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"Homeopathic" Palladium Nanoparticle Catalysis of Cross Carbon–Carbon Coupling Reactions

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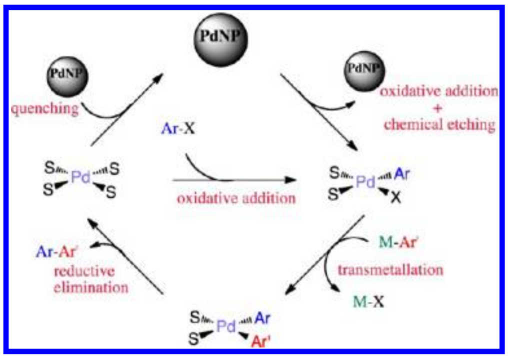

Catalysis by palladium derivatives is now one of the most important tools in organic synthesis. Whether researchers design palladium nanoparticles (NPs) or nanoparticles occur as palladium complexes decompose, these structures can serve as central precatalysts in common carbon–carbon bond formation. Palladium NPs are also valuable alternatives to molecular catalysts because they do not require costly and toxic ligands.

In this Account, we review the role of "homeopathic" palladium catalysts in carbon–carbon coupling reactions. Seminal studies from the groups of Beletskaya, Reetz, and de Vries showed that palladium NPs can catalyze Heck and Suzuki–Miyaura reactions with aryl iodides and, in some cases, aryl bromides at part per million levels. As a result, researchers coined the term "homeopathic" palladium catalysis. Industry has developed large-scale applications of these transformations.

In addition, chemists have used Crooks' concept of dendrimer encapsulation to set up efficient nanofilters for Suzuki–Miyaura and selective Heck catalysis, although these transformations required high PdNP loading. With arene-centered, ferrocenyl-terminated dendrimers containing triazolyl ligands in the tethers, we designed several generations of dendrimers to compare their catalytic efficiencies, varied the numbers of Pd atoms in the PdNPs, and examined encapsulation vs stabilization. The catalytic efficiencies achieved "homeopathic" (TON = 540 000) behavior no matter the PdNP size and stabilization type. The TON increased with decreasing the Pd/substrate ratio, which suggested a leaching mechanism.

Recently, we showed that water-soluble arene-centered dendrimers with tri(ethylene glycol) (TEG) tethers stabilized PdNPs involving supramolecular dendritic assemblies because of the interpenetration of the TEG branches. Such PdNPs are stable and retain their "homeopathic" catalytic activities for Suzuki–Miyaura reactions for months. (TONs can reach 2.7×10^6 at 80 °C for aryl bromides and similar values for aryl iodides at 28 °C.) Sonogashira reactions catalyzed by these PdNPs are quantitative with only 0.01% Pd/mol substrate. Kato's group has reported remarkable catalytic efficiencies for mesoporous catalysts formed by polyamidoamine (PAMAM) dendrimer polymerizations. These and other mesoporous structures could allow for catalyst recycling, with efficiencies approaching the "homeopathic" behavior.

In recent examples of Suzuki–Miyaura reactions of aryl chlorides, chemists achieved truly "homeopathic" catalysis when a surfactant such as a tetra-*n*-butylammonium halide or an imidazolium salt was used in stoichiometric quantities with substrate. These results suggest that the reactive halide anion of the salt attacks the neutral Pd species to form a palladate. In the case of aryl chlorides, the reaction may occur through the difficult, rate-limiting oxidative-addition step.

Introduction

Palladium-catalyzed cross carbon–carbon coupling reactions that include Heck, Suzuki–Miyaura, Sonogashira, Negishi, Stille, Hiyama, and Kumada–Corriu reactions (Scheme 1) are among the most useful organic reactions.[1−5]

Although molecular palladium catalysts containing various tertiary phosphines[1−5] or singlet *N*-heterocyclic carbene ligands[6] have long proven to be efficient and very popular, these ligands are toxic, expensive, or both, and therefore continuous investigations are pursuing the search of "green", so-called "ligandless", palladium precatalysts for applications to large-scale industrial processes.[2] Along this line, palladium nanoparticles (PdNPs) have appeared as a valuable alternative with several benefits relevant to

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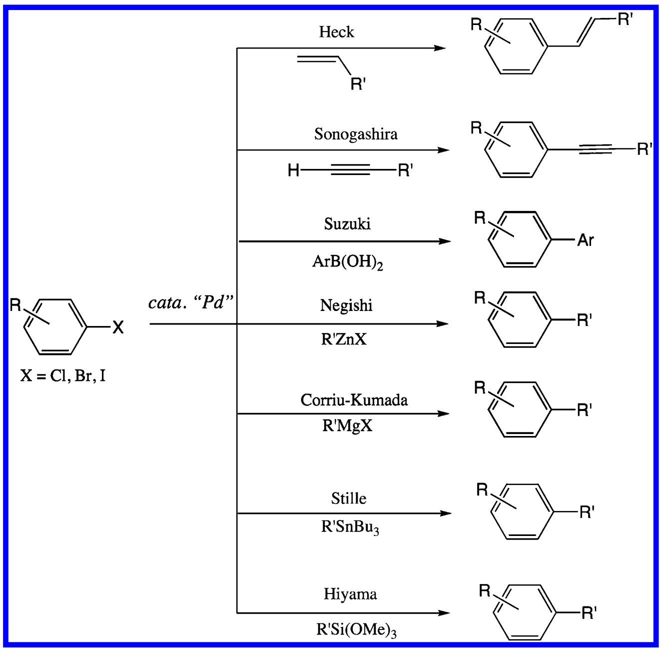
SCHEME 1. Main Palladium Catalyzed Cross Carbon–Carbon Coupling Reactions

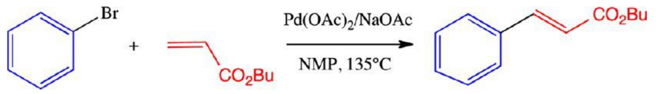


"green" chemistry. PdNPs generated by reduction of palladium salts were shown in the 1990s by pioneering studies of the groups of Bönneman[7] and Reetz[8] to be active catalysts of Heck and Suzuki–Miyaura reactions. In parallel, it was found that Pd^0 or Pd^{II} complexes that were intended to behave as molecular catalysts were in fact thermally decomposed to PdNPs, which were the actual catalysts or precatalysts under the catalytic reaction conditions of high-temperature Heck reactions (usually between 120 and 160 °C).[9,10] One of the most critical cases was that of palladacycles that were shown by Beller and Herrmann to be excellent C–C cross-coupling catalysts and initially believed to involve Pd^{IV} palladacycle intermediates in the catalytic cycles[11,12] until it was realized, in particular following studies by Hartwig's group, that PdNPs were the actual precatalysts resulting from palladacycle decomposition.[9,10,13] Indeed, seminal reports by Takahashi,[14] Mizoroki,[15] and Heck[16] already in the early 1970s used the "ligandless" complexes Pd(dba) (dba = dibenzylideneacetone), $PdCl_2$ in the presence of sodium acetate, and $Pd(OAc)_2$, respectively, as sources of PdNPs.

The "Homeopathic" Mechanism of PdNP-Catalyzed Heck Reaction

One of the key advantages of PdNPs is that they are catalytically active in much lower amounts than molecular Pd catalysts. Indeed, the use of very low PdNP catalyst amounts led to the term "homeopathic" doses. Beletskaya reported that 5 ppm Pd/mol iodobenzoic acid catalyzed Heck heterocoupling,[2] Reetz's group reported that 9 ppm Pd/substrate catalyzed Heck bromobenzene coupling to styrene,[9] and de Vries' group showed that homeopathic amounts of Pd catalysts were efficient to carry out Heck reactions of a variety of aryl bromides in *N*-methylpyrrolidone (NMP) at 135 °C (Scheme 2).[10]

SCHEME 2. Heck Reaction between Bromobenzene and Butyl Acrylate in NMP with a Homeopathic Amount of $Pd(OAc)_2$



Sometimes, the PdNP amount was so low that reactions first appeared as proceeding in their absence,[17] before the authors realized that they were occurring with "homeopathic" quantities of PdNPs.[10,18]

The past decade has provided a large body of literature data whereby cross-coupling reactions are catalyzed by designed PdNPs in catalytic amounts on the order of 0.01 to 0.1 mol % and sometimes lower.[19–23] Mechanistically, it has been proposed by de Vries (Figure 1) that for the Heck reaction oxidative addition of an aryl iodide onto the PdNP surface is followed by detachment (chemical etching) of metal atoms from the surface followed by highly efficient turnover in solution of the "ligandless" atoms that are possibly negatively charged as a result of attack by halide anions.[24]

The fact that palladate Pd^0 species are better activators than neutral Pd^0 species had been proposed by Tchoubar[24] and demonstrated electrochemically in the case of Pd–-phosphine catalysts by Amatore and Jutand.[25] de Vries' group discovered by ES-MS experiments that anionic Pd^0 species such as $PhPdCl_2^-$ were indeed present in the catalytic reaction medium when NaCl was used as an additive.[26,27] Thus, the roles of the anions are multiple and complex in the "homeopathic" mechanism (*vide infra*).

These reactive atoms in some form are quenched by the mother PdNP in sufficiently concentrated solutions, whereas upon dilution less frequent quenching due to higher distance between the two species results in increasing efficiency. Indeed, in all ligand-free Heck reactions on aryl bromides, the turnover frequency increases with decreasing catalyst concentration, which confirms the "homeopathic" designation. A "dead-end" point is the formation of Pd black (Scheme 3) resulting from agglomeration of the mother PdNPs depending on its stabilization, concentration

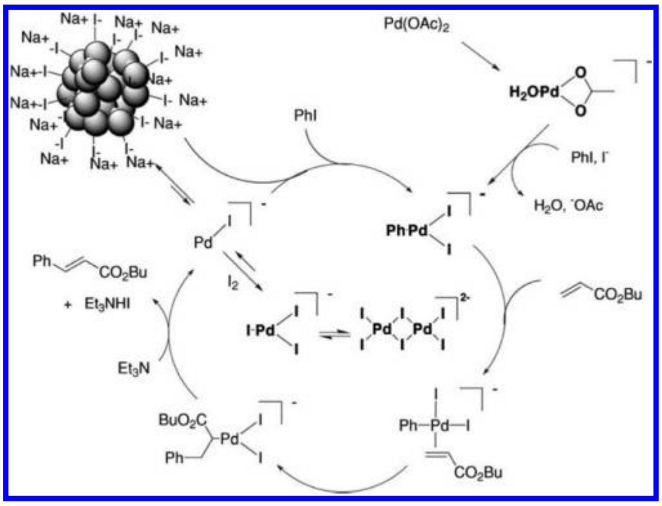
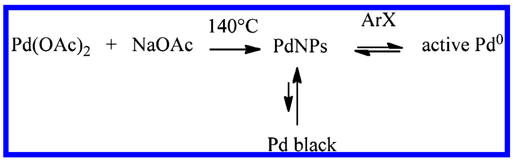


FIGURE 1. Mechanistic proposal for ligand-free Heck reactions of aryl iodide by de Vries (intermediates in bold have been observed by ES–MS or by EXAFS). Reprinted with permission from ref 10 (de Vries). Copyright 2006 Royal Society of Chemistry.

SCHEME 3. High-Temperature Generation of PdNPs from a Pd Precursor Complex with Formation of Pd Black (Heck Reaction Conditions)



(less or no Pd black forms with diluted PdNPs), and reaction temperature.[9,10]

The Pd doses used are all the lower because only surface PdNP atoms are reactive, whereas the interior PdNP atoms do not participate in the catalysis; thus the actual % Pd atoms used per substrate is lower than the nominal ones.

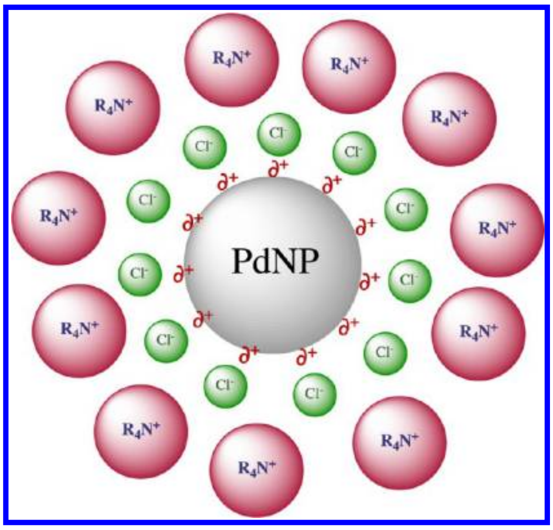


FIGURE 2. "Electrosteric" (that is electrostatic and steric) stabilization of Pd nanoparticles obtained by reduction of $PdCl_2$ in the presence of a tetra-*n*-alkylammonium salt. The halide anions provide electrostatic stabilization, and the tetra-*n*-butylammonium cations provide steric stabilization.

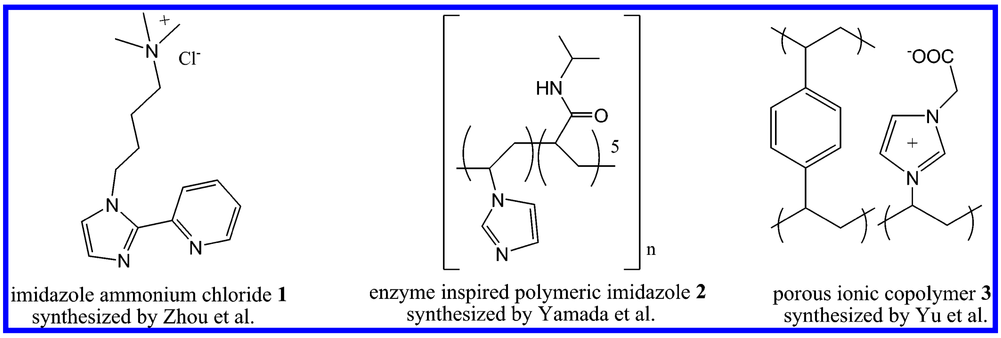
Industrial Applications and Extension to Other Cross C–C Coupling Reactions

The method is of industrial interest, because the Heck reaction is of considerable use for applications, and various syntheses have been scaled up to kilogram size to prepare drug intermediates.[28,29] In these seminal examples, the catalytic systems are homogeneous, but various heterogeneous PdNP systems with solid support have also been greatly developed, although the PdNP amount is not so low.[21,26,27] The above indications are characteristic of the Heck reaction, but the de Vries' group also reported "homeopathic" ligand-free PdNP catalysis of Suzuki–Miyaura and Negishi reactions. For instance, with the Suzuki reaction, the best results were obtained using the $Pd(OAc)_2$ catalyst precursor in toluene with K_2CO_3 as the base (25 ppm Pd/mol bromoacetophenone and phenylboronic acid substrates), although aryl chlorides were poorly reactive; for Negishi coupling, a 75% yield was obtained upon reaction between ethyl 4-bromobenzoate and PhZnBr at 50 °C in DMF catalyzed by 0.02% $Pd(OAc)_2$.[30] Altogether, the application of PdNP catalysis to organic chemistry is considerable and has been recently reviewed.[31−33] Finally, the principles developed here with PdNPs are rather general and have also been applied to other late transition metal NPs for catalysis, although not yet with "homeopathic" doses,[34−36] detailed analysis being beyond the scope of this Account.

Stabilization of the Pd Nanoparticles

At high temperatures required for productive Heck reactions, it was shown that PdNPs are stabilized by the presence of polar solvents such as propylene carbonate, tetra-*n*-alkylammonium salts, or ionic liquids (imidazolium salts or else).[9,19−21] Since the first report by Grätzel of ammonium salt-stabilized transition-metal nanoparticles (with PtNPs),[37] it has been shown that the first layer surrounding the NP core was that of the anions (Figure 2),[38] and stabilization was improved upon increasing the anion size.[39]

Altogether, two components, steric and ionic (electrostatic), are essential to stabilize transition-metal NPs for catalytic use as shown, for instance, by the extensive use of such surfactants in high-temperature Heck reactions.[28,29,40−42] The nature of the organic stabilizer is important for the determination and design of the PdNP size, but the nature and addition rate of the reductant of Pd^{II} to Pd^0 also is decisive in order to reach the ideal size between 1 and 2 nm



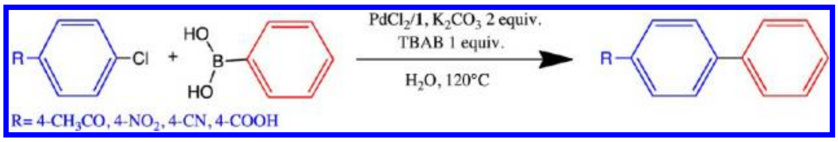
imidazole ammonium chloride **1** synthesized by Zhou et al.

enzyme inspired polymeric imidazole **2** synthesized by Yamada et al.

porous ionic copolymer **3** synthesized by Yu et al.

FIGURE 3. Examples of supports and ligands used for the stabilization of PdNPs active in C–C coupling with a parts per million scale of Pd in the presence of stoichiometric amounts of salt.[46,48,49]

SCHEME 4. Suzuki–Miyaura Reaction of Various Chloroarenes in Water in the Presence of 1 equiv of TBAB and between 100 and 10 ppm of PdNP Stabilized by Ligand **1**



R= 4-CH$_3$CO, 4-NO$_2$, 4-CN, 4-COOH

that provides the optimal proportion of surface Pd atoms while preserving the PdNP nature. Fast reduction of Pd^{II} leads to the formation of such small NPs if the organic stabilizer is efficient. According to Marcus theory, a strong driving force, that is, a large difference of potentials between the standard reduction potential of the metal ion precursor and that of the reductant, results in fast reduction, but experience shows that in this concern the rate of reductant addition (most often NaBH$_4$ but various other reductants are also used[35,43]) is crucial. Sometimes, no reductant is necessary at the high temperatures required by Heck reactions, because at such temperatures the anion of the Pd^{II} salt serves at the reductant of Pd^{II} to Pd^0. Even alkylthiolate ligands, however, provide excellent stability and reactivity of PdNPs in minute amounts for Suzuki–Miyaura coupling of aryl halides under ambient conditions in toluene despite the absence of ionic stabilizer, and no poisoning occurs.[44] However, the most successful organic stabilizers in terms of stability and catalytic efficiency of PdNPs at the level of a few parts per million of Pd atoms per mol substrate (or sometimes even less) for Heck or Suzuki–Miyaura cross coupling of aryl halides are those containing a large ammonium or imidazolium cation (Figure 3).[28,29,45–50]

The amount of such salts in homogeneous catalytic reaction conditions was always very high, usually as high as that of the substrates and base, and the reaction mixture also contained a nitrogen ligand (eventually bonded to the cationic surfactant), whereas the PdNP amount was "homeopathic".[48,49] Under these conditions, the Heck and Suzuki–Miyaura cross coupling reactions of aryl chloride can occur efficiently in water (or in aqueous solvent) at high temperatures (Scheme 4).

The halide anion of these salts not only serves as the first protecting layer of the PdNP. Also, the fact that aryl chlorides are activated in their presence in huge excess indicates that their coordination to reactive Pd atoms that produces palladate species is crucial for the difficult oxidative addition of these aryl halides (Scheme 5). This factor and de Vries' detection of palladates strongly argue in favor of the intermediacy of these palladate species in the catalytic activation mechanism.

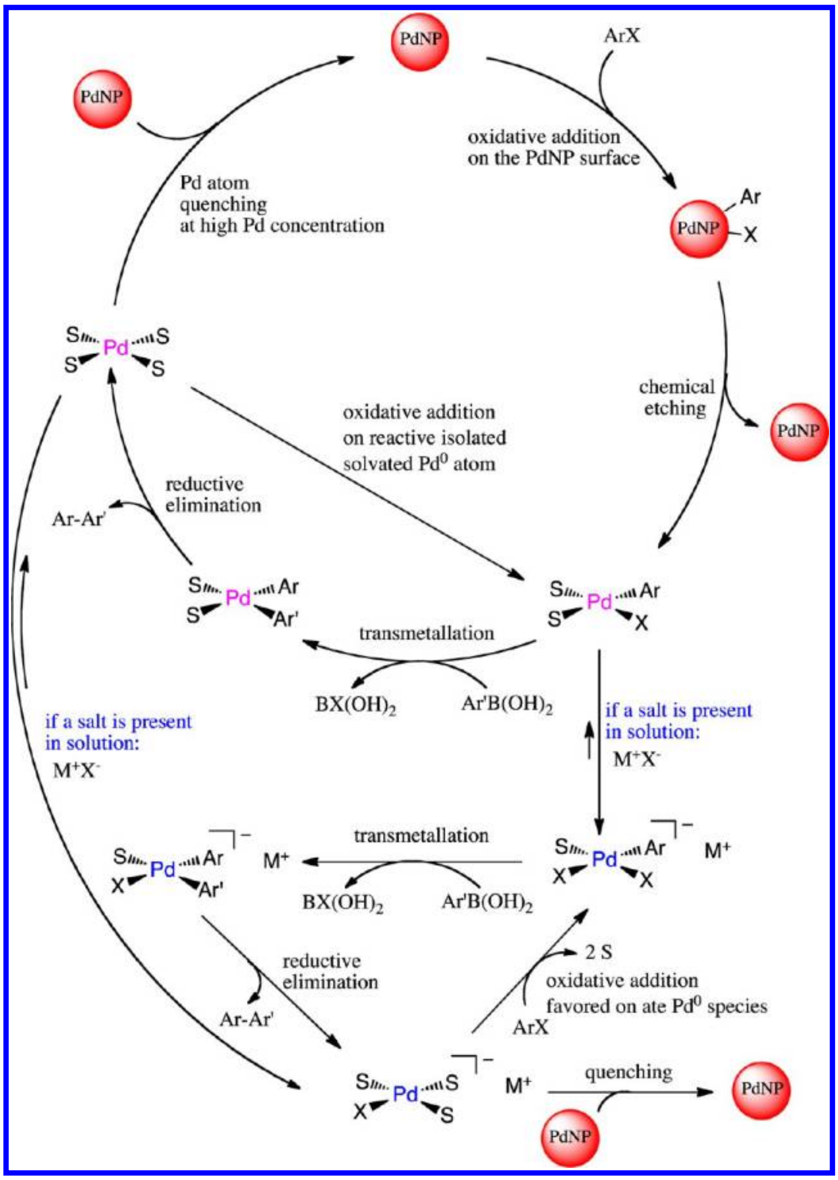
Heterogeneous supports (sometimes binding the ammonium or imidazolium salt) are also valuable alternatives to high salt concentrations.[45–47]

Catalysis by Dendrimer-Encapsulated and Stabilized Pd Nanoparticles

In 1999, Crooks' group pioneered catalysis by PdNPs and PtNPs encapsulated in Tomalia's commercial polyamidoamine (PAMAM) dendrimers (Scheme 6).[51]

These studies followed catalysis by NPs stabilized by polymers such as NMP studied in particular by Toshima's group in the 1990s.[52] These two types of macromolecules have in common their large size, their neutrality, and the presence of functional groups stabilizing NPs by coordination. The dendrimers have the advantage of a spherical topology and precise molecular definition with size control upon progressive increase of the generation number, Gn,

SCHEME 5. Homeopathic Mechanism for the Suzuki–Miyaura Reaction Inspired from the de Vries Mechanism[a]



[a] S = solvent molecule; X = halide. The quantity of salt (typically a tetra-*n*-butylammonium halide in which the halide is reactive) is very high in aryl chloride-activating system favoring palladate formation and thus the rate-limiting oxidative addition step.

SCHEME 6. Crook's Synthesis of a Nanoparticle inside a PAMAM Dendrimer[a]

[a] Reprinted with permission from ref 53. Copyright 2011 Royal Society of Chemistry.

and according to Crooks they serve as substrate nanofilters for encapsulated NPs whereby the filtering efficiency increases along with Gn.[53,54] In the early 2000s, several groups investigated the Heck and Suzuki reaction catalyzed by PdNPs encapsulated in PAMAM and polypropyleneimine (PPI) dendrimers.[53−60] The latter PdNPs provided 100% selectivity in Heck reaction between iodobenzene and *n*-butyl acrylate at 363 K.[48] With Gn-PAMAM dendrimer PdNPs, G2 yielded a more reactive catalyst than G4, but G4 provided a more stable catalyst.[55] For catalysis of the Stille reaction, the size of PAMAM-dendrimer-encapsulated PdNPs was shown to increase, which may be an indication of leaching during catalysis,[61] and this point was debated using G6-PAMAM-encapsulated PdNPs whereby leaching was only observed in the presence of N_2 or air but not H_2.[62]

Heterogeneous PAMAM dendrimer templates that are polymerized with an acrylate are a valuable microporous host for excellent PdNP catalysis reported by Kato et al. (Figure 4). This group recently conducted Suzuki–Miyaura cross coupling of bromoacetophenone with phenyl boronic acid with TONs reaching 8.5×10^4. In addition, this catalyst could be recycled more than 8 times with >90% yield even until the last run. ICP-MS analysis indicated a loss of only 0.27% Pd in solution showing the absence of leaching or recombination of leached Pd atoms as in the "homeopathic" mechanism.[45]

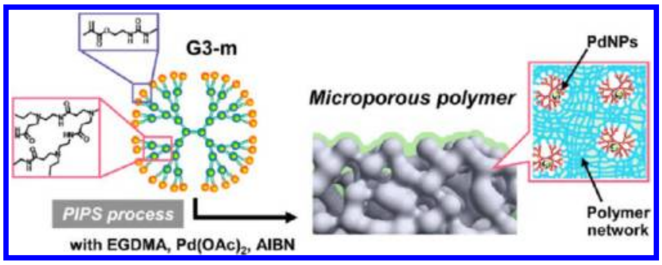


FIGURE 4. Schematic outline of the preparation of microporous network polymers that contain PdNPs. Reprinted with permission from ref 45. Copyright 2010 American Chemical Society.

Homeopathic C–C Cross Coupling by "Click" Dendrimer-Stabilized Pd Nanoparticles

Whereas commercial PAMAM and PPI dendrimers usually required relatively high Pd loading, the design of "click" ferrocenyl dendrimers[63] allowed evaluation of the coordination

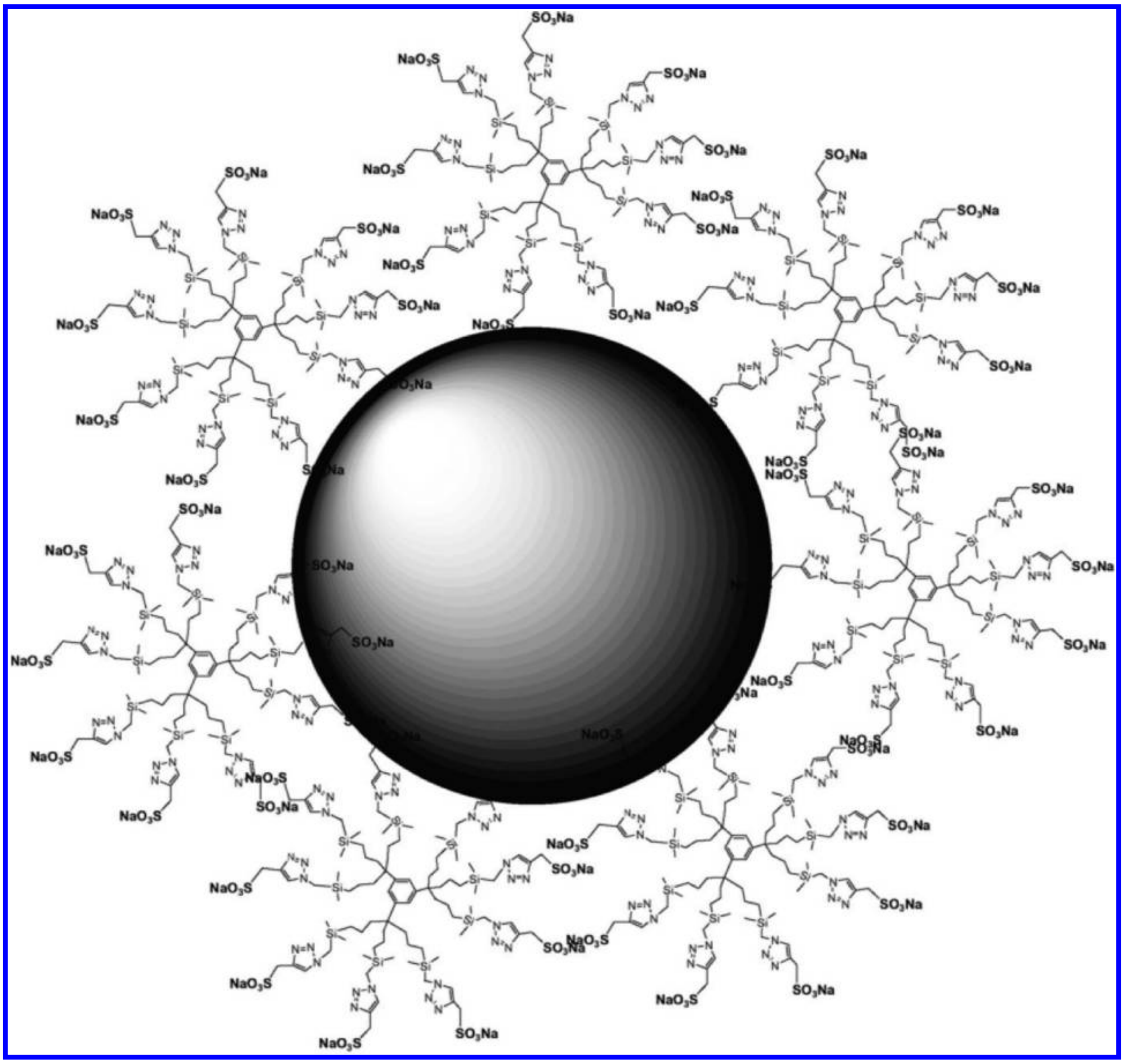


FIGURE 5. PdNP stabilized by several G0 arene-centered dendrimers with sulfonate termini.[67]

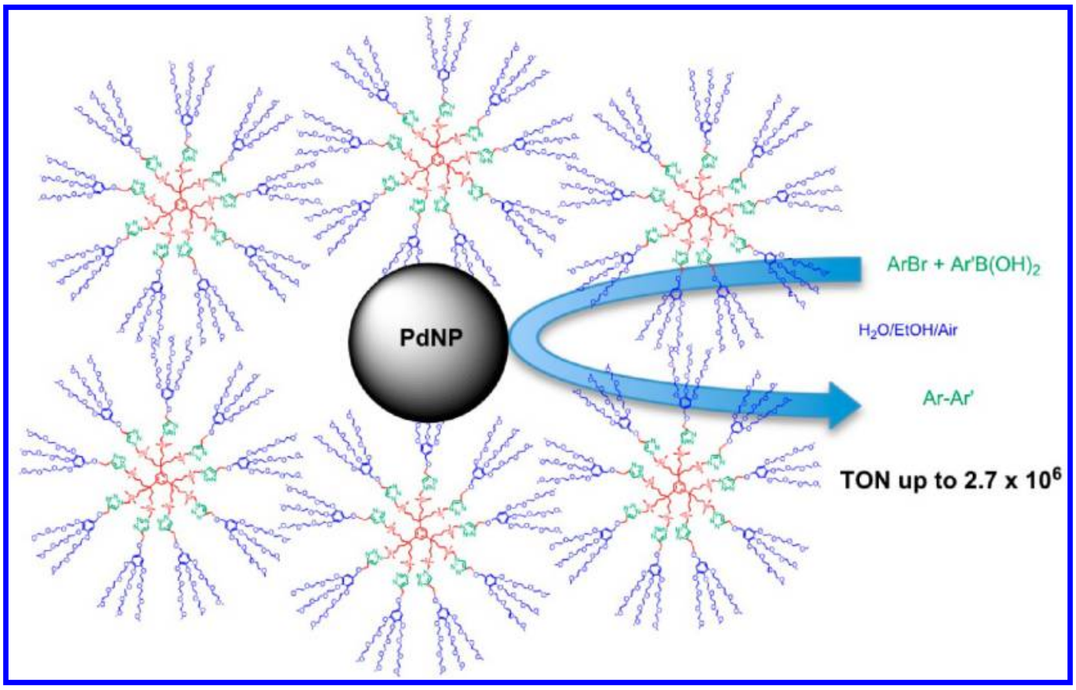


FIGURE 6. Stabilization of a PdNP by a supramolecular assembly of several G0 27-TEG dendrimers after reduction of Pd^{II} by NaBH$_4$. The Suzuki–Miyaura reaction of various bromoarenes has been carried out in H$_2$O/EtOH media with Pd amount between 10 ppm to 0.3 ppm. Turnover numbers reached 2.7 × 10^6.[71]

of metal cations including Pd^{II} upon redox recognition of these cations using a ferrocenyl group attached to triazolyl dendrimer branch termini.[64] Indeed, the electrochemical titration indicated a 1:1 Pd^{II}/triazole branch stoichiometry. After reduction of Pd^{II} to Pd^0, the forecasted number of Pd atoms encapsulated inside the "click" dendrimers could be verified by TEM for the G1 and G2 dendrimers containing, respectively, 27 and 81 ferrocenyltriazole termini, resulting in encapsulated PdNPs that were 1.3 ± 0.2 nm and 1.6 ± 0.3 nm, respectively. With the G0 dendrimer containing 9 ferrocenyl triazole termini, the PdNPs were larger (2.8 nm), because they were surrounded by several dendrimers rather than being encapsulated inside a single dendrimer. Whereas hydrogenation of diene to monoene was all the faster because the PdNPs were smaller as expected for a surface mechanism,[65] C–C coupling between iodobenzene and phenylboronic acid in toluene was independent of the PdNP size and of whether the PdNP was encapsulated inside a large G1 or G2 dendrimer or stabilized by small G0 dendrimers. Catalysis was all the more efficient as the PdNP concentration was lower, and at high PdNP concentration, the yield was not quantitative, which was taken into account by atom quenching by the PdNP in analogy to the high-temperature Heck "homeopathic" mechanism. With 1 ppm Pd, a TON of 540 000 was obtained at room temperature, although the reaction was slow.[66] When the terminal "click" dendrimer groups were sulfonates, they were water-soluble and stabilized PdNPs (but did not encapsulate them, Figure 5), and the Suzuki–Miyaura coupling of iobenzene with phenylboronic acid was conducted in aqueous solvents resulting in TONs up to almost 10000 (almost quantitative) under ambient conditions with TOFs up to 1500 mol PhI (mol Pd)$^{-1}$ h^{-1},[67] these values being higher than with the comparable "click" sulfonate polymer.[68]

The next series of "click" dendrimers were designed to contain both triazolyl linkages and tri(ethylene glycol) (TEG) termini in Percec-type tripodal dendrons.[69] These new water-soluble dendritic nanoreactors were efficient in both molecular[70] and PdNP catalysis.[71] The G0 dendrimer contains 27 TEG termini and 9 triazole linkers, whereas the G1 dendrimer contains 81 TEG termini and 27 triazole linkers. Addition of Pd^{II} ions as K$_2$PdCl$_4$ in water was shown by UV–vis spectroscopy to coordinate efficiently only to the triazole ligands according to a 1:1 Pd/triazole stoichiometry. Reduction to PdNPs yielded a large supramolecular assembly that required several dendrimers to stabilize a single truncated bipyramid PdNP of 1.4 ± 0.7 nm core size containing approximately 100 Pd atoms. On the other hand, the dendrimer size of G1 hardly increases upon PdNP encapsulation. The dendrimer-stabilized PdNPs are stable in air and water and retain their catalytic activity for months, the G0-stabilized PdNPs being the most active catalyst.

TABLE 1. Selected Examples of Extremely Active PdNP Catalysts Discussed in the Text[a]

catalyst	PdNP (nm)	R	solvent	temp (°C)	Pd loading, TON
$Pd(OAc)_2$		H	DMF/H_2O, $HMPA/H_2O$	85	5 ppm,[2] 200000
$Pd(OAc)_2$		H	NMP/H_2O (19/1)	90	0.9 ppm,[9] 94444
$Pd(OAc)_2$ + n-Bu_4NBr		S	NMP/H_2O	90	50 ppm,[30] 16600
		N	DMF	50	200 ppm, 4050
Pd/C	2.4	H	NMP	140	50 ppm,[29] 18000
$Pd(OAc)_2$/G3-P3	2.0	S	H_2O	80	10 ppm,[45] 85000
$Pd(OAc)_2$/**3** + TBAB	2.0−5.0	S	H_2O	100	10 ppm,[46] 95000
K_2PdCl_4, PVP	10	S	H_2O/EtOH (3/1)	90	8 ppm,[47] 117500
$(NH_4)_2PdCl_4$/**2** + TBAF	4.9	S	H_2O	100	0.28 ppm,[48] 3570000 (ArI) 66 ppm, 14848 (ArCl)
$PdCl_2$/**1**	3.0	S	H_2O	120	10 ppm,[49] 100000 (ArBr)
$PdCl_2$/**1**+ TBAB	3.0	S	H_2O	120	10 ppm,[49] 66000 (ArCl)
H_2PdCl_4/SBA-15 + TBAB	6.4	S	H_2O	80	6 ppm,[50] 121666
K_2PdCl/PPPI		H	Et_3N	90	(3−5) × 10^4 ppm,[54] low
K_2PdCl_4/G4-OH		H	DMA	140	25 ppm,[56] 36800
K_2PdCl_4/G4-OH	1.4	S	H_2O/EtOH (6/4)	80	1.5 × 10^4 ppm,[57] low
K_2PdCl_4/G4-OH	3.2	S	EtOH	78	550 ppm,[58] 1771
K_2PdCl_4/G4-OH	1.6	St	H_2O	40	3 × 10^3 ppm,[61]low
$Pd(OAc)_2$/G0-9Fc	2.8	S	$CHCl_3$/MeOH (2/1)	rt	1 ppm[65] 540000 (ArI)
K_2PdCl_4/ G0-$9SO_3^-$	2.3	S	H_2O/EtOH (1/1)	rt	100 ppm,[67] 9200 (ArI)
K_2PdCl_4/ G1-$27SO_3^-$	2.8	S	H_2O/EtOH (1/1)	rt	100 ppm,[67] 9400 (ArI)
K_2PdCl_4/ G0-27TEG	1.4	S	H_2O/EtOH (1/1)	80	0.3 ppm,[71] 2700000 (ArBr)
K_2PdCl_4/ G1-81TEG	2.7	S	H_2O/EtOH (1/1)	80	1 ppm,[71] 390000 (ArBr)

[a] Catalyst, Pd source/stabilizer + additive; R, reaction (S, Suzuki; H, Heck; St, Stille; and N, Negishi). G4-OH, 4th generation PAMAM dendrimer with OH termini. PPPI, perfluorinated polyether-derivatized poly(propylene) imine. G0-9Fc: zeroth-generation dendrimer with 9 ferrocene termini; G0-$9SO_3^-$ and G1-$27SO_3^-$, zeroth- and first-generation dendrimers with, respectively, 9 and 27 sulfonated termini; G0-27TEG and G1-81TEG, zeroth- and first-generation dendrimers with, respectively, 27 and 81 tri(ethylene glycol) termini.

These PdNPs catalyze Suzuki−Miyaura coupling of inactivated bromoarenes with phenylboronic acids at 80 °C with TONs that reach or overtake 1 million and that of iodoarenes also at the sub-part per million level at 28 °C.[71] It appears that the TEG tethers, in addition to bringing biocompatibility,[72] allow interpenetration of a set of dendrimers to create large assemblies favoring PdNP stabilization (Figure 6). Comparatively, "click" polymers containing TEG tethers are also extremely active but less stable, lacking the nanocontainer property of the related "click" dendrimers.[73] For Heck or Suzuki−Miyaura coupling of chloroarenes, the results are less impressive, because these PdNPs decompose above 100 °C, and classic surfactants used in large quantities remain superior for "homeopathic" catalysis. Note, however, that the "click" TEG dendrimers are fully recycled and also used in very small quantities contrary to surfactants.

The "click" TEG dendrimer-stabilized PdNPs also efficiently catalyze *inter alia* the more demanding Sonogashira reactions at 100 °C, and the amount of Pd vs substrate that is required reaches 0.01%, that is, higher than "homeopathic" quantities. Nevertheless, the "ligand-free" nature of the PdNP precatalyst is of interest in terms of "green" chemistry despite the lack of mechanistic information.

In Table 1, we compare the "homeopathic" catalysis for a variety of carbon−carbon bond formation reactions catalyzed by PdNPs. The data show the advantage of recyclable dendrimers that stabilize highly active PdNP precatalyst in Miyaura−Suzuki reactions.

Conclusion and Propects

The "ligand-free" Pd-catalyzed Heck reaction was a considerable breakthrough from both standpoints of saving costly or toxic ligands and requiring so-called "homeopathic" quantities of PdNP catalysts; moreover, it provided the occasion of a novel mechanistic insight into NP catalysis. The "homeopathic" nomenclature should not be taken here strictly as in the traditional meaning of infinite dilution, but the analogy only involves (i) activity at extremely low, sometimes sub-part per million Pd concentration and (ii) catalytic activity increasing with dilution (until a certain point) because the mother PdNP quenches the active Pd atoms, a process disfavored upon dilution. Consequently, industrial applications resulted from this new generation of catalysts. Recently, the principle of "homeopathic" catalysis by PdNPs could be extended to room-temperature Suzuki−Miyaura catalysis in aqueous solvents using preformed PdNPs that were precisely designed in terms of size and shape using dendrimers that permitted the optimization of the PdNP stability and efficiency. There are also an increasing number of recent reports on homeopathic PdNP catalysis using stoichiometric amounts of cationic (ammonium or imdazolium) stabilizers that allow chloroarene Heck and Suzuki−Miyaura coupling in water. The requirement of these salts containing reactive anions in large excess facilitates the formation of palladate species that are better candidates than neutral Pd species for the difficult oxidative addition of aryl chlorides.

Alternatively, sophisticated microporous solid supports that are eventually functionalized with cationic PdNP stabilizers also lead to excellent catalysis results in terms of catalytic Heck and Suzuki–Miyaura reactions sometimes using almost "homeopathic" PdNP amounts.[74]

The forthcoming challenges leading to improved simultaneous stabilization and catalytic efficiency of Pd catalyst now involve (i) "homeopathic" PdNP catalysis requiring as little salt as possible in aqueous solvents, (ii) activation of chloroarenes with "homeopathic" dendrimer-stabilized PdNPs, (iii) continuous improvements of recyclable "homeopathic" heterogeneous catalysts, and (iv) extension of the "homeopathic" PdNP catalysis beyond the Heck and Suzuki–Miyaura reactions to other PdNP-catalyzed cross coupling reactions for which the PdNP is still relatively high as reported in known studies.[35,74]

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FOOTNOTES

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