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Continuous Nanofiltration and Recycle of an Asymmetric Ketone Hydrogenation Catalyst

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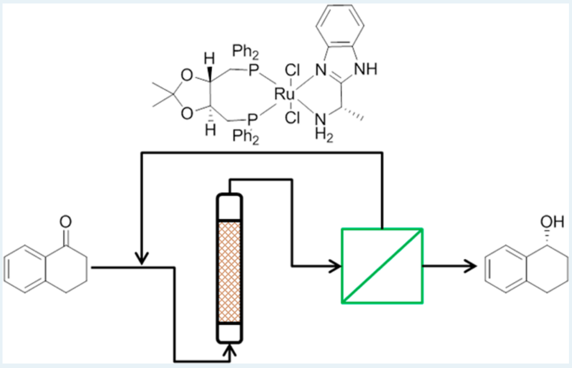
Supporting Information



ABSTRACT: The continuous nanofiltration and recycle of a ruthenium diphosphine/diamine catalyst for the asymmetric hydrogenation of α-tetralone is demonstrated in a small scale flow system. Batch experiments show that the catalyst can be recycled under hydrogen pressure. Subsequent transient packed bed experiments serve to characterize the reaction and inform the design of the recycle experiments. The total internal volume of the resulting system is ∼50 mL, making this pilot useful for testing catalyst recyclability via nanofiltration during the early stages of process development. The high-pressure catalyst recycle system is run with an automatic control system to respond to membrane flux decline during the course of operation and enable long duration runs. In 24 h, we achieved a turnover number approaching 5000 for ruthenium diphosphine/diamine catalyst used in the asymmetric hydrogenation of α-tetralone, demonstrating significant reuse of the catalyst since the substrate-to-catalyst ratio in the reactor approaches 250. During the 24 h period, the equivalent of 60 batch separation/recycle experiments is automatically performed. Ruthenium concentration in the product stream remains below 200 ppb. A slow decline in enantiomeric selectivity from 96% to 93% is observed during the run.

KEYWORDS: *continuous flow, nanofiltration, homogeneous catalyst, recycle, asymmetric hydrogenation*

■ INTRODUCTION

Homogeneous organometallic catalysts are frequently applied in the production of fine chemicals,[1,2] but the transition metal center and ligands of these catalysts can pose separation problems downstream from the reactor.[3,4] Heavy metal contamination is strictly regulated in the pharmaceutical industry with often less than 5 ppm heavy metal content allowed in the final product.[4] Moreover, the cost of the metal and ligands provides motivation to separate catalysts from the product stream and preserve their activity. The pharmaceutical industry is finding new benefits of converting processes from batch to flow[5−7] that adds further incentive to recycling catalyst in flow. Although batch experiments are indispensable in early process development, the complications that could arise when recycling a catalyst in a flow system are best understood with a pilot flow system. Here, we demonstrate the design and operation of a small-scale (∼50 mL) pilot flow system to study the viability of nanofiltration as a separation technique for reusing a high pressure, second-generation Noyori asymmetric hydrogenation catalyst.

Asymmetric hydrogenation of ketones is an important transformation in pharmaceutical synthesis.[8] For aryl ketones lacking an additional coordinating group, this transformation can use molecular hydrogen, an alcohol, or borane as the reductant.[9] The latter approach often uses Corey−Bakshi−Shibata (CBS) oxazaborolidine catalysts[10] that have been recycled previously using nanofiltration membranes.[11−13] In these cases, recycling generally increased turnover numbers (TONs) substantially while exhibiting some percent decline in enantiomeric excess (ee). Efficient ruthenium-containing organometallic catalysts have been developed to perform asymmetric ketone hydrogenation using both alcohol and hydrogen sources.[9] Flow systems have been used to investigate the recyclability of asymmetric transfer hydrogenation catalysts.[14−16] Herein, we focus on a catalyst using molecular hydrogen as the reductant. The separation and recycle of diphosphine/diamine catalysts has been performed mostly in batch recycle experiments. Some examples include the modification of the catalyst using dendrimers,[17] magnetic nanoparticles,[18] mesoporous silica,[19] zirconium phosphonates,[20] and polystyrene.[21] These approaches have the potential disadvantage of significant catalysts modification that could cause large reductions in turnover frequencies (at least 1 order of magnitude compared to the native catalyst species for all those cases). As an alternative, we apply organic solvent nanofiltration (OSN), also known as solvent-resistant nanofiltration (SRNF), to separate an unmodified diphosphine/diamine catalyst that has not been recycled to date.[22] This

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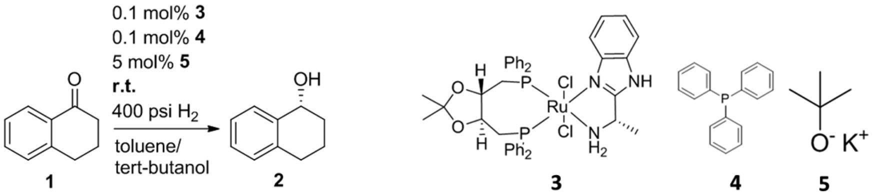
Scheme 1. Asymmetric Hydrogenation of α-Tetralone Using a Diphosphine/Diamine Catalyst[a]



[a] An ee of 97% was obtained for this substrate. Previous batch operating conditions are shown in ref 22.

approach has the advantages of eliminating the catalyst modification step in process development and allowing operation at turnover frequencies (TOFs) of the original homogeneous catalyst. With the relatively high molecular weight (MW) of this catalyst (832 amu), smaller products and intermediates could be used in the system without any catalyst modification.

A variety of membrane separation process blocks have been developed and applied in the literature to enact surface tension-based phase separation,[23] partial pressure gradient-based gas removal,[24] and gravity-based separation approaches.[25−27] OSN membranes can be used to separate large molecules (200−1000 amu) from smaller molecules and are compatible with a variety of nonpolar, polar protic, and polar aprotic solvents.[28] OSN membranes can be made from a variety of materials including polyamide, polyimide, and polydimethylsiloxane material.[29] In this paper, we make use of poly(ether ether ketone) (PEEK) nanofiltration membranes, which were made by the Livingston Group at Imperial College, London.[30] These PEEK membranes are compatible with a wide range of solvents and have the advantage of being stable in strong bases.[31,32] Nanofiltration membranes have been used to separate organometallic, enzymatic, metallic, and organic catalysts from smaller product molecules.[33−35] Continuous catalyst recycling experiments have been applied to metathesis reactions,[36,37] hydroformylation,[38−40] hydrogenation,[41−43] and other important reactions.[33,34,44]

Our system performs small-scale flow tests of catalyst recyclability without the need of building larger scale, more expensive pilots. For example, our system can test whether, after 24 h of continuous catalyst recycling, problems arise which inhibit the application or require new process solutions. Some of these potential problems that can arise in flow, but might not be noticed after a few batch recycles are catalyst degradation into smaller species which pass through the nanofiltration membrane, accumulated degraded catalyst causing side reactions, steady-state membrane flux decline due to fouling, membrane rejections changing due to fouling, membrane clogging, and inhibited catalyst activity under closed-loop conditions. Our system is able to investigate all of the concerns above to develop a more accurate understanding of how recycling a catalyst in flow affects throughput, yield, and metal contamination in the product stream.

■ RESULTS AND DISCUSSION

Process Development in Batch. We consider the asymmetric hydrogenation of α-tetralone using a ruthenium diphosphine/diamine catalyst (Scheme 1).[22] This substrate has been run at a 200 L pilot scale with a transfer hydrogenation catalyst at Avecia.[45] The large (832 amu) catalyst is used with two base cocatalysts: triphenylphosphine (TPP) and potassium *tert*-butoxide. The large nonlabile ligands of this catalyst make nanofiltration a good choice for the catalyst separation and recycle. After being activated by the strong base, the catalyst is quickly oxidized by air so oxygen contamination must be avoided for safety and preserving catalyst activity.

We reproduced Li et al.'s results[22] for a 5 h batch experiment with substrate **1**. Upon increasing the pressure to 2.76 MPa, we were able to reduce the residence time in batch to 40 min. These shorter residence times allowed us to test catalyst recyclability more efficiently. Since this particular catalyst system had not yet been recycled in the literature, batch catalyst recycling experiments were first employed to test catalyst stability after a reaction. In order to do so, a high-pressure hydrogenation reaction was first performed. After the reaction, the cell was depressurized and allowed to stir under argon bubbling for an additional 40 min. Next, more substrate was added to the reaction mixture and the cell was repressurized. This procedure resulted in a fully deactivated catalyst. When stirring under low pressures of hydrogen after a reaction (instead of bubbling argon), some active catalyst remained, and 40% conversion was obtained after the first cycle for a 40 min residence time. This observation implied that high pressures of hydrogen might be required to keep the catalyst stable once it was activated. As result, we constructed a high-pressure batch reactor with the ability to add additional substrate without depressurizing the batch reaction mixture. (Figure 1, further detail in the Supporting Information). Since additional substrate could be added with the reactor at 1.38 MPa of hydrogen, with reactions being performed at 2.76 MPa, the reaction mixture was always in contact elevated pressures of hydrogen at all times. Under those conditions, substantial reuse of the catalyst was possible (Figure 2). This behavior could be attributed to beta-hydride elimination of the diamine ligand being more likely in the absence of hydrogen.[46−48] Accurate quantification of catalyst stability in this experiment was not the goal, rather these batch experiments served to identify that continual presence of high pressures of hydrogen was necessary

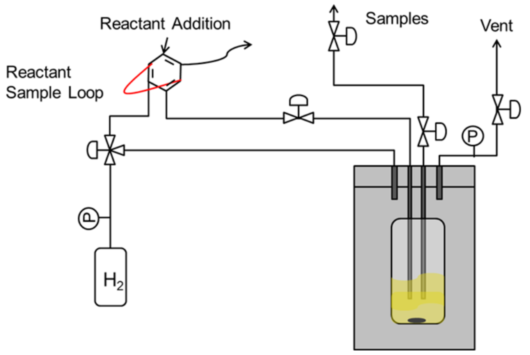


Figure 1. Batch system for reusing catalyst without reducing hydrogen pressure below 1.38 MPa in between catalyst reuses.

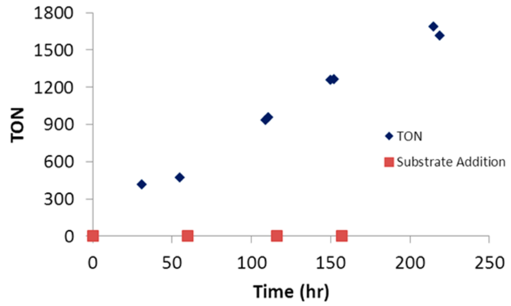


Figure 2. Batch catalyst reuse result obtained with the setup shown in Figure 1. Data represent three separate reuses of the catalyst, showing that catalyst activity is maintained between cycles.

for a reuseable catalyst. As result, the design of the recycle system had to accommodate high pressures of hydrogen (~2.76 MPa) at all points in the catalyst recycle loop, even in the surge tank.

Process Development in Flow. Once the batch reaction was optimized to 40 min, and the catalyst was shown to be recyclable, kinetic screening in flow was chosen as an efficient way to fine-tune the conditions of operation. Although flow systems generally take a few residence times to reach a steady-state, it has recently been shown that transient performance of a plug flow reactor can generate very efficient and accurate kinetic data.[49] Residence time distribution experiments performed on our packed bed reactor confirmed approximate plug flow behavior in the liquid phase so the technique was applicable (see the Supporting Information).

The layout of our flow system to screen kinetic behavior is shown in Figure 3, the details of which are described in the experimental methods section and the Supporting Information. Multiple pumps are used to deliver separate feeds that are mixed with hydrogen before entering the packed bed reactor. A packing of inert stainless steel enhances gas–liquid mass transfer.

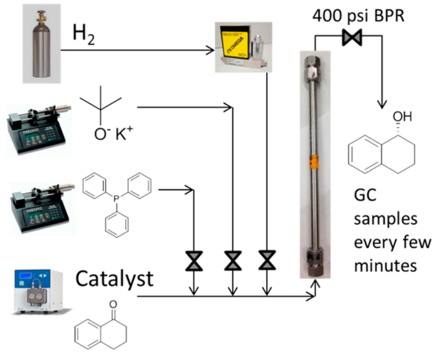


Figure 3. Flow system used to screen kinetics efficiently using a transient upflow packed bed reactor.

In order to screen the dependence of the reaction rate on concentration of *tert*-butoxide, the system was run with a linear ramping of the flow rate of *tert*-butoxide while all other flows remained constant. At low *tert*-butoxide concentrations, the reaction rate is inhibited (Figure 4a), but at increasingly higher *tert*-butoxide concentrations, the reaction rate plateaus. TPP was found to have little effect on the reaction rate over this concentration range (Figure 4b). Thus, there is a wide range of *tert*-butoxide and TPP concentrations that can be maintained without affecting the process significantly. This is an important consideration since maintaining concentrations within a narrow range in our catalyst recycle system would require additional control loops.

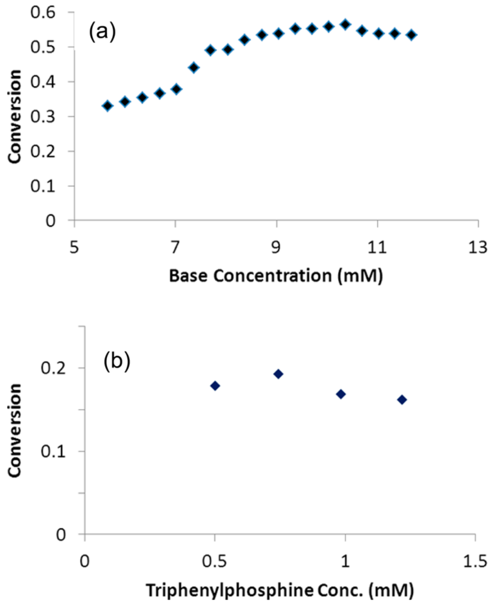


Figure 4. (a) Base and (b) TPP concentrations have little effect on kinetics near the operating point.

The substrate concentration was also ramped using a setup similar to that in Figure 3 (see the Supporting Information). When ramping the substrate concentration, the same amount of product was formed regardless of the inlet concentration of substrate (see Figure 5). Thus, under the conditions investigated, the reaction is approximately zero order in substrate, which has a number of implications on our process design. For a catalyst recycle system involving a nanofiltration membrane, we expect the product rejections to increase with time and plateau during startup. This, combined with the "snowball effect"[50] associated with a closed loop recycle system, implies that we will build up a high concentration of product in our recycle loop. However, at steady state, product output equals reagent input, and there is no loss of product. If the reactor is operated at higher substrate concentrations, this will likely result in significant loss of permeation at steady-state due to concentration polarization and/or fouling at the membrane surface.[51] For first-order kinetics, we would pay a penalty in reaction rate when trying to reduce substrate concentration. For zero-order kinetics there is, however, no rate penalty for

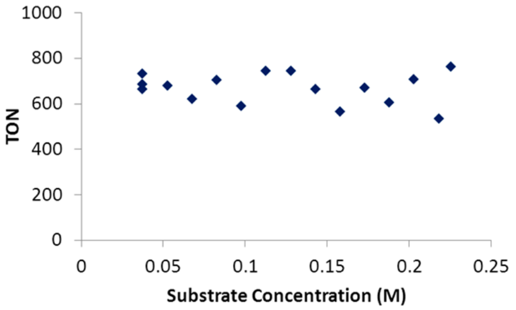


Figure 5. TON obtained as a function of inlet substrate concentration. Substrate concentration has no significant effect on reaction rate.

operating at lower substrate concentrations. Using this information, we chose to operate at lower concentration of **1** (0.08 M) to reduce fouling of the nanofiltration membrane without decreasing the reaction rate in our reactor.

The residence time could be screened by linearly ramping all of the pump flow rates simultaneously, similar to the approach of Moore and Jensen,[49] though in their case nonlinear pump flow rate changes were employed. The residence time of a fluid exiting the reactor was calculated using techniques in the Supporting Information. The linearity of the resulting yield as a function of residence time (Figure 6) is consistent with our zero-order rate dependence on substrate concentration (for this present range of conversion). The characterization data were obtained in a few hours in contrast to cumbersome steady-state flow experiments, which would have taken over 10 h to produce 10 data points, assuming three reactor residence times would be needed to reach each steady state.

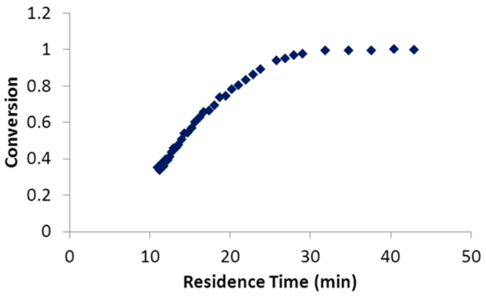


Figure 6. Yield as a function of residence time obtained during a ramping experiment.

Finally, catalyst concentration was ramped under our optimized conditions at a 5 min residence time and 2.76 MPa pressure of hydrogen. Since our yield has a strong dependence on catalyst concentration even at this 5 min residence time (Figure 7), the reaction is not mass-transfer limited under the operating conditions. These results imply that the mass transfer coefficient is greater than 0.0045 s^{-1}, which is consistent with literature values for small scale upflow packed bed reactors near our flow rates (also referred to as flooded bed reactors).[52,53] A catalyst concentration of 0.225 mM was chosen for the subsequent recycle experiments to achieve high conversion. The steady-state data included in Figure 7 verify that the approach of Moore and Jensen[49] extends to high pressure multiphase packed bed reactors.

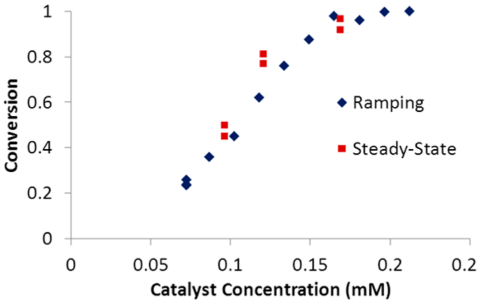


Figure 7. Conversion as a function of catalyst concentration obtained during a concentration ramping experiment. Steady-state data were obtained afterward to verify the accuracy of the more efficient ramping approach.

Catalyst Recycle Flow System. After verifying the recyclability of the catalyst in batch and exploring the reaction characteristics in flow, a small-scale flow system was built to recycle catalyst **3** (Figure 8). The different process blocks are discussed in detail in the Supporting Information. Here, we give a general overview of the process flow diagram and discuss the performance of the system. When scaling up an oxygen-sensitive chemistry, much better oxygen exclusion is typically observed at scale.[1] We used the most rigorous oxygen exclusion techniques practical on a laboratory scale to predict more accurately what could be achieved in larger scale systems. All the reagents were handled in a glovebox prior to being loaded into the continuous recycle system. This was not the case for the earlier batch reactions.

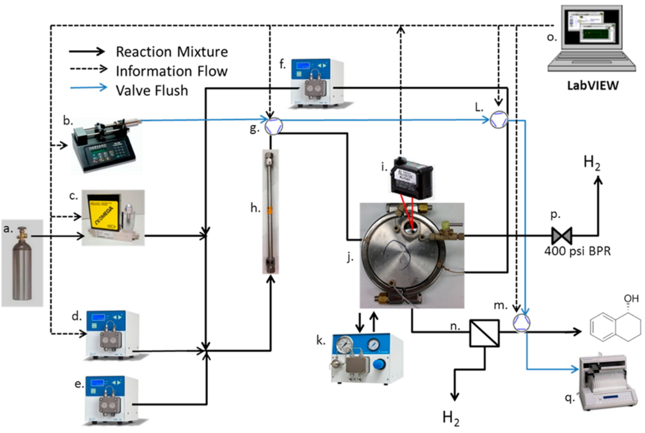


Figure 8. Process diagram for our small scale continuous recycle system. The major pieces of the system include the following: (a) hydrogen cylinder with regulator; (b) syringe pump for valve-flushing; (c) mass flow controller; (d) inlet pump for catalyst/substrate; (e) inlet pump for base/TPP; (f) recycle HPLC pump; (g) reactor outlet sample valve; (h) packed bed reactor; (i) laser for liquid level measurement; (j) nanofiltration flow cell with built in high pressure holding tank; (k) recirculation pump for nanofiltration cell; (l) retentate sampling valve; (m) permeate sample valve; (n) gas/liquid membrane separator for permeate stream based on wetting characteristics;[54,55] (o) computer running LabVIEW; (p) series of pressure regulators adding up to 2.76 MPa; (q) fraction collector. The total internal volume of the system is less than 50 mL.

Starting with the left-hand side of Figure 8, an inlet substrate solution is mixed with an inlet potassium *tert*-butoxide/TPP solution and the recycled membrane retentate stream. Before combining with the two inlet feeds, this recycle stream is mixed with a hydrogen source at a fixed mass flow rate. This allows the flow direction and approximate flow rate to be verified visually through the clear tubing of the recycle stream. The two inlet streams and recycle stream are mixed in a four-way cross and enter the packed bed reactor at 2.76 MPa. After the reaction, the mixture proceeds to the nanofiltration module. In this module, gas/liquid separation occurs by gravity and hydrogen is vented through 2.76 MPa of backpressure. The level of the liquid in the module is measured with a laser proximity sensor and used to control automatically the inlet flows via a LabVIEW script. The product stream permeates through the nanofiltration module while a concentrated catalyst solution from the retentate side enters the in-line HPLC pump, repressurizing the recycle line back to the inlet conditions. In this way, our catalyst is continuously separated and recycled back to the reactor. At no point in the system does the pressure fall below 2.76 MPa, which increases the stability of our catalyst. At three points in the system, automatic sampling valves with sample loops probe the conditions in the system. At the experimental times defined by the LabVIEW script, these valves switch and their loops are flushed out into a fraction collector by a controlled syringe pump.

Throughout all the runs, the control system responded to membrane flux decline due to fouling and concentration polarization by reducing inlet flow rates. During normal operation, significant hydrogen outgassing was observed from the permeate stream. An gas/liquid surface-tension-based separator was used to continuously remove this hydrogen before the permeate sample valve using a separator based on wetting charateristics.[54,55] As a result, the sample loop on the permeate stream was always filled with liquid, allowing the direct quantification of absolute concentrations by the use of isobutylbenzene as an external standard.

In order to test the recyclability of the catalyst in our flow system, catalyst and base were first loaded into the entire system (see the Experimental Methods). Next, substrate, base, and TPP were loaded into the inlet pumps, and the system was allowed to operate automatically for 19 h. With no fresh catalyst cofeed during this time, the initial charge of catalyst gradually deactivated as reflected by the product fraction in the retentate declining (Figure 9). The catalyst solution did not become a darker orange (indicative of oxidation), so oxidation is not likely to be the major mechanism of catalyst deactivation. Loss of the catalyst through the membrane during this run was insignificant, with an average catalyst rejection of 99.6%. Our ruthenium concentration in the product stream was maintained below 200 ppb. A catalyst turn over number (TON) of 10 800 was obtained for this run. The residence time in our reactor under these conditions was 5 min.

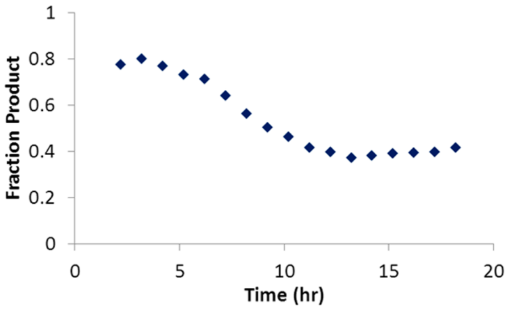


Figure 9. Fraction of product in the retentate of our system as a function of time. Data from the retentate valve was automatically actuated/flushed every hour during the run.

On the basis of the previous experience, we designed an experiment with catalysts cofeed that would produce high conversions over 24 h. The system was started up similarly to the previous example except that, in this case, catalyst was cofed along with the substrate into the system. The cofeed ratio of substrate to catalyst of 9400:1 was much higher than the ratio of substrate to catalyst within the reactor near 250, reflecting the reuse of the catalyst in the system. Conversions in the permeate, retentate, and reactor outlet remained high throughout the 24 h experiment (Figure 10). Near the end of the experiment, the substrate feed was cut in half to combat membrane fouling. A TON of 4750 was obtained for this 24 h run. The TON per pass in the reactor approached only 250, demonstrating that the catalyst was reused over 15 times on average. The flow system performed the equivalent of 60 reactions, separations, and recycles during this time period, with catalyst being partially purged (via sampling) and partially made-up every cycle. Furthermore, the ruthenium measured in the permeate (via atomic absorption spectroscopy) remained below 200 ppb, corresponding to a membrane rejection of 99.6%. During the run, the enantioselectivity declined from 97% to 93% likely due to the partial degradation of the catalyst into a species catalyzing nonstereo-specific hydrogenation. For example, racemization of the diamine ligand via a beta hydride elimination has been observed in the literature for similar catalysts.[47]

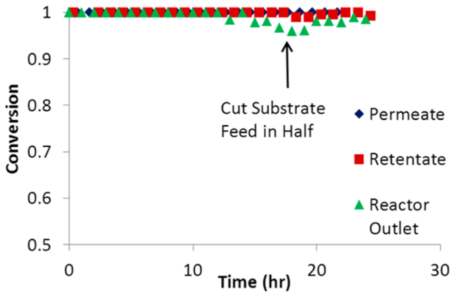


Figure 10. Conversion as a function of time for a 24 h operation with 9440:1 substrate to catalyst feed.

The product rejection by the membrane versus time shows an initial rise and plateau (Figure 11) despite the low concentrations of substrate employed. The product rejection increases from an initial value of −20% to ∼40% during the 24 h run. The negative rejection initially is consistent with independent rejection tests for the product and implies that, under dilute conditions with no fouling, our product is actually more permeable than our solvent system.[56] Increases in rejection via membrane fouling and concentration polarization are challenges for nanofiltration applications and can be probed efficiently and automatically with our system. The increase in rejection from concentration polarization was reduced via a high recirculation rate through the retentate side of the membrane (see the Supporting Information). For an unfouled membrane, potassium *tert*-butoxide was found to have high rejections (>80% according to titration experiments) despite the small size of the molecule, possibly due to the hydrophobicity of the PEEK membrane.

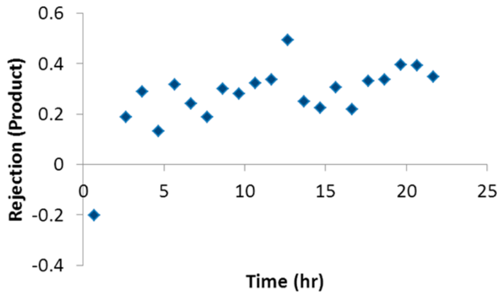


Figure 11. Rejection of product by the membrane as a function of experimental time for the 24 h run with a catalyst cofeed.

Rejection and permeate data were incorporated into a dynamic process model based on residence time distributions of the individual process blocks (see the Supporting Information). With this semiempirical model, the expected permeate, retentate, and reactor outlet product concentrations could be calculated assuming full conversion. The good agreement between experiments and predictions from the dynamic process model (Figure 12) supports our understanding of the dynamic mass balances in the system under actual operation, and ensures that the system is operating as intended. Moreover, the model could serve as a good starting point for exploring future systems-level improvements in performance.

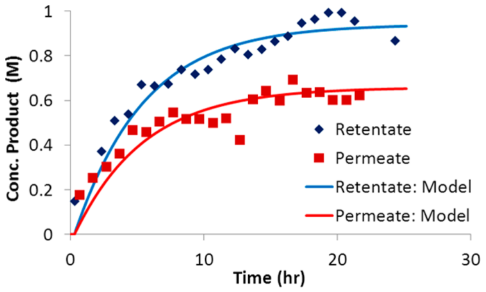


Figure 12. Dynamic process model predictions are in good agreement with experimental product concentrations in the product and retentate streams.

CONCLUSION

A small-scale nanofiltration flow system was developed to continuously separate and recycle a ruthenium diphosphine/diamine catalyst for asymmetric hydrogenation of α-tetralone. Batch scale experiments revealed that the catalyst was most stable when kept under high pressures of hydrogen, which prompted the design of a nanofiltration module with a high-pressure holding tank and controlled liquid. Transient operation of a small scale packed bed reactor showed that the cocatalyst concentrations were not major drivers of reaction rate, and so control systems to maintain their concentrations in the recycle loop were not necessary. Moreover, at the operating conditions, the reaction rate was zero-order in substrate concentration, which allowed experiments at lower concentrations of substrate to help reduce membrane fouling without impacting the reaction rate. During a 24 h run, we were able to maintain high yields with a turnover number near 5000 for the process, which represented a significant catalyst reusage since the approximate substrate-to-catalyst ratio in the reactor is only 250. After 24 h of operation, contents of the reaction loop had been recycled approximately 60 times (on average). The PEEK nanofiltration membrane survived the strong base that would have destroyed commercial membranes while providing 99.6% rejection throughout the run. As a result, ruthenium leaching in the permeate stream remained less than 200 ppb. The enantioselectivity (ee) of our transformation reduced from 97% to 93% during the run, implying that some deactivated catalyst species catalyzed the hydrogenation non stereospecific. Finally, a dynamic process model provided further insight into the performance of the small-scale nanofiltration system for catalyst recycle process. Future improvements on the system could add additional control loops to maintain constant cocatalyst concentrations during longer runs. Additional long duration experiments with this and other catalyst systems could form a strong foundation for scale-up and implementation of nanofiltration systems for recycling expensive homogeneous catalysts with simultaneous reduction of metal levels in products.

EXPERIMENTAL METHODS

Batch Hydrogenation. Batch experiment reagents were all handled using a Schlenk line. In open air, 5.5 mg of dichloro[(4*S*,5*S*)-(+)-4,5-bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolane][(*S*)-(−)-2-(alpha-methylmethanamine)-1*H*-benzimidazole]ruthenium(II) (Strem Chemicals, 44-0955) and 1.2 mg of triphenylphosphine (Sigma-Aldrich, 93092) was weighed, added to a Schlenk vial, and cycled with argon (Airgas, grade 5.0) five times. Using purged needles, 0.25 mL of substrate was added to the catalyst vial. The contents of this vial were diluted with 4.25 mL of a 9:1 toluene (Sigma-Aldrich, 244511) tert-butanol (Sigma-Aldrich, 471712) solution. In a separate vial, 46.9 mg of potassium *tert*-butoxide (Sigma-Aldrich, 659878) was weighed, cycled, and diluted with 1 mL of tert-butanol. Sonication was necessary to dissolve efficiently the base. Argon was flowed continuously into the empty in-house aluminum batch reactor to remove trace oxygen. After 10 min of argon purging, the base was added to the catalyst solution, and this mixture was then added to the batch reaction chamber. With a purged needle, 0.175 mL of this base mixture was added to the catalyst vial. This solution was quickly added to the batch reaction chamber with the cap taken off. The batch chamber was then closed. Hydrogen pressure was adjusted to 2.76 MPa in the batch reaction chamber, and the stir plate was turned on. The hydrogen was slowly vented down to 5 bar. This hydrogen pressure cycling procedure was repeated three times to remove trace oxygen, and the reaction is then run for 40 min under 2.76 MPa of hydrogen. Adequate stirring was verified via a sight-glass in the batch reactor. The solution with an active catalyst appeared as a transparent light yellow.

High Pressure Batch Recycle. The set up shown in Figure 1 was used to perform high-pressure batch recycling experiments. During these catalyst recycling experiments, the hydrogen pressure never dropped below 1.38 MPa in between catalyst uses. First, the normal batch hydrogenation procedure was followed, with the exception that all of the lines in Figure 1 were purged with argon prior to use. Once the batch reaction mixture was put into the chamber, the chamber was drilled shut and the argon source (connected to what became the vent valve) was closed. The valve positions were set such that hydrogen could be used to pressurize the reaction chamber. The stir plate was activated and stirring was visually verified via the sight glass. The reaction was allowed to proceed for the 40 min. Afterward, a sample was carefully extracted from the series of two way valves. This was done by starting with both valves closed, opening the valve closest to the reaction chamber, and then closing it again after a few seconds. The second valve was then opened to let the sample expand out into the GC vial. Normally, this was done three times to reduce cross-contamination from previous samples. After the reaction, the hydrogen regulator pressure was reduced to 1.38 MPa, the chamber was vented until it was at 1.38 MPa, and the reaction mixture was allowed to stir under this reduced hydrogen pressure for 20 min. The six-way valve was switched such that the loop was not exposed to the high-pressure hydrogen line. The sample loop (0.25 mL) was then filled with pure substrate **1** from the Schlenk line. The hydrogen cylinder's (Airgas, grade 5.0) regulator was set back to 2.76 MPa, and the six-way valve was manually actuated. This caused the substrate in the sample loop to be pushed into the reaction chamber by the high-pressure stream of hydrogen. The reactor pressure continued to rise until its pressure matched the hydrogen cylinder's regulator pressure. The reaction began again, and after 40 min another sample was taken as described earlier. This catalyst recycle procedure was repeated two more times. It should be noted that no additional solvent or base was added during these cycles. These experiments provided an initial evaluation of catalyst recyclability under hydrogen pressure to guide the design of the recycle system.

Kinetic Ramping Experiments. The experimental layout is shown in Figure 3. Unlike the batch experiments, all the reagents were handled in a glovebox (VAC, 101965) prior to being loaded into the continuous system. Toluene (anhydrous) and *tert*-butoxide (anhydrous) were purchased from Sigma-Aldrich and degassed in the glovebox by stirring prior to use. The Schlenk line was used afterward to load syringes when necessary. The reactor was connected to the three pumps using a four-way cross from Upchurch Scientific. An HPLC pump (Lab Alliance Series 1500 HPLC pump) was used to deliver the solvent mixture to the reactor. A 3.45 MPa Upchurch Scientific back pressure regulator was tuned with an Allen key until the system reached a steady state pressure of 2.76 MPa. Five reactor volumes of liquid were put through the system at this pressure to degas the system thoroughly and to reach a hydrodynamic steady state. Next, the solvent mixture was switched out for the catalyst/substrate mixture from the glovebox. Flow was paused intermittently during this switch to prevent argon from entering the HPLC pump. Next, the base and TPP stainless steel syringes were loaded with their respective solutions (from the glovebox) using the Schlenk line. The pumps (Harvard PHD Ultra) were made to flow two reactor volumes, at which point the LabVIEW script was started and the experiment began. Samples for GC were manually collected from the reactor outlet every few minutes.

Continuous Recycle Startup. In a glovebox, 60 mg of potassium *tert*-butoxide was weighed out and added to a 40 mL vial. Next, 40 mL of solvent mixture 9:1 toluene:*tert*-butanol was added. While the control system for the (fully degassed) system was running, the base solution was loaded into the HPLC feed pumps. The recycle pump was set to 1.05 mL/min. This solution was loaded into the system at a rate equal to the permeation rate. In a glovebox, 14 mg of catalyst and 5 mg of triphenylphosphine was weighed and added to a 40 mL vial. A 40 mL portion of the same solvent mixture was added to this catalyst. When the base was fully loaded into the system, the catalyst solution was then loaded onto the HPLC pump. Loading the catalyst required roughly 1.5 h. This was the amount of time required to permeate almost 40 mL under these conditions. To prepare a base cofeed, 100 mg of base was added to 500 mL of solvent mixture. To prepare a substrate/catalyst cofeed, 17.2 mg of catalyst, 26 mL of substrate, and 30.5 mg of triphenylphosphine were mixed in a 40 mL vial. These materials were diluted by the 9:1 solvent mixture to 40 mL. After the startup, catalyst solution was loaded, the catalyst cofeed and base cofeed was loaded onto the two inlet HPLC pumps. The catalyst/substrate cofeed has a fixed 32 μL/min flow rate. The base cofeed was loaded onto the HPLC pump that was connected to the control system. At this point, the fraction collector was started and the associated LabVIEW script was run. This program controlled the flushing pump and automatic six-way valves so that samples could be automatically obtained.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The following file is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b00149.

> Descriptions of individual kinetic ramping experiments, process block residence time distributions, and the dynamic process model (PDF)

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Notes

The authors declare no competing financial interest.

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