

This item is the archived peer-reviewed author-version of:

Synthesis of Pd complexes containing tailed NHC ligands and their use in a semicontinuous membrane-assisted Suzuki cross-coupling process

Reference:

Ormerod Dominic, Dorbec Matthieu, Merkul Eugen, Kaval Nadya, Lefèvre Nicolas, Hostyn Steven, Eykens Lies, Lievens Jo, Sergejev Sergey, Maes Bert.-
Synthesis of Pd complexes containing tailed NHC ligands and their use in a semicontinuous membrane-assisted Suzuki cross-coupling process
Organic process research and development - ISSN 1083-6160 - 22:11(2018), p. 1509-1517
Full text (Publisher's DOI): <https://doi.org/10.1021/ACS.OPRD.8B00273>
To cite this reference: <https://hdl.handle.net/10067/1543510151162165141>

Synthesis of Pd complexes containing tailed NHC ligands and their use in a Semi-continuous membrane assisted Suzuki cross coupling process.

Dominic Ormerod,^{a,*} Matthieu Dorbec,^a Eugen Merkul,^b Nadya Kaval,^b Nicolas Lefèvre,^b Steven Hostyn,^b Lies Eykens,^a Jo Lievens,^a Sergey Sergeev,^b Bert U. W. Maes.^b

^a VITO (Flemish Institute for Technological Research), Separation and Conversion Technology, Boeretang 200, B-2400 Mol, Belgium.

^b University of Antwerp, Organic Synthesis, Department of Chemistry, Groenenborgerlaan 171, B-2020 Antwerp, Belgium

Corresponding author:

Dominic Ormerod

Vito NV

Boeretang 200

B-2400 Mol

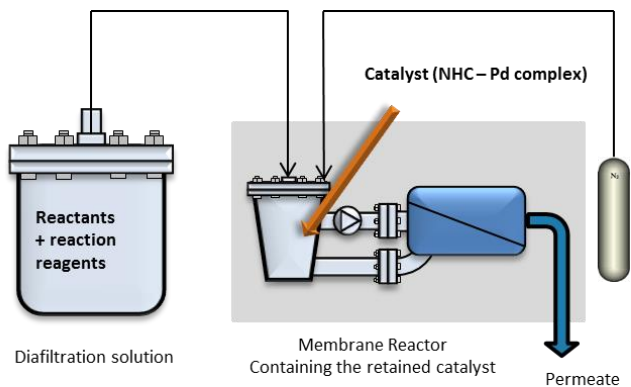
Belgium

Tel: +32 14 33 5650

Fax: +32 14 32 1186

E-mail: dominic.ormerod@vito.be

Table of contents graphic



In-line processing
((semi)-Continuous conversion-separation process)

Abstract

Homogeneous catalysis has proved to be a reliable method of preparing numerous molecular entities, but catalysts can be expensive and difficult to remove. Because of this, industry targets catalysts which are easily separated, recovered and feature increased turnover numbers. The ongoing shift from multi-purpose batch reactors towards continuous manufacturing in fine chemicals synthesis results in a new set of catalyst requirements. This paper reports the design and use of Pd complexes suitable for a semi-continuous Suzuki cross coupling reaction based on a membrane assisted reactor. These Pd complexes contain tailed NHC ligands allowing internal catalyst recovery by Organic Solvent Nanofiltration (OSN) with top layer modified ceramic membranes. These membranes give selective nanofiltration of catalyst based on a combination of size exclusion and affinity separation (solvent – solute – membrane interaction). The semi-continuous system developed led to significantly improved turnover numbers, simplified product isolation and consequently reduced mass intensity by simply adding more of the reactants and reagents to the reaction vessel.

Keywords: Pd catalysts, organic solvent nanofiltration, ceramic membranes, mass intensity, reduced catalyst load, semicontinuous processing.

Introduction

Recent decades have witnessed a significant growth in industrial interest in solvent based separations using membranes stable to organic solvents,¹⁻² due in part to the non-thermal, hence mild and energy efficient nature of the technique. Indeed, as up to 90% of chemical production processes contain a separation procedure and these separations account for 40 to 70% of the global capital and operational costs incurred by the process industry, there exists a clear need for the development of cost efficient separation techniques. Separations with membranes stable to organic solvents, often called Organic Solvent Nanofiltration (OSN), have also been shown to be sustainable.³ Recent membrane developments include ceramic membranes with modified top layers designed to effect separation not simply on size exclusion alone, but by additionally exploiting solvent – membrane – solute interactions.⁴⁻⁶ These new membranes open up new unique possibilities for homogenous catalysis. By designing the membrane surface and the catalyst ligand a desired rejection profile and reaction performance should be achievable. Moreover, the mild nature of membrane separations makes them particularly suited to integration within reaction systems in which reaction and separation occur simultaneously, a particularly salient example being catalyst reuse through efficient recovery.⁷⁻⁹

Homogeneous metal based catalysis is a technique that has achieved a high level of maturity, and is often an indispensable and reliable method of synthesizing molecular entities produced within several chemical industry sectors and especially in the fine chemicals industry.¹⁰ These catalysts efficient as they are, can be expensive and difficult to remove after reaction. Because of this, for industrial applications emphasis is placed upon increasing catalyst turnover numbers (TON) and catalyst recovery. Strategies to increase catalyst TON are often based either on increasing their stability or reaction rate (i.e. increase TOF), or developing methods to reuse the catalyst.¹¹ In a recent publication¹² we demonstrated that it was possible to efficiently separate NHC based palladium catalysts under different OSN processing methods namely, online, at-line and off-line (Figure S1, supporting information) in a model Suzuki reaction of 4-chlorotoluene with (*p*-methoxyphenyl)boronic acid. Though organometallic species were efficiently removed from reaction products under all three processing methods, online (semi-continuous) processing failed, with the palladium catalysts employed, as efficient catalyst separation was only achieved at the expense of reaction efficiency. In contrast good yield and rejection of the organometallics could be achieved with the at-line or off-line processing methods.

Because the catalyst load into the reaction is pre-determined with the off-line or at-line processing, increasing TON by employing an internal membrane catalyst recycling system is somewhat more complex than with the continuous process in which TON's can be increased by simply continuing the addition of reactants in to the reaction during the process. Therefore, determining the minimum catalyst load for a reaction can be achieved in a single reaction, especially if in-line monitoring is used. Something that usually requires several reactions with off-line or at-line processes.

Under the semi-continuous reaction conditions previously used without success, at 30°C moderate reaction yield was obtained with the NHC catalyst [1,3-Bis(2,6-diisopropylphenyl)imidazol-2-

ylidene]chloro[3-phenylallyl]palladium(II), produced and sold by Umicore as CX-31. Under these conditions rejection of the organometallics by the membrane was only 50%. By increasing the operating temperature of the reaction – separation system to 50°C, high membrane rejection of the organometallic species was obtained, thus accomplishing efficient separation but unfortunately no internal catalyst recovery as the reaction yield falls to a poor 21%. The reason for the catalyst deactivation was attributed to cluster formation, a known catalyst deactivation pathway.¹³ In order to improve the performance of the continuous flow – membrane reactor system, not only are improvements to the catalyst stability required but also harmonization of the catalyst performance and desired rejection, so that the requisite membrane performance can be achieved without deactivation of the catalyst.

The modified ceramic membranes have already demonstrated that where there is high interaction between the membrane surface and the solute in solution, rejection tends to be low and conversely low interaction between the membrane surface and the solute gives high rejection.⁵ At first glance the simplest method of varying the membrane – solvent – solute interactions, and thus achieving the desired rejection profile, is to change the membrane. However, changing the membrane does not affect the catalyst stability and therefore will not lead to a suitable internal recovery system. To simultaneously achieve the goals of high rejection and improved catalyst stability, changes need to be made to the catalyst itself. Thus, the requirements are a ligand that is susceptible to the introduction of functional groups to achieve high membrane rejection by exploiting the affinity aspects of the separation and not easily lost from the metal complex to ensure the required catalyst stability. One such ligand type that is thermally and oxidatively stable, forms thermodynamically strong M-L bonds and is susceptible to functionalization are the N-heterocyclic carbenes (NHC).¹⁴ Furthermore, it has also been demonstrated that substitution in the NHC ligand can inhibit cluster formation of the catalysts.¹⁵ The separation via OSN of palladium and ruthenium complexes containing molecular weight increased NHC ligands has already been reported.¹⁶⁻²⁰ However, in these reported cases the OSN separation was exclusively based upon size exclusion. Moreover, for the Pd catalysis there are a very limited number of examples reported of the use of membranes in continuous processing; namely a Heck reaction²¹⁻²² and a Tsuji – Trost reaction, both of which rely upon size exclusion to effect OSN separation.²³ The object of this work is, via judicious catalyst design, achieve internal recovery of the Pd catalyst in a semi-continuous Suzuki reaction by means of OSN with modified ceramic membranes allowing separation based on both size exclusion and affinity. A successful system will require the active catalyst to have improved thermal and hydrolytic stability, be preferably easily synthesized and to give the desired membrane rejection profile, this being the case not just for the organometallic species but for all the reaction components. The Suzuki reaction of 4-chlorotoluene with (*p*-methoxyphenyl)boronic acid was selected as a model reaction.

Experimental

General

Synthesis of Pd complexes is detailed within the supplementary information. The solvents used in this study were ethanol and isopropanol, both of 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, C₈ or C₈H₄F₁₃ 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 or 250 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, potassium formate and potassium *tert*-butoxide were purchased from Sigma- Aldrich (Belgium), Umicore cross coupling series catalysts, CX-21, was purchased from Sigma- Aldrich (Belgium). All membrane experiments were performed in an in house made cross-flow nanofiltration unit on lab scale.

Cross-coupling reactions were analyzed 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.

Thin layer chromatography (TLC) was carried out on silica-gel plates (Merck F254). Spots were detected with UV light and revealed with KMnO₄ or ninhydrin solutions.

General cross coupling procedure with on-line membrane assisted processing

To the filtration apparatus fitted with a 120 mm single tube C₈ functionalized ceramic membrane (2.05.10⁻³ m²) was added 700 ml of a solution of Pd complex **8-c** (69 mg, 0.05 mmol, 500 ppm) and potassium formate (3.15 g, 37.5 mmol) in ethanol, previously degassed by bubbling nitrogen through for 10 minutes. The circulation pump was switched on and the mixture circulated at 0.5 bar of nitrogen pressure until the internal temperature was 20°C. Connected to the filtration apparatus via a pump and set up to perform constant volume diafiltration was a 300 ml solution of 4-chlorotoluene (12.66 g, 100 mmol, 1.0 eq), (4-methoxyphenyl)boronic acid (16.7 g, 110 mmol, 1.1 eq), potassium formate (1.05 g, 12.5 mmol) and potassium *tert*-butoxide (14.59 g, 130 mmol, 1.3 eq) in ethanol (diafiltration solution) also degassed by bubbling nitrogen through for 10 minutes and kept under nitrogen atmosphere. The filtration loop system was brought under pressure (10 bar) and the diafiltration was started. It was realized in a semi-continuous mode (with valve V-1 closed and V-2 open, figure S1 supporting information) at 10 bars and a measured temperature in the filtration loop between 23 ±2°C, while maintaining constant feed level. The volume inside the filtration loop is kept constant via the controlled addition of the diafiltration solution containing the reagents and base added slowly to a solution of the catalyst in the filtration loop, by the diafiltration process. Addition of reagents to catalyst was used in the flow system to allow the catalysts to be pushed towards higher turn-over numbers, simply by adding more reagent. The permeate generated was added to the diafiltration solution maintained under N₂ atmosphere. The membrane flux was continually monitored. The reaction was allowed to proceed in such a manner for 44 hours (corresponding here to 1.3 diafiltration volume)* with regular sampling of the

filtration loop contents (retentate) and the membrane permeate (diafiltration solution which is here the permeate in this semi-continuous mode) for analysis. The content of the diafiltration tank A was then poured in a permeate tank. The diafilter tank A was then charged with fresh ethanol, the valve V-1 was opened and the valve V-2 was closed. The diafiltration was continued till having used more than 3 diafiltration volumes of EtOH (2.21 L which corresponds to 3.15 diafiltration volumes) the permeate being collected in the permeate tank.

The permeate (2.44 L) contained more than 90 % of the desired product with a palladium content of 12 ppm, metal content was analyzed by ICP-MS.

The initial flux was 13 L/h.bar.m² at 40 °C with a mixture EtOH/water 1/1 and 28 L/h.bar.m² at 21 °C with pure EtOH, went down to 0.8 L/h.bar.m² during the reaction and went up to 0.95 L/h.bar.m² during the constant diafiltration with fresh EtOH. The original flux of 13 L/h.bar.m² at 40 °C with a mixture EtOH/water 1/1 was recovered after a wash with a hot mixture of EtOH/Water.

The permeate was evaporated and dried in an oven at 100 °C for 48 h and the resulting powder (23.8 g) was further analyzed. A purity of 66.1 % w/w was found while having a clean chromatogram (Figure S2) the presence of salts explaining most certainly this value. The residual palladium content was found to be 20 mg/Kg of the crude material which corresponds to a slightly higher palladium contamination of 16 ppm than previously found. The yield of the reaction was 88%.

*This reaction time could be adapted by using a larger membrane surface.

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.

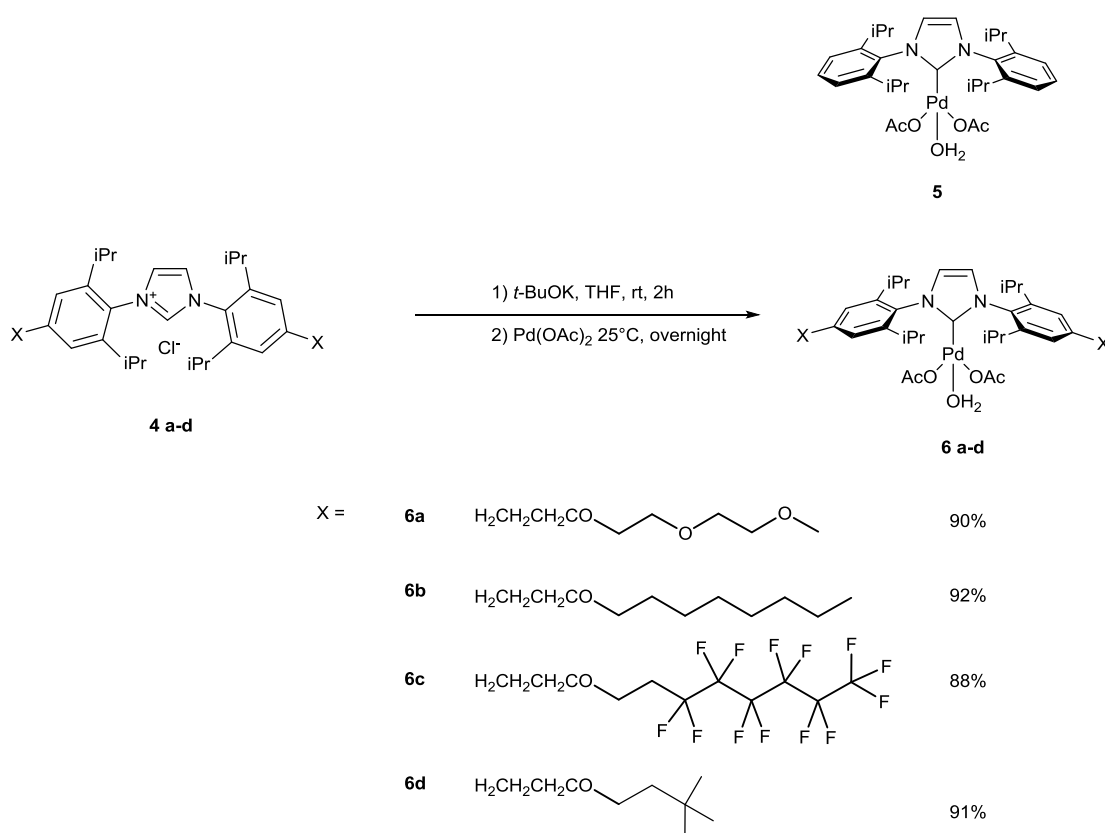
Results & Discussion

Tailed NHC ligands and Tailed Palladium NHC complex synthesis

The chosen NHC ligand that formed the foundation for these tailed versions was the 1,3-*bis*-2',6'-diisopropylphenylimidazol-2-ylidene (IPr). Substitution of the 4-position of the aryl rings was chosen as this would be remote from the catalytic center of the metal complex and therefore

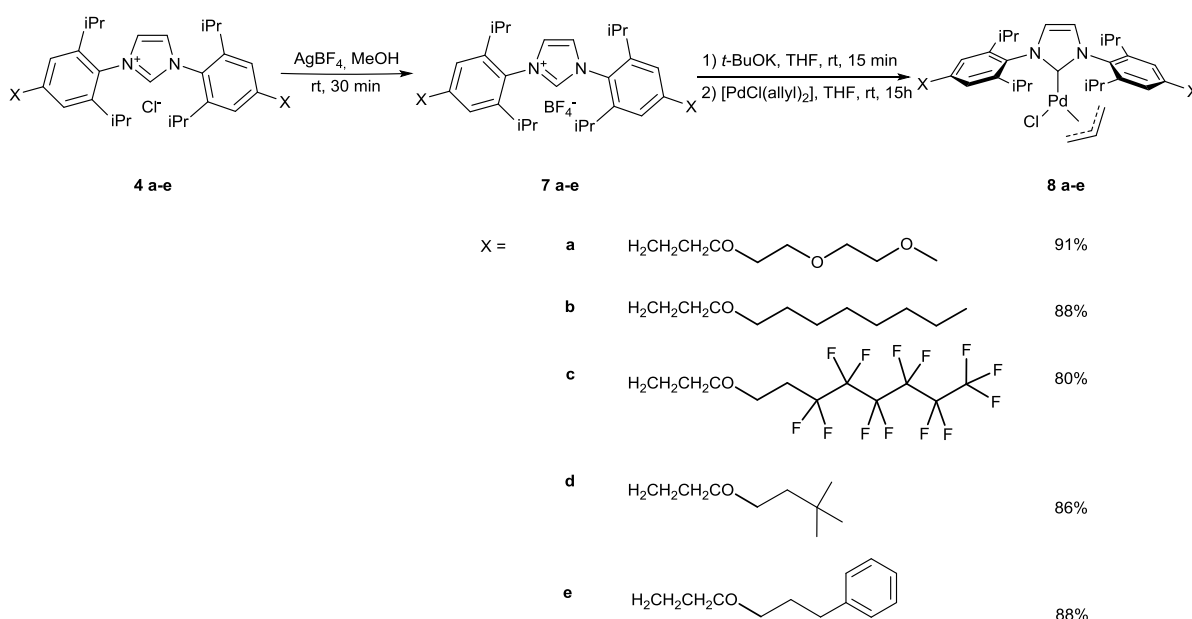
expected to minimally impact catalysis. Moreover substitution with highly bulky trityl groups in this position has been previously shown to be possible without loss of catalytic activity of the Pd complexes.¹⁵ The selected tails were intended to be hydrophobic, hydrophilic and fluorophilic to exploit the affinity OSN. A concise and general synthetic method for their introduction was therefore required. The synthetic strategy of choice was the diversity-oriented route shown in Scheme S1. Introduction of the tail was performed in a late stage of the synthesis using a Sonogashira cross-coupling reaction. A chromatography-free, five step procedure afforded the desired NHC precursors **4a-d** with overall yields in the range of 21-28%, while the nature of the tail only marginally affected the yield. Gram quantities of the tailed imidazolium chloride salts were easily produced with this strategy.

The first generation tailed Pd NHC complexes targeted were those resulting from the reaction of the imidazolium chlorides **4a-d** with Pd(OAc)₂ in the presence of base (Scheme 1).²⁴ This route however, proved to be troublesome and low yielding mainly due to the required generation and manipulation of the free carbene. Generation of the carbene *in-situ* and subsequent reaction with Pd(OAc)₂ did successfully lead to a chromatography free procedure to prepare the target Pd complexes, of structure **6** containing a coordinated water molecule. Complex **5**, synthesized using the method described elsewhere,¹² has previously been described in the literature as a catalyst for aerobic oxidations rather than cross couplings.²⁵



Scheme 1: Structure of Pd complex **5** and synthesis of tailed Pd NHC complexes **6 a-d** from imidazolium chloride salts **4 a-d**

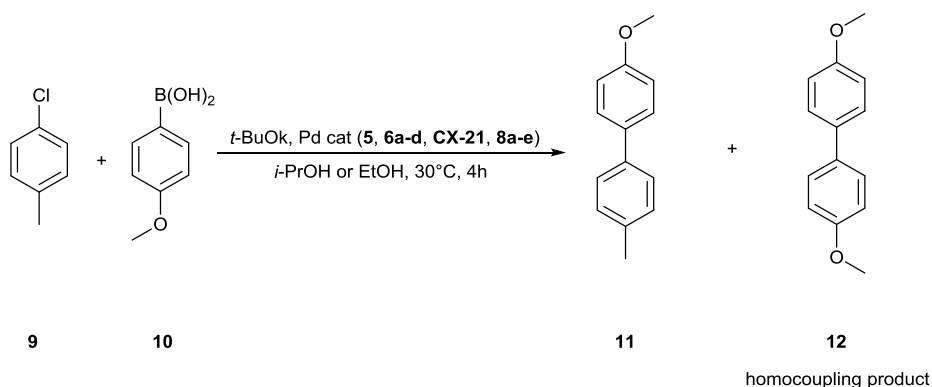
These, aqua complexes tended to have somewhat limited stability and would decompose both, on storage and in solution. Thus, a second generation of complexes were synthesized, the allyl palladium complexes **8a-e**, Scheme 2. The untailed version (CX-21) was introduced by Nolan²⁶ and is now commercially available (called CX-21) as part of the Umicore cross coupling portfolio. Synthesis of the imidazolium salts was improved by performing an ion exchange reaction on the chlorides **4a-e** to yield the corresponding tetrafluoroborate salts **7a-e**. These salts facilitated the purification of the imidazolium salts and further enabled isolation of NHC Pd allyl chloride complexes **8a-e** in high purity.



Scheme 2: Synthesis of tailed Pd allyl chloride complexes **8 a-e**, yields shown are for the final complex formation from the imidazolium tetrafluoroborate salts **7 a-e**.

Tailed Pd NHC complex performance in model Suzuki cross coupling reaction

All Pd NHC complexes of types **6** and **8** proved to be effective catalysts for this model cross coupling reaction, Table 1, when carried out under batch conditions; i.e. addition of catalyst to the reactants and reagent at 30°C in an alcohol as solvent. The nature of the tail appears to be having minimal effect on the yield of biphenyl **11** in a batch reaction. In a lab simulation of the semi-continuous processing, in which a solution of *t*-BuOK, **9** and **10** are added to a solution of the catalyst at 30°C, significant quantities of homocoupled product **12** are formed which were observed to a far lower extent in the batch process. This could be suppressed when a mild reducing agent such as potassium formate is added.^{12, 27}



*Scheme 3: The model reaction chosen to investigate the membrane process with tailed NHC Pd complexes **6** and **8** was the Suzuki cross coupling of 4-chlorotoluene **9** and (p-methoxyphenyl)boronic acid **10***

Table 1: Catalyst performance in Suzuki cross coupling of 9 & 10 ^a			
Entry	Pd complex	Solvent	Yield 11 (%)
1	5	<i>i</i> PrOH	83
2	5	EtOH	0
3	6a	<i>i</i> PrOH	86
4	6b	<i>i</i> PrOH	84
5	6c	<i>i</i> PrOH	85
6	6d	<i>i</i> PrOH	83
7	CX-21	EtOH	99
8	8a	EtOH	98
9	8b	EtOH	97
10	8c	EtOH	99
11	8d	EtOH	89
12	8e	EtOH	89

a) Reaction concentration 500 mM with respect to chlorotoluene **9**, 1 mol% catalyst, *t*-BuOK (1.3 eq), 30°C, 4 h, solvents degassed.

Membrane characteristics and requirements

Two parameters generally used to characterize a membrane are solute rejection and permeate flux. Rejection is a measure of a solutes ability to permeate through the membrane thus, if a solute has high rejection its concentration is low in the permeate. Membrane rejection (R) is a function of

the solute concentration in both the permeate (C_p) and retentate (C_r) and is expressed as a percentage, eq 1.

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

Membrane flux is a measure of the flow rate through the membrane and is determined by measuring the permeate volume (V) per unit time (t) over a membrane of area (A), expressed as $\text{Lm}^{-2}\text{h}^{-1}$, or if normalized to the applied pressure as $\text{Lm}^{-2}\text{h}^{-1}\text{bar}^{-1}$ and termed permeance. Equations 2 & 3.

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

$$L = \frac{J}{\Delta P} \quad (3)$$

The membranes used in this study are principally ceramic membranes; chosen in part due to their high chemical stability and resistance to swelling but also because the surface of the membrane can be modified, resulting in a range of surface polarities. This leads to separations that are not based on size exclusion alone but also the solvent-solute-membrane interactions (affinity aspects). By way of comparison a tight and chemically highly stable polymeric membrane has also been used in a number of experiments. Membrane characteristics are listed in table S1. Both contact angle and water permeance are a measure of the membrane surfaces hydrophilicity and consequently surface polarity.^{4, 28-29} The more hydrophilic a membrane is, the more the contact angle tends to zero and also its water flux will be higher. Accordingly, hydrophilic membranes are more efficient in highly polar solvent systems.

For the model cross coupling reaction used in this work the intention is to have a membrane that is capable of high rejection of the catalyst and rejection as low as possible for the reaction product. In an initial phase the rejection of the Pd aqua complexes **5** & **6 a-d** in isopropanol at room temperature was determined over a number of membranes (table 2). This was done in a unit of set up very similar to that in Figure 1, V-2 is closed and V-1 open and there is no addition (solvent or reactant and reagent solution) to the filtration unit under operation. A solution of the catalyst is added to feed tank (B), the system brought under pressure and permeate collected. This gives the rejection of the complexes alone and not under reaction conditions. The fact that the reference untailed Pd complex **5** in general gives a higher rejection than the tailed counterparts is likely to be due to its greater tendency to form clusters than membrane affinity aspects.

Table 2: Rejection and permeance data for aqua complexes 5 & 6a-d in isopropanol over 3 different membranes				
Entry	Membrane	Pd complex	Rejection (%)	Permeance ($\text{L m}^{-2}\text{h}^{-1}\text{bar}^{-1}$)
1	0.9nm TiO ₂	5	86	0.6
2		6a	58	1.0
3		6b	48	0.7
4		6c	36	0.4
5		6d	67	1.3
6	1.0 nm C ₅ TiO ₂	5	94	1.4
7		6a	84	1.3
8		6b	78	1.0
9		6c	95	0.45
10		6d	92	1.5
11	Duramem-200	5	98	0.12
12		6a	97	0.14
13		6b	97	0.14
14		6c	≥99	0.14
15		6d	96	0.12
a) Trans membrane pressure ceramic membranes 10 bar, polymeric membranes 20 bar. Cross flow velocity 2 m/s, temperature rt.				

The switch from the aqua complexes to the palladium allyl chloride complexes **8** was principally due to the instability of the aqua complexes observed upon storage and the fact that the Pd allyl chloride complexes allowed the use of ethanol as solvent (table 1). Moreover, ethanol is less viscous than isopropanol and therefore also gives better membrane permeance than isopropanol. The rejection and permeance data observed with complexes **5** and **6a-d** indicated the type of membranes that would be most suited for use under reaction conditions thus, rejection measurements with the palladium allyl chloride complexes **8a-e** were carried out directly in the reaction mixture.

On-line semi-continuous OSN processing in cross-coupling reactions

As we earlier reported efficient removal of untailed commercial NHC Pd catalysts and good reaction yield in the Suzuki reaction of **9** and **10** with either down-stream membrane processing (off-line) or in a system in which a flow reactor is attached to an OSN filtration unit (at-line)¹² is

feasible. However, these untailed catalysts give poor performance in the semi-continuous mode of operation (on-line), the latter was explored with tailed NHC Pd catalysts **8**. A solution of base (*t*-BuOH), potassium formate, **9** & **10** were added via a constant volume diafiltration to the OSN system containing a solution of the catalyst. Constant volume diafiltration is the addition into the OSN unit at the same rate that solution permeates through the membrane, thus the volume within the unit remains constant.³⁰ The object in these reactions is high rejection of the organometallic species and as low as possible rejection of the reaction product. Because the tailed Pd NHC complex is maintained under reaction conditions during the addition of reactant solution, catalyst stability becomes of greater importance than in a batch reaction in which the catalyst is added in a short time period at the start of the reaction. The membrane set – up used is shown in Figure 1. Reactions are carried out in a semi-continuous mode, thus to remove issues related to residence time of reactants and reagents with the catalyst, allowing complete conversion, total return of the permeate is used during the reaction phase by having V-1 closed and V-2 open. The solution that permeates the membrane contains reaction product as well as possibly starting materials. This permeate solution is returned to the reaction vessel (feed tank **B**) via the diafiltration tank **A**. Total return of permeate can be continued until it is deemed, via reaction monitoring, that the reaction is either complete or catalyst efficiency is no longer sufficient. Whereupon V-2 is closed and V-1 opened allowing the separation of reaction product from the organometallic species.

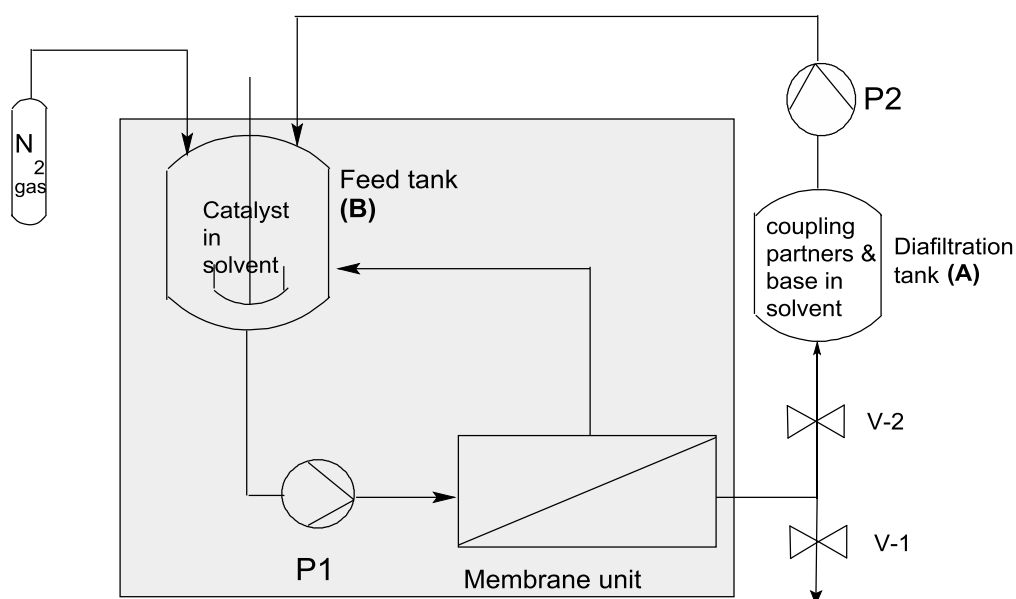


Figure 1: Schematic view of the OSN system used for the semi-continuous reactions, everything in the shaded zone is under pressure during operation. P1 is a circulation pump, P2 a diafiltration pump. V1 and V2 are valves allowing either return of permeate via the diafiltration tank or permeate removal. Trans membrane pressure: 10 bar, solvent: ethanol, membrane cross flow velocity: 2 m/s.

Table 3: Rejection over ceramic membranes of untailed & tailed Pd NHC catalysts used in the semi-continuous reactions							
entry	catalyst	Reaction temperature (°C)	Molecular mass (g/mol)	Yield (%)	Pd rejection (%)		
					0.9 nm TiO ₂	1.0 nm C ₈ TiO ₂	0.9 nm C ₈ H ₄ F ₁₃ TiO ₂
1	CX-21	23	571.5	63	0	/	20
2	8a	23	891.9	62	24	57	60
3	8b	23	912.1	62	54	89	65
4	8c	23	1379.9	75	32	≥99	67
5	8d	23	856.0	0	/	/	/
6	8e	23	924.1	80	/	87	/

Reaction scale: 10 mmol with respect to chlorotoluene **9**, 1 mol % catalyst, trans membrane pressure: 10 bar, solvent: ethanol, membrane cross flow velocity: 2 m/s.

All reactions in table 3 were carried out with a catalyst loading of 1 mol% i.e. a substrate to catalyst ratio of 100. Highest rejections were observed with the 1.0 nm C₈ TiO₂ membrane and the perfluoroalkyl tailed Pd NHC complex **8c**, being ≥ 99%. No reaction was observed with complex **8d**, the branched alkyl tail in this complex did appear to be unstable and decompose on standing. Though CX-21 gave reaction yields comparable to the other tailed catalysts its rejection at 23°C was low. At higher temperature untailed catalyst **CX-21** forms Pd⁰ clusters which gives a good rejection in membrane separation but then avoids catalyst reuse in a semi-continuous set-up. The obvious consequence of the low rejection of untailed catalyst CX-21 are ineffective internal separation and recovery of the catalytically active Pd complex. The reaction yields in table 3 are somewhat lower than those observed in the batch reactions listed in table 1. This in part at least is due to the higher concentration of the batch reactions as compared to the continuous membrane assisted reaction i.e. at higher concentration complete conversion is achieved in a shorter time period.

Origins of Catalyst rejection profile

Catalyst rejection over the membranes can be clarified by taking Spiegler – Kedem theory into consideration. A method of describing solute transport through a membrane that consists of two terms, the first related to diffusion i.e. solubility effects and the second related to convection, pore size and molecular volume. It has already been shown that further solution of this equation can give solute rejection and that this rejection is a function of the reflection coefficient (σ), which is dependent on the ratio of the solute size and the membrane pore size, and the ratio of solvent and solute permeabilities (J/P_{diff}).^{6, 31} If the J/P_{diff} ratio is large (≥ 10), solute rejection approaches a limiting value equal to the reflection coefficient and thus, solute transport is dominated by convection and is due to size exclusion. If J/P_{diff} is low then diffusion dominates the solute transport and rejection is lower than the reflection coefficient (σ). Calculation of P_{diff} and J/P_{diff} for catalysts **8a**, **8b** and **8c** in the same manner as previously reported³¹ shows clear differences in J/P_{diff} between the membranes (Table 4). Indeed, the rejection profile of catalysts **8b** and **8c** follow size exclusion with the 1.0 nm C₈ TiO₂ membrane as would be expected from the J/P_{diff} ratio. In contrast

the rejection of the catalysts over the tighter 0.9 nm C₈H₄F₁₃ TiO₂, that might be expected to give higher rejection than that of a membrane with pore size of 1.0 nm, give the best illustration that solute transport is diffusion controlled because, not only do they give lower rejection than the 1.0 nm membrane but also there is little difference between the rejection of the three catalysts. With the unmodified membrane again, diffusion is the controlling factor in the observed catalyst rejection.

Table 4: P_{diff} & J/P_{diff} results for catalysts **8a**, **8b** & **8c** in ethanol over numerous membranes

entry	Catalyst	membrane	Temp (°C)	J (Lm ⁻² h ⁻¹)	P _{diff} (Lm ⁻² h ⁻¹)	J/P _{diff}	Rejection (%)
1		0.9 nm TiO ₂	23	3	5	0.3	24
2	8a	1.0 nm C ₈ TiO ₂	23	46	9	1.4	57
3		0.9 nm C ₈ H ₄ F ₁₃ TiO ₂	23	14	32	1.7	60
4		0.9 nm TiO ₂	23	1.4	1	1.4	54
5	8b	1.0 nm C ₈ TiO ₂	23	8	0.25	11.4	89
6		0.9 nm C ₈ H ₄ F ₁₃ TiO ₂	23	12	5	2.4	65
7		0.9 nm TiO ₂	23	2.9	5.75	0.5	32
8	8c	1.0 nm C ₈ TiO ₂	23	60	1	60	≥99
9		0.9 nm C ₈ H ₄ F ₁₃ TiO ₂	23	35	16	2.2	67

Process intensification with catalyst **8c**

As highest rejection was observed with complex **8c** this was the obvious choice of catalyst to use to demonstrate the increased catalyst efficiency. Experiments were carried out in which initially the substrate to catalyst ratio of 100 was increased to 400 (1 mol% to 0.25 mol% of catalyst) and then further to 2000 (0.05 mol % catalyst). The results are summarized in table 5. Practically this was carried out by simply increasing the concentration of the diafiltration solution in tank (**A**) (Figure 1), and keeping the absolute quantity of catalyst in the system the same. The observed reduction in membrane permeance as catalyst load is reduced is explained by the increase in concentration of the solutions. The reaction was again carried out in the semi-continuous mode as above and allowed to run with total return of the permeate (i.e. V-2 open V-1 closed, figure 1) until a volume equivalent to at least one diafiltration volume³² had been added to feed tank (**B**) containing catalyst from the diafiltration tank (**A**). For the experiments with the substrate/catalyst ratio of 100 and 400 the total return of permeate was allowed to run for 24 hours and for the substrate/catalyst ratio of 2000 this was for 44 hours³³, during which time the volume of solution added to tank (**B**) was equivalent to two diafiltration volumes.

Once this reaction phase is complete V-2 was closed and V-1 opened. The contents of the diafiltration tank (**A**) was added to the unit feed tank (**B**) and then the reaction product washed

through the membrane into the permeate using three diafiltration volumes of ethanol. Between 90 and 95% of the reaction product is then found in the permeate phase.

The results in Table 5 show a clear and substantial improvement in mass intensity of the reaction.³⁴⁻³⁵ The large reduction in mass intensity observed is principally due to the fact that on increasing the scale of the reaction the solvent volume used to carry out the process remained the same as that used with a substrate to catalyst ratio of 100. With just 500 ppm loading of catalyst, 88% yield of **11** product is obtained containing only 16 ppm of Pd contamination without performing any post metal scavenging treatments. It should be noted that catalyst retention as noted in Table 5 represents the quantity of Pd recovered in the final retentate solution i.e. after washing the reaction product through the membrane after reaction.

Table 5: Comparison of membrane and reaction performance on reduction of load of the catalyst 8c in the Suzuki cross coupling of 9 & 10 .			
Substrate/catalyst ratio	100 ^b	400 ^c	2000 ^d
Pre-catalyst load (ppm)	10000	2500	500
Yield (%) ^a	75	86	88
Av. Process Permeance (Lm ⁻² h ⁻¹ bar ⁻¹)	6	2	0.8
Catalyst retention (%)	96	90	96
Mass intensity (reaction)	424	155	51
Mass intensity (reaction & product isolation)	/	355	167
^a Yield determined after evaporation of the permeate and HPLC purity analysis.			
^b Reaction scale: 10 mmol with respect to chlorotoluene 9 .			
^c Reaction scale: 20 mmol with respect to chlorotoluene 9 .			
^d Reaction scale: 100 mmol with respect to chlorotoluene 9 .			

Conclusions

Pd complexes containing a N-heterocyclic carbene backbone that have been modified with tails in the aryl rings of the imidazolidene structure have been designed and synthesized. The substituent in the Pd complex has a double role: a) to provide greater resistance to cluster formation than their untailed commercial counterparts and thus increase the catalytic productivity in semi-continuous reactions b) achieve high membrane rejection of the tailed Pd NHC complexes with top layer modified ceramic membranes based on both size exclusion and affinity to render them suitable for use in a membrane assisted process.

The tailed Pd NHC complexes synthesized proved to be efficient catalysts in a model Suzuki cross coupling reaction and unlike the commercial untailed counterparts high ($\geq 99\%$) membrane

rejection was achieved with modified ceramic membranes. Their successful use in a semi-continuous membrane assisted reactor was demonstrated allowing high yield, high TON values and low residual Pd in the reaction product. Moreover, significant improvement of Process mass intensity and high product recovery was achieved. A further advantage of the disclosed system is that no specialist reactors or adaption of existing reactors is necessary as a nanofiltration unit is a stand-alone commercially available unit that can be connected to existing reactors via standard connections. Further studies are underway to further investigate the scope and limitations of these tailed Pd NHC complexes.

Conflicts of Interest

There are no conflicts to declare

Acknowledgements

This study has been partially funded by the Flemish government agency for Innovation by Science and Technology (IWT) within the framework of the SBO project, FunMem4Affinity, grant number (IWT 110019) and the Hercules foundation (grant agreement AUHA/13005). The research leading to these results has also received funding from the Innovative Medicines Initiative (www.imi.europa.eu) Joint Undertaking under grant agreement no. 115360, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.

Supporting information

Supporting information figures, shemes and tables
Synthesis of Pd complexes **6a-d** and **8a-e**.
NMR spectra of synthesized compounds

References

1. Marchetti, P.; Solomon, M. F. J.; Szekely, G.; Livingston, A. G., Molecular Separation with Organic Solvent Nano filtration : A Critical Review. *Chem. Rev.* **2014**, *114*, 10735-10806.
2. Vandezande, P.; Gevers, L. E. M.; Vankelecom, I. F. J., Solvent resistant nanofiltration: separating on a molecular level. *Chemical Society reviews* **2008**, *37* (2), 365-405.
3. Szekely, G.; Jimenez-Solomon, M. F.; Marchetti, P.; Kim, J. F.; Livingston, A. G., Sustainability assessment of organic solvent nanofiltration: from fabrication to application. *Green Chem.* **2014**, *16* (10), 4440-4473.
4. Rezaei Hosseinabadi, S.; Wyns, K.; Meynen, V.; Carleer, R.; Adriaensens, P.; Buekenhoudt, A.; Van der Bruggen, B., Organic solvent nanofiltration with Grignard functionalised ceramic nanofiltration membranes. *J. Membr. Sci.* **2013**, *454*, 496-504.
5. Rezaei Hosseinabadi, S.; Wyns, K.; Buekenhoudt, A.; Van der Bruggen, B.; Ormerod, D., Performance of Grignard functionalized ceramic nanofiltration membranes. *Sep. Purif. Technol.* **2015**, *147*, 320-328.

6. Hosseinabadi, S. R.; Wyns, K.; Meynen, V.; Buekenhoudt, A.; Van der Bruggen, B., Solvent-membrane-solute interactions in organic solvent nanofiltration (OSN) for Grignard functionalised ceramic membranes: Explanation via Spiegler-Kedem theory. *J. Membr. Sci.* **2016**, *513*, 177-185.
7. Vural Gürsel, I.; Noel, T.; Wang, Q.; Hessel, V., Separation/Recycling Methods of Homogeneous Transition Metal Catalysts in Continuous Flow. *Green Chem.* **2015**, *17*, 2012-2026.
8. Priske, M.; Wiese, K.-D.; Drews, A.; Kraume, M.; Baumgarten, G., Reaction integrated separation of homogenous catalysts in the hydroformylation of higher olefins by means of organophilic nanofiltration. *Journal of Membrane Science* **2010**, *360* (1-2), 77-83.
9. Cseri, L.; Fodi, T.; Kupai, J.; Balogh, G. T.; Garforth, A.; Szekely, G., Membrane-assisted catalysis in organic media. *Adv. Mater. Lett.* **2017**, *8* (12), 1094-1124.
10. Magano, J.; Dunetz, J. R., Large-scale applications of transition metal-catalyzed couplings for the synthesis of pharmaceuticals. *Chemical reviews* **2011**, *111* (3), 2177-2250.
11. Hübner, S.; de Vries, J. G.; Farina, V., Why Does Industry Not Use Immobilized Transition Metal Complexes as Catalysts? *Advanced Synthesis & Catalysis* **2016**, *358* (1), 3-25.
12. Ormerod, D.; Lefevre, N.; Dorbec, M.; Eyskens, I.; Vloemans, P.; Duyssens, K.; Diez de la Torre, V.; Kaval, N.; Merkul, E.; Sergejev, S.; Maes, B. U. W., Potential of Homogeneous Pd Catalyst Separation by Ceramic Membranes. Application to Downstream and Continuous Flow Processes. *Org. Process Res. Dev.* **2016**, *20* (5), 911-920.
13. Crabtree, R. H., Deactivation in Homogeneous Transition Metal Catalysis : Causes , Avoidance , and Cure. *Chem. Rev.* **2014**, *115* (1), 127-150.
14. Fortman, G. C.; Nolan, S. P., N-Heterocyclic carbene (NHC) ligands and palladium in homogeneous cross-coupling catalysis: a perfect union. *Chemical Society reviews* **2011**, *40* (10), 5151-5169.
15. Dible, B. R.; Cowley, R. E.; Holland, P. L., Remote Substitution on N-Heterocyclic Carbenes Heightens the Catalytic Reactivity of Their Palladium Complexes. *Organometallics* **2011**, *30* (19), 5123-5132.
16. Schoeps, D.; Sashuk, V.; Ebert, K.; Plenio, H., Solvent-Resistant Nanofiltration of Enlarged (NHC) Pd (allyl) Cl Complexes for Cross-Coupling Reactions. *Organometallics* **2009**, *28* (13), 3922-3927.
17. Schoeps, D.; Buhr, K.; Dijkstra, M.; Ebert, K.; Plenio, H., Batchwise and continuous organophilic nanofiltration of Grubbs-type olefin metathesis catalysts. *Chem. - Eur. J.* **2009**, *15* (12), 2960-2965.
18. Kajetanowicz, A.; Czaban, J.; Krishnan, G. R.; Malińska, M.; Woźniak, K.; Siddique, H.; Peeva, L. G.; Livingston, A. G.; Grela, K., Batchwise and Continuous Nanofiltration of POSS-Tagged Grubbs-Hoveyda-Type Olefin Metathesis Catalysts. *ChemSusChem* **2013**, *6* (1), 182-92.
19. Rabiller-Baudry, M.; Nasser, G.; Renouard, T.; Delaunay, D.; Camus, M., Comparison of two nanofiltration membrane reactors for a model reaction of olefin metathesis achieved in toluene. *Sep. Purif. Technol.* **2013**, *116*, 46-60.
20. Nasser, G.; Renouard, T.; Shahane, S.; Fischmeister, C.; Bruneau, C.; Rabiller-Baudry, M., Interest of the Precatalyst Design for Olefin Metathesis Operating in a Discontinuous Nanofiltration Membrane Reactor. *ChemPlusChem* **2013**, *78* (7), 728-736.
21. Peeva, L.; Da Silva Bural, J.; Vartak, S.; Livingston, A. G., Experimental strategies for increasing the catalyst turnover number in a continuous Heck coupling reaction. *J. Catal.* **2013**, *306*, 190-201.
22. Peeva, L.; Da Silva Bural, J.; Heckenast, Z.; Brazy, F.; Cazenave, F.; Livingston, A., Continuous Consecutive Reactions with Inter-Reaction Solvent Exchange by Membrane Separation. *Angew Chem Int Ed Engl* **2016**, *55* (43), 13576-13579.
23. Ronde, N. J.; Totev, D.; Müller, C.; Lutz, M.; Spek, A. L.; Vogt, D., Molecular-Weight-Enlarged Multiple-Pincer Ligands: Synthesis and application in Palladium-Catalyzed Allylic Substitution Reactions. *ChemSusChem* **2009**, *2* (6), 558-574.

24. Singh, R.; Viciu, M. S.; Kramareva, N.; Navarro, O.; Nolan, S. P., Simple (imidazol-2-ylidene)-Pd-acetate complexes as effective precatalysts for sterically hindered Suzuki-Miyaura couplings. *Organic letters* **2005**, *7* (9), 1829-32.
25. Jensen, D. R.; Schultz, M. J.; Mueller, J. a.; Sigman, M. S., A well-defined complex for palladium-catalyzed aerobic oxidation of alcohols: design, synthesis, and mechanistic considerations. *Angew. Chem. Int. Ed.* **2003**, *42* (32), 3810-3813.
26. Nolan, S. P.; Navarro, O., Large-Scale One-Pot Synthesis of N-Heterocyclic Carbene-Pd(allyl)Cl Complexes. *Synthesis* **2006**, (2), 366-367.
27. Miller, W. D.; Fray, A. H.; Quatroche, J. T.; Sturgill, C. D., Suppression of a palladium-mediated homocoupling in a Suzuki cross-coupling reaction. Development of an impurity control strategy supporting synthesis of LY451395. *Org. Process Res. Dev* **2007**, *11* (3), 359-364.
28. Darvishmanesh, S.; Degrève, J.; Van der Bruggen, B., Performance of Solvent-Pre-treated Polyimide Nanofiltration Membranes for Separation of Dissolved Dyes from Toluene. *Industrial & Engineering Chemistry Research* **2010**, *49* (19), 9330-9338.
29. Darvishmanesh, S.; Degrève, J.; Van der Bruggen, B., Mechanisms of solute rejection in solvent resistant nanofiltration: the effect of solvent on solute rejection. *Physical chemistry chemical physics : PCCP* **2010**, *12*, 13333-13342.
30. Sereewatthanawut, I.; Lim, F. W.; Bhole, Y. S.; Ormerod, D.; Horvath, A.; Boam, A. T.; Livingston, A. G., Demonstration of Molecular Purification in Polar Aprotic Solvents by Organic Solvent Nanofiltration. *Organic Process Research & Development* **2010**, *14* (3), 600-611.
31. Ormerod, D.; Buekenhoudt, A.; Bongers, B.; Baramov, T.; Hassfeld, J., From Reaction Solvent to Crystallization Solvent, Membrane Assisted Reaction Workup and Interpretation of Membrane Performance Results by Application of Spiegler-Kedem Theory. *Organic Process Research & Development* **2017**, *21* (12), 2060-2067.
32. 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.
33. A batchwise experiment with the same catalyst load and concentration achieved maximum conversion after 20 hours.
34. Jimenez-Gonzalez, C.; Ponder, C. S.; Broxterman, Q. B.; Manley, J. B., Using the right green yardstick Why Process Mass Intensity is used in the Pharmaceutical Industry to drive more sustainable processes. *Org. Process Res. Dev.* **2011**, *15*, 912-912.
35. McElroy, C. R.; Constantinou, A.; Jones, L. C.; Summerton, L.; Clark, J., Towards a holistic approach to metrics for the 21st Century pharmaceutical industry. *Green Chem.* **2015**, *17*, 3111-3121.