# Carbon–Carbon Cross-Coupling Reactions under Continuous Flow Conditions Using Poly(vinylpyridine) Doped with Palladium

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Abstract: Coordinative immobilization of an oxime-based palladacycle to poly(vinylpyridine)/glass composite materials shaped as Raschig rings or placed within the PASSflow<sup>TM</sup> microreactor affords technical devices that are well suited for performing palladium-catalyzed carbon–carbon cross-coupling reactions in the flowthrough mode. Reusability of the immobilized precatalyst as well as applications in the microwave field were investigated. Experiments with thiol- and pyridine-based scavengers were carried out, which revealed that the active palladium species is likely to be composed of nanoparticles of unknown nature and that the poly(vinylpyridine) carrier has scavenging properties for these particles.

**Key words:** palladium catalyst, immobilization, microreactor, microwave, C–C cross-coupling reactions

Advances in organic synthesis and catalysis from academic laboratories are often not rapidly transferred into industrial applications.<sup>1,2</sup> In many cases, developments from research laboratories lack practicability as far as scale-up, easy and rapid workup, product isolation, and recyclability of catalysts are concerned. New synthetic methods need to be combined with new techniques which are termed 'enabling technologies for organic synthesis' in order to achieve better incorporation into industrial processes (Figure 1). Microwave assistance,<sup>3</sup> new solvent systems,<sup>4</sup> continuous flow reactors,<sup>2,5</sup> and immobilization of chemically active species such as reagents and homogeneous catalysts<sup>6</sup> can be regarded as typical enabling technologies. Truly new synthetic technology platforms, however, will not be based on the individual use of these new techniques, but will require the integration of two or more of these enabling techniques. By exploiting synergic effects higher efficiency and better controlling of chemical processes should be achieved. Various successful examples of combining two or more of these techniques in order to achieve faster synthesis or improved workup have recently appeared in the literature. Particularly the field of catalysis with heterogenized homogeneous catalysts, which are incorporated inside continuous flow reactors is a very active area of research.<sup>2</sup>

For example, continuous flow processes with immobilized catalysts were utilized for the reduction of organic compounds (Pd/C-mediated hydrogenations<sup>7,8</sup> and ruthe-nium-catalyzed asymmetric transfer hydrogenations<sup>9</sup>),



Figure 1 Enabling technologies for organic synthesis

Suzuki cross-coupling reactions [using precipitated palladium(0) nanoparticles,<sup>10</sup> polyurea-encapsulated palladium(II) acetate precatalyst,<sup>11</sup> and salen-type palladium(II) complexes12], Heck-Mizoroki and Sonogashira crosscoupling reactions [using precipitated palladium(0) nanoparticles<sup>9</sup>], Kumada–Corriu cross-coupling reactions [using salen-type nickel(II) complex immobilized on Merrifield resin<sup>13</sup> or on functionalized silica gel<sup>14</sup>], and for the kinetic resolution of terminal epoxides [using an immobilized chiral cobalt(II)-salen complex<sup>15</sup>]. These examples illustrate the various techniques applied for immobilization of metal catalysts inside continuous flow devices. These are the physisorption on charcoal<sup>7,8</sup> or organic polymers,<sup>10</sup> and encapsulation within a polymer matrix.<sup>11</sup> Undoubtedly, the most popular method relies on covalent attachment of ligands to a polymeric or inorganic solid supports (grafting) followed by loading with the transition-metal catalyst.9,13-15

For some time, we have been involved in the development of continuous flow reactors suitable for organic synthesis. Our PASSflow<sup>TM</sup> reactors contain a megaporous monolithic glass/polymer composite material, which can be further functionalized. This experimental set up allows an almost workup-free procedure for carrying out many different reactions including nucleophilic substitutions, reductive aminations, oxidations, Horner–Wadsworth– Emmons, and palladium-catalyzed carbon–carbon coupling reactions in the flow-through mode.<sup>16</sup>

From a technological point of view, particularly when upscaling and economical aspects are in focus, the mode of immobilization should allow easy loading of the reactor with active catalyst or precatalyst and simple removal, and reloading after the catalytic species has lost its activity. In this context, ionic or coordinative interactions between the transition-metal complex and the solid phase represent promising concepts. In both cases, the inactive transition-metal complex or degradation products derived

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Figure 2 Catalysts 1 and 2 (Mes = mesityl) bound to PVP

thereof can easily be removed by simple washing steps before the solid phase is regenerated with a fresh portion of the active complex under flow-through conditions.

Recently, we have shown that poly(4-vinylpyridine) (hereafter abbreviated as PVP) is a well suited solid phase for immobilizing transition-metal complexes such as the Grubbs III complex<sup>17</sup> or Najera's oxime-based palladacycle.<sup>18</sup> The resulting functionalized polymeric phases **1** and 2 showed very good activity in olefin metathesis<sup>17</sup> and carbon-carbon cross-coupling reactions,19 respectively (Figure 2). In analogy to findings by Reetz and de Vries,<sup>20</sup> we suggested that the latter complex 2 is a reservoir for palladium nanoparticles of unknown nature, which are formed after reduction. We further speculated that the palladium(0) species can carry on the catalytic cycle or can be recaptured by PVP. This hypothesis gained support from ICP measurements of the cooled reaction mixture because a residual palladium level as low as 1.1–2.1 ppb was detected. The easy reusability of functionalized resin 2, its air-, moisture- and thermal stability in carbon-carbon cross-coupling reactions and the very low degree of leaching makes this precatalyst an ideal study object for applications under continuous flow conditions. In fact, when switching from batch to flow-through conditions with heterogenized homogeneous catalytic systems, the convective flow can strongly alter the reaction profile as contact times between the solid phase and the fluid are commonly shorter and leaching of metals can increase. In this report, we disclose the studies on Suzuki-Miyaura and Heck-Mizoroki reactions with PASSflow<sup>TM</sup> reactors that are loaded with polymer 2. Additionally, we use the flow-through device to shed light on how 'homogeneous' the carbon-carbon coupling reactions actually are by employing resins with scavenging properties, which are located in a separate reactor.

### **Preparation of Immobilized Palladium**

Complex 2 was prepared by coordination of palladacycle  $3^{18}$  to PVP [cross-linked with 5.3% divinylbenzene (DVB)] (Table 1).<sup>19</sup> The proposed structure of this immobilized precatalyst 2 is based on an X-ray study of a related complex.<sup>21</sup> We prepared three different types of samples of precatalyst 2 using a) PVP as a powder prepared by precipitation polymerization, b) the same PVP matrix as a coating of the glass surface inside a megapor-

ous glass rod which is part of a PASSflow<sup>TM</sup> microreactor,<sup>22</sup> and c) megaporous glass Raschig rings coated with this PVP matrix<sup>23</sup> (Table 1). The powder was used in batch processes while the two glass/polymer composites were incorporated inside the reactor for being studied in continuous flow processes. The Raschig ring microreactor (case c) has an advantage over the rod-type reactor (case b) because it can be easily unscrewed and functionalized Raschig rings can be removed or fresh rings can be easily inserted.

 Table 1
 Immobilization of Palladacycle 3 on Different PVP Matrices



# Applications in Palladium-Catalyzed Carbon– Carbon Coupling Reactions

First, we investigated the catalytic activity of precatalyst **2** loaded on the Raschig rings (optimized loading:  $3.57 \times 10^{-5}$  mmol Pd/mg ring as judged by elemental analysis). The composite rings were placed inside a flow-through reactor (Table 1, case c) and Suzuki–Miyaura cross-coupling reactions were performed under continuous flow conditions. As the monolithic material doped with palladium is composed of irregular microchannels ( $\leq 50 \mu$ m) one has to choose homogeneous conditions in order to prevent clogging of the channels.

The results obtained are listed in Table 2. In some cases (entries 2 and 3), an unusual solvent system consisting of DMF–water–amyl alcohol (10:1:1) was employed. This mixture guaranteed homogeneous conditions during the whole process, however, with the price of prolonged reaction times. Several boronic acids gave good to very good yields with *p*-bromoacetophenone as coupling partner. Aryl bromides that contain electron-donating substituents (entries 7 and 8) gave only moderate yields of coupling products with phenylboronic acid. The sterically congested 2,6-dimethylbromobenzene gave a low yield (9%) of coupling product with phenylboronic acid (**5a**) while 2-

 Table 2
 Continuous Flow Suzuki–Miyaura Reactions Using the Precatalyst 2 Immobilized on the Raschig Rings<sup>a</sup>



<sup>a</sup> Conditions: Boronic acid (1.5 equiv), aryl bromide (1 equiv), CsF (2.4 equiv), **2** (1 mol% immobilized on Raschig rings; loading  $3.57 \times 10^{-5}$  mmol Pd/mg ring), DMF–H<sub>2</sub>O (10:1), 100 °C (preheated), flow rate 2 mL/min.

<sup>b</sup> Isolated yields.

<sup>c</sup> Solvent: DMF-H<sub>2</sub>O-amyl alcohol (10:1:1); time and yield in parentheses refer to DMF-H<sub>2</sub>O (10:1).

bromothiazole, 3-bromothiophene or 2-bromothiophenol practically are not suited for achieving cross-coupling products under continuous flow conditions.

Stability of the precatalyst 2 under conditions described above was investigated using coupling of phenylboronic acid with *p*-bromoacetophenone (4a) (Table 2, entry 1). This reaction was repeated with the same Raschig rings carrying the precatalyst 2, each run was carried out for 24 hours. The results clearly showed the good stability (after the fifth run small degree of reduced activity was encountered) of the catalyst. No formation of palladium black could be observed on the surface of the used rings after several runs.

The heterogeneous catalyst 2 was active also in the arylation of olefins with aryl halides (Heck-Mizoroki reaction). The coupling between iodobenzene and methyl acrylate in DMF at 110 °C in the presence of triethylamine as base and 2 [1 mol% immobilized on PVP (powder)] under air (Scheme 1) proceeded quantitatively within 1.5 hours under batch conditions.

The catalyst **2** after this reaction was washed with ethyl acetate and used immediately for another Heck-Mizoroki coupling between iodobenzene and tert-butyl acrylate under similar conditions. Again, the reaction was completed within 1.5 hours, and the product – trans-cinnamic acid tert-butyl ester - was isolated in 93% yield. After washing with ethyl acetate, the same portion of catalyst 2 was used for the third Heck reaction of *p*-iodoanisole with methyl acrylate. After completion of the reaction (6 h), the coupling product - trans-4-methoxycinnamic acid methyl ester - was isolated in 87% yield. Thus, precatalyst 2 showed high reusability, in contrast to the related cyclopalladated imine catalyst covalently immobilized on polystyrene resin, which completely lost all of its activity after the first Heck coupling.<sup>24</sup>

These recycling experiments demonstrate the high affinity of PVP to the palladium species with simultaneous preservation of the catalytic activity. Precatalyst 2 (powder) was also active in Heck-Mizoroki couplings of variWhen microwave irradiation (300 W) was applied to carry out the Heck-Mizoroki reaction between coupling partners shown in Table 3, the results obtained were comparable to those observed for conventional thermal heating except for a reduced E/Z ratio for 8e-g, and no product formation in the case of the reaction of 4a with 7c.

However, for conducting continuous flow experiments these conditions had to be optimized so that homogeneous conditions for the fluid are guaranteed throughout the whole process. Poly(4-vinylpyridine) was incorporated inside a rod-type PASSflow<sup>TM</sup> microreactor as well as in a Raschig ring-type PASSflow<sup>TM</sup> microreactor and employed in Heck-Mizoroki reactions under continuous flow conditions. Again, the reactors were preheated to 110-120 °C and the reaction mixture was circulated through the reactors. Initially, iodobenzene (1 equiv) and methyl acrylate were coupled in DMF inside the glass rod microreactor, which resulted in quantitative conversion (76% isolated yield) within 24 hours. As the performance of both reactor types turned out to be comparable we switched to the Raschig ring microreactor which can be handled more conveniently (Table 4). Thus, under flowthrough conditions the Heck-Mizoroki reaction was carried out in DMF at 120 °C [in order to prevent thermal destruction of some reactor parts (e.g., sealings)] and with tributylamine (3 equiv) instead of triethylamine. The results are listed in Table 4.

Aryl iodides gave satisfactory results. However, under continuous flow conditions, aryl bromides furnished only low to moderate yields of coupling products. For example, only 64% and 72% of products 8e and 8k were isolated

.COOMe







2 (1 mol%)

Scheme 2 Heck-Mizoroki reaction of p-bromoacetophenone (4a) and acrylic ester 7a in batch mode (2, powder)

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4a,b,e,f	r <sub>+</sub>	$\xrightarrow{2} \xrightarrow{R^{1}} \xrightarrow{R^{2}} \xrightarrow{8a-g}$		f Br 7a	CO <sub>2</sub> <i>t</i> -Bu <b>7b</b>	CO <sub>2</sub> Me 7c	CN 7d	Ph 7e
Entry	ArBr Alkene		Time (h)	Product		Yield (%) <sup>b</sup>		
				0	$\int R^2$			
1	<b>4</b> a	7a	0.5	$8a R^2 = CO_2Cy$		99		
2	4a	7b	0.5	<b>8b</b> $R^2 = CO_2 t$ -Bu		64		
3	4a	7c	0.5	$8c R^2 = CO_2 Me$		99		
4	<b>4</b> a	7d	0.5	$8d R^2 = CN$		99 (5.6:1)		
5	4b	7e	0.6	Ph Ph		78 (18:1)		
6	4e	7e	0.6		33 (14:1)			
7	4f	7e	0.6	8f	86 (13:1)			

Table 3 <sup>25</sup>	Heck-Mizoroki Reactions	n Batch Mode	Using the	Precatalyst 2 in a	a Powder Form and	Conventional Heating <sup>a</sup>
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<sup>a</sup> For bromides also refer to Table 2. Conditions: Aryl bromide (1 equiv), alkene (1.2 equiv),  $Et_3N$  (2 equiv), and precatalyst **2** (1 mol% immobilized on powder with a loading of 0.8 mmol Pd/g resin) in DMF (3.5 mL/mmol aryl bromide), 150 °C in a screw-cap vial, 30–40 min. <sup>b</sup> Isolated yield; unless otherwise noted, only the *E*-isomer was detected; data in parentheses refer to *E/Z* ratio.

when *o*-bromobenzonitrile (4e) or *p*-bromoacetophenone (4a), respectively, were coupled with styrene (7e) (Table 4, entries 4 and 8). When the other aryl bromides listed in Table 3 were employed in Heck–Mizoroki reactions with styrene, the yields did not exceed 50%.

For testing the stability of functionalized PVP **2**, ten consecutive Heck–Mizoroki reactions of *p*-iodoacetophenone (**4g**) with cyclohexyl acrylate (**7a**) were carried out in the flow-through mode. For each run the same Raschig rings containing palladium-doped PVP **2** was used. The catalytic performance of the polymeric material did not erode under these conditions. The catalyst is stable for ten runs without loss of activity. Noteworthy, we observed some formation of palladium black on the surface of the glass/ composite material an observation which contrasts to the corresponding test for the Suzuki–Miyaura cross-couplings. This may be ascribed to the higher temperature

employed. De Vries et al. noted that the mechanism of ligand-free palladium-catalyzed Heck reactions may change when increasing reaction temperatures from 100 to 150 °C.<sup>20,25</sup> At lower temperatures only aryl iodides react, likely on the solid surface while at higher temperatures palladium particles released into solution are the catalytically active species. Our flow-through experiments were carried out at 120 °C because at higher temperatures we encountered technical problems such as damage of the reactor sealings.

Reloading of inactive PVP phase was simply achieved by pumping dilute hydrochloric acid though the reactor which leads to removal of the palladium species. This was followed by a washing protocol [aq 1 N NaOH, water (to neutral pH), methanol, and toluene]. At this point the palladacycle **3** could be recoordinated onto the polymeric phase as described above.



Scheme 3 Three-phase test with precatalyst 2 (PVP powder, batch mode)

# On the Nature of the Catalytic Species

Up to this point we have demonstrated that PVP is a versatile solid phase for attaching palladacycles like **3** by direct coordination. Under batch conditions, a highly active catalytic species is present, which is even able to promote Suzuki–Miyaura cross coupling reactions with activated aryl chlorides. It can be repeatedly used and only a very small amount of palladium (1.1–2.1 ppb) is present in the cooled reaction mixture. However, when comparing the results of the batch reactions with those observed under continuous flow conditions one has to encounter that the material performs less well under the latter conditions. For the Heck–Mizoroki reaction this effect can be explained by the lower temperature used in the flow mode (120 vs. 150 °C in the batch process).

We speculated that PVP may serve as a reservoir of a catalytically active but ill-defined species of palladium(0) which exerts its activity in solution.<sup>19,25</sup> The low degree of leaching observed could be ascribed to the possibility that the catalytically active species is efficiently scavenged by the large excess of uncoordinated pyridyl sites present which would also retard the formation and growth of colloids. In fact similar observations for inorganic supports (zeolites MCM-41, NaY and SAPO-31, mesoporous silica SBA-15, Mordenite and hydroxyapatite) have been reported.<sup>26,27</sup> This hypothesis was further supported by our observation that higher loading of the PVP phase (0.8 mmol Pd/g polymer) yields a catalyst which more rapidly loses its activity than PVP containing a smaller amount of palladium. It can be concluded, that the higher concentration of palladium species on the polymeric phase more rapidly leads to inactive palladium black under thermal stress. De Vries and co-workers pointed out that also low concentrations of palladium(0) in solution will aggregate and deactivate much more slowly than high concentrations.<sup>20,25</sup> In order to gain further evidence on the double role of PVP, we conducted several additional experiments. First, we carried out the three phase test.<sup>28</sup> Thus, cross coupling of p-chloroacetophenone (4k) with phenylboronic acid (5a) was performed in the presence of polymer-bound aryl bromide 9. The latter halide should be more reactive in Suzuki-Miyaura cross coupling reactions than the former halide (Scheme 3). In fact, the anchored aryl bromide 9 did not react under the typical reaction conditions, which could be an indication that low level metal leaching occurred during catalysis and that probably a biphasic process is under operation.<sup>29</sup>

In order to get further insight, we coupled two microreactors in a row. The first reactor contained palladium-doped



Scheme 4 Influence of the thiol- and pyridine-based scavengers on the course of the test Heck reaction

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<sup>a</sup> For other halides and alkenes, refer to Tables 1 and 2. Conditions: Aryl halide (1 equiv), alkene (3 equiv),  $Bu_3N$  (3 equiv), Pd precatalyst 2 (1 mol% immobilized on Raschig rings; loading  $3.57 \times 10^{-5}$  mmol Pd/mg ring), DMF, 120 °C; flow rate 2 mL/min.

<sup>b</sup> Isolated yields; unless otherwise noted, only the *E*-isomer was detected; data in parentheses refer to *E/Z* ratio.

PVP **2** (Raschig ring; loading  $3.57 \times 10^{-5}$  mmol Pd/mg of ring, 10 µmol Pd/ring) while the second reactor contained differently functionalized glass/polymer composite Raschig rings (Scheme 4). The first reactor was heated at 120 °C while the second reactor was kept at room temper-

ature. The polymeric phase of the Raschig rings incorporated into the second microreactor was functionalized with groups that potentially are able to trap any soluble palladium species from solution. As polymeric phase we chose thiol **10**, bispyridine **11**, amino-bispyridine **12** (all three based on polystyrene), or PVP **13**. Additionally, we also incorporated a blank Raschig ring (pure glass) in the second reactor which served as a 'dummy' in order to guarantee identical parameters for all experiments such as the total volume of the reaction mixture, concentrations of reactants, the flow inside the reactors, temperature gradients.

The results of these experiments are summarized in Figures 3 and 4. When the second microreactor contained the 'dummy' rings the test Heck–Mizoroki reaction went to completion within two hours. When the thiol scavenger **10** (one Raschig ring) was introduced the carbon–carbon coupling reactions proceeded much slower and full transformation was reached only after 23 hours. When three thiol rings **10** were placed inside the second reactor, the retardation of the reaction rate was even more pronounced. Additionally, we observed a deposit of some palladium black on the thiol Raschig rings. This deposit showed no catalytic activity under batch as well as flow conditions.

In contrast, the pyridine-based scavengers **11–13** exerted a much smaller influence on the test Heck–Mizoroki reaction. Importantly, they had adopted high catalytic activity after having served as scavenger inside the second microreactor. In fact, when these rings, after being applied in the scavenging experiments, were used under the described conditions, but with a 'dummy' ring in the first reactor, the Heck–Mizoroki reaction went to completion within 4.5 hours for **11**, 3.5 hours for **12**, and 24 hours for **13** (81% isolated product).

These results strongly support the role of the palladiumdoped PVP-phase 2 as a depot for active palladium species which are released into solution (refer to Table 1).



**Figure 3** Influence of the thiol scavenger **10** on the course of the test Heck–Mizoroki reaction. *Reagents and conditions: p*-iodoacetophenone (1 equiv), cyclohexyl acrylate (3 equiv), Bu<sub>3</sub>N (3 equiv), Pd precatalyst **2** (reactor 1:1 mol%, immobilized on Raschig rings, loading  $3.57 \times 10^{-5}$  mmol Pd/mg ring, 10 µmol Pd/Raschig ring), DMF, 120 °C, 2 mL/min flow rate; reactor 2: thiol scavenger **10** (0.185 mmol thiol groups/Raschig ring).

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**Figure 4** Influence of the pyridine-based scavengers **11–13** on the course of the test Heck reaction. *Reagents and conditions: p*-iodoace-tophenone (1 equiv), cyclohexyl acrylate (3 equiv), Bu<sub>3</sub>N (3 equiv), Pd precatalyst **2** (reactor 1:1 mol%, immobilized on Raschig rings, loading  $3.57 \times 10^{-5}$  mmol Pd/mg ring, 10 µmol Pd/Raschig ring), DMF, 120 °C, 2 mL/min flow rate; reactor 2: scavengers **11–13** (loading: 0.067 mmol/Raschig ring for **11**, 0.046 mmol/Raschig ring for **12**, and 0.181 mmol/Raschig ring for **13**).

These species can be trapped by polymeric scavengers **10–13**. In the case of thiol scavenger **10**, the trapped palladium is completely deactivated, while the pyridinebased scavengers create palladium species still showing excellent catalytic activity at elevated temperature. The results prove that the PVP resin can serve as a solid phase for immobilizing palladium precatalysts, which themselves create palladium particles during the Heck–Mizoroki reaction conditions. Additionally, PVP is able to recapture these particles, which explains the low amount of palladium detected in the cooled solution.

At this point it has to be noted that our results contradict a report by Jones et al.<sup>30</sup> They considered PVP to be an 'effective poison of active soluble palladium species in Heck reactions'. This statement is based on the strong inhibition of the reaction in the presence of a large excess of PVP (molar ratio 1:300 of Pd to PVP). Similarly, Weck and coworkers<sup>31</sup> described a dramatic retardation of palladium-catalyzed Suzuki–Miyaura reactions in the presence of a large excess (molar ratio 1: 500) of either PVP or polystyrene (only about 15% conversion after 24 h for both resins). In our case the ratio is about 1:15. Thus, we have shown that retardation of the reaction not necessarily has to be associated with poisoning properties of PVP, particularly as polystyrene is generally not considered to be a poison for palladium catalysts.

The fact that switching from batch to flow-through conditions leads to a less active catalytic system can be ascribed to shorter contact times between the solid phase and the fluid and a more pronounced wash-out effect for the released palladium particles.

We have demonstrated that PVP is well suited to accommodate Najera's palladium precatalyst. It can be employed in continuous flow devices for Suzuki–Miyaura cross-coupling and Heck–Mizoroki reactions. The use of additional scavenger reactors shed light on the role of the polymer support. Besides serving as an anchor for the precatalyst **2**, PVP also acts as a scavenger for the palladium species that are released into solution in the course of the catalytic reaction. Remarkably, the trapped palladium species retain their catalytic activity. It is our belief that PVP has a broad potential for the facile and repeated immobilization of transition-metal complexes. However, the fundamental problem of metal leaching is not prevented with this phase.

All reactions were carried out in the air (in the absence of an inert gas atmosphere). NMR spectra were recorded on a Bruker DPX-400 spectrometer at 400 MHz (<sup>1</sup>H NMR) or 100 MHz (<sup>13</sup>C NMR) in CDCl<sub>3</sub> using TMS as internal standard. IR spectra were recorded on a Bruker FT-IR Vector 22 apparatus using Golden-Gate-ATR system on the film of the neat liquid compounds or on the compressed samples for the solid substances. Mass spectra (EI) were obtained at 70 eV on a VG Autospec apparatus. Melting points were determined in open glass capillaries on an Electrothermal IA 9200 apparatus and are uncorrected. GC analyses were conducted using a Hewlett-Packard HP 6890 Series GC System equipped with a SE-54 capillary column (25 m, Macherey-Nagel) and a FID detector 19231 D/E. Microwave experiments were carried out in the apparatus Labmate Discover from CEM. Analytical TLC was performed using precoated silica gel 60 F254 plates (Merck, Darmstadt), and the spots were visualized with UV light at 254 nm or with vanillin reagent. Merck silica gel 60 (230-400 mesh) was used for flash column chromatography. Pyridine-based scavengers 11 and 12 (Raschig rings) were purchased from Chelona GmbH (Potsdam). Commercially available reagents and anhydrous solvents were purchased from Fluka and Aldrich and used as received. Homogeneous product samples were isolated via flash chromatography and their purity was checked by TLC, GC and NMR analyses. All products are known and have been published with full characterization. Characterization of the products was commonly achieved spectroscopically (1H and 13C NMR, IR, high-resolution mass spectrometry). Additionally, for known compounds the physical (e.g., melting points) and spectroscopic data were compared with those in the literature.

The preparation of the PVP polymeric phase as a powder or as a glass/polymer composite material (shaped as rods or as Raschig rings) as well as immobilization of palladacycle **3** were described previously.<sup>19,22b,23</sup>

# Precatalyst 2 Immobilized on Glass/PVP Composite Raschig Rings (Exemplified for Loading of $3.57\times10^{-5}$ mmol Pd/mg Raschig Ring)

Palladacycle **3** (128 mg, 0.23 mmol) and Raschig rings coated with PVP<sup>19,23</sup> (total weight 14.11 g, 0.55 mmol pyridine loading per ring) were carefully shaken in DMSO (40 mL) at r.t. for 24 h. Then, the Raschig rings were thoroughly washed with DMSO, then H<sub>2</sub>O, and dried in vacuo. The loading was determined to be ca.  $3.57 \times 10^{-5}$  mmol Pd/mg ring as judged by weight increase and by Pd inductive-ly coupled plasma mass spectrometry (ISP-MS).<sup>19</sup> This corresponds to a loading of ca. 10 mmol Pd/ring (all Raschig rings used had the same standard size and weight). No decrease of catalytic activity of precatalyst **2** immobilized on the Raschig rings was noted after storing for at least 7 months in the air at r.t.

### Suzuki–Miyaura Cross-Coupling Reactions Under Continuous Flow Conditions Using Precatalyst 2; General Procedure

A solution of aryl halide (1 mmol), arylboronic acid (1.5 mmol), and CsF (364 mg, 2.4 mmol) in DMF–H<sub>2</sub>O (10:1, 5 mL) was circulated (flow rate 2.5 mL/min) through the reactor charged with one Pd-doped PVP Raschig ring 2 (10 mmol Pd) at 100 °C. After com-

pletion of the reaction (GC monitoring), the reactor was washed with DMF–H<sub>2</sub>O (10:1, 40 mL). The combined reaction mixture and washings were diluted with H<sub>2</sub>O (50 mL), and extracted with EtOAc ( $3 \times 20$  mL). The combined organic phases were dried (MgSO<sub>4</sub>) and concentrated in vacuo. The products were commonly sufficiently pure. Final purification was possible by flash column chromatography on silica gel. The reactor was ready for use in the next experiment.

### Heck–Mizoroki Reaction Using Precatalyst 2 Immobilized on PVP; General Procedure A (Powder, Batch Mode, Conventional Heating)

A mixture of aryl iodide (1 mmol), acrylic acid ester (1.2 mmol), palladium precatalyst **2** (10 mg of powder, 1 mol%), and  $Et_3N$  (142 mg, 1.4 mmol) in DMF (2 mL) was stirred at 110 °C. After completion of the reaction (GC monitoring), the mixture was diluted with EtOAc (5 mL) and filtered. The filtrate was diluted with H<sub>2</sub>O (10 mL) and extracted with EtOAc (2 × 15 mL). The combined organic extracts were washed with H<sub>2</sub>O (10 mL), dried (MgSO<sub>4</sub>), and concentrated in vacuo. The products were commonly sufficiently pure. Final purification was possible by flash column chromatography on silica gel. The recovered precatalyst **2** (on filter paper) was carefully washed with EtOAc and immediately used for the next Heck–Mizoroki reaction.

### Heck–Mizoroki Reactions Using Precatalyst 2 Immobilized on PVP; General Procedure B (Powder, Batch Mode, Conventional Heating)

A mixture of aryl bromide (1 mmol), alkene (1.2 mmol), palladium precatalyst **2** (10 mg of powder, 1 mol%), and Et<sub>3</sub>N (202 mg, 2 mmol) in DMF (3.5 mL) was stirred at 150 °C in a sealed tube. After completion of the reaction (GC monitoring), the mixture was diluted with EtOAc (5 mL), and filtered. The filtrate was diluted with H<sub>2</sub>O (10 mL) and extracted with EtOAc (2 × 15 mL). The combined organic extracts were washed with H<sub>2</sub>O (10 mL), dried (MgSO<sub>4</sub>), and concentrated in vacuo. The products were commonly sufficiently pure. Final purification was possible by flash column chromatography on silica gel.

# Heck-Mizoroki Reactions Using Precatalyst 2 Immobilized on PVP; General Procedure (Powder, Batch Mode, Microwave Irradiation)

The reactions were carried out as described above for the general procedure B, but employing microwave irradiation at 300 W to reach 150 °C within 3 min, which was then kept for 30 min. After cooling to r.t., the coupling products were isolated using the usual workup procedure.

#### Heck–Mizoroki Reactions Using Precatalyst 2 Immobilized on PVP General Procedure (Monolithic PASSflow<sup>TM</sup> Reactor, Continuous Flow)

A solution of iodobenzene (306 mg, 1.5 mmol), *tert*-butyl acrylate (269 mg, 2.1 mmol) and Et<sub>3</sub>N (212 mg, 2.1 mmol) in anhyd DMF (3 mL) was circulated through the PASSflow<sup>TM</sup> microreactor (2.5 mL/min) loaded with the precatalyst **2** (ca. 0.8 mmol)<sup>19</sup> at 110 °C (oven temperature). After completion of the reaction (24 h), the microreactor was rinsed with DMF (10 mL) and EtOAc (15 mL). The solution was diluted with EtOAc (50 mL), washed with H<sub>2</sub>O (2 × 50 mL), and dried (MgSO<sub>4</sub>). After concentration in vacuo, the products were commonly sufficiently pure. Final purification was possible by flash column chromatography on silica gel.

# Heck–Mizoroki Reactions Using Precatalyst 2 Immobilized on PVP; General Procedure (Raschig Ring PASSflow<sup>TM</sup> Reactor, Continuous Flow)

A solution of aryl halide (1 mmol), alkene (3 mmol), and  $Bu_3N$  (556 mg, 3 mmol) in anhyd DMF (3 mL) was circulated at 120 °C

through the reactor (flow rate: 2 mL/min) charged with a Raschig ring bearing immobilized precatalyst **2** ( $3.57 \times 10^{-5}$  mmol Pd/mg, 10 mmol Pd). After completion of the reaction (GC-monitoring), the reactor was rinsed with DMF (40 mL). The solution was diluted with H<sub>2</sub>O (80 mL), extracted with EtOAc ( $3 \times 50$  mL), and the combined EtOAc layers were dried (MgSO<sub>4</sub>). After concentration in vacuo, the products were commonly sufficiently pure. Final purification was possible by flash column chromatography on silica gel. The reactor was ready for use in the next experiment.

### Three-Phase Test for Suzuki–Miyaura Cross-Coupling Reactions (Batch Mode)

Polymer-bound aryl bromide 9 (loading 0.72 mmol/g) was prepared according to a literature protocol<sup>28b</sup> using aminomethylated polystyrene (0.9 mmol/g, 1% DVB, 200-400 mesh) and p-bromobenzoyl chloride. For the 3-phase test, a mixture of *p*-chloroacetophenone (4k; 1 mmol), phenylboronic acid (5a; 1.5 mmol), K<sub>2</sub>CO<sub>3</sub> (2 mmol), TBAB (0.5 mmol), precatalyst 2 (1 mol%; immobilized on PVP, powder), and polymer-bound aryl bromide 9 (0.4 mmol) in H<sub>2</sub>O (5 mL) was stirred for 17 h at 100 °C. The polymers were filtered off and washed with several portions of EtOAc and H2O. 4-Acetyl-1,1'diphenyl (6a) was isolated from the combined filtrates in 92% yield after the usual workup. The polymer was extracted in a Soxhlet with CHCl<sub>3</sub> for 12 h, dried in vacuo, and heated in an excess of 2 M KOH in EtOH-H<sub>2</sub>O (2:1) for 4 days at 90 °C. The solution was neutralized with aq 2 N HCl and extracted with  $CH_2Cl_2$  (3 × 10 mL). The combined CH2Cl2 layers were concentrated, and the residue was analyzed by GC-MS.

# **Thiol Scavenger 10**

A solution of thiourea (2.04 g, 26.5 mmol) in DMA (50 mL) was added to Raschig rings (10 g, coated with a Merrifield-type polymer, 5.3% DVB, loading 0.53 mmol benzyl chloride groups/g composite material). The mixture was degassed and then heated at 85 °C for 24 h under N<sub>2</sub>. After cooling to r.t., the Raschig rings were thoroughly washed with *i*-PrOH, dioxane, a mixture of dioxane–H<sub>2</sub>O (1:1), finally with *i*-PrOH, and dried in high vacuo. The Raschig rings were immersed in a mixture of pyrrolidine–dioxane (1:4, 50 mL), the mixture was degassed and then heated at 110 °C for 3 h under N<sub>2</sub>. After cooling, the Raschig rings were thoroughly washed with DMA and *i*-PrOH, and dried under high vacuum. According to combustion analyses (S: 1.8%), the Raschig rings prepared were loaded with thiol groups (0.56 mmol/g).

### Continuous Flow Heck–Mizoroki Reaction Using Precatalyst 2 Immobilized on Raschig Rings in Combination with Scavenger Rings; General Procedure

A solution of aryl halide (1 mmol), alkene (3 mmol) and Bu<sub>3</sub>N (556 mg, 3 mmol) in anhyd DMF (3 mL) was pumped through the two consecutive connected flow-through reactors at the flow rate 2 mL/ min in a cycle mode. The first reactor was charged with a Raschig ring bearing immobilized precatalyst **2** ( $3.57 \times 10^{-5}$  mmol Pd/mg, 10 mmol Pd) and held at 120 °C. The second reactor was charged with a Raschig ring bearing scavenger **10**, **11**, **12**, or **13**, or 'dummy' and was held at r.t. (in the course of circulation, the temperature increased slowly to ca. 50 °C because of the heat transfer from the first reactor). After completion of the reaction (GC-monitoring), the reactors were rinsed with DMF (ca. 40 mL). The solution was diluted with H<sub>2</sub>O (80 mL), extracted with EtOAc (3 × 50 mL), and dried (MgSO<sub>4</sub>). After concentration in vacuo, the pure coupling product was isolated by flash chromatography on silica gel.

### Catalytic Activity Test of Scavenger Rings after Heck–Mizoroki Reaction (Continuous Flow Mode)

After performing the Heck–Mizoroki reaction with two linearly linked reactors as described above, the Raschig ring bearing precatalyst **2** was removed from the first reactor and replaced with a 'dummy' Raschig ring. Then, a solution of aryl halide (1 mmol), alkene (3 mmol), and  $Bu_3N$  (556 mg, 3 mmol) in anhyd DMF (3 mL) was circulated through the connected reactors under the general conditions. Conversion was determined by GC (Figures 3 and 4).

### Test of Catalytic Activity of Thiol Raschig Rings 10 after Heck-Mizoroki Coupling (Batch Mode)

A solution of aryl halide (1 mmol), alkene (3 mmol) and  $Bu_3N$  (556 mg, 3 mmol) in anhyd DMF (3 mL) was added to the thiol Raschig ring **10**, which was previously used as a scavenger in the linear reactor setup for performing the Heck–Mizoroki reaction. The mixture was gently shaken at 50 °C. Conversion was determined by GC.

#### **Supporting Information**

Supporting information on further coupling reactions carried out with the precatalyst **2** are available.

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