Ultrafine palladium nanoparticles immobilized into poly(4-vinylpyridine)-based porous monolith for continuous-flow Mizoroki-Heck reaction

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ABSTRACT

Ultrafine Pd nanoparticles (d_m = 2.3 nm), obtained by metal vapor synthesis technique, were immobilized into a poly(4-vinylpyridine)-based porous monolith by means of a new synthetic approach. The synthesis involves stabilization of Pd nanoparticles with 4-vinylpyridine ligand and their subsequent immobilization into the monolith by radical co-polymerization of the resulting metal-embedding monomer with ethylene glycol dimethacrylate in presence of porogenic agents (i.e. DMF and PEG-400) inside stainless-steel columns (HPLC type). The hybrid monolithic reactors containing highly dispersed Pd nanoparticles were effectively used as catalyst for Mizoroki-Heck cross-coupling reactions carried out under continuous-flow conditions. The devices showed long life-time (> 65 h) and very low Pd leaching (< 2 ppm).

1. Introduction

The palladium-catalyzed cross-coupling of an aryl or vinyl halide with a terminal olefin, commonly termed Mizoroki-Heck (M-H) reaction, is one of the most relevant reactions for the formation of carbon-carbon bonds in organic synthesis.[1-4] In the last decade, the possibility to combine the favorable features of continuous-flow reactors with heterogeneous catalysts has attracted a great deal of interest in view of the economic and environmental sustainable production of fine chemicals.[5-7] Several approaches have been pursued to prepare robust supported catalysts for carbon-carbon bond formation in flow-through mode.[8] These include typical packed bed reactors, filled with Pd systems anchored on a broad range of conventional [9-11] and unconventional solid supports [12] or the in situ formation of a continuous porous structure (monolith) containing the immobilized catalyst.[13-27]

As far as systems of the latter type are concerned, both discrete Pd complexes and nanostructured catalysts have been reported. Examples of the first type were described by Guijt and co-workers, who developed polymeric macroporous monoliths containing nitrogen-based ligands for anchoring palladium salts or organometallic complexes in capillary microreactors.[24-26] The resulting microfluidic devices proved effective for continuous-flow M-H reactions of *n*-butyl acrylate with iodobenzene and, to a lesser extent, bromobenzene.[26]

Kirschning and co-workers immobilized Pd particles next to polymer-bound ammonium cations on highly porous polymer/glass composites (termed PASSflow, from polymer assisted solution phase synthesis).[16-20] Operating in cyclic mode within a closed loop reactor, the devices led to good-to-high yields in the M-H reaction of various iodoarenes with styrene or *n*-butyl acrylate.[17-19] Similarly, Luis and co-workers reported Pd systems onto monolithic polymers containing IL-

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like moieties, which could be used with DMF, as a conventional organic solvent, or with near critical EtOH at temperatures > 150°C.[21-22]

While these studies demonstrated unequivocally the possibility of carrying out the M-H reaction in monolithic micro- and mesofluidic devices, several opened questions still remain. A very fundamental one regards the extent to which the catalyst support can prevent Pd leaching into the solution. In this context, it is worth mentioning that many of the heterogenized Pd sources for M-H and related reactions have been shown to serve as "reservoirs" of active species leached in solution in the course of the catalytic runs. [28,29] Under favorable conditions, however, a catch-release mechanism may be operating to relieve the problem.[21] As consequence, metal losses of 0.04-0.05 % per run of the initial Pd amount are not unfrequent to be met in these studies, which concur to extend catalyst life-time and reduce product contamination to the low ppm range.[19, 26]

A second point of concern is the possibility of controlling the supported catalyst structure in a very precise manner. In this respect is worth to note that the procedures reported to date involve multi-step synthetic schemes for anchoring onto pre-formed polymeric monoliths suitable ligands and, eventually, the Pd catalyst or pre-catalyst.[13,21-24] In the case of nanostructured systems, this latter step proved especially critical for what it regards particles size. In fact, unless special techniques for the pore-size-selective functionalization of the monolith are adopted,[30] the reduction of immobilized Pd(II) species with chemical agents like, e.g., $NaBH_4$ [13,19] has been shown to lead to supported metal clusters of relatively large size (e.g. 7-10 nm)[19] or size distribution (e.g. 5-50 nm).[13,31] Because these properties of metal clusters are known to impact strongly on the their performance as catalysts[17,19,31] it has to be expected that benefits could be gained by developing novel procedures for the size-controlled preparation of monolithic Pd(0)-polymer composites. Besides overcoming limitations like, e.g., the occurrence of significant induction periods or the need of relatively high temperatures (e.g. > 150°C) for prompt conversion of even the most active iodide substrates, these efforts should obviously address the still open

challenge of the effective use the monoliths in continuous-flow with very low Pd contamination of the final products. [32]

Poly(4-vinylpyridine) (PVPy) is an effective scavenger for soluble Pd complexes or salts, due to the ability of the pyridine moiety to bind Pd species.[33,34] Pd complexes immobilized on a PVPy/glass composite materials afforded efficient devices to perform carbon-carbon cross-coupling reactions in continuous flow-through mode.[20,35]

Previously, metal vapor synthesis (MVS)-derived Pd nanoparticles (NPs) supported onto commercially available PVPy resins were reported as effective catalysts for M-H-type alkenylations in batch conditions.[36,37] The catalyst showed high activity and stability in the reaction run under air, ensuring also very low palladium leaching (< 1 ppm).

Herein we report the synthesis and the structural characterization of PVPy-based porous monoliths containing ultrafine Pd NPs polymerized inside standard HPLC columns. Following a novel synthetic approach, MVS-derived Pd NPs were stabilized by 4-vinylpyridine (VPy) and further immobilized into the porous monolith by VPy ligand free-radical mold polymerization with ethylene glycol dimethacrylate (EGDMA) as cross-linking agent in presence of porogenic agents. The procedure allowed to obtain catalytic monoliths devoid of impurities, such as residual chlorine or other ions, with a high dispersion of the Pd NPs and a remarkable homogeneity in their distribution across the polymer. The hybrid reactors were effectively used in M-H alkenylations carried out under continuous flow-through conditions showing long life-time together with very low metal leaching.

2. Experimental

2.1. Materials and apparatus

N-methylpyrrolidone (NMP), N,N-dimethylformamide (DMF), HPLC-grade THF, VPy, EGDMA, poly(ethylene glycol) Mn = 400 (PEG-400), and 2,2'-azobisisobutylnitrile (AIBN) were purchased from Sigma-Aldrich and used without further purification. VPy was passed through a column of basic alumina to remove inhibitors prior to use. EGDA used as received from Sigma-Aldrich. Mesitylene and 1-hexene (Sigma-Aldrich) were distilled and stored under argon. Palladium (shots, ca. 6 mm, 99.9 %) was a Strem product. The co-condensation of palladium vapor together with solvent vapors was carried out in a previously described static reactor [30], equipped with an alumina-coated tungsten crucible heated by Joule effect. The solvated metal atoms (SMA) solutions were handled under argon atmosphere by standard Schlenk techniques. The amount of palladium in SMA solution was determined by Inductively Coupled Plasma-Optical Emission Spectrometers (ICP-OES) with a iCAP 6200 Duo upgrade, Thermofisher. For ICP-OES, a sample (0.5 mL) of SMA solutions was heated in a porcelain crucible in order to remove the organic solvents. The solid residue was dissolved by heating with aqua regia (4 x 2 mL) for four times, and then dissolved in 0.5 M aqueous HCl. The limit of detection (lod) calculated for palladium was 1 ppb. The amount of leached palladium was similarly assessed by means of ICP-OES analysis of the reactions mixtures mineralized as described above. GC analyses were performed with an Agilent 6890 Series equipped with a HP-5 column (30 m × 0.25 mm) and FID detector, while GC-MS analysis were performed with an Agilent 5975C equipped with an HP-5 column (30 m × 0.25 mm). BET analyses were performed with a Micrometrics ASAP2020 instrument. Thermogravimetric analysis (TGA) were performed on Perkin Elmer 7 HT thermobalance by heating the sample from 50 °C to 1000 °C with a temperature ramp of 5 °C/min. High resolution transmission electron microscopy (HRTEM) analyses of the Pd-NPs embedded in the polymer were carried out by a Zeiss LIBRA 200FE analytical transmission electron microscope (TEM), equipped with: 200 kV FEG, in column second-generation omega filter, high angle annular dark field (HAADF) scanning transmission electron microscopy (STEM) facility and Energy Dispersive X-ray Spectrometry (EDX) probe for chemical analysis. The samples were ultrasonically suspended in a 1:1 solvent mixture of

isopropanol/toluene and one drop of the obtained suspension was deposited on a holey-carbon film supported on a copper TEM grid of 300 mesh. Histograms of the particle size distribution were obtained by counting at least 500 particles. The mean particle diameter (d_m) was calculated by using the formula $d_m = \sum d_i n_i / \sum n_i$, where n_i is the number of particles with diameter d_i. The monolith morphology was characterized using a XL30 Environmental Scanning Electron Microscopy (ESEM-FEG Philips). A piece of monolith were cut, dried overnight and analyzed at environmental condition and low electron voltage: 1.2 Torr and 5kV. These conditions were used in order to preserve the micro- and nano-porosity by avoiding any deposition of conductive layer onto the material. EDX (EDAX Sirion 200/400) analyses were carried at low vacuum condition 0.8 Torr and 16 kv. Every EDX spectra was recorded at 500× magnification, collecting data for 300s on an analytical area of 0.049104 mm^2 per frame.

2.2. Synthesis of Pd-PVPy monolith

Pd NPs were prepared by means of MVS technique, as described elsewhere.[37,38] Thus, Pd vapors were co-condensed in a glass reactor, at the liquid nitrogen temperature, with a 1:1 mixture of mesitylene (30 mL) and 1-hexene (30 mL). The palladium content of the resulting Pd SMA solution (55 mL) was 1.3 mg·mL^{-1}, as determined by ICP-OES analysis. To the Pd SMA was added 2.66 equiv. of VPy (188 mg, 1.79 mmol). The mixture was allowed to warm to RT and the brown precipitate thus obtained was separated by centrifugation and washed with *n*-pentane (3 × 10 mL). The Pd-VPy stock solution was prepared by dissolving the residue in DMF (6.0 mL) (concentration of Pd = 11.9 mg·mL^{-1}). The feed mixture for polymerization was prepared under argon by mixing monomers, porogenic solvents, and the radical initiator. In a Schlenk tube under argon was added VPy (0.149 g, 15 % of monomers), EGDMA (0.847 g, 85 % of monomer), PEG-400 (0.399 g), Pd-Vpy stock solution in DMF (0.51 g), DMF (2.038 g) and AIBN (10 mg, 1 wt.%). The feed mixture was degassed while stirring, by slow bubbling of nitrogen for 5 minutes. A portion of degassed feed

was poured in stainless steel HPLC column (0.46 cm i.d. × 15 cm) sealed at the bottom end, paying attention to fill completely the available volume. After sealing the top end under argon, the column was weighed in order to determine the exact amount of the feed mixture (2.479 g). The formation of the monolith was carried out by placing the column vertically into a preheated oil bath (70°C) and allowing the polymerization to proceed for 18 h at the same temperature. After cooling to RT, the seals were replaced by metal frits and the soluble components were removed by flushing the column with 50 mL dry toluene followed by 50 mL of NMP. The final Pd content in the PVPy-based monolith support was evaluated by taking a sample (12 mg) of the monolith which was treated by heating with aqua regia (4 x 2 mL), and then dissolved in 0.5 M aqueous HCl. ICP-OES measurements revealed a Pd content of 0.30 wt.%.

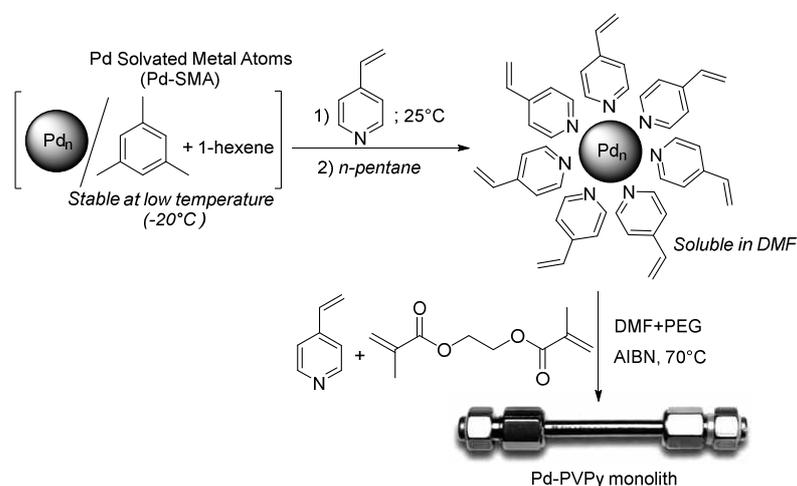*2.3 Mizoroki-Heck reaction under continuous flow conditions*

The reaction feed was prepared under argon in a Schlenk tube, by mixing NMP (3.6 mL), the aryl halide (2.0 mmol, 1 equiv.), butyl acrylate (574 µL, 513 mg, 4.0 mmol, 2 equiv.), and triethylamine (279 µL, 203 mg, 2.0 mmol, 1 equiv.). After stirring for 5 minutes, the solution was loaded under argon into a reservoir placed in-line between a HPLC pump and the column containing the Pd-PVPy monolith. The latter was placed in a preheated oil-bath and the reaction feed from reservoir was forced to flow through the monolithic catalyst bed by pumping NMP at constant flow rate (see Table 1). The output of the reaction was collected in a Schlenk tube, diluted with water and extracted with diethyl ether for GC analysis (conditions: helium as carrier, 6.7 mL/min, 40°C//10°C/min//100°C//2min//20°C/min//270°C//2 min).

2. Results and discussion

3.1. Synthesis and characterization of Pd-PVPy monolith

Pd NPs were synthesized by means of the MVS technique (Scheme 1).[36-39] To the obtained Pd

solvated metal atoms (SMA) containing Pd NPs stable at low temperature (-20°C) (Fig. 1S), was

added an excess of 4-vinylpyridine (VPy). Upon warming to 25°C a brown precipitate containing

VPy-stabilized Pd NPs was obtained (Scheme 1). The VPy-stabilized Pd NPs were isolated and

easily dissolved in DMF solvent. HRTEM analysis (Fig. 2S) showed ultrafine Pd NPs (mean

diameter 2.1 nm), very similar in size to those present in the Pd SMA precursor.

Porous PVPy-monoliths containing Pd NPs were prepared inside standard HPLC columns (0.46 cm

i.d. × 15 cm), according to Fréchet mold polymerization technique.[40] In brief, VPy-stabilized Pd

NPs were mixed with VPy (diluting monomer) and EGDMA (crosslinking agent) and subjected to

AIBN-initiated radical copolymerization at 70°C, in the presence of DMF and PEG-400 as

porogenic agents. Then, THF and NMP were pumped through the monolithic column to remove the

porogens and any residual non-polymeric material.

Scheme 1. Synthesis of Pd-PVPy monolith.

The average final Pd content in the PVPy-monolith resulted 0.30 wt.%, as evidenced by ICP-

OES measurements. In order to evaluate the metal distribution into the polymer, SEM-EDX spectra

of different frames of a cross-section of the monolith were collected along two perpendicular axis,

X and Y, and the Pd wt.% plotted against the frame position (Fig. 1). The Pd content obtained by this technique (0.2 - 0.3 Pd/C %) agrees well with that resulting from ICP-OES analysis of the bulk material. Moreover a high spatial homogeneity of the Pd distribution across the monolith was evidenced, with some drop in metal concentration only in proximity of the edges of the section.

Figure 1, near here

ESEM image of the cross-section at higher magnifications (Fig. 2 a)) revealed the presence of a continuous inter-connected network of macropores and nanopores, the latter approx. 120 nm in diameter. Not surprisingly, this translated into a satisfactory BET surface area of 305 m^2/g (Fig. 3S).

Figure 2, near here

STEM (Fig. 2b)) and HRTEM (Fig. 3) micrographs revealed the polymer densely populated with highly dispersed roundish Pd NPs, mostly limited in the size range 1.5 - 3.5 nm. Notably, the latter was comparable to that observed in the starting VPy-stabilized Pd NPs (Figure 2S), to confirm that no extensive particle aggregation occurred during the polymerization step at 70°C.

Figure 3, near here

Thermogravimetric analysis (TGA) of the Pd-PVPy monolith was performed in order to evaluate the thermal stability of the material. The TGA results (Fig. 4S) showed that the polymer undergoes thermal degradation beginning at 220℃ and with a total mass loss of 99.2%. Eventually, this leaves a small amount of inert residue (0.80 %) which contains also the metal.

3.2 In continuo Mizoroki-Heck reactions

MVS-derived Pd NPs supported on commercially available cross-linked polyvinylpyridine powder, showed good catalytic efficiency, high stability, and very low palladium leaching in M-H alkenylations.[36,37] Given these promising results in batch, the same reaction was selected for testing the Pd NPs containing PVPy monoliths under continuous flow conditions. The catalytic runs were carried out by pumping through the monolithic reactor, preheated at the chosen temperature (100-150°C), a solution of the aryl halide (1 equiv.), *n*-butyl acrylate (2 equiv.), and triethylamine (1 equiv) in NMP. A single pass configuration with constant flow-rate (ϕ = 25-100 µL·min^{-1}) was adopted in these experiments, monitoring the composition of the solution collected at the reactor outlet by GLC analysis.

Initial runs with iodobenzene as the halide substrate (Table 1) revealed a promising catalytic activity at 150°C and the selective formation of *n*-butyl trans-cinnamate. Interestingly, no induction period was observed under these conditions, which agrees with the presence of highly reactive Pd(0) NPs, commonly accepted as the actual active species of the first step of the reaction.[41-43]

As expected, reduction of the flow-rate led to an increase in the substrate conversion (from 45 to 99 %, entries 1-3), as well as a significant decrease (from 14 to 1.5 MPa) of the back pressure caused by the column. Both results made it viable to explore next the reduction of reaction temperature (entries 4 and 5), which confirmed that the residence time at ϕ = 25 µL·min^{-1} was sufficient for attaining complete conversion of phenyl iodide at temperatures as low as 100°C. The raise in back-

pressure upon decreasing the temperature can be related to the increase of viscosity of the reaction components in the liquid phase.

Table 1, near here

Nevertheless, the concurrent raise of column back-pressure registered under these conditions suggested that $\phi = 25$ µL·min^{-1} and T = 125°C could be a better compromise in order to conjugate high catalytic efficiency with less severe operative conditions for the polymeric material inside the reactor.

This latter experimental set-up was selected for studying the recyclability of the Pd-PVPy monolith. With this aim, 14 consecutive runs were carried out inside the same reactor (Fig. 4), with intermediate washing of the device with an equal amount of NMP (4 mL) and same temperature as that used the for reactions. Gratifyingly, an essentially complete conversions of iodobenzene (96-99%) and the selective formation of *n*-butyl trans-cinnamate were attained in each run, corresponding to a total productivity of the catalyst of 1604 mmol of product/mmol of Pd. The Pd leached into the solution containing the crude product and in the washings was determined by ICP-OES (Fig. 4). The highest levels of Pd contamination (7.7 and 5.1 ppm, respectively) were observed in the course of the first two catalysis runs, then, as the experiments went on, the metal leaching levelled down substantially (1.1 ppm). In any case, it is worth noting that the low Pd leaching obtained ranks our monolith among the most effective catalytic systems operating in continuo, reported to date [13-27, 42,43]

Figure 4, near here

The commonly accepted mechanism for the M-H reaction catalyzed by supported Pd NPs is: 1) oxidative addition of the halide on the NPs leading to haloaryl Pd(II) species, 2) insertion of the double bond in the Pd(II)-aryl bond and 3) reductive elimination with the formation of Pd(0) species. It has been demonstrated that the [Pd(II)(Ar)X] species formed during the first step can diffuse into the liquid phase and are therefore could be one of the main reason of the observed metal leaching.[17,28,29,44-47] Other factors like presence of different coordinating chemicals (ammonium salt, acrylic and cynnamic esters) could also increase the Pd-leaching during reaction. Examination of Fig. 4 lends further support to these two ideas, because the metal concentration in the intermediate washings with pure NMP at 125°C (max 0.5 ppm) appears significantly lower in most cases than in the solutions collected from actual catalysis runs.

It is also worth to note the fact that in runs 3-5 the leaching level is not appreciably higher than in the washings, but it rises then in the following catalysis experiments. No apparent correlation with the conversion degree can be seen, thus suggesting the occurrence of some other unknown factor that could affects the leaching. Nonetheless, the very low Pd leaching registered during the coupling reactions can be ascribed to the ability of the pyridyl groups to coordinate the different palladium species formed in the catalytic cycle.[33,34,36,37] HRTEM investigation of the Pd-PVPy monolith recovered after 14 runs showed the presence of the starting Pd NPs (ca. 2 nm) along with occurrence of Pd NPs with somewhat increased sizes (10-15 nm) (Fig. 5S). Therefore, the same strong interactions that allowed to control metal leaching to a large extent, were apparently effective in extending the life-time of the catalytic monolith by preventing also the uncontrolled growth of the Pd NPs and the eventual formation of inactive bulk Pd.

In order to further study the applicability of the Pd-PVPy monolithic devices, the substrate scope was briefly examined (Table 2). With this aim, a new Pd-PVPy monolith was prepared and employed to sequentially promote the M-H alkenylations in continuo of differently substituted aryl

iodides (entries 1-6) and bromides (entries 7-9), with *n*-butyl acrylate. The monolith was washed with fresh NMP before new reaction. The catalytic reactor showed excellent activity and high conversions with aryl iodides bearing electron-withdrawing substituents at the para position, like 4-nitroiodobenzene (entry 2) and 4-iodoacetophenone (entry 3). Good activity was registered also with substrates containing weaker electron-withdrawing groups, such as ethyl 4-iodobenzoate (entry 4) and 4-bromoiodobenzene (entry 5), as well as with the more electron-rich aryl iodides 4-iodotoluene (entry 6) and 4-iodoaniline (entry 7), which are generally less reactive in the M-H reaction. By contrast, the results obtained by testing a few aryl bromides (entries 8-11) were less satisfactory. In fact, only the activated 4-nitrobromobenzene (entry 9) led to a good yield, albeit at higher temperature (175°C). On the other hand, yields did not exceed 20% with 4-bromotoluene (entry 10) and 4-bromoacetophenone (entry 11).

In order to rule out stability issues for the Pd-PVPy monolith under the more severe reaction conditions required by bromides, a run was carried out again with the standard iodobenzene substrate at $\phi = 25$ µL·min^{-1} and T = 125°C (entry 12).

Table 2, near here

The attainment of the usual high conversion in this benchmark run confirmed the substantial integrity of the monolith. Therefore, the less satisfactory results with 4-bromotoluene and 4-bromoacetophenone have largely to be related to the much reduced reactivity of these aryl bromides, already noted a number of times with supported Pd-pyridine catalysts in batch.[36,37]

3. Conclusions

New porous monoliths containing immobilized Pd Nps were synthesized inside standard stainless-steel HPLC columns, by starting with MVS-derived Pd NPs stabilized by the VPy monomer. Besides avoiding the use of additional ligands and the presence of residual reducing agents or metal salts inside the monolith. A detailed structural characterization of the monoliths performed by SEM and TEM microscopies revealed a remarkable homogeneous dispersion of very small Pd NPs (d_m = 2.3 nm) across the monoliths. Remarkably, the NP sizes appeared to be controlled at the stage of formation of the VPy stabilized clusters, as no further growth or sintering was observed during the radical copolymerization with the cross-linking agent EGDMA at 70°C.

The Pd-PVPy monoliths were active catalysts for in continuo M-H cross-coupling reactions on a variety of aryl iodides. Moreover, the continuous-flow mini-fluidic devices could be effectively used for 12-14 consecutive runs (more than 65 hours, 1604 mmol of product/mmol of Pd) with no reduction in activity and very low Pd leaching (levelled at an average value of 1.1 ppm). Efforts to expand the new approach described herein to the synthesis of porous polymers containing metal NPs to be used in other selective organic transformations are currently ongoing.
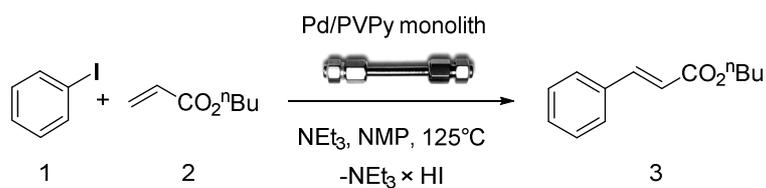
Acknowledgements

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at…

Table Captions:

Table 1. Flow-rate and temperature dependence for the continuous flow Mizoroki-Heck reaction in the Pd-PVPy monolith.
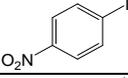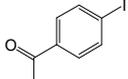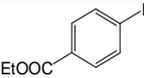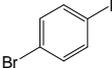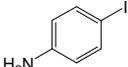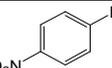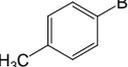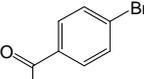
Table 2. Scope of the continuous-flow Mizoroki-Heck alkenylation reaction using Pd-PVPy monolith.

Table 1.

Entry[a]	ϕ^{b} ($\mu L \cdot min^{-1}$)	T (°C)	P (MPa)	Conversion[c] (%)	SA[d] (h^{-1})
1	100	150	14	45	68
2	50	150	6.5	83	63
3	25	150	1.5	> 99	
4	25	125	5	> 99	38
5	25	100	12	> 99	

a) Reaction conditions: iodobenzene (2.0 mmol, 1 equiv.), n-butyl acrylate (4.0 mmol, 2 equiv.), triethylamine (2.0 mmol, 1 equiv.), catalyst ($1.7 \cdot 10^{-2}$ mmol. Pd, loading 0.30 Pd wt. %), NMP (3.6 mL). b) Flow-rate. c) Determined by GLC. d) Specific Activity (SA) = mmol substrate (converted) $\times$ (mmol Pd $\times$ h)$^{-1}$.

Table 2

Entry[a]	Substrate	T (°C)	Conversion (%) [b]
1		125	> 99
2	O$_2$N	125	> 99
3		125	> 99
4	EtOOC	125	87
5	Br	125	82
6		125	92
7	H$_2$N	125	75
8	O$_2$N (Br)	150	65
9		175	87
10	H$_3$C (Br)	175	< 10
11	(Br)	175	< 20
12		125	> 99

a) Reaction conditions: phenyl halide (2.0 mmol, 1 equiv.), *n*-butyl acrylate (4.0 mmol, 2 equiv.), triethylamine (2.0 mmol, 1 equiv.), catalyst (1.7 ·10^{-2} mmol. Pd, loading 0.30 wt. Pd %), NMP (3.6 mL), ϕ = 25 μL min^{-1}. After each cycle, the monolith was washed with NMP (4 mL). b) Determined by GC.

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