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Benchmarking Immobilized Di- and Triarylphosphine Palladium Catalysts for Continuous-Flow Cross-Coupling Reactions: Efficiency, Durability, and Metal Leaching Studies

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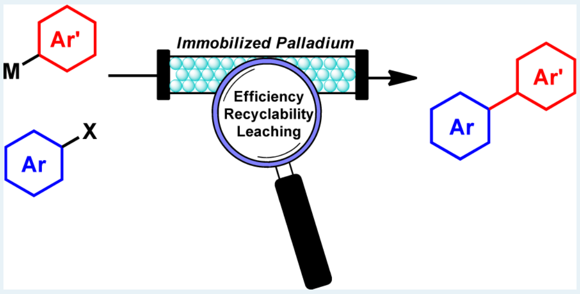
Supporting Information



ABSTRACT: Leaching resistance and recyclability, in addition to efficiency, are key parameters which constrain the choice of a catalyst for performing metal-catalyzed cross-coupling reactions in continuous-flow mode. Comparison of commercially available immobilized catalysts is often difficult because literature data are typically obtained under a wide range of reaction conditions. Here we present a comparative investigation on some of the most common immobilized phosphine-based Pd catalysts, namely Pd Tetrakis (polymer bound), FiberCat 1001, EnCat TPP30, and SiliaCat DPP-Pd. The efficiency, recyclability, and leaching resistance of each of the catalysts has been carefully investigated under a standard set of conditions as well as a selection of literature-based protocols. The data presented herein enable a direct comparison of these catalysts and provide further insights into the leaching phenomena of these types of ligand-based palladium catalysts.

KEYWORDS: *continuous flow, cross-coupling, palladium, immobilized catalysts, leaching*

INTRODUCTION

There is little doubt that the development of cross-coupling chemistry over the past decades has revolutionized modern synthetic organic chemistry.[1] These transition-metal-catalyzed carbon−carbon and carbon−heteroatom bond forming reactions have had a significant impact on the synthesis of pharmaceuticals, agrochemicals, and natural products.[1,2] As a recognition of their seminal work, Richard Heck, Ei-ichi Negishi, and Akira Suzuki were awarded with the Nobel Prize in Chemistry in 2010.[3] The discoveries by these authors of Pd-catalyzed C−C bond formations changed how many organic syntheses are conceived and later on inspired other chemists to develop a wide range of additional cross-coupling reactions, including carbon−heteroatom coupling.[1,2,4] In the case of carbon−carbon bond forming reactions palladium is the most commonly used transition-metal catalyst. In a few cases metals other than palladium are used to perform these cross-couplings (typically copper or nickel), although the catalytic activity of these metals is generally significantly lower in comparison to that of palladium.[5]

The intense research in the field of cross-coupling chemistry during the past two decades has led to the development of "greener" reaction conditions as well as a large number of highly efficient catalyst/ligand combinations.[1−5] Apart from a plethora of homogeneous catalytic systems, several immobilized palladium catalysts have also been developed[6] and have been extensively utilized as heterogeneous catalysts, on the premise that the the solid-supported active metal could be easily removed from the reaction mixture and reutilized. In this context, several immobilized catalysts have been employed both in batch procedures and in continuous-flow applications.[7] In a continuous-flow process the catalyst is typically placed in a packed-bed reactor and the reaction mixture is flown through the reactor using an appropriate pumping system.[8] The catalytically active material remains located in a specific part of the reactor during processing of the reaction mixture, and therefore, the reaction and separation of the catalyst from the solution (including the product) take place simultaneously. In this way, catalyst reuse and recycling is simplified, as a catalyst separation/filtration step can be avoided. Furthermore, as small amounts of the reaction mixture are in contact simultaneously with the packed-bed reactor, high local concentrations of catalyst are achieved, resulting in increased reaction rates in comparison to that of a batch reaction.[8] Thus, high conversions can be obtained within residence times of a few seconds or minutes, although on the other hand the same local concentration effect can also sometimes lead to lower selectivities.

When cross-coupling chemistry and continuous flow using a packed-bed heterogeneous catalyst are combined, substantial amounts of "dissolved" palladium are typically observed in the reaction mixture collected from the reactor output.[9] Ultimately, deactivation of the catalyst bed and reduced product formation are inevitable. The leaching phenomenon in cross-coupling

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reactions is ascribed to the fact that the reaction mechanism for these kinds of transformations is (quasi)homogeneous and involves the transformation of Pd^0 species into soluble Pd^{II} during the oxidative addition step.[10] When an immobilized catalyst is used in a batch cross-coupling reaction, the leaching of palladium is not obvious because upon completion the metal readsorbs onto the solid support (thus acting as a "reservoir" of soluble, active Pd species). When continuous flow is used, the situation is different: in continuous-flow mode, the palladium metal will progressively be "chromatographed" through the packed-bed catalyst until eventually all Pd will be removed from the support owing to continuous metal leaching/readsorption.[9] This effect, which becomes especially relevant when long-run experiments are performed, leads to significant amounts of transition metal being leached out of the reactor, contaminating the product.

In 2009 our group carried out a detailed investigation on the mechanism and leaching phenomena for the Pd/C-catalyzed Mizoroki−Heck reaction of 4-iodobenzonitrile with butyl acrylate in microwave batch and continuous flow.[11] Although Pd/C is one of the most widely used catalysts for (batch) cross-coupling chemistry,[12] under the applied continuous-flow conditions a rapid metal leaching and catalyst deactivation was observed. Notably, novel and more sophisticated supported Pd catalysts for cross-coupling chemistry are being continuously reported in the literature.[1−5] In particular, incorporation of ligands to the immobilized catalyst often results in improved stability and leaching resistance of the solid material.[2] In some instances, continuous-flow applications have been also performed to test the leaching resistance and hence the recyclability and durability of the catalysts. However, the flow experiments have often been performed under very specific conditions (solvent, temperature) and at very low substrate concentrations. Low substrate concentrations obviously result in low amounts of metal being leached from the packed-bed reactor but compromise the practical use of a procedure that has no possibility of being scalable. A comparison of the performance of the different commercially available catalysts is therefore difficult, as the existing literature data have been obtained under a wide range of reaction conditions. Herein we present a benchmarking study of some of the most common immobilized diarylphosphine- and triarylphosphine-based palladium catalysts: namely, Pd Tetrakis (polymer-bound), FiberCat 1001, EnCat TPP30, and SiliaCat DPP-Pd. The efficiency, durability, and leaching resistance of these supported catalysts have been studied for continuous-flow Mizoroki−Heck and Suzuki−Miyaura reactions under analogous as well as selected literature conditions. The data presented herein enable a direct comparison of these catalysts and will help to understand the leaching phenomena of these types of ligand-based supported Pd catalysts.

■ RESULTS AND DISCUSSION

Initial Considerations. Four popular Pd-supported catalysts have been considered in our comparative study (Figure 1). Polymer-bound Pd Tetrakis, FiberCat 1001, EnCat TPP30, and SiliaCat DPP-Pd differ in the solid matrix hosting the active metal catalyst and the way in which the ligand is attached to the support (covalent bonding, encapsulation) (Figure 1). All of the catalysts evaluated herein have in common the presence of a substituted diphenylphosphine (DPP) or triphenylphosphine (TPP) as ligand. It has been shown that the presence of a ligand has beneficial effects in terms of catalyst stability and durability, as well as reaction selectivity and efficiency in some cases.[2] Two cross-coupling reactions have been selected as models for our continuous-flow experiments: the Mizoroki−Heck reaction of 4-iodobenzonitrile (**IBN**) with *n*-butyl acrylate (**BA**) (in analogy to our previous study on the Pd/C catalyst[11]) and the Suzuki−Miyaura reaction of **IBN** with phenylboronic acid (**PBA**) (Scheme 1). The use of aryl bromides in these transformations was troublesome, since their lower reactivity resulted in only moderate conversions in flow after a single pass through the packed-bed reactor.[11]

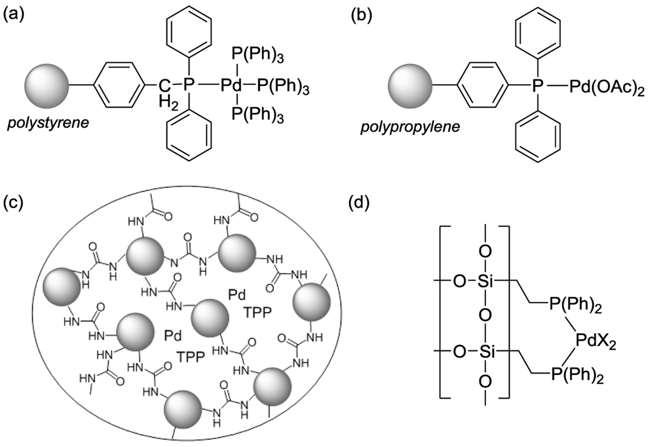
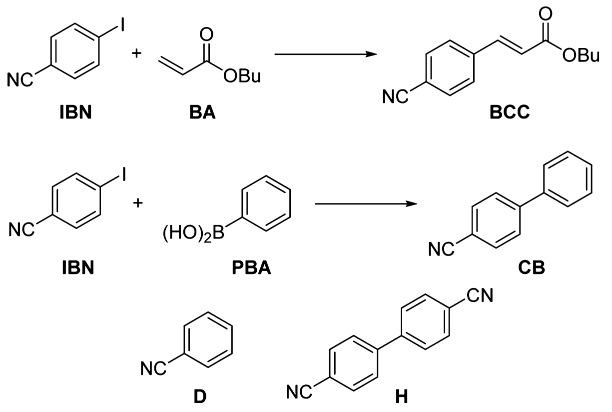


Figure 1. Structures of the (a) polymer-bound Pd Tetrakis, (b) FiberCat 1001, (c) EnCat TPP30, and (d) SiliaCat catalysts used in this work.

Scheme 1. Cross-Coupling Reactions Selected as Models in the Present Study[a]



[a]Dehalogenation (**D**) and homocoupling (**H**) side products typically observed in these reactions are also shown.

In all cases the temperature has been kept below 120 °C, even when low conversions were observed. It has been shown that at temperatures above 120 °C Pd catalysts are prone to form Pd black nanoparticles[13] which could provoke a faster deactivation and leaching of the active metal species. Selected literature-based reaction conditions (temperature, concentration, base, solvent) have been applied for each of the immobilized catalysts to independently assess their efficiency and stability. Furthermore, a set of reaction conditions which utilizes acetonitrile as solvent and triethylamine (TEA) or diisopropylethylamine (DIPEA) as base has been concurrently utilized in all cases. Acetonitrile is a relatively inert, weakly complexing solvent compatible with all solid-supported catalysts considered in this study.

Each of the immobilized catalysts has been tested for both the model Mizoroki–Heck and Suzuki–Miyaura reactions. In all cases a set of preliminary microwave (MW) batch experiments was performed to estimate an appropriate range of temperatures for the flow experiments.[14] Fresh catalyst cartridges were used for all flow runs, and typically 20 mL of the reaction mixture or 10 mmol of substrate was processed. For this purpose a commercial flow instrument (X-Cube, ThalesNano) was utilized (Figure 2).[15] Conversion profiles were obtained by GC-FID monitoring of samples collected from the reactor output. To assess the amount of metal leaching produced during the flow processing, the Pd content of the crude reaction mixtures was determined by ICPMS analysis (see the Experimental Section for details).

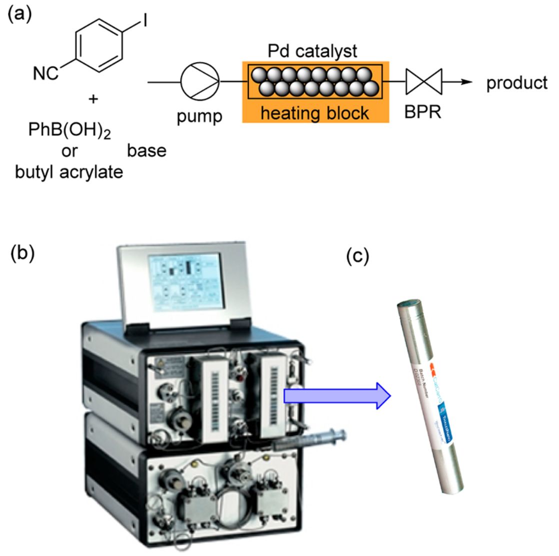


Figure 2. Schematic representation of the flow setup (a), performed in a X-Cube reactor from ThalesNano (b). The immobilized catalysts were loaded in a CatCart stainless steel column reactor (c).

Polymer-Bound Pd Tetrakis. This supported catalyst, developed by Fenger and Le Drian in 1998, consists of a diphenylphosphinated divinylbenzene (DVB) cross-linked polystyrene matrix treated with a solution of Pd(PPh$_3$)$_4$ in benzene.[16] In their original work the catalyst was tested for the batch Suzuki–Miyaura reaction of 4-bromopyridine with phenylboronic acid. Excellent yields analogous to those obtained when Pd(PPh$_3$)$_4$ was used as homogeneous catalyst were obtained, with the advantage that the heterogeneous catalyst could be easily separated from the reaction mixture and reused more than five times without any activity decrease. Recently, it has been shown by Gordon and co-workers that this catalyst can be applied for continuous-flow Suzuki–Miyaura reactions involving furylboronic acids,[17] although a detailed investigation on the stability of this particular catalyst was not carried out.

Our study started with a series of preliminary microwave batch experiments to evaluate the most appropriate reaction conditions. As an established literature protocol for cross-coupling reactions in flow using this catalytic system was not available, we decided to carry out all our experiments using acetonitrile as solvent and TEA or DIPEA as base. Thus, ~0.5 M solutions of the substrate in MeCN were treated with 1.5 equiv of the coupling partner (phenylboronic acid or *n*-butyl acrylate) and 1.5 equiv of base and mixed with 0.5 mol % of the supported catalyst. The mixture was heated in a single-mode microwave reactor for 15 min at temperatures ranging from 70 to 100 °C and the crude product analyzed by GC-FID (see Table S1 in the Supporting Information). A temperature of 100 °C was not exceeded, as this is the maximum working temperature recommended by the catalyst vendor. As expected, the best conversions were obtained at this temperature (56–57% and 36–40% for the Suzuki and Heck reactions, respectively) and a relatively good selectivity (90%) was observed for both transformations. The base employed did not affect the reaction outcome, and DIPEA and TEA gave analogous results.

We thus decided to move forward and utilize these conditions (100 °C, TEA or DIPEA as base in MeCN) in continuous-flow mode (see the Experimental Section for details). A volume of 20 mL of a 0.5 M reaction mixture was prepared for both cross-coupling reactions and pumped through the reactor utilizing fresh catalyst cartridges preheated at 100 °C. The reactor pump was set to a flow rate of 0.2 mL min^{-1}, which results in a residence time within the packed-bed reactor of approximately 2–3 min. Samples were collected from the reactor output and analyzed by GC-FID to monitor the reaction conversion and selectivity over time (Figure 3). In the case of the Heck reaction (Figure 3a) an essentially constant reaction profile was obtained under steady-state conditions. Full conversion was obtained within the relatively short contact time of the reaction mixture with the catalyst bed, although with a significantly lower selectivity with respect to batch processing (with formation of ~25% dehalogenation product and ~15% homocoupling). Both effects are typically ascribed to the high local concentrations of catalyst achieved using a packed-bed reactor.[11] Importantly, after 180 min working time and 10 mmol of starting material processed no drop in the conversion was noticeable.

For the Suzuki reaction the picture looked completely different (Figure 3b). In this case the substrate was fully consumed during the first 40 min of processing (after an initial period of stabilization) but then dropped dramatically to a conversion of <10%. Obviously the catalyst was rapidly degraded during this reaction, and significant amounts of metal were most likely leached from the support, contaminating the product.

The irregular contour of the conversion profiles during the first minutes of the continuous-flow processing is worth noting. Seemingly, only the desired cross-coupling is initially observed, followed by a drop in the selectivity until the system stabilizes. This effect, particularly pronounced for the Suzuki–Miyaura reaction, is due to the different affinities of each of the reaction components to the solid phase of the packed-bed reactor. Thus, the reactants as well as the formed products are "chromatographed" through the catalyst column, causing an initial incorrect reaction stoichiometry until steady-state conditions are reached. As could be observed in Figure 4, the cross-coupling product is eluted through the packed bed faster than other reaction products and therefore is the first species observed in the conversion profile. Butyl acrylate is also separated and eluted more rapidly than other reagents. This "chromatographic effect" results in an apparent poor selectivity at the initial stage of processing, with a greater amount of homocoupling product being obtained, due to the lower

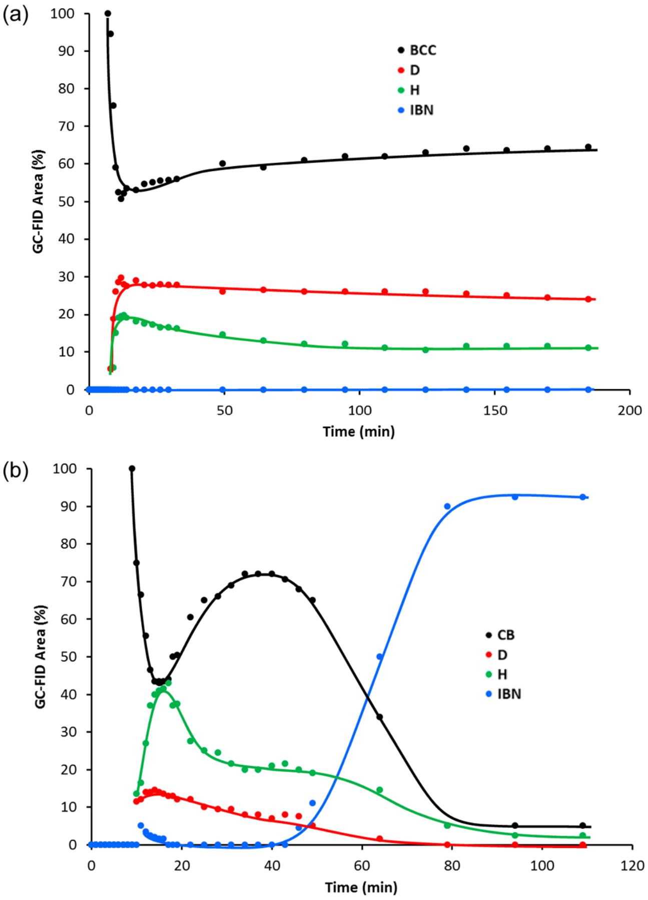


Figure 3. Conversion profiles obtained for the continuous-flow Mizoroki–Heck (a) and Suzuki–Miyaura (b) reactions catalyzed by polymer-bound Pd Tetrakis. The first ∼10 min, in which no compound is observed in the GC-FID, corresponds to the dead volume of the reactor. Conditions: 0.5 M substrate in MeCN, 1.5 equiv of TEA, 1.5 equiv of $PhB(OH)_2$ or *n*-butyl acrylate, 100 °C, 0.2 mL min^{-1}.

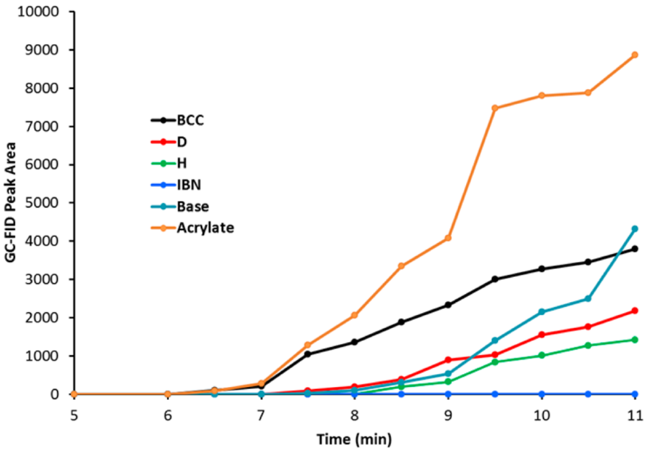


Figure 4. Differences in the retention of the components of the Mizoroki–Heck reaction within the polymer-bound Pd Tetrakis catalyst cartridge. Base: TEA.

effective amount of coupling partner until steady-state concentrations are reached. The effect is even more pronounced for the Suzuki–Miyaura reaction (for an analysis of the corresponding chromatographic effect, see Figure S9 in the Supporting Information).

ICPMS analyses revealed that significant amounts of Pd had leached from the packed-bed reactors for both cross-coupling reactions. Not surprisingly, a higher amount was determined for the Suzuki–Miyaura (4.61 mg) in comparison to that for the Mizoroki–Heck crude reaction mixture (2.25 mg) (the amount of palladium refers to that amount contained in the total crude reaction mixture), as in the former case the reaction conversion dramatically dropped after 40 min of processing. However, the amount of metal measured was small in comparison to the total amount of palladium contained in each catalyst cartridge. A close inspection of the packed-bed reactor denoted a substantial degradation of the material, with copious amounts of Pd black particles found in the reactor tubing and connections.

FibreCat 1001. A matrix of triphenylphosphine-functionalized polypropylene fibers serves as support for this palladium acetate based catalyst (Figure 1b).[18] Apart from a number of batch mode applications,[19] this immobilized catalyst has been utilized in continuous-flow mode for Sonogashira[20] and Suzuki–Miyaura[17,21] cross-coupling reactions. In this context, a catalyst reusability study was carried out by Dormán and co-workers for continuous-flow Sonogashira reactions.[20] The results revealed important substrate-dependent reductions in conversion after reusing the packed-bed reactors more than five times.

Our own initial microwave batch experiments showed excellent conversion (95%) and selectivity (>99%) for the Mizoroki–Heck reaction on heating to 120 °C for 15 min using DIPEA as base (see Table S2 in the Supporting Information). The Suzuki–Miyaura coupling was less efficient with this catalyst, and at the same temperature only 60% conversion was achieved. This temperature was thus selected for the long-run continuous-flow experiments. In this case DIPEA performed slightly better than TEA as the base for the reaction.

The conversion profiles resulting from the continuous-flow experiments were somewhat similar to those obtained with the polystyrene Pd Tetrakis immobilized catalyst (Figure 5). In the case of the Heck reaction, after an initial period of erratic selectivity due to the chromatographic effect, a more or less constant profile with full conversion and ca. 60% selectivity was achieved (Figure 5a). Evaluation of the retention of the reaction components in the FiberCat support was analogous to that for the polystyrene matrix, and similar chromatography curves were observed (see Figures S10 and S11 in the Supporting Information). Notably, after 80 min of processing the conversion started to drop slowly. Similar to the case for polymer-bound Pd Tetrakis, the Suzuki–Miyaura reaction provoked a very rapid degradation and deactivation of the supported catalyst, starting after approximately 20 min of flow processing (Figure 5b).

ICPMS analyses of the crude reaction mixtures again revealed significant amounts of Pd leached from the packed-bed reactors after processing 20 mL of the reaction mixture (2.58 and 2.43 mg of Pd for the Mizoroki–Heck and Suzuki–Miyaura reactions, respectively). However, the quantity of leached palladium was again relatively moderate in comparison with the total amount contained in the catalyst cartridge (ca. 15 mg), despite the rapid drop of conversion observed for the Suzuki–Miyaura reaction. In this particular case the content of the solid material inside the used catalyst cartridge was also examined (Figure 6). Apparently, the reaction provoked the formation of Pd black particles, which gradually moved through

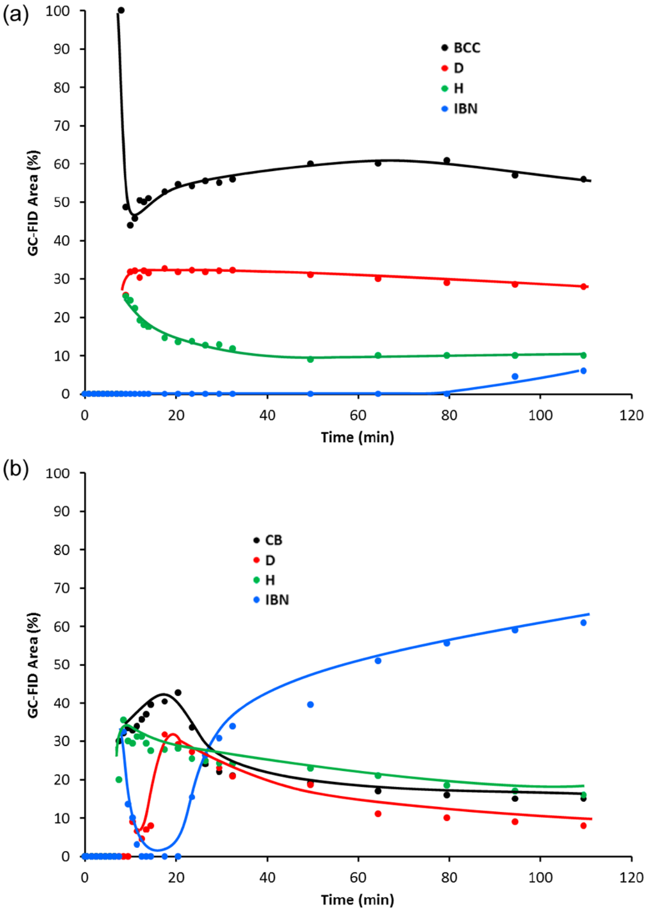


Figure 5. Conversion profiles obtained for the continuous flow Mizoroki–Heck (a) and Suzuki–Miyaura (b) reactions catalyzed by Fibercat 1001. The first ~10 min, in which no compound is observed in the GC-FID, corresponds to the dead volume of the reactor. Conditions: 0.5 M substrate in MeCN, 1.5 equiv of DIPEA, 1.5 equiv of $PhB(OH)_2$ or *n*-butyl acrylate, 120 °C, 0.2 mL min^{-1}.

the column with the flow of the reaction mixture. Thus, at the end of the flow run most of the metal was deposited in the final part of the packed-bed reactor. ICPMS analyses of the different portions of the solid material confirmed higher amounts of Pd in the final part of the packed-bed reactor after the Suzuki–Miyaura reaction (Figure 6). This catalyst degradation with migration of Pd through the supported catalyst would indeed result in a much shorter contact time of Pd-containing material with the reaction mixture. This effect, together with the metal leaching, can explain the significant reduction in conversion observed.

PdEncat TPP30. Polyurea encapsulated Pd is a popular, commercially available class of heterogeneous catalysts introduced by the Ley group in 2002.[22] The polyurea matrix provides the material with a good ability to ligate metal species and has been used in a wide range of applications, including cross-coupling reactions.[23] Although considered a heterogeneous catalyst, it was shown by Broadwater and McQuade[24] that most likely soluble, catalytically active Pd species leached from the support are responsible for catalysis in cross-coupling reactions, with the encapsulated palladium species serving as a reservoir for soluble palladium. Suzuki–Miyaura cross-coupling reactions using PdEncat in a packed-bed reactor in continuous-flow mode have also been described.[25] Importantly, metal contamination in the products was observed in some cases and a metal scavenging resin had to be installed into the flow setup. Attempts to process large-scale reaction mixtures failed, and the conversions dropped dramatically after a few hours of processing.[25c]

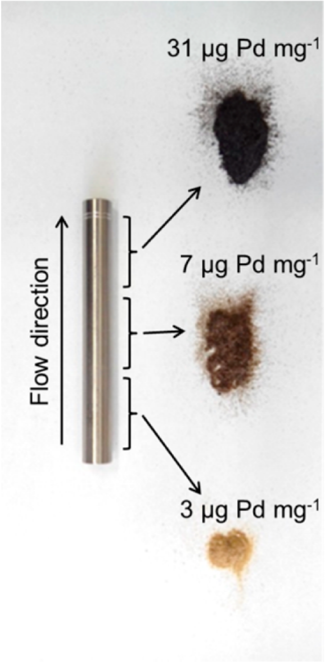


Figure 6. Visual representation of the contents of a used Fibrecat 1001 catalyst cartridge after a continuous-flow Suzuki–Miyaura reaction. The Pd black particles are clearly concentrated in the final part of the packed-bed reactor after the flow run.

Our study again started with a series of preliminary microwave batch experiments to establish adequate reaction conditions for this catalyst (see Table S3 in the Supporting Information). Apart from an evaluation of the general acetonitrile/DIPEA conditions, other base and solvent systems utilized in the literature[25] were tested. In MeCN and DIPEA or TEA as base, low conversions (<25%) were observed in all cases after 15 min at 120 °C, in contrast to the high conversions achieved with Pd Tetrakis and FibreCat 1001 under analogous conditions. When EtOH was used as solvent instead and tetrabutylammonium acetate (TBAOAc) was used as base, higher conversions (60% and 75% for Suzuki–Miyaura and Mizoroki–Heck reactions, respectively) and excellent selectivities were achieved (Table S3, entries 4 and 13). Ultimately both solvent/base systems were translated into flow for comparative purposes.

The flow experiments carried out using the two systems and the Pd Encat catalyst highlight the importance of the solvent/base choice on the stability of the packed-bed reactor. When the Mizoroki–Heck coupling was performed in acetonitrile with TEA as base, a constant amount of product was observed (after the initial irregular selectivity due to the chromatographic effect) on processing 20 mL of the reaction mixture (10 mmol) (Figure 7a). Even when the amount of reaction mixture was doubled (40 mL), no drop in conversion could be seen (see Figure S1 in the Supporting Information). In stark contrast, when EtOH was used as the solvent in combination with TBAOAc as base (conditions based on the work of the Ley group[25]) a constant decrease in the product formation was observed during flow processing (Figure 7b). Again, Suzuki–Miyaura reactions resulted in much faster degradation of the

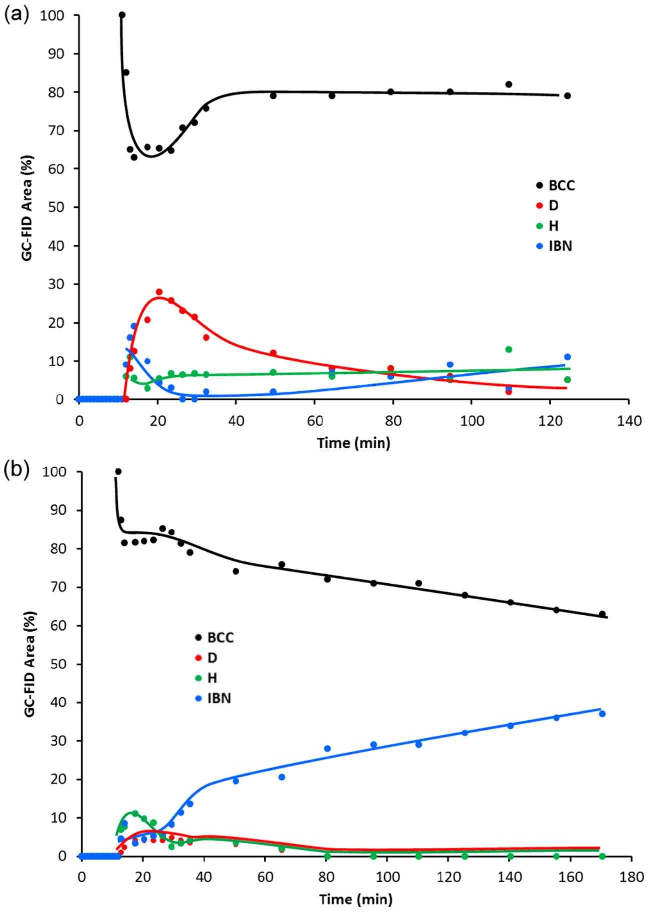


Figure 7. Conversion profiles obtained for the continuous-flow Mizoroki–Heck reactions catalyzed by Pd Encat TPP30 using the (a) acetonitrile/TEA and (b) ethanol/TBAOAc solvent/base systems. The first ~10 min, in which no compound is observed in the GC-FID, corresponds to the dead volume of the reactor. Conditions: (a) 0.5 M or (b) 0.25 M substrate, 1.5 equiv of base, 1.5 equiv of *n*-butyl acrylate, 120 °C, 0.2 mL min^{-1}.

immobilized catalyst (Figures S2 and S3 in the Supporting Information).

Despite the constant production of the desired Mizoroki–Heck cross-coupling product using acetonitrile as solvent, significant amounts of Pd (6.25 mg) were detected in the crude reaction mixture by ICPMS after processing 20 mmol of the substrate. Interestingly, lower amounts of Pd were found in the ethanolic crude mixture (1.03 mg), probably reflecting the fact that the catalyst is degraded or poisoned but that the Pd does not pass the packed-bed reactor filter. As for the previous catalyst studies, higher amounts of Pd were found in the Suzuki–Miyaura reaction mixtures (detailed information on the ICPMS Pd determination for all reactions is collected in Table S5 in the Supporting Information).

SiliaCat DPP-Pd. SiliaCat DPP-Pd is a commercially available sol–gel entrapped catalyst made out of an amorphous organosilica matrix functionalized with a diphenylphosphine ligand bound to Pd(II).[26] This immobilized catalyst has previously been evaluated for continuous-flow applications by the groups of Alcázar[27] and Pagliaro.[28,29] Notably, Alcázar and co-workers were able to perform a continuous Suzuki–Miyaura reaction in H_2O/THF for more than 8 h (0.125 M, 0.2 mL min^{-1}) without observing a decrease in the catalytic activity.[27a] In contrast, in the work by Pagliaro and co-workers a long-run experiment (also 8 h) utilizing this catalyst for a continuous-flow Suzuki–Miyaura reaction in THF/H_2O/EtOH as solvent clearly exhibited a significant decrease in conversion.[28a]

A wide range of reaction conditions and solvent/base combinations were evaluated for the SiliaCat DPP-Pd catalyst in our preliminary batch experiments. These incorporated THF/H_2O and THF/H_2O/EtOH mixtures as solvents as well as K_2CO_3, KOH, and KOAc as bases, in addition to our standard MeCN/DIPEA (or TEA) conditions concurrently used for all catalysts (see Table S4 in the Supporting Information). Remarkably, this catalyst had a relatively low performance in acetonitrile in batch processing, for both the Suzuki–Miyaura and Mizoroki–Heck reactions. Conversions considerably increased when mixtures including protic solvents and inorganic bases were employed. Thus, full conversion and complete selectivity were observed in H_2O/THF and H_2O/THF/EtOH mixtures and K_2CO_3 and KOH as bases, even at temperatures as low as 60–70 °C (see entries 5 and 6 in Table S4).

Given the good results obtained for a variety of solvent/base combinations, a large number of flow experiments were carried out using the SiliaCat catalyst. Although the conversion for the Mizoroki–Heck reaction in acetonitrile was not very high (Figure 8a), excellent selectivity was achieved. Interestingly, the

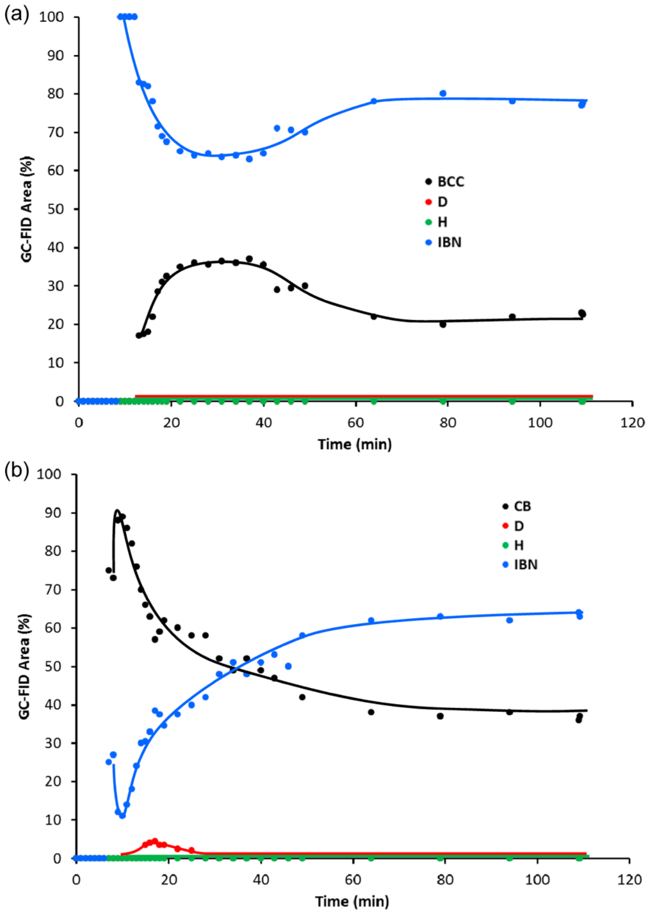


Figure 8. Conversion profiles obtained for the continuous-flow Mizoroki–Heck (a) and Suzuki–Miyaura (b) reactions catalyzed by SiliaCat DPP-Pd. The first ~10 min, in which no compound is observed in the GC-FID, corresponds to the dead volume of the reactor. Conditions: 0.5 M substrate in MeCN, 1.5 equiv of TEA, 1.5 equiv of $PhB(OH)_2$ or *n*-butyl acrylate, 120 °C, 0.2 mL min^{-1}.

conversion profile was not stable until ca. 40 min of processing time. During the first stage of the processing a higher conversion (~35%) was obtained, which then dropped and stabilized at ca. 20% after 40 min. This behavior is possibly due to a modification of the metal species upon contact with the reaction mixture that partially decreases its initial activity. A similar pattern was observed for the Suzuki–Miyaura reaction (Figure 8b), with higher initial conversion rates which slowly stabilized during flow processing.

We decided to increase the residence time for the Mizoroki–Heck reaction by using a larger packed-bed reactor containing 2 g of supported catalyst. Under these conditions full conversion was obtained during the complete processing time but with decreased selectivity (~80%) (see Figure S4 in the Supporting Information). An Ommifit column reactor was utilized for this experiment. In contrast to the stainless steel CatCart catalyst cartridges, the Omnifit columns are made out of transparent borosilicate glass and we therefore could observe in situ changes in the appearance of the solid material during the processing (Figure 9). The SiliaCat DPP-Pd catalyst has an intense orange color which is maintained in contact with acetonitrile even when the temperature is increased (Figure 9a). However, as soon as the reaction mixture was introduced in the packed-bed reactor (Figure 9b) the catalyst material gradually turned black, indicating the formation of Pd(0) in the supported catalyst. Ultimately all of the supported catalyst acquired a black coloration (Figure 9c,d). This catalyst modification during the reaction is most probably responsible for the decrease of catalytic activity observed for the smaller scale experiment (Figure 8a).

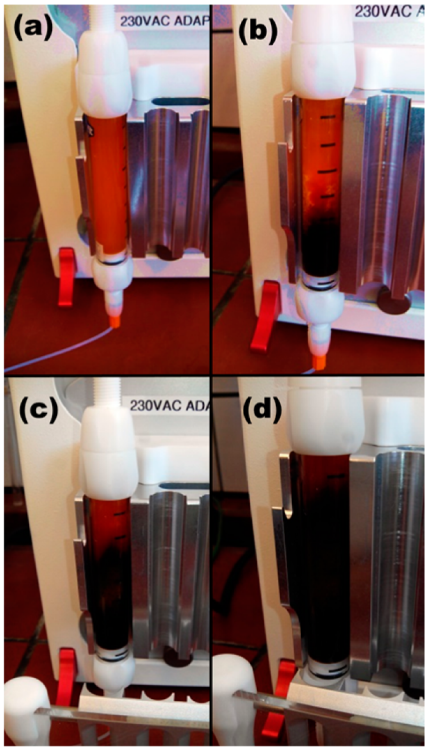


Figure 9. Visual appearance of SiliaCat DPP-Pd packed in a column reactor during the processing of a Mizoroki–Heck reaction using acetonitrile as solvent and TEA as base (a) in contact with hot solvent, (b) after 30 min, (c) after 60 min, and (d) after 120 min. The reaction stream flows from the bottom to the top of the packed-bed reactor.

As was experienced in batch processing, combinations with a protic solvent and an inorganic base resulted in very good conversions and selectivities in continuous flow. The conversion profiles depicted in Figure 10 were obtained using the THF/EtOH/H_2O and K_2CO_3 system described by Pagliaro and co-workers.[28] The reaction outcome rapidly stabilized, and a constant profile was achieved. It is possible that in this case the Pd catalyst is "preactivated" in contact with the hot protic solvent, with can be easily oxidized by Pd(II) to form Pd(0),[30] thus avoiding the initial stabilization time necessary when MeCN was used as solvent. Interestingly, under these conditions SiliaCat DPP-Pd performed much better for the Suzuki–Miyaura reaction (Figure 10b) than for the Mizoroki–Heck reaction (Figure 10a). Almost full conversion and excellent selectivity was obtained during all of the processing for the coupling with $PhB(OH)_2$. For the Mizoroki–Heck reaction a constant 65% conversion was obtained. This solvent/base system gave the best results in terms of conversion and catalyst stability. Several other solvent/base systems were tested, including THF/H_2O/KOH, THF/H_2O/K_2CO_3, and MeOH/H_2O/K_2CO_3 (the corresponding conversion profiles are collected in the Supporting Information).

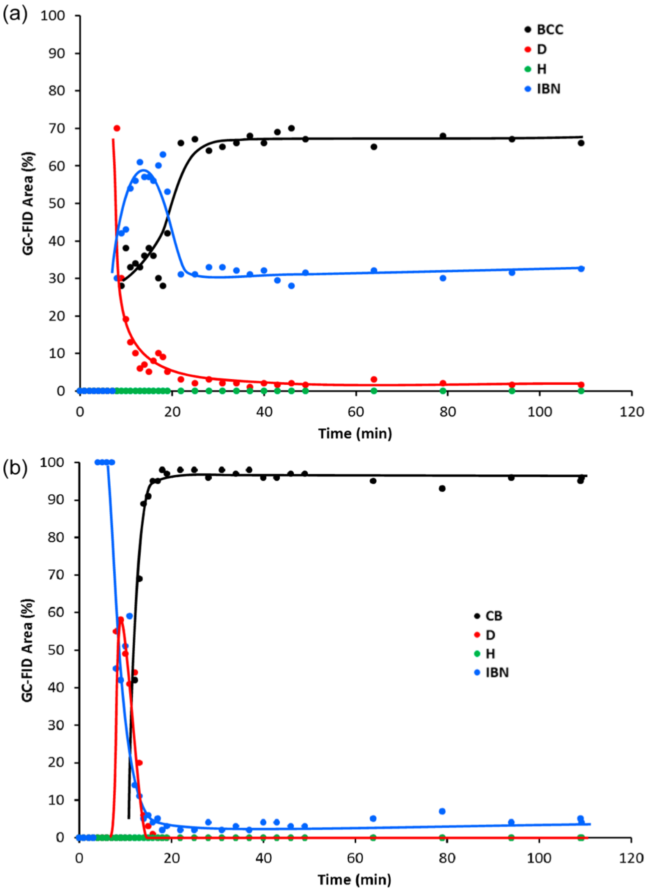


Figure 10. Conversion profiles obtained for the continuous-flow Mizoroki–Heck (a) and Suzuki–Miyaura (b) reactions catalyzed by SiliaCat DPP-Pd. The first ~10 min, in which no compound is observed in the GC-FID, corresponds to the dead volume of the reactor. Conditions: 0.25 M substrate in THF/EtOH/H_2O, 1.5 equiv of K_2CO_3, 1.25 equiv of $PhB(OH)_2$ or *n*-butyl acrylate, 80 °C, 0.2 mL min^{-1}.

ICPMS analyses of all crude reaction mixtures obtained from the reactor output indicated a significantly lower amount of Pd being leached from the solid support with respect to that for the three previously studied supported catalysts. The amounts of metal encountered in the mixtures obtained with the MeCN/TEA system (Figure 8) were 0.81 and 1.25 mg for the Mizoroki−Heck and Suzuki−Miyaura reactions, respectively. For the THF/EtOH/H_2O/K_2CO_3 system the amount was even lower (332 and 39 μg for the Mizoroki−Heck and Suzuki−Miyaura reactions). The solid material from the catalyst cartridge utilized for this Suzuki−Miyaura reaction (Figure 10b) was placed out of the steel cylinder for a closer inspection. Similar to the reaction carried out in acetonitrile, the catalyst had acquired a black color as a result of the formation of Pd(0) black. More importantly, clear catalyst degradation could be visually observed at the first part of the material (Figure 11). Apparently, the Pd had been gradually moved through the packed-bed reactor during the reaction processing, becoming a gray material. This hypothesis was confirmed by ICPMS analyses of the used solid material (Figure 11), which detected a higher concentration of Pd in the final part of the catalyst cartridge. Although no drop of conversion was observed during our flow experiment and the amount of metal contaminating the reaction mixture was not very high, this analysis revealed that most likely when larger reaction mixtures are processed all of the catalyst material will be degraded, ultimately losing its activity. A negligible amount of Pd leaching could only be obtained when very dilute reaction mixtures were processed. Thus, following a procedure described by the group of Pagliaro,[29] solutions for the Mizoroki−Heck and Suzuki−Miyaura reactions containing 0.05 M substrate concentration were processed using fresh catalyst cartridges. Although, as expected, the metal leached from the reactor was very low (15 μg and 5 μg of Pd), such dilute conditions arguably are not very useful for practical preparative purposes.

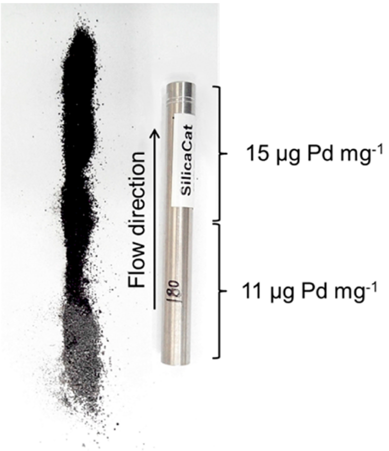


Figure 11. Visual appearance of the content of a used SiliaCat DPP-Pd catalyst cartridge after a continuous-flow Suzuki−Miyaura reaction with the THF/EtOH/H_2O/K_2CO_3 system. The Pd content of different fragments of the solid material, as determined by ICPMS analyses, is also incorporated. Degradation of the solid material at the beginning of the reactor is visually observable (gray coloration).

The results described above show SiliaCat DPP-Pd to be a superior catalyst with respect to those in the other case studies, especially in terms of stability and durability, even though metal leaching and catalyst degradation were still observable. An obvious question arises from the possibility that the silica matrix itself can retain Pd species by a simple physical affinity with the polar media and whether the presence of the phosphine ligand covalently bound to the support is essential for the low leaching. In order to address this question, a simple packed-bed reactor was built in a column containing unmodified silica gel. Then, a solution of $Pd(PhPh_3)_4$ in acetonitrile was pumped through the column reactor at room temperature. The solid material rapidly acquired a dark coloration while, after a second pass of the Pd solution, the solvent became completely colorless. The column was then utilized for a Suzuki−Miyaura reaction using the MeCN/TEA system. Notably, when only solvent was passed through the reactor, no leaching was appreciable even on heating to 120 °C. However, as soon as the reaction mixture was introduced, a rapid leaching was observed. The conversion rapidly dropped, and it could be clearly observed how the Pd Tetrakis was "washed out" from the silica (for a detailed description, see Figures S12 and S13 in the Supporting Information). This simple experiment demonstrated that the polarity of the silica matrix itself has no crucial effect on the recyclability of the SiliaCat DPP-Pd and the immobilized ligand plays an essential role in the Pd retention. This effect is in agreement with previous observations which indicated that the addition of external ligands often induces leaching of the metals.[31]

■ CONCLUSION

A comparative study of the efficiency, durability, and metal leaching resistance of some of the most common immobilized diarylphosphine- and triarylphosphine-based palladium catalysts toward continuous flow cross-coupling reactions has been performed. Pd Tetrakis (polymer-bound), FiberCat 1001, EnCat TPP30, and SiliaCat DPP-Pd have been independently evaluated using two model reactions: the Mizoroki−Heck reaction of 4-iodobenzonitrile with butyl acrylate and the Suzuki−Miyaura reaction of the same halide with phenylboronic acid. A set of reaction conditions combining acetonitrile as solvent and triethylamine or diisopropylethylamine as base has been concurrently used in all cases to directly compare the performance of the immobilized catalyst. Furthermore, selected literature protocols have been also reevaluated in terms of catalyst efficiency and durability.

Except for SiliaCat DPP-Pd, the Suzuki−Miyaura cross-coupling produced a much higher amount of metal leaching and catalyst degradation than the Mizoroki−Heck reaction. The choice of an appropriate solvent/base system is crucial for the durability of the supported catalyst. Thus, in the case of Pd EnCat TPP30 a constant drop in conversion was observed when EtOH as solvent and TBAOAc as base were utilized for the Mizoroki−Heck reaction, while in MeCN a much more constant conversion profile was achieved.

Variable amounts of Pd leached from the packed-bed reactors were always present in the crude reaction mixtures collected from the reactor output (for a comparison of Pd leaching data for all experiments performed, see Table S5 in the Supporting Information). In this context, SiliaCat DPP-Pd combined with THF/EtOH/H_2O as solvent and K_2CO_3 as base gave the best results regarding catalyst efficiency and leaching resistance. However, significant degradation of the immobilized catalyst was also observable in these cases. Negligible amounts of metal leaching are only achieved when rather diluted reaction mixtures (e.g., 0.05 M) are processed; this is not practical for preparative purposes.

The role of the covalent bonding of the ligand with the silica matrix for the stability of the SilicaCat DPP-Pd catalyst could be assessed by using a packed-bed reactor of unmodified silica loaded with $Pd(PPh_3)_4$. In this case, a rapid metal leaching and drop of conversion was observed during a continuous Suzuki–Miyaura reaction.

Given the problem of metal leaching and catalyst stability observed in most continuous-flow metal-catalyzed cross-coupling reactions,[7,9] it appears that in many cases it would be more appropriate to use a suitable homogeneous metal catalyst/ligand system. This would lead to more predictable and reproducible transformations, as the catalyst loading could be accurately adjusted. If necessary, recycling of the homogeneous metal catalyst could also be implemented and likely future research in this area will become increasingly important.[32] Notably, the SiliaCat DPP-Pd catalyst system described herein has shown superior leaching resistance and stability with respect to the other three case studies. Further development of this or other silica-based immobilized catalysts might lead to more leaching-resistant supports in the future, at least on a laboratory scale. Other strategies to circumvent the problem of metal leaching in continuous-flow cross-couplings using immobilized catalysts, such as "capture and release" systems[33] and recirculating reactors,[34] can also be useful on a small scale when telescoped reactions are not required.

EXPERIMENTAL SECTION

General Considerations. GC-FID analysis was performed on a standard GC instrument with a flame ionization detector, using an HP5 column (30 m, 0.250 mm, 0.025 mm). After 1 min at 50 °C the temperature was increased in 25 °C min^{-1} steps up to 300 °C and kept at 300 °C for 4 min. The detector gas for the flame ionization was H_2 and compressed air (5.0 quality). Curves drawn in the conversion profiles correspond to average plots of the experimental data. Solvents and chemicals were obtained from standard commercial vendors and were used without any further purification. The following catalyst cartridges were obtained from ThalesNano: Pd Tetrakis, polymer bound (0.5 mmol of Pd/g, THS X1178, ca. 565 mg of catalyst/cartridge); Pd Fibrecat 1001 (0.5 mmol of Pd/g, THS X1187, ca. 300 mg of catalyst/cartridge); Pd EnCat TPP30 (0.4 mmol of Pd/g, THS X1125, ca. 530 mg of catalyst/cartridge); SiliaCat DPP-Pd (0.2 mmol of Pd/g, ca. 220 mg of catalyst/cartridge). A fresh cartridge was used for every continuous-flow experiment described herein.

Leaching Studies. The amount of Pd leached from the immobilized catalyst for each of the flow runs was determined by ICPMS analysis of the crude reaction mixture. Thus, the solution collected from the reactor was evaporated under reduced pressure to remove all volatile compounds. The resulting residue was dissolved in acetonitrile/concentrated nitric acid to give a homogeneous solution, and the solution was diluted with nitric acid to 40 mL and placed in a vial for microwave digestion. Microwave-assisted acid digestion was carried out in an MLS UltraClave IV instrument. The temperature was ramped up in 30 min to 250 °C and kept at this temperature for a further 30 min. After appropriate dilution Pd was quantitatively determined at m/z 105 with an Agilent 7500ce inductively coupled plasma mass spectrometer. A calibration was performed with an external calibration curve established from 1.000 g of Pd/L standard (CPI International). Indium served as the internal standard.

General Procedure for Microwave Batch Experiments. In a 2 mL Pyrex vial were placed the Pd catalyst (0.5 mol %), 4-iodobenzonitrile (0.5 mmol), phenylboronic acid (Suzuki–Miyaura) (1.5 equiv) or *n*-butyl acrylate (Mizoroki–Heck) (1.5 equiv), the corresponding base (see Tables S1–S4 in the Supporting Information), and 1 mL of solvent. The vial was capped and heated in a single-mode microwave reactor (Biotage Initiator) for 15 min at the desired temperature. The reaction mixture was subsequently cooled to room temperature with compressed air, filtered, and analyzed by GC FID.

Continuous-Flow Procedures. *Procedure 1: Flow Reactions in MeCN as Solvent and TEA or DIPEA as Base (Figures 3, 5, 7, and 8).* A stock solution containing 4-iodobenzonitrile (0.5 M), phenylboronic acid (Suzuki–Miyaura) or *n*-butyl acrylate (Mizoroki–Heck) (1.5 equiv), and the corresponding base (1.5 equiv) in MeCN was prepared. A fresh catalyst cartridge was placed in the X-Cube flow reactor, and the system was set at the desired temperature and 20 bar of back pressure while pure acetonitrile was pumped at a rate of 0.2 mL min^{-1}. When the temperature and pressure were stable, the reactor inlet was switched to the reaction mixture, and 20 mL of the stock solution was pumped through the reactor before switching the inlet back to solvent. The crude reaction mixture was collected from the output, and the conversion was monitored by GC-FID.

Procedure 2: Flow Reactions in THF/EtOH/H_2O and K_2CO_3 as Base (Figure 10). Two separate stock solutions (A and B) were prepared. Solution A contained 4-iodobenzonitrile (0.83 M) in THF. Solution B contained phenylboronic acid (Suzuki–Miyaura) or *n*-butyl acrylate (Mizoroki–Heck) (0.45 M) and K_2CO_3 (0.55 M) in 1/1 EtOH/H_2O. A modified flow setup incorporating two feeds was employed. Feed A was set to 0.055 mL min^{-1} using THF as solvent. Feed B containing 1/1 EtOH/H_2O was set to 0.155 mL min^{-1}. At these flow rates the substrate/coupling partner proportion is 1/1.25 and the substrate/ base proportion is 1/1.5. A fresh catalyst cartridge was placed in the X-Cube flow reactor, and the system was set at the desired temperature and 20 bar of back pressure while pure THF and EtOH/H_2O were pumped through the system. When the temperature and pressure were stable, the reactor inlets were switched to the corresponding stock solutions A and B. The two reaction streams were mixed immediately before the heated column reactor in a T-mixer. The system was run until 10 mmol of the substrate had been processed (8.3 mL of solution A) before switching the inlets back to solvent. The crude reaction mixture was collected from the output, and the conversion was monitored by GC-FID.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Supplementary Tables and Figures. This material is available free of charge via the Internet at http://pubs.acs.org.The following file is available free of charge on the ACS Publications website at DOI: 10.1021/cs5020089.

> Preliminary MW-batch experiments, ICPMS data, continuous-flow conversion profiles, separation of the reaction components within the catalysts, and continuous-flow experiment with packed unmodified silica (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062−5085.

(2) (a) *Science of Synthesis: Cross Coupling and Heck Type Reactions*; Molander, G. A., Wolf, J. P., Larhed, M., Eds.; Georg Thieme Verlag: Stuttgart, Germany, 2013; Vols. *1*−*3*. (b) *Metal Catalyzed Cross-Coupling Reactions and More*; de Meijere, A., Bräse, S., Oestreich, M., Eds.; Wiley-VCH: Weinheim, Germany, 2014.

(3) (a) Negishi, E.-i. *Angew. Chem., Int. Ed.* **2011**, *50*, 6738−6764. (b) Suzuki, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6722−6737.

(4) (a) Bariwal, J.; van der Eycken, E. *Chem. Soc. Rev.* **2013**, *42*, 9283−9303. (b) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954−6971. (c) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400−5449.

(5) (a) Takahashi, T.; Kanno, K.-i. In *Modern Organonickel Chemistry*; Tamaru, Y., Ed.; Wiley-VCH: Weinheim, Germany, 2005; pp 41−53. (b) *Copper-Mediated Cross-Coupling Reactions*; Evano, G., Blanchard, N., Eds.; Wiley: Hoboken, NJ, 2014.

(6) (a) Molnár, A. *Chem. Rev.* **2011**, *111*, 2251−2320. (b) Anderson, E. B.; Buchmeiser, M. R. *ChemCatChem* **2012**, *4*, 30−33.

(7) Noël, T.; Buchwald, S. L. *Chem. Soc. Rev.* **2011**, *40*, 5010−5029.

(8) Frost, C. G.; Mutton, L. *Green Chem.* **2010**, *12*, 1687−1703.

(9) Cantillo, D.; Kappe, C. O. *ChemCatChem* **2014**, *6*, 3286−3305.

(10) (a) Pagliaro, M.; Pandarus, V.; Ciriminna, R.; Bland, F.; Demma Carà, P. *ChemCatChem* **2012**, *4*, 432−445. (b) Ananikov, V. P.; Beletskaya, I. P. *Organometallics* **2012**, *31*, 1595−1604. (b) Kashin, A. S.; Ananikov, V. P. *J. Org. Chem.* **2013**, *78*, 11117−11125.

(11) Glasnov, T. N.; Findenig, S.; Kappe, C. O. *Chem. Eur. J.* **2009**, *15*, 1001−1010.

(12) Yin, L.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133−173.

(13) de Vries, J. G. *Dalton Trans.* **2006**, 421−429.

(14) Glasnov, T. N.; Kappe, C. O. *Chem. Eur. J.* **2011**, *17*, 11956−11968.

(15) The ThalesNano X-Cube system is no longer commercially available and has been replaced by the H-Cube Pro, which enables working with identical cartridges, but under slightly decreased maximum conditions (150 °C, 100 bar) in "no hydrogen" mode.

(16) Fenger, I.; Le Drian, C. *Tetrahedron Lett.* **1998**, *39*, 4287−4290.

(17) Trinh, T. N.; Hizartidis, L.; Lin, A. J. A.; Harman, D. G.; McCluskey, A.; Gordon, C. P. *Org. Biomol. Chem.* **2014**, *12*, 9562−9571.

(18) Carole, W.; Colacot, T. J. *Chim. Oggi* **2010**, *28*, XXIII−XXV.

(19) (a) Colacot, T. J.; Carole, W. A.; Neide, B. A.; Harad, A. *Organometallics* **2008**, *27*, 5605−5611. (b) Colacot, T. J. *Top. Catal.* **2008**, *48*, 91−98.

(20) Borcsek, B.; Bene, G.; Szirbik, G.; Dormán, G.; Jones, R.; Ürge, L.; Darvas, F. *ARKIVOC* **2012**, *5*, 186−195.

(21) Estrada, G. O. D.; Flores, M. C.; Silva, J. F. M.; de Souza, R. O. M. A.; e Miranda, L. S. M. *Tetrahedron Lett.* **2012**, *53*, 4166−4168.

(22) Ramarao, C.; Ley, S. V.; Smith, S. C.; Shirley, I. M.; DeAlmeida, N. *Chem. Commun.* **2002**, *10*, 1132−1133.

(23) (a) Kuang, Y. Y.; Chen, F. R. *Helv. Chim. Acta* **2009**, *92*, 897−903. (b) Carpita, A.; Ribecai, A. *Tetrahedron Lett.* **2009**, *50*, 204−207.

(24) Broadwater, S. J.; McQuade, D. T. *J. Org. Chem.* **2006**, *71*, 2131−2134.

(25) (a) Lee, C. K. Y.; Holmes, A. B.; Ley, S. V.; McConvey, I. F.; Al-Duri, B.; Leecke, C. A.; Santos, R. C. D.; Seville, J. P. K. *Chem. Commun.* **2005**, 2175−2177. (b) Leeke, G. A.; Santos, R. C. D.; Al-Duri, B.; Seville, J. P. K.; Smith, C. J.; Lee, C. K. Y.; Holmes, A. B.; McConvey, I. F. *Org. Process Res. Dev.* **2007**, *11*, 144−148. (c) Baxendale, I. R.; Griffiths-Jones, C. M.; Ley, S. V.; Tranmer, C. K. *Chem. Eur. J.* **2006**, *12*, 4407−4416.

(26) (a) Pandarus, V.; Gingras, G.; Béland, F.; Ciriminna, R.; Pagliaro, M. *Org. Process Res. Dev.* **2012**, *16*, 117−122. (b) Lemay, M.; Pandarus, V.; Simard, M.; Marion, O.; Tremblay, L.; Béland, F. *Top. Catal.* **2010**, *53*, 1059−1062.

(27) (a) Muñoz, J. M.; Alcázar, J.; de la Hoz, A.; Díaz-Ortiz, A. *Adv. Synth. Catal.* **2012**, *354*, 3456−3460. (b) Egle, B.; Muñoz, J. M.; Alonso, N.; De Borggraeve, W. M.; de la Hoz, A.; Díaz-Ortiz, A.; Alcázar, J. *J. Flow. Chem.* **2014**, *4*, 22−25.

(28) (a) Pandarus, V.; Gingras, G.; Béland, F.; Ciriminna, R.; Pagliaro, M. *Org. Process Res. Dev.* **2014**, *18*, 1550−1555. (b) Pandarus, V.; Gingras, G.; Béland, F.; Ciriminna, R.; Pagliaro, M. *Org. Process Res. Dev.* **2014**, *18*, 1556−1559.

(29) Pandarus, V.; Ciriminna, R.; Gingras, G.; Béland, F.; Drobod, M.; Jina, O.; Pagliaro, M. *Tetrahedron Lett.* **2013**, *54*, 1129−1132.

(30) Brazier, J. B.; Nguyen, B. N.; Adrio, L. A.; Barreiro, E. M.; Leong, W. P.; Newton, M. A.; Figueroa, S. J. A.; Hellgardt, K.; Hii, K. K. M. *Catal. Today* **2014**, *229*, 95−103.

(31) Kobayashi, S.; Miyamura, H. *Aldrichim. Acta* **2013**, *46*, 3−19.

(32) (a) Li, P.; Moore, J. S.; Jensen, K. F. *ChemCatChem* **2013**, *5*, 1729−1733. (b) Ormerod, D.; Bongers, B.; Porto-Carrero, W.; Ciegas, S.; Vijt, G.; Lefevre, N.; Lauwers, D.; Brusten, W.; Buekenhoudt, A. *RSC Adv.* **2013**, *3*, 21501−21510. (c) Peeva, L.; Arbour, J.; Livingston, A. *Org. Process Res. Dev.* **2013**, *17*, 967−975. (c) Peeva, L.; da Silva Burgal, J.; Vartak, S.; Livingston, A. G. *J. Catal.* **2013**, *306*, 190−201.

(33) Suzuki, Y.; Laurino, P.; McQuade, D. T.; Seeberger, P. H. *Helv. Chim. Acta* **2012**, *95*, 2578−2588.

(34) (a) Pavia, C.; Ballerini, E.; Bivona, L. A.; Giacalone, F.; Aprile, C.; Vaccaro, L.; Gruttadauria, M. *Adv. Synth. Catal.* **2013**, *355*, 2007−2018. (b) Petrucci, C.; Strappaveccia, G.; Giacalone, F.; Gruttadauria, M.; Pizzo, F.; Vaccaro, L. *ACS Sustainable Chem. Eng.* **2014**, *2*, 2813−2819.