Competing commercial catalysts

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Competing commercial catalysts: Unprecedented catalyst activity and stability of Mizoroki-Heck reaction in a continuous packed bed reactor

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ABSTRACT

Main obstacle for adopting continuous processes as a standard technology for Mizoroki-Heck reaction usually lies in its specific reaction mechanism. Here we present an important step forward answering the challenges unraveled through a comprehensive study that provides deeper understanding on the Mizoroki-Heck reaction, in particular the case when iodobenzene and butyl acrylate react in a continuous packed bed reactor in the presence of a Pd Supported Ionic Liquid Catalyst (SILCA). On-line UV–VIS spectrometry supported by ICP-OES, TEM and XPS measurements were carried out and the catalyst leaching was minimized. Finally, simple continuous flow process was proposed resulting in a high catalytic activity (up to 1470 mol_{ArI} $mol_{Pd}^{-1}h^{-1}$) and reaching productivity in the range of 12,000 to 16,000 mol_{ArI} mol_{Pd}^{-1} thus competing with the performance of commercial catalysts.

1. Introduction

The growing interest in the production of fine chemicals, pharmaceuticals and agrochemicals by continuous process technology is reflected by several studies found in open literature [1–9]. The main driving force is the advantage of the processes that valorise the benefits of continuous flow technologies, *i.e.* better production economy, good heat and mass transfer, waste reduction and enhanced product purity, higher throughput, safety and lower environmental impact [8]. In addition, continuous flow processes allow easier control of reaction parameters, easier process development and scale-up with a reduced time from laboratory scale to market [10]. In the past, the main obstacles appeared to be the additional economical investments, namely, the small production volumes cannot justify additional investments into utilisation of continuous flow technologies. Other issues are related to the safety and break-down of the equipment, availability of sufficiently active reactants and their cost, as well as the development of the reliable downstream process for continuous separation since strict regulations on purity and metal contamination are valid for pharmaceuticals (0.5 to 5 ppm) [11–14]. Therefore is why many efforts have been put in designing highly active and stable catalysts and developing simple technical solutions.

For the production of pharmaceuticals, carbon–carbon couplings are very important branch of reactions, often they are the key step in formulating more complex molecules for the synthesis of fine chemicals and active pharmaceutical ingredients (APIs) [15–18]. Moreover, Mizoroki-Heck coupling reaction is a highly valuable tool in organic and organometallic chemistry [19,20], mainly because of its versatility towards different reactants, solvents, reaction conditions and computability with many types of functional groups as compared to other reactions [11,21]. For these reactions, palladium is a most commonly used catalyst, while in a few cases also copper or nickel can be used but with a limited activity [22,23]. Mizoroki-Heck reaction has been a topic of intensive debates within the scientific community due to the controversial mechanism and the nature of the palladium catalysing the reaction. Nowadays it is widely accepted that the reaction is based on the Pd^0 catalysis and throughout the reaction cycle, palladium alternates between the oxidation states Pd^0 and Pd^{2+} (detailed reaction mechanism given in Supplementary information, SI) [24–31]. While some scientists have been sternly advocating a purely heterogeneous reaction mechanism, many investigators have found that the real nature of the palladium is more dynamic and that active palladium circulates between the support and reactants, later titled as the release-and-catch mechanism. It seems that there is a vast amount of studies reporting the emission of the active palladium from the surface of the catalyst or metallic nanoparticles, followed by participation in the reaction cycle and then

redepositing back to the surface, or re-entering the cycle or deactivation through the Pd black formation (see Scheme 1) [32–38]. Evidently, this reaction feature imposes the challenge for the application in a continuous flow process, because it could result in leaching of Pd that finally leads to catalyst deactivation [39]. Unfortunately, in the batch reactors this migratory phenomenon is often overlooked because the apparent reaction time is sufficient for palladium re-deposition but, under continuous flow, loss of Pd will most certainly require a significant down-stream separation effort in order to recycle the valuable metal and, moreover, to satisfy regulatory requirements on the final product purity.

By virtue of the problems with the palladium leaching and catalysts reusability in many Mizoroki-Heck reactions in continuous flow reactors, it may appear hard to justify efforts leading towards the direction of abounding homogeneous batch systems. It is known that the predictability of the heterogeneous continuous flow reactor performance is still incomparable with homogeneous systems, since in the first case the catalyst loading can be precisely tuned. Also, a purely heterogeneous catalyst often displays drastically lover activity and selectivity compared to a homogeneous one [40]. Still, the foremost important reason why pseudo-heterogeneous systems with release-and-catch mechanism attracts attention is that this kind of systems combine the benefits of both types of catalysis - high activity and easiness in separation. Driven by the growing demand for the molecules produced by C–C coupling reactions and with the constant advancement of the pseudo-heterogeneous catalysts, reactor system optimization is inevitable.

As an encouragement, few inspiring concepts can be found in literature. The PASSflow reactors which performed in a flow-through mode were efficiently used for Mizoroki-Heck couplings and other reactions. For this purpose highly active polymer composite catalyst were developed [41–43]. It was found that the ionic nature of the polymer catalysts was responsible for the palladium stabilization [44,45]. Similarly, other systems with polymer based catalysts have appeared. Micro-reactors constructed of fused silica capillaries and glass chips that were covalently bonded to the porous polymer monoliths and loaded with $PdCl_2$ have been described and used for Suzuki-Miyaura reaction demonstrating stability for 96 h and turnover numbers (TON) in range 2080–2200 $mol_{product}/mol_{Pd}$ [46]. Elsewhere, catalyst stability of 65 h on stream (1600 $mol_{product}/mol_{Pd}$) with 2 ppm of Pd leaching have been observed in Mizoroki-Heck reaction of a various aryl iodides inside HPLC type reactor column [47]. Also, Mizoroki-Heck reaction can be performed in a flow system with a supported liquid-phase catalyst with ethylene glycol coating and with a low catalyst loading but it is essential to address the catalyst poisoning by accumulated salts [48].

More complex approaches have been proposed, too. Some of them have implemented integrated crystallization as a continuous downstream protocol was proposed in case of Suzuki-Miyaura reaction in packed bed reactors. When appropriate catalyst-solvent-base system was selected, the catalyst showed a good stability for up to 30 h on stream [49]. Alternatively, palladium leaching from the system can be suppressed by means of two separate columns, one loaded with catalysts (supported ionic liquid-like phases) that serves as the reservoir of active palladium and the other one scavenging column loaded with a heterogenized base. For Mizoroki-Heck reaction this approach seems to work [50]. More importantly, it has been emphasized necessity for defining the origin of the catalyst reusability problems for retaining active catalyst in the reactor. One example of a successful use of continuous flow technology for production and purification has been demonstrated by an end-to-end integrated continuous manufacturing plant for the production of pharmaceuticals based on aliskiren hemifumarate by the MIT-Novartis Center [51].

The systems found in literature have been operated under very specific conditions and require a clever process design containing elements such as metal scavenging units or require reverse flow actions or flow circulation reactors that forces the system to operate more like a batch reactor. In addition, it is hard to use these systems for comparison, since different reactions are involved, usually using activated halides which are more reactive. Above all, the investigations do not assess the Pd leaching and long time-on-stream experiments. Studies that enable direct comparison of the different catalysts under identical conditions are rare [52].

In the present study, a simple packed bed reactor system was designed and used to investigate the catalyst performance for the Mizoroki-Heck reaction of iodobenzene and butyl acrylate in the presence of triethanolamine base. The main goal was minimizing metal leaching and promoting SILCAs as suitable catalysts for C–C coupling reactions in flow. The Pd supported ionic liquid catalyst (SILCA) that was synthesized and fully characterized in our previous work was used [53]. Catalysts with palladium loaded on propyl imidazolium bromide-tetramethylguanidinium pentanoate SiO_2 allowed a localised catalytic cycle within the ionic liquid layer. On-line UV–VIS spectrometry analysis was used as a main tool for monitoring effects of various parameters on metal leaching. This new investigation approach enabled to correlate the reaction conditions with palladium leaching. Different reaction parameters were optimised to obtain a metal-free product and to achieve a high catalyst activity. With the support of ICP-OES, TEM and XPS analysis, insight in catalytic and deactivation mechanisms was obtained, which guided to the simple methodology for catalyst recovery and extension of catalyst life cycle by at least 40 %. To the best of our knowledge, we designed one of the simplest and long-performing processes for Mizoroki-Heck reaction in a continuous flow reactor (with productivity in the range 12,000 to 16,000 $mol_{ArI}\ mol_{Pd}^{-1}$), comparable with commercial catalysts and susceptible to further upgrade.

2. Materials and methods

2.1. Materials

All the chemicals were obtained from commercial sources Sigma Aldrich and Alfa Aeser and they were used as obtained without additional purification. Commercially catalysts SiliaCat® Pd^0 and SiliaCat® DPP-Pd were obtained from SiliCycle®, Canada.

2.2. Catalysts preparation

The catalysts were prepared according to the procedure previously published for the palladium supported silica modified with 3-propyl imidazolium bromide-tetramethylguanidinium pentanoate [53]. In the first stage imidazole auxiliary was introduced on the surface of the SiO_2 via reaction of silanol groups with (3-chloropropyl)trimethoxysilane in toluene. 1 g of SiO_2 was treated with 5 mmol of the silylating agent. This was followed by the reaction with imidazole (10 mmol) in refluxing toluene and washing with ethanol. Subsequently, 1.5 mmol of esterified 5-bromo-pentanoic acid was reacted with 1 g of imidazole modified SiO_2
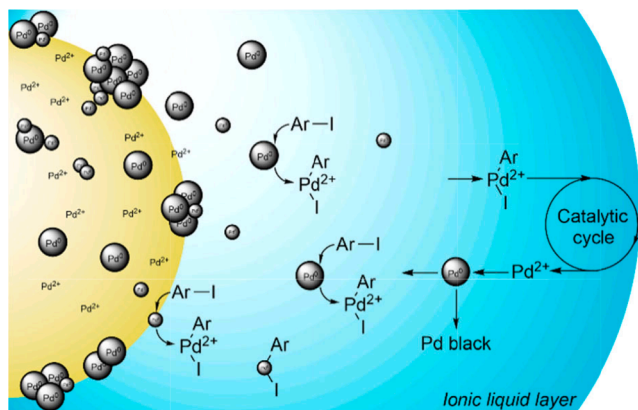
Scheme 1. Presumed palladium lifecycle.

in DMF thus forming an ionic liquid layer on the surface. The ester group was then converted to acidic species in the presence of a strong base in methanol, followed by carefully washing and drying of the solids. Thus obtained material was exposed to the coordination of the acid groups with strong bases. Ethanol solution of 5 mmol 1,1,3,3-tetramethylguanidine was reacted with 1 g of 3-propyl imidazolium bromide pentanoic acid modified silica. In the end, 1 g of this material was loaded with the PdCl$_2$ (0.1 mmol) that finally yielded SILCA with 1 wt% or 0.096 mmol g^{-1} of Pd loading (detected by ICP-OES). For those catalysts in which lower Pd loading was targeted, namely 50, 25 and 10 % of the above-mentioned loading, correspondingly lower amounts of palladium were used, *i.e.* 0.05, 0.025 and 0.01 mmol of PdCl$_2$ per 1 g of modified SiO$_2$. This yielded SILCAs with 0.61 wt% (0.057 mmol g^{-1}), 0.34 wt% (0.032 mmol g^{-1}) and 0.14 wt% (0.013 mmol g^{-1}) loadings, respectively.

2.3. General experimental procedure

All the experiments were performed in a designed tubular reactor shown in Fig. S2 (Supplementary information) with 0.7 cm internal diameter and 15 cm length equipped with HPLC pump. The reactor was heated by a heating block, and temperature was monitored with four thermocouples in order to control the temperature in the bottom, middle and top segment of the catalyst bed. The total length of the heated part was 11 cm out of which catalyst bed length was 9 cm. Outlet of the reactor was passed throughout the UV–VIS analyzer, while the system of valves allowed collecting GC aliquots before and after reactor and UV–VIS analyzer. In order to load the reactor quartz particles of 125–250 μm size were used as filling. In a down-joint part of the reactor quartz wool was placed, following with approx. 2 g of fine quartz granules that filled the first 3 cm of reactor, above which catalyst bed was loaded. In a typical experiment, the catalyst bed was prepared by diluting 0.2 g catalysts with 4.8 g of quartz to give a total of 5 g of 4 wt% diluted catalyst. Above the catalyst bed, the reactor was filled with quartz particles and capped with quartz wool. To perform the experiments after the loading, the reactor was firstly heated to the desired temperature and then the pumping was started. In the determined time intervals, GC samples were collected and UV–VIS spectra were collected.

2.4. Characterization

The reaction progress was monitored with gas chromatograph GC-HP 6890 series hawing HP-5 (5%-phenyl)-methylsiloxane capillary column (30.0 m, 320 μm, 0.25 μm) with FID detector (Agilent Technologies Inc., Santa Clara, CA, USA) running at the temperature of 300 °C. The injector temperature was 280 °C and the gas flow rate was 9.5 ml min^{-1}. The column was heated from 40 to 250 °C with a heating rate of 10 °C min^{-1}. As an internal standard, hexadecane was used. The collected GC aliquots were diluted to 16 % prior to analysis.

In-line UV–VIS spectra were recorded on a Shimadzu UV-2550 series spectrophotometer with a diode array detector. The quartz flowing cuvette with 1 cm path length was used and the wavelength was recorded in the range of 300–500 nm.

The palladium amount in the solid and liquid samples were analyzed with inductively coupled plasma optical emission spectroscopy (ICP-OES) with Optima 4300 DV optical atomic emission spectrometer (Perkin Elmer, Waltham, MA, USA). Before any analysis, the samples were digested in a solution of hydrochloric and nitric acid.

The palladium size and distribution were studied by the transmission electron microscopy (TEM) performed on a JEM 1400 plus (120 kV, 0.38 nm) with OSIS Quemesa 11 Mpix digital camera (Jeol Ltd, Tokyo, Japan). The image processing was carried out by imageJ.

The oxidation state of the metal was done with X-ray photoelectron spectroscopy (XPS). The spectra were recorded with a Kratos Axis Ultra DLD electron spectrometer (Kratos Analytical Ltd., Manchester, UK), supplied with a monochromated Al Ka source operating at 150 W. For individual photoelectron lines, the energy of 20 eV was used while for a

spectra analyzer pass energy of 160 eV was set. The binding energy (BE) scale was referenced to the Si 2p line of silica at 103.4 eV. The Kratos Software was used for spectra processing. To avoid reduction of Pd^{2+} ions during XPS measurements, Pd 3d spectrum was acquired during the first 5 min of exposure, and then again with other photoelectron lines

2.5. Residence time distribution

Residence time distribution (RTD) was determined by step response experiments with the use of reaction slurry as a tracer (0.5 M ArI) and UV–VIS spectroscopy to monitor concentration differences at the reactor outlet. Peak at the 500 nm wavelength was determinate as the most dominant and reliable to track. In the first experiment, the RTD was determined just for the pipeline conducting the flow (without reactor on line). This was done by switching the flow from solvent (DMF) to the reaction slurry and at the same time monitoring changes in the peak size at 500 nm in UV–VIS spectra. The residence time for the pipeline was calculated as the maximal value of the first derivative of absorbances at 500 nm. Analogously, in the second experiment, the RTD was determined for the reactor connected to the pipeline. The thus obtained result was used to determine RTD just for the reactor by discarding RTD value for the pipeline from RTD of the reactor connected with the pipeline. The obtained time (42.5 min) represents the residence time for the total length of the reactor (15 cm) with connectors filled with quartz wool (2 × 0.7 cm), meaning that approximated catalyst bed (9 cm length) residence time can be calculated as $RTD_{reactor} * (l_{cat.bed}/l_{reactor})$.

2.6. Catalysts recovery

Catalyst bed recovery and Pd reactivation was done by a simple flushing method. After determined time on stream, the flow was stopped and the reaction was quenched by cooling the reactor to room temperature, followed by flashing catalyst bed with the DMF at 0.1 ml min^{-1} flow rate for 8 h without removing it from the reactor. Thus reactivated catalyst bed was used as a fresh catalyst bed in restarted continuous flow reaction. After every 10 h on stream, this action was repeated.

3. Results and discussion

For studying the Mizoroki-Heck reaction under continuous flow conditions, a simple tubular reactor with 7 mm internal diameter of the tube and 9 cm length of the diluted catalyst bed was applied. The bed was heated by a heating block, shown in Fig. S2 (Supplementary Information).

Getting insight in the palladium lifecycle is difficult and it may require various *in operando* analyses [54]. In this work UV–VIS spectroscopy analysis is proposed as a simple qualitative method to determine the existence of palladium in the solution. For a more detailed, numerical values on the metal species present, advanced UV–VIS data processing is required, comprising the combined net analyte signal and principal component analysis [55,56]. This is the consequence of the fact that many transition metals do not show distinct peaks. The presence of metal ions, nanoparticles and clusters gives rise to overlapping bands in spectra that are difficult to deconvolute [56,57]. Alternatively, ICP analysis of the samples periodically collected at the reactor outlet could also provide answer on the total amount of the leached metal. Nevertheless, both of the methodologies are time consuming and technically requiring. As a straightforward solution an on-line UV–VIS analysis of the reactor outlet was used. It provided an overview of the palladium leaching depending on a different reaction conditions and confirmation whether leaching occurs or not. Obtained signals were compared and the best conditions for minimized metal leaching were defined. With this approach necessity for often quantifications was omitted and a facile and user friendly technique was implemented. To verify this approach ICP-OES analysis was used in the most relevant experimental cases.

The simplest way to illustrate the nature of palladium in the mixture is through the observation of the UV–VIS spectra of diluted PdCl$_2$ samples in different commonly used solvents for Mizoroki-Heck reaction as shown in Fig. 1. When looking at their UV–VIS spectra, DMF, DMA and NMP showed distinguishable broad peaks in the area of 420 nm and other ones that are less evident at 320 nm. In order to verify relation of the peaks size and palladium amount in solution, samples with the different Pd concentrations in solvents of interest were analysed (see Fig. S3). Indeed, peak size is related to the Pd amount.

It is known that these conventional dipolar aprotic solvents bind with soluble palladium species thus usually facilitating Pd leaching from catalyst surface, but also improving the reaction rate [50,58]. Therefore, it can be accepted that at the wavelength area of 420 nm (and 320 nm), Pd^{2+} ions mostly contribute to the spectral line [55,56]. The metallic Pd^0 nanoparticles do not give rise to a pronounced peak, but they do absorbs photons in the broad range of 350–390 nm, due to the oscillations of the conducting band electrons. These are also known as the surface plasmons [56,59].

Exploring the impact of the individual compounds on the palladium leaching from the catalyst surface in a continuous reactor system unravelled the catalyst stability (Fig. S4). When just DMF solvent passed the catalyst bed, only in the initial slurry fraction (time on stream 0 min) it was observed presence of the reduced Pd^0 with an associated peak at 360 nm in the UV–VIS spectra. This is probably associated to the palladium nanoparticles loosely deposited on the support surface. Furthermore, when each of the reactants in the solvent were passed through the catalyst bed under similar conditions, constant leaching could be observed in case of iodobenzene and acrylate. Pd^{2+} was monitored at 420 nm and 320 nm, which are supposed to originate from oxidised palladium originating from the metallic Pd^0 nanoparticles [60]. Interestingly, when all the reactants were passed together, as will be shown with reaction mixture, the leaching was possible to control.

In case of continuous flow Mizoroki-Heck reaction, the reaction temperature seems to have the most significant impact. In most of the cases published, the required reaction temperatures are much higher (up to 220 °C) in comparison with what is needed for common batch reactor systems [39]. Only at increased temperatures, the cross-coupling can be achieved with full conversion in a single pass through the reactor [45,50]. The high temperature influences the activation of the aryl halides, nevertheless this increase has to be done consciously in order to promote the reaction and avoid the formation of Pd black that can take place at high temperatures [61]. Experiments were performed at three different temperatures as presented in Fig. 2. In cases when reaction temperature was 100 and 120 °C, high yields were achieved only
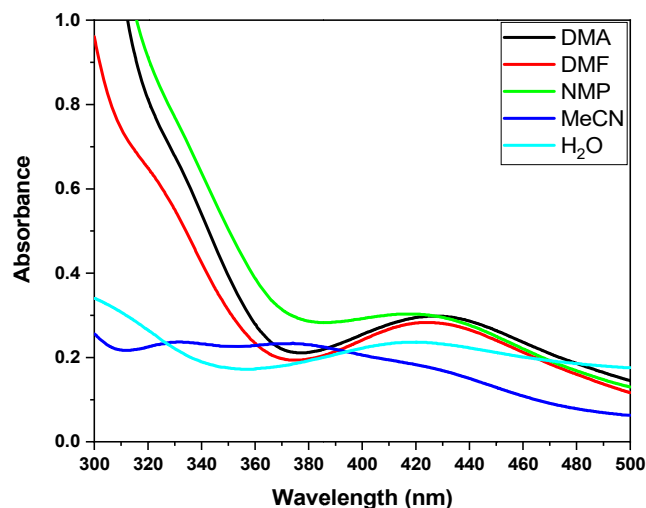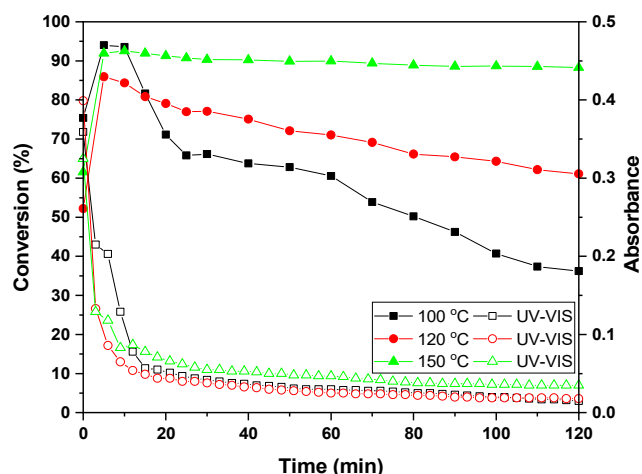

Fig. 2. Influence of temperature on the conversion in the continuous reactor Mizoroki-Heck reaction plotted with UV–VIS absorbance values at 420 nm wavelength. Reaction conditions: flow rate 0.1 ml min^{-1}, catalyst loading 0.2 g (0.096 mmol g^{-1}), 0.25 M iodobenzene, 0.5 M butyl acrylate and 0.5 M triethanolamine.

initially, when the concentration of active catalyst was at the highest. As the reaction temperature was increased to 150 °C, the catalyst seemed to be stable on stream maintaining a high conversion of 90 % of iodobenzene's initial amount. This value is assumed to correspond to the maximal conversion of iodobenzene under the actual reaction conditions due to the design of the catalyst bed *i.e.* lack of back mixing.

Parallel to monitoring the conversion, leaching of the Pd with UV–VIS was monitored. In Fig. S5 it is visible that within the range of operating wavelength, a wide absorption peak can be observed in the area less than 360 nm originating from the main reaction product, butyl cinnamate [62]. This disqualified the wavelength of 320 nm for identification of Pd^{2+}, leaving the absorbance values at 420 nm as the primary "witness" for the presence of metal in the stream. It is accepted that for the case of the Mizoroki-Heck reaction with iodobenzene, the olefin insertion is most likely the rate-determining step [63,64]. An important consequence of the rate-determining step is the stability of the catalyst resting state. For the present case, it means that after initial local leaching (if it happens) most of the released palladium would be in state in which it is found before the olefin insertion takes place, namely arranged in the Pd^{2+} complexes. In addition, it is expected that excess of unreacted compounds capable to oxidise Pd^0 implies that, at the reactor outlet, mostly Pd^{2+} species could be identified. Finally, the XPS analysis made at later stage of study (Table S2) showed that in the spent catalyst palladium is exclusively present as the Pd^0 on the surface of the SILCA. These nanoparticles are actual source of active Pd^{2+}. By plotting the data obtained by UV–VIS measurements at the value of 420 nm together with the conversion values at different temperatures in Fig. 2, it become evident that metal leaching is not a reason for the catalyst deactivation. The deactivation probably takes place due to the catalyst poisoning and Pd black formation. This means that at 150 °C, reaction dominates over the metal agglomeration and deactivation.

The following study disclosed optimal flow rate for performing the reaction at 150 °C (see Fig. 3). As expected, the long residence time and flow rate of 0.05 ml min^{-1} gave the highest conversion, but from the practical view such low flow rates are not applicable. Similar results were obtained with 0.1 ml min^{-1} flow rate, corresponding to the residence time 23.5 min (Fig. S6), while a slight drop of activity and yield of 82 % was detected when the flow rate was 0.2 ml min^{-1}. Nevertheless, experiments with prolonged time-on-stream (24 h) revealed that the flow rate 0.2 ml min^{-1} eventually leads to drop in the conversion, while in case of 0.1 ml min^{-1}, the high activity was maintained (Fig. S7). A further increase of the flow rate to 1 ml min^{-1} was associated with a

Fig. 1. UV–VIS spectra of PdCl$_2$ dissolution (0.001 mmol ml^{-1}) in different solvents.
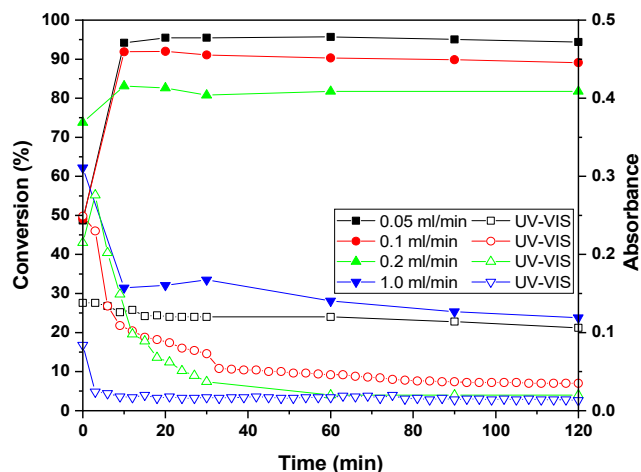
Fig. 3. Influence of flow rate on the conversion in the continuous reactor Mizoroki-Heck reaction plotted with UV–VIS absorbance values at 420 nm wavelength. Reaction conditions: temperature 150 °C, catalyst loading 0.2 g (0.096 mmol g^{-1}), 0.25 M iodobenzene, 0.5 M butyl acrylate and 0.5 M triethanolamine.

much lower catalyst activity. Based on the UV–VIS measurements (Fig. S8) and due to the absence of leaching, it could be concluded that this low yield of the products can be ascribed to short residence time in the bed. Next to it, this result may be due to the fact that at this flow rate the reaction solution was not heated in time and the actual temperature in the reactor did not reach the set temperature. Consequently, a flow rate of 0.1 ml min^{-1} was chosen as the most suitable from the point of efficiency and applicability.

Further attempts were made to increase the yields by decreasing reactant ratios among each other, with subsequently increasing the iodobenzene concentration from 0.25 M to 0.4, 0.45 and 0.5 M. At a first glance, this gave a good outcome (Fig. 4), but prolonged time on stream study revealed that for the case of 0.4 M of iodobenzene a slow decrease in the product yield from 89 to 82 % occurred in 24 h (Fig. S7). The probable reason is the faster catalyst poisoning and Pd black formation. For these reasons, two molar equivalents of the acrylate and base with respect to halide was rendered as the optimal ratio.

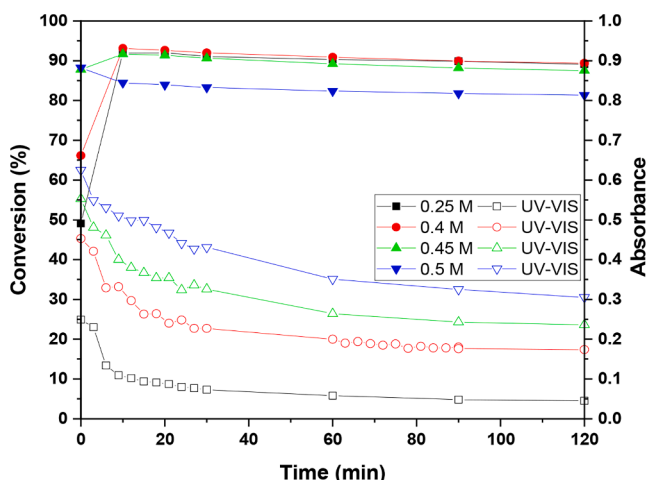This study prioritised that high catalyst activity is retained and Pd^0

Fig. 4. Influence of iodobenzene concentrations on the conversion in the continuous reactor Mizoroki-Heck reaction plotted with UV–VIS absorbance values at 420 nm wavelength. Reaction conditions: flow rate 0.1 ml min^{-1}, temperature 150 °C, catalyst loading 0.2 g (0.096 mmol g^{-1}), 0.5 M butyl acrylate and 0.5 M triethanolamine.

agglomeration into palladium black is prevented. The presence of the metallic species accelerates the Pd agglomeration and can result in the deposition of the metallic Pd in the reactor system and, finally, to leaching [48,60]. In general, an excessive Pd concentration can lead to slow deactivation of the catalyst trough the growth of the Pd nano-particles nucleated on the metal excluded from the reaction. This means that the palladium found in the reactor can be subjected to two competing processes: self-catalysed aggregation and catalytic reaction cycle (Scheme 1). Still, the reaction rate is of a lower order with respect to catalyst concentration while agglomeration is of the higher order [65]. For the case of olefin insertion being the rate-determining step, it practically means that catalyst to substrates ratio should be reduced to the value at which olefin insertion surpasses the aggregation [64]. This can be achieved by increasing the amount of reactants upon use of equal catalyst loading, as shown in Table 1 (entry 1) and Fig. 5. The experiment performed with doubled concentration of reactants (0.5 M of ArI) and with preserved reactant ratios (2 eq. of acrylate and base) demonstrated a good catalyst activity and long lasting stability for no less than 94 h time-on-stream. Further lowering of the catalyst-to-substrate ratio was made by decreasing the catalyst loading, because higher reactants concentrations lead to an increase in the reaction mixture viscosity, pressure increase and leaching of Pd.

Experiments with a lower catalyst loading (entry 2 to 4) revealed a "masked" catalyst activity. Which implies that even in the case of 0.02 g of catalyst loading, which represents one-tenth part of the initial catalyst loading, managed to provide a sufficient local catalyst concentration for reaching a high yield of the product for at least 8 h on stream (more detailed in Table S1). Almost a linear dependence of the catalyst specific activity on the catalyst loading indicates that a small local concentration of the catalyst takes part in the reaction at a time, while the rest of the catalyst bed stands by for the moment to step-in and overtakes its role in the catalytic cycle. We assume that this moment is determined by the time needed for the total poisoning of the ionic liquid layer of the initially active catalyst with the reaction side producing salts and with that loss of its ability to stabilise palladium and prevent agglomeration.

On the other hand, similar values of the productivity in experiments 1 to 4 implies on the constant stability of the catalyst and supports the claim that just a small fraction of the catalyst is included in the catalytic cycle. This is in contrast to what was expected that an increase in the catalyst amount would decrease the catalyst stability. Authors believe that the main reason for a high activity of the catalyst and good stability is the result of the supported ionic liquid catalyst nature as previously discussed [53]. It is known that in purely homogeneous systems the Pd

Table 1
Activities of different catalyst loadings for the Mizoroki-Heck reaction.

Entry	Catalyst[a]	Mass, g	TOS, h[b]	SA, mol$_{ArI}$ mol$_{Pd}$$^{-1}$h^{-1}[c]	Productivity, mol$_{ArI}$ mol$_{Pd}$$^{-1}$[d]
1	100 %	0.2	94	146.6	13780
2	100 %	0.1	50	295.2	14758
3	100 %	0.05	20	588.5	11770
4	100 %	0.02	8	1473.7	11790
5	50 %	0.2	7	243.0	1701
6	25 %	0.2	7	432.0	3024
7	10 %	0.2	4	1079.2	4317
8[e]	100 %	0.05	28	583.8	16347
9	SiliaCat® Pd^0	0.02	8	596.7	4773
10	SiliaCat® DPP-Pd	0.016	20	604.2	12083

[a] Reaction parameters: 0.1 ml min^{-1} flow rate, temperature 150 °C, 0.5 M Iodobenzene.
[b] Time on stream at which conversion was maintained above 90 %.
[c] Calculated as amount of converted iodobenzene per amount of used catalyst and time on stream.
[d] Calculated as specific activity × time on stream.
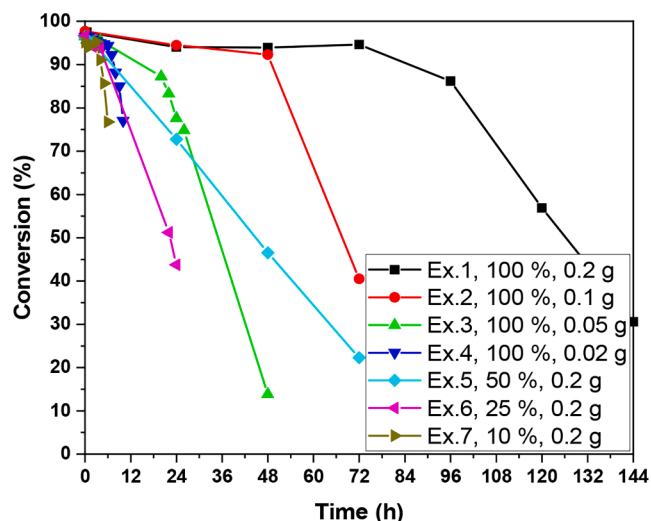[e] Flushing with DMF after every 10 h on stream.

Fig. 5. Influence of the catalyst loading on the conversion in the continuous reactor Mizoroki-Heck reaction. Reaction conditions: flow rate 0.1 ml min^{-1}, temperature 150 °C, 0.5 M iodobenzene, 1 M butyl acrylate and 1 M triethanolamine.

agglomeration can be suppressed with the use of ligands, while in case of pseudo-heterogeneous systems (release-and-catch mechanism) ligand-like species must be permanently anchored to the surface of the catalyst. So, in addition to the optimal catalyst-to-substrate rate, aggregation is suppressed by coordination of the ligands with Pd, which are supposed to sterically prevent the interaction between individual Pd atoms in the absence of reactants. It can be considered that the reason for such a high activity and stability of catalysts used lies in the structure of the ionic liquid layer that bears quaternary ammonium cations (R_4N^+) and carboxylate anions (RCO_2^-) [53]. In this context, the catalyst stabilising effect is associated with the coordination of the nitrogen derived ions with Pd^0 species obtained from Pd^{2+} precursors [66–69], as well as with potential coordination of Pd^{+2} complexes by carboxylates [70]. Finally, this leads to hypothesise that the actual reaction cycle takes place in the ionic liquid layer of the catalyst and not in the voids of the catalyst bed particles.

With the intention to make the catalyst more stable by increasing the amount of the ligand moieties to the Pd ratio, a series of catalysts with lower loadings were synthesized. Catalysts with approximately 50, 25 and 10 % of the original Pd loading (marked as 100 %) were prepared, characterized and tested (entries 5–7, Table 1). For these materials, it was hard to identify nanoparticles in the TEM images presented in Fig. S9, since they were certainly much smaller in size and had a small
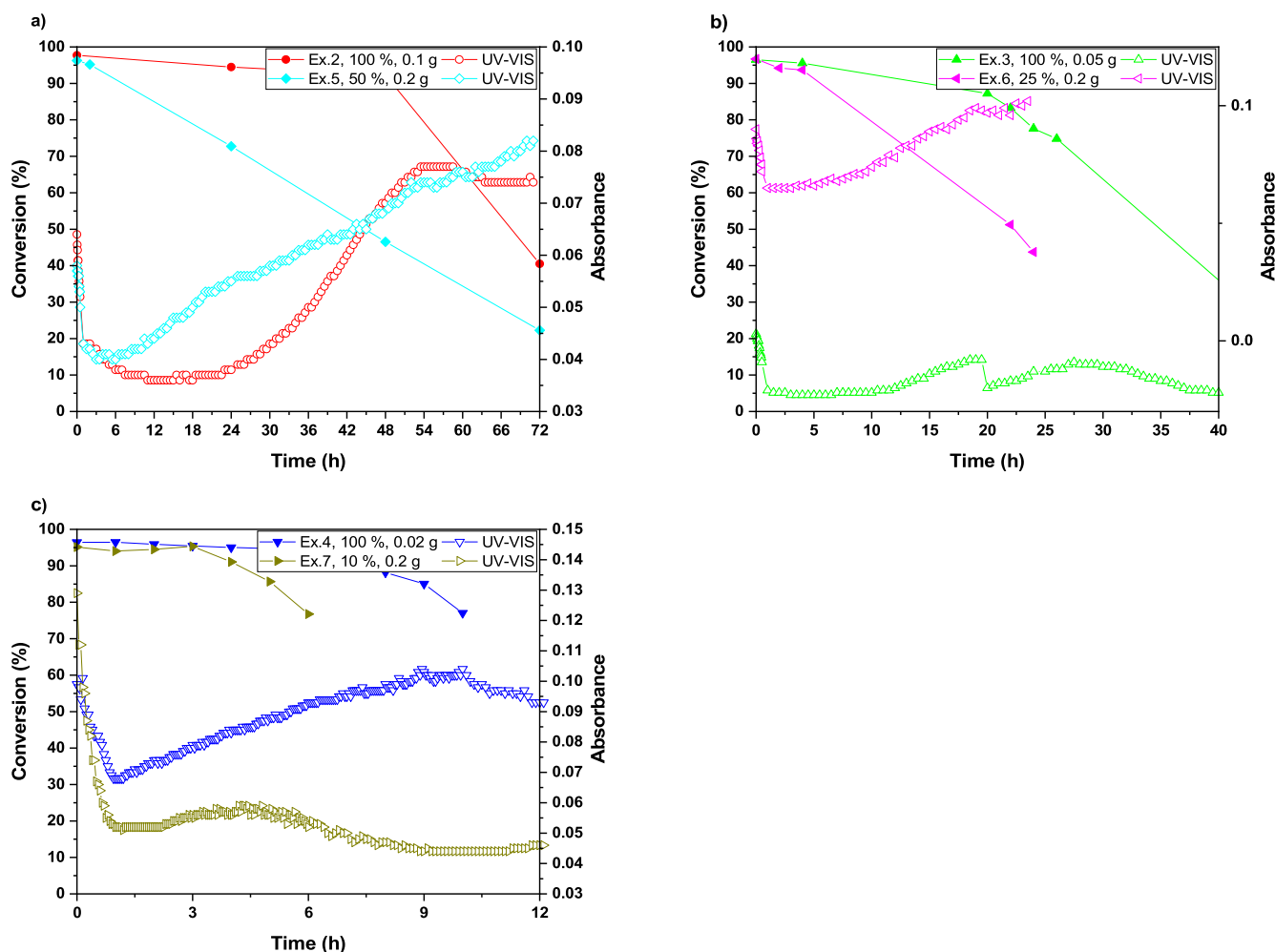

Fig. 6. Influence of the catalyst loading on the conversion in the continuous reactor Mizoroki-Heck reaction plotted with UV–VIS absorbance values at 420 nm wavelength. Reaction conditions: flow rate 0.1 ml min^{-1}, temperature 150 °C, 0.5 M iIodobenzene, 1 M butyl acrylate and 1 M triethanolamine.

Table 2
ICP-OES investigation of palladium leaching in Experiment 3.

Time, h[a]	Pd (ppm)	Loss of initial Pd amount (%)[b]	Average UV–VIS absorbance at 420 nm
0–10	<0.01	/	0.287
10–20	0.026	0.25	0.313
20–30	0.016	0.15	0.306

[a] Reaction parameters: catalyst amount 0.05 g (0.51 mg Pd), 0.1 ml min^{-1} flow rate, temperature 150 °C, 0.5 M Iodobenzene.

[b] Calculation based on the total amount of leached palladium collected during 10 h on stream.
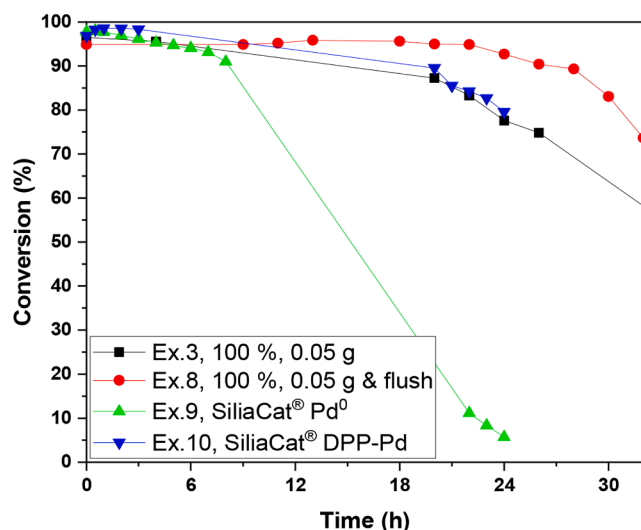

Fig. 7. Catalytic performance of the flushed catalyst and commercial catalysts in the continuous reactor Mizoroki-Heck reaction. Reaction conditions: flow rate 0.1 ml min^{-1}, temperature 150 °C, Pd loading 0.0048 mmol, 0.5 M Iodobenzene, 1 M Butyl acrylate and 1 M Triethanolamine.

amount of metal. Also, XPS analysis data are given in supplementary file and presented in tabulated form in Table S2 confirming the presence of predominantly Pd^{2+} complexes in all fresh catalysts.

Fig. 6 compares the results of the experiments with lower loadings of the original catalyst with results of the experiments with equivalent Pd loading of deprived catalysts, *i.e.* experiment 2 vs. 5, 3 vs. 6 and 4 vs. 7. By plotting UV–VIS data and observing the shape of the activity curve in Fig. 6, it can be deduced that in experiments 2 to 4 the initial stability of the catalyst performance corresponds to the slow poisoning and nanoparticles agglomeration, followed with rapid deactivation corresponding to leaching of ripe Pd agglomerates. It was evident that increased amount of moieties affected negatively on catalyst activity and more prominently on stability. Much faster catalyst poisoning caused by the loss of stabilising effect with almost constant palladium leaching, as confirmed by UV–VIS, can explain the drastic drop in yields in experiments 5–7.

More interest was dedicated to the investigation of experiment 3 with 0.05 g of catalyst loading (0.51 mg Pd). In this case, although the yields were high in 20 h on stream, the non-leaching time was much shorter (10 h), after which loss of Pd can be detected, while for the experiment 6 it is even shorter (Fig. 6b). This was confirmed by a separate experiment by ICP-OES analysis of samples collected in different periods of time as showed in Table 2. Namely, for the experiment 3, in the sample collected during the first 10 h on stream, the amount of Pd collected at the reactor outlet was below the instrument detection limit, from 10 to 20 h on stream 0.026 ppm were detected and in 20 to 30 h it was 0.016 ppm. Highest level of leaching occurred during the 10–20 h period, and it presented 0.25 % of total amount of Pd found in catalyst bed. The data obtained are in line with what was expected from UV–VIS monitoring. Also, after comparing the TEM images in Fig. S9 of the fresh catalyst (S9a) and those performed 10 h on stream, respectively, it was evident that this period corresponds to nanoparticle maturing and growth from 4 nm in the fresh sample to the range of 5–45 nm in the spent sample (S9e). Meanwhile the sample exposed 30 h on stream (S9f) evidenced the presence of agglomerated nanoparticles with 34 nm averaged diameter which are presumably more prone to leach.

Insight in the catalyst deactivation mechanism helps to suppress it. In order to demonstrate a potential solution in fighting the deactivation of the catalyst used in experiment 3, the reaction was quenched before the leaching occurred (after 10 h on stream) by cooling the reactor to the room temperature. Subsequently, flushing was performed with 50 ml of DMF (0.1 ml min^{-1}) to strip deposited salts and, consequently, the reaction was run again. The catalytic performance of the purified catalyst bed was tested demonstrating prolonged activity (Fig. 7 and Table 1, entry 8). By repeating the flushing in every 10 h on stream, the life cycle of the catalyst was extended from original 20 h on stream ($X_{ArI} > 90$ %) to 28 h on stream and 16,347 mol$_{ArI}$ mol$_{Pd}$$^{-1}$ productivity which is equivalent to 40 % improvement in catalysts performance. This is direct confirmation of poisoning as the major cause for the catalysts deactivation. It is anticipated that by optimizing the catalyst flushing procedure by varying the temperature, solvent type, flow-rates and volume can lead to much better outcome.

The results obtained were compared with systems which operate in continuous mode and utilise Mizoroki-Heck reaction. This kind of evaluation can be difficult due to the often misleading terminology related to continuous flow processes and due to scarcity of long time on stream experiments in the published literature. Nevertheless, most relevant studies are summarized in Table 3 and compared. Even though the observed systems are operating under different conditions, the data can certainly be used to position this study and imply on its significance, as the drastically higher productivity was observed in this work.

Additional benchmarking of the catalyst was made by comparing the obtained results with the performance of commercially available catalysts Silia*Cat*® Pd^0 2.51 wt% and Silia*Cat*® DPP-Pd 3.2 wt% produced by SiliCycle®. Tests were made with 0.0048 mmol Pd loading, same as in entry 3. From results shown in Table 1 (entry 9 and 10) it was obvious that Silia*Cat*® Pd^0 underperformed the catalyst used in this study preserving activity for 8 h on stream, while Silia*Cat*® DPP-Pd showed

Table 3
Comparison of the presented systems with similar previously reported systems used for Mizoroki-Heck reaction in continuous-flow conditions.

Catalyst	Pd, mg	Reaction	Temperature, °C	Flow-rate, ml/min	Productivity, mol$_{ArI}$ mol$_{Pd}$$^{-1a}$	Reference
SILCA packed bed	2.0–0.2	Iodobenzene/Butyl acrylate	150	0.1	14800-11800[b]	This study
Pd(0)-polymeric monolith /IL[c]		Iodobenzene/Methyl acrylate	200	0.05	217	[44]
Pd-PVPy monolith[d]	1.8	Iodobenzene/Butyl acrylate	125	0.025	1604	[47]
SILP-Pd[e]	34.3	Iodobenzene/Methyl acrylate	100	0.1	62	[67]

[a] Given as total amount (mol) of converted iodobenzene per amount of catalyst (mol).

[b] Calculated for the time on stream at which the conversion was maintained above 90 %.

[c] Calculated during the stable performance of 420 min on stream, in near critical EtOH at 8 MPa.

[d] Corresponds to the total performance in 14 experiments.

[e] Calculated for the best performing catalyst in the study (CAT-4) with use of 0.5 M of halide, during 10.5 h.

similar performance and activity. Fig. 7 shows visible that both of the commercial catalysts are less stable than the catalyst flushed with DMF. Flushing of the commercial catalyst was not made, because of potentially different catalyst deactivation reasons, which would require extensive study for identifications and be out of the scope of this work. This clearly demonstrates outstanding performance of materials and system discussed here, setting it *on par* with commercially available solutions.

4. Conclusions

The presented study discussed the utilization of continuous packed bed reactor technology for the Mizoroki-Heck reaction of iodobenzene and butyl acrylate with the use of Pd supported ionic liquid catalyst (SILCA). For the optimization of the reaction conditions and investigation of the catalyst stability, on-line UV–VIS spectrometry was used, allowing correlation of Pd leaching with temperature, flow rate, the amount of reactants and catalyst loading. Thus the obtained insights together with the information received with ICP-OES, TEM and XPS led to expanded understanding of the catalytic cycle, deactivation mechanism and to the hypothesis that the reaction is proceeding in the ionic liquid layer. All this served to design the efficient continuous process with low Pd loading and leaching, activity as high as 1470 mol_{ArI} $mol_{Pd}^{-1}h^{-1}$, reaching productivity in the range 12,000 to 16,000 mol_{ArI} mol_{Pd}^{-1} and competing commercially available catalysts. Additionally, simple catalyst bed flushing sequences enabled the extension of the catalyst stability for at least 40 %. Moreover, the disclosed study presents a potential approach for the investigation and utilisation of other SILCAs together with other types of catalysts for continuous Mizoroki-Heck reactions.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cej.2021.134432.

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