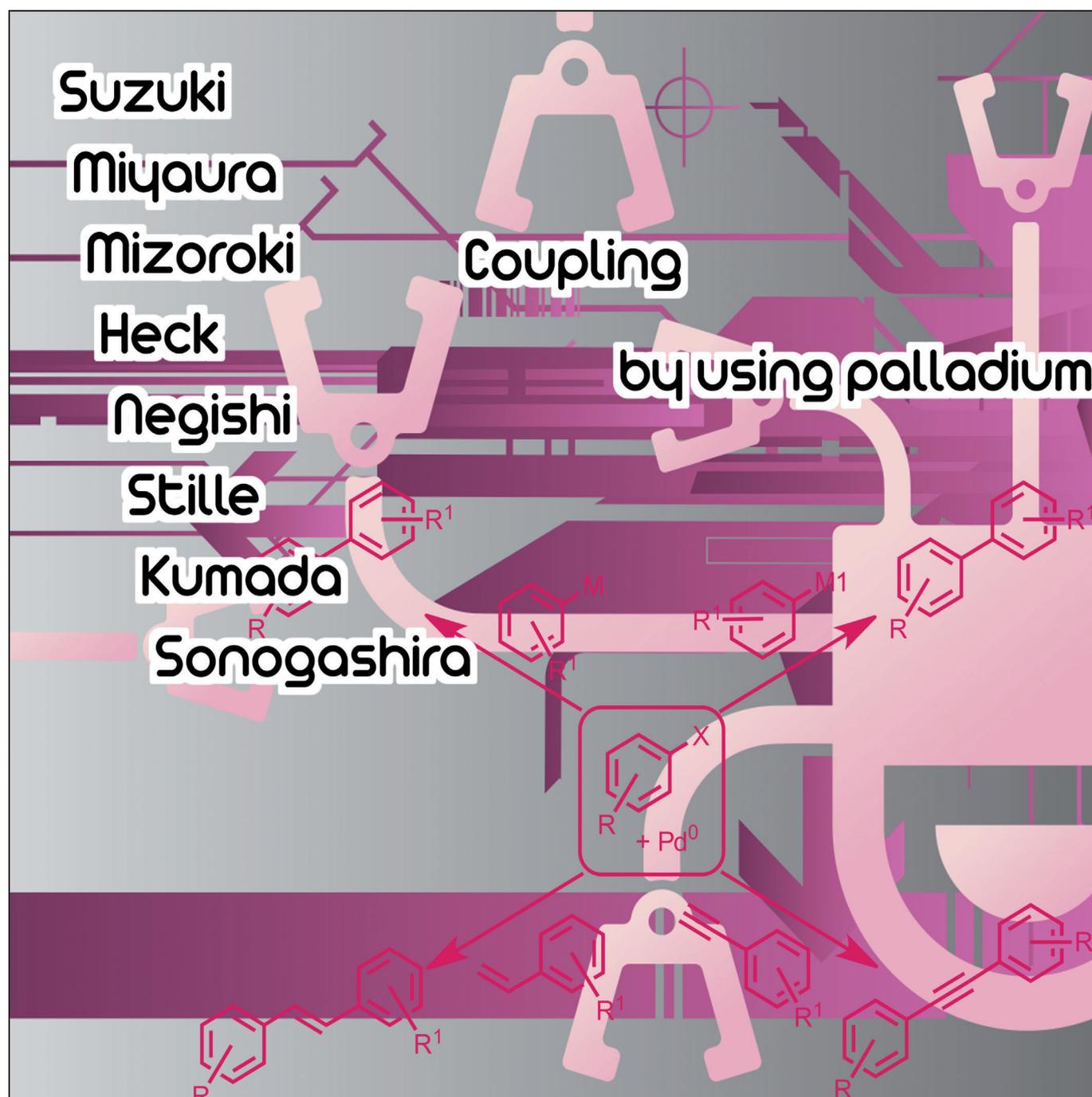


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Heterogeneous versus Homogeneous Palladium Catalysts for Cross-Coupling Reactions

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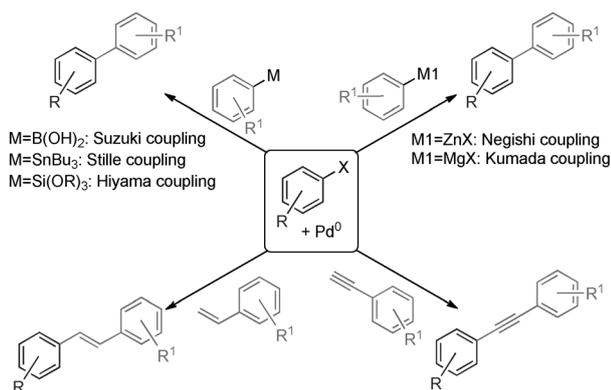
A large number of immobilized-Pd-catalysts for cross-coupling reactions have been introduced in the last decade. Are the observed catalyzed reactions truly heterogeneous or are they homogeneous due to leached palladium? This account critically addresses the leaching issue by selectively referring to some of

the newly developed catalytic systems in an attempt to evaluate said systems based on uniform criteria. The report is concluded by identifying the relevant chemical and structural challenges in the field.

1. Introduction

Palladium-catalyzed cross coupling reactions, such as those named after Suzuki, Miyaura, Mizoroki, Heck, Negishi, Stille, Kumada, and Sonogashira, developed over the last thirty years have changed the practice of synthetic organic chemistry from a linear pattern of slow, consecutive reaction steps with protected substrates into the parallel synthesis of key precursors that are linked together at a late stage in the process.^[1] This is possible because, along with broad versatility, these reactions generally tolerate the presence of functional groups in the coupling partners, and thus do not require tedious protection and deprotection steps of functional groups in the reagents.

In general, in these reactions (Scheme 1) a homogeneous palladium catalyst mediates the reaction between a less-reactive organic electrophile, typically aryl halides, and different carbon nucleophiles.^[2]



Scheme 1. Palladium-catalyzed C-C coupling reactions classified according to the carbon nucleophiles. [Adapted from Ref. [2], with kind permission].

In the Suzuki–Miyaura carbon–carbon bond formation takes place between phenylboronic acid and vinyl or aryl halides;^[3] whereas in the Sonogashira reaction, reaction makes use of terminal alkynes.^[4] In both cases, the reaction is catalyzed by Pd⁰ formed in situ. The base, in the Suzuki–Miyaura coupling, plays multiple roles, favoring both the (rate-determining) transmetalation and reductive elimination, while limiting the reaction by formation of the unreactive anionic species, so that the overall reactivity is controlled by the concentration of OH[−] and passes through a maximum as the concentration of base is increased.^[5]

Homogeneous cross-coupling reactions, however, have several shortcomings, such as limited reusability of the expensive catalyst and palladium contamination in the product.^[6] Removal-

ing residual palladium in a pharmaceutical substance to reduce its content to the maximum acceptable concentration limit (Table 1) requires a slow and costly purification process (that often makes use of silica-based scavengers).^[7]

Table 1. Specification limits for residues of metal catalysts in the EU.

Metal	Concentration [ppm]	
	Oral	Parenteral
Pt, Pd, Ir, Rh, Ru, Os	5	0.5
Mo, V, Ni, Cr	10	1.0
Cu, Mn	15	1.5
Zn, Fe	20	2.0

Source: European Medicines Agency (EMA)—Guidelines on the Specification Limits for Residues of Metal Catalysts and Metal Reagents, 2008.

Clearly, there is a need to efficiently heterogenize the palladium catalytic species to obtain selective and reusable solid catalysts, avoiding or limiting the subsequent product contamination associated with use of expensive and non-reusable homogeneous Pd catalysts and their undesired tendency to remain in the final products.

Pd/C and Pd/Al₂O₃ were the first commercially available solid catalysts and today both are frequently used in academia and industry. For example, an optimized Pd/C commercial catalyst for Heck, Suzuki, and Sonogashira reactions achieves TON values up to 36 000.^[8] However, recovery of the catalyst, especially in the case of Pd/C, is difficult.^[9]

Many new catalytic materials have since been introduced and the first comprehensive review^[10] on solid supported Pd-catalysts for cross-coupling appeared in 2007, following accounts on coupling reactions catalyzed by Pd/C^[11] and by SiO₂/Pd.^[12] Most recently, Molnár thoroughly reviewed the existing solid Pd catalysts categorizing the available materials for the different coupling reactions.^[13]

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In 2012 one can rightly claim that research chemists and fine chemical companies can access a diverse selection of commercially available solid catalysts, some of which show astonishingly high selective activity in different cross-coupling reactions. The field, in other words, may appear as a mature branch of chemical science with limited room for improvement. Alas, this is not the case, as many of the solid catalysts developed thus far are actually homogeneous, namely they behave as reservoirs, or “pre-catalysts”^[14] of the catalytically active species in solution.

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François Béland obtained his Ph.D. in 1999 from Laval University in Quebec City, Canada, where he studied silica-based catalysts by different spectroscopy methods. He moved to Montpellier for post-doctoral studies at the ENSCM. There, he studied different reactions in organic chemistry catalyzed by silica-based heterogeneous catalysts. He started working at SiliCycle as a researcher after his post-doc. A year later he was promoted to R&D Director and his focus was to develop the *SiliaBond* (functionalized silica gels) product line. Recently he has been promoted to Vice-president of R&D.



Valerica Pandarus studied chemistry at the University of Bucharest. In 2007 she obtained her Master Degree in Organometallic Chemistry and Catalysis from the Université de Montréal under the supervision of Professor Davit Zargarian. She then joined the research group of Dr. François Béland at SiliCycle Inc. as a researcher where she began to work on *SiliaCat* sol-gel heterogeneous catalysts. Her research interests include the preparation of heterogeneous catalysts to explore their applications in heterogeneous catalysis and green chemistry.



Indeed, in 2007, according to experienced practitioners of the pharmaceutical industry, “scavenging leached Pd” appeared to be “the method of choice to solve the leaching problem”^[15]. Moreover, the activation of inexpensive aryl chlorides, rather than aryl bromides or iodides, remains an elusive goal for many supported Pd catalysts. Accordingly, reviewing the use of immobilized-Pd catalysts in environmentally benign water,^[16] Felpin and co-workers recently concluded that many heterogeneous catalysts deactivate upon successive reuses (owing to palladium leaching and/or support degradation), with the simplest support, such as polyaniline (PANI) and active carbon (charcoal), still providing the most active solid Pd catalysts.

As mentioned above, a wide variety of immobilized Pd-catalysts for cross coupling reactions have been reported including methods based on exotic supports such as tobacco mosaic virus,^[17] dendrimers,^[18] chitosan,^[19] graphene^[20] and carbon nanotubes.^[21] The recent review^[13] of Molnár comprehensively addresses most of the existing methods. However, the leaching issue remains a rather elusive topic that requires to be fully addressed. Are the observed catalyzed reactions truly heterogeneous, or are they homogeneous because of Pd leached in solution? Indeed, for the latter case, which species is responsible for the observed catalysis? Catalytic systems, we argue, should be evaluated based on uniform criteria. This account hence

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Piera Demma Carà is currently a PhD student in sustainable technologies at the University of Palermo. Her work, performed also at Palermo's CNR Institute of nanostructured materials, aims at the development of new heterogeneous sol-gel Pd catalysts for cross coupling reactions. In 2009 she undertook a 6 months internship at Québec City's Silicycle and in late 2011 she joined Professor G. Rothenberg's research group at the University of Amsterdam.



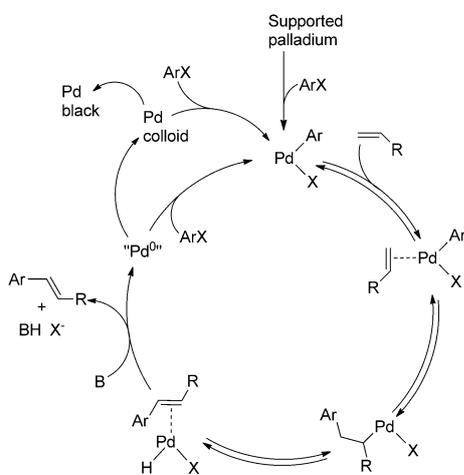
critically addresses the leaching issue by selectively referring to some of the newly developed catalytic systems. The report is concluded by identifying the relevant chemistry (and nanochemistry) challenges in the field.

2. The Leaching Issue

In 2000, a report of Arai and co-workers^[22] clearly showed that several supported palladium catalysts (commercial Pd/C, Pd/SiO₂ and Pd over magnesium-containing smectite-like porous material) employed in the Heck vinylation of iodobenzene actually leached significant amounts of palladium into the solvent and that it was these dissolved Pd species that catalyzed the reaction. The same authors, however, noted that almost all the palladium species in the solution redeposited onto the surface of the supports after the reaction, so that the solid catalysts, and in particular 10 wt.% Pd/C, were recyclable with minor loss of activity. Remarkably, both inorganic and organic bases used to enhance the reaction rate were found to promote the palladium dissolution and redeposition.

Shortly afterwards, Basato and co-workers confirmed that in Heck-type reactions, promoted by either Pd/Al₂O₃ and Pd/ion-exchange resin, the solids actually acted as sources of soluble catalytically active palladium(II) complexes.^[23] By investigating the mechanism of metal leaching they also demonstrated that leaching of palladium only occurs in the presence of an aryl halide, as a consequence of the oxidative addition of the halide to surface atoms of the metal particles with soluble palladium(II) species directly entering the catalytic cycle after being generated from the supported metal (Scheme 2).

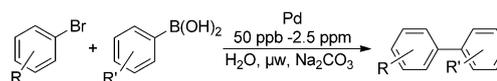
As palladium is released in the +2 oxidation state, good coordinating agents towards palladium(II), such as acetate ions, enhance the extent of metal leaching. Basato explained why some authors did not observe significant catalytic activity in the filtrate after removal of the solid catalyst *shortly* after the onset of the reaction. This suggests that the accumulation of active palladium(II) species in the solution is a relatively slow process. Indeed, the ICP chemical analysis of the filtrate and



Scheme 2. The catalytic cycle for the Heck reaction catalyzed by supported Pd catalysts. [Reproduced from Ref. [23], with kind permission].

the Maitlis filtration test (comparison of catalytic activity before and after hot-filtering the active catalyst solution)^[24] will show, respectively, whether Pd is leached or not, and if the leached palladium is still in active form.^[25]

Surprisingly enough, in 2005 Arvela and co-workers reported that Suzuki homogeneous coupling reactions under microwave irradiation were catalyzed at completion even by 50 ppb of Pd contaminating the potassium carbonate (Scheme 3).^[26] In other words, ultralow palladium concentrations down to a level of 50 ppb found as a *contaminant* in commercially available sodium carbonate were found to be responsible for the generation of the biaryl.



Scheme 3. Suzuki coupling reactions catalyzed by ultralow palladium concentrations. [Reproduced from Ref. [26], with kind permission].

In the following we review the test reaction and the leaching experiments for solid catalysts obtained by selected immobilization methodologies. The scope and intrinsic catalytic activity of the material are of clear, primary relevance. However, following Sheldon's approach,^[27] we argue that the main criterion to evaluate the performance of immobilized-Pd catalysts is i) the lack of reaction of the reaction filtrate obtained under the actual reaction conditions (hot filtration test). Indeed, it is not surprising that reactions that are known to be catalyzed even by ppb quantities of Pd are also catalyzed, for example, by 5 wt.% Pd/C in 5 consecutive runs; ii) to differentiate these systems the actual values of Pd leached in solution should always be measured; iii) the activity of the catalyst in further recycles should also be assessed.

General leaching of palladium is responsible for most catalytic processes observed for most "heterogeneous" Pd catalysts developed thus far. This does not necessarily limit the practical synthetic advantages of these materials, although the cases for which the catalyst is recyclable and leaching is limited must be distinguished from options for which the catalyst is strongly modified and the original activity is dramatically reduced after one run.

For example, a TEM investigation of an highly active Pd/C catalyst tested for the Heck coupling of bromobenzene and styrene at 140 °C before and after a 20 h reaction shows that the uniform distribution of the Pd nanoparticles in the fresh catalyst is lost after the reaction (Figure 1).^[28]

After cross-coupling, the Pd crystallites average size increases from 2.4 nm to 23 nm (one order of magnitude) and the same crystallites agglomerate into larger particles. In addition, and detrimental to catalysis efficiency, Pd precipitation occurs only on the *outer* surface of carbon grains. This example shows also that, being a dissolution/reprecipitation process, leaching is generally a surface (slow) heterogeneous reaction often limiting the overall reaction rate. Hence, as emphasized by Basato,^[23] a strong influence of the support structure on the re-

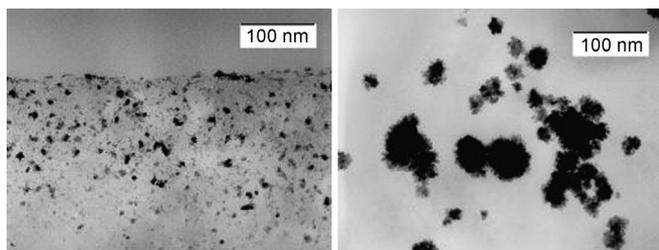


Figure 1. TEM images of a Pd/C catalysts before Heck coupling of bromobenzene with styrene (left) and after the Heck reaction (right). [Reproduced from Ref. [28], with kind permission].

lease of the active Pd species can be almost invariably expected.

Most often, the leached palladium contains catalytically active molecular Pd species and catalytically inactive Pd clusters, both remaining in equilibrium in the reaction mixture, such as in the case of the Heck synthesis of diarylated functionalized olefins catalyzed by Pd^{II}/Al₂O₃.^[29] The reaction mixture was hot-filtered after 1 h, when the yield of product was 45%. The solution was left for 3 h at 140 °C without catalyst and the yield increased to 54%.

A similar leaching and equilibrium mechanism was first proposed by Reetz and de Vries to explain the high catalytic activity in Heck reactions of extremely low amounts (few ppm) of Pd-salts in the absence of ligands.^[30] Authors ascribed the observed activity to formation of soluble Pd nanoclusters that were clearly identified in solution. However, further investigation of the mechanism of Pd nanoparticles catalyzed Heck and Suzuki reactions by Rothenberg and co-workers enabled the conclusion concluded either Pd⁰ atoms or Pd^{II} leached in solution are the true active catalytic species, and not the original Pd nanoclusters (Figure 2).^[31] Actually, the researchers evaluated the behavior of 15 nm Pd nanoparticles stabilized by tetraoctylammonium glycolate using a nanoporous alumina membrane reactor, so that palladium clusters of less than 5 nm in diameter would in any case cross the membrane and promote catalysis at their surface.

Indeed, more recently, Fairlamb and co-workers has shown rather conclusive experimental evidence (real-time X-ray absorption measurements under working conditions) for a heterogeneous active site in the Suzuki–Miyaura catalyzed by polyvinylpyrrolidone-stabilized Pd⁰ nanoparticles (diameter = 1.8–4.0 nm).^[32] Reaction was performed in MeOH at 60 °C and neither sintering nor dissolution was evident, whereas high-resolution TEM showed no size or shape changes between fresh and spent nanoparticles. Fairlamb also suggested that catalysis involves the direct participation of surface palladium defect sites (surface Pd atoms or in five- or six-coordinate sites) in the catalytic cycle (Figure 3).

In 2006 McQuade revealed evidence that the polyurea-encapsulated PdEnCat, a commercial catalyst employed in Heck and Suzuki coupling reactions, was actually acting as a Pd reservoir of catalytic species in solution.^[33] TEM analysis was used to analyze the supernatant from the Heck reaction catalyzed by PdEnCat 30 by sampling the reaction mixture at 85% con-

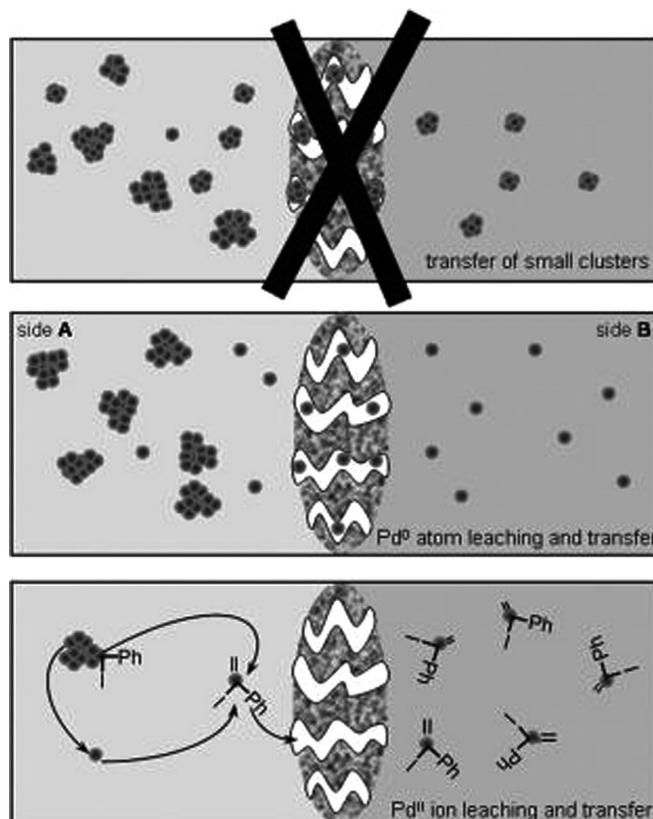


Figure 2. Suggested mechanisms for palladium transfer from side A to side B. Top: cluster fragmentation followed by small cluster transfer; middle: Pd⁰-atom leaching and transfer under non-oxidizing conditions; and bottom: formation and subsequent transfer of Pd^{II} complexes. [Reproduced from Ref. [31], with kind permission].

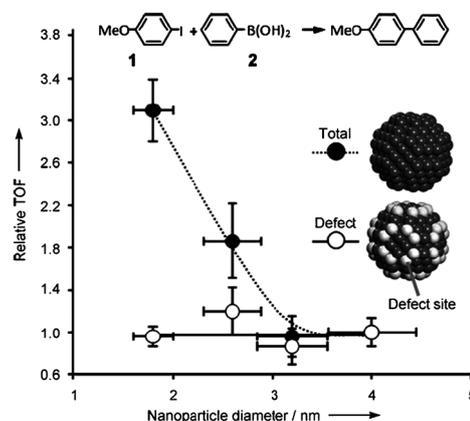


Figure 3. Structure-sensitive Suzuki coupling of 1 and 2 over size-selected PVP-stabilized Pd nanoparticles. Turnover frequencies are normalized relative to the surface-atom densities of the largest nanoparticle: total surface atoms (●) or defect surface atoms (○). The normalized cross-coupling rate should be independent of nanoparticle size if the correct active site has been identified. [Reproduced from Ref. [32], with kind permission].

version. The analysis clearly revealed the formation of Pd nanoparticles in the size range of 5–10 nm (Figure 4). Soon afterwards, Jones reached analogous conclusions for entrapped Pd pincers, Pd salts, and Pd N-heterocyclic carbenes complexes.^[34]

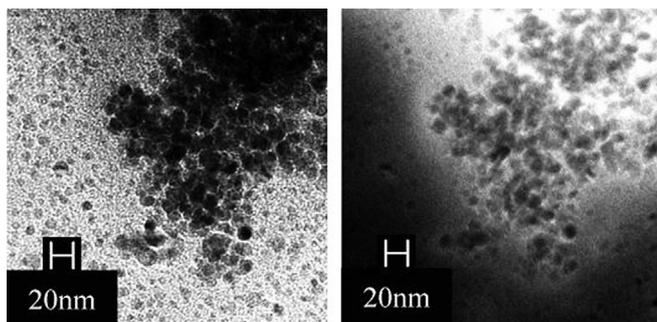


Figure 4. TEM image of Heck reaction supernatant catalyzed by PdEnCat 30 in isopropyl alcohol (left). TEM image of the same sample using energy filtration imaging specific for Pd (right). [Reproduced from Ref. [33], with kind permission].

In 2003, Kobayashi reported^[9] a “coacervation”, a polymer-based heterogenization method, using polymers containing pendant epoxide and alcohol functionalities to create insoluble precipitates that are then thermally cross-linked to produce polymer incarcerated (PI) palladium catalysts starting from inexpensive Pd^{II} salts and a polystyrene-based copolymer under reducing conditions.

Such catalysts show high catalytic activity in Mizoroki–Heck reactions and Suzuki–Miyaura couplings with a range of substrates including an aryl chloride^[35] and can be recovered and reused. As described by McQuade,^[36] however, the high catalyst loading required by PI-mediated reactions lead to the use of coordinating solvents. Additionally, many of the Pd-catalyzed transformations require excess phosphine ligands in the reaction mixture to achieve good reactivity, which suggests that PI catalysts are also serving as reservoirs for catalytically active species dispersed in solution.

3. Available Heterogeneous Catalysts

Heterogeneous Pd-based catalysts for cross coupling reactions mainly differ in i) chemical nature (organic, inorganic, or hybrid organic-inorganic) of the solid matrix entrapping the Pd catalyst, and ii) the nature of the catalyst attachment (chemical or physical entrapment), which, in turn, is related to the nature of the entrapped catalyst (a Pd organometallic complex or Pd nanoparticles). In the following we focus on selected examples for all these catalytic classes.

3.1. Heterogenization using organic materials

As mentioned above, Pd/C remains the main commercial catalyst employed in heterogeneously catalyzed cross-coupling reactions. However, owing to dissolution and re-precipitation of Pd during reaction, the activity of even the best catalyst^[7] is reduced by more than 50% when the catalyst is reused, thus impacting the overall economy of the process. A number of organic polymers in new shapes and forms have thus been used to heterogenize Pd catalysts and avoid degradation. Traditional polymeric resins indeed have poor accessibility of reactive

sites, are mechanically unstable (break into fine residues that block filters) and undergo swelling in organic solvents.

3.1.1. Catalytic organic fibers

First introduced by Colacot and co-workers at Johnson & Matthey in 2006, polypropylene fiber-supported palladium complexes tradenamed FibreCat and SMOPEX are low leaching mediators for various coupling reactions.^[37] FibreCat is a class of functionalized phosphine-based supported homogeneous catalyst system; whereas SMOPEX is a fiber originally designed to scavenge metals that is now also employed for supporting [Pd(OAc)₂] to afford a supported catalyst (Pd-SMOPEX-111) for coupling of aryl iodides and bromides.^[38]

These fibers (typical size 2 mm, Figure 5) are produced by graft copolymerization under electron beam irradiation of polyolefin fiber with functionalized monomers.^[39] The catalytic centers are located at the exterior of the fiber where they are easily accessible, while the resulting mechanically and chemically robust catalytic fibers alleviate the swelling problem typical of traditional polymeric beads.

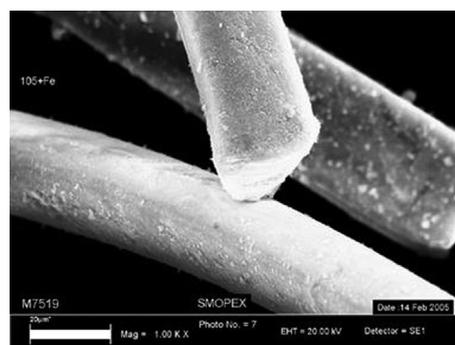
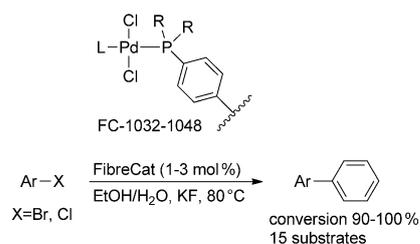


Figure 5. FibreCat fibers under the scanning electron microscope [Reproduced from Ref. [39], with kind permission]. Scale bar represents 20 μm .

The design of these catalysts allows them to be tuned in three ways, namely by changing: i) the Pd precursors, ii) the ligand on the support, and iii) the ligand on the metal. Highlighting that there is no universal C–C bond forming catalyst, Colacot^[38] emphasized that electronic and steric matches between the substrate and the catalyst is the key in developing new efficient catalysts for the reactions required by the customer. The first generation FibreCat catalysts made of Ph₃-based systems with various Pd precursors were designed for conversion of aryl bromides and aryl iodides only, consequently, a second generation of FibreCat was introduced for the coupling of deactivated aryl chlorides. These materials incorporate an additional electron-rich and bulky monodentate ligand such as Q-Phos, tBu₃P, (Me₂NC₆H₄)P(tBu)₂ (Ata-Phos), and IPr-carbene, as well as bidentate ligands such as BINAP, dppf, and dippf, bound to the heterogenized Pd center (Scheme 4).

Leaching of Pd from the FibreCat and SMOPEX first generation materials is typically low and in the acceptable range for APIs (active pharmaceutical substances) in the first 2–3 reac-



Scheme 4. Basic structure of 2nd generation FibreCats (FC-1032-1048) designed for cross-coupling of chloroarene substrates. [Reproduced from Ref. [39], with kind permission].

tion recycles, but then rapidly increases from 1 to 20 ppm pointing to catalyst dissolution (Table 2).^[40] The 2nd generation of palladium FibreCat catalysts, however, show leaching values below 1 ppm in five consecutive Suzuki coupling of aryl chlorides and bromides with consistent product conversions up to 100%.^[41]

Table 2. Recycling of FibreCat and SMOPEX 111 catalysts used in a Suzuki coupling of 4-bromoanisole with phenyl boronic acid in EtOH-H₂O solvent (n.d.= not detected). [Reproduced from Ref. [40], with kind permission].

Catalyst	Loading [mol%]	Cycle	Yield (isolated) [%]	Leaching [ppm]
FC-1032	1	1	100 (94)	< 1
		2	100 (92)	< 1
		3	100 (93)	5
		4	95 (87)	10
FC-1039	0.5	1	100 (93)	< 1
		2	98 (91.5)	< 1
		3	94 (88)	1
		4	16	20
FC-1029	0.5	1	100 (94)	n.d.
		2	100 (91)	< 1
		3	92 (88)	1
		4	26	3
Pd SMOPEX 111	1	1	100 (92)	n.d.
		2	100 (91)	< 1
			77 (65)	1
			5	65

3.1.2. Polyurea-microencapsulated catalysts

Polyurea-microencapsulated palladium catalysts were first reported by Ley and co-workers in 2002^[42] and are obtained by microencapsulation of [Pd(OAc)₂] in a polyurea framework formed upon hydrolytic polycondensation of multi-functional oligo-arylisocyanates. Unlike most palladium catalysts then available on the market, the resulting materials (Figure 6) were stable to storage and use in air and could be used in both conventional solvents and supercritical carbon dioxide (scCO₂). They were soon commercialized by Reaxa (now part of S Amit & Co.) with the tradename PdEnCat. Products include Pd(II)EnCat (encapsulated palladium acetate plus co-encapsulated li-



Figure 6. SEM image of PdEnCat beads. [Reproduced from Ref. [43], with kind permission]. Scale bar represents 200 μm.

gands)^[43] and Pd(0)EnCat (encapsulated palladium metal nanoparticles).

PdEnCat act as reservoirs (solid sources) for catalytically active species during the course of Heck and Suzuki couplings. Coordinating solvents (such as *N,N*-dimethylacetamide and *N,N*-dimethylformamide) swell the polyurea matrix affording increased palladium leaching.^[33] However, upon lowering the temperature in most polar and alcoholic solvents in which Pd(II)EnCat works best, the levels of Pd leached into products are reduced, which makes these materials suitable for the synthesis of APIs (Figure 7).^[44] For example, in a Suzuki commercial coupling process, the synthesis previously in use employed

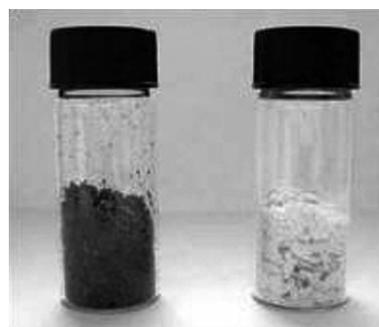


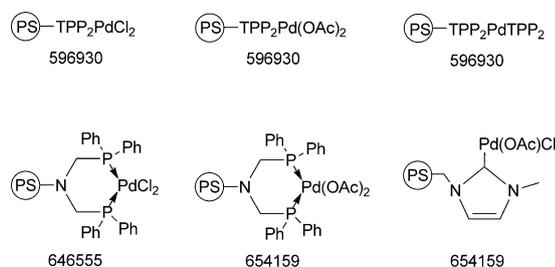
Figure 7. Contaminated crude Suzuki coupling product made with homogeneous [Pd(OAc)₂] (left), and product made using PdEnCat 30 catalyst with no extra purification (right) [Reproduced from Ref. [44], with kind permission].

2.5 mol% Pd/C affording a 94% product yield with impurities at 5% and 1% and a reaction time of 60 min.^[47] Following extensive work-up and recrystallization, Pd levels of > 50 ppm were still present in the product. Using a 0.25 mol% catalytic amount of Pd(II)EnCat30 gave instead a 99% product yield after 30 min with both impurities reduced to < 1% and Pd levels reduced to < 10 ppm without recrystallization.

In agreement with the dissolution–re-deposition mechanism typical of many solid catalysts, under microwave irradiation the selective activity of microencapsulated palladium acetate PdEnCat 30 catalyst in the Suzuki cross-coupling reaction is significantly enhanced (and the lifetime of the immobilized catalyst prolonged).^[45]

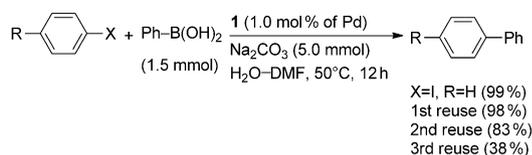
3.1.3. Polystyrene-entrapped catalysts

Polystyrene (cross-linked with divinylbenzene) beads doped with palladium catalysts are stable to heat and air and can be reused several times with minor decrease in activity in many cross coupling reactions.^[46] Sigma Aldrich, for instance, offers a wide variety of resins made of polystyrene-supported (PS) Pd species for cross coupling reactions (Scheme 5).^[47] However, in



Scheme 5. Selected examples of commercial polystyrene resins functionalized with palladium species for cross coupling reactions. [Reproduced from Ref. [47], with kind permission].

many cases these resins leach palladium in organic solvents (such as DMF, dioxane, toluene, etc.) and are broken by vigorous, long-lasting stirring. For example, the PS-Pd catalyst developed by Park and co-workers^[48] rapidly loses the original activity in the Suzuki–Miyaura reaction, owing to palladium leaching and Pd nanoparticle aggregation, with yield in the third reuse lowered to only 38% from the original 98% (Scheme 6).



Scheme 6. Suzuki–Miyaura coupling reaction mediated by a PS-Pd catalyst developed by Park and co-workers. [Adapted from Ref. [48], with kind permission].

In water the performance of polystyrene-supported catalysts improves, with decreased leaching. Wang and co-workers for instance reported that sodium tetraphenylborate rapidly reacts with aryl bromides in water at 120 °C, under microwave irradiation, in the presence of a PS palladium catalyst to afford polyfunctional biaryls in good yields over 10 consecutive reaction runs without noticeable decrease in activity.^[49] However, the scope of these materials is often limited to one specific reaction and leaching is almost invariably responsible for the observed catalysis.

3.2. Heterogenization using inorganic materials

A number of different inorganic materials have been used to heterogenize Pd catalysts. The main advantage of using an in-

organic matrix, in principle, lies in its superior chemical and physical stability, which is a requirement of relevance for reactions that are typically carried out in liquid phase at 80–120 °C.

Conventional inorganic solid catalysts, however, most often show poor chemical stability. For example, Pd-doped zeolites, such as Pd/SBA-15 and $[\text{Pd}(\text{NH}_3)_4]^{2+}/\text{NaY}$, give complete conversions in various Sonogashira coupling reactions of aryl halides with acetylenes, but are both strongly deactivated during the first run, owing to complexation of phosphine ligand during reaction.^[50] Similarly, a Pd⁰-loaded NaY zeolite was able to mediate the Suzuki reaction of aryl bromides even at room temperature.^[51] Even in this case, the catalyst activity was reduced to 31% after one run, requiring cumbersome regeneration of the catalyst by consecutive treatments with O₂ and H₂.

Newly developed Au@Pd nanoparticles consisting of 16 nm Au cores surrounded by Pd shells catalyze Suzuki–Miyaura cross-coupling reactions in water at room temperature, owing to the leaching of Pd species from the capsule outer surface.^[52] Once again, interestingly, leaching is ascribed to the synergistic action of base and arylboronic acid.

3.2.1. Polyoxometalate and metal–organic frameworks Pd catalysts

The first example of an active heterogeneous palladium catalyst for Suzuki coupling of inexpensive and readily available aryl chlorides was reported by Neumann and co-workers in 2002.^[53] The catalyst is made of 15–20 nm Pd⁰ particles prepared by reduction with H₂ of Pd_x-([PW₁₁O₃₉]⁷⁻)_y nanoparticles clusters supported on $\gamma\text{-Al}_2\text{O}_3$ (Figure 8).

These supported nanoparticles were shown to be effective catalysts for Suzuki-, Heck-, and Stille-type carbon–carbon coupling and carbon–nitrogen coupling reactions of bromoarenes in mixed a H₂O–EtOH reaction medium. Furthermore, chloroar-

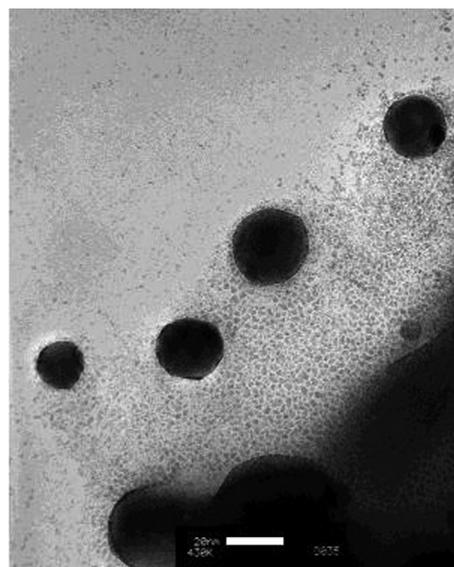


Figure 8. Pd_x-([PW₁₁O₃₉]⁷⁻)_y nanoparticles developed by Neumann and co-workers. [Reproduced from Ref. [53], with kind permission]. Scale bar represents 20 nm.

enes successfully underwent Suzuki cross-coupling with phenylboronic acid in the absence of solvent.

The coupling reaction is initiated by reaction of the haloarene with the Pd catalyst at the surface of the nanoparticle rather than with dissolved Pd species. Indeed, to investigate on whether the $\text{Pd}_x\text{-(PW}_{11}\text{O}_{39})_y^7^-$ on alumina catalyst is a true heterogeneous catalyst insoluble poly(4-bromostyrene) was reacted with 3-formylphenylboronic acid ($\text{mp} = 110^\circ\text{C}$) in the presence of the solid catalyst at 140°C for 12 h. The polymer was recovered after the reaction. IR analysis showed no characteristic aldehyde peak at $\tilde{\nu} = 1700\text{ cm}^{-1}$, indicating that 3-formylphenylboronic acid had not reacted with the 4-bromopolystyrene substrate.

More recently, a similarly versatile heterogeneous catalyst supported on a metal-organic framework (MOF) suitable for Suzuki coupling of different aryl chlorides with phenylboronic acid in water was reported.^[54] The MIL-101 $[(\text{Cr}_3(\text{F},\text{OH})(\text{H}_2\text{O})_2\text{O}-[(\text{O}_2\text{C})-\text{C}_6\text{H}_4-(\text{CO}_2)]_3 \cdot n\text{H}_2\text{O})]_n$ ($n \approx 25$), zeolite-type framework structure has a huge specific surface area ($4000\text{ m}^2\text{g}^{-1}$) whereas the hybrid nature of the 30 \AA pore surface made of both hydrophilic and hydrophobic networks facilitates selective adsorption of the aryl substrates in water.

The entrapped Pd nanoparticles are not air-stable and reactions need to be carried out under N_2 . High catalytic activities were observed for chlorobenzene and both electron-rich and electron-poor aryl chlorides, affording the corresponding biphenyl compounds in good yields in 20 h at 80°C . The crystalline structure of the catalyst after five catalytic cycles is retained and the TEM image of the reused catalyst indicates that the mean diameter of the nanoparticles is $(2.0 \pm 0.6)\text{ nm}$ is unvaried (Figure 9).

The solution isolated at the reaction temperature after approximately 50% conversion did not exhibit any further reactivity indicating that palladium leached in solution (less than 0.2% of the total palladium detected by atomic absorption spectroscopy) is in *non*-active form. The same MOF-based catalyst could be reused in 10 consecutive reaction runs for the one-pot synthesis of indole by coupling 2-iodoaniline and phenylacetylene in water at 90°C .^[55] Again, the remarkable stability of the catalyst in 10 consecutive reaction runs was ascribed to effective confinement of the Pd^0 nanoparticles in the cages of MIL-101.

3.2.2. LaPCat perovskite catalysts

Perovskites containing palladium are applicable for Suzuki-Miyaura cross coupling reactions (and, to a lesser extent, for Ullmann and Sonogashira reactions).^[56] Reaxa offers a kit of 6 palladium (and copper) LaPCat perovskite (Table 3) that, again, act as reaction pre-catalysts.^[57]

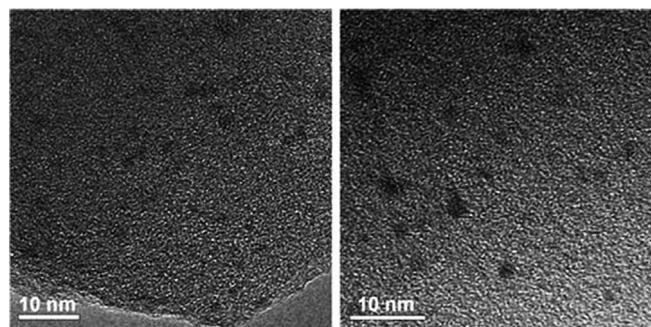


Figure 9. TEM images of Pd/MIL-101 before the reaction (left) and after five cycles (right). [Reproduced from Ref. [54], with kind permission].

Table 3. Reaxa heterogeneous Perovskites containing palladium kit sample series. [Reproduced from Ref. [58], with kind permission].

Catalyst	Formulation	Formula weight	Pd [wt %]	Cu [wt %]	Surface area [m^2g^{-1}]	Mean particle size [μm]
FP2	$\text{LaFe}_{0.95}\text{Pd}_{0.05}\text{O}_3$	245.29	2.169	–	5.5	41.1
FP8	$\text{LaFe}_{0.80}\text{Pd}_{0.20}\text{O}_3$	252.87	8.417	–	5.7	3.3
CoP	$\text{LaFe}_{0.57}\text{Co}_{0.38}\text{Pd}_{0.05}\text{O}_3$	246.46	2.159	–	3.4	4.0
CuP	$\text{LaFe}_{0.57}\text{Cu}_{0.38}\text{Pd}_{0.05}\text{O}_3$	248.21	2.144	8.20	12	3.7
CoCu	$\text{LaFe}_{0.9}\text{Ce}_{0.1}\text{Co}_{0.60}\text{Cu}_{0.40}\text{O}_3$	247.81	–	8.64	7.9	5.4
YBCu	$\text{YBa}_2\text{Cu}_3\text{O}_7$	666.22	–	24.1	0.3	10.6

For example, the $\text{LaFe}_{0.57}\text{Co}_{0.38}\text{Pd}_{0.05}\text{O}_3$ material can be applied to the Suzuki coupling of numerous boronic acids and esters with aryl bromides, iodides and chlorides in a wide range of aqueous solvent mixtures at $80\text{--}100^\circ\text{C}$.^[58] Low palladium loadings of as little as 0.1 mol% Pd (corresponding to perovskite loading of 2 mol%) can be successfully employed.

Monitoring the reaction (Suzuki coupling of 4-bromoanisole and phenylboronic acid) shows that the catalyst is actually a pre-catalyst with a four minutes induction period and a typical sigmoidal kinetics (Figure 10).^[59]

Once again, detailed investigation into the mode of action of these catalysts shows that these heterogeneous materials operate by a solution-phase mechanism which involves the generation of a soluble, catalytically active palladium species that is desorbed from the bulk inorganic phase and probably

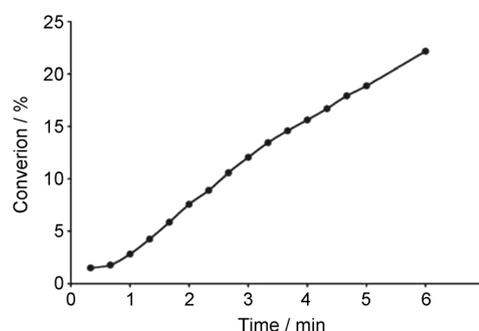


Figure 10. Kinetic investigation of $\text{LaFe}_{0.57}\text{Co}_{0.38}\text{Pd}_{0.05}\text{O}_3$ in the first 7 min of reaction between phenylboronic acid and 4-bromoanisole. [Reproduced from Ref. [59], with kind permission].

redeposited on a modified solid phase after the reaction is complete. Whereas the surface of the unused catalyst is relatively uniform and appears amorphous, the post-reaction catalyst has undergone a profound morphological change and appears to consist predominantly of a new crystalline phase (Figure 11). This phenomenon clearly limits the reusability of these catalysts.

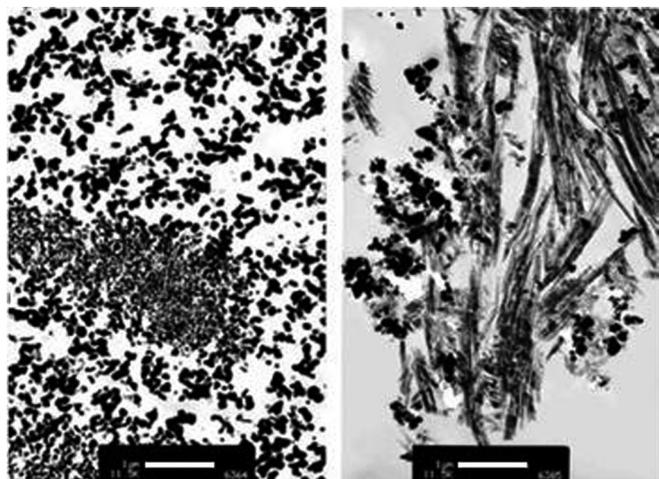


Figure 11. TEM images of the catalyst before (left) and after (right) reaction in the Suzuki coupling of phenylboronic acid with 4-bromoanisole. [Reproduced from Ref. [59], with kind permission]. Scale bar represents 1 μm .

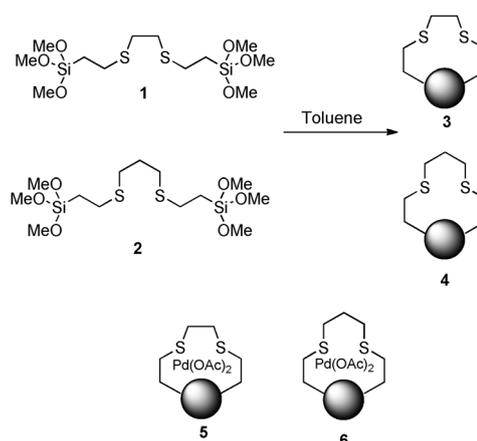
3.3. Sol-gel heterogenization in silica-based materials

Among the new heterogenization technologies, the sol-gel entrapment in silicate materials is rapidly emerging, owing to a number of benefits originating from the combination of catalyst entrapment in solid matrices of high chemical and physical stability typical of inorganic oxides; along with the ability to tune the properties of the matrix, typical of organic polymers.^[60]

3.3.1. Silica-based palladium catalysts

First reported by Sullivan and co-workers in 2007,^[61] a number of heterogeneous functionalized silicas act as low leaching catalysts for palladium-mediated cross-coupling reactions for a wide range of different substrates. Shown in Scheme 7 is a typical polycondensation of these catalytic systems affording two dithio palladium modified silicas. Typical 2 mol% catalyst loads effectively catalyze Suzuki cross-coupling reactions of bromo- and iodoarenes. No reactivity of the hot filtrate collected after 50 min is typically observed, pointing to truly heterogeneous catalysis.

In general, the strong chemical bond linking the active functionality to the silica-based support ensures that no bond cleavage can occur in the challenging environments of many cross-coupling reactions and, since 2009, the British company Phos-



Scheme 7. Synthesis of two dithio palladium modified silicas according to Sullivan and co-workers. [Reproduced from Ref. [61], with kind permission].

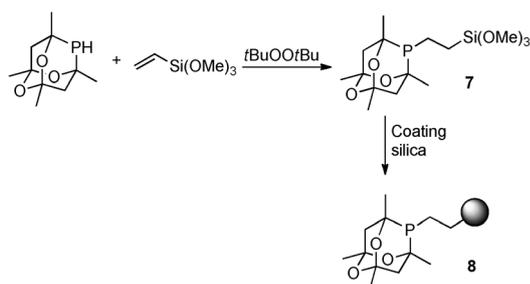
phonicS commercializes a portfolio of such silica-based catalysts (Table 4).^[62]

Another catalyst of this series is Pd ethylthioglycolate-modified silica. Using a 5 mol% catalyst amount, close to quantitative conversions can be achieved for many Suzuki-Miyaura reactions in less than 2 h.^[63] However, use of a 2.5 mol% catalytic amount requires considerably longer reaction times, which is an indication of Pd leaching. Indeed, lower conversions (90%) were achieved in the 2nd and 3rd cycles even after increasing the reaction times. The authors concluded that together the hot filtration and recycling data suggest that the equilibrium between solid and solution phase palladium lies in the direction of the solid-bound palladium.^[69]

Table 4. PhosphonicS heterogeneous palladium catalyst kit sample series. [Reproduced from Ref. [63], with kind permission].				
Structure name	Loading [mmol g ⁻¹]	Particle size [μm]	Diameter [Å]	Product Code
	0.1–0.4	60–200	60	SCR-Pd
	0.1–0.4	60–200	60	SEM2-Pd
	0.1–0.4	60–200	60	SPM3-Pd
	0.01–0.03	60–200	110	PAPd1r
	0.01–0.03	60–200	110	PAPd2r

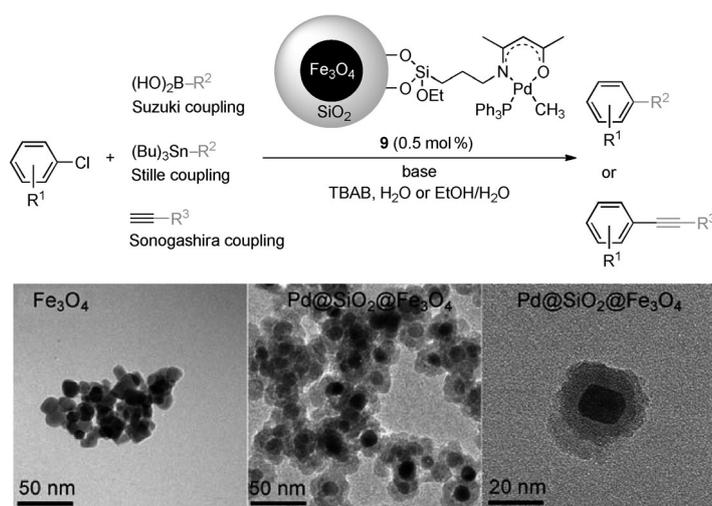
Heterogeneous Palladium Catalyst Kit: 1 g format (CP-06-KITD31) (5 × 1 g samples); 5 g format (CP-06-KITD35) (5 × 5 g samples); 10 g format (CP-06-KITD310) (5 × 10 g samples)

The most active catalyst of this series is made of silicaethylphosphatrioxadamantane palladium, wherein the phosphine is immobilized from compound **7**. The precursor catalytic material **8** is formed by radical addition of phosphatrioxadamantane to vinyltrimethoxysilane which is subsequently grafted onto silica (Scheme 8).^[64] Applied in low catalytic amounts (0.1 mol % in xylene at 120 °C or under microwave irradiation of EtOH:H₂O:DME solutions) to a broad range of Suzuki substrate pairs, this Pd catalyst was found effective, reusable, and resistant to leaching, even if the hot filtration test was performed after only 2 min, a time frame that may be too short to observe accumulation of leached Pd in solution



Scheme 8. Synthesis of silicaethylphosphatrioxadamantane palladium according to Sullivan and co-workers. [Reproduced from Ref. [64], with kind permission].

As mentioned above, the electronic and steric pairing between the substrate and the catalyst needs to be taken into consideration in the design of sol-gel entrapped Pd catalysts. Following this approach, Lee and co-workers recently reported successful synthesis of an highly stable silica-entrapped catalyst suitable for Suzuki, Sonogashira, and Stille couplings of a wide variety of deactivated aryl chlorides (Scheme 9).^[65]



Scheme 9. TEM images of aggregated Fe₃O₄ (left); aggregated Pd@SiO₂@Fe₃O₄ (**9**) (middle); individual Pd@SiO₂@Fe₃O₄ (**9**) (right). [Reproduced from Ref. [65], with kind permission].

The authors entrapped a monodentate electron-rich phosphine and bulky imine ligands complexing Pd²⁺ in the inner porosity of a thin layer of SiO₂ sol-gel coated around commercially available 20 nm Fe₃O₄ nanoparticles. Said ligands cooperatively facilitate the key step oxidative activation of less reactive aryl chlorides, as well as the reductive elimination step mediated by magnetic nanoparticle-supported (β -oxoiminato)(-phosphanyl) palladium catalyst **9** (Scheme 9). Furthermore, the sol-gel entrapment within the inner porosity of the resulting materials results in effective stabilization of the entrapped catalyst.^[66] As a result, catalyst **9** showed full retention of the original high activity over 10 consecutive coupling reactions of 4-chloroanisole with phenylboronic acid, as well as with phenylacetylene. Finally, being supported on commercially available magnetite, the material was easily and efficiently separated from the reaction medium by an external permanent magnet, therefore, minimizing the loss of catalyst during separation, whereas the silica layer protects the magnetite core from abrasion under shaking.

3.3.2. ORMOSIL Pd catalysts

Organically modified silicates (ORMOSIL) doped with catalytic species are often superior heterogeneous catalysts in a number of different synthetically relevant organic reactions.^[67] In 2010, a new series (tradenamed *SiliaCat*) of ORMOSIL-entrapped palladium catalysts for cross-coupling reactions was introduced by Canada's company SiliCycle.

*SiliaCat*DPP-Pd and *SiliaCat*S-Pd are, respectively, diphenylphosphine and thiol based palladium(II) heterogeneous catalysts synthesized from a mercapto and diphenylphosphine functionalized organosilica matrix.^[68] These catalysts can effectively catalyze Mizoroki-Heck, Sonogashira, Suzuki-Miyaura, Stille, Buchwald, and Kumada cross-coupling reactions with low leaching and good selectivity. For example, relative to [Pd(OAc)₂] in solution, *SiliaCat*DPP-Pd employed in the Mizoroki-Heck reaction between aryl iodides and bromides and styrene offers superior selectivity in the formation of the desired *trans*-stilbene.

The organosilica-based matrix of these catalysts facilitates work-up whereas the low leaching prevents the use of metal scavengers and affords good catalyst recyclability in Suzuki, Sonogashira, and Heck reactions (Table 5). For example, the catalyst *SiliaCat*DPP-Pd can perform over 9 cycles in the Suzuki-Miyaura coupling between 1-iodo-4-nitrobenzene and phenylboronic acid without noticeable loss of activity.

More recently, a new nanostructured Pd⁰ catalyst *SiliaCat*Pd⁰, able to catalyze a number of C-C bond formation reactions, was introduced.^[69] The material is made of a mesoporous organosilica gel doped with ultrasmall (3–5 nm) Pd⁰ nanocrystallites. A very low amount (0.1 mol %) of the catalyst rapidly mediates the Sonogashira coupling of phenylacetylene and 4-iodo-acetophenone in ethanol at reflux without the need of deaerated conditions typical of So-

Table 5. Leaching in crude products from SiliaCatDPP-Pd and SiliaCatS-Pd in Suzuki, Sonogashira and Heck coupling reactions. [Reproduced from Ref. [69], with kind permission].

Entry	Aryl halide	Substrate	Catalyst [mol %]	Solvent ^[a] (Conc. [M])	t	Conv. [%]	Leaching [ppm]	
							Pd	Si
1	1-iodo-4-nitrobenzene	PhB(OH) ₂	0.2 S-Pd	MeOH (0.1)	15 min	99	4.3	0
2	1-bromo-4-nitrobenzene	PhB(OH) ₂	0.2 DPP-Pd	MeOH (0.1)	15 min	99	4.6	0
3	1-iodo-4-nitrobenzene	PhC≡CH	0.5 DPP-Pd	MeOH/H ₂ O (0.07)	5 min	98	36	12
4	iodobenzene	Styrene	0.1 DPP-Pd	CH ₃ CN (0.8)	20 h	99	0.5	19

Reactions performed at reflux. Aryl halide/substrate/base = 1:1.1:1.5 equiv (K₂CO₃ entry 1–3, Et₃N entry 4); [a] MeOH/H₂O in a 10:1 ratio.

sonogashira reactions using Pd⁰ complexes that are typically unstable in air (oxygen promotes formation of homocoupled acetylenes).

The SiliaCatPd⁰ catalyst can be similarly employed in the Suzuki–Miyaura coupling reaction of iodide and bromide substrates with phenylboronic acid with reaction proceeding in excellent yields for substrates with different electron withdrawing or electron donating groups, as well as with different heteroatoms such as pyridine and quinoline.

Reusing the catalyst in 7 consecutive cycles in the Suzuki coupling of 4-iodo-nitrobenzene and phenylboronic acid did not result in catalytic activity losses, with minimal Pd leaching (<0.2 ppm). Complete substrate conversion was achieved even after the seventh cycle, with 99.5% selectivity. This is not the case, for comparison, for each of the palladium catalysts obtained by reduction of [Pd(OAc)₂] supported on amorphous silica, mercapto-functionalized and amine functionalized silica for which in similar Heck reactions leached Pd was the active phase for all of the catalysts tested.^[70]

All SiliaCat palladium catalysts (SiliaCatDPP-Pd, SiliaCatS-Pd, and SiliaCatPd⁰) were recently applied to the conversion of

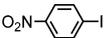
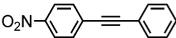
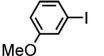
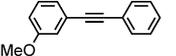
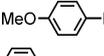
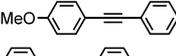
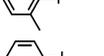
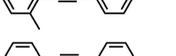
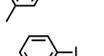
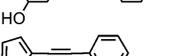
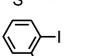
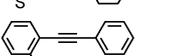
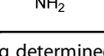
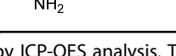
widely different substrates in Suzuki, Sonogashira, and Heck coupling reactions run in a parallel synthesizer.^[71] The method enables quick screening with identification of the best reaction conditions and rapid library generation. Leaching test for all catalysts employed show, invariably, that minimal leaching values are obtained with the SiliaCatPd⁰ catalyst (Table 6). In general, furthermore, leaching increases with decreasing reactivity, with nitrogen-coordinating substrates such as pyridines and quinoline affording the highest release levels.

Outlook and Conclusions

Numerous Pd-immobilized catalysts for cross-coupling reaction have been introduced in the last decade. Some of them are truly heterogeneous, others are pre-catalysts capable to re-adsorb the palladium leached in solution and recycle; whereas many of them are not recyclable and are irreversibly modified upon single use. A critical analysis of selected examples from the recent literature has led us to propose that uniform criteria should be followed to evaluate the performance of Pd-immobilized catalysts. These criteria are: i) the lack of reaction of the reaction filtrate obtained under the actual reaction conditions (to rule out catalysis by leached species); ii) quantitative analysis of the actual values of Pd leached in solution; and iii) assessment of the catalyst activity in further recycles.

Two general findings emerging from the literature review are that encapsulation in the inner porosity of both small Pd

Table 6. Conversion and Leaching of Pd from the SiliaCatDPP-Pd, SiliaCatS-Pd, and SiliaCatPd⁰ catalysts employed in Sonogashira reactions. [Reproduced from Ref. [71], with kind permission].

Entry	Substrate	Product	SiliaCatDPP-Pd			SiliaCatS-Pd			SiliaCatPd ⁰		
			Conv/Select	Pd [ppm]	Si [ppm]	Conv/Select	Pd [ppm]	Si [ppm]	Conv/Select	Pd [ppm]	Si [ppm]
1			100:100	1.5	5	100:100	4	1.4	100:100	1.1	8
2			100:100	11	50	100:100	0.4	7	99:99	0.3	30
3			99:98	9	35	100:100	0.6	8	99:98	0.4	35
4			100:100	8	12	99:100	0.7	4	91:98	0.4	16
5			100:100	6	29	100:100	1.2	4	100:100	0.4	21
6			90:98	18	24	30:90	0.8	9.8	85:94	1.8	6
7			83:98	6	18	80:98	3	4	75:99	5	6
8			55:95	18	33	30:93	3	7	36:97	14	11

Leaching determined by ICP-OES analysis. The solvent was evaporated and replaced by DMF/EtOH (3:1 v/v).

nanoclusters and Pd complexes is required to enhance stabilization of the entrapped species by the surrounding cages; and that, when Pd complexes catalyst are entrapped, a strong chemical bond between the entrapped ligands and Pd²⁺ is important to prevent release of palladium.

In the latter case, furthermore, the electron density in the palladium atom ligands has a crucial role in promoting the activation of the activity of the haloarene substrates.

Now, Colacot is right in pointing out that no universal Pd catalysts is available for cross-coupling reactions.^[42] Yet, the development of a versatile catalyst systems such as his own FibreCat remains a primary goal in advancing the field. For example, as emphasized by Felpin,^[16] the Heck and Sonogashira heterogeneous couplings of aryl chlorides, which are the most industrially relevant haloarene substrates, are far from being fully developed.

In general, hundreds of pharmaceutical, agrochemical, and fine chemical companies worldwide are in need of recyclable Pd catalysts for cross-coupling reactions meeting demanding requirements in terms of product contamination and economic viability.^[1] Once available, the price of these solid catalysts will mostly depend on the manufacturing cost that, in its turn, is given by the palladium market price added to the cost of the materials synthesis.

Basically, the cost trend will follow the Pd market pricing because the cost of synthesis will remain largely unvaried as the local cost of energy, starting material, capital and labor will only slightly change. As a result, the total catalyst price will fluctuate with the precious metal market pricing (Figure 12) that is currently affected by the increasing demand of Pd as alternative catalyst in automotive catalytic converters.^[72] In this volatile context, competing technologies using lower amounts of entrapped Pd compared to, say, conventional 10 wt.% Pd/C will benefit from lower production cost and lesser volatility.

To ensure therefore widespread diffusion of Pd heterogeneous catalysis in the fine chemicals and pharmaceutical industry, new immobilized-Pd catalysts using lesser amounts of Pd and also of higher stability will be needed, such as in the case of the Pd/MIL-101 or SiliaCatPd⁰ catalysts mentioned above. Consequently, significant progress is needed to merge knowledge

from the once separated domains of organic and materials chemistry to guide the assembly of Pd molecular or nanocrystalline species to optimize their chemical composition, size, shape, and surface to give enhanced chemical and physical properties.

The first attempts towards advanced solid-phase palladium catalysis for high-throughput organic synthesis based on cross-coupling reactions were described by synthetic organic chemists in 2005.^[73] Along this evolutionary path, we argue that future chemical synthesis will be carried out in flow, as it currently happens with the construction of a car: namely by conducting waste-free catalytic reactions one after another in reactors containing solid-supported catalysts in a designed sequential and multistep fashion without the use of conventional work-up procedures.^[74]

In 1997, one of us was among the attendees of a seminar given by Avnir where he invoked the need "to shift organic chemistry from the flask to the inside of sol-gel glasses". An incredible program, clearly, but a trendsetting one that numerous chemical companies worldwide are gradually translating into reality.^[75] This account will hopefully assist in this progress.

Acknowledgements

This article is dedicated to the memory of University of Palermo's Prof. Sergio Hauser (1945–2011), great geochemist, teacher and mentor of two generations of Sicily's geochemists.

Keywords: cross-coupling · heterogeneous catalysis · immobilization · palladium · parallel synthesis



Figure 12. 5 year palladium price (2006–2011). [Reproduced from Kitco.com, with kind permission].

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