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Extending Ru-BINAP Catalyst Life and Separating Products from Catalyst Using Membrane Recycling

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Abstract:

Organic solvent nanofiltration (OSN) is a new membrane technology with many applications in pharmaceutical and fine chemicals development and manufacture, from laboratory through production scales. One application of particular industrial relevance is the ability to recover and recycle homogeneous catalysts, in particular asymmetric, organometallic, homogeneous transition metal catalysts. Industrial application of this group of catalysts is often limited due to the cost of applying these catalysts to single reactions and the subsequent product yield losses associated with removal of the catalyst from solution. OSN provides a technique that can maximise the value of the catalyst through catalyst recycle from one reaction batch to the next, whilst minimising the concentration of catalyst present in the reaction product. This contribution describes the development and demonstration of OSN catalyst recycle on an example catalytic system, the homogeneous, asymmetric hydrogenation of dimethyl itaconate (DMI) to dimethyl methylsuccinate (DMMS) with Ru-BINAP. The first step of the development process was to demonstrate that Ru-BINAP was sufficiently stable that the process concept, i.e., catalyst recycling, was feasible. A dilute solution (0.8 wt %) of DMI in methanol with a high catalyst loading (S/C = 500) was used, and 14 successive reactions were carried out with constant reaction rate and without yield or enantiomeric excess (ee) reduction. In industrial practice, the goal is always to operate a reaction at the highest, practical S/C ratio, and thus the next stage of development was to optimise the S/C ratio. The limiting, practical S/C ratio was found to be 7000. The process was then run with the optimised dilute reaction system, which allowed 10 reaction cycles to be carried out with only 20% addition of the initial (reaction 1) mass of catalyst to reactions 2−10 to maintain reaction rate, conversion, and ee. This leads to a 5 times increase in the overall S/C ratio. In addition, this optimisation reduced the amount of metal present in the product solution from 130 μg Ru per gram of product to <6 μg Ru per gram of product. The process was then scaled up to an industrially relevant substrate concentration (20 wt % DMI in methanol), and it was found that both the reaction (in terms of reaction rate, conversion, and yield) and the ability to recycle the catalyst were unaffected by the scale-up in concentration.

1. Introduction

Many homogeneous organic syntheses are catalysed by transition metals complexed with organic ligands.[1−4] Many transition metal catalysts (TMCs) are expensive, and the organic ligands can be difficult to synthesise, which may lead to the ligands being more valuable than the metal, especially if they are chirally directing.[5] A major drawback of using TMCs is that they must be separated from the product at the end of the reaction. Generally, a pure (metal-free) product is only obtained with energy intensive and/or waste-generating downstream processing that destroys the catalyst and reduces the final product yield.[6,7] Even after this extensive, destructive postreaction processing[8−10] only a fraction of the metal value can typically be recovered by returning separation residues to the catalyst suppliers, while the ligands are irreversibly lost. A nondestructive separation method to recover the catalyst in an active form could remove these disadvantages of using TMCs by providing a product stream with reduced metal content and allowing the catalyst value to be maximised through its reuse. Such technology would be particularly useful in regulated industries where metal content in products is tightly controlled. For example, in pharmaceutical products the daily dosage of transition metals must be minimised to prevent any unwanted

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side effects. In particular, the platinoid group metals (Pt, Pd, Ru, Rh, etc.) have particularly low concentration specifications, 10 μg or less of metal per g product, due to their toxicity.[11] Organic solvent nanofiltration (OSN) is a membrane technology that can be used to achieve this process concept.

OSN is a membrane technology capable of retaining large homogeneous TMCs, usually $MW_{TMC} > 500$ Da, from postreaction organic solvent mixtures,[12] while allowing smaller product molecules to permeate through the membrane. As many TMCs are significantly larger than the reactants they act on and the product molecules they generate, it is possible to use OSN to retain the catalyst molecule, whilst allowing the product and unused reactants to permeate through the membranes.

Several authors have studied the use of homogeneous TMC recovery and recycle using membrane-coupled catalytic systems, with the first reported study by Gosser et al.[13] published in 1977. A summary of the subsequent application of this technique is provided in Vankelecom et al.[14] and Vandezande et al.[15] These studies have typically been carried out at dilute, "non-industrial" substrate loadings, with the aim of understanding the maximum turnover number (TON) for a particular catalytic system. A different perspective on the technology is provided by Nair et al.,[16] who have investigated the final product purity attainable using OSN recycle technology for a Heck coupling reaction. In many industrial applications, achieving a sufficient purity (i.e., low metal level in the product) is at least as important as the ability to recover and reuse the catalyst.

To date, catalyst recycle using OSN membranes has only been reported in the literature with systems using dilute substrate concentrations (typically <1 wt %) and the influence of higher, more industrially relevant substrate concentrations (>5 wt %) on this process has not been investigated, and it remains unclear whether scale-up of OSN processes by increasing substrate concentration affects process performance.

In this report we demonstrate the increase in catalytic productivity possible through TMC recycle in a batch-operated OSN cell, allowing the TMC to be reused for multiple consecutive reactions. The enantioselective hydrogenation of dimethyl itaconate (DMI) to dimethyl methylsuccinate (DMMS), catalysed by Ru-BINAP, was selected as the model reaction. The reaction scheme and TMC are shown in Figure 1. Excellent performance in asymmetric hydrogenation reactions has been observed using Ru-BINAP,[17,18] and it is known to catalyse industrially important reactions;[19,2,3,20] thus, we chose to use it for this study. The usefulness of the OSN technology for TMC recycle and obtaining a high purity product will be examined at high and low TMC loadings at 0.8 wt % DMI concentrations. The process will then be scaled up with a low TMC loading to 20 wt % DMI, to demonstrate that the process can be a useful tool at industrially relevant substrate loadings.

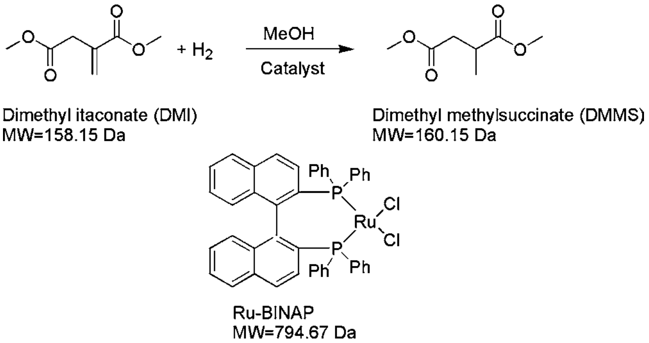

Figure 1. **DMI hydrogenation catalysed by Ru-BINAP.**

2. Experimental Section

2.1. Chemicals. Methanol (99+ %), dimethyl itaconate (97%) and dimethyl methylsuccinate (98%) were all obtained from Aldrich Chemical Co. (Poole, Dorset, U.K.). (*R*,*R*)-Ru-BINAP was obtained from Strem Chemicals (Kehl, Germany). All preparations were carried out using standard Schlenk techniques in a dry nitrogen atmosphere. The solvent was dried by standard methods prior to use, to exclude moisture. All other starting materials were used as supplied.

2.2. Analytical Techniques. Concentrations of dimethyl itaconate (DMI) and dimethyl methylsuccinate (DMMS) were determined using a Shimadzu GC-14A gas chromatograph with a flame ionisation detector (FID) equipped with a BP1 capillary column (length 25 m, 0.32 mm i.d.) (SGE, Australia). The oven temperature was held at 50 °C for 2.5 min and then increased to 300 °C at a rate of 25 °C min^{-1}. The coefficient of variation of the assay was 1.2% for DMI concentration fixed at 0.8 wt %. A 0.1 mL amount of organic sample was evaporated and then dissolved in 10 mL of a 10 wt % aqueous nitric acid solution for ICP spectroscopy. Concentrations of Ru and P were measured with a Jobin Yvon Ultima spectrometer. Coefficients of variation for Ru and P, measured at initial experimental concentrations, were 0.69% and 0.61% respectively. Enantiomeric excess was measured using a Unicam Crystal 200 HPLC system. The column used was a CHIRALCEL OD-H, 250 mm long and 4.6 mm diameter, containing 5 μm packing. The mobile phase, 9:1 hexane: IPA, was pumped through the column at a flow rate of 500 $\mu\text{L min}^{-1}$, and a diode array detector at a fixed wavelength of 200 nm was used to detect the elluents. The major product from the reaction is the *S* enantiomer, and the ee of the *S* enantiomer is calculated as $([S] - [R])/([S] + [R])$.

2.3. OSN Membrane and Filtration/Reaction Cells. Samples of Davison Membranes STARMEM 122 (STARMEM is a trademark of W.R. Grace), an integrally skinned, asym-

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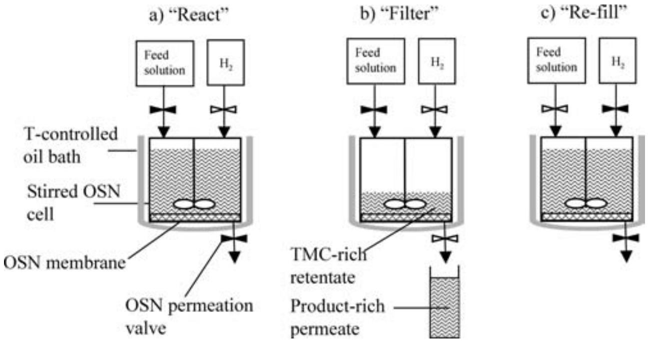

Figure 2. **TMC recycle sequence "React"−"Filter"−"Re-fill" using OSN (shaded valves are closed).**

metric OSN membrane with a polyimide active surface, were provided by Membrane Extraction Technology Ltd. (London, U.K.). STARMEM 122 has a nominal molecular weight cutoff (MWCO) of 220 Da (manufacturer values, using toluene as a solvent and based on 90% rejection of *n*-alkanes). Prior to use, each new membrane disk was conditioned (prepared for use) by permeating pure methanol under 30 bar pressure until a constant flux was obtained. This was to ensure complete removal of the preserving agent (lube oil) and minimise the influence of flux decline, due to irreversible membrane compaction, on the results.[21]

Reaction and filtration of the dilute (0.8 wt %) DMI systems were performed in a Sepa ST cell (GE Osmonics, Minnetonka, MN, U.S.A.) set up in an oil bath controlled to within 0.1 °C of the required reaction temperature. The stainless steel OSN cell was mixed at 900 rpm with a PTFE stirrer bar. Membrane disks of 49 mm diameter were mounted in the pressure cell using a FEP-coated ring-seal. The cell was connected to a hydrogen cylinder (to provide a necessary reaction substrate and the pressure for nanofiltration) and filled with a degassed feed solution. The available membrane area for filtration, A_m, was 1.69×10^{-3} m^2.

Reaction and filtration for the concentrated (20 wt %) DMI system was performed in a METcell (Membrane Extraction Technology Ltd., London, U.K., www.membrane-extraction-technology.com). The temperature was controlled by switching the hot plate section of a magnetic stirrer/hot plate on and off, based on readings from a thermocouple inserted into the reaction mixture. The temperature was controlled to within 0.1 °C of the required reaction temperature. The METcell was mixed at 450 rpm with a dedicated PTFE stirrer disk using a magnetic stirrer. Membrane disks of 90 mm diameter were mounted in the pressure cell using a FEP-coated ring-seal. The cell was connected to a hydrogen cylinder (to provide a necessary reaction substrate and the pressure for nanofiltration) and filled with a degassed feed solution. The available membrane area for filtration, A_m, was 5.1×10^{-3} m^2.

2.4. TMC Recycle Procedure. The TMC recycle scheme is shown in Figure 2 and can be considered as three stages per cycle: react, filter, and refill. First, the reaction feed solution was placed into the cell (containing a conditioned membrane disk) under inert conditions. The reaction solution was then allowed to reach the reaction temperature, and the hydrogen valve was opened to pressurise the cell to 10 bar and initiate the reaction (as shown in Figure 2a). Regular sampling was carried out until a 95−100% conversion of DMI had been obtained. The pressure was then increased to 30 bar, and the OSN permeation valve was opened (as shown in Figure 2b) to allow the solvent and DMMS to permeate across the membrane under the applied pressure into a collection receptacle. Once 40 mL (80% of the reaction volume) had permeated, the cell was depressurised. The time, *t*, to collect the permeate volume, V_p, was recorded, and the permeate was sampled for analysis.

A fresh 40 mL feed solution was prepared under inert conditions and fed to the OSN reactor to replenish the consumed substrate and restore the original 50 mL reaction volume (Figure 2c), again under inert conditions. The cell was then closed and allowed to reach reaction temperature, and the hydrogen valve was opened to reinitiate the reaction. This TMC recycle procedure was repeated multiple times. A single membrane disk was used in each recycle system, since the feed solution or retentate would always be in contact with the membrane until the end of a sequence, thus preventing damage to the membrane through drying out.

2.5. Detailed Reaction Compositions. Five different reaction solutions were used during this development work. The initial and fresh feeds for Systems 1−5, with substrate/catalyst (S/C) ratios, are given below. In all cases, reactions were conducted at 30 °C. In System 2, 80% of the postreaction volume was not filtered but poured away and instead diluted with the fresh feed. In all other systems the TMC was recycled by the procedure outlined in section 2.4.

Reaction System 1 (initial S/C = 500): Initial Feed = 0.337 g (2.13 mmol) DMI, 0.0034 g (0.00427 mmol) Ru-BINAP, 50 mL MeOH; Fresh Feed = 0.337 g (2.13 mmol) DMI, 40 mL MeOH. TMC recycled by OSN.

Reaction System 2 (initial S/C = 500): Initial Feed = 0.337 g (2.13 mmol) DMI, 0.0034 g (0.00427 mmol) Ru-BINAP, 50 mL MeOH; Fresh Feed = 0.337 g (2.13 mmol) DMI, 40 mL MeOH. TMC not recycled by OSN.

Reaction System 3 (initial S/C = 7000): Initial Feed = 0.337 g (2.13 mmol) DMI, 0.00024 g (0.00031 mmol) Ru-BINAP, 50 mL MeOH; Fresh Feed = 0.337 g (2.13 mmol) DMI, 40 mL MeOH. TMC recycled by OSN.

Reaction System 4 (initial S/C = 7000): 0.337 g (2.13 mmol) DMI, 0.00024 g (0.00031 mmol) Ru-BINAP, 50 mL MeOH; Fresh Feed = 0.337 g (2.13 mmol) DMI, 0.000048 g (0.000061 mmol) Ru-BINAP, 40 mL MeOH. TMC recycled by OSN.

Reaction System 5 (initial S/C = 4000): 16 g (94.9 mmol) DMI, 0.02 g (0.0252 mmol) Ru-BINAP, 64 g MeOH; Fresh Feed = 16 g (94.9 mmol) DMI, 0.006 g (0.0076 mmol) Ru-BINAP, 64 g MeOH. TMC recycled by OSN.

2.6. Experimental Calculations. For each reaction−separation cycle, all calculations were based on volume permeated, V_p, permeation time, *t*, and measurement of Ru, P, and DMMS concentrations in each permeate and in the final retentate.

Reaction performance was assessed in terms of turnover number (TON). TON, a measure of catalyst efficiency, was calculated as:

$$\mathrm{TON} = \left(\frac{\text{total moles DMI converted over all cycles}}{\text{total moles Ru fed over all cycles}}\right) \tag{1}$$

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The membrane performance was assessed in terms of solute rejection (eq 2) and solvent flux (eq 3). The rejection of species i, rej$_i$, for a given membrane is a measure of its separation performance and is defined by:

$$\mathrm{rej}_i = \left(1 - \frac{C_{\mathrm{p}i}}{C_{\mathrm{r}i}}\right) \times 100\% \tag{2}$$

where C_{pi} and C_{ri} are the concentration of solute i in the permeate and retentate respectively, as measured at the end of a batch filtration. A rejection of 100% corresponds to perfect retention of the species and 0% to no separation.

The flux, J (measured in L m^{-2} h^{-1}), was calculated using:

$$J = \left(\frac{V_{\mathrm{p}}}{A_{\mathrm{m}}t}\right) \tag{3}$$

where A_{m} is the area of the membrane disk used in the filtration (V_{p} and t are defined above). The flux is the volume of solution permeated per unit membrane area per unit time at a given transmembrane pressure.

The mass balance error (ΔMB) was calculated for Ru, P, and DMMS at the end of a sequence of reactions and separations using the following equation:

$$\Delta\mathrm{MB} = \left(\frac{X^i_{\mathrm{in}} + X^i_{\mathrm{gen}} - X^i_{\mathrm{perm}} - X^i_{\mathrm{ret}}}{X^i_{\mathrm{in}} + X^i_{\mathrm{gen}}}\right) \times 100\% \tag{4}$$

where X^i_{in}, X^i_{gen}, X^i_{perm}, and X^i_{ret} are the total moles of species i respectively input, generated, permeated, and retained during the course of the reactions. Clearly, $X^{\mathrm{DMMS}}_{\mathrm{in}} = 0$, and only $X^{\mathrm{DMMS}}_{\mathrm{gen}} \neq 0$. ΔMB was within ±7% for all species in every system.

3. Results and Discussion

3.1. Proof of Concept (Reaction System 1). The first aim of this work was to demonstrate that the TMC catalyst recycle concept was feasible when using Ru-BINAP. This initial work was carried out with Reaction System 1.

Fourteen consecutive reaction−separation cycles were attempted, with each reaction taking approximately 2.5 h to reach complete conversion of DMI to DMMS. The conversion profiles over time for the first and fourteenth reactions demonstrated that no reaction rate decline was occurring during this sequence (Figure 3), and a cumulative TON of 6950 was reached. Calculations of DMMS rejection for System 1 showed that it increased from 49% for the first filtration to 70% after five filtrations, and ultimately reached 73% for the last eight filtrations. This is most likely caused by irreversible compaction of the membrane during the first six filtration cycles. After these six filtrations, the compaction is complete, and no further change in DMMS rejection is observed. At steady state, with a DMMS rejection of 73%, it is expected that almost two reaction equivalents of DMMS will be held up in the reactor at steady state, while only one reaction equivalent is permeated. After the ninth reaction in the sequence, it was noted that the postreaction concentration of DMMS became constant at a value of 1.9 equiv of DMMS, as expected. During the filtrations, the permeate flux averaged 35.9 L m^{-2} h^{-1}.

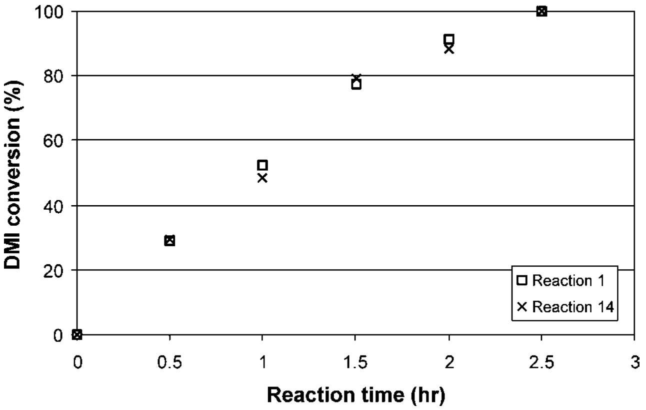

Figure 3. **DMI conversion in Reaction System 1 for the 1st and 14th reactions.**

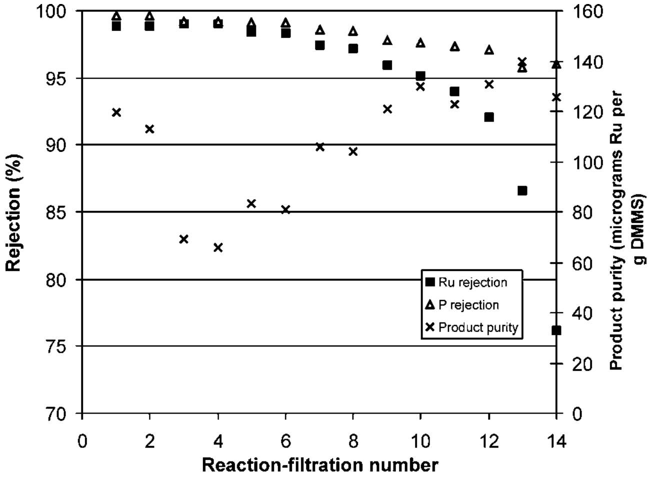

Figure 4. **Rejection of TMC species and product purity in Reaction System 1.**

As it is not possible to measure directly the concentration of intact, active Ru-BINAP, the concentrations of Ru and P are measured as indicators of the catalyst-related species present in a particular solution. It should be noted that this technique does not distinguish between active catalyst, deactivated catalyst, and catalyst degradation products. Figure 4 shows Ru and P rejection and product purity (defined as mass of Ru per unit mass of product) after each filtration in Reaction System 1. Ru rejection decreased from 98.8 to 76.8% during the sequence of filtrations, while P rejection decreased from 99.6 to 96.0%. It is thought that under the reaction conditions the TMC fragments into separate metal and ligand species, with the resulting metal species more easily able to permeate the membrane than the ligand-related species. As P, rather than the whole ligand group, was detected using ICP, it was not possible to determine whether the BINAP ligand had degraded or was still intact. It is expected that if the catalyst remains intact, then the molar ratio of P and Ru in the permeate should be the same as the fresh feed of Ru-BINAP (i.e., Ru:P = 1:2). From the change in Ru and P permeate concentrations over time (Figure 5), it was evident that they were not permeating in the ratio expected for intact Ru-BINAP and in fact the final permeate Ru:P ratio at 1:1.3 was significantly less than the expected 1:2. This was confirmed through both the mass balances and the measured Ru:P ratio of 1:8.1 in the retentate, which should also be 1:2 if the Ru-BINAP was permeating intact. To test if any of the Ru species

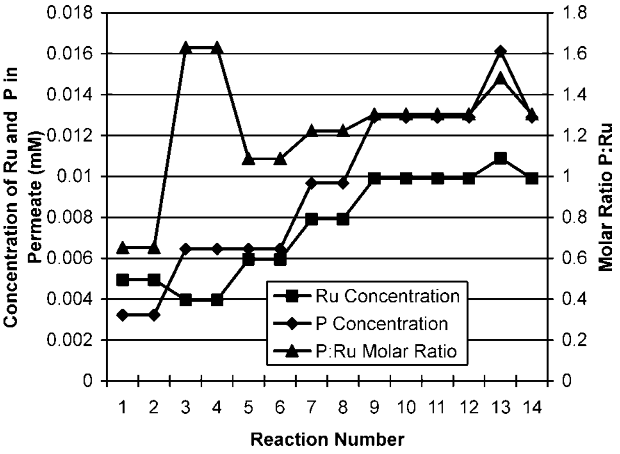

Figure 5. **Permeate concentrations of TMC species in Reaction System 1.**

in the permeate was intact catalyst or demonstrated any catalytic activity, fresh DMI/methanol solution was added back to samples of the permeate, hydrogen pressure applied, and the conversion monitored. No conversion was obtained, which suggests that the permeated TMC species was no longer catalytically active.

Metal contamination of the product (product purity) only reaches steady state when both DMMS and the metal permeate are at their respective steady state values. Since metal permeation rates were increasing over time and DMMS concentration increased over the first nine reactions, a steady state value was not reached. Product purity for the first two reactions was close to 120 μg Ru per g DMMS, which improved to 65 μg Ru per g DMMS (due to increasing DMMS permeation) and then worsened to 120−140 μg Ru per g DMMS as Ru permeation across the membrane increased. It should be noted that, without filtration, 1309 μg Ru per g DMMS would be expected in the postreaction mixture, showing that even with this nonoptimised reaction/filtration system there is significant benefit in product purity using OSN.

By the final reaction, the working S/C ratio had increased from an initial value of 500 to 5000, due to TMC losses. This increase in S/C ratio was not observed to be reaction rate limiting.

3.2. Optimisation of S/C Ratio (Reaction System 2). Having demonstrated the proof of concept for the process, the next stage of work was to optimise the S/C ratio. Reaction System 2 was used to investigate the effect of S/C ratio on conversion. The work carried out for this optimisation was very similar to the proof-of-concept work, except that rather than filtering the postreaction mixture, 80% of postreaction liquid was simply poured out of the filtration cell rather than carrying out a filtration. That is, every reaction contained only 20% of the catalyst present in the previous one, with the exception of the initial reaction. The results of this experiment are shown in Figure 6.

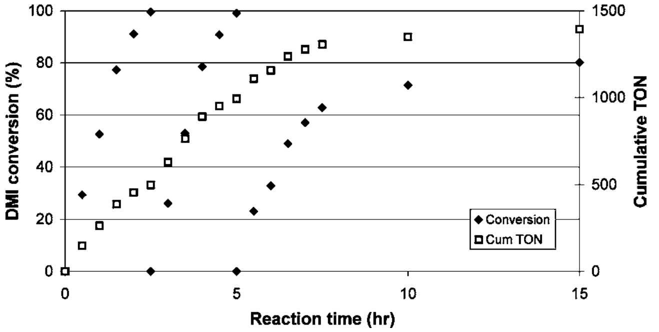

Figure 6. **DMI conversion and cumulative TON for Reaction System 2.**

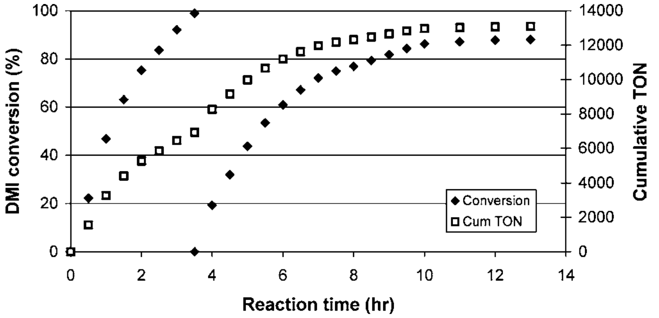

Figure 7. **DMI conversion and cumulative TON for Reaction System 3.**

The initial reaction, with an S/C ratio of 500, reached complete conversion of DMI after 2.5 h (as expected from the proof-of-concept results). The second reaction, with an S/C ratio of 2500 also took only 2.5 h to reach completion. This was expected, since the proof-of-concept work demonstrated that an S/C ratio of 5000 was not rate limiting. However, the third reaction, with an S/C ratio of 12,500 started to slow down significantly and achieved only 80% conversion in 10 h. At an S/C ratio between 5000 and 12,500, the reaction appeared to become controlled by the limiting catalyst concentration. A cumulative TON (based on the original TMC loading and the total DMMS produced in the 3 reactions) of 1400 was achieved in a total of 15 h. The product purity in the produced DMMS streams from reactions 1, 2, and 3 by calculation would be 1,309, 262, and 65 μg Ru per g DMMS, respectively. The product purity was improving due to dilution as TMC was lost from the system in each unfiltered permeate volume.

This data demonstrated that membrane recycle of the TMC was important to achieve more than a single repeated reaction. It also suggested that the reaction could be achieved without reaction rate decline at an S/C ratio between 5000 and 12,500.

3.3. Verification of S/C = 7000 as Limiting Catalyst Concentration (Reaction System 3). An S/C ratio of 7000 was chosen because it not only fulfilled the requirement of being close to the rate-limiting S/C ratio, but it also represented a system that could match the cumulative TON of the initial S/C = 500 catalyst recycle system with a single reaction (instead of 14 reactions). The results of testing this S/C ratio are shown in Figure 7. The initial reaction took 3.5 h (an hour longer than with the S/C = 500 system) to reach 100% conversion, indicating that the catalyst loading was indeed rate limiting. The second reaction reached 88% conversion in just under 10 h, giving a cumulative TON of 13,100 in just under 14 h. The significant reaction rate decline during the second reaction suggested that TMC losses during filtration and/or catalyst deactivation were sufficient to increase the working S/C ratio above the reaction rate-limiting value.

Rejection of Ru was 98.4% for the filtration between the initial and second reactions, which gave a product purity of

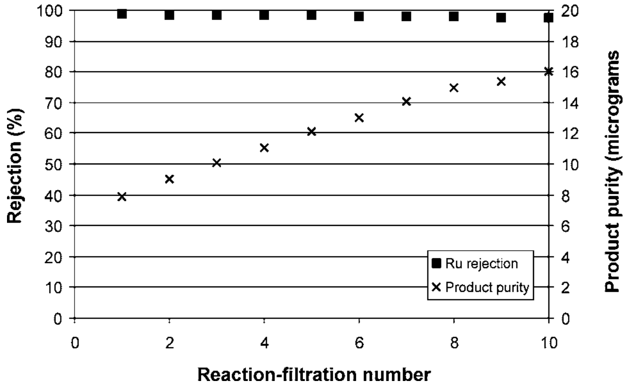

Figure 8. **Ru rejection and product purity for Reaction System 4.**

7.1 μg Ru per g DMMS in the filtered product solution. In comparison, without filtering the product solution and assuming 100% conversion, a product purity of only 89.1 μg Ru per g DMMS would have been obtained. Certainly for pharmaceutical applications, this Ru concentration from the unfiltered solution would be regarded as too high, and further workup would be required, whereas the product from the filtered solution would not require additional workup.

3.4. Application of Optimised S/C Ratio in OSN Catalyst Recycle Process (Reaction System 4). The rapid reaction rate decline observed during the second reaction of the S/C = 7000 verification test is avoidable only by maintaining the TMC loading above the reaction rate-limiting concentration. This can be achieved by adding a fraction of the initial catalyst mass to the system with each successive batch of fresh reactant solution. In this way, the TMC loading per batch can be kept at a relatively low level, such that the membrane can still provide low metal concentration in the product, whilst preventing reaction rate decline and reaction stalling observed in cases where the S/C ratio becomes rate limiting.

In approaching the problem of what fraction of the TMC added to the initial reaction batch should be added to each subsequent recycle batch, it seemed logical to simply replenish the amount of TMC observed leaving the system through the permeate in each reaction cycle. In the reaction verification work at S/C = 7000, only 8.6% of the Ru fed to the system was detected in the permeate. Hence, 10% of the initial mass of TMC was added to each subsequent reaction, operating with an initial S/C of 7000. Although some improvement in reaction rate was observed, the second reaction still suffered from reaction rate decline, stalling at 95% conversion after 7 h (data not shown). This suggested that some of the Ru species retained by the membrane was also deactivated or degraded and needed replacing by the additional catalyst.

Recognising that TMC degradation may be higher than that implied by the concentration of permeated Ru alone, the amount of TMC added to reaction 2 onwards was 20% of the initial catalyst mass. By applying this strategy, 10 consecutive reactions (including nine catalyst recycles) were conducted with complete conversion and no reaction rate decline.

DMMS rejection increased, as observed during the S/C = 500 proof of concept work, from 64.3% to 89.5%. As in the proof of concept work, this is believed to be due to irreversible compaction of the membrane during the first five filtrations. During the filtrations, the permeate flux averaged 35.7 L m^{-2} h^{-1}. A cumulative TON of 40,900 over the 10 reactions (taking into account each new catalyst addition) was achieved in 35 h.

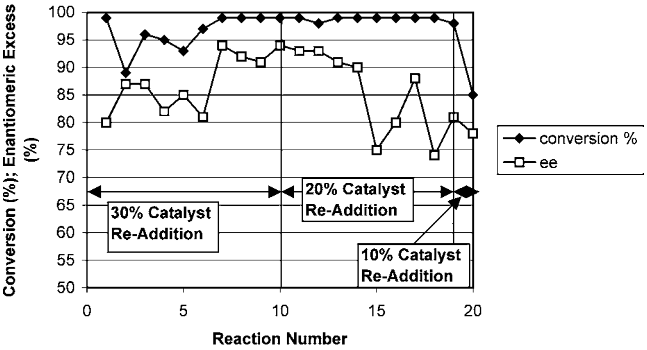

Figure 9. **DMI conversion and ee for 20 wt % DMI reactions (Reaction System 5).**

Ru rejection and product purity for the S/C = 7000 recycle system is shown in Figure 8. Ru rejection did not decrease below 97.5% during the reaction sequence, although product purity increased from 7.9 to 16 μg Ru per g DMMS. The increase in Ru content in the product is due to a fraction of the Ru added to each reaction accumulating in the system, until steady state is reached. At steady-state, the mass of Ru fed per batch equals the rate at which the Ru permeates. By assuming 100% conversion of DMI to DMMS, i.e. at no point is the rate-limiting S/C ratio exceeded, and that steady-state permeation rates of DMMS and Ru can be achieved, 18.4 μg Ru per g DMMS would be expected in the product at steady state. From the results in Figure 8, it can be seen that the product purity is tending towards this value. If an additional 5−10 reactions had been carried out, it is expected that the steady-state product purity value would have been attained.

Again, during these 10 reactions it was observed that Ru permeated faster than expected from stoichiometry, based on the P permeation rate (mean Ru:P ratio during the 10 reactions was 1:1.27, stoichiometry predicts Ru:P = 1:2), suggesting that degradation of the catalyst was still occurring.

3.5. Scale-Up to Industrially Relevant Substrate Concentration (Reaction System 5). To maximise productivity in commercial applications, as high a substrate concentration as practically feasible is used. For asymmetric hydrogenations, this is typically in the range 10−40 wt % substrate. Thus, following demonstration and optimisation of the OSN catalyst recycle system with the dilute (0.8%) DMI solution, the process was scaled up to the more industrially relevant substrate concentration of 20 wt % DMI.

It was observed during initial tests that at this higher substrate concentration a lower S/C ratio (S/C = 4000 rather than S/C = 7000 for the dilute system) was required to maintain the same reaction batch time as was attained with the optimised dilute system. Therefore, demonstration of the catalyst recycle system at 20 wt % DMI was carried out at the higher catalyst loading of S/C = 4000.

The amount of catalyst added to the reaction system with each batch of fresh substrate solution was reduced sequentially from 30% initial catalyst mass, to 20% initial catalyst mass, and finally to 10% initial catalyst mass. The goal was to verify that the fraction of initial catalyst mass addition identified in

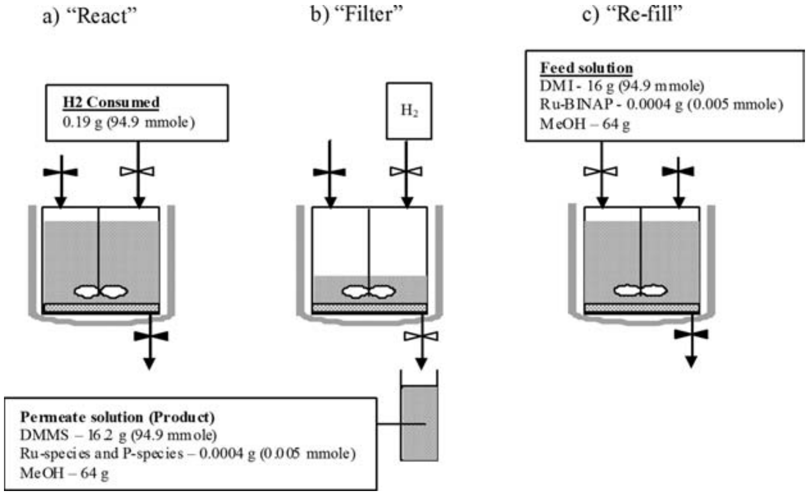

Figure 10. **Steady-state mass balance for one reaction−filtration cycle for Reaction System 5 with 20% of initial catalyst loading added per reaction−filtration cycle.**

the dilute system optimisation was also appropriate for the 20 wt % DMI system. By bracketing the previously identified 20% readdition rate, it would be possible to verify if this addition rate still remained optimal.

Figure 9 shows the evolution of DMI conversion and DMMS ee over the course of 20 reactions, incorporating 19 catalyst recycles. The desired end-point of the reaction during each cycle was DMI conversion >95% and DMMS ee >80%. The first 10 reaction/recycles were carried out with the maximum readdition of catalyst, 30% addition of the initial catalyst mass. During these 10 reactions, the conversion averaged 96.5% and the ee averaged 87.3%, with the conversion and ee stabilising at 99% and 93%, respectively, by reactions 7−10. Given this successful demonstration with 30% catalyst readdition, the readdition fraction was reduced to 20% for reactions 11−19. With 20% readdition, the conversion and ee averaged 98.8 and 85%, respectively, which is comparable with the results for 30% readdition. However, although the conversion is constant with 20% catalyst readdition, there does appear to be a trend of reducing ee after reaction 15, perhaps due to degradation of the chirally directing BINAP ligand. Figure 10 shows the steady-state mass balance for each reaction−filtration cycle at these operating conditions. Also, as reaction 20 (Figure 9) shows, adding only 10% of catalyst has a significant affect on the conversion in addition to the ee. As both conversion and ee were both below the desired reaction end-point values, the recycles were terminated at reaction 20. During these reaction/filtrations, the permeate flux averaged 40 L m^{-2} h^{-1}.

4. Conclusions

It has been shown that applying OSN technology to recycle a homogeneous TMC (Ru-BINAP) has substantially increased the catalyst TON and lifetime for a hydrogenation reaction. The membrane performance at high catalyst loadings (S/C = 500) allowed sufficient catalyst to permeate through the membrane that further downstream product purification would be necessary. By reducing and optimising the catalyst loading (S/C = 7000), product purities <20 μg Ru per g DMMS could be achieved, potentially removing the need for any further posreaction processing, and the turnover number of the catalyst was increased from 6950 (14 reactions at S/C = 500) to 13,100 (two reactions at S/C = 7000 with no readdition of catalyst).

The TON was further increased to >40,000 by feeding small amounts of the TMC to each repeat reaction to maintain an acceptable reaction rate with the recycled TMC. The optimal solution for high TON and product purity required system operation close to the S/C limiting ratio (working S/C = 7000) with a small addition of TMC to compensate for catalytic and filtration losses (20% addition of initial catalyst charge). Clearly, a completely stable catalyst that is present at a reaction rate-limiting S/C ratio, and completely retained by a membrane, should require no further addition of catalyst after the initial loading. Nevertheless, in the system presented in this study the requirement to add only 20% of the initial catalyst load to all subsequent reactions is equivalent to a 5-fold increase in catalyst life and a 5-fold reduction in catalyst quantity/cost—this represents a significant cost saving in processes where TMCs are used.

The overall productivity was improved by increasing the DMI concentration by an order of magnitude from 0.8 wt % to 20 wt %, showing that application of this technology at industrially relevant substrate concentrations is feasible.

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