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Separation of Reaction Product and Palladium Catalyst after a Heck Coupling Reaction by means of Organic Solvent Nanofiltration

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Organic solvent nanofiltration (OSN) is a recently commercialized technology, which we have used to develop a method for the separation of a target product and the Pd catalyst from a Heck coupling postreaction mixture. The experimental setup included commercially available polyimide copolymer membranes with molecular weight cut-off (MWCO) values in the range of 150–300 Da, acetone as the solvent, and a working pressure (N_2) of 3 MPa. The investigation of the membranes revealed that a membrane with a MWCO of 200 Da provided quantitative retention of the Pd catalyst and quantitative recovery of the target product by means of a cross-flow dianofiltration procedure.

Introduction

One of the fundamental goals in organic synthesis is the formation of new C–C bonds and thus new carbon frameworks.[1] A wealth of reactions and processes that involve transition-metal catalysis have enhanced the organic chemist's repertoire of reactions and methods to provide access to new and shorter synthetic pathways towards highly complex molecules.[2] Although transition-metal catalysis plays an almost indispensable role in organic synthesis, such catalytic reactions are encumbered with drawbacks. To obtain sound process economy for an industrial process, it is necessary to establish effective unit operations that will separate the transition-metal catalyst from the reaction product. This will enable catalyst recycling[3] and allow the utilization of the reaction products as pharmaceutical chemicals, active pharmaceutical ingredients (APIs), nutraceuticals, or as food or feed additives. Guidelines from the European Medicines Agency[4] state that the daily permitted oral exposure to Pd in a pharmaceutical ingredient should be less than 10 mg of Pd per kilo of API (<10 ppm),[5] which places strict requirements on the purification process.

There are a number of methods that can be utilized for removing Pd catalysts from APIs,[6] which are based on classical unit operations and include distillation, extraction, crystallization, and adsorption.

When such unit operations are to be used, various experimental variables need to be investigated: the reaction environment, the physical and chemical characteristics of the compound that is treated in the purification process,[5,7] and the behavior and properties of the catalyst. To accomplish an acceptable residual Pd level,[8] classical purification methods often call for repeated purification cycles or a combination of several methods. When several purification cycles or steps are needed, the operating cost of the overall process increases at the same time as the throughput and yield decreases.

Organic solvent nanofiltration (OSN) has been introduced as a new separation/purification method and is still an emerging technology in membrane science.[9] At this time, a few solvent-resistant nanofiltration membranes are commercially available: the DuraMem,[10] SelRO,[11] SolSep,[12] and Starmem[13] series of membranes and the Inopor series of ceramic membranes.[14]

OSN is a pressure-driven membrane-based separation technique that permits the use of organic solvents instead of water, which is used in many other liquid filtration techniques. The nanofiltration membranes are manufactured from polyimide copolymers, such as the polyimide copolymer P84 (Figure 1).[15] The flow diagrams of two different setups for OSN are shown in Figure 2.

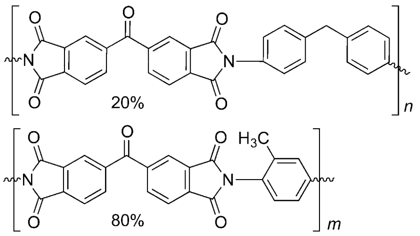

Figure 1. The chemical structures of the two polymers that constitute the polyimide copolymer P84.

The polyimide copolymer (Figure 1) is an excellent material for the preparation of membranes for nanofiltration because of its outstanding resistance to a wide range of both polar and

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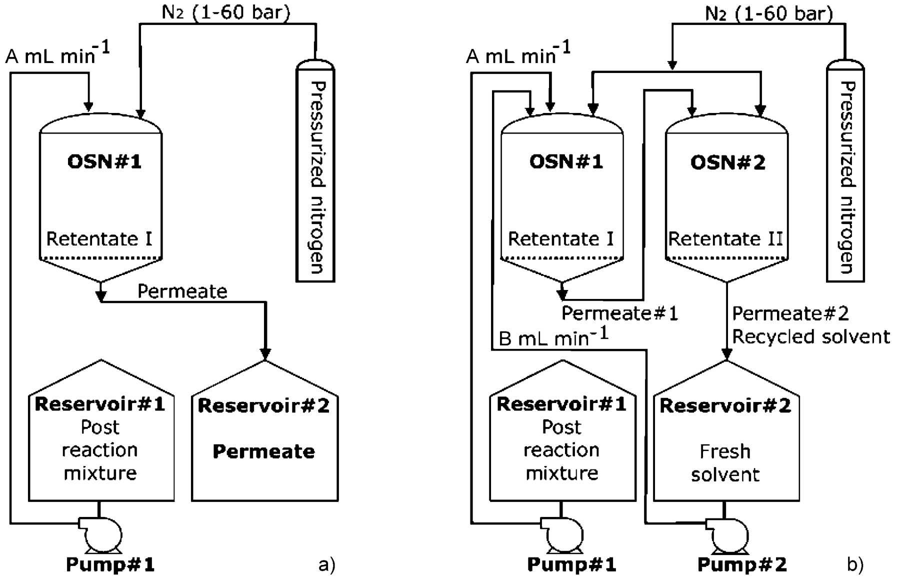
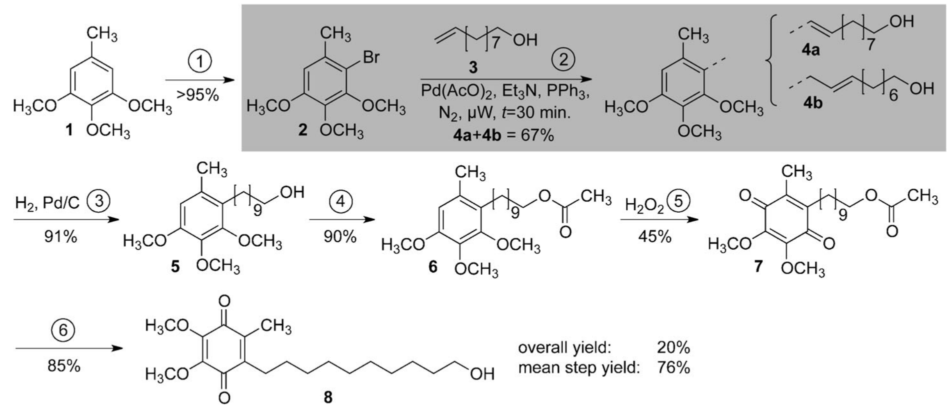


Figure 2. a) Flow diagram for organic solvent dead-end nanofiltration. b) Organic solvent dia-nanofiltration. The retentate of the OSN step 1 constitutes of the Pd catalyst, and the permeate contains the organic products and the solvent. The retentate of the OSN step 2 constitutes of the target product, and the permeate is the solvent, which can be recycled in the next filtration process cycle.

polar aprotic solvents.[16] Such membranes have also been shown to provide cost-effective and environmentally benign separation and purification techniques that minimize the requirement of solvents and waste side-streams compared to classical separation/purification methods. Previously, OSN technology was utilized with first generation membranes (Starmem, Membrane Extraction Technology Ltd., UK) to isolate transition-metal catalysts from Suzuki and Heck coupling postreaction mixtures.[17,18] These studies revealed that the methodology was suitable for 1) the removal of residual Pd up to approximately 95%, and 2) the separation of the product from the catalyst and ionic liquid after ruthenium-catalyzed hydrogenation and Suzuki coupling reactions.[19,20] The results from these studies combined with the recent achievements in membrane development spurred us to undertake the study disclosed herein with the goal to separate the target molecule from the Pd catalyst that was used in a Heck coupling reaction,[21] which was the key step of a new total synthesis of idebenone (**8**, Scheme 1, Step 2).[22] An important aspect of this project was to design and develop a green, efficient, and high yielding process. Moreover, the total synthesis should preferably involve readily available starting materials and cost-optimized synthetic methods because **8** is of potential industrial interest for use in pharmaceutical applications. 2-Bromo-3,4,5-trimetoxymethylbenzene (**2**) and 9-decen-1-ol (**3**) were coupled in the presence of a Pd^0 catalyst with microwave or thermal heating. The Heck coupling reaction produces two productive isomers, **4a** (major isomer) and **4b**, in a good yield (67%) by using microwave (μW) heating.



Scheme 1. Total synthesis of **8**.[23]

Results and Discussion

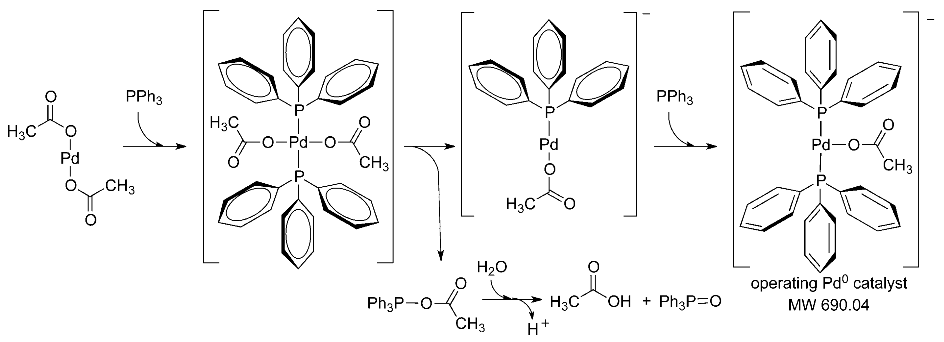
In general, the design and development of efficient, functional methods for the isolation of transition-metal catalysts from postreaction mixtures by means of OSN requires a significant molecular weight difference between the catalyst and the product to be separated.[16b,24]

To identify 1) an appropriate membrane that can deliver transition metal-free products, and 2) a suitable flow rate (membrane flux), it is mandatory to screen various membranes that possess different molecular weight cut-off (MWCO) values.[26]

The model Heck coupling reaction (Scheme 1, Step 2)[23d] is catalyzed by Pd^0. $Pd^{II}(OAc)_2$ was added to the reaction mixture with PPh_3, which reacted in situ to produce the operational catalyst $[Pd^0(PPh_3)_2OAc]^-$ (MW = 690.04 Da, 1 Da = 1.66×10^{-27} kg, Scheme 2). The molecular weight (MW) difference between the target intermediate **4** (MW = 336.5 Da) and the Pd catalyst appeared to be sufficient ($\Delta MW = 690.04-336.5 = 353.54$ Da) to separate the catalyst from **4a** and **4b**.

Commercially available second-generation membranes (Evonik MET Ltd, UK) with MWCOs of 300 Da (M_1), 200 Da (M_2), and 150 Da (M_3) were screened, and the results of the rejection of Pd and the product are shown in Figure 3.

M_2 exhibited an excellent rejection (100%) of Pd and a high rejection (77%) of **4a** and **4b**. M_1 demonstrated the complete permeation of the product, but only a relatively low selectivity



Scheme 2. In situ production of the active catalytic species for the Heck reaction.[25]

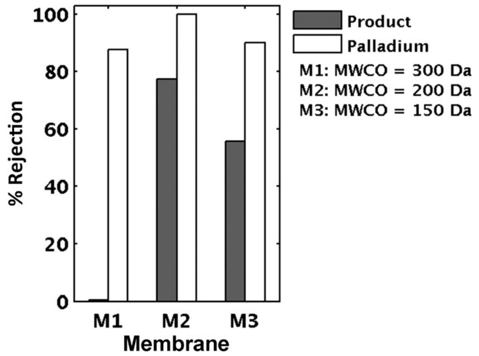


Figure 3. Rejection (%) of Pd and product from the nanofiltration of the postreaction mixture by M_1–M_3.

towards Pd and retained just 80 %. This behavior may be related to the formation of Pd species with molecular weights lower than 300 Da that cannot be retained by M_1. M_3 also possessed a high selectivity towards Pd with a rejection of 90 % and a permeability of 50 % for the product. The results with M_3 were unexpected as it has the lowest MWCO of the three membranes. The trials performed with M_2 revealed both suitable flux and Pd catalyst rejection (Figure 4) for the separation of the catalyst and product.

The performance and permeability of a membrane is correlated to the membrane flux,[27] and the oligostyrene test can be used to explore the flux of a membrane.[25a] The results of the exploration of the flux [$\mathrm{L\,m^{-2}\,h^{-1}}$] of M_1, M_2, and M_3 are shown in Figure 5.[28] M_2 and M_3 provided a lower flux than M_1. However, all three membranes demonstrate suitable fluxes for our application. Although M_1 displayed the highest flux, M_2 displayed the best total performance for our postreaction mixtures, as it showed both a high retention of the Pd catalyst and a relatively low retention of **4a** and **4b**.

The investigation of the performance of M_1, M_2, and M_3 revealed that M_2 quantitatively trapped the Pd catalyst. However, the recovery of the product from the postreaction mixture was a problem, as it was also trapped. Dia-nanofiltration allows the nanofiltration process to be repeated in a continuous fashion (Figure 2 b).

The results of the dia-nanofiltration experiments are displayed in Figure 6, and reveal that the reaction product was quantitatively recovered from the postreaction mixture after six filtration cycles, and the Pd level was much lower than the requirements set for pharmaceutical applications.[5]

Conclusions

We have successfully developed an OSN process for the separation of $[\mathrm{Pd^0(PPh_3)OAc}]^-$ and **4a** and **4b** found in a Heck coupling postreaction mixture. A commercially available membrane with a molecular weight cut-off value of 200 Da was identified to be the most appropriate for the purpose.

The purified product (a mixture of **4a** and **4b**) was quantitatively recovered from the postreaction mixture after five suc-

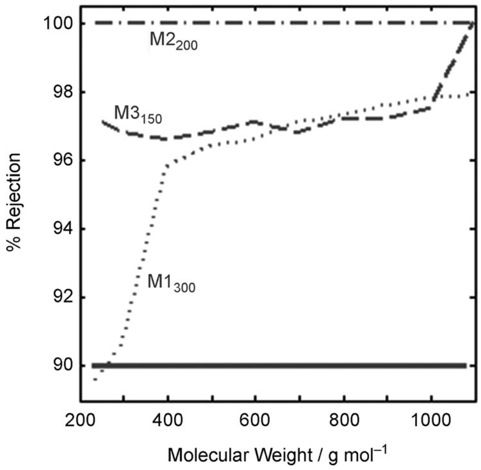


Figure 4. Molecular weight cut-off curves of M_1–M_3. Rejections (%) for the membranes from the oligostyrene test.

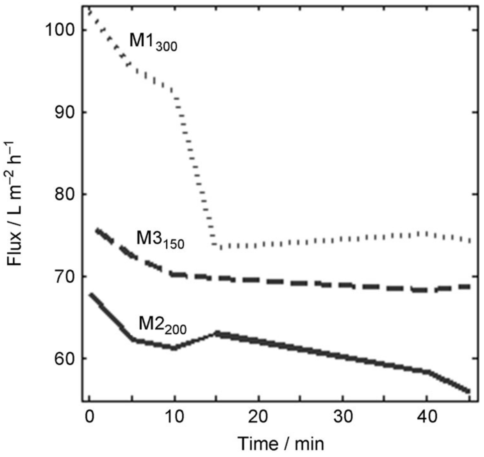


Figure 5. The flux of the membranes M_1 (MWCO 300 Da), M_2 (MWCO 200 Da), and M_3 (MWCO 150 Da).

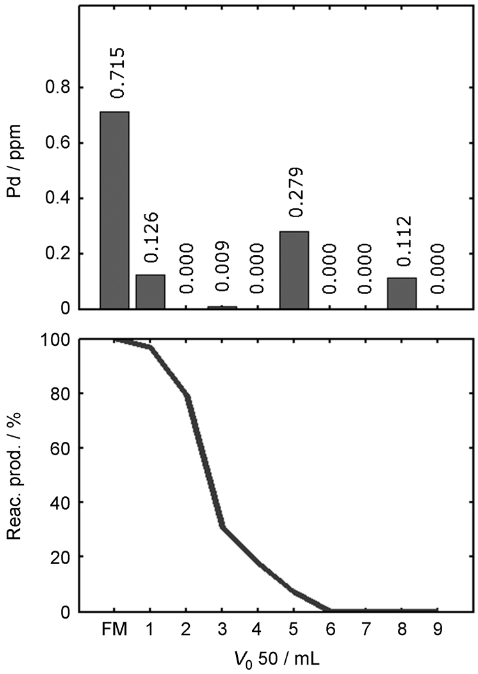


Figure 6. Results of the dia-nanofiltration process for the separation of reaction product and catalyst. The quantities of the reaction product in the permeate fraction were determined by using GC. The Pd quantities were determined by using ICP [ppm Pd]. FM = feeding mixture, which contained a Pd quantity of 0.715 ppm.

cessive filtrations in a purity that meets the health and safety specifications stated by the European Medicines Agency for a product to be used in a pharmaceutical product.

Our catalyst/product separation process is beneficial from several environmental and process points of view: 1) the expensive Pd catalyst is recovered for recycling, 2) the need for solvent is substantially reduced compared to other separation techniques, 3) the process waste streams are reduced, and 4) there is a reduction in energy consumption as this process does not need energy to strip off large volumes of solvent.

Our process can be used directly or be an excellent starting point for other syntheses based on $[Pd^0(PPh_3)_2OAc]^-$ with a MW of 690.04 Da as a catalytic system.

For application with other Pd-catalyzed coupling reactions, a requirement is that the difference in molecular weight between the operating catalyst and the target molecule (with a molecular weight lower than 337 Da) is at least 354 Da (ΔMW).

Experimental Section

Starting materials, reagents, and solvents were purchased commercially and were used without further purification unless otherwise stated. The DuraMem membranes were purchased from Evonik MET Ltd., U.K. The Heck coupling reactions were conducted by using microwave irradiation as the energy source by using a Biotage Initiator Sixty EXP Microwave System, which operates at 0–400 W at 2.45 GHz in a temperature range of 40–250 °C, pressures of 0–20 bar (1 bar = 10^5 Pa), and reactor tube volumes of 0.2–20 mL.

Synthesis of the olefin isomers

The olefin isomers **4a** and **4b** were synthesized by using a a mixture of 2-bromo-3,4,5-trimethoxytoluene (**2**, 7.66 mmol, 2 g), dec-9-en-1-ol (**3**, 12.5 mmol, 2.3 mL), triethylamine (14.3 mmol, 2 mL), Pd acetate (0.20 mmol, 45 mg, 2.61 mol%), and triphenylphosphine (0.80 mmol, 210 mg), which was heated by using two methods. 1) Thermal heating: The reaction mixture (without solvent) was transferred to a thick-walled sealed tube reactor (Ø = 20 mm, h = 150 mm). The reactor tube was flushed with nitrogen for 3 min, the valve was closed, and the tube was heated at 120 °C for 3 days. 2) Microwave irradiation: The reaction mixture was added to tetrahydrofuran (1.5 mL) and transferred to a reactor tube (2.5 mL), which was then placed in the microwave reactor. The reaction was conducted at approximately normal pressure at 120° C for 30 min.

Isolation and purification of the postreaction mixture

Method 1 (classical): The sealed tube reactor (or microwave reactor tube) was cooled to room temperature, and the reaction mixture was filtered through a pad (1 cm) of celite to remove precipitated catalyst. The celite pad was washed with diethyl ether (3 × 10 mL) and the organic phases were combined, washed with water (1 × 25 mL), and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the isolated solid was purified by using flash chromatography. The product was isolated as a mixture of **4a** and **4b** in a yield of 60% (thermal) and 67% (microwave). The yields were measured by using ^{1}H NMR spectroscopy with 3,4-dimethoxyacetophenone as internal standard. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.28$ (br, s, 9H), 1.54 (qn, 2H), 1.95 (q, 2H), 2.23 (s, 3H), 3.27 (d, 2H), 3.62 (t, 2H), 3.80 (t, 9H), 5.39 (m, 2H), 6.50 ppm (s, 1H); MS: m/z (%) = 336 (75), 221 (56), 195 (100), 190 (80), 182 (95), 167 (25), 91 (22), 79 (12), 55 (34). $R_f = 0.32$ (hexane and ethyl acetate, 8:2).

Method 2 (OSN): The filtration experiments were performed by using a dead-end Sepa ST pressure cell (Osmonics, USA) with a nanofilter (DuraMem membrane, Evonik MET, UK). The experiments were conducted at room temperature under a pressure of 30 bar (N_2) as the driving force of the filtration. Acetone was used as the filtration solvent.[29] M_1–M_3 possessed an effective membrane area of 14 cm^2 (circular form, Ø = 42 mm). The OSN membrane was placed on a sintered metal disk that was inserted into the filter housing and sealed to the filter body by using O-rings. A magnetic stirrer plate and a Teflon coated magnetic stirrer bar were used to avoid concentration gradients. The membranes were preconditioned by using pure acetone.[27a] The filter cell was charged with acetone (200 mL) and loaded at a pressure of 30 bar. The permeate (150 mL) was collected and discarded, and the pressure was slowly reduced to atmospheric pressure. The system was used to investigate the MWCO of the membranes by using the oligostyrene method[25a] after the preconditioning step and before OSN to evaluate the integrity of the membrane and the equipment and to identify the presence of possible leaks owing to defects in the membrane or around the membrane seal. A solution of oligostyrene in acetone (100 mL) was transferred to the filtration cell. Pressure was applied (3 MPA); and 50 mL of the solution was permeated through the membrane and collected. Three samples (1.5 mL each) were withdrawn from the permeate, the retentate, and the feed (the oligostyrene mixture) for analysis by using HPLC to determine the concentration of oligostyrene in the permeate ($C_{permeate}$) and retentate ($C_{retentate}$). The rejection of each solute (R_i) was estimated by using Eq. (1).

$$R_i = \left[1 - \frac{C_{\text{permeate,i}}}{C_{\text{retentate,i}}}\right] \times 100\% \quad (1)$$

The estimated values of R_i were plotted against the molecular weight of each membrane. After completing the oligostyrene test run, the membrane was washed thoroughly with the filtration solvent (acetone); and the preconditioning step was repeated.

OSN filtration: Triethylamine (leftover from the Heck coupling reaction) was removed from the post reaction mixture by using a rotary evaporator. A sample (0.2 g) of the amine-free mixture was withdrawn, dissolved in acetone (50 mL), and transferred to the filtration cell. The cell was pressurized (3 bar), and the permeate (25 mL) was collected. The pressure was then reduced slowly to normal atmosphere. Samples (1.5 mL) were drawn from the permeate and the retentate. These samples were analyzed by using inductively coupled plasma (ICP) spectroscopy and HPLC to determine the quantities of Pd and **4a** and **4b**, respectively. Rejection of solutes (Pd and product) was estimated by means of Eq. (1), and the results for M_1–M_3 are presented in Figure 2.

Determination of flux

The flux of the membranes was measured for the three filtration steps 1) the preconditioning step, 2) the oligostyrene test, and 3) the OSN. The flux, J_v, was estimated according to Eq. (2) and plotted against time (Figure 4), in which V corresponds to the volume of the permeate in L, A to the filter area in m^2, and t to time in h.

$$J_v = \frac{V}{A \times t} \quad (2)$$

Chemical analysis of the olefin isomers by using HPLC

The quantity of the Heck coupling products **4a** and **4b** was determined by using GC (6850 Series II, Agilent Technologies) equipped with a flame ionization detector and a fused silica column (L = 30 m, 0.25 mm inner diameter, 0.25 μm film thickness, nonpolar, MDN-12 Supelco) with He as the carrier gas. For each membrane, three samples (1.5 mL each) were drawn from 1) the permeate, 2) the retentate, and 3) the feed mixture. Each sample was injected (1 μL) directly into the gas chromatograph.

Chemical analysis of Pd by means of ICP

ICP optical emission spectroscopy (PerkinElmer 2000DV ICP-OES) was used for the determination of the Pd concentration in the nanofiltration feed mixture, the permeate, and the retentate. A sample (2 mL) was drawn from each of the three mixtures, the solvent was evaporated, and aqua regia (4 mL) was added to destroy organic materials and dissolve Pd. Purified water (50 mL) was added when the digestion step was completed (usually after 24 h), and the solution was analyzed by using ICP. Each sample was analyzed three times, and the coefficient of variation for the values obtained was estimated to be lower than 4%. The results of the ICP analyses for M_1–M_3 are summarized in Table 1, which displays the Pd content in the permeate, retentate, and the rejection of Pd.

Table 1. ICP analysis of Pd in permeate and retentate from M_1–M_3.

M	MWCO [Da]	Pd concentration [ppm] permeate	retentate	Rejection [%]
M_1	300	0.079	0.639	87.6
M_2	200	0.000	0.400	100
M_3	150	0.040	0.414	90.0

Chemical analysis of oligostyrene samples by using HPLC

An HPLC system (Gilson) equipped with a Gilson 118 UV/Vis detector and an ACE 5-C18-300 column (Advance Chromatography Technologies, ACT, UK) was used for the analysis of the styrene oligomers. The mobile phase was composed of 35 vol% analytical grade water, 64.9 vol% tetrahydrofuran, and 0.1 vol% trifluoroacetic acid. The styrene oligomers were analyzed in the permeate, retentate, and the feed mixture. A sample (1.5 mL) was taken from each, the solvent was evaporated under reduced pressure, the residue was redissolved in *N*,*N*-dimethylformamide (1.5 mL), and injected into the HPLC.

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Keywords: heck reaction · homogeneous catalysis · nanofiltration · palladium · recycling

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[29] The DuraMem membranes (Evonik MET, UK) show long-term stability in numerous polar aprotic solvents, for example acetone, ethanol, methanol, tetrahydrofuran, dimethylformamide, dimethylacetamide, isopropanol, acetonitrile, methyl ethyl ketone, and ethyl acetate. We selected acetone as the solvent because of its low boiling point and low toxicity as well as the good solubility of our product.

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