poor  $Y_{\text{react}}$  and *ees* were observed using  $(DHQD)_2PYR$  as an alternative chiral ligand for 1-hexene and methyl *trans*-cinnamate.

Several reports<sup>[18,19]</sup> described that the organic solutes interact with micelles (spherical arrangement of surfactant monomers) according to their polarity: non-polar solutes are buried in the interior of the micelle; moderately polar molecules are located closer to the polar surface, while polar solutes will be found at the external surface of the micelle.

Some solutes prefer to bind just below the surface of the micellar aggregates, taking advantage of hydrophobic microdomains in the Stern region.

This organization of solutes may be responsible for the observed catalytic or inhibitory influence on organic reactions in micellar media. In the case of the AD reaction, the presence of some cationic or anionic surfactants seems to improve the observed catalytic efficiency depending of their concentration in the aqueous medium. As a general rule, we can conclude that the water/surfactant systems allowed comparable or higher  $Y_{\text{react}}$  and enantioselectivities (*ees*) than the previous approaches reported (water/*tert*-butanol; water/ILs or ILs media) for a representative range of olefins.

### Scaling Up of the AD Reaction for Reaction-Nanofiltration Feasibility Study

Results in Table 2, Table 3 and Table 4 show that AD reactions can be successfully performed in aqueous media when combined with an appropriate surfactant. However, the addition of surfactants poses additional challenges for the isolation of the final product and disposal of an osmium-enriched streams. Processing of the post-reaction solution by membrane nanofiltration may provide for a direct isolation of the product in the permeate, as the surfactants and the catalytic system (osmium/chiral ligand) are retained by the membrane.

Retention of the catalytic system contributes to product isolation and osmium detoxification of the permeate stream, and also allows recycling of the catalytic system into successive reactions, improving the economics of the synthesis of chiral diols. Once fresh substrate and co-oxidant are added to the retentate, another AD reaction can take place with production of further chiral diol without the need of using additional expensive catalyst. In other words the method-

ology described in Figure 2 aims at improving the catalytic cumulative turn-over number (TON).<sup>[28]</sup> The proposed approach requires low membrane rejections to the product and high rejections to the catalytic system, i.e., osmium, chiral ligand and surfactants. The following parameters have to be selected for a feasibility study of the proposed methodology: (a) a suitable nanofiltration membrane, (b) a model substrate (and respective concentration), (c) co-oxidant, (d) ligand/osmium (L/Os) molar ratio, (e) substrate/osmium (S/Os) molar ratio, (f) surfactant type and respective concentration. The rationale used for the selection of each of these parameters is discussed below.

**a) Desal DK**, a nanofiltration composite membrane with a polyamide selective top layer and a polysulfone support, was selected to operate the reaction-nanofiltration (R-NF) cycles. This membrane, with a nominal molecular weight cut-off (MWCO)<sup>[29]</sup> of  $250 \text{ g}\cdot\text{mol}^{-1}$ , is suitable to retain the model catalytic system, comprised of  $K_2OsO_2(OH)_4$  salt ( $MW = 368 \text{ g}\cdot\text{mol}^{-1}$ ) and the chiral ligand  $(DHQD)_2PHAL$  ( $MW = 779 \text{ g}\cdot\text{mol}^{-1}$ ).

**b) 1-Hexene was selected as a model substrate** for the R-NF cycles since it is the smallest of the olefins tested as substrate, thus facilitating permeation of the corresponding product, 1,2-hexanediol ( $MW = 118 \text{ g}\cdot\text{mol}^{-1}$ ) throughout the membrane. An average Desal DK rejection<sup>[30]</sup> of 51.9% (with a coefficient of variation of 6%) was obtained for 1,2-hexanediol in water under applied pressures in the range of 8.5 to 20.5 bar. A 10 bar applied pressure was selected to operate the R-NF cycles. The feasibility and optimization studies of AD reaction using water/surfactant media, reported in Table 2, Table 3, Table 4 and Table 5, were performed at a 1.5-mL scale. Surfactant concentration was either 0.1 or 0.01 M. However, our nanofiltration equipment<sup>[31]</sup> requires a considerable higher volume and, therefore, R-NF cycles were performed at a 50-mL scale.

Studies performed in *tert*-butanol/water (50:50 v/v %) show that the AD reaction of 1-hexene is not significantly affected with substrate concentrations decreasing from 255 to 45 mM, but a steep decrease in yield was observed for substrate concentrations<sup>[32]</sup> below 45 mM. Therefore, 2.42 mmol of 1-hexene were added in each cycle, corresponding to a concentration of 48.4 mM.

**c) The co-oxidant selected was NMO.** The co-oxidant is consumed in the dihydroxylation reaction, therefore fresh co-oxidant was added together with substrate at the beginning of each reaction-nanofiltration (R-NF) cycle. Only 1 mol equiv. of NMO to substrate (NMO/S molar ratio 1.0) is required by the AD reaction, whereas the use of  $K_3Fe(CN)_6$  would imply a  $K_3Fe(CN)_6/S$  molar ratio higher than 3.0 and co-addition of  $K_2CO_3$  salt, which would increase significant-

ly the salt concentration and viscosity of the retentate solution. Accumulation of the reduced form of the co-oxidant species in the retentate phase would contribute to an undesirable increase of the solution viscosity or development of heterogeneities, leading to decreasing filtration fluxes. Since NMO is a co-oxidant with a molecular weight (MW 135 g·mol<sup>-1</sup>), significantly lower than the K<sub>3</sub>Fe(CN)<sub>6</sub> salt (MW 329 g·mol<sup>-1</sup>) and well below the Desal DK MWCO of 250 g·mol<sup>-1</sup>, it was selected as co-oxidant for the R-NF cycles.

**d) Higher ligand to osmium (L/Os) molar ratios** are directly related with the higher enantioselectivity observed. For the model solvent system (water/*tert*-butanol, 50:50 v/v %) *ees* of 70%, 83% and 97% were obtained, respectively for 1, 2 and 4 molar L/Os ratios. No significant effects on the reaction yield were observed for the range of L/Os tested (*Y*<sub>react</sub> of 89%, 85% and 89% were obtained for L/Os=1, 2 and 4 mol·mol<sup>-1</sup>, respectively). These data are in agreement with the proposed mechanism for AD, where the catalytic complex is formed by two molecules of chiral

ligand per each osmium molecule.<sup>[1b]</sup> An initial L/Os molar ratio higher than 4 was also tested in order to minimize the amount of free osmium (MW 190 g·mol<sup>-1</sup>) dissolved in solution, and therefore the potential Os permeation throughout the membrane.

**e) Similar substrate to osmium (S/Os)<sup>[33]</sup>** molar ratios of 100–200, reaction times of about 40 h and normal addition of substrate were employed in both reaction scales. However, due to budget limitations, the substrate concentration was decreased. The different experimental conditions used for each set of experiments are compared in Table 6.

**f) Surfactant concentrations** of 0.1 and 0.01 M were used at a 1.5-mL scale experiments. To select the surfactant for R-NF cycles, we compared the *Y*<sub>react</sub> and *ee* obtained in independent reactions performed at a 40-mL scale for the three surfactants with higher molecular weights, since these are easily retained by the membrane. The results are shown in Figure 4. The surfactant concentration used in these experiments, as well as in the successive R-NF cycles, was reduced to 1.5 mM (near the CMC). The best *Y*<sub>react</sub> and *ee* were

**Table 6.** Comparison of reaction conditions at different volume scales for asymmetric dihydroxylation of 1-hexene into 1,2-hexanediol in aqueous/surfactant media.

Experiment type:	(i) Feasibility and optimization studies <sup>[a]</sup>	(ii) Single reaction <sup>[a]</sup> (Figure 4)	(iii) Reaction-Nanofiltration cycles <sup>[a]</sup>	(iv-a) Single reaction <sup>[b]</sup> (reference)	(iv.b) Single reaction <sup>[b]</sup> with product inhibition <sup>[f]</sup>	(iv-c) Single reaction <sup>[b]</sup> with substrate load 6-fold higher
Volume scale (mL)	1.5	40	50	50	50	10
Substrate (mM)	339.0	60.5	48.4	48.4	48.4	290.6
L/Os (mol·mol <sup>-1</sup> )	2.0	4.0	4.3	4.7	4.7	4.7
S/Os (mol·mol <sup>-1</sup> )	187	143	109	115	115	689
NMO/S (mol·mol <sup>-1</sup> )	1.5	1.1	1.6	<1.6	<1.6	<1.6
Surfactant (mM)	10 (or 100)	1.5	1.5	1.6	1.6	1.6
Initially load of product (mM)					38.7	
Reaction time (hour)	48	40	40	40	40	40
[Na][cholate] as surfactant:						
<i>Y</i> <sub>react</sub> [%] <sup>[c]</sup>	91	84	{23–35}	88	56	79
{ <i>Y</i> <sub>process</sub> [%] <sup>[d]</sup> }						
<i>ee</i> [%]	85	76	74–79	79	Not measured	67
TON <sup>[e]</sup> [mol·mol <sup>-1</sup> ]	170	120	203	101	64	546

<sup>[a]</sup> Room temperature 25 °C.

<sup>[b]</sup> Room temperature 18 °C.

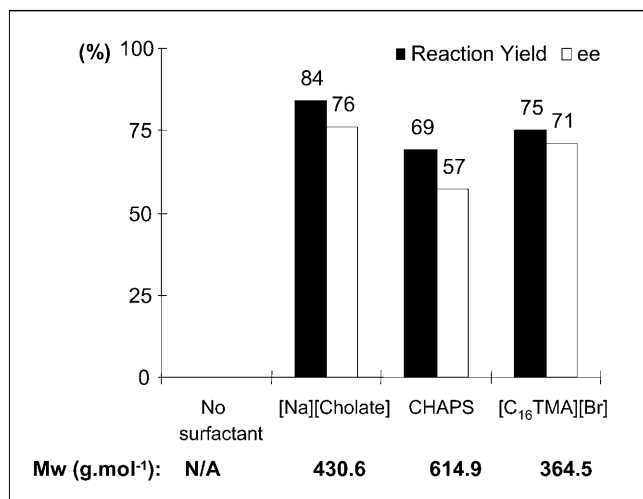
<sup>[c]</sup>  $Y_{\text{react}} (\%) = \frac{\text{diol produced (mol)}}{\text{olefin/substrate added (mol)}} \times 100$ .

<sup>[d]</sup>  $Y_{\text{process}} (\%) = \frac{\text{diol in permeate (mol)}}{\text{olefin substrate (mol)}} \times 100$  [*Y*<sub>process</sub> differs from *Y*<sub>react</sub> since there is accumulation of product in retentate].

<sup>[e]</sup>  $\text{TON} = \frac{\sum \text{diol produced (mol)}}{\text{catalyst used (Os mol)}}$  [notice that enantioselectivity is not taken into account in this calculation.].

<sup>[f]</sup> This reaction was carried out in the presence of 2 mmol of racemic 1,2-hexanediol.





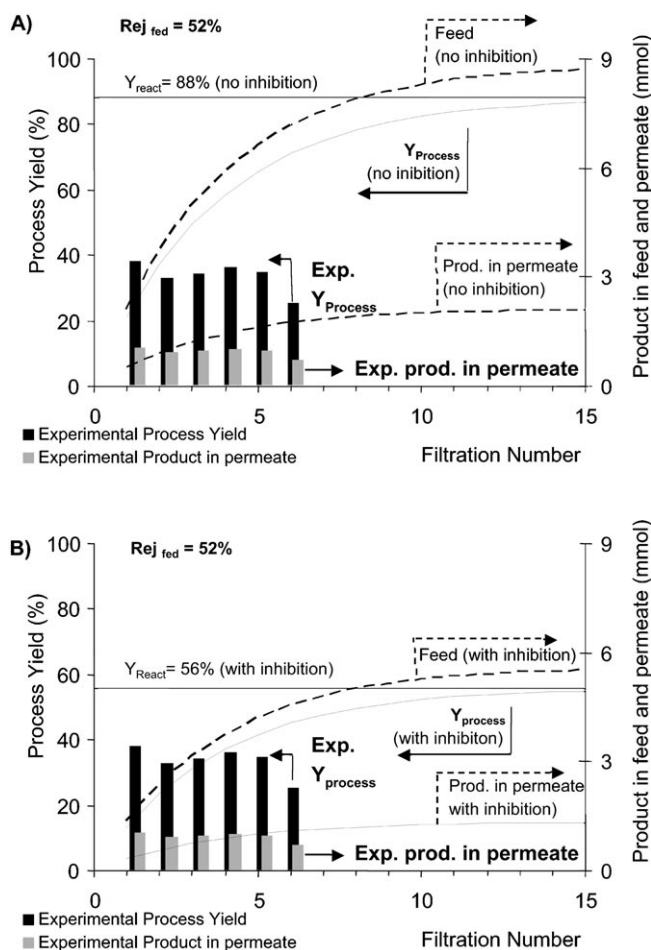
**Figure 4.** Surfactant screening at a 40-mL scale for dihydroxylation of 1-hexene. Reaction conditions: 40-mL scale, 1 h, 60.5 mM, L/Os = 4.0 mol·mol<sup>-1</sup>, S/Os = 143 mol·mol<sup>-1</sup>, NMO/S = 1.1 mol·mol<sup>-1</sup>. Reaction proceeded over 40 h at room temperature.

obtained for the sodium cholate with values of 84% and 76%, respectively. Therefore this surfactant was selected to be used on the R-NF cycles. The rejection of sodium cholate by Desal DK was measured by total organic carbon (TOC) at a value of (99.5 ± 0.1)%, using as feed solution a 1.5 mM aqueous solution of sodium cholate.

### Yields and ees in the Reaction-Nanofiltration (R-NF) Cycles Process

R-NF cycles were carried out as schematically illustrated in Figure 2. The detailed reaction conditions are summarized in Table 6 (column iii). An average ee of (76 ± 2)% was obtained for the R-NF cycles (Table 6, column iii). This value is quite similar to the ones obtained in single reactions, performed also using sodium cholate as surfactant at 40-mL or 50-mL scale (Table 6, ii and iv-a, respectively).

Whereas in single reaction experiments the entire post-reaction solution is analyzed for diol production, in the R-NF cycles only the diol in the permeate solution is quantified. Therefore, two different yields were defined for each of the experiment types: reaction yield ( $Y_{\text{react}}$ )<sup>[25]</sup> and process yield ( $Y_{\text{process}}$ )<sup>[25]</sup>, respectively, for single reaction and R-NF cycles experiments. After a given number of successive R-NF cycles at constant catalytic activity, it is expected that accumulation of the product in the retentate reaches a steady state and therefore the  $Y_{\text{process}}$  values tends to the  $Y_{\text{react}}$  value. Figure 5 shows the calculated expected values of diol (in moles) in the post-reaction feed and permeate solutions, as well as the  $Y_{\text{process}}$  over the



**Figure 5.** Experimental and calculated data on process yield and product amounts. Accumulation of product in the retentate is taken into account on the basis of a membrane rejection of 51.9%, a feed and a permeate volumes of 50 mL and 25 mL, respectively, and 1,2-hexanediol production was calculated based on substrate addition of 2.42 mmol and either (A) in a  $Y_{\text{react}} = 88\%$ , which does not take product inhibition into account or (B) in a  $Y_{\text{react}} = 56\%$ , accounting for product inhibition.

first cycles before such a steady state is reached. These calculations were based on diol mass balances, on a rejection of 51.9% measured for 1,2-hexanediol and on feed and permeate volumes of 50 mL and 25 mL, respectively. Production of fresh 1,2-hexanediol in each cycle was assumed to be constant on the basis of the addition of 2.42 mol of substrate (1-hexene) and a constant  $Y_{\text{react}}$  value.

The obtained experimental  $Y_{\text{process}}$  (and diol on the permeate) of the six R-NF cycles maintained a value relatively constant with a slight decrease towards the last cycle. With the exception of the 1<sup>st</sup> cycle, the experimental  $Y_{\text{process}}$  values are below the ones calculated on the basis of a  $Y_{\text{react}}$  of 88%, which led us to suspect reaction inhibition by the product as it accumulates in the retentate.

Therefore an additional single reaction was performed at the same conditions of the R-NF cycles, but with an initial addition of 2 mmol of product (1,2-hexanediol), an intermediate value between the one expected at the beginning of the first R-NF cycle (zero) and the one measured in the retentate of the 6<sup>th</sup> R-NF cycle (4.19 mmol). A  $Y_{\text{react}}$  of 55.8% (column iv b of Table 6) was obtained for this single reaction, showing a significant decrease in the reaction performance, therefore product inhibition was indeed confirmed. In this context, the  $Y_{\text{process}}$  and the amount of the 1,2-hexanediol in the permeate and feed solutions for the first filtrations were recalculated on the basis of a constant  $Y_{\text{react}}$  of 55.8% and the obtained values are illustrated in Figure 5 B.

Product accumulation and consequent inhibition definitely seem to contribute to decreases in diol production over R-NF cycle, as illustrated by the sudden drop in  $Y_{\text{process}}$  from the first to the second R-NF cycle. However, the decrease in diol production may also result from losses of catalytic activity due to either physical losses of catalyst or catalyst deactivation, which may justify further decreases in  $Y_{\text{process}}$  such as the one observed in the sixth cycle.

Therefore, the first identified limitation of this system is the relatively high product rejection (51.9%), which for the AD reaction leads to product inhibition and, consequently, a decrease of the catalytic activity and yields.

### Evaluation of Catalyst Losses and Product Contamination

The osmium content in post-reaction solution fed to the nanofiltration, and the obtained retentate and permeate streams were analyzed by inductively coupled plasma spectroscopy (ICP). An average osmium concentration of  $(4.9 \pm 0.4)$  ppm was measured in the permeate, which is 94% lower than the initial osmium concentration (84 ppm). Therefore the larger osmium fraction is retained by the membrane, ensuring that the following downstream purification steps are less demanding. With a membrane rejection for sodium cholate of 99.5%, virtually all of the surfactant was retained by the membrane and the permeate stream is an aqueous solution enriched in product, contaminated by a smaller amount of osmium. Contrary to the conventional medium for AD reactions, the proposed system does not employ organic solvents, thus further improvements for osmium removal became simplified. For example, it may be easier to apply adsorption techniques for removal of the osmium traces from the permeate solution; and the selection and tailoring of nanofiltration membranes for the separation of product from osmium species is not restricted by membrane material swelling due to processed organic solvents.

The osmium fraction in each permeate<sup>[33]</sup> was determined at 2.9% of the initial osmium fed to the first cycle. These values are indicative of permeate stream contamination and are comparable with the ones reported in other studies for alternative recycling techniques.<sup>[12b,d]</sup> Leaching of osmium into the permeate solution has two implications: product contamination (as discussed above) and losses of catalytic activity. Over the six R-NF cycles carried out in this study, 17.3% (3.9  $\mu\text{mol}$ ) of the total osmium fed in the 1<sup>st</sup> cycle (22.3  $\mu\text{mol}$ ) left the system through the six permeate streams; this value represents a decrease of the S/Os molar ratio from 109  $\text{mol}\cdot\text{mol}^{-1}$  in the 1<sup>st</sup> cycle to 132  $\text{mol}\cdot\text{mol}^{-1}$  in the 6<sup>th</sup> cycle, which can explain the decrease in  $Y_{\text{process}}$  observed.

These two drawbacks result from the second identified limitation of this system, which is the membrane rejection for osmium: an average rejection of  $(87.7 \pm 2.7)\%$  was estimated on the basis of dissolved osmium in the feed and permeate solutions.

A value of about 9  $\mu\text{mol}$  of osmium was measured to be dissolved in the last feed solution; this value is 40% of the 22.3  $\mu\text{mol}$  of osmium initially added in the first cycle, significantly superior to the 3.9  $\mu\text{mol}$  of osmium that left the system through the six permeate solutions, and therefore indicates the existence of other sources for osmium losses not accounted by analysis of the liquid solutions, such as segregation and/or adsorption in the experimental apparatus/membrane surface.

### Improvement of the Overall Turn-Over Number (TON) and Catalyst Recycling

In spite of the two limitations identified and the existence of product inhibition, the diol in the 6<sup>th</sup> retentate solution was measured at a value of 4.19 mmol which, added with the diol measured in the six permeates, represents a total diol production over the six cycles of 8.71 mmol. This value corresponds to an overall a cumulative TON<sup>[28]</sup> of 391  $\text{mol}\cdot\text{mol}^{-1}$  and an overall reaction yield of 71%; this value lies between the  $Y_{\text{react}}$  values of 88% and 52% obtained for single reactions with and without initial addition of product, respectively. Considering only the product isolated in the permeate, the TON obtained over the six R-NF cycles was 203  $\text{mol}\cdot\text{mol}^{-1}$ , which is about the double of the one found for a single reaction without product inhibition (101  $\text{mol}\cdot\text{mol}^{-1}$ ).

An additional single experiment was carried out at a 10-mL scale and at a substrate concentration six times higher than the one employed in the R-NF cycles, but maintaining the catalytic system concentrations (Table 6, column iv-c). These experimental conditions can be translated as an increase in S/Os ratio of about 6 times. A  $Y_{\text{react}}$  of 79%, lower than the refer-

ence single reaction ( $Y_{\text{react}}=88\%$ ), was obtained. However, since less catalyst was used, the TON increased dramatically to a value 5.4 times higher than the reference single reaction (Table 6, column iv-a and c). This result would avoid the need of using nanofiltration to recycle the catalyst, since that higher amount of diol could be obtained in a single reaction using the same amount of substrate and catalytic system. However, in the analysis of these data it is critical to notice two aspects: 1) The first is that TON is a parameter that does not capture the enantiomeric purity of the product. In this single reaction experiment, with a 6 times higher load of substrate, part of the enantiomeric reaction selectivity was lost, as illustrated by a drop of the *ee* from 79% to 67%, when comparing with reactions performed under the same conditions (Table 6, column iv-a and iv-c, respectively); such a negative impact was not observed when the catalyst was recycled through the R-NF cycles methodology (Table 6, column ii, iii and iv-a). 2) A second aspect that requires some attention is the experimental concentrations employed in these experiments. The experiments at a 50-mL scale were diluted in both substrate and catalytic system, about 7 times when compared with the 1.5-mL scale. This dilution was done only due to research resources rationing; actually, for industrial application of the R-NF methodology, where maximization of the product obtained for each operation is crucial, higher loads of substrate concentrations are desirable in order to yield also a higher amount of product.

Therefore, the R-NF methodology can provide for an effective recycling of catalyst, improving TON and, more importantly, maintaining high enantiomeric purity. The first identified limitation of the R-NF cycle methodology can be overcome by optimization of the nanofiltration stage towards higher product elution into the permeate, and thus minimization of inhibition. However, for this specific system, with the existing gap between the rejections for product (51.9%) and for osmium catalyst (87.7%), higher elution of solution would promote not only higher recoveries of the product, but also undesirable elution of the osmium into the permeate. The proximity between product and catalyst rejections is surprising when taken into account that the Desal DK membrane has a MWCO of  $250 \text{ g}\cdot\text{mol}^{-1}$  and the two solute molecular weights are rather different (the MW of the possible osmium-chiral ligand complex is around  $1750 \text{ g}\cdot\text{mol}^{-1}$  and the MW of 1,2-hexanediol is only  $118 \text{ g}\cdot\text{mol}^{-1}$ ). Therefore, this result suggests that a significant part of the osmium is free in solution [e.g.,  $\text{K}_2\text{OsO}_2(\text{OH})_4$ ,  $\text{MW} = 368 \text{ g}\cdot\text{mol}^{-1}$ ], making easy its permeation throughout the membrane, leading to the observed osmium catalyst rejection. Enlargement of the osmium salt and its charge can be explored to enhance its membrane rejection.

## Conclusions

This study presents for the first time the use of water/surfactant as a medium for AD of olefins. The use of water as the unique solvent offers an alternative greener medium for this reaction previously optimized by Sharpless in *tert*-butanol/water (50/50 v/v %). Several cationic and anionic surfactants were tested to assist AD reaction of a range of olefins. Yields and enantioselectivities obtained through this methodology were higher than or comparable with the ones obtained in conventional media (*tert*-butanol/water). Additionally, when using the new proposed medium with NMO as co-oxidant, slow addition of olefin into the reaction medium is no longer required to obtain high *ees*. Nanofiltration was presented as a useful technique to isolate the product from the toxic osmium catalyst, allowing us to re-use the catalytic system (osmium and chiral ligand) and surfactant over successive reaction cycles, enhancing the TONs. An inhibition by the product of this reaction was identified and therefore it is crucial to remove the product between successive reactions. Therefore, continuous elution of product can be advantageous for this system.

Using successive reaction-nanofiltration cycles, 94% of osmium was retained in the system and the respective contamination in the product stream was reduced to 5 ppm. A relatively low osmium rejection, high product rejection and product inhibition were observed. In spite of such limitations, catalyst retention was enough to improve significantly the reaction TONs. To overcome the limitations posed by the high product rejections we first need to increase osmium rejections. Such an objective can be achieved either by stabilization of osmium in a larger molecule, either by optimizing the reaction conditions that promote binding between osmium and ligand, using osmium species of higher molecular weight (such as e.g., diimidoosmium species<sup>[34]</sup>) or by seeking membranes in which the rejection is not only based on size exclusion, but also on electrostatic interactions with the membrane surface. This last strategy would allow the permeation of the neutral diol, but will reject the osmium salt. Once high catalyst and low product rejections are achieved, the proposed R-NF methodology can be applied continuously.

## Experimental Section

### Reaction-Nanofiltration Cycles Process

R-NF cycles were carried out as schematically illustrated in Figure 2. For the first reaction, we dissolved the osmium salt  $\text{K}_2\text{OsO}_2(\text{OH})_4$  (8.2 mg, 0.022 mmol; 0.43 mM), chiral ligand [(DHQD)<sub>2</sub>PHAL, 75.1 mg, 0.096 mmol], and surfactant

[sodium cholate, 32.5 mg, 0.075 mmol, 1.5 mM] in 52 mL of water. The resulting catalytic solution was vigorously mixed.

The nanofiltration MetCell<sup>[31]</sup> was filled with 200 mL of distilled water, from which 150 mL were pushed through the membrane to obtain a stable water flux. A 10 bar pressure was applied using N<sub>2</sub> gas. The cell was emptied and 50 mL of the previously prepared catalytic solution were transferred into the nanofiltration cell. Co-oxidant (NMO 0.51 g, 3.75 mmol) was added and dissolved into this solution. Reaction was initiated by adding 1-hexene (0.3 mL, 2.42 mmol, 48.4 mM) without slow addition. A magnetic stirrer was used to continuously stirrer the solution over 40 h at room temperature.

A surfactant concentration of 1.5 mM, an L/Os molar ratio of 4.3 and S/Os molar ratio of 109 were employed in this first reaction. Assuming complete membrane rejection of surfactant, ligand and osmium, these parameters would be maintained over successive reaction cycles. Every reaction took place in 50 mL solution with a substrate initial concentration of 48.4 and an NMO/S molar ratio of 1.5.

After each 40 h reaction, 10 bar of pressure using N<sub>2</sub> were applied to the 50 mL of feed post-reaction solution. The nanofiltration was stopped by depressurizing the cell, when 25 mL of permeate solution were obtained. This permeate solution was analyzed for quantification of 1,2-hexanediol and osmium. The 25 mL of retentate were topped up with other 25 mL of distilled water, making up to 50 mL volume for the next reaction. Again, fresh co-oxidant (NMO 0.51 g, 3.75 mmol) was added and dissolved and the following reaction was initiated by adding 1-hexene (0.3 mL, 2.42 mmol, 48.4 mM) without slow addition. A magnetic stirrer was used to continuously stirrer the solution over 40 h at room temperature. A 0.5 mL aliquot each of retentate and feed solution were used for quantification of osmium. The retentate of the 6<sup>th</sup> nanofiltration was also used for 1,2-hexanediol analysis.

## Acknowledgements

This work was supported by REQUIMTE and Fundação para a Ciência e Tecnologia, (POCI 2010) and FEDER (POCI/QUI/60175/2004), SFR/BPD/19369/2004 and SFR/BPD/24969/2005).

## References

- [1] a) C. Bolm, J. P. Hildebrand, K. Muniz, in: *Catalytic Asymmetric Synthesis*, 2<sup>nd</sup> edn., (Ed.: I. Ojima), VCH, Weinheim, **2000**, p 399; b) R. A. Johnson, K. B. Sharpless, in: *Catalytic Asymmetric Synthesis*, 2nd edn., (Ed.: I. Ojima), VCH, Weinheim, **2000**, p 357.
- [2] a) C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483; b) A. B. Zaitsev, H. Adolffson, *Synthesis* **2006**, 1725; c) P. Wu, R. Hilgraf, W. Fokin, *Adv. Synth. Catal.* **2006**, *348*, 1079.
- [3] a) Z.-M. Wang, K. B. Sharpless, *J. Org. Chem.* **1994**, *59*, 8302; b) L. Ahrgren, L. Sutin, *Org. Process Res. Dev.* **1997**, *1*, 425; c) X. Lu, Z. Xu, G. Yang, *Org. Process Res. Dev.* **2000**, *4*, 575; d) S. Y. Jonsson, H. Adolffson, J. E. Bäckvall, *Chem. Eur. J.* **2003**, *9*, 2783; e) J. S. Prasad, T. Vu, M. J. Totleben, G. A. Crispino, D. J. Kaesur, S. Swaminathan, J. E. Thornton, A. Fritz, A. K. Singh, *Org. Process Res. Dev.* **2003**, *7*, 821; f) P. Dupau, R. Epple, A. A. Thomas, W. Fokin, K. B. Sharpless, *Adv. Synth. Catal.* **2002**, *344*, 421.
- [4] S. Kobayashi, M. Sugiura, *Adv. Synth. Catal.* **2006**, *348*, 1496–1504.
- [5] a) S. Kobayashi, M. Endo, S. Nagayama, *J. Am. Chem. Soc.* **1999**, *121*, 11229; b) S. Kobayashi, T. Ishida, R. Akiyama, *Org. Lett.* **2001**, *3*, 2649; c) T. Ishida, R. Akiyama, S. Kobayashi, *Adv. Synth. Catal.* **2003**, *345*, 576; d) S. V. Ley, C. Ramarao, A.-L. Lee, N. Østergaard, S. C. Smith, I. M. Shirley, *Org. Lett.* **2003**, *5*, 185.
- [6] a) B. M. Choudary, N. S. Chowdari, M. L. Kantam, K. V. Raghavan, *J. Am. Chem. Soc.* **2001**, *123*, 9220; b) B. M. Choudary, N. S. Chowdari, K. Jyothi, M. L. Bantam, *J. Am. Chem. Soc.* **2002**, *124*, 5341; c) B. M. Choudary, N. S. Chowdari, S. Madhi, M. L. Kantam, *J. Org. Chem.* **2003**, *68*, 1736; d) B. M. Choudary, K. Jyothi, S. Madhi, M. L. Kantam, *Adv. Synth. Catal.* **2003**, *345*, 1190.
- [7] A. Sevreus, D. E. De Vos, L. Fiermans, F. Verpoort, P. J. Grobet, P. A. Jacobs, *Angew. Chem. Int. Ed.* **2001**, *40*, 586.
- [8] a) S. Chandrasekhar, Ch. Narsihmulu, S. S. Sultana, N. R. Reddy, *Chem. Commun.* **2003**, 1716; b) J. W. Yang, H. Han, E. J. Roh, S. Lee, C. E. Song, *Org. Lett.* **2002**, *4*, 4685.
- [9] a) H. Li, Y.-Y. Luk, M. Mrksich, *Langmuir* **1999**, *15*, 4957; b) B. M. Choudary, K. Jyothi, M. Roy, M. L. Kantam, B. Sreedhar, *Adv. Synth. Catal.* **2004**, *346*, 1471.
- [10] E. K. Kwueon, D. S. Choi, H. Y. Choi, Y. J. Lee, C. H. Jo, S. H. Hwang, Y. S. Park, C. E. Song, *Bull. Korean Chem. Soc.* **2005**, *26*, 1839–1842.
- [11] a) G. Bolm, A. Gerlach, *Angew. Chem. Int. Ed.* **1997**, *36*, 741; b) P. H. Toy, K. D. Janda, *Acc. Chem. Res.* **2000**, *33*, 546; c) Y.-O. Kuang, S.-Y. Zhang, *Tetrahedron Lett.* **2001**, *42*, 5925; d) I. Motorina, C. M. Crudden, *Org. Lett.* **2001**, *3*, 2315; e) B. M. Choudary, N. S. Chowdari, K. Joyothi, M. L. Kantam, *Adv. Synth. Catal.* **2003**, *345*, 1190; f) A. Köckritz, M. Bartoszek, C. Döbler, M. Beller, W. Mägerlein, H.-C. Miltzer, *J. Mol. Cat. A* **2004**, *218*, 55.
- [12] a) Q. Yao, *Org. Lett.* **2002**, *4*, 2197; b) R. Yanada, Y. Takemoto, *Tetrahedron Lett.* **2002**, *43*, 6849; c) L. C. Branco, C. A. M. Afonso, *Chem. Commun.* **2002**, 3036; d) C. E. Song, D. Jung, E. J. Roh, S. Lee, D. Y. Chi, *Chem. Commun.* **2002**, 3038; e) L. C. Branco, C. A. M. Afonso, *J. Org. Chem.* **2004**, *69*, 4381; f) R. Jiang, Y. Kuang, X. Sun, S. Zhang, *Tetrahedron: Asymmetry* **2004**, *15*, 743.
- [13] a) L. C. Branco, A. Serbanovic, M. N. da Ponte, C. A. M. Afonso, *Chem. Commun.* **2005**, 107; b) L. C. Branco, A. Serbanovic, M. N. da Ponte, C. A. M. Afonso, *Patent Applications* PT 10293703 and PCT/PT2005/000007; c) A. Serbanovic, L. C. Branco, M. N. da Ponte, C. A. M. Afonso, *J. Organometallic Chemistry* **2005**, *690*, 3600.
- [14] A. Closson, M. Johansson, J.-E. Bäckvall, *Chem. Commun.* **2004**, 1494.



- [15] M. Johansson, A. A. Lindén, J.-E. Backvall, *J. Organometallic Chemistry* **2005**, *690*, 3600.
- [16] L. C. Branco, P. M. P. Gois, N. M. T. Lourenço, V. B. Kurteva, C. A. M. Afonso, *Chem. Commun.* **2006**, 2371.
- [17] F. C. Ferreira, L. C. Branco, K. K. Verma, J. G. Crespo, C. A. M. Afonso, *Tetrahedron: Asymmetry* **2007**, doi:10.1016/j.tetasy.2007.06.032.
- [18] a) C. J. Li, T. H. Chan, *Organic Reactions in Aqueous Media*, John Wiley & Sons, New York, **1997**; b) B. Cornils, W. A. Hermann, *Aqueous-Phase Organometallic Catalysis*, VCH-Wiley, Weinheim, **1998**; c) S. Kobayashi, in: *Organic Synthesis in Water*, (Ed.: P. A. Grieco), Blackie Academic & Professional, London, **1998**; d) C.-J. Li, L. Chen, *Chem. Soc. Rev.* **2006**, *35*, 68; e) C. Li, *Chem. Rev.* **2005**, *105*, 3095; f) U. M. Lindstrom, *Chem. Rev.* **2002**, *102*, 2751; g) A. Lubineau, J. Auge, Y. Queneau, *Synthesis* **1994**, 741; h) D. G. Blackmond, A. Armstrong, V. Coombe, A. Wells, *Angew. Chem. Int. Ed.* **2007**, *46*, 3798; i) U. M. Lindstrom (Ed.), *Organic Reactions in Water*, Blackwell Publishing, London, **2007**.
- [19] S. Tascioğlu *Tetrahedron* **1996**, *52*, 11113.
- [20] a) P. Eriksson, *Environ. Prog.* **1988**, *7*, 58; b) M. Schmidt, S. Mirza, R. Schubert, H. Röddicker, S. Kattaneck, J. Malisz, *Chemie Ingenieur Technik* **1999**, *71*, 199.
- [21] a) C. H. Linder, M. Nemas, M. Perry, R. Katrarro, US Patent 5,265,734, **1993**; b) L. S. White, I. Wang, Minhas, S. Bhupender, US Patent 5,264,166, **1993**; c) L. S. White, *J. Membrane Sci.* **2002**, *205*, 191; d) D. Bhanushali, D. Bhattacharyya, in: *Advanced Membrane Technology*, (Ed.: N. N. Li, E. Drioli, W. S. W. Ho), *Ann. NY Acad. Sci.* **2003**, 984, 159.
- [22] a) H. P. Dijkstra, G. P. M. van Klink, G. van Koten, *Acc. Chem. Res.* **2002**, *35*, 798; b) D. Nair, J. T. Scarpello, L. S. White, L. M. Freitas dos Santos, I. F. J. Vankelecom, A. G. Livingston, *Tetrahedron Lett.* **2001**, *42*, 8219–8222; c) K. De Smet, S. Aerts, E. Ceulemans, I. F. J. Vankelecom, *Chem. Commun.* **2001**, 597.
- [23] H. T. Wong, Y. H. See-Toh, F. C. Ferreira, R. Crook, A. G. Livingston, *Chem. Commun.* **2006**, 2063.
- [24] a) L. García-Río, P. Hervés, J. R. Leis, J. C. Mejuto, J. Perez-Juste, *J. Phy. Org. Chem.* **1998**, *11*, 584–588; b) H. Nakamura, A. Sano, K. Matsuura, *Anal. Sci.* **1998**, *14*, 379–382; c) value to be found at: <http://www.sigmaaldrich.com/catalog/search/ProductDetail/SIAL/C5070>.
- [25] Reaction yield ( $Y_{\text{react}}$ ):  

$$Y_{\text{react}} (\%) = \frac{\text{diol produced (mol)}}{\text{olefin/substrate added (mol)}} \times 100;$$
 reaction process ( $Y_{\text{process}}$ ):  

$$Y_{\text{process}} (\%) = \frac{\text{diol in permeate (mol)}}{\text{olefin/substrate added (mol)}} \times 100.$$
- [26] Specific yield: ( $Y_{\text{react}}$ ):  

$$\text{R-Yield} (\%) = \frac{\text{diol (mol)}}{\text{substrate added (mol)}} \times 100 = \frac{Y_{\text{react}} (\%)}{2} \left(1 + \frac{ee (\%)}{100}\right).$$
- [27] Values consistent with experimental log P reported in C. Hansch, A. Leo, D. Hoekman, *Exploring QSAR – Hydrophobic, Electronic, and Steric Constants*, American Chemical Society, Washington, DC, **1995**. Estimated by Interactive LogKow (KowWin) Demo, which can be found at: [http://www.syrres.com/esc/est\\_kowdemo.htm](http://www.syrres.com/esc/est_kowdemo.htm).
- [28] Turn-over number (TON):  

$$\text{TON}(i) = \frac{\sum_{j=1}^n \text{diol in permeate (j) (mol)}}{\text{Catalyst added in 1st cycle (Os mol)}}.$$
- [29] Molecular weight cut-off (MWCO) of a membrane is the molecular weight of the solute which 90% is rejected by the membrane.
- [30] Rejection (Rej):  $\text{Rej} (\%) = \left(1 - \frac{[\text{Solute}]_{\text{permeate}}}{[\text{Solute}]_{\text{feed}}}\right) \times 100;$  in this study, the solute is either osmium or diol.
- [31] A stainless steel MetCell with a membrane area of 0.0052 m<sup>2</sup> purchased from Membrane Extraction Technology, Ltd., UK, was used as nanofiltration equipment. Details on equipment to be found under <http://www.membrane-extraction-technology.com/MET-Cell.php>.
- [32] NMO/S, S/Os and L/Os were maintained at about 1.5, 187 and 2.0 mol·mol<sup>-1</sup>, respectively.
- [33] Osmium in permeate  

$$(\%) = \frac{\text{permeate (mL)} \times \text{osmium in permeate (nM)}}{\text{osmium added (μmol)}} \times 100.$$
- [34] T. J. Donohoe, R. M. Harris, S. Butterworth, J. N. Burrows, A. Cowley, J. S. Parker, *J. Org. Chem.* **2006**, *71*, 4481.