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Potential of homogeneous Pd catalyst separation by ceramic membranes. Application to down-stream and continuous Flow processes.

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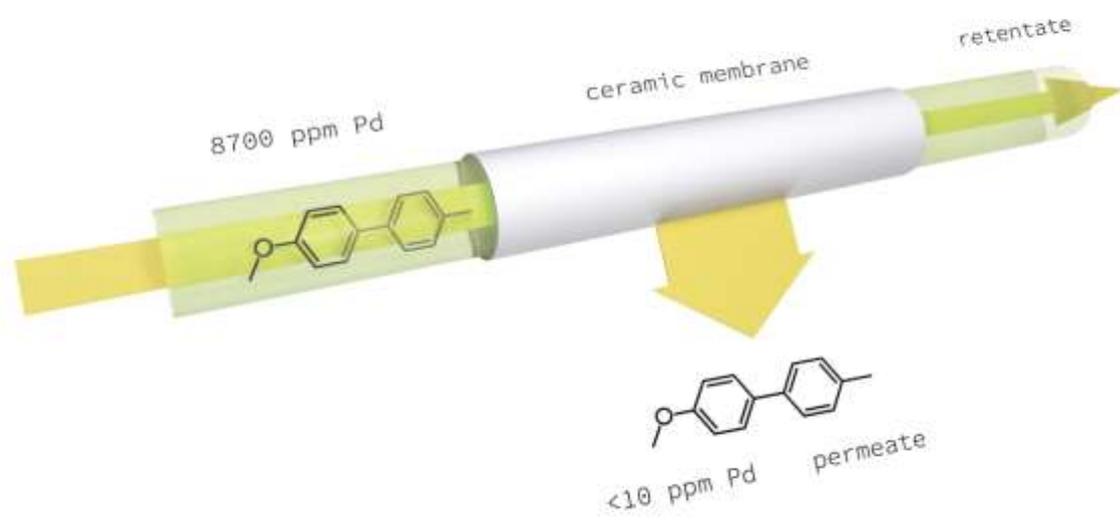
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TOC Graphic



Abstract

Successful chemical production of molecules whilst simultaneously reducing the environmental impact of the process relies not only on more efficient reactions but also on developments in reactor and separation technology. Recent decades have also witnessed a significant growth in industrial interest in solvent based separations using membranes stable to organic solvents. The incorporation of membranes into a chemical process can be via a simple downstream processing method or an integrated reaction membrane method. This paper deals with homogeneous organometallic catalysed reactions and probes the separation of a number of readily available Palladium complexes from reaction mixtures with highly stable ceramic membranes. A number of different processing methods namely on-line, at-line and off-line are compared and contrasted. High rejection of Palladium species and consequently very low Palladium contamination of reaction products with a single organic solvent nanofiltration (OSN) step has been demonstrated.

Keywords: Organic solvent nanofiltration, Suzuki cross coupling reaction, Catalyst separation, downstream processing, flow reactor processing.

Introduction

The use of platinum group metals as homogeneous catalysts in the fine chemical and pharmaceutical industries has gained importance during recent years, resulting in a number of examples in which these catalysts are used on large scale.^{1,2} Transition metal catalysed coupling have even become a reliable and indispensable tool for the synthesis of pharmaceuticals over the last two decades. In particular the role of Pd has become preponderant for several transition metal-catalysed reactions since Pd allows for reactions at low temperature, provide high turnover number and can promote the couplings of a wide array of substrates with high tolerance to many functional groups. In 2010, 22% of all reactions in pharma were Pd-catalyzed couplings.³ However, despite their high selectivity and efficiency their general implementation has been somewhat hampered by their relatively high cost and the sometimes rather problematic removal of metal species after reaction. A consequence of implementing transition-metal coupling is indeed the need to purge residual metals from product to meet the stringent specifications. This being especially the case for transformations used within the pharmaceutical industry (< 10 ppm in oral formulations and < 1 ppm in parenterally administered formulation).⁴

Because of this significant efforts have been, and are still being invested in methods to not only increase their efficiency but also to facilitate their removal from reaction mixtures. Consequently numerous methods have been developed to scavenge efficiently metals but also to allow recovery and recycling.⁵⁻⁷ Indeed, for large scale reactions recovery of metal species from reaction mixtures, even in a deactivated form can have a significant effect upon costs.

There are now many options to scavenge and/or remove metals beyond the crystallization and the distillation of products including amongst others activated charcoal, dicalite, Celite, Smopex, amine-modified silicas, trimercaptotriazine, aqueous sodium bisulfite, (nBu)₃P, BH₃.NMe₃.⁸ These options however, tend to be rather specific to certain compounds and/or processes and the combination of several metal removal techniques are often necessary to meet specifications. The removing of metals is often labour-intensive, tedious and delicate to optimize. A general method to purge residual metal from API and offering the opportunity to recover the metal is then highly desirable.

Membrane techniques⁹ are a sustainable^{10,11} way of effecting catalyst recovery. Such membrane procedures when performed in organic solvents with membranes stable in these solvents is often called Organic Solvent Nanofiltration (OSN).^{12,13} Separation and recovery of catalysts using OSN, is a technique that is non-thermal and does not require any phase transition, unlike some of the more traditional methods such as distillation. The fact that OSN can occur in the same phase and often the same temperature as a reaction makes it amenable to application to continuous flow systems.

Recent decades have witnessed a significant growth in interest in catalyst recycling via OSN techniques^{14 - 27} with some leading to applications on scale.²⁸ The already published work tends to be centred on the use of polymeric membranes and also makes use of size exclusion to separate the catalyst from other reaction components. Furthermore, only scant attention is paid to the reaction processing method being used and the ensuing consequences.

The metal removal/recycling via OSN is far from being trivial though since good membrane performance and stability associated with a high metal rejection is a delicate goal to achieve. Furthermore, the reported high rejection of metals are sometimes insufficient to meet pharma specifications and hence a hybrid approach has to be considered.²⁹ In other words a single OSN step to separate the molecule of interest from the metal impurities is not straightforward.

Ceramic membranes are chemically more resistant than polymeric membranes, but due to their hydrophilic nature tend to be somewhat less performant in apolar solvents. To counter this we have recently introduced membranes in which the surface has been modified with organic groups.^{30,31,32} This results in a membrane with amphiphilic character that is chemically stable and also resistant to swelling. Furthermore, due to lowering of the hydrophilicity of the membrane surface an improved performance in lower polarity solvents is observed. These membranes have also demonstrated that separation with them is not simply size exclusion and that molecules of very similar molecular mass and size can be successfully separated.³³ This being because of the solvent-solute-membrane interactions that play a key role in their mode of action.

In this work the potential of these surface modified ceramic membranes as a means of separating and if possible recycling catalysts will be explored. This has been done by studying their performance with N-heterocyclic carbene (NHC) complexes of Pd, a class of stable well defined pre-catalysts used in numerous cross coupling reactions.³⁴ In this case the NHC ligand on all complexes used was the same with differences being within the ancillary ligands on the metal. The dual intention of achieving designed for rejection profile and also the required catalyst stability under reaction conditions are key to this work. This catalyst stability was of greater importance if the complexes are to be used in a flow reaction. Four Pd-complexes were used, two commercial complexes from the Umicore cross coupling catalyst portfolio namely, CX31 and Peppsi-IPr and two non – commercial, though literature known, complexes **3** and **4** (Figure 1).

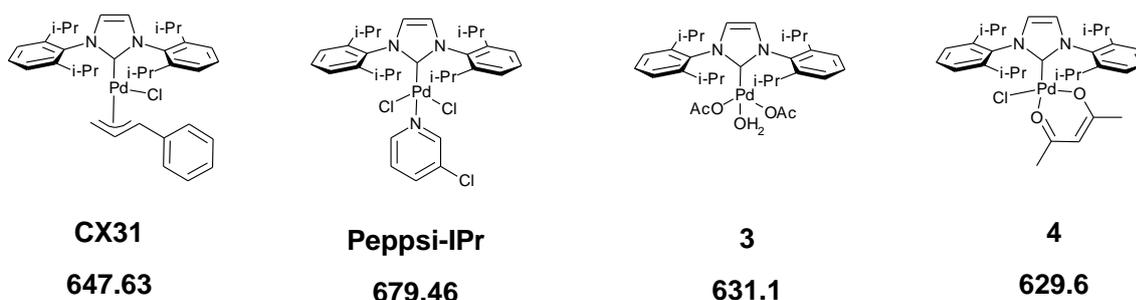


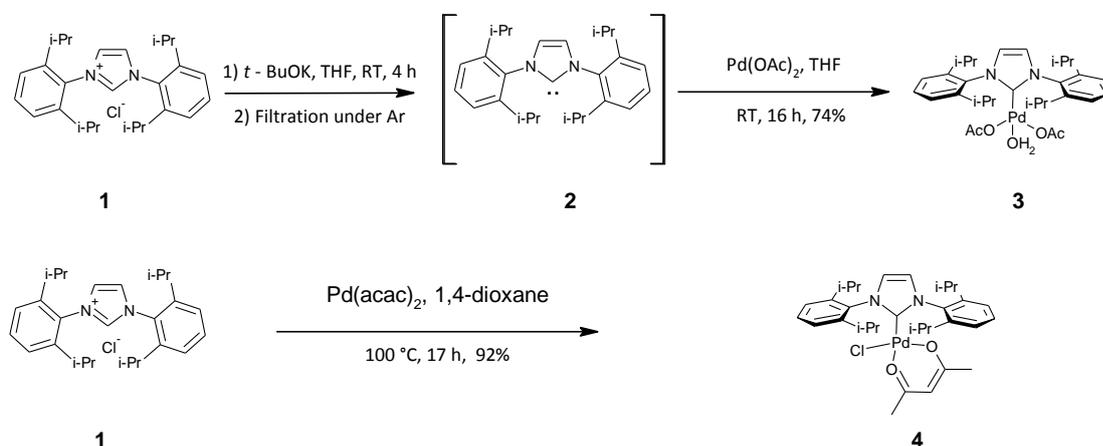
Figure 1: Pd-NHC complexes used in this study

Results and Discussion

Preparation of complexes 3 & 4

Synthesis of aqua complex **3** was via the stable imidazolium chloride **1**, forming carbene **2** *in-situ* by treatment with potassium *tert*-butoxide (Scheme 1). After filtration under argon, to remove KCl, the resulting solution was treated with palladium acetate and stirred at 22°C overnight to yield on isolation complex **3**. The presence of water in the complex was confirmed by ¹H-NMR at -40°C in CDCl₃ and are in accordance with the data reported by Sigman³⁵ and co-workers.

Complex **4** was synthesized by a method adapted from the literature.³⁶ Imidazolium chloride **1** was stirred with Pd(acac)₂ in 1,4-dioxane at 100°C, after isolation of complex **4** analytical data is in accordance with the reported literature data.³⁷



Scheme 1: Synthesis of complexes 3 & 4

Model reaction studied

The reaction used to investigate the membrane processing methods was the model Suzuki cross-coupling of 4-chlorotoluene **5** and (*p*-methoxyphenyl)boronic acid **6** to yield **7** (scheme 2).

Entry	Membrane	MWCO	Surface area (m ²)	Water permeance at 20 °C (Lm ⁻² h ⁻¹ bar ⁻¹)	EtOH permeance at 20 °C (Lm ⁻² h ⁻¹ bar ⁻¹)	i-PrOH permeance at 20 °C (Lm ⁻² h ⁻¹ bar ⁻¹)
1	0.9 nm TiO ₂	450 ^[a]	0.002	31	7.5	1
2	1.0 nm TiO ₂	750 ^[a]	0.002	41		
3	1.0 nm C ₅ TiO ₂	1500 ^[b]	0.002	16	9.5	1.1
4	1.0 nm C ₈ TiO ₂	1500 ^[b]	0.002	22	11.8	2.4
5	0.9 nm C ₈ H ₄ F ₁₃ – TiO ₂	/	0.004794	11	5.5	0.18

[a] MWCO = molecular weight cut-off (see reference 38)³⁸
[b] based on the rejection of polyethylene glycols in water

Separation of organometallic species within a reaction mixture can occur either post reaction, in a down-stream process, or in-line with the reaction in a flow system. For both processing methods important aspects are the rejection profile, of all reaction species, as well as the membrane flux. Membrane rejection is a function of the solute concentrations in the permeate C_p and retentate C_r and expressed as a percentage, equation (1).

$$R = \left(1 - \frac{C_p}{C_r}\right) * 100 \quad (1)$$

Flux is a measure of the flow rate per unit area per unit time and can be determined by measuring the permeate volume (V) per unit time (t) over a membrane of area (A) using equation (2). It is expressed as L m⁻² h⁻¹, or if normalized to the applied pressure it is expressed in terms of L m⁻² h⁻¹bar⁻¹ and called permeance.

$$J = \frac{V}{At} \quad (2)$$

Coupling of the reaction and a membrane separation can be achieved in three ways i.e.

- On-line: reagents are added into the filtration loop, charged with catalyst, within which there is concomitant reaction and OSN separation. This process is easily converted into a continuous process the reagents being constantly added to the filtration loop housing the catalyst.
- At-line: Catalyst and reagents are mixed and reacted in a flow system. The output of which is directly subjected to OSN separation. This configuration is thus a conventional continuous flow system coupled with a membrane separation process.
- Off-line: the reaction is carried out using standard laboratory techniques and equipment. On completion, the reaction mixture is subjected to OSN separation to remove organometallic species from reaction products in a downstream processing procedure.

All the membrane assisted methods require a large difference between catalyst rejection and product rejection. For this particular reaction a high catalyst rejection and a low product rejection was envisaged.

On-line processing

Three different membrane assisted flow reaction set-ups were used and compared. The first is shown schematically in figure 2. In this set-up a solution of the reagents and base was added slowly to a solution of the catalyst in the filtration loop, by a constant volume diafiltration process. A process in which an equivalent volume of solvent is added to the system as permeates through the membrane.³⁹ Thus, one diafiltration volume is the volume of solvent, washed through the membrane via a diafiltration process, that is equivalent in volume to the volume of the original feed solution. Addition of reagents to catalyst was opposite to that used in lab experiments to test the efficiency of the catalyst (table 1); where catalyst was added to a solution of reagents and base. Addition of reagents to catalyst was used in the flow system to allow the catalysts to be pushed towards their maximum turn-over number, simply by adding more reagent. Results with this set-up were however, disappointing (table 3, entries 1 - 6). With Pd complex **3** the principle observed reaction was the homocoupling of (*p*-methoxyphenyl)boronic acid **6**, suggesting that the catalyst was reacting preferentially with residual oxygen in the solvent to form a palladium peroxo complex as reported by Amatore, Jutand and co-workers.⁴⁰ The origin of this residual oxygen is possibly due to incomplete removal of oxygen during the degassing of the solvents or present within the nitrogen gas used to pressurize the system, other complexes proved to be less sensitive to oxygen than complex **3**. The other issue was the already observed low permeance (Table 2 & Table 3, entries 1-2) and the impossibility to switch the solvent to ethanol due to a poor reactivity in this solvent (*vide supra* table 1). Commercial complex CX-31 in the presence of the mild reducing agent potassium formate (*vide infra*) performed better in that **7** was formed, albeit in moderate yield of 57% (table 3, entry 3). Also during the reaction, which was carried out at 30°C, significant precipitation was observed. These solids tended to foul the membrane resulting in a substantial reduction in membrane permeance.

The catalyst rejection results were obtained by ICP-AES and so there was no differentiation between the different organopalladium species within the samples. With the C5 membrane a significant rejection above 90 % was obtained on raising the temperature to 50°C. For the CX 31 catalyst in ethanol, rejection was lower at 30°C than observed at 50°C, the formation of Pd clusters or nanoparticles at the higher temperature being a possible explanation of this effect.⁴¹ A further advantage of performing the filtration at 50°C was that all solids dissolved at 50°C thus countering the effects of the solids formed during the reaction provoking the observed reversible fouling.

However, performing the process at 50°C with palladium complex CX-31 has a negative influence on the catalyst performance (table 3, entry 4). In contrast to the batch reaction reported in table 1, under the relatively low concentration that was used with this on-line membrane assisted processing method complex **4** gave no reaction (table 3, entries 5 & 6). A combination of the low concentration of the reagents and greater stability of the pre-catalyst which in turn resulted in a concentration of active catalyst in the reactor being too low to allow reaction could explain this observation.

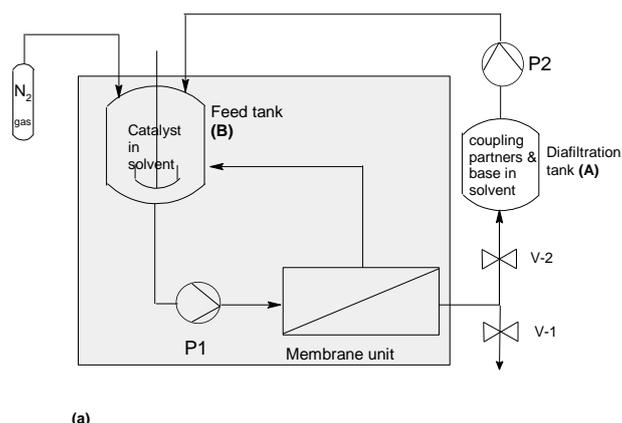


Figure 2: Schematic set up of the OSN system used with on-line processing. P1 is a circulation pump and P2 a diafiltration pump; V-1 & V-2 are valves allowing either return of permeate via the diafiltration tank or permeate removal. Everything in the shaded zone is under pressure during operation.

Table 3. Summary of OSN characteristics under on-line processing method using a 1 nm C ₅ TiO ₂ membrane								
Entry	Processing method	Catalyst	Reaction temp (°C)	Filtration temp (°C)	Solvent	Yield 7 (%)	Catalyst rejection (%)	Pemeance (Lm ⁻² h ⁻¹ bar ⁻¹)
1		3 ^[a]	30	30	isopropanol	0 ^[b]	97	0.01
2		3 ^[a]	50	50	isopropanol	0.5 ^[b]	97	0.05
3	On-line	CX-31 ^{[a][c]}	30	30	ethanol	57	56	9.2 – 1.2
4		CX-31 ^{[a][c]}	50	50	ethanol	21	≥99	2.5
5		4 ^[a]	50	50	ethanol	0	94	1.39
6		4 ^{[a][c]}	50	50	ethanol	0	92	1.2

[a] Catalyst in the filtration loop other reaction reagents added slowly to catalyst solution, reaction as in figure 4. Molar concentration with respect to reagent **5** for reaction and filtration was < 17mM
 [b] Main product is **8**
 [c] Potassium formate added to the reaction mixture

Laboratory simulation of the on-line membrane flow system as in figure 2 was carried out by adding a solution of the reaction reagents to a solution of Pd complex at 30°C, over 6 hours. In all cases yields were lower (table 4) than with the previous batch reactions (table 1). Addition of the mild reducing agent potassium formate⁴² resulted in some improvement, under these conditions the formation of a mixture of **7** and **8** in a 2:1 ratio with complex **3** was observed, albeit in low yield. Clearly, the combined factors of catalyst stability and residual oxygen was a serious issue in this case. Using Pd complex CX-31 under the same conditions was more performant; though again good results were only achieved when potassium formate was used (table 4). Without potassium formate besides **7** in 40% yield, dehalogenated and deboronated products were also formed.

Table 4. Performance of the complexes in Suzuki cross-coupling of 5 & 6 at 30 °C in EtOH when adding reagents slowly to catalyst				
Catalyst	Concentration (M) ^[b]	Yield 7 (%)	Yield 8 (%)	
CX31	0.1	40	/	
CX31 ^[a]	0.1	75	/	
3	0.1	/	traces	
3 ^[a]	0.1	20	10	

[a] Potassium formate added to the reaction mixture
[b] molar concentration with respect to reagent **5**

The results obtained in this on-line system enabled the identification of conditions in which the catalysts were efficiently retained during the membrane filtration process, a catalyst rejection of more than 99 % with the CX31 being observed. However this process showed that the balance between an efficient rejection of the catalyst and an acceptable conversion was difficult to reach mainly due to:

- 1- the physical properties (molecular mass, structure etc.) of the precatalysts used whose molecular weight are lower than the MWCO of the membrane used leading to a somewhat low rejection when used at 30 °C (table 3, line 3)
- 2- The limited catalyst stability at higher temperature leading to higher rejections but lowering the TON when used in such a continuous process. Though ultimate catalyst deactivation is inevitable, this deactivation rate needs to be sufficiently slow to allow addition of all the reaction reagents

It is also important to note that the physical size of the nanofiltration loop imposed a certain volume of solvent to allow efficient operation of the system, also the mixer/reaction tank size used imposed a certain solvent volume. On small laboratory scale reactions this has the effect of diluting the reaction, resulting in a negative effect on the catalyst performance.

At-line processing

The second membrane assisted flow system is shown schematically in figure 4, a solution of the catalyst and a solution of the reaction reagents were added simultaneously to a continuous-flow coil now becoming the site of reaction, the contents of which are also being added to the nanofiltration loop via constant volume diafiltration. This system couples a classical continuous-flow system to a membrane filtration process.

The effect of the concentration of the reaction was investigated and is shown in figure 3, clearly low reaction concentration at 30°C gives lower yield. These are conversion versus time plots for batch reactions in which catalyst was added to reagents in a single addition and thus, long term stability of the catalyst under reaction conditions was not here an issue.

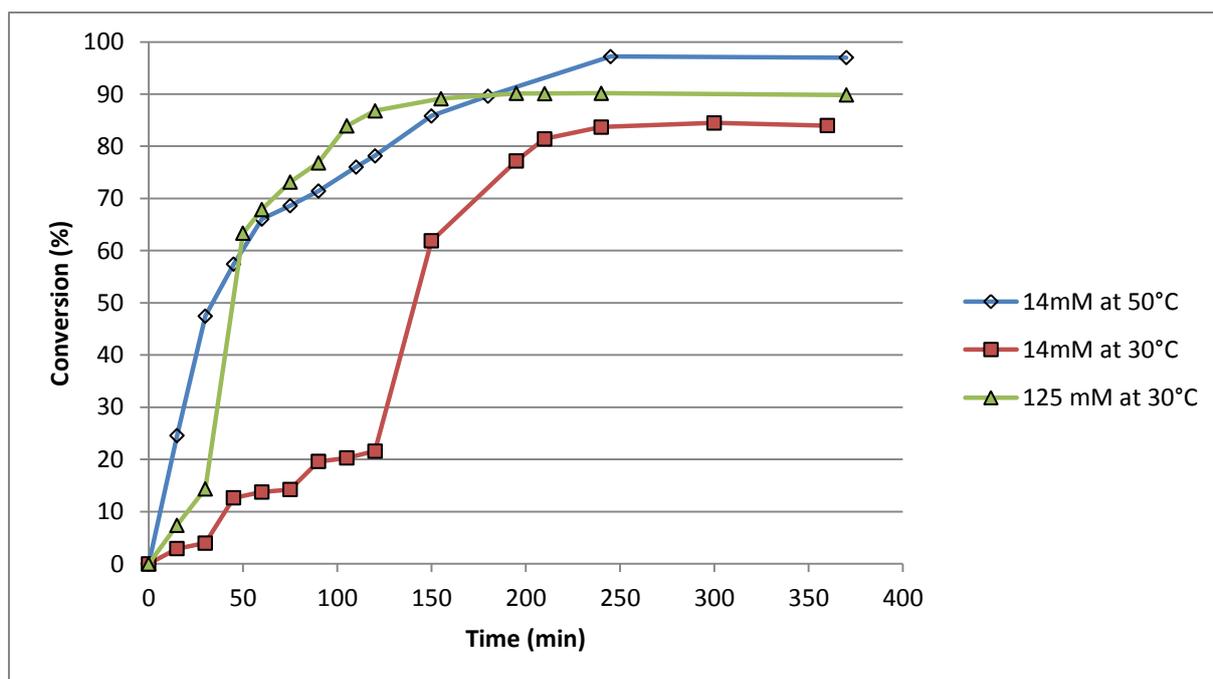


Figure 3: conversion of boronic acid 6 vs time plot (batch condition) for Suzuki coupling with Pd complex CX-31 at low concentration (14 mM) at 30°C and 50°C and at higher concentration (125 mM) at 30°C.

Beyond the known advantages of a continuous flow system,⁴³ this at-line processing allowed the use of lower quantities of solvent thus addressing the unfavorable effect of low reaction concentration. This process configuration offers also the possibility to adjust various parameters independently such as solvents, temperature and concentration in which the coupling reaction is performed and different conditions for the filtration. In other words the best reaction conditions could be easily coupled with the best filtration conditions while still being continuous.

The continuous flow process part was achieved by performing the reaction in tubing, fluorinated ethylene propylene (FEP) of 1.6 mm in diameter and between 2 m and 30 m in length (figure 4). Mixing occurred in a T-shaped adaptor shown in figure 4 and residence time was adjusted by changing the rate of the addition into the tubing and/or by the length of the tubing. During the reaction the outlet of the FEP tubing was being added directly into the NF loop which was under pressure and operating (shaded area figure 4). On completion of the reaction the contents of the tubing could be washed into the filtration loop with solvent by opening V-2. The filtration loop did still contain the required volume of solvent (400 ml of EtOH) to allow efficient operation thus, the reaction mixture was diluted for the filtration step.

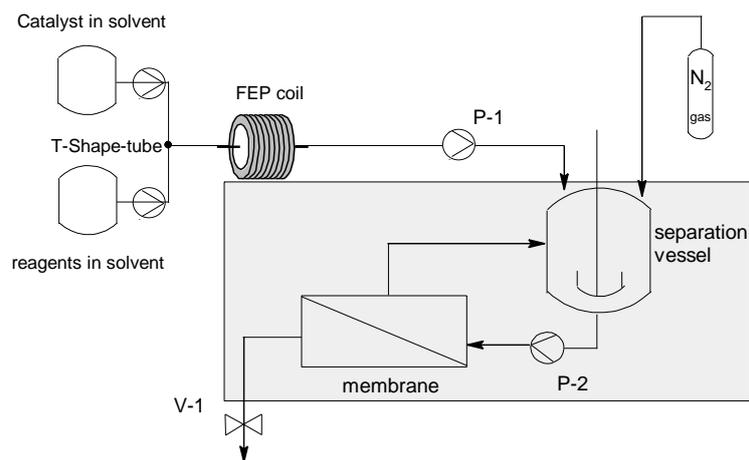


Figure 4: Schematic of the membrane assisted flow reactor used with concentrated reaction systems. Reaction occurs in the FEP cable of 1.6 mm internal diameter, mixing points are shown as black dot in the diagram. P-1 is a diafiltration pump, P-2 circulation pump.

Table 5 gives a summary of the results; in the most concentrated reaction (entry 1, table 5) significant precipitation lead to the tubing being blocked and significant loss of reaction product. Use of THF/ethanol/water⁴⁴ in v/v ratio of 3/2/2 (entry 2, table 5) still resulted in the blockage of the system by precipitation. Replacement of THF by DMF in the solvent mixture (entry 3, table 5) resulted in less precipitation of reaction products, but the Pd-complex tended to precipitate resulting in lower conversion. Reducing the concentration of the reaction in ethanol as solvent (entries 4 - 8, table 5) prevented precipitation and high conversion and yield from the reactions were observed, along with high catalyst rejection. The use of isopropanol with complex **3** gave a moderate conversion associated with a solubility problem leading to the clogging of the continuous flow reactor (entry 9, table 5). No reaction was observed with complex **4** (entry 10, table 5).

All the reactions were performed in the presence of potassium formate to limit the formation of the homocoupling product **8** and at 50 °C to prevent clogging problems (observed at 30 °C).

Table 5: Summary of reaction performances for the membrane assisted flow reactor (at-line OSN processing)								
Entry	Membrane	catalyst	Reaction solvents	Residence time (h)	Conversion 6 (%)	Yield 7 (%)	Catalyst rejection (%)	Permeance (L.m ⁻² .h ⁻¹ .bar ⁻¹)
1 ^{[a], [c]}	/	CX-31	ethanol	2.5h	90	16	/	/
2 ^{[b], [c]}	1 nm C ₅ TiO ₂	CX-31	THF/ethanol/water (3/2/2)	3.5h	74	16	≥99	1.02
3 ^{[b], [c]}	1 nm C ₅ TiO ₂	CX-31	DMF/ethanol/water (3/2/2)	4h	36.9	30.2	≥99	1.55
4 ^[b]	1 nm C ₈ TiO ₂	CX-31	ethanol	4h	96	71	≥99	6.5
5 ^[b]	1 nm TiO ₂	CX-31	ethanol	4h	96	71	98	16
6 ^[b]	0.9 nm C ₈ H ₄ F ₁₃ – TiO ₂	CX-31	ethanol	3h	95	64	≥99	4.0
7 ^[b]	1 nm C ₈ TiO ₂	Peppi-IPr	ethanol	2h	94	73	98	1.8
8 ^[b]	1 nm TiO ₂	Peppi-IPr	ethanol	2h	94	73	97	0.68
9 ^{[b], [c]}	1 nm C ₅ TiO ₂	3	IPA	2 h	61	/	≥99	/
10 ^[b]	1 nm C ₅ TiO ₂	4	ethanol	2 h	/	0	79	2.3

[a] molar concentration of the reaction solution with respect to reagent **5** = 250 mM; [b] molar concentration of the reaction solution with respect to reagent **5** = 125 mM; [c] Solubility problems of the reagents and/or the catalyst leading to lower yield and clogging problems of the continuous flow system.
For all experiments reaction & filtration were realized at 50°C and the filtration was performed with EtOH (400 ml) at 50 °C (concentration was then comprised between 16 to 25 mM)

It is interesting to note that both commercial catalyst CX31 and Peppi gave excellent conversion with satisfactory yield associated with a high catalyst rejection with both unmodified (entries 5 and 8) and modified ceramic membranes (entries 4, 6 and 7). The better results observed here are linked to a higher concentration of the reagents. The former on-line process had the effect of diluting the reaction, resulting in a negative effect on the catalyst performance. The unfavorable effects of low reaction concentration was here simply addressed by increasing the concentration of the reaction.

On completion of the reaction phase the separation vessel contained a mixture of reaction product and organometallic species, some of the product had already permeated through the membrane. Due to the high rejection of the organometallic species and low product rejection (< 35 % in the conditions used with all the ceramic membranes) a diafiltration process washes the product through the membrane into the permeate resulting in separation of the organometallic species from the reaction products.

Off-line processing

Off-line processing was carried out using the membrane set-up outlined in figure 5. Thus, 1 mol% of catalyst was used and the reaction carried out at a concentration of 500 mM (2L/mol), with respect to reagent **5**, then on completion of the reaction diluted to a concentration of 17 mM (60 L/mol) prior to OSN processing. This dilution of the reaction mixture was principally to avoid concentration polarization of the membrane, an effect in which a high concentration boundary layer can form at the membrane affecting flux and rejection, but also to ensure there was sufficient solvent volume to operate the filtration unit. Reaction products, unreacted starting material and reagents were washed

through the membrane during the filtration phase using fresh solvent under conditions of constant volume diafiltration.

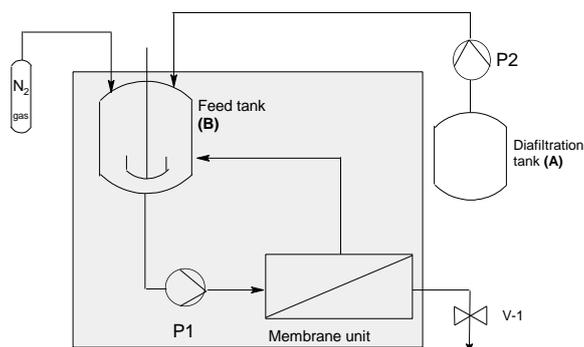


Figure 5: Schematic set up of the OSN system used with off-line processing; P-1 is a circulation pump, P-2 a diafiltration pump.

Under these reaction conditions the most performant catalysts were CX-31 and PEPSSI where yields of 90% were obtained. All the off-line separation experiments gave high catalyst rejection, table 6. The best separation was achieved using ethanol as solvent as this gives the combination of high catalyst rejection, low product rejection and reasonable membrane flux. Again filtrations were carried out at 50°C, the best conditions for this operation.

The efficiency of this separation can be demonstrated by calculating the % of the solute left in the retentate using equation (3), where % R_i is the percentage of solute i in the retentate, N is the number of diafiltration volumes and r_i is the rejection of solute i during the process.

$$\%R_i = 100 * e^{-N(1-r_i)} \quad (3)$$

This simulation is shown graphically in figure 6. Assuming 90% recovery of the reaction product in the permeate, in ethanol this requires 2 diafiltration volumes and 90% of the organometallic species remain in the retentate. Similar recovery of product in the permeate in isopropanol requires seven diafiltration volumes. In isopropanol the quantity of organometallic species leached into the permeate is lower, even after seven diafiltration volumes, but due to the far lower flux the processing time would be far longer.

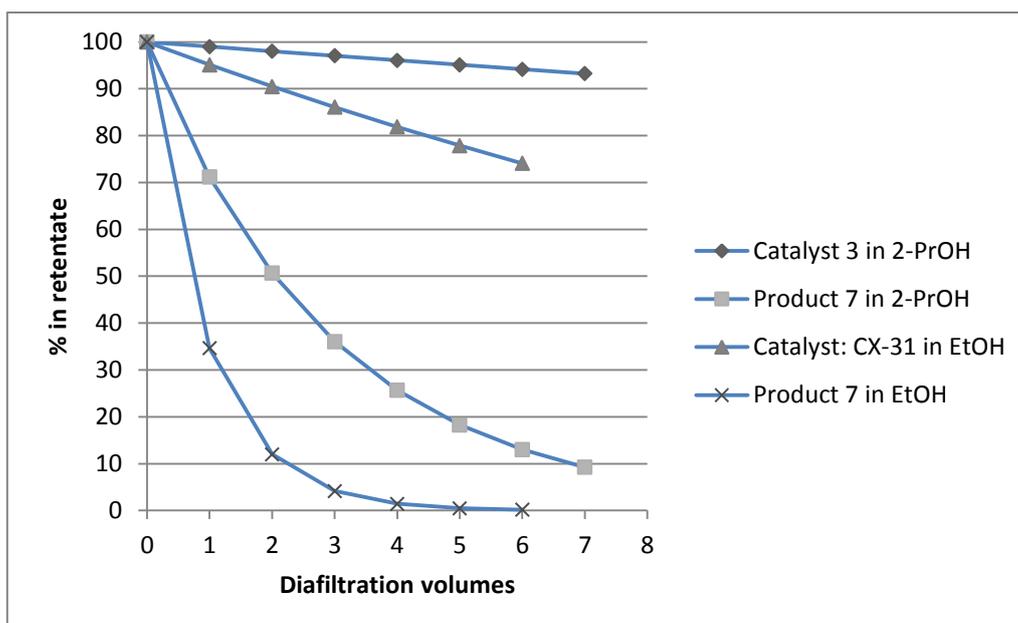


Figure 6: Diafiltration simulation for off-line reaction mixtures in isopropanol and ethanol.

The downstream processing or off-line processing showed as in the case of the at-line processing a very simple methodology based on a single filtration step to efficiently remove the residual palladium while maintaining a good conversion.

Table 6. Summary of OSN characteristics under the off-line processing method using a 1 nm C ₅ TiO ₂ membrane								
Entry	Membrane	Catalyst	Reaction temp (°C)	Filtration temp (°C)	Solvent	Yield 7 (%)	Catalyst rejection (%)	Permeance (L·m ⁻² ·h ⁻¹ ·bar ⁻¹)
1	1 nm C ₅ TiO ₂	3	30	50	isopropanol	68	≥99	0.02
2	1 nm C ₅ TiO ₂	CX-31	30	50	ethanol	90	95	0.9
2'	1 nm TiO ₂	CX-31	50	50	ethanol	92	≥99	7.2
3	1 nm C ₅ TiO ₂	Peepsi-IPr	30	50	ethanol	80	93	1.0
3'	0.9 nm C ₈ H ₄ F ₁₃ – TiO ₂	Peepsi-IPr	50	50	ethanol	89	≥99	3.0

[a] Molar concentration with respect to reagent **5** for reaction was 0.5 M, for the filtration was 17mM

The relative permeance stability of the modified TiO₂ membranes was also observed. The modified membrane had indeed the tendency to show relatively stable permeances demonstrating their anti-fouling ability, previously established in aqueous systems.⁴⁵. The 1 nm C₅ modified TiO₂ membrane had for this Suzuki coupling processes (7 reactions performed with the same membrane) an average permeance in EtOH at 30 °C of 1.7 L·m⁻²·h⁻¹·bar⁻¹ with an absolute deviation of 0.97 L·m⁻²·h⁻¹·bar⁻¹ and with values comprised between 0.88 and 2.00 L·m⁻²·h⁻¹·bar⁻¹. The same membrane had an average permeance (5 reactions performed) in EtOH at 50 °C of 1.9 L·m⁻²·h⁻¹·bar⁻¹ with an absolute deviation of 0.25 L·m⁻²·h⁻¹·bar⁻¹ with values comprised between 1.5 and 2.55 L·m⁻²·h⁻¹·bar⁻¹. Several membranes were

used several times for different experiments demonstrating the reusable character of ceramic membranes unlike polymeric membranes.

An important aspect in all these processes was the necessity to perform the filtration with the modified membrane at a pH below 11 to maintain its characteristics (permeances and antifouling properties) with a sufficient cross-flow velocity to limit reversible and irreversible fouling.

Pd Contamination of products

Though high rejection of the catalyst, or its degradation products, is possible with the membranes used, quantities of palladium contamination of the reaction product after the OSN processing are of fundamental importance for any industrial process within the pharmaceutical or fine chemical industries. As such to demonstrate this the reaction was performed on gram-scale (10 mmol) using the off-line and at-line processing using CX-31 and Pepsii as catalysts. On completion of the reaction the mixture was added to the filtration unit and subjected to a diafiltration process with 3 diafiltration volumes of fresh ethanol. This reaction process was carried out several times, each time with a different membrane and for each the palladium contamination of the reaction product assessed (ICP), the results of which are shown in table 7. Very low Pd contamination can be achieved with a single nanofiltration operation. Similar levels of Pd contamination with a membrane process have previously only been achieved with a hybrid membrane-scavenging system.⁴⁶

Entry	Initial Pd content	Processing	Membrane	Catalyst	Final Pd content
1	8700 ppm	at-line	1 nm C ₈ – TiO ₂	CX31	67 ppm
2	8700 ppm	at-line	0.9 nm C ₈ H ₄ F ₁₃ – TiO ₂	CX31	6.0 ppm
3	8700 ppm	Off-line	0.9 nm TiO ₂	CX31	7.0 ppm
4	8700 ppm	Off-line	0.9 nm C ₈ H ₄ F ₁₃ – TiO ₂	CX31	5.8 ppm
5	8700 ppm	Off-line	0.9 nm C ₈ H ₄ F ₁₃ – TiO ₂	PEPPSI	2.7 ppm

Conclusions

In conclusion a number of Pd-complexes with the same N-heterocyclic carbene backbone but differing ancillary ligands have been applied in three different membrane assisted processing methods. High rejection of the organometallic species and low rejection of the reaction product can be achieved with the ceramic membranes used in all processing methods thus, separation is feasible with minimal loss of reaction product. While off-line processing proved to be highly performant from a reaction as filtration point of view, with on-line or at-line processing the stability of the catalyst and reaction concentration played a central role in attaining high reaction yield. Furthermore, though the off-line processing may seem to be the most performant from the results presented here this does not take

into account the numerous other advantages of using flow reactors. The physical properties of the catalysts used associated with a limited catalyst stability when employed in such a continuous process being the main limiting factors for an efficient and scalable on-line processing. Further investigations on modified precatalysts and highly reactive and stable catalysts are underway.

These results also demonstrate the importance of the metal complexes ancillary ligands, an aspect that is easily overlooked.

With both the unmodified and the modified membranes high rejection of Pd species and consequently ultra-low Pd contamination of reaction products is possible. One advantage of this membrane assisted method to separate reaction products from organometallic compounds over more conventional use of adsorbents is losses of product on the adsorbents is minimized.

Experimental Section

General

The solvents used in this study were ethanol, isopropanol, THF and DMF were all technical grade purchased from VWR (Belgium) and used without prior purification. Water was reverse osmosis purified water. Commercially available membranes selected for this study were Inopor[®] ceramic membranes from Inopor (Veilsdorf, Germany). The C₅ or C₈ modified ceramic membranes were Inopor membranes modified in house to have n-alkyl chains on the membranes top layer. The membranes used in this work were asymmetric tubular TiO₂ membranes; length 120 mm, outer diameter 10 mm, inner diameter 7 mm and top layer thickness of about 50 nm. All membrane experiments were performed in a cross-flow filtration unit made in-house, pressurized with nitrogen gas. Filtration experiments were performed with crossflow velocity of 2 m/s and unless otherwise stated a transmembrane pressure of 10 bar.

4-Chlorotoluene, (4-methoxyphenyl)boronic acid and potassium *tert*-butoxide were purchased from Sigma- Aldrich (Belgium), Umicore cross coupling series catalysts, CX-31, and Peppi-IPr were donated by Umicore AG & Co. KG (Hanau, Germany). All membrane experiments were performed in an in house made cross-flow nanofiltration unit on lab scale.

Cross-coupling reactions were analysed on a waters UPLC with a UV/Vis PDA detector. A Waters Acquity BEH C18 column with dimensions of 2.1 x 50 mm, 1.7µm and a gradient of water, acetonitrile buffered with 0.1% formic acid. The column temperature was 40°C and the detector was used at a wavelength of 270 nm.

Analysis of Pd species was carried out using inductively coupled plasma atomic emission spectroscopy (ICP-AES). After evaporation of the solvent from the sample the residue was digested using *aqua regia* and diluted with deionized water to the required concentration range. The samples were then analysed for metal content.

^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a Bruker Avance 400 instrument. For ^1H NMR spectra, chemical shifts (δ) are given relative to external TMS (0.00 ppm). For ^{13}C NMR spectra, chemical shifts (δ) are given relative to CDCl_3 (77.0 ppm). Coupling constants (J) are reported in Hz. The following abbreviations are used: s, singlet, d, doublet, t, triplet, q, quartet, quint, quintuplet, sept, septuplet, m, multiplet, br, broad.

Melting points were measured with a Büchi B-545 melting point apparatus. Thin layer chromatography (TLC) was carried out on silica-gel plates (Merck F254). Spots were detected with UV light and revealed with KMnO_4 or ninhydrin solutions.

Synthesis of $\text{IPrPd}(\text{OAc})_2\text{OH}_2$ (**3**)

A 25 mL flask under an atmosphere of argon was charged with 1,3-bis(2,6-diisopropylphenyl)-1*H*-imidazol-3-ium chloride (**1**) (213 mg, 0.50 mmol, 1.00 eq.). Subsequently, 10 mL of THF (degassed with argon by purging the gas through the solvent for 15 min.) was added and the mixture degassed with argon for an additional 5 min. To this suspension, potassium *tert*-butoxide (112 mg, 1.00 mmol, 2.00 eq.) was added in a single portion. The beige-yellowish mixture was stirred for 4 h. It was then filtered, under argon, through glass filter with 0.5 g of Celite[®] and a pad of cotton directly into a 25 mL flask and washed portion wise with 5 mL of degassed THF. Palladium(II) acetate (135 mg, 0.60 mmol, 1.20 eq.) was added in one portion to give an orange-brown homogeneous mixture that was stirred o/n at room temperature. Solvent was evaporated under reduced pressure and the residue dissolved in 10 mL of DCM and washed with 10 mL of water. The aq. phase was extracted with DCM (2 x 5 mL; org. phase became colorless). After evaporation, the orange-brown solid was dissolved in 1 mL of DCM and 10 mL of pentane was added. The resulting precipitate was sonicated in ultrasound bath, filtered and rigorously washed with pentane. After drying under reduced pressure, an orange-brown solid was obtained (235 mg, 0.37 mmol, 74 % yield).

^1H NMR (CDCl_3 , 400 MHz): δ 7.61 – 7.55 (m, 2 H), 7.43 – 7.39 (m, 4 H), 7.10 (s, 2 H), 2.76 (sept, J = 6.8 Hz, 4 H), 1.74 (s, 6 H), 1.34 (d, J = 6.7 Hz, 12 H), 1.09 (d, J = 6.9 Hz, 12 H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 182.2 (C_{quat}), 151.0 (C_{quat}), 146.4 (C_{quat}), 134.7 (C_{quat}), 131.0 (CH), 125.5 (CH), 124.5 (CH), 28.5 (CH), 26.3 (CH_3), 24.7 (CH_3), 23.1 (CH_3).

Low temperature NMR to confirm presence of water in the complex.

^1H NMR (CDCl_3 , 400 MHz, $-40\text{ }^\circ\text{C}$): δ 8.5 (br, 2 H, H_2O), 7.67 – 7.60 (m, 2 H), 7.48 – 7.41 (m, 4 H), 7.17 (s, 2 H), 2.70 (sept, J = 6.5 Hz, 4 H), 1.80 (s, 6 H), 1.31 (d, J = 6.1 Hz, 12 H), 1.09 (d, J = 6.6 Hz, 12 H).

Synthesis of acac complex $\text{IPr-Pd}(\text{acac})\text{Cl}$ (**4**)

A 10 mL flask was charged with 1,3-bis(2,6-diisopropylphenyl)-1*H*-imidazol-3-ium chloride (**1**) (425 mg, 1.00 mmol, 1.00 eq.) and $\text{Pd}(\text{acac})_2$ (308 mg, 1.00 mmol, 1.00 eq.; purity: 99 %) under argon. Then, 1,4-dioxane (5 mL) was added and the mixture was heated to $100\text{ }^\circ\text{C}$ (preheated oil bath). A yellow suspension resulted that after several minutes turned orange and was stirred for 17 h giving a yellow-orange homogeneous mixture. The reaction progress was monitored by TLC (50 % acetone/heptanes). Upon cooling a precipitate formed. Celite[®] was added, the solvent was evaporated, and the residue was purified chromatographically on silica (20 g; step wise gradient; eluent: 5 - 10 % acetone/heptanes). After drying under reduced pressure a yellow solid (582 mg, 0.92 mmol, 92 % yield) was obtained.

Mp = 220 – 222 °C (dec.). R_f (50 % acetone/heptanes) = 0.56. ¹H NMR (CDCl₃, 400 MHz): δ 7.52 – 7.47 (m, 2 H), 7.36 – 7.32 (m, 4 H), 7.10 (s, 2 H), 5.11 (s, 1 H), 2.95 (sept, *J* = 6.7 Hz, 4 H), 1.83 (s, 3 H), 1.81 (s, 3 H), 1.33 (d, *J* = 6.6 Hz, 12 H), 1.09 (d, *J* = 6.9 Hz, 12 H). ¹³C NMR (CDCl₃, 100 MHz): δ 186.8 (C_{quat}), 183.6 (C_{quat}), 156.1 (C_{quat}), 146.7 (C_{quat}), 135.1 (C_{quat}), 130.5 (CH), 125.3 (CH), 124.2 (CH), 99.5 (CH), 28.6 (CH), 27.2 (CH₃), 27.1 (CH₃), 26.4 (CH₃), 23.1 (CH₃).

General cross coupling procedure batch process.

A flask equipped with a magnetic stirring bar was charged with a Pd catalyst (0.025 mmol, 0.5 mol %) , 4-methoxyphenylboronic acid (6 mmol, 1.2 eq) and potassium *tert*-butoxide (6.5 mmol, 1.3 eq). The flask was sealed with septum, and ethanol (4 mL,) was added *via* syringe. The mixture was degassed for 3 min, the flask was filled with argon and the reaction mixture was stirred in a preheated bath at 30° for 30 min. A degassed solution of 4-chlorotoluene (5 mmol, 1 eq) in ethanol (2 mL) was added, and the reaction mixture was stirred at 30°C for 4 hours. 100 µl samples of the reaction mixture were taken every 15 minutes and quenched by adding the sample to a vial containing 500 µl of an aqueous saturated ammonium chloride solution.

General cross coupling procedure with on-line membrane assisted processing

To the filtration apparatus fitted with a 120 mm single tube ceramic membrane was added 450 ml of a solution of Pd complex **CX-31** (65 mg, 0.1 mmol, 0.01 eq) in ethanol, previously degassed by bubbling nitrogen through for 10 minutes. The circulation pump was switched on and the mixture circulated at atmospheric pressure until the internal temperature was 30°C. A sample was taken for ICP-AES analysis. Connected to the filtration apparatus via a pump and set up to perform constant volume diafiltration was a 150 ml solution of 4-chlorotoluene (1.27 g, 10 mmol, 1.0 eq), (4-methoxyphenyl)boronic acid (1.67 g, 11 mmol, 1.1 eq), potassium formate (0.42 g, 5 mmol, 0.5 eq) and potassium *tert*-butoxide (1.45 g, 13 mmol, 1.3 eq) in ethanol (diafiltration solution) also degassed. The system brought under pressure (10 bar) the membrane flux was continually monitored. The reaction was allowed to proceed in such a manner for 5 hours with regular sampling of the filtration loop contents (retentate), diafiltration solution and the membrane permeate (permeate) for analysis. After this period of time the reagent solution addition was complete. Diafiltration with ethanol was continued for a further 16 hours with sampling for analysis.

General cross coupling procedure with at-line membrane assisted processing

A degassed solution of Pd complex **CX-31** (65 mg, 0.1 mmol, 0.01 eq.) in degassed ethanol (40 ml) was charged to a syringe pump. A second syringe pump was filled with a solution of 4-chlorotoluene (1.27 g, 10 mmol, 1.0 eq), (4-methoxyphenyl)boronic acid (1.67 g, 11 mmol, 1.1 eq), potassium formate (0.42 g, 5 mmol, 0.5 eq) and potassium *tert*-butoxide (1.45 g, 13 mmol, 1.3 eq) in degassed ethanol (40 ml). The two solutions were simultaneously added via a T-shaped mixer into FEP tubing of internal diameter 1.6 mm and 25 m in length, filled in advance with degassed ethanol and in a water bath warmed to 50°C. The two solutions were passed through the FEP tubing at a rate of 6.25 ml/h, the output of which was added directly into a nanofiltration apparatus fitted with a 120 mm single tube ceramic membrane. The nanofiltration apparatus was filled with 400 ml ethanol at 50°C and operated at 10 bar of nitrogen pressure. On completion of the addition of the catalyst and

reagent solutions into the FEP tubing a further 80 ml of degassed ethanol was passed through the tubing at a rate of 12 ml/h.

General cross coupling procedure with off-line membrane processing

A flask equipped with a magnetic stirring bar was charged with 4-chlorotoluene (1.27 g, 10 mmol, 1.0 eq), (4-methoxyphenyl)boronic acid (1.82 g, 12 mmol, 1.2 eq), potassium *tert*-butoxide (1.45 g, 13 mmol, 1.3 eq) and ethanol (20 ml). The mixture was degassed by bubbling nitrogen through for 5 minutes. Pd complex CX-31 (65 mg, 0.1 mmol, 0.01 eq) was added and the resulting mixture degassed a further 5 minutes before the flask was filled with argon. The reaction mixture was heated to 30°C and stirred for 16 hours. Ethanol (580 ml) was added to the reaction mixture and the resulting solution charged to the filtration apparatus fitted with a 120 mm single tube ceramic membrane, heated to 50°C and circulated at maximum 1 bar pressure for 2 hours. Pressure was increased to 10 bars and filtration system subjected to constant volume diafiltration with ethanol until 3 diafiltration volumes had been washed through the membrane. The total permeate volume and the retentate were both evaporated to dryness for palladium determination analysis.

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