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Synthesis of Pd Complexes Containing Tailed NHC Ligands and Their Use in a Semicontinuous Membrane-Assisted Suzuki Cross-Coupling Process

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Supporting Information

ABSTRACT: Homogeneous catalysis has proved to be a reliable method for preparing numerous molecular entities, but catalysts can be expensive and difficult to remove. Because of this, industry targets catalysts that are easily separated and recovered and feature increased turnover numbers. The ongoing shift from multipurpose batch reactors toward 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 semicontinuous Suzuki cross-coupling reaction based on a membrane-assisted reactor. These Pd complexes contain tailed N-heterocyclic carbene (NHC) ligands, allowing internal catalyst recovery by organic solvent nanofiltration with top-layer-modified ceramic membranes. These membranes give selective nanofiltration of the catalyst based on a combination of size exclusion and affinity separation (solvent–solute–membrane interactions). The semicontinuous 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 that are stable toward organic solvents,^{1,2} due in part to the nonthermal and 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 40–70% 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 toward 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 the basis of size exclusion alone but by additionally exploiting solvent–membrane–solute interactions.^{4–6} These new membranes open up new unique possibilities for homogeneous catalysis. By design of 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, as 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 (TONs) and catalyst recovery. Strategies to increase catalyst TONs are often based on either increasing their stability or reaction rate (i.e., increasing the turnover frequency (TOF)) or developing methods to reuse the catalyst.¹¹ In a recent publication,¹² we demonstrated that it is possible to efficiently separate N-heterocyclic carbene (NHC)-based palladium catalysts with different OSN processing methods, namely, on-line, at-line, and off-line (Figure S1 in the [Supporting Information](#)), in a model Suzuki reaction of 4-chlorotoluene with (*p*-methoxyphenyl)boronic acid. Though organometallic species were efficiently removed from reaction products using all three processing methods, on-line (semicontinuous) processing failed with the palladium catalysts employed, as efficient catalyst separation was achieved only at the expense of reaction efficiency. In contrast, good yield and rejection of the organometallics could be achieved with the at-line and off-line processing methods.

Because the catalyst loading in the reaction is predetermined with off-line or at-line processing, increasing the TON by employing an internal membrane catalyst recycling system is

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somewhat more complex than with a continuous process, in which the TON can be increased simply by continuing the addition of reactants to the reaction mixture during the process. Therefore, determining the minimum catalyst loading for a reaction can be achieved in a single reaction, especially if in-line monitoring is used, whereas this usually requires several reactions with off-line or at-line processes.

Under the semicontinuous reaction conditions previously used without success, at 30 °C a 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, the rejection of the organometallics by the membrane was only 50%. When the operating temperature of the reaction–separation system was increased 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 fell to a poor 21%. The catalyst deactivation was attributed to cluster formation, a known catalyst deactivation pathway.¹³ Thus, improving the performance of the continuous flow membrane reactor system requires not only improvements in the catalyst stability 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 a strong interaction between the membrane surface and the solute in solution, rejection tends to be low, and conversely, a weak 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 cannot 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 but is 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 NHCs.¹⁴ Furthermore, it has also been demonstrated that substitution in the NHC ligand can inhibit cluster formation by the catalysts.¹⁵ The separation of palladium and ruthenium complexes containing molecular-weight-increased NHC ligands via OSN has already been reported.^{16–20} However, in those reported cases the OSN separation was exclusively based upon size exclusion. Moreover, for Pd catalysis only a very limited number of examples of the use of membranes in continuous processing have been reported, namely, a Heck reaction^{21,22} and a Tsuji–Trost reaction, both of which rely upon size exclusion to effect OSN separation.²³ The object of this work was to achieve via judicious catalyst design the internal recovery of the Pd catalyst in a semicontinuous Suzuki reaction by means of OSN with modified ceramic membranes allowing separation based on both size exclusion and affinity. A successful system required the active catalyst to have improved thermal and hydrolytic stability, to 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 of the reaction components. The Suzuki reaction of 4-chlorotoluene with (*p*-methoxyphenyl)boronic acid was selected as a model reaction.

■ EXPERIMENTAL SECTION

General. The synthesis of the Pd complexes is detailed in the [Supporting Information](#). The solvents used in this study were ethanol and isopropanol, both of technical grade, which were purchased from VWR (Belgium) and used without prior purification. Water was purified by reverse osmosis. 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 membrane top layer. The membranes used in this work were asymmetric tubular TiO₂ membranes with a length of 120 or 250 mm, an outer diameter of 10 mm, an inner diameter of 7 mm, and a top layer thickness of about 50 nm. All of the membrane experiments were performed at lab scale in a cross-flow filtration unit made in-house and pressurized with nitrogen gas. Filtration experiments were performed with a cross-flow velocity of 2 m/s and unless otherwise stated a transmembrane pressure of 10 bar.

4-Chlorotoluene, (4-methoxyphenyl)boronic acid, potassium formate, potassium *tert*-butoxide, and Umicore CX-21 cross-coupling series catalysts were purchased from Sigma-Aldrich (Belgium).

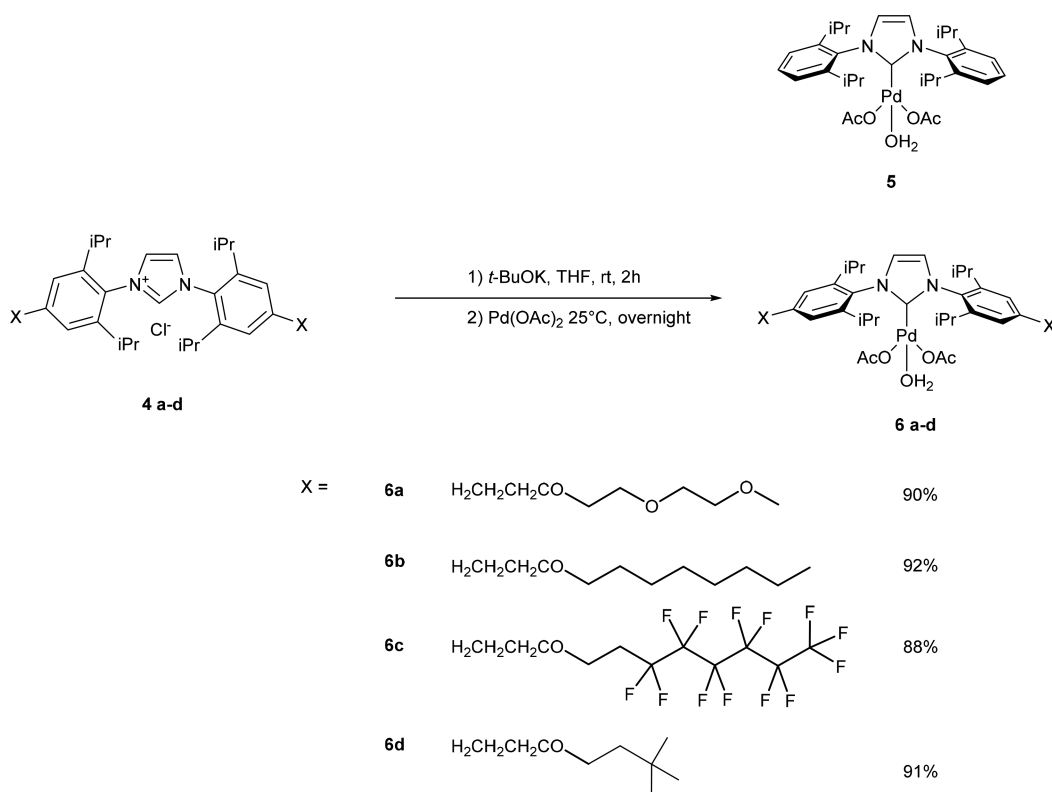
Cross-coupling reactions were analyzed on a Waters UPLC with a UV/vis photodiode array detector, a Waters Acquity BEH C18 column with dimensions of 2.1 mm × 50 mm, 1.7 μm, and a gradient of water and acetonitrile buffered with 0.1% formic acid. The column temperature was 40 °C, and the detector was used 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 analyzed 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 **8c** (69 mg, 0.05 mmol, 500 ppm) and potassium formate (3.15 g, 37.5 mmol) in ethanol that was previously degassed by bubbling nitrogen through it for 10 min. The circulation pump was switched on, and the mixture was circulated at a nitrogen pressure of 0.5 bar 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 equiv), (4-methoxyphenyl)boronic acid (16.7 g, 110 mmol, 1.1 equiv), potassium formate (1.05 g, 12.5 mmol), and potassium *tert*-butoxide (14.59 g, 130 mmol, 1.3 equiv) in ethanol (diafiltration solution), which was also degassed by bubbling nitrogen through it for 10 min and kept under a nitrogen atmosphere. The filtration loop system was brought under pressure (10 bar), and the diafiltration was started. It was realized in semicontinuous mode (with valve V-

Scheme 1. Structure of Pd Complex 5 and Synthesis of Tailed Pd NHC Complexes 6a–d from Imidazolium Chloride Salts 4a–d



1 closed and V-2 open; Figure S1) at 10 bar and a measured temperature in the filtration loop between $23 \pm 2^\circ\text{C}$ while a constant feed level was maintained. The volume inside the filtration loop was kept constant via the controlled slow addition of the diafiltration solution containing the reagents and base to a solution of the catalyst in the filtration loop by the diafiltration process. Addition of reagents to the catalyst was used in the flow system to allow the catalysts to be pushed toward higher turnover numbers simply by adding more reagent. The permeate generated was added to the diafiltration solution maintained under an atmosphere of N_2 . The membrane flux was continually monitored. The reaction was allowed to proceed in such a manner for 44 h (corresponding here to 1.3 diafiltration volumes;³² this reaction time could be adapted by using a larger membrane surface) with regular sampling of the filtration loop contents (retentate) and the membrane permeate (the diafiltration solution, which is here the permeate in this semicontinuous mode) for analysis. The content of the diafiltration tank (A) was then poured into a permeate tank. The diafiltration tank was then charged with fresh ethanol, valve V-1 was opened, and valve V-2 was closed. The diafiltration was continued until more than 3 diafiltration volumes of EtOH (2.21 L, which corresponds to 3.15 diafiltration volumes) was used, 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. The metal content was analyzed by ICP-MS.

The permeance was initially $13 \text{ L h}^{-1} \text{ bar}^{-1} \text{ m}^{-2}$ at 40°C with a 1:1 EtOH/water mixture or $28 \text{ L h}^{-1} \text{ bar}^{-1} \text{ m}^{-2}$ at 21°C with pure EtOH, went down to $0.8 \text{ L h}^{-1} \text{ bar}^{-1} \text{ m}^{-2}$ during the reaction, and then went up to $0.95 \text{ L h}^{-1} \text{ bar}^{-1} \text{ m}^{-2}$ during the

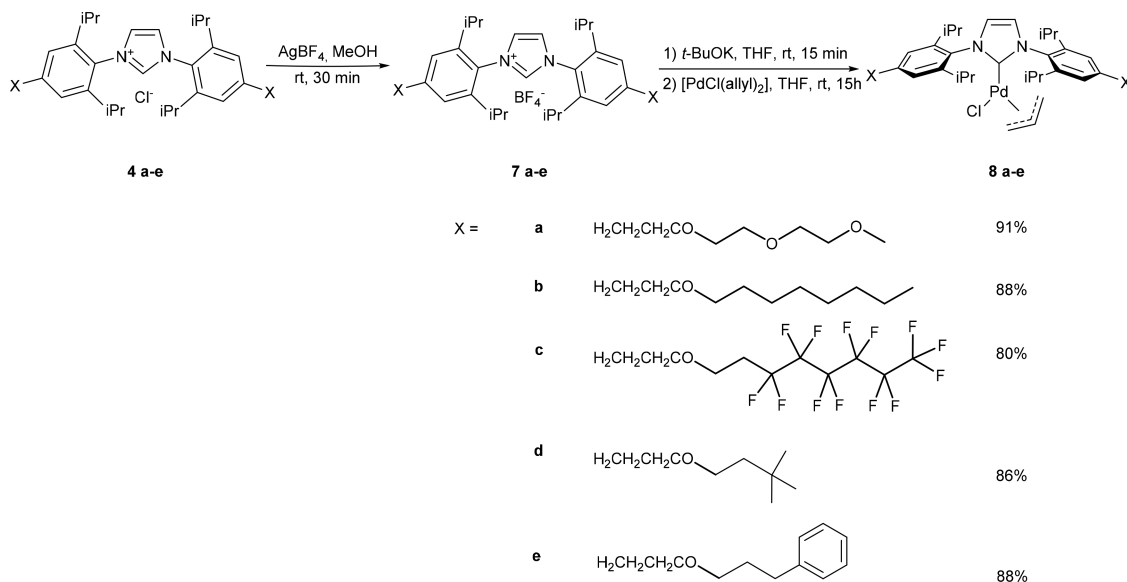
constant diafiltration with fresh EtOH. The original permeance of $13 \text{ L h}^{-1} \text{ bar}^{-1} \text{ m}^{-2}$ at 40°C with a 1:1 EtOH/water mixture was recovered after a wash with a hot EtOH/water mixture.

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 with a clean chromatogram (Figure S2); the presence of salts most certainly explains 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%.

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-methoxyphenyl)boronic acid (6 mmol, 1.2 equiv), and potassium *tert*-butoxide (6.5 mmol, 1.3 equiv). The flask was sealed with a septum, and ethanol (4 mL) was added via syringe. The mixture was degassed for 3 min, and the flask was filled with argon. Then the reaction mixture was stirred in a preheated bath at 30° for 30 min. A degassed solution of 4-chlorotoluene (5 mmol, 1 equiv) in ethanol (2 mL) was added, and the reaction mixture was stirred at 30°C for 4 h. A $100 \mu\text{L}$ sample of the reaction mixture was taken every 15 min, and the reaction was quenched by addition of the sample to a vial containing $500 \mu\text{L}$ of an aqueous saturated ammonium chloride solution.

RESULTS AND DISCUSSION

Tailed NHC Ligands and Tailed Palladium NHC Complex Synthesis. The chosen NHC ligand that formed the foundation for these tailed versions was 1,3-bis(2',6'-diisopropylphenyl)imidazol-2-ylidene (IPr). Substitution at the 4-position of the aryl groups was chosen, as this would be remote

Scheme 2. Synthesis of Tailed Pd Allyl Chloride Complexes 8a–e^a

^aYields shown are for the final complex formation from imidazolium tetrafluoroborate salts 7a–e.

from the catalytic center of the metal complex and therefore would be expected to minimally impact the catalysis. Moreover, substitution with highly bulky trityl groups at this position had 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 in overall yields 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 imidazolium chlorides 4a–d with Pd(OAc)₂ in the presence of base (Scheme 1).²⁴ However, this route proved to be troublesome and low-yielding, mainly because of 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 6 containing a coordinated water molecule. Complex 5, synthesized using a method described elsewhere,¹² has previously been described in the literature as a catalyst for aerobic oxidations rather than cross-couplings.²⁵

These aqua complexes tended to have somewhat limited stability and would decompose both during storage and in solution. Thus, a second generation of complexes were synthesized, allylpalladium complexes 8a–e (Scheme 2). The untailed version, known as CX-21, was introduced by Nolan²⁶ and is now commercially available as part of the Umicore cross-coupling portfolio. The synthesis of the imidazolium salts was improved by performing an ion exchange reaction on 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 with high purity.

Performance of the Tailed Pd NHC Complexes in the Model Suzuki Cross-Coupling Reaction. As shown in Table 1, all of the Pd NHC complexes of types 6 and 8 proved

Table 1. Catalyst Performance in the Suzuki Cross-Coupling of 9 and 10^a

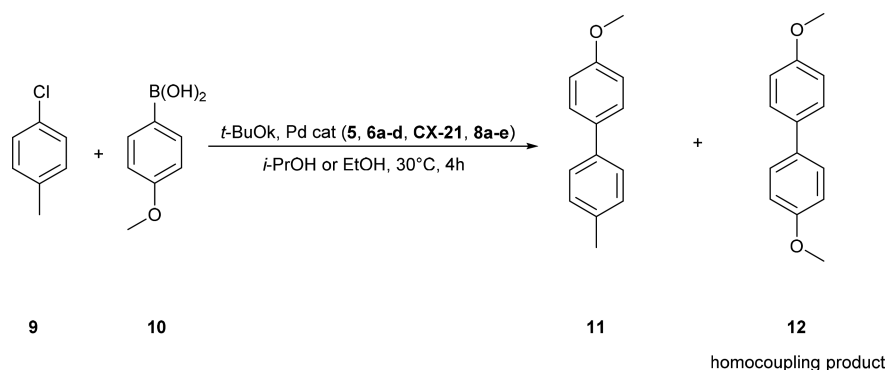
entry	Pd complex	solvent	yield of 11 (%)
1	5	<i>i</i> PrOH	83
2	5	EtOH	0
3	6a	<i>i</i> PrOH	86
4	6b	<i>i</i> PrOH	84
5	6c	<i>i</i> PrOH	85
6	6d	<i>i</i> PrOH	83
7	CX-21	EtOH	99
8	8a	EtOH	98
9	8b	EtOH	97
10	8c	EtOH	99
11	8d	EtOH	89
12	8e	EtOH	89

^aReaction concentration 500 mM with respect to 9, 1 mol % catalyst, *t*-BuOK (1.3 equiv), 30 °C, 4 h, solvents degassed.

to be effective catalysts for the model cross-coupling reaction (Scheme 3) when it was carried out under batch conditions (i.e., addition of the catalyst to the reactants and reagent at 30 °C in an alcohol as the solvent). The nature of the tail appears to have a minimal effect on the yield of biphenyl 11 in the batch reaction. In a lab simulation of the semicontinuous processing, in which a solution of *t*-BuOK, 9, and 10 is added to a solution of the catalyst at 30 °C, significant quantities of the homocoupled product 12 were formed; the formation of 12 was observed to a far lower extent in the batch process. This could be suppressed when a mild reducing agent such as potassium formate was added.^{12,27}

Membrane Characteristics and Requirements. Two parameters generally used to characterize a membrane are

Scheme 3. Model Reaction Chosen To Investigate the Membrane Process with Tailed NHC Pd Complexes 6 and 8: Suzuki Cross-Coupling of 4-Chlorotoluene (9) and (*p*-Methoxyphenyl)boronic Acid (10)



solute rejection and permeate flux. Rejection is a measure of a solute's ability to permeate through the membrane. Thus, if a solute has high rejection, its concentration is low in the permeate. The 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):

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

The membrane flux (J , in units of $\text{L m}^{-2} \text{h}^{-1}$) is a measure of the flow rate through the membrane and is determined from the measured permeate volume (V) per unit time (t) and the membrane area (A) according to eq 2:

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

The permeance (L , in units of $\text{L m}^{-2} \text{h}^{-1} \text{bar}^{-1}$) is the membrane flux normalized to the applied pressure (eq 3):

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

The membranes used in this study were principally ceramic membranes. They were chosen not only because of 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 based on not only size exclusion but also the solvent–solute–membrane interactions (affinity aspects). For comparison, a tight and chemically highly stable polymeric membrane was also used in a number of experiments. Membrane characteristics are listed in Table S1. Both the contact angle and water permeance are measures of the hydrophilicity and consequently the surface polarity of the membrane surface.^{4,28,29} The more hydrophilic a membrane is, the more its contact angle tends to zero and the higher its water flux is. Accordingly, hydrophilic membranes are more efficient in highly polar solvent systems.

For the model cross-coupling reaction used in this work, the intention was to have a membrane 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 and 6a–d in isopropanol at room temperature was determined over a number of membranes (Table 2). This was done using a setup very similar to that shown in Figure 1, in which V-2 was closed and V-1 was open and there was no addition (solvent or reactant and reagent solution) to the

Table 2. Rejection and Permeance Data for Aqua Complexes 5 and 6a–d in Isopropanol over Three Different Membranes^a

entry	membrane	Pd complex	rejection (%)	permeance ($\text{L m}^{-2} \text{h}^{-1} \text{bar}^{-1}$)
1	0.9 nm 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	Duramem-200	6d	92	1.5
11		5	98	0.12
12		6a	97	0.14
13		6b	97	0.14
14		6c	≥99	0.14
15		6d	96	0.12

^aThe transmembrane pressure was 10 bar for ceramic membranes and 20 bar for polymeric membranes. The cross-flow velocity was 2 m/s. The data were obtained at room temperature.

filtration unit under operation. A solution of the catalyst was added to the feed tank (B), the system was brought under pressure, and the permeate was collected. This procedure gave the rejection of the complexes alone and not under the reaction conditions. The fact that the reference untailed Pd complex 5 in general gives a higher rejection than the tailed counterparts is likely due to its greater tendency to form clusters rather than membrane affinity aspects.

The switch from the aqua complexes to the allylpalladium chloride complexes 8 was principally due to the instability of the aqua complexes observed upon storage and the fact that the allylpalladium chloride complexes allowed the use of ethanol as the 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 the reaction conditions, and thus, rejection measurements with the allylpalladium chloride complexes 8a–e were carried out directly in the reaction mixture.

Online Semicontinuous OSN Processing in Cross-Coupling Reactions. As we reported previously, efficient

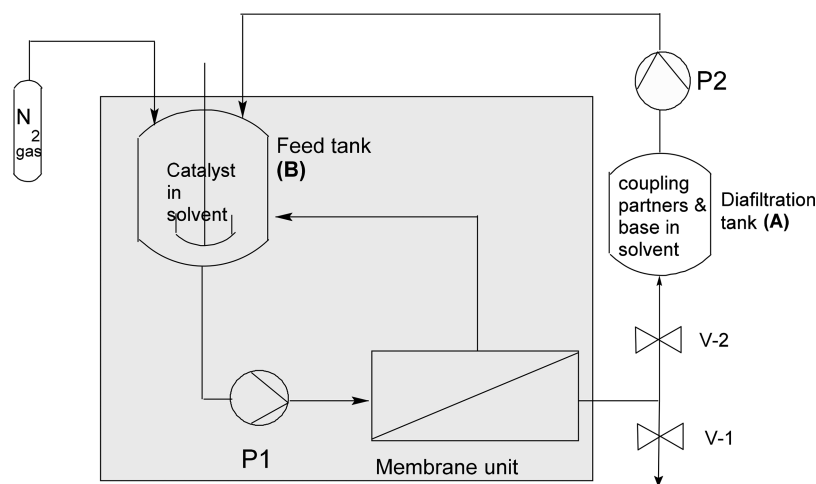


Figure 1. Schematic view of the OSN system used for the semicontinuous reactions. Everything in the shaded zone is under pressure during operation. P1 is the circulation pump, and P2 is the diafiltration pump. V1 and V2 are valves allowing either return of permeate via the diafiltration tank or permeate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

Table 3. Rejection over Ceramic Membranes of Untailed and Tailed Pd NHC Catalysts Used in the Semicontinuous Reactions^a

entry	catalyst	reaction temperature (°C)	molar 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	–

^aReaction scale, 10 mmol with respect to **9**; catalyst loading, 1 mol %; transmembrane pressure, 10 bar; solvent, ethanol; membrane cross-flow velocity, 2 m/s.

removal of commercial untailed NHC Pd catalysts and a good reaction yield in the Suzuki reaction of **9** and **10** with either downstream 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 exhibit poor performance in the semicontinuous mode of operation (on-line), so the latter was explored with tailed NHC Pd catalysts **8**. A solution of base (*t*-BuOH), potassium formate, **9**, and **10** was added via constant-volume diafiltration to the OSN system containing a solution of the catalyst. Constant-volume diafiltration involves addition into the OSN unit at the same rate that solution permeates through the membrane, thus keeping the volume within the unit 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 the reaction conditions during the addition of the 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 setup used is shown in Figure 1. Reactions were carried out in semicontinuous mode. To remove issues related to residence time of reactants and reagents with the catalyst, allowing complete conversion, total return of the permeate was 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 was returned to the reaction vessel (feed tank B) via

the diafiltration tank (A). The total return of permeate was continued until it was deemed, via reaction monitoring, that either the reaction was complete or the catalyst efficiency was no longer sufficient, whereupon V-2 was closed and V-1 was opened, allowing the separation of the reaction product from the organometallic species.

All of the reactions in Table 3 were carried out with a catalyst loading of 1 mol %, i.e., a substrate to catalyst ratio of 100. The highest rejections (≥99%) were observed with the 1.0 nm C₈ TiO₂ membrane and perfluoroalkyl-tailed Pd NHC complex **8c**. No reaction was observed with complex **8d**; the branched alkyl tail in this complex did appear to be unstable and decomposed upon standing. Though CX-21 gave reaction yields comparable to those with the other tailed catalysts, its rejection at 23 °C was low. At higher temperature, the untailed catalyst CX-21 forms Pd⁰ clusters, which gives a good rejection in membrane separation but then avoids catalyst reuse in a semicontinuous setup. The obvious consequences 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. In part at least, this is due to the higher concentration of the batch reactions compared with the continuous membrane-assisted reaction, i.e., at higher concentration complete conversion is achieved in a shorter time period.

Origins of the Catalyst Rejection Profile. Catalyst rejection over the membranes can be clarified by taking

Table 4. P_{diff} and J/P_{diff} Results for Catalysts 8a, 8b, and 8c in Ethanol over Numerous Membranes

entry	catalyst	membrane	T ($^{\circ}\text{C}$)	J ($\text{L m}^{-2} \text{h}^{-1}$)	P_{diff} ($\text{L m}^{-2} \text{h}^{-1}$)	J/P_{diff}	rejection (%)
1	8a	0.9 nm TiO_2	23	3	5	0.3	24
2		1.0 nm $\text{C}_8 \text{TiO}_2$	23	46	9	1.4	57
3		0.9 nm $\text{C}_8\text{H}_4\text{F}_{13} \text{TiO}_2$	23	14	32	1.7	60
4	8b	0.9 nm TiO_2	23	1.4	1	1.4	54
5		1.0 nm $\text{C}_8 \text{TiO}_2$	23	8	0.25	11.4	89
6		0.9 nm $\text{C}_8\text{H}_4\text{F}_{13} \text{TiO}_2$	23	12	5	2.4	65
7	8c	0.9 nm TiO_2	23	2.9	5.75	0.5	32
8		1.0 nm $\text{C}_8 \text{TiO}_2$	23	60	1	60	≥ 99
9		0.9 nm $\text{C}_8\text{H}_4\text{F}_{13} \text{TiO}_2$	23	35	16	2.2	67

Spiegler–Kedem theory into consideration. This is 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 the 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 the solvent and solute permeabilities (J/P_{diff}).^{6,31} If J/P_{diff} 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 the 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} among the membranes (Table 4). Indeed, the rejection profiles of catalysts 8b and 8c follow size exclusion with the 1.0 nm $\text{C}_8 \text{TiO}_2$ membrane, as would be expected from the J/P_{diff} ratio. In contrast, the rejection of the catalysts over the tighter 0.9 nm $\text{C}_8\text{H}_4\text{F}_{13} \text{TiO}_2$ membrane, which might be expected to give higher rejection than a membrane with a pore size of 1.0 nm, gives the best illustration that the solute transport is diffusion-controlled not only because they give lower rejection than the 1.0 nm membrane but also because there is little difference in rejection among the three catalysts. With the unmodified membrane again, diffusion is the controlling factor in the observed catalyst rejection.

Process Intensification with Catalyst 8c. As the 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 the substrate to catalyst ratio was increased initially from 100 to 400 (1 mol % to 0.25 mol % catalyst) and then further to 2000 (0.05 mol % catalyst). The results are summarized in Table 5. Practically this was carried out simply by 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 the catalyst loading is reduced is explained by the increase in concentration of the solutions. The reaction was again carried out in the semicontinuous mode as above and allowed to run with total return of the permeate (i.e., V-2 open and V-1 closed; Figure 1) until a volume equivalent to at least one diafiltration volume³² had been added to the feed tank (B) containing catalyst from the diafiltration tank (A). For the experiments with the substrate/catalyst ratios of 100 and 400, the total return of permeate was allowed to run for 24 h, and for the substrate/catalyst ratio of 2000, this was done for 44 h,³³

Table 5. Comparison of Membrane and Reaction Performance upon Reduction of the Loading of Catalyst 8c in the Suzuki Cross-Coupling of 9 and 10

substrate/catalyst ratio	100 ^b	400 ^c	2000 ^d
precatalyst load (ppm)	10000	2500	500
yield (%) ^a	75	86	88
av. process permeance ($\text{L m}^{-2} \text{h}^{-1} \text{bar}^{-1}$)	6	2	0.8
catalyst retention (%)	96	90	96
mass intensity (reaction)	424	155	51
mass intensity (reaction and product isolation)	–	355	167

^aYields were determined after evaporation of the permeate and HPLC purity analysis. ^bReaction scale: 10 mmol with respect to 9. ^cReaction scale: 20 mmol with respect to 9. ^dReaction scale: 100 mmol with respect to 9.

during which time the volume of solution added to tank B was equivalent to two diafiltration volumes.

Once this reaction phase was complete, V-2 was closed and V-1 opened. The contents of the diafiltration tank were added to the unit feed tank, and then the reaction product was washed through the membrane into the permeate using three diafiltration volumes of ethanol. Between 90 and 95% of the reaction product was then found in the permeate phase.

The results in Table 5 show a clear and substantial improvement in the mass intensity of the reaction.^{34,35} The large reduction in mass intensity observed is principally due to the fact that as the scale of the reaction was increased, the solvent volume used to carry out the process remained the same as that used with a substrate/catalyst ratio of 100. With a catalyst loading of just 500 ppm, product 11 was obtained in 88% yield and contaminated with only 16 ppm Pd without performing any postreaction 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 the reaction product was washed through the membrane following the reaction.

CONCLUSIONS

Pd complexes containing an N-heterocyclic carbene backbone that has 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 semicontinuous reactions and (b) to achieve high membrane rejection of the tailed Pd NHC complexes with top-layer-modified ceramic membranes on the basis of 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 untailored counterparts, high membrane rejection ($\geq 99\%$) was achieved with modified ceramic membranes. Their successful use in a semicontinuous membrane-assisted reactor was demonstrated, allowing high yield, high TONs, and low residual Pd in the reaction product. Moreover, a significant improvement in the process mass intensity and high product recovery were achieved. A further advantage of the disclosed system is that no specialized reactors or adaptation of existing reactors is necessary because the nanofiltration unit is a stand-alone commercially available unit that can be connected to existing reactors via standard connections. Additional studies are underway to further investigate the scope and limitations of these tailed Pd NHC complexes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.oprd.8b00273](https://doi.org/10.1021/acs.oprd.8b00273).

Supporting figures, schemes, and tables, synthesis of Pd complexes **6a–d** and **8a–e**, and NMR spectra of the synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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