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Forum

Palladium Nanoparticles as Efficient Green Homogeneous and Heterogeneous Carbon–Carbon Coupling Precatalysts: A Unifying View

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Pd catalysis of C–C bond formations is briefly reviewed from the angle of nanoparticles (NPs) whether they are homogeneous or heterogeneous precatalysts and whether they are intentionally preformed or generated from a Pd derivative such as $Pd(OAc)_2$. The most studied reaction is the Heck coupling of halogenoarenes with olefins that usually proceeds at high temperature (120–160 °C). Under such conditions, the Pd^{II} precursor is reduced to Pd^0, forming PdNPs from which Pd atom leaching, subsequent to oxidative addition of the aryl halide onto the PdNP surface, is the source of very active molecular catalysts. Other C–C coupling reactions (Suzuki, Sonogashira, Stille, Negishi, Hiyama, Corriu–Kumada, Ullmann, and Tsuji–Trost) can also be catalyzed by species produced from preformed PdNPs. For catalysis of these reactions, leaching of active Pd atoms from the PdNPs may also provide a viable molecular mechanistic scheme. Thus, the term “PdNP catalysis of C–C coupling” used in this review refers to this function of PdNPs as precursors of catalytically active Pd species (i.e., the PdNPs are precatalysts of C–C coupling reactions).

1. Introduction

If Pd has the reputation of being one of the very most efficient metals in catalysis, especially for the formation of C−C bonds,[1] the role of palladium nanoparticles (PdNPs) often is overlooked.[2] Metal NPs have been known for about two millenniums, however [AuNPs were used to decorate glasses (see, for instance, the Lycurgus cup, 4th century AD, British Museum) and were famous in the Middle Age for therapeutic uses].[3] The catalytic role of AgNPs was disclosed in the middle of the XIXth century in photography, while synthetic and optical aspects were rationalized by Faraday during that same period.[4] Pioneering catalytic applications of NPs were reported in 1940 by Nord and co-workers for nitrobenzene reduction.[5] Since the 1970s, transition-metal NPs have been more frequently used in catalysis[6] and are even suspected to be involved in organometallic catalysis

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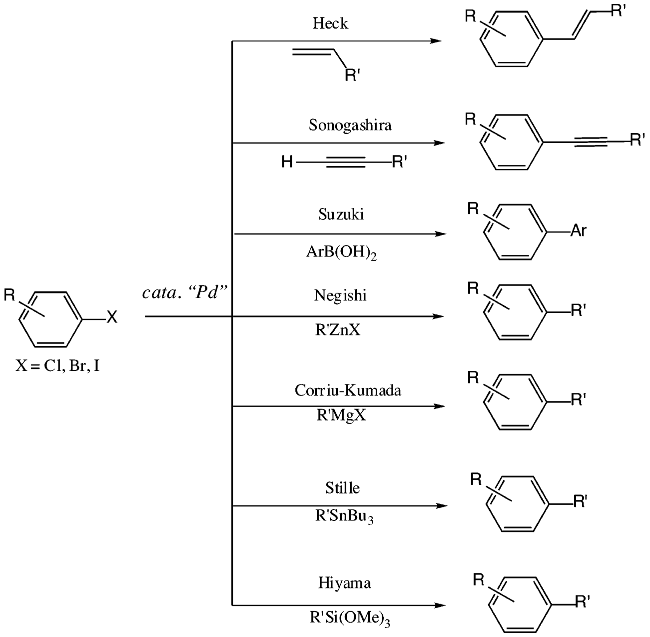
(the Crabtree test[7a] and other recent tests[7b,c]). Since the turn of the millennium, interest in NP catalysis has considerably increased because this class of catalysts appears as one of the most promising solutions toward efficient reactions under mild, environmentally benign conditions in the context of *Green Chemistry*.[2,8] Pd now appears as the most frequently investigated metal for catalytic coupling in the synthesis of C−C bonds. On the one hand, numerous methods of synthesis of metal NPs have been reported, followed by catalytic studies involving either homogeneous or heterogeneous systems (NPs supported on oxides such as silicas, aluminas, or other metal oxides and forms of carbon supports including carbon nanotubes). On the other hand, Pd^0 species systematically and rapidly generated from homogeneous molecular Pd catalysts may eventually aggregate to form PdNPs that can reasonably be suspected to be involved as active species in catalytic processes. Although these two approaches of PdNP catalysis seem to be far away from each other, we will see in this Forum Article that multiple literature data indicate that they are, in fact, intimately related and even often relevant to the same kind of mechanism.

2. Pd-Catalyzed C−C Coupling Reactions

Examples of Pd-catalyzed C−C coupling reactions include the Heck, Sonogashira, Suzuki, Stille, Negishi, Hiyama, Corriu−Kumada, Tsuji−Trost, and Ullmann reactions (Scheme 1). The former two reactions are especially easy to carry out because they do not involve the preparation of an organoelement compound, whereas the four latter do. In this second group, the Suzuki reaction now is most useful and popular because the development of the synthesis of B compounds is now well spread, and these compounds are nontoxic, contrary to other organometallics such as the organotins. Thus, the Heck reaction is the most frequently used, and it has also been much studied using PdNP catalysis. In this reaction, PdNPs are all the more probably involved starting from molecular Pd catalysts because reaction temperatures (required above 100 °C) are high.[8n] The other C−C coupling reactions have been less studied with the purpose of involving PdNPs because such reactions almost systematically involved molecular Pd complexes that were believed to work per se as true catalysts; a few reports are known, however (see sections 8−10). This does not mean that PdNPs are rarely involved in Pd catalysis of these reactions. Indeed, Pd^0 species formed tend to more or less lose ligands if the latter are not strongly bound to the Pd atom in a polypodal form. Indeed, in various cases, molecular Pd precursors were found to form PdNPs that are the sources of catalytically active species, but these in situ generated PdNPs have often not been considered as possible intermediates.

Scheme 1. Pd-Catalyzed C−C Bond Formation with Aryl Halides and Triflates



3. Preparation of Metal NPs

Since the 1980s, metal salts, a molecular stabilizer, and a reductant were used by Bönnemann as represented in eq 1, and this method has become the most used one in the presence of any stabilizer selected among a large variety of more or less sophisticated possibilities (vide infra).[9]

$$MX_n(NR_4)_m + (n - m)\mathrm{Red} \xrightarrow{\mathrm{THF}} M_{NP} + (n - m)(\mathrm{Red}^+X^-) + m(NR_4{}^+X^-) \quad (1)$$

M = group 8−10 metal, X = Cl or Br, R = C_{4-12} alkyl, and Red = M′H (M′ = H, Li, $LiBEt_3$, $NaBEt_3$, $KBEt_3$).

In this mode of PdNP synthesis, the PdNPs are stabilized by a first layer of anions, itself surrounded by a layer of bulky cations. The surface of the NP itself bears some positive charge (Figure 1).

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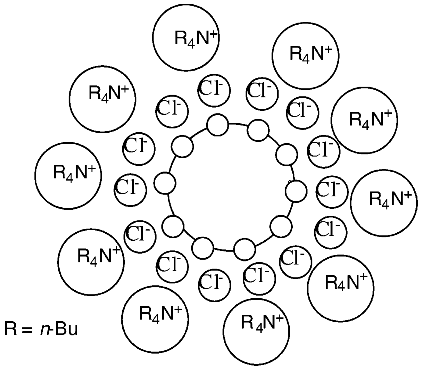

Figure 1. "Electrosteric" (i.e., *electrostatic* with the halide anions located between the positively charged NP surface and the tetrabutylammonium cations and *steric* with the tetrabutylammonium cation) stabilization of metal NPs obtained by reduction of a metal chloride salt in the presence of a tetra-*N*-alkylammonium cation (Bönnemann-type synthesis of eq 1). The presence of chloride or other anions (rather than ammonium cations) near the NP surface was demonstrated. Finke showed that the order of stabilization of IrNPs by anions followed the trend polyoxometallate > citrate > polyacrylate ∼ chloride. Thus, the stabilization of metal NPs by anions can also have an important steric component.[9g]

For instance, Gittins and Caruso recently reported the synthesis and stabilization of PdNPs using Na_2PdCl_4 and (4-dimethylamino)pyridine.[10] Another even earlier, popular NP synthetic method used the thermal decomposition of metal(0) precursors. Zerovalent metal complexes such as $Pd(dba)_2$ and $M_2(dba)_3$ (M = Pd, Pt) were reported in 1970 by Takahashi et al.[11] Since 1979, Smith and co-workers reported that metal carbonyls (Fe, Co, Ni, Ru, Rh, and Ir) can be thermally decomposed to form metal NPs in the presence of stabilizing polymers.[12] In 1990, the Gallezot group at IRC produced efficient NP catalysts or precatalysts upon reaction with either H_2 or CO,[13] and then the Bradley−Chaudret groups reported hydrogenation of zerovalent complexes of olefinic ligands.[14] The metal−vapor technique to produce metal NPs, conceptually (but not practically) an ideal one, was first published in 1927 by Roginski and Schalnikoff[15] and was made popular in modern times by work from the groups of Green, Timms, and Ozin.[16] Physical synthetic means[17,18] became numerous in the 1980s for the synthesis of transition-metal NPs that were subsequently used in catalysis. In particular, electrochemistry was developed by Reetz and co-workers in studies that were systematically followed up by PdNP-catalyzed formation of C−C bonds.[17] More recently, the modes of preparation have included impregnation,[19] coprecipitation,[19,20] deposition−precipitation,[21] sol−gel,[19,22] gas-phase organometallic deposition,[23] sonochemistry,[24] microemulsion,[25] laser ablation,[26] electrochemistry,[17,27] and cross-linking.[28] Classic organic supports of PdNPs include polymers and dendrimers (vide infra).[2] PdNPs have been reported with a variety of solid supports for heterogeneous catalysis, i.e., oxides, mostly of Si but also of Al, Ti, Zr, Ca, Mg, and Zn. These supports are in the form of SiO_2 aerogels or sol−gels such as Gomasil G-200, high-surface silica, M41S silicates and alumimosilicates, MCM-41 mesoporous silicates such as HMS and SBA-15 silica, silica spheres, microemulsions (SiO_2), hydroxyapatite (Ca^{2+}), hydrotalcite (Mg^{2+} and Al^{3+}), zeolites (SiO_2 and Al_2O_3), molecular sieves, and alumina membranes.[2]

4. Stabilizers for PdNPs in Homogeneous Catalysis: Micelles, Microemulsions, and Surfactants

It is essential to stop the agglomeration of Pd atoms at a colloidal stage in order to prevent the formation of Pd black precipitate. A large choice of organic and inorganic stabilizers has been reported to synthesize PdNPs that were further used in catalysis. In particular, the use of micelles, microemulsions, and surfactants has been common. These stabilizers are a compromise between the protection of PdNPs against further agglomeration and free access to the PdNP surface for the substrate activation and transformation. Ultrafine

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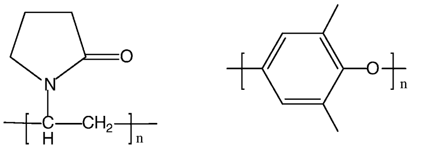
Chart 1. Most Used Polymers for the Stabilization of Catalytically Efficient PdNPs



PVP
poly(vinylpyrrolidone)

PPO
poly(2,5-dimethylphenylene oxide)

PdNPs in reverse micelles using KBH_4 as a reducing agent of Pd^{II} precursors led to catalytic hydrogenation of allylic alcohol and styrene in isooctane, although the bis(2-ethylhexyl)sulfosuccinate surfactant inhibited the hydrogenation activity.[29] Note that, in PdNP-catalyzed hydrogenation, the PdNP itself is expected to be the true catalyst because all of the catalytic reactions supposedly occur on the very PdNP surface, contrary to the cases of C−C formation. Microemulsions were found to be efficient for catalysis of the Heck reaction in ligand-free systems (vide infra; section 7).[30] Functional olefins such as 4-methoxycinnamic acid as well as nitrobenzene (to aniline) were selectively hydrogenated in supercritical CO_2 using PdNPs in a water-in-CO_2 microemulsion.[31] Fluorous strategies[32] have been used on various occasions for NP catalysis such as, for instance, by the Crooks[33] and Gladysz[34a] groups. Fluoro surfactants can also serve as micellar stabilizers for PdNPs in water-in-supercritical CO_2 microemulsions that were used as hydrogenation catalysts for simple olefins[34b] and citral.[34c]

5. Polymers and Dendrimers

Polymers have long been obvious stabilizers for NPs. Poly(*N*-vinyl-2-pyrrolidone) (PVP) is the most used polymer for NP stabilization and catalysis (Chart 1), and PdNPs stabilized by PVP are synthesized by a refluxing ethanolic reduction of the corresponding metal halide.[13]

Many other polymers have most recently been used in an efficient way for catalysis: poly(2,5-dimethylphenylene oxide) (Chart 1), polyurea,[35a] polyacrylonitrile, and/or poly(acrylic acid) (Figure 2),[35b] multilayer polyelectrolyte films (Figure 3),[35c] polysilane shell-cross-linked micelles (Figure 4),[35d] polysiloxane,[35e] oligosaccharides,[35f] copolymers synthesized by aqueous reversible addition−fragmentation chain-transfer polymerization,[35g] π-conjugated conducting polypyrrole,[35h] poly(4-vinylpyridine),[35h] poly(*N*,*N*-dialkylcarbodiimide,[35i] poly(ethylene glycol) (PEG),[35j] chitosan,[35k] and hyperbranched aromatic polyamides (aramids).[35l] Classic surfactants such as sodium dodecylsulfate are also used as NP stabilizers for catalysis.[35m]

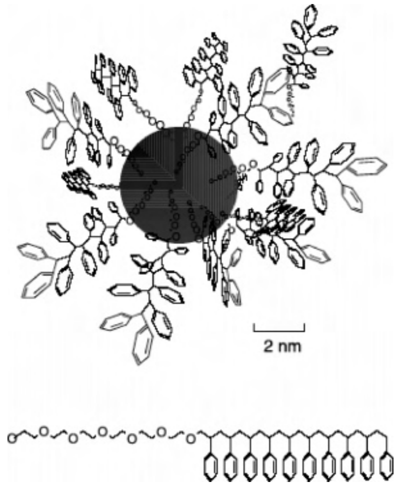


Figure 2. PdNPs adsorption on poly(acrylic acid) particles: stabilizing effect of a PdNP due to adsorbed block copolymer. Reprinted with permission from ref 35c. Copyright 2004 Kluwer.

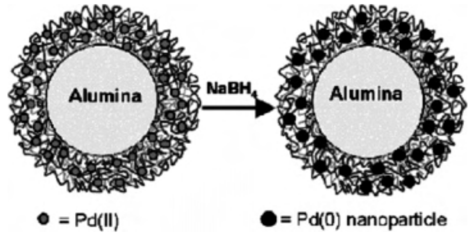


Figure 3. Principle of the formation of PdNPs in multilayer polyelectrolyte films (the layer-by-layer deposition is both convenient and versatile). Reprinted with permission from ref 35d.

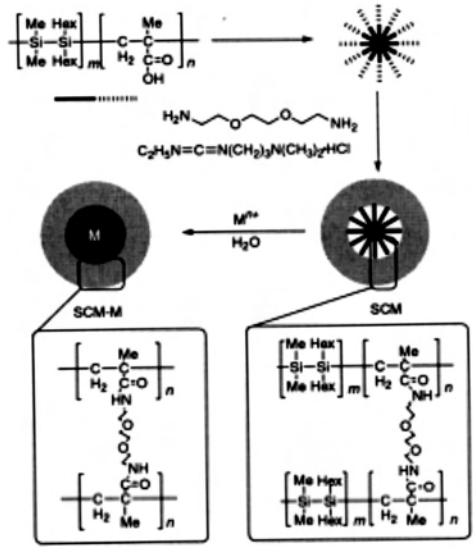


Figure 4. Schematic illustration of the synthesis of metal NPs derived from polysilane shell cross-linked micelle templates. Reprinted with permission from ref 35f.

The use of two different metals such as Au and Pd in the same NP[35n,o] was developed by Toshima's group, who used PVP to stabilize core/shell bimetallic Au−PdNPs, i.e., for instance, NPs in which the core is Au whereas Pd atoms are located on the shell.[35p] Subsequent to coreduction, this structure is controlled by the order of reduction potentials

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of both ions and the coordination abilities of both atoms to PVP. The location of Au in the core and Pd on the shell was demonstrated by extended X-ray absorption fine structure (EXAFS), and it was shown that such heterobimetallic Au-cored PdNPs are more active in catalysis than simple PVP-stabilized PdNPs. Thus, the Au core enhances the catalytic properties of PdNPs at the PdNP surface.[6f,g]

Dendrimers can stabilize NPs in view of catalytic applications either by encapsulation of the NP within a single dendrimer or by stabilization of NPs by surrounding the NPs with several dendrimers. The formation of NPs stabilized by dendrimers was proposed in 1998 by the three research groups of Crooks,[36a] Tomalia,[36b] and Esumi.[36c] Crooks, who pioneered this field with Cu^{2+} ions,[33,36a,d] showed that complexation of inner N atoms of tertiary amines by metal cations (Cu^{2+}, Au^{3+}, Pt^{2+}, Pd^{2+}, Fe^{3+}, and Ru^{3+}) could be followed by reduction by $NaBH_4$ to metal(0), provoking the agglomeration of metal atoms to NPs inside the PAMAM dendrimers.[33] When the terminal amino groups were protonated at pH 2 prior to complexation by metal ions, the later proceeded selectively onto the inner N atoms, resulting in water solubility and subsequent catalytic activity in water. For instance, selective hydrogenation of allylic alcohol and *N*-isopropylacrylamide was catalyzed in water by such PAMAM dendrimer−PdNPs. The addition of decanoic acid solubilizes the dendrimer−NP catalyst in toluene by a terminal amino group−carboxylic acid reaction. The catalytic activity of the dendrimer-encapsulated NPs depended on the number of Pd atoms in the NP, i.e., on the generation of the dendrimer and, of course, on its nature (PAMAM vs PIP) and the kind of functional group at the periphery. Crooks rationalized the results as the dendrimer periphery acting as a size- and shape-selective nanofilter.[33] In addition to the highly selective Heck reaction, dendrimer-encapsulated PdNPs were also found to be efficient for catalysis of the Suzuki C−C coupling. Narayanan and El Sayed compared thus PAMAM G4-OH-terminated dendrimers to PVP− or polystyrene−poly(sodium acrylate) block copolymers. The G4 dendrimer-encapsulated PdNPs were found to have higher stability but lower activity than the polymer-stabilized PdNPs, the results having shown that there was an inverse relationship between PdNP stability and catalytic activity.[36e] Further sophistication uses bimetallic NPs containing Pd and another metal located in the NP core and supported dendrimer-templated PdNPs, but these materials have almost exclusively been studied for hydrogenation and oxidation reactions. PdNP-encapsulated dendrimers also serve as templates to deliver size-controlled PdNPs onto solid oxide supports subsequent to thermal removal of the dendrimer coating. Catalysis using such PdNPs provides promising results in terms of efficiency and selectivity because of the small size and relatively narrow dispersity of the PdNPs, despite some Oswald ripening during the thermal treatment that somewhat broadens this dispersity.[36f]

6. Ionic Liquids (ILs) in PdNP Catalysis

ILs were introduced in catalysis by Chauvin in the 1990s[37] and have received considerable attention in this field.[37] Chauvin introduced the imidazolium salts that are the most frequently used ILs in catalysis. They are valuable media for catalysis with PdNPs because the substituted imidazolium cation is bulky, favoring the electrosteric stabilization of NPs

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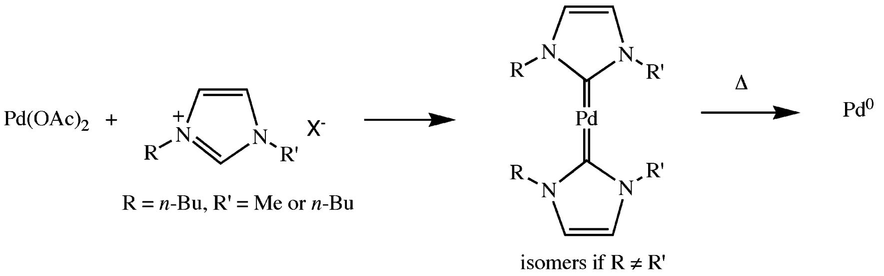
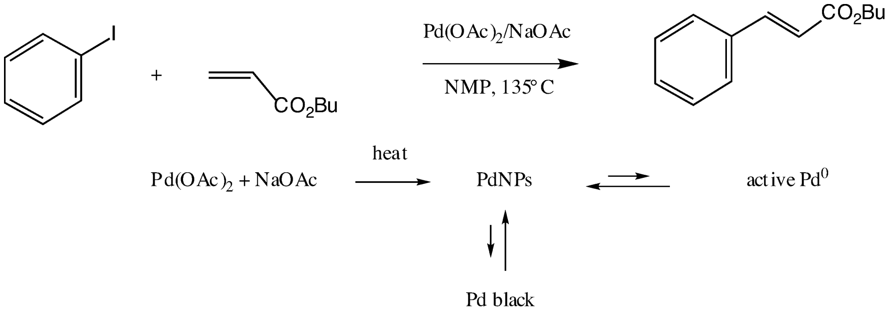
Scheme 2. Formation of Pd−Carbene Complexes by Reaction between Palladium Acetate and Imidazolium Salts Followed by Decomplexation at High Temperature and Formation of PdNP Precatalysts for Heck-Type Reactions[40]



Scheme 3. Heck Reaction between Aryl Bromides (or Iodides) and Olefins Catalyzed by Homeopathic Amounts of $Pd(OAc)_2$: Intermediacy of PdNPs and Leaching Active Pd Atoms Proposed by de Vries (Scheme 4)



as $t\text{-}Bu_4N^+$ salts do in Figure 1. The size of the cation (that can eventually be tuned by the choice of the *N*-alkyl substituents) also has an important influence on the stabilization, size, and solubility of the NPs, with these factors playing a role in catalysis. ILs are also noninnocent, however, because they readily produce N-heterocyclic Pd−carbene complexes upon deprotonation of the imidazolium salt at sufficiently high temperature. Thus, these carbene ligands can be bound to the NP surface or give mononuclear mono- or bis-carbene complexes subsequent to leaching of Pd atoms from the PdNP surface (vide infra).[38]

As indicated in the beginning of this section, the role of the ILs is crucial in both the PdNP formation and stereospecifity of C−C coupling that could not be obtained in previous studies of PdNP-catalyzed Heck reactions.[39] Salts of a *N*-butyronitrile pyridinium cation react with $PdCl_2$ to give dinitrile complexes that turn black upon the addition of phenyltributylstannane, and the PdNPs formed are the sources of catalysts for Stille and Suzuki C−C coupling reactions. It is believed that the nitrile groups coordinate to the PdNP surface, which results in PdNP stabilization.[40]

Palladium acetate led to the formation of PdNPs in the presence of the IL 1,3-dibutylimidazolium salts. It was suggested that the formation of N-heterocyclic Pd−carbene complexes is at the origin of the formation of PdNPs (Scheme 2) that are the sources of catalyst in Suzuki coupling.[41]

Such carbene complexes were shown to form and serve as precatalysts for the Heck reaction, with the formation of PdNPs under these conditions being highly suspected to be involved as precatalysts.[42] Indeed, heating these N-heterocyclic Pd−carbene complexes leads to PdNP formation subsequent to ligand loss (Scheme 3). The selectivity of the reactions in such IL media also depends on the solubility,

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and the solubility difference can be used for the extraction of the product. In summary, ILs are favorable media for the electrostatic stabilization of preformed PdNPs at room temperature, but they give Pd−carbene complexes upon deprotonation of the imidazolium cation, yielding PdNP precatalysts at high temperature. Indeed, Dupont and co-workers have shown using detailed spectroscopic ad kinetic studies that PdNPs in IL leach active molecular species in Heck C−C coupling reactions.[41]

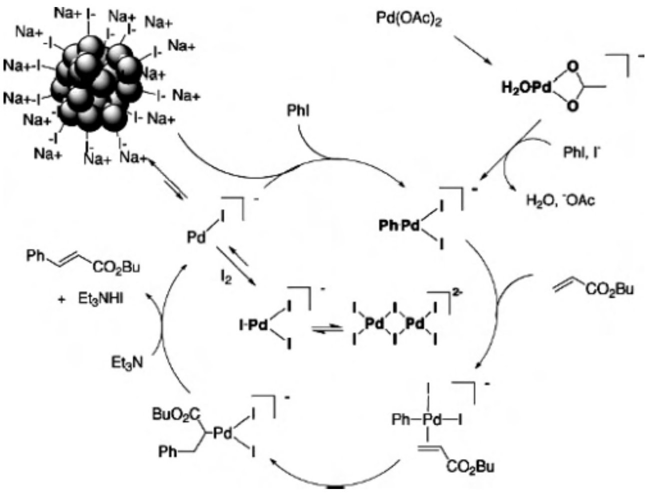
7. "Ligand-Free" Heck Reaction Using a Low Loading of a Pd^{II} Derivative

The original reports by Mizoroki et al. in 1971,[42a] and then by Heck and Nolley in 1972,[42b] on catalyzed coupling reactions of aryl iodides with olefin used $PdCl_2$ or $Pd(OAc)_2$ as the catalyst, a base (NaOAc and N-*n*-Bu_3, respectively), and a solvent (methanol and *N*-methylpyrolidone, respectively) but no phosphine or other ligand. Beletskaya and Cheprakov reported a similar phosphine-free reaction of iodo- and bromoarenes in water, and the Pd loading was as low as 0.0005 mol % (the term "homeopathic" dose was used) in the case of 3-iodobenzoic acid.[42c] The Reetz[42d,n] and de Vries[42e,n] groups reported extremely efficient Heck catalysis of coupling between aryl bromides and styrene in organic solvents with such very low Pd loading. Reetz also found that PdNPs are formed when $PdCl_2$, $Pd(OAc)_2$, or $Pd(NO_3)_2$ is warmed in THF in the presence of a tetrabutylammonium carboxylate, which functions as a reducing and stabilizing agent.[42f] Polar solvents such as propylene carbonate also generated such PdNPs upon heating of $Pd(OAc)_2$. PdNPs generated in this way from $Pd(OAc)_2$[42d−f] or palladacycles[42g−i] are active precatalysts in the Heck reaction, which was demonstrated by following reactions using transmission electron microscopy.[42j] Very interestingly, it was found that the Pd catalyst "improves" upon lowering of the Pd loading, which was taken into account by an equilibrium between PdNPs serving as a catalyst reservoir and small (monomeric or dimeric) catalytically active Pd species.[42d,h,k] When the catalyst concentration is too high, inactive Pd black forms.

This indicates that the rate of the catalytic reaction is extremely high because most of the Pd is in the form of PdNPs. This type of Heck reaction seems quite general with aryl bromides.[42e]

Likewise, a range of enantiopure substituted *N*-acetylphenylalanines were obtained from methyl *N*-acetamidoacrylate and various bromoarenes at very low Pd loading in the absence of other ligands, followed by Rh-catalyzed hydrogenation.[42l] de Vries and co-workers reported a similar behavior for the Suzuki reaction of aryl bromides with turnover frequencies (TOFs) up to 30 000.[42m] The precise nature of the active species in these Pd-catalyzed C−C coupling reactions is not known, and it may well be an anionic mono- or dimeric Pd^0 species to which an anionic ligand (Cl^- or OAc^-) is bound. The mechanism proposed by de Vries (Scheme 4) involves these anionic intermediates as in the molecular mechanism shown by Amatore and Jutand on the basis of electrochemical kinetics. The suggestion by de Vries of these anionic intermediates was supported by the detection of $PhPdI_2^-$ and PdI_3^- by electrospray ionization mass spectrometry[49a] and $Pd_2I_6^-$ by EXAFS[42s] in the Heck reaction of PhI.

Scheme 4. Mechanism Proposed by de Vries[49a] for the "Homeopathic" Heck Reaction[42] between Phenyl Iodide and Butyl Acrylate Catalyzed by $Pd(OAc)_2$ (Reprinted with Permission from ref 49a. Copyright 2006 Royal Society of Chemistry)



In terms of *Green Chemistry*, this process is of great interest because waste is largely minimized here in the absence of added ligand and such low Pd loading.[42n] It also suggested that supported PdNP catalysts (heterogeneous catalysts, vide infra) could well behave in a related way. The very efficient use of a tetraalkylammonium salt in ligand-free Heck catalysis, i.e., so-called Jefferey conditions, was shown to produce exclusively the trans coupling product between butyl acrylate and bromobenzene in the absence of a base.[42o]

8. Catalysis of the Heck Reaction by Preformed PdNPs

Both the Herrmann[43] and Reetz[17e] groups using stabilized PdNPs obtained by reduction of Pd^{II} salts to Pd^0 before catalysis reported the high-temperature-catalyzed Heck reaction of aryl bromides in 1996 using PdNP precatalysts. The Reetz system even allowed one to couple aryl chlorides to olefins. The latter group developed ongoing pioneering studies with applications such as ethenylation of 2-bromo-6-methoxynaphthalene, a precursor of Naproxen.[17] Polymers and copolymers derived from 2- and 4-vinylpyridine, PVP, PEG, chitosan, functional resins, lyotropic liquid crystals, imidazolium ILs, and various silicas were found to be good PdNP stabilizers, and catalytic efficiency herewith was sometimes found to increase when the PdNP size decreased. Pd leaching was observed in several of these studies although the organic solution analyzed after the reactions did not contain Pd. Thus, a hypothesis was formulated, according to which the PdNP was a reservoir of Pd atoms that returned to the colloid after catalysis. This means that both the Pd^{II}

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salt (Mizoroki−Heck) catalysts and the PdNP catalysts seem to work according to the same mechanism involving leaching of active Pd atoms that are recovered by the PdNPs after catalysis.[44]

Herrmann's group,[45] followed by many others,[46] found the excellent catalytic efficiency of Pd-containing metallocycles, but Louie and Hartwig later showed that their activity was presumably due to the formation of PdNPs.[47] Such catalytic reactions are poisoned by Hg,[9] confirming the activity of Pd^0 species resulting from the thermal decomposition of these palladacycles to PNPs (Hg should poison both Pd^0NPs and relatively naked mono- or dinuclear Pd^0 species). Reviews on the topic of catalysis by Pd cycles and pincers have appeared.[48,49] Following the Amatore−Jutand mechanism with Pd complexes,[50] it has been proposed that mono- or dinuclear anionic Pd species (complexes) are intermediate of the catalysis occurring in solution subsequent to leaching.[49] It results that PdNPs are probably responsible for the oxidative addition of ary bromides and chlorides at their surfaces, giving palladium(II)(aryl)(halide), although the more demanding reaction of aryl chlorides might require the use of phosphine-activated or N-heterocyclic carbene-activated Pd complexes.[49b] Dupont recently reported convincing evidence based on kinetic, poisoning, and leaching studies that PdNPs generated from palladacycle precatalysts were sources of active intermediates in Heck coupling reactions in a mechanism similar to that proposed by de Vries.[49c]

In principle, fixation of PdNPs on solid supports should provide catalysts prepared at low cost and allow easy separation by filtration in view of multiple recycling and continuous processing. A major drawback of this technique reported in the publications is leaching, however. These aspects of heterogeneous PdNP catalysis have been reviewed,[49b,51] and Köhler's group convincingly discusses solid PdNP-containing precursors of Heck catalysts in another Article of this Forum.[51b] Catalysis in zeolites and noncrystalline mesoporous silicates (molecular sieves), such as MCM-41 (which are extremely robust supports), should also avoid aggregation.[52] The PdNPs are generally less reactive in these zeolites, although high turnover numbers (TONs; up to 47.000) could be obtained by Kaneda and co-workers for the coupling of bromobenzene with styrene and butyl acrylate on a new support, hydroxyapatite.[52] In this way, aryl iodides and activated aryl bromides only could be activated.[53] Djakovitch and Köhler showed that the structure and Si/Al ratio had little influence on the catalytic activity and that complete conversion of aryl bromides could be obtained at 140 °C with 0.2 mol % Pd.[54a] Oxides of Mg, Ti, Zn, and Zr were also investigated.[54b] Very few heterogeneous Pd catalysts were found to convert activated aryl chlorides at high temperatures (see Köhler et al.'s work, however),[51b,54c] although microwave activation helps. C also is a support of choice, as is well-known with the commercially available Pd/C catalyst that was optimized, although it still remains very slow compared to simple Pd compounds.[55] There also is promising research on C nanotubes as the PdNP support.

In summary, key parameters are high dispersion, the use of Pd^{II} rather than Pd^0, and the presence of some water. On the other hand, the nature of the support has little influence. Zeolite encapsulation of PdNPs works best probably because the zeolite cavities prevent coagulation of the PdNPs to Pd black.

Aryl chlorides are very difficult to activate (the choice of parameters is even more crucial). It is thus clear that aryl chlorides are best activated by a monometallic Pd complex containing a specific electron-rich bulky phosphine or an N-heterocyclic carbene with bulky *N*-aryl substituents.[56] The electron-releasing properties of these ligands in these complexes favor the difficult oxidative addition of the aryl−chloro bond, whereas the bulk of the ligand favors the final reductive elimination step in the catalytic cycle of the monometallic Pd complex to give the final coupled product. In the case of the aryl iodides and bromides, Pd^{II} ligands are useless at high temperature and the catalyst amount is homeopathic.[49a] The PdNPs formed work as reservoirs of Pd atom catalysts. The Pd^{II} salts as well as palladacycles and pincer Pd complexes that are excellent catalysts are, in fact, sources of PdNP precursors of catalytically active species at the rather high temperature required for the Heck

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reactions, although the molecular mechanism is possible using these catalysts with aryl chlorides.[49] With preformed PdNP catalysts, Pd atom leaching, first proposed by Arai and co-workers,[57a] could possibly be caused by oxidative addition of the aryl−halide bond on the PdNP surface, a hypothesis confirmed by experimental data. Then, the mechanism is purely homogeneous whatever the PdNP source (homogeneous or supported), and the Pd atoms return to PdNP after catalysis, as shown by several experiments, indicating the absence of any catalytic activity of the solutions separated after catalysis. Zeolites provide the best heterogeneous PdNP-supported catalysts, and palladium oxides or hydroxide improve the activity of nearby Pd^0 in NPs by $Pd^{II}-Pd^0$ synergistic activation.[49b,57b,58] Recently, PdNPs were stabilized by a star-shaped block copolymer, and these PdNPs are precatalysts for the Heck coupling (vide infra) between styrene and 4-bromoacetophenone with up to 99% conversion within 24 h at a catalyst loading of 0.1%.[59a] Another very efficient technique is ultrasonic irradiation providing catalysis of numerous Heck coupling reactions at 25 °C with regioselectivity in water.[59b] Finally, diatomite, which is a type of natural porous material, was shown to be adequate for the synthesis of supported PdNPs (20−100 nm), and this supported catalyst was efficient for the Heck and Suzuki reactions and could be recovered with numerous uses.[59c]

9. PdNP-Catalyzed Suzuki C−C Coupling Reactions

Beletzkaya and co-workers reported in 1989 the ligand-free Pd-catalyzed Suzuki reaction in water between iodobenzoates and phenylboronic acid using $Pd(OAc)_2$ as the catalyst,[60] and this finding was followed by others under comparable conditions,[61] also including the use of ILs and C supports.[62] The latter can be efficient under more drastic conditions to also activate aryl bromides and chlorides especially if microwave conditions are applied. de Vries showed that homeopatic Pd catalysis also applies to the Suzuki reactions of bromoarenes at 90 °C with a 0.005% Pd catalyst.[49] Under microwave conditions, Suzuki reactions were first believed by Leadbeater and Marco to be uncatalyzed[63] but could later be explained by de Vries[64] using the principle of the homeopathic Pd catalysis with down to a 1 ppm Pd catalyst. Leadbeater's reinvestigation confirmed the validity of this principle.[65] The Suzuki reaction of aryl bromides and iodides was shown by Reetz et al. to be catalyzed by *tert*-butylammonium-stabilized PdNPs, and bimetallic Pd/NiNPs were found to also catalyze the reaction of aryl chlorides.[17d] Polymers (PVP),[66] micelles,[67a] ILs,[67b] thiolate ligands,[68] and dendrimers were used to stabilize PdNPs in view of catalytic use in the Suzuki and other C−C coupling reactions. In contrast to PAMAM dendrimers of second-generation (noted G2) PVP polymers, G3 PAMAM dendrimers were found to be good stabilizers.[69] Palladacycles have also been found to be good Suzuki catalyst precursors in the presence of n-Bu_4NBr via the formation of PdNPs,[70] sometimes when they were anchored on inorganic supports[71a] and resins.[71b] Dendronic thiolate-stabilized PdNPs have been shown to be so-called catalysts (obviously precatalyst, however, with our nomenclature) for high-temperature Suzuki reactions of iodo- and bromobenzene and Heck reaction

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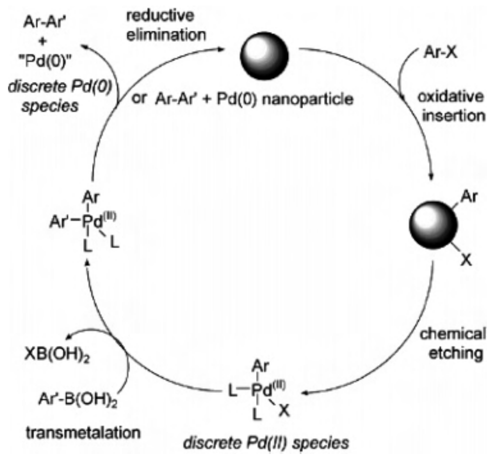
Scheme 5. Mechanism Proposed for the Catalysis of the Suzuki Reaction by Pregenerated PdNPs Proceeding via Pd Atom Leaching into Solution with a Molecular Mechanism Resembling That Given by de Vries for the Heck Reaction (Reprinted with Permission from ref 49b. Copyright 2006 Wiley)[a]



[a] The ancillary ligands include anions so that the mechanism is most probably relevant to the Amatore−Jutand type with anionic intermediates.

of iodobenzene with high TONs and modest yields.[72a] On the other hand, simple alkylthiolate−PdNPs were shown to be precatalysts or catalysts of the Suzuki reaction of iodo- and bromobenzene with $PhB(OH)_2$ quantitatively at 20 °C. Moreover, the PdNPs could be filtered and recycled six times with very little loss of activity (from 100% to 87% yields for PhI).[68] Even chlorobenzene yielded the coupled product with $PhB(OH)_2$ in 52% yield at 20 °C. Dendronic phosphine-stabilized PdNPs are highly active and recyclable precatalysts and catalysts for the Suzuki and hydrogenation reactions, respectively.[72b] The mechanism proposed for the Heck reaction involving Pd atom escape (leaching) from the PdNPs and recombination after catalysis probably does also apply to Suzuki catalysis (Scheme 5).[49b] For instance, the studies by Biffis's group[57b] and by Liu and Hu[35i] described the catalytic activity in the Suzuki reaction of microgel- and polymer-encapsulated PdNPs, respectively, to leaching Pd^0 species.

10. PdNP-Catalyzed Sonogashira Coupling

The Sonogashira coupling of aryl halides with terminal alkynes is carried out using most of the time both Pd and Cu catalysts. The latter forms alkynyl cuprates that further transmetalate the alkynyl group in situ onto the Pd center. In this way, the preparation of the organometallic cuprate is avoided because the Cu salt is regenerated subsequent to transmetalation. The presence of the Cu cocatalyst is not indispensable, however, because Pd can also play the role of Cu but with more difficulty. Thus, the Suzuki reaction without Cu salt can be performed but at higher temperatures than that of the analogous reaction carried out in the presence of the Cu salt.[73] For instance, Cu-free Sonogashira reactions were reported using $Pd(OAc)_2$/DABCO/air/CH_3CN with only 0.01% mol of Pd.[74] Thus, PdNPs that are precatalysts for the Heck and Suzuki reactions should, in principle, also be efficient for Sonogashira coupling. A few examples follow. PVP-stabilized PdNPs were found to be efficient precatalysts for Sonogashira coupling of aryl bromides and iodides with phenylacetylene after 6 h in methanol using K_2CO_3 as the base, and the catalyst could be recycled eight times without significant loss of activity. Silica-stabilized PdNPs exhibited good Sonogashira activity in tetraethylene glycol.[75] The counteranion of the Pd salt that is a precursor of the TBAB-stabilized PdNPs was shown to have a strong influence on the Sonogashira coupling activity, which decreased in the order $NO_3^- > Cl^- > OAc^-$. The binding strength of the anions to Pd decreases in the reverse order, and it was suggested that Pd leaching is determined by the bond strength, following the de Vries leaching mechanism discussed above for the Heck reaction.[76] Reports concern polymer-stabilized PdNPs,[77] dendrimers,[33,72,78] and layered double hydroxide active for aryl chlorides.[79] Djakovitch and co-workers have published interesting results with zeolites, mesoporous materials, metal oxides, and fluorides for the Sonogashira coupling of aryl iodides and bromides.[80] The MCM-41-supported PdNPs were found to be efficient for the Sonogashira coupling of aryl chlorides, and ligand-free Pd/C-induced catalysis of aryl iodide coupling was reported.[81] Again, one can assume that Pd leaching of Pd species in solution provides the basis for a homogeneous mechanism such as that for the Heck reaction followed by recombination of these Pd atoms with the PdNP reservoir.

11. Other PdNP-Induced Catalysis of C−C Coupling Reactions

Other C−C coupling reactions that are catalyzed by Pd are the Stille, Corriu−Kumada, Negishi, and Hiyama reactions (Scheme 1). There is no reason to believe that these reactions could not be catalyzed by species produced by PdNPs or Pd complexes decomposing in situ into PdNPs in

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the same way as they do with the Heck, Suzuki, and Sonogashira reactions. There is extensive literature concerning the catalysis of these reactions by Pd complexes that could be reexamined in view of this possibility. There are only relatively few reports, however, concerning the catalysis of these reactions with preformed PdNPs. For instance, ligand-free Pd-catalyzed Negishi and Corriu−Kumada reactions are known,[44,82] and PdNPs have also been characterized in the use of palladacycles in the Stille[44,83] and Hiyama reactions.[84] PdNPs stabilized by poly(4- and 2-vinylpyridine) have been reported to catalyze inter alia the Stille coupling.[85] PdNPs have been shown to form during the carbonylation reaction catalyzed by the reduced Pd^0 form of $[PdCl_2(COD)]$ (COD = η^4-cyclooctadiene).[86] A BINAP ligand bearing a C-8 alkyl chain terminated by a methyl thioether group was found to stabilize PdNPs that were shown to be active in Suzuki and Stille catalysis.[87] Ullmann coupling reactions were catalyzed in ILs by electrochemically generated PdNPs.[88]

12. Conclusion

The high-temperature Heck reaction between aryl iodides, aryl bromides, or activated aryl chlorides catalyzed by simple Pd^{II} derivatives as well as by heterogeneously supported catalysts proceeds by leaching of Pd atoms from PdNPs, formed upon the reduction of Pd^{II}, into solution. The catalytic mechanism proceeds homogeneously via anionic Pd^0 species following the Amatore−Jutand mechanism. On the other hand, inactivated aryl chlorides most often need mononuclear Pd^0 catalysts containing electron-rich, bulky phosphines or N-heterocyclic carbenes. Homogeneous and heterogeneous Heck reactions can also be catalyzed by species produced from preformed PdNPs stabilized by various organic or inorganic stabilizers, in particular tetraalkylammonium salts, ligands, macromolecules (the most sophisticated being dendrimers), ILs, microemulsions and micelles, or solid oxides of a variety of elements. The other Pd-catalyzed C−C bond formation reactions (Suzuki, Sonogashira, Stille, Corriu−Kumada, Hiyama, Ullman, carbonylation, and Tsuji−Trost allylic substitution) have been less studied than the Heck reaction (except the Suzuki coupling) but can be catalyzed by PdNPs as well according to mechanisms that may resemble the Heck NP mechanism. There is also considerable progress concerning the efficiency (high TOFs and TONs), recovery, and recycling of catalysts using various methods (precipitation, filtration of solid supports, magnetic separation,[89] etc.). These considerable improvements have brought PdNPs at the forefront of catalytic C−C bond syntheses, and a large number of applications in synthesis are expected in the near future. Some of these applications have already appeared (e.g., Naproxen synthesis).[90]

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