

## Efficient, Selective, and Recyclable Palladium Catalysts in Carbon–Carbon Coupling Reactions

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### 1. INTRODUCTION

Carbon–carbon cross-coupling reactions are among the most useful and most widely studied synthetic transformations. The three most important processes, the Heck reaction, the Suzuki–Miyaura coupling, and the Sonogashira reaction characteristically catalyzed by palladium, have been abundantly used in syntheses and widely studied in recent decades. Because of their great practical and theoretical importance, a book<sup>1</sup> and general review articles covering the field are available. These address the topic in general<sup>2–6</sup> or treat specific subjects such as the use of cross-coupling reactions in total synthesis,<sup>7,8</sup> coupling reactions performed in ionic liquids (ILs),<sup>9</sup> the use of silica-supported<sup>10</sup> and polymer-supported<sup>11</sup> catalysts, the nature of active species,<sup>12,13</sup> recyclable catalysts used in pure water,<sup>14–17</sup> the use of Pd/C in coupling reactions,<sup>18</sup> and issues with respect to the difficulties

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associated with the use of chloroaromatics,<sup>19,20</sup> the synthetic importance of C–C couplings,<sup>21</sup> and industrial applications in the production of fine chemicals.<sup>22,23</sup> The great significance of palladium-catalyzed C–C coupling reactions has been recognized by awarding the 2010 Nobel Prize in Chemistry to Professors Heck, Negishi, and Suzuki. The coupling methods, which they and others originated, are appropriately considered to be the cornerstones in organic synthesis.

An excessive array of new, highly effective, mostly heterogeneous catalysts has been developed in recent years. They can be repeatedly used and, consequently, provide an efficient and economic way to perform coupling reactions. Such catalysts do not require the use of phosphanes, they are not sensitive to air and moisture, afford coupling products in high yields at short reaction times, and can often be applied under mild conditions. It is not exceptional that reactions can be carried out in water, or, in a few rare cases, even solventless operations are possible. Such catalyst systems are valuable alternatives to homogeneous complexes. An equally important possibility is the use of ionic liquids.<sup>9,24</sup> They can serve as immobilization solvents and coordinating ligands to the catalysts and allow convenient catalyst recycling as well. The use of solvent mixtures composed of an IL and an organic solvent or water offers additional advantages.<sup>25</sup> Cross-coupling reactions performed under such conditions are of high practical importance.

Catalyst recycling, in general, is enormously important from the point of view of industrial applications and the environment. Despite these issues and the excessively large number of reports, a thorough treatment of the topic of recyclability is lacking. Therefore, it appears to be timely to give a comprehensive survey and a thorough analysis of the available data and discuss the questions related to recyclability in general. An additional important reason for the need of this Review is the fact that the majority of these new catalyst materials have been developed for synthetic purposes, and recycling studies, consequently, were of secondary importance in most cases. Characteristically, the consistently high yields of a catalyst in a few repeated runs are taken as evidence to prove its high recycling potential. Because of this shortcoming and the excessive number of reported data, a selection was necessary: with a few notable exceptions, only the results reporting at least five uses are treated. Furthermore, five-run studies are cited provided yields are high and stable, and the results are described in well-documented form with appropriate characterization information. It is necessary, however, to emphasize here that it is not the number of recycles that is important. Rather, true and valid measures of recycling performance are total TON and derived TOF values as well as reaction kinetics that is measuring true rates (rates of conversion) versus yields at long times (see further discussion of this point in section 3 below). Still, high consistent yields in repeated runs testify to the robust nature of a catalyst system, which is a necessary requirement for long-term applications.

The majority of the results are about the three most important coupling reactions, that is, the Heck, Suzuki–Miyaura, and Sonogashira couplings. Other methods, the Stille reaction, a few examples of coupling reactions studied less frequently (Kumada, Hiyama, and Negishi reaction), allylations including the Tsuji–Trost reaction, and relevant homocoupling processes are also covered. The main emphasis, naturally, is on palladium with a few additional examples for the use of other metals (Cu, Ni, Co, Rh). Discussions will also include a short description of catalyst synthesis and a brief, general evaluation of the performance of the

catalyst systems in the related coupling reaction. This Review includes results having been disclosed since the beginnings of Pd-catalyzed C–C coupling chemistry, albeit only a handful of the studies qualified from the 1990s.

The organization of the material, within each major reaction type, is made according to the type of the active palladium species inducing the coupling reaction (palladium nanoparticles and palladium complexes) and the supports used (silica and ordered mesoporous silica materials, other inorganic supports, as well as polymeric materials). Recycling studies with homogeneous palladium complexes are treated in separate subsections. In the final section, coupling reactions carried out in continuous operations are discussed. Strictly speaking, these methods cannot be considered as catalyst recycling. Because of the advantages of such processes, precise control of reaction variables particularly heat and mass transfer as well as residence time, no need for separation, the possibility to enhance TON, and future perspectives of practical importance, they are worth being included in this Review.

At the end of five chapters (Heck, Suzuki–Miyaura, Sonogashira, and Stille reaction, as well as homocoupling processes) with sufficient information to draw general conclusions, summary analyses are given. These are made by selecting well-characterized robust catalyst systems, which afford consistently high yields in recycling studies or give high cumulative TON numbers. These results are also tabulated and discussed in the final section (section 12, Conclusions and Outlook).

## 2. CATALYSTS AND CATALYST SYNTHESIS

The majority of the catalyst systems developed and studied is heterogeneous in nature. These catalysts can simply be removed from the reaction mixture by filtration or centrifugation and reused following appropriate washing processes. The supports most widely used are various silica materials and polymers. In addition, a wide range of solids including hybrid organic–inorganic supports, oxides, and carbon either commercially available or appropriately fine-tuned for specific purposes have been used to fabricate efficient heterogeneous palladium catalysts. About one-half of the studies covered here use palladium nanoparticles. Summaries of their application are available.<sup>26–29</sup>

Amorphous silica and ordered mesoporous siliceous materials with anchored functional groups have been widely used to synthesize palladium catalysts for coupling reactions. These organic–inorganic hybrid materials are made by grafting trialkoxysilanes bearing an appropriate functional group, most often (3-aminopropyl)trialkoxysilane and (3-mercaptopropyl)trialkoxysilane.<sup>30–32</sup> The method is called postsynthesis modification. Alternatively, hydrolysis–polycondensation (cogelification) of a silica source, most often tetraethyl orthosilicate (TEOS), and a functionalized trialkoxysilane may be applied (sol–gel process). When performed in the presence of a structure-directing (templating) agent, ordered mesoporous silica materials may be formed.<sup>32–34</sup> The two solids used most frequently are MCM-41 and SBA-15 with periodic pore structure, hexagonal symmetry, and large surface area. MCM-41 (Mobil composition of matter, no. 41) synthesized with the use of cationic surfactants has a long-range hexagonal framework with a uniform pore structure. SBA-15, developed at the University of California, Santa Barbara, in turn, is prepared with neutral triblock polyether templates and characterized by highly ordered mesoporous structure with larger pore size and thicker pore walls. SBA-16

used also in coupling chemistry, in turn, has 3D cubic symmetry and a cage-like structure with open frameworks accessible to metal ions and reagents. Among other interesting and important properties, their highly specific surfaces render them attractive in catalysis. The functional group introduced is capable of complexing Pd ions. The solids thus prepared are used as such or reduced, most often with hydrazine hydrate or flowing hydrogen, to form Pd<sup>0</sup> particles usually in the nanometer size. Nanoparticles may also be formed in situ under reaction conditions. The grafting method can also be used to functionalize any solids bearing surface OH groups. Alternatively, the synthesis of the silica material may be performed with the Pd source in the reaction mixture (in situ approach).

Polymers often functionalized with phosphane groups<sup>35</sup> may also serve as suitable carriers for depositing or complexing appropriate palladium sources. These systems can be seen as a borderline class of catalysts, which retain the advantages of homogeneous catalysts while securing the ease of recovery and workup of heterogeneous systems. Polymer-supported palladium catalysts have been successfully applied in varied coupling reactions.<sup>36</sup> Discussions will include dendritic Pd catalysts as well.<sup>37</sup> Recent progress in homogeneous nanosized catalysts including palladated dendrimers has been summarized.<sup>38</sup>

Another important method is to carry out the reaction in ionic liquids with dissolved palladium species. Recycling, in this case, is made by recharging the ionic liquid phase containing the catalyst with new educts and the base after product extraction, washing, and drying. The palladium sources most often applied are PdCl<sub>2</sub>, Pd(OAc)<sub>2</sub>, and *N*-heterocyclic carbene (NHC) Pd complexes.<sup>39</sup>

Two types of acronym are used for the designation of catalysts: (i) Pd-X and Pd-X-support stand for catalysts where X refers to a formula, which describes exactly the catalyst structure; (ii) when formula X is in parentheses [Pd-(X), Pd-support-(X)], then it refers to a ligand, a precursor used in catalyst synthesis, or the active catalyst center formed.

### 3. CATALYST RECYCLING

Recycling of palladium catalysts in coupling reactions has a few important general issues to be discussed. As mentioned, in the majority of cases, consistently high conversions or yields in a few repeated runs are taken as evidence to prove the high potential of a catalyst. It is often the case, however, that a sudden drop in yields is experienced after the fifth or sixth reuse. More importantly, a few successful reuses of a catalyst with consistently high conversions, yields, or TON numbers alone do not necessarily prove high efficiency and constant high activity in longer uses.

The evaluation of the recycling ability of a catalyst system in the long run, consequently, is problematic and requires high-quality studies. For example, if an unnecessarily long time is selected for the first run, comparable yields may be found in successive reactions. To measure TOF values at incomplete conversion and kinetic profiles, in turn, are the reliable tools to gather information of the nature of the catalytically active species. Kinetic data provide information for an induction period if present and allow a comparison of initial rates determined in successive reactions. As summarized by Gladysz,<sup>40</sup> the “recycled” species is certainly not the active catalyst when (i) inductions periods are detected, together with observations (ii) indicating catalytic activity of the separated reaction mixture and (iii) observing induction periods in repeated runs of the recovered catalyst often with decreased activity. If induction periods do

exist in successive catalytic cycles, it is an indication for the regeneration of the active catalyst in every run that is it is the catalyst resting state, which is actually recycled. As will be clear in the discussion sections, kinetic analysis has been rarely performed in the recycling studies covered here. Another crucial problem in any recycling study is the efficiency of catalyst recovery with the ideal case being quantitative recovery. Direct measurements, however, are quite rare, which is not surprising considering the small quantities used.

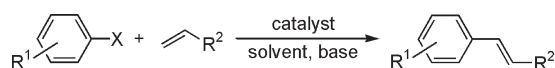
Considering practical applications, a high cumulative TON is more crucial than good recycling ability of a catalyst, that is, yields as a function of cycles. Furthermore, average TOF values giving the rate of product formation measured in each cycle are valid and meaningful data as pointed out by Gladysz.<sup>41</sup> In case of an induction period often observed in coupling reactions, catalytic activity may be better expressed by the slope of tangent line after the induction period as suggested by Beletskaya.<sup>42</sup> Useful advice recommended by Jones<sup>12</sup> is to plot kinetic data (conversions vs time) for comparison with quantitative values (rate constants, initial rates, TOFs). Data sets collected by such careful and thorough studies will certainly allow the unequivocal assessment of catalyst systems with respect to recyclability, stability, and deactivation if any.<sup>43</sup> It should also be an obvious necessity to characterize and evaluate catalysts before and after reaction and monitor continuously the working catalyst systems to collect information of recyclability, catalyst recovery, and deactivation. Readers are advised to consult papers by Jones<sup>12,43</sup> and Gladysz<sup>41,44</sup> for intriguing detailed discussions.

When catalysts with supported Pd particles are used, important reasons bringing about decreasing yields are as follows:

- (i) The aggregation of nanoparticles results in diminishing of available active metal species as shown by the changes in particle size distribution and/or metal surface area of the recovered catalyst after recycling.
- (ii) Leaching of palladium occurs in successive runs as evidenced by inductively coupled atomic absorption and mass spectroscopic measurements (ICP-AAS/MS) and atomic or optical emission spectroscopy (ICP-AES/OES). Leaching is also shown by the residual activity of the reaction mixture after catalyst removal. In most cases, leached species are deposited again on the support (see below); however, this process may also be accompanied by decreasing metal surface area.
- (iii) Poisoning the active surface sites and salt accumulation hinder the access to surface active sites and redeposition of Pd species from solution. The overall result is a diminishing concentration of palladium species participating in the catalytic cycle.
- (iv) When palladium complexes either in heterogenized form or applied under homogeneous conditions are used in coupling reactions, in situ reduction may transform the active complex into metallic palladium particles. Even when these act as active catalytic species, their activity is often inferior to that of the original complex.

Mechanistic issues of palladium-catalyzed cross-coupling reactions are beyond the scope of this Review. Nevertheless, the question of mechanism inevitably arises in connection with catalyst recycling. A few major points and relevant experimental techniques, consequently, are briefly discussed here. Important additional readings are related forum articles published in *Inorganic Chemistry*.<sup>45–47</sup>



**Table 1.** Heck Coupling of Haloaromatics with Styrene and Acrylic Esters Catalyzed by Palladium Nanoparticles Supported on Amorphous Silica

entry	R <sup>1</sup>	X	R <sup>2</sup>	catalyst <sup>a</sup>	reaction conditions:		number of reuses	average yield, <sup>b</sup> (%)	ref
					solvent/base/temperature/time				
1	H	Br	Ph	0.48% Pd-SiO <sub>2</sub> (1)	H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /80 °C/4 h		6	quantitative	68
2	4-Me	I	Ph	0.70% Pd-SiO <sub>2</sub> -(1) (0.5)	DMF/Na <sub>2</sub> CO <sub>3</sub> /140 °C/6.6–11.5 h <sup>c</sup>		10	88 (91–86)	69
3	4-Ac	Br	Ph		DMF/Na <sub>2</sub> CO <sub>3</sub> /140 °C/2–28.5 h <sup>c</sup>		8	89.5 (96–65)	
4	H	I	COOMe	1.22% Pd-FSG-(2a) (0.1)	MeCN/Et <sub>3</sub> N/100 °C/24 h		10	93 (100–86)	71
5	H	I	COOMe				15	98 (98–80)	
6	H	I	COOBu	3.47% Pd-SiO <sub>2</sub> -(3) (2)	MeCN/Et <sub>3</sub> N/130 °C/24 h		6	99 (99) <sup>d</sup>	73
7	H	I	COOBu		MeCN/Et <sub>3</sub> N/130 °C/3 h <sup>c</sup>		6	96.5 (97–96) <sup>d</sup>	
8	H	I	COOBu	12.50% Pd-SiO <sub>2</sub> -(4) (2)	MeCN/Et <sub>3</sub> N/130 °C/24 h		6	98 (99–97)	74

<sup>a</sup> Percentage data show Pd loading (wt %) when available; data in parentheses indicate mol % of Pd used. <sup>b</sup> Data in parentheses indicate range of yields.

<sup>c</sup> Under inert atmosphere. <sup>d</sup> Conversion. <sup>e</sup> Under microwave irradiation.

It has been well-documented that active palladium species leach from supported catalysts and then redeposit on the catalyst surface (dissolution–redeposition or release–capture mechanism).<sup>48–52</sup> This occurs even when palladium particles present as such or formed in situ under reaction conditions are involved. As a result of complex formation or oxidative addition of the aromatic halide at the beginning of the catalytic cycle, highly active soluble species are generated (Pd<sup>0</sup> → Pd<sup>2+</sup>). Characteristically, the Pd content of the reaction mixture after complete conversion is very low (in or below the ppm range). On the other hand, studies with immobilized molecular Pd<sup>2+</sup> complexes have shown that these tend to decompose and release ligand-free soluble Pd<sup>0</sup> species (Pd<sup>2+</sup> → Pd<sup>0</sup>).<sup>12,45,53</sup> Relevant information about the involvement of leached Pd species can be collected by appropriate experimental techniques listed below. Examples of these methods will be mentioned in the discussions.

- In a hot filtration (also called split) test, the reaction is interrupted at a low conversion and then continued after catalyst removal, and a new reaction is started with the recovered catalyst. If no further conversion in the catalyst-free solution phase is detected, it may be concluded that soluble species even when formed are not active in the reaction. However, when fast redeposition of soluble species occurs, the test may lead to erroneous conclusion.<sup>54</sup> Consequently, the distinction between heterogeneous and homogeneous catalysis cannot be based solely on the hot filtration test. On the other hand, if both activity and an induction period are observed, the immobilized species is definitely not the active catalytic species (see above).
- In the three-phase test developed by Rebek,<sup>55</sup> one of the reactants is anchored on a solid support and then reacted in the presence of the other reactant in solution and a solid catalyst. The immobilized reactant is able to react only if soluble palladium species are involved.
- Finally, poisoning by elemental mercury (Hg<sup>0</sup>) via amalgamation has also been used to test the nature of active species involved in the coupling process, that is, to show the participation of metallic Pd. See, however, comments by Jones about the proper interpretation of this test.<sup>56,57</sup> Poly(4-vinylpyridine) (PVPy) and Quadrapure

TU, a thiourea-functionalized polymer,<sup>57</sup> as well as 3-mercaptopropyl-functionalized silicas,<sup>58</sup> in turn, have been used as selective trapping agents to probe the involvement of leached palladium species.

A final remark is about the merits of recoverable catalyst systems producing an overall large amount of product molecules in repeated cycles (large combined TON) versus the use of catalysts of high activity yielding an equally high amount of product in a single run. From a green chemistry point of view, the use of catalysts with high TON and TOF values, characteristic of homogeneous systems, should be considered the ideal case. Nevertheless, studies with respect to the development of stable and recyclable catalysts of high efficiency constitute an important research field and may have practical implications. Additional readings are the papers by Gladysz<sup>41,44</sup> and Jones<sup>12,43</sup> already mentioned, a related thematic issue in *Chemical Reviews*,<sup>59</sup> and a review by Farina.<sup>54</sup>

## 4. HECK COUPLING

The Heck coupling, often referred to as the Mizoroki–Heck reaction first reported by Heck in 1968,<sup>60</sup> is the alkenylation of aromatic compounds through the reaction of substituted aromatics (halides, triflates, or diazonium derivatives called the Matsuda–Heck reaction, etc.) and alkenes. In the great majority of the studies, however, haloaromatics are reacted with styrene and acrylic acid derivatives (acrylic acid, alkyl acrylates, acrylonitrile). The topic is widely reviewed.<sup>22,52,61–67</sup>

### 4.1. Coupling Reactions Catalyzed by Palladium Nanoparticles

**4.1.1. Palladium Particles Supported on Silica Materials.** Results with respects to the use of palladium particles supported on amorphous silica and ordered silica materials are collected in Tables 1 and 2, respectively.

Tselikhovsky and Blum<sup>68</sup> have designed a catalyst with Pd(OAc)<sub>2</sub> entrapped within a silica gel matrix. The catalyst was prepared by cogelification of tetramethoxysilane and octyltriethoxysilane in the presence of Pd(OAc)<sub>2</sub> (0.48% Pd-SiO<sub>2</sub>). The long alkyl chains make the matrix hydrophobic. The catalyst containing Pd nanoparticles was used in the Heck, Suzuki, and Stille coupling by making a microemulsion of the substrates in water as solvent in the presence of sodium dodecyl sulfate as surfactant and an alcohol (propan-1-ol or butan-1-ol) as cosurfactant. The role of

**Table 2.** Heck Coupling of Haloaromatics with Styrene, Acrylic Acid, and Esters Catalyzed by Palladium Nanoparticles Supported on Ordered Silica Materials

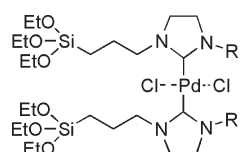
entry	R <sup>1</sup>	X	R <sup>2</sup>	catalyst <sup>a</sup>	reaction conditions: solvent/base/temperature/time	number of reuses	average yield, <sup>b</sup> (%)	ref
1	H	I	COOBu	1.46% Pd-SBA15 (0.02)	DMAc/Et <sub>3</sub> N/140 °C/1 h	7	89 (98.5–69)	75
2	H	I	COOMe	5.7% Pd-SBA15 (0.04)	NMP/Et <sub>3</sub> N/140 °C/1 h	6	92 (99–70)	76
3	H	I	COOMe	1.39% Pd-MCM41 (0.3)	NMP/Et <sub>3</sub> N–Na <sub>2</sub> CO <sub>3</sub> /150 °C/1 h	20	quantitative	77
4	H	I	COOMe	5.85% Pd-MCM41 (0.3)	NMP/Et <sub>3</sub> N–Na <sub>2</sub> CO <sub>3</sub> /175 °C/45 min	20	quantitative	
5	H	Br	Ph	Pd-SBA15 (0.002)	NMP/Et <sub>3</sub> N/140 °C/2 h	6	52.5 (54–49)	82
6	H	I	COOMe	1.06% Pd-TMG-SBA15 (0.05)	–/Et <sub>3</sub> N/140 °C/50 min	7	90.5 (91–90)	83
7	H	I	COOH	4.30% Pd-5a-SBA15 (0.04)	DMF/Et <sub>3</sub> N/120 °C/0.5 h	7	91 (98–78)	84
8	4-CHO	Br	Ph	0.23% Pd-SBA16-(6+7a) (0.02)	NMP/NaOAc/130 °C/16–49 h <sup>c</sup>	8	94 (99–87)	85
9	H	I	Ph	3.9% Pd-HS-Si(HIPE) (0.004)	DMF/Et <sub>3</sub> N/155 °C/3 h <sup>c</sup>	9	93 (99–75)	86
10	H	I	Ph	4.1% Pd-grHS-Si(HIPE) (0.004)		7	97 (98–97)	
11	H	I	COOBu	5% Pd-MCF-(8a) (1)	toluene/Et <sub>3</sub> N/100 °C/20 h <sup>c</sup>	5	92 (92)	87
12	H	I	COOMe	7.8% Pd-MSS-zeolite (0.025)	NMP/Et <sub>3</sub> N/120 °C/3 h	10	95 (99–92)	88

<sup>a</sup> Percentage data show Pd loading (wt %) when available; data in parentheses indicate mol % of Pd used. <sup>b</sup> Data in parentheses indicate range of yields.

<sup>c</sup> Under inert atmosphere.

the surfactants is to carry the substrates into the entrapped Pd species. The catalyst gave quantitative yields in six successive runs in the coupling of bromobenzene and styrene to produce pure (*E*)-stilbene (Table 1, entry 1; average yields are calculated as the average of all individual yield data). Varied yields were reported for the coupling of bromobenzenes with styrenes (47 to >99%), whereas the reaction of bulky substrates such as 2-bromotoluene and 1-bromonaphthalene was found to be strongly inhibited.

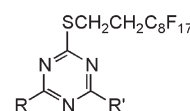
Pd-silica catalysts with Pd loadings of 0.13 and 0.70 wt % were prepared by grafting amorphous silica with derivatized complex **1**.<sup>69</sup> Coupling reactions of bromoarenes and butyl acrylate progressed smoothly with catalyst 0.13% Pd-silica under inert atmosphere to afford high yields. Large TON numbers could be realized with low Pd loadings under “homeopathic” conditions<sup>70</sup> (840 000, 4-bromoacetophenone and butyl acrylate, 0.0001 mol % of Pd). Recycling studies with 0.70% Pd-SiO<sub>2</sub>-(**1**) gave decreasing yields, requiring the use of prolonged reactions (entries 2 and 3). Pd particles formed under reaction conditions were detected by transmission electron microscopy (TEM). An average particle size diameter of 36.7 nm was measured for the catalyst recovered after the first use in contrast to a value of 8.7 nm after the eighth run. Hot filtration and mercury poisoning tests, as well as reaction in the presence of poly(4-vinylpyridine) capable of strongly coordinating to Pd<sup>2+</sup> species, indicated that the reaction is catalyzed mainly by soluble Pd species. Furthermore, 3.6 ppm of Pd (3.4% of Pd loaded) was detected in the reaction mixture after interrupting the reaction at 16% conversion.



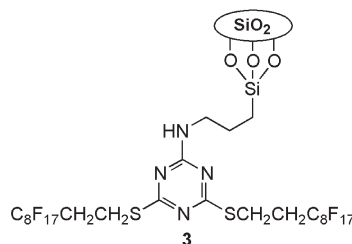
**1:** R = 2,4,6-trimethylbenzyl

Two types of catalyst with immobilized, perfluoro-tagged Pd nanoparticles have been prepared and evaluated in the Heck and

Suzuki reactions by Vallribera and co-workers.<sup>71</sup> In the synthesis of catalyst 1.22% Pd-FSG-(**2a**), Na<sub>2</sub>[Pd<sub>2</sub>Cl<sub>6</sub>] generated in situ was reduced with methanol in the presence of the perfluoro-tagged stabilizing agent **2a**, and then the formed nanoparticles (mean diameter = 1.5 ± 0.7 nm) were deposited onto commercial fluorosilica gel (FSG).<sup>71,72</sup> Catalyst 3.47% Pd-SiO<sub>2</sub>-(**3**), in turn, was prepared by first synthesizing the fluorosilica-inorganic hybrid material **3** by polycondensation of the silylated precursor **2b** and TEOS and then carrying out the reduction of Na<sub>2</sub>[Pd<sub>2</sub>Cl<sub>6</sub>] in the presence of **3**.<sup>73</sup> Catalyst 3.47% Pd-SiO<sub>2</sub>-(**3**) contains Pd nanoparticles with an average particle size of 3.9 ± 0.9 nm. Reactions were conducted, and catalyst recovery was made in the presence of air without the necessity of any special precaution.

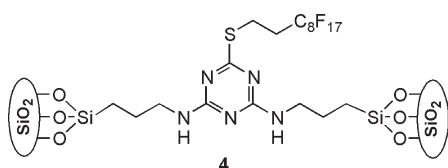


**2a:** R, R' = SCH<sub>2</sub>CH<sub>2</sub>C<sub>8</sub>F<sub>17</sub>  
**2b:** R = SCH<sub>2</sub>CH<sub>2</sub>C<sub>8</sub>F<sub>17</sub>, R' = NH(CH<sub>2</sub>)<sub>3</sub>Si(OEt)<sub>3</sub>  
**2c:** R, R' = NH(CH<sub>2</sub>)<sub>3</sub>Si(OEt)<sub>3</sub>



Both catalysts afforded high yields in the coupling of iodoaromatics with methyl acrylate (74–98%). Catalyst 1.22% Pd-FSG-(**2a**) exhibited high but slowly decreasing yields in recycling studies in 10 and 15 runs (entries 4 and 5). No agglomeration was detected upon recycling (particle size of the recovered

catalyst after 15 runs was about  $1.9 \pm 0.3$  nm). The analysis of the crude reaction mixture revealed the loss of about 5% of **2a** and 2–7 ppm of palladium. The residual activity of the reaction mixture after separation of the catalyst was significant (40% yield at 100 °C after 23 h). This shows that leached palladium species are, obviously, participating in the catalytic process. Catalyst 3.47% Pd-SiO<sub>2</sub>-(**3**) displayed consistently high yields in six runs using either conventional or microwave heating<sup>73</sup> (entries 6 and 7) with 6 ppm of Pd detected in the reaction mixture. In their latest communication,<sup>74</sup> the authors have reported the synthesis of catalyst Pd-SiO<sub>2</sub>-(**4**) performed by reducing Na<sub>2</sub>[Pd<sub>2</sub>Cl<sub>6</sub>] in the presence of **4**. The latter was prepared by the condensation of bis-silylated **2c** without TEOS to have a catalyst with increased Pd loading. Indeed, the palladium content of the resulting catalyst is significantly higher (12.50 wt %) with Pd particles of an average size of 4 nm. The catalyst could be reused with only a negligible decrease in yields in six runs (entry 8).



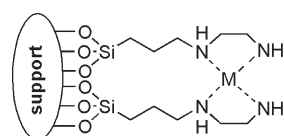
The 1.46% Pd-SBA15 catalyst (Table 2, entry 1), prepared by performing the synthesis of SBA-15 in the presence of Pd<sup>2+</sup> acetylacetonate [Pd(acac)<sub>2</sub>] followed by reduction (H<sub>2</sub>, 300 °C, 2 h), has highly dispersed uniform particles (3 nm) located inside the pore channels of the mesoporous silica.<sup>75</sup> The catalyst used in air gave high yields, which, however, dropped significantly in the seventh run with a loss of 6.2% of Pd. Furthermore, both metal dispersion (from 36% to 30%) and metal surface area (from 161 to 134 m<sup>2</sup> g<sup>-1</sup>) decreased slightly as measured by CO chemisorption. A similar method that is the sol-gel process was applied in the preparation of the catalyst used in entry 2 (5.7% Pd-SBA15), but palladium was loaded as PdCl<sub>2</sub>.<sup>76</sup> The Pd nanoparticles (5–10 nm) formed after reduction (H<sub>2</sub>, 80 °C, 0.5 h) are confined in the hexagonal channels of the SBA-15 structure. The few iodo- and bromoarenes tested gave high conversion with this catalyst (90–99%). In recycling studies, it exhibited characteristics similar to those of 1.46% Pd-SBA15 discussed above, giving a significantly decreased yield already in the sixth run.

MCM-41, another ordered mesoporous silica material, was also used as support for Pd nanoparticles.<sup>77</sup> The sol-gel method was applied for catalyst synthesis with a reaction mixture consisting of TEOS, cetyltrimethylammonium bromide (CTMABr, a structure-directing agent), and PdCl<sub>2</sub>. Catalysts were made via simultaneous self-assembling of mesoporous MCM-41 and particle generation. A particle size distribution of 5–17 nm was found by TEM, indicating that Pd nanoparticles are located mainly on the surface.<sup>78</sup> Among the catalysts thus prepared, Pd-MCM41 with low and high palladium loadings (1.39%, 5.85%) proved to be active and stereoselective in the coupling of bromoarenes including deactivated bromo derivatives (yields of 54–100%, selectivities of 71–100%). They also displayed excellent characteristics in recycling studies. The best results were achieved using the mixed base Et<sub>3</sub>N–Na<sub>2</sub>CO<sub>3</sub> to form methyl (*E*)-cinnamate in quantitative yields in 20 runs (entries 3 and 4). No precautions against air or moisture needed to be taken when using these catalysts.

Nadkarni and Frey in 1993 disclosed the method of in situ reduction with immobilized surface Si–H functions for the controlled deposition of metals.<sup>79</sup> The method was later used to prepare organic–inorganic hybrid Pd-SiO<sub>2</sub> catalysts<sup>80,81</sup> and deposit metallic Pd onto the surface of SBA-15 for the Heck coupling.<sup>82</sup> The latter catalyst gave medium to excellent yields in the coupling of a few aromatic halides with styrene and methyl acrylate (yields of 51–100%). It affords medium yields with a sudden drop in the last run of a recycling study (entry 5). Nevertheless, it gives a total TON of 157 500.

Material 1.06% Pd-TMG-SBA15 was applied in solvent-free Heck couplings and reused after a thorough washing with ethanol and drying at 50 °C. The catalyst was prepared by the reaction of Pd(OAc)<sub>2</sub> and 1,1,3,3-tetramethylguanidinium lactate (TMG) in the presence of SBA-15 followed by reduction (H<sub>2</sub>, 180 °C, 2 h) and heat treatment (200 °C, 3 h) to remove the anion.<sup>83</sup> Reactions took place with complete regio- and stereoselectivity except those of styrene (5% of 1,1-disubstituted product) and acrylonitrile (12% of *Z* isomer). In contrast to the reaction of iodoarenes (yields of 60–94%), low yields were reported for the coupling of bromobenzene and 4-bromoacetophenone with methyl acrylate (33% and 54%, respectively). High and stable yields were observed in the recycling study (entry 6). The filtration test showed further reaction and complete consumption of iodobenzene, whereas less than 0.3% of Pd was detected after completion of the reaction. This shows that soluble Pd species are efficiently recaptured, which is attributed to the stabilizing effect of the guanidinium ion in the catalyst. Nanoparticles (3–6 nm) were shown to exist in the channels of SBA-15, and only a few larger particles were detected after recycling.

Derivatization of SBA-15 with 3-[(2-aminoethyl)amino]propyltriethoxysilane (AAPTES) followed by reaction with PdCl<sub>2</sub> gave immobilized complex **5a**. Subsequent reduction with hydrazine hydrate furnished catalyst 4.30% Pd-**5a**-SBA15 with an average particle diameter of 3 nm.<sup>84</sup> Iodobenzenes and activated bromobenzenes reacted smoothly with styrene, acrylic acid, and butyl acrylate to afford high yields (78–98%). Bromobenzene, however, gave similar high yields only after prolonged reaction with increased amount of Pd (0.4 mol % vs 0.04 mol %). The catalyst showed high but decreasing yields in recycling with a significant drop in the last run (entry 7). This was attributed to a decreased metal dispersion indicative of agglomeration and a Pd loss of 2.1% determined after the sixth run.

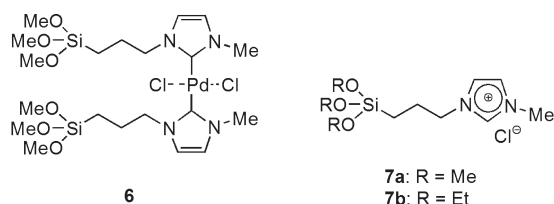


**5a:** M = Pd<sup>0</sup>, support = SBA-15  
**5b:** M = Pd<sup>2+</sup>, support = SiO<sub>2</sub>  
**5c:** M = Cu<sup>2+</sup>, support = SiO<sub>2</sub>

Catalyst 0.23% Pd-SBA16-(**6+7a**) (entry 8) is composed of an ionic liquid and an NHC complex covalently attached to the inner cage surface of SBA-16. Functionalization was made by grafting derivative **7a** and derivatized complex **6**.<sup>85</sup> Good to high yields (76–95%) were reported in the coupling of bromobenzene and derivatives with styrene and methyl acrylate. Fine Pd nanoparticles (~5 nm) are formed during the reaction, which are

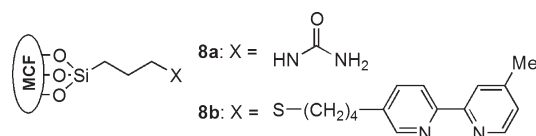


located in the cages of SBA-16. Heterogeneity was tested by interrupting the reaction at 69% conversion and continuing the reaction after removal of the catalyst (hot filtration test). No further conversion after 35 h and less than 0.1 ppm Pd measured in the filtrate after the first run were taken by the authors as evidence for the heterogeneous nature of the reaction. See further discussion of this catalyst in section 5.1.1 (Table 9, entry 4).



The first “high internal phase emulsion” (HIPE) open-cell hybrid matrixes were prepared by either hydrolysis–polycondensation of (3-mercaptopropyl)trimethoxysilane and TEOS [3.9% Pd-HS-Si(HIPE)] or first synthesizing a native Si(HIPE) by the template-directed hydrolysis of TEOS followed by grafting with (3-mercaptopropyl)trimethoxysilane [4.1% Pd-*gr*HS-Si(HIPE)] or (3-aminopropyl)trimethoxysilane.<sup>86</sup> The macrocellular monoliths with hierarchical porosities thus prepared were immersed in a solution of Pd(OAc)<sub>2</sub> and PPh<sub>3</sub>, and then the resulting materials were reduced with NaBH<sub>4</sub>. The formed Pd nanoparticles with average diameters of about 5–10 nm are located on the inner surface of macropores. The catalysts handled under argon afforded high yields (entries 9 and 10) and gave (*E*)-stilbene with high selectivity (96%) in the coupling of iodobenzene with styrene. Moreover, both catalysts afforded high cumulative TON values (157 500 and 209 200). Kinetic studies showed similar behavior of the three samples tested, but mercapto-derivatized catalysts proved to be less sensitive to deactivation and leaching than the catalyst functionalized with the amino group (3.5–15 ppm Pd detected in successive runs). The decrease in yields in the eight and ninth runs (entry 9) is attributed to the gradual loss of Pd from sample 3.9% Pd-HS-Si(HIPE).

A siliceous mesocellular foam (MCF) modified with propyleneurea (**8a**) was reacted with Pd(OAc)<sub>2</sub> to generate catalyst 5% Pd-MCF-(**8a**) with uniformly dispersed nanoparticles (2–3 nm).<sup>87</sup> Couplings of varied bromo- and iodoarenes with butyl acrylate proceeded in high yields (84–96%). The catalyst could easily be recovered by filtration and gave consistently high yields in successive runs with a loss of <5% of Pd after five cycles (entry 11). This, however, is not a promising sign for long-time applications.



Material 7.8% Pd-MSS-zeolite is a novel catalyst with nanopalladium particles entrapped in the zeolitic matrix.<sup>88</sup> First, the surface of mesoporous silica spheres (MSS) was modified with (3-aminopropyl)trimethoxysilane followed by impregnation with Pd(acac)<sub>2</sub>. The surface of the resulting material was then seeded with zeolite nanocrystals and subjected to hydrothermal treatment. Finally, the product was treated with flowing

hydrogen (100 °C) to yield a catalyst with Pd particles of about 11 nm in size. Pd leaching was not detected in coupling reactions, but X-ray photoelectron spectroscopy (XPS) showed the presence of Pd<sup>2+</sup> species in the recovered catalyst, and the growth of Pd particles was also observed. The latter, however, did not affect kinetic curves, which were practically unchanged. These results have been taken as evidence that the reaction is quasi-homogeneous, that is, dissolving–redeposition of Pd species occurs. The coupling reaction was suggested to take place in the micrometer-sized hollow cavities preventing Pd leaching, which affords stable catalytic activity (high yields) in 10 runs (entry 12). This conclusion is based on the high reactivity of 4-iodotoluene and the almost complete lack of reaction of 5-iodo-*meta*-xylene: the latter is not able to reach the active Pd species through the zeolitic shell.

**4.1.2. Palladium Particles Supported on Other Inorganic Materials.** Numerous reports have been published with respect to the excellent properties including recyclability of commercial Pd/C catalysts.<sup>18</sup> In fact, the characteristic feature in recycling experiments, in most cases, is decreasing yields. Consequently, only a few studies are deserved to be discussed here. Commercial 10% Pd/C applied in [bmim][PF<sub>6</sub>], for example, was shown to be easily recyclable after extraction of the reaction mixture with hexane or ethyl acetate.<sup>89</sup> Because the catalyst remained suspended in the IL, the IL phase was used directly in subsequent runs. However, yields dropped from 92% to 80% in the fifth run upon recycling (Table 3, entry 1), which was attributed to the accumulation of Et<sub>3</sub>NH<sup>+</sup>I<sup>−</sup>. Indeed, washing with water restored the activity (95% yield); that is, aqueous workup proved to be necessary.

Vallribera, Roig, and co-workers have developed a Pd/C aerogel catalyst<sup>90</sup> containing Pd nanoparticles (19 ± 4 nm) by reacting 2,4-dihydroxybenzoic acid and formaldehyde in K<sub>2</sub>CO<sub>3</sub>. The resulting gel was treated with Pd(OAc)<sub>2</sub>, and the product was subjected to drying with supercritical CO<sub>2</sub> and then carbonized by pyrolysis at 1050 °C. The catalyst afforded quantitative conversions in five reuses (Table 3, entry 2) with a 3% of Pd leaching detected after the first use. Pd/C aerogel with higher loading (46 wt %) and larger particles (27 ± 8 nm), in contrast, displayed rapidly decreasing yields in recycling. Another sample, 3.7% Pd/SiO<sub>2</sub> aerogel (mean particle size = 39 nm), was less active (reaction time = 4–5 days) with significant leaching observed (11% of Pd).

The catalytic application of magnetic particles loaded with metal nanoparticles has aroused great interest in recent years.<sup>91</sup> The main attractive feature is easy separation by an external magnet with minimal catalyst loss that is the usual filtration or centrifugation can be avoided. Medium yields and low stabilities were generally reported in early studies with the use of Pd on magnetic supports in coupling reactions. For example, Shen, He, and co-workers prepared two catalysts by using Fe<sub>3</sub>O<sub>4</sub> or silica-coated Fe<sub>3</sub>O<sub>4</sub>. Catalyst Pd-Fe<sub>3</sub>O<sub>4</sub> gave an initial yield of 81% in the coupling of iodobenzene and acrylic acid, which, however, dropped to 53% in the fifth reuse.<sup>92</sup> A similar large drop of yield (from 67% to 37% in the sixth run) was observed for silica-coated catalyst Pd-SiO<sub>2</sub>/Fe<sub>3</sub>O<sub>4</sub>.<sup>93</sup> The reason for unsatisfactory catalyst stability, in the first case, is the aggregation of Pd particles, while in the second case decreasing activity was attributed to Pd leaching. Another catalyst, 3.4% Pd-9-MNP, was made by anchoring starch on the surface of magnetic nanoparticles (MNP) through phosphate groups.<sup>94</sup> Pd nanoparticles (less than 1 nm in size) were generated by absorbing Pd(acac)<sub>2</sub> through electrostatic interaction followed by reduction with ethylene glycol. Medium

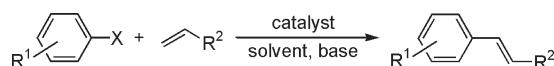
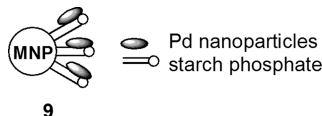
**Table 3.** Heck Coupling of Haloaromatics with Styrene, Acrylic Acid, and Esters Catalyzed by Palladium Nanoparticles Supported on Other Inorganic Materials

Table 1. Catalytic activity of various catalysts in the hydrogenation of 1-phenyl-2-methyl-2-butene (1) to 2-phenyl-2-butanol (2) under various reaction conditions.									
entry	R <sup>1j</sup>	X	R <sup>2</sup>	catalyst <sup>a</sup>	reaction conditions: solvent/base/temperature/time	number of reuses	average yield, <sup>b</sup> (%)	ref	
1	H	I	COOEt	10% Pd/C (3.1)	[bmim][PF <sub>6</sub> ]/Et <sub>3</sub> N/100 °C/12 h <sup>c</sup>	6	87.5 (95–80)	89	
2	H	I	COOEt	35% Pd/C aerogel (2)	MeCN/Et <sub>3</sub> N/reflux/24–25 h	5	quantitative <sup>d</sup>	90	
3	H	I	COOH	3.3% Pd-C/Au@Fe (0.5)	DMF/Et <sub>3</sub> N/100 °C/4 h	10	93 (100–90) <sup>d</sup>	95	
4	H	I	COOMe	7.26% Pd-DOPA-pine-Fe <sub>2</sub> O <sub>3</sub> (6.8)	DMF/Et <sub>3</sub> N/100 °C/30 min <sup>e</sup>	5	86 (87–85)	97	
5	H	I	COOH	4.57% Pd-10-polym/Fe <sub>3</sub> O <sub>4</sub> (0.5)	DMF/Bu <sub>3</sub> N/95 °C/3 h	6	94.5 (98–92)	98	
6	H	Br	Ph	5% Pd-MgO (0.1)	DMAc/NaOAc/140 °C/20 h	6	41 (96–4)	99	
7	H	Cl	Ph	10.53% Pd-MgO (1)	DMAc/NaOAc/135 °C/15 h <sup>f</sup>	5	n.r. (78–73)	101	
8	4-Ac	Cl	Ph	10.53% Pd-MgO (1)	DMAc/NaOAc/135 °C/10 h <sup>f</sup>	5	n.r. (92–89)		
9	H	I	Ph	10.53% Pd-MgO (1.43)	DMAc/NaOAc/100 °C/4 h <sup>c</sup>	6	97 (98–96) <sup>g</sup>	102	
10	H	I	Ph	0.4% Pd-ZrO <sub>2</sub> (0.3)	H <sub>2</sub> O/TBAOH/90 °C/4–7 h	10	72 (81–67)	103	
11	R <sup>3</sup>	I	Ph	0.4% Pd-ZrO <sub>2</sub> (0.3)	H <sub>2</sub> O/TBAOH/90 °C/7 h	5	— <sup>h</sup>		
12	R <sup>4</sup>	Br	Ph	0.4% Pd-ZrO <sub>2</sub> (0.3) <sup>i</sup>	H <sub>2</sub> O/TBAOH/110 °C/14 h	3	— <sup>h</sup>		
13	4-MeO	Cl	Ph	10.1% Pd-LDH (3)	Bu <sub>3</sub> N/130 °C/40 h <sup>f</sup>	5	74 (75–73) <sup>d</sup>	105	
14	4-MeO	Cl	Ph	10.1% Pd-LDH (3)	Bu <sub>3</sub> N/130 °C/1 <sup>e,f</sup>	5	79 (80–78) <sup>d</sup>		
15	H	I	Me	3.66% Pd-diatomite (0.1)	NMP/Et <sub>3</sub> N/120 °C/20–70 min	6	95.5 (97–95)	106	

<sup>a</sup> Percentage data show Pd loading (wt %) when available; data in parentheses indicate mol % of Pd used. <sup>b</sup> n.r. = not reported. Data in parentheses indicate range of yields. <sup>c</sup> Under inert atmosphere. <sup>d</sup> Conversion. <sup>e</sup> Under microwave irradiation. <sup>f</sup> Under inert atmosphere, in the presence of TBAB. <sup>g</sup> Yield of bibenzyl because Heck coupling was followed by hydrogenation in one pot. <sup>h</sup> See footnote. <sup>i</sup> The catalyst recovered from previous runs (entry 11) was used. <sup>j</sup> R<sup>3</sup>: Successive reactions with R<sup>1</sup> = 4-MeO (80%), 4-Me (95%), 4-Br (99%), 4-CF<sub>3</sub> (99%), 4-NO<sub>2</sub> (78%). R<sup>4</sup>: Successive reactions with R<sup>1</sup> = 4-MeO (34%), 4-Me (31%), H (76%).

yields (56%) were determined in five runs with a low level of Pd leaching (less than 5 ppm).

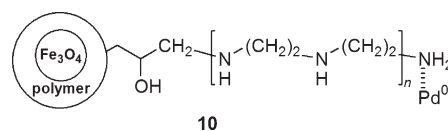


A significantly improved catalyst performance has been reported in a subsequent study<sup>95</sup> by using palladium particles (~12 nm) deposited onto carbon-encapsulated gold-coated Fe nanoparticles (C/Au@Fe).<sup>96</sup> Catalyst 3.3% Pd-C/Au@Fe exhibited high activity in the coupling of iodobenzene with styrene, acrylic acid, and methyl acrylate (yields of 89–96%). Bromobenzene was less reactive (47–57%) even at elevated temperature in prolonged reactions (140 °C, 12 h vs 100 °C, 4 h). *E* isomers were formed exclusively with the exception of styrene giving *E/Z* isomer ratios of about 75:25. The catalyst showed good stability in a 10-run recycling study (entry 3) as compared to a commercial 3% Pd/C giving a mere 48% conversion in the tenth run. A small degree of aggregation and a 2% loss of Pd were detected when the catalyst was analyzed after the recycling study.

α-Fe<sub>2</sub>O<sub>3</sub> particles of single-crystal structure with a unique micropine morphology were functionalized with dopamine and then treated with Na<sub>2</sub>[PdCl<sub>4</sub>] and hydrazine hydrate.<sup>97</sup> According to TEM images, the support in catalyst 7.26% Pd-DOPA-pine-Fe<sub>2</sub>O<sub>3</sub> is decorated with fine Pd particles. A variety of iodo- and bromoaromatics reacted smoothly with styrene and methyl acrylate to give coupled products in high yields (84–96%). Satisfactory activity and high stability were maintained in five successive uses (entry 4).

Superparamagnetic Fe<sub>3</sub>O<sub>4</sub> nanoparticles coated with a copolymer of glycidyl methacrylate, methyl methacrylate, and acrylic

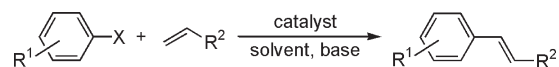
acid were aminated with triethylenetetramine, then reacted with Pd(OAc)<sub>2</sub>, and, finally, reduced with KBH<sub>4</sub> to produce catalyst 4.57% Pd-10-polym/Fe<sub>3</sub>O<sub>4</sub>.<sup>98</sup> The Pd-loaded composite microspheres thus prepared have fine Pd particles with diameters less than 1 nm and contain a small amount of unreduced Pd<sup>2+</sup> ions. Iodobenzenes coupled with acrylic acid to afford high yields of coupling products (92–98%, 95 °C, 3 h), whereas yields were much lower for bromobenzenes (45–88%, 140 °C, 12 h). Gradually decreasing yields and minimal leaching (0.5 wt %) were observed in recycling experiments (entry 5). In addition, Pd<sup>2+</sup> ions were shown to undergo reduction.



Catalysts with Pd particles supported on oxides (Pd-MgO, Pd-TiO<sub>2</sub>, Pd-Al<sub>2</sub>O<sub>3</sub>, Pd-SiO<sub>2</sub>) were tested in an early study to show that they exhibit medium activity in the Heck coupling of aryl bromides at low Pd loading (0.01 mol %).<sup>99</sup> Correlations between catalytic activity, the nature of the support, and Pd surface area were reported and discussed. Recycling studies of the four catalysts, with washing the samples with CH<sub>2</sub>Cl<sub>2</sub> between uses, gave very similar results (data for 5% Pd-MgO are shown in entry 6 as an example). Initial medium yields increased in the third run (from 49% to 96%), but washing with water resulted in significant deactivation. A breakdown was experienced in the sixth use.

A highly basic Pd-MgO catalyst developed by Kantam and co-workers with palladium stabilized by nanocrystalline MgO



**Table 4.** Heck Coupling of Haloaromatics with Styrene, Acrylic Acid, or Alkyl Acrylates Catalyzed by Polymer-Supported Palladium Nanoparticles

entry	R <sup>1</sup>	X	R <sup>2</sup>	catalyst <sup>a</sup>	reaction conditions:		number of reuses	average yield, <sup>b</sup> (%)	ref
					solvent/base/temperature/time				
1	4-Cl	I	COOH	5.53% Pd-PVC-AE (1)	EtOH/Et <sub>3</sub> N/reflux/4 h		6	79 (82–77)	110
2	H	I	COOMe	Pd-PVPy (0.1)	NMP/Et <sub>3</sub> N/100 °C/80–180 min		6	93 (93)	111
3	H	I	COOMe	2.2% Pd-11a-PS (0.1)	DMF/Et <sub>3</sub> N/130 °C/3 h		5	96 (99–92)	112
4	H	I	COOH	Pd-12-PVC-EDA (0.125)	DMF/Bu <sub>3</sub> N/90 °C/3–5 h		12	87.5 (94.5–68)	113
5	H	I	COOH	Pd-12-PVC-DETA (0.125)			12	90 (94.8–78)	
6	H	I	COOBu	1.28% Pd-chitosan (0.35)	TBAAC/100 °C/5 min <sup>c</sup>		10	86 (95–72)	114
7	H	I	COOH	1.21% Pd-polysaccharide (0.06)	DMF/Et <sub>3</sub> N/100 °C/1.5 h		6	89.5 (92–88)	115
8	H	I	COOBu	29.32% Pd-dendr-(13) (2)	THF/Bu <sub>3</sub> N/60 °C/24 h		5	96 (96)	116
9	4-MeO	I	COOEt	0.6% Pd-PEG2000 (4.5)	toluene–EtOH/Et <sub>3</sub> N/100 °C/8 h		9	80 (91–52)	117
10	H	Cl	Ph	5% Pd-MSiC (1)	H <sub>2</sub> O/Na <sub>2</sub> CO <sub>3</sub> /100 °C/24 h		21	n.r. (26–23)	118
11	H	I	COOMe	1.28% Pd-14-PS (0.1)	DMF/Et <sub>3</sub> N/110 °C/1.6–10 h		8	95 (97–90)	120
12	4-Cl	I	COOtBu		H <sub>2</sub> O/Cy <sub>2</sub> NMe/120 °C/2–3 h		8	97.5 (99–93)	
13	H	I	COOMe	Pd-15-PS (0.02)	DMF/Et <sub>3</sub> N/90 °C/3 h		6	99 (99)	121

<sup>a</sup> Percentage data show Pd loading (wt %) when available; data in parentheses indicate mol % of Pd used. <sup>b</sup> n.r. = not reported. Data in parentheses indicate range of yields. <sup>c</sup> Under nitrogen, in the presence of TBAB. TBAAc = tetrabutylammonium acetate. Cy<sub>2</sub>NMe = dicyclohexylmethylamine.

displayed much better characteristics.<sup>100</sup> When aerogel-prepared nanocrystalline MgO is reacted with Na<sub>2</sub>[PdCl<sub>4</sub>], the Na<sup>+</sup> ions interact with O<sup>x−</sup> sites (anionic vacancies), whereas PdCl<sub>4</sub><sup>−</sup> ions will interact with Mg<sup>2+</sup> sites (cationic vacancies). The precursor formed by such counterionic stabilization was reduced with hydrazine hydrate to give an air-stable, black-colored powder with Pd particles of 30–40 nm in diameter. Catalyst 10.53% Pd-MgO showed high efficiency in the Heck coupling of all types of aromatic halides including activated chloroaromatics with styrenes and acrylates (78–95% yields).<sup>101,102</sup> Recycling studies with styrene gave good results (entries 7–9) even with chlorobenzene (entry 7). The decrease in activity was attributed by the authors to the decrease in surface area because of the hydration of the catalyst by water formed in the reaction. Note, however, that there is no water formation in this case. Moreover, the catalyst works efficiently in water as solvent in Suzuki coupling (Table 10, entry 9) and the Sonogashira reaction (Table 15, entry 1). Morphology of the catalyst as shown by TEM did not change, and no leached Pd was detectable by atomic absorption spectroscopy (AAS). In fact, this is one of the rare recycling experiments for the coupling of chlorobenzene, a nonactivated compound performed with the use of a heterogeneous catalyst containing Pd particles. For the other examples, see Table 4, entry 10; Table 10, entries 12 and 18; Table 17, entry 6; and Table 18, entries 1–3.

An efficient Pd-ZrO<sub>2</sub> catalyst exhibiting high durability in various coupling reactions has been developed by Nacci, Cioffi, and co-workers.<sup>103</sup> The method of preparation included electrochemical impregnation of nanostructured tetragonal ZrO<sub>2</sub> powders to afford catalyst 0.4% Pd-ZrO<sub>2</sub> with palladium nanoparticles of an average diameter of 6.9 ± 1.8 nm.<sup>104</sup> It works in aqueous conditions in air and in the presence of tetrabutylammonium hydroxide (TBAOH), which acts both as base and as phase-transfer agent. High yields were found in a recycling study with iodobenzene and styrene with necessary increases in reaction time in the

third and fourth runs (entry 10). Five iodobenzenes were coupled successively with similar efficiency in another study (entry 11). Of three bromobenzenes tested in subsequent runs with the same catalyst sample at elevated temperature in prolonged reactions, only bromobenzene gave satisfactory yield (entry 12).

Choudary and co-workers exchanged Cl<sup>−</sup> ions of a layered double hydroxide (LDH) for PdCl<sub>4</sub><sup>2−</sup> ions and reduced the resulting material with hydrazine hydrate to get catalyst 10.1% Pd-LDH.<sup>105</sup> The catalyst with palladium nanoparticles (4–6 nm) was studied in four coupling reactions of chloroarenes. High yields were measured in Heck reaction with styrene under both thermal conditions (76–98%, 130 °C, 15–40 h) and microwave irradiation (80–96%, 130 °C, 0.5–1 h) in the presence of tetrabutylammonium bromide (TBAB) as phase-transfer catalyst. The stability of the catalyst in recycling studies is also satisfactory (entries 13 and 14) without any change in particle size and morphology. When the reaction of 4-chloroanisole and styrene was interrupted at 25% conversion, 4.5% of leached Pd was detected in the reaction mixture; however, the filtrate gave almost no further conversion for an additional 40 h. This was taken by the authors as evidence that the coupling process takes place predominantly on the surface of Pd particles.

Wang and Zhang prepared air-stable supported nanoparticles (20–100 nm) by refluxing a mixture of diatomite treated with SnCl<sub>2</sub>, poly(vinylpyrrolidone), and H<sub>2</sub>[PdCl<sub>4</sub>] in water (catalyst 3.66% Pd-diatomite).<sup>106</sup> Iodo- and bromoarenes including bromobenzene reacted rapidly to the corresponding coupling products in high to excellent yields (76–96%). In recycling studies, reaction time had to be increased in the last two runs to 40 and then 70 min to maintain high catalytic activity (entry 15). In the hot filtration test, a conversion of 95% in 40 min was found with 8.48 ppm of Pd in the filtrate, which suggests the release of Pd<sup>2+</sup> ions into the solution formed in the oxidative addition of iodobenzene to surface Pd species.

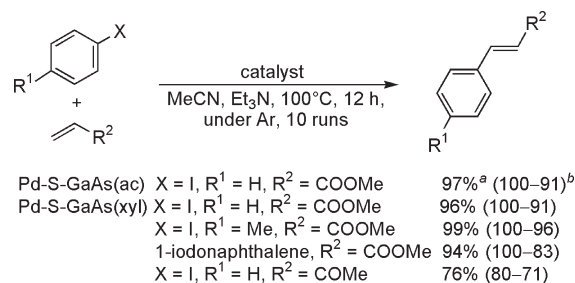
Arisawa and co-workers have developed low-leaching Pd catalysts and applied them in both Heck and Suzuki couplings. A semiconducting GaAs(001) plate (13 × 11 × 0.6 mm) modified by a treatment with aqueous (NH<sub>4</sub>)<sub>2</sub>S<sub>x</sub> solution (60 °C, 30 min) gave after appropriate washing and drying a sulfur-terminated sample.<sup>107,108</sup> Pd loading was performed in acetonitrile (100 °C, 12 h) with varied Pd sources followed by washing with various solvents under argon. Of the 15 samples prepared, the two best catalysts were made with Pd(OAc)<sub>2</sub> and applying acetonitrile (100 °C, 12 h) or xylene (135 °C, 12 h) in the final washing process [catalysts Pd-S-GaAs(ac) and Pd-S-GaAs(xyl), respectively]. The final catalysts have Pd loadings of 104–209 μg. In a subsequent study using catalyst Pd-S-GaAs(xyl) in Suzuki coupling (section 5.1.3, Scheme 17), particles of 3–5 nm were detected.<sup>109</sup> Selected examples of 10-run studies made under argon without stirring are collected in Scheme 1, indicating high stability of the prepared catalysts in the coupling of the reactant pairs shown. In contrast, significant decreases in activity were observed for isomeric bromo- and iodo-methylbenzenes (average yields = 54–68%). Moreover, catalyst Pd-S-GaAs(xyl) was completely deactivated after five cycles in the reaction of 4-iodonitrobenzene and 4-iodoacetophenone, whereas bromobenzene and phenyl triflate did not react under the reaction conditions applied. A comparison of the XPS spectra of catalyst Pd-S-GaAs(ac) before and after recycling showed that the Pd<sup>0</sup> oxidation state did not change during reactions. Changes in the surface structure, in turn, were detected by scanning electron microscopy (SEM), but these did not seem to affect catalytic activity. Extremely low levels of Pd leaching (0.04–0.26 ppm in each run) were measured for Pd-S-GaAs(xyl) attributed to the use of xylene as a noncoordinating solvent in the final washing. Both the hot filtration test and the three-phase test showed, however, the leaching of active Pd species of low activity into solution.

**4.1.3. Polymer-Supported Palladium Particles.** Results with respect to recycling studies of palladium nanoparticles supported on polymeric materials in the Heck coupling are collected in Table 4.

When PdCl<sub>2</sub> and poly(vinyl chloride) modified with 2-aminoethanol (PVC-AE) are stirred in ethanol, Pd nanoparticles (20–40 nm) are formed and immobilized on the polymer surface.<sup>110</sup> The catalyst (5.53% Pd-PVC-AE) is stable against air and moisture and affords medium to high yields in the Heck coupling of iodoarenes with styrene and acrylic acid (62–90%). Moderate activity was reported in a recycling study (Table 4, entry 1) with the appearance of smaller particles and a slight agglomeration observed after six uses. Pd nanoparticles prepared by metal vapor synthesis were deposited onto poly(4-vinylpyridine) to fabricate catalyst Pd-PVPy.<sup>111</sup> Coupling products were isolated in low to high yields (47–93%) with complete *E* selectivity for most bromobenzenes when reacted at elevated temperature and in longer reaction as compared to iodobenzene. Chloroarenes and 4-bromoanisole gave low product yields (15–34%) even after 24 h with increased catalyst loading (0.01 vs 0.001 mol %). The catalyst is characterized by minimal leaching: 0.5–0.9% corresponding to 0.4–0.6 ppm of Pd was detected in the reaction of iodobenzene with methyl acrylate (100 °C, 3 h) and 1.0–1.5% (0.6–0.7 ppm) in the coupling of 4-bromonitrobenzene with butyl acrylate (140 °C, 4 h). Yields were high and stable in six successive reactions (entry 2). No appreciable differences between the pristine and recovered samples could be detected by XPS.

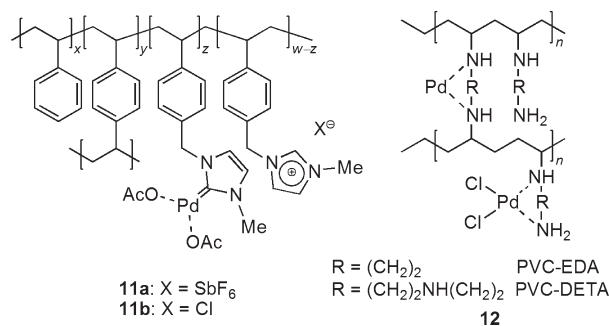
Catalyst 2.2% Pd-11a-PS was made by functionalizing Merri-field resin by covalent attachment of ionic liquid-like units and an

**Scheme 1.** Heck Couplings Induced by Pd-S-GaAs Catalysts<sup>a</sup>



<sup>a</sup> (a) Average yields. (b) Range of yields.

NHC Pd complex.<sup>112</sup> When used in recycling studies at lower temperature (90 °C), significant aggregation occurred, requiring the addition of an oxidizing agent in successive runs. At increased temperature (130 °C), however, consistently high yields were observed without decreasing tendency (entry 3). It appears that the ionic liquid-like gel support with immobilized Pd nanoparticles has the ability to efficiently release and recapture soluble palladium species (Pd was not detected in the reaction mixture). Kinetic profiles for the first and subsequent uses are significantly different (first run, 95% yield in 80 min; fifth run, 97% yield in 180 min), indicating the stabilization of nanoparticles during the first application. The catalyst is insensitive to air and moisture, but characteristics depend on composition: higher loading of ionic liquid-like units and strongly coordinating anions result in lower yields but better recovery. Catalysts with weakly coordinating anions, in contrast, give higher yields associated with poorer recovery. The scope of the catalyst system was evaluated by using catalyst 3.6% Pd-11b-PS. It afforded excellent yields (89–97%) in the coupling of iodo- and bromoarenes with various alkenes. Bromobenzene and 4-bromoanisole, in turn, reacted reluctantly (30% and 15% yield, respectively, in 18 h).



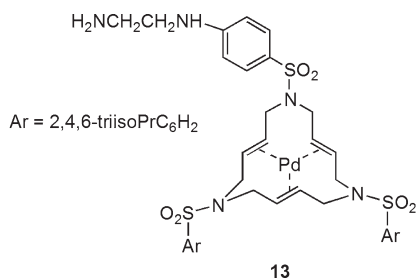
Poly(vinyl chloride)-ethylenediamine (PVC-EDA) and poly(vinyl chloride)-diethylenetriamine (PVC-DETA) polymeric materials were reacted with PdCl<sub>2</sub> to get polymer-supported catalysts (Pd-12-PVC-EDA, Pd-12-PVC-DETA).<sup>113</sup> Both Pd<sup>0</sup> and Pd<sup>2+</sup> were detected by XPS, whereas TEM images showed the presence of nanosized Pd particles in uniform distribution (Pd-12-PVC-EDA = 10 nm, Pd-12-PVC-DETA = 15 nm). Iodoarenes were rapidly converted to the corresponding coupling products in high yields in air at 90 °C (80–95%). Similar yields in the coupling of bromobenzene and 4-bromotoluene were found when reactions were carried out in the presence of

$\text{PPh}_3$  at 120 °C. Catalyst performance in recycling experiments was almost unchanged in the first seven runs, and then yields decreased despite the increase in temperature in the last three runs (entries 4 and 5).

Chitosan, a polymeric material prepared by partial deacetylation of the polysaccharide chitin, served to support Pd nanoparticles (average diameter = 3.3 nm) generated by sacrificial anode electrolysis in the presence of TBAB in acetonitrile (catalyst 1.28% Pd-chitosan).<sup>114</sup> The process gives Pd nanoparticles surrounded by a shell composed of a monolayer of  $\text{Bu}_4\text{N}^+$  ions as well as  $\text{Br}^-$  and  $[\text{PdBr}_4]^{2-}$ . Reactions were run in tetrabutylammonium acetate (TBAAc) as base in the presence of TBAB. The acetate ion of TBAAc is assumed to reduce  $\text{Pd}^{2+}$  ions to  $\text{Pd}^0$  and increase the reaction rate by fast neutralization of the  $\text{PdH}$  intermediate, thereby reforming the active catalyst. Coupling products of bromoaromatics and activated chloro derivatives with butyl acrylates were formed in high yields in very short reaction times (85–98% in 5 min–1.5 h). High yields dropped significantly in the last reuses in a 10-run recycling study (entry 6).

The support used in preparing 1.21% Pd-polysaccharide is the natural polysaccharide konjac glucomannan consisting of  $\beta$  1,4-linked D-glucose and D-mannose units.<sup>115</sup> A range of substituted iodoaromatics and various alkenes reacted smoothly and gave the corresponding alkenes in high to excellent yields (83–99%) with nearly complete *E* selectivity. The catalyst has good thermal stability and afforded high yields in six runs (entry 7) with the  $\text{Pd}^{2+}$  ions undergoing reduction during the coupling reaction to form Pd particles.

A series of phosphorus dendrimers containing azamacrocycles with various ring sizes attached to their surface were prepared by Caminade, Sebastián, and co-workers.<sup>116</sup> Depending on reaction variables,  $\text{Pd}^0$  sources complexed by the macrocycle form nanoparticles of 2.5–7.9 nm in size. Reusability was tested with a catalyst bearing the 15-membered azatriolefinic macrocycle **13** [29.32% Pd-dendr-(**13**)]. It furnished high yields and proved to be stable in the coupling of iodobenzene with butyl acrylate (entry 8).

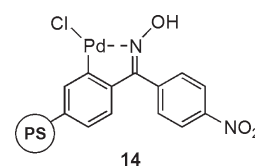


Pd nanoparticles with narrow size-distribution ( $\sim 5$  nm) were formed when  $\text{Pd}(\text{OAc})_2$  was stirred with poly(ethylene glycol) at 80 °C.<sup>117</sup> Reduction of  $\text{Pd}^{2+}$  ions is induced by the hydroxyl groups of PEG as evidenced by detecting formyl groups by NMR. The reducing ability of PEG strongly depends on its molecular weight, and the application of PEG-2000 gave the best catalyst: it is not sensitive to air or moisture and afforded high but considerably decreasing yields in nine runs (entry 9) with a Pd leaching of 0.3 ppm (0.064%). Iodo and activated bromo derivatives could be transformed to coupling products with high efficiency (yields of 80–95%).

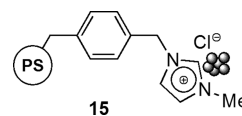
For the synthesis of 5% Pd-MSC (entry 10), a surfactant templating method by using a soluble phenolic resin (carbon precursor), TEOS (silica precursor), and the triblock copolymer

F127 (structure-directing agent) was applied.<sup>118</sup> The resulting mesoporous silica–carbon nanocomposite (MSC) was impregnated with  $\text{PdCl}_2$  and reduced with flowing hydrogen (200 °C, 3 h). Extensive instrumental characterization showed that the catalyst has highly ordered mesopore structure and uniform mesopores. Pore size distribution of MSC (6.3 nm) did not change significantly after deposition of Pd and after 15 runs (6 nm). Metallic particles of high dispersion (about 3 nm) are located inside the pores, showing no aggregation after 15 successive reactions. The catalyst is not sensitive to air or moisture, affords very low yields, but exhibits high stability and complete selectivity (100% *trans*-stilbene) in the coupling of chlorobenzene and styrene (entry 10) with a negligible degree of leaching ( $<0.2\%$ ).

Various oxime-derived palladacycles have been synthesized and used in coupling reactions by Alacid, Nájera, and co-workers<sup>119</sup> including catalyst 1.28% Pd-**14**-PS. It was prepared by treating a polystyrene-based Kaiser oxime resin (oxime loading = 1.1 mmol  $\text{g}^{-1}$ ) with  $\text{Li}_2[\text{PdCl}_4]$ .<sup>120</sup> When used in the coupling of iodobenzene and methyl acrylate in DMF, significantly increasing reaction times were necessary to obtain high yields (entry 11) with a Pd leaching of 0.4–5%. Much better performance was shown, however, in the reaction of 4-chloriodobenzene and *tert*-butyl acrylate using water as solvent (entry 12) with a lower degree of Pd leaching (2–2.7%). No reaction was observed in the presence of Hg, which indicates that the complex is a precatalyst and Pd nanoparticles formed by decomposition are the actual active species. Very high turnover numbers (up to  $10^5$ ) were achieved when the reaction of 4-chloriodobenzene and *tert*-butyl acrylate was carried out with low catalyst loading (0.001 mol %).

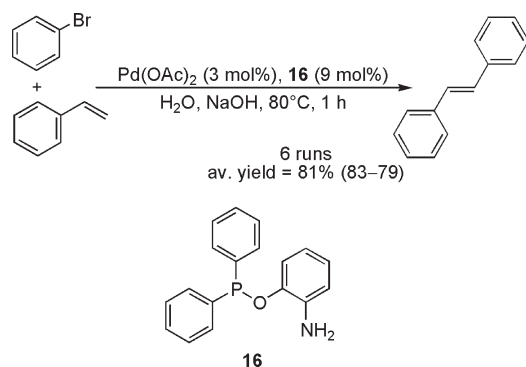


Catalyst Pd-**15**-PS was prepared by reacting the polymer bearing the grafted imidazolium moiety with  $\text{Pd}(\text{OAc})_2$  in the presence of HCl and THF followed by reduction with  $\text{NaBH}_4$  in ethanol.<sup>121</sup> In the hot filtration test, the reaction was even faster than in the original run, showing the participation of soluble Pd species. The catalyst, however, proved to be robust in a recycling study, showing no sign of deterioration (entry 13). These features were accounted for by the ionic-liquid-like fragment stabilizing the formed Pd particles and improving the release–capture mechanism. The catalyst was also tested in a continuous flow system (see section 11).



**4.1.4. Other Nanoparticle Systems.**  $\text{Pd}(\text{OAc})_2$  in combination with the ligand 2-aminophenyl diphenylphosphinite (**16**) has been used in aqueous solution in the Heck reaction.<sup>122</sup> The coupling of haloarenes including halogen derivatives of heteroarenes with alkenes proceeded smoothly to afford high yields in



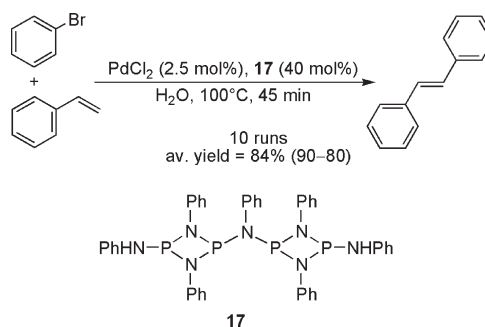
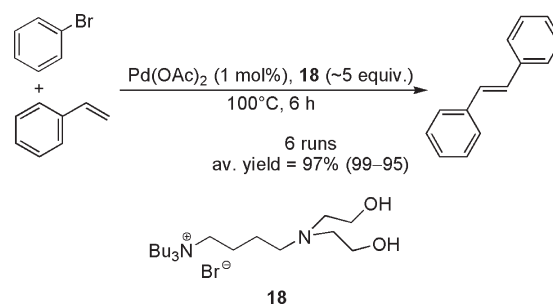
**Scheme 2.** Heck Coupling Catalyzed by Pd Particles Formed under Reaction Conditions

the presence of NaOH as the base (68–90%). The reaction of chloroaromatics, however, had to be performed in a sealed tube at higher temperature ( $130^\circ\text{C}$ ). Coupling with butyl acrylate carried out in the presence of  $\text{Cs}_2\text{CO}_3$  instead of NaOH showed similar features (yields of 73–89%). Chloroaromatics under these conditions were, however, completely unreactive. In all cases, small amounts of the homocoupled products (less than 10%) were formed.  $\text{Pd}(\text{OAc})_2$  is a precatalyst and forms a black solid mass with the ligand containing Pd particles as detected by SEM and XRD. The coupling of bromobenzene with styrene proceeded in high yields in recycling (Scheme 2).

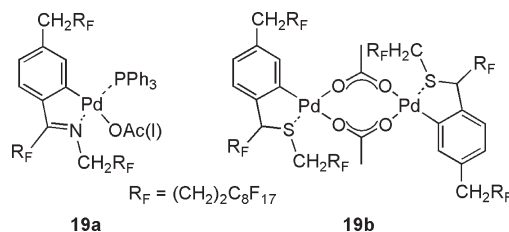
Of various diazadiphosphetidines, the dimeric phosphazane **17** has been used as bidentate ligand and base in the Heck reaction in water.<sup>123</sup>  $\text{PdCl}_2$  and ligand **17** are suggested to form an  $\text{ML}_2$  structure  $[(\text{PdCl}_2)_2\text{17}]$ , which serves as the precatalyst and undergoes reduction to give Pd particles under reaction conditions. Varied iodo- and bromoarenes react smoothly with styrene and butyl acrylate to give good to high product yields under mild conditions (70–91%,  $100^\circ\text{C}$ ). Yields are similar for chloroarenes reacted in a sealed tube at  $120^\circ\text{C}$  (65–86%, 10 h). The catalyst system proved to be active in the coupling of unsubstituted alkenes as well (oct-1-ene, cyclohexene, 69–77% yields). High but decreasing yields were found in recycling experiments in 10 runs (Scheme 3).

High efficiency is also characteristic of the novel, diethanolamine-functionalized IL **18** acting as base, ligand, and solvent in the  $\text{Pd}(\text{OAc})_2$ -catalyzed alkenylation of various iodo-, bromo-, and chloroarenes with styrene and ethyl acrylate.<sup>124</sup> Interestingly, while  $\text{Pd}(\text{OAc})_2$ , in general, is stable in ILs, this catalyst system turned black, which is indicative of the formation of Pd particles. Indeed, these could be isolated and were found to have an average diameter of 4 nm. It is argued that the ethanolamine moiety stabilizes the Pd colloid and prevents aggregation of particles. High yields were found in the recycling study (Scheme 4) with a minimal amount of Pd leaching (<0.2 ppm). Recycling was made by washing the IL phase after product extraction with  $\text{K}_2\text{CO}_3$  and ethanol. The centrifugate, after centrifugal separation, was evaporated under reduced pressure, washed with diethyl ether,  $\text{CH}_2\text{Cl}_2$ , and hexane, and reused after drying.

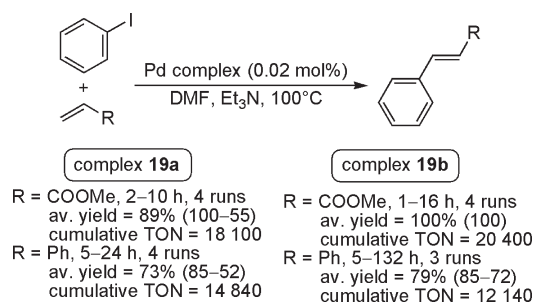
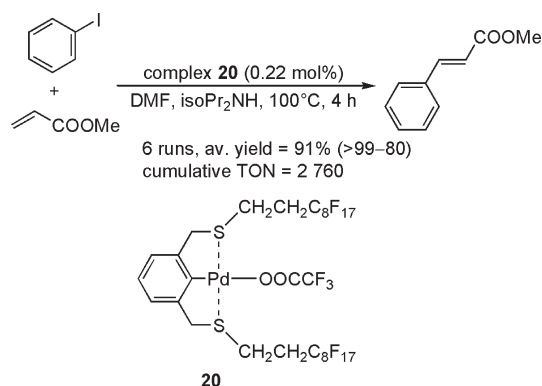
Gladysz and Rocaboy have studied thermomorphic fluorosolv N-donor and S-donor palladacycles in Heck coupling.<sup>40</sup> Experimentations were made by using the technique of fluorosolv biphasic catalysis successfully applied in organic synthesis including coupling reactions.<sup>125</sup> Although the complexes did not show high stability in recycling experiments, additional detailed studies

**Scheme 3.** Heck Coupling Catalyzed by Pd Particles Formed in situ**Scheme 4.** Heck Coupling Catalyzed by in situ-Generated Pd Particles

gave important information with respect to the nature of active species involved. The fluorinated complex **19a** and its sulfur analogue **19b** are not soluble in the organic solvent (DMF) but dissolved at the reaction temperatures ( $80$ – $140^\circ\text{C}$ ) in DMF. Upon cooling and adding  $\text{C}_8\text{F}_{17}\text{Br}$ , two phases are formed, which allows convenient product isolation and catalyst recycling: the upper DMF layer containing the products is separated, whereas  $\text{C}_8\text{F}_{17}\text{Br}$  is removed by evaporation from the lower phase and the residue is charged with fresh reactants and reused. Both catalysts exhibit outstanding activity in coupling reactions. The TON values measured in the coupling of iodobenzene and methyl acrylate induced by complex **19a** and **19b** are  $1.46 \times 10^6$  and  $1.51 \times 10^6$ , respectively.

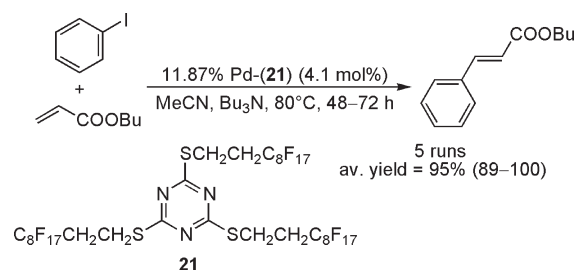
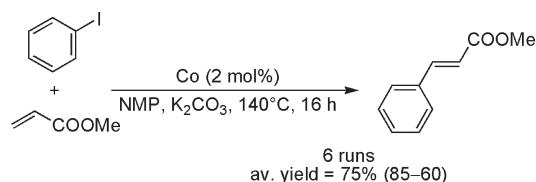


In recycling studies, significantly extended reaction times were necessary to maintain complete conversion (Scheme 5). Complex **19b** displayed somewhat lower stability, being inactive in the fourth cycle in the coupling of iodobenzene and styrene. Coupling with methyl acrylate took place with high stereoselectivity [exclusive formation of methyl (*E*)-cinnamate], whereas *E/Z* mixtures (87:13) were formed with styrene. Decreasing yields

**Scheme 5.** Heck Coupling with the Use of Palladacycles **19a** and **19b****Scheme 6.** Heck Coupling Performed in the Presence of Complex **20**

were assumed to result from the formation of nonfluorous colloidal nanoparticles, whereas complexes with bridging halides formed as a result of anion exchange serve as recyclable sources of nanoparticles. Kinetic studies at 80 and 100 °C provided supporting evidence, indicating an induction period in the first application of complex **19a**. A similar induction period was detected in the second run with a slightly lower rate. In another experiment, the C<sub>8</sub>F<sub>17</sub>Br layer containing the catalyst was washed with DMF, and this latter solution was then combined with the DMF layer after catalyst separation. The reaction with the combined solution charged with new substrates occurred without an induction period although at a lower rate. Obviously, leached catalytic species generated during the induction period are involved in the coupling process. Finally, TEM measurements of the reaction mixture showed the presence of nanoparticles (mean diameter = 10 nm). The formation of the catalytically active nanoparticles is attributed to the interaction of the Pd complexes with one of the reactants, and they are stabilized by the triethylammonium salt byproduct. In summary, it is not the active catalytic species, which are recycled in repeated uses; rather, the complexes serve as steady-state sources to generate highly active colloidal nanoparticles in each cycle. Because the complexes are consumed in each cycle, this process leads to decreasing catalytic activities, and ultimately catalysis ceases.

In a recent study, Gladysz and co-workers have evaluated fluorinated Pd complexes of S<sub>2</sub>C(sp<sup>2</sup>)S pincer ligands.<sup>126</sup> Recycling experiments were conducted with complex **20**. After the first run, the reaction mixture was charged with the reactants and the base,

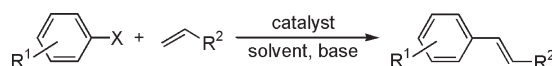
**Scheme 7.** Heck Coupling Catalyzed by Stabilized Nanoparticles**Scheme 8.** Heck Coupling Catalyzed by Flower-like Co Nanostructures

and a new cycle was performed. High yields in the first runs decreased slowly (Scheme 6). A reddish color was also observed in the first hours of the first reaction. Furthermore, an extract of the reaction mixture with CF<sub>3</sub>C<sub>6</sub>F<sub>11</sub> showed no further activity. A reaction in the presence of Hg<sup>0</sup>, again, resulted in no significant conversion. On the basis of these observations, it is clear that the Pd complex is not recyclable but serves as a precursor of a nonfluorous active catalytic species. Similar to that discussed above, TEM images showed the presence of Pd particles. Colloidal Pd nanoparticles or molecular species were concluded to be the active catalysts.

A heavily fluorinated 1,3,5-triazine-based aromatic sulfur compound bearing functional groups with high affinity for metals was synthesized and used as stabilizer of Pd nanoparticles.<sup>127</sup> The star-shaped material **21** was prepared by reaction of cyanuric chloride with the corresponding thiol in the presence of Cs<sub>2</sub>CO<sub>3</sub> in THF. Next, the material thus formed was treated with PdCl<sub>2</sub> in methanol to afford catalyst 11.87% Pd-(**21**) with nanoparticles of an average diameter of 2.7 ± 0.8 nm. When used in five consecutive cycles, the reaction time was increased after the second run, resulting in increasing yields (Scheme 7).

A unique example in Heck coupling is the use of flower-like Co nanostructures prepared by sonicating a mixture of CoCl<sub>2</sub> and NaBH<sub>4</sub>.<sup>128</sup> Instrumental analysis reveals that the sample has a porous structure and it is free of boron; that is, the product is not a CoB alloy. Yields decrease continuously upon reuses because of aggregation of particles (Scheme 8). Iodobenzene and all types of activated haloaromatics gave medium to good yields of coupling products (67–86%).

Unfortunately, the authors have not addressed the possible contribution of Pd contamination in the reaction. In 2003, Leadbeater reported about a transition-metal-free Suzuki-type coupling protocol.<sup>129,130</sup> In a follow-up paper, however, the findings were corrected to show that palladium contaminants (a level of 50 ppb) in sodium carbonate are responsible for the coupling taking place.<sup>131</sup>

**Table 5.** Heck Coupling of Halobenzenes with Styrene and Acrylic Esters Catalyzed by Palladium Complexes Immobilized on Inorganic Supports

entry	R <sup>1</sup>	X	R <sup>2</sup>	catalyst <sup>a</sup>	reaction conditions:		average yield, <sup>b</sup> (%)	ref
					solvent/base/temperature/time	number of reuses		
1	H	I	Ph	3.7% Pd-22a-MCM41 (0.3)	NMP/Bu <sub>3</sub> N/100 °C/6 h	10	96 (98–94)	132
2	H	I	COOBu	4.04% Pd-22b-MCM41 (0.3)	NMP/Bu <sub>3</sub> N/100 °C/6 h	5	~94 (94)	133
3	4-AcO	Br	COOEt	3.4% Pd-HS-FSM16 (1)	NMP/KOAc/130 °C <sup>c</sup>	6	96 (99–92)	134
4	4-AcO	Br	COOEt	3.6% Pd-HS-SiO <sub>2</sub> (1)	NMP/KOAc/130 °C <sup>c</sup>	6	91 (99–84)	
5	H	I	COOMe	2.34% Pd-23-SiO <sub>2</sub> (1.5)	DMAc–H <sub>2</sub> O/Na <sub>2</sub> CO <sub>3</sub> /125 °C/0.8 h	6	96 (100–88)	135
6	4-MeO	I	COOBu	2.76% Pd-24-SiO <sub>2</sub> (1)	DMF/K <sub>2</sub> CO <sub>3</sub> /100 °C/12 h	14	95.5 (99–91)	136
7	H	Br	Ph	Pd-SiO <sub>2</sub> -(25) (1)	benzene/Et <sub>3</sub> N/80 °C/4 h	6	quantitative	137
8	H	I	Ph	4.41% Pd <sup>2+</sup> -5b-SiO <sub>2</sub> (0.08)	DMAc/K <sub>2</sub> CO <sub>3</sub> /130 °C/12 h	10	93 (96–90)	139
9	H	I	COOMe	8.65% Pd-SiO <sub>2</sub> -(26) (1.3)	DMF/Et <sub>3</sub> N/130 °C/12–15 h	5	94.5 (95–93)	140
10	H	I	COOCy	0.46% Pd(OAc) <sub>2</sub> -[bmim][PF <sub>6</sub> ]- (27a) (5)	H <sub>2</sub> O/Bu <sub>3</sub> N/100 °C/10.5–1 h	6	95 (98–93)	142
11	H	I	Ph	0.8% Pd-K10-(28) (0.1)	DEAc/Et <sub>3</sub> N/180 °C/2 h	10	88.5 (>99–79)	144
12	4-CHO	Br	Ph		DEAc/NaOAc/180 °C/1 h <sup>d</sup>	8	77 (>99–25)	
13	H	I	COOEt	3.3% Pd-HS-SiO <sub>2</sub> /Fe <sub>3</sub> O <sub>4</sub> -(29) (0.5)	DMF/Et <sub>3</sub> N/110 °C/2.5–10 h	6	98 (99–95) <sup>e</sup>	145

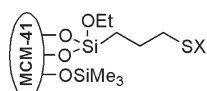
<sup>a</sup> Percentage data show Pd loading (wt %) when available; data in parentheses indicate mol % of Pd used. <sup>b</sup> Data in parentheses indicate range of yields.

<sup>c</sup> Under nitrogen atmosphere. Reaction time was not specified. <sup>d</sup> In the presence of TBAB. <sup>e</sup> Conversion.

## 4.2. Couplings Catalyzed by Immobilized Palladium Complexes

Results reported on the Heck coupling performed by using immobilized palladium complexes are collected in Tables 5 and 6.

**4.2.1. Palladium Complexes Immobilized on Inorganic Supports.** Cai and co-workers have reported the synthesis of a range of Pd catalysts supported on MCM-41 and applied them in various coupling reactions. These were prepared by first modifying MCM-41 with appropriately substituted trialkoxysilanes followed by reaction with a Pd source. The formed supported mono- or bidentate Pd complexes were used as such or applied after reduction. In the synthesis of catalyst 3.7% Pd-22a-MCM41, surface functionalization of MCM-41 was performed with 3-(2-cyanoethylsulfanyl)propyltriethoxysilane, and then unreacted SiOH groups were capped with Me<sub>3</sub>SiCl. Next, the modified MCM-41 was reacted with PdCl<sub>2</sub> and reduced with hydrazine hydrate to yield the MCM-41-supported thioether Pd<sup>0</sup> complex.<sup>132</sup> The coupling of iodobenzene with styrene occurred in high yields in 10 runs (entry 1). Functionalized MCM-41 made by grafting with (3-mercaptopropyl)trimethoxysilane was reacted with PdCl<sub>2</sub> followed by reduction to yield an immobilized mercapto Pd<sup>0</sup> complex<sup>133</sup> (catalyst 4.04% Pd-22b-MCM41). The air-stable catalyst gave consistently high yields in five runs (entry 2). (*E*)-Stilbenes are formed in high to excellent yields with almost complete selectivities in the coupling of iodo- and bromoarenes with styrene induced by either catalyst (3.7% Pd-22a-MCM41 = 73–96%; 4.04% Pd-22b-MCM41 = 78–98%). Similar features were reported in the reaction of haloarenes with acrylic acid and derivatives (71–98% yields).



22a: X = (CH<sub>2</sub>)<sub>2</sub>CN]<sub>2</sub>Pd<sup>0</sup>  
22b: X = H]<sub>2</sub>Pd<sup>0</sup>

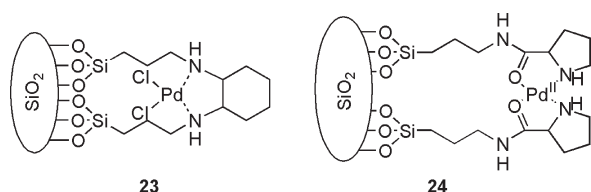
The FSM-16 mesoporous silica with a structure very similar to that of MCM-41 prepared from kanemite a layered silicate was

functionalized with (3-mercaptopropyl)trimethoxysilane followed by reaction with Pd(OAc)<sub>2</sub> to give catalyst 3.4% Pd-HS-FSM16.<sup>134</sup> A similar catalyst with amorphous silica was also prepared for comparative studies (3.6% Pd-HS-SiO<sub>2</sub>). Structural studies were performed by means of varied surface characterization techniques. Pd<sup>2+</sup> ions coordinated to the sulfur ligands were shown to be the dominating species on the former catalyst with small Pd clusters as minor species after recovery from Heck coupling. On 3.6% Pd-HS-SiO<sub>2</sub>, in contrast, a large amount of Pd<sup>2+</sup> species was transformed into Pd clusters during reaction. It appears that HS ligands in the mesopores of FSM-16 are able to prevent aggregation of complexed Pd<sup>2+</sup> species to form large particles. As a consequence, catalyst 3.4% Pd-HS-FSM16 exerted better stability in a six-run recycling study (entry 3; compare to entry 4), although neither catalyst showed decreasing tendencies of activity. The heterogeneous nature of the reaction was concluded by the authors solely on the hot filtration test.

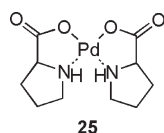
The immobilized bidentate complex (catalyst 2.34% Pd-23-SiO<sub>2</sub>) is insensitive to air and was prepared by grafting silica gel with *N,N*-bis[(triethoxysilyl)propyl]-1,2-diaminocyclohexane followed by the reaction with PdCl<sub>2</sub>(PhCN)<sub>2</sub>. High initial yields decreased continuously in successive runs (entry 5), and 0.25 ppm of leached Pd was detected.<sup>135</sup> No further reactivity was observed in a filtration test after catalyst removal. Various activated and deactivated iodo derivatives, bromobenzene, as well as 4-bromonitrobenzene gave very high yields in coupling reactions (91–100%). Excellent stability and reusability were demonstrated in 14 successive reactions with the use of catalyst 2.76% Pd-24-SiO<sub>2</sub> (entry 6).<sup>136</sup> Furthermore, only a minimal amount of leached Pd was found (less than 0.1 ppm), and only a trace amount of product could be isolated in a filtration test. The catalyst was highly active in the coupling of various iodo- and bromoarenes (yields of 84–99%) and gave a yield of 45% in the transformation of 4-chloronitrobenzene and butyl acrylate. In the synthesis of the catalyst, aminopropyl-functionalized silica gel



was reacted with Boc-protected L-proline, and then the solid after deprotection was treated with  $\text{Pd}(\text{OAc})_2$ .

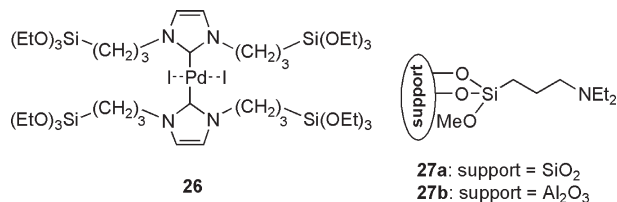


Blum and co-workers entrapped amino acid derivatives of  $\text{Pd}(\text{OAc})_2$  in silica.<sup>137</sup> In contrast to the catalyst described above (0.48%  $\text{Pd-SiO}_2$ , section 4.1.1, Table 1, entry 1), Pd nanoparticles were not formed. XPS clearly indicated that these catalysts contain  $\text{Pd}^{2+}$  ions immobilized in the silica matrix. Furthermore, coupling reactions had to be carried out in benzene because of the easy leaching of Pd compounds into water. As well as 0.48%  $\text{Pd-SiO}_2$ , catalyst  $\text{Pd-SiO}_2$  (**25**) with the *cis*-bis(L-prolinato) complex **25** gave quantitative yields (entry 7), but proved to be more active when measured in short reaction time. Palladium species could not be detected in the reaction mixture, and filtration tests showed no catalytic activity. Yields in the coupling of 4-bromochlorobenzene and 4-bromotoluene under identical conditions shown in entry 7 were 100% and 48.5%, respectively.



Wang et al. carried out derivatization of silica gel with the functionalized trimethoxysilane AAPTES (3-[(2-aminoethyl)-amino]propyltriethoxysilane) followed by reaction with  $\text{Pd}(\text{OAc})_2$  to furnish silica-supported catalysts with complexed  $\text{Pd}^{2+}$  ions.<sup>138</sup> Catalyst 4.41%  $\text{Pd}^{2+}$ -**5b-SiO**<sub>2</sub> was applied directly in the Heck coupling,<sup>139</sup> providing high yields in the coupling of haloarenes with styrene, ethyl acrylate, and acrylonitrile (yields of 83–99%). Chloroarenes also gave fair to high yields (72–90%) under modified conditions (0.02 mol % of Pd, 24 h). The catalyst recovered after filtration was washed, dried, and then successfully reused in 10 runs affording consistently high yields (entry 8). Without thorough cleaning, however, only a yield of 72% could be achieved. Leaching of Pd was found to be less than 0.2 ppm.

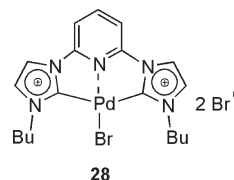
An N-heterocyclic carbene (NHC) Pd complex immobilized by the sol–gel process using triethoxysilylated precursor **26** gave a hybrid material [catalyst 8.65%  $\text{Pd-SiO}_2$ -(**26**)] with low porosity and low specific surface area ( $5 \text{ m}^2 \text{ g}^{-1}$ ).<sup>140</sup> Despite these features, it showed medium to high catalytic activity in Heck couplings of aromatic and heteroaromatic iodo and bromo derivatives (yields of 59–95%). To maintain high yields in recycling, however, reaction times had to be increased in successive runs (entry 9). This may be due to the loss of the NHC complex at the relatively high reaction temperature as indicated by the high amount of Pd leached (22 ppm).



Hagiwara and co-workers have explored the use of catalysts prepared by immobilizing  $\text{Pd}(\text{OAc})_2$  and IL [bmim][PF<sub>6</sub>] on

various support materials. Although the catalyst made by using silica gel as support showed high and stable activity in recycling (range of yields = 89–93% in six runs),<sup>141</sup>  $\text{Pd}(\text{OAc})_2$  was found to undergo reduction under reaction conditions.<sup>142</sup> The use of diethylaminopropylated supports (**27**), in turn, gave catalysts with improved characteristics. Coupling reactions with  $\text{Pd}(\text{OAc})_2$  and [bmim][PF<sub>6</sub>] immobilized on such reversed-phase amorphous silica (**27a**) were carried out in water with cyclohexyl acrylate because other alkenes such as styrene decomposed under the reaction conditions applied. High isolated yields were reported for iodobenzenes (90–98%), 1-iodonaphthalene (90%), and 4-bromonitrobenzene (76%).<sup>142</sup> TON and TOF values measured for iodobenzene (TON = 200 000, TOF = 20 000  $\text{h}^{-1}$ , catalyst loading = 0.0004 mol %) are exceptionally high for a ligandless heterogeneous catalyst. High yields could be maintained with decreasing reaction time in repeated runs (entry 10) with a Pd leaching of 1.1 ppm after the first reaction. Increasing activities were attributed to the accumulation of tetrabutylammonium iodide on the catalyst surface acting as phase-transfer agent. This is an active and useful catalyst system; however, the use of cyclohexyl acrylate as the only suitable substrate greatly hinders practical application.

The rigid CNC-tridentate pincer bis-carbene Pd complex **28** prepared by Crabtree and co-workers<sup>143</sup> has been studied in the Heck coupling (section 4.3, Table 7, entry 34). Catalyst 0.8% Pd-K10-(**28**) made upon immobilization of the complex in montmorillonite K-10, an acid-treated bentonite clay material with partially destroyed layered structure, was also tested.<sup>144</sup> It gave sharply decreasing yields in the coupling of iodobenzene and styrene when applied in the presence of NaOAc as base with washing between runs with  $\text{CH}_2\text{Cl}_2$ . This was attributed to the adsorption and accumulation of NaOAc on the support. Much higher stability was found when the reaction was performed in  $\text{Et}_3\text{N}$  (entry 11). Interestingly, NaOAc combined with TBAB was found to work best in the coupling of 4-bromobenzaldehyde and styrene: yields did not change in the first four runs but dropped sharply in the last two runs (entry 12). In the coupling of bromobenzene, in turn, activity decreased significantly (a yield of 40% in the third run). A significant drawback of this catalyst is the high reaction temperature (180 °C).



In a recent report,<sup>145</sup> Shen et al. described the synthesis of catalyst 3.3%  $\text{Pd-HS-SiO}_2/\text{Fe}_3\text{O}_4$ -(**29**) inspired by the work of Corma et al.<sup>146</sup> The catalyst was synthesized by first coating  $\text{Fe}_3\text{O}_4$  nanoparticles stabilized by poly(vinylpyrrolidone) with a silica shell by reacting it with TEOS in the presence of CTAB. The product was treated with (3-mercaptopropyl)trimethoxysilane, and then the resulting thiol-functionalized material was grafted with the functionalized oxime palladacycle **29**. The yields in the coupling of iodobenzenes performed in the presence of  $\text{Et}_3\text{N}$  at 110 °C are high (95–99%). In turn, much lower yields could be obtained with bromobenzenes (47–55%, TBAB,  $\text{K}_2\text{CO}_3$ , 130 °C, 24 h). Iodobenzene and ethyl acrylate used in recycling coupled in high yields

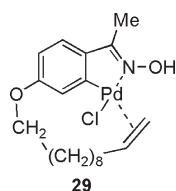
Table 6. Heck Coupling of Halobenzenes and Styrene, Acrylic Acid, and Esters Catalyzed by Polymer-Immobilized Palladium Complexes

entry	R <sup>1</sup>	X	R <sup>2</sup>	catalyst <sup>a</sup>	reaction conditions: solvent/base/temperature/time	number of reuses	average yield, <sup>b</sup> (%)	ref
1	4-CN	Br	COOMe	Pd-PS-( <b>30a</b> ) (0.2)	DMAc/Et <sub>3</sub> N/100 °C/10 h	7	>99 (>99)	147
2	H	I	COOBu	1.17% Pd- <b>31</b> -PS (1)	DMAc/Bu <sub>3</sub> N/120 °C/3 h	6	94.5 (95–94)	149
3	H	I	COOMe	4.36% Pd- <b>32</b> -PS (0.02)	DMF/Et <sub>3</sub> N/130 °C/2.5 h	5	99 (99)	150
4	H	I	Ph	5.3% Pd- <b>33</b> -PS (0.5)	DMF/K <sub>2</sub> CO <sub>3</sub> /80 °C/12 h	5	94 (95–93)	151
5	H	Br	Ph	5.45% Pd- <b>34</b> -PS (1)	DMF/K <sub>2</sub> CO <sub>3</sub> /90 °C/10 h	8	94.5 (96–92.5) <sup>c</sup>	152
6	4-NO <sub>2</sub>	Br	Ph	12.8% Pd- <b>35</b> -PVCarb (0.5)	DMF/K <sub>2</sub> CO <sub>3</sub> /80 °C/8 h	6	92 (95–89)	153
7	H	I	COOMe	1.5–1.6% Pd- <b>36</b> -FDU (0.5)	DMF/Et <sub>3</sub> N/100 °C/3 h	8	92 (98–85)	154
8	H	I	COOH	3.40% Pd- <b>37</b> -TGR (10)	H <sub>2</sub> O/KOH/25 °C/14 h	5	92 (95–90)	155
9	H	I	COOtBu	3.04% Pd- <b>38</b> -TGR (1)	DMAc/Et <sub>3</sub> N/165 °C/48 h <sup>d</sup>	14	83 (83)	156
10	H	I	COOtBu	Pd- <b>39</b> -polym (0.005)	toluene/Et <sub>3</sub> N/100 °C/15 h <sup>d</sup>	5	94 (95–92)	158
11	H	I	COOH	Pd-chitosan-( <b>40</b> ) (0.5)	DMF/Bu <sub>3</sub> N/90 °C/3–5 h	10	85.5 (94–75)	159
12	H	I	COOH	Pd-cellulose-xanth (0.0073)	NMP/Bu <sub>3</sub> N/90 °C/8 h	10	70 (89–52)	160
13	H	I	COOBu	3% Pd- <b>41</b> -Au (8)	toluene-d <sub>8</sub> /Pr <sub>3</sub> N/108 °C/30 min	15	92 (99–79)	161

<sup>a</sup> Percentage data show Pd loading (wt %) when available; data in parentheses indicate mol % of Pd used. <sup>b</sup> Data in parentheses indicate range of yields.

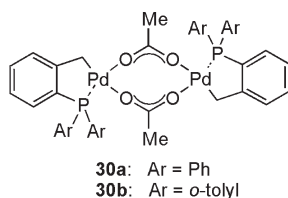
<sup>c</sup> Conversions. <sup>d</sup> Under argon atmosphere.

with slight drops only in the last two runs (entry 13). No further conversion was observed in a split (hot filtration) test.

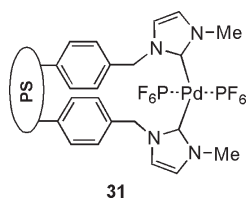


#### 4.2.2. Palladium Complexes Immobilized on Polymers.

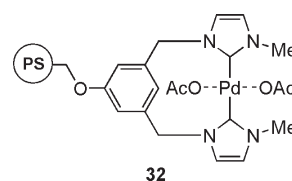
Palladacycle **30a** immobilized on polystyrene [Pd-PS-(**30a**)] afforded high yields and showed high durability in a seven-run recycling study when catalyst recovery was made by precipitation with ether (Table 6, entry 1).<sup>147</sup>



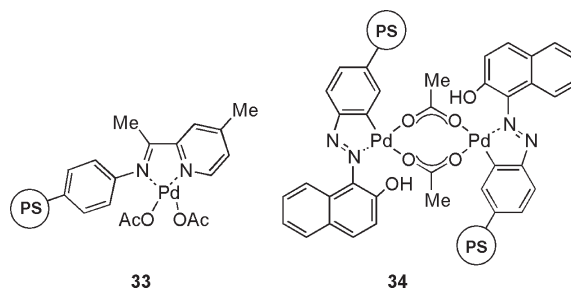
Catalyst 1.17% Pd-**31**-PS with a surface-grafted NHC complex well-characterized in an earlier study<sup>148</sup> also provided high and stable yields in recycling experiments without any Pd leaching<sup>149</sup> (entry 2). The catalyst was prepared by the copolymerization of the ionic liquid monomer 1-methyl-3-(4-vinylbenzyl)imidazolium hexafluorophosphate with styrene and divinylbenzene followed by reaction with Pd(OAc)<sub>2</sub>.



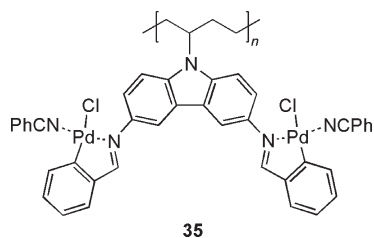
Catalyst 4.36% Pd-**32**-PS has a robust pincer-type complex anchored to Merrifield resin modified by functionalization with dimethyl 5-hydroxyisophthalate. Reduction and treatment with SOCl<sub>2</sub> followed by reaction with 1-methylimidazole and Pd(OAc)<sub>2</sub> furnished the final catalyst.<sup>150</sup> Samples with monodentate ligands gave high but rapidly decreasing yields at 90 °C (from yields of 99% to 51% and 12%). In contrast, yields with catalyst 4.36% Pd-**32**-PS were lower, but the catalyst proved to be more stable to give nearly quantitative yields in five runs at higher temperature (entry 3). The coupling products of iodo- and bromoarenes with styrene and methyl acrylate are formed in medium to high yields (66–100%) with exclusive *E* selectivity with the exception of acrylonitrile (*E/Z* = 85:15). Bromobenzene and 4-bromoanisole were found to be unreactive under such conditions.



Ligand 2-acetyl-4-methylpyridine was anchored to *para*-aminopolystyrene, and then the modified polymer was reacted with Pd(OAc)<sub>2</sub> to get the corresponding Schiff-base complex (catalyst 5.3% Pd-**33**-PS).<sup>151</sup> It showed good activity toward iodo- and bromoarenes to afford high product yields (65–95%). The poisoning and three-phase test indicated the absence of leached palladium. High, consistent yields were observed in recycling (entry 4).

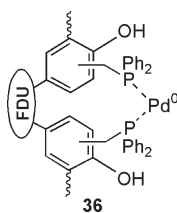


The air-stable polymer-anchored  $\text{Pd}^{2+}$  azo complex (catalyst 5.45% Pd-34-PS) is a highly active catalyst in Heck coupling of iodo- and bromobenzenes with styrene and methyl acrylate (yields of 76–100%).<sup>152</sup> 4-Substituted chlorobenzenes, however, coupled with much lower efficiency (14–60%), whereas chlorobenzene and 4-chloroanisole were unreactive with methyl acrylate. In a recycling study, a slow progressive decrease was detected (entry 5). The palladium content of the recovered catalyst decreased to 5.40 wt % after eight uses. Similar catalyst performance, that is, high yields in the coupling of iodo- and bromoarenes (76–100%) and high but decreasing yields in recycling (entry 6), have been observed with catalyst 12.8% Pd-35-PVCarb bearing a  $\text{Pd}^{2+}$  complex anchored to functionalized poly(*N*-vinylcarbazole) with 0.5 ppm of leached Pd detected.<sup>153</sup>



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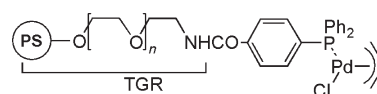
A chloromethylated FDU-type phenolic mesopolymer (FDU = Fu-Dan University) was reacted with  $\text{LiPPh}_2\text{Cl}$  to incorporate phosphane ligands. A subsequent treatment with tris(dibenzylideneacetone)dipalladium(0) [ $\text{Pd}_2(\text{dba})_3$ ] yielded the air-stable catalyst 1.5–1.6% Pd-36-FDU loaded with a  $\text{Pd}^0$  phosphane complex.<sup>154</sup> The catalyst induced the coupling of all types of haloaromatics and various alkenes to give medium to excellent yields (50–96%) with the exception of bromobenzene and chlorobenzene (traces of coupling products). High yields were found in recycling with drops in the last runs (entry 7) without detectable Pd leaching.



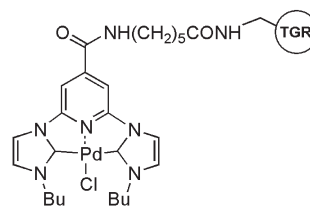
36

Uozumi and Kimura used TentaGel S resin for immobilizing Pd following phosphonation.<sup>155</sup> TentaGel is an amphiphilic resin [polystyrene grafted with *O*-(2-aminoethyl)polyethylene glycol; see structure 37], which swells both in water and in polar organic solvents and is widely used in preparing combinatorial libraries. The catalyst 3.40% Pd-37-TGR gave excellent yields (92–99%) under optimized conditions in the coupling of varied iodoarenes including deactivated derivatives (bromobenzene = 52%). In recycling, however, slight decreases were observed (entry 8). Another catalyst with TentaGel resin (TGR) as support (3.04% Pd-38-TGR), in contrast, gave high, stable yields in 14 successive applications when the reactions were run under argon (entry 9).<sup>156</sup> The catalyst was made by immobilizing a pincer-type *N*-heterocyclic carbene ligand on modified TentaGel. Although the catalyst is air-stable, repeated uses in air results in the formation of Pd black and decreasing yields. Further characterizations performed in

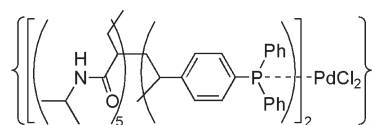
connection with the Suzuki reaction will be discussed (see section 5.2.2, Table 13, entry 18).



37

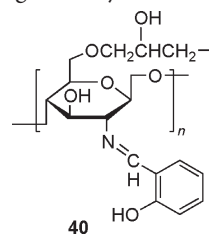


Ikegami and co-workers have developed new amphiphilic polymers, which were reacted with  $[(\text{NH}_4)_2][\text{PdCl}_4]$  to give insoluble catalyst Pd-39-polym.<sup>157,158</sup> Catalyst Pd-39-polym with improved cross-linking characteristics exhibited extremely high activities: a TON value of  $1.15 \times 10^6 \text{ h}^{-1}$  was measured in the Heck coupling of iodobenzene and methyl acrylate (catalyst loading =  $8 \times 10^{-7} \text{ mol equiv}$ ).<sup>158</sup> All iodobenzenes studied under optimized conditions reacted with high efficiency to furnish coupling products in high yields (>90%). The catalyst is active and durable in recycling (entry 10) with a total TON of 94 000.



39

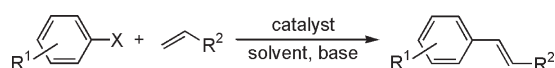
Cross-linked chitosan condensed with salicylaldehyde provided polymer 40, which upon reacting with  $\text{PdCl}_2$  gave catalyst Pd-chitosan-(40).<sup>159</sup> It can be used in air, affording high yields (>93%) in the Heck coupling of iodoarenes with styrene and acrylic acid. It also proved to be efficient in recycling experiments with decreasing yields in consecutive runs requiring prolonged reactions (entry 11). A catalyst sample prepared by using cross-linked chitosan with free nonfunctionalized amino functions was less stable in recycling (range of yields in five runs = 92–62%). Whereas catalysts were well-characterized by various instrumental techniques, leaching studies were not performed. A report from the same group disclosed the synthesis of a supported  $\text{Pd}^0$  complex (Pd-cellulose-xanth) by reacting cellulose xanthate with  $\text{PdCl}_2$ .<sup>160</sup> The catalyst gave high yields in the coupling of iodobenzenes with styrene and acrylic acid (83–100%). In a 10-run recycling study, a TON of 95 900 could be realized despite steadily and significantly decreasing yields (entry 12).



40

Yu and co-workers have developed a nonleaching colloidal Pd complex catalyst by reacting octanethiolate-protected Au



**Table 7.** Heck Coupling of Haloaromatics with Styrene and Acrylic Esters Catalyzed by Palladium Complexes under Homogeneous Conditions

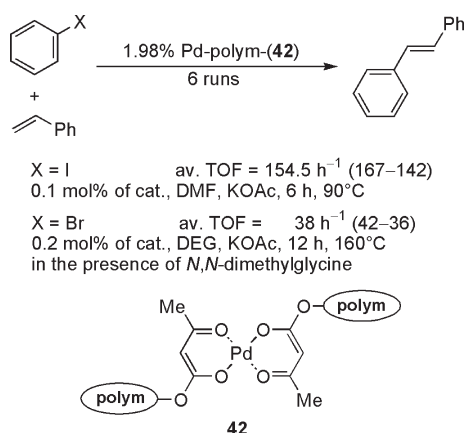
entry	R <sup>1h</sup>	X	R <sup>2</sup>	catalyst <sup>a</sup>	reaction conditions:		number of reuses	average yield, <sup>b</sup> (%)	ref
					solvent/base/temperature/time				
1	H	Br	Ph	<b>30b</b> (1)	TBAB/NaOAc/130 °C/12 h <sup>c</sup>		8	95.5 (99–89)	164
2	H	Br	Ph	<b>30b</b> (1)	TBAAc–TBAB/NaOAc/130 °C/12 h <sup>c</sup>		12	97 (100–94)	
3	H	I	COOMe	<b>44</b> (2)	<b>43</b> /Na <sub>2</sub> CO <sub>3</sub> /100 °C/4 h		5	91.5 (94–90)	165
4	H	Cl	COOMe	<b>44</b> (2) <sup>d</sup>			3	74.5 (78–75)	
5	H	Cl	Ph	<b>44</b> (2) <sup>d</sup>			3	83.5 (86–81)	
6	H	I	COOBu	<b>46a</b> (2)	<b>45</b> /Et <sub>3</sub> N/110 °C/3 h <sup>c</sup>		9	>99 (>99)	166
7	H	I	COOBu	<b>46a</b> (2)	<b>47</b> /Et <sub>3</sub> N/110 °C/3 h <sup>c</sup>		9	>99 (>99)	
8	H	I	COOBu	PdCl <sub>2</sub> (2)	<b>48</b> /Et <sub>3</sub> N/110 °C/3 h <sup>c</sup>		9	>99 (>99)	
9	R <sup>3</sup>	I	COOBu	<b>46a</b> (2)	<b>45</b> /Et <sub>3</sub> N/110 °C/3 or 15 h <sup>c</sup>		12	— <sup>e</sup>	
10	R <sup>4</sup>	Br	COOBu				12	— <sup>e</sup>	
11	H	I	COOBu	<b>49</b> (2)	[bmim][PF <sub>6</sub> ]/Et <sub>3</sub> N/120 °C/8 h <sup>c</sup>		6	91 (93–87)	167
12	R <sup>5</sup>	I	Ph				5	— <sup>e</sup>	
13	R <sup>6</sup>	I	COOBu	<b>50</b> (2)	<b>51</b> /Na <sub>2</sub> CO <sub>3</sub> /120 °C/12 h <sup>c</sup>		5	— <sup>e</sup>	168
14	R <sup>7</sup>	I	Ph				5	— <sup>e</sup>	
15	H	I	COOBu	<b>52</b> (2)	<b>53a</b> /Et <sub>3</sub> N/120 °C/3 h <sup>c</sup>		10	>99 (>99–>98)	169
16	H	I	COOBu	<b>52</b> (2)	<b>53b</b> /Et <sub>3</sub> N/120 °C/3 h <sup>c</sup>		10	>99 (>99–>98)	
17	R <sup>8</sup>	I	COOY	<b>52</b> (2)	<b>53a</b> /Et <sub>3</sub> N/120 °C/5 h <sup>c</sup>		5	— <sup>e</sup>	
18	R <sup>9</sup>	Br	COOBu	<b>52</b> (2) <sup>d</sup>			4	— <sup>e</sup>	
19	R <sup>10</sup>	Br	Ph	<b>52</b> (2) <sup>d</sup>			4	— <sup>e</sup>	
20	H	I	COOEt	<b>54</b> (0.0025)	[bpy][BF <sub>4</sub> ]/Et <sub>3</sub> N/100 °C/1 h		7	89 (98–80)	170
21	4-Ac	I	Ph	PdCl <sub>2</sub> (NH <sub>3</sub> ) <sub>2</sub> (1)	<b>55</b> –H <sub>2</sub> O/Bu <sub>3</sub> N/140 °C/24 h <sup>f</sup>		5	92.5 (94–90)	171
22	H	Br	Ph	PdCl <sub>2</sub> (0.03)	<b>56</b> –Et <sub>3</sub> N/80 °C/1 h		7	90 (93–84)	172
23	H	I	COOEt	PdCl <sub>2</sub> (0.05)	<b>57</b> –DMF/K <sub>2</sub> CO <sub>3</sub> /130 °C/0.5 h		10	97 (98–96)	173
24	H	I	COOEt	PdCl <sub>2</sub> (0.5)	<b>58</b> –[bmim][PF <sub>6</sub> ]/NMM/110 °C/2 h		7	84 (88–80)	175
25	H	I	COOEt	PdCl <sub>2</sub> (0.5)	<b>59</b> –[bmim][PF <sub>6</sub> ]/NMM/110 °C/2 h		7	97 (99–95)	
26	H	I	COOEt	PdCl <sub>2</sub> (0.5)	<b>58</b> + <b>60</b> /130 °C/3 h		7	91 (100–75) <sup>g</sup>	174
27	H	I	COOEt	PdCl <sub>2</sub> (0.5)	<b>58</b> + <b>60</b> –[bmim][PF <sub>6</sub> ]/130 °C/3 h		7	98 (100–94) <sup>g</sup>	
28	H	I	COOBu	<b>61</b> (2)	[bmim][PF <sub>6</sub> ]/Et <sub>3</sub> N/120 °C/1 h		5	99 (99)	176
29	4-MeO	I	COOBu				5	92 (94–91)	
30	R <sup>11</sup>	I	COOBu	<b>61</b> (2)	[bmim][PF <sub>6</sub> ]/Et <sub>3</sub> N/120 °C/1 or 2 h		5	— <sup>e</sup>	
31	H	I	COOBu	<b>62</b> (2)	[bmim][NTf <sub>2</sub> ]/Pr <sub>3</sub> N/100 °C/1 h <sup>c</sup>		7	96.5 (98–95)	177
32	H	I	Ph	Pd(OAc) <sub>2</sub> (2)	<b>63</b> /K <sub>3</sub> PO <sub>4</sub> /130 °C/16 h <sup>c</sup>		6	95 (97–93)	178
33	H	Br	Ph	Pd(OAc) <sub>2</sub> (0.5)	<b>64</b> /K <sub>2</sub> CO <sub>3</sub> /140 °C/10 h		6	93 (96–82)	179
34	4-MeO	Br	Ph	<b>28</b> (0.2)	DMAc/NaOAc/165 °C/10 h		6	82 (88–76)	143

<sup>a</sup> Data in parentheses indicate mol % of Pd used. <sup>b</sup> Data in parentheses indicate range of yields. <sup>c</sup> Under nitrogen atmosphere. <sup>d</sup> The catalyst recovered from previous runs was used. <sup>e</sup> See footnote for data. <sup>f</sup> In the presence of TBAB. <sup>g</sup> Conversion. <sup>h</sup> R<sup>3</sup>: Successive, repeated reactions with R<sup>1</sup> = H (91%, 91%), 4-Me (92%, 93%), 4-MeO (90%, 92%), 2-iodothiophene (84%, 87%), 4-NO<sub>2</sub> (90%, 89%), 4-F (91%, 92%). R<sup>4</sup>: Successive, repeated reactions with R<sup>1</sup> = H (47%, 63%), chlorobenzene (<1%), 4-Me (10%, 15%), 4-CF<sub>3</sub> (75%, 90%), 4-Ac (76%, 86%), 4-F (69%, 85%), 4-NO<sub>2</sub> (81%, 89%). Reaction times are 3 h in the first run, 15 h in repeated use. R<sup>5</sup>: Successive reactions with R<sup>1</sup> = H (89%), 4-Me (93%), 4-MeO (90%), 4-F (91%), 4-NO<sub>2</sub> (93%). R<sup>6</sup>: Successive reactions with R<sup>1</sup> = H (93%), 4-Me (92%), 4-MeO (90%), 4-F (95%), 4-NO<sub>2</sub> (92%). R<sup>7</sup>: Successive reactions with R<sup>1</sup> = H (94%), 4-Me (88%), 4-MeO (90%), 4-F (91%), NO<sub>2</sub> (93%). R<sup>8</sup>: Successive reactions with R<sup>1</sup> = H (93%), Y = Bu, 4-Me (94%), Y = Bu, 4-MeO (91%), Y = Bu, 4-F (93%), Y = Bu, H (91%), Y = Me. R<sup>9</sup>: Successive reactions with R<sup>1</sup> = H (62%), 4-MeO (47%), 4-CF<sub>3</sub> (89%), 4-NO<sub>2</sub> (90%). R<sup>10</sup>: Successive reactions with R<sup>1</sup> = H (65%), 4-Ac (91%), 4-F (85%), 4-NO<sub>2</sub> (88%). R<sup>11</sup>: Successive reactions with R<sup>1</sup> = H (>99%), 4-CF<sub>3</sub> (95%), 4-CH<sub>3</sub> (98%), 4-NO<sub>2</sub> (93%, 2 h), 4-MeO (98%). [bpy][BF<sub>4</sub>] = *N*-butylpyridinium tetrafluoroborate. NMM = *N*-methylmorpholine.

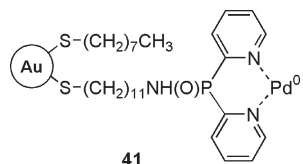
nanoparticles with ligand HS(CH<sub>2</sub>)<sub>11</sub>NHP(O)(2-py)<sub>2</sub>. In the final step of catalyst synthesis, the ligand was partially palladated with PdCl<sub>2</sub>(PhCN)<sub>2</sub>.<sup>161</sup> As shown by XPS, the loaded Pd<sup>2+</sup> complex underwent reduction under reaction conditions to form catalyst 3% Pd-**41**-Au. The catalyst applied in a DMSO stock solution exhibited extreme activity in the

coupling of iodobenzene with styrene and various alkyl acrylates to afford TOF values in the range of 44 700–48 700 h<sup>−1</sup>. In a 15-run recycling experiment, the catalyst applied in deuterated toluene and separated by centrifugation showed high durability with yields dropping below 90% only in the 12th cycle (entry 13). High durability is attributed to the

### Scheme 9. Heck Couplings Catalyzed by Polymer-Supported Complex 42



presence of uncapped ligands capable of capturing leached Pd species during recycling.



Catalyst 1.98% Pd-polym-(42) obtained by copolymerizing the Pd derivative of 2-(acetoacetoxy)ethyl methacrylate with ethyl methacrylate and ethylene glycol has a polymer-supported  $\beta$ -ketoesterate palladium complex. It gave high yields in the coupling of iodobenzenes (90–100%) with low stereoselectivities in the reaction of acrylonitrile (*E/Z* ratios with iodobenzene and 4-iodotoluene are 52:48 and 68:32, respectively).<sup>162</sup> Slight increases in yields could be achieved with the use of additives such as *N,N*-dimethylglycine. In addition, higher temperature ( $160^\circ\text{C}$  vs  $90^\circ\text{C}$ ) was required to have similar high yields with bromobenzenes. Negligible catalytic activity was found in the filtration test. Decreasing TOF values were reported in six-run recycling studies with iodobenzene and bromobenzene (Scheme 9). All manipulations were carried out in air with nondried solvents.

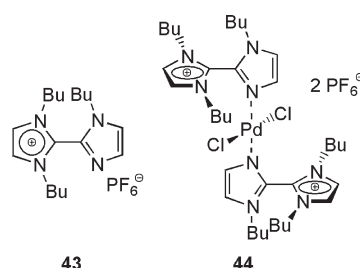
### 4.3. The Use of Palladium Complexes under Homogeneous Conditions

All studies collected in Table 7 with the exception of results shown in the last entry have been performed in ionic liquids. Catalyst recycling is usually made by recharging the ionic liquid phase after product extraction, and washing and drying with a new batch of substrates and the base. Reviews about ionic liquids and their applications in catalytic processes<sup>24,163</sup> and, specifically, their use in C–C coupling reactions<sup>9</sup> are available.

Böhm and Herrmann applied palladacycle 30b in the presence of NaOAc and TBAB as nonaqueous ionic liquid solvent under nitrogen.<sup>164</sup> The degree of drying and degassing was found to be critical. Varied yields (18–99%) were reported for the coupling of various bromo- and chloroarenes with substituted styrenes and acrylic derivatives. Styrene and 4-bromoacetophenone gave a TON value of 1 million at a Pd loading of 0.0001 mol %. In recycling studies made with bromobenzene, starting materials and products were distilled off under vacuum after reaction, and

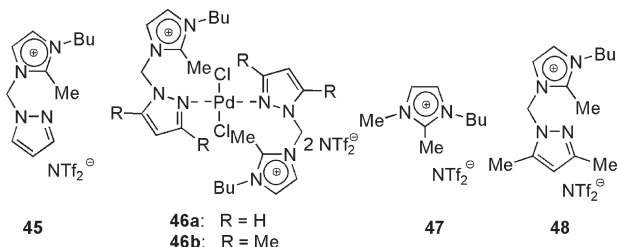
the residue was reused. When NaOAc was used as base, the formed NaBr could not be removed before catalyst reuse. This is assumed to be the reason for decreasing yields (entry 1). The use of TBAAc, however, solves this problem by furnishing the solvent TBAB. Indeed, much better efficiency was detected in a 12-run study (entry 2) despite visible Pd black formation after the fourth run. The presence of 23% of structurally unchanged palladacycle was measured after the eighth run. Yields decreased significantly in the fifth cycle, and heavy Pd black formation already in the first run was experienced in recycling with  $\text{PdCl}_2$ . This method is characterized by the authors as the first leach-free Heck coupling protocol without reporting any observation with respect to the nature of the catalytically active species.

Shreeve and co-workers have carried out wide-ranging studies by developing varied ionic liquids (43–53) and testing them in C–C coupling reactions. When used as solvent, they play a dual role by immobilizing palladium species and as coordinating ligands. The air- and moisture-insensitive complex 44 was prepared by reacting IL 43 bearing a 2,2'-biimidazole moiety with  $\text{PdCl}_2$ .<sup>165</sup> The formed catalyst was evaluated in the coupling of three reactant pairs in 11 consecutive runs. High and stable yields were measured in the reaction of iodobenzene and methyl acrylate (entry 3). The results with the recovered catalyst in the coupling of less reactive chloro derivatives are also satisfactory (entries 4 and 5), indicating the high durability of the catalyst system.

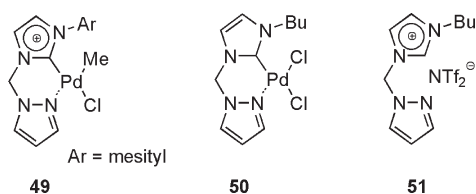


Pyrazolyl-functionalized *N*-heterocyclic carbene complexes of  $\text{Pd}^{2+}$  were also used in various cross-coupling reactions in the presence of ionic liquids. In this study, they focused on evaluating catalytic activity and recyclability with thorough characterizations of both the complexes and the ionic liquids. Complex 46a prepared by reacting  $\text{PdCl}_2$  with 2 equiv of IL 45 has been tested in the Heck coupling of iodobenzene and butyl acrylate.<sup>166</sup> Outstanding catalyst performance in nine runs was found by using the complex in ILs 45 or 47 (entries 6 and 7). Moreover,  $\text{PdCl}_2$  itself gave similar performance when applied in IL 48 (entry 8). Catalyst recycling was made by extracting the reaction mixture with diethyl ether, and then the IL solution containing the  $\text{Pd}^{2+}$  catalyst was washed with water to remove excess base and the salt formed and dried under reduced pressure ( $60^\circ\text{C}$ , 4 h). Next, according to their usual recycling protocol, complex 46a was tested in the coupling of various haloarenes in successive runs. Furthermore, in this case, each reactant was used repeatedly. The coupling of substituted iodobenzenes (entry 9) proceeded in high yields. In all cases, the corresponding cinnamates were formed with complete regio- and stereoselectivity ( $\beta$ -substitution and *E* products, respectively). In the reaction with

bromobenzenes (entry 10), significant substituent effects were observed, whereas chlorobenzene proved to be unreactive. Palladium leaching was not detected.

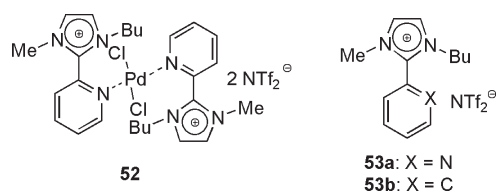


In another study,<sup>167</sup> complex **49** in [bmim][PF<sub>6</sub>] was found to exhibit sufficient stability in the coupling of iodobenzene and butyl acrylate (entry 11). Reactions were run under nitrogen because in an open system palladium black was formed. A five-run study was also performed by reacting five different iodobenzenes with styrene in successive runs (entry 12) with similar yields and stability found in entry 11. The catalyst system offered high yields (68–94%) and complete selectivity in the reaction of substituted iodo- and bromobenzenes as well as 2-iodothiophene with butyl acrylate without loss of efficiency in three runs with each substrate.

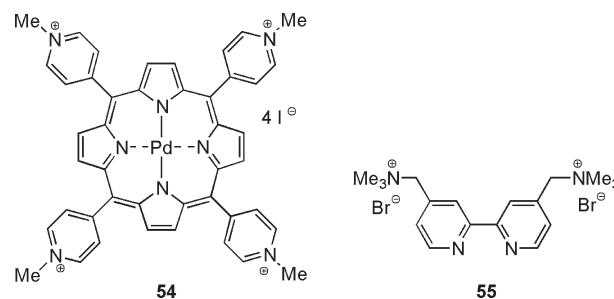


In their next communication, the authors assayed the effect of the *N*-alkyl substituent and the anion on the properties of a range of ionic liquids.<sup>168</sup> The results of recycling experiments carried out with complex **50** and IL **51** (entries 13 and 14) were similar to those observed with complex **49** (entries 11 and 12).

In their following study,<sup>169</sup> Shreeve et al. tested the Pd<sup>2+</sup> complex of a pyridyl-functionalized IL **52** in ILs **53a** and **53b** in the coupling of iodo- and bromobenzenes with styrene and butyl acrylate. After they found excellent results in the coupling of iodobenzene with butyl acrylate (entries 15 and 16), the catalyst system (**52** and **53b**) was applied in a 13-run study, again, with the use of various substrates in each subsequent cycle. In the first five runs (entry 17), high and stable yields were recorded in the reaction of substituted iodobenzenes with butyl acrylate (in the fifth cycle, methyl acrylate was tested). Among the bromobenzenes used in the next cycles (runs 6–9, entry 18), bromobenzene and 4-bromoanisole gave lower yields. In continuous catalyst recycling, bromobenzenes showed much higher reactivity in couplings with styrene (runs 10–13, entry 19). A yield of 92% observed in the last run (coupling of iodobenzene with butyl acrylate) proves unequivocally the high efficiency and excellent stability of the catalyst system (compare to the yield of 93%, entry 17, first run).

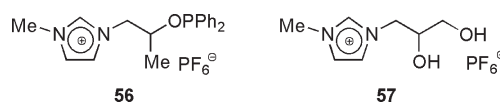


The ionic Pd complex **54** with a pyridinium-tagged porphyrin base serving as a tetradentate pincer ligand applied in IL [bpy][BF<sub>4</sub>] provided high yields in the coupling of activated iodobenzenes with ethyl acrylate under mild, aerobic conditions.<sup>170</sup> Pd leaching was below the detection limit of 0.1 ppm. Bromo derivatives did not react under such conditions, and steric effects were observed for *ortho*-substituted derivatives. Decreasing yields in recycling studies (entry 20) were attributed to salt accumulation because the IL phase, after product extraction, was used directly in the next cycle. Nevertheless, a high cumulative TON of 249 000 could be realized.



PdCl<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub> in dicationic 2,2'-bipyridyl salt **55** and water under air has proved to be a highly efficient system for the coupling of iodoarenes with alkenes, affording high TON values: coupling of 4-iodoacetophenone and butyl acrylate with a Pd loading of 0.0001 mol % gave a TON of 9.2 × 10<sup>5</sup>.<sup>171</sup> However, only activated bromoarenes were reactive with butyl acrylate with 1 mol % of Pd and in the presence of TBAB. Similar conditions were required to get high yields in the coupling of iodoarenes with styrene. High but decreasing yields were detected in five runs in recycling studies with 4-iodoacetophenone with butyl acrylate and ethyl acrylate in the presence of 0.01 mol % of Pd (a drop of 9% from 99% and 90%, respectively, in the fifth run). The stability of the catalyst system was only slightly better in the coupling with styrene using 1 mol % of Pd (entry 21).

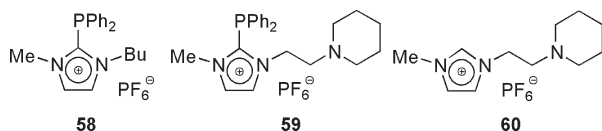
PdCl<sub>2</sub> applied in imidazolium-based phosphinite IL **56** afforded medium to high product yields in Heck coupling of varied aromatic halides with styrene (60–97%) and butyl acrylate (59–95%).<sup>172</sup> Even the coupling of chlorobenzene was successfully accomplished at higher temperature in a prolonged reaction. The catalyst system gave gradually decreasing yields in seven cycles in the reaction of iodobenzene and styrene after removing the ammonium salt after each run (entry 22). A variety of iodo- and bromoarenes were efficiently coupled with alkyl acrylates in the presence of PdCl<sub>2</sub> and IL **57** in air (yields of 76–98%), whereas 4-chloronitrobenzene gave only a yield of 29% even in a prolonged reaction (48 h) with increased amount of PdCl<sub>2</sub> (0.01 mol % vs 0.005 mol %).<sup>173</sup> Both IL **56** and **57** are insensitive to air and moisture; however, the stability of the PdCl<sub>2</sub>-**57** catalyst system (entry 23) is higher than that of PdCl<sub>2</sub>-**56** (entry 22): it provides high steady yields in 10 runs with Pd leaching below the detection limit of 1 ppm.



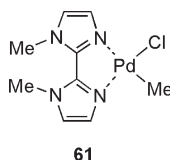
*P,N*-Donor-functionalized ionic liquids **58** and **59** have been developed and applied in the Heck coupling of iodo- and



bromoarenes with ethyl acrylate by Wan, Liu, and co-workers.<sup>174,175</sup> Reactions were carried out with  $\text{PdCl}_2$  in a mixture of the new IL **58** or **59** in combination with **60** or  $[\text{bmim}][\text{PF}_6]$  in an open atmosphere. Electronic effects of the substituents in the coupling of iodobenzenes could not be detected, whereas bromobenzenes required longer reaction time, increased amount of  $\text{PdCl}_2$ , and elevated temperature ( $130^\circ\text{C}$ , 15–25 h vs  $110^\circ\text{C}$ , 2 h). Selectivities of ethyl (*E*)-cinnamate were at least 99%. In recycling studies,  $\text{PdCl}_2$  in **58** gave somewhat lower yields and showed lower stability when compared to the performance of IL **59** under identical reaction conditions (entries 24 and 25). Yields in IL **60**, in contrast, dropped significantly in each run (from 97% to 49% conversion in seven runs) with the concomitant formation of Pd black. Recycling of the catalyst systems was made by first drying the IL phase containing  $\text{PdCl}_2$  (in vacuo at room temperature) and then recharging it with a new batch of reactants and *N*-methylmorpholine (NMM). When using complex mixtures of the various ionic liquids, high yields were obtained in a combination of ILs **58** and **60**, but yields decreased considerably in the last three cycles (entry 26) despite additional charging of IL **60** in the fourth and seventh cycles. This was necessary because the low solubility of **60** in water resulted in a loss during the treatment of the HI salt with NaOH between runs. This also contributed to a loss of about 28% of Pd in seven cycles. The performance, however, improved significantly when the recycling study was carried out with added  $[\text{bmim}][\text{PF}_6]$  (entry 27). It is surmised that Pd is reduced to  $\text{Pd}^0$ , but it is not clear whether it forms Pd carbene species or it is coordinated to **58** and/or **60**. In this system, **58** is used as a phosphane ligand to stabilize  $\text{Pd}^0$ , **60** serves as a base, whereas  $[\text{bmim}][\text{PF}_6]$  is the solvent.

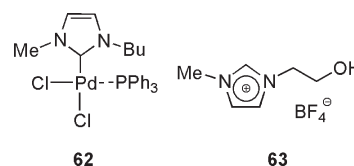


The  $\text{Pd}^{2+}$  complex with 2,2'-biimidazole ligand (catalyst **61**) applied in  $[\text{bmim}][\text{PF}_6]$  is an efficient system in the coupling of iodoaromatics and butyl acrylate used in air (yields of 76 to >99%).<sup>176</sup> Iodobenzene (entry 28) and 4-iodoanisole (entry 29) reacted smoothly to give consistently high yields in recycling experiments. Prolonged reactions, however, were necessary in the reaction of 2-iodoanisole because of small steric effects: the yield dropped from 99% to 76% in the third run but increased again to 99% when running the reaction for 2 and 3 h in subsequent uses. 2-Iodothiophene also reacted with full conversion but with decreased selectivity (bisthiophene as homocoupling product was formed in ~20% yield). Excellent performance was found for recycling the catalyst in successive runs with various iodoarenes (entry 30).

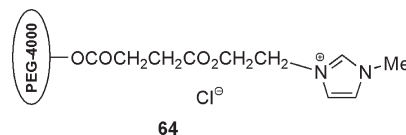


The Pd-carbene complex **62** used in the low-viscosity IL  $[\text{bmim}][\text{NTf}_2]$  worked efficiently in the coupling of iodoarenes (yields of 61–95%).<sup>178</sup> It is also durable when recycled (entry 31). In a comparative study with various 1-substituted-3-methylimidazolium ILs, the functionalized ionic liquid

1-(2-hydroxyethyl)-3-methylimidazolium tetrafluoroborate **63** displayed the best catalyst performance when applied with  $\text{Pd}(\text{OAc})_2$  as the catalyst and  $\text{K}_3\text{PO}_4$  as the base.<sup>177</sup> Medium to high yields (52–97%) and excellent selectivity (>99% *E* products) were found in the coupling of varied iodo- and bromoarenes with styrene, acrylates, and acrylonitrile. The catalyst system worked with high efficiency in recycling by simply recharging the IL phase after product extraction (entry 32).



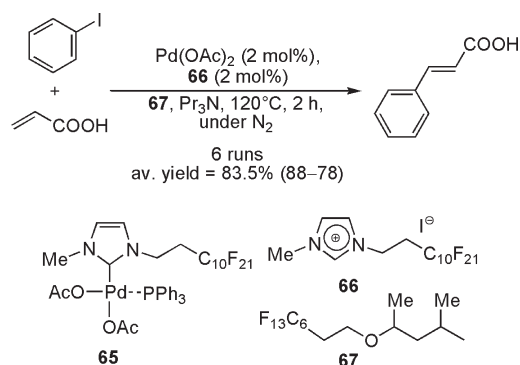
$\text{Pd}(\text{OAc})_2$  in the PEG-supported IL **64** as the reaction medium exhibited high activity in the Heck coupling of bromoarenes and activated chlorobenzenes with styrene and ethyl acrylate (yields of 91–97%).<sup>179</sup> Prolonged reaction, however, had to be applied in the reaction of deactivated bromoarenes (10 h vs 8 h). High yields were also found for activated chlorobenzenes at  $160^\circ\text{C}$  under nitrogen in the presence of  $\text{Cs}_2\text{CO}_3$  instead of  $\text{K}_2\text{CO}_3$  (yields of 62–97%; chlorobenzene = 23%). An NHC Pd complex formed in situ is suggested to be the active catalyst. High yields and high stability were observed in the first five runs in recycling by reusing the IL phase after product extraction without any regeneration (entry 33). The cleavage of the succinic ester bond, however, was observed, resulting in about a 10% loss in each cycle. This is the possible reason for the significant drop of yields in the sixth run.



Complex **28** already discussed when used as an immobilized catalyst (section 4.2.1, Table 5, entries 11 and 12) was applied at relatively high temperature ( $165^\circ\text{C}$ ) without any special precaution to exclude air and moisture.<sup>143</sup> It showed high activity in the coupling of varied haloarenes and styrene to form (*E*)-stilbenes and 8–15% of 1,1 products. 4-Chlorobenzaldehyde gave a TON of 75 000 in the presence of TBAB (catalyst loading =  $2 \times 10^{-4}$  mol %). The complex proved to be active in the reaction of 4-bromoanisole, but yields dropped in the last cycles (entry 34). Catalyst recycling with 4-chloroacetaldehyde, however, failed. Recycling was made by adding new educts and base to the reaction mixture after each run without removing the product. The monocarbene complex showed similar characteristics with lower stability: the formation of Pd black was detected.

Fluorous carbene complex **65** was prepared in situ by mixing fluorous IL **66**,  $\text{Pd}(\text{OAc})_2$ , and  $\text{PPh}_3$  in fluorous solvent **67** under nitrogen.<sup>180</sup> The system allows facile product separation and efficient catalyst recycling. The reaction mixture is monophasic at reaction temperature ( $120^\circ\text{C}$ ). The products precipitating at room temperature are separated by filtration under argon, whereas the IL solution of the catalyst is reused. The catalyst system worked efficiently in Heck couplings of varied iodoarenes and acrylic acid and esters (yields of 80–99%). Reactions with methacrylic acid gave lower yields (iodobenzene = 56%, 4-iodoanisole = 47%). The system was successfully applied in a recycling study (Scheme 10) with 95.5% of the solvent recovered.

### Scheme 10. Heck Coupling Catalyzed by Complex 65 in the Presence of IL 66 and Fluorous Solvent 67



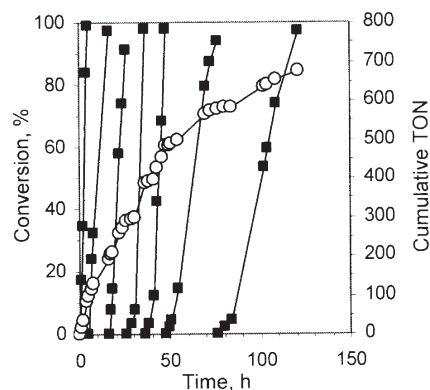
Livingston and co-workers have studied C–C cross-coupling reactions by using nanofiltration<sup>181</sup> (see also Suzuki coupling, section 5.3, Table 14, entries 4 and 5). Instead of the conventional solvent extraction technique, catalyst separation for recycling was performed by organic solvent nanofiltration (OSN). This technology allows the separation of large molecules from small reaction products and subsequent recycle and reuse of the catalyst. In this approach, the catalytic reaction and separation by nanofiltration operate independently but coupled, thereby improving productivity and achieving ultralow Pd contamination. Reactions were run until 95–100% conversion. The reaction mixture after quenching with water was filtered through a solvent resistant nanofiltration (SRNF) membrane until 85% of the volume permeated. The remaining solution with the catalyst was charged with fresh educts and solvent, and a new run was started.

The coupling of iodobenzene and styrene was used in their studies of Heck reaction. In a preliminary report,<sup>182</sup> the technique was shown to allow cumulative TON values of about 1200 in five repeated runs in various solvent systems. The reaction rates, however, decreased in the last runs. In a subsequent study, four catalysts were tested.<sup>183</sup> Bis(1,3-dibenzylimidazoline-2-ylidene)-diiodopalladium(II) applied in the presence of  $\text{P}(o\text{-tolyl})_3$  as stabilizer proved to be an active and stable catalyst; the first reaction was completed in less than 3 h, only a minor rate decrease was observed during subsequent runs, and a cumulative TON value of 1050 was realized. Catalyst  $[\text{Pd}(\text{OAc})_2(\text{PPh}_3)_2]$  used in the presence of  $\text{P}(o\text{-tolyl})_3$  also exhibited high initial activity (near complete conversion in 4 h). However, the reaction was accompanied by Pd black formation, and the activity decreased significantly in the seventh run (Figure 1). Similar, even more serious problems arose with the use of the  $\text{Pd}(\text{OAc})_2-[\text{PPh}_4]\text{Br}$  catalyst system. All three reactions were carried out in  $\text{THF}-\text{H}_2\text{O}$  solvent mixture. Because the STARMEM 122 membrane deteriorates in  $\text{THF}-\text{H}_2\text{O}$ , a new membrane was used for each filtration.

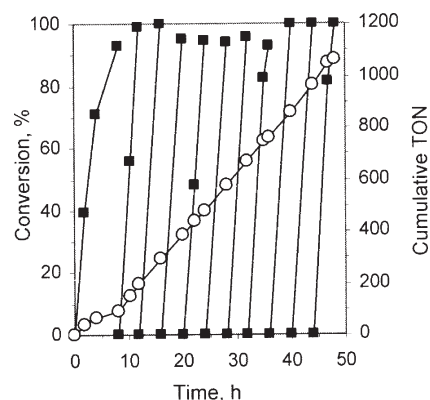
In the fourth test, the  $\text{Pd}(\text{OAc})_2-[\text{PPh}_4]\text{Br}$  catalyst system was used again, but reactions were run in acetonitrile applying the hydrophobic silicone-based composite membrane MPF-60. Each consecutive run after the first reaction (8 h, 93% conversion) was completed in 4 h, and 11 cycles gave a cumulative TON of 1063 in 48 h (Figure 2). Formation of Pd black, in this case, was not observed.

#### 4.4. Related Coupling Reactions

Alacid and Nájera used polymer-supported Kaiser oxime resin catalyst 1.25% Pd-14-PS to perform the Heck reaction of allyl



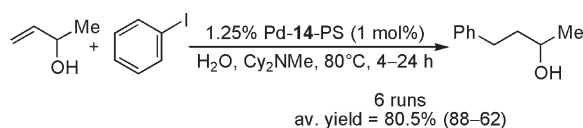
**Figure 1.** Conversion of iodobenzene (■) and cumulative TON values (○) as a function of reaction time. Reaction conditions:  $[\text{Pd}(\text{OAc})_2(\text{PPh}_3)_2]$ , 1 mol % with respect to styrene,  $\text{P}(o\text{-tolyl})_3$ ,  $\text{THF}-\text{H}_2\text{O}$ ,  $\text{Et}_3\text{N}$ ,  $60^\circ\text{C}$ . Reproduced with permission from ref 183. Copyright 2002 The Royal Society of Chemistry.



**Figure 2.** Conversion of iodobenzene (■) and cumulative TON values (○) as a function of reaction time. Reaction conditions:  $\text{Pd}(\text{OAc})_2$ , 1 mol % with respect to styrene,  $[\text{PPh}_4]\text{Br}$ ,  $\text{MeCN}$ ,  $\text{Et}_3\text{N}$ ,  $160^\circ\text{C}$ . Reproduced with permission from ref 183. Copyright 2002 The Royal Society of Chemistry.

alcohols with haloaromatics to afford  $\beta$ -arylated carbonyl compounds.<sup>184</sup> Iodoarenes react in water, in the presence of dicyclohexylmethylamine ( $\text{Cy}_2\text{NMe}$ ) or  $\text{Cs}_2\text{CO}_3$  as bases at low Pd loading (0.1 mol %), to give coupling products in yields of 54–97%. Byproducts are  $\alpha$ -arylated carbonyl compounds and  $\alpha$ - and  $\beta$ -arylated allyl alcohols. Bromo- and chloroarenes required the use of TBAB and aqueous DMAc as well as higher Pd loading (1 mol %) to achieve yields of 46–88%. Despite an increase in reaction time in every run in recycling, a large drop was experienced in the last run (Scheme 11). The performance in the coupling of 2-bromo-6-methoxynaphthalene was inferior (a yield of 86% dropped to 38% in the fourth run). The Pd content of the polymer after the last cycle was determined to be 51%; that is, about 8% of Pd was lost in every run.

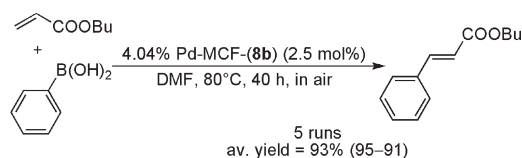
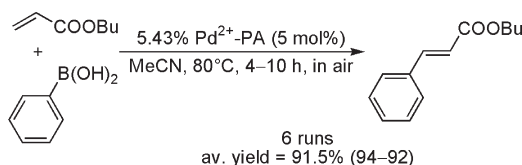
The use of acrolein diethyl acetal as a three-carbon homologation reagent was also demonstrated with the above catalyst.<sup>185</sup> It affords ethyl 3-arylpropanoates under optimized Heck conditions (0.1 mol % Pd, aqueous DMAc,  $\text{Cy}_2\text{NMe}$ , TBAB,  $90-120^\circ\text{C}$ ) to give yields of 61–92%. The products under Cacchi conditions (1 mol % Pd, DMAc,  $\text{K}_2\text{CO}_3$ , KCl, TBAB,  $120^\circ\text{C}$ ) are cinnamaldehydes (yields of 78–99%; 3-bromopyridine = 46%). Competitive dehalogenation was not observed. A

**Scheme 11. Heck Reaction of Allyl Alcohol Induced by Catalyst 1.25% Pd-14-PS****Scheme 12. Coupling of Acrolein Diethyl Acetal Catalyzed by 1.25% Pd-14-PS**

lower leaching of 0.08 ppm of Pd was detected in the former reaction as compared to the formation of cinnamaldehydes (0.8 ppm). The results of recycling studies are similar to those discussed above, that is, decreasing yields despite prolonged reactions (Scheme 12). Pd leaching in the first three runs is 0.51, 0.53, and 0.63 ppm. Decreasing yields are attributed to both Pd leaching and the partial loss of the polymer. The palladacycle works as a source of Pd<sup>0</sup> species in these reactions. Pd particles of 6–8 nm were detected by TEM, and Hg<sup>0</sup> inhibited the reaction.

Palladium induces the oxidative Heck coupling of arylboronic acids with alkenes.<sup>186</sup> Jones and co-workers performed the reaction in air, which allows the reoxidation of Pd without using a co-oxidant. Catalyst 4.04% Pd-MCF-(8b) consists of a Pd(OAc)<sub>2</sub>–bipyridine complex immobilized on mesocellular silica foam.<sup>187</sup> Excellent yields (86–98%) with high selectivities (>94%) over the product of 1,4-addition were observed in the coupling of varied boronic acids and alkyl acrylates. 4-Vinylphenylboronic acid, however, was unreactive. The electronic nature of the substituents does not seem to affect reactivities. High yields and selectivity were found with small stability decrease typical for five-run recycling studies (Scheme 13). Kinetic profiles for the first and second cycles are practically identical.

Choudary, Kantam, and co-workers have developed polymer-supported Pd catalysts by depositing PdCl<sub>2</sub> onto polyaniline (PA).<sup>188</sup> Catalyst 5.43% Pd<sup>2+</sup>-PA afforded high yields (88–94%) and high selectivities over the corresponding saturated product (>92%) in the reaction of acrylate derivatives with phenylboronic acids under optimized base-free conditions (5 mol % Pd, MeCN, 80 °C, air).<sup>189</sup> Again, substituents effects are hardly observed. A few alkenes gave, however, medium yields with phenylboronic acid (acrylonitrile = 60%, 4-vinylanisole = 52%, cyclohex-2-enone = 55%; no reaction of 2-methyl-but-2-yl acrylate). In the last run of recycling, longer reaction time was needed to maintain high yield (Scheme 14). According to an XPS study of the catalyst recovered after the fifth run, 20% of Pd<sup>2+</sup> was found to be reduced to Pd<sup>0</sup>, which was suggested to account for decreasing activity. No activity was observed in the hot filtration test, and leached Pd could not be detected. See the further use of this catalyst in the Suzuki coupling (section 5.2.2, Table 13, entry 7).

**Scheme 13. Oxidative Heck Coupling with Catalyst 4.04% Pd-MCF-(8b)****Scheme 14. Oxidative Heck Coupling with Catalyst 5.43% Pd<sup>2+</sup>-PA**

## 4.5. Summary

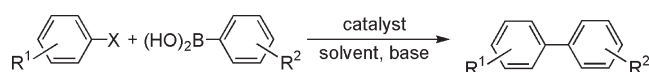
A number of catalysts show good performance in recycling studies of Heck couplings. Evaluations have been made here on the basis of their stability either to afford consistently high yields or to provide sufficiently high cumulative TON numbers. Criteria for selection are either (i) constant yields or only a 1% decrease (in 5–9 cycles) or a maximum loss of 2% in at least 10 cycles or (ii) a minimum of total TON number of about 100 000. Furthermore, sufficient catalyst stability must be demonstrated.

Both amorphous and ordered silica materials proved to be useful supports for palladium nanoparticles. It appears, however, that these require modification such as a long-chain alkyl groups making the silica matrix hydrophobic [0.48% Pd-SiO<sub>2</sub> with entrapped Pd(OAc)<sub>2</sub>, Table 1, entry 1], the perfluoro-tagged stabilizing agent 3 [catalyst 3.47% Pd-SiO<sub>2</sub>-(3), Table 1, entries 6 and 7], tetramethylguanidinium lactate [1.06% Pd-TMG-SBA15, Table 2, entry 6], or silica grafted with (3-mercaptopropyl)trimethoxysilane [4.1% Pd-grHS-Si(HIPE), Table 2, entry 10]. Exceptions are two Pd-MCM41 samples made by simultaneous synthesis of MCM-41 and particle generation with palladium loadings of 1.39% and 5.85% (Table 2, entries 3 and 4), and catalyst 35% Pd/C aerogel (Table 3, entry 2). Further examples with polymer-supported nanoparticles are Pd-PVPy made with poly(4-vinylpyridine) matrix (Table 4, entry 2), the polystyrene-based Pd-15-PS with grafted imidazolium moiety (Table 4, entry 13), and dendrimeric 29.32% Pd-dendr-(13) with azamacrocyclic 13 (Table 4, entry 8).

Similar high yields and stability may be realized by the immobilization of complexes on inorganic supports [4.04% Pd-22b-MCM41, Table 5, entry 2; Pd-SiO<sub>2</sub>-(25), Table 5, entry 7]. Polymeric materials can be equally useful as shown by the performance of polystyrene-based catalysts with palladacycle 30a [Pd-PS-(30a), Table 6, entry 1] and anchored N-heterocyclic carbene (NHC) Pd complexes (1.17% Pd-31-PS, Table 6, entry 2; 4.36% Pd-32-PS, Table 6, entry 3; 3.04% Pd-38-TGR, Table 6, entry 9).

The combined use of varied ionic liquids and related homogeneous complexes is of particular interest. Pyrazolyl-functionalized N-heterocyclic carbene complex 46a and PdCl<sub>2</sub> proved to be highly efficient, giving near quantitative yields when applied in ionic liquids 45, 47, or 48 (Table 7, entries 6–8). Complex 46a



**Table 8.** Suzuki Coupling of Aromatic Halides with Phenylboronic Acids Catalyzed by Palladium Nanoparticles Immobilized on Amorphous Silica

entry	R <sup>1</sup>	X	R <sup>2</sup>	catalyst <sup>a</sup>	reaction conditions:		number of reuses	average yields, <sup>b</sup> (%)	ref
					solvent/base/temperature/time				
1	4-Ac	Br	H	6.05% Pd-68-SiO <sub>2</sub> (0.2)	DMF-H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /110 °C/0.75 h		10	97 (100–94)	198
2	4-Ac	Br	H	3.88% Pd-68-SiO <sub>2</sub> (0.2)	DMF-H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /110 °C/0.75 h		10	97 (100–94)	
3	4-Ac	Br	H	2.63% Pd-68-SiO <sub>2</sub> (0.2)	DMF-H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /110 °C/1 h		10	97 (100–95)	
4	4-Me	Br	H	0.48% Pd-SiO <sub>2</sub> (1)	H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /80 °C/20 h		6	>99 (>99)	68
5	H	I	H	2.30% Pd-69-SiO <sub>2</sub> (1)	DMAc/K <sub>2</sub> CO <sub>3</sub> /100 °C/2 h <sup>c</sup>		15	95.5 (99–93)	199
6	4-CO <sub>2</sub> H	I	2-Me	1.22% Pd-FSG-(2a) (0.1)	H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> -KF/110 °C/5 h		15	89 (99–84)	71
7	4-CO <sub>2</sub> H	I	2-Me	3.47% Pd-SiO <sub>2</sub> -(3) (0.1)			15	94 (100–85)	

<sup>a</sup> Percentage data show Pd loading (wt %) when available; data in parentheses indicate mol % of Pd used. <sup>b</sup> Data in parentheses indicate range of yields.

<sup>c</sup> Under nitrogen atmosphere.

and IL **45** gave consistently high yields with varied substrate combinations tested sequentially in duplicate runs (Table 7, entry 9). The pyridyl-functionalized complex **52** in ILs **53a** or **53b** applied in similar studies exhibited analogous features (Table 7, entries 15–19). Additional examples are the use PdCl<sub>2</sub> and IL **57** (Table 7, entry 23) and catalyst **61** applied in [bmim][PF<sub>6</sub>] (Table 7, entry 28).

The best performance with respect to cumulative TON numbers has been reported for catalyst Pd-SBA15 (157 500, Table 2, entry 5), 3.9% Pd-HS-Si(HIPE), and 4.1% Pd-grHS-Si(HIPE) (209 200 and 169 700, respectively; Table 2, entries 9 and 10), Pd-**39**-polym with PdCl<sub>2</sub> anchored to an amphiphilic polymer (94 000, Table 6, entry 10), PdCl<sub>2</sub> deposited on cellulose xanthate (95 900, Table 6, entry 12), and complex **54** with a pyridinium-tagged porphyrin base applied in [bmim][PF<sub>6</sub>] (249 000, Table 7, entry 20). Unfortunately, no attempts have been made to acquire high TONs with high-yielding homogeneous complexes.

From this summary, the following general conclusions may be drawn:

- There are a number of examples for all three types of catalysts (supported Pd particles and complexes either immobilized or used under homogeneous conditions), which give good yields when reused in Heck couplings.
- Homogeneous complexes applied in ILs are thoroughly studied, stable catalyst systems to give high yields.
- High yields and stable catalyst activity do not parallel high efficiency considering total TON numbers. The reason is that most catalyst recycling studies are carried out with relatively high Pd concentrations typically in the range of 0.1–2 mol %. Of the six catalyst systems selected above, which provide high TONs, only 4.1% Pd-grHS-Si(HIPE) gave consistent high yields in recycling. Furthermore, in all cases, highly specific support materials or a particular complexing agent (last example) have been applied.

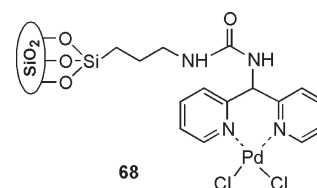
## 5. SUZUKI COUPLING

The reaction reported first by Suzuki and Miyaura<sup>190</sup> is the cross-coupling reaction between aromatic (or vinyl) halides and boranes, boronic acids, or esters to form biaryls. The topic has been reviewed.<sup>191–197</sup> The results are organized according to the type of catalysts used similar to that for Heck coupling.

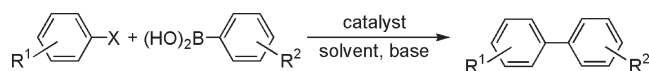
### 5.1. Coupling Reactions Catalyzed by Palladium Nanoparticles

**5.1.1. The Use of Silica Materials as Supports.** Tables 8 and 9, respectively, summarize the results reported for Suzuki couplings with palladium particles supported on amorphous silica and ordered silica materials.

In the synthesis of catalyst Pd-68-SiO<sub>2</sub>, a silylated urea precursor was treated with PdCl<sub>2</sub>(MeCN)<sub>2</sub>, and then the product was used in hydrolysis–polycondensation with various amounts of TEOS (sol–gel process).<sup>198</sup> Three samples with different Pd loadings were applied in Suzuki couplings, giving high and progressively decreasing yields (Table 8, entries 1–3). The initial pale yellow catalysts were observed to darken in successive runs. High-resolution transmission electron microscopy (HR-TEM) showed the formation of nanoparticles (~5 nm), which are stabilized by both the inorganic matrix and the bipyridyl ligand. A significant amount of leached Pd was measured in the product (12 ppm) isolated in a reaction catalyzed with 6.05% Pd-68-SiO<sub>2</sub>. Furthermore, additional conversion (from 47% to 88%) was measured in the hot filtration test, indicative of the involvement of a homogeneous pathway.



Catalyst 0.48% Pd-SiO<sub>2</sub> designed by Tselikhovsky and Blum<sup>68</sup> gave high to excellent product yields in the coupling of iodo- and bromoarenes with phenylboronic acids (80% to >99%). The performance of the catalyst sample in recycling (Table 8, entry 4) is practically identical to that in the Heck reaction (Table 1, entry 1). Catalyst 2.30% Pd-69-SiO<sub>2</sub> was made by treating 3-aminopropyl-functionalized silica gel with Pd(OAc)<sub>2</sub> in ethanol at room temperature for 4 h.<sup>199</sup> A wide range of haloaromatics including chloro derivatives reacted to give fair to high yields (53–99%). The catalyst could be reused 15 times without significant loss of yields (entry 5) with only 0.17 ppm of leached Pd. According to TEM, the catalyst has Pd

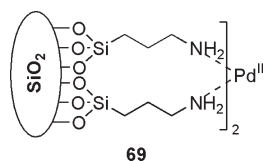
**Table 9.** Suzuki Coupling of Aromatic Halides with Phenylboronic Acids Catalyzed by Palladium Nanoparticles Immobilized on Ordered Silica Materials

entry	R <sup>1</sup>	X	R <sup>2c</sup>	catalyst <sup>a</sup>	reaction conditions: solvent/base/temperature/time	number of reuses	average yields, <sup>b</sup> (%)	ref
1	H	I	4-MeO	5% Pd-MCF-( <b>8a</b> ) (1)	EtOH–H <sub>2</sub> O/Na <sub>2</sub> CO <sub>3</sub> /80 °C/12 h <sup>c</sup>	5	99 (99)	87
2	4-Ac	Br	H	5.7% Pd-SBA15 (0.2)	EtOH–H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /85 °C/5 h	5	98 (99–95)	76
3	H	I	4-MeO	0.53% Pd-SBA15-( <b>70</b> ) (1)	H <sub>2</sub> O/K <sub>3</sub> PO <sub>4</sub> /50 °C/10 h	5	91 (92–89)	200
4	H	Br	H	0.23% Pd-SBA16-( <b>6+7a</b> ) (0.02)	EtOH–H <sub>2</sub> O/K <sub>3</sub> PO <sub>4</sub> /50 °C/5–49 h	10	92 (99–83)	85
5	H	Br	H	0.86% Pd-SBA16-( <b>71a+b</b> ) (0.05)	EtOH–H <sub>2</sub> O/K <sub>3</sub> PO <sub>4</sub> /50 °C/35 min–15 h	7	90.5 (99–77)	201
6	4-Ac	Br	R <sup>3</sup>	1.06% Pd-HS-KIT6(60) (1)	DMF–H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /80 °C/12 h <sup>c</sup>	7	93 (100–74)	202
7	4-Ac	Br	R <sup>3</sup>	1.28% Pd-HS-KIT6(100) (1)		8	93 (100–69)	
8	4-Ac	Br	H	0.037% Pd-PMO-( <b>72</b> ) (10)	H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /reflux/24 h	6	82.5 (95–68)	203
9	4-Ac	Br	H	Pd(OAc) <sub>2</sub> + <b>73cg</b> (0.2)	DMF–H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /110 °C/1 h	5	99 (100–97)	204
10	4-Ac	Br	H	3.24% Pd-Y (0.01)	DMF–H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /RT/0.5 h	15	91 (98–81) <sup>d</sup>	205

<sup>a</sup> Percentage data show Pd loading (wt %) when available; data in parentheses indicate mol % of Pd used. <sup>b</sup> Data in parentheses indicate range of yields.

<sup>c</sup> Under argon atmosphere. <sup>d</sup> Conversions. <sup>e</sup> R<sup>3</sup> = pinacol ester of phenylboronic acid was used.

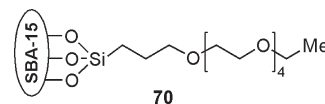
nanoparticles with a typical size of 3 nm located on the surface of silica.



The two perfluoro-tagged catalysts developed by Vallribera et al. discussed above (Heck coupling, section 4.1.1, Table 1, entries 4–7) have been tested in the Suzuki coupling as well.<sup>71</sup> Both catalysts gave good to excellent yields (71–99%) in the coupling of haloarenes with arylboronic acids, tolerating all types of substitution patterns. Even electron-deficient arylboronic acids reacted smoothly. Yields in 15-run recycling studies (entries 6 and 7) varied without showing decreasing tendencies. A TON of 333 000 was measured with 1.22% Pd-FSG-(**2a**) at a Pd loading of 0.001 mol % in the coupling of 4-iodobenzoic acid with 2-tolylboronic acid in four runs. Pd leaching levels in the water phase and in the raw product after the 15th run were found to be 1–2.4 and 3–23 ppb, respectively. Particle size distribution did not change significantly in recycling [ $1.7 \pm 0.3$  and  $3.6 \pm 0.6$  nm for 1.22% Pd-FSG-(**2a**) and 3.47% Pd-SiO<sub>2</sub>-(**3**), respectively].

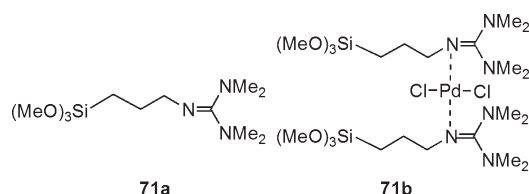
Catalyst 5% Pd-MCF-(**8a**) used in the Heck coupling (section 4.1.1, Table 2, entry 11) proved also to be a highly active and stable catalyst in the Suzuki reaction with a similar amount of Pd loss (<5% after five cycles)<sup>87</sup> (Table 9, entry 1). This catalyst with nanoclusters of 2–3 nm outperformed those having nanoclusters of 4–6 nm and commercial Pd/C in a kinetic study. The scope of the catalyst system encompasses the coupling of iodo- and bromoarenes with a variety of phenylboronic acids to give high to excellent product yields (89–99%). The stability of 5.7% Pd-SBA15 in the Suzuki coupling appears to be better than that observed when applied in the Heck reaction<sup>76</sup> (Table 9, entry 2; compare to Table 2, entry 2) albeit with the use of a higher catalyst loading and studied only in five cycles.

Another catalyst based on SBA-15 has been synthesized by first coating the mesoporous silica with poly(ethylene glycol) accomplished by grafting with the corresponding triethoxysilylated reagent.<sup>200</sup> Treatment of **70** with [Pd(Ph<sub>3</sub>)<sub>4</sub>] gave the final catalyst with a 0.53% metal loading [0.53% Pd-SBA15-(**70**)]. The catalyst gave high yields in the Suzuki coupling of a range of substrates (81–95%) including the reaction of chlorobenzene with 4-methoxyphenylboronic acid (84% yield, 0.1 mol % catalyst, 10 h). Reactions were performed in water without the necessity to exclude air. The observed catalyst performance, high but decreasing yields (entry 3), is characteristic of numerous five-run recycling studies. Pd leaching was not detected. On the basis of TEM images, Pd is assumed to be finely dispersed on the walls of the support material.



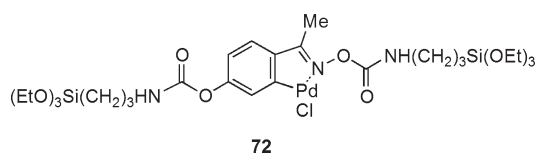
The synthesis and use in the Heck coupling of catalyst 0.23% Pd-SBA16-(**6+7a**) was already discussed above<sup>85</sup> (section 4.1.1, Table 2, entry 8). It is highly effective in the Suzuki coupling of bromoarenes and phenylboronic acid (yields of 87–99%). Significantly increasing reaction times were necessary to maintain high yields in recycling from the fifth cycle (entry 4). X-ray photoelectron spectroscopy (XPS) and TEM analyses of the catalyst sample isolated after the third reuse provided strong evidence that the Pd<sup>2+</sup> complex of the as-prepared catalyst transformed into Pd particles with the concomitant partial collapse of the mesoporous cage-like structure. Still, fine particles (~5 nm) were dispersed in the cages. A total TON of 45 400 for 10 reuses was achieved. It was argued that the stability of the catalyst as compared to that of the silica-supported analogue is attributed to the location of the particles in the isolated nanocages of SBA-16, which prevents the formation of large aggregates. Nevertheless, significant structural changes result in deteriorating catalyst performance (entry 4). Because the mesoporous cage structure collapses, aggregation, that is, formation of larger particles (10–25 nm) of lower activity, follows.

In a recent attempt, Wang and co-workers grafted SBA-16 with both trimethoxysilylated guanidine derivative **71a** and palladium–guanidine complex **71b** in one pot. Instrumental studies indicated that the grafting process had practically no effect on structural characteristics of the mesoporous SBA-16 silica material.<sup>201</sup> The performance of this new catalyst sample [0.86% Pd-SBA16-(**71a+b**)] is similar to that of 0.23% Pd-SBA16-(**6+7a**): bromobenzenes reacted smoothly with phenylboronic acid and substituted derivatives in high yields (79–99%); however, a yield of only 8% was realized in the reaction of chlorobenzene. A TOF of 45 700 h<sup>−1</sup> was determined for bromobenzene. The recycling study, however, proves again the unsatisfactory stability of the catalyst (entry 5) despite the statement by the authors about impressive recyclability.



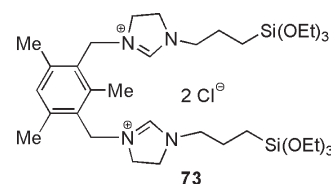
Mesoporous silica with KIT-6 structure was functionalized with (3-mercaptopropyl)trimethoxysilane followed by the adsorption of [Pd(Ph)<sub>3</sub>]<sub>4</sub> dissolved in benzene to give Pd-HS-KIT6(X) catalysts (X denotes the temperature of hydrothermal treatment).<sup>202</sup> XPS analysis of the samples before reaction showed the presence of Pd<sup>2+</sup>, whereas after reaction a new species with lower binding energy appeared. The latter is consistent with the formation of Pd nanoparticles (size range = 10–20 nm), that is, the reduction of the complex during reaction. Among four catalysts evaluated in recycling studies, Pd-HS-KIT6(80) and Pd-HS-KIT6(130) afforded high yields in the first five runs followed by significant drops in the next run (data not shown). 1.06% Pd-HS-KIT6(60) and 1.28% Pd-HS-KIT6(100), in turn, were more stable with decreasing yields only in the seventh and eight cycles (entries 6 and 7, respectively). Pd leaching of about 1–2 ppm was detected with decreasing values after reuses.

Hydrolysis–polycondensation of silylated carboxypalladacycle **72** and TEOS in the presence of CTMABr gave a periodic mesoporous organosilica (PMO) with an MCM-like structure [catalyst 0.037% Pd-PMO-(**72**)].<sup>203</sup> In a kinetic study, the initial activity of the catalyst was shown to be similar to the catalyst prepared by grafting of MCM-41 but significantly higher than that of a sample prepared without the structure-directing agent. Both the hot filtration test and a three-phase test indicated that leached Pd species contribute to the overall catalytic activity. Significant decrease in activity was observed in a recycling experiment (entry 8). Because Pd leaching was not detected, decreasing yields were attributed to drastic changes in catalyst structure: the PMO structure completely collapses, and the carboxypalladacycle complex decomposes during the reaction to form Pd particles.



Pleixats and co-workers synthesized various hybrid silica materials with the use of imidazolium and dihydroimi-

dazolium salts in the presence of 1-cetyl-3-methylimidazolium chloride as cationic surfactant and tested them in Suzuki reactions including recycling studies in the presence of Pd(OAc)<sub>2</sub>.<sup>204</sup> Composite **73g** was prepared by gelification of monomer **73**, whereas cogelification with TEOS gave composite **73cg**. The latter composite has a worm-like mesoporous structure (surface area = 266 m<sup>2</sup> g<sup>−1</sup>), whereas **73g** shows no mesoporosity and has very low surface area (2 m<sup>2</sup> g<sup>−1</sup>). Very high isolated yields were reported for the coupling of 4-bromoanisole and 4-bromoacetophenone with phenylboronic acid (94–100%). 4-Chloroacetophenone, in turn, showed much lower reactivity (34–46% yields, 150 °C, 24 h). In a recycling study with **73g** in the presence of Pd(OAc)<sub>2</sub>, a significant increase in reaction time after the first run was necessary to maintain high yields (data not shown). In contrast, catalyst **73cg** used under identical conditions proved to be more stable (entry 9). An HR-TEM study showed the presence of Pd nanoparticles (mean particle size = 3.1 nm), whereas the hot filtration test indicated that a homogeneous pathway is operative. Furthermore, both catalysts showed rapidly decreasing activities when reused in the coupling of 4-bromoanisole and 4-chloroacetophenone (data not shown).



Pd-Y catalysts with Pd nanoclusters confined in the zeolite cages were prepared by reduction with NaBH<sub>4</sub> of Pd<sup>2+</sup>-exchanged zeolite-Y.<sup>205</sup> Very high efficiency (conversions better than 98%) was reported in Suzuki coupling of bromobenzene derivatives and phenylboronic acid under mild conditions (room temperature in air, 0.5–6 h). Chlorobenzene could also be transformed with a yield of 58.5% (100 °C, 24 h). 3.24% Pd-Y is a robust catalyst in recycling experiments (entry 10) with a cumulative TON of 136 000. The palladium content of the catalyst did not change after use, indicating negligible Pd leaching. Decreasing activity was attributed to passivation of the surface of nanoclusters.

**5.1.2. Palladium Particles Supported on Other Inorganic Materials.** Pd/C is an easy to handle catalyst and can be used under mild conditions in aqueous solutions to induce the Suzuki coupling although with decreasing yields in recycling experiments.<sup>206,207</sup> This general feature is illustrated well in the coupling of 2-iodocyclohexenone with phenylboronic acid carried out by Felpin<sup>208</sup> (Scheme 15). A similar observation has been made in a recent study when the reaction of bromobenzene was conducted over 5% Pd/C in DMF–H<sub>2</sub>O in much shorter reaction time<sup>209</sup> (Table 10, entry 1). This catalyst efficiently induced the coupling of bromobenzenes with 4-substituted phenylboronic acids (yields of 88–97%).

A detailed study has demonstrated the high efficiency of 10% Pd/C in the Suzuki reaction of varied aromatic compounds under appropriately selected reaction conditions.<sup>210</sup> Bromobenzenes with both electron-withdrawing and electron-donating substituents coupled with high efficiency (yields of 78–100%) when applied in MeOH/Na<sub>2</sub>CO<sub>3</sub>, 50% EtOH/Na<sub>2</sub>CO<sub>3</sub>, or 50% isopropyl alcohol/Na<sub>3</sub>PO<sub>4</sub> under argon at



Scheme 15. Suzuki Coupling of 2-Iodocyclohex-2-enone with Phenylboronic Acid over Pd/C

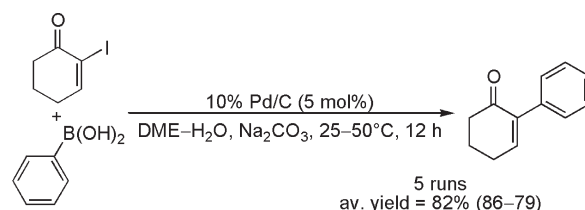
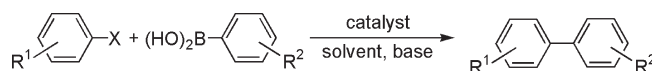


Table 10. Suzuki Coupling of Aromatic Halides with Phenylboronic Acids Catalyzed by Palladium Nanoparticles Immobilized on Other Inorganic Materials



reaction conditions:									
entry	R <sup>1j</sup>	X	R <sup>2</sup>	catalyst <sup>a</sup>	solvent/base/temperature/time	number of reuses	average yields, <sup>b</sup> %	ref	
1	H	Br	4-Pr	5% Pd/C (1)	DMF–H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /75 °C/0.5 h	6	88 (93–80)	209	
2	4-NO <sub>2</sub>	Br	H	10% Pd/C (1.5)	EtOH–H <sub>2</sub> O/Na <sub>2</sub> CO <sub>3</sub> /RT/4–5 h <sup>c</sup>	5	98 (99–97)	210	
3	H	I	H	3% Pd-MWCNT (0.3)	MeOH/NaOAc/reflux/2 h	7	95 (96–94)	213	
4	4-Ac	Br	H	5% Pd/BaSO <sub>4</sub> (1)	PEG–H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /80 °C/24 h	6	83 (95–67)	214	
5	H	Br	4-Me	2% Pd/CeO <sub>2</sub> (1)	EtOH–H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /25 °C/9 h	11	98.5 (99.9–97)	215	
6	R <sup>3</sup>	I	R <sup>4</sup>	0.4% Pd-ZrO <sub>2</sub> (0.1)	H <sub>2</sub> O/TBAOH/90 °C/14 h	5	— <sup>d</sup>	103	
7	R <sup>5</sup>	Br	R <sup>6</sup>	0.4% Pd-ZrO <sub>2</sub> (0.1) <sup>e</sup>		5	— <sup>d</sup>		
8	4-NO <sub>2</sub>	Cl	H	10.53% Pd-MgO (3)	DMAc/K <sub>3</sub> PO <sub>4</sub> /130 °C/2–6 h <sup>cf</sup>	5	n.r. (90–85)	100	
9	H	I	H	10.53% Pd-MgO (0.5)	H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /RT/5–6 h	5	n.r. (95–92)		
10	H	I	4-Me	5% Pd-KF/Al <sub>2</sub> O <sub>3</sub> (47)	100 °C/4 h <sup>g</sup>	6	94 (96–93)	216	
11	H	I	4-Me	5% Pd-KF/Al <sub>2</sub> O <sub>3</sub> (47)	70 °C/2 min <sup>g,h</sup>	6	81.5 (84–76)		
12	H	Cl	H	10.1% Pd-LDH (1)	dioxane–H <sub>2</sub> O/KF/100 °C/10 h <sup>c</sup>	5	90.5 (91–89) <sup>i</sup>	105	
13	H	Br	H	5% Pd-DS-LDH (0.5)	DMF–H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /80 °C/5 h	7	82 (99–60)	217	
14	H	Br	H	Pd-Fe <sub>3</sub> O <sub>4</sub> (0.5)	DMF–H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /80 °C/0.5 h	7	82 (95–60)	218	
15	H	I	H	7.26% Pd-DOPA-pine-Fe <sub>2</sub> O <sub>3</sub> (3.4)	DMF–H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /100 °C/10 min <sup>h</sup>	5	95 (97–94)	97	
16	H	Br	H	2.1% Pd-Fe <sub>2</sub> O <sub>3</sub> -(74) (1)	dioxane/Cs <sub>2</sub> CO <sub>3</sub> /80 °C/15 h	7	94 (>99–92)	219	
17	H	Br	H	8.68% Pd-PEI-Fe <sub>3</sub> O <sub>4</sub> (0.816)	MeOH/K <sub>3</sub> PO <sub>4</sub> /50 °C/18 h	5	94 (95–93)	220	
18	H	Cl	H	8.68% Pd-PEI-Fe <sub>3</sub> O <sub>4</sub> (0.816)	MeOH/K <sub>3</sub> PO <sub>4</sub> /60 °C/24 h	5	93 (94–92)		
19	4-Ac	Br	H	0.12% Pd-HAP (0.3)	H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /100 °C/4 h <sup>f</sup>	5	93 (94–92)	221	

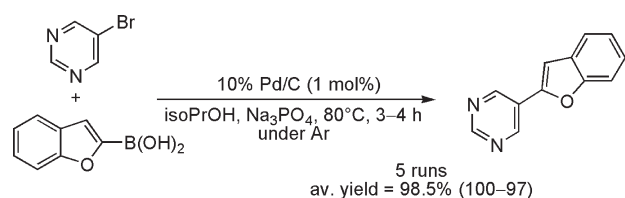
<sup>a</sup> Percentage data show Pd loading (wt %) when available; data in parentheses indicate mol % of Pd used. <sup>b</sup> n.r. = not reported. Data in parentheses indicate range of yields. <sup>c</sup> Under inert atmosphere. <sup>d</sup> See footnotes. <sup>e</sup> The catalyst recovered from previous runs (entry 6) was used. <sup>f</sup> In the presence of TBAB. <sup>g</sup> KF is added in every cycle. <sup>h</sup> Under microwave irradiation. <sup>i</sup> Conversion. <sup>j</sup> R<sup>3</sup> and R<sup>4</sup>: Successive reactions with R<sup>1</sup> = R<sup>2</sup> = H (90%); R<sup>1</sup> = H, R<sup>2</sup> = 4-MeO (88%); R<sup>1</sup> = 4-MeO, R<sup>2</sup> = H (75%); R<sup>1</sup> = Me, R<sup>2</sup> = H (84%); R<sup>1</sup> = 4-NO<sub>2</sub>, R<sup>2</sup> = H (78%). R<sup>5</sup> and R<sup>6</sup>: Successive reactions with R<sup>1</sup> = R<sup>2</sup> = H (75%); R<sup>1</sup> = H, R<sup>2</sup> = 4-MeO (88%); R<sup>1</sup> = 4-AcO, R<sup>2</sup> = H (90%); R<sup>1</sup> = 4-MeO, R<sup>2</sup> = H (40%); R<sup>1</sup> = H, R<sup>2</sup> = Me (79%).

room temperature. Aryl triflates gave coupling products in similar high yields (50% EtOH/Na<sub>2</sub>CO<sub>3</sub>), and styrylboronic acids also reacted successfully (yields of 80–91% in 50% isopropyl alcohol/Na<sub>3</sub>PO<sub>4</sub>). Trace amounts of homocoupling products of the corresponding arylboronic acids were also detected. The reaction of a few substrates did not go to completion (1-bromonaphthalene, 4-bromoanisole), and 2,6-dimethylbromobenzene, as expected, was unreactive. Wet-type 10% Pd/C containing 50 wt % of water could be used with approximately the same results under aerobic conditions. Consistently high yields were achieved by performing recycling reactions in aqueous ethanol but with a prolonged

reaction in the fifth run (entry 2). In the hot filtration test, only a conversion of 1% was found, and no leached Pd was detected. Köhler and Lysén<sup>211</sup> have observed even larger drops in yields in the third and fourth reuses (from yields of 99% to 25–47%). Moreover, I<sub>2</sub> as additive had to be used to partially reoxidize Pd to Pd<sup>2+</sup> to restore activity. They studied, however, the more demanding reaction of 4-chloroacetophenone with phenylboronic acid at a lower Pd loading (0.2 mol %) as compared to those used in entries 1 and 2.

Sajiki and co-workers have shown 10% Pd/C to be an efficient catalyst to couple substituted bromobenzenes and heteroaryl bromides with substituted phenylboronic acids and heteroarylboronic

### Scheme 16. Suzuki Coupling of 5-Bromopyrimidine with 2-Benzofurylboronic Acid over Pd/C



acids in aqueous isopropyl alcohol under mild conditions.<sup>212</sup> In most cases, products were isolated in good to excellent yields (72–97%). Exceptions are 3- and 4-bromopyridine (27% and 59%) and 3-bromoquinoline (24%), whereas 3- and 4-pyridinylboronic acid were unreactive. In heteroaryl–heteroaryl couplings, the use of nonaqueous isopropyl alcohol proved to be more suitable. High yields were found in a five-run recycling study (Scheme 16). Kinetic investigation and Pd leaching test clearly indicated the involvement of a release–capture mechanism.

The reduction of  $\text{Pd}^{2+}$  hexafluoroacetate (150 atm  $\text{H}_2$ , 80 °C) dissolved in supercritical  $\text{CO}_2$  in the presence of multi-walled carbon nanotube (MWCNT) was used to synthesize 3% Pd-MWCNT containing spherical particles with narrow size distribution.<sup>213</sup> Various activated iodobenzenes and bromobenzenes gave excellent product yields (92–95%). Only minor changes in the activity of the catalyst in recycling experiments performed in air were observed (Table 10, entry 3) with the formation of only a few large particles (40 nm) detected after the sixth reuse.

Activity characteristics in recycling studies of Pd supported on  $\text{BaSO}_4$  applied in a PEG–water mixture<sup>214</sup> (entry 4) are similar to those of Pd/C. Recycling was made by charging the reaction mixture with new educts without separating the catalyst. Because the reaction medium after catalyst removal by filtration gave a yield of 74%, it was concluded that active species leached are involved in the transformation. Catalyst 2% Pd/ $\text{CeO}_2$  used in the coupling of a range of bromoarenes, in turn, displayed high durability in a longer recycling study<sup>215</sup> (entry 5). Interestingly, metallic Pd nanoparticles could not be detected by HR-TEM. This may be explained by the very small size of particles (<2 nm) or having PdO particles covered by a thin Pd shell.

The results in the Suzuki coupling with catalyst 0.4% Pd-ZrO<sub>2</sub> are similar to those found in its use in Heck coupling<sup>104</sup> (section 4.1.2, Table 3, entries 11 and 12). The yields testify to high efficiency in the coupling of iodobenzenes and phenylboronic acids in the first five cycles (entry 6). The successive use of the same catalyst sample in the coupling of bromobenzenes shows the usual activity pattern of substituted derivatives. A comparison of the yields with bromobenzene in the sixth and tenth rounds (75% vs 79%) proves unequivocally the high efficiency and excellent stability of the catalyst (entry 7).

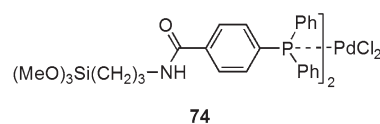
The Pd-MgO catalyst discussed earlier (Heck reaction, section 4.1.2, Table 3, entries 7–9) composed of Pd nanoparticles stabilized by nanocrystalline MgO exhibited excellent catalyst performance in coupling reactions with arylboronic acids: yields were high in the coupling of iodo- and bromoarenes (90–95%), whereas fair to high yields were measured in the reaction of chloroarenes (45–90%).<sup>100</sup> The yields in recycling studies were high but decreased slightly in five runs (entries 8 and 9). Noteworthy, however, is the result displayed in the coupling of 4-chloronitrobenzene (entry 8).

Kabalka and co-workers used a mixture of KF on alumina and palladium black (submicrometer powder) to carry out solventless Suzuki reactions (catalyst 5% Pd-KF/ $\text{Al}_2\text{O}_3$ ).<sup>216</sup> Yields in the coupling of iodobenzene, bromobenzene, and chlorobenzene with *para*-tolylboronic acid are 99%, 60%, and 5%, respectively. Results in the reaction of alkenyl halides and alkyl- and alkenylboronic acids varied widely (yields of 0–66%). Microwave-assisted coupling reactions gave similar results. Catalyst performance in recycling was better under thermal condition (entry 10) than using microwave heating (entry 11).

The nanopalladium catalyst supported on LDH studied in the Heck coupling (section 4.1.2, Table 3, entries 13 and 14) gave good to high yields of biaryls in the coupling of chloroarenes and arylboronic acids (60–93%).<sup>105</sup> Good yields were reported for the reaction of chlorobenzene with phenylboronic acid (entry 12). A layered double hydroxide with embedded dodecyl sulfate (DS) anions treated with  $\text{Na}_2[\text{PdCl}_4]$  was subjected to reduction with ascorbic acid to provide catalyst 5% Pd-DS-LDH.<sup>217</sup> According to TEM, the surface of LDH is covered with Pd clusters (diameter = 2–2.5 nm). Because of the increased interlayer spacing between hydrophobic LDH layers, diffusion of organic molecules is believed to be favored. The limited interlayer space, at the same time, may also hinder the growth of Pd particles. Haloarenes displayed high reactivity to afford high yields under mild conditions in the coupling with phenylboronic acid (85–96%; 4-chloronitrobenzene = 49%). In the recycling study, high yields dropped significantly in the last two runs (entry 13).

$\text{PdCl}_4^{2-}$  immobilized on superparamagnetic cationic  $\text{Fe}_3\text{O}_4$  colloids through electrostatic interaction followed by reduction with ascorbic acid results in the formation of Pd clusters.<sup>218</sup> The catalyst afforded high yields in the coupling of bromoarenes with phenylboronic acid (85–96%). It could be easily recycled by a permanent magnet providing high product yields in Suzuki coupling. Yields, however, decreased considerably with repeated uses (entry 14). Catalyst 7.26% Pd-DOPA-pine- $\text{Fe}_2\text{O}_3$ , an active and stable catalyst in the Heck coupling (section 4.1.2, Table 3, entry 4), exhibited similar features in both the Suzuki coupling of iodo- and bromoarenes with varied arylboronic acids (yields of 96–92%), in general, and the recycling of iodobenzene and phenylboronic acid (entry 15).<sup>97</sup>

Magnetic nanoparticles (~10 nm) coated with a dense silica layer were functionalized by grafting with silylated complex **74**.<sup>219</sup> Palladium species were shown to be uniformly dispersed over the nanocomposite support. Catalyst 2.1% Pd- $\text{Fe}_2\text{O}_3$ -**74** affords high yields in the coupling of iodo- and bromoarenes with phenylboronic acid (73 to >99% yields). Low yields were found for *ortho*-substituted derivatives and chlorobenzene. A slight leaching was detected in the hot filtration test. TEM analysis of the recovered catalyst after the first run of the recycling study revealed that  $\text{Pd}^{2+}$  ions underwent reduction. This and the leaching are assumed to be responsible for a drop of high initial yields in reuses (entry 16).



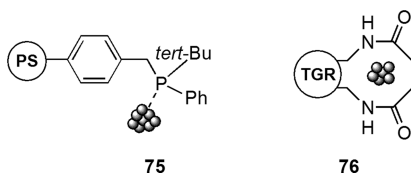
Another similar, magnetically separable catalyst was generated by using citrate-modified  $\text{Fe}_3\text{O}_4$  nanoparticles ( $10 \pm 0.5$  nm) followed by functionalization with poly(ethylene imine) (PEI).

Pd ions entrapped by surface amino groups after treatment with  $\text{Na}_2[\text{PdCl}_4]$  followed by reduction gave 8.68% Pd-PEI- $\text{Fe}_3\text{O}_4$  with high metal loading.<sup>220</sup> XRD and XPS studies indicate a bimodal distribution of Pd particles ( $>10$  nm and 5–7 nm). All haloarenes studied gave good to high yields (75–95%) in coupling with phenylboronic acid. The catalyst collected by a magnet for reuse retained high activity in five runs (entries 17 and 18). Pd leaching was negligible ( $\sim 0.03\%$ ), and the morphology of the catalyst and the average crystallite size remained almost unchanged after repeated uses (2–6 nm).

Supported Pd particles (average size = 20 nm) were prepared by treating hydroxyapatite and  $\text{Pd}(\text{OAc})_2$  in ethanol followed by reduction with hydrazine hydrate (catalyst 0.12% Pd-HAP).<sup>221</sup> The catalyst gave high yields (78–95%) in the coupling of aryl bromides with arylboronic acids including heteroaryl derivatives in the presence of TBAB in aqueous solution. Yields were also high in a recycling experiment (entry 19). Product 4-acetylbi-phenyl was isolated in a yield of 92% in a scale-up study (50 mmol of 4-bromoacetophenone, 12 g of catalyst, 250 mL of  $\text{H}_2\text{O}$ , 7.5 h). No additional studies with respect to Pd leaching and the nature of active species were reported.

**5.1.3. Polymer-Supported Palladium Particles.** An easy and straightforward access to generate stabilized Pd nanoparticles is the thermal decomposition of  $\text{Pd}(\text{OAc})_2$  in water in the presence of polystyrene.<sup>222</sup> The resultant black material (catalyst 26.6% Pd-PS) used successfully in Suzuki coupling contains uniform particles ( $2.3 \pm 0.3$  nm) and shows no deactivation in 10 runs (Table 11, entry 1). Pd leaching was not detected, and the catalyst could be recovered quantitatively. It gave high yields in the coupling of bromoarenes with arylboronic acids (89–99%), and a yield of 99% was achieved in the reaction of 4-chloroacetophenone and 4-methylphenylboronic acid in a prolonged reaction (12 h).

Becht and co-workers have reported the synthesis of an air- and moisture-stable Pd catalyst (0.10% Pd-75-PS) by functionalizing the Merrifield resin with *tert*-butylphenylphosphano groups followed by treatment with  $[\text{Pd}(\text{PPh}_3)_4]$ .<sup>223</sup> It was shown to provide high yields (61–98%) in the Suzuki coupling of activated aromatic chlorides with arylboronic acids in toluene containing traces of water (0.3%).<sup>224</sup> Similar efficiency was found when the catalyst was reused in seven runs (entry 2). A TEM study showed a very small amount of Pd crystallites in the pristine catalyst, whereas they became abundant in a very short reaction (diameters up to 15 nm). No further changes were observed, however, even after seven uses. The hot filtration test gave only negligible additional conversion after 20 h (1%) with a very low amount of Pd leaching ( $<0.1\%$ ).

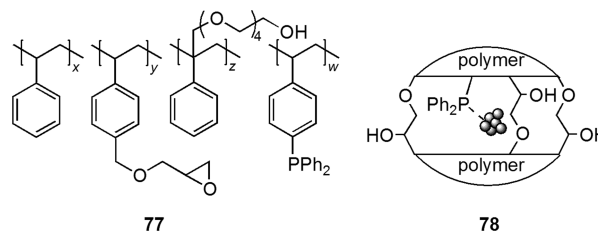


Aminomethylated TentaGel resin (TGR, see structure 37) when treated with  $\text{Pd}(\text{OAc})_2$  in toluene traps the complex, which is then transformed to Pd particles upon reduction with hydrazine hydrate. Subsequent cross-linking with succinyl chloride results in the formation of catalyst 3.83% Pd-76-TGR with resin-captured palladium particles ( $7.4 \pm 1.4$  nm).<sup>225</sup> Coupling

products of bromoarenes and arylboronic acids were isolated in medium to high yields (62–99%). 4-Chloroacetophenone and 4-chlorotoluene, however, reacted in very low yields (25% and 14%, respectively). High, stable yields are observed in recycling (entry 3) with minimal Pd leaching (9 ppb) and without noticeable change in particle size. Marginal activity (a conversion of 4%) was detected in a three-phase test with polymer-bound 4-bromobenzamide. These results indicate the robust nature of the catalyst.

The performance of catalyst 5.3% Pd-33-PS in Heck coupling reactions and recycling was already discussed<sup>151</sup> (section 4.2.2, Table 6, entry 4). A comparison with data shown in entry 4 (Table 11) indicates similar features in Suzuki coupling.

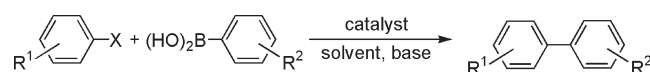
Phosphanated copolymer 77 ( $x:y:z:w = 72:12:5:11$ ) was used by Kobayashi and co-workers to immobilize Pd through reaction with  $[\text{Pd}(\text{PPh}_3)_4]$ , microencapsulation, and cross-linking the polymeric chains.<sup>226</sup> The polymer-incarcerated catalyst 0.36% Pd-PI-(78) has extremely small Pd clusters (1 nm) dispersed on the polymer surface and in the bulk. Substituted bromobenzenes including bulky substrates (2-bromonaphthalene, 1-bromo-2-methylnaphthalene) were converted with phenylboronic acid to the corresponding coupling products in high to excellent yields (84–100%). It also afforded high yields in recycling reactions (entry 5), showing only a small degree of aggregation of the particles. The hot filtration test and X-ray fluorescence (XRF) analysis of the reaction mixture after catalyst removal did not show detectable Pd leaching. This was attributed to the strong coordination by both the aromatic  $\pi$  electrons and the phosphane groups to the Pd clusters without adversely affecting catalytic activity.



Zhang and co-workers have reported the synthesis and application in the Suzuki coupling of a series of catalysts consisting of a polystyrene (PS) core and Pd particles embedded in an outer shell layer. The prepared colloid catalysts were kept in water and used as such. The core-shell nanospheres made by copolymerizing styrene with 4-vinylpyridine (VPy) were treated with  $\text{PdCl}_2$  and then reduced with  $\text{NaBH}_4$  to form catalyst Pd-PS-co-PVPy with Pd particles of an average particle size of 3.8 nm.<sup>227</sup> Excellent yields were found for activated iodo- and bromoarenes in aqueous solution (yields of 90–99%). Difficulties were, however, experienced with 4-bromophenol and chloroarenes (yields of 6–14%). The catalyst in recycling showed outstanding robustness with excellent and steady yields (entry 6) without Pd leaching and without any activity of the isolated liquid phase after catalyst separation.

A similar catalyst prepared by following the above protocol has a pH-responsive chelating shell. Copolymerizing styrene with glycidyl methacrylate (GMA) and iminodiacetic acid (IDA) provided catalyst Pd-PS-co-PGMA-IDA (average particle size =  $\sim 6$  nm).<sup>228</sup> The catalyst is dispersed in water at pH = 3–11 and exhibits excellent activity in the coupling of varied haloarenes and



**Table 11. Suzuki Coupling of Aromatic Halides with Phenylboronic Acids Catalyzed by Polymer-Supported Palladium Nanoparticles**

entry	R <sup>1</sup>	X	R <sup>2</sup>	catalyst <sup>a</sup>	reaction conditions:	number of reuses	average yields, <sup>b</sup> (%)	ref
					solvent/base/temperature/time			
1	H	Br	4-Me	26.6% Pd-PS (1.5)	H <sub>2</sub> O/KOH/80 °C/1 h	10	99 (99)	222
2	4-Ac	Cl	H	0.10% Pd-75-PS (0.4)	toluene–H <sub>2</sub> O(0.3%)/CsF/reflux/20 h	7	98 (99–95)	224
3	4-Ac	Br	H	3.83% Pd-76-TGR (10)	H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /80 °C/4 h	6	98 (99–97)	225
4	H	I	H	5.3% Pd-33-PS (0.5)	DMF–H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /80 °C/5 h	5	98.5 (100–97)	151
5	4-Ac	Br	H	0.36% Pd-PI-(78) (5)	toluene–H <sub>2</sub> O/K <sub>3</sub> PO <sub>4</sub> /reflux/4 h	5	99.5 (100–98)	226
6	4-Ac	Br	H	Pd-PS-co-PVPy (0.25)	H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /90 °C/4 h <sup>c</sup>	5	99 (99)	227
7	4-Ac	Br	H	Pd-PS-co-PGMA-IDA (0.1)	H <sub>2</sub> O/Et <sub>3</sub> N/90 °C/2 h <sup>c</sup>	5	98.5 (99–97)	228
8	H	I	H	Pd-12-PVC-DETA (0.25)	DMF–H <sub>2</sub> O/NaHCO <sub>3</sub> /90 °C/4–10 h	8	96 (100–93)	231
9	4-NO <sub>2</sub>	I	H	1.14% Pd-79 (1)	95% EtOH/K <sub>2</sub> CO <sub>3</sub> /reflux/0.5 h	6	93 (98–80)	232
10	4-MeO	Br	H	Pd-80-PPIL (1)	EtOH–H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /80 °C/5 h <sup>c</sup>	9	92 (96–89)	233
11	4-Ac	Cl	H	10.9% Pd-PA (0.05)	H <sub>2</sub> O/NaOH/80 °C/4 h	10	94 (99–89)	234
12	Br	Br	H	0.35% Pd-Amberlite (0.04)	DMF/Na <sub>2</sub> CO <sub>3</sub> /110 °C/5 h	5	82 (84–80)	235
13	4-Ac	I	H	15.5% Pd-chitosan (0.5)	H <sub>2</sub> O/K <sub>3</sub> PO <sub>4</sub> /150 °C/5 min <sup>d,e</sup>	5	93.5 (94–93)	236
14	4-NO <sub>2</sub>	I	H	6.28% Pd-81-EDA-cell (0.6)	95% EtOH/K <sub>2</sub> CO <sub>3</sub> /reflux/0.5–5 h	6	98 (99–95)	237
15	H	I	3-Me	Pd-polymer micelles (1)	MeOH/KOH/20 °C/20 h <sup>f</sup>	5	83.5 (85–82)	238
16	3-COOH	I	H		H <sub>2</sub> O/KOH/20 °C/10 h <sup>g</sup>	5	91 (94–87)	
17	4-OH	I	H	Pd-(82) (0.2)	dioxane/K <sub>3</sub> PO <sub>4</sub> /reflux/20–48 h	9	91.5 (98–75)	239
18	H	I	H	Pd-Sn-dendr1 (n.r.)	toluene/K <sub>2</sub> CO <sub>3</sub> /reflux/4 h	10	95 (95)	240
19	H	I	H	Pd-Sn-dendr2 (n.r.)	MeOH/K <sub>2</sub> CO <sub>3</sub> /reflux/2 h	10	99 (99)	
20	4-Ac	Br	H	3.3% Pd-dendr (1)	H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /80 °C/4 h	6	90 (94–87.5)	241
21	H	I	Me	Pd-dendr-SBA15 (0.5)	EtOH–H <sub>2</sub> O/K <sub>3</sub> PO <sub>4</sub> /100 °C/30 min <sup>e</sup>	5	97 (99–95)	242
22	4-Ac	Br	H	1.28% Pd-14-PS (0.01)	MeOH–H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /60 °C/1.5–4 h	6	94 (99–90)	243
23	4-Ac	Br	H	1.28% Pd-14-PS (0.01)	H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /reflux/0.5–3 h	7	97 (99–94)	
24	H	CH <sub>2</sub> Cl	H	1.28% Pd-14-PS (0.1)	acetone–H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /reflux/1–4 h <sup>d</sup>	6	93 (99–89)	

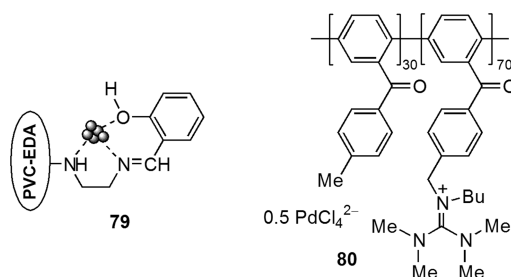
<sup>a</sup> Percentage data show Pd loading (wt %) when available; data in parentheses indicate mol % of Pd used. <sup>b</sup> n.r. = not reported. Data in parentheses indicate range of yields. <sup>c</sup> Under inert atmosphere. <sup>d</sup> In the presence of TBAB. <sup>e</sup> Under microwave irradiation. <sup>f</sup> Catalyst separated by centrifugation.

<sup>g</sup> Catalyst separated by ultrafiltration.

phenylboronic acid at 90 °C (yields of 94–99%). Chlorobenzoic acid, in turn, reacted only in the presence of TBAB (50% yield, 24 h). At room temperature, only hydrophilic substrates showed high reactivity. The bases used were Et<sub>3</sub>N and K<sub>2</sub>CO<sub>3</sub> for hydrophobic and hydrophilic substrates, respectively. The catalyst gave high and stable yields in recycling (entry 7). The aqueous phase containing the catalyst was charged with the substrates and the base after extraction and used directly in the next run. No activity was detected in a filtration test, and Pd was not found in the filtrate (detection limit = 0.03 ppm). Another catalyst made by an analogous method<sup>229</sup> and a raspberry-like colloid-supported sample prepared by using block polymer micelles,<sup>230</sup> in turn, proved to be less stable in a five-run recycling experiment.

Pd-12-PVC-DETA (see also Heck reaction, section 4.1.3, Table 4, entry 5) has spherical Pd particles with a uniform particle size distribution of 15 nm. It can easily be recovered and affords slightly decreasing yields in successive runs despite significantly prolonged reactions<sup>231</sup> (entry 8). The catalyst has a limited use because low yields were found for 4-iodotoluene (56%) and 4-iodoanisole (53%) even after 8 h. PVC modified with ethylenediamine served to support a Schiff base used in the synthesis of catalyst 1.14% Pd-79.<sup>232</sup> Nanoparticles (~40 nm) are shown by TEM to be distributed on the polymer surface. The

significant drop of the yield in the sixth run (entry 9) was attributed to the formation of large aggregates (~200 nm). Only iodo- and bromoarenes could be coupled with this catalyst (product yields of 40–99%).



Catalyst Pd-80-PPIL has been prepared by grafting a functionalized rigid poly(*para*-phenylene) with a pentaalkylguanidinium ionic liquid. Reduction with NaBH<sub>4</sub> forms Pd particles uniformly embedded into the surface IL layer of the nonswelling microspheres.<sup>233</sup> Iodo- and bromobenzenes reacted smoothly with boronic acid and derivatives to give products in high to excellent yields under mild conditions (71–100%), whereas

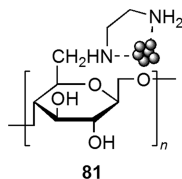
chlorobenzene gave a yield of 36% in the presence of TBAOH as base. The heterogeneous nature of the reaction is based by the authors on the result of the hot filtration test and the extremely low Pd leaching (9 ppb). TEM, XRD, and XPS did not show any change in particle size distribution ( $3.1 \pm 1$  and  $4 \pm 1$  nm by TEM and XRD, respectively). The catalyst proved to be highly efficient with gradually decreasing yields in recycling experiments (entry 10).

Diaconescu and co-workers fabricated the exceptionally active catalyst 10.9% Pd-PA by depositing Pd particles onto polyaniline nanofibers of high surface area and high porosity by mixing the polymer with  $\text{Pd}(\text{NO}_3)_2$ .<sup>234</sup> It gave high yields (71–97%) in the coupling of varied chloroarenes including 4-chloropyridine and dichloropyridines with phenylboronic acids in aqueous solution (0.05 mol % of catalyst, 4 equiv of NaOH as base, 80–100 °C, 2–8 h). Even 1,4-difluorobenzene reacted to afford triphenyl in 60% yield under optimized conditions (0.1 mol % of catalyst, 100 °C, 24 h). A 40% yield was measured in a hot filtration test, but no activity was found in a reuse indicative of the stabilizing effect of polyaniline nanofibers. The catalyst exhibited high and slowly decreasing yields in 10 consecutive runs (entry 11). Pd leaching was determined to be in ppm levels, and the bimodal particle size distribution of the catalyst (2 nm and 50–100 nm) did not change after two cycles.

When the formate form of Amberlite IRA 900 was treated with  $\text{Pd}(\text{OAc})_2$  or  $\text{Na}_2[\text{PdCl}_4]$ , the resin beads turned black to give a Pd-Amberlite catalyst.<sup>235</sup> XPS indicated that the great majority of  $\text{Pd}^{2+}$  underwent reduction to form  $\text{Pd}^0$  particles. The Heck, Suzuki, and Sonogashira reactions were studied with varied results. The catalyst displayed high stability when reused in the coupling of 1,4-dibromobenzene with phenylboronic acid in five consecutive runs to give 1,1':4',1''-terphenyl in good yields (entry 12). Significant leaching of Pd after the first use was detected by monitoring the Pd/N ratio, which is the possible reason for slow activity decrease.

The water-compatible biopolymer chitosan (partially deacetylated chitin) was used in the preparation of the bead-type catalyst 15.5% Pd-chitosan.<sup>236</sup> The stability of the polymer was increased by cross-linking with diglycidyl ether PEG. Anchoring  $\text{Pd}(\text{OAc})_2$  to the surface amino groups followed by reduction with  $\text{NaBH}_4$  resulted in the formation of nanoparticles of 3–10 nm in diameter. The catalyst is very effective when used under microwave conditions in the presence of TBAB (entry 13) with palladium leaching of 3.3% after the fifth use. It gives high yields in the coupling of iodo- and bromoarenes (70–98%) but displays low activity in the coupling of 4-chloroacetophenone (40%).

Ethylenediamine-functionalized cellulose treated with  $\text{PdCl}_2$  in ethanol gave 6.28% Pd-81-EDA-cell.<sup>237</sup> The catalyst has spherical nanoparticles (10–20 nm), it is insensitive to air and moisture, works under mild conditions, and gives high product yields in the coupling of activated iodobenzenes with boronic acid and derivatives (70–98%). Yields, however, are much lower in the coupling of other compounds, whereas chloroarenes are unreactive. High yields could be attained in a six-run recycling study (entry 14).

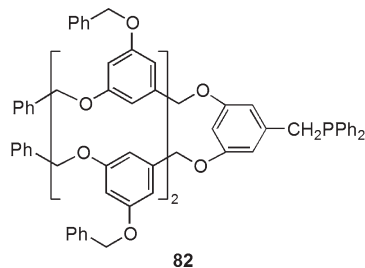


81

Beletskaya and co-workers have developed a catalyst system consisting of a water-soluble micelle formed by

polystyrene–poly(ethylene oxide) copolymer, the surfactant *N*-cetylpyridinium chloride, and Pd nanoparticles prepared by the reduction of  $\text{K}_2[\text{PdCl}_4]$  with  $\text{NaBH}_4$ .<sup>238</sup> This system was studied in the Suzuki reaction in water and methanol. Performing the reaction of iodobenzene with 3-tolylboronic acid in methanol, the Pd nanoparticles can be separated by centrifugation and reused with a minimal loss of activity (entry 15). In the reaction of 3-iodobenzoic acid with phenylboronic acid in water, however, a part of the catalyst could not be separated by centrifugation, and the activity decreased sharply with repeated uses (data not shown). It was also observed that the separated catalyst (about 75% of the load) gave a yield of 35% as compared to a 86% yield using the separated solution (containing 25% of Pd). Furthermore, the latter fraction of the catalyst exhibits the same activity in successive runs. TEM analysis revealed that the precipitated catalyst contains aggregated micelles with Pd nanoparticles of increased size (2.4–3.1 nm versus 1.7 nm of the original catalyst). In contrast, the particle size of the catalyst remained in solution is 1.9 nm. No such phenomena were observed when the catalyst was separated by ultrafiltration capable of removing all catalyst particles (entry 16). Additional studies revealed that both centrifugation and the organic iodide contributed to catalyst aggregation.

The reduction of  $\text{Pd}(\text{acac})_2$  with hydrogen (25 atm, 60 °C, 18 h) in the presence of polyaryl ether dendritic phosphane ligands gave Pd nanoparticles stabilized by phosphane oxide formed during the synthesis process.<sup>239</sup> At a Pd/ligand ratio of 1, Pd black was formed, which could be dissolved in solvents of low polarity but was insoluble in methanol and ethanol. This gave a possibility for catalyst separation and recycling by solvent precipitation. The air-stable catalyst synthesized using ligand **82** [catalyst Pd-(**82**)] tested in the recycling study has a mean particle diameter of 3.2 nm. High initial yields dropped significantly in the fifth run to 79%, but yields could be increased again by prolonged reactions (entry 17). Recycling was made by removing the solvent dioxane under reduced pressure and then adding methanol to the residue, which results in the precipitation of the catalyst. Leaching in the second and third runs was 8.1 and 3.6 ppm, respectively. The nanoparticles in the recovered catalyst were shown to have an irregular shape and increased size (10 nm) because of aggregation. This and the high product yield in the coupling between dendritic bromobenzene and 4-acetylphenylboronic acid indicated the involvement of soluble species in the catalytic process, which are deposited to the surface of the nanoparticles (release–capture mechanism). The catalyst showed good activity toward various haloarenes including deactivated or sterically hindered *ortho*-substituted chlorobenzenes (yields of 80–100%). TON values up to 65 000 could be achieved with this catalyst.



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Chandrasekhar and co-workers generated Pd nanoparticles with an average size of ~3 nm by the reduction of  $\text{PdCl}_2$  with  $\text{NaBH}_4$  in the presence of a phosphane-rich hexameric

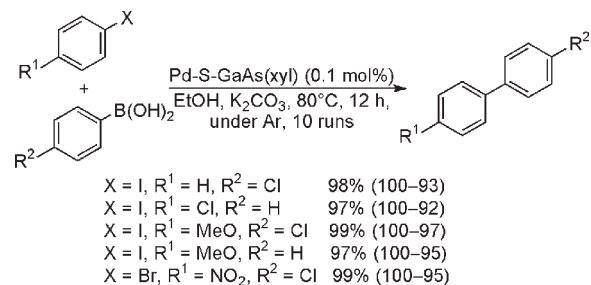
organostannoxane cage acting as a dendrimer-like ligand (Pd-Sn-dendr1).<sup>240</sup> The formed nanocomposite can be dispersed in various solvents and successfully reused after drying and redissolving. Recycling was made by adding fresh reactants to the reaction mixture after completion of the first cycle. High yields were sustained in 10 runs (entry 18). Agglomeration of particles ( $\sim 45$  nm) detected after the first run had no effect on catalytic activity. Catalyst Pd-Sn-dendr2 was made by treating Pd-Sn-dendr1 in methanol/chloroform for 6 h, then kept at  $-25$  °C for one day after adding hexane to remove the excess organostannoxane cage. Palladium particles then were separated by filtering through a PTFE [poly(tetrafluoroethylene), Teflon] membrane filter. The performance of this latter catalyst sample was very similar (entry 19) without the change in particle size distribution (average size = 4.3 nm). A wide variety of haloaromatics including chloro derivatives, bulky substrates, and heteroaromatics afforded medium to high product yields (67–99%).

Ogasawara and Kato used polymerization-induced phase separation to synthesize catalyst 3.3% Pd-dendr.<sup>241</sup> A generation-3 poly(amidoamine) dendritic monomer (PAMAM) was treated with a radical initiator (AIBN) in the presence of ethylene glycol dimethacrylate and Pd(OAc)<sub>2</sub>, in the solvent mixture dimethylformamide–diethylene glycol dimethyl ether. PAMAM serves as ligand for complexation of Pd<sup>2+</sup> ions, and it stabilizes Pd particles (diameter =  $\sim 2.0$  nm). The exact mechanism of the reduction is unclear, but the growing polymer chains are assumed to take part in the process. High yields could be achieved in the reaction of substituted bromobenzenes and boronic acids under mild conditions in aqueous solution (81–96%). The microporous polymer formed has high specific surface area and hinders Pd leaching: a loss of 0.27% of Pd was determined, and a conversion of 3.1% was measured in the hot filtration test. The catalyst proved to be effective in recycling (entry 20) with a drop of yield in the fifth run without noticeable structural changes. Furthermore, TON numbers close to  $10^5$  could be realized at a catalyst loading of 0.00001 mol % in the coupling of 4-bromoacetophenone and phenylboronic acid.

In a report by Cao and co-workers, a generation-4 dendritic PAMAM was planted in the channels of SBA-15. Treatment of the material thus prepared with K<sub>2</sub>[PdCl<sub>4</sub>] resulted in the formation of monodisperse Pd particles evenly distributed in the channels.<sup>242</sup> Catalyst Pd-dendr-SBA15 made by using a Pd<sup>2+</sup>/dendrimer molar ratio of 10 (particle size =  $1.4 \pm 0.4$  nm) exhibited the best performance in the coupling of iodobenzene and phenylboronic acids under microwave irradiation (yields of 68 to >99%; 2,6-dimethylphenylboronic acid = 31%). In contrast, poor performance (yields of 13–56%) was found for bromobenzenes. Much better yields were, however, measured by using a Pd-Au bimetallic catalyst (10–92%), which was attributed to complete reduction of Pd<sup>2+</sup> ions. The five-run recycling study showed the well-known progressive decrease of yields (entry 21).

Nájera and Alacid have made a thorough study with the use of catalyst 1.28% Pd-14-PS in Suzuki coupling (see also Heck coupling, section 4.1.3, Table 4, entries 11 and 12).<sup>243</sup> In recycling studies, the coupling of activated bromo- and chloroarenes with phenylboronic acid required prolonged reactions in successive runs to maintain high product yields (entries 22 and 23). As well as in the Heck coupling, the catalyst showed high levels of leaching (up to 45% loss of Pd). The lack of reactivity in the presence of Hg, again, is indicative of the transformation of the catalyst complex into Pd<sup>0</sup>. Indeed, particles of 3–10 nm in size were detected by TEM. High yields were found in the first

### Scheme 17. Suzuki Couplings Induced by Pd-S-GaAs(xyl)



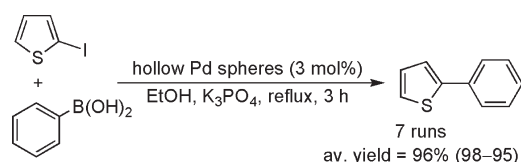
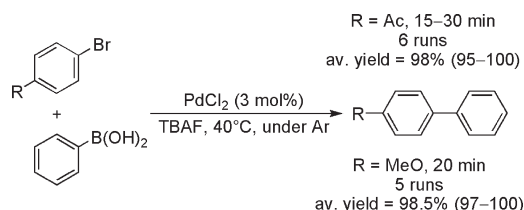
run in the coupling of rarely used boron derivatives [(MeBO)<sub>3</sub>, BuB(OH)<sub>2</sub>, (CH<sub>2</sub>=CHBO)<sub>3</sub>·Py, (E)-PhCH=CHB(OH)<sub>2</sub>] with 4-bromoacetophenone and 4-bromoanisole in the presence of TBAB. Yields, however, decreased significantly in subsequent runs despite prolonged reactions. The reaction of benzyl chloride and phenylboronic acid, however, gave better results (entry 24).

Catalyst Pd-S-GaAs(xyl) (54 μg of Pd, particle diameter = 3–5 nm) developed by Arisawa and co-workers<sup>107</sup> has been studied in the Suzuki coupling<sup>108,109</sup> using the same 10-run protocols applied in the Heck reaction (section 4.1.2, Scheme 1). The catalyst, again, is robust with a low amount of leached Pd (1.7 ppm) detected in the coupling of iodobenzene and 4-chlorophenylboronic acid in 10 cycles (Scheme 17). The results of a three-phase test with a yield of 93% indicated that palladium species leached in low amounts to the solution are the catalytically active species. Poisoning by thiol-functionalized silica provides additional evidence to this conclusion. Also in accordance is the induction period detected in runs 5 and 10 of the coupling of iodobenzene and 4-chloroboronic acid. This indicates that the supported catalyst acts as a reservoir of the active species. On the basis of these pieces of information, calculations were made using the amount of leached Pd to give a combined TON value of  $1.5 \times 10^6$  for the coupling of iodobenzene and 4-chlorophenylboronic acid. A calculation with the actual Pd loading (54 μg) gives a more realistic value of  $\sim 10$  000.

**5.1.4. Other Nanoparticle Systems.** Silica spheres upon reacting with (3-mercaptopropyl)trimethoxysilane yield a product serving as template to fabricate Pd spheres. Treatment of the functionalized material with Pd(acac)<sub>2</sub> followed by heat treatment (250 °C, 3 h) and, finally, removal of the silica template with HF gave uniform hollow Pd spheres of 300 nm.<sup>244</sup> According to TEM, the shell is composed of Pd particles of  $\sim 10$  nm in size, and the shell thickness of individual particles is 15 nm. The hollow spheres worked efficiently in the coupling of iodobenzene, 1,4-diiodobenzene, and 2-iodothiophene with phenylboronic acid (yields of 96–99%). For the reaction of bromobenzene, an increased amount of catalyst (15 mol %) was necessary to get a yield of 90%, whereas chloroarenes were unreactive. High, consistent yields were found in a seven-run recycling experiment (Scheme 18). Pd leaching was not detected.

Pd particles ( $\sim 200$  nm) generated in situ from PdCl<sub>2</sub> in tetrabutylammonium fluoride (TBAF) gave high product yields in coupling reactions with phenylboronic acid (Scheme 19), but an increase in reaction time was necessary to maintain yields in the reaction of 4-bromoacetophenone.<sup>245</sup> Recycling of the catalyst system was made by extracting the reaction mixture with cyclohexane after complete conversion and using the remaining solid material after evaporation in the next run. The yield (93% in 5 h) in the coupling of 4-bromoacetophenone was still satisfactory



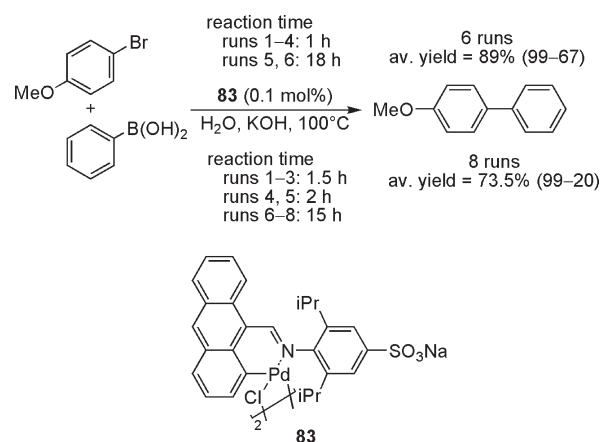
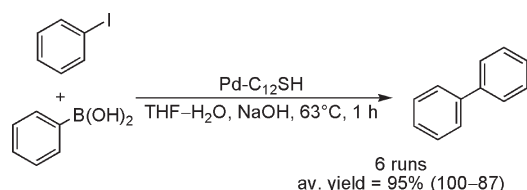
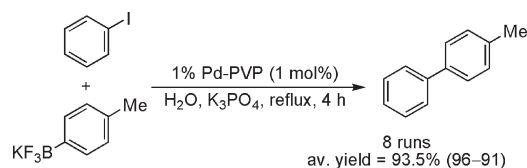
**Scheme 18.** Suzuki Coupling of 2-Iodothiophene and Phenylboronic Acid Using Hollow Pd Spheres**Scheme 19.** Suzuki Couplings in the Presence of Pd Particles Generated in TBAF

at a Pd loading of 0.005 mmol. Various bromo- and chloroarenes as well as heteroaromatic compounds reacted with high efficiency (yields of 58–100%) with low yields for chlorotoluenes (20–28%).

Cyclopalladated complexes with five- and six-membered rings and a sulfonated *N*-phenyl group have been evaluated in the Suzuki coupling of bromoarenes and phenylboronic acid.<sup>246</sup> Preliminary studies showed that the complexes decompose under reaction conditions to form Pd particles with a wide size distribution. Of the prepared complexes, compound **83** (particle size range = 20–150 nm) gave the best results (82–98% yields in the coupling of bromoarenes and phenylboronic acid) and was used in recycling studies. The results were satisfactory for the first few runs, but prolonged reactions were necessary in subsequent uses because of decreasing yields (Scheme 20; note differences in reaction times in the six-run and eight-run reactions). The dramatic change in catalyst performance is attributed to the formation of very large Pd aggregates.

Astruc and co-workers have elucidated the catalytic properties of dodecanethiol-stabilized Pd nanoparticles (Pd-C<sub>12</sub>SH) in Suzuki reaction in a biphasic mixture of THF–H<sub>2</sub>O.<sup>247</sup> The catalyst was easily prepared by reducing PdCl<sub>2</sub>(MeCN)<sub>2</sub> with LiEt<sub>3</sub>H in THF in the presence of tetraoctylammonium bromide. The resulting black suspension was treated with dodecanethiol, and then ethanol was used to precipitate the monodisperse Pd nanoparticles (mean diameter = 2.3 ± 0.5 nm). Good results were observed for the reaction of iodo- and bromobenzenes with phenylboronic acid under mild conditions (yields of 87–100%), whereas chlorobenzene and 4-chlorotoluene gave lower yields in THF (52% and 27%, respectively, in 3–5 days at 20 °C). This catalyst, as many others, shows insufficient stability for longer uses (Scheme 21).

A colloidal solution of Pd particles (mean diameter = 7 nm) generated by refluxing a solution of Pd(OAc)<sub>2</sub> and poly(vinylpyrrolidone) in methanol (1% Pd-PVP) was used in the Suzuki coupling with potassium aryltrifluoroborates in water.<sup>248</sup> Varied aryl iodides and bromides including *ortho*-substituted compounds reacted easily to give medium to high yields (51–96%). The activity and stability in eight runs were

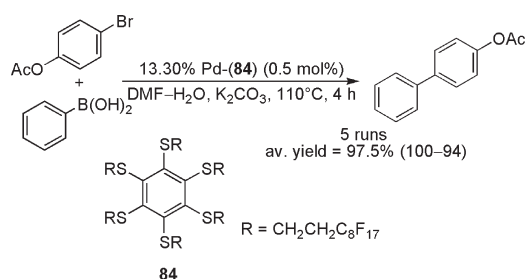
**Scheme 20.** Suzuki Coupling in the Presence of Pd Particles Formed in the Decomposition of Complex **83****Scheme 21.** Suzuki Coupling in the Presence of Pd-C<sub>12</sub>SH Nanoparticles**Scheme 22.** Suzuki Coupling with Potassium 4-Methylphenyltrifluoroborate in the Presence of 1% Pd-PVP Catalyst

also satisfactory (Scheme 22). Recycling was made by charging the precipitate formed upon ethereal extraction with new reactants and K<sub>3</sub>PO<sub>4</sub>.

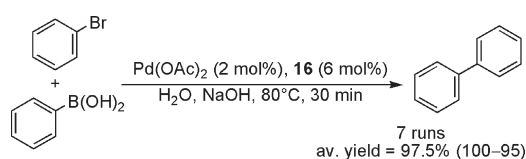
Catalyst 13.30% Pd-(**84**) with the star-shaped hexasubstituted fluorinated material stabilizing Pd nanoparticles (mean diameter = 2.2 ± 0.8 nm) exhibited better performance in a five-run recycling study (Scheme 23)<sup>127</sup> than an analogous 1,3,5-triazine-based, trisubstituted sample with lower Pd loading [catalyst 11.87% Pd-(**21**)] applied in the Heck reaction (section 4.1.4, Scheme 7).

2-Aminophenyl diphenylphosphinite (**16**) introduced as a new ligand for heterogeneous Heck coupling<sup>122</sup> (section 4.1.4, Scheme 2) has recently been tested in the Suzuki reaction with Pd(OAc)<sub>2</sub>.<sup>249</sup> All haloarenes studied coupled efficiently with phenylboronic acid in the presence of NaOH as base in water (yields of 70–94%). TBAB was used in a few cases to increase the solubility of substrates. Iodo- and bromoarenes including 3-bromopyridine reacted to afford yields of 52–90% even at room temperature. The system proved to be robust in a seven-run recycling study (Scheme 24).

### Scheme 23. Suzuki Coupling Catalyzed by Stabilized Nanoparticles



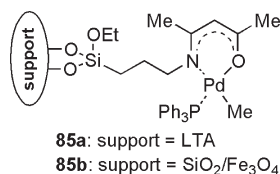
### Scheme 24. Suzuki Coupling Catalyzed by Pd Particles Formed under Reaction Conditions



## 5.2. Couplings Catalyzed by Immobilized Palladium Complexes

Results reported on the Suzuki coupling of aromatic halides with phenylboronic acids catalyzed by immobilized palladium complexes are collected in two tables: data about the use of complexes immobilized on inorganic supports are summarized in Table 12, whereas Table 13 contains results for the application of polymer-supported palladium catalysts.

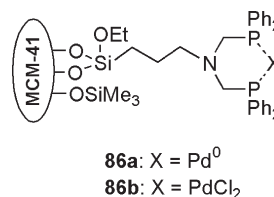
**5.2.1. Palladium Complexes Immobilized on Inorganic Supports.** Postsynthesis modification of mesoporous LTA (Linde Type A, more commonly abbreviated as NaA) zeolite with a triethoxysilylated  $\beta$ -ketoiminatophosphanyl palladium complex resulted in catalyst 3.19% Pd-85a-LTA. Varied chloroaromatics including chloro-substituted heteroarenes and deactivated chloro derivatives reacted to give high yields in the range of 84–95%. The catalyst proved to be robust and stable in recycling studies under mild conditions in aqueous solution<sup>250</sup> (Table 12, entry 1). The reaction mixture after catalyst separation did not show activity, and only an extremely small amount of leached Pd (0.0009%) was detected. The catalyst retained its mesoporosity after 10 cycles, and particle formation was not observed. These features are attributed to the robust nature of the crystalline mesoporous zeolite under basic reaction conditions. In contrast, many other less satisfactory Pd-MCM41 and Pd-SBA15 preparations gave decreasing yields in recycling.



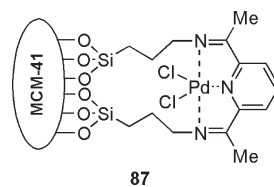
Zeolite NaA and mesoporous sodalite were used by the same group to prepare catalysts by ion-exchange with Pd(NO<sub>3</sub>)<sub>2</sub>.<sup>251</sup> The resulting samples were found to allow conversions in the range of 83–96% with iodo-, bromo-, and chlorobenzene in the Heck, Suzuki, and Sonogashira reaction under aerobic

conditions. Mesoporous sodalite (Pd<sup>2+</sup>-sodalite) proved to be highly stable in recycling studies, giving constant conversions in five runs without detectable Pd leaching in the coupling of chlorobenzene and phenylboronic acid. Because of the basicity of the zeolite framework, the catalyst works without added base (entry 2). At low catalyst concentration, however, the zeolite is destroyed, but this can be prevented by running the reaction in the presence of an external base (entry 3). Catalytic activity significantly decreases under nitrogen because Pd<sup>2+</sup> undergoes reduction and agglomeration of Pd<sup>0</sup> follows. Oxygen, in turn, is capable of preventing these processes and maintains catalyst activity.

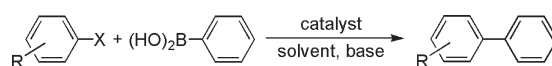
Cai et al. used (3-aminopropyl)triethoxysilane and diphenylphosphanomethanol to functionalize MCM-41.<sup>252</sup> The product was then reacted with PdCl<sub>2</sub>, and reduction with hydrazine hydrate gave catalyst 5.53% Pd-86a-MCM41. The supported bidentate phosphane Pd<sup>0</sup> complex afforded high yields in the coupling of varied iodo- and bromoarenes with arylboronic acids (84–98%) and proved to be robust in 10 runs (entry 4). Furthermore, no activity was observed in the hot filtration test in the reaction of iodobenzene with 4-chlorophenylboronic acid. In further studies, the palladated catalyst was used without the final reduction step (catalyst 5.62% Pd<sup>2+</sup>-86b-MCM41, section 5.4.3, Scheme 38).



Amino-functionalized MCM-41 was grafted with 2,6-diacetylpyridine, and then the formed immobilized Schiff-base was reacted with PdCl<sub>2</sub> to get catalyst 0.03% Pd-87-MCM41.<sup>253</sup> It is highly active toward Suzuki coupling of bromobenzenes and phenylboronic acid (yields of 90–98%) including 2-substituted derivatives with TOF values in the range of 2200–5500 h<sup>−1</sup>. Consistently high yields (entry 5) and a total TON of 117 600 were measured in a recycling study. Reaction time, however, had to be increased after the first cycle from 8 to 10 h to get complete conversion. The three-phase test with anchored *para*-bromoacetophenone indicated the true heterogeneous nature of the supported complex.



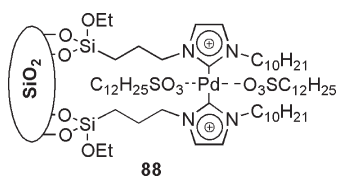
The oxime carbapalladacycle complex **29** was anchored to 3-mercaptopropyl-modified amorphous silica, and the catalyst thus formed [2.87% Pd-HS-SiO<sub>2</sub>-(**29**)] afforded near quantitative yields in the coupling of 4-chloroacetophenone and phenylboronic acid in an eight-run catalyst recycling study<sup>146</sup> (entry 6). Thorough mechanistic studies (hot filtration and three-phase test as well as analysis of the Pd content of the recovered catalyst after recycling) indicated that the coupling process is completely heterogeneous. Varying product yields (34–93%) were reported for the reaction of bromo- and chloroarenes with phenylboronic

**Table 12.** Suzuki Coupling of Aromatic Halides with Phenylboronic Acid Catalyzed by Palladium Complexes Immobilized on Inorganic Supports

entry	R	X	catalyst <sup>a</sup>	reaction conditions:	number of reuses	average yields, <sup>b</sup> (%)	ref
				solvent/base/temperature/time			
1	4-MeO	Cl	3.19% Pd- <b>85a</b> -LTA (1)	EtOH–H <sub>2</sub> O/Na <sub>2</sub> CO <sub>3</sub> /50 °C/4.5 h	10	94 (95–93)	250
2	H	Cl	Pd <sup>2+</sup> -sodalite (1)	EtOH–H <sub>2</sub> O/80 °C/12 h	5	95 (95) <sup>c</sup>	251
3	H	Cl	Pd <sup>2+</sup> -sodalite (0.1)	EtOH–H <sub>2</sub> O/Na <sub>2</sub> CO <sub>3</sub> /100 °C/24 h	5	84 (84) <sup>c</sup>	
4	H	I	5.53% Pd- <b>86a</b> -MCM41 (0.6)	dioxane/K <sub>2</sub> CO <sub>3</sub> /80 °C/2 h	10	~96 (96)	252
5	4-MeO	Br	0.03% Pd- <b>87</b> -MCM41 (0.005)	DMF/KF/100 °C/8–10 h <sup>d</sup>	6	98 (98)	253
6	4-Ac	Cl	2.87% Pd-HS-SiO <sub>2</sub> - <b>(29)</b> (4)	H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /100 °C/2 h	8	>99 (>99)	146
7	4-Me	I	2.54% Pd- <b>88</b> -SiO <sub>2</sub> (2)	2-PrOH–H <sub>2</sub> O/Na <sub>2</sub> CO <sub>3</sub> /50 °C/2 h	5	91.5 (95–90)	254
8	H	Br	3.2% Pd- <b>89a</b> -SiO <sub>2</sub> (1.2)	<i>o</i> -xylene/K <sub>2</sub> CO <sub>3</sub> /95 °C/1–2 h	10	69 (98–20)	255
9	H	Br	1.06% Pd- <b>89b</b> -SiO <sub>2</sub> (0.4)	<i>o</i> -xylene/K <sub>2</sub> CO <sub>3</sub> /95 °C/1.5–3 h <sup>d</sup>	7	n.r. (100–95)	256
10	4-Ac	Br	Pd-HS-SBA15 (1)	DMF–H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /80 °C/8 h <sup>d</sup>	5	96 (98–95)	257
11	4-MeO	Br	2.55% Pd- <b>90</b> -MFI (0.3)	H <sub>2</sub> O/K <sub>3</sub> PO <sub>4</sub> /65 °C/0.5 h <sup>e</sup>	5	97 (99–96)	258
12	4-NO <sub>2</sub>	Br			5	99.5 (100–99)	
13	4-MeO	Br	2% Pd- <b>91</b> -SiO <sub>2</sub> (1)	H <sub>2</sub> O/Na <sub>2</sub> CO <sub>3</sub> /100 °C/8 h	10	98.5 (100–96)	259
14	4-NO <sub>2</sub>	I	Pd <sup>2+</sup> -SiliaCat (1)	methanol/K <sub>2</sub> CO <sub>3</sub> /reflux/30 min	9	100 (100) <sup>c</sup>	260
15	4-Ac	Br	0.29% Pd(OAc) <sub>2</sub> -[bmim][PF <sub>6</sub> ]- <b>(27b)</b> (4.9)	EtOH–H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /100 °C/1–60 min	5	95 (100–92)	261
16	2-Me	I	15.96% Pd- <b>92</b> -Fe <sub>2</sub> O <sub>3</sub> (7.3)	DMF/Na <sub>2</sub> CO <sub>3</sub> /50 °C/12 h	5	94 (95–93)	262
17	4-Ac	Br	6.17% Pd- <b>93</b> -SiO <sub>2</sub> /Fe <sub>3</sub> O <sub>4</sub> (0.2)	DMF/K <sub>2</sub> CO <sub>3</sub> /100 °C/3 h	5	98 (99–95)	263
18	4-MeO	Cl	2.23% Pd- <b>85b</b> -SiO <sub>2</sub> /Fe <sub>3</sub> O <sub>4</sub> (0.5)	H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /60 °C/5 h <sup>e</sup>	10	95.5 (96–95)	264

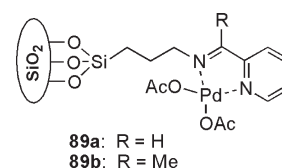
<sup>a</sup> Percentage data show Pd loading (wt %) when available; data in parentheses indicate mol % of Pd used. <sup>b</sup> n.r. = not reported. Data in parentheses indicate range of yields. <sup>c</sup> Conversion. <sup>d</sup> Under inert atmosphere. <sup>e</sup> In the presence of TBAB.

acid depending on the substitution pattern, and even 4-fluoro-2-nitrobenzaldehyde gave coupling product in a yield of 30% in 24 h. In the synthesis of catalyst 2.54% Pd-88-SiO<sub>2</sub> bearing an *N*-heterocyclic carbene Pd complex, first the corresponding 3-triethoxysilylpropyl-modified imidazolium salt was immobilized on silica nanoparticles of ~10 nm. Treatment of the functionalized silica with Pd(OAc)<sub>2</sub> gave the final catalyst.<sup>254</sup> It gives high yields under mild conditions in the coupling of iodo- and bromoarenes (76–94%) but exhibits poor performance in the reaction of chlorobenzene (29% yield). No loss of activity was observed in recycling studies in five runs (entry 7; yields did not show decreasing tendency), but only 85% of the catalyst could be recovered after the first run.



Clark and co-workers have prepared functionalized silica materials by the reaction of aminopropyl-modified silica with 2-pyridinecarbaldehyde or 2-acetylpyridine. Further treatment with Pd(OAc)<sub>2</sub> furnished catalysts 3.2% Pd-89a-SiO<sub>2</sub> and 1.06% Pd-89b-SiO<sub>2</sub>. Both catalysts showed high activity in the coupling of bromobenzene and derivatives with phenylboronic acid (yields of 60–98% and 67–100%, respectively).<sup>255,256</sup> Furthermore, the latter catalyst was highly active in forming polyaryls in the reaction of di- and tribromoarenes (yields of 60–80%). In a 10-run recycling study with catalyst 3.2% Pd-89a-SiO<sub>2</sub>, high initial yields decreased slowly with drastic drops in the last two

runs despite prolonged reactions (entry 8). Unfortunately, catalyst 1.06% Pd-89b-SiO<sub>2</sub> was assayed only in a seven-run recycling experiments (entry 9). Neither catalyst showed any appreciable activity in hot filtration tests.

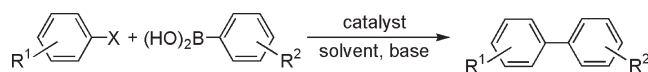


Mercaptopropyl-modified SBA15 (HS-SBA15) is capable of absorbing Pd ions by treatment with Pd(OAc)<sub>2</sub> to form catalyst Pd-HS-SBA15 loaded with complexed Pd<sup>2+</sup> ions.<sup>257</sup> High and reproducible yields were observed for bromo- and chloroarenes (82–98%) including chlorobenzene (67%) in water, DMF, or a mixture of the two solvents. High initial yields decreased slowly when reused in the solvent mixture (entry 10) with catalyst recovery made under inert atmosphere. In contrast, Pd-HS-SiO<sub>2</sub> applied in a comparative study displayed significantly decreasing yields (from 95% to 77% in four runs). Pd-HS-SBA15 is almost leach-free, and the major reaction pathway is considered to be truly heterogeneous on the basis of the hot filtration as well as a three-phase test.

A hierarchical MFI zeolite, commonly known as ZSM-5, modified by grafting with ionic liquid derivative 7b served as support material for the immobilization of Pd(OAc)<sub>2</sub>. MFI zeolite has uniform, tailored mesopores (diameters = 3–10 nm) with a surface rich in silanol groups, which allow easy functionalization. The treatment of the functionalized zeolite with [bmim][PF<sub>6</sub>] and Pd(OAc)<sub>2</sub> in THF gave catalyst 2.55% Pd-90-MFI with Pd embedded in the thin IL phase on the pore walls of zeolite.<sup>258</sup>



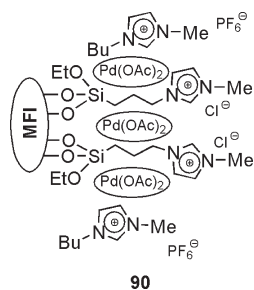
Table 13. Suzuki Coupling of Aromatic Halides with Phenylboronic Acids Induced by Palladium Complexes Immobilized on Polymers



entry	R <sup>1</sup>	X	R <sup>2</sup>	catalyst <sup>a</sup>	reaction conditions: solvent/base/temperature/time	number of reuses	average yields, <sup>b</sup> %	ref
1	4-MeO	Br	H	1.06% Pd-PS-( <b>96</b> ) (0.4)	DMF-H <sub>2</sub> O/Na <sub>2</sub> CO <sub>3</sub> /RT/24 h	5	96 (99–94)	267
2	3-NO <sub>2</sub>	N <sub>2</sub> <sup>+</sup>	4-Me	1.06% Pd-PS-( <b>96</b> ) (2)	EtOH/-/RT/8 h	10	92 (96–86)	268
3	4-NO <sub>2</sub>	Br	H	0.67% Pd <sup>2+</sup> -PS-( <b>97</b> ) (0.25)	EtOH-H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /RT-40 °C/0.3–48 h	7	96.5 (99–91)	271
4	H	I	4-Me	2.66% Pd <sup>2+</sup> - <b>98</b> -PEG-AA (2.5)	H <sub>2</sub> O/Cs <sub>2</sub> CO <sub>3</sub> /50 °C/6 h	8	94 (96–92)	272
5	H	I	H	1% Pd <sup>2+</sup> -polym-( <b>99</b> ) (0.9)	dioxane-H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /90 °C/24 h	5	98.5 (99–98)	273
6	4-Me	I	H	3.72% Pd <sup>2+</sup> -PA (2)	dioxane/Cs <sub>2</sub> CO <sub>3</sub> /100 °C/4 h <sup>c</sup>	5	91 (92–88)	188
7	4-Ac	Cl	H	5.43% Pd <sup>2+</sup> -PA (2)	H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /100 °C/12 h <sup>c,d</sup>	5	92.5 (93–92)	274
8	4-Ac	Br	H	Pd-PS-( <b>30a</b> ) (0.2)	<i>o</i> -xylene/K <sub>2</sub> CO <sub>3</sub> /130 °C/5 h	7	99 (100–98)	147
9	H	I	H	1.17% Pd-31-PS (1)	DMF-H <sub>2</sub> O/Na <sub>2</sub> CO <sub>3</sub> /50 °C/1 h	10	94 (95–92)	148
10	R <sup>3</sup>	Cl	4-Me	2.72% Pd-100a-PS (2.5)	toluene-H <sub>2</sub> O/K <sub>3</sub> PO <sub>4</sub> /80 °C/24 h	6	n.r. (86–96)	275
11	4-Ac	Br	H	2.17% Pd-100b-PS (1)	2-PrOH/K <sub>2</sub> CO <sub>3</sub> /80 °C/2 h	12	94.5 (98–82)	276
12	4-Ac	Br	H	5.28% Pd-101-PS (0.5)	DMF/K <sub>2</sub> CO <sub>3</sub> /70 °C/8 h	5	94 (95–92)	277
13	4-Ac	Br	R <sup>4</sup>	0.96% Pd-102-comp (0.7)	H <sub>2</sub> O/KOH/100 °C/2 h <sup>d</sup>	10	94.5 (100–67) <sup>e</sup>	278
14	4-Ac	Br	R <sup>4</sup>	0.96% Pd-102-comp (0.7)	H <sub>2</sub> O/KOH/160 °C/3 min <sup>d,f</sup>	10	86 (100–45) <sup>e</sup>	
15	4-Ac	Br	H	10.6% Pd-103-PVPy (1)	toluene/K <sub>2</sub> CO <sub>3</sub> /110 °C/45 min	10	93 (100–80) <sup>e</sup>	279
16	4-NO <sub>2</sub>	Cl	H	21.6% Pd-104-dendr (2)	DMF/K <sub>2</sub> CO <sub>3</sub> /110 °C/100–130 min <sup>d</sup>	5	97.5 (98–95)	280
17	H	I	H	Pd-39-polym (0.005)	H <sub>2</sub> O/Na <sub>2</sub> CO <sub>3</sub> /100 °C/24 h	10	95 (95)	157
18	H	I	4-MeO	3.04% Pd-38-TGR (1)	DMAc/K <sub>2</sub> CO <sub>3</sub> /165 °C/48 h <sup>c</sup>	14	95 (95)	156
19	H	I	H	5.07% Pd-105-PNIPAM (0.2)	DMF-heptane-H <sub>2</sub> O/Et <sub>3</sub> N/95 °C/20 h	5	65 (32–92)	285
20	4-Ac	Br	H	3.51% Pd-106-PS (1)	DMF-H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /50 °C/1 h	5	94 (94–89)	287
21	4-NO <sub>2</sub>	Cl	H	Pd <sup>2+</sup> -PEG-PS-( <b>107</b> ) (0.2)	toluene-EtOH-H <sub>2</sub> O/Na <sub>2</sub> CO <sub>3</sub> /80 °C/20 h	6	90 (100–79)	288
22	4-Ac	Br	H	0.12% Pd-108-PE (1.55)	DMF/Cs <sub>2</sub> CO <sub>3</sub> /100 °C, 120 °C/6 h	5	97 (98–96) <sup>e</sup>	289
23	4-Me	Br	H	12.8% Pd-35-PVCarb (1)	H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /70 °C/8 h <sup>d</sup>	5	92 (94–90) <sup>e</sup>	290
24	H	I	H	Fe <sub>2</sub> O <sub>3</sub> -( <b>109</b> ) (1.96)	Tx-H <sub>2</sub> O/NaOH/65 °C/1 h <sup>c</sup>	25	92 (100–89) <sup>e</sup>	291
25	4-CN	Br	H	Pd-graphite-( <b>110</b> ) (0.16)	toluene-MeOH/K <sub>2</sub> CO <sub>3</sub> /85 °C/16 h	6	95 (98–90)	292
26	4-CHO	Cl	H	<b>111</b> (0.05)	H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /80 °C/20 h	6	92 (100–79)	293
27	3-NO <sub>2</sub>	Br	H	<b>112</b> (0.2)	H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /100 °C/1 h	6	99 (99)	294
28	4-Ac	Br	H	Pd(OAc) <sub>2</sub> , <b>113a</b> (0.5)	toluene/K <sub>3</sub> PO <sub>4</sub> /100 °C/1 h	9	99 (99–90)	296

<sup>a</sup> Percentage data show Pd loading (wt %) when available; data in parentheses indicate mol % of Pd used. <sup>b</sup> n.r. = not reported. Data in parentheses indicate range of yields. <sup>c</sup> Under inert atmosphere. <sup>d</sup> In the presence of TBAB. <sup>e</sup> Conversion. <sup>f</sup> Under microwave irradiation. Tx = nonionic surfactant triton X405. R<sup>3</sup>: 2-Chloropyridine was used. R<sup>4</sup>: 3,4-Methylenedioxyphenylboronic acid was used.

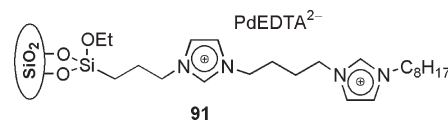
Yields are high for the coupling of all types of bromoarenes and arylboronic acids in short times in water (yields of 71–98%) with the exception of the hindered 2,6-dimethylbromobenzene (51%). Results shown in entries 11 and 12 are characteristic of five-run recycling studies. Minimal Pd leaching (1.5 ppm) and inactivity of the separated reaction mixture were attributed to strong binding of Pd(OAc)<sub>2</sub> to and isolation of the complex by the supported IL.



90

An efficient and reusable catalyst was generated by immobilizing Pd-EDTA<sup>2-</sup> on a silica-supported diimidazolium ionic liquid

brush<sup>259</sup> (catalyst 2% Pd-**91**-SiO<sub>2</sub>). No significant decrease in yields was observed in 10 consecutive reactions conducted in water (entry 13). Furthermore, only a loss of 0.45% of Pd was measured, and no activity was detected in a filtration test. A range of substituted haloaromatics gave excellent yields (89–100%) in the coupling with substituted phenylboronic acids including the reaction of chlorobenzene with phenylboronic acid (66%, 24 h).



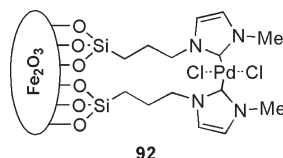
91

A highly active and robust catalyst (Pd<sup>2+</sup>-SiliaCat) was made by anchoring (2-triethoxysilylethyl)diphenylphosphane on the surface of glassy silica beads of high surface area with the concomitant co-condensation with TEOS followed by immobilizing Pd<sup>2+</sup> ions.<sup>260</sup> The catalyst gave full conversion in every run of a nine-run recycling experiment (entry 14) with Pd and P leaching between 0.3–1.8 and 1.4–3.2 ppm, respectively, in each cycle.

The catalyst prepared by immobilizing  $\text{Pd}(\text{OAc})_2$  and  $[\text{bmim}][\text{PF}_6]$  on reversed-phase alumina (**27b**) was tested in Suzuki reactions.<sup>261</sup> Bromoarenes reacted smoothly with phenylboronic acids at room temperature in short reactions and gave coupling products in medium to high yields (61–100%). Because of Pd leaching, a catalyst with low Pd loading was used (0.020–0.025 mmol  $\text{g}^{-1}$ ). Remarkably high TON (up to  $2 \times 10^6$ ) and TOF values ( $3 \times 10^4 \text{ h}^{-1}$ ) could be realized with this catalyst in the coupling of *para*-bromoacetophenone and phenylboronic acid. The stability of the catalyst system with higher loading used in recycling was, however, rather low, requiring significantly longer reaction times in consecutive runs (entry 15; compare to Heck coupling, section 4.2.1, Table 5, entry 10).

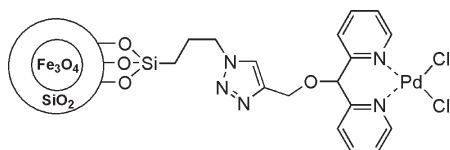
In the final entries in Table 12, reports about the use of magnetically separable iron oxide-based catalysts in the Suzuki coupling are summarized.

Catalyst 15.96% Pd-**92**- $\text{Fe}_2\text{O}_3$  is a supported, air-stable NHC Pd complex synthesized and studied by the group of Gao.<sup>262</sup> A monodisperse, highly crystalline  $\gamma\text{-Fe}_2\text{O}_3$  (maghemite) coated with an oleate layer was functionalized with (3-chloropropyl)-trimethoxysilane, and then loaded with 1-methylimidazole and reacted with  $\text{Pd}(\text{OAc})_2$  in the presence of  $\text{Na}_2\text{CO}_3$ . A combination of organic coating and very small particle size ( $\sim 11 \text{ nm}$ ) results in partial dissolution of the catalyst in many organic solvents. High yields were measured in the coupling of a few iodo- and bromoarenes (yields of 84–93%). Features are similar in recycling (entry 16) with easy recovery by a permanent magnet. Interestingly, high yields were also recorded in successive applications in the Suzuki, Heck, and Sonogashira coupling (94%, 95%, and 92%, respectively).



92

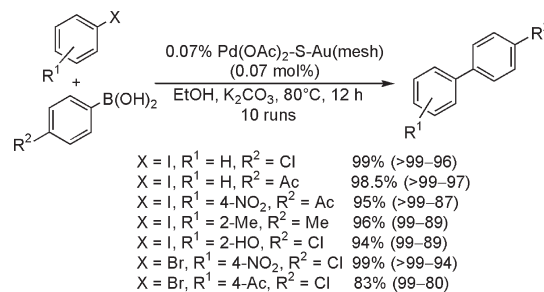
The dipyrindin-2-yl-methanol-derived Pd complex supported on silica-coated magnetic  $\text{Fe}_3\text{O}_4$  nanoparticles has also been prepared Gao and co-workers<sup>263</sup> (catalyst 6.17% Pd-**93**- $\text{SiO}_2/\text{Fe}_3\text{O}_4$ ). The synthesis was accomplished by treating silica-coated magnetic  $\text{Fe}_3\text{O}_4$  with (3-azidopropyl)triethoxysilane, then reacting the formed functionalized material with dipyrindin-2-yl-methyl propargyl ether, and, finally, treating the immobilized ligand with  $\text{PdCl}_2(\text{MeCN})_2$  in toluene at reflux temperature. The air- and moisture-stable catalyst gave the coupling products of bromoarenes with phenylboronic acids in high yields (83–99%), but much lower yields were found for 2-bromopyridine (<20%) and chlorobenzene (46%). It could be efficiently used in recycling studies after magnetic recovery, washing, and drying (entry 17).



93

Jin and Lee used a silica-coated magnetic iron oxide and functionalized it with the same complex used in the preparation

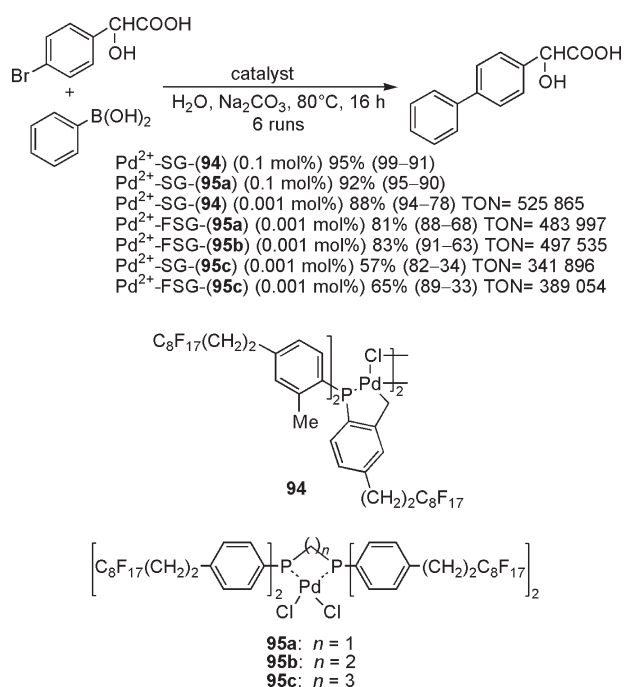
### Scheme 25. Suzuki Coupling of Iodo- and Bromobenzenes and Phenylboronic Acids over $\text{Pd}(\text{OAc})_2$ Supported on Sulfur-Treated Au



of 3.19% Pd-**85a**-LTA. Catalyst 2.23% Pd-**85b**- $\text{SiO}_2/\text{Fe}_3\text{O}_4$  has a core-shell structure with a silica coating of about 7 nm. It exhibited unprecedented performances in various cross-coupling reactions including Suzuki coupling.<sup>264</sup> Chlorobenzene and substituted derivatives reacted smoothly to afford coupling products in high yields (77–95%) under mild conditions in the presence of TBAB. Chloroanilines and *ortho*-substituted derivatives exhibiting, in general, low reactivity were also successfully reacted, and even 2,6-dimethylchlorobenzene gave a yield of 71%. Similar excellent catalyst performance was experienced in recycling (entry 18; compare the results with those reported for catalyst 3.19% Pd-**85a**-LTA in Table 12, entry 1). ICP-AES showed only a minimal loss of Pd (0.06%), and no aggregation of  $\text{Pd}^0$  to visible Pd nanoparticles could be detected after the tenth use. Furthermore, the filtered solution did not show any activity. These excellent features are attributed to the high durability of the silica-coated support and the robust nature of the palladium complex.

Arisawa and co-workers have observed by synchrotron radiation hard X-ray photoelectron spectroscopy analysis (SR-HXPS) the inclusion of sulfur into the surface of  $\text{Au}(111)/\text{mica}$  upon treatment by the strongly oxidizing Piranha solution.<sup>265</sup> Sulfur is in the oxidized state but undergoes reduction when palladium is adsorbed, which indicates that Pd is chemically bonded to sulfur. The electronic state of Pd was shown by photoelectron spectroscopy to be close to  $\text{Pd}^0$ . On the basis of these observations, unique Pd catalysts have been developed. The catalyst prepared by treating sulfur-modified Au mesh with  $\text{Pd}(\text{OAc})_2$  [ $\text{Pd}(\text{OAc})_2\text{-S-Au}(\text{mesh})$ ] was tested in 10-run recycling studies (16 combinations of varied reactant pairs). As shown by selected examples in Scheme 25, the catalyst gave excellent yields and displayed satisfactory stabilities in the coupling of various iodo- and bromobenzenes with varied phenylboronic acids. TON values of 12 000–14 000 can be calculated. Furthermore, extremely low levels of Pd leaching (a few hundred ng) were measured. Despite the excellent features reported, the practical significance of these catalysts emphasized by the authors can be questioned because of the highly specific method of catalyst fabrication.

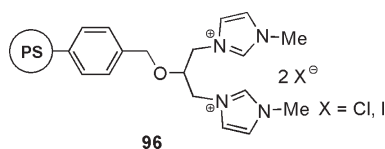
Bannwarth and co-workers have performed a detailed study using a range of perfluoro-tagged palladated monodentate and bidentate phosphane ligands including **94**, **95a**–**95c** immobilized on silica gel (SG) and fluorosilica gel (FSG).<sup>266</sup> The results reported include thorough kinetic studies in the coupling of 4-bromomandelic acid with phenylboronic acid, reactions with varied catalyst loadings, and, for comparison, the use of untagged complexes on silica gel and FSG. Selected results (conversion data) are shown in Scheme 26. Activities decreased upon recycling in organic solvents, which was attributed to decomposition of the

**Scheme 26. Suzuki Coupling of 4-Bromomandelic Acid with Phenylboronic Acid over Silica-Supported Pd Complexes**

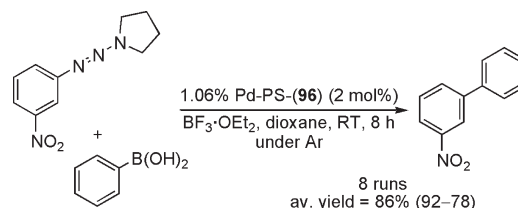
$\text{Pd}^0$  intermediate. In water, in contrast, consistently high activities and high cumulative TON values were observed. The nature of the support does not seem to affect catalyst performance, but prewetting with methanol of the highly hydrophobic FSG was beneficial. Catalyst  $\text{Pd}^{2+}\text{-SG-(94)}$  and  $\text{Pd}^{2+}\text{-SG-(95a)}$  displayed the best results at high catalyst loading, whereas high TON values could be realized with four ligands. The cumulative TON values at low catalyst loading shown are extremely high for immobilized complexes. In fact, cumulative TONs in the range 114 000–526 000 were reported in 10 six-run recycling experiments.

### 5.2.2. Palladium Complexes Immobilized on Polymers.

In the first three studies listed in Table 13, functionalized Merrifield resin catalysts were applied. The resin modified with an appropriate bis-imidazolium reagent provided the corresponding polystyrene-supported bis-imidazolium salt **96**, which, upon reacting with  $\text{Pd}(\text{OAc})_2$ , gave catalyst 1.06%  $\text{Pd-PS-(96)}$  bearing the corresponding NHC complex.<sup>267</sup> Inductively coupled atomic absorption spectroscopy (ICP-AAS) indicated, however, only the partial participation of the imidazolium groups in forming the complex. Varied substituted bromoarenes underwent coupling with phenylboronic acids to provide coupling products in good to excellent yields at ambient conditions (73–99%). All reactions were carried out in air without noticeable formation of Pd black. The original high yields decreased slightly in the recycling study performed without any regeneration of the recovered catalyst (entry 1).



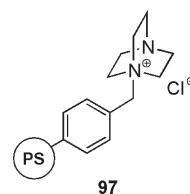
The same catalyst was successfully applied in the coupling of arenediazonium tetrafluoroborates with 4-methylphenylboronic

**Scheme 27. Suzuki Coupling of 1-Aryltriazenes**

acid.<sup>268</sup> It displayed small decreases in yields in recycling experiments in 10 runs in the absence of a base (entry 2). After an initial Pd leaching of 0.2%, low and decreasing levels of Pd were detected in further applications (90–50 ppm). No further activity was observed in a hot filtration test in 10 h. Interestingly, the catalyst recovered from the first, fifth, and tenth runs was also used in the coupling of 4-methoxybenzenediazonium tetrafluoroborate and phenylboronic acid, affording, respectively, 84%, 80%, and 74% yields. In a recycling study with 3-nitrophenylsulfonyl chloride and phenylboronic acid (desulfative Suzuki coupling), decreasing yields from 87% to 81% in five runs were observed.<sup>269</sup>

The Suzuki coupling of 1-aryltriazenes and phenylboronic acid induced by catalyst 1.06%  $\text{Pd-PS-(96)}$  has also been reported to afford good to high product yields (71–96%).<sup>270</sup> In an eight-run recycling study, yields gradually dropped from 92% to 78% (Scheme 27). The recovered catalyst from the first, fifth, and eighth runs was used in the coupling of 1-phenyl-2-(pyrrolidin-1-yl)diazene and 4-methoxyphenylboronic acid to give products with 85%, 80%, and 72% yields, respectively. Pd leaching measured after the first, second, and fifth runs was 0.4%, 90 ppm, and 45 ppm, respectively. No further reactivity was detected in a filtration test.

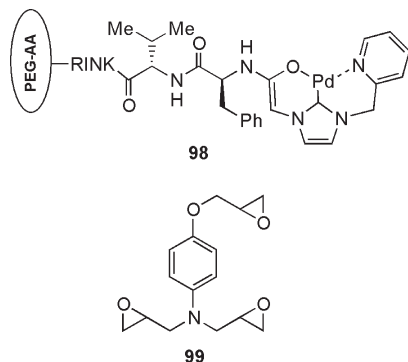
With the polymer-supported DABCO-Pd complex [catalyst 0.67%  $\text{Pd}^{2+}\text{-PS-(97)}$ ], prolonged reactions in the first four runs (from 0.3 to 48 h) and then increased reaction temperature (reactions at 40 °C instead of room temperature in 12–18 h) were required to maintain high product yields in recycling studies (entry 3).<sup>271</sup> Similar observations were made in the five-run recycling of heteroaryl bromides (5-bromopyrimidine and 2-bromopyrazine; data not shown). The catalyst was synthesized by using the functionalized Merrifield resin **97** and  $\text{Pd}(\text{OAc})_2$ , and it provided high to excellent yields (73–100%) in the coupling of bromo- and chloroarenes with phenylboronic acids.



A poly(ethylene glycol)-dimethylacrylamide copolymer (PEG-AA) was functionalized with a RINK-amide linker to attach pyridine and imidazolium moieties. Palladation was carried out with  $[\text{PdCl}_2\text{COD}]$  to form catalyst 2.66%  $\text{Pd}^{2+}\text{-98-PEG-AA}$  with an NHC complex as the active site.<sup>272</sup> The catalyst is robust and allowed the synthesis of coupling products in the reaction of iodo- and bromobenzene with varied arylboronic acids in yields of 79–96%. Furthermore, only minor changes in yields were observed in an eight-run recycling study (entry 4).



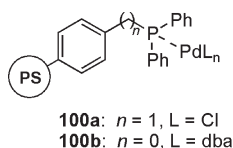
Catalyst 1% Pd<sup>2+</sup>-polym-(**99**) has been fabricated by polymerizing the triglycidyl derivative of aminophenol (**99**) using metal complexes as initiators.<sup>273</sup> This catalyst with a higher Pd loading displayed higher stability (entry 5) and lower Pd leaching (0.21–0.08%) than 0.5% Pd<sup>2+</sup>-Mo-polym-(**99**) (a drop of yields from 97% to 89% in five runs and 0.70–0.19% leached Pd in five runs).



Two polyaniline-supported catalysts 5.43% Pd<sup>2+</sup>-PA discussed earlier (section 4.4, Scheme 14) and 3.72% Pd<sup>2+</sup>-PA prepared by depositing Pd(OAc)<sub>2</sub> have been tested in the Suzuki reaction affording excellent yields in the coupling of iodo- and bromoarenes with phenylboronic acids (90–98%).<sup>188,274</sup> Catalyst 5.43% Pd<sup>2+</sup>-PA was efficient even in the coupling of chloroarenes, but in these cases TBAB was required (yields of 62–94%). The two catalysts exhibited very similar performance in recycling studies (entries 6 and 7). Catalyst 5.43% Pd<sup>2+</sup>-PA lost 2% of Pd during reaction; however, no further conversion in the hot filtration test occurred after 10 h with no detectable Pd in the filtrate. The three-phase test with silica-bound 4-bromobenzamide indicated the leaching of a certain amount of Pd from the polyaniline support. A much smaller amount of leaching (0.05% of Pd) was measured for catalyst 3.72% Pd<sup>2+</sup>-PA. As shown by XPS, an induction period (3 and 25 min, respectively, in water and dioxane as solvents) was necessary for Pd<sup>2+</sup> to undergo reduction to Pd<sup>0</sup>, the latter being the actual active species for catalyst 5.43% Pd<sup>2+</sup>-PA.

The characteristics of catalyst Pd-PS-(**30a**) in the Suzuki coupling (entry 8) are similar to those observed in the Heck reaction (section 4.2.2, Table 6, entry 1).<sup>147</sup> In a similar way, the modified polystyrene-supported catalyst 1.17% Pd-**31**-PS found to give high yields in Heck coupling (section 4.2.2, Table 6, entry 2) exhibited excellent characteristics in the Suzuki reaction in a longer recycling study (entry 9).<sup>148</sup>

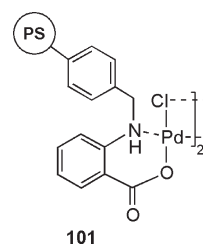
Reactions with the polystyrene-supported phosphanated catalyst 2.72% Pd-**100a**-PS were found to be slow in polar solvents.<sup>275</sup> In a heterogeneous, three-phase system, in turn, satisfactory yields could be achieved in couplings of chloroaromatics and 4-tolylboronic acid (72–92%; 3-chloroanisole = 35%). High yields were measured in recycling experiments (entry 10).



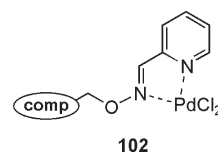
Highly monodisperse cross-linked hollow polystyrene microcapsules (average diameter = 7.78  $\mu\text{m}$ ) were prepared by copolymerizing diphenyl(4-vinylphenyl)phosphane and divinylbenzene. Treatment of the microcapsules with Pd<sub>2</sub>(dba)<sub>3</sub> gave a polymer-supported Pd catalyst with Pd species anchored inside

the microcapsules (2.17% Pd-**100b**-PS).<sup>276</sup> Bromobenzenes with varied substitution patterns and 3-bromopyridine coupled with phenylboronic acids to afford the corresponding biphenyls in medium to high yields (58–98%; 2-bromobenzaldehyde = 15%). The three-phase test provided evidence that the catalyst is almost leach-free and reactions are characteristically heterogeneous in nature. High, consistent yields were found in 11 runs in a recycling study (yields >90%), but a large drop was measured in the 12th run (entry 11).

Catalyst 5.28% Pd-**101**-PS was easily prepared by reacting anthranilic acid with chloromethylated polystyrene followed by anchoring PdCl<sub>2</sub> in methanol at 90 °C.<sup>277</sup> The application of this catalyst allowed the coupling of aromatic iodo and bromo derivatives with phenylboronic acids in yields of 83–100%, and chlorobenzene also reacted with a satisfying yield of 72%. Yields decreased only slightly in recycling (entry 12). No reactivity was found in a filtration test, and no Pd leaching was detected by atomic absorption spectroscopy. The latter observation was further confirmed by a poisoning test: mercaptopropyl-modified silica did not affect the conversion in the reaction of 4-bromoanisole and phenylboronic acid.

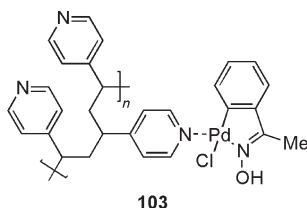


Kirschning and Dawood used a glass composite material prepared by copolymerizing chloromethylpolystyrene and divinylbenzene inside the pores of porous glass as support to covalently anchor a pyridine-2-carboxamide-based Pd complex (catalyst 0.96% Pd-**102**-comp).<sup>278</sup> It proved to be highly active under both thermal conditions and microwave irradiation in water in the presence of KOH and TBAB. 4-Bromoacetophenone and heteroaryl bromides gave high yields in couplings with phenylboronic acid, 3,4-methylenedioxyphenylboronic acid, and 3-thiophenylboronic acid (thermal heating = yields of 78–98%, microwave heating = yields of 50–98%). 4-Chloroacetophenone also coupled efficiently with phenylboronic acid (85% yield) and 3,4-methylenedioxyphenylboronic acid (98%). Results with 3-thiophenylboronic acid and couplings with 2-bromo-1,3-thiazole were inferior. In recycling studies, reactions were complete in 2 h under thermal heating in the first seven runs, and then conversions decreased and dropped suddenly in the tenth cycle (entry 13). Similar efficiency was experienced in the recycling study under microwave irradiation (entry 14). The catalyst is a precatalyst and assumed to be the source of coordinatively unsaturated “PdL<sub>n</sub>” species or colloidal Pd<sup>0</sup>. The scavenging action of the pyridine ligand accounts for the low amount of leached Pd (0.0016–0.00128%). In addition, it is also suggested to retard the formation and agglomeration of colloidal species.



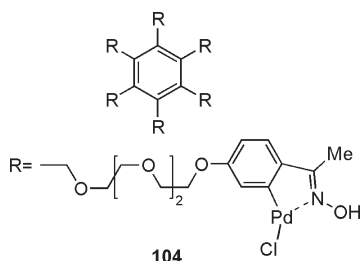
An oxime-based palladacycle immobilized on poly(4-vinylpyridine) (10.6% Pd-**103**-PVPy) was reported by Kirschning's

group to afford high to excellent yields (63–97%) in the reaction of 4-bromoacetophenone with aryl- and vinylboronic acids (toluene,  $\text{K}_2\text{CO}_3$ , 110 °C).<sup>279</sup> Varied yields were found for the coupling of 4-chloronitrobenzene and 4-chloroacetophenone in aqueous solution, in the presence of TBAB (3–99%). 2-Chlorobenzonitrile and 3-chloropyridine gave medium to high yields (65–91%) under thermal and microwave heating. Small decreases in yields were observed from the fifth run on in a recycling study (entry 15). An induction period at 80 °C is indicative of the formation of an active catalytic species from the polymer-supported oxime precatalyst.



103

The self-supported star-shaped catalyst composed of ethylene glycol tethers attached to the core ring and functionalized with the oxime-palladacycle (21.6% Pd-**104**-dendr) displayed good performance in Suzuki couplings.<sup>280</sup> Oxime-palladacycles are assumed to form cross-linkages between star-shaped units. Bromo compounds afforded excellent yields (85–98%) in aqueous ethanol under aerobic conditions (1 mol % of Pd,  $\text{K}_2\text{CO}_3$  as base, room temperature). The yields were lower in couplings of 3,5-difluorophenylboronic acid with activated 3-nitrobromobenzene (79%) and 4-bromoanisole (70%). Pyridine derivatives gave similar yields (75–87%) at 60 °C. A wider range of reactivities (yields of 45–98%; chlorobenzene = 33%) were observed for the reaction of chloroaromatics performed under more forcing conditions (2 mol % of Pd, DMF, TBAB, 110 °C). Couplings in a five-run recycling study proceeded in high yields (entry 16). The drop of activity in the last cycle and the need of extended reaction time, however, are indications of unstable catalytic activity in the long run.

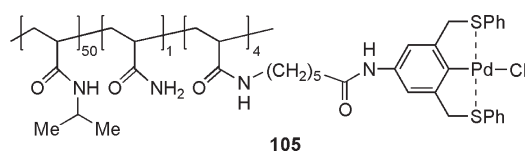


104

The assembled catalyst of palladium and a non-cross-linked amphiphilic polymer (catalyst Pd-**39**-polym) developed by Ikegami and co-workers<sup>157</sup> displayed excellent performance in the coupling of varied iodo- and bromoarenes with phenylboronic acids (yields of 84–99%). 4-Tolyl triflate and 3-acetylphenylboronic acid also reacted with similar efficiency to give the product in 93% yield. A TON of  $1.25 \times 10^6$  was reported in the coupling of iodobenzene and phenylboronic acid (Pd loading =  $8 \times 10^{-5}$  mol %, 96 h). The catalyst system afforded high, stable yields and a TON of 190 000 in a 10-run recycling study (entry 17; see also the use of the catalyst in Heck coupling, section 4.2.2, Table 6, entry 10).

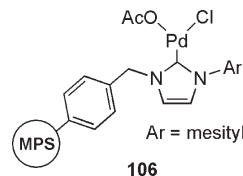
The immobilized pincer-type *N*-heterocyclic carbene ligand discussed previously<sup>156</sup> (catalyst 3.04% Pd-**38**-TGR, section 4.2.2, Table 6, entry 9) displays high, stable activity in the Suzuki coupling (entry 18). Catalytic activity was not detected either in a hot filtration test or using a three-phase reaction with the Wang resin derivatized with 4-iodobenzoic acid. After the initial run with 3 ppb of Pd leaching, only very low levels of leaching were detected (<0.05 ppb). As mentioned, the catalyst was less stable when used in air: Pd black was precipitating, and yields decreased after several runs. Furthermore, yields with iodides (>95%) were considerably higher than those with bromides (55–57%).

Bergbreiter and co-workers developed varied polymer-bound phosphane ligands with Pd attached and used them under thermomorphic conditions.<sup>281</sup> Similar to fluoruous biphasic catalysis, the system is homogeneous at elevated temperature, and product separation is easily performed in a biphasic system. The catalysts were used in various cross-coupling reactions;<sup>282–284</sup> however, only results with the Suzuki coupling induced by catalyst 5.07% Pd-**105**-PNIPAM are qualified for a discussion here.<sup>285</sup> The air-stable catalyst was synthesized by reacting phosphane-functionalized poly(*N*-isopropylacrylamide) with  $\text{PdCl}_2(\text{PhCN})_2$  to form the anchored tridentate SCS moiety. Reactions with iodoarenes and phenylboronic acid were performed in DMAc–heptane solvent mixture to have products in high isolated yields. Low yields were observed in the first recycling runs, but high isolated yields were achieved in the fifth cycle (entry 19). This was attributed to the dissolution of the product into the polar DMAc phase. However, it was shown later by Jones and co-workers<sup>286</sup> that the pincer complex decomposes under reaction conditions to release  $\text{Pd}^0$  species, and these are responsible for catalysis.



105

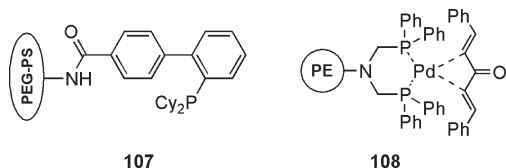
The synthesis of polymer-supported catalyst 3.51% Pd-**106**-PS was started by reacting mesoporous chloromethylpolystyrene with 1-mesitylimidazole. The formed NHC precursor after treatment with  $\text{Pd}(\text{OAc})_2$  gave the stable supported complex.<sup>287</sup> The catalyst provided moderate to high yields in the coupling of varied haloaromatics and phenylboronic acid (yields of 58–99%) with prolonged reaction at higher temperature for chloro derivatives (24 h, 100 °C). The high and gradually dropping yields in a recycling study (entry 20) are accompanied by small Pd leaching (3.0–1.1%).



106

Ligand **107** was synthesized by reacting an amino-functionalized poly(ethylene glycol)–polystyrene copolymer with 2'-(dicyclohexylphosphano)-biphenyl-4-carboxylic acid.<sup>288</sup> When used in Suzuki coupling, a mixture of **107**,  $\text{Pd}(\text{OAc})_2$ , 4-chloronitrobenzene, and phenylboronic acid was stirred under

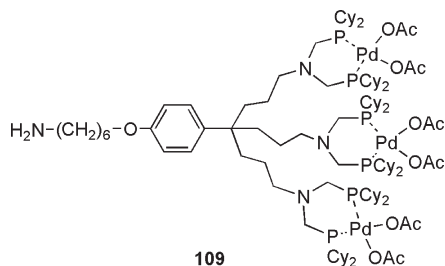
reaction conditions indicated in entry 21. The polymer-supported palladium complex formed in the first run [ $\text{Pd}^{2+}$ -PEG-PS-(**107**)] can be recovered by filtration and used in subsequent runs after washing. Yields in toluene as solvent were usually lower and decreased drastically in recycling in contrast to the use of a solvent mixture.



Haag and co-workers used a sintered polyethylene sheet, functionalized with primary amino groups, to anchor bis-(diphenylphosphanyl)methyl groups, followed by reaction with  $\text{Pd}(\text{dba})_2$  to have the immobilized, polymer chip-supported palladium complex **108** (0.12% Pd-**108**-PE).<sup>289</sup> The catalyst applied in the Suzuki reaction afforded high, consistent yields with a necessary increase in temperature after the first two runs (entry 22). Furthermore, it could simply be removed from the reaction flask by a pair of tweezers and was also successfully used in scale-up experiments.

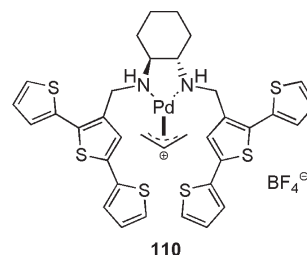
High yields were achieved with catalyst 12.8% Pd-**35**-PVCarb in the Suzuki coupling of varied haloarenes and arylboronic acids (68–100%; chlorobenzene = 40%).<sup>290</sup> In the recycling study (entry 23), catalyst performance is similar to that found in the Heck coupling (section 4.2.2, Table 6, entry 6). No activity was observed in the hot filtration test.

For the immobilization of palladium, carboxyl groups of polymer-coated  $\gamma$ - $\text{Fe}_2\text{O}_3$  nanoparticles were reacted with pallada-dendron **109**.<sup>291</sup> Catalyst Pd-polym/ $\text{Fe}_2\text{O}_3$ -(**109**) gave quantitative conversion in the reaction of iodobenzene and phenylboronic acid, and high conversions were measured for the coupling of bromobenzenes and varied arylboronic acids (yields of 79 to >99%). Even *ortho*-substituted reactants coupled smoothly, while chlorobenzenes exhibited lower reactivity (29–79%). The catalyst proved to be highly efficient in a 25-run recycling study with acceptable stability (entry 24).

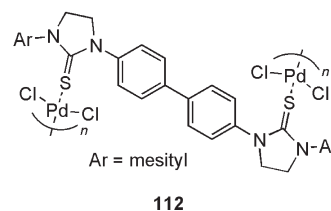
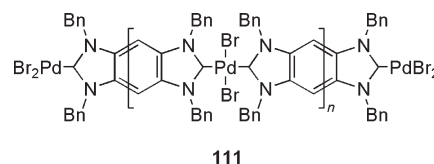


Oxidative electrochemical polymerization of monomer **110** using carbon paper as the working electrode was applied to generate a polymeric film [Pd-graphite-(**110**)].<sup>292</sup>  $\alpha$ -Position of each terthienyl moiety are available for polymerization. This graphite-based catalyst, after a short induction period, gave high yields in the coupling of iodo- and bromoarenes (conversions of 50–98%), and high initial yields with a large drop were observed in recycling (entry 25). The separated reaction mixture after full conversion charged with a new batch of substrates gave no further reaction in 48 h. This, however, is not a valid test to

conclude the heterogeneous nature of the reaction and the lack of leaching.

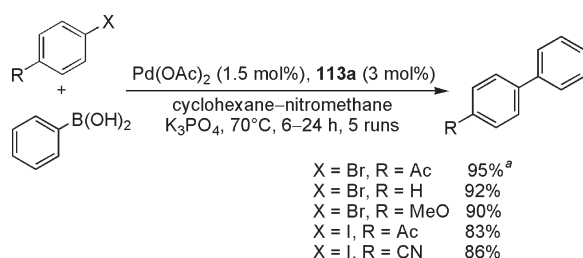


In the next two entries in Table 13, results with respect to the use of self-supported NHC-palladium organometallic polymers used as catalysts are summarized. Karimi and Akhavan treated tetrabenzyl benzo-bis(imidazolium) dibromide with a stoichiometric amount of  $\text{Pd}(\text{OAc})_2$  and isolated catalyst **111** in 80–85% yield.<sup>293</sup> Reactions, in general, were performed by injecting a solution of **111** in dimethyl sulfoxide into the reaction mixture, whereas chloro compounds were reacted by adding the catalyst directly into the reaction mixture. Yields decreased slowly in five successive uses, and then dropped in the sixth run, affording an average yield of 92% (entry 26). Only 69% of the catalyst could be recovered after five runs. It showed high activity in the presence of mercury, indicating that it is not a precatalyst. In the hot filtration test, only a marginal reactivity was detected (4% conversion in 18 h). An additional important feature of catalyst **111** is its significant activity in the Suzuki coupling of 4-fluorobenzaldehyde (51% yield,  $\text{H}_2\text{O}$ ,  $\text{NaOH}$ , TBAB, 90 °C, 30 h). Chen and co-workers used the self-supported thiourea-PdCl<sub>2</sub> complex **112** in recycling studies.<sup>294</sup> The catalyst, prepared by treating a bis-thiourea ligand with  $\text{PdCl}_2(\text{MeCN})_2$ , was found to be highly efficient and durable (entry 27) with 2 ppm of Pd in the filtrate in each run. All types of bromoarenes afforded high to excellent yields in coupling with phenylboronic acids (75–99%).

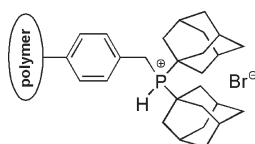


Plenio and co-workers have performed biphasic Suzuki couplings by using Pd-phosphane catalysts phase-tagged with soluble polymers (**113a**, **113b**). The air-stable polymer phosphonium salts were used directly because the corresponding Pd complex is formed as a result of deprotonation under basic reaction conditions. The cyclohexane–nitromethane solvent combination was found to give the best performance with ligand **113a** and  $\text{Pd}(\text{OAc})_2$ .<sup>295</sup> Both iodo- and bromoarenes reacted smoothly to afford excellent combined yields (Scheme 28). In these studies, phase yields per cycle were reported corresponding



**Scheme 28.** Suzuki Coupling with Phenylboronic Acid in the Presence of  $\text{Pd}(\text{OAc})_2$  and Ligand **113a**<sup>a</sup><sup>a</sup> (a) Yield of isolated products after chromatographic purification.

to the amount of product isolated after separation of the product phase from the catalyst phase. These values reflect the partition coefficients and can be higher than 100%. Moreover, phase yields may increase in subsequent runs because salt formation changes polarity and partition coefficients. TOF values per cycle, however, are more informative with respect to the stability of the catalyst system. These are 180, 182, 175, 168, and 165 h<sup>-1</sup> in the reaction of 4-bromoacetophenone and phenylboronic acid. The high and stable activity testifies to the practically quantitative retention of the catalyst in the cyclohexane phase.



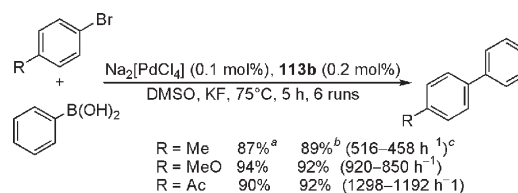
**113a:** poly(methylstyrene)  
**113b:** MeOPEG<sub>2000</sub>OCH<sub>2</sub>

The same catalyst system was also used in a study by applying a solvent-resistant nanofiltration technique.<sup>296</sup> A membrane composed of a porous layer of poly(acrylonitrile) covered with a dense poly(dimethylsiloxane) layer is capable of practically quantitatively retaining the polymeric phosphane (palladium in the permeate was less than 0.05%). Very high yields were maintained in a nine-run study (Table 13, entry 28). More importantly, TOF values for the first four cycles are 290, 305, 300, and 300 h<sup>-1</sup>. High yields were reported for the coupling of both bromo- and chloroarenes and even for *ortho*-substituted phenylboronic acids (87–96% and 72–93%, respectively). A study similar to that summarized in Scheme 28 was performed with  $\text{Na}_2[\text{PdCl}_4]$  and ligand **113b** in DMSO, indicating again high activity and stability<sup>297</sup> (Scheme 29).

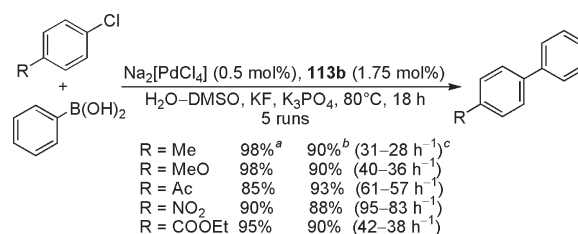
The catalyst system was also applied in the more challenging recycling study of 14 chlorobenzene derivatives. 4-Substituted compounds were tested in five-run recycling experiments (Scheme 30; only five selected examples are shown) with stabilities similar to those shown above. TOF values decreased to some extent after the first cycle, and then remained relatively constant. Shortening the time between cycles was shown to be beneficial. Pd leaching determined by spectrophotometry was below the detection limit of 0.05%.

### 5.3. Recycling Studies with Palladium Complexes under Homogeneous Conditions

The pyrazolyl-functionalized *N*-heterocyclic carbene complexes **46a** and **49** developed by Shreeve and co-workers and used in Heck couplings in the presence of ionic liquids (section

**Scheme 29.** Suzuki Coupling of Bromobenzenes with Phenylboronic Acid in the Presence of  $\text{Na}_2[\text{PdCl}_4]$  and Ligand **113b**<sup>a</sup>

<sup>a</sup> (a) Yield of isolated products after chromatographic purification. (b) Residual activity after five cycles relative to the first cycle normalized to 100% activity. (c) Range of TOF values determined on incomplete conversion at 0.5 h.

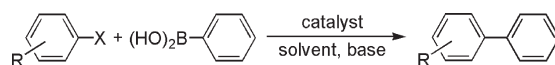
**Scheme 30.** Suzuki Couplings of Chlorobenzenes with Phenylboronic Acid in the Presence of  $\text{Na}_2[\text{PdCl}_4]$  and Ligand **113b**<sup>a</sup>

<sup>a</sup> (a) Yield of isolated products after chromatographic purification. (b) Residual activity after five cycles relative to the first cycle normalized to 100% activity. (c) Range of TOF values determined on incomplete conversion at 1 h.

4.3, Table 7, entries 6, 7, and 9–12) were tested in the Suzuki reaction as well using  $\text{Na}_2\text{CO}_3$  as the base in water to increase the solubility of the inorganic salt formed. Five iodobenzenes were reacted successively in the presence of complex **49** and [bmim][PF<sub>6</sub>] with high efficiency<sup>167</sup> (Table 14, entry 1). The difference in yields between activated and deactivated reactants is negligible. The combination of complex **46a** and IL **45** was also studied in the coupling of seven reactants (bromobenzenes and 4-chloroacetophenone) with phenylboronic acid with the repeated use of each reactant<sup>166</sup> (entry 2). As expected, substituent effects are significant, and in each case prolonged reaction time was used in repeated runs. 4-Chloroacetophenone gave low yields.

The monoquaternary 2,2'-biimidazolium-based ionic liquid **43** was demonstrated to serve as an excellent ligand and solvent in Suzuki cross-coupling.<sup>298</sup> The catalyst complex was generated by stirring a solution of  $\text{PdCl}_2$  and **43** in methanol at room temperature followed by concentrating the solution. The catalyst system performed efficiently in the recycling of five bromoarenes tested in triplicate runs to provide good product yields (entry 3).

Livingston et al. have studied Suzuki reactions in an IL–ethyl acetate solvent mixture (1:1) using  $\text{Pd}_2(\text{dba})_3$  as catalyst in the presence of  $\text{PPh}_3$ .<sup>299</sup> The use of the solvent mixture allows one to carry out the reaction in homogeneous solution. Catalyst separation for recycling was performed by organic solvent nanofiltration (OSN) (see also Heck coupling, section 4.3). Of the three ILs tested, trihexyl(tetradecyl)phosphonium chloride (CyPhos101) gave the best performance in the coupling of 4-bromoacetophenone

**Table 14.** Suzuki Coupling of Haloaromatics with Phenylboronic Acid Induced by Palladium Complexes under Homogeneous Conditions

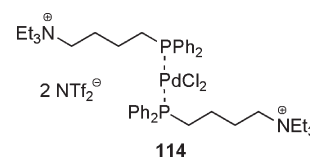
entry	R <sup>g</sup>	X	catalyst <sup>d</sup>	reaction conditions: solvent/base/temperature/time	number of reuses	average yield, <sup>b</sup> %	ref
1	R <sup>1</sup>	I	<b>49</b> (2)	[bmim][PF <sub>6</sub> ]-H <sub>2</sub> O/Na <sub>2</sub> CO <sub>3</sub> /110 °C/1 h <sup>c</sup>	5	— <sup>d</sup>	167
2	R <sup>2</sup>	Br	<b>46a</b> (2)	<b>45</b> -H <sub>2</sub> O/Na <sub>2</sub> CO <sub>3</sub> /110 °C/1 h <sup>c</sup>	14	— <sup>d</sup>	166
3	R <sup>3</sup>	Br	PdCl <sub>2</sub> (2)	<b>43</b> /Na <sub>2</sub> CO <sub>3</sub> /100 °C/24 h	15	— <sup>d</sup>	298
4	4-Ac	Br	Pd <sub>2</sub> (dba) <sub>3</sub> , PPh <sub>3</sub> (5)	CyPhos101-EtOAc/K <sub>3</sub> PO <sub>4</sub> /70 °C/1 h <sup>c</sup>	13	72 (82–56) <sup>e</sup>	299
5	4-Ac	Br			13	79 (88–62) <sup>e</sup>	
6	2-Me	Br	<b>114</b> (1)	[bmip][NTf <sub>2</sub> ]-H <sub>2</sub> O/K <sub>3</sub> PO <sub>4</sub> /65 °C/2 h <sup>c</sup>	6	90 (92–88)	300
7	H	I	<b>115</b> (1.2)	[C <sub>3</sub> H <sub>6</sub> CNpy][Tf <sub>2</sub> N]-H <sub>2</sub> O/Na <sub>2</sub> CO <sub>3</sub> /110 °C/12 h	9	86 (88–82)	301
8	H	Br	PdCl <sub>2</sub> (1)	[Dppc][PF <sub>6</sub> ]-[bmim][PF <sub>6</sub> ]/Na <sub>2</sub> CO <sub>3</sub> /110 °C/2 h	9	93 (96–90)	302
9	4-Me	Br	Pd(OAc) <sub>2</sub> (1.8)	[bmim][PF <sub>6</sub> ]-H <sub>2</sub> O/Na <sub>2</sub> CO <sub>3</sub> /100 °C/0.5 h	9	82 (99–72)	303
10	R <sup>4</sup>	Br	Pd(OAc) <sub>2</sub> (2.2)	[bmim][PF <sub>6</sub> ]-H <sub>2</sub> O/Na <sub>2</sub> CO <sub>3</sub> /80 °C/12 h <sup>c</sup>	7	87 (92–69)	304
11	4-Me	I	Pd(OAc) <sub>2</sub> , PPh <sub>3</sub> (2)	PEO-MeOH/K <sub>3</sub> PO <sub>4</sub> /60 °C/3 h	7	91.5 (81–98)	305
12	4-Me	Br	Pd(OAc) <sub>2</sub> , PPh <sub>3</sub> (2)	PEO-MeOH/K <sub>3</sub> PO <sub>4</sub> /60 °C/24 h	12	95 (70–100)	
13	R <sup>5</sup>	X*			6	— <sup>d</sup>	
14	4-Ac	Br	Pd(OAc) <sub>2</sub> (0.01)	DABCO/K <sub>2</sub> CO <sub>3</sub> /110 °C/14 h <sup>f</sup>	5	94 (96–92)	306
15	4-MeO	Br	<b>116a</b> (1)	THF-H <sub>2</sub> O/Na <sub>2</sub> CO <sub>3</sub> /90 °C/4 h <sup>c</sup>	5	90.5 (77–95)	307
16	4-MeO	Br	<b>116b</b> (1)		5	95 (82–99)	
17	4-Me	Br	<b>118</b> (2)	<b>119</b> -H <sub>2</sub> O/Na <sub>2</sub> CO <sub>3</sub> /80 °C/1 h <sup>c</sup>	13	94.5 (>99–50)	308

<sup>a</sup>Data in parentheses indicate mol % of Pd used. <sup>b</sup>n.r. = not reported. Data in parentheses indicate range of yields. <sup>c</sup>Under inert atmosphere. <sup>d</sup>See footnote for data. <sup>e</sup>Process yields as defined in reference. <sup>f</sup>In the presence of TBAB. <sup>g</sup>R<sup>1</sup>: Successive reactions with R = H (90%), 4-Me (91%), 4-MeO (88%), 4-F (90%), 4-NO<sub>2</sub> (87%). R<sup>2</sup>: Successive, repeated reactions with R = H (76%, 91%), 4-MeO (53%, 82%), 4-chloroacetophenone (10%, 31%), 4-Ac (91%, 93%), 4-F (92%, 90%), 4-CF<sub>3</sub> (91%, 95%), 4-NO<sub>2</sub> (89%, 91%). In repeated runs, reaction time was increased to 15 h (first four compounds) and 3 h (last three compounds). R<sup>3</sup>: Successive reactions in triplicate uses with R = H (83%, 84%, 80%), 4-F (86%, 86%, 85%), 4-CF<sub>3</sub> (85%, 90%, 88%), 4-NO<sub>2</sub> (86%, 86%, 90%), 4-Me (85%, 80%, 82%). R<sup>4</sup>: 3-Bromopyridine. R<sup>5</sup>: Successive reactions with R = 4-Me, X\* = I (83%); R = CF<sub>3</sub>, X\* = Br (62%); R = 4-MeO, X\* = Br (71%); R = H, X\* = CH<sub>2</sub>Br (68%); 1-bromonaphthalene (81%); 2-bromonaphthalene (83%).

and phenylboronic acid. Solid byproducts were removed after reaction by an aqueous wash, and then the reaction mixture was filtered (STARMEM 122 membrane, 30 bar, 30 °C) and the catalyst phase reused. The results determined in two parallel tests shown in entries 4 and 5 indicate good catalyst performance. In the first case, yields dropped in the last run (entry 4, 56%), whereas in the second test, yields decreased significantly in subsequent runs (54% yield in the 18th cycle). More importantly, however, nanofiltration turned out to be an unsuitable technique for catalyst separation. Analysis showed unacceptably high Pd concentrations (100–1000 ppm) in the filtrate even at a low catalyst loading of 0.1 mol %. Interestingly, even higher levels of Pd (up to 3000 ppm) were detected after the fifth cycle.

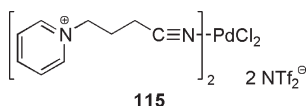
Lombardo and co-workers have conducted a study by using the preformed triethylammonium-tagged diphenylphosphane Pd<sup>2+</sup> complex **114** in 1-butyl-1-methylpyrrolidinium bis(trifluoromethylsulfonyl)imide [bmip][NTf<sub>2</sub>].<sup>300</sup> Bromoaromatics and arylboronic acids afforded very high yields (84–99%) under mild reaction conditions in short reaction times without an induction period. Reactions were carried out under argon because increased amounts of biphenyls (up to 15%), the homocoupling product of phenylboronic acids, were formed in air. Surprisingly, the reactivity order was found to be ArBr > ArI >> ArOTf, whereas chloroaromatics proved to be unreactive. The lower

reactivity of iodoaromatics was attributed to the retarding effect of the KI byproduct. The catalyst system offered high, slightly decreasing yields in recycling (entry 6) with an extremely low level of leached Pd (<10 ppb). The ionic phase was reused after washing with water and drying in vacuo (6–8 h).



Dyson and co-workers have designed ILs based on the *N*-butyronitrile-substituted pyridinium salts [C<sub>3</sub>H<sub>6</sub>CNpy][X] (X = PF<sub>6</sub>, BF<sub>4</sub>, Tf<sub>2</sub>N). The salts were reacted with PdCl<sub>2</sub> to have precatalysts, which were characterized (XRD) and tested in the Suzuki and Stille couplings.<sup>301</sup> Complex **115** when used in the IL [C<sub>3</sub>H<sub>6</sub>CNpy][Tf<sub>2</sub>N] displayed the best catalyst performance in the Suzuki reaction of iodobenzene and phenylboronic acid (entry 7). Coupling in the presence of *N*-butyl-substituted IL [C<sub>4</sub>H<sub>9</sub>py][Tf<sub>2</sub>N], in contrast, showed significant drops of yields, and the system became inactive in the sixth run. Furthermore, Pd leaching was much larger (28 ppm vs <5 ppm). The catalyst system in the Suzuki coupling was homogeneous (compare to

the Stille coupling; section 7.1, Table 17, entry 7), but the real nature of the catalytically active species remains unclear.



The Suzuki coupling proceeded efficiently in the air-stable catalyst system composed of  $\text{PdCl}_2$  and two ionic liquids,  $[\text{bmim}][\text{PF}_6]$  and  $[\text{Dppc}][\text{PF}_6]$  ( $[1,1'\text{-bis(diphenylphosphano)-cobaltocenium hexafluorophosphate}]$ ).<sup>302</sup> Bromoarenes reacting with phenylboronic acid gave high yields (85–94%) independent of substitution patterns and the nature of substituents. A simple washing with water of the IL phase containing the catalyst was sufficient for the reuse of the catalyst system to get high yields in recycling (entry 8). No leaching of Pd and  $[\text{Dppc}][\text{PF}_6]$  and no change in catalyst performance was observed in an unprecedented 140 reuses (no specific data were reported). The total TON achieved was, however, only 13 000.

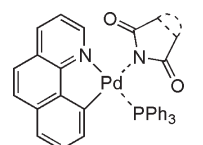
Xin and co-workers have made extensive studies with the use of the  $[\text{bmim}][\text{PF}_6]$ –water solvent mixture in combination with  $\text{Pd}(\text{OAc})_2$  in C–C coupling reactions. Water was found to exert a significant accelerating effect on the Suzuki coupling with the highest yields at an IL–water ratio of 3:1.<sup>303</sup> The reaction of varied iodo- and bromoarenes proceeded in high yields (85–98%; 100 °C, 20–40 min, 1.8 mol % of Pd). The transformation of 4-chloroacetophenone and 4-chloronitrobenzene, in contrast, was sluggish, affording low yields (30% and 49%, respectively) despite the higher temperature, longer reaction, and the use of an increased amount of Pd (150 °C, 24 h, 2.5 mol %). The catalyst system was successfully reused in the coupling of 4-bromotoluene and phenylboronic acid with high product yields in the first seven cycles after washing with water of the IL phase (entry 9). Significant drops in yields occurred, however, in the eighth and ninth reuses (83% and 72%, respectively). Coupling products were isolated in fair to high yields (48–96%) in the reaction of bromopyridines and phenylboronic acids in the presence of the same catalyst system applied under nitrogen.<sup>304</sup> 3-Chloropyridine, in contrast, gave only a yield of 36%, whereas 2-methyl-5-chloropyridine was unreactive. Catalyst performance in recycling experiments (entry 10) is similar to that observed above (entry 9); that is, neither catalyst system appears to be a promising candidate for longer uses. Recycling was performed by washing the residue after solvent extraction with water and recharging it with new reactants.

Monteiro and co-workers reported a simple and efficient protocol for catalyst recycling by carrying out reactions in poly(ethylene oxide) (PEO) and methanol.<sup>305</sup> After the product was extracted with heptane, the organic phase was reused in further runs. The catalyst system provided high yields in the coupling of 4-iodo- and 4-bromotoluene with phenylboronic acid in recycling studies (entries 11 and 12) with incomplete conversions in the first runs. Neither this phenomenon was commented on, nor were any characterization data reported. Good performance was found for the coupling of six iodo- and bromoarenes in successive runs (entry 13).

$\text{Pd}(\text{OAc})_2$  in combination with DABCO in PEG-400 as solvent proved to be an extremely active catalyst system in the Suzuki cross-coupling of iodo- and bromoarenes with arylboronic acids (yields of 74–100%).<sup>306</sup> It provides high TON values (up to 910 000) in the coupling of 4-iodonitrobenzene

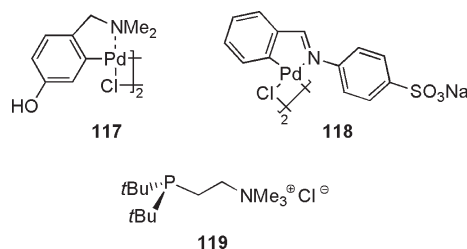
with phenylboronic acid with a Pd loading of 0.0001%. Low to high yields were also found for chloroarenes in the presence of TBAB (yields of 32–92%). As seen in many other cases, this catalyst also gives decreasing yields already in five runs in the recycling of 4-iodoacetophenone and phenylboronic acid (entry 14). Recycling was made by charging the solidified mixture after product extraction and evaporation with reactants and  $\text{K}_2\text{CO}_3$ .

Fairlamb and co-workers developed and tested a range of imidato– $\text{Pd}^{2+}$  complexes in the Suzuki coupling.<sup>307</sup> High yields were reported with the use of **116a** and **116b** in recycling studies in the reaction of 4-bromoanisole with phenylboronic acid (entries 15 and 16). Both complexes gave lower yields in the first run, indicative of a precatalyst activation. After the initial run at 90 °C, the catalysts could be reused in subsequent reactions at 25 °C, affording similar yields.



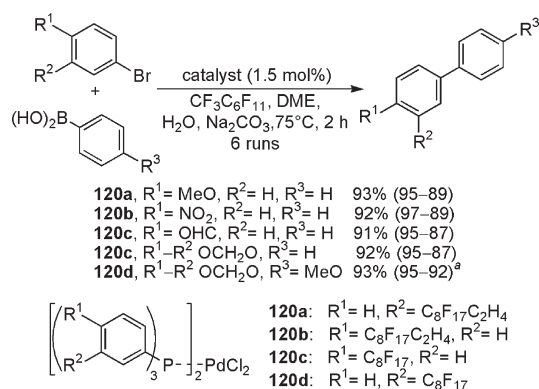
**116a:** = CH=CH  
**116b:** = benzene

Shaughnessy and Huang have developed a family of water-soluble palladacycles. When combined with (2-di-*tert*-butylphosphanoethyl)trimethylammonium chloride (*tert*-Bu-Amphos, **119**), two of the palladacycles (**117**, **118**) proved to be efficient and recyclable in the Suzuki coupling of bromoarenes and activated chloroarenes in aqueous solution.<sup>308</sup> Even the hindered 2,6-dimethylbromobenzene coupled with phenylboronic acid in yields of 43% and 64%. Catalyst **117** gave near quantitative yields in the first four cycles in the reaction of 4-bromotoluene and phenylboronic acid with a drop to 66% in the fifth reuse (not shown). Catalyst **118**, in contrast, was found to be more stable to afford better than 99% yields in the first 11 cycles (entry 17). After the eighth reuse, the aqueous phase was allowed to stand overnight, and then was removed from the precipitated salt and used again in five additional cycles. Yields decreased in the last two runs (85% and 50%). The palladacycles served as effective precatalysts to give the (*tert*-Bu-Amphos)<sub>2</sub> $\text{Pd}^0$  complex as the catalytically active species. Recycling was made by recharging the aqueous phase containing the catalyst and ligand with a new batch of reactants and  $\text{Na}_2\text{CO}_3$  after extraction.

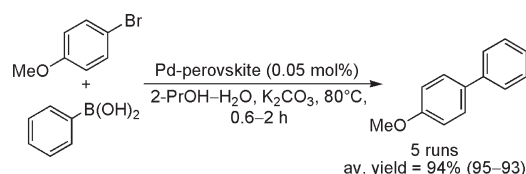


Perfluoro-tagged Pd complexes **120a**–**120d** were prepared by reacting the corresponding phosphanes with  $\text{Na}_2[\text{PdCl}_4]$ . They were applied in a fluorous biphasic system in the Suzuki reaction of bromobenzenes with varied substitution patterns in six-run recycling experiments.<sup>309</sup> Consistently high yields were observed in all cases (selected examples are shown in Scheme 31). Three of



**Scheme 31. Suzuki Coupling of Bromobenzenes and Phenylboronic Acids in the Presence of Catalysts 120a–120d<sup>a</sup>**

<sup>a</sup> (a) Carried out in a mixture of DME–MeOH.

**Scheme 32. Suzuki Coupling of 4-Bromoanisole with Phenylboronic Acid in the Presence of Pd-Containing Perovskite**

the complexes were also studied in the Stille coupling (see section 7.1, Table 17, entries 9–11).

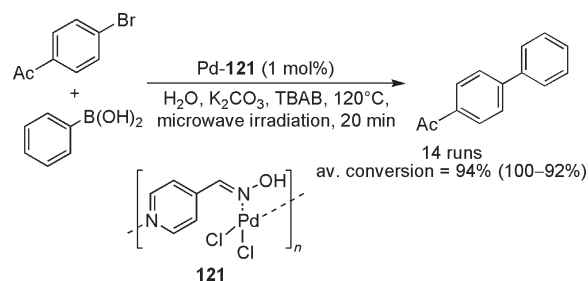
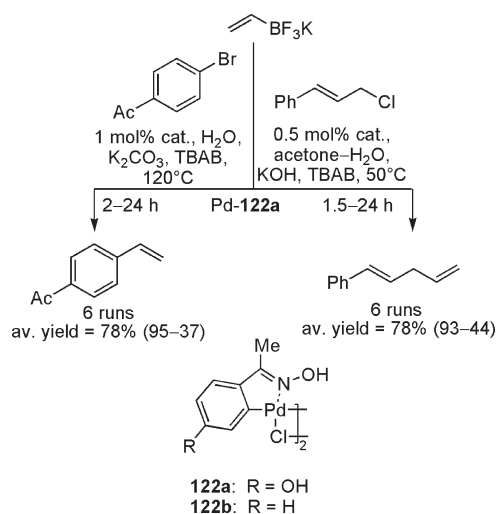
## 5.4. Miscellaneous Examples

**5.4.1. Couplings with Other Catalysts.** The Pd-containing perovskite LaFe<sub>0.57</sub>Co<sub>0.38</sub>Pd<sub>0.05</sub>O<sub>3</sub> gave high yields (70–95%) in the coupling of iodo- and bromoarenes with phenylboronic acids in aqueous alcohols.<sup>310</sup> The use of TBAB was beneficial in a few cases. Chlorobenzenes reacted under microwave heating to give the coupling products in lower yields (26–71%). The three-phase test indicated that, at least partially, a homogeneous mechanism is operative. A low level of Pd leaching (0.5–2.4 ppm) in the crude product was determined. High yields with a minor decline were measured in recycling experiments performed by varying the reaction time (Scheme 32).

The robust, insoluble precatalyst Pd-121 with a quasi-polymeric structure was prepared by reacting pyridine-4-carbaldehyde oxime with Na<sub>2</sub>[PdCl<sub>4</sub>].<sup>311</sup> The exact nature of the catalyst was not clarified, but the absence of a Pd–C σ-bond excludes a palladacycle structure. Pd-121 turned dark after an induction period in Suzuki reactions, which indicates the probable formation of Pd particles. 4-Halo- and 4-trifluoroacetophenones as well as 4-bromoanisole coupled with phenylboronic acids in the presence of TBAB under microwave irradiation (yields of 48–100%). High conversions and a combined TON of >1200 were observed in a recycling study (Scheme 33).

**5.4.2. The Use of Other Boron Reagents.** In addition to arylboronic acids, organotrifluoroborates<sup>312,313</sup> and sodium tetraphenylborate have been shown to be useful reagents in Suzuki coupling in recent years.

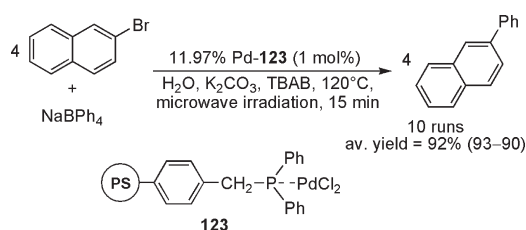
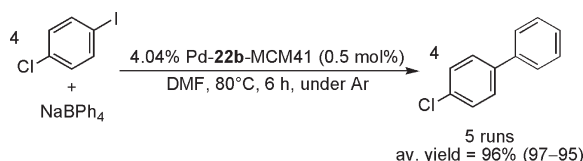
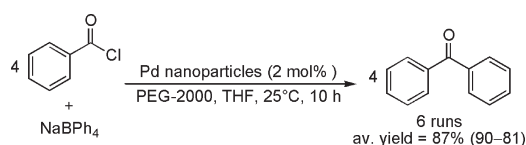
Alacid and Nájera have used palladacycle 122a derived from 4-hydroxyacetophenone oxime to induce coupling reactions with

**Scheme 33. Suzuki Coupling of 4-Bromoacetophenone and Phenylboronic Acid in the Presence of Pd-121****Scheme 34. Vinylations with Potassium Vinyltrifluoroborate Induced by Palladacycle 122a**

potassium alkenyltrifluoroborates.<sup>314</sup> The complex allowed the synthesis of coupling products of bromoarenes in high yields under both thermal conditions and microwave irradiation (57–93% in 2–24 h and 63–93% in 20–30 min, respectively) under optimized conditions (1 mol % of Pd, 1.5 equiv of alkenyltrifluoroborates, water reflux, 2 or 3 equiv of K<sub>2</sub>CO<sub>3</sub>, TBAB, pressure tube). Slightly lower yields could be realized in comparative studies with Pd(OAc)<sub>2</sub>. The results with 5-bromothiophene-2-carbaldehyde and 3-bromopyridine (yields of 75–86%) are also satisfactory. Alkenylation of allyl and benzyl chlorides to yield 1,4-dienes and allylbenzenes, respectively, occurred with similar high efficiency (yields of 59–89%). Because of the lower reactivity of potassium alkenyltrifluoroborates, couplings of chloroarenes could not be performed. Both palladacycle 122a and Pd(OAc)<sub>2</sub> act as precatalyst and efficient source of Pd particles, which are stabilized by TBAB.

Significantly prolonged reactions had to be used in recycling studies of potassium vinyltrifluoroborate with 4-bromoacetophenone and cinnamyl chloride (Scheme 34). Nevertheless, large drops of yields in the sixth cycle were experienced. ICP-OES (optical emission spectroscopy) analyses indicated about 50–110 ppm of Pd in the crude coupling products. See also the use of complex 122a in the Hiyama coupling (section 8, Scheme S6).

Wang and Bai have reported the synthesis of diphenylphosphanomethyl-functionalized polystyrene, which then was mixed

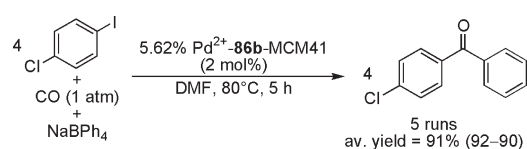
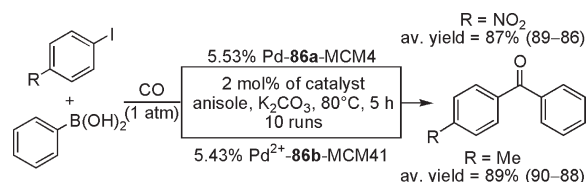
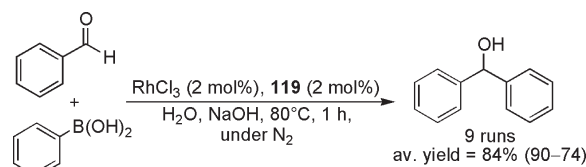
**Scheme 35. Suzuki Coupling of 2-Bromonaphthalene with NaBPh<sub>4</sub> in the Presence of Polymer-Anchored PdCl<sub>2</sub>****Scheme 36. Suzuki Coupling of 4-Chloriodobenzene with NaBPh<sub>4</sub> in the Presence of 4.04% Pd-22b-MCM41****Scheme 37. Coupling Reaction To Produce Diaryl Ketones Catalyzed by Pd Nanoparticles**

with an ethanol–benzene solution of PdCl<sub>2</sub> and irradiated with ultrasound to get catalyst 11.97% Pd-123-PS.<sup>315</sup> High yields (~90%) were observed in the Suzuki reaction of bromoarenes in aqueous solution under microwave irradiation. The catalyst proved to be highly efficient in the recycling of 2-bromonaphthalene with phenylboronic acid (93.5% average yield in five runs, range of yields = 95–93%)<sup>315</sup> or NaBPh<sub>4</sub> (Scheme 35).<sup>316</sup>

Catalyst 4.04% Pd-22b-MCM41 induces the coupling of iodo- and bromoarenes with NaBPh<sub>4</sub> to give the corresponding non-symmetrically substituted biaryls in high yields (81–97%).<sup>317</sup> Similar efficiency was observed in a recycling study (Scheme 36).

**5.4.3. Related Coupling Reactions.** In addition to biaryls, diaryl ketones may also be synthesized using the Suzuki reaction. Cho has described a method to carry out the coupling of aryl chlorides with NaBPh<sub>4</sub> in the presence of Pd nanoparticles generated by reacting Pd(OAc)<sub>2</sub> and PEG-2000 as described earlier<sup>117</sup> to furnish diaryl ketones<sup>318</sup> (Scheme 37). Recycling was made by cooling the reaction mixture and using the solidified mass after filtration.

The palladium complexes supported on MCM-41 prepared by Cai and co-workers proved to be effective in the carbonylative Suzuki coupling of aryl iodides and bromides (yields of 48–94%).<sup>319</sup> The product ketone was formed in consistently high yields in the coupling of 4-chloriodobenzene with NaBPh<sub>4</sub> over catalyst 5.62% Pd<sup>2+</sup>-86b-MCM41 (Scheme 38). Different bases tested did not affect the reaction. No further reaction was observed in the hot filtration test in the coupling of 4-bromonitrobenzene.

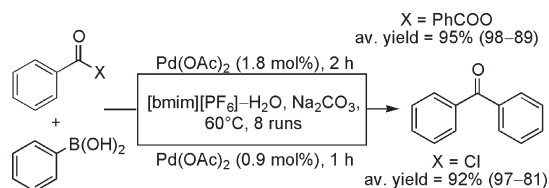
**Scheme 38. Carbonylative Suzuki Reaction with NaBPh<sub>4</sub> Catalyzed by 5.62% Pd<sup>2+</sup>-86b-MCM41****Scheme 39. Carbonylative Suzuki Reactions with Phenylboronic Acid****Scheme 40. Coupling of Benzaldehyde with Phenylboronic Acid Induced by RhCl<sub>3</sub> To Produce Benzhydrol**

The features of carbonylative couplings with phenylboronic acid in the presence of either catalyst 5.53% Pd-86a-MCM41<sup>320</sup> or catalyst 5.43% Pd<sup>2+</sup>-86b-MCM41<sup>321</sup> (Scheme 39) are very similar to those shown in Scheme 38. No further reaction was observed in the hot filtration test in either reaction using 4-iodonitrobenzene, and only 2% Pd was lost in the presence of Pd<sup>2+</sup>-86b-MCM41. These properties were attributed to the mesoporous structure of MCM-41 and the chelating action of the bidentate phosphorus ligand toward Pd species located inside the mesoporous channels. The coupling of varied aromatic iodo derivatives with arylboronic acids proceeded smoothly in high yields (67–90%) under the optimized reaction conditions shown.

RhCl<sub>3</sub> in combination with the ligand *tert*-Bu-Amphos (119) developed by Shaughnessy and Huang gives a recyclable catalyst for the coupling of aldehydes with boronic acids to yield the corresponding secondary alcohols.<sup>322</sup> Aromatic aldehydes with electron-withdrawing groups reacted efficiently with phenylboronic acid in aqueous solution under nitrogen to give the corresponding benzhydrols in good yields (77–89%). Conversely, anisaldehyde and aliphatic aldehydes offered lower yields (52–59%). High yields were also obtained in couplings with alkenylboronic acids (71–84%). Good efficiency was found in a recycling study with benzaldehyde and phenylboronic acid (Scheme 40). After the sixth use, the aqueous phase was allowed to stand overnight, and then removed from the precipitated salt and used in three consecutive cycles. The yield in the first run was rather low (79%), and then yields increased up to 90%, but significant drops in the last two runs followed (74% and 76%).

Pd(OAc)<sub>2</sub> used in aqueous solution with PEG-2000 or [bmim][PF<sub>6</sub>] offered good yields with a few exceptions in the

**Scheme 41. Couplings To Synthesize Ketones Catalyzed by  $\text{Pd}(\text{OAc})_2$  in Aqueous Solution in the Presence of  $[\text{bmim}][\text{PF}_6]$**



coupling of carboxylic anhydrides or acyl chlorides with aryl-boronic acids to form ketones.<sup>323</sup> Illustrative are the yields in PEG-2000–H<sub>2</sub>O and  $[\text{bmim}][\text{PF}_6]$ –H<sub>2</sub>O of hexanoyl chloride (0% and 54%, respectively), phenylacetic anhydride (20% and 73%), and phenylacetyl chloride (15% and 78%). Furthermore, the solvent mixture  $[\text{bmim}][\text{PF}_6]$ –H<sub>2</sub>O showed, in general, somewhat better performance. High efficiency in recycling was observed only for the  $\text{Pd}(\text{OAc})_2$ – $[\text{bmim}][\text{PF}_6]$ –H<sub>2</sub>O system (Scheme 41).

### 5.5. Summary

The catalyst systems with supported Pd nanoparticles exhibiting good activity and stability in Suzuki couplings qualified to be mentioned here are silica-supported sample 0.48% Pd–SiO<sub>2</sub> (Table 8, entry 4), nanoparticles deposited onto polystyrene (26.6% Pd–PS, Table 11, entry 1), Pd–PS-co-PVPy with a polystyrene–4-vinylpyridine core–shell structure (Table 11, entry 6), and organostannoxane-based materials Pd–Sn–dendr1 and Pd–Sn–dendr2 (Table 11, entries 18 and 19). A few other samples with similar performance are characterized by significant activity decrease, Pd loss, or the necessity to use prolonged reactions to maintain high yields.

Immobilized complexes with varied supports include samples with functionalized ordered silica materials (3.19% Pd–85a–LTA, Table 12, entry 1; Pd<sup>2+</sup>–sodalite, Table 12, entries 2 and 3; 5.53% Pd–86a–MCM41, Table 12, entry 4; 5.43% Pd<sup>2+</sup>–86a–MCM41, Scheme 39; 0.03% Pd–87–MCM41, Table 12, entry 5), amorphous silica [2.87% Pd–HS–SiO<sub>2</sub>–(29), Table 12, entry 6] and silica beads (Pd<sup>2+</sup>–SilicaCat, Table 12, entry 14), as well as a sample with magnetic iron oxide (2.23% Pd–85b–SiO<sub>2</sub>/Fe<sub>3</sub>O<sub>4</sub>, Table 12, entry 18). Polymer-supported samples Pd–39–polym (Table 13, entry 17) and 3.04% Pd–38–TGR (Table 13, entry 18), the self-supported thiourea–PdCl<sub>2</sub> complex 112 (Table 13, entry 27), as well as complex 49 and PdCl<sub>2</sub> in ILs under homogeneous conditions (Table 14, entries 1 and 3) show similar performance.

Catalyst samples with the highest TON values in Suzuki couplings are 1.22% Pd–FSG–(2a) (333 000, Table 8, entry 6), 3.24% Pd–Y (136 000, Table 9, entry 10), 0.03% Pd–87–MCM41 (117 600, Table 12, entry 5), and Pd–39–polym (190 000, Table 13, entry 17). Note that the latter was also found to exhibit similar efficiency in the Heck reaction. Perfluoro-tagged palladated phosphane ligands 94, 95a–95c immobilized on silica gel afforded by far the best TON values [Pd<sup>2+</sup>–SG–(94), 525 865; Pd<sup>2+</sup>–FSG–(95a), 483 997; Pd<sup>2+</sup>–FSG–(95b), 497 535, Scheme 26].

Two important notes are made here.

- (i) In contrast to Heck couplings, which may be induced with varied catalyst types (see section 4.5), efficient immobilized complexes are more dominant for the Suzuki reaction.

- (ii) As was already pointed out, total TON values and not the number of recycles are true and valid measures of recycling performance. An illustrative example is the use of PdCl<sub>2</sub> applied in the mixture of ILs  $[\text{Dppc}][\text{PF}_6]$  and  $[\text{bmim}][\text{PF}_6]$ . This system was reused 140 times with only a meager total TON of 13 000 achieved. Similarly, 1.22% Pd–FSG–(2a) gave a TON of 333 000 in four runs at a Pd loading of 0.001 mol %, whereas cumulative TONs of the same catalyst in extended reuses are 55 300 (six runs, Pd loading = 0.01 mol %) and 13 360 (15 runs, Pd loading = 0.1 mol %).

## 6. SONOGASHIRA COUPLING

Sonogashira coupling of haloarenes with terminal alkynes, that is, alkynylation of aromatics, may be induced by Pd in the presence of Cu salts.<sup>324–330</sup> Most catalysts reported recently, however, are active without Cu (so-called Heck-type alkynylation).

### 6.1. Couplings with Pd Particles

As well as in other coupling reactions (Heck reaction, section 4.1.2, Table 3, entries 7–9; Suzuki coupling, section 5.1.2, Table 10, entries 8 and 9), 10.53% Pd–MgO with Pd particles (30–40 nm in diameter) displays good performance in the Sonogashira reaction of haloarenes with various terminal acetylenes (yields of 65–96%) with the exception of the coupling of chlorobenzene with phenylacetylene (20% yield in 24 h).<sup>101</sup> Yields and stabilities are also satisfactory in recycling studies (Table 15, entries 1 and 2).

Sonogashira couplings proceeded smoothly with fluoro-tagged 1.22% Pd–FSG–(2a) and 3.47% Pd–SiO<sub>2</sub>–(3) developed by Vallribera and co-workers.<sup>71,331</sup> Reactions were performed under aerobic, copper-, and phosphane-free conditions in aqueous solution, in the presence of pyrrolidine. Iodoarenes with varied substituent patterns and various terminal alkynes gave the corresponding coupled products in high to excellent yields (70–95%). Similar or slightly lower yields (50–99%) for bromoarenes, in turn, required prolonged reactions (up to 48 h). However, the performance of 1.22% Pd–FSG–(2a) in recycling was inferior to that of 3.47% Pd–SiO<sub>2</sub>–(3): yields dropped significantly after a few runs even with increased Pd loading (data not shown) because of the loss of high amounts of Pd detected in the crude product (39–240 ppm). This was attributed to the weak fluorine–fluorine interactions between nanoparticles, fluorine stabilizing agent 2a, and FSG. Indeed, <sup>19</sup>F NMR analysis of the reaction mixture showed the loss of about 50% 2a in every run. Interestingly, such phenomenon was not observed in the Heck coupling and the Suzuki reaction. In contrast, high, constant yields were found over 3.47% Pd–SiO<sub>2</sub>–(3) with a decrease only in the last run from 86% to 70% (Table 15, entry 3). Compare the above data to those reported for the use of catalysts 1.22% Pd–FSG–(2a) and 3.47% Pd–SiO<sub>2</sub>–(3) in other coupling reactions (Heck coupling, section 4.1.1, Table 1, entries 4–7; Suzuki reaction, section 5.1.1, Table 8, entries 6 and 7).

As discussed, the Pd/C aerogel catalyst containing Pd nanoparticles prepared by Vallribera, Roig, and co-workers proved to be a good catalyst in the Heck coupling (section 4.1.2, Table 3, entry 2). It was found to display interesting characteristics in the Sonogashira reaction carried out in deoxygenated DMF, in the presence of CuI, under argon<sup>332</sup> (Table 15, entry 4). Despite the strict reaction protocol, the catalyst could be recycled 15 times after recovering by simple decantation in air without any particular precaution. The yield decreased significantly in the



Table 15. Sonogashira Coupling of Halobenzenes with Terminal Acetylenes Induced by Pd Particles

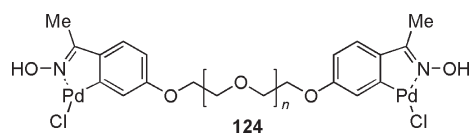
entry	R <sup>1</sup>	X	R <sup>2</sup>	catalyst <sup>a</sup>	reaction conditions:			ref
					solvent/base/temperature/time	number of reuses	average yield, <sup>b</sup> (%)	
1	4-MeO	I	Ph	10.53% Pd-MgO (1)	THF-H <sub>2</sub> O/Et <sub>3</sub> N/RT/24 h	5	n.r. (92–90)	101
2	4-Me	Br	Ph		DMF/Et <sub>3</sub> N/80 °C/14 h	5	n.r. (90–88)	
3	3-CF <sub>3</sub>	I	Ph	3.47% Pd-SiO <sub>2</sub> -(3) (0.5)	H <sub>2</sub> O/pyrrolidine/100 °C/60 min	11	89 (95–70)	331
4	3-MeO	I	C <sub>5</sub> H <sub>11</sub>	35.6% Pd/C aerogel (6)	DMF/isoPr <sub>2</sub> NH/100 °C/16 h <sup>c,d</sup>	15	81 (98–63)	332
5	H	I	Ph	22.69% Pd-CNF (1)	2-PrOH-H <sub>2</sub> O/Na <sub>3</sub> PO <sub>4</sub> /reflux/3 h	10	85 (88–84)	333
6	H	I	Ph	7.26% Pd-DOPA-pine-Fe <sub>2</sub> O <sub>3</sub> (6.8)	DMF/K <sub>2</sub> CO <sub>3</sub> /100 °C/30 min <sup>e</sup>	5	83.5 (85–82)	97
7	4-Ac	Br	Ph	0.6% Pd-124-PEG (5)	PEG/CsOAc/150 °C/24 h	10	94 (>99–75)	334
8	H	Br	Ph	Pd(OAc) <sub>2</sub> , 16 (2)	H <sub>2</sub> O/NaOH/80 °C/1 h	6	85 (87–82)	335
9	4-MeO	I	Ph	13.30% Pd-(84) (1)	EtOH/K <sub>2</sub> CO <sub>3</sub> /80 °C/2 h <sup>d</sup>	6	97.5 (100–72)	127
10	H	I	Ph	26.6% Pd-PS (1.5)	H <sub>2</sub> O/Et <sub>3</sub> N/80 °C/6 h	5	98.5 (99–97)	336
11	H	I	Ph	Pd-Co-sphere (2)	H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /80 °C/5 h <sup>c,d</sup>	7	96 (99–90)	337

<sup>a</sup> Percentage data show Pd loading (wt %) when available; data in parentheses indicate mol % of Pd used. <sup>b</sup> n.r. = not reported. Data in parentheses indicate range of yields. <sup>c</sup> Under inert atmosphere. <sup>d</sup> In the presence of CuI and PPh<sub>3</sub>. <sup>e</sup> Under microwave irradiation.

third run (a yield of 63%) but could be increased by a washing process (DMF, 120 °C, 2 days). A similar treatment was necessary after the sixth and 12th run. Very high yields (>90%) were reported for the coupling of iodoaromatics with phenylacetylene, hept-1-yne, and propargyl alcohol over a 46% Pd/C aerogel catalyst.

Hou and co-workers reported the synthesis of catalyst 22.69% Pd-CNF based on a carbon nanofiber material (CNF) made by carbonizing and reducing an electrospun poly(acrylonitrile)/Pd(OAc)<sub>2</sub> composite.<sup>333</sup> Pd particles with diameters in the range of 5–40 nm were detected by TEM. The catalyst afforded high, stable yields in a 10-run recycling test (entry 5) with 7.8% of the catalyst lost. As well as in Heck coupling (section 4.1.2, Table 3, entry 4) and the Suzuki reaction (section 5.1.2, Table 10, entry 15), catalyst 7.26% Pd-DOPA-pine-Fe<sub>2</sub>O<sub>3</sub> afforded high yields in the coupling of varied iodo- and bromoaromatics with phenylacetylene and 4-fluorophenylacetylene (79–88%). Catalyst performance was also similar in the recycling of iodobenzene and phenylacetylene (entry 6).

A carbapalladacycle complex anchored to PEG-6000 (catalyst 0.6% Pd-124-PEG) was evaluated by Corma and co-workers in various coupling reactions.<sup>334</sup> High yields could be achieved in the first seven runs in a recycling study in the Sonogashira reaction with significant drops in the last three uses (entry 7). The majority of the anchored palladacycle complex was found to decompose during the first cycle to form Pd particles with a broad size distribution of 4–40 nm (average particle size = 14 nm). The particle size distribution, however, did not change significantly in subsequent runs. This was attributed to PEG as ligand, which stabilizes Pd particles and prevents their agglomeration. The catalyst system proved to be inferior in recycling in the more demanding reaction of 4-bromoanisole and in the Heck and Suzuki coupling.



The use of 2-aminophenyl diphenylphosphinite (16) introduced as a new ligand for heterogeneous Heck coupling (section

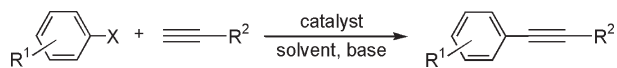
4.1.4, Scheme 2) has recently been tested in the Sonogashira reaction with Pd(OAc)<sub>2</sub>.<sup>335</sup> High yields were demonstrated for the coupling of various iodoarenes (at 80 °C) and bromoarenes (at 95 °C) with phenylacetylene in aqueous solution using NaOH as the base (73–93% isolated yields). The yields for chloroarenes are lower (36–73%). Iodobenzenes reacted at room temperature in the presence of TBAB (70–92%). Continuously decreasing yields were found in a six-run recycling study (entry 8).

The highest efficiency of the catalyst with the fluorinated star-shaped material stabilizing Pd nanoparticles [13.30% Pd-(84)] was observed in the Sonogashira reaction with yields of 100% dropping only in the sixth cycle<sup>127</sup> (entry 9). Compare these results to those reported for the Heck coupling [catalyst 11.87% Pd-(21), section 4.1.4, Scheme 7] and the Suzuki reaction (section 5.1.4, Scheme 23).

Catalyst 26.6% Pd-PS exhibiting excellent robustness in the Suzuki coupling (section 5.1.3, Table 11, entry 1) displayed similar efficiency in copper-free Sonogashira reactions in the coupling of iodoarenes with phenylacetylenes in the presence of 3 equiv of Et<sub>3</sub>N in water (yields of 74–99%).<sup>336</sup> Similar high yields were observed in reactions with oct-1-yne (80%) and trimethylsilylacetylene (74%), whereas bromobenzene reacted with phenylacetylene in a lower yield of 49%. Yields changed only slightly in a five-run recycling study (entry 10). Leaching levels were barely detectable, and the particle size practically did not change during recycling (2.7 ± 0.6 vs 2.6 ± 0.6 nm).

Pd-Co hollow nanospheres (average diameter = 100 nm) were prepared by the vesicle-assisted chemical reduction of PdCl<sub>2</sub> and CoCl<sub>2</sub> in an aqueous solution of TBAB.<sup>337</sup> The shell of the spheres contains nanoparticles of 3 nm with uniform distribution of Pd and Co and has a mesoporous structure. The best performance in the Sonogashira reaction was displayed by the catalyst with a Pd/Co ratio of 53:47 at. %, affording excellent yields (93–99%) in the coupling of iodobenzenes with phenylacetylene. Both bromobenzene and chlorobenzene reacted efficiently (yields of 87% and 70%, respectively). High yields decreased progressively in the last three runs of the recycling study (entry 11). Because atomic emission spectrometric analysis did not show changes in catalyst composition, the decrease was attributed to

Table 16. Sonogashira Coupling of Halobenzenes with Terminal Acetylenes Induced by Immobilized Palladium Complexes



entry	R <sup>1</sup>	X	R <sup>2</sup>	catalyst <sup>a</sup>	reaction conditions: solvent/base/temperature/time	number of reuses	average yield, <sup>b</sup> (%)	ref
1	H	I	Ph	4.18% Pd <sup>2+</sup> - <b>5b</b> -SiO <sub>2</sub> (1)	EtOH/K <sub>2</sub> CO <sub>3</sub> /80 °C/6 h <sup>c</sup>	30	96 (96)	138
2	H	I	Ph	3.7% Pd- <b>22a</b> -MCM41 (0.5)	H <sub>2</sub> O/piperidine/25 °C/18 h	5	91 (92–90)	338
3	4-NO <sub>2</sub>	I	Bu		H <sub>2</sub> O/piperidine/25 °C/12 h	5	94 (95–93)	
4	4-MeO	I	SiMe <sub>3</sub>		H <sub>2</sub> O/piperidine/25 °C/24 h	5	87 (89–86)	
5	H	I	SiMe <sub>3</sub>	4.04% Pd- <b>22b</b> -MCM41 (0.5)	piperidine/RT/2 h <sup>d,e</sup>	10	92 (93–91)	339
6	H	I	Bu	5.53% Pd- <b>86a</b> -MCM41 (0.5)	piperidine/RT/2 h <sup>d,e</sup>	10	97 (98–96)	340
7	4-MeO	Cl	Ph	2.23% Pd- <b>85b</b> -SiO <sub>2</sub> /Fe <sub>3</sub> O <sub>4</sub> (0.5)	H <sub>2</sub> O/piperidine/60 °C/6 h <sup>f</sup>	10	95 (96–94) <sup>g</sup>	264
8	H	I	Ph	1.94% Pd- <b>125</b> -Amberlyst (1)	H <sub>2</sub> O/Et <sub>3</sub> N/80 °C/1 h	5	96.5 (98–95)	341
9	H	I	Ph	Pd- <b>126</b> -DAB-dendr (2)	H <sub>2</sub> O/80 °C/48 h	7	62.5 (78–39) <sup>g</sup>	342
10	H	I	Ph	12.8% Pd- <b>35</b> -PVCarb (1)	Et <sub>3</sub> N–H <sub>2</sub> O/70 °C/10 h <sup>f</sup>	5	97 (99–95) <sup>g</sup>	290
11	4-Cl	I	Ph	12.8% Pd- <b>127</b> -polym (0.1)	pyrrolidine/H <sub>2</sub> O/reflux/1 h <sup>f</sup>	10	99 (99)	343
12	4-MeO	I	Ph			5	94 (96–92)	
13	4-Ac	Br	Ph	PdCl <sub>2</sub> (PhCN) <sub>2</sub> , <b>113a</b> (0.5)	toluene/isoPr <sub>2</sub> NH/60 °C/2 h <sup>d</sup>	7	89 (98–80)	296
14	4-Ac	Br	Ph	4.7% Pd-EnCat <sup>TM</sup> TPP30 (3.5)	MeCN/DBU/120 °C/10–15 min <sup>h</sup>	6	94 (98–90) <sup>g</sup>	344
15	4-MeO	I	Ph	5.48% Cu- <b>128</b> -SiO <sub>2</sub> (5)	DMF/K <sub>2</sub> CO <sub>3</sub> /110 °C/8 h <sup>c</sup>	6	89.5 (92–88)	345

<sup>a</sup> Percentage data show Pd loading (wt %) when available; data in parentheses indicate mol % of Pd used. <sup>b</sup> Data in parentheses indicate range of yields.

<sup>c</sup> Under nitrogen atmosphere. <sup>d</sup> In the presence of CuI. <sup>e</sup> Piperidine serves as both solvent and base. <sup>f</sup> In the presence of TBAB. <sup>g</sup> Conversion. <sup>h</sup> Under microwave irradiation with simultaneous cooling.

the loss of catalyst during centrifugal separation. Unfortunately, Pd leaching was not determined.

## 6.2. Studies with Immobilized Palladium Complexes

Catalyst 4.18% Pd<sup>2+</sup>-**5b**-SiO<sub>2</sub> developed by Wang and co-workers and discussed in connection with the Heck reaction (section 4.2.1, Table 5, entry 8) exhibited high efficiency in copper-free Sonogashira coupling in 30 consecutive reactions<sup>138</sup> (Table 16, entry 1). Varied iodoaromatics, activated bromo derivatives, and 2-bromo- and 3-bromopyridine reacted smoothly to give very high product yields (85–98%).

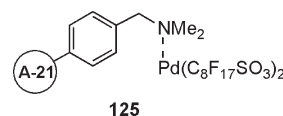
The thioether Pd<sup>0</sup> complex supported on MCM-41 (catalyst 3.7% Pd-**22a**-MCM41) found to afford high yields in 10 runs in the Heck reaction (section 4.2.1, Table 5, entry 1) has also been effective in copper-free Sonogashira coupling in water under aerobic conditions<sup>338</sup> (Table 16, entries 2–4). Only iodoarenes including 3-iodopyridine and 2-iodothiophene were tested and found to form products in yields of 78–93%. According to experimental observations, no further reaction in the filtration test, no Pd in the filtrate, and about the same Pd content of the fresh and recycled catalyst, the catalyst is leach-free. The related catalyst with the immobilized mercapto Pd<sup>0</sup> complex (catalyst 4.04% Pd-**22b**-MCM41), again, tested in other coupling reactions (Heck coupling, section 4.2.1, Table 5, entry 2; Suzuki reactions, section 5.4.2, Scheme 36), showed good catalyst performance in the Sonogashira coupling.<sup>339</sup> High yields were observed in 10 runs in the coupling of iodobenzene and trimethylsilylacetylene in the presence of CuI (Table 16, entry 5). Bromoarenes, however, failed to react under identical reaction conditions.

The MCM-41-supported bidentate phosphane Pd<sup>0</sup> complex (5.53% Pd-**86a**-MCM41) developed by Cai and co-workers and applied in Suzuki couplings (section 5.2.1, Table 12, entry 4; section 5.4.3, Scheme 39) has also been tested in the Sonogashira coupling of iodobenzene and hex-1-yne. The catalyst, used in the

presence of CuI, was found to be highly efficient and could be recycled at least in 10 runs<sup>340</sup> (Table 16, entry 6). The outstanding durability was attributed to bidentate chelation, the location of palladium species on the inner surface of the mesopores of MCM-41, and the low reaction temperature applied.

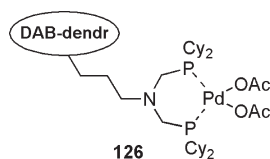
Silica-coated and functionalized magnetic iron oxide (2.23% Pd-**85b**-SiO<sub>2</sub>/Fe<sub>3</sub>O<sub>4</sub>) developed by Jin and Lee and studied in the Suzuki coupling of aryl chlorides (section 5.2.1, Table 12, entry 18) exhibited similar outstanding catalyst performance in the Sonogashira reaction.<sup>264</sup> Varied chloro derivatives afforded coupling products in good to high yields (74–96%). As shown by data in entry 7 (Table 16), the catalyst is fairly stable in recycling experiments.

The treatment of Amberlyst A-21 with Pd perfluorooctanesulfonate [Pd(C<sub>8</sub>F<sub>17</sub>SO<sub>3</sub>)<sub>2</sub>] gave the polymer-supported fluororous catalyst 1.94% Pd-**125**-Amberlyst.<sup>341</sup> High efficiency was shown in the coupling of varied terminal acetylenes with iodo-, bromo-, and chloroarenes (70–96% yields) under ligand- and copper-free conditions used in air in aqueous solution. High yields decreased slightly in reuse (entry 8). A small amount of leaching (11.6 ppm of Pd) was detected in the last run.



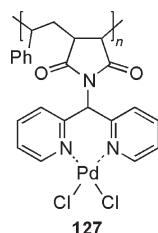
The performance of monomeric and dendritic Pd complexes based on commercial polyamino dendrimers was evaluated in the Sonogashira reaction under copper-free conditions.<sup>342</sup> With a monomeric bis-(*tert*-butylphosphane)-functionalized complex, TON values as high as 71 000 were achieved in the coupling of iodoarenes and phenylacetylene. Among the dendritic Pd complexes, catalytic activity was shown to decrease with increasing

dendrimer generation. In recycling studies, in turn, Pd-126-DAB-dendr exhibited somewhat better catalyst performance (DAB-dendr = generation 3 dendrimer with 16 NH<sub>2</sub> groups functionalized with bulky dicyclohexylphosphanes; in formula 126, only one of the ligands is shown for clarity). High yields were measured up to four runs with significant drops in subsequent uses (entry 9).



As was already discussed, catalyst 12.8% Pd-35-PVCarb afforded high yields in the Heck coupling (section 4.2.2, Table 6, entry 6) and the Suzuki reaction (section 5.2.2, Table 13, entry 23). Similar performance was observed in the Sonogashira coupling.<sup>290</sup> Iodo- and bromoarenes reacted with phenylacetylene to give high product yields (78–99%; chlorobenzene = 18%), and high yields with small drops were measured in recycling experiments (entry 10).

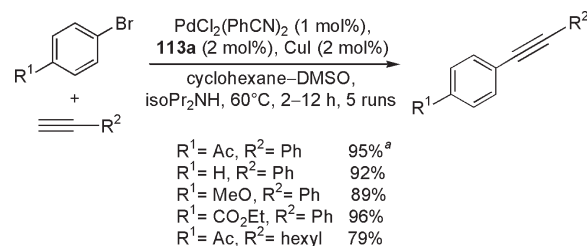
A commercially available poly(styrene-*alt*-maleic anhydride) resin was reacted with di(2-pyridyl)methylamine, and then the supported ligand thus prepared was treated with Na<sub>2</sub>[PdCl<sub>4</sub>] to get catalyst 12.8% Pd-127-polym.<sup>343</sup> It gave high yields in the coupling of phenylacetylene with iodo- and bromobenzenes (96–99%) and 2-bromothiophene (92%) under copper-free conditions. These values are comparable to those found with the corresponding monomeric homogeneous complex. At low Pd loading (0.001 mol %), however, the polymer-anchored complex showed much better efficiency (TOF of 3225 vs 730 h<sup>−1</sup>). High and stable yields were observed in varied recycling studies (Table 16, entries 11 and 12). Outstanding robustness was found in the recycling experiments with 4-chloriodobenzene (entry 11): the catalyst was reused in the first five runs without separation, and then filtered, washed with water and ethyl acetate, vacuum-dried, and reused in five additional cycles. The stability of the catalyst in other coupling reactions is inferior. Moreover, in the Suzuki coupling, Pd particles were formed and observed to be dispersed into the polymer matrix after the first run with 2.4% of Pd leached.



The solvent-resistant nanofiltration technique has been applied for the Sonogashira coupling using PdCl<sub>2</sub>(PhCN)<sub>2</sub> and polymer 113a.<sup>296</sup> Recycling occurred with slightly lower efficiency (entry 13) as compared to that in the Suzuki reaction (section 5.2.2, Table 13, entry 28) with TOF values of 237, 230, 220, and 218 h<sup>−1</sup> in the first four cycles.

Pd-EnCat TPP30 is a commercially available catalyst with Pd(OAc)<sub>2</sub> and triphenylphosphane microencapsulated in a polyurea matrix with a Pd loading of 4.7 wt %. Ley and co-workers

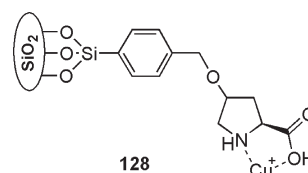
**Scheme 42. Sonogashira Coupling of Bromoarenes and Terminal Acetylenes in the Presence of PdCl<sub>2</sub>(PhCN)<sub>2</sub> and Ligand 113a<sup>a</sup>**



<sup>a</sup> (a) Amounts of isolated products after chromatographic purification.

have found it highly efficient in the rapid synthesis of functionalized acetylenes.<sup>344</sup> Results showed unequivocally that the catalyst outperforms other Pd-EnCat preparations in the coupling of iodo- and bromoarenes with varied terminal acetylenes. Coupling products are formed in good to excellent yields (53–99%) under copper-free conditions in the presence of DBU under microwave irradiation with simultaneous cooling. This is necessary to prevent thermal decomposition and furnishes products with significantly higher purity. Although 4.7% Pd-EnCat TPP30 operates in air, isomeric 1,2-dichloroethylenes reacted only in dry toluene as solvent under inert atmosphere in the presence of a catalytic amount of CuI to yield enynes (67–89%). Slightly decreasing yields were detected in a recycling study with a significantly longer reaction in the sixth run to maintain high conversion (entry 14). The filtrate of the reaction solution did not show any activity, albeit, it was separated after full conversion. Formation of Pd black, however, was observed, which could be prevented by running the reaction in the presence of the thiourea-functionalized strong polymeric scavenger Quadrapure TU resin.

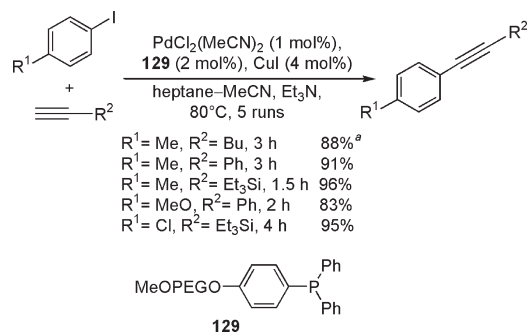
The final entry is a unique example for the application of copper catalysts in Sonogashira coupling. Catalyst 5.48% Cu-128-SiO<sub>2</sub> with a proline-copper(I) active site anchored to modified silica is efficient and recyclable in the Sonogashira reaction of 4-iodoanisole with phenylacetylene (Table 16, entry 15) and gives moderate to high yields in the coupling of other reactant pairs (62–96% isolated yields).<sup>345</sup> The issue of the involvement of Pd contamination, however, can also be raised here (see also the discussion for Scheme 8 with the use of flower-like Co nanostructures in the Heck coupling).



Plenio et al. have carried out comprehensive studies of Sonogashira couplings. Pd-phosphane catalysts phase-tagged with soluble polymers were formed in situ and used under biphasic conditions. Nonpolar biphasic catalysis was applied with PdCl<sub>2</sub>(PhCN)<sub>2</sub> and polymer 113a similar to that used in the Suzuki coupling (section 5.2.2, Scheme 28) except that in this case the cyclohexane–DMSO solvent combination was used<sup>295</sup> (Scheme 42). Yields in the last two runs of each test are nearly constant, testifying to high catalyst stability. In the reaction of 4-bromoacetophenone and phenylacetylene, the more informative

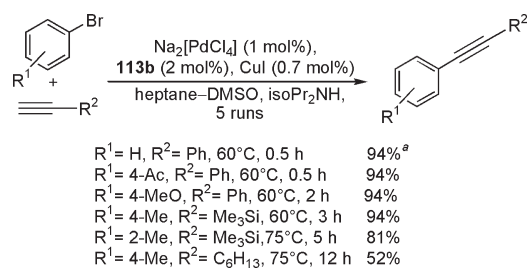


**Scheme 43.** Sonogashira Couplings of Iodoarenes and Terminal Acetylenes in the Presence of  $\text{PdCl}_2(\text{MeCN})_2$  and Ligand **129**<sup>a</sup>



<sup>a</sup> (a) Amounts of isolated products after chromatographic purification.

**Scheme 44.** Sonogashira Coupling of Bromoarenes and Terminal Acetylenes in the Presence of  $\text{Na}_2[\text{PdCl}_4]$  and Ligand **113b**<sup>a</sup>



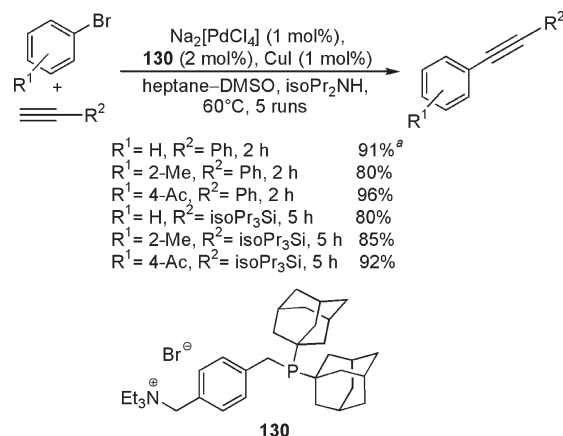
<sup>a</sup> (a) Amounts of isolated products after chromatographic purification.

TOF values per cycle were found to be practically constant (220, 220, 215, 210, and 210  $\text{h}^{-1}$ ).

$\text{PdCl}_2(\text{MeCN})_2$  and  $\text{MeOPEG}_{2000}$ -linked phosphane **129** in acetonitrile–heptane induced the smooth biphasic coupling of iodoarenes and varied acetylenes in five-run recycling experiments<sup>346</sup> (Scheme 43, selected examples). Coupling of bromoarenes under the same conditions, however, gave only poor yields. The use of  $\text{Na}_2[\text{PdCl}_4]$  with the sterically demanding electron-rich phosphane covalently linked to  $\text{MeOPEG}_{2000}$  (**113b**, see its use in Suzuki coupling, section 5.2.2, Schemes 29 and 30), in turn, resulted in excellent catalyst performance (Scheme 44, selected examples) similar to that of **129**. TOF data at low conversion for the coupling of phenylacetylene with bromobenzene (for 20 min: 440/432/390/336/312  $\text{h}^{-1}$ ), 4-bromoanisole (for 30 min: 336/320/292/260/252  $\text{h}^{-1}$ ), and 4-bromoacetophenone (for 10 min: 1150/1120/1020/912/880  $\text{h}^{-1}$ ) show, however, significant decreases. Addition of CuI to the reaction mixture before reuse reactivated the catalyst: the TOF of 880  $\text{h}^{-1}$  for 4-bromoacetophenone in the fifth run increased to 1000  $\text{h}^{-1}$  in the sixth run. Pd leaching to the heptane phase was detected to be 0.005%.

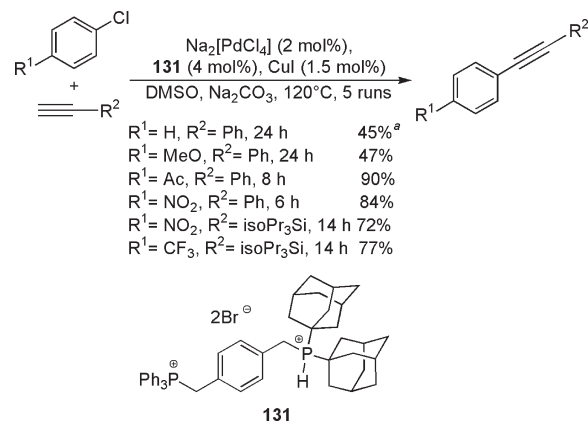
The new phase-tagged phosphanes **130** and **131** have been applied in similar studies in DMSO.<sup>347</sup> Products were extracted with heptane, and then the DMSO phase with the phase-tagged catalysts was reused. Alternatively, a biphasic mixture of heptane–DMSO was applied, and the heptane layer was separated. Bromoarenes and terminal acetylenes coupled in the presence of CuI with the catalyst system  $\text{Na}_2[\text{PdCl}_4]$  and **130** in five runs in overall yields of 72–96% (Scheme 45, selected examples).

**Scheme 45.** Sonogashira Coupling of Bromoarenes and Terminal Acetylenes in the Presence of  $\text{Na}_2[\text{PdCl}_4]$  and Ligand **130**<sup>a</sup>



<sup>a</sup> (a) Amounts of isolated products after chromatographic purification.

**Scheme 46.** Sonogashira Coupling of Chloroarenes and Terminal Acetylenes in the Presence of  $\text{Na}_2[\text{PdCl}_4]$  and Ligand **131**<sup>a</sup>

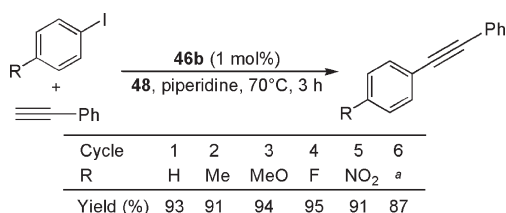
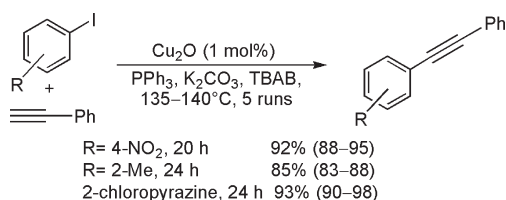
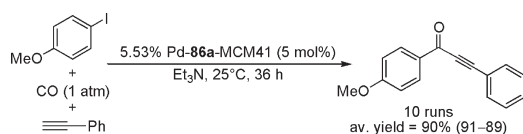


<sup>a</sup> (a) Amounts of isolated products after chromatographic purification.

Coupling of chlorobenzenes could be performed with similar efficiency with increased amount of catalysts and  $\text{Na}_2\text{CO}_3$  as base at higher temperature.<sup>347</sup> Both catalyst systems with phase-tagged phosphanes **130** (data not shown) and **131** retained high yields in five runs (Scheme 46, selected examples). Overall yields are in the range of 72–90% for electron-deficient compounds, but deactivated chloroarenes gave yields below 50%. TOF values determined for the reaction of phenylacetylene with 4-bromoacetophenone are close to constant (103/102/100/97/96  $\text{h}^{-1}$ ), but those for 4-chloroacetophenone (60/58/56/54/48  $\text{h}^{-1}$ ) decrease by about 20%. The amount of Pd retained in the DMSO phase was >99.95%.

### 6.3. Miscellaneous Examples

Pyrazolyl-functionalized ionic liquid **48** developed by Shreeve and co-workers and evaluated in combination with *N*-heterocyclic carbene  $\text{Pd}^{2+}$  complexes (Heck coupling, section 4.3, Table 7, entry 8) has been tested in the Sonogashira cross-coupling.<sup>166</sup> Recycling studies were performed with complex **46b** in IL **48**

**Scheme 47. Sonogashira Coupling Induced by Complex 46b in IL 48<sup>a</sup>**<sup>a</sup> (a) 2-Iodothiophene.**Scheme 48. Sonogashira Coupling Induced by Octahedral Cu<sub>2</sub>O Particles****Scheme 49. Carbonylative Sonogashira Coupling Induced by Catalyst 5.53% Pd-86a-MCM41**

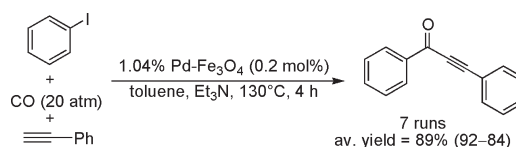
with the consecutive reaction of various iodoarenes (Scheme 47). Yields are high with no significant effect of the substituents and without the formation of homocoupling products. The method for catalyst recycling was already discussed (see section 4.3 for the use of the related complex 46a in Heck couplings).

Octahedral Cu<sub>2</sub>O particles were shown by Li, Zhang, and co-workers to be highly efficient in the presence of PPh<sub>3</sub> and TBAB in Sonogashira reaction.<sup>348</sup> The coupling of a range of haloarenes and alkynes gave varied yields (40–98%). The catalyst exhibits an interesting property in recycling studies by displaying increasing yields in consecutive reactions (Scheme 48), but this phenomenon was not commented on.

#### 6.4. Carbonylative Sonogashira Couplings

Two samples have been tested in carbonylative Sonogashira coupling. The characteristics of catalyst 5.53% Pd-86a-MCM41 in a recycling study in the carbonylative coupling under atmospheric pressure of CO<sup>349</sup> (Scheme 49) are very similar to those found in Sonogashira coupling (section 6.2, Table 16, entry 6).

According to TEM characterization, the superparamagnetic 1.04% Pd-Fe<sub>3</sub>O<sub>4</sub> catalyst, prepared by wet impregnation of Fe<sub>3</sub>O<sub>4</sub> with Na<sub>2</sub>[PdCl<sub>4</sub>] followed by reduction with KBH<sub>4</sub>, consists of Pd particles of 5 nm in diameter entrapped in iron oxide nanoparticles<sup>350</sup> (25–50 nm). The catalyst was active in the carbonylative Sonogashira coupling under copper- and phosphane-free conditions and offered medium to high yields in the coupling of various iodoarenes and terminal acetylenes (50–95%). It was recycled seven times after magnetic separation,

**Scheme 50. Carbonylative Sonogashira Coupling over 1.04% Pd-Fe<sub>3</sub>O<sub>4</sub>**

showing gradual decreases of yields (Scheme 50). Pd leaching after the first and seven cycles was, respectively, ~6% and ~2%.

#### 6.5. Summary

In the Sonogashira coupling, only complexes exhibit catalyst performance, which matches the criteria for inclusion in this summary. These are supported complexes 4.18% Pd<sup>2+</sup>-5b-SiO<sub>2</sub> (Table 16, entry 1), 4.04% Pd-22b-MCM41 (Table 16, entry 5), 2.23% Pd-85b-SiO<sub>2</sub>/Fe<sub>3</sub>O<sub>4</sub> (Table 16, entry 7), and 12.8% Pd-127-polym (Table 16, entry 11) as well as complex 46b used in IL 48 (Scheme 47). MCM-41-supported complex 5.53% Pd-86a-MCM41 showed stable activity in both Sonogashira reaction (Table 16, entry 6) and carbonylative Sonogashira coupling (Scheme 49). However, none of the catalysts tested in the Sonogashira reaction give high TON values comparable to those mentioned in the Heck reaction and Suzuki coupling.

### 7. STILLE COUPLINGS

The palladium-catalyzed coupling of organostannanes with organic halides is the Stille cross-coupling.<sup>351–355</sup> This method has been studied less frequently and applied less widely when compared to the three major C–C coupling reactions discussed above. Particular concerns are the toxicity of organotin reagents and difficulties to control selectivity.

#### 7.1. Stille Coupling

The results of recycling studies with various catalysts (supported Pd particles and complexes as well as homogeneous complexes) are included in Table 17.

Catalyst 0.48% Pd-SiO<sub>2</sub> with entrapped nanopalladium clusters within the silica matrix shown to be recyclable affording high yields in other coupling reactions<sup>68</sup> (Heck coupling, section 4.1.1, Table 1, entry 1; Suzuki reaction, section 5.1.1, Table 8, entry 4) has also been used successfully to perform the Stille reaction. The four bromoarenes tested gave good to high product yields (73–98%). The catalyst gives high yields and exhibits excellent reusability in the coupling of bromobenzene (Table 17, entry 1), whereas drops of yields are experienced with deactivated 4-bromotoluene (entry 2).

The bidentate phosphane Pd<sup>0</sup> complex supported on MCM-41 (catalyst 5.53% Pd-86a-MCM41) has been applied successfully in Suzuki couplings (section 5.2.1, Table 12, entry 4; section 5.4.3, Scheme 39) and Sonogashira reactions (section 6.2, Table 16, entry 6; section 6.4, Scheme 49). It displayed high stability and excellent reusability in the Stille coupling as well<sup>356</sup> (Table 17, entry 3). Good product yields (around 80–90%) were reported for the reaction of a range of iodo- and bromoarenes with alkynyl-, vinyl-, and arylstannanes. Catalyst 4.04% Pd-22b-MCM41 has been widely tested in important C–C coupling processes (Heck coupling, section 4.2.1, Table 5, entry 2; Suzuki reaction, section 5.4.2, Scheme 36; Sonogashira reaction, section 6.2, Table 16, entry 5). It was successfully applied in the Stille coupling of a wide variety of iodoarenes with

Table 17. Stille Coupling of Aromatic Halides with Tributylstannanes

entry	R <sup>1</sup>	X	R <sup>2</sup>	catalyst <sup>a</sup>	reaction conditions: solvent/temperature/time	number of reuses	average yield, <sup>b</sup> (%)	ref
1	H	Br	Ph	0.48% Pd-SiO <sub>2</sub> (1)	H <sub>2</sub> O/80 °C/7 h	6	quantitative	68
2	4-Me	Br	Ph			6	72.5 (75–70)	
3	3-CN	I	(Z)-1-hexenyl	5.53% Pd- <b>86a</b> -MCM41 (0.5)	DMF-H <sub>2</sub> O/60 °C/6 h	10	90 (91–89)	356
4	4-CO <sub>2</sub> Me	I	PhC≡C	4.04% Pd- <b>22b</b> -MCM41 (1)	DMF-H <sub>2</sub> O/60 °C/3 h	10	89 (90–88)	357
5	4-Me	I	Ph	10.53% Pd-MgO (1)	NMP/100 °C/2.5 h <sup>c</sup>	5	n.r. (92–90)	100
6	H	Cl	Ph	10.53% Pd-MgO (3)	NMP/100 °C/12 h <sup>c</sup>	5	n.r. (85–84)	
7	H	I	Ph	<b>115</b> (5)	[C <sub>3</sub> H <sub>6</sub> CNpy][Tf <sub>2</sub> N]/80 °C/12 h	9	50 (53–47)	301
8	H	I	vinyl	Pd-( <b>132</b> + <b>133</b> ) (0.5)	–/80 °C/4 h	6	88 (93–85)	358
9	4-CO <sub>2</sub> Me	Br	2-furyl	Pd- <b>120b</b> (1.5)	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> -DMF/80 °C/3 h <sup>d,e</sup>	6	87 (91–83)	359
10	4-CO <sub>2</sub> Me	Br	2-furyl	Pd- <b>120c</b> (1.5)		6	87 (89–84)	
11	4-CO <sub>2</sub> Me	Br	2-furyl	Pd- <b>120d</b> (1.5)		6	85 (90–81)	
12	4-MeO	I	Ph	Cu <sub>2</sub> O (10)	P( <i>o</i> -tolyl) <sub>3</sub> /125–130 °C/12 h <sup>f</sup>	5	93.5 (87–98)	360

<sup>a</sup> Percentage data show Pd loading (wt %) when available; data in parentheses indicate mol % of Pd used. <sup>b</sup> n.r. = not reported. Data in parentheses indicate range of yields. <sup>c</sup> In the presence of NaOAc. <sup>d</sup> In the presence of LiCl. <sup>e</sup> Under argon atmosphere. <sup>f</sup> In the presence of KF and TBAB.

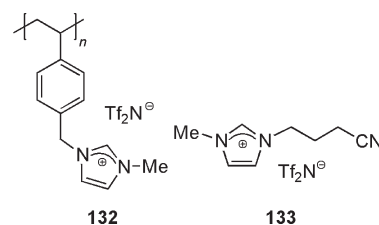
organostannanes to afford products in medium to high yields (72–90%).<sup>357</sup> Bromoarenes required prolonged reaction and gave lower yields (62–80%). No further reaction in the hot filtration test and no leached Pd were detected. Furthermore, XPS analysis of the used catalyst did not reveal any significant changes. The performance of the catalyst in recycling (entry 4) is practically identical to that of 5.53% Pd-**86a**-MCM41 (entry 3).

Various halobenzenes have been reported to give coupling products in high yields (70–95%) with the use of catalyst 10.53% Pd-MgO. Consistently high yields were found in the Stille reaction in five runs with both 4-iodotoluene (entry 5) and chlorobenzene with increased catalyst loading (3 mol %) in longer reactions<sup>100</sup> (entry 6). These features are very similar to those found in the Heck coupling (section 4.1.2, Table 3, entries 7–9), Suzuki reaction (section 5.1.2, Table 10, entries 8 and 9), and Sonogashira coupling (section 6.1, Table 15, entries 1 and 2). Leaching was also analyzed, but Pd was not detected in the reaction mixture.

The precatalyst **115** in combination with IL [C<sub>3</sub>H<sub>6</sub>CNpy][Tf<sub>2</sub>N] developed by Dyson et al. was evaluated in the Stille reaction to give medium and slightly decreasing yields in nine runs<sup>301</sup> (entry 7). Interestingly, the catalyst system in the Suzuki coupling was homogeneous (section 5.3, Table 14, entry 7), whereas nanoparticles (~5 nm) were detected in the Stille reaction. Results determined by using the *N*-butyl-substituted IL [C<sub>4</sub>H<sub>9</sub>py][Tf<sub>2</sub>N] were inferior with a yield of a mere 10% in the sixth run and more significant Pd leaching (46 vs 7 ppm). Furthermore, large aggregates could be detected in the presence of the latter IL. Such differences indicate the possible role of the complexing ability and stabilizing effect of the nitrile function.

Dyson and co-workers<sup>358</sup> prepared Pd nanoparticles (mean particle size = 5 nm) protected by an imidazolium-based ionic polymer (**132**) in functionalized ionic liquid (**133**). In generating the nanoparticles, first PdCl<sub>2</sub> was dissolved in the mixture of **132** and **133**, and then PdCl<sub>2</sub> coordinated to the nitrile groups was reduced with NaBH<sub>4</sub> to produce a black solution [catalyst Pd-(**132**+**133**)]. Pd nanoparticles are remarkably stable in the mixture of the ionic polymer and ionic liquid. High yields were

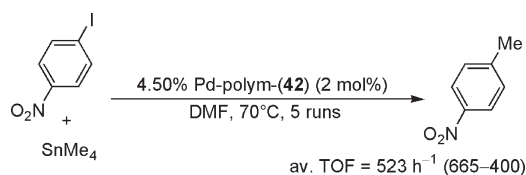
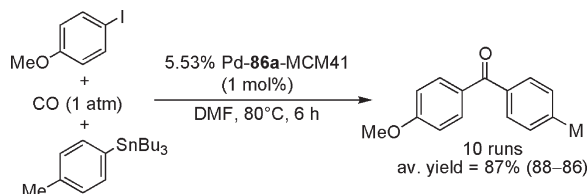
measured for the reaction of activated iodo and bromo compounds (74–100%). Bromobenzene and 4-cyanobromobenzene, in turn, were less reactive (yields of 10% and 35%, respectively). Yields in recycling experiments were high but decreased slightly (entry 8), whereas the Pd content in the organic fraction was shown to be below the detection limit of 1 ppm. The catalyst is also active in Heck and Suzuki coupling but gives an orange solution because oxidative addition results in the formation of Pd<sup>2+</sup> species that are solubilized and stabilized by the IL. In contrast, the formation of Pd<sup>2+</sup> species in Stille coupling was hardly detectable.



Bannwarth and Schneider used perfluoro-tagged Pd complexes **120b**–**120d** in a fluorous biphasic system to couple aromatic bromo compounds and aromatic tributylstannyl derivatives.<sup>359</sup> Yields with 2-tributylstannylfuran and 3-tributylstannylanisole vary in the range of 55–98%. Lower efficiency (yields of 39–82%) for 2-tributylstannylanisole is probably due to steric hindrance. Yields in six-run recycling studies in the coupling of methyl 4-bromobenzoate and 2-tributylstannylfuran are comparably high with small decreases for all three complexes (entries 9–11). See also the use of this catalyst system in the Suzuki coupling (section 5.3, Scheme 31).

The last example in Table 17 shows the use of Cu<sub>2</sub>O nanoparticles in the presence of tri(*ortho*-tolyl)phosphane.<sup>360</sup> A variety of aromatic halides including chloroarenes underwent smooth reaction with organotin reagents to give the coupling products in high yields. An exception is the transformation of deactivated 4-chloroanisole (10% yield in 72 h). Cu<sub>2</sub>O afforded



**Scheme 51.** Stille Coupling of 4-Iodonitrobenzene with Tetramethyltin**Scheme 52.** Carbonylative Stille Coupling Catalyzed by Catalyst 5.53% Pd-86a-MCM41

high and increasing yields in recycling with 4-iodoanisole (entry 12). These features are similar to those found in Sonogashira coupling (section 6.3, Scheme 48). A similar study with 4-bromoanisole gave a low yield of 55% in the second run. Recycling of the catalyst system was made by charging the solid residue with the reactants and KF after product extraction and evaporation.

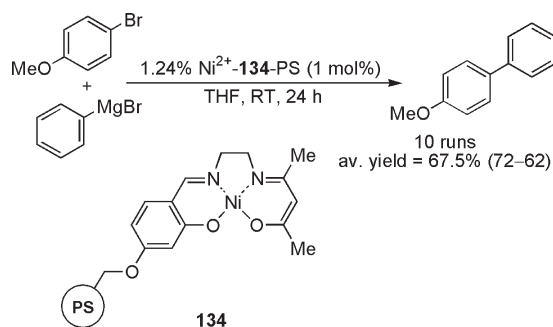
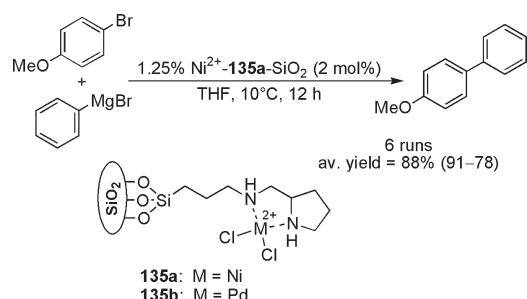
Catalyst Pd-polym-(42) tested in the Heck reaction with a lower loading (section 4.2.2, Scheme 9) displayed high efficiency in the Stille coupling of iodobenzenes and substituted bromobenzenes with varied trimethyltin and tributyltin derivatives (yields of 63 to >99%).<sup>361</sup> Bromobenzene showed similar reactivity in the presence of TBAB (90% vs 38%), but it is related to increased Pd leaching. TON values in the recycling study decreased considerably (Scheme 51) attributed to the accumulation of tin derivatives on the polymer. Further conversions in hot filtration tests (10–20%) were interpreted by a mainly homogeneous reaction route with a short lifetime of the leached palladium species.

## 7.2. Carbonylative Stille Coupling

The MCM-41-supported bidentate phosphane Pd<sup>0</sup> complex (catalyst 5.53% Pd-86a-MCM41) has been widely used in coupling reactions (section 5.2.1, Table 12, entry 4; section 6.2, Table 16, entry 6; section 7.1, Table 17, entry 3) including carbonylative couplings (section 5.4.3, Scheme 39; section 6.4, Scheme 49). It was successfully applied in the first heterogeneous carbonylative Stille coupling of a variety of organostannanes and aryl iodides (isolated yields = 72–90%).<sup>362</sup> Consistently high yields were observed in a 10-run recycling study (Scheme 52).

## 7.3. Summary

The three catalyst systems affording consistently high yields in Stille couplings (0.48% Pd-SiO<sub>2</sub>, Table 17, entry 1; supported complexes 5.53% Pd-86a-MCM41, Table 17, entry 3; 4.04% Pd-22b-MCM41, Table 17, entry 4) or in carbonylative Stille reaction (5.53% Pd-86a-MCM41, Scheme 52) were shown to exhibit similar properties in other coupling reactions. There is no report on catalysts with high TON.

**Scheme 53.** Kumada Coupling Catalyzed by Ni<sup>2+</sup> Anchored to Merrifield Resin**Scheme 54.** Kumada Coupling Catalyzed by Ni<sup>2+</sup> Anchored to Silica

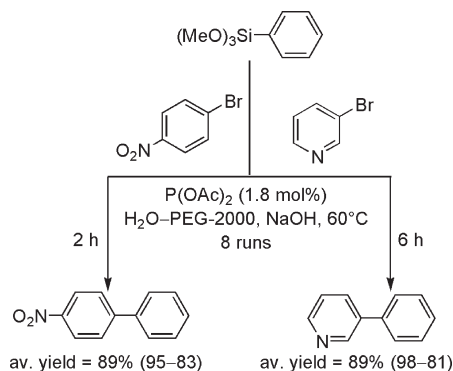
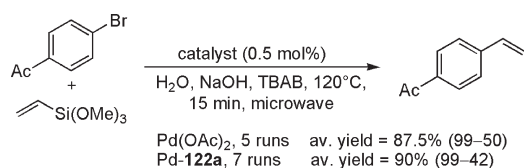
## 8. MISCELLANEOUS CROSS-COUPLING REACTIONS

The following coupling reactions are all unique examples because they are less frequently applied and less studied particularly considering catalyst recycling.

Both Ni and Pd catalysts are active in the coupling of Grignard reagents with organic halides called the Kumada reaction.<sup>363</sup> Unfortunately, results of recycling studies are available only for Ni-mediated reactions. A Ni complex anchored to Merrifield resin (0.88% Ni<sup>2+</sup>-134-PS) proved to be an active catalyst in room-temperature Kumada couplings.<sup>364</sup> Bromobenzenes coupled with Grignard reagents of bromobenzene, 2-bromothiophene, and methyl bromide to afford varied yields of the corresponding biaryls (37 to >99%). Yields changed irregularly in a 10-run recycling study (Scheme 53). Nickel leaching was not detected even at subppm sensitivities.

*N*-Boc-protected proline was anchored to silica modified with (3-aminopropyl)triethoxysilane. After removal of the protecting group and reduction of the carbonyl function, reaction with NiCl<sub>2</sub> gave catalyst 1.25% Ni<sup>2+</sup>-135a-SiO<sub>2</sub>.<sup>365</sup> Decreasing yields are observed in repeated uses in six runs (Scheme 54). In the last cycle with a lower yield (78%), the color of the originally pale yellow catalyst changed to dark grayish, which is presumably due to the formation of Ni and NiO. Nickel concentrations in the filtrates were detected to be less than 0.5 ppm.

Zhang and Shi have reported the cross-coupling of aryl bromides and arylsiloxanes catalyzed by Pd(OAc)<sub>2</sub><sup>366</sup> (Hiyama coupling<sup>367,368</sup>). Good to high yields (60–99%) were found in aqueous medium under mild conditions in an open atmosphere. The catalyst system showed high efficiency with decreasing yields in recycling studies (Scheme 55). Recycling was made by adding

Scheme 55. Hiyama Couplings Catalyzed by Pd(OAc)<sub>2</sub>Scheme 56. Hiyama Couplings Induced by Pd(OAc)<sub>2</sub> and Pd-122a

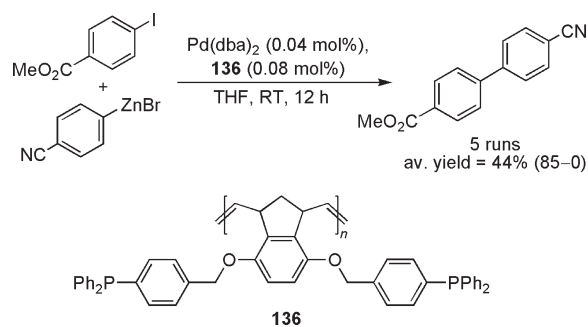
new reactants, NaOH, and, after the third, fifth, and seventh runs, water to the catalyst phase after the extraction of the products.

Alacid and Nájera have performed the coupling of aromatic halides and alkenyltrialkoxysilanes in aqueous NaOH.<sup>369</sup> Pd(OAc)<sub>2</sub> and oxime-derived palladacycle Pd-122a served as catalysts under thermal or microwave heating. Both catalysts are assumed to be precatalyst and the source of Pd nanoparticles. Medium-to-high yields (60–99%) were observed in the reaction of haloarenes with vinyltrialkoxysilanes. Alkenyltrialkoxysilanes reacted with similar efficiency (70–99%) with moderate to high  $\beta/\alpha$  regioselectivities and varied stereoselectivities ( $E/Z = 96:4$ – $55:45$ ). Both catalysts gave high initial product yields in recycling experiments (Scheme 56) with large drops in the last run. Furthermore, significant Pd leaching into the product was measured [Pd(OAc)<sub>2</sub>, fifth run = 192 ppm; Pd-122a, seventh run = 219 ppm].

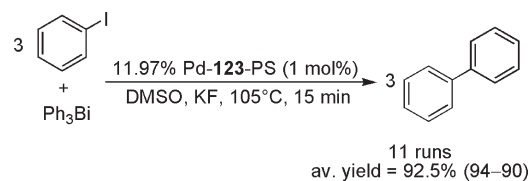
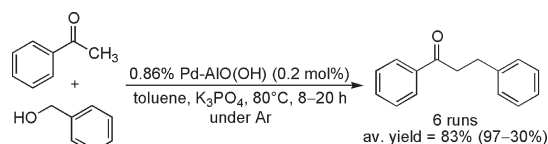
A single example of Negishi coupling<sup>370</sup> is barely qualified by affording high but rapidly diminishing yields in the reaction of methyl 4-iodobenzoate and 4-cyanophenylzinc bromide induced by Pd(dba)<sub>2</sub> in the presence of polymeric phosphane ligand **136**.<sup>371</sup> Catalytic activity is completely lost in the last run (Scheme 57), whereas somewhat better still unsatisfactory performance was observed in the Heck and Sonogashira reaction (10% and 30% activity loss in five cycles).

The polystyrene-supported Pd<sup>2+</sup> catalyst (11.97% Pd-123-PS) proved to be highly efficient in the rapid coupling reaction of aryl iodides and bromides with triarylbiaryl.<sup>372</sup> The reaction is atom-efficient, requires the use of KF, works in air, and gives polyfunctional biaryls in fair to high yields (43–94%). High yields and stability were reported when the catalyst was reused in 11 runs (Scheme 58).

Park and co-workers have developed a method for the  $\alpha$ -alkylation of ketones with alcohols using a catalyst that contains palladium nanoparticles embedded in aluminum hydroxide.<sup>373</sup> The synthesis mixture composed of tetra(ethylene glycol),

Scheme 57. Negishi Coupling Induced by Pd(dba)<sub>2</sub> in the Presence of Ligand **136**

Scheme 58. Coupling of Iodobenzene with Triphenylbismuth Catalyzed by 11.97% Pd-123-PS

Scheme 59.  $\alpha$ -Alkylation of Ketones with Alcohols Catalyzed by Pd Particles

(*sec*-BuO)<sub>3</sub>Al, butan-1-ol, and [Pd(PPh<sub>3</sub>)<sub>4</sub>] at 120 °C produced a black powder with 0.86 wt % of Pd loading.<sup>374</sup> To maintain high yields in recycling, the addition of 1 equiv of K<sub>3</sub>PO<sub>4</sub> was required after the second run (a yield of 30%), and the reaction time was increased to 20 h in the last run to have a yield of 96% (Scheme 59).

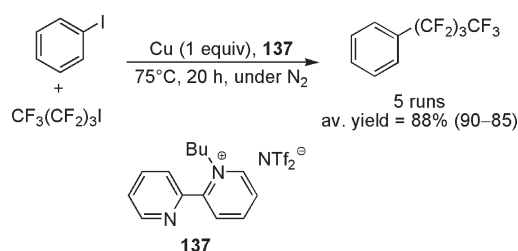
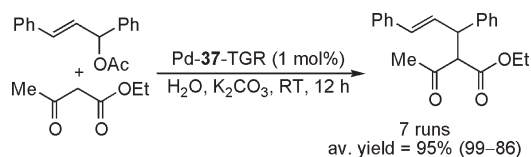
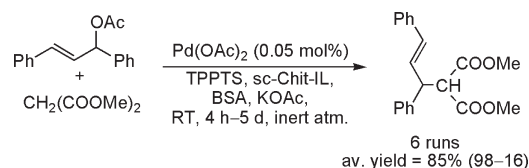
Shreeve et al. performed the copper-catalyzed coupling of iodoarenes with perfluoroalkyl iodides and bromoperfluorobenzene.<sup>375</sup> The bipyridinium salt **137** in the presence of activated copper was shown to act both as an efficient ligand and as a recyclable solvent to afford high product yields (84–91%). Ullmann-type homocoupling products (symmetric biaryls) under these conditions were not detected. High yields were also reported in the reuse of the catalyst system (Scheme 60).

## 9. ALLYLATIONS

Pd catalysts can induce the coupling of varied allylic derivatives to form C–C coupling products. In the Tsuji–Trost allylation,<sup>376,377</sup> activated C-nucleophiles are reacted. Allylation of boron reagents with allyl alcohol derivatives affords the synthesis allyl-substituted aromatics and 1,4-dienes.<sup>378</sup>

### 9.1. Tsuji–Trost Allylation

Catalyst Pd-37-TGR with a Pd-phosphane complex supported on the amphiphilic resin TentaGel developed by Uozumi and

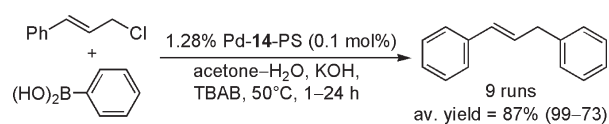
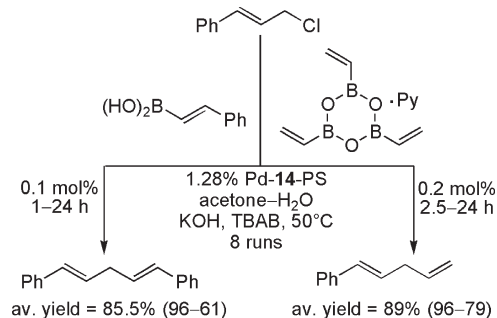
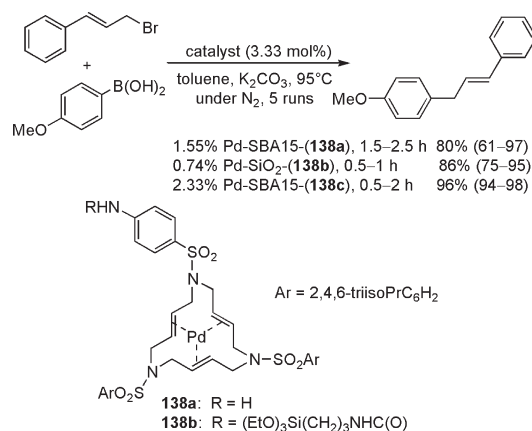
**Scheme 60.** Perfluorobutylation of Iodobenzene Induced by Copper**Scheme 61.** Allylation of Ethyl Acetoacetate Induced by Catalyst Pd-37-TGR**Scheme 62.** Allylation of Dimethyl Malonate

co-workers<sup>379</sup> worked efficiently in the allylation of ethyl acetoacetate with (*E*)-1,3-diphenyl-1-acetoxyprop-2-ene in water (Scheme 61).

Chitosan beads impregnated with [bmim][BF<sub>4</sub>] have been applied in the allylation of dimethyl malonate with the same allyl derivative. The catalyst system composed of Pd(OAc)<sub>2</sub>, PPh<sub>3</sub> as ligand, and lyophilized chitosan beads in the presence of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and KOAc as bases was shown to display low stability in recycling studies (a drop of conversion from >98% to 52% in the fifth run).<sup>380</sup> This was attributed to significant Pd leaching (19% in five cycles). Improvements were achieved by using ligand P(*m*-C<sub>6</sub>H<sub>4</sub>SO<sub>3</sub>Na)<sub>3</sub> (TPPTS) and chitosan prepared by supercritical CO<sub>2</sub> drying (sc-Chit-IL). Reaction time had to be prolonged to have high yields; nevertheless, a drastic drop was experienced in the final use despite a 5-day reaction (Scheme 62). Interestingly, the quantity of leached palladium in the first four runs (20%) was even higher. Accumulation of base-derived products in the ionic liquid layer and mechanical degradation of the chitosan support are suggested to account for unsatisfactory catalyst performance. High yields and enantiomeric ratios as high as 97:3 were reported for reactions performed in the presence of chiral ligands.

## 9.2. Allylation of Boron Reagents

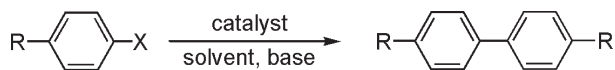
Catalyst 1.28% Pd-14-PS has been applied in the allylation of various boron derivatives with cinnamyl chloride with satisfactory results<sup>243</sup> (Schemes 63 and 64). Nevertheless, the general features of these processes are decreasing yields and the necessity of extended reactions in successive runs.

**Scheme 63.** Allylation of Phenylboronic Acid with (*E*)-Cinnamyl Chloride in the Presence of Catalyst 1.28% Pd-14-PS**Scheme 64.** Allylation of Boron Derivatives with (*E*)-Cinnamyl Chloride in the Presence of Catalyst 1.28% Pd-14-PS**Scheme 65.** Allylation of 4-Methoxyphenylboronic Acid with Cinnamyl Bromide in the Presence of Azamacrocyclic Pd Complexes 138 Anchored to Silica Materials

Pleixats, Mehdi, and co-workers have developed new air-stable catalysts containing a 15-membered azatriolefinic macrocyclic Pd<sup>0</sup> complex anchored to silica materials.<sup>381</sup> The grafting method (postsynthesis modification) was applied to prepare catalyst 1.55% Pd-SBA15-(138a) by the reaction of 138a and SBA-15 functionalized with silylbenzyl iodide. Another catalyst [0.74% Pd-SiO<sub>2</sub>-(138b)] was synthesized by cogelification of complex 138b and TEOS. The third sample was made by grafting triethoxysilylated nonpalladated precursor 138b to SBA-15 followed by complexing with Pd(dba)<sub>2</sub> [sample 2.33% Pd-SBA15-(138c)]. When evaluated in the Suzuki coupling of deactivated 4-iodoanisole with phenylboronic acid, all three catalysts gave rapidly decreasing yields (98%–48%) in five consecutive runs. In the reaction of cinnamyl bromide with 4-methoxyphenylboronic acid, in contrast, the product was isolated in medium to high yields (Scheme 65). An increase in reaction time, however, was



Table 18. Homocoupling of Aromatic Halides or Arylboronic Acids



entry	R	X	catalyst <sup>a</sup>	reaction conditions:	number of reuses	average yields, <sup>b</sup> (%)	ref
				solvent/base/temperature/time			
1	H	Cl	10% Pd/C (0.5)	PEG-400–H <sub>2</sub> O/NaOH/110 °C/2.5 h <sup>c</sup>	7	76 (76)	385
2	H	Cl	5% Pd/C (0.53)	MeOH–H <sub>2</sub> O/HCOONa/NaOH/65 °C/35 min <sup>d</sup>	5	70.5 (72–68)	386
3	H	Cl	5% Pd-OMC (0.53)	H <sub>2</sub> O/HCOONa/KOH/100 °C/6 h	11	40.5 (42–38)	387
4	H	I	2.2% Pd-135b-SiO <sub>2</sub> (0.1)	DMAc/Bu <sub>3</sub> N/120 °C/12 h <sup>e</sup>	5	93 (93)	388
5	H	Br	PdCl <sub>2</sub> (5)	56/Et <sub>3</sub> N/80 °C/0.25 h <sup>e</sup>	6	90 (90)	389
6	4-MeO	I	2.55% Cu <sup>2+</sup> -5c-SiO <sub>2</sub> (10)	DMSO/KF/130 °C/20 h <sup>e</sup>	5	90 (92–88)	390
7	4-Me	B(OH) <sub>2</sub>	4.3% Pd-EnCat 30 (3)	MeOH/26 °C/24 h	5	63 (65–60)	391
8	H	B(OH) <sub>2</sub>	Pd(OAc) <sub>2</sub> (3.6)	[bmim][PF <sub>6</sub> ]–H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /60 °C/3 h <sup>f</sup>	8	82.5 (92–66)	392
9	H	B(OH) <sub>2</sub>	Pd(OAc) <sub>2</sub> (3.6)	[bmim][PF <sub>6</sub> ]–H <sub>2</sub> O/K <sub>2</sub> CO <sub>3</sub> /60 °C/3 h	8	63.5 (75–47)	

<sup>a</sup> Percentage data show Pd loading (wt %) when available; data in parentheses indicate mol % of Pd used. <sup>b</sup> Data in parentheses indicate range of yields.

<sup>c</sup> Under hydrogen pressure (4 atm). <sup>d</sup> In the presence of TBAB. <sup>e</sup> Under nitrogen atmosphere. <sup>f</sup> In the presence of 1 mmol of ethyl 2-bromoacetate.

necessary to have complete conversion. Pd leaching in the first cycle for 1.55% Pd-SBA15-(138a), 0.74% Pd-SiO<sub>2</sub>-(138b), and 2.33% Pd-SBA15-(138c) was 0.7%, 3.5%, and 0.4%, respectively. The grafting process appears to give somewhat better catalysts. It was also found that all three catalysts exhibited better performance than those made by anchoring azamacrocyclic Pd complexes to polystyrene<sup>382</sup> or other silica-immobilized macrocycles.<sup>383</sup>

## 10. HOMOCOUPINGS

The results summarized in this section are examples for the synthesis of symmetric biaryls formed in the reaction of haloaromatics or arylboronic acids called Ullmann-type reaction.<sup>384</sup> Results with respect to the homocouplings of terminal acetylenes are also discussed.

When chlorobenzenes are reacted in the presence of 10% Pd/C, PEG, and NaOH under hydrogen pressure, the corresponding symmetric biaryls are formed as a result of reductive coupling (yields = 36–79%, selectivities = 33–79%).<sup>385</sup> Hydro-dehalogenated compounds are formed as byproducts. The catalyst system worked efficiently in recycling with high stability (Table 18, entry 1). Similar selectivities (30–73%) were observed when the reductive coupling of chloro- and bromobenzenes catalyzed with 5% Pd/C was performed in aqueous methanol in the presence of HCOONa, NaOH, and phase-transfer catalyst TBAB.<sup>386</sup> Efficient catalyst recycling with a small drop of conversion from 100% to 96% in the last run and an average biphenyl yield of 70.5% was found in the homocoupling of chlorobenzene under optimized conditions (entry 2).

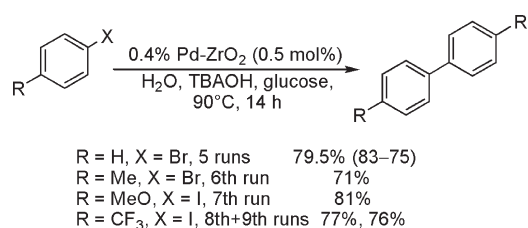
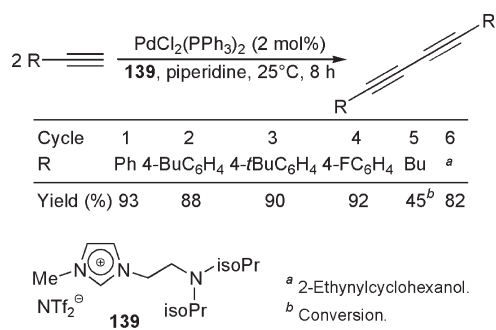
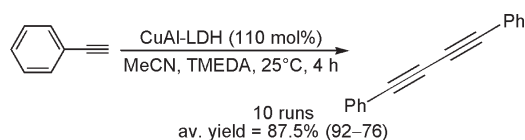
Ordered mesoporous carbon (OMC) with a large surface area (2200 m<sup>2</sup> g<sup>−1</sup>) and bimodal pores (6.3 and 1.7 nm) was impregnated with an aqueous solution of PdCl<sub>2</sub>, and then reduced with hydrogen (10% H<sub>2</sub> in N<sub>2</sub>, 200 °C, 3 h) to give catalyst 5% Pd-OMC containing Pd particles of ~2 nm.<sup>387</sup> Yields are high and stable but selectivity is low for biphenyl in the reaction of chlorobenzene (entry 3), with hydro-dehalogenation being the main reaction (57–62% of benzene formed). Pd leaching, however, was not detected.

Catalyst 2.2% Pd<sup>2+</sup>-135b-SiO<sub>2</sub> (see also the use of the Ni analogue in Kumada coupling, section 8, Scheme 54) gave the homocoupling products of iodo- and bromoarenes in good to high yields (73–95%; 42% for 2-bromopyridine). High and

stable product yields were observed in the homocoupling of iodobenzene<sup>388</sup> (entry 4). In recycling experiments, the catalyst was separated by filtration and reused after washing and drying to constant weight. PdCl<sub>2</sub> and the imidazolium-based phosphinite IL 56 were found to be an efficient catalyst system for the homocoupling of a range of halogen derivatives of haloarenes including heteroarenes (yields of 60–95%).<sup>389</sup> It was easily recovered and reused with stable, high yields in the homocoupling of bromobenzene (entry 5). Catalyst 2.55% Cu<sup>2+</sup>-5c-SiO<sub>2</sub> has been prepared by immobilizing Cu(OAc)<sub>2</sub> on amino-functionalized SiO<sub>2</sub>.<sup>390</sup> Good to excellent yields (68–96%) were observed in the homocoupling of varied haloarenes, and 2-bromopyridine was also reactive (47%). Yields in recycling are also high with small decreases in every reuse (entry 6).

In addition to haloarenes, arylboronic acids also undergo homocoupling under appropriate reaction conditions. Varied arylboronic acids gave homocoupling products in medium to high yields (50–100%) in the presence of Pd(OAc)<sub>2</sub> under base- and ligand-free conditions in air under mild conditions.<sup>391</sup> Formation of Pd black and gradually decreasing yields, however, were observed in recycling (data not shown). In contrast, commercial 4.3% Pd-EnCat 30 with Pd(OAc)<sub>2</sub> encapsulated in polyurea was found to be more stable (entry 7). Moderate yields were attributed to a side-reaction (oxidation of 4-methylphenylboronic acid to *para*-cresol). Homocoupling of phenylboronic acid induced by Pd(OAc)<sub>2</sub> in [bmim][PF<sub>6</sub>]–H<sub>2</sub>O (IL/water ratio = 1) gave moderate yield of biphenyl. The oxidizing agent ethyl 2-bromoacetate showed a strong promoting effect, resulting in smooth homocoupling reactions of various aromatic and heteroaromatic boronic acids with fair to good isolated yields (46–79%).<sup>392</sup> High yields decreased significantly in recycling in the presence of ethyl 2-bromoacetate (entry 8). Similar stability but lower yields were observed when recycling was carried out without the oxidizing agent (entry 9).

Copper-free Ullmann-type couplings were performed with the use of catalyst 0.4% Pd-ZrO<sub>2</sub> containing Pd nanoparticles in the presence of 0.5 equiv of glucose as reductant.<sup>103</sup> Bromobenzene was tested in a five-run recycling study followed by the coupling of three other haloarenes (Scheme 66). The good catalyst stability observed here is comparable to those reported for the Heck reaction (section 4.1.2, Table 3, entries 10–12) and Suzuki

**Scheme 66. Homocoupling of Halobenzenes Mediated by 0.4% Pd-ZrO<sub>2</sub>****Scheme 67. Product Yields in the Homocoupling of Terminal Acetylenes Catalyzed by PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> in IL 139****Scheme 68. Homocoupling of Phenylacetylene Induced by CuAl-LDH**

coupling (section 5.1.2, Table 10, entries 6 and 7) performed with this catalyst.

The coupling of terminal acetylenes, originally carried out with Cu<sup>+</sup> ions in the presence of oxygen (Glaser-type coupling),<sup>393,394</sup> can also be mediated by Pd catalysts. Ionic liquids with tertiary amine function have been found to be effective as both solvent and base in alkyne homocoupling to form symmetrically substituted 1,3-diynes. PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> served as the catalyst used in IL **139** to test six alkynes sequentially under aerobic conditions.<sup>395</sup> Products of homocoupling were isolated in high yields with the exception of hex-1-yne (Scheme 67).

CuAl-LDH prepared by coprecipitation works under similar mild conditions to afford high yields (73–89%) in the homocoupling of substituted acetylenes bearing an alcohol or ester function as well as trimethylsilylacetylene in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) as base.<sup>396</sup> High yields in a recycling study dropped only in the last run (Scheme 68).

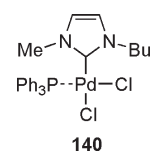
### 10.1. Summary

The three catalysts qualified for inclusion are 10% Pd/C (Table 18, entry 1) and PdCl<sub>2</sub> either in IL **56** (Table 18, entry 5) or immobilized on functionalized silica (2.2% Pd-**135b**-SiO<sub>2</sub>, Table 18, entry 4). There is no report on catalysts with high TON.

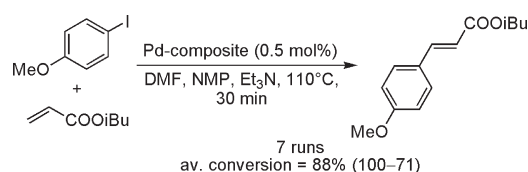
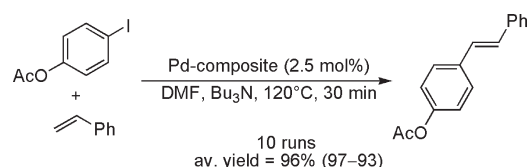
## 11. C–C COUPLINGS IN CONTINUOUS SYSTEMS

The studies discussed in this section are not always about catalyst recycling. Continuous flow methods, however, offer specific advantages.<sup>397</sup> They allow the precise control of reaction variables particularly heat and mass transfer as well as residence time. When solid catalysts are used, the separation of the catalyst from the product is not needed, and workup processes are highly simplified. Regeneration of catalysts in the reactor also makes operations easier. Further advantages are the possibility for scale-up and, consequently, possible practical importance. Continuous operations are often performed under microwave irradiation, which allows very short reaction times.<sup>398</sup> It is not surprising, therefore, that combinatorial libraries using capillary microreactors for microwave-assisted Suzuki reactions<sup>399,400</sup> have been prepared. Selected examples reporting long-term studies and sequential use of catalyst systems are summarized and discussed here.

Ryu and co-workers have performed Heck couplings in an automated microflow system using *N*-heterocyclic carbene (NHC) Pd complex **140** in low-viscosity IL [bmim][NTf<sub>2</sub>].<sup>401</sup> The solution of the reagents and the base (iodobenzene, butyl acrylate, Pr<sub>3</sub>N) and the solution of the catalyst (5 mol %) in the IL are pumped into a micromixer with a flow rate of 0.5 mL min<sup>−1</sup>. The mixed reaction solution then enters into a tube reactor (a 1 m × 1 mm capillary kept at 130 °C), which serves to extend the residence time, which is 17 min at a total flow rate of 1 mL min<sup>−1</sup>. The product is extracted with hexane, and the IL phase containing the catalyst is washed with water then used again. Product yields of 90–99% were observed in repeated uses. The process was then fully automated by connecting the residence time unit into a dual microextraction system. In a scale-up study, 115.3 g of butyl (*E*)-cinnamate in 80% yield was isolated by running the system with two residence time units for 11.5 h with the recycling of the Pd-IL five times (total volume of reagent solution = 408 mL, flow rates = 0.8 and 1 mL min<sup>−1</sup>). The cumulative TON achieved is 3800. Unfortunately, leaching studies were not performed.



The polymer-supported catalyst Pd-**15**-PS, which was used in a batch study of Heck reaction (section 4.1.3, Table 4, entry 13), was also tested in a continuous flow system in the form of a monolithic unit in a minireactor with a free volume of 230 μL.<sup>121</sup> In preliminary tests, iodobenzene and methyl acrylate were reacted for 745 min detecting a yield of 100% in the whole operation (DMF, Et<sub>3</sub>N, 200 °C, 8 bar, cumulative TON = ~300). Under similar conditions, a yield of 85% could be achieved using near-critical ethanol as solvent. A long-term study was then performed under these conditions. First, the effect of flow rate was optimized (50 μL min<sup>−1</sup>), running the system for 420 min followed by the coupling of iodobenzene with acrylonitrile (480 min), affording 66% yield and 70:30 *E/Z* selectivity. Finally, the reaction of iodobenzene with methyl acrylate gave the same results as above. Overall, about 50 mL of reagent solution was tested with a minimal amount of Pd leaching (<1 ppm) to have a total TON of about 420.

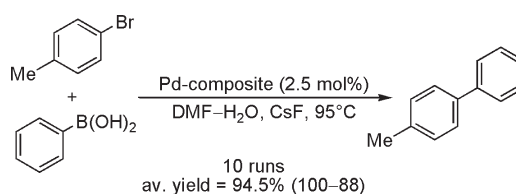
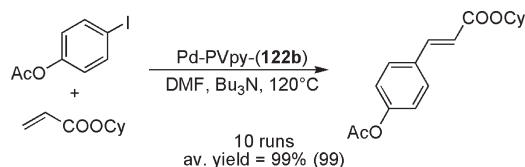
**Scheme 69.** Heck Coupling Performed in a Continuous System (PASSflow Technique)**Scheme 70.** Heck Reaction with Pd-Composite in Continuous Operation

A series of papers have been published by Kirschning and co-workers demonstrating the advantages of a well-designed continuous flow system in coupling reactions. The reactor (10 cm × 0.5 cm) contains a monolith composite of chemically functionalized highly porous polymer and megaporous glass carrier. This is made by polymer-assisted solution-phase synthesis in a flow-through mode (PASSflow technique)<sup>402,403</sup> to ensure high loading and good accessibility of the reactants in solution to the immobilized species.

The monolith catalyst was made by reacting the trimethylammonium chloride form of a vinylbenzyl chloride polymer with  $\text{Na}_2[\text{PdCl}_4]$  and then was reduced ( $\text{NaBH}_4$  or hydrazine hydrate) to form supported  $\text{Pd}^0$  particles.<sup>404</sup> Larger Pd clusters on the surface and nanoparticles embedded in the polymer could be located by EPMA and EDX studies. Heck coupling was performed by circulating the reaction mixture through the microreactor. Full conversion was achieved in 30 min at 110 °C. The catalyst washed with DMF after each run was reused six times (Scheme 69). After deactivation, the monolith was washed with ethanol,  $\text{H}_2\text{O}$ , aqueous  $\text{NaOH}$ ,  $\text{H}_2\text{O}$ , 1 M  $\text{HCl}$ , and  $\text{H}_2\text{O}$  and then palladated again as described.

In a recent study, much better performance could be achieved using a highly optimized composite (5.3% divinylbenzene, 1:1 mixture of vinylbenzyl chloride and styrene) with a Pd content of 0.03 wt % with nanoparticles of 7–10 nm.<sup>405</sup> Reactions were performed in a cyclic mode operating the system as a closed loop reactor. High yields were observed for both Heck reactions with iodoarenes (77–99%) and Suzuki couplings with bromoarenes (60–99%). The catalyst did not show decreasing tendency in either reaction in 10-run recycling studies (Schemes 70 and 71). Washing after each run was made with DMF (Heck coupling) or  $\text{DMF-H}_2\text{O}$  (Suzuki reaction). 0.04% (0.7 ppm) of Pd was detected to be leached in each run.

In a different approach, the arylboronic acid was immobilized on the monolith (in the hydroxide form) by pumping a boronic acid solution in degassed THF through the reactor.<sup>405</sup> The immobilized tetrahedral arylboronate anions formed are more reactive in Suzuki coupling. Coupling took place by circulating the degassed solution of the halobenzene and  $[\text{Pd}(\text{PPh}_3)_4]$  in anhydrous THF under nitrogen at 60 °C (yields of 67–93%,

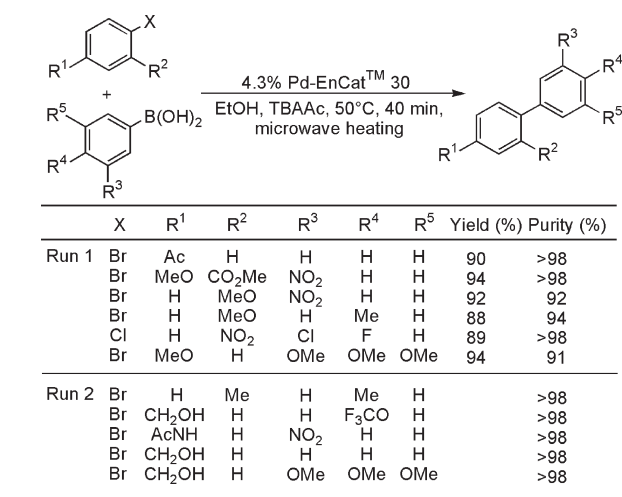
**Scheme 71.** Suzuki Reaction with Pd-Composite in Continuous Operation**Scheme 72.** Heck Coupling Performed in a Continuous System with Catalyst Pd-PVpy-(122b)

reaction times = 1.5–48 h). The reactor was reused more than 20 times after washing with 2 M  $\text{HCl}$ , 1 N  $\text{NaOH}$ , and water before each run. The two methods discussed were combined by using the monolith loaded with  $\text{Pd}^0$  particles in the hydroxide form, that is, without prior immobilization of the boronic acids to achieve similar yields.

The same reactor system was used with immobilized complex **122b** loaded on megaporous glass Raschig rings coated with poly(4-vinylpyridine) (loading = 10 mmol Pd/ring).<sup>406</sup> Medium to excellent yields were reported in both the Heck reaction and the Suzuki coupling (yields of 64–99% and 50–99%, respectively) operating the reactor in the flow-through mode. In repeated applications, the activity of the catalyst in the Suzuki coupling (4-bromoacetophenone, phenylboronic acid) decreased slightly in the fifth run in a 10-run study. In the Heck reaction, in turn, it showed excellent robustness (Scheme 72). Blackening of the rings, that is, formation of Pd particles was, however, observed, which was attributed to the higher reaction temperature (120 vs 100 °C). In further experiments, the nature of the active catalytic species was tested by using a two-reactor system in the Heck reaction. The second reactor contained rings coated with PVPy or polystyrene functionalized with thiol, bispyridine, or amino-bispyridine groups capable of trapping soluble Pd species. In all cases reaction rates decreased, which suggests that active Pd species are released into solution. The thiol scavenger brought about significant rate decreases, whereas pyridine-based materials showed a much smaller effect, indicating that pyridine-based scavengers are able to create, capture, and release such species. This explains the very low concentration of Pd found in cooled reaction mixtures (1.1–2.1 ppb).

Ley and co-workers have reported a continuous flow study<sup>407</sup> using a polymer monolith with Pd nanoparticles similar to that developed by Kirschning et al.<sup>404</sup> First, the polymer prepared in a 70 × 6.6 mm glass column by radical polymerization of divinylbenzene and vinylbenzyl chloride was transformed into the triethylammonium form. Next, Pd nanoparticles (5–50 nm) were generated by further treatment with  $\text{Na}_2[\text{PdCl}_4]$  followed by reduction ( $\text{NaBH}_4$ ). High yields (73–88%) were found in the coupling of substituted iodobenzenes with varied alkenes including 2-vinylpyridine and 2-vinylpyridazine in superheated ethanol

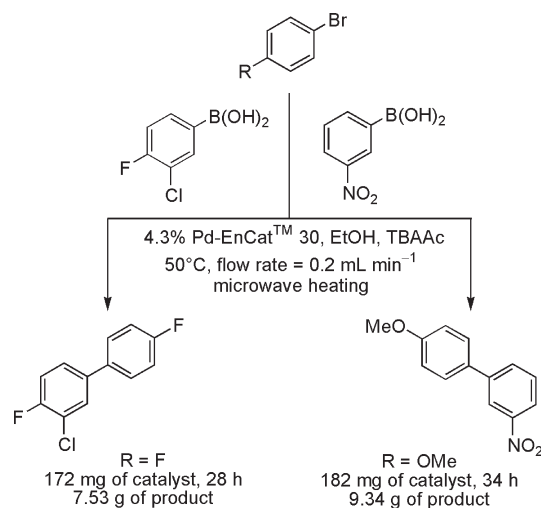


**Scheme 73. Sequential Processing of Substrates Induced by Pd-EnCat 30 in a Flow Reactor**

(Et<sub>3</sub>N, 130 °C). The reactor was reused 25 times, displaying high efficiency without regeneration. Significant Pd leaching (~270 ppm) was, however, observed. The problem was resolved by inserting a column packed with Quadrapure TU, the thiourea-functionalized scavenger, after the reactor to reduce Pd concentrations below 5 ppm.

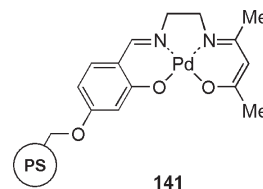
In another report, they disclosed the use of 4.3% Pd-EnCat 30 packed into a microreactor to study the Suzuki reaction.<sup>400</sup> Reactions were performed under microwave irradiation with simultaneous cooling with compressed air. For other recycling applications of Pd-EnCat catalysts, see Sonogashira Coupling, section 6.2, Table 16, entry 14, and Homocouplings, Section 10, Table 18, entry 7. In batch studies, high yields (78–99%) were found for bromobenzenes (10 mol % of catalyst, MeCN, TBAAc, 140 °C, 15 min). A combinatorial library of 341 compounds was generated with 31 aromatic bromides and triflates and 11 boronic acids. Dramatic increases in both yield and product purity were observed when couplings were carried out in a flow system. A stock solution of the bromoarene, boronic acid, and TBAAc in ethanol was fed into the reactor placed into the microwave cavity (0.06–0.07 mmol of catalyst, flow rate = 0.1 mL min<sup>-1</sup>, residence time = 65 s) with pulsed microwave heating (50 W for 30 s, 18 s off). Sequential processing of substrate pairs was made without catalyst regeneration. The product stream was fed into a column filled with Amberlyst 15 resin to remove residual base and salts, and then ethanol was pumped through the column to flush the system. Ten substrate pairs giving incomplete conversion in batch experiments afforded coupling products of very high yields and purity (Scheme 73, run 1; six examples are shown). Of four heterocyclic substrate pairs (results not shown), 3-bromopyridine and pyridyl-3-boronic acid, which were unreactive in the batch experiment, gave similar good results (95% yield, 82% purity). Product purities were also high in another sequential study (Scheme 73, run 2; five examples of nine reactions are shown). In the two scale-up studies summarized in Scheme 74, TON values of 469 and 560 were realized. The activity of the catalyst, however, fell dramatically at the end of the trials.

In a study with Pd-EnCat 40 by Leeke and co-workers,<sup>408</sup> the catalyst was used in toluene–methanol or supercritical CO<sub>2</sub>–methanol in a flow system. In eight repeated runs with a column of 22.5 cm × 25.4 mm, the coupling of iodobenzene with

**Scheme 74. Scale-Up Studies with Pd-EnCat 30 in a Flow Reactor**

4-methylphenylboronic acid was tested under varied experimental conditions. The highest conversion of 81% was achieved in CO<sub>2</sub>–methanol (10:1) in the presence of TBAOME as base (100 °C, 166 bar, flow rate = 5.5 g min<sup>-1</sup>). The originally free-flowing catalyst, however, turned into a black cake, indicating the reduction of Pd<sup>2+</sup> to Pd<sup>0</sup>. Tests with the used catalyst in batch mode showed significantly reduced activity (conversions of 52% and 41% in the two solvent systems).

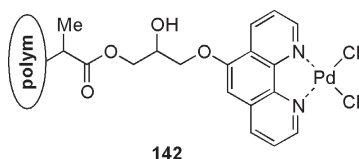
The polymer-supported salen Pd<sup>2+</sup> complex Pd-141-PS with a Pd content of 2 wt % was prepared by reacting Merrifield resin with the HO-functionalized complex in the presence of NaH.<sup>409</sup> Preliminary batch studies were performed by the coupling of 4-bromoanisole and phenylboronic acid. Transferring the reaction into a mini-continuous flow reactor required one to select an appropriate combination of solvents to have a completely homogeneous system to avoid blockage in the reactor. Studies with an Omnifit mini flow reactor (25 mm × 3 mm) packed with 110 mg of 2% Pd-141-PS were conducted using a DMF–H<sub>2</sub>O (1:1) solvent mixture, in the presence of isoPr<sub>2</sub>Et as the base (100 °C, flow rate = 3 μL min<sup>-1</sup>, residence time = 21 min). In a 6 h run, the conversion values determined in every hour were 42%, 57%, 61%, 65%, 62%, and 54%. The catalyst could be reused after washing (DMF, water, THF) and drying in vacuo to show a similar trend in catalyst performance. A range of various activated and deactivated bromoarenes and heterocyclic bromo derivatives were also tested, showing the known difference in reactivities. Exceptions are 4-bromonitrobenzene, 4-bromoaniline, 5-bromoisatine, and 2-bromopyridine, which proved to be unreactive. Finally, the stopped-flow technique that is injecting the reaction mixture to the reactor for a designated period followed by a pause (10 min on and 20 min off) allowed the improvement of the conversion to 86%.



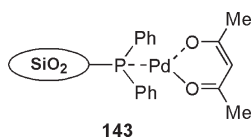
Xia et al. developed a simple method to functionalize with metal nanoparticles the surface of TiO<sub>2</sub> and ZrO<sub>2</sub> nanofiber

membranes (porous, nonwoven mats) prepared by electrospinning<sup>410</sup> by immersing them in a polyol reduction bath.<sup>411</sup> Of the products thus prepared, the Pd-decorated anatase fiber membranes (mean Pd particle size =  $5 \pm 0.5$  nm) were tested in the reaction of 4-bromonitrobenzene and phenylboronic acid in a continuous flow reactor. A solution of the two reactants in ethanol–deionized water was passed through 5 mg of the catalyst (flow rate =  $0.5 \text{ mL min}^{-1}$ ). Complete conversion was found for the first 10 mL of solution followed by a drop to 93% for the next 20 mL. The catalyst, however, could easily be regenerated by treatments with 1 M  $\text{HNO}_3$  solution ( $1 \text{ mL min}^{-1}$ , 4 min), water, and  $\text{Na}_2\text{CO}_3$  solution. The acid etching resulted in a decrease of mean particle size ( $4.7 \pm 0.74$  nm) and an increase in polydispersity.

Guijt, Smith, and co-workers reported the use of a fused silica capillary reactor ( $20 \text{ cm} \times 250 \mu\text{m}$ ) packed with a copolymer of glycidyl methacrylate and ethylene dimethacrylate. Attachment of the phenanthroline ligand followed by palladation with  $\text{PdCl}_2 \cdot (\text{MeCN})_2$  gave catalyst Pd-142-polym with a Pd loading of  $0.02 \text{ mmol g}^{-1}$ .<sup>412</sup> A yield of 68% was measured during an 18 h trial for the coupling of iodobenzene with *p*-tolylboronic acid (toluene–methanol = 1:1, TBAOMe as base,  $80^\circ\text{C}$ , flow rate =  $0.05 \text{ mL min}^{-1}$ ). The monolith was further used for 4 days with a yield of 68% observed in the last 4 h showing the high efficiency of the catalyst. Considering, however, the small reactor diameter and the low flow rate, the overall solvent quantity pumped through in 114 h was only 0.342 mL.



A silica-immobilized, phosphane-bound complex (catalyst 5.92% Pd-143- $\text{SiO}_2$ ) has also been used in a continuous flow system for Hiyama coupling.<sup>413</sup> The reaction was performed by pumping two solutions, aromatic bromo derivative and a mixture of  $\text{PhSi}(\text{OMe})_3$  and TBAF ( $35 \mu\text{L min}^{-1}$ ), both in *para*-xylene, through a tube ( $1 \text{ m} \times 3.96 \text{ mm}$ ) filled with 10 g of catalyst (flow rate =  $0.45 \text{ mL h}^{-1}$ ). The reaction of 4-bromotoluene gave the coupling product in 99% yield in 40 h at  $120^\circ\text{C}$ . Bromobenzene and methyl 4-bromobenzoate reacted with similar efficiency, whereas lower conversions were observed for 2-bromopyridine (72%) and 2-bromothiophene (45%).



## 12. CONCLUSIONS AND OUTLOOK

Literature information of palladium-catalyzed coupling reactions performed with efficient and recyclable catalyst systems with focus on the three major transformations (Heck, Suzuki–Miyaura, and Sonogashira reaction) and relevant data for related coupling reactions studied less frequently have been collected. The experimental observations with respect to the most efficient catalyst systems discussed in the corresponding subsections of

summary analyses (sections 4.5, 5.5, 6.5, 7.3, and 10.1) are collected in Tables 19 and 20. These reliable data allow a few general conclusions to be drawn, and an analysis of major trends in the field is also possible.

In Table 19, catalyst systems providing high, consistent yields are summarized (for selection criteria, see section 4.5). A few general statements can be made.

- (i) As was already discussed, there are varied catalysts with Pd particles and complexes either immobilized or used under homogeneous conditions, which give good yields in Heck couplings. In contrast, efficient immobilized complexes are more dominant for both the Suzuki reaction and the Sonogashira coupling. It appears, therefore, that Pd particles are well-suited for good performance in the Heck coupling.
- (ii) Of the supported catalyst systems collected, eight are based on ordered silica materials (SBA-15, MCM-41, LTA zeolite, sodalite), and these exhibit good catalyst performance in all reactions listed with the exception of homocouplings (no data are available). This may be attributed to the confinement effect of the channel structure to prevent the agglomeration of nanoparticles and, when the support is functionalized, to the chelation by ligands toward Pd species located inside the mesoporous channels.
- (iii) Efficient catalyst performance with supported palladium nanoparticles, that is, high yields and high stability, requires the careful selection of inorganic support materials and functionalization with appropriate functional groups. Polymeric supports must also be functionalized in a similar manner. Groups such as nitrogen-containing functions or anchored ionic liquid-like units play important role in the release and recapture of soluble palladium species. This notion is illustrated by data for catalyst Pd-15-PS and materials Pd-PVPy and Pd-PS-*co*-PVPy with Pd particles deposited onto poly-(4-vinylpyridine). The double bonds of azatriolefinic macrocycle **13** play a similar role in dendrimeric 29.32% Pd-dendr-(**13**). Electron-donating ligands certainly contribute to catalyst efficiency and stability. In fact, this also applies to catalysts with complexes supported on polymers.
- (iv) Varied complexes, even simple ligandless  $\text{PdCl}_2$  applied in ILs, particularly complex–IL combinations with related structures, exhibit outstanding stability providing near quantitative yields in repeated runs. Unfortunately, no attempts have been made to acquire high TONs with these catalyst systems.

Data for the most efficient catalysts affording high cumulative TON numbers are collected in Table 20. As can be seen, such systems are less numerous than those shown in Table 19. In other words, catalysts with consistently high yields are not necessarily effective to provide high TON values. These efficient systems comprise mostly catalysts with Pd particles and immobilized complexes, indicating that both methodologies are useful in fabricating highly active catalyst systems. A comparison of the two tables shows that there are only three catalysts, which can be characterized by both high yields and high TON. One is catalyst 4.1% Pd-*gr*HS-Si(HIPE) with Pd particles located on the inner surface of macroporous silica modified with 3-mercaptopropyl groups. The other two have  $\text{PdCl}_2$  either anchored to an

Table 19. Catalyst Systems Providing High, Consistent Yields in Recycling Studies

	Pd particles	complexes	
		immobilized	homogeneous <sup>a</sup>
Heck reaction	0.48% Pd-SiO <sub>2</sub>	4.04% Pd- <b>22b</b> -MCM41	<b>46a</b> in IL <b>45</b> or <b>47</b>
	3.47% Pd-SiO <sub>2</sub> -( <b>3</b> )	Pd-SiO <sub>2</sub> -( <b>25</b> )	PdCl <sub>2</sub> in IL <b>48</b> or <b>57</b>
	1.06% Pd-TMG-SBA15	Pd-PS-( <b>30a</b> )	<b>52</b> in IL <b>53a</b> or <b>53b</b>
	4.1% Pd- <i>gr</i> HS-Si(HIPE)	1.17% Pd- <b>31</b> -PS	<b>61</b> in [bmim][PF <sub>6</sub> ]
	1.39% Pd-MCM41	4.36% Pd- <b>32</b> -PS	
	5.85% Pd-MCM41	3.04% Pd- <b>38</b> -TGR	
	35% Pd/C aerogel		
	Pd-PVPy		
	Pd- <b>15</b> -PS		
	29.32% Pd-dendr-( <b>13</b> )		
Suzuki reaction	0.48% Pd-SiO <sub>2</sub>	3.19% Pd- <b>85a</b> -LTA	<b>49</b> in [bmim][PF <sub>6</sub> ]
	26.6% Pd-PS	Pd <sup>2+</sup> -sodalite	PdCl <sub>2</sub> in IL <b>43</b>
	Pd-PS- <i>co</i> -PVPy	5.53% Pd- <b>86a</b> -MCM41	
	Pd-Sn-dendr1	0.03% Pd- <b>87</b> -MCM41	
	Pd-Sn-dendr2	2.87% Pd-HS-SiO <sub>2</sub> -( <b>29</b> )	
		Pd <sup>2+</sup> -SilicaCat	
		2.23% Pd- <b>85b</b> -SiO <sub>2</sub> /Fe <sub>3</sub> O <sub>4</sub>	
		Pd- <b>39</b> -polym	
		3.04% Pd- <b>38</b> -TGR	
		<b>112</b> <sup>b</sup>	
Sonogashira reaction		5.43% Pd <sup>2+</sup> - <b>86b</b> -MCM41 <sup>c</sup>	
		4.18% Pd <sup>2+</sup> - <b>5b</b> -SiO <sub>2</sub>	<b>46b</b> in IL <b>48</b>
		4.04% Pd- <b>22b</b> -MCM41	
		5.53% Pd- <b>86a</b> -MCM41	
		2.23% Pd- <b>85b</b> -SiO <sub>2</sub> /Fe <sub>3</sub> O <sub>4</sub>	
		12.8% Pd- <b>127</b> -polym	
Stille reaction	0.48% Pd-SiO <sub>2</sub>	5.53% Pd- <b>86a</b> -MCM41 <sup>d</sup>	
		5.53% Pd- <b>86a</b> -MCM41	
		4.04% Pd- <b>22b</b> -MCM41	
		5.53% Pd- <b>86a</b> -MCM41 <sup>e</sup>	
homocoupling	10% Pd/C	2.2% Pd- <b>135b</b> -SiO <sub>2</sub>	PdCl <sub>2</sub> in IL <b>56</b>

<sup>a</sup> Used under homogeneous conditions. <sup>b</sup> Self-supported complex. <sup>c</sup> Used in carbonylative Suzuki coupling. <sup>d</sup> Used in carbonylative Sonogashira coupling. <sup>e</sup> Used in carbonylative Stille reaction.

Table 20. Catalyst Systems Providing the Highest Cumulative TON Values in Recycling Studies

	catalysts with Pd particles	TON <sup>a</sup>	ref	complexes <sup>b</sup>	TON <sup>a</sup>	ref
Heck reaction	Pd-SBA15	157	82	Pd- <b>39</b> -polym	94	158
	3.9% Pd-HS-Si(HIPE)	209	86	Pd-cellulose-xanth	96	160
	4.1% Pd- <i>gr</i> HS-Si(HIPE)	169	86	<b>54</b> in IL [bpy][BF <sub>4</sub> ]	249	170
Suzuki reaction	1.22% Pd-FSG-( <b>2a</b> )	333	71	0.03% Pd- <b>87</b> -MCM41	118	253
	3.24% Pd-Y	136	205	Pd- <b>39</b> -polym	190	157
				Pd <sup>2+</sup> -SG-( <b>94</b> )	525	266
				Pd <sup>2+</sup> -FSG-( <b>95a</b> )	484	
				Pd <sup>2+</sup> -FSG-( <b>95b</b> )	498	
				Pd <sup>2+</sup> -SG-( <b>95c</b> )	342	
				Pd <sup>2+</sup> -FSG-( <b>95c</b> )	389	

<sup>a</sup> Values must be multiplied by 10<sup>3</sup>. <sup>b</sup> Immobilized complexes with the exception of complex **54**.

immobilized Schiff-base applied in Suzuki reaction (catalyst 0.03% Pd-**87**-MCM41) or immobilized on a phosphane-modified amphiphilic polymer (Pd-**39**-polym) exhibiting efficient performance in both the Heck and the Suzuki reactions. This comparison nicely underlies the notion formulated before that it is

not the number of recycles what is important; rather, valid assessment of recycling performance should only be based on total TON or derived TOF values.

Despite the abundance of catalysts, major general trends of the field are not easy to extract. First, reliable data for catalysts



collected in Tables 19 and 20 are far fewer than those included in this Review. Furthermore, only a handful of these have been tested in all three major coupling reactions. Nevertheless, a few important conclusions may be arrived at.

- (i) An analysis of the active Pd species provides interesting results. Most of the effective catalysts, which are active in varied applications, contain immobilized Pd species. For example, 3.04% Pd-38-TGR was found to be high-yielding in Heck and Suzuki coupling, whereas catalyst Pd-39-polym gave high total TONs in the same processes. Other similar catalysts are 4.04% Pd-22b-MCM41, which performs well in all three reactions tested (Heck, Sonogashira, and Stille reaction), whereas 5.53% Pd-86a-MCM41 with Pd<sup>0</sup> species gave high yields in five reactions (Suzuki, Sonogashira, and Stille reaction as well as the carbonylative Sonogashira and Stille coupling). The related complex 5.43% Pd<sup>2+</sup>-86b-MCM41 with Pd<sup>2+</sup> ions, however, is less effective (one satisfactory performance in the carbonylative Suzuki coupling). Moreover, 0.48% Pd-SiO<sub>2</sub> with Pd particles proved also to be high-yielding in the Heck, Suzuki, and Stille reaction. Catalytic efficiency, consequently, cannot exclusively be associated with one type of active Pd species involved.
- (ii) The immobilized  $\beta$ -ketoiminatophosphanyl palladium complex is useful when grafted either into LTA zeolite (3.19% Pd-85a-LTA, Suzuki reaction) or into SiO<sub>2</sub>/Fe<sub>3</sub>O<sub>4</sub> (2.23% Pd-85b-SiO<sub>2</sub>/Fe<sub>3</sub>O<sub>4</sub>, Suzuki and Sonogashira reaction). It appears, consequently, that it is the immobilized complex and not the support structure that plays the decisive role in determining catalytic properties. The silica support used in the synthesis of catalyst 0.48% Pd-SiO<sub>2</sub> with Pd particles and Pd-SiO<sub>2</sub>-(25) containing the *cis*-bis(L-prolinato) complex was modified with long-chain alkyl groups. The former catalyst gives high yields in the Heck reaction, whereas the latter shows similar efficiency in the Suzuki coupling. In this case, in turn, catalyst performance may be linked to the nature of the support material. The results with ordered silica materials (SBA-15, MCM-41, LTA, sodalite) discussed above also underline the latter conclusion.
- (iii) A general conclusion that may follow is that either the catalytically active species, Pd particles and immobilized species, or the support material employed may play the decisive role in efficient catalysis. It is obvious, however, that only an appropriate combination of active and stable metal species and a suitable support material can result in good catalyst performance. In fact, it is a major trend of the field to develop new, highly specific support materials and design new complexes and then combine them with the aim to have stable, high-yielding catalyst systems of high leaching resistance. It appears, however, that the performance of these systems rarely exceeds those already reported. As shown, varied catalysts exhibiting suitable properties have been designed with the use of the simple salt PdCl<sub>2</sub>. Considering the supports, new results for catalysts prepared with magnetic iron oxides and applied in coupling reactions have been reported in recent years. Most of these, even exotic samples such as Pd-C/Au@Fe, however, do not offer any specific catalytic property as compared to other support materials except the easy separation by a permanent magnet. It is not surprising, therefore, that 2.23% Pd-85b-SiO<sub>2</sub>/

Fe<sub>3</sub>O<sub>4</sub> is the single related catalyst, which is included in Table 19.

- (iv) The efficient use of every catalyst system requires fine-tuning the reaction conditions for each reaction. Illustrative is 5.53% Pd-86a-MCM41 with immobilized Pd<sup>0</sup> species, which gave high yields in five reactions. It has been applied in a different solvent in every case with K<sub>2</sub>CO<sub>3</sub>, piperidine, or Et<sub>3</sub>N as bases. In a similar way, solvents applied in the use of 4.04% Pd-22b-MCM41 are NMP (Heck reaction), DMF (Suzuki coupling with NaBPh<sub>4</sub>), and piperidine (Sonogashira reaction).

As documented in this Review, wide-ranging research efforts with the use of varied palladium catalysts in recycling studies in important C–C coupling reactions have resulted in the accumulation of a wealth of information in recent years. Numerous novel catalysts have been developed, which display outstanding properties providing high yields and selectivity, even being capable of inducing the transformation of chloroaromatics. The great majority of these studies, however, have mainly focused on the development of catalysts, which are effective for a wide range of substrate materials in a single coupling reaction. Many of the new catalysts are easy to handle and can be used under mild conditions in an open atmosphere. Indeed, high yields (>90%) have been reported often without significant substituent effects. Unfortunately, with such excellent results in hand, much less attention has been paid to recycling experiments, and the performance of many of these catalysts in recycling experiments is not convincing. Authors are satisfied to show and report a few repeated uses of the catalyst with the most reactive substrates; 107 of the 278 entries listed in Tables 1–18 are about the coupling of iodobenzene. Slow, progressive drop of yields and the necessity of extended reactions and increased reaction temperature, however, are revealing signs of unsatisfactory catalytic activity in the long run. As summarized above, high cumulative TON numbers could be realized only in a few cases. More importantly, data for catalyst characterization and additional important information (leaching study, the use of selective poisons, filtration and three-phase test, kinetic study) are often inadequate or lacking. Without such data of key importance, the recycling ability cannot be adequately assessed.

It is obvious from earlier studies, particularly those by Gladysz, Plenio, Shreeve, Bannwarth, and Vallribera, concerning their approach, methodologies, and the quality of data collection as well as related discussions by Gladysz and Jones treated in introductory sections that the reliable assessment of the recycling ability of catalysts and the closely related issue of the nature of active species require high-quality studies. The use of methods enabling quantitative characterization and evaluation of catalysts and recycling systems before and after reaction and continuous monitoring of changes during reactions are absolutely necessary to gather information of recyclability and catalyst recovery. Kinetic studies, the combined use of various selective poisons, the application of the three-phase test, and hot filtration test may provide additional valuable data. The information acquired will certainly fuel the development of new catalysts and appropriate reaction conditions matching the best homogeneous catalysts of high efficiency. The fabrication of new catalyst materials with high leaching resistance, which are also highly active in the coupling of chloroarenes, is of particular importance. Deeper

understanding of mechanistic issues involved will certainly contribute to the design of new catalyst systems.

Finally, an evaluation and comparison of the productivity and, consequently, the merit of using recoverable catalysts and the “homeopathic” approach may be useful here. The word was coined by Beletskaya<sup>62</sup> and refers to the effective use of simple ligandless Pd sources [PdCl<sub>2</sub>, Pd(OAc)<sub>2</sub>] as catalysts in the coupling of bromoarenes. de Vries and co-workers demonstrated<sup>70,414</sup> increasing TOF values with decreased palladium loading down to 0.01 mol % and described the possibility of practical Pd recycling.<sup>415</sup> Köhler et al. have recently reported a very high TON value of  $4.7 \times 10^7$  in the coupling of bromobenzene and styrene with the use of Pd(OAc)<sub>2</sub> in ultralow concentration ( $3 \times 10^{-7}$  mol %).<sup>416</sup> In contrast, the highest cumulative TON achieved with recoverable catalysts is  $5.3 \times 10^5$  reported by Bannwarth et al. (Table 20). In the light of these data, it is really not worth preparing expensive catalysts and trying to achieve high productivity (high total TONs) by repeated uses. As formulated nicely by Gladysz “the pursuit of higher-turnover-number catalysts represents a more important research direction than recoverable catalysts”.<sup>41</sup> However, not all supported catalysts are expensive and difficult to prepare. The latest example is a catalyst with ultrastable Y zeolite (USY) as support developed by Okumura and co-workers.<sup>417</sup> It is easily prepared by impregnation of the H-form of the zeolite with Pd(NH<sub>3</sub>)<sub>4</sub>Cl<sub>2</sub> and gave high TON values ( $(1.1\text{--}1.3) \times 10^7$ ) in the Suzuki coupling of bromobenzene, 4-bromotoluene, and 4-bromoacetophenone. Unfortunately, the ability of this catalyst in recycling has not been explored. On the other hand, studies with respect to the development of stable and recoverable catalysts of high efficiency still represent an important research field. Studies such as those performed and reported by Bannwarth cited above may yield additional useful general information, and the results may eventually have practical implications.

Despite the shortcomings and flaws discussed in detail, research efforts exploring new avenues in catalyst synthesis have made significant contributions to our understanding of the desired characteristics of a catalyst exhibiting the necessary stability for prolonged use. These recent developments provide a good basis and give an exceptional opportunity to make further improvements. The synthesis of well-characterized heterogeneous catalysts including solids functionalized with appropriately selected surface groups to ensure the release and capture of active catalytic species and the exploitation of the confinement effect of ordered materials with appropriately tailored structure capable of stabilizing nanoparticles deserve further studies. The idea of embedding nanoparticles into polymer matrices to control particle size and prevent agglomeration has been demonstrated and is also worth pursuing. The key issue of practical importance here is to prevent the agglomeration of monomeric, dimeric, or colloidal Pd species, that is, to prevent the formation of Pd black. Finally, a highly promising area with already outstanding examples is the use of homogeneous complexes in IL, with the latter playing the dual role as solvent and coordinating ligand immobilizing palladium species, and even as base.

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