Experimental strategies for increasing the catalyst turn-over number in a continuous Heck coupling reaction

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Abstract

This work presents a continuous Heck coupling reaction combined with organic solvent nanofiltration (OSN) separation of the catalyst *in situ*, using polymeric membranes at high temperature (80 °C) and high concentration of base ($>0.9 \text{ mol.L}^{-1}$). Two reactor configurations are investigated: a continuous single stirred tank reactor/membrane separator (m-CSTR); and a plug flow reactor (PFR) followed by m-CSTR (PFR-m-CSTR). The combined PFR-m-CSTR configuration was found to be the most promising, achieving conversions above 98 % and high catalyst turn-over numbers (TONs) of $\sim 20,000$. In addition, low contamination of the product stream ($\sim 27 \text{ mg Pd per kg of product}$) makes this process configuration attractive for the pharmaceutical industry.

Keywords: Continuous Heck coupling reaction; Pd retention *in situ*; organic solvent nanofiltration (OSN); PEEK membrane; low contamination of the product stream; high catalyst TON.

1 Introduction

Many organic syntheses require expensive homogeneous transition metal catalysts (TMCs) to effect the reactions. Separation of these catalysts from the reaction products and solvents is difficult, requiring the use of energy intensive and waste-generating downstream processing [1, 2]. In addition, distillation, the most commonly used separation method, requires high temperatures (unless the product is very volatile) and most homogeneous catalysts are

thermally labile (even at reduced pressure usually decomposition can occur). Other conventional processes such as chromatography or extraction also lead to catalyst loss [3].

Recovery of a (noble) metal catalyst is useful not only for obvious economic reasons but also because contamination of a product by heavy metal impurities is undesirable and must be limited to sub-ppm levels [2]. A lot of research has been done to heterogenize TMCs with different techniques such as encapsulation, interphase chemistry, phase-tagging for biphasic catalysis or ionic liquids and various techniques for the immobilization of molecular catalysts on solid or colloidal supports [4]. For example, Gröschel et al. [5], employed a catalytically active membrane based on poly(acrylic acid) networks containing palladium nanoparticles for the partial hydrogenation of propyne. In order to test the long term stability a membrane was kept under constant reaction conditions for about 6 days (reactants flow rate of 20 mL.min⁻¹ and temperature of 298 K) and a conversion and selectivity of about 50% and 88% were obtained, respectively (TON data not presented). Another work from Milano-Brusco et al. [6], used a different approach based on the potential of surfactant based reaction media in different homogeneous catalytic reactions. The reaction under study was the enantioselective catalytic hydrogenation of dimethyl itaconate (DMI) using two different reaction media. In the first one, the Rh catalyst is complexed with the chiral ligand (2S,4S)-1-tert-butoxycarbonyl-4-diphenylphosphino-2-(diphenylphosphinomethyl)-pyrrolidine (BPPM) (T = 30 °C and P = 1.1 bar). After complete hydrogenation was achieved, micellar enhanced ultrafiltration (MEUF) with a polyethersulfone membrane (Nadir P010) was used to recycle the catalyst achieving up to 95% retention; in this configuration three repetitive batches of DMI were performed and an enantiomeric excess (ee) of up to 69% was obtained (TON data not presented). In the second reaction medium, Triton X-100 was used for the hydrogenation of DMI with a Rh catalyst complexed with the water-soluble tris(3-sulfophenyl)phosphine trisodium salt (TPPTS) at 50 °C and 1.1 bar. With this system, phase separation by temperature induced separation allowed for up to four repetitive batches of DMI hydrogenations, resulting in a TON of 1530. Nevertheless, anchoring the catalyst on, for instance, inorganic supports or organic polymers often results in a loss of activity and selectivity [1]. Zhan et al., 2011 [7], reported a novel type of Heck reaction catalyst, composed of hydrophilic interpenetrating polymer networks (PINs) and palladium (Pd)

nanoparticles that could be recycled 20 times in DMF; however, the yields were not stable from cycle to cycle, with variations from 60 to 90 %.

The recent development of organic solvent nanofiltration (OSN) provides an alternative to the classical heterogenization of homogeneous complexes. An OSN-membrane is used to separate the homogeneous catalyst from the reaction mixture and thus recycle the homogeneous complex. OSN has already been performed at laboratory scale to recycle homogeneous catalysts and its importance and relevance has been emphasised by works such as: Nair et al., 2001 [4], who performed a semi-continuous nanofiltration-coupled catalysis for a well-known Heck coupling reaction. They permeated the post-reaction mixture through a polyimide OSN membrane achieving an overall 90 % catalyst retention after four catalyst recycles (five reaction-filtration sequences) and a total catalyst turnover number (TON, moles of product synthesised per mol catalyst added) of 1200; Datta, et al., 2003 [8], developed catalysts for the Heck, Sonogashira and Suzuki type coupling reactions, which were retained by poly(dimethylsiloxane) (PDMS) membranes (retention higher than 99.5 %) but the catalysts lost activity after a series of catalyst recycles; Aerts, et al., 2006 [1], who used silicon-based OSN-membranes to recycle the Co-Jacobsen catalyst four times in diethylether (Et_2O), achieving 98.5 % retention and a minor decrease in the conversion from one cycle to another; Janssen et. al, 2009 [9], reported the synthesis of multiple phosphine ligands attached to a dendritic support via 'click' chemistry (molecular weight enlargement – MWE – catalysts) and their application in the Pd-catalyzed Suzuki coupling as well as their recovery and reuse by means of nanofiltration. In this work the reaction performed was the Suzuki–Miyaura coupling between 4-bromotoluene and phenyl boronic acid at 60 °C for 16 h with three different ligands. A ceramic membrane (Nanofiltration Inopor® nano 450 Da) with retention higher than 99 % for the three MWE catalysts was employed and four catalyst recycles were performed achieving initial yields of 99 % but decreasing from cycle to cycle (TON data not presented).

All previous examples of OSN stated above were performed in discontinuous or semi-continuous mode but current interest in the continuous flow production of fine chemicals has motivated a re-evaluation of how synthetic transformations are performed at the laboratory, intermediary, and manufacturing scales. Although continuous operations might require more

time initially to set up equipment and find the optimum conditions - concentrations, temperatures and flow rates - other parameters such as mixing and temperature can be more easily controlled when compared to batch processes ([10],[11]). Few works have been published in the literature about continuous flow production with catalyst retention using OSN. One of the very first works in continuous catalysis was performed by Brinkmann et al., 1999 [12]. These authors focused on the usage of diaminopropyl-type dendrimers bearing palladium phosphine complexes as catalysts for the allylic substitution in a continuously operating chemical membrane reactor. Retention rates by ultra- or nanofiltration membranes -Nadir UF-PA-5 and SELRO MPF-50, respectively - higher than 99.9% resulted in a total TON for the Pd catalyst of circa 95. However, in the reactions of $T = 25\text{ }^{\circ}\text{C}$ and a flow rate of $20\text{ mL}\cdot\text{h}^{-1}$ the conversion starting at 100 % decreased to around 80 % after 40 h (80 residence times) and the experiment was stopped. Dijkstra, et al., 2003 [13] developed a shape-persistent nanosize dodecakis (NCN-Pd^{II}-aqua) complex [14] that was applied as a homogeneous catalyst under continuous reaction conditions in a nanofiltration membrane reactor. The reaction performed was the double Michael reaction between methyl vinyl ketone and ethyl-cyanoacetate and the membrane used was Koch MPF-50 flat-membrane (catalyst rejection of 99.5%). Under the reaction conditions of $T = 23\text{ }^{\circ}\text{C}$ and $P = 20\text{ bar}$ a TON of 3000 and a conversion of 85 % was obtained (26 h, 65 exchanged reactor volumes). De Smet, et al., 2001 [15], have performed a continuous enantioselective hydrogenation of dimethyl itaconate with Ru-BINAP catalyst and of methyl 2-acetamidoacrylate with Rh-EtDUPHOS catalyst in a hybrid process composed of a CSTR followed by a NF unit (NF-coupled catalysis). For the first reaction they achieved a conversion of 100 % throughout the entire run and for the second reaction the conversion was 100 % initially but then decreased to 90 % in the later stages. The catalyst retention was above 97 % for both reactions. The TON for the hydrogenation with Ru-BINAP and Rh-EtDUPHOS was, respectively, 1950 and 930. Fang, et al., 2011 [16], reported a continuous homogeneous hydroformylation with bulky rhodium catalyst complexes retained by nanofiltration membranes (STARMEM[®]) but in practice those experiments were performed in a semi-continuous mode. Sequential batches of 16 to 22 hours were performed at 50 - 60 °C and at different pressures (maximum 3.0 MPa syngas) achieving high catalyst retention (> 99 %) but relatively low yields;

for instance, for 1-octene hydroformylation catalysed by PBB10d at 3.0 MPa the conversion was around 50 % (TON data not presented).

More recently the use of continuous-flow reactors for multistep synthesis has gained a considerable amount of interest because they allow for integration of the individual reaction steps and subsequent separations in one single streamlined process. For instance Noel, et al., 2011 [17], used a microreactor (100 μ L) for the palladium-catalyzed Suzuki-Miyaura cross-coupling reactions (synthesis of biaryls starting from substituted phenols) in flow connected to a microfluidic extraction operation with a porous fluoropolymer membrane to remove impurities and a packed-bed reactor to increase the mixing and efficiency of the biphasic Suzuki-Miyaura cross-coupling reaction. They were able to obtain, on average, isolated yields of 95 %. A comprehensive review of recycling of homogeneous catalysts using membrane separation could be found elsewhere [18].

The main hurdle towards implementing OSN in the catalytic processes has been the compatibility of the existing OSN membranes (particularly the polymeric ones) with the reaction conditions. Typically the TMC reactions are performed at high temperatures (100 °C and above) in aggressive solvents (e.g. DMF) and at high concentrations of base/acid – quite challenging conditions for the polymeric membranes. Although successful, all of the above cited catalytic reactions combined with membrane separations have been performed in a batch or semi-continuous mode and at mild conditions (non-aggressive solvents, low concentration of acids or bases, moderate temperature of 30 - 50 °C) and/or the membrane separation step has been performed separately after temperature reduction and post-reaction media workup to make it compatible with the membrane material. In addition, the catalyst loadings employed are usually high (0.5 – 2 mol %) and the reported TONs (usually varying from 50 to 2,000) are too low to be of commercial interest to the industry.

In this work we report for the first time a continuous process for a Heck coupling reaction combined with *in situ* separation of the TMC using polymeric membrane. In contrast to the previous works, the reaction and the separation are performed simultaneously in the same

vessel, both performed at 80 °C (high temperature) and in dimethylformamide (DMF) containing $>0.9 \text{ mol.L}^{-1}$ triethylamine (high base content). In addition, a high catalyst TON and low TMC contamination of the product was achieved by maintaining the catalyst loading at minimal levels throughout the runs. A summary of the state of the art and a comparison with the results presented in this work can be found in Table 1 in the last section of the manuscript. Two reactor configurations are investigated: continuous single stirred tank reactor/membrane separator (m-CSTR); and a plug flow reactor (PFR) followed by m-CSTR (PFR-m-CSTR in series). It was demonstrated that the combined PFR-m-CSTR configuration is the most promising achieving catalyst TONs of $\sim 20,000$.

2 Materials and methods

2.1 Chemicals

Analytical grade palladium (II) acetate [Pd(OAc)₂], 1,3-Bis(diphenylphosphino)propane (dppp), iodobenzene (IB), methyl acrylate, anhydrous *N,N*-dimethylformamide (DMF), triethylamine (NEt₃), ethyl acetate, diethyl ether, fuming nitric acid (100 %) and hydrochloric acid (37 %) were all purchased from Sigma-Aldrich.

2.2 Membrane

Poly (ether ether ketone) (PEEK) membrane was prepared at Imperial College London using the wet phase inversion method. The membrane was cast on a non-woven polypropylene support using an automatic film applicator (Elcometer 4340 Automatic) with a transverse speed of 0.5 cm/s. The thickness of the membrane was set by adjusting the casting knife to 250 µm.

2.3 Heck coupling reaction

The reaction between iodobenzene **1** (MW 204 g.mol⁻¹) and methyl acrylate **2** (MW 86 g.mol⁻¹) to form *E*-methyl cinnamate **3** (MW 162 g.mol⁻¹) (Figure 1) was selected and carried out because it would proceed regioselectively and form a stable product. The by-product of this reaction is triethylamine hydroiodide **4** (MW 229 g.mol⁻¹).

Figure 1 – Scheme of Heck coupling reaction to form *E*-methyl cinnamate (3).

2.3.1 Temperature studies

In a reaction carousel (Radleys, UK) a series of batch experiments were performed at two different temperatures: 80 °C (temperature selected as a trade-off between reaction kinetics and the boiling points of methyl acrylate, 80⁰ C and triethylamine, 88.8⁰ C) and 110 °C [19] [20]. In a carousel tube 5.4 mg (0.024 mmol) of Pd(OAc)₂ and 19.8 mg (0.048 mmol) of dppp were stirred for 15 minutes at room temperature in DMF (2 mL). 0.273 mL (2.45 mmol) of iodobenzene, 0.264 mL (2.93 mmol) of methyl acrylate, 0.5 mL (3.58 mmol) of triethylamine and 1 mL of DMF were then added and the solution was stirred throughout the experiment. For catalyst pre-

activation the same amount of $\text{Pd}(\text{OAc})_2$ and dppp were added to 2 mL of DMF and the mixture was stirred for an additional 30 minutes at 80 °C. 0.273 mL (2.45 mmol) of iodobenzene, 0.264 mL (2.93 mmol) of methyl acrylate, 0.5 mL (3.58 mmol) of triethylamine and 1 mL of DMF were then added and the solution was stirred throughout the experimental run. 0.1 mL samples were taken for analysis.

2.3.2 Catalyst concentration studies

In order to determine the minimum catalyst loading that allows the reaction to achieve completion within a working day, a series of experiments were performed as batches in a reaction carousel at 80 °C with different catalyst, $[\text{Pd}(\text{OAc})_2]$, concentrations: 0.002 mol %, 0.004 mol %, 0.0078 mol %, 0.0156 mol %, 0.03125 mol %, 0.0625 mol %, 0.125 mol %, 0.25 mol %, 0.5 mol % and 1 mol %. For each concentration the same procedure described in 2.3.1 for catalyst pre-activation was applied.

2.3.3 Reaction kinetics

From the batch experiments it was determined that the reaction rate could be approximated by a first order reaction (Equation 1A, Appendix) with respect to the limiting substrate IB (C_s) by using the isolation method. Plotting the graph $\ln(C_s/C_{s_0})$ vs. time (Figure 14A, Appendix) a kinetic rate of 0.0219 min^{-1} ($T_{ref.} = 80 \text{ }^\circ\text{C}$; $p_{ref.} = 1 \text{ bar}$) was determined for a catalyst loading of 0.031 mol %.

2.4 Continuous Heck coupling reaction combined with OSN membrane separation

2.4.1 System setup: m-CSTR and PFR

The two configurations used in this study are shown in Figure 2. The first configuration was a single reactor system consisting of a one pot reactor/ membrane separator cell (m-CSTR) where the reaction and catalyst separation from the reaction mixture were performed at the same time. A constant flow of feed solution was supplied to the cell via a HPLC pump. Equivalent flow of the post-reaction mixture was collected as permeate through the membrane. The cell was equipped with a pressure relief valve set to 50 bar relief pressure in order to avoid over-pressurising the system. The m-CSTR was equipped with a magnetic stirrer bar, and placed on a hotplate stirrer. The second configuration consisted of two reactors in series. A

constant flow of the feed solution was first passed through a U-shaped PFR, placed in a heating chamber. The outlet of the PFR was directly connected to the inlet of the m-CSTR.

The m-CSTR (Figure 3) was made of 316 SS, could operate under high pressure (69 bar), and hold circular flat sheet membranes with an effective area of 51 cm². The m-CSTR was operated in a bottom-to-top permeation mode and contained a magnetic stirrer in the feed/retentate chamber. This is to ensure that any dissolved gas released from a feed stream which enters the cell will move to the top of the cell and exit through the membrane. The liquid capacity of the m-CSTR was ~60 mL. Six ports surround the bottom section of the cell, and were used as inlet ports (feed) or outlet ports (permeate), or were connected to a thermocouple or a pressure gauge for temperature control and pressure monitoring [21].

The PFR was made of 316 SS ½" tube with a length of 0.64 m (total volume of 60 mL).

Figure 2 - Scheme of the single-reactor system (top). Scheme of the two reactors in series system (bottom). Legend: A - Feed solution flask; B - HPLC pump; C - m-CSTR with PEEK membrane (stirred membrane cell); D - Permeate collector flask; E - Heating/stirring plate; F - PFR; G - PFR outlet sampling valve. 0 - PFR inlet stream; 1 -m-CSTR inlet stream; 2 - m-CSTR outlet stream/ permeate; 3 - Nitrogen supply.

Figure 3 – Stirred tank reactor/membrane separator (m-CSTR) layout. Legend: 1 - Inlet/outlet ports; 2 - Feed/retentate chamber; 3 – Inner o-ring; 4 – Membrane; 5 - Sintered plate; 6 - Outer o-ring; 7 - Cover.

2.4.2 Operating procedure

For 100 mL of the initial feed solution, 0.0044 g $\text{Pd}(\text{OAc})_2$ ($2.0 \times 10^{-4} \text{ mol.L}^{-1}$, ~ 0.033 mol %) and 0.016 g dppp ($4.0 \times 10^{-4} \text{ mol.L}^{-1}$, ~ 0.063 mol %) were added into a 500 mL two-neck round bottom flask. The flask was vacuum degassed and then placed under an N_2 atmosphere. After that, and always under an N_2 atmosphere, 65.2 mL of anhydrous DMF were added and the solution was mixed using a magnetic stirrer. Then, 6.8 mL of iodobenzene (final concentration of 0.6 mol.L^{-1}), 10 mL of methylacrylate and 18 mL of triethylamine were added to the flask and mixed. The flask was then connected to the system as a feed solution and kept under an N_2 blanket (~ 0.5 bar overpressure). More feed solution was prepared throughout the running of the system by using the procedure described above but with 10 times lower catalyst and ligand concentrations.

Note: The single-reactor system was run initially in a batch mode. 50 mL starting solution (0.6 mol.L^{-1} iodobenzene; $3.2 \times 10^{-4} \text{ mol.L}^{-1}$ $\text{Pd}(\text{OAc})_2$, $6.4 \times 10^{-4} \text{ mol.L}^{-1}$ dppp and the other reagents were added into the m-CSTR chamber and stirred for ~ 12 hours at 80 °C (overnight). On the following day the system was started in continuous mode using a feed stream containing 0.6 mol.L^{-1} iodobenzene and $2 \times 10^{-5} \text{ mol.L}^{-1}$ Pd catalyst. **Note that since we were not sure how the**

membrane would perform in a continuous process and whether a constant rejection of 90% would be obtained we started the batch using slightly higher catalyst concentration than the estimated limiting equilibrium concentration ($3.2 \times 10^{-4} \text{ mol.L}^{-1}$ instead of $2.0 \times 10^{-4} \text{ mol.L}^{-1}$).

2.5 Analytical methods

2.5.1 Conversion

An Agilent 6890 Series II gas chromatograph equipped with a HP - 5 column (5 % phenyl methyl siloxane; capillary: $30\text{m} \times 0.530 \text{ mm} \times 1.50 \text{ }\mu\text{m}$) and a flame ionization detector (FID) was used for determining the conversion of limiting substrate to product by comparing the area of the individual characteristic peaks [Conversion = Area product/(Area product + Area substrate)]. The programme ran from 40 °C (1 min hold) to 200 °C with a ramp of 15 °C.min⁻¹.

2.5.2 Product extraction

In order to confirm that the right product has been obtained, permeate solution was mixed initially with distilled water (1:1) and ethyl acetate (1:4) and the mixture was allowed to phase-separate in a separating funnel. Brine solution (1:15) was added to facilitate phase separation and the organic phase was then subjected to three washes with water using brine in-between. The resultant organic phase was partially evaporated in a rotary evaporator. The paste residue consisted mostly of methyl cinnamate with traces of iodobenzene and DMF. A thin layer of this was spread on a petri dish to allow evaporation of the residual DMF. An ¹H-NMR scan (not shown) confirmed the methyl cinnamate presence and also the traces of iodobenzene.

2.5.3 Triethylamine hydroiodide salt extraction and analysis

The retentate was subjected to vacuum filtration to separate the salt from the liquid component, consisting of DMF and the substrates. After washing with ether the cake was left at room temperature to evaporate remaining traces of ether. ¹H-NMR revealed it to be exclusively triethylamine hydroiodide.

The solubility of the salt in the retentate was determined at 80 °C and atmospheric pressure for two post-reaction mixture compositions of the initial iodobenzene concentration: 0.6 mol.L^{-1} and 1.2 mol.L^{-1} . Though the reactor was operated under a pressure of 20-40 bar, salt solubility is expected to change negligibly within this pressure range. The experiments were performed on

the reaction carousel by adding known amounts of salt to the post-reaction mixture until the solubility limit was reached. The saturation concentrations of the salt were found to be $\sim 3.35 \text{ mol.L}^{-1}$ and $\sim 2.14 \text{ mol.L}^{-1}$ for the initial substrate concentrations of 0.6 mol.L^{-1} and 1.2 mol.L^{-1} respectively. The membrane rejection of the salt was determined by analysing permeate and retentate samples using an Agilent 1100 HPLC equipped with ELSD detector (Varian 385-LC). A reverse-phase HPLC column (ACE C-18, 250 mm $\times$ 4.6 mm) packed with $5\mu\text{m}$ diameter silica particles with 300 Å pores size was operated at 30 °C. Water (adjusted to pH ~ 6.5 with 0.1 mol.L^{-1} ammonium acetate buffer) and methanol were used as the mobile phase, at 1 mL.min^{-1} flow rate. A ramp from 50% methanol / 50% water to 95% methanol / 5% water in 35 minutes was followed by 4 minutes at 95% methanol and then a ramp back to 50% methanol / 50% water in 1 minute. Rejection is given by Equation 2A (Appendix) and it was found to be 45.6 %.

2.5.4 Palladium analysis

0.5 mL feed, permeate and retentate samples were heated at 90 °C on a hotplate stirrer. After complete drying, 1.5 mL of aqua regia (nitric acid and hydrochloric acid 1:3 v/v) was added to each dried sample to digest the organic content (digestion within ~ 24 hours). Each sample was then diluted in 10 mL centrifuge tubes with distilled water and mixed (the small residual organic matter was found not to interfere with the analysis). The samples were analysed using Inductively Coupled Plasma Optical Emission Spectrometry (ICP-OES) on a Perkin-Elmer Optima 2000DV spectrometer and compared against a calibration curve of 2 ppm, 5 ppm and 10 ppm palladium standard samples.

3 Results and discussion

3.1 Batch experiments for the Heck coupling reaction

3.1.1 Temperature studies

For the carousel experiments at two different temperatures the reaction reached 98% conversion after 40 minutes at 110 °C whereas for a temperature of 80 °C the reaction reached 99.5% conversion after 2 hours (Figure 4). Nevertheless, the conversion of starting material to product was slow at 80 °C, increasing sharply after 100 minutes of reaction time. This indicates that formation of the *in situ* catalyst complex was the rate limiting step. Hence, a complementary

experiment was performed by stirring $\text{Pd}(\text{OAc})_2$ and dppp together in DMF (2 mL) for 30 minutes at 80 °C (for pre-activation) prior to the addition of the remaining reagents. The reaction proceeded to full conversion in 50 minutes with catalyst pre-activation (Figure 4). As the boiling point of methyl acrylate is 80 °C and of triethylamine is 88.8 °C it was decided to investigate the kinetics and perform all membrane experiments at 80 °C in order to minimise the evaporation of these reagents. In addition, the glass transition temperature (T_g) of the PEEK polymer used for membrane preparation is ~ 140 °C and the lower operational temperature will minimise any membrane structural changes.

Figure 4 – Conversion over time of the Heck coupling reaction at 110 °C and at 80 °C with and without catalyst pre-activation. The reaction was performed as batch in a reaction carousel.

3.1.2 Catalyst concentration studies

As described earlier, in order to determine the minimum catalyst concentration essential for reaction completion within a working day, a series of experiments were performed on a reaction carousel at 80 °C, varying the catalyst concentrations. This experiment allows for a direct comparison between the maximum TONs achieved in a simple batch reactor and those in a continuous process combined with membrane separation. It was found that the reaction rate decrease starts somewhere between 0.0078 - 0.0156 mol % catalyst loading (Figure 5). From this experimental data it was established that the optimal catalyst concentration (as a trade-off

between high reaction rate and catalyst loading) should be around ~ 0.03 mol %, which corresponds to a catalyst concentration of $\sim 2 \times 10^{-4}$ mol.L $^{-1}$. The former value was fixed as the limiting concentration in the continuous reactor so at any given moment the catalyst concentration in the reactor should be maintained above or equal to this value.

Figure 5 - Effect of the catalyst concentration on the Heck coupling reaction performed in batch on the reaction carousel expressed as conversion values as a function of time. For each catalyst concentration the TON is presented in brackets.

3.2 Continuous Heck coupling reaction combined with OSN membrane separation

3.2.1 Single-reactor system: m-CSTR

The first experiment was performed using only the m-CSTR. Preliminary experiments performed using the PEEK membrane have shown ~ 90 % rejection of the Pd catalyst (~ 10 % losses).

Therefore, in order to compensate the 10 % losses and to maintain and run the continuous reactor at the target concentration of 2×10^{-4} mol.L $^{-1}$, the feed stream should contain 2×10^{-5}

mol.L⁻¹ catalyst. An added benefit of this strategy is that the Pd concentration in the permeate stream will remain low, 2×10^{-5} mol.L⁻¹, throughout the experiment. As stated in the operating procedure, the system was started initially in batch mode and then run in continuous mode. It was found that for batch mode the reaction proceeded to full conversion in approximately 5 hours (hence in Figure 6 at time 0 the conversion is 100 %).

The kinetics of the reaction was used to perform a theoretical simulation (using gPROMS v3.4, Process System Enterprise Ltd.) of the process performance. The rejections of product and substrate by the membrane were assumed to be negligible. The catalyst preactivation period is only 30 minutes while the catalyst residence time in the reactor is 300-600 minutes, an order of magnitude higher, which we assume should be sufficient for catalyst preactivation. According to the model predictions (Equation 3A, Equation 4A, Equation 5A, Appendix) the expected conversion at 300 minutes residence time (0.2 mL.min⁻¹ flow rate, operating pressure ~ 35 bar) was 86.7 %, while at a residence time of 600 minutes (0.1 mL.min⁻¹ flow rate, operating pressure ~ 20 bar) the model estimation was for 92.9 % conversion. As can be seen from Figure 6 the experimental and theoretical results for the conversion in continuous mode correlate reasonably well, although for the residence time of 600 minutes the experimental values of conversion are higher than the predicted ones. There could be various reasons for the increase in conversion including some changes in the rejection of product and substrate or variations in the feed flow rate (most likely). In fact the assumption for 0% rejection of the product and substrate may not be quite accurate as for example assuming 30% rejection of the product and the substrate will increase the apparent conversion measured in the permeate from 93 to 95 %. Overall it is a complex system and in our opinion is described reasonably well by a relatively simple model, and we consider the simplicity of the model, which describes the principal phenomena we have observed, as an advantage.

The Pd concentration in the permeate (calculated from Equation 6A, Appendix) was within the expected range of $2-3 \times 10^{-5}$ mol.L⁻¹ but on average it was slightly higher than the predicted value (Figure 7). The Pd concentration in the retentate is again within the expected range but lower than the predicted one: 1.6×10^{-4} mol.L⁻¹ vs. 2×10^{-4} mol.L⁻¹ (Figure 7). These results

suggest that the Pd rejection is lower than 90 %, with the Pd mass balance closed within 10 % error. In this experiment ~ 0.97 mol (~ 157 g) of product was produced and $\sim 5.4 \times 10^{-5}$ mol (~ 12 mg) of catalyst was utilised, resulting in a catalyst TON of approximately 17,963. On average there was ~ 25.8 mg Pd.kg product $^{-1}$ in the permeate stream.

We have to admit that the assumption for a single rejection value for the catalyst is a simplified one. In fact according to the Heck reaction mechanism, the Pd can be found in various molecules, so called catalytic species, which may actually co-exist. Since these species have different sizes and molecular weights the membrane rejection may also vary. However according to the reaction mechanism proposed by Amatore et al [22] all Pd complexes co-existing during the reaction have molecular weight within the range of 600 g.mol $^{-1}$ and above and should be well rejected by the membrane. If we look at a typical rejection curve Figure 15A (Appendix) for the PEEK membrane (although it is obtained using a mixture of polystyrene oligomers as marker molecules), it can be seen that for the species with MW higher than 500 g.mol $^{-1}$ the rejection varies only slightly and is within the range of 90%, in other words in an ideal case we would expect similar rejections for most of the Pd species present. Thus the only specie with rejection considerably lower than the others is Pd(OAc) $_2$ with MW of 224.51 g.mol $^{-1}$. Assuming its rejection is similar to the marker molecules it could be estimated as $\sim 50\%$. On the other hand according to the same work [22] the formation of the first Pd complex Pd(OAc) $_2$ dppp (MW 636.95 g.mol $^{-1}$) is fast, irreversible and thus the probability of free Pd(OAc) $_2$ permeating through the membrane is diminished. Literature data [22] suggest that the formation of Pd complex is a first order reaction with respect to Pd and zero order toward the ligand. Using a rate constant for the first Pd complex formation from the literature [23] of 3×10^{-3} s $^{-1}$, 50% rejection value for the Pd(OAc) $_2$ and 90% rejection for the first Pd complex, from Equations 3A and 4A we estimated Pd(OAc) $_2$ losses within 0.92% (for 300 minutes residence time) and 0.46% (for 600 minutes residence time) which are negligible compared to the 10% catalyst losses in the form of other species. Of course this is an idealised case, where the membrane performs in the same way for any type of molecule depending only on their molecular weight. In reality there are other factors also affecting the separation (e.g. membrane-catalytic species interactions) and further extensive study is necessary to elucidate this interesting topic. To the

best of our knowledge there is no published work describing the permeation rate of various Pd species through a membrane. To include these factors would be very complex and would rightly be the subject of a further extensive study and a further separate publication (even several publications): this is beyond the scope of the current paper.

Although the result was rather encouraging in terms of catalyst TON the achieved conversion was still below that obtained in a batch process. One possible way to increase the conversion is to increase the residence time. Once the reactor (or reactors) already has (or have) a fixed volume this can be achieved either by decreasing the flow rate (which might not be feasible practically) or to combine several types of reactors in series. In fact, for a reaction with first order kinetics the CSTR is not the best possible reactor configuration. For such types of reaction a PFR configuration is more efficient as a smaller volume is required compared to a CSTR for substrate conversions near 99% [24]. As a further strategy for improving conversion, a combination of PFR followed by membrane CSTR was investigated. This specific sequence of reactors was obtained using the Levenspiel plots – which are a useful tool for sequencing reactors in such a way to obtain the best overall conversion with smaller reactor volumes. An added benefit to having the PFR before the m-CSTR reactor is that the Pd catalyst would be pre-activated fully before entering the m-CSTR, thus eventually accelerating the reaction. In addition, reduced Pd losses through the membrane could be expected, due to the fact that the low molecular weight $\text{Pd}(\text{OAc})_2$ (MW of $224.51 \text{ g.mol}^{-1}$) will be fully converted to high molecular weight Pd complexes with dppp ligand (active species) (MW higher than 600 g.mol^{-1}) and therefore rejected better by the membrane.

Figure 6 - Theoretical and experimental results of conversion for the continuous Heck coupling reaction in the single m-CSTR system operated close to the limiting catalyst concentration ($2 \times 10^{-4} \text{ mol.L}^{-1}$). Experimental points are obtained for the permeate stream. The conversion was estimated using initial conditions from the batch start-up of the reactor - 60 mL starting solution, with 100% conversion - 0.6 mol.L^{-1} initial concentration of product and $3.2 \times 10^{-4} \text{ mol.L}^{-1}$ $\text{Pd}(\text{OAc})_2$. The continuous run was simulated using a feed stream containing 0.6 mol.L^{-1} iodobenzene and $2 \times 10^{-5} \text{ mol.L}^{-1}$ Pd catalyst at 0.2 mL.min^{-1} flow rate (residence time of 300 minutes) for the first 75 hours and 0.1 mL.min^{-1} flow rate (600 minutes residence time) thereafter. 90% rejection was assumed for the Pd catalyst and 0% for the product and substrate.

Figure 7 - Theoretical and experimental results of Pd concentration for the continuous Heck coupling reaction in the single m-CSTR system operated close to the limiting catalyst concentration. The estimation for the Pd concentrations was performed using initial conditions from the batch start-up of the reactor - 60 mL starting solution, with 100% conversion - 0.6 mol.L⁻¹ initial concentration of product and 3.2×10⁻⁴ mol.L⁻¹ Pd(OAc)₂. Note that since we were not sure how the membrane would perform in a continuous process and whether a constant rejection of 90% would be obtained we started the batch using slightly higher catalyst concentration than the estimated limiting equilibrium concentration (3.2×10⁻⁴ mol.L⁻¹ instead of 2.0×10⁻⁴ mol.L⁻¹). The continuous run was simulated using a feed stream containing 0.6 mol.L⁻¹ iodobenzene and 2×10⁻⁵ mol.L⁻¹ Pd catalyst at 0.2 mL.min⁻¹ flow rate (residence time of 300 minutes) for the first 75 hours and 0.1 mL.min⁻¹ flow rate (600 minutes residence time) thereafter. 90% rejection was assumed for the Pd catalyst and 0% for the product and substrate.

3.2.2 Two-reactors in series system: PFR-m-CSTR

- 1.2 mol.L⁻¹ Iodobenzene with membrane

After the promising results from the first set of m-CSTR experiments it was decided to investigate further options for increasing the catalyst TON in a PFR-m-CSTR system. One option is to increase the concentration of reagents and/or the feed flow rate. In order to challenge the system, both parameters were doubled and the experiment was started using a feed of 1.2 mol.L⁻¹ iodobenzene at 0.2 mL.min⁻¹ flow rate (10 hours residence time, 5 in the PFR and 5 in the CSTR). To avoid delays at start-up, the m-CSTR was used as it was, already pre-filled with the post-reaction mixture from the last single m-CSTR continuous experiment. The m-CSTR was directly connected to the empty PFR. A continuous run was started using a feed solution of 1.2 mol.L⁻¹ iodobenzene and 2×10^{-5} mol.L⁻¹ catalyst and the start-up time for the experiment was considered to be approximately 5 hours after initiating the feed supply, when the PFR-m-CSTR system was completely filled and permeation through the membrane occurred.

From the results in Figure 8 one can observe that the conversion was around 98 % throughout the process except for an isolated drop in the conversion (to a value around 92 %) after 5 hours (reasons unknown). The pressure in the system was constant at ~ 35 bar but after 23 hours of operation it increased to around 40 bar. Therefore, the flow rate in the system was decreased to 0.1 mL.min⁻¹, which in turn made the pressure drop to a value of ~ 26 bar. However, the pressure started to build up again, reaching 40 bar after 49 hours and still increasing, so for safety reasons the experiment was stopped. Crystalline triethylamine hydroiodide was found inside the m-CSTR after disassembling the system. This result underlined one potential problem when running the m-CSTR in a continuous process: accumulation of side products.

Figure 8 – Conversion values in the m-CSTR outlet stream/permeate (left axis) and pressure values (right axis) inside the m-CSTR as a function of time for the two-reactors in series system operated at 1.2 mol.L^{-1} iodobenzene concentration. The system was stopped after 7 hours and restarted after 22 hours.

▪ Salt accumulation in the m-CSTR study

The salt accumulation observed during the last reaction could cause a serious problem during continuous process operation and further investigation was necessary. Measurements were performed in order to obtain the salt solubility limits at different post-reaction media compositions (0.6 mol.L^{-1} and 1.2 mol.L^{-1}). As mentioned earlier the saturation concentrations of the salt were found to be 3.35 mol.L^{-1} and 2.14 mol.L^{-1} respectively. The salt rejection by the membrane was also determined to be 45.6 %. A mathematical model was used (Equation 6A) to determine the time after which the concentration of the salt in the m-CSTR reaches its saturation limit under the reaction conditions employed. For simplicity, the salt formation was assumed to be instantaneous, with a conversion of 100 %. This model also helps to predict whether precipitation would pose a problem for a feed having an iodobenzene concentration of 0.6 mol.L^{-1} . Estimated salt concentration in the m-CSTR as a function of time is shown in Figure 9.

Figure 9 - Salt concentration with time at two different iodobenzene concentrations in the feed solution – 0.6 mol.L⁻¹ and 1.2 mol.L⁻¹. IB denotes ‘Initial iodobenzene concentration’. The estimation for IB=0.6 mol.L⁻¹ was performed using a flow rate of 0.1 mL.min⁻¹ and an initial salt concentration of 0.6 mol. L⁻¹, as expected after starting the experiment as batch; For the IB=1.2 mol.L⁻¹ estimation, a flow rate of 0.2 mL.min⁻¹ for 8 hours was used and 0.1 mL.min⁻¹ for the rest of the run. For the last run, an initial salt concentration of 1.1 mol. L⁻¹ was used (the steady state concentration at the end of the 0.6 mol. L⁻¹ m-CSTR run) in order to simulate the actual experiments.

As is evident from Figure 9, the salt concentration never reaches its solubility limit with a feed iodobenzene concentration of 0.6 mol.L⁻¹ and salt precipitation will not occur. However, doubling the initial substrate concentration causes the salt concentration to reach its saturation value of 2.14 mol.L⁻¹ after approximately 44 hours (the initial salt concentration in the m-CSTR was expected to be ~ 1.1 mol.L⁻¹; the experiment was started using post-reaction mixture from the m-CSTR continuous experiment of 0.6 mol.L⁻¹ IB, where the steady state concentration has already been achieved). In our process, rapid crystallisation and reactor clogging seemed to have occurred at ~ 50 hours (~ 35 hours operational time) which is in reasonable agreement with the model estimations (between 40 and 50 hours). However in a membrane filtration unit operating with concentrated solutions, concentration polarisation phenomenon often occurs [25] where next to the membrane surface, concentrations several times higher than in the bulk solution may exist. **The crystallisation may have also been initiated in the membrane pores (if these exist) as a result of concentration effects due to confinement [26]. Thus we do not exclude**

the possibility that the salt crystallisation started earlier than expected at the membrane surface (due to concentration polarisation effects) or in the membrane pores. At 0.6 mol.L⁻¹ IB

concentration salt crystallisation was not observed even though several experiments were performed with durations of more than 250 hours. Overall, this undesired phenomenon should be carefully considered and monitored in continuous membrane reactors.

- 0.6 mol.L⁻¹ Iodobenzene with membrane

For this experiment with the two-reactors system, a residence time of 20 hours (10 h in the m-CSTR and 10 h in the PFR) was implemented (flow rate of 0.1 mL.min⁻¹) in order to make a direct comparison with the single m-CSTR reactor performance. The system was started in continuous mode and was fed initially with 100 mL feed solution with $\sim 2 \times 10^{-4}$ mol.L⁻¹ Pd concentration followed by feed solution with $\sim 2 \times 10^{-5}$ mol.L⁻¹ Pd concentration (all at 0.1 mL.min⁻¹ flow rate). It was expected that this reactor configuration would be able to achieve and continuously maintain a ~ 100 % conversion throughout the entire run (Equation 7A, Equation 8A, Equation 9A, Appendix, were used to estimate conversion). Indeed, the results showed that for 142 h operational time the conversion was stable at ~ 100 % but after that it started to decrease slowly and by the end of the run (~ 254 h) reached values around 96 % (Figure 10). From the Pd concentration measurements (Figure 11) it may be concluded that this decrease in conversion is related to the lower Pd rejection of the membrane - 75 % rejection instead of the assumed 90 % rejection - which means that the palladium concentration of 2×10^{-5} mol.L⁻¹ present in the feed is not enough to compensate the palladium loss throughout the system run (the Pd concentration in the retentate at the end of the run was $\sim 5 \times 10^{-5}$ mol.L⁻¹, 5 times lower than anticipated). On average the palladium concentration in the permeate was around 2.6×10^{-5} mol.L⁻¹ (2.75 ppm). After the system was disassembled it was possible to verify that the membrane was swollen. Such phenomenon was not observed during the previous experiment and is probably due to the fact that the experiment was started directly in a continuous mode (not in batch, as with the single m-CSTR reactor experiment); the m-CSTR was not initially pre-filled with liquid and the dry membrane was heated for several hours at the beginning of the experiment.

In addition, samples from the PFR outlet were also taken during the run in order to verify the efficiency of the PFR and also to prove that the m-CSTR with PEEK membrane was necessary for achieving conversions near 100 %. From Figure 12 one can observe that the conversion in the PFR was below 80 % and that it decreased throughout the run. In fact, based on a rough estimation from the batch experiments (Figure 5) it was expected that the conversion in the PFR (operating at ~ 0.0033 mol % catalyst, 2×10^{-5} mol.L⁻¹) should be in the range of not more than 40 - 50 % throughout most of the run. The observed higher efficiency of the PFR was attributed to a laminar flow with back mixing and/or existence of dead zones in the PFR (non-ideal plug flow reactor) resulting in a higher than anticipated catalyst concentration (Figure 12). This could be expected since with the current flow rate of 0.1 mL.min⁻¹ the Re number in the PFR is <1. In this experiment ~ 0.96 mol (~ 156 g) product was produced and $\sim 4.65 \times 10^{-5}$ mol (~ 10 mg) of catalyst was utilised, resulting in a catalyst TON of approximately 20,645. On average there was ~ 26.8 mg Pd.kg product⁻¹ in the permeate stream, with Pd mass balance closing within 6 % error. Overall improved system performance in terms of conversion and catalyst TON was obtained as compared to the single m-CSTR system.

Figure 10 – Conversion values in the CSTR outlet stream (permeate) as a function of time for the two-reactors system operated at 0.6 mol.L^{-1} iodobenzene concentration for the experiments performed with and without membrane (left axis); Pd concentration in the outlet stream of the CSTR vs. time for the experiments performed with and without membrane (right axis). (Points marked with red circles denote sudden drops in the conversion of the CSTR outlet stream possibly due to by-pass streams coming directly from the PFR).

Figure 11 - Experimental results and theoretical calculated curves of Pd concentration for the continuous Heck coupling reaction in the two-reactors in series system operated at 0.6 mol.L^{-1} iodobenzene concentration. The system was started in continuous mode and was fed initially with 100 mL feed solution with $\sim 2 \times 10^{-4} \text{ mol.L}^{-1}$ Pd concentration (the actual measured $1.96 \times 10^{-4} \text{ mol.L}^{-1}$ Pd was used as initial condition) followed by feed solution with $\sim 2 \times 10^{-5} \text{ mol.L}^{-1}$ Pd concentration (all at 0.1 mL.min^{-1} flow rate).

Figure 12 - Conversion obtained for the PFR outlet and m-CSTR outlet/permeate at the same time points in the two-reactors in series system operated at 0.6 mol.L^{-1} iodobenzene concentration (left axis); Pd concentration at the PFR outlet (right axis). (Data for the experiment with membrane).

- 0.6 mol.L⁻¹ Iodobenzene without membrane (blank test)

In the last experiment (0.6 mol.L⁻¹ iodobenzene with membrane) the Pd rejection was around 75 % and the conversion only started to decrease after 142 h of running even though the concentration in the retentate was 5 times lower than the one expected – 5×10^{-5} mol.L⁻¹ instead of 2×10^{-4} mol.L⁻¹. From these results it was rather obvious to question the importance of the membrane in terms of function and whether or not the PFR-CSTR system could reach the same values of conversion without it. An experiment was therefore performed without membrane (blank experiment) in order to assess the membrane contribution. The membrane was removed from the cell and the system was fed initially with 100 mL feed solution with 2×10^{-4} mol.L⁻¹ Pd concentration followed by feed solution with 2×10^{-5} mol.L⁻¹ Pd concentration (all at 0.1 mL.min⁻¹ flow rate) in order to closely reproduce the conditions at the experiment with membrane. Comparison between the experimental results obtained with and without membrane is also shown on Figure 10. Although in the beginning both experimental runs gave similar conversion the conversion started clearly to diverge after 59 hours. By the end of the run without membrane, at around 263 hours, the conversion dropped to ~ 82 % (~ 84 % at 255 hours vs. 96 % for the membrane experiment). As could be expected the Pd concentration in the outlet stream was higher for the experiment without membrane. Occasionally there were sharp drops in the conversion of the outlet stream (red circled points); a possible cause for these sudden fluctuations could be by-pass streams coming directly from the PFR reactor. The measured conversion at the PFR reactor outlet for the experiment without membrane was also lower than the experiment with membrane, although the measured Pd concentration was within the same range (Figure 13).

In this experiment ~ 1.06 mol (~ 172 g) product were produced and ~ 6×10^{-5} mol (~ 13.5 mg) of catalyst were utilised resulting in catalyst TON of approximately 17,667. As an average there was ~ 34.3 mg Pd.kg product⁻¹ in the permeate stream and the Pd mass balance closed within 11 % error. Overall the membrane experiment showed higher conversion, higher catalyst TON and lower Pd content per kg product. This effect will be more pronounced for longer runs and improved membrane performance, where the catalyst will be better retained and the conversion would remain stable at ~ 100 %.

Figure 13 - Conversion obtained for the PFR outlet and CSTR outlet at the same time points in the two-reactors in series system operated at 0.6 mol.L^{-1} iodobenzene concentration (left axis); Pd concentration at the PFR outlet (right axis). (Data for the blank experiment).

3.3 Process considerations and comparison with other processes and configurations

A comparison of our results with others reported in the literature for catalytic processes integrating membrane separation clearly demonstrates the **advantages** of our process configuration not only in terms of productivity but also in terms of downstream purification (see Table 1). While other processes tackle the problem of catalyst retention or catalyst recycle, attention has been paid neither to the productivity and the overall TON nor to the optimisation of the catalyst loading. In fact, comparing the catalyst loading of different processes only the one reported in [7] uses lower catalyst loading $0.030 \text{ mol } \%$ vs. $0.032 \text{ mol } \%$ and reports higher overall TON, 46,823, and lower downstream contamination ($0 \text{ mg Pd.kg product}^{-1}$) than the PFR-m-CSTR configuration reported in this study (see Table 1). However, the manufacture of Pd nanoparticles encaged in nanoporous interpenetrating polymer networks is not simple and might not be ready for immediate scale-up (see Table 1). In addition, the conversion reported in [7] is lower than the one obtained in our system, 70% versus 98% . One weakness of our

process is the relatively low catalyst retention obtained (most of the published works, demonstrate catalyst retention ~99%, see Table 1). In this respect, further optimisation of PEEK membrane production will be essential in bringing even better efficiency to the process.

As a proof-of-concept it is interesting to compare the productivity of our continuous process with the same process performed in batch with and without a membrane. The calculations were performed using the same initial feed composition and a reactor volume of 1 L for the batch modes and a volume of 1 L and 5 x 200 mL (5 small reactors operated in parallel) for the continuous mode. A production of 100 kg was set as a target for this process. A summary of the calculated results is presented in Table 2 below. As can be seen from the table, the continuous process gave again a superior performance in terms of catalyst TON and the product purity. Although the reactor volumetric productivity for the PFR-m-CSTR is slightly lower than the batch reactors (longer operation time required) it would be compensated by the savings in downstream purification and catalyst usage. In addition, in terms of material inventory a small continuous reactor is safer, for example, by running 5 continuous membrane reactors of 200 mL in parallel rather than a larger membrane reactor of 1 L (as could be seen from the table the process parameters would remain the same). On the other hand using multiple small batch reactors operating in parallel would not be economically feasible since the total number of non-productive hours will increase considerably (e.g. 2 hours for maintenance, filling, and emptying periods per each reactor). Overall the estimated productivity of a simple batch reactor is higher than that obtained in a continuous PFR-m-CSTR system, but this is achieved in expense of ~10 times higher catalyst consumption, ~10 times lower TON and ~10 times higher product contamination. These results clearly demonstrate the potential of OSN technology in continuous catalytic processes.

Table 1 – Comparison of different process configurations published in literature in terms of reaction type, solvent(s) employed, independency of reaction with separation, type of catalyst employed, catalyst loading (mol %), catalyst retention (%), conversion (%), contamination (mg TM per kg of product) and overall TON.

Reference	Reaction	Solvent	Reaction and separation performed independently	Catalyst employed	Catalyst loading (mol %)	Catalyst retention (%)	Conversion (%)	Contamination (mg TM.kg product ⁻¹)	Overall TON ^{a,b}
[4]	Heck coupling	Ethyl acetate and acetone	Yes	Pd(OAc) ₂ (PPh ₃) ₂	0.275	90.0	98	141	1,200
[8]	Heck coupling	NMP and cyclohexane	Yes	Pd(dba) ₂	0.500	99.95	55	11.9	87.80
[1]	Hydrolytic kinetic resolution (HKR) of epoxides	Et ₂ O	Yes	Co-Jacobsen	0.963	98.0	40	240	166.1
[1]	Hydrolytic kinetic resolution (HKR) of epoxides	IPA	Yes	Co-Jacobsen	0.985	93.0	45	764	91.4
[7]	Heck coupling	DMF	No	Pd nanoparticles in the IPNs	0.030	100	70	0	46,823
[15] ^c	Enantioselective hydrogenation of dimethyl itaconate	Methanol	Yes	Ru-BINAP	0.563	98.0	98	6.47	1,963
[15] ^d	Methyl 2-acetamidoacrylate	Methanol	Yes	Rh-EtDUPHOS	0.565	97.0	90	23.1	926
[16] ^e	Hydroformylation of 1-octene	Toluene	No	Modified rhodium complex (PBB10d)	0.100	99.99	50	0.22	2640
[17]	Suzuki–Miyaura Cross-Coupling Reactions	Toluene	Not applicable	XPhos	2.000	Not applicable	95	Not applicable	47.8
m-CSTR	Heck coupling	DMF	No	Pd(OAc) ₂ + dppp	0.032/0.002	90	~ 95	25.8	17,963
PFR-m-CSTR	Heck coupling	DMF	No	Pd(OAc) ₂ + dppp	0.032/0.002	75	98 - 100	26.8	20,645

^a Calculated taking into account all catalyst recycles (if applicable). ^b These numbers should not be compared explicitly because of different operating parameters (e.g. number of catalyst recycles, operation time, heterogeneous or homogeneous catalysis, process design, recovery, etc). ^c Calculated based on a flow-rate of 3.6 mL.h⁻¹ and 40 hours of operation. ^d Calculated based on a flow-rate of 3.5 mL.h⁻¹ and 22 hours of operation. ^e Calculated for the hydroformylation of 1-octene with PBB10d under 3.0MPa syngas and based on a flow-rate of 0.288 mL.min⁻¹. Note that in a continuous filtration mode rejection and retention are equivalent terms.

Table 2 – Comparison between batch mode and continuous process mode with PFR-m-CSTR for the Heck reaction under study in terms of total mass (g, produced/consumed), reactor productivity, operation time, catalyst loading (mol %), contamination (mg Pd per kg of product) and TON for theoretical process producing 100 kg of product.

	Total mass (g) ^a		Operation time (days)	Productivity (g product. L ⁻¹ reactor.h ⁻¹)	Catalyst loading (mol %)	Contamination ^b (mg Pd.kg product ⁻¹)	TON
	Palladium consumed	E-methyl cinnamate (product) formed					
Batch without membrane ^c	21.0	100 × 10 ³	286	14.57	0.032	210.1	3,123
Batch with membrane ^d	4.292	100 × 10 ³	343	12.18	0.032/0.002	42.71	15,286
Continuous PFR-m-CSTR (I) ^e	2.165	100 × 10 ³	415	10.06	0.032/0.002	21.43	30,305
Continuous PFR-m-CSTR (II) ^f	5 × 0.433	5 × 20 × 10 ³	415	10.06	0.032/0.002	21.43	30,305

^a Total mass consumed/produced after 286 days, 343 days and 415 days for batch without membrane, batch with membrane and continuous PFR-m-CSTR respectively. ^b Assuming 90 % rejection of Pd. ^c Assuming a reactor volume of 1 L, 3.43 batches per day (5 hours reaction and 2 hours for maintenance, filling, and emptying periods), a conversion of 100 % and catalyst and iodobenzene concentrations of 2×10^{-4} mol.L⁻¹ and 0.6 mol.L⁻¹, respectively. ^d Assuming a reactor volume of 1 L, 3.37 batches per day (including 5 hours for reaction, 0.12 hours for filtering 85 % of the reactor medium and 2 hours for maintenance, filling, and emptying periods), a membrane area of 5.37 m² (flux = 1.3 L.m⁻².h⁻¹), a rejection of 90 % (in respect to palladium), a conversion of 100 %, a iodobenzene concentration of 0.6 mol.L⁻¹ and a catalyst feed concentration of 2×10^{-4} mol.L⁻¹ for the first batch and 2×10^{-5} mol.L⁻¹ for the following batches. ^e Assuming a reactor volume of 1 L, 1.67 mL.min⁻¹ flow rate, an average conversion of 98 %, a catalyst feed concentration of 2×10^{-4} mol.L⁻¹ for the initial batch and 2×10^{-5} mol.L⁻¹ throughout the continuous run; iodobenzene concentration of 0.6 mol.L⁻¹. ^f Assuming a reactor volume of 0.2 L, 0.33 mL.min⁻¹ flow rate, an average conversion of 98 %, a catalyst feed concentration of 2×10^{-4} mol.L⁻¹ for the initial batch and 2×10^{-5} mol.L⁻¹ throughout the continuous run; iodobenzene concentration of 0.6 mol.L⁻¹.

4 Conclusions

This work has shown the potential for performing Heck catalytic reactions in continuous mode and achieving high catalyst TON, stable productivity and low Pd content per kg product.

Coupling the continuous process with a membrane separation step improves the continuous process performance, the catalyst productivity (TON) even further and reduces undesired metal content in the product stream. It also revealed the potential adverse effect of side product accumulation in the combined continuous reactor-membrane separation units, which may lead to serious process disruptions. Finally the excellent potential of PEEK membranes as separation materials in high temperature catalytic processes has been demonstrated.

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Appendix

A: Heck reaction kinetics

$$(-r_S) = \frac{dC_S}{dt} = K \cdot (C_S)^n \xrightarrow{n=1} (-r_S) = K \cdot C_S \quad \text{Equation 1A}$$

Figure 14A - Determination of the rate constant for the first order reaction approximation of the Heck coupling reaction. A rate constant of 0.0219 min^{-1} was obtained at 0.031% catalyst loading.

B: PEEK membrane rejection characteristics

Figure 15A - Polystyrenes rejection data (DMF solution of polystyrenes) for PEEK membrane at 80°C, 30 bar pressure and flux of ~2 L.m⁻².h⁻¹ (the conditions were chosen to simulate the continuous Heck reaction conditions).

C: Equations used to calculate rejection, catalyst TON, conversion, salt and catalyst concentrations

$$R_i(\%) = \left(1 - \frac{C_{perm,i}}{C_{ret,i}}\right) \cdot 100\% \quad \text{Equation 2A}$$

$$V_{CSTR} \frac{dC_{CSTR,S}}{dt} = C_{in,S} \cdot Q_{in} - Q_{out} \cdot (1 - R_s) \cdot C_{CSTR,S} - V_{CSTR} \cdot K \cdot C_{CSTR,S} \quad \text{Equation 3A}$$

$$V_{CSTR} \frac{dC_{CSTR,P}}{dt} = C_{in,P} \cdot Q_{in} - Q_{out} \cdot (1 - R_p) \cdot C_{CSTR,P} + V_{CSTR} \cdot K \cdot C_{CSTR,S} \quad \text{Equation 4A}$$

$$x_{CSTR} = \frac{C_{CSTR,P}}{C_{CSTR,S} + C_{CSTR,P}} \quad \text{Equation 5A}$$

$$V_{CSTR} \frac{dC_{CSTR,i}}{dt} = C_{in,i} \cdot Q_{in} - Q_{out}(1 - R_i)C_{CSTR,i}$$

Equation 6A

$$t_r = \frac{V}{Q}$$

Equation 7A

$$x_{PFR} = 1 - e^{-k \cdot t_{rPFR}}$$

Equation 8A

$$x_{CSTR} = \frac{x_{PFR} + k \cdot t_{rCSTR}}{1 + k \cdot t_{rCSTR}}$$

Equation 9A

$$V_{PFR} = L \cdot \frac{\pi D^2}{4}$$

Equation 10A

$$v = \frac{Q}{A}$$

Equation 11A

$$Re = \frac{\rho v D}{\mu}$$

Equation 12A

$$TON = \frac{\text{total moles of product synthesised}}{\text{total moles of catalyst added through the run}}$$

Equation 13A

List of symbols

A_s	Cross sectional area (cm ² or m ²)
C	Concentration at T_{ref} and P_{ref} (mol.L ⁻¹)
D	Diameter (cm)
K	pre-exponential factor/kinetic rate constant (min ⁻¹)
L	Length (cm)
$\dot{m}$	Molar flow rate (mol.min ⁻¹)
n	reaction order, dimensionless
p	Pressure (bar)
Q	Volumetric flow rate (mL.min ⁻¹)
R	Rejection, dimensionless (note that in a continuous filtration mode rejection and retention are equivalent terms)
r	Reaction rate (mol.L ⁻¹ .min ⁻¹)
Re	Reynolds number
Salt	Triethylamine hydroiodide
T	Temperature (°C)
t_r	Residence time (min)
V	Reactor volume (mL)
v	Velocity of the fluid (cm.min ⁻¹ or m.s ⁻¹)
X	Conversion, dimensionless
μ	Viscosity (Pa.s)
ρ	Density (kg.m ⁻³)

Subscripts

cat.	Catalyst
CSTR	Continuous Stirred Tank Reactor
gen	Generated in the CSTR
<i>i</i>	Component <i>i</i> of the solution
IB	Iodobenzene
in	System inlet stream
out	CSTR outlet stream
P	Product
perm	Permeate
PFR	Plug flow reactor
ref.	reference
ret	Retentate
S	Substrate

Figure Captions

Figure 1 – Scheme of Heck coupling reaction to form E-methyl cinnamate (3).

Figure 2 - Scheme of the single-reactor system (top). Scheme of the two reactors in series system (bottom). Legend: A - Feed solution flask; B – HPLC pump; C – m-CSTR with PEEK membrane (stirred membrane cell); D – Permeate collector flask; E – Heating/stirring plate; F – PFR; G – PFR outlet sampling valve. 0 – PFR inlet stream; 1 –m-CSTR inlet stream; 2 – m-CSTR outlet stream/ permeate; 3 – Nitrogen supply.

Figure 3 – Stirred tank reactor/membrane separator (m-CSTR) layout. Legend: 1 - Inlet/outlet ports; 2 - Feed/retentate chamber; 3 – Inner o-ring; 4 – Membrane; 5 - Sintered plate; 6 - Outer o-ring; 7 - Cover.

Figure 4 – Conversion over time of the Heck coupling reaction at 110 °C and at 80 °C with and without catalyst pre-activation. The reaction was performed as batch in a reaction carousel.

Figure 5 - Effect of the catalyst concentration on the Heck coupling reaction performed in batch on the reaction carousel expressed as conversion values as a function of time. For each catalyst concentration the TON is presented in brackets.

Figure 6 - Theoretical and experimental results of conversion for the continuous Heck coupling reaction in the single m-CSTR system operated close to the limiting catalyst concentration ($2 \times 10^{-4} \text{ mol.L}^{-1}$). Experimental points are obtained for the permeate stream. The conversion was estimated using initial conditions from the batch start-up of the reactor - 60 mL starting solution, with 100% conversion - 0.6 mol.L^{-1} initial concentration of product and $3.2 \times 10^{-4} \text{ mol.L}^{-1} \text{ Pd(OAc)}_2$. The continuous run was simulated using a feed stream containing 0.6 mol.L^{-1} iodobenzene and $2 \times 10^{-5} \text{ mol.L}^{-1} \text{ Pd}$ catalyst at 0.2 mL.min^{-1} flow rate (residence time of 300 minutes) for the first 75 hours and 0.1 mL.min^{-1} flow rate (600 minutes residence time) thereafter. 90% rejection was assumed for the Pd catalyst and 0% for the product and substrate.

Figure 7 - Theoretical and experimental results of Pd concentration for the continuous Heck coupling reaction in the single m-CSTR system operated close to the limiting catalyst concentration. The estimation for the Pd concentrations was performed using initial conditions from the batch start-up of the reactor - 60 mL starting solution, with 100% conversion - 0.6 mol.L^{-1} initial concentration of product and $3.2 \times 10^{-4} \text{ mol.L}^{-1} \text{ Pd(OAc)}_2$. Note that since we were not sure how the membrane would perform in a continuous process and whether a constant rejection of 90% would be obtained we started the batch using slightly higher catalyst concentration than the estimated limiting equilibrium concentration ($3.2 \times 10^{-4} \text{ mol.L}^{-1}$ instead of $2.0 \times 10^{-4} \text{ mol.L}^{-1}$). The continuous run was simulated using a feed stream containing 0.6 mol.L^{-1} iodobenzene and $2 \times 10^{-5} \text{ mol.L}^{-1} \text{ Pd}$ catalyst at 0.2 mL.min^{-1} flow rate (residence time of 300 minutes) for the first 75 hours and 0.1 mL.min^{-1} flow rate (600 minutes residence time) thereafter. 90% rejection was assumed for the Pd catalyst and 0% for the product and substrate.

Figure 8 – Conversion values in the m-CSTR outlet stream/permeate (left axis) and pressure values (right axis) inside the m-CSTR as a function of time for the two-reactors in series system operated at 1.2 mol.L^{-1} iodobenzene concentration. The system was stopped after 7 hours and restarted after 22 hours.

Figure 9 - Salt concentration with time at two different iodobenzene concentrations in the feed solution – 0.6 mol.L^{-1} and 1.2 mol.L^{-1} . IB denotes 'Initial iodobenzene concentration'. The

estimation for $IB=0.6 \text{ mol.L}^{-1}$ was performed using a flow rate of 0.1 mL.min^{-1} and an initial salt concentration of 0.6 mol. L^{-1} , as expected after starting the experiment as batch; For the $IB=1.2 \text{ mol.L}^{-1}$ estimation, a flow rate of 0.2 mL.min^{-1} for 8 hours was used and 0.1 mL.min^{-1} for the rest of the run. For the last run, an initial salt concentration of 1.1 mol. L^{-1} was used (the steady state concentration at the end of the 0.6 mol. L^{-1} m-CSTR run) in order to simulate the actual experiments.

Figure 10 – Conversion values in the CSTR outlet stream (permeate) as a function of time for the two-reactors system operated at 0.6 mol.L^{-1} iodobenzene concentration for the experiments performed with and without membrane (left axis); Pd concentration in the outlet stream of the CSTR vs. time for the experiments performed with and without membrane (right axis). (Points marked with red circles denote sudden drops in the conversion of the CSTR outlet stream possibly due to by-pass streams coming directly from the PFR).

Figure 11 - Experimental results and theoretical calculated curves of Pd concentration for the continuous Heck coupling reaction in the two-reactors in series system operated at 0.6 mol.L^{-1} iodobenzene concentration. The system was started in continuous mode and was fed initially with 100 mL feed solution with $\sim 2 \times 10^{-4} \text{ mol.L}^{-1}$ Pd concentration (the actual measured $1.96 \times 10^{-4} \text{ mol.L}^{-1}$ Pd was used as initial condition) followed by feed solution with $\sim 2 \times 10^{-5} \text{ mol.L}^{-1}$ Pd concentration (all at 0.1 mL.min^{-1} flow rate).

Figure 12 - Conversion obtained for the PFR outlet and m-CSTR outlet/permeate at the same time points in the two-reactors in series system operated at 0.6 mol.L^{-1} iodobenzene concentration (left axis); Pd concentration at the PFR outlet (right axis). (Data for the experiment with membrane).

Figure 13 - Conversion obtained for the PFR outlet and CSTR outlet at the same time points in the two-reactors in series system operated at 0.6 mol.L^{-1} iodobenzene concentration (left axis); Pd concentration at the PFR outlet (right axis). (Data for the blank experiment).

Figure 14A - Determination of the rate constant for the first order reaction approximation of the Heck coupling reaction. A rate constant of 0.0219 min^{-1} was obtained at 0.031% catalyst loading.

Figure 15A - Polystyrenes rejection data (DMF solution of polystyrenes) for PEEK membrane at 80°C , 30 bar pressure and flux of $\sim 2 \text{ L.m}^{-2}.\text{h}^{-1}$ (the conditions were chosen to simulate the continuous Heck reaction conditions).