REVIEW

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On the Nature of the Active Species in Palladium Catalyzed Mizoroki–Heck and Suzuki–Miyaura Couplings – Homogeneous or Heterogeneous Catalysis, A Critical Review

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Abstract: A wide array of forms of palladium has been utilized as precatalysts for Heck and Suzuki coupling reactions over the last 15 years. Historically, nearly every form of palladium used has been described as the active catalytic species. However, recent research has begun to shed light on the *in situ* transformations that many palladium precatalysts undergo during and before the catalytic reaction, and there are now many suggestions in the literature that narrow the scope of types of palladium that may be considered true "catalysts" in these coupling reactions. In this work, for each type of precatalyst, the recent literature is summarized and the type(s) of palladium that are proposed to be truly active are enumerated. All forms of palladium, including discrete soluble palladium complexes, solid-supported metal ligand complexes, supported palladium nano- and macroparticles, soluble palladium nanoparticles, soluble ligand-free palladium, and palladium-exchanged oxides are considered and reviewed here. A considerable focus is placed on solid precatalysts and on evidence for and against catalysis by solid surfaces *vs.* soluble species when starting with various precatalysts. The review closes with a critical overview of various control experiments or tests that have been used by authors to assess the homogeneity or heterogeneity of catalyst systems.

Keywords: C–C coupling; colloidal particles; heterogeneous; homogeneous; leaching; 3-phase test

1 Introduction

Aromatic carbon-carbon bond coupling reactions have recently emerged as exceedingly important methodologies for the preparation of complex organic molecules such as pharmaceuticals. Of the many commonly used coupling reactions such as Heck,[1–4] Suzuki,[5,6] Sonogashira[7] and Stille[8] reactions, perhaps the two most important are the Heck and Suzuki reactions.

The Heck and Suzuki couplings are fascinating reactions from a catalysis science perspective. Virtually all forms of palladium can be used as precatalysts for the simpler reactions (e.g., activation of aryl iodides), yet specifically designed catalysts are required for activa-

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Christopher W. Jones was born in Michigan (USA) in 1973. He obtained his B. S. E. degree in chemical engineering Summa Cum Laude from the University of Michigan (UM) in 1995, where he first studied catalysis under the guidance of Prof. L. T. Thompson. At UM, he became intrigued by catalyst design and catalyst synthesis, and he thus chose to further study these topics in his graduate work at the California Institute of Technology. There he obtained M.S. (1997) and Ph.D. (1999) degrees in chemical engineering while working with Prof. Mark E. Davis. His PhD thesis focused on zeolites and the incorporation of organic active sites into zeolites and all-silica molecular sieves. During his studies, he developed the first zeolite-like materials with covalently-tethered organic catalytic sites within the micropores of the solid. From 1999–2000, he worked as a post-doctoral researcher with Profs. John E. Bercaw and Mark E. Davis on Group 4 metal complexes for olefin polymerization and mixed transition metal oxide catalysts for light alkane oxidation. In the Fall of 2000, he joined the Georgia Institute of Technology as an Assistant Professor of chemical engineering. In 2005, he was promoted to Associate Professor and named the J. Carl. & Sheila Pirkle Faculty Fellow in chemical and biomolecular engineering. While at Georgia Tech, he has built a research group that works at the interface of homogeneous and heterogeneous catalysis in a diverse array of topics including (i) polymerization catalysis and reaction engineering, (ii) organic and organometallic catalysts in fine chemistry, and (iii) design of single-sited solid catalysts and adsorbents. In 2003, he first became involved in palladium-catalyzed carbon-carbon bond forming reactions, and his curiosity about this intriguing area of catalysis science eventually led to this review.

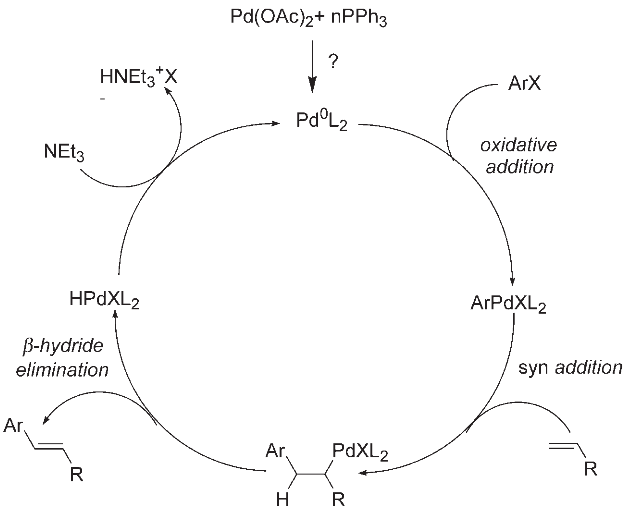
tion of bulky or electronically unactivated substrates. Additionally, in many cases, extremely small amounts of palladium (ppm or ppb levels) are sufficient to give very high turnover frequencies, whereas in others, 10% or higher precatalyst loadings are required to obtain sufficient product yields.

Two critical questions have dominated modern research on Heck and Suzuki couplings. The first is (1) how can a catalyst be designed to activate aryl chlorides,[9] as these are the cheapest and most abundant class of aryl halides available for use as substrates? While many of the catalysts recently developed to activate aryl chlorides will be discussed in this review, the design of new, molecular metal ligand complexes to achieve these transformations is not our primary focus. This has been the topic of several other recent reviews.[9,10] The second key question researchers have focused on is (2) how can minimization of catalyst cost and catalyst contamination of the product be best achieved?[11] Researchers have addressed this topic in several ways, including development of high turnover number catalysts and *via* the design and utilization of "heterogeneous" Heck and Suzuki precatalysts. It has been in the pursuit of this second question that the Heck and Suzuki coupling literature has grown into a morass, with an endless list of hypothesized or claimed "true catalytic species." In most research papers, the active form of palladium is not discussed, while in others educated guesses are proposed based on limited data. Only recently have researchers focused on the question – what is the form of the true, catalytic palladium species in these coupling reactions? Identifying the true catalyst is critically important for future advances in the rational design of coupling catalysts. While for some classes of catalysts the nature of the active species is fairly well established by direct or accumulated circumstantial evidence (e.g., bulky monodentate phosphine complexes developed for aryl chloride activation under low temperature conditions – $T < 80\,°C$), in other cases, the nature of the true catalyst is ambiguous. For example, claims exist in the literature supporting both soluble molecular and nanoparticle catalysts as well as truly heterogeneous insoluble Pd catalysts.

In this work, we review the literature on catalyzed Heck and Suzuki coupling reactions with a critical eye aimed at identification of the true catalytic species. While the primary focus is placed on the recent literature, important historic publications are also noted. In most cases, only Heck and Suzuki couplings of aryl halides are discussed, although occasional examples of other coupling reactions are presented, those being the rare cases where the nature of the true catalytic species is addressed. Both homogeneous and heterogeneous precatalysts are discussed, with the use of the traditional definitions of homogeneous and heterogeneous catalyst employed (homogeneous = soluble catalyst; heterogeneous = solid catalyst) *in lieu* of the modern definitions of Schwartz.[12] Soluble and insoluble nanoparticle precatalysts are reviewed together. A particular emphasis is placed on the nature of the catalytic species and the recovery/recycle of the catalyst when using heterogeneous precatalysts or "ligand-free" systems.

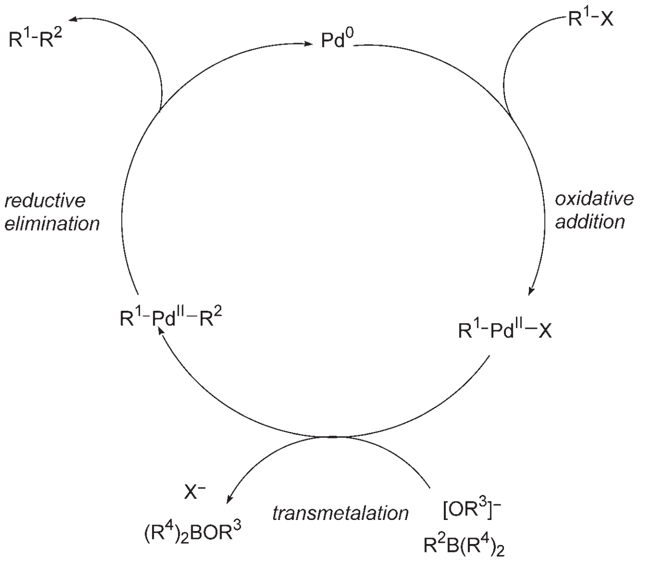
2 Mechanism

The standard catalytic cycle[13] described for both the Heck and Suzuki reactions in most organic chemistry textbooks involves a postulated molecular, homogeneous palladium catalyst that cycles between the Pd(0) and Pd(II) oxidation states during the course of the catalytic reaction. Usually, a precatalyst in the Pd(II) oxidation state is used, and this precatalyst is presumed to be reduced to Pd(0) *in situ*, allowing it to then oxidatively add the aryl halide forming a Pd(II) intermediate as shown in Scheme 1 for the Heck reaction. The Pd(II) complex can next bind to the olefin, inserting it into the aryl–Pd bond, creating a new carbon-carbon bond. β-Hydride elimination gives the product species, generating an L_2PdHX species. It is often proposed that the base then removes the bound HX from the palladium regenerating the $L_2Pd(0)$ intermediate, although it has been suggested that the equilibrium between XPdH and Pd is fast and may not need base. The exact role of the base is still being debated.[14] The Suzuki reaction is conceptually quite similar to the Heck reaction, with the nucleophile for transmetalation being derived from an arylboronic acid rather than from an olefin (Scheme 2).[15,16]



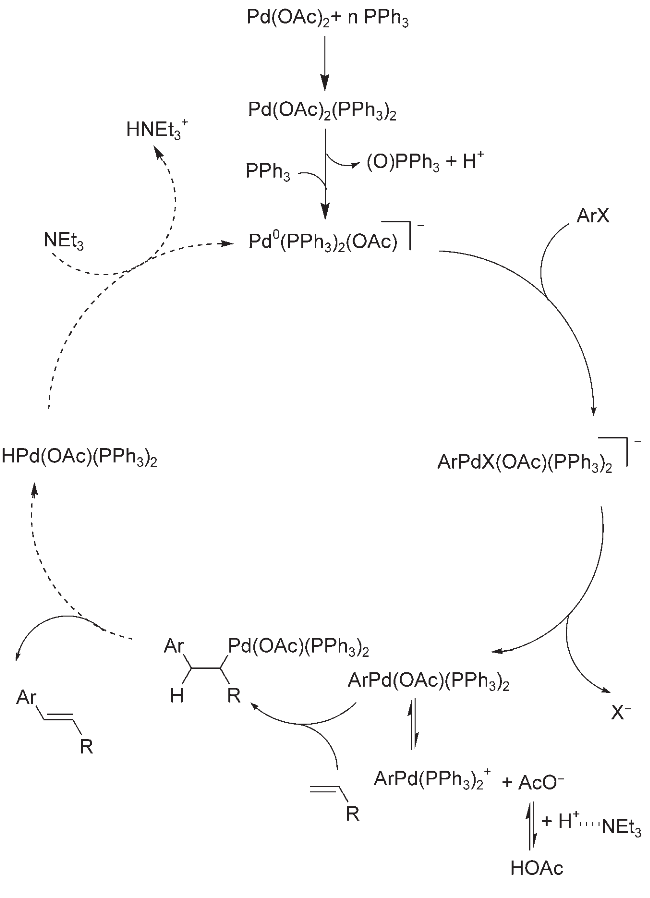
Scheme 1. The typical, textbook catalytic cycle of the Heck reaction.

Recently, Amatore and Jutand have developed significant experimental evidence for the existence of an anionic version of the proposed textbook cycle for Heck and other palladium-catalyzed coupling reactions (Scheme 3).[17] The overall cycle is similar to the standard cycle discussed above except that anionic, pentacoordinated species are proposed to be the important Pd(II) intermediates. In practice, it is highly likely that most traditional, high temperature Heck reactions follow this Amatore/Jutand mechanistic cycle, with the widely recognized textbook cycle only important for triflates or other arylating groups that have non-ligating leaving groups (not halides). Unfortunately, most chemists continue to think of the Heck reaction with the textbook cycle (Scheme 1) in mind.

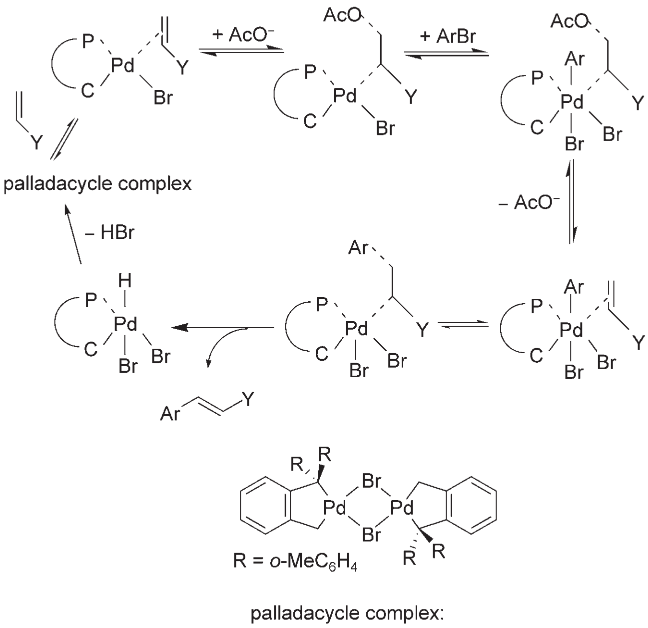


Scheme 2. The typical, textbook catalytic cycle for the Suzuki reaction.

The final proposed catalytic cycle that will be discussed in this review is the Pd(II)-Pd(IV) cycle outlined by Shaw for Heck coupling reactions.[18,19] As a consequence of the purported stability of some palladacycle complexes in Heck reactions, early on in the development of these precatalysts, it was hypothesized that a new catalytic cycle might operate. This cycle, a Pd(II)-Pd(IV) cycle, was invoked relatively often in the mid to late 1990s for Heck couplings involving palladacycle precatalysts, and this cycle continues to be invoked today. A Pd(II)-Pd(IV) cycle as outlined by Shaw is described in Scheme 4.



Scheme 3. The catalytic cycle involving anionic intermediates as proposed by Amatore and Jutand for the Heck reaction.



Scheme 4. The Pd(II)-Pd(IV) catalytic cycle outlined by Shaw for the Heck reaction.

3 Homogeneous Precatalysts

3.1 Homogeneous Precatalysts with N, O, P or S Donor Ligands

3.1.1 Phosphorus Ligands

Many of the earliest precatalysts for Heck and Suzuki couplings relied on the use of triphenylphosphine as a ligand.[20] Indeed, until the mid 1990s, most coupling protocols still relied on use of palladium-triphenylphosphine complexes as catalysts despite the fact that it was demonstrated early on that other ligands, like tri-(*o*-tolyl)phosphine, could give better results.[21,22] However, even after many years, these well-known precatalysts are still being studied and basic trends such as the effect of solvent and Pd:P ratio are being probed.[23] Herrmann showed that the conditions required for many Heck reactions (such as elevated temperatures) yielded significant ligand decomposition when $Pd(OAc)_2$-triarylphosphine complexes were used, with significant P−C bond cleavage being observed.[24] Similar observations were reported for bidentate phosphines, and the authors pointed out that all phosphines studied other than P(*o*-Tol)$_3$ and P(Mes)$_3$ underwent such decomposition reactions under specific conditions.[25]

In an effort to find catalysts that activate aryl chlorides, a variety of different ligands has been screened over the years. Milstein and co-workers studied the use of bidentate phosphines such as 1,4-bis[(diisopropyl)phosphino]butane (dippb) in combination with Pd(OAc)$_2$ in the Heck coupling of aryl chlorides with various olefins.[26] Later they reported the use of Pd complexes of 1,4-bis[(diisopropyl)phosphino]propane, (dippp), for Heck couplings in the absence of a base but with added zinc,[27] as well as mechanistic studies of the oxidative addition of aryl chlorides to dippp-ligated Pd(0).[28] Later, in a more detailed study, the authors outlined the role of the various bidentate *vs.* monodentate ligands in Heck reactions.[29] Similar catalyst systems were used in carbonylation and formylation reactions as well.[28,30,31]

Osborn reported in 1989 that chlorobenzene could be carbonylated with the use of a palladium source with phosphine ligands such as P(Cy)$_3$.[32] Subsequently, Alper published an account of P(Cy)$_3$ in combination with palladium chloride salts in the carbonylation of aryl chlorides.[33] Years later, Shen showed that aryl chlorides could be activated in Suzuki couplings using P(Cy)$_3$ or (diphenylphosphino)butane (dppp).[34] Monteith verified Shen's observations while developing a manufacturing route for 2-cyano-4′-methylbiphenyl.[16] Interestingly, tricyclopentylphosphine and triisopropylphosphine were both found to be poorly active in Suzuki couplings of alkyl chlorides despite that fact that they are sterically and electronically similar to PCy$_3$.[35]

In the late 1990s, a number of authors including Fu, van Leeuwen, Beller, Buchwald and others published accounts of bulky, monodentate ligands as effective components of palladium Suzuki coupling catalysts[36] (it should be noted that N-heterocyclic carbenes also represent important electron-donating monodentate ligands, *vide infra*). Bulky ligands had been previously shown to facilitate other cross-coupling reactions (e.g., see the work of Nishiyama[37] and Hartwig[38–41]), although their use in Suzuki couplings was not widespread until later. In 1998, Fu and co-workers described the use of the bulky trialkylphosphine P(*t*-Bu)$_3$ as a ligand in palladium-catalyzed Suzuki coupling reactions of a broad array of aryl halides.[42] In mechanistic studies published in 2000,[43] the authors found that the Pd:P ratio played a large role in the catalytic performance of the *in-situ* formed complexes. Whereas high activity was achieved at a Pd:P ratio of 1:1 or 1:1.5, a ratio of 1:2 only gave lethargic reactions. In NMR studies, the only identifiable phosphine species observed at a Pd:P ratio of 2:1 to 1:1.5 was the complex containing two phosphines, Pd[P(*t*-Bu)$_3$]$_2$. In further NMR studies during the reaction of an aryl chloride and a boronic acid at a Pd:P ratio of 1:1, the only species observed was also Pd[P(*t*-Bu)$_3$]$_2$. Since the Pd:P ratio was 1:1, this suggested that about half of the Pd contained no phosphine ligands and half contained two ligands. As the complex containing two ligands did not appear to be active under the conditions they employed, the authors concluded that small amounts of the palladium-monophosphine adduct may represent the true catalytic species. Thus, they attributed the excellent reactivity of the palladium-P(*t*-Bu)$_3$ system to both its bulky size and its electron-rich character. Later studies by Hartwig and co-workers showed that the dimer {Pd$_2$(μ-Br)$_2$[P(*t*-Bu)$_3$]}$_2$ could be used as a single-component precatalyst for Suzuki couplings and amination reactions.[44] Again, the high reactivity of this compound was attributed to the *in-situ* formation of monoligated species. Low P:Pd ratios were also required to achieve good catalytic properties when using palladacycles as catalyst precursors, as these precursors have been found to liberate ligand free palladium.[10] These catalysts are discussed further in Section 3.3.

In 1999, van Leeuwen, de Vries and co-workers reported a palladium-catalyzed Heck reaction using different bulky monodentate phosphorus ligands. Bulky phosphoramidites were used as ligands in the Heck coupling of iodobenzene and styrene. A variety of phosphines, phosphites and phosphoramidite ligands of different bulk were screened at a Pd:P ratio of 1:2, where all ligands gave reasonable results. However, upon addition of excess phosphine, only the bulky phosphorus amidite, **1**, gave similar rates. Indeed, with this ligand, the reaction was quite fast and under optimized conditions, no palladium black was formed. The steric bulk of the ligand was thought effective in keeping some fraction of the palladium bound by a single monodentate ligand, a coordination environment that was proposed to promote fast catalytic reactions. When a less bulky phosphorus amidite ligand was used, NMR studies showed that the palladium was bound by two ligands and reaction rates decreased.[45] Figure 1 shows the structure of ligand **1** as well as many other ligands discussed in this review.

Buchwald reported a very important class of monodentate, bulky phosphines in the late 1990s based on functionalized biphenyls.[46–49] These ligands, when combined with a palladium source, led to effective catalysts for a variety of cross-coupling reactions including aminations and Suzuki couplings. Beginning with the bulky **2**, Buchwald and co-workers successively optimized the system, moving to ligand **3** and finally to the simple ligands **4** and **5** in, for example, Suzuki coupling reactions of aryl chlorides.[49] Ligands **4** and **5**, which unlike P(*t*-Bu)$_3$ are air-stable [it should be noted that the air-stable phosphonium salt of the P(*t*-Bu)$_3$ ligand can be used[50]], are now commercially available.[48] The outstanding cat-

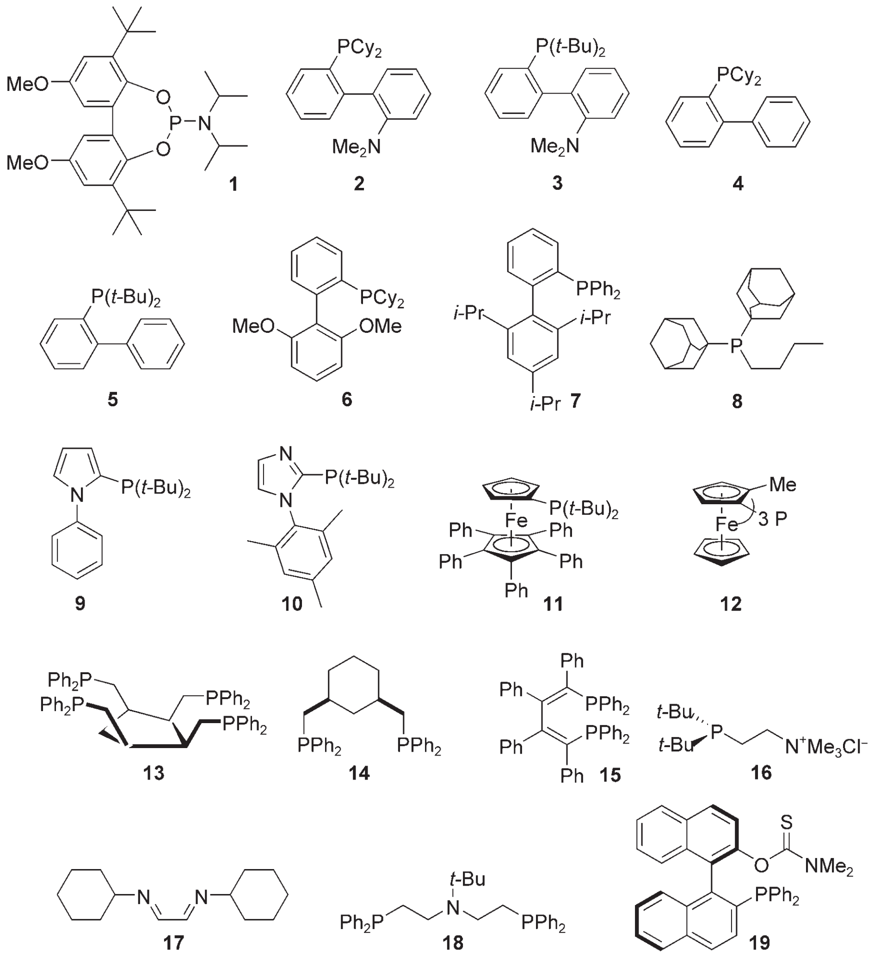


Figure 1. A variety of monodentate, bidentate, tridentate and tetradentate ligands have been used in conjunction with palladium in Heck and Suzuki coupling reactions.

alytic performance of these ligands in conjunction with a palladium source has been attributed to a combination of electronic and steric properties that favor both the oxidative addition and reductive elimination steps in the catalytic cycle.[51] It was suggested that the electron-rich phosphine facilitates the oxidative addition step even when using normally sluggish aryl chlorides, and the steric bulk of the ligand promotes reductive elimination. Additionally, the phosphine appears to bind strongly enough to the Pd(0) intermediate to prevent its significant aggregation and precipitation.[49] It was suggested by others that the biphenyl-based phosphines may contribute to stabilization of the Pd(0) intermediate by forming π interactions with the aryl ring.[36,52] This was later probed in some detail in a study of the SPhos ligand **6**.[53] Like with other bulky monodentate ligands, the performance of these systems depends strongly on the Pd : P ratio and the palladium source. Although steric bulk alone was important, an electron-rich phosphine was also valuable, as was evident upon comparing the use of **3** or **4** to the tris(2,4-di-*t*-butylphenyl)-phosphite ligand,[54] which was bulky but not electron-rich enough to activate aryl chlorides in Suzuki reactions under the conditions employed.[48] Buchwald and co-workers further described this class of ligands in a study of the related SPhos ligand, **6**, in Suzuki coupling reactions.[53] Noting that the exceptional ability of some bulky monodentate phosphine ligands to promote coupling reactions was often attributed to the two factors discussed above, they sought to understand the relative importance of these. On the one hand, the ligands were deemed highly active due to their ability to donate electron density to the intermediate Pd(0) complex, facilitating oxidative addition. On the other hand, it was proposed that these ligands allowed a reasonable amount of PdL_1 species to form under the reaction conditions, which were hypothesized to be highly active. By studying Sphos **6** and the ligand **7**, which is roughly isostructural to SPhos but less electron-rich, they found that ligand **7** was also an excellent ligand for room temperature Suzuki reactions of aryl chlorides. Thus, the authors concluded that perhaps the most important factor in the ability of these types of ligands to promote coupling reactions was their ability to stabilize PdL_1 intermediates.[53] It should be noted that related ligands also promote the Suzuki coupling of aryl tosylates.[55] Water-soluble analogues have also been recently reported.[56]

Beller and co-workers reported in 2000 the use of the bulky monodentate phosphine, diadamantyl-*n*-butyl phosphine **8**, in the Suzuki coupling of aryl chlorides.[57] Later they described monophosphine-Pd(0) complexes based on other bulky ligands and used them as precatalysts in Suzuki coupling reactions.[58] At the same time, Hartwig and co-workers developed similar ligands for coupling reactions,[44,59–61] as did several other groups.[46,62–69] Beller's group also showed that diadamantylphosphonium salts were useful ligands in coupling reactions.[70] Later, they described *N*-arylpyrroles as effective ligands (PAP ligands, see, for example, **9**) for aryl chloride activation.[71,72] Bulky *N*-aryl-2-(dialkylphosphino)imidazoles (see, for example, ligand **10**) were also effective ligands for activation of chlorides in Suzuki couplings and Buchwald–Hartwig aminations.[73] Again, an important component of their reactivity was suggested to be the stabilization of monoligated palladium species.

Several groups have reported the use of ferrocene-based ligands in coupling reactions. Fu reported a bulky, ferrocene-based triarylphosphine ligand that was effective in Suzuki couplings of aryl chlorides.[74] Hartwig studied ferrocene-based triarylphosphine ligands in conjunction with palladium salts in Suzuki couplings and amination reactions[75] and also in Heck couplings.[61] The ligand **11** generated highly active palladium catalysts that were stable towards air in solution and in the solid state, with Pd(0) complexes even showing some stability towards air. Richards also studied a bulky triferrocenylphosphine, TomPhos **12**, in Suzuki couplings of aryl chlorides.[76,77] The ligand **12**, when complexed with $Pd_2(dba)_3$, produced a very active but short-lived catalyst that decomposed to palladium black after about 5 hours. Characterization of the system indicated that the ferrocenylphosphine ligand was slightly more electron-rich than its phenyl analogue but quite electron-poor compared to trialkylphosphines. Johannsen and co-workers also studied ferrocene-based phosphine ligands in conjunction with palladium salts as catalysts for Suzuki couplings of aryl chlorides and bromides.[78] As in the cases discussed above with other bulky monodentate phosphines, the authors attributed the excellent reactivity of their system to the stabilization of reactive palladium complexes containing a single phosphine ligand. As in the other cases, Pd:P ratios played a critical role, with ratios around 1:1 optimum in most cases. Ferrocenyl moieties containing two phosphines have also been used as bidentate ligands in cross-coupling reactions, as reported by Hierso, Doucet and co-workers.[79] Shaughnessy et al. showed that di-*t*-butyl(ferrocenylmethyl)phosphine was also a useful monodentate ligand in coupling reactions.[80] As have others, they noted that Pd:P ratios near 1:1 were useful in creating active catalysts, with additional phosphine adversely affecting the catalysis. Hong studied mono/bidentate ligands based on other transition metals such as cobalt, using them in Suzuki couplings of aryl bromides.[81,82] Mathey and Le Floch utilized ferrocenyl ligands containing bidentate phosphorus donors in Suzuki couplings of aryl bromides.[83] Ferrocene-based ligands have also been and used for asymmetric Suzuki reactions,[78,84] and they have been incorporated into polymeric structures.[85]

A variety of ligands containing P–O bonds has proven to be useful in Heck and Suzuki coupling reactions. Pd(II)-phosphate complexes were found to be excellent complexes for the activation of aryl chlorides in Suzuki couplings,[86] and air-stable phosphine oxides have been shown to be useful in the Suzuki coupling of aryl chlorides by Li and co-workers.[87–89] Phosphites have been effectively used as ligands for Suzuki couplings of aryl chlorides and bromides,[86,90,91] as well as in Heck couplings of aryl bromides and chlorides.[92] Interestingly, the hydrolysis of palladacycles based on phosphinite or phosphate ligands has also been proposed to play a role in their catalytic activity in Suzuki couplings, indicating that the presence of P–OH groups in the ligand may be beneficial in promoting coupling reactions in the system as well.[93]

Many other complexes based on simple phosphines are good precatalysts in Heck and Suzuki coupling reactions. For example, Beller has shown that a simple Pd(0)-triphenylphosphine-diene complex is effective in Suzuki couplings of aryl chlorides.[58] Additionally, a tetrapodal phosphine, **13**, has been shown by Doucet and Santelli to activate aryl bromides or chlorides in Suzuki couplings.[94–102] The fact that this ligand and others that do not have high σ-basicity can activate aryl chlorides provides evidence that high σ-basicity is not a prerequisite for catalytic activity.[10]

Sémeril, Matt and co-workers have used calixarene-supported diphosphines as ligands for palladium in Heck, Suzuki and other coupling reactions.[103] The presence of a chelating ligand on the true catalyst was inferred, as triphenylphosphine ligated palladium was an ineffective precatalyst in some coupling reactions under identical conditions. Andersson also reported a bidentate phosphine ligand, **14**, that seemed to give stable palladium catalysts for Suzuki couplings,[104] as they observed no palladium black formation in reactions of iodoarenes and bromoarenes. The bidentate ligand NUPHOS (see, for example, **15**) was also shown to be useful in Suzuki couplings of bromoarenes with phenylboronic acid.[105]

Due to the large number of Suzuki and other coupling reactions that are carried out in aqueous[106] or biphasic systems, there has been an increased interest in the development of water-soluble ligands for these reactions. Shaughnessy and co-workers utilized both sterically demanding water-soluble alkylphosphines[107] and triarylphosphines[108] in Suzuki and Heck/Suzuki couplings of aryl bromides, respectively. They have also demonstrated that bulky cationic and anionic phosphine ligands are useful, with *t*-Bu-Amphos, **16**, giving a system that could be recycled several times using water/toluene mixtures, although with notable losses in yield.[109] Beller reported sugar-linked triarylphosphines as effective ligands in aqueous coupling reactions.[110] Miyaura disclosed a gluconamide-substituted triphenylphosphine ligand for coupling reactions as well.[111] A variety of more standard water-soluble phosphines have also been used.[106,112–116] For instance, Genêt and coworkers describe the use of a Pd(0)/TPPTS precatalyst in water that was effective in Suzuki couplings of aryl bromides with areneboronic acids. It was claimed that the catalyst could be recycled three times without a loss of activity, although it is clear from the data presented that the activity decreases upon recycle (although the yields do not).[112] Arcadi and co-workers utilized traditional precatalysts such as $Pd[PPh_3]_4$ or Pd/C in aqueous Suzuki couplings using surfactants to facilitate contact between the reagents and the catalysts in water.[117] Using the solid precatalyst, the authors reported that the solid could be recovered and reused, although the activity decreased upon recycle. Using $Pd(OAc)_2$ in their system also gave good results, which they concluded was due to the formation of catalytically active Pd(0) nanoparticles.

In some cases, biphasic systems were used in combination with palladium salts and water-soluble phosphines with the specific aim of aiding catalyst recovery as exemplified in the Heck coupling reactions studied by Arai et al.[118] Oehme used biphasic systems with surfactants to promote transfer between the phases in their studies of Suzuki couplings.[119] Palladium deposition was shown to be affected by the Pd:P ratio and under optimized conditions, deposition could be prevented with no metal being found in the organic phase.

Enantioselective coupling reactions have also been studied extensively. These will not be explicitly addressed here, although it should be stated that enantioselective Heck[120] and Suzuki[84,121–123] reactions are well known.

Overall, recent studies of phosphorus-based ligands suggest that a useful and increasingly explored way of creating active coupling catalysts is through the use of electron-rich ligands that are bulky, making them capable of stabilizing finite amounts of PdL_1 complexes that are hypothesized to be the true active species in these reactions. A variety of bidentate ligands has also been used, and in these cases it seems often assumed that the catalytically active palladium atom is ligated by both donor atoms. A broader variety of ligands is available for the activation of bromides and iodides. It should be noted that the beneficial use of phosphorus donor ligands in coupling reactions has generally been observed under low temperature conditions (below 100 °C), with higher temperatures potentially leading to decomposition of the well-defined complexes to give more ill-defined palladium species (*vide infra*).

3.1.2 Non-Phosphorus and Mixed Phosphorus Ligands

Although phosphorus-based ligands have been the most often studied, there has been an increased emphasis on the use of ligands with other donor atoms in recent years. For example, simple palladium complexes with thioether donor ligands, such as $PdCl_2(SEt_2)_2$ have been shown to be good precursors for catalytically active Pd(0) in Heck and Suzuki couplings by Dupont.[124,125] Interestingly, tetrabutylammonium bromide (TBAB), which has a beneficial effect on Suzuki couplings using $Pd(OAc)_2$ precatalysts (*vide infra*), had no significant effect when using the sulfur-containing precursor complexes.[16,125]

Nolan described Pd(II) complexes of bidentate diazabutadiene (DAB) ligands as effective precatalysts for Heck[126] and Suzuki[127] couplings. In Heck reactions, the authors surmised that the DAB-bound Pd(II) species was reduced to Pd(0) and the ligand-bound palladium affected the catalytic reaction. This suggestion was due to the observation that catalysis readily occurred at low temperatures in the presence of the DAB ligand (see, for example, **17**) whereas in the absence of the ligand the reaction was sluggish. At higher temperatures, the activity of the DAB system was similar to homeopathic $Pd(OAc)_2$.

Following Buchmeiser's reports[128–133] of supported bidentate di-2-pyridylmethylamine-based palladium complexes (*vide infra*), Nájera and co-workers evaluated these complexes as homogeneous precatalysts for Heck, Suzuki and other coupling reactions.[134,135] Pd(II) precatalysts based on this ligand system allowed activation of aryl iodides, bromides and chlorides in various coupling reactions.

Gade studied tridentate NNN ligands based on bis(oxazolinyl)pyrrole to form palladium complexes for use in Heck and Suzuki reactions, noting that under no circumstance was palladium black observed.[136] At temperatures of interest for reaction Pd atoms that were bound intramolecularly by the ligand were in equilibrium with monomeric species and simple Pd-ligand complexes were thought to be the active species. In a related ligand system, Boykin reported the use of 2-aryl-2-oxazoline ligands with $Pd(OAc)_2$ in the Suzuki coupling of aryl bromides with areneboronic acids.[137]

Liang studied bidentate NP ligand-Pd(II) complexes in Suzuki reactions, and the complexes were described as extremely stable complexes under a variety of conditions. They reported no obvious formation of palladium black during the catalytic reactions.[138] Aminophosphine complexes have also been successfully used in Suzuki coupling reactions. A variety of aminophosphine ligands has been screened and, in some cases, aryl chlorides were readily activated.[139–141]

Scrivanti et al. reported a Pd(0) complex of an iminophosphine ligand as an active precatalyst in the Heck coupling of aryl bromides with styrene or butyl acrylate.[142] They reported that polar solvents were necessary to achieve high reaction rates and that an induction period was clearly present based on the shape of the kinetic plots. In assessing the true nature of the catalyst, the authors noted that Hg(0) addition quenched all activity, whereas purported homogeneous catalyst poisons such as PPh_3 had no effect at low loading (a detailed discussion of catalyst poisons is presented later in this review). Although they did not assign a structure to the true active species in the reaction, these data were consistent with catalysis by either Pd nanoparticles or a "naked" molecular palladium complex (*vide infra*) that spends some time in a Pd(0) oxidation state.

Liang[143] and Ozerov[144] independently reported on the use of structurally similar PNP ligand-Pd(II) pincer complexes in Heck coupling reactions. Liang observed no formation of palladium black under the reaction conditions and suggested, based on Hammett plots, that the rate-limiting step in the cycle was not oxidative addition. Citing previous work that suggested a Pd(II)-Pd(IV) catalytic cycle, it may be interpreted that the authors imply that such a cycle might be operative, although it should be noted that this was not explicitly stated.

Chelating PO ligands have also been reported for Suzuki couplings of aryl bromides and chlorides. The catalytic properties of these complexes have been attributed to the stabilization of electron-rich palladium species with the bidentate, chelating PO ligand.[145,146]

Hii's group reported the hemilabile ligand **18** that cycles between PP and PNP coordination of palladium. This ligand was used as a component of an aryl bromide and iodide activating Heck catalyst system.[147] They reported that the multiple coordination modes of the ligand could help to stabilize the system, leading to high TONs.

Many phosphine-free systems behave similarly to the "naked" ligand-free catalysts described below in Heck reactions.[148] Even ligands that might be surmised to be "dead," like the tetradentate salen ligand, were found to be reasonable ligands for palladium precatalysts.[149] Ligands in this class could convert aryl iodides and activated bromides giving high TOFs, with some converting unactivated aryl bromides and aryl chlorides in the presence of Pd(0) stabilizing species such as TBAB under Jeffery conditions.[150,151] While the activity of phosphine-free systems was often better in Suzuki couplings, longevity was better in Heck reactions, with the highest achieved TOFs several orders of magnitude higher for Heck than Suzuki reactions, perhaps due to the stabilizing nature of the olefin reagent.[148]

Welton reported the use of commercially available imidazoles as ligands for Suzuki coupling reactions,[152] although in many cases extensive catalyst decomposition was noted. Sarkar et al. have utilized a triazole-functionalized triarylphosphine ligand in Suzuki couplings and suggested that palladium chelation may play a role in stabilizing catalysts derived from the ligand.[153]

Shi has reported binaphthyl-based PS bidentate ligands (see, for example, **19**) in Suzuki couplings.[154] Kostas has utilized tridentate ONS ligands with palladium chloride salts as precatalysts for Suzuki couplings of aryl bromides and chlorides.[155] Chen, Yang and coworkers utilized a monodentate thiourea ligand with PdI_2 to generate an effective Suzuki coupling catalyst system for conversion of aryl iodides and bromides.[156] The authors claimed that an L:Pd ratio of 2:1 was ideal, and that their system behaved well because the Pd–S bond in their complexes was stronger than most Pd–P bonds in more traditional catalyst formulations.

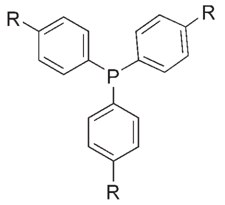
Pringle and colleagues evaluated bulky triarylarsines as ligands in Heck couplings of bromoarenes and *n*-butyl acrylate,[157] noting that, although the ligands have toxicity issues, the arsines often outperform comparable phosphine ligands in the coupling reactions.

Overall, much less mechanistic detail has been uncovered in the Heck and Suzuki coupling reactions using non-phosphorus based systems. Indeed, the vast majority of the ligands have simply been applied in reactions under a limited scope of conditions, with many reports representing simple reactivity screens. It is not clear at this juncture how many of the ligands described in this section remain ligated to palladium in the active catalytic form and how many simply are lost in the initial stages of the reaction.

3.1.3 Soluble Catalysts in Non-Traditional Media

In addition to being used in traditional organic and aqueous solvents, some of the ligands described above and some new ligands have been used in a variety of non-traditional solvents. Sinou carried out Heck reactions of aryl iodides with methyl acrylate in perfluorinated solvents using fluorine-tagged triarylphosphines (see, for example, **20** in Figure 2) in conjunction with $Pd_2(dba)_3$.[158] The catalyst system was not completely stable and lost activity upon recycle. Gladysz studied the use of fluorous dialkyl sulfides as ligands for Pd in fluorous-phase Suzuki couplings of aryl bromides.[159] The precatalysts were effective and the palladium-containing phase was reused multiple times. In primary uses, palladium black formation was not observed, although when runs were allowed to linger under heating after complete conversion, palladium deposition was often noted. Average TOFs also diminished upon recycle. The authors hypothesized that the metallic, ligand-free palladium being formed under reaction conditions may be the actual catalytic species.

Bannwarth studied Pd(II) phosphine complexes based on fluoroalkyl-tagged triarylphosphines in the Su-



20 **a** R = $OCH_2C_7F_{15}$ (%F = 58.7)
b R = C_6F_{13} (%F = 60.9)
c R = $O(CH_2)_2OCH_2CF_2[OCF(CF_3)CF_2]_p(OCF_2)_qOCF_3$
$\bar{p} = 3.38$; $\bar{q} = 0.11$ (%F = 56.1)

Figure 2. Fluorine-tagged triarylphosphine ligands.

zuki coupling of bromoarenes with arylboronic acids.[160] Using a fluorous biphasic reaction system, the authors demonstrated recycle up to six times without a decrease in yield. Later, they studied a similar system in conjunction with fluorous silica as a catalyst sequestration phase.[161] They reported effective recycle of the catalyst without a significant loss in "activity" based on steady yields in multiple reaction cycles and a Pd content in the product phase of 5.4 ppm. The authors interpreted this as only a limited washing off of palladium from the fluorous support. Upon re-examining this system in more detail,[162] the authors found that the perfluoro-tagged complex and fluorous silica behaved very similarly to a traditional, fluorine-free catalyst and bare silica. Additionally, they showed through a three-phase test (this special test reaction is described in detail further below) that significant palladium leaching had occurred, as a solid-bound aryl iodide was converted to a large extent. Thus, like traditional heterogeneous catalysts such as Pd/C, this catalyst operated by a palladium release and recapture mechanism (*vide infra*). Bannwarth also used fluorous tagged phosphines coupled with fluorous hyperbranched polymers to manipulate Pd-phosphine complexes in Suzuki reactions.[163] The fluorous complexes could be precipitated, recovered and reused multiple times. However, upon reuse, activities were noticeably decreased. The authors found that the presence of the hyperbranched support was important, as catalyst performance without this additive was diminished.

Palladium complexes have also been used in conjunction with supercritical carbon dioxide ($scCO_2$) as a solvent. For instance, Tumas and co-workers[164] and Holmes and Carroll[165] independently reported the application of fluorinated phosphines coupled with a palladium source in Heck and Suzuki couplings in $scCO_2$. Arai and co-workers reported the use of water-soluble palladium complexes bearing sulfonated phosphines in supercritical carbon dioxide with an added polar cosolvent for Heck reactions.[166] An overview of their use of non-traditional solvents in Heck coupling reactions was recently published.[167] Heterogeneous catalysts have also been used in supercritical media.[168]

3.2 "Naked" Homogeneous Precatalysts

Most of the original studies of the Heck reaction involved "ligandless" palladium (free of η^2 donor ligands like phosphines), including the original studies by Heck[1] and Mizoroki.[2] Jeffery later showed that catalysts derived from ligand-free precursors could be stabilized by quaternary ammonium compounds, with researchers now commonly referring to couplings conducted in the presence of TBAB as being "under Jeffery conditions."[151] Recently, catalyst systems based on these simple Pd sources [$Pd(OAc)_2$, $PdCl_2$, etc.] have attracted increased attention due to their low cost. In particular, they can be used at such low loadings that Beletskaya recently coined the term "homeopathic palladium," to describe these systems.[169] Ligand-free Pd catalysts such as $Pd(OAc)_2$ are among the most well-studied systems for coupling reactions, and they are effective under a variety of conditions including in water,[170] ionic liquids,[171,172] and other solvents as well as in conjunction with both conventional[173,174] and microwave heating.[175–177]

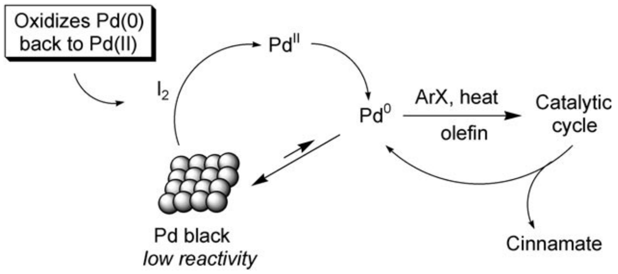
A wide variety of reactants has been employed in ligand-free Heck and Suzuki couplings. Rossi and coworkers present a good overview of the variety of ligandless Suzuki couplings that has been carried out in recent years in their review.[16] These range from Novák's report of ligandless Suzuki couplings of aryl iodides and bromides under mild conditions in 1994,[178] to Bumagin and Bykov's illustration that simple, ligand-free systems could activate aryl chlorides using sodium tetraphenylborate as a phenyl source,[179] to Bedford's report in 2003 that $Pd(OAc)_2$ in conjunction with TBAB converted deactivated aryl chlorides.[173]

In 1999, Herrmann and co-workers utilized catalytic amounts of palladium salts and palladacycles in nonaqueous ionic liquids (e.g., TBAB, imidazolium salts) for activation of chloroarenes in Heck chemistry.[180,181] Using such systems, they showed that even simple salts such as $PdCl_2$ could effectively activate deactivated aryl bromides. The ionic liquid containing the palladium catalysts could be effectively recycled, in some cases up to 12 times. Because the products were recovered by distillation, the authors established that the ionic liquid system represented the first recycling procedure for catalytic Pd where no leaching of Pd into the products was possible. The nature of the true catalyst was not directly confirmed, although palladium colloids were considered, as palladium metal is clearly formed under the reaction conditions.

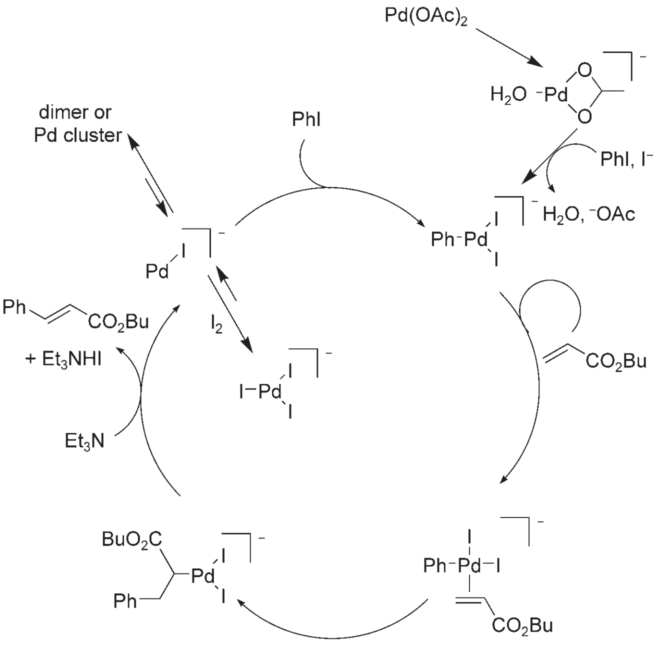
In an interesting study of the nature of the actual catalyst when "naked" Pd precatalysts [e.g., $Pd(OAc)_2$] were used, Reetz and Westermann showed conclusively that Pd nanoparticles were either the true catalytic species or important intermediates in Heck couplings with aryl iodides or bromides.[182] In the Heck reaction of bromobenzene and styrene using NMP as solvent, they observed that the reaction went nearly to completion, but that an induction period was observed. Only after the induction period did they detect Pd nanoparticles *via* TEM analysis. When preformed Pd colloids were used, their data indicated that the induction period was much shorter, signaling that the pronounced induction period seen by many investigators may largely be due to the formation of colloids. The colloids can be further stabilized using Jeffery conditions, with quaternary ammonium ions giving added stability. The authors were able to definitively show that the nanoparticles can participate in the reaction, as they showed that they can be easily oxidized by addition of stoichiometric aryl iodide to give either PdIAr or $[PdArX_3]^{2-}$. Addition of styrene and base then gave rapid conversion to the coupling product. The analogous experiment with chlorobenzene did not work, as chlorobenzene could not convert the Pd(0) nanoparticles. Ultimately, the authors called the Pd nanoparticles the true catalytic species, although they could not rule out dissolution of the nanoparticles to molecular active species, such as the Pd(II) complexes described above.

In 2002, de Vries and co-workers at DSM studied the use of homeopathic $Pd(OAc)_2$ in Heck couplings and developed a simple and effective method for recycle of the palladium.[183] After reaction, the residual palladium (mostly palladium black) was removed from the organic products *via* filtration over celite or silica and the Pd(0) was subsequently reoxidized to Pd(II) using iodine (Scheme 5). During mechanistic studies aimed at elucidating the intermediate palladium species during the Heck coupling reaction of iodobenzene and *n*-butyl acrylate, they uncovered strong evidence *via* negative ion electron spray mass spectroscopy in support of anionic Pd(II) species as intermediates in the catalytic cycle (Scheme 6).

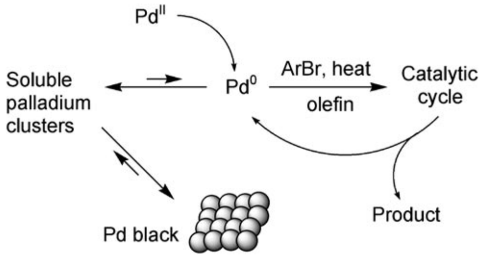
In 2003, the same group from DSM provided strong evidence that the active species derived from homeopathic palladium $[Pd(OAc)_2]$ and from the well-known palladacycle **21** (Figure 3) were most probably of the same type, as both precatalysts gave similar kinetic profiles.[184] The homeopathic catalysts were able to catalyze the conversion of a wide variety of aryl bromide substrates with low catalyst loadings. Their observation that the turnover frequency increased as the catalyst loading decreased (also seen by Beletskaya and Cheprakov[148]) is critically important and is most consistent with a monomeric or dimeric, molecular Pd catalyst that may be in equilibrium with nanoparticulate species. Indeed, they proposed a catalytic cycle that involved monomeric Pd species in equilibrium with soluble Pd clusters (Scheme 7). Similar results were also reported by Schmidt[185] at about the same time as de Vries' first suggestion of this phenomenon.[183] It should also be pointed out that more recently Schmidt has offered an alternate explanation for the observation of increased TOFs at low Pd loadings.[186] Yao also reported the use of ligand-free palladium for Heck couplings, invoking palladacycle-like molecular Pd species in a catalytic cycle that involved Pd(IV) species.[187]



Scheme 5. Palladium recycle strategy utilizing I_2 to redissolve Pd black in ligand-free Heck couplings.

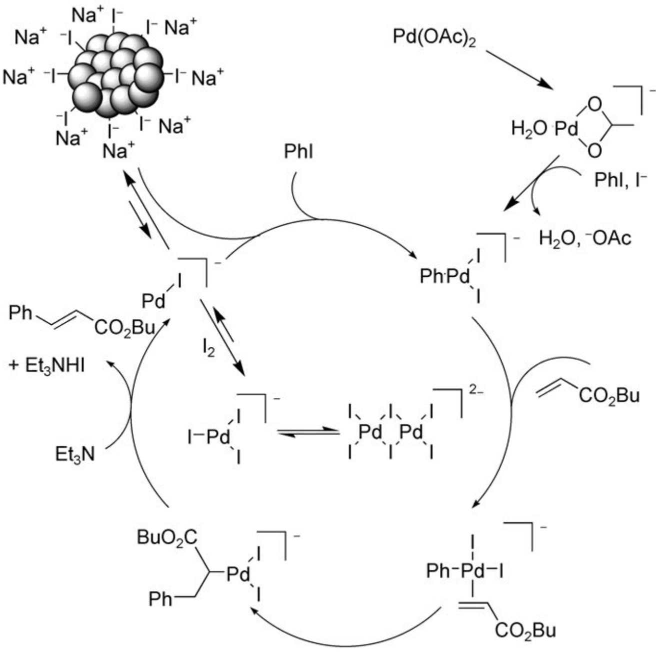


Scheme 6. A catalytic Heck cycle illustrating the presence of anionic palladium intermediates akin to those proposed by Amatore/Jutand.



Scheme 7. The catalytic cycle that involved active molecular Pd species in equilibrium with soluble Pd clusters as proposed by de Vries in 2003.

More recently, de Vries has summarized the results of many studies to propose a general catalytic cycle for the



Scheme 8. The general catalytic cycle for the homeopathic Heck reaction as proposed by de Vries in 2006.

homeopathic Heck coupling reaction (Scheme 8).[188] This mechanistic picture is essentially similar to that of Schemes 6 and 7, with the exception that it is made clear that the colloids and reaction intermediates both have anionic characters resulting from the halide anions that are ligated to them. These charges are in turn stabilized by cations in the system, with some cations such as the tetrabutylammonium cation (or acid salts of common bases like triethylamine) being very soluble and therefore supporting substantial quantities of stabilized palladium in solution. This hypothesis explains the commonly observed long-term stability under Jeffery conditions. The halide-ligation of the nanoparticles and the monomeric or dimeric palladium species are thought to play a key role in stabilizing the palladium species and preventing formation of palladium black.

The DSM group utilized ligand-free Pd as a precatalyst in Suzuki, Kumada and Negishi couplings as well.[189] For the Suzuki reaction of aryl chlorides with phenylboronic acid, it was demonstrated that the homeopathic approach could also be effectively used so long as small amounts of water were present in the system. No discussion of the nature of the active species was included, although it might be assumed that the authors attribute the chemistry to the same active molecular Pd species as they advocated for the Heck reaction.

Zhang et al. utilized $Pd(OAc)_2$ in a mixture of poly(ethylene glycol) (PEG) and water as a solvent for the efficient Suzuki coupling of aryl iodides or bromides with various areneboronic acids.[190] The PEG-stabilized palladium could be recycled multiple times with consistent yields in three cycles. $Pd(OAc)_2$ has also been used by Li et al. in conjunction with DABCO as a stabilizer in Suzuki coupling reactions.[191] Very low palladium loadings were possible and in some cases it was claimed that the polymer-stabilized palladium could be reused in several recycles based on consistent reaction yields. In both the work of Li and Zhang, the nature of the true catalytic species was not identified. Recycle of ligand-free catalysts was also explored in Heck reactions using low molecular weight PEG as a polar catalyst sequestration phase.[192] The PEG phase was reused five times with slight decreases in yield. Unfortunately, only 90% of the palladium was retained.

Hagiwara and co-workers immobilized $Pd(OAc)_2$ in ionic liquids, which were in turn immobilized on a porous silica support.[172] The catalysts were studied in the Heck coupling of aryl halides and cyclohexyl acrylate. The catalyst could be effectively used multiple times and only traces of Pd leached into the organic phase from the ionic liquid (0.24 ppm). The authors did not evaluate the leached species as possible catalytic agents. Zou and co-workers also used ionic liquids as media for ligandless palladium ($PdCl_2$) in conjunction with toluene or water to make a biphasic system in Suzuki and Heck couplings.[171] They saw formation of Pd black in their system and attributed the reaction to catalysis by solid Pd nanoparticles in the ionic liquid phase. In contrast, Welton et al. carried out Heck couplings in imidazolium ionic liquids and surmised that *in-situ* formed Pd-carbene complexes were the active species.[193] Subsequently, Shreeve et al. showed good recyclability using catalysts based on $PdCl_2$ in imidazolium ionic liquids,[194] recycling the ionic liquid phase 14 times and still maintaining some finite activity.[195] Dyson and co-workers stabilized palladium species in nitrile-functionalized ionic liquids and utilized them in Suzuki and Stille couplings.[196] In the ionic liquid (IL) containing nitriles, the ionic liquid phase could be effectively reused 9 times giving similar yields, whereas in the absence of the additive all activity was lost after five cycles. Palladium losses from the ionic liquid phase ranged from <5 ppm to ~30 ppm. Although the nature of the active species was not identified in Suzuki couplings, the authors hypothesized that palladium nanoparticles were active in Stille couplings. TEM and visual observation supported their existence, although it is not clear how the authors concluded that they were the active species. Hardacre and co-workers evaluated a variety of ligand-free catalysts including $Pd(OAc)_2$, $PdCl_2$ and Pd/C in both ionic liquid media and NMP.[197] The authors noted a better catalytic performance in the ionic liquid media and decreased palladium black formation using palladium salts as precatalysts. Significant palladium leaching was noted using the heterogeneous catalyst, making its utility limited in regard to catalyst recovery. The authors indicated that leached palladium from the solid catalyst or the ligand-free salts form nanoparticles in the ionic liquid media and they attributed the catalytic activity observed to these nanoparticles. The authors stated that the data were consistent with the reagents causing palladium dissolution and leaching and that the leaching was not inherent to the use of the ionic liquids. Other studies of ionic liquid stabilized catalysts did not identify an active species in Suzuki couplings.[198] It is noteworthy that many of these systems may not involve ligandless palladium, as the ionic liquid can sometimes act as a ligand.[193] Solid-supported Pd(II) precatalysts have also been used with ionic liquid solvents.[199]

In an alternate approach to recycle ligand-free catalysts, Livingston and co-workers utilized continuous reactors with nanofiltration membranes for sustained production of coupling products *via* the Heck reaction.[200,201] Reaction rates were modest but both the $Pd(OAc)_2$ and Pd(II)-N-heterocyclic carbene (NHC) precatalyst systems could be effectively used for many hours. Decent sequestration of palladium was achieved, with up to 96% of the palladium retained within the reactor system in the cases studied.

The collected data on ligand-free, homeopathic palladium studies are consistent with the view that catalysis is achieved by molecular (or dimeric), Pd(0) species that are in equilibrium with Pd(0) nanoparticles. Recently, de Vries nicely summarized the collected data on these systems in a paper that describes a unified catalytic cycle for homeopathic Pd-catalyzed Heck couplings at high temperatures.[188] The collected data including (i) increased TOFs with decreased palladium loading,[184] (ii) mass spectrometry[183] and EXAFS[202] results showing the presence of anionic palladium intermediates (Amatore cycle), (iii) observations that the nanoparticles represent a reservoir of Pd(0) that can be released *via* oxidative addition of the aryl halide to generate soluble, free Pd(II) species in solution,[184,203,204] all support this unified mechanism. The occurrence of some complete catalytic turnovers on the nanoparticle surface cannot be ruled out at this point, although no definitive evidence exists to support the hypothesis that it occurs.

3.3 Palladacycle-Based Homogeneous Precatalysts

3.3.1 PC, NC, and SC Palladacycles

Palladacycles were introduced as new Heck and Suzuki coupling precatalysts by Herrmann and Beller in 1995.[205,206] In those first publications, a hypothesis was put forth that these catalysts may operate *via* a Pd(II)–Pd(IV) catalytic cycle.[205–207] The precatalysts were a major departure from precatalysts that were previously known, as phosphine stability was not an issue, limited or no palladium black deposited after use in coupling reactions, and the catalysts could activate aryl chlorides that reacted only sluggishly with other palladium sources. Beller studied the PC palladacycle **21** (Figure 3) in Heck coupling reactions of olefins with various aryl bromides.[208,209] A detailed account of the development of these palladacycle precatalysts has been published.[22] Kinetic studies led the authors to conclude that the Pd(II) precatalyst was reduced under the reaction conditions to give a monophosphine-Pd(0) species as the true catalyst. Nonetheless, as noted above, a hypothesis was put forth that these catalysts may operate *via* a Pd(II)–Pd(IV) catalytic cycle,[207] and the concept of a new catalytic cycle propagated through the literature rapidly (although from the early publications, it should be noted that this new idea was put forward with caution). In 1998, the idea gained a more solid footing with the publication by Shaw that described the hypothesized cycle in some detail.[18] In 2000, a publication describing the isolation of a Pd(IV) species from a coupling reaction that utilized a chiral aminophosphine ligand with a palladium source as a precatalyst (where it was inferred that a palladacycle formed *in situ*) seemed to put the idea of a Pd(II)–Pd(IV) cycle on solid ground.[210] However, in 2002, this publication was withdrawn. Indeed, it has now been established that these precatalysts are effective due to their ability to release active palladium species (that might be ligated by a single monodentate phosphine or a “naked” species, *vide infra*) that resist ligand degradation due to aryl-aryl scrambling.[22,25] Herrmann evaluated the use of palladacycle **21** in the Heck reaction of bromo- and chloroarenes in ionic liquid solvents (e.g., molten TBAB), showing that use of such a solvent system could facilitate catalyst recycle.[181] Although the palladacycle gave good conversions of substrate and did not form visible palladium black, the authors found that use of $Pd(OAc)_2$ gave lower TONs and noticeable palladium black formation. Palladium catalysts in the ionic liquid could be reused multiple times by distillation of the volatile products, with only slightly decreasing yields in each run. Palladium black had visibly formed by the fourth run, although the system could still be recycled.

In 1999, Herrmann reviewed the use of palladacycles in coupling reactions, pointing out that most evidence pointed towards decomposition of these catalyst precursors to form Pd(0) species in coupling reactions such as Stille, Grignard, Negishi, and perhaps Suzuki couplings.[211] In particular, early work by Hartwig highlights the reduction of these Pd(II) precatalysts to form Pd(0).[212] At that time, speculation about a possible Pd(II)-Pd(IV) pathway in coupling reactions with such complexes was still widespread and the fact that no observed decomposition of the palladacycle during reaction was obvious supported this possibility indirectly. Nonetheless, the authors at this time indicated that unknown reduction pathways to small amounts of Pd(0) could not be ruled out. The summary of the evidence available at that point caused the authors to conclude that coupling chemistries using palladacycle **21** proceeded *via* a Pd(0)–Pd(II) route, although the possibility of a small amount of chemistry occurring by a Pd(II)–

Pd(IV) pathway could not be excluded. Later, the same group revisited the issue of a classical Pd(0)–Pd(II) cycle *vs.* the hypothetical Pd(II)–Pd(IV) cycle using phosphapalladacycle **21** in Heck chemistry. They studied three different precatalysts, palladacycle **21** and two palladium-phosphine complexes. They found that the behavior of the palladacycle **21** was different enough from the complexes that did not contain a Pd–C bond to speculate that the precatalysts had different active species, although all catalysts were believed to involve a Pd(0)–Pd(II) cycle. Ultimately, a unique, dimeric Pd(0) anionic species that still contained an intact Pd–C bond was hypothesized to be involved in Heck couplings using palladacycle **21** as a precatalyst. In kinetic studies of palladacycle **21** and the related NC palladacycle **22**, Blackmond and co-workers found that both these precatalysts likely operated by the same mechanism.[213] In this study, the authors proposed that the dimeric palladacycle was reduced to a Pd(0) species that was the active catalyst. This active species was suggested to be in equilibrium with a halide-bridged dimer, which was the major species present under the reaction conditions. The authors argued that the stability of these systems was due to the influx of active monomeric species from a reservoir of dimer, although it is unclear if they were referring to the activated dimer (without a Pd–C bond) or the precatalyst dimer (with Pd–C bonds). Interestingly, the equilibrium between dimer and monomer with the palladacycle **21** in NMP solution has been confirmed by EXAFS.[214] The presence of most of the palladium in the form of a halide-bridged species is consistent with the EXAFS studies of homeopathic Pd(OAc)$_2$ as a catalyst as well, where the majority species in solution was likely $[Pd_2I_6]^{2-}$.[202] Later, de Vries and co-workers showed that homeopathic Pd(OAc)$_2$ and palladacycle **21** kinetically behave identically, indicating that the same catalytic species may be produced from both systems.[184]

Milstein reported imino-NC palladacycle complexes such as **23** as precatalysts for Heck coupling reactions of aryl iodides and bromobenzene with various olefins.[215] They reported that the complexes could be recovered after reaction unchanged, and that additional aliquots of reagents could be readily converted at the end of the first reaction. NC palladacycles were also used in Suzuki couplings, with the authors indicating that the complex could be recovered after reaction and that the reaction likely occurred *via* a Pd(II)–Pd(IV) cycle.[216] Similarly, Dupont et al. studied SC palladacycles in Heck and Suzuki couplings and mused about Pd(II)–Pd(IV) catalytic cycles.[217,218]

In 2000, Nowotny et al. studied poly(styrene)-bound imine-based NC palladacycle complexes (**24**) in the Heck reaction of iodobenzene and styrene.[219] They showed that all catalysts displayed an induction period and it was demonstrated that a large amount of soluble, active palladium species was produced. Nanoparticles were proposed to be the catalytically active species.[219,220] In 2001, Beletskaya and co-workers published similar findings with a variety of SC, PC and NC palladacycles, suggesting that the accumulated evidence strongly supported a Pd(0)–Pd(II) catalytic cycle.[221] As such, they cite complexes of this type as highly effective Heck precatalysts due to their ability to slowly release[222] active catalytic species. Additives that bind to the palladacycle and might inhibit the reduction of Pd by other reagents (such as triphenylphosphine or 2,2′-dipyridyl), were shown to decrease the reaction rates. Interestingly, they hypothesized that all palladacycles were precatalysts that decompose to form Pd(0) active species, except possibly the "truly robust" PCP pincer palladacycles that they reported later as Heck catalysts.[223]

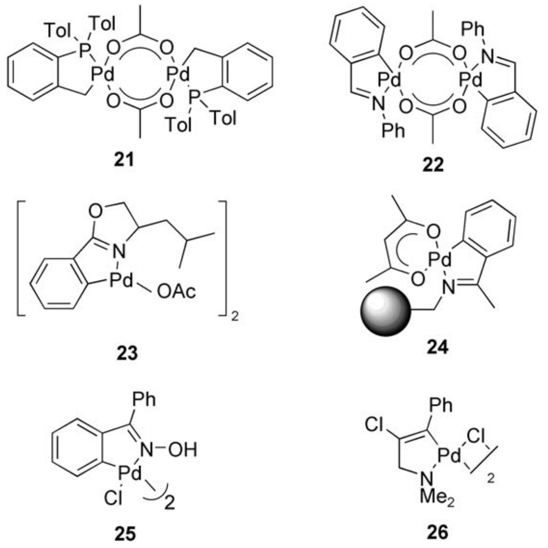


Figure 3. Palladacycle complexes **21**–**26**.

Bedford et al. have studied a variety of NC, SC and PC palladacycle precatalysts, primarily in Suzuki couplings, for a number of years. Early on, they indicated that coupling reactions using these palladacycles likely occurred *via* loss of ligand and operation of a Pd(0)–Pd(II) cycle, as palladium black[224] sometimes formed in reactions and silica-supported complexes were not recyclable[225] (*vide infra*). With aryl chloride substrates, additives such as ammonium or phosphonium salts were needed to effect Heck and Suzuki couplings using many palladacycle precatalysts. Bedford argued that the main role of the additive was to stabilize "catalytically active" colloidal species that were derived from most palladacycles.[10,173] This was partly because TEM studies of reaction media sometimes showed the presence of nanoparticles.[10,134] However, it is possible that the nanoparticles, while important, were not the true catalytic species, as they may simply serve as a reservoir for soluble "naked" molecular Pd(0) species that were truly active[204] (*vide supra*). In extensive studies of aryl chloride activation in the Suzuki reaction, the authors hypothesized that the excellent reactivity associated with complexes such as PC phosphinite palladacycles was associated with the significant long-term stability of reduced, Pd(0) species.[226] Assuming that oxidative addition was the slow step, they theorized that Pd(0) species were the likely resting state in the cycle, and ligands that stabilize these species led to long catalyst lifetimes. Interestingly, in Heck couplings of iodoarenes, the primary species in solution were found to be Pd(II)-iodo complexes,[202] indicating that in this chemistry the relative rates of oxidative addition and olefin insertion were quite different. Bedford et al. also showed that phosphinite palladacycles exhibited better activity than structurally similar phosphite and phosphine complexes, and when combined with small amounts of tricyclohexylphosphine, could effectively activate aryl chlorides.[227] Again, improved reactivity was attributed to catalyst longevity. Activation of the Pd(II) complex by reduction with phenylboronic acid was thought to result in a free 2-arylated ligand. The authors showed that use of ligands of this type have markedly higher activity compared to their parent ligands.[227] Similar PC palladacycle phosphite catalysts also can be stabilized by added phosphine, although too much deactivated the system by over-coordination (poisoning).[228,229] NC[230–232] and SC[233] palladacycles were stabilized in the same way. The catalysts of this type could also be effectively used under microwave conditions.[234]

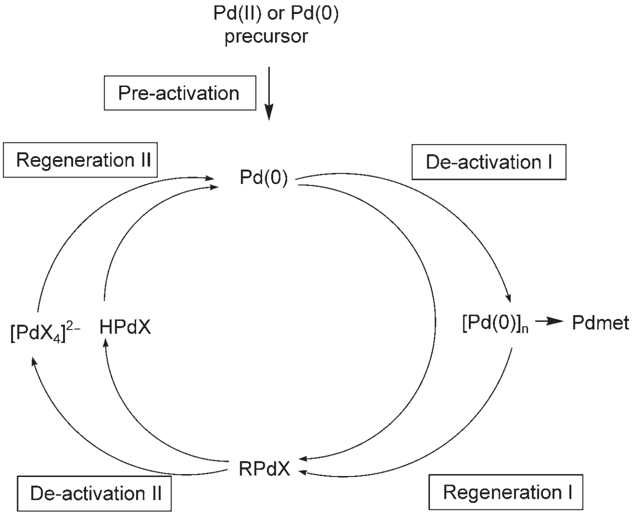
Indolese, Studer and co-workers showed that a variety of different, bulky secondary phosphines could effectively facilitate Heck and Suzuki reactions when coupled with NC palladacycles.[63] Bulky NHC ligands could also be combined with palladacycles to facilitate formation of active catalysts. Nolan and co-workers added an NHC ligand to an NC palladacycle and showed that the resulting catalyst was more effective in room temperature Suzuki couplings of aryl chlorides than the corresponding NC palladacycle catalysts with added phosphine.[235] The organic fragment liberated upon activation of the palladacycle, an aromatic secondary amine arising from reductive elimination of the palladacycle ligand from a presumed Pd(II) hydride, was isolated and purified.

Chiral non-racemic SC palladacycles were prepared and evaluated in Heck couplings by Dupont, with a focus placed on potential asymmetric induction with these catalysts. Unfortunately, racemic products were obtained, giving further evidence to the notion that these complexes were simply precursors for Pd(0) species, moieties that in this case were not chiral.[236]

Nájera[237] reported thermally stable NC oxime carbapalladacycles (e.g., **25**) as precatalysts for various coupling reactions including Heck,[237,238] Suzuki,[237,239–241] Stille[237] and Sonogashira[237,242] reactions. As in the case of the other bidentate palladacycles, there was significant evidence that the metal complex was simply a precursor for free Pd(0). For example, in the Heck couplings, the authors reported that the metal complex exhibited an induction period in its first use, attributable to reduction to Pd(0), and then in subsequent uses there was not an induction period. The authors hypothesized that Pd(0) nanoparticles could be the active catalysts, although they could not rule out catalysis by soluble molecular species. They reported that the systems could be reused four times with equal activity, although it should be noted that progressively longer times were needed to achieve comparable yields, indicating that activities dropped upon recycle. In some cases Pd black was observed, although XPS experiments only showed the presence of Pd(II) in the system. In Suzuki couplings, again recycle with a constant yield in each cycle (not rate of conversion) was reported, and it was noted that some homocoupling product derived from the aryl iodides was found.[241] This may be attributable to heterogeneous palladium that formed in the reaction, as Djakovitch[243] suggested that soluble Pd(0) species catalyze Heck couplings whereas heterogeneous Pd(0) particles catalyze homocoupling *via* a radical reaction. Interestingly, Nájera et al. only observed homocoupling in the absence of hydroquinone, an effective radical trap. Similar homocoupling was observed by Luo,[244] who studied other palladacycle systems and offered a mechanism based on homogeneous Pd complexes. Immobilized oxime palladacycle complexes are discussed further below.

Following their study of fluorous-tagged Pd(II) thioether complexes,[159] Gladysz and co-workers evaluated similarly-tagged NC palladacycles under fluorous and non-fluorous Heck reaction conditions.[245] In recycling studies under two-phase conditions, decreases in average TOF were observed in each cycle and colloidal palladium was found to be formed. Kinetic studies showed that repeated use of the catalyst system resulted in depressed initial rates. All catalysts showed an induction period, *including during recycle*, indicating that the palladacycle was a precursor for non-recyclable catalysts. The authors assert that the new nanoparticles were generated in each cycle and that they were likely the true catalysts.[245,246] Similar conclusions were drawn for Suzuki couplings.[246]

Dupont studied NC palladacycles based on chloropalladated propargylamine[247] (e.g., **26**). Noting previous studies[182] that cited the decomposition of palladacycles to liberate catalytic Pd(0) species and a positive Hg(0) test (which was assigned as probable evidence for catalysis by Pd nanoparticles), the authors speculated that the active components were palladium nanoparticles, although the presence of these could not be characterized in this system by TEM or other means. Interestingly, this catalyst system proved to be effective for Heck coupling even at room temperature. In a later, very detailed study, DuPont and co-workers provided a thorough description of the activation of NC palladacycles yielding first colloidal Pd(0) that was transformed into active molecular palladium species that use a catalytic Pd(0)–



Scheme 9. *In situ* transformation of palladium proposed to occur during Heck coupling based on DuPont's detailed studies of NC palladacycle precatalysts.

Pd(II) cycle.[248] Building off from previously published studies of pincer[249–252] or half-pincer palladacycles,[208,219,221,225,245,246] that utilized a combination of kinetic, poisoning and/or leaching studies to elucidate the nature of the true catalytic species, DuPont goes perhaps the furthest in establishing a detailed view of the molecular events that lead to active palladium species when exposed to Heck reaction conditions. Spectroscopic and kinetic studies under conditions with excess iodoarene or olefin indicated that different dominant solution species were formed in each case, giving soluble Pd(II) species when excess iodoarene was used and Pd(0) species that can aggregate when excess olefin was present (Scheme 9).[248] Their work also brings to light the difficulties that can be associated with kinetic studies of precatalysts, as initial rate measurements can be highly distorted due to different decomposition paths of the various intermediates under different reaction conditions.

Richards et al. described a ferrocene-containing PC palladacycle precatalyst that was effective for Suzuki coupling reactions of aryl chlorides.[253] Moyano later studied NC ferrocenyl-based palladacycles in Heck couplings of iodo- and bromoarenes with various olefins.[254] In this work, the authors were able to verify the release of palladium from the original complex to liberate ligand-free palladium species, as postulated in previous works discussed above. They showed that the free ligand was recovered as a Heck coupling product of the ligand plus the olefin that was added to the reaction.

A variety of additional reports of palladacycle precatalysts for coupling reactions has recently appeared. Liu studied structurally different NC palladacycles in Suzuki couplings.[255] Palladium nanoparticles were found to form in solutions containing the NC palladacycle complex, and it was implied that these species might be the true active catalysts. Other palladacycles reported recently include CNN tridentate palladacycles for Heck reactions,[256] furancarbothioamide SC complexes for Heck and Suzuki reactions,[257] aminophosphine PC palladacycles in hydroarylations[258] and NC complexes in Heck reactions.[259] For information on these, the reader is referred to several excellent reviews on palladacycles including Beletskaya and Cheprakov's review of their use in catalysis[148] and DuPont's initial[220] and recent comprehensive review with Spencer.[260]

Today, the collected data for the NC, SC and PC palladacycle precatalysts are consistent with the hypothesis that these species represent sources of low-ligated, homeopathic palladium. Indeed, kinetic studies comparing palladacycles to homeopathic palladium showed that their behavior was quite similar.[184] It is now widely accepted that these precatalysts operate *via* a traditional Pd(0)–Pd(II) catalytic cycle.

3.3.2 Pincer Palladacycle Precatalysts

In 1997, Milstein and coworkers reported the use of pincer palladacycles, PCP Pd(II) complexes (e.g., **27**) in this case, in Heck coupling reactions of aryl iodides and bromides.[261,262] They reported no noticeable degradation of the catalysts under the reaction conditions and that the system continued to convert the reagents when additional aliquots were added at the end of the reaction. They interpreted these observations as evidence that the catalyst was stable for long periods of time, although an alternate interpretation in light of all the new data presented above is that the system could continuously generate new catalytic species (*vide supra*). Based on reaction tests with Pd–Ph and Pd–H pincers, they hypothesized that the suggested pathways for the decomposition of the complexes to Pd(0) species were unlikely.

Shibasaki described bulky phosphite Pd(II) PCP pincer complexes and their use as highly active catalysts in the Heck coupling reaction.[263] Studying iodoarenes, they noted that the rates of reaction of two similar arenes were different, which they argued was inconsistent with the rate-limiting step being oxidative addition of the halide to Pd(0). They found that several different palladacycle precatalysts gave different reaction rates, which they interpreted as inconsistent with the generation of active Pd(0). Thus, they assigned the activity to a Pd(II)–Pd(IV) catalytic cycle.

DuPont and co-workers reported both SCS (e.g. **28)** and SC palladacycle precatalysts for the Heck coupling of iodoarenes and olefins.[217] It was speculated that these highly active precatalysts may have utilized a Pd(II)-Pd(IV) cycle, as they could be recovered unchanged after catalysis and there were marked differences in activity depending on the nature of the thioether ligand. Similar precatalysts were also studied in the Suzuki couplings of aryl bromides and chlorides with phenylboronic acids, giving high rates at room temperature.[218]

Phosphine-based PCP palladacycles were evaluated by Jensen et al. in the Heck coupling of aryl bromides and iodides.[264] In that work, they proposed that pincer complexes operated by a different mechanism than the half-palladacycles of Hermann and Beller, which had been proposed by that time to operate by a Pd(0)–Pd(II) cycle.[208] Citing previous work by Milstein,[262] a Pd(II)–Pd(IV) catalytic cycle was considered. Indeed, subsequently, Jensen et al. reported the Heck coupling of aryl chlorides using phosphinito PCP–Pd(II) complexes as the precatalyst,[265] and in that work, they proposed a Pd(II)–Pd(IV) catalytic cycle whereby the olefin oxidatively adds to the Pd(II) species in the first step, creating a 6-coordinate Pd(IV) complex. In that same year, Beletskaya and van Koten reported on acetylene-linked PCP pincer complexes, describing them as catalyst *precursors* for Heck couplings, although no further data about the activity or stability of the complexes were provided. Later, although they noted that the Heck reaction is generally catalyzed by Pd(0) complexes, the authors reported on the use of monomeric and dendritic PCP Pd(II) complexes as Heck catalysts.[223] They found intriguing results, where the TON depended on the nature of the pincer (one molecule containing a single Pd complex **29** *vs.* three **30**). Perhaps the steric bulk of the complexes affected that ability to generate free Pd(0) from the systems, influencing the observed TOFs.

PCP pincer complexes based on an sp^3 carbon as the central carbon atom in the PCP ligand were reported by Andersson and evaluated in the Heck coupling of iodo- and bromoarenes.[266] They observed no noticeable formation of elemental palladium and hypothesized that a Pd(II)–Pd(IV) catalytic cycle could be operational, citing the work of Milstein[262] and Jensen,[265] although they could not rule out formation of Pd(0) and catalysis *via* a classic Heck cycle.

As late as 2004, it was suggested that pincer palladacycles offered the best "hope" that a Pd(II)–Pd(IV) catalytic Heck cycle might be operational, as most of the catalysts for which such a cycle was originally proposed had been shown to decompose to Pd(0) at that point.[10,148] However, many researchers still clung to the idea that the stability imparted by the tridentate pincer ligands was so significant that indeed the metal-ligand complex remained intact during the catalytic Heck coupling with these systems, although it should be noted that Beletskaya suggested that, while they appeared stable, they likely just released palladium species more slowly than their related PC, NC and SC palladacycle systems.[148]

Early on with Heck couplings using pincers such as SCS Pd(II) complexes, there were indications that some complex decomposition to liberate Pd(0) may occur.[267] However, *via* clever use of ligand design, it seemed that this decomposition could be eliminated. Bergbreiter et al. uncovered signs that polymer-supported SCS pincers that were seemingly stable under the reaction conditions might liberate soluble Pd(0) species that were active catalysts.[252,268] However, the amount of leached Pd was exceedingly small and catalysis by polymer-bound, intact palladium could not be ruled out.[252] In 2004, Weck and Jones presented the first conclusive evidence that intact SCS pincer species were wholly inactive in Heck couplings of iodobenzene and *n*-butyl acrylate.[250] By designing solid-supported and soluble polymer-supported analogues of known SCS-Pd(II) complexes, they were able to demonstrate that no activity was associated with intact pincer species and that all catalysis was due to leached Pd(0) species operating in a classic Pd(0)–Pd(II) cycle. At about the same time, Eberhard showed that phosphite PCP-Pd(II) pincers also decomposed to form Pd(0) species.[269] Based on poisoning studies, they concluded that the likely active moieties were Pd(0) nanoparticles. However, they were unable to rule out catalysis by intact pincers potentially occurring in parallel with the cataly-

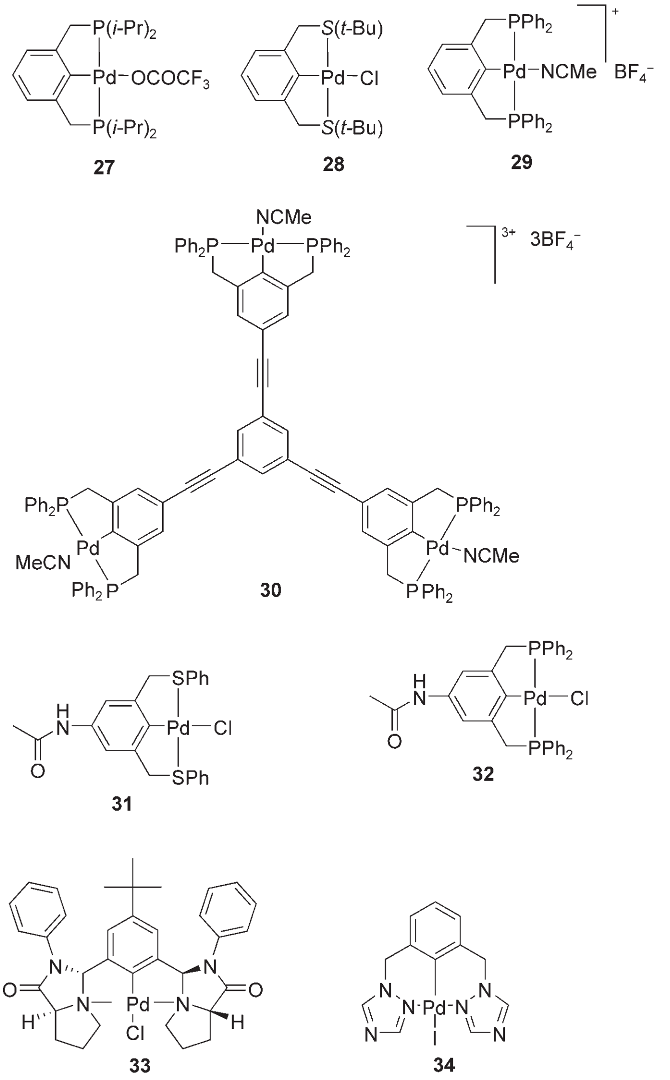


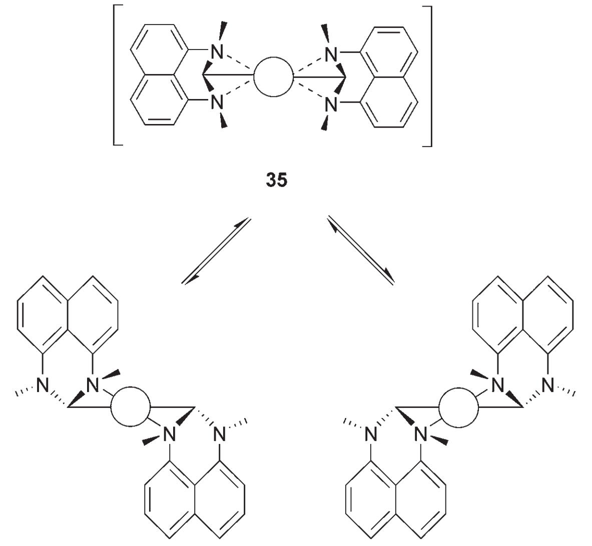
Figure 4. Pincer palladacycle complexes **27**–**34**.

sis by leached Pd(0). After their early studies on the relatively unstable SCS-O Pd(II) complexes, Weck and Jones communicated two additional studies of SCS[249] and PCP[270] Pd(II) pincer complexes (**31** and **32**, respectively) in Heck catalysis and conclusively showed that these also showed no activity in their native form, although they liberate soluble Pd(0) species that were catalysts. Although catalysis by palladium nanoparticles could not be ruled out, they hypothesized that molecular Pd(0) was the active species, based on poisoning tests using poly(4-vinylpyridine) as a poison for soluble palladium species. Subsequently, Wendt and co-workers showed that PCP-Pd(II) complexes also decomposed to form active Pd(0) in Stille couplings.[271] Poisoning studies were used to elucidate the nature of the active species, and it was concluded that Pd(0) nanoparticles were the likely heterogeneous catalysts, although they were not observed by TEM. More discussion of these studies is presented below in the heterogeneous section of this review.

Dupont and colleagues prepared non-symmetric pincer palladacycles based on NCP and NCS ligands and studied them in the Heck reaction of aryl halides and *n*-butyl acrylate.[272] The authors noted that palladacycles with different ligand structures offer different reaction rates, and they indicated that the rates may correlate with the release of catalytically active Pd(0) species, as they noted most palladacycles are reservoirs of active Pd(0) species. In a different twist on non-symmetric pincer ligands, Jensen et al. prepared PCP pincer complexes with different alkyl or aryl components on each phosphorus atom.[273] These precatalysts were used in the Heck coupling of iodobenzene and styrene.

Uozumi reported the synthesis of a bulky NCN Pd(II) pincer (**33**) and utilized it in the Heck coupling of iodobenzene and methyl acrylate.[274] They noted that the reaction profile was similar to that reported by Eberhard,[251] where catalyst decomposition was important. Interestingly, Uozumi's pincer was active at concentrations as low as 10^{-6} mol Pd per mol substrate. In a later study of the use of NCN palladacycles in the Heck coupling of iodobenzene and methyl acrylate,[275] the authors reported good catalytic performance in the presence of water and TBAB. The authors asserted that the catalysis likely followed the established paths described for SCS[249,250,252] and PCP pincers,[251,270] involving a Pd(0)–Pd(II) cycle.

Díez-Barra et al. reported CNC imidazole-carbene palladacycles (e.g., **34** in Figure 4) as precatalysts for the Heck coupling of aryl halides and *n*-butyl acrylate.[276] Aryl iodides, bromides, and chlorides were readily converted. Unfortunately, there was no discussion of the nature of the active site presented. At about the same time, Chung and co-workers reported the use of a fluxional NCN Pd(II) palladacycle as a precatalyst for Heck couplings of aryl bromides and iodides.[277] Also, the authors studied the use of a simpler, previously reported NCN Pd(II) complex in Heck coupling reactions of iodobenzene and observed that it decomposed quite readily to palladium black under the reaction conditions employed. In contrast, the authors' new, fluxional NCN pincer did not visibly decompose and was capable of activating both aryl iodides and bromides. The nature of the true active species and the catalytic mechanism were not explicitly addressed in the work, although the authors argued that the fluxional behavior of the complex (e.g., **35** in Scheme 10) may contribute to its enhanced catalytic activity, whatever mechanism it might follow.



Scheme 10. Proposed fluxional behavior of the NCN palladium complex **35**.

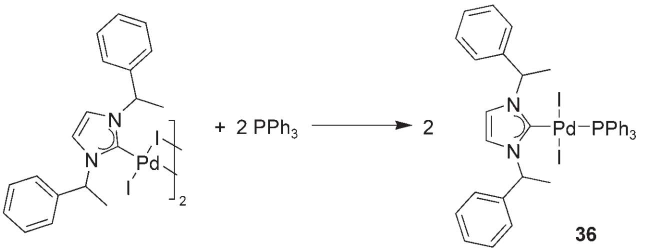
Finally, although not a true pincer complex due to the different length arms on each side,[148] Monteiro, DuPont and co-workers developed tridentate PCN palladacycles as precatalysts in Suzuki reactions of aryl chlorides at high temperatures.[278]

Derivatives of Pd(II) pincers that are claimed to be true, active catalysts in coupling reactions continue to be reported. For example, Yao et al. reported SeCSe ligated pincers in the Heck coupling of bromobenzene and *n*-butyl acrylate.[279] A ditopic double pincer palladacycle that was active even in the presence of Hg(0) was reported by Bowman-James in the Heck coupling of 4-iodotoluene and styrene.[280]

Thus, in the years since the first application of tridentate pincer palladacycles in Heck and Suzuki reactions, the nature of the true catalytic species has been debated vigorously. Now, when looking at the non-NHC palladacycle and pincer palladacycle work reported to date as a whole, it is clear that the overwhelming evidence supports catalysis by a traditional Pd(0)–Pd(II) cycle mediated by palladium species expelled from the original Pd–C-containing ligand. A few complexes, such as the CNC-based pincer of Díez-Barra[276] still have not been conclusively shown to decompose to expel active, ligand-free palladium species, and hence there remain some open questions in this area. However, for the PCP-, SCS-, and NCN-based palladacycles discussed above, all the data are consistent with catalysis by potentially homeopathic palladium.[188]

3.4 N-Heterocyclic Carbene Containing Precatalysts

Herrmann et al. reported the use chelating N-heterocyclic carbene (NHC) complexes of Pd(II) salts (**37**) as effective precatalysts in Heck and Suzuki couplings, demonstrating that they can activate chloro- and bromoarenes.[281] Monodentate NHCs (e.g., **36** in Scheme 11) were also used in conjunction with phosphine ligands, and it was shown that use of NHCs suppressed the formation of palladium black relative to the bis-triarylphosphine complex.[282] For long reaction times, palladium black often still formed, indicating some breakdown of the Pd–C bonds under the reaction conditions.[283] Whereas Herrmann's related phosphapalladacycles were hypothesized to operate by a Pd(II)–Pd(IV) mechanism for a short while, the NHC complexes were always associated with a standard Pd(0)–Pd(II) cycle,[284] with the observed induction periods assigned to reduction of the Pd(II) precursor complexes to Pd(0).[211] For most NHC complexes, reduction does not require rupture of the Pd–C bond, as the NHC ligand is a two-electron sigma donor like a phosphine. As such, the NHC ligand appeared to be an excellent handle for catalyst immobilization onto solid supports. Herrmann et al. investigated NHC Pd(II) complexes immobilized on Wang resins and showed that they were reusable palladium sources for Heck couplings (*vide infra* – **83** in Scheme 24).[285] Unfortunately, palladium leaching was observed in most cases, indicating that although Pd–C bond rupture appeared not to be a requirement for catalytic activity, the bond can still break under typical reaction conditions. In addition to use of Pd(II) precatalysts, Herrmann, Beller and others showed that NHC complexes of Pd(0) (**38**, **39**, **40**, Figure 5) could also be prepared and used in coupling reactions.[286,287] Interestingly, Beller showed that *in-situ* produced catalysts behaved better than purified, well-defined Pd(0) complexes of monodentate NHC ligands in various coupling reactions.[288] *In-situ* produced catalysts have also been used for intramolecular Heck reactions.[289]



Scheme 11. Generation of a Pd(II) complex containing one monodentate NHC and one triarylphosphine **36**.

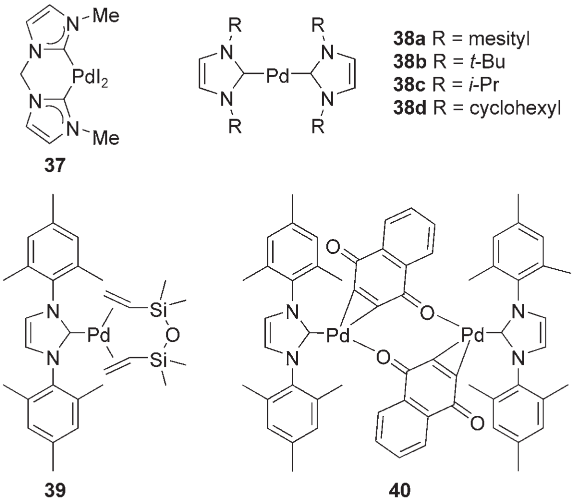


Figure 5. NHC complexes of Pd(II) **37**, and Pd(0) **38–40**.

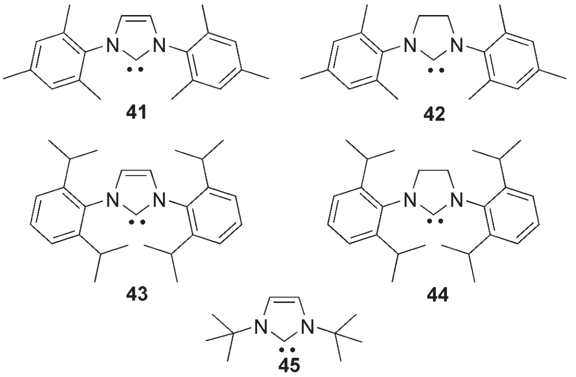
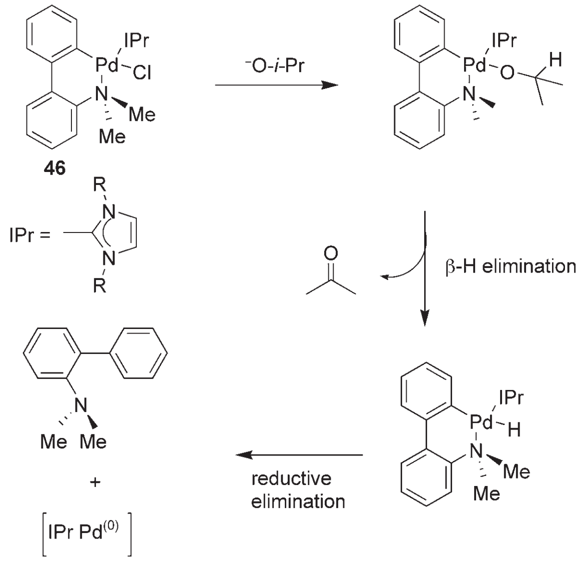


Figure 6. Monodentate NHC ligands **41–45** used in conjunction with palladium in coupling reactions.

Nolan and co-workers have also extensively studied NHC ligated Pd(0) and Pd(II) species in coupling reactions, including Heck and Suzuki couplings.[290,291] Phosphine-free Pd(II) complexes bound by monodentate NHCs (**41–45**, Figure 6) were excellent precatalysts in Suzuki couplings of aryl chlorides.[292–297] Furthermore, bidentate NHC-phosphine complexes prepared *in situ* were effective in Heck couplings of aryl bromides.[298] The steric conditions associated with the NHC ligand seemed to play an important role in the varying catalytic activities seen with different ligands.[291,294] For monodentate NHCs, the authors indicated that mechanistic studies were most consistent with an active species bound by a single NHC,[293] although, in some cases, it was shown that a second NHC can take on an unusual binding mode.[299] When running reactions in isopropyl alcohol as solvent, a mechanism for generation of NHC-Pd(0) species was proposed based on nucleophilic attack of the palladium by deprotonated isopropyl alcohol.[294,300] Nolan et al. also have reported the use of bidentate NC palladacycles (**46**) with an additional NHC ligand in the Suzuki coupling of aryl chlorides and other coupling reactions. They proposed that the palladacycle was lost following nucleophilic attack of isopropoxide anion, generating an active NHC-ligated Pd(0) species[235,297,301] (Scheme 12). Herrmann and co-workers have also studied palladacycle complexes (in this case PC palladacycles) in combination with NHC ligands, showing that they activate aryl chlorides effectively in Heck couplings.[302] Interestingly, the authors reported that, while nitrogen-containing palladacycles gave palladium black after reaction, phosphapalladacycles did not. They suggested that leaching from the phosphapalladacycles was non-existent, although no definitive evidence was presented.

Cavell and co-workers evaluated various Pd complexes containing one or two monodentate NHC ligands (**47–49**, Figure 7) in Heck and Suzuki couplings.[303,304] The authors studied the reduction and decomposition pathways associated with the complexes and established that Pd–NHC–Me complexes were capable of all the steps associated with the standard Heck reaction following a Pd(0)–Pd(II) cycle.[304] Reduction of the Pd(II) complexes *in situ* was rapid when starting with methyl complexes, in contrast to what was observed previously for iodo-Pd–NHC complexes.[305] Initial reaction rates were comparable for complexes substituted with one *vs.* two NHC ligands, although the complex with two of the bulky ligands remained active longer, leading to higher TONs.[304] Studying the mechanism of olefin insertion in the Heck reaction using these complexes, they found that the migratory insertion and elimination steps were quite fast following halide abstraction, in agreement with Albert's theoretical results.[306] In the Suzuki coupling, they found that Pd–NHC dihalide complexes required long reduction times, resulting in induction periods, whereas monohalide complexes were easily reduced. In a follow-up study using non-symmetrical NHC ligands,[307] Cavell showed that complexes derived from these NHC ligands were effective precatalysts in a wide variety of coupling reactions. Although they appeared stable during reaction, the authors pointed out that palladium black formed after the substrate was consumed in Heck couplings if the reaction mixture was kept at high temperatures. Subsequently, a wider variety of monodentate, bidentate and tridentate pincer NCN carbene complexes (**50**) was prepared and evaluated in various coupling reactions.[308] Cavell and other authors have also discussed the importance of the ligand on the palladium precursor species when working with NHC palladium complexes, with Cavell[303,307,308] reporting the ease of activation of Pd–Me complexes, and Fairlamb[309] showing that substituents on DBA influence activity, as examples.



Scheme 12. Proposal for the generation of an active NHC-ligated Pd(0) species, following the nucleophilic attack of isopropoxide anion.

Cavell, Biffis and co-workers recently reported on the use of Pd(II) complexes with *N*-benzyloxazolin-2-ylidene ligands (**51**) as precursors for Heck couplings of bromoarenes.[310] They showed that these complexes appeared more active than the related, well-known NHC complexes and were of similar activity to Calò's bis-benzothiazolin-2-ylidene complexes[311] that were used in molten TBAB. Chugaev-type carbene ligands were also effective ligands for palladium complexes in coupling reactions, with Slaughter demonstrating their use in Suzuki couplings of aryl bromides.[312]

Roland and Jutand carried out a detailed study of Pd(II) and Pd(0) bis-diaminocarbene complexes (**52**)

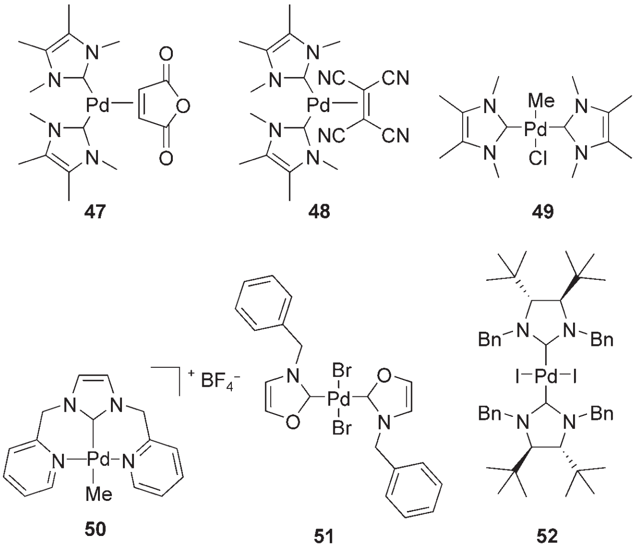


Figure 7. Pd complexes containing one or two monodentate NHC ligands **47–49**, pincer NCN carbene, **50**, *N*-benzyloxazolin-2-ylidene **51**, and bis-diaminocarbene **52**.

in Heck coupling reactions.[313] Pd(II) complexes containing two monodentate carbene ligands proved quite stable in the coupling reaction, with no sign of palladium metal deposition and recovery of 90% or more of the starting complex after reaction at 120 °C. In most cases, the complex could be recovered by recrystallization and reused in subsequent reactions. At lower temperatures such as 80 °C, the system was not as effective, as reduction of the Pd(II) precursor was not as facile. In contrast, the mixed complex containing one carbene ligand and one phosphine ligand could not be recovered after reaction, although still no palladium black deposition was noticed. Although the "quantitative" recovery and reuse of the Pd(II) complex after oxidation and lack of palladium black formation argues for the stability of the complex, it should be noted that only small amounts of decomposition products could account for some or all of the catalytic reactivity.

Multidentate NHC-containing ligands have been reported by several groups, including Herrmann (e.g., **37**).[281] Trudell evaluated several bidentate NHC ligands (**53**–**56**, Figure 8) in the Suzuki coupling of aryl chlorides with arylboronic acids.[314] Later, Peris and Crabtree reported the use of CNC pincer Pd(II) complexes, where each Pd–C bond is to an NHC moiety, in the Heck coupling of chlorides, bromide and iodides.[315,316] The activity was maintained in the presence of Hg(0) and there was no observable induction period, and hence, the authors hypothesized that the active species still contained the CNC ligand, as it could fit the generic formula for an active species as described by the Amatore–Jutand cycle,[17] $[Pd(0)XL_2]^-$. Suzuki and Sonogashira couplings were also reported, again with a Pd(0) catalyst proposed.[317] Further studies of this complex immobilized on a clay support are described below.

Recently, Glorius and co-workers introduced another variation of the carbene ligand, reporting the use of NHCs derived from bisoxazolines (IBiox) (**57**, **58**, Figure 9) in Suzuki couplings of aryl chlorides.[318,319] They pointed out that, in some cases, the steric bulk of the ligand could be modulated without changing the electronics, a rare observation for monodentate ligands.

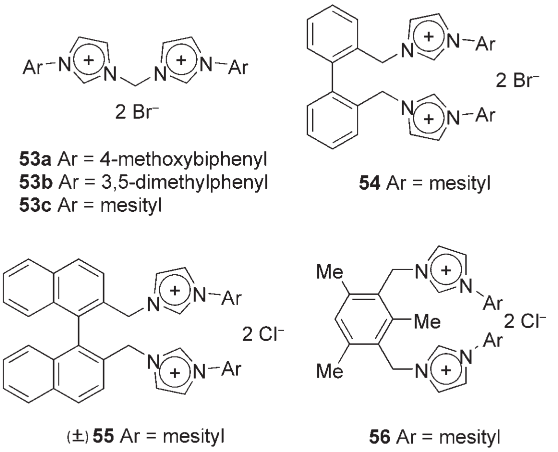


Figure 8. Bidentate NHC ligands evaluated by Trudell.

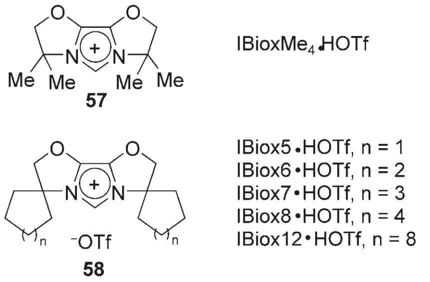


Figure 9. NHC ligands derived from bisoxazolines (IBiox) **57** and **58**.

Gade and Bellemin-Laponnaz[320] reported the design of chiral oxazolinyl-imidazolyl bidentate CN ligands (**59**) that, when complexed with Pd(II), gave effective precatalysts for Heck and Suzuki coupling reactions. Both bromoarenes and chloroarenes could be converted by this system. Palencia, Takacs and co-workers reported a different variation of the NHC ligand, showing that *N*-acyl-NHCs (**60**) could be used to create effective Suzuki coupling catalysts that operated at extremely low catalyst concentrations approaching 1 ppm.[321]

Pd-carbene complexes are natural fits for use in ionic liquids, especially imidazolium-based systems. Ionic liquids have been shown to be useful media for carrying our Heck reactions using Pd(II) salts in combination with various phosphine ligands.[322] Srinivasan proposed that the combination of imidazolium ionic liquids with $PdCl_2$ or $Pd(OAc)_2$ in conjunction with ultrasound creates Pd–NHC$_2$ complexes.[323] The ionic liquid containing palladium could be easily separated from the reaction products and the liquid phase could be reused in subsequent reactions. TEM analysis showed that the ionic liquid contained palladium nanoparticles and the authors argued that these were derived from the Pd–NHC$_2$ precursor, forming during sonication. Later they studied a similar precatalyst system in the Suzuki coupling of aryl halides, including aryl chlorides, again under sonication.[324] They provided evidence that palladium nanoparticles do not form in this system *via* TEM images and argued that the Pd–NHC$_2$ complex was stable under the reaction conditions, being quantitatively recovered after acting as the catalytic species. Welton et al. presented evidence that $Pd(OAc)_2$ or $Pd(PPh_3)_4$ complexes in imidazoylidene ionic liquids form *in-situ* Pd–NHC complexes at room temperature.[325] Later, they showed that ionic liquid solutions containing added $Pd(PPh_3)_4$ that were active for Suzuki coupling were all found to contain mixed phosphine-imidazoylidene-palladium complexes, whereas those that were inactive did not contain such complexes.[326] Welton also showed that Pd(II) complexes with added imidazole gave effective catalysts for Suzuki reactions in butylmethylimid-

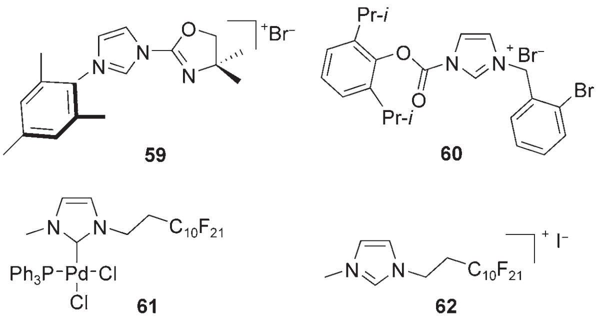


Figure 10. Variations on NHC ligands including the bidentate CN ligand, **59**, the *N*-acyl-NHC ligand, **60**, and fluorous-tagged NHCs **61** and **62**.

azolium (BMIM) ionic liquids.[327] The catalyst could be reused with stable TOFs over five consecutive cycles using bromobenzene and tolylboronic acid as substrates. Ryu et al.[328] also reported on the use of Pd(II) complexes with monodentate NHC and phosphine ligands in BMIM ionic liquids for Heck and Suzuki reactions, indicating that the IL phase containing palladium species could be effectively reused. Shreeve et al. have incorporated palladium species into an ionic liquid based on 2,2-biimidazole and utilized the system for Heck couplings too.[194]

Fluorous-tagged Pd–NHC complexes (**61**) have also been recycled using fluorous solvents (see, for example, **62**) in Heck coupling reactions.[329] The recycled fluorous phase was reused for five runs with similar *yields* in each run, although similar *activities* were claimed.

Overall, NHC ligands have proven to be versatile components of active catalyst systems for both Heck and Suzuki coupling reactions. The majority of the evidence gathered to date supports catalysis by traditional Pd(0)–Pd(II) cycles. However, it is less clear how robust the Pd–C bond in NHC systems is, with some authors reporting rupture of the bonds and others suggesting that they remain intact during catalysis. Like many of the bulky, monodentate phosphines described above, the steric bulk of NHC ligands can be important in stabilizing active species under the reaction conditions.

4 Heterogeneous Precatalysts

Solid catalysts for C–C coupling reactions have been primarily developed as a means to separate the reaction products from the catalyst, potentially facilitating decreased catalyst cost due to reduced catalyst loss and simplified product purification.[330,331]

4.1 Pd(0) Particles on Oxide or Carbon Supports

In the early development of the Heck reaction, it was widely regarded that both homogeneous and heterogeneous Pd species could catalyze the reaction. Indeed, very early on, it was surmised that Pd black, formed *in situ via* reduction of Pd(II) precatalysts, was a crucial intermediate in Heck couplings.[2,3] However, Mizoroki noted that the catalytic activity was independent of the amount of palladium black that was added and therefore concluded that the reaction was not taking place on the surface of the metal particles. At about the same time, Julia and co-workers studied Pd/C as precatalysts in the Heck reaction, showing that this system was capable of activating aryl chlorides and achieving moderate coupling yields.[332,333] After these early reports, only few papers detailing Heck couplings with solid catalysts of this type were reported until the 1990s.[331,334–339] In 1995, Augustine and co-workers, in an effort to explain regiochemistry effects in the Heck arylation reaction using *aroyl* chlorides, described the active sites in a solid supported Pd catalyst as coordinatively unsaturated corner atoms and adatoms on the Pd surface.[340,341] These assignments were made based on the observation that there was no activity in the liquid phase after solid catalyst removal and the extinguishing of activity in the presence of Hg(0). Both observations were assigned as evidence for heterogeneous catalysis. The authors also suggested that palladium black formed from $Pd(OAc)_2$ was truly active also, and that homogeneous species were not the catalyst with this precatalyst system. In the light of more recent data on aryl halide activation, these assignments now appear dubious, although it is possible that aroyl halides react differently (*vide supra* and *infra*). Palladium deposited on porous glass was shown to be an active precatalyst in Heck coupling reactions of iodo- and bromoarenes.[342] Similarly, palladium encapsulated between the layers of graphite was observed to be active in Heck couplings of iodoarenes, but inactive in converting chloroarenes.[343] In that case, the authors concluded that the palladium was completely stable based on the fact that there were no observed changes in the palladium nanoparticle structure after reaction. At the same time, they could not conclude that the reaction occurred on the palladium metal surface given the data they had gathered.

In 1996, Shmidt and Mametova published a report that suggested only soluble, leached palladium species were active catalysts in the Heck reaction of iodobenzene with styrene when using heterogeneous catalysts such as Pd/C or Pd/SiO_2.[344] This rarely cited work was the first report to strongly assert that the surface of palladium metal particles was not active for a Heck coupling reaction, and that all of the activity was associated with leached species. The authors also suggested that the primary mode of the leaching was due to the oxidative addition of the aryl iodide to the Pd(0) surface, releasing soluble Pd(II) species into solution. Nonetheless, it would still be a few years before it became relatively broadly accepted that leached species were the true active catalysts when starting with supported palladium metal precatalysts in many cases. It is noteworthy that in the 1990s Shmidt[344] and Augustine[340,341] came to opposite conclusions in their studies of the Heck reaction using solid catalysts.[331] This may be a consequence of the fact that they studied the activation of aryl iodides and *aroyl* chlorides, respectively.

Buchecker et al. studied Suzuki couplings of aryl halides with phenylboronic acids using supported Pd(0) precatalysts.[345] The precatalysts used were a variety of commercial supported palladium hydrogenation catalysts. The authors attributed the reactions observed using the Pd/C catalysts to surface-catalyzed, heterogeneous reactions, owing to results of an array of test reactions studied. Mercury poisoning results were ambiguous. Filtration tests suggested that activity was not associated with the liquid phase, which the authors accepted as evidence of heterogeneous catalysis, a reasonable conclusion at the time. Later studies that are described below indicated that redeposition of leached active species can occur in coupling reactions, sometimes quite rapidly[346] under the reaction conditions, masking leaching if filtration tests are used as the only or the primary mode of evaluating leaching.

Wali et al. studied the Heck coupling of acrylonitrile with iodobenzene using Pd(0)/MgO as a precatalyst.[347] Addition of PPh_3 improved the efficiency of the catalyst. The authors noted that the supported precatalyst behaved quite similarly to a homeopathic catalyst derived from $Pd(OAc)_2$. After reaction, the authors studied the precatalyst using XPS and showed that the surface was covered with hydrocarbon and no Pd(0) remained. The recovered catalyst showed lower activity for the reaction in subsequent uses. Leaching of some palladium into solution was observed. Nonetheless, the authors concluded that the reaction was truly surface-catalyzed based on their ability to reuse the solid catalyst.

Ying and co-workers described Pd metal loaded Nb-MCM-41 materials that they called Pd-TMS-11 and utilized them in the Heck reaction of aryl bromides and *n*-butyl acrylate.[348,349] The authors discovered that by loading the solid *via* vapor phase deposition of a volatile, reactive organometallic precursor, good films of Pd could be loaded within the mesopores of the support. The reduced Pd material was then utilized in the Heck reaction at 120 and 170 °C. The system rapidly and effectively converted the substrates, and it was found that induction periods could be minimized by preheating the reactants before addition of the catalyst. However, the presence of notable induction periods, loss of 5% of the palladium after use and clear metal restructuring after reaction (visible by TEM) were signs that leached species may be important.[331] The authors attributed the catalytic activity to a heterogeneous mechanism involving the Pd surface, as a filtration test showed that the filtrate did not exhibit any activity and addition of elemental Hg(0) poisoned the reaction. This latter test is commonly used to characterize catalysis by heterogeneous surfaces, as this is the way the test was originally introduced in the literature. However, we believe that this interpretation may be incorrect in Pd-catalyzed coupling reactions where homeopathic Pd, palladacycles, or heterogeneous precatalysts are used.[249,250,270] This will be discussed further below.

In the late 1990s, it became more widely appreciated that leached species from Pd(0)- or Pd(II)-loaded solid supports could play a large role in Heck coupling reactions. Independently, groups in Munich and Sendai studied the leaching of soluble Pd species from heterogeneous Pd precatalysts in Heck coupling reactions. Arai and co-workers presented clear evidence that leached, soluble Pd species were the true catalysts in typical Heck reactions using solid Pd catalysts.[350–352] In particular, their use of cross-transfer experiments, whereby palladium leached from one support and deposited on another, was particularly convincing. In addition, they showed that excellent recovery of the Pd could be achieved due to a redeposition process that occurred after consumption of the reactants.[350–352] Furthermore, the amount of leaching and the reaction rates could be controlled to a certain degree by choice of solvent.[353] At about the same time, Köhler and Djakovitch together studied a variety of Pd-loaded zeolite catalysts for Heck couplings of aryl halides and olefins. Their early work showed definitively *via* filtration tests that there was significant activity associated with leached Pd species in these reactions, although they were unable to rule out catalysis by some solid-supported palladium.[354,355] Early indications suggested that soluble, leached Pd(0) nanoparticles could be responsible for much of the activity, although some reactivity was still ascribed to solid Pd particles.[355–357] Later, Köhler suggested that soluble, leached species were wholly responsible for Heck couplings of aryl bromides[358,359] and even chlorides[360,361] when using Pd/C as a catalyst. Careful studies where the palladium concentration in solution was tracked and correlated with the reaction rate provided compelling evidence that *all* the activity was associated with leached, soluble palladium species.[358,359] Again, a dissolution/redeposition process was suggested to operate. Catalyst recycle in the conversion of aryl chlorides was found to be problematic, with the authors suggesting that the redeposition of the palladium after reaction left it in a form that was less active than in the starting Pd/C material.[361] Subsequently, Köhler and Djakovitch et al. concluded that soluble species leached from a variety of solid precatalysts such as Pd/C, Pd/SiO_2, Pd/MgO, Pd/Al_2O_3, and Pd(0) or Pd(II) in zeolites were responsible for Heck couplings, whereas side reactions including aryl dehalogenation occurred on solid Pd particles.[243] Zhao and Arai reached a similar conclusion in a parallel study.[362] Along these lines, Biffis and co-workers[331,363] proposed that soluble, leached molecular Pd species were active in the Heck reaction when using metallic Pd precursors, ruling out catalysis by palladium colloids due to the large excess of aryl halide in their system, as stoichiometric amounts of iodobenzene could quickly and quantitatively oxidize Pd nanoparticles.[182] A further observation supporting catalysis by leached species made by Nishida and co-workers was that a soluble phosphine had to be added to allow activation of halopyridines in Suzuki couplings using Pd/C.[364] Kotschy and co-workers have similarly shown that Pd(0)-catalyzed Sonogashira couplings using Pd/C also proceed with soluble, leached catalytic species.[365]

Kabalka et al. reported the use of palladium black with KF-loaded alumina as a solid precatalyst in the Suzuki reaction under microwave conditions.[366] The precatalyst was reportedly recovered and reused, although no discussion of palladium leaching or the nature of the true active phase was presented. Later they reported solventless Suzuki couplings using the same precatalyst system which was active in six recycles with fresh KF added in each run.[367]

Shi and co-workers studied mesoporous silica materials derivatized with Si–H groups as novel supports for Pd nanoparticles.[368,369] Addition of Pd(II) precursor species to the silane-functionalized supports led to reduction of the Pd(II) to form Pd(0) nanoparticles and these Pd(0)-loaded solids were used as precatalysts in the Heck coupling of iodo- and bromoarenes with terminal olefins. The solid displayed an induction period; however, the kinetics of reaction were reproducible from one run to another. A filtration test was carried out and, after removal of the solid material, the solution was found to be inactive for further conversions of the substrates.[369] The authors therefore concluded that the reactivity must be due to heterogeneous palladium.

Molnar and co-workers studied a similar system, Si–H capped silica materials loaded with Pd(II).[370,371] They also reported that the Si–H groups were capable of reducing the palladium salt to metallic species, and they found the Pd(0) had very low dispersion. In the Heck reaction with iodo- and bromoarenes and olefins, they found *via* application of a filtration test (actually separation by centrifuge),[371] that leached Pd species were not active in the reaction when triethylamine was used as base. However, they were able to detect leached Pd at levels of 1–2 ppm present in solution after each recycle. In further studies, they showed that the presence of acetate ions led to greatly enhanced activity with leached Pd species, and suggested that these anions play an important role in stabilizing the activity of leached, soluble palladium. Additionally, the authors found that the activity profile and recyclability of their precatalysts closely mimicked that of a commercial Pd/C catalyst.

In a study of Pd/C precatalysts for the Suzuki coupling of an aryl bromide and 3-formylphenylboronic acid, Conlon and co-workers presented evidence for catalysis by soluble Pd species.[372] The leaching of Pd from the solid catalyst was shown to correlate well with the conversion of substrate. They also found that leaching was caused by the oxidative addition of the aryl bromide at the Pd(0) surface. They reported that this oxidative addition was not the slow step in the overall reaction. Catalysis by soluble Pd nanoparticles *vs.* soluble molecular species was not discussed.

Sowa et al. also studied Pd/C catalysts for Suzuki couplings, focusing their studies on the conversions of aryl chlorides.[373] They found that the simple Pd/C catalyst was capable of activating a variety of aryl halides and that proper choice of solvent was critical in preventing the homocoupling reaction. Only very limited leaching of Pd was observed (~1 ppm) and addition of small amounts of triphenylphosphine was found to inhibit the reaction significantly. These observations led the authors to conclude that the heterogeneous metal particle surface was the true active catalyst, and that activation of metal halides was made possible by synergistic anchimeric and electronic effects occurring in the presence of adsorbed species on the catalyst surface.[373] Another potential interpretation is that a dissolution/redeposition process occurred and that the amount of PPh_3 added (one equivalent with respect to the surface palladium) was enough to deactivate traces of potentially active, leached species *via* overcoordination.

Choudary et al. prepared Pd nanoparticles on basic layered hydroxide supports *via* reduction of the $PdCl_4^{2-}$-exchanged solids. The catalysts were then evaluated in the Heck, Suzuki, Sonogashira and Stille couplings of aryl chlorides in non-aqueous ionic liquids.[374] The heterogeneity of the catalysts was analyzed by testing the clear, solid-free filtrate in the Heck reaction and it was determined that the filtrate showed no activity. Additionally, the Pd content of this phase was evaluated, and it was found to vary over the course of the reaction from 1–5% of the total palladium in the reaction vessel. The authors also found no change in the size or shape of the nanoparticles after reaction based on TEM analysis. XPS analysis of the used catalyst indicated that both aryl halide and olefin fragments could be seen on the solid after reaction. The authors interpreted this as proof that only Pd bound to the LDH was active. Using iodoarenes, they suggested that the major contribution of catalysis comes from the solid particles, with a minor contribution coming from soluble species. The Suzuki reaction was carried out in more traditional solvent systems (e.g., water/dioxane) using the same catalyst. The authors found that the catalyst could be reused five times with little loss in yield from cycle to cycle. However, there was a large solvent effect, as has been seen in other coupling reactions by other authors. It should be noted that the reaction temperatures for Heck coupling in particular were fairly high (130 °C), conditions where typically, catalysis occurs by a soluble, ligand-free catalytic species.[188]

Corma et al. prepared 2–10 nm Pd(0) nanoparticles supported on single-wall carbon nanotubes and studied them in the Heck coupling of iodo- or bromobenzene and styrene.[375] The supported nanoparticle catalysts were found to be more active than a typical Pd/C precatalyst. Using DMF, the activity was found to be associated with leached Pd species, with the authors speculating that these species were leached Pd(0) nanoparticles. As reported previously, by moving to more non-polar supports such as xylenes or toluene, the leaching of Pd could be suppressed.[376–378] The solids were effectively recycled with similar rates, with the cause for this in the light of the observed leaching attributed to palladium redeposition as described by Davies[379] and Lipshutz.[346]

Okumura and co-workers evaluated various Pd-loaded zeolites in the Heck reaction of bromobenzene and styrene.[380] Zeolites mordenite, Y, and ZSM-5 were ion-exchanged with a Pd(II) salt and then used as Heck coupling catalysts in Pd(II) or reduced Pd(0) forms. They found that zeolites in their proton form provided better supports than alkali-exchanged zeolites in stabilizing Pd clusters. Utilizing an oxidation/reduction regeneration process, the authors were able to effectively recycle the precatalysts, with Pd−HY catalysts appearing the most stable. When Pd(0) nanoparticle-containing precatalysts were used, only small amounts of leaching were detected by elemental analysis of the filtrate ($<0.5\%$ of Pd present in the catalyst), even using a polar solvent such as *N,N*-dimethylacetamide. Application of a hot filtration test showed the authors that the filtrates did not have activity in the Heck reaction, and thus they concluded that the activity was associated with stable Pd clusters in the zeolite pores. In the case of the HY catalyst, EXAFS analysis showed that the nature of the clusters did not change significantly after use in a Heck reaction, and this gave the authors confidence that the intracrystalline Pd clusters were the true active catalysts.

Pd/C was reported as a precatalyst for the aqueous Suzuki coupling of iodo- and bromoarenes with phenylboronic acid with catalyst recovery and reuse.[381] The yields dropped with each catalyst reuse and the nature of the active catalyst was not discussed. Leadbeater showed that the combination of a Pd/C catalyst with aqueous systems and microwave heating and cooling was an effective way to carry out Suzuki couplings of aryl chlorides and phenylboronic acid.[382] $Pd(OH)_2/C$ has also been effectively used in Suzuki couplings, although the nature of the true active site was not clearly elucidated.[383]

Artok and Bulut studied the Suzuki coupling of aryl bromides and phenylboronic acid with Pd(0)-loaded NaY zeolite in water/DMF.[384] The authors found that the reaction rates depended strongly on the base used, a common observation in many coupling reactions. Catalysts were reused successfully, but they required regeneration. Application of a filtration test followed by elemental analysis of the filtrate showed that very little Pd was present in the solution (<1 ppm) and that the solid-free filtrate did not promote the reaction any further. Finally, the authors reported that leaching from Pd(II)-exchanged NaY zeolites was substantially higher than when the Pd species were reduced to Pd(0) before use in catalytic reactions.[384] The authors argued that the small amounts of leached Pd could not cause all of the observed catalysis, based on an experiment with an equivalent concentration of Pd(OAc) giving very limited conversions. This conclusion does not appear justified given the dynamic nature of Pd in these systems.

Sastry and co-workers studied aminopropyl-functionalized NaY zeolite as a support for Pd nanoparticles and utilized the resulting solids as precatalysts in the Heck reaction of iodobenzene with styrene.[385] The authors claimed that the nanoparticles were exclusively tethered to the outer surface of the zeolite crystals based on nanoparticle size arguments, XRD data and TEM images. Unfortunately, they did not report any porosity measurements that could have more conclusively shed light on this issue. TGA studies showed an increased weight loss associated with amino-NaY materials that were loaded with Pt or Pd nanoparticles, with the authors arguing that desorption of surface-bound amino groups leads to loss of the metal nanoparticles in the TGA as well, a quite dubious hypothesis. They also interpreted these unique TGA data as proof that the nanoparticles were associated with the amine groups on the zeolite surface. The organic-modified zeolite support was asserted to be excellent for stabilizing Pd nanoparticles as no change in the nanoparticle size was observed after reaction. The authors reused the solids three times, achieving similar reaction yields and average TOFs in each run. Based on these results, a negative hot filtration test, and low levels of leached Pd as measured by elemental analysis (less than 1 ppm with respect to total metal loading), the authors concluded that these materials were stable catalysts for this Heck reaction. Interestingly, other reports of Pd(0) particles on aminosilica-based supports in Heck couplings all reported significantly poorer results in regard to activity, leaching, recyclability or other factors.[370,386,387] This may indicate something unique about use of the aminosilane-functionalized zeolite support.

Kirschning and co-workers studied Heck and Suzuki couplings in a continuous, tubular reactor loaded with monolithic glass/polymer composite catalyst.[388] For Suzuki couplings of aryl iodides and bromides, the conversion could be accomplished by loading an anion-exchange resin (hydroxide form) into the reactor, followed by loading of the boronic acid, washing, and then circulating the aryl halide and $Pd(PPh_3)_4$ in THF at 60 °C to yield the product. In a second approach, the reaction was also successfully run without preliminary immobilization of the boronic acid. These approaches did not address catalyst contamination issues, so the authors also pursued loading the glass/polymer composite catalyst with Pd(0) particles to give a solid catalyst. No direct characterization of the state of the palladium was given, although the authors hypothesized that nanoparticles of

Pd(0) were formed. Heck reactions of iodobenzene and butyl acrylates were also studied in DMF solvent over seven consecutive runs. The precatalyst effectively produced coupling product, although yields dropped noticeably in each run. Leaching of palladium to form soluble, potentially catalytic species was only addressed in terms of catalytic transfer hydrogenation experiments, not coupling reactions. This reactor would be an excellent arrangement to study catalyst leaching over long periods of time, although in this initial study, such experiments were not undertaken. Prior to Kirschning's work, Haswell and co-workers reported the use of a flow microreactor for Suzuki couplings using Pd(0) on silica as a catalyst.[389] Although this catalyst system is now known to operate by a solution mediated mechanism (*vide supra*), the authors were able to show that the palladium loss from the catalyst bed was nonetheless quite low, with concentrations of 1.2–1.6 ppb found in the crude product.

Bedford et al. studied the Suzuki coupling of aryl bromides with phenylboronic acid using nanoparticulate Pd supported on aminosilane-functionalized mesoporous silicas.[390] Primary amine, diamine, triamine and quaternary ammonium silanes were used to functionalize the silica support, and the best results were obtained with monoamine and triamine-loaded supports. Despite the expected good behavior of Pd nanoparticles on quaternary ammonium loaded supports (due to the similarity to solution phase Jeffery conditions), it was determined that these silica materials were not as effective. Small amounts of palladium leaching were observed in most runs, but no tests were carried out to check if these species were catalytically active. Even the best catalyst lost activity after the third or fourth runs. Based on the data presented, it was not clear whether the activity was associated with leached species or with the nanoparticle surface.

Samant and co-workers used Pd/C as a precatalyst in the Heck coupling of iodobezene and methyl acrylate at room temperature using ultrasound.[391] Using NMP and DMAC as solvents, leaching of palladium into solution was minor, with ~5 ppm Pd remaining in solution after reaction. Addition of the reducing agent sodium formate to the system and application of ultrasound brought the soluble Pd concentration down to 1.85 ppm. Using this approach, the precatalyst was recycled two times, with noticeably decreasing conversions in each recycle.

Pd/C has also been effectively used as a precatalyst in polymerization reactions, for example, in the polymerization of diolefins with diiodoarenes to give linear polymers.[392] A heterogeneous Pd/C precatalyst was also utilized in supercritical carbon dioxide solvents for the Heck reaction of aryl iodides with olefins.[393]

Overall, the cumulative evidence to this point indicates that most supported forms of Pd(0) metal particles are in fact precursors for soluble palladium species that are the real catalysts in C–C coupling reactions when using aryl iodides as reagents. There are still some reports of couplings involving primarily aryl or aroyl chlorides where catalysis by the metal particle surface is suggested. However, in nearly all cases, given the small amount of soluble palladium needed to affect the catalytic reaction and the occurrence of a palladium dissolution/reprecipitation process, catalysis by soluble species is difficult to conclusively eliminate. There appears no *definitive* evidence for surface-catalyzed Heck and Suzuki coupling reactions. It is suggested that future investigations in using solid catalysts for bromide and chloride conversion should focus on developing definitive methods to assess the potential for true surface catalysis. Again, it should be noted that for catalysis by supported Pd(0) particles or nanoparticles, the catalytic trends can be best explained by a solublization/redeposition[350–352,358–361] process and such a mechanistic picture fits well with the data supporting the high-temperature homeopathic palladium mechanism described by de Vries.[188] Whereas in this work and in those of Beletskaya the term "homeopathic" is primarily used to imply that small amounts of ligand-free palladium are effective precatalysts in coupling reactions, de Vries appears to use this term with the added constraint that TOFs should increase as the catalyst loading decreases.[188] This implies that the substrate to catalyst ratio plays a key role, with high ratios leading to maximized rates. If supported forms of Pd(0) particles truly act as precursors for homeopathic palladium as suggested by Kohler, Arai, de Vries and others, it would be interesting in the future for investigators to focus on the role of the substrate/catalyst ratio using these precatalysts.

4.2 Pd(II)-Exchanged Supports

Although many authors who have utilized Pd(II) ion-exchanged solids as precatalysts in Heck and Suzuki reactions also report the use of pre-reduced Pd(0) in the same communications, there are still several reports that only utilize Pd(II)-exchanged, solid precatalysts and have therefore not been discussed above. These precatalysts are discussed here.

In the late 1990s, Sudalai and co-workers reported the use of Pd- and Cu-exchanged montmorillonite clays as precatalysts for the Heck coupling of aryl bromides and iodides with styrene and acrylates.[394] It was reported that the catalyst could be recovered by filtration and reused three times without loss of activity, although no data are included regarding recycle in the paper.

In a short contribution, Jacobs and co-workers showed that Pd(II)-exchanged mordenite and Pd(0)-loaded mordenite represented truly heterogeneous Heck catalysts, whereas oxidized materials containing PdO or other forms of Pd(II) in an all-oxygen environment were prone to leaching.[395] At about the same time, in a more detailed report, Jacobs et al. studied the Heck coupling of aryl bromides and olefins using a variety of Pd-loaded zeolites.[378] Precatalysts based on zeolites with low loadings of $Pd(NH_3)_4^{2+}$, high loadings of the palladium amine, oxidized palladium, and reduced palladium were evaluated. Most of the zeolites tested were shown to leach active Pd species into solution when polar solvents were used. However, the authors reported that several zeolite precatalysts were truly heterogeneous when toluene and tributylamine were used as solvent and base, respectively, although the reaction rates were markedly lower. It was also determined that the state of the palladium determined to a large degree the extent of leaching. Calcined or oxidized zeolite samples showed a high propensity for leaching active Pd species, whereas Pd-exchanged solids with a low Pd loading or pre-reduced catalysts that contained Pd(0) nanoparticles were judged to be fully heterogeneous. Rates were also found to be enhanced by addition of tetrabulyammonium compounds, reagents suggested to stabilize soluble Pd colloids.[151,182,204] The authors used a hot filtration test coupled with elemental analysis of the filtrate to determine if there were significant leached active Pd species or leached Pd species at all, respectively. All the data presented were consistent with catalysis by solid Pd(0) species, with a filtration test being the key methodology used to judge heterogeneity. However, it is still possible that the catalysis was associated in most or all cases with soluble species. In particular, it is difficult to envision how the anionic palladium intermediates formed during the Heck reaction are retained by an anionic zeolite framework. While hot filtrations work well in many cases as a proof for soluble heterogeneous species, it can be dangerous to use this test alone to disprove the existence of soluble active species.[396] This is because redeposition of the soluble active species can be very rapid, especially in M(0)-catalyzed coupling reactions.[350,351,397] This issue is discussed further below. In a final, intriguing study, Jacobs et al. developed unique new chemistries to produce Heck products without the use of aryl halides.[398]

Djakovitch and Rollet studied a similar system, Pd-loaded zeolite NH_4-Y, in the copper-free Sonogashira coupling reaction.[399] Application of a hot filtration test showed that leaching had occurred, although the reaction rate after filtration was low. They concluded that the small amount of leached Pd (about 10 ppm) could not be responsible for most of the activity and assigned the majority of the activity to reaction on heterogeneous sites. Later, Davis et al. studied Pd(II)-exchanged Y zeolites as precatalysts in the continuous-flow Heck coupling of iodobenzene and *n*-butyl acrylate.[387] Using elemental analysis, poisoning studies and experiments with the solid-free liquid eluent of the tubular reactor, they showed that essentially all activity when using this precatalyst was associated with soluble, leached palladium species.

Shimizu et al. reported the Suzuki coupling of aryl bromides with phenylboronic acid and sodium tetraphenylboronate in water using Pd(II)-exchanged sepiolites.[400] The catalysts were carefully characterized before and after reaction, and X-ray absorption spectroscopic results indicated that the precatalysts were largely unchanged after reaction. The fresh precatalyst contained largely Pd(II) species, with the used precatalyst also showing small amounts of Pd(0) contributions. The presence of Pd(0) nanoclusters was confirmed by TEM observations. A filtration test was undertaken to probe for the presence of soluble active species and it was concluded that the catalysis was due to heterogeneous sites. This was supported by elemental analysis results of the filtrate showing trace amounts of solubilized Pd were solublized (<1 ppm). Catalyst activity was reported to be similar both in the first and subsequent uses in a reaction, although only yields were reported for long reaction times. The *in-situ* formed, supported Pd(0) nanoclusters were hypothesized to be the active species.

At the same time as Shimizu's study, García and coworkers also reported Heck and Suzuki couplings with Pd(II)-supported sepiolites.[401] Interestingly, García et al. utilized the alkali species in the alkali-exchanged sepiolite as base sites in the reactions, and they successfully carried out the couplings in the absence of an external base. A hot filtration test resulted in a clear filtrate that did not continue to promote the Heck reaction when *o*-xylene was used as solvent. Elemental analysis of the used catalyst and the filtrate did not provide evidence for leaching of Pd species. Perhaps the leaching of Pd from solid catalysts was promoted by excess, external base, and in the absence of such species, a truly heterogeneous catalyst was possible. Although this may be the case, the catalyst was hampered by low rates overall (compared to when more polar solvents were used and leaching occurred)[376] and loss of activity due to neutralization of base sites with the HX that was produced. Some activity could be regained by mild steaming.

Ley introduced the use of Pd(II)-exchanged perovskites as precatalysts in the Suzuki coupling of bromoarenes and arylboronic acids.[402] Small levels of Pd leaching were found to occur during reaction (~2 ppm in solution) and application of a 3-phase test proved that at least part of the reactivity was associated with these leached species. Leaching was caused by addition of aryl halides to the catalyst, as observed in other systems. A detailed poisoning study similar to those carried out on other systems,[249,250] including use of an insoluble, polymeric poison to trap homogeneous species, indicated conclusively that the catalysis was associated with soluble species.[403] A plausible mechanism for catalyst formation was given, with the true catalyst possibly being Pd(0) nanoclusters or molecular, "naked" Pd species.

Sivasankar prepared Pd-loaded hydrotalcites and evaluated them in the Heck reaction of iodobenzene and methyl acrylate.[404] Based on a negative filtration test result, they concluded that the catalysis observed was heterogeneous in nature, although they did not identify whether Pd(0) nanoparticles were formed during the reaction. It may be assumed that Pd(0) species were formed, as the authors observed a higher activity upon catalyst reuse.

Srinivas, Ratnasamy and co-workers utilized the Pd-exchanged silicoaluminophosphate SAPO-31 in the Heck coupling of aryl chlorides and olefins.[405] They found that significant Pd leaching took place, although most of the Pd redeposited on the solid support after the reactants were consumed, making the system recyclable.

Yokoyama et al. showed that Pd(II)-exchanged oxide supports could also be used in conjunction with ionic liquids as solvents.[199] The authors showed that roughly half of the supported palladium dissolved in the ionic liquid phase under the reaction conditions. Nonetheless, the ionic liquid phase containing the palladium could be effectively recovered and recycled, giving similar yields in subsequent runs.

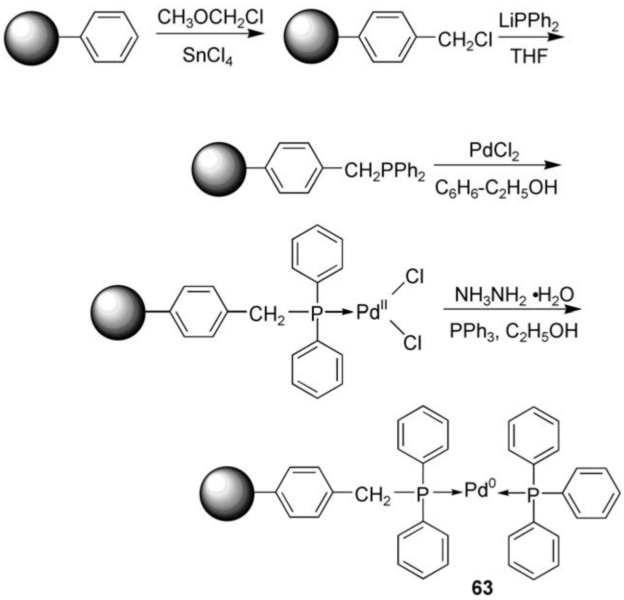
Overall, the results using Pd(II)-exchanged supports mirror those found when using supported Pd(0) species. Both reports of catalysis by leached, soluble species and truly heterogeneous catalyst systems are abundant. Most often, a filtration test has been used as the primary or sole evidence for catalysis by heterogeneous sites, and as noted above, given the small amount of soluble palladium needed to effect the catalytic reaction and the occurrence of a palladium dissolution/reprecipitation process, complete or partial catalysis by soluble species is difficult to conclusively eliminate. This will be discussed further below.

4.3 Supported Metal-Ligand Complexes

4.3.1 Polymer-Supported Metal-Ligand Complexes

4.3.1.1 Phosphorus Ligand Systems

Over the last few decades, a diverse array of polymers, especially poly(styrenes), has been prepared with a number of phosphine-based functional groups. These phosphine-functionalized polymers have been used quite often as supports for palladium species in coupling reactions.[406] Teranishi et al. studied triarylphosphine-loaded poly(styrene) as a support for "coordinatively unsaturated Pd(0)", and evaluated the materials in various coupling reactions.[407] After loading the phosphine-containing polymer with $PdCl_2$, the material was reduced with hydrazine in the presence of soluble triphenylphosphine to give what the authors suggested was two-coordinate Pd(0) (**63**), based on XPS characterization (Scheme 13). They concluded that Pd(0) metallic particles were not formed. They did not rule out the presence of a mixture of differently ligated Pd(0) phosphine complexes, with one, two or three Pd−P coordinations. The insoluble polymer was shown to be a catalyst or precatalyst for the coupling of styrene with iodobenzene. The authors also showed that the solid could be reused with some loss in activity.



63

Scheme 13. The synthesis of phosphine-functionalized polymers containing Pd(0) species **63** bound by two phosphines.

Miyaura and Inada reported the use of PPh_3-functionalized polymer resins as supports for $PdCl_2$ in the Suzuki coupling of aryl chlorides and arylboronic acids.[408] The solid worked best in three-phase media including the solid polymer, toluene and water. The authors reported that the solid material could be reused multiple times, although limited data were presented. Jang also reported the use of palladium-loaded PPh_3-functionalized polymer resins in Suzuki couplings, reporting good recyclability with stable activity, although only reaction yields were reported.[409]

Andersson, Hallberg and co-workers completed one of the earliest in-depth studies of polymer-immobilized Pd-phosphine complexes in Heck arylations.[410] They studied poly(styrene)-supported triphenylphosphine-$PdCl_2$ complexes with a variety of different Pd : P ratios, along with Pd/C and $Pd(OAc)_2$. For the precatalysts with the largest loading of Pd, it was clear that metallic Pd formed during reaction and the system was able to effectively couple iodobenzene and methyl acrylate or styrene. Highly-loaded polymers were easier to reduce to form Pd(0), likely as a consequence of bridging $PdCl_2$ moieties between phosphine-ligated $PdCl_2$ species. Very different reactivity patterns were seen when bromobenzene was used, with the catalysts that were least active for iodobenzene conversions being most active for bromobenzene coupling. This was ascribed to the theory that only molecular Pd species ligated by phosphines would promote bromobenzene coupling, whereas naked, metallic Pd could not promote this reaction (this is now known to be untrue under some conditions[148,411]). Thus, catalysts that have the most metallic Pd formation were observed to be the least active in bromobenzene conversion, but the most reactive with iodobenzene. The most reactive catalyst with bromobenzene was found to have a pale yellow color, consistent with the presence of $Pd(PPh_3)_n$ complexes, with no visible sign of Pd black.

Whereas Anderrson et al.[410] evaluated polymer-supported monodentate phosphines as supports for palladium in coupling chemistry, Fox and Wang[412] studied polymer-supported bidentate phosphines and found very different catalytic behavior in the Heck reaction of iodobenzene and olefins. Poly(styrene)-supported 1,2-bis-(diisopropylphosphino)benzene-Pd(II) complexes (**64**) were shown to be more active and stable than the corresponding homogeneous complexes. This was ascribed to the stability of the chelated Pd species on the polymeric support relative to the soluble molecular species that was susceptible to bimolecular decomposition in the Pd(0) state to give naked Pd(0), which was unstable, and tetraphosphine-ligated Pd(0), which was inactive. The polymeric catalyst could be effectively recycled 5 times and was claimed to be stable in air. As the authors pointed out, it is unusual for a supported complex to be more active than the homogeneous analogue. This could be a sign that the materials were simply precatalysts for other species, or that the monomeric species was more susceptible to deactivation pathways that were prevented in the supported solid. The authors argued for the later based on XPS characterization of the used catalyst that showed no sign of Pd(0). While it was possible that the majority of the activity was associated with supported Pd species, there was insufficient data to rule out catalysis by leached, soluble species.

Ruckenstein and co-workers developed a unique polymeric support for palladium-catalyzed Heck reactions. Recognizing the utility of tetrabutylammonium salts as cocatalysts, they prepared random copolymers that contained monomer units with ligands such as alkyl(triaryl)-phosphines and also monomer units containing trialkylammonium salts.[413] Upon metallation of the polymers with palladium salts, they were found to be excellent precatalysts for Heck couplings of iodobenzene with acrylate esters. They showed that the copolymer gave catalysts that were more active than simple homogeneous systems of similar components or polymers with only one of the polymerizable units and all other species in homogeneous solution. The authors inferred from the results that the quaternary ammonium sites were the loci for the adsorption of the reagents. Subsequently, the authors reported the immobilization of tetraalkylammonium groups and palladium-phosphorus complexes as a non-uniform layer on cross-linked poly(styrene) beads.[414] The immobilizations were facilitated using the resin's pendant chloride groups and then the precatalysts were used in the Heck coupling of iodobenzene with methyl acrylate. It was found that when the two groups were attached to the same polymer chain alternately that the catalytic performance was better than when the two groups were on different polymer chains. The nature of the true active species in both reports[413,414] was unclear.

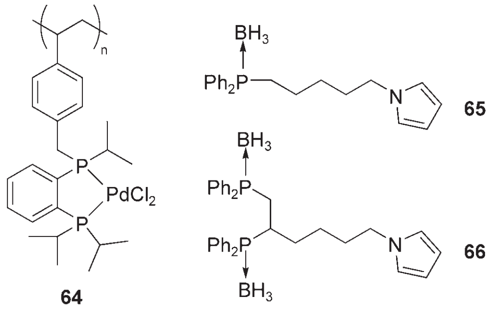
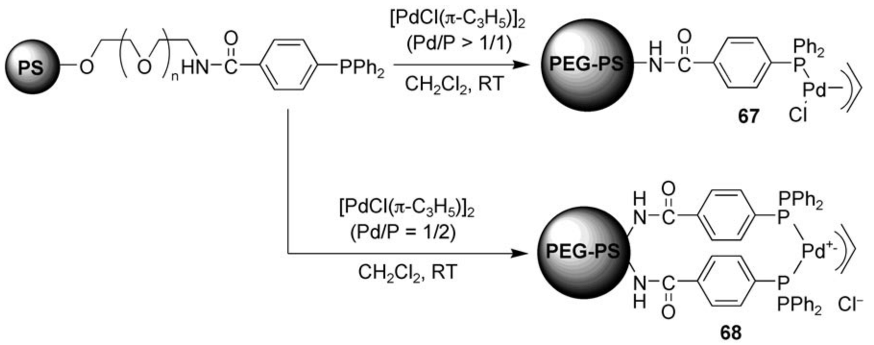


Figure 11. Poly(styrene)-supported 1,2-bis(diisopropylphosphino)benzene Pd(II) complex **64**, and pyrrole-based phosphine ligands **65** and **66**.

Juge and coworkers prepared poly(pyrrole) supported mono- and diphosphine ligands (see **65**, **66** in Figure 11 for the monomer structure), contacted them with $Pd(OAc)_2$, and utilized the resulting solids as precatalysts in Heck couplings of iodoarenes with olefins.[415] The yields obtained were modest and the materials were inactive upon reuse without the addition of a fresh aliquot of $Pd(dba)_2$. This can be interpreted as strong evidence that the precatalysts were unstable and the palladium took on an inactive form during and/or after reaction.

Buchwald and Parrish reported Merrifield resin-supported dialkylphosphinobiphenyl ligands in the palladium-catalyzed Suzuki coupling of chloroarenes and areneboronic acids.[416] Under some reaction conditions, substantial leaching of palladium and phosphine into the solution phase was observed, whereas under optimized conditions, significant leaching of phosphine could be avoided. The precatalysts effectively converted the chloroarenes, although under some conditions a competitive hydrolytic deboronation was observed. The solids could be recycled, although rates and selectivity suffered after the fourth use. Explicit analysis of the solution for leached catalyst was not carried out, although the activation of hard-to-convert chloroarenes was consistent with ligation by the bulky monodentate polymeric phosphine.

Le Drian et al.[417] found different trends in the Suzuki coupling of phenylboronic acid with 4-bromopyridine compared to Andersson et al.'s work that was discussed above in the Heck reaction with Merrifield resin-supported $Pd(PAr_3)$ precatalysts. In the Suzuki coupling, the reactivity was found to be independent of the Pd:P ratio, unlike in the Heck couplings described by Ander-



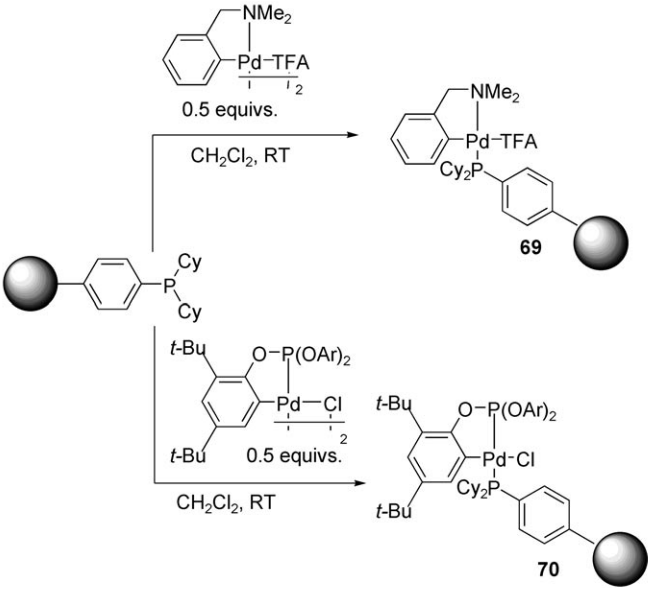
Scheme 14. The immobilization of Pd(II) triarylphosphine complexes on poly(ethylene glycol)-poly(styrene) graft copolymers, **67** and **68**.

sson. However, like the earlier work, the authors found that the solids could be effectively recovered from solution. Furthermore, only 0.6% of the palladium was found to have leached into solution during reaction.

Uozumi et al. immobilized Pd(II) complexes on poly(ethylene glycol)-poly(styrene) graft copolymers (precatalysts **67** and **68** in Scheme 14) and utilized the materials in the Suzuki coupling of aryl iodides and bromides with areneboronic acids.[418] The catalytic materials could be reused in subsequent reactions, although few details on catalyst stability and recycling were given. Later, they reported a similar, high-throughput screening study of the Suzuki coupling of aryl bromides and iodides with a variety of areneboronic acids, reporting good results in three successive cycles in one case.[419] They also studied triarylphosphines immobilized on amphiphilic PEG-poly(styrene) resins as supports for palladium species in Heck coupling reactions.[406,420] The reaction of iodobenzene and acrylic acid was carried out in water using palladium immobilized on the resin, with five consecutive recycles giving an average of 92% yield (no activity information was presented).

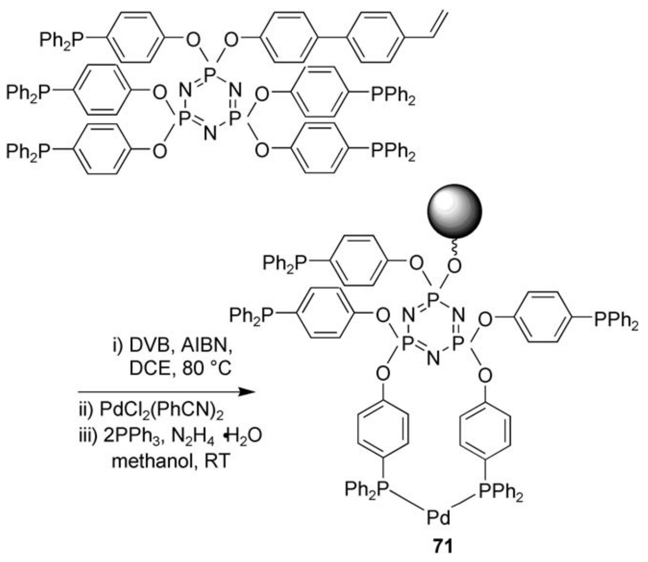
Sauer et al. studied commercial FibreCat-supported Pd(II) in the microwave-heated Suzuki coupling of aryl chlorides, bromides and iodides.[421] FibreCat supports are poly(ethylene)-supported phosphines from Johnson Matthey. A wide variety of aryl halides were effectively converted, although no discussion of the nature of the catalytic species was presented. In some cases, soluble P(t-Bu$_3$) was used in conjunction with the supported phosphine. Leaching of palladium has been observed with these supported catalysts.[422]

Bedford et al. utilized a commercial dicyclohexyl(phenyl)phosphine-functionalized poly(styrene) as a support for PC and NC palladacycles (precatalysts **69** and **70** in Scheme 15).[423] After immobilization, only 55–75% of the supported phosphines were bound to Pd species according to elemental analysis. The supported Pd(II) species were then utilized in Suzuki reactions of aryl chlorides and areneboronic acids. The catalysts effectively coupled the reagents, although immobilization significantly changed the reactivity of the PC palladacycle. Unfortunately, complex stability was a problem, as the solids could not be recycled. As it had been already established that palladacycles decompose to give catalytic species potentially similar to homeopathic palladium,[184,225] it is not surprising that the supported complexes could not be recycled and that palladium black formed. Despite the catalyst decomposition, though, the crude product in a typical reaction showed very little Pd, only about 12 ppm.

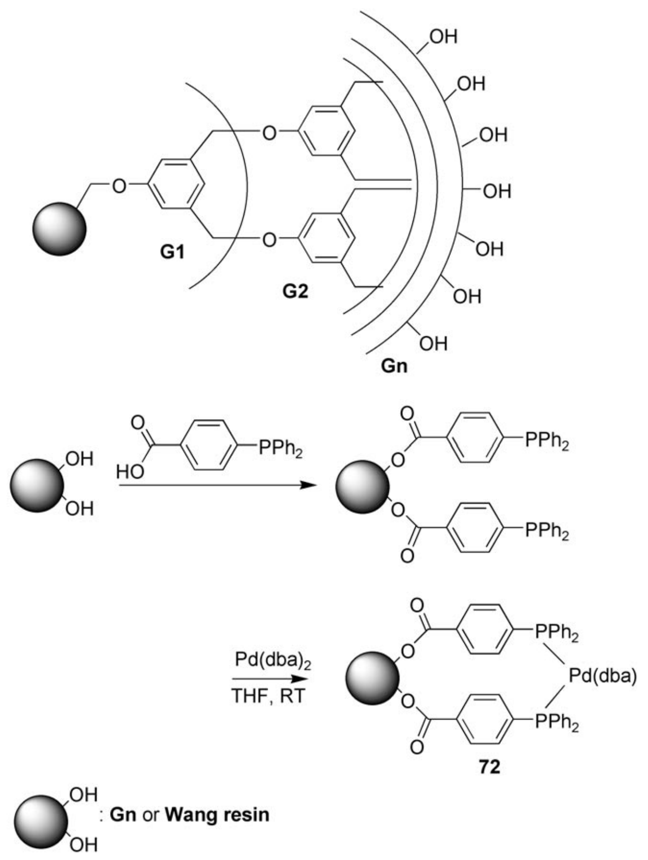


Scheme 15. PC and NC palladacycle precatalysts immobilized on commercial dicyclohexyl(phenyl)phosphine functionalized poly(styrene) to create precatalysts **70** and **69**, respectively.

Chandrasekhar et al. supported Pd(0)–PPh$_3$ complexes of unknown speciation on a unique cyclophosphazene-containing polymer (e.g., **71** in Scheme 16) and studied their ability to promote the Heck reaction of iodoarenes and olefins.[424] The precatalyst was reused several times, with the yield decreasing with each use. The authors ascribed the catalysis to polymer-supported sites, as a filtration test showed no activity in the filtrate



Scheme 16. The immobilizaion of Pd(0) PPh$_3$ complexes on a unique cyclophosphazene-containing polymer.



Scheme 17. Pd(0) species immobilized on dendrimer or Wang resin supports to give precatalyst **72**.

once the polymer was removed. Elemental analysis of the used polymer showed that no significant change in the Pd loading was observed after reaction.

Kaneda and co-workers immobilized a Pd phosphine complex within a protonated poly(propylene imine) dendrimer *via* ionic interactions between the cationic polymer and the anionic, acetate-containing phosphine ligand.[425] Based on product distributions in the coupling of 1,4-diiodobenzene with olefins in the Heck reaction, the authors concluded that the reaction took place with Pd complexes inside the dendrimer core.

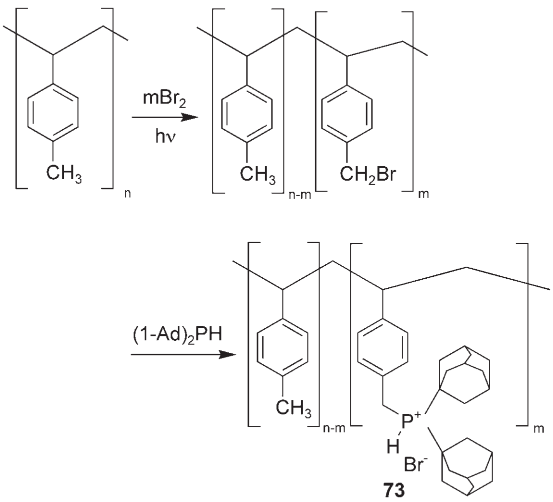
Shieh and co-workers studied the Suzuki coupling of 2-bromoanisole and phenylboronic acid using a commercial triarylphosphine-poly(styrene) resin.[426] The polymer was loaded with PdCl$_2$ and the effect of the reaction conditions on catalyst leaching was studied. In all cases, Pd was shown to have leached from the polymer support (41–920 ppm), although tailoring of the reaction conditions could be done to minimize this. Leaching could be minimized by reducing the Pd(II) to Pd(0) before the reaction. It was also discovered that leaching occurred to a lower extent in subsequent reactions after the first use of the precatalyst. As in other systems, polar solvents enhanced leaching. The authors ascribed the activity to 14-electron Pd(PPh$_3$)$_2$ complexes attached to the solid support.

Portnoy and Dahan studied dendrimers with terminal triphenylphosphine moieties, as well as Wang resin-supported phosphines (e.g., **72** in Scheme 17) that were loaded with palladium and used in the Heck reaction of bromobenzene and olefins.[427] In some cases, the homocoupling product was observed, which may be interpreted as a sign of the presence of solid Pd species. Indeed, the authors observed formation of Pd black during the reaction. Improved catalytic performance was seen using higher generation dendrimers and a number of hypotheses was proposed to account for the observed effects. Astruc et al. also studied dendrimer-immobilized Pd(OAc)$_2$, although they worked with bidentate diaryl(alkyl)phosphines.[76] Dendrimers from G1 to G3 were used, with a slightly negative dendritic effect being observed. In some cases the dendrimer precatalyst could be recycled several times before decreased reactivities were noted.

Ikegami et al. functionalized an amphiphilic, non-cross-linked polymer with triarylphosphine ligands and immobilized Pd(II) on it. The insoluble polymer was effectively used as a precatalyst in the Heck reaction of iodoarenes and olefins,[428,429] even at loadings as low as 1 ppm. The precatalyst was reportedly recycled 5 times, with little change in activity. A similar precatalyst was also used in aqueous-phase Suzuki couplings of iodo- and bromoarenes and arylboronic acids. With only 5×10^{-5} mol equivalents of palladium, the polymer could be recycled 10 times with essentially no change in yield.[430] In a more detailed study,[431] it was shown that the polymer-supported precatalyst was active in organic media, that turnover numbers as high as 1.25 million could be achieved, that the filtrate from a reaction did not promote additional conversion of the reactants, and that most Pd species were ligated by two dialkylarylphosphines in the precatalyst.

Plenio developed a soluble polymer-immobilized triarylphosphine-Pd(II) material and demonstrated its use in Heck, Sonogashira and Suzuki couplings in conjunction with a nanofiltration membrane for catalyst sequestration.[432] The phosphine-functionalized polymer (e.g., **73** in Scheme 18) was prepared and palladium species were immobilized *in situ* before use in a coupling reaction. The activity of the catalyst was found to be independent of the molecular weight of the polymer. The precatalysts were fairly stable over long-term use, with TOFs slowly decreasing over several cycles in the Sonogashira reaction and remaining relatively stable in the Suzuki coupling. Stability in the Heck reaction was limited by fouling of the nanofiltration membrane by the solvents used. The authors were unable to detect any leached Pd using multiple analytical techniques and thus concluded that the membrane retained 99.95% of the polymeric catalyst. Poly(ethylene glycol)-immobilized phosphines were also used as supports for Pd(II) species in the biphasic Suzuki coupling of aryl bromides and chlorides with arylboronic acids.[433] The authors found that the activity of the catalysts depended on the P:Pd ratio, with a maximum near 3.5:1 rather than 2:1 or 1:1 as is commonly found in many homogeneous systems. The precatalysts could be effectively recycled for 5 or more cycles for most substrates, with TOFs dropping marginally in each run. Analysis of the non-catalytic phase in these biphasic experiments (heptane phase) by spectrophotometric analysis led to the conclusion that most of the palladium, 99.95% or more, was kept within the polar phase. It is not clear whether this analysis was specific to the Pd-phosphine complex, or whether it would also detect naked Pd species or Pd nanoparticles. Although the recycling ability and analysis of the non-polar phase shows the ability of the reaction system to sequester Pd, it does not give any information on the state of the active Pd species. The authors also reported poly(methylstyrene)-supported palladium-alkyl(diaryl)phosphines in Suzuki and Sonogashira couplings.[434] The solids could be effectively reused in both cases, although there was a slight drop in TOFs upon recycle in Suzuki couplings of 4-bromoacetophenone and phenylboronic acid. Plenio also reported polar-phase tagged phosphine ligands for biphasic Sonogashira couplings.[65,66]

Immobilized Pd(II)-phosphine complexes on polymeric supports have also been utilized in other coupling reactions such as aminations[416] and Sonogashira couplings.[435] Astruc et al. prepared bis(*t*-butylphosphine)- and bis(cyclohexylphosphine)-functionalized Pd(II) complexes on dendritic supports and compared them to the monomeric complexes in the Sonogashira coupling of aryl halides and alkynes.[435] The dendritic precatalysts were recovered by precipitation and reused several times, being stable until the fifth recycle, where the activity dropped considerably. The activity drop was associated with decomposition of the ligand, rather than being due to Pd leaching.

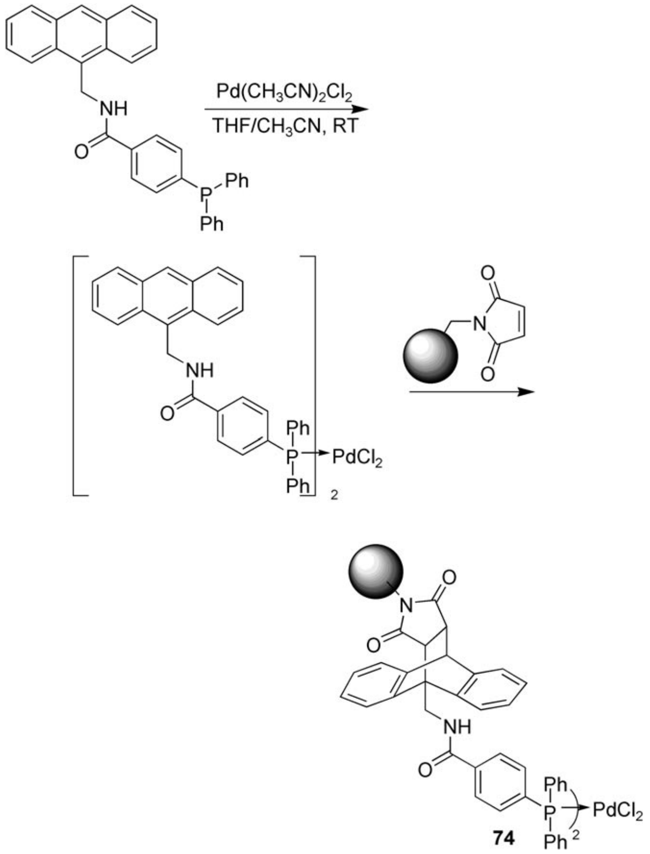


73

Scheme 18. Preparation of a dialkylarylphosphonium salt polymer. Upon addition of palladium metal under basic conditions, a phosphine-ligated palladium complex is formed *in situ*.

Kobayashi et al. have published several examples of polymer-encapsulated palladium moieties for use in coupling chemistries (*vide infra*). In most cases, the resulting supported palladium was ligand-free [ignoring possible electron donation from the poly(styrene) to the metal]. However, in their earliest work in this area,[436] they found that encapsulation of $Pd(PPh_3)_4$ resulted in recovery of 3 equivalents of phosphine, and thus they described their materials as polymer-loaded $PdPh_3$ species, with the rest of the palladium coordination shell filled by interactions with the polymer, giving a hypothetical 18 e complex. Applying the precatalyst first in allylation reactions, they found that it displayed no activity unless an external phosphine was added. Subsequently, they reported effective catalysis of the Suzuki coupling of aryl bromides with aryboronic acids in the presence of external phosphine. It was discovered that the nature of the external phosphine affected the progress of the reaction. One noteworthy item about this work is the extremely high precatalyst and ligand loadings used, 20 mole percent. It was assumed that the external phosphine displaced the interaction of the Pd(0) species with the polymer, creating a 14 or 16 e complex from the 18 e complex that was originally proposed. No discussion was given about catalyst leaching or Pd black formation, although the authors stated that the catalyst can be recovered “quantitatively”. When using 20 mole percent precatalyst, it may be doubtful whether it would be noticed if small amounts of Pd leached from the polymer.

Bradley and co-workers reported the impregnation of polymer resin plugs composed of HDPE and Merrifield



74

Scheme 19. Removal of an anthracene-tagged Pd(II) complex *via* Diels–Alder immobilization to a resin support to give the recoverable palladium-containing material **74**.

resin that were derivatized with triarylphosphine groups, covalently.[437] The polymer was loaded with Pd(PPh$_3$)$_4$ to give a black solid that was used in Suzuki couplings. The state of the Pd in the reaction (nanoparticles *vs.* molecular) was unclear.

Monteiro dosed poly(ethylene oxide) with palladium complexes and utilized it in two-phase Suzuki couplings.[438] The polar catalyst-containing phase was reused several times, with the claims of no loss of activity. Reactions were run for 24 hours and yields were measured, which certainly is long enough for most reactions to go to completion even with significant deactivation, thus the claim of no loss in activity is questionable. Leaching from the polar polymer phase was 5% in the first run and about 2% in the recycled runs.

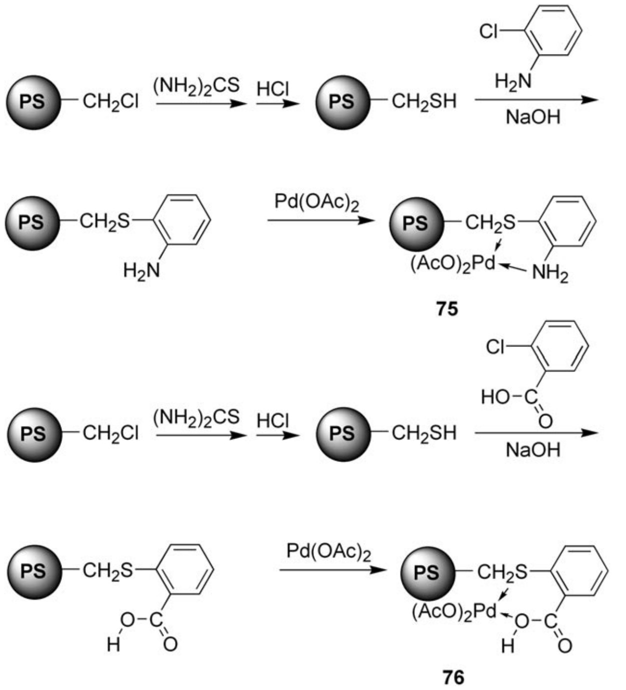
Parlow used an anthracene-tagged palladium complex (e.g., **74** in Scheme 19) with polymer-bound base in Suzuki couplings.[439] Following reaction, the palladium species still attached to anthracene-containing ligands were removed from solution *via* a Diels–Alder reaction between the ligand and maleimide resin. Assuming no palladium was free of the anthracene-containing phosphine ligand, complete recovery of palladium can in principle be achieved. Residual palladium in the product was measured to be less than 1 ppm.

4.3.1.2 Non-Phosphorus and Mixed Ligand Systems

Liu and co-workers studied polymer- and silica-supported thiol, SO and SN (e.g., **75**, **76** in Scheme 20) ligands loaded with Pd(II) in the Heck reaction of iodobenzene and olefins.[440] Like the control material, polymer-supported Pd(II) ligated by triarylphosphines, the silica-supported thiol precatalyst lost palladium to solution, although to a much lesser extent (9% *vs.* 90%). After reaction, the state of the Pd was not observed to have changed from Pd(II) in the S-containing catalysts, although the sulfur was oxidized, based on XPS analysis. The oxidation was assigned to interactions with iodine, rather than exposure to air. Catalytic activity was thought to be associated with a supported Pd(0) complex. Later, Liu and Wang studied polymers containing potentially bidentate hydroxyl-thiol ligands as supports for palladium species in Heck coupling reactions.[441] The low molecular weight polymers were metalated with Pd(OAc)$_2$ and then a silica support was added to adsorb the polymeric precatalyst, giving a higher surface area material than just a neat polymer. Binding of the thiols with the palladium was verified by XPS and UV-vis spectroscopic analysis. Ideal S:Pd ratios were determined to be between 3 and 6, with deviations outside this range leading to lower catalytic productivities. Induction periods associated with reduction of Pd(II) to Pd(0) were noted initially, whereas the recycled solids lacked these delays. Loss of palladium into the homogeneous solution was shown only to occur appreciably in the presence of both the reactants and the base. The authors proposed a mechanism of leaching involving oxidative addition of the aryl halide to the supported Pd(0) species followed by leaching of the resulting Pd(II) species with the action of the base. The authors indicated that the Pd(II) could be readsorbed if fresh, Pd-free polymer were added to the system, indicating that poor readsorption of the leached palladium under reaction conditions was likely a consequence of loss of thiols during the reaction due to oxidation.

Phenanthroline-modified polymers were loaded with Pd(II), reduced, and used as precatalysts for Heck couplings by Zhang et al.[442–445] The reduced catalysts were found to contain Pd(0) particles of about 5 nm in size by microscopy. The authors found that leaching of the palladium from the support was a problem when using tributylamine as a base in DMF/water, however, substitution of NaOAc as the base gave a more stable system, although the possibility of the presence of leached, active species was not evaluated. Using the inorganic base, the solid could be recovered and reused in multiple reactions (up to 10) with moderately decreasing yields in each reuse. The authors found that both aryl iodides and bromides (such as bromobenzene) could be activated by the catalytic system.

Zhang et al. immobilized Pd(OAc)$_2$ on a commercial thiourea-containing resin, Deloxan THP, and utilized the polymer-supported palladium in the Suzuki coupling

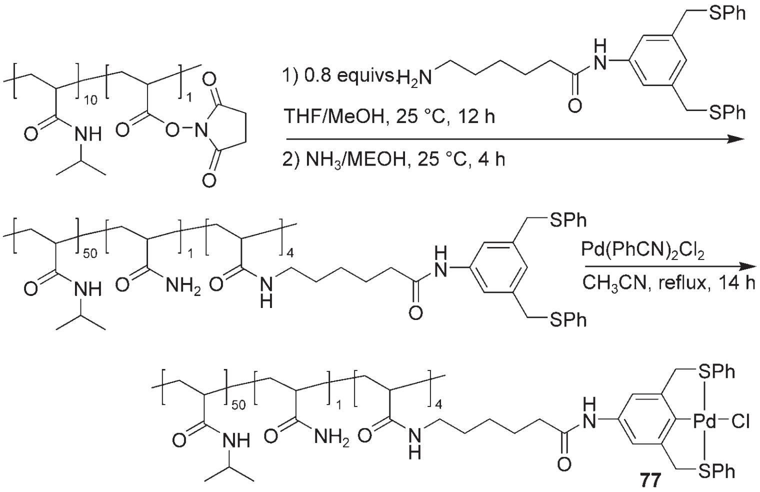


Scheme 20. Polymer- and silica-supported SO and SN ligands loaded with Pd(II) to give precatalysts **76** and **75**, respectively.

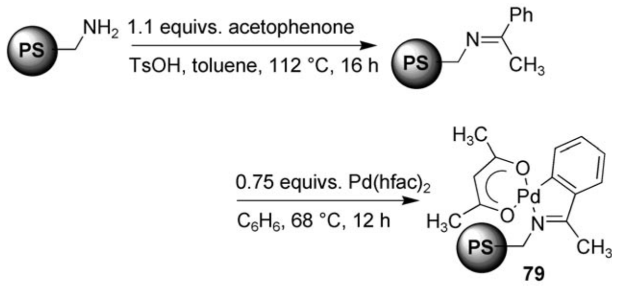
of aryl iodides and bromides with arylboronic acids.[446] The solid catalyst converted a variety of substrates with good yield and could be recycled up to three times before rates started to noticeably decrease. Residual palladium found in crude product was low, about 3 ppm or less. The authors did not evaluate whether the catalyst was truly heterogeneous or whether the leached species promoted the reaction.

Bergbreiter and co-workers introduced several novel, thermomorphic polymers (e.g., **77** in Scheme 21) for use as catalysts supports in the Heck reaction in 1999.[268] To these supports, they immobilized Pd(II) complexes of SCS palladacycle pincer ligands. These polymer-supported complexes were shown to be stable at high temperatures and in the presence of oxygen. Under high-temperature Heck conditions, these Pd-polymers effectively promoted the coupling of iodoarenes and olefins. Polymers based on SCS ligands with an ether linkage between the aromatic ring and the polymer linker (**78**, Figure 12) were shown to form palladium black during the reaction, a tell-tale sign of catalyst decomposition, making catalysis by leached Pd possible.[267] However, the related complexes with SCS ligands linked *via* an amide group (e.g., **77**) appeared to be more stable and catalyst decomposition was not detected. The seemingly stable precatalysts could be recovered (nearly quantitatively) and recycled multiple times, with no decrease in rate observed.[268] A variety of polymers was used as supports, proving the methodology to be very versatile.[447–449] Other authors, building from this work, also developed polymer supports for SCS pincer complexes and utilized them in the Heck reaction.[450] Subsequently, in 2005, Bergbreiter and co-workers[252] and Jones and Weck[249,250] independently showed that supported SCS Pd(II) pincer complexes are simply sources of active, soluble palladium. *Via* a combination of kinetic and poisoning studies, filtration tests and three phase tests, it was conclusively shown that there was no activity associated with supported SCS pincer complexes and that all activity was due to leached homogeneous species.[249,250] Thus, the dendrimer-ligated SCS pincers of Portnoy are almost certainly soluble Pd sources as well.[451] Later studies of PCP systems[270] demonstrated that these behave in the same way (*vide infra*).

Nowotny et al. studied poly(styrene)-bound imine-based NC palladacycle complexes (e.g., **79** in Scheme 22) in the Heck reaction of iodobenzene and styrene.[219] Prior to use, the corresponding homogeneous analogues were also prepared and, in both systems, it was confirmed that ligated Pd(II) complexes were



Scheme 21. Pd(II) SCS pincer complexes immobilized on a thermomorphic polymer to give precatalyst **77**.



Scheme 22. Poly(styrene)-immobilized NC imine palladacycle **79**.

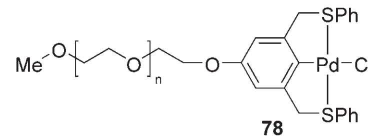


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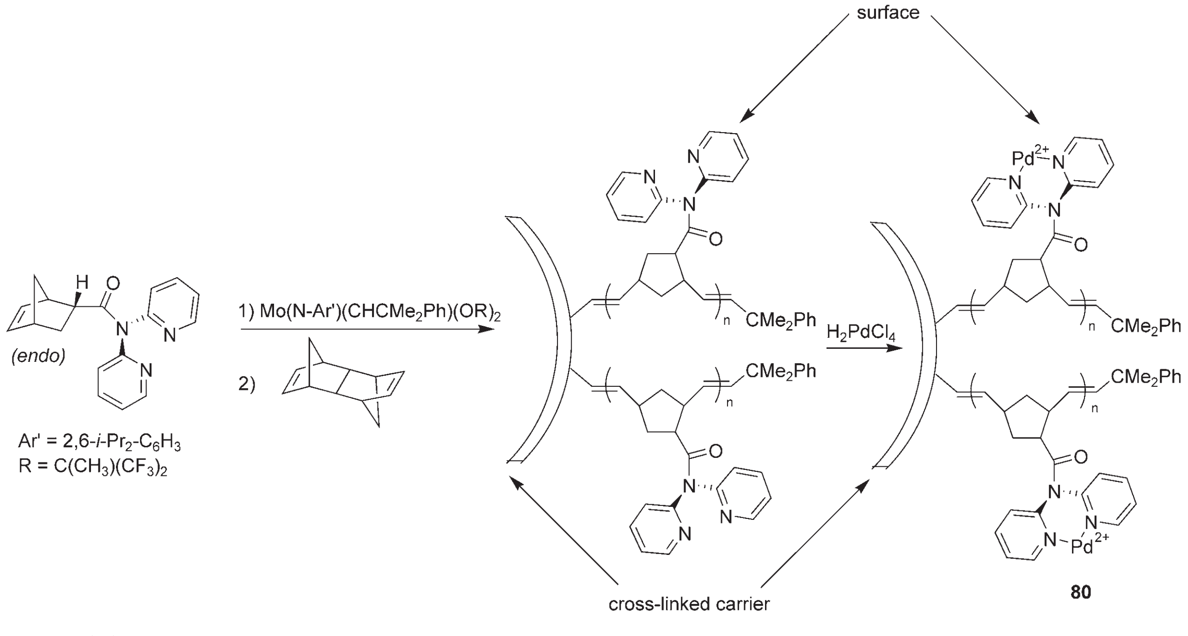
Figure 12. PEG linked to an SCS Pd(II) pincer complex *via* an ether linkage.

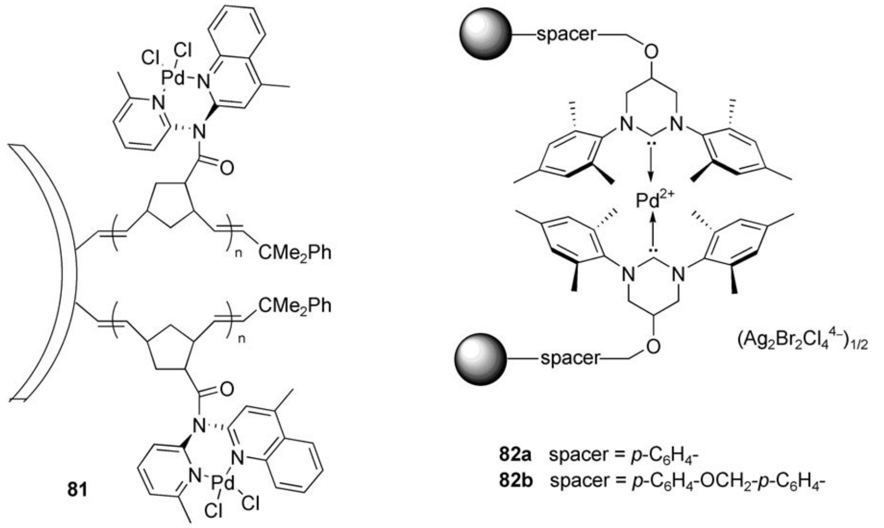
formed. All precatalysts displayed an induction period and it was shown that large amounts of soluble, active palladium species were produced. At high temperatures, the solids were not recyclable at all, whereas at lower temperatures the solid maintained enough palladium precatalyst on the surface to be used a second time. The authors surmised that the soluble species were formed *via* loss of ligand, and that finely divided, soluble palladium nanoparticles were the true catalysts.

Luo studied PC palladacycles immobilized on poly(styrene) in Heck, Suzuki and Sonogashira reactions.[452] The solid was reported as a recyclable catalyst, with good yields obtained in 7 consecutive cycles in Heck and Suzuki reactions in diethyl ether. In other reaction/solvent combinations, a significant loss of activity was observed. Of course, in light of the discussion presented above, it is likely that the polymer was simply a source for soluble, leached Pd(0).

Buchmeiser and co-workers studied two classes of metal complexes immobilized on polymeric (prepared *via* ROMP) and other supports, complexes based on dipyridyl ligands and 3,4,5,6-tetrahydropyrimidin-2-ylidene ligands, in the Heck and Suzuki reaction[131] (e.g., **80** in Scheme 23). In the earliest work, they studied polymer-bound and homogeneous dichloropalladium-di(pyrid-2-yl)amide complexes (e.g., **80**) in the Heck coupling of iodo-, bromo- and chloroarenes. The catalysts effectively converted the iodo and bromo compounds and even were able to react chloro compounds in the presence of tetrabutylammonium bromide. In most cases, only very small amounts of Pd were needed to promote the reactions. Couplings carried out with the homogeneous complexes led to minor, but detectable amounts of Pd metal formation. In contrast, this was not detected with the supported precatalysts, and the authors surmised that the support was able to retain active Pd(0) species as ligated, molecular species or as adsorbed nanoparticles. The authors gave an interesting and plausible hypothesis for why this might occur – they noted that the supported catalysts have only ~35% of the ligands metalated, and thus there are many ligands available to readsorb the free Pd should it leach from one of the metalated ligands. In contrast, such a situation does not exist for the homogeneous catalysts. Reproducible kinetics upon recycle of the precatalyst and increased rates without the formation of Pd black upon pre-reduc-



Scheme 23. Pd(II) ligated by polymer-supported dipyridyl ligands **81** or by 3,4,5,6-tetrahydropyrimidin-2-ylidene ligands **82**.



82a spacer = p-C$_6$H$_4$-
82b spacer = p-C$_6$H$_4$-OCH$_2$-p-C$_6$H$_4$-

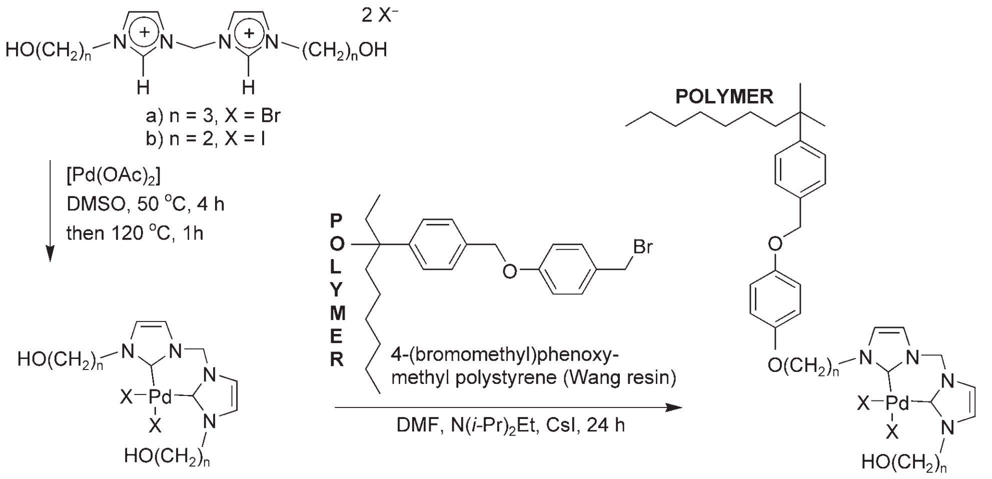
Figure 13. Polymers containing substituted the dipyridyl-type ligand **81**, and 3,4,5,6-tetrahydropyrimidin-2-ylidene-based ligands **82** loaded with palladium.

ing the supported Pd(II) species were also signs that a stable, truly heterogeneous catalyst might be in hand.

These initial studies were followed with studies of the Sonogashira coupling and amination reactions,[130] as well as systems based on flow reactors. In the flow studies, the catalysts were found to be fairly stable with less than 2.5% of the Pd lost from the solid over the course of the experiments.[129] The authors followed up the initial work by evaluating related, but slightly different systems (e.g., **81**, Figure 13) based on substituted dipyridyl-type ligands.[128] The authors found that these substituted ligands had relatively large dissociation constants, and as a result they hypothesized that leached Pd species were potentially important in coupling reactions promoted by these immobilized complexes. Despite this, levels of leaching were limited (unless a redeposition process was at play[351]), as elemental analysis of the supported catalysts before and after reaction showed less than 10% loss of palladium. Reuse of the support showed that it had lower activity, unlike the previous study, yet the filtrate showed no activity, showing that any soluble Pd had become inactive during or after the reaction.

Studies of supported 3,4,5,6-tetrahydropyrimidin-2-ylidene-based ligands (e.g., **82a**, **82b**, Figure 13) in the Heck reaction of acrylates and styrene were also conducted using various aryl iodides and bromides.[132] A variety of precatalysts was prepared using the same complex on different supports and it was observed that catalytic properties varied widely. The precatalysts deactivated after a single use by about 30% and leaching of Pd into the solution phase occurred. However, the authors assigned most of the reactivity to sites on the supports. A more detailed study was reported later, where the authors showed that supported precatalysts of this type were able to convert both chlorides and bromides in the Heck reaction with high TONs.[133] In some cases Pd black was observed during reaction, indicating decomposition of the catalyst, whereas in others, the authors found that the catalysts appeared to be highly stable. When filtration tests were conducted, the activity of the solution phase was found to be low but not zero. Addition of Hg(0) to a reaction did not shut down catalytic activity, even when traces of catalyst were used (0.001 mol %), although the authors do not comment on whether there were reduced rates under these conditions. Recharging the reactor with fresh reactants after the first reaction led to rapid conversion of the substrate, with rates comparable to or slightly lower than the first use.

Herrmann et al. studied the use of bidentate N-heterocyclic carbine-Pd(II) complexes immobilized on Wang resins *via* ether linkages (e.g., **83** in Scheme 24) in the Heck reaction of aryl bromides.[285] Complexes of this type appeared to be good candidates for immobilization due to the strength of the C–Pd bond, as the carbenes can bind both Pd(II) and Pd(0) as strong or stronger than most phosphines. The loading of Pd sites on the polymer was substantially less than the calculated number of total binding sites (~6–7% of the total), indicating that only some of the reactive bromo groups in the polymer were accessible. The Pd-loaded polymer contained residual hydroxy groups as well, indicating that some or all of the complexes were bound to the polymer at one point, rather than off of both ends of the bidentate phosphine. Reactions of aryl bromides with styrene or n-butyl acrylate proceeded with very low Pd loadings (0.02–0.15 mol%) and the reaction selectivity and yield were not different than when using the corresponding homogeneous analogues. However, the TOFs for the supported catalysts were about one order of magnitude lower. Whereas addition of TBAB allowed the homogeneous



Scheme 24. Preparation of bidentate NHC Pd(II) complexes **83** immobilized on Wang resin.

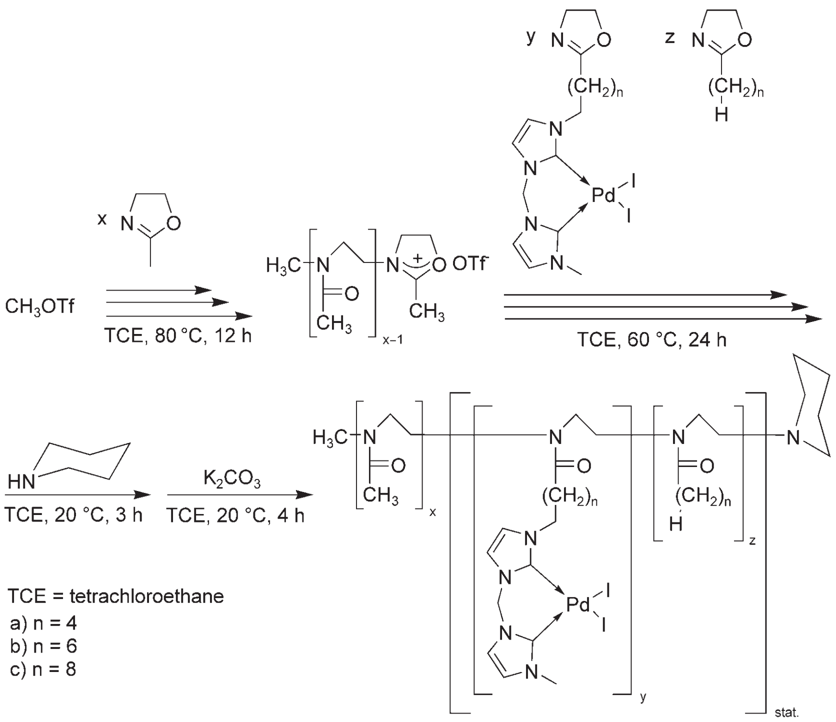
complexes to convert some aryl chlorides, the additive did not affect the reactivity of the supported catalyst, which was inert to aryl chlorides. The precatalyst was recyclable, with the authors claiming reuse 15 times without detectable loss of activity in some cases. The polymer was shown to leach Pd into solution, with the largest loss occurring in the first use of the system (losing 60% of the Pd in some cases). The authors ascribed the catalysis to immobilized sites based on a filtration test. Leaching in subsequent uses after the primary use was found to be much lower, with loses of only 7% of the remaining Pd after three additional runs.

Other authors have also reported NHC-containing supported catalysts. Lee and Byun reported the preparation of poly(styrene)-immobilized NHC ligands following a simple, one-step procedure.[453] Relatively low NHC loadings were obtained, but the metalated polymer proved to be a good precatalyst for Suzuki couplings using iodo- and bromoarenes. No discussion about the nature of the catalyst, catalyst recovery, or stability was presented. Weberskirch et al. prepared amphiphilic, water-soluble diblock copolymers, with pendant N-heterocyclic carbene-Pd(II) complexes in the hydrophobic block (e.g., **84** in Scheme 25). Akin to the work of Uozumi,[418,419] they used the amphiphilic precatalysts in a micellar Heck reaction to effect the reaction of iodobenzene and styrene.[454] The precatalysts composed of Pd(II) species chelated by bidentate N-heterocyclic carbene ligands displayed an induction period, presumably due to reduction of Pd(II) to Pd(0), and then the reactions proceeded smoothly with a TOF of 150–570 h^{-1}. The authors determined that a minimum spacer of six methylene units was needed between the polymer backbone and the metal complex to give good activities. Precatalysts were recyclable and reusable, although rates were reduced in subsequent cycles. The authors ascribed this to micelle restructuring effects rather than to catalyst deactivation or leaching. The authors suggested that future studies would focus on the nature of the true catalyst – immobilized *vs.* leached Pd.

Portnoy and Mansour screened a variety of polymer-supported, bidentate NP or PP ligands for activity in the Heck reaction of bromobenzene and methyl acrylate.[455] Solid Pd black formed during the reactions with the polymer-supported complexes. However, the authors argued that the Heck activity observed was likely associated with the supported complexes, as "naked" Pd was thought to be inactive for conversions of less reactive aryl halides like bromobenzene and chloroarenes. Of course, this supposition has since been proven to be untrue in the general sense, although the reactivity in the system they studied could still be associated with the supported complexes.

Toy, Chiu and coworkers studied poly(styrene) supports (both soluble and insoluble) functionalized with triarylarsine groups.[456] The polymers were added to the reaction with external Pd(II) salt and used (As:Pd ratio was 2:1) in the Suzuki coupling of aryl iodides. The insoluble polymer was found to react sluggishly, although good results were observed with the soluble support. Under most conditions, significant palladium black was observed, although its formation could be minimized by adjusting the reaction temperature. The precatalyst was recovered and reused, with the authors hypothesizing that polymer-encapsulation of the Pd(0) species akin to Kobayashi's work[436] made this possible. The nature of the active species in this work was unclear.

Styring et al. studied the Suzuki coupling of 4-bromoanisole with phenylboronic acid using a Merrifield resin-supported tetradentate ONNO-Pd(II) complex (e.g., **85** in Scheme 26).[457] Interestingly, the supported precatalyst was demonstrated to be significantly more useful than the corresponding homogeneous analogue, suggesting that the support may serve to stabilize the



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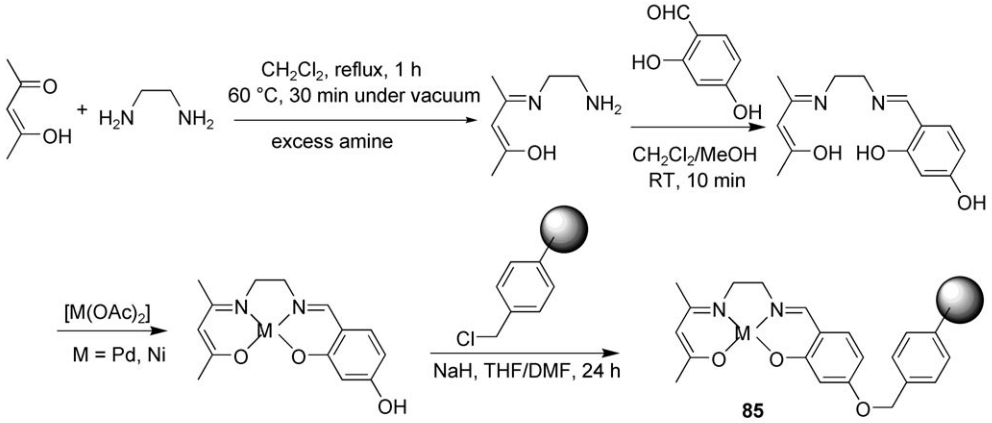
Scheme 25. Synthesis of supported precatalyst **84**, Pd(II) species ligated by bidentate NHC ligands attached to the hydrophobic block of amphiphilic diblock copolymers.



85

Scheme 26. Immobilization of the Pd(II)-loaded tetradentate ONNO ligand on a polymer resin to create precatalyst **85**.

Pd species. Nonetheless, it is clear that some restructuring of the Pd likely occurred under the reaction conditions, as the ligand likely must depart from its tetradentate structure or the Pd must leach for the reaction to proceed by the common Pd(0)–Pd(II) cycle. Nonetheless, the polymers were reported to be recyclable catalysts, as a filtration test indicated that the filtrate did not promote the coupling. Additionally, the precatalyst could be recovered and reused, although the rate dropped with each recycle. Less than 1% of the Pd that was added to the reaction was lost, indicating low leaching levels based on ICP-MS analysis of the crude reaction media after evaporation to dryness. The authors studied a similar complex immobilized on a Merrifield resin and on a silica support in the Heck reaction of 4-bromoanisole and styrene.[458] They found that the reaction did not proceed except at very high temperatures (140 °C) and that these high temperatures degraded the resin (although potentially leaving the active species intact). Both the silica- and resin-supported materials were effectively reused in multiple cycles, with the conversions and TOFs slowly dropping with each cycle. Filtration tests were used to characterize the materials as heterogeneous, with the solid-free solution giving almost no

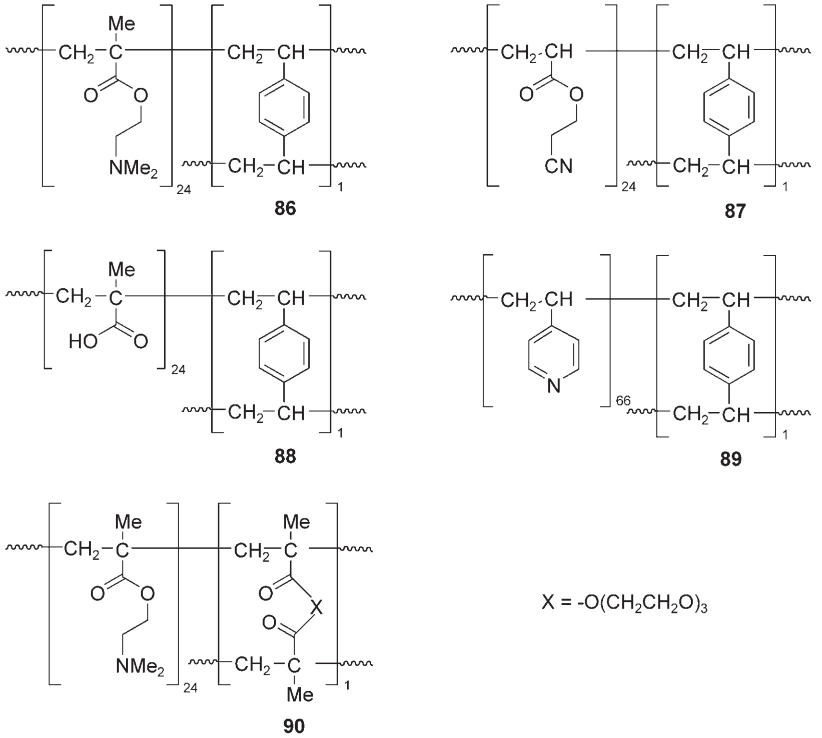


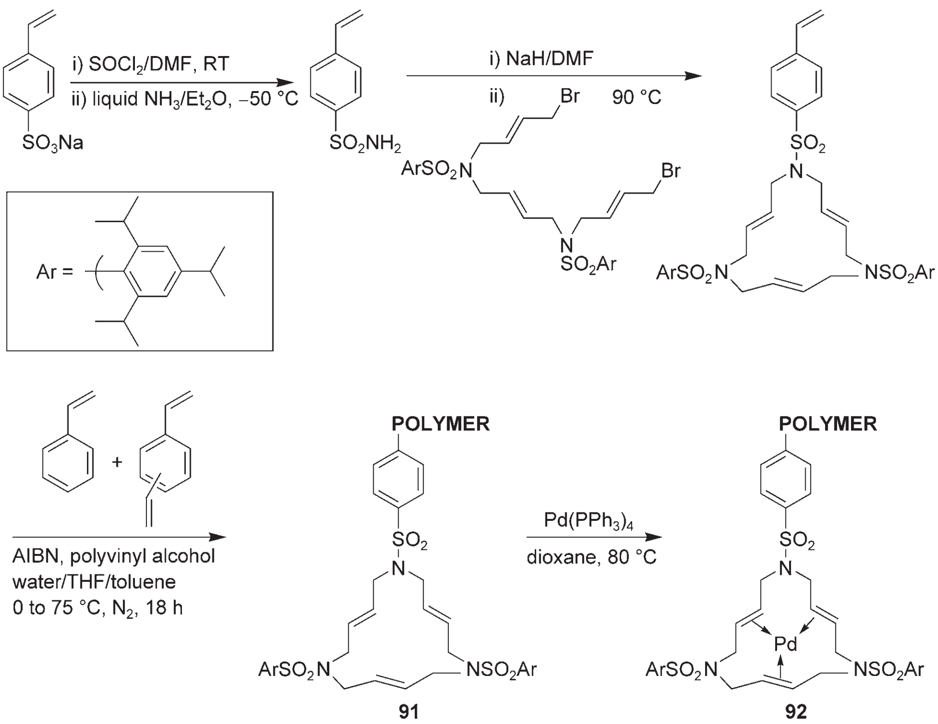
Figure 14. Copolymers containing tertiary amino, cyano, carboxyl or pyridyl groups **86–90**.

conversion of substrate. The authors indicated that 1% of the Pd or less was lost in each run, although they highlighted the importance of solvent washing before use as a critical step to remove any physisorbed material. The authors also reported similar supported ligands containing nickel for other coupling reactions as well.[458,459]

Caporusso, Biffis and co-workers recently reported several different copolymers containing tertiary amino, cyano, carboxyl or pyridyl groups (e.g., **86–90** in Figure 14) loaded with Pd as precatalysts in Heck reactions in NMP solvent.[460] The Pd-loaded polymers were reduced to generate supported Pd(0) nanoparticles before use in Heck reactions. The authors found that the activity and stability to leaching of the various precatalysts depended on the method of Pd loading and the nature of the polymeric ligands. In all cases, some contribution to catalysis was associated with leached palladium species, although for one material that contained tertiary amine groups, a series of careful experiments gave significant evidence for catalysis by truly heterogeneous Pd species.

Cui and Zheng reported use of poly(vinyl chloride)-poly(ethylene)-poly(amine)-supported Pd(0) nanoparticles as precatalysts in the Heck coupling of acrylic acid with aryl iodides.[461] The solids were recovered and reused and were claimed to be quite stable. Nonetheless, reaction yields decreased in subsequent reactions and possible palladium leaching was not investigated.

Moreno-Manas reported an interesting ligand for the stabilization of Pd(0) complexes in Heck and Suzuki reactions – a cyclic triolefin ligand (e.g., **91** in Scheme 27). Pd(0) complexes in solution as well as immobilized onto a poly(styrene) resin (**92**) were evaluated in the Suzuki coupling of aryl bromides with arylboronic acids.[462] Using the homogeneous complex, the authors reported that they could "quantitatively" recover the metal ligand complex *via* column chromatography. The polymer-supported catalyst also could be recovered almost quantitatively after use in five consecutive runs, starting with 8.1 mg of catalyst and recovering 7.9 mg. Interestingly, the yield increased after run 1, stabilized and then dropped slightly, perhaps a sign that the polymer was a precatalyst and not a true catalyst. No characterization was done to check for active, leached Pd species in solution. Structural characterization of the metal-ligand complex indicated that not all Pd-olefin bonds were the same, and that the complex should be best represented as a PdL_2L' complex. The authors hypothesized that the atypical Pd-olefin decoordinates to free up a binding site for the reactants. In a follow-up study involving Roglans' group in collaboration with the original authors, the homogeneous complexes were altered to contain ferrocenyl groups at the periphery, and the catalysts were evaluated in both Heck and Suzuki coupling reactions of iodoarenes.[463] The reactions were effectively catalyzed, but only 95% and 55% of the metal ligand complex were recovered after reaction in the Suzuki and Heck couplings, respectively. In the case of the



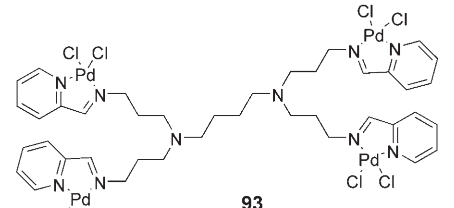
Scheme 27. Cyclic triolefin ligand **91** immobilized onto a polymeric support followed by metalation to create precatalyst **92**.

Heck reaction, the other 45% of the ligand was recovered without the Pd metal, indicating that leaching from the complex had occurred and that possibly homeopathic Pd was the active catalyst. In a related study, the authors used a similar homogeneous complex in the Heck reaction, substituting arenediazonium salts for aryl halides.[464] In this case, they were able to observe evidence *via* mass spectrometry for the oxidative addition product of the arene to the Pd atom within the macrocyclic complex. After reaction, the catalyst was recovered in 97% yield *via* silica chromatography. The authors also immobilized the macrocyclic olefin complex on a carbon electrode as a means of heterogenizing the system.[465] They studied this new system in the Suzuki coupling of aryl bromides and iodides with areneboronic acids. At low temperatures, they found that the reaction was effectively deactivated after one use. However, increasing the reaction temperature and regenerating the system with a cleaning and soaking step led to better recyclability when using aryl bromides as substrates. When iodoarenes were used, the catalyst was almost fully deactivated after two uses. Elemental analysis of the liquid phase showed that 5% of the Pd had leached from the solid, although the authors concluded that these species were not responsible for the activity based on their monitoring of the filtrate after the solid was removed midway through the reaction. For the reader, it is difficult to judge based on the data presented whether there was truly no reaction from the soluble species. In the most recent study,[466] the authors immobilized the macrocyclic Pd complexes at the ends of a central triazine core and studied their use in the Suzuki cross-coupling of iodobenzenes and areneboronic acids. They observed that quantitative recovery of the precatalyst was possible in all reactions and they claimed that no decomplexation of the palladium complex took place. In the Heck reaction, precatalyst recovery was lower, but still as high 95%. Characterization to probe reactivity associated with leached, active Pd was not carried out in any study.

Wu, Song and co-workers immobilized imidazolinyl ligands onto poly(acrylonitrile) fibers *via* a single-step functionalization and loaded the resulting materials with $PdCl_2$.[467] The precatalysts were applied in the Heck coupling of iodobenzene with olefins such as ethyl acrylate. The authors claimed that the precatalysts could be recycled up to 20 times without degrading selectivity, although no discussion of the activity upon recycle was presented.

Screttas and co-workers immobilized Pd(II) species on iminophosphine-containing dendrimers and studied their use in the Heck reaction of aryl bromides.[468] The authors found a strong influence of the L:M ratio, with higher numbers leading to inactive catalysts. The authors hypothesized that this was due to strong inter-arm interactions within the dendrimer. Under the reaction conditions, they observed extensive formation of Pd black. Also, the precatalysts were not recoverable or recyclable.

Mapolie studied iminopyridine-ligated Pd(II) on poly(propyleneimine) dendrimers (e.g., **93** and **94** in Figure 15) in the Heck coupling of iodobenzene with meth-



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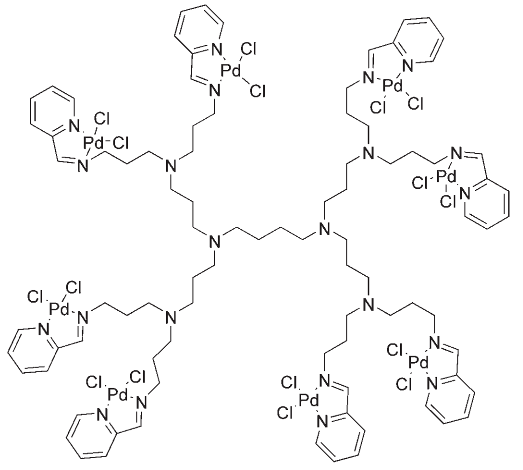
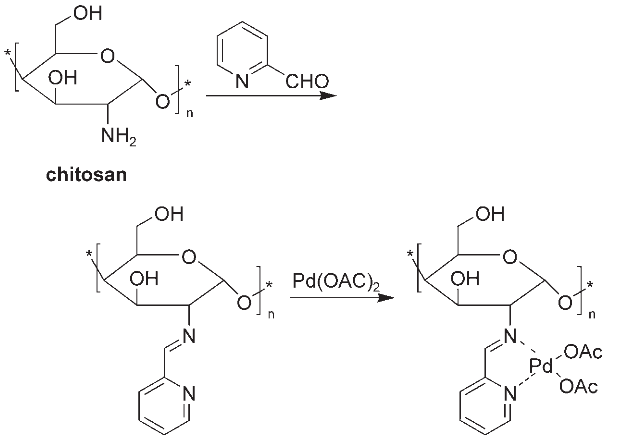


94

Figure 15. Iminopyridine ligated Pd(II) on poly(propylene-imine) dendrimers **93** and **94**.

yl acrylate, styrene and 1-octene.[469] The metallodendrimer was found to give higher reaction rates compared to the homogeneous ligand and $PdCl_2$. Palladium black formation was observed with both non-dendrimer precatalysts, although it was not observed with the dendritic system. There were no studies performed aimed at reuse of the precatalyst or probing whether leached Pd might promote the reaction.

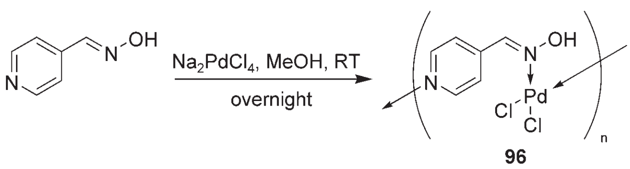
Macquarrie and co-workers immobilized an iminopyridine ligand on the sugar-based polymer chitosan (Scheme 28), metalated it with $Pd(OAc)_2$, and evaluated the supported material in the Suzuki and Heck reactions of bromobenzene or iodobenzene.[470] Immobilization of the palladium resulted in a solid with 18% of the ligands coordinating palladium. The catalyst was conditioned by prolonged reflux in ethanol, toluene and acetonitrile to remove any physisorbed, leachable Pd[471]. Catalyst reuse without a washing and regeneration process proved problematic, although it could be effectively recycled five times if it was washed with aqueous methanol, pure methanol and then dried. The homogeneous analogue was tested in the Suzuki reaction, giving increased initial rates but decreased long-term stability. It was proposed that the supported catalyst stopped deactivation by impeding solution-phase clustering. Reactions that proceeded for a long time were characterized by a simultaneous deboronation of the phenylboronic acid occurring alongside the coupling reaction. It should be noted that both the side-reaction rates and overall rates decreased substantially upon lowering the reaction temperature, perhaps a sign that some catalyst restructuring took place at higher temperatures. Later, Macquarrie, Clark and co-workers studied silane-functionalized starch as a support for Pd in various coupling reactions.[472] The support was of relatively low surface area, but decent Pd loadings were still obtained, with much of the Pd in the form of Pd(0) nanoparticles that formed during the immobilization process. Using the conditioning process they reported previously (*vide supra*) to insure removal of physisorbed Pd, solid precatalysts were obtained that displayed excellent properties. In particular, hot filtration tests showed no indication of leached active species and ICP analysis of the liquid phase also showed no palladium leaching. This was the case for Heck, Suzuki and Sonogashira reactions. It should be noted that very high reaction temperatures were used in most cases, conditions where normally some palladium restructuring and leaching would be expected. Perhaps the nature of the catalyst support, with many potentially ligating hydroxy groups, helps to prevent palladium loss to some degree.



Scheme 28. Immobilization of an iminopyridine ligand on the natural polymer chitosan followed by metalation with Pd(II) to create precatalyst **95**.

Although not of the same type as the catalysts described above, Kirschning and co-workers also reported the use of polymer-supported Pd(II) complexes in Suzuki couplings.[473] In their work, the authors prepared intramolecular, bidentate iminopyridine ligands to create a polymeric material composed of ligated Pd(II) units (e.g., **96** in Scheme 29). The solid was successfully used in a “tea-bag” approach for Suzuki couplings, including 14 consecutive successful recycles, achieving a modest TON of 2100. The nature of the active species was not clear, although the authors could not rule out catalysis associated with soluble, naked Pd(0) species.[184]

A huge variety of polymer-ligated metal ligand complexes has been reported for Heck and Suzuki couplings. In essentially all cases, some leaching of palladium was



Scheme 29. Polymeric Pd(II) iminopyridine material **96** with palladium part of the polymer backbone.

noted when the potential for leaching was considered. In most cases, some supported palladium could be recovered after reaction and often used subsequently in another reaction. Only in rare cases was strong evidence for the presence of truly supported, active palladium species reported. In nearly all cases it is possible that some fraction of the observed activity was associated with soluble, leached species. Nonetheless, the potential for leaching-free, highly active supported metal-ligand complexes exists if supports can be designed that retain both Pd(0) and Pd(II). As an alternative, supported systems that slowly release trace amounts of active palladium to solution may also be useful, especially if the redeposition of the leached palladium is possible, as is observed with many traditional oxide and carbon-supported Pd(0) metal particle systems.

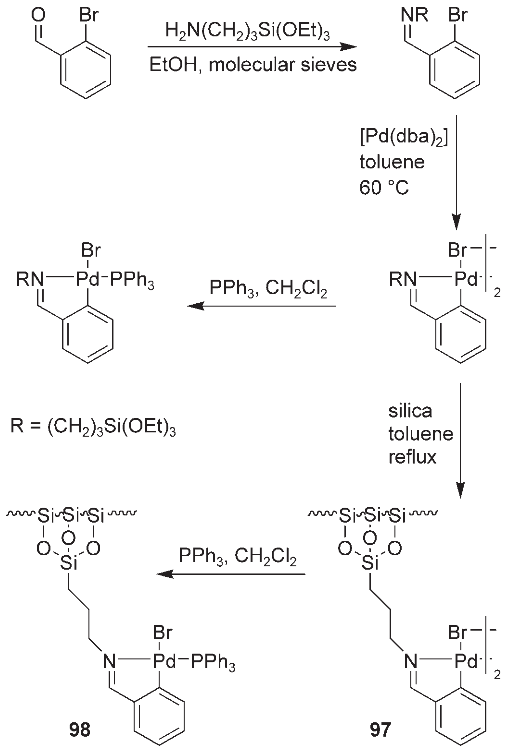
4.3.2 Oxide-Supported Metal-Ligand Complexes

In addition to polymer-supported ligands, a myriad of inorganic solid supported ligands has been used to complex palladium salts in an effort to generate recoverable, recyclable precatalysts. In the 1990s, a variety of short reports of ligand-functionalized oxides loaded with palladium salts in catalytic coupling reactions appeared. Zhang and co-workers immobilized Pd(II) species on various amine-containing silica materials and reduced them to form Pd(0) before using them in the Heck coupling of aryl halides and olefins.[474] The ligands attached to silica included poly(benzimidazole), *N*-methylaniline, and 2- and 3-methylpyridines. Whereas polymer-supported phenanthroline-Pd(0) catalysts were capable of converting bromobenzene,[442] these silica-supported precatalysts were essentially inert to this reactant. However, iodoarenes were converted. In some cases, Pd leaching was evident and recycle and reuse of the solid precatalysts was problematic, whereas others were reused, in some cases up to 10 times. As with the work on polymeric supports,[442–444] the state of Pd [other than that some Pd(0) was present] was unclear in these solids. Cai et al. have studied Pd(0) and Pd(II) species supported on functionalized silicas as precatalysts in coupling reactions for a number of years. Examples of supported ligands used include thiols,[475–477] thioethers,[478,479] diaryl(alkyl)phosphines,[480,481] diaryl(alkyl)arsines,[482–487] bidentate diaryl(alkyl)arsines,[488,489] γ-methylselenopropyl groups[490,491] and others.[492–496] In many cases, the precatalysts were recoverable and reusable, although often palladium leaching was encountered. In most cases, the nature of the true catalytic species was unclear. Zhou et al. immobilized $PdCl_2$ on primary, secondary and tertiary amine-functionalized silica materials and reduced them using KBH_4.[497] The solids were used in the Heck reaction of iodobenzene and olefins. Significant leaching was found to have occurred over several cycles with the Pd content of the solids changing from 2.52 to 1.57 to 1.4% after the first three cycles. No discussion about the nature of the catalytic species was presented. Varma et al. reported clay-intercalated Pd(II) complexes in Heck and Suzuki couplings, including recycle of the precatalyst.[498–500]

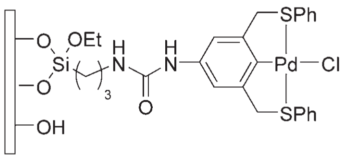
Kiviaho and co-workers studied $PdX_2(PPh_3)_2$ complexes loaded on functionalized silica materials as precatalysts in the Heck reaction of iodobenzene and methyl acrylate.[501] Silica materials were functionalized with poly(alumazane), poly(titanazane), or poly(stanazane), leaving primary amine ligands on the surface for binding to the palladium. The precatalysts could be recycled and behaved better in the second use, compared to the first, with regard to selectivity to Heck products *vs.* iodobenzene decomposition to form benzene. In the first run, a small fraction of the palladium was leached from the solid. Some precatalysts displayed induction times, although they all behaved similarly after a few hours of reaction. It was reported that the solids did not lose any activity after recovery *via* filtration, washing and drying. XPS was used to corroborate the chemical bonds between palladium and nitrogen. During reaction, the authors postulated that the two phosphine ligands were lost from the reduced Pd(0) species, but that the Pd(0) remained bound to the surface amines. The authors indicated that breakage of the Pd–N bonds could also occur, creating soluble $Pd(0){-}P(Ph_3)_2$ species, although they argued that these only play a minor role if they are formed at all.

Alper et al. prepared poly(amidoamine) dendrimers with bidentate arylphosphines at the periphery and a silica surface at the core.[502] The phosphine ligands were loaded with Pd(II) species and the resulting solid material was studied in the Heck reaction of bromobenzene with styrene. Precatalysts with 0, 1 or 2 generation dendrimers were effective, whereas rates dropped for generation 3 and 4 dendrimers. At high temperatures, the authors noted that palladium black formed, indicating that the palladium species may be labile under the reaction conditions. Application of a filtration test *after* a reaction and addition of fresh reactants to the filtrate were used by the authors to rule out homogeneous catalysis, as no further reaction was observed.

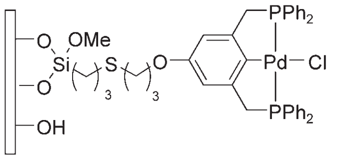
Bedford et al. prepared silica-supported NC imine palladacycles (e.g., **97** and **98** in Scheme 30) and evaluated their use as precatalysts in the Suzuki coupling of bromoarenes and phenylboronic acid.[225] Two different



Scheme 30. Silica-supported NC imine palladacycles **97** and **98**.



99



100

Figure 16. Silica-supported tridentate palladacycle complexes based on SCS **99**, and PCP **100** ligands.

supported palladacycles were studied, one with an added PPh_3 ligand and one without. Both were shown to decompose to form significant soluble catalytic species under the reaction conditions. Reaction brought about a significant color change in the solid catalyst, going from pale yellow to a brownish red, consistent with formation of Pd(0) nanoparticles. Unlike Nowotny's work on a poly(styrene) support,[219] Bedford et al. showed that the silica-supported precatalysts could be recycled at least a few times, although with decreased yields, in the absence of triphenylphosphine. Thus, the silica surface may serve to stabilize the nanoparticles formed, acting as a palladium nanoparticle reservoir, allowing the solid to perhaps operate by a release and capture mechanism.[350,351] For the phosphine-containing system, recycle was found to be more problematic, with the authors hypothesizing that this was due to enhanced solublization of palladium *via* low-coordinated palladium-phosphine complexes. The authors surmised that catalyst decomposition occurred by reductive elimination of the ligand after addition of an arylboronic acid to the palladium.

Alper and Chanthateyanonth studied silica-tethered PCP palladacycles in the Heck reaction of iodo- and bromoarenes and olefins.[503] Significant palladium loss was observed after one use (13%), and after three uses, 58% of the palladium was lost from the solid. Nonetheless, the solids could be reused in a few runs, albeit with diminishing yields. The authors referred to the solid as a recyclable catalyst with good stability. It is now known in the light of more recent results on the stability of pincers in coupling reactions that these supported PCP systems are likely simply precatalysts for active, ligand-free palladium.

Jones, Weck and co-workers demonstrated that the tridentate palladacycles (SCS, PCP) (e.g., **99** and **100** in Figure 16), decomposed to form soluble, catalytic Pd(0) species in the Heck coupling of iodoarenes and olefins, much like the bidentate palladacycles (NC, PC, etc.).[249,250,270] Using a battery of tests, including kinetic studies, poisoning studies, filtration tests, and three phase tests, they showed that SCS complexes with ether, amide and urea groups acting as tethers and PCP complexes with the same tethering groups all decomposed. Furthermore, using an insoluble, polymeric poison that was selective for soluble catalytic species, the authors were able to show that there was no activity associated with both silica and polymer-supported catalysts, and that all activity came from the solution. Addition of Hg(0) completely extinguished the activity. The combination of the Hg(0) results and polymeric-poisoning results together strongly suggested that catalysis by a Pd(II)-Pd(IV) cycle using intact Pd pincers was not possible under the conditions employed. This was the first study where catalysis by such a cycle could be rather conclusively ruled out.

Clark et al. studied bidentate iminopyridine ligands (i.e., **102** in Figure 17) grafted onto mesoporous silica gel as heterogeneous ligands for Pd(II) in the Heck coupling of aryl iodides and olefins.[504] After a single use in which there was a long induction period, they observed that the precatalyst could be recycled, with the authors demonstrating use in five consecutive reactions without any regeneration. They noted that there was no induction period after the first use, indicating that some precatalyst restructuring likely took place. The authors presented data that indicated that Pd leaching may not be important, as less than 0.1 ppm of Pd was detected in the final reaction solution. Of course, this does not preclude a solvation/redeposition process as has been seen by other authors.[350,351] Hot filtration tests showed that the solution after the precatalyst had been removed had only moderate activity, about 1/8 that of the fresh catalyst. Following up on the original study, the same authors reported the use of the precatalyst (e.g., **102** in Figure 17) in Suzuki couplings of bromobenzene and phenylboronic acid.[471] In that work, the authors claimed excellent recyclability and "total catalyst stability under reaction conditions." The iminopyridine-based solid precatalyst, after being loaded with $Pd(OAc)_2$, was used in 10 consecutive reactions after solid recovery by filtration. In doing so, a TON of several thousand was achieved, although the yields dropped after every cycle, with a steep drop after the first 5 cycles. No Pd could be detected in the liquid reaction mixtures using atomic absorption spectroscopy and hot filtration tests showed no activity in the solid-free solution. A variety of aryl bromides was converted, although aryl chlorides were found to be unreactive with the system. Although some leaching of active palladium cannot be ruled out based on (i) use of a filtration test alone and the fact that (ii) ppb and ppt levels of soluble palladium can catalyze the Suzuki coupling of aryl bromides and iodides (*vide infra*), this work represents a promising approach to build a truly heterogeneous Suzuki coupling catalyst.

Later, Clark and Paul studied a subtly different iminopyridine grafted onto silica (**101**) in the Suzuki coupling of aryl bromides and phenylboronic acid.[505] Again, easy to convert aryl bromides were used as reactants and the authors claimed the catalyst displayed "total stability under the reaction conditions." This new precatalyst displayed a rate substantially higher than that of the first generation precatalyst, reported as a unitless rate constant of 0.0364 *vs.* 0.00198 for the original system. About 10% of the available bidentate ligands were metalated with $Pd(OAc)_2$ to give the new catalyst. A myriad of different aryl bromides was coupled, and upon precatalyst removal from solution, no further reaction was observed in the filtrate. The authors successfully used the precatalysts in seven consecutive runs, achieving high yields in each run with progressively longer reaction times. Analysis of the solid after several uses showed no change in the surface area of the solid, a moderate change in pore volume, and the same weight loss in thermogravimteric analysis as with the fresh precatalyst. A slight loss of Pd was detected, from 0.1 mmol/g to 0.098 mmol/g.

In their most recent work, Clark and Paul studied a wider variety of bidentate ligands grafted onto a silica surface in the Suzuki coupling reaction, including NN, NS and NO ligands.[506] Eight solid precatalysts in total were prepared, including the two previously reported (e.g., **101**–**108** in Figure 17).[471,505] The precatalysts were characterized by a variety of techniques, and based on thermogravimetric analyses in the gas phase, the authors concluded that 100 °C would be a safe reaction temperature to carry out the solution reaction without any chance of catalyst decomposition. FT-IR analysis was used to confirm that Pd species coordinated to the imine groups, based on shifts in the bands for the C=N peak. Larger shifts were assigned to stronger binding. Unfortunately, these shifts did not correlate with the rate constants observed in the Suzuki reaction of bromobenzene and phenylboronic acid. Instead, the authors found a correlation between activity and XPS binding energy of Pd, with a lower energy corresponding to increased reactivity. This was interpreted as increased reaction rates correlating with electron-rich Pd.

Sugi et al. studied the same supported ligand as Clark[504] (e.g., **102** in Figure 17), focusing on the Heck reaction of aryl iodides and bromides with methyl acrylate using $PdCl_2$-loaded solids.[507] As in other studies, only a small fraction of the supported ligands were metalated by Pd, ~20%. The catalysis was studied in the presence of TBAB, and it was found that this additive induced the Pd to leach from the solid support to a significant extent (based on a filtration test). This observation raises an interesting question about the utility of a hot filtration result where active leached species are not detected. TBAB is proposed to stabilize homeopathic, active palladium species. Hence, it might be possible that leaching of active species was detected in this work[507] due to the prolonged lifetime of the leached species, whereas in the absence of TBAB, any leached active species might deactivate so quickly that they may be undetectable by a hot filtration test.[504] Sugi and co-workers noted that leaching was observed to be more significant using polar solvents, as others have reported. Several precatalysts were recovered from the reaction and reused up to seven times. Based on reported yields after 10 hours, the authors stated that the precatalysts do not lose any activity after the seven uses. Results were also reported for the Suzuki coupling of aryl bromides and phenylboronic acid.

Moggi and Lagasi studied a similar system in the Heck reaction of iodobenzene and olefins, although in their work they reduced the iminiopyridine to an aminopyridine (e.g., **109**–**111** in Figure 18) before adding the Pd(II) source.[508] The anchored Pd(II) was then reduced using $NaBH_4$ to give a supported Pd(0) material. The solid precatalysts were studied alongside their homogeneous analogues, which were also prepared. Metalation of the ligands was confirmed by FT-IR, with a 20 cm^{-1} shift to lower wavenumbers of the 1600 cm^{-1} peak. The solid was effectively used in a number of consecutive runs, sometimes numbering as high as 13, with virtually no change in TON. The new solid precatalysts showed a better stability than a Pd/C catalyst used as a control. Although the precatalysts were described as stable, TOFs were not tracked with each test and the extent of Pd leaching was not reported.

Kihinast has also recently reported silica-supported aminosilane-Pd complexes (e.g., **112**–**114** in Scheme 31) as precatalysts for the Suzuki coupling of aryl bromides with arylboronic acids.[509] Both supported precatalysts

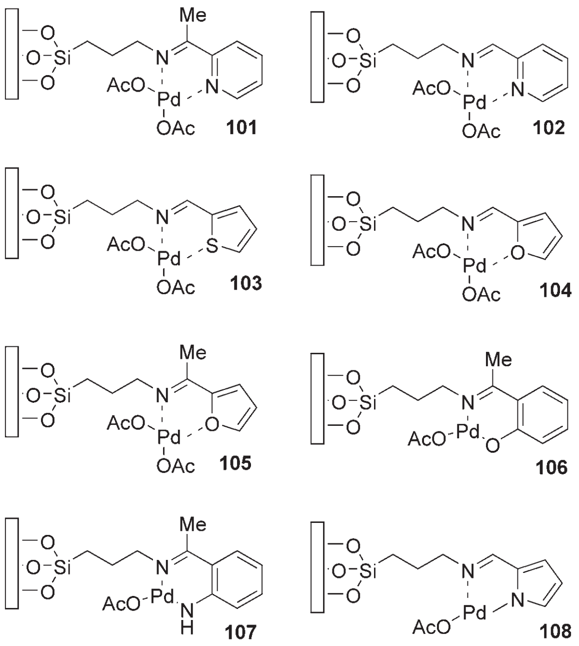


Figure 17. Pd(II) complexes of bidentate NN, NS, and NO ligands grafted onto silica **101**–**108**.

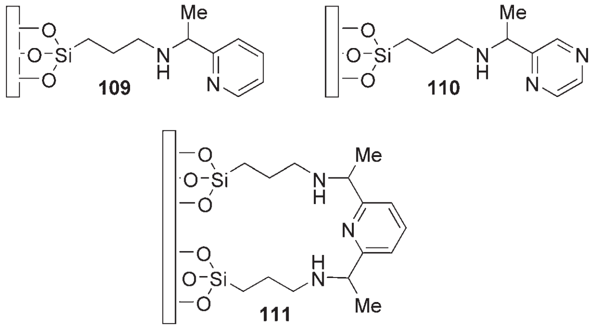
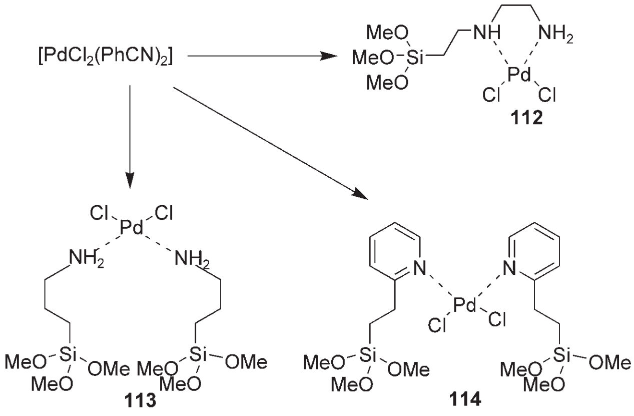


Figure 18. Aminopyridine-ligands grafted onto silica **109**–**111**.

and homogeneous analogues were prepared and well-characterized. Based on a calculated average spacing of aminosilane groups on the support surface, the authors concluded that the Pd species were ligated by a single organic ligand, although it should be noted that the well-known clustering of silanes on surfaces was not considered or ruled out. Upon carrying out the coupling reaction in isopropyl alcohol/water mixtures as solvent, the authors found that leaching was negligible in most cases as measured by ICP-MS analysis of the liquid phase. Additionally, hot filtration tests were used to show that the liquid phase displayed little or no activity in most cases. The higher observed activity of the solid precatalysts compared to the homogeneous analogue was suggested as evidence for truly heterogeneous catalysis.

Liu, Mou and co-workers immobilized bipyridyl ligands on mesoporous silica surfaces and loaded them with Pd(II) species.[510] The solid precatalysts were used in Heck couplings of aryl iodides and bromides with acrylates and styrene. The precatalysts were found to be active and recyclable, with the authors claiming the same activity in four runs. They concluded that the catalysis occurred with immobilized Pd species, as the Pd content of the solution *after* reaction was found to be negligible. A leaching/redeposition process was not considered.

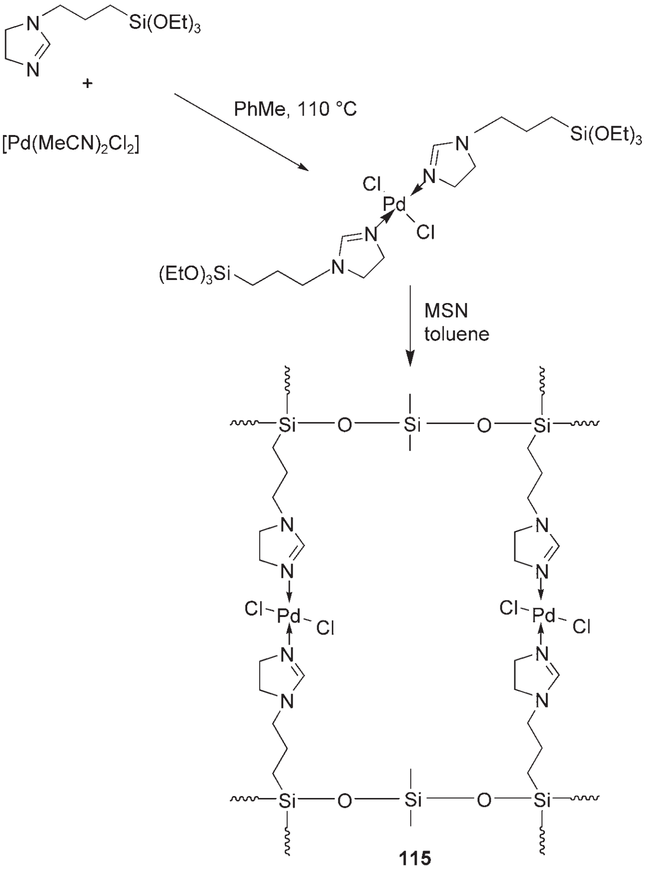


Scheme 31. Aminosilane-derived Pd(II) complexes **112**–**114**.

Ozdemir immobilized Pd(II) species on silica supports *via* ligation to 3-(4,5-dihydroimidazol-1-yl)-propyl tethers (e.g., **115** in Scheme 32) and utilized them in Heck and Suzuki coupling reactions.[511] Iodo-, bromo- and chloroarenes were studied, and in all cases where recycling was studied, the reused catalyst showed slightly depressed activity. The authors hypothesized that the ligand prevented decomposition to Pd metal.

Corma, García and co-workers immobilized oxime-carbapalladacycle palladium complexes **116** on mercaptopropyl-modified silica and evaluated these precatalysts in the Suzuki coupling of aryl bromides and chlorides in water.[512] This was achieved by preparation of a carbapalladacycle palladium complex with a pendant terminal olefin. This terminal olefin was coupled with thiols using a catalytic amount of a radical generator like AIBN to give thioether linkages to the silica support (Scheme 33).

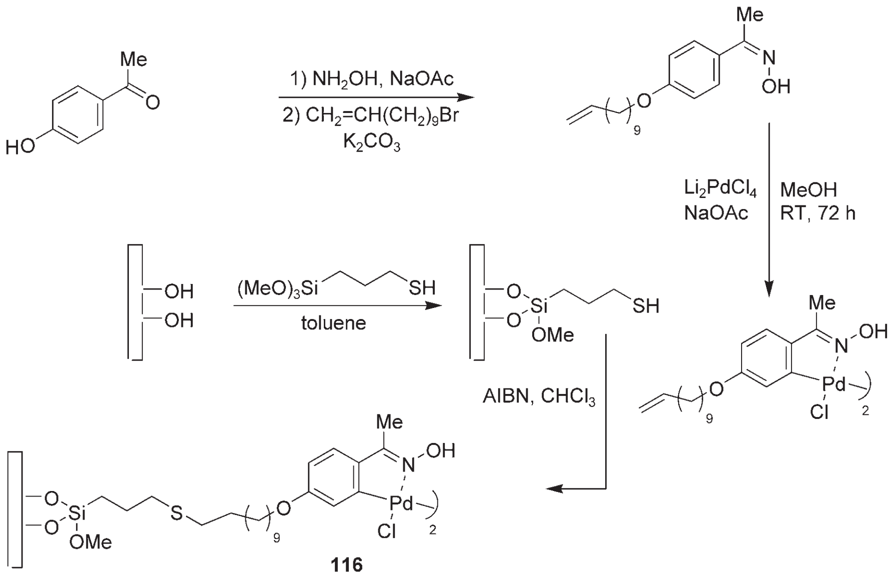
Elemental analyses showed that only about 50% of the thiol groups were consumed to form thioether linkages for the supported metal complexes.[513] In a more detailed publication, the authors expanded upon their initial results to include cross-linked poly(styrene)-supported complexes and poly(ethylene glycol dimethacrylate)-supported species as well.[513] Elemental analyses of the solids, UV-vis spectra, and FT-IR spectra all supported the hypothesis that the palladium complex was incorporated into the solid without significant decomposition. In the Suzuki coupling of phenylboronic acid with 4-chloroacetonphenone in water, dioxane, or water/dioxane mixtures, all precatalysts were found to generate



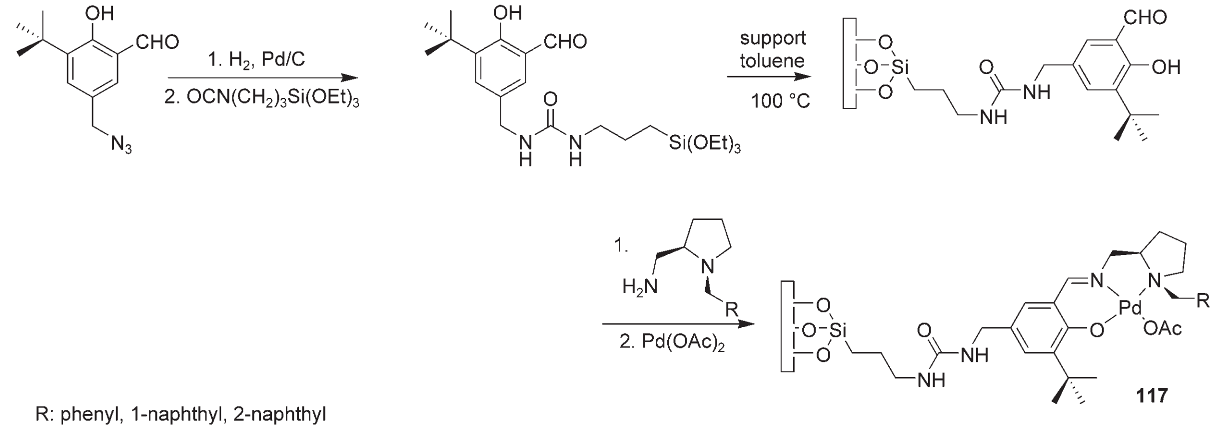
Scheme 32. $PdCl_2$ immobilized on silica functionalized with η^2 nitrogen donor ligand to give immobilized complex **115**.

active species, although the polymeric and silica catalysts behaved differently from a rate perspective in aqueous *vs.* organic solvents. Other aryl bromides, chlorides and even a fluoride were also effectively converted. Detailed studies focusing on the nature of the true catalyst were carried out for the silica-supported carbapalladacycle catalyst. Application of a filtration test and a three phase test indicated that small amounts of leached species that can convert iodoarenes were present, although they could not convert chloroarenes. It is interesting to note that these leaching tests were performed on a silica material with free thiol groups and no data were given for the polymer-supported precatalysts that lack thiols. It has been shown by others[514,515] that thiols may represent good ligands for retaining potentially labile palladium species from entering solution (*vide infra*). Thus, one new hypothesis for the mechanism for this action by this catalyst is (i) decomposition of the palladacycle to liberate small amounts of free Pd species (most non-NHC palladacycles have been shown to be sources of free palladium – *vide supra*), (ii) trapping of these free Pd species by the excess thiol groups on the surface, (iii) heterogeneous conversion of chloroarenes on these immobilized sites.

These initial studies were followed up by additional work whereby the dimeric, molecular alkoxysilane-containing carbapalladacycle complex was incorporated into a periodic mesoporous organosilica by direct synthesis.[516] This new material was studied alongside a mesoporous silica material that was loaded with the complex by a more traditional grafting approach. It is noteworthy that these complexes utilized a urea linkage between the complex and the support tether, and no thiol groups were incorporated into the solid, nor were there any thioether groups in the material. Characterization of the periodic mesoporous organosilica material



Scheme 33. Synthesis of the silica-supported oxime-carbapalladacycle complex **116** *via* radical coupling of the olefin-containing metal complex with the thiol-functionalized surface.



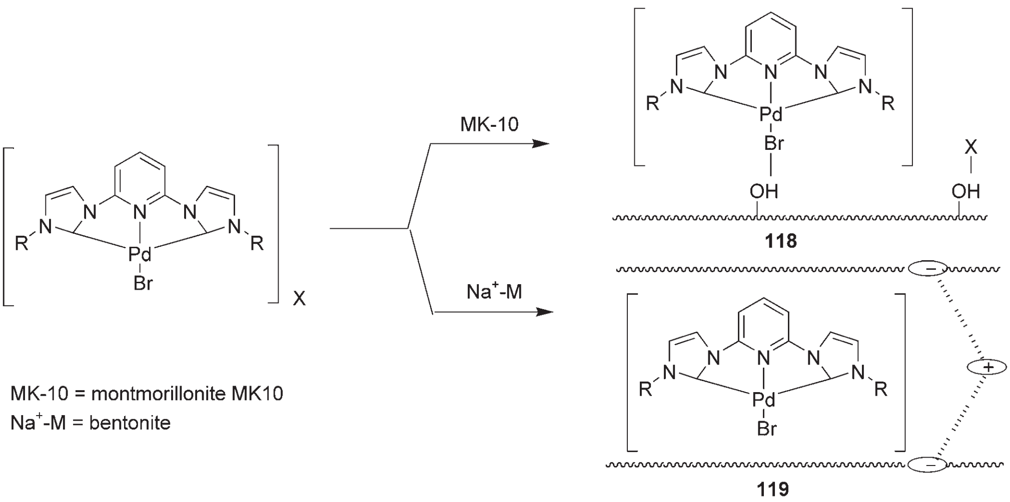
Scheme 34. Immobilization of a tridentate NNO ligand on silica followed by metalation with palladium to give precatalyst **117**.

suggested that the complex had remained largely intact during the synthesis. The catalysts were active in the Suzuki coupling of 4-bromobenzoic acid and phenylboronic acid in water, although the reactivity of the materials was found to depend significantly on palladium loading, perhaps due to the inaccessibility of some sites. Leaching studies indicated that some or all of the activity was associated with leached, soluble species (filtration test, three phase test). Characterization of the precatalyst upon recycle indicated that, by the end of the second use, no intact palladacycle remained. However, there was no significant variation in the palladium content of the solid, indicating that only trace amounts of leached palladium may account for much of the reactivity and that a leaching/deposition process may occur. The authors hypothesized that the active species might be nanosized palladium particles. Unlike the previous work on chloroarenes[513], there was no evidence to suggest activity associated with immobilized sites, and this may be a consequence of a lack of stabilizing thiol species on the surface (*vide infra*).

Iglesias, Sanchez and co-workers studied a tridentate NNO Pd(II) complex **117** immobilized on mesoporous and delaminated, layered silica materials (Scheme 34) as a precatalyst for the Heck and Suzuki coupling reactions in mixed polar/non-polar media.[517] The precatalysts could effectively convert bromo- and iodoarenes, although they did not work with chloroarenes. Like in the work of Styring,[457,458] if the active catalysts were truly immobilized ligand-bound palladium species, they presumably must drop one of the ligand bonds to become bidentate if the traditional Heck or Suzuki coupling cycle with square planar tetracoordinated palladium species was followed. When NMP was used as a solvent, significant amounts of leaching were observed, whereas in the biphasic liquid, ethylene glycol/toluene, no leaching of active species was noted. Relatively large concentrations of precatalyst were needed, with 2 mol% being the minimum amount required. Compared to the homogeneous complex, the solid precatalysts had longer lifetimes and it was presumed that this was due to prevention of palladium clustering *via* immobilization. The precatalyst was recycled by reusing the ethylene glycol phase up to six times with addition of fresh toluene and base. After the first use, yields increased markedly, presumably due to the presence of Pd(0), and then slowly dropped with successive cycles. Based on FT-IR, UV-vis and ^{13}C NMR characterization after reaction, the authors claimed that the supported palladium species remained intact. Elemental analysis of the solid showed minimal palladium loss after several uses and filtration experiments indicated that there was no reaction in the absence of the solid and, thus, the authors concluded they had a truly heterogeneous catalyst.

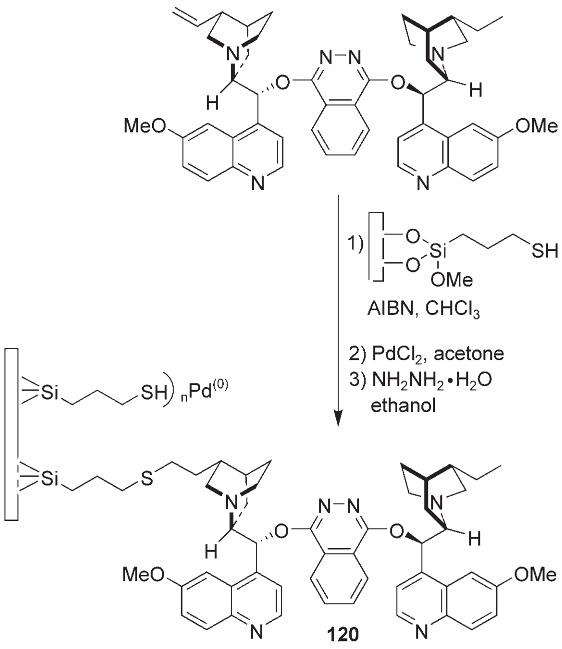
Singh and co-workers immobilized Pd on hydroxypropyl-functionalized silicas, claiming that OC palladacycle complexes were formed.[518,519] In some cases, evidence for the formation of bulk palladium metal was also observed. These solids were used in the Heck coupling of bromobenzene and styrene, and were claimed to be heterogeneous catalysts based on filtration tests. However, in light of the findings that nearly all palladacycles decompose to liberate active, potentially ligand-free Pd(0) species, it is questionable whether the immobilized palladacyclic species were truly active in this case.

Peris, Fernandez and co-workers immobilized Pd(II) CNC pincer complexes on clay materials *via* solvent impregnation (Scheme 35).[520] The precatalysts were then evaluated in the Heck reaction of iodobenzene and styrene. The authors concluded that the structures of the metal complexes were unchanged after immobilization based on characterization of the solids using FT-Raman spectroscopy. Two different clays were used as hosts and it was surmised that they offered different types of immobilized species. In the case of the montmorillonite clay MK-10, hydrogen bonding was proposed as the key means of immobilization (giving **118**), whereas in Na^{+}–M, electrostatic interactions between the countercation and the bentonite clay layers were proposed (giving **119**). The authors found that the reaction kinetics us-



Scheme 35. Pd(II) CNC complexes immobilized on clay materials *via* hydrogen bonding (**118**) and *via* electrostatic interactions (**119**).

ing the homogeneous and supported species (on MK-10) were similar at all temperatures tested (120–180 °C). It appeared that activity associated with leached palladium was discounted because the hot filtrate used *after* the first run was found to be inactive when additional reactants were charged to it in the absence of the solid catalyst. A palladium redeposition process was apparently not considered. The recycled solid precatalyst, however, was observed to be significantly deactivated after a single use. After three uses, the palladium loading was found to have decreased significantly, (0.8% wt–0.5% by wt or 0.43% by wt after a water/methanol wash to remove adsorbed salts), based on bulk elemental analyses. XPS was also used for elemental analysis and it showed that the surface Pd loading was also changing with recycle relative to the silicon content. Interestingly, XPS studies showed that the palladium remained in the Pd(II) state after use, with no sign of Pd(0) (although this might be expected if the precatalysts were not milled – *vide infra*[521]). This was consistent with homogeneous studies by others[522] where it appeared the authors hypothesized that the catalyst potentially could operate *via* a Pd(II)–Pd(IV) cycle, although the authors never explicitly stated this. Using triethylamine as base, it was possible to greatly increase the precatalyst longevity and recyclability. Conversion of aryl bromides, including relatively unreactive species, was possible upon addition of TBAB.[520] The same authors studied the solid precatalyst in Sonogashira couplings as well, finding the solid to be active and recyclable with similar overall conversions for several different monomers.[523] Whereas the washed precatalysts were not observed to contain any palladium black, the authors noted that Pd black was observed in some experiments after all the substrate had been consumed, which is a sure sign of some complex decomposition. Overall, this system represents a very interesting case for further study, as the precatalyst appears not to generate Pd(0) in some cases, yet the tridentate, 6-electron donating ligand would appear to need to partially decoordinate to allow conversion by a typical Heck reaction cycle involving square planar metal species.



Scheme 36. Grafting of palladium and a chiral ligand for dihydroxylation chemistry onto mercaptopropyl-modified silica to give precatalyst **120**.

Four different research groups recently studied the use of thiol groups anchored on silica surfaces as ligands for Pd(II) and Pd(0) species in Heck and Suzuki reactions. Although they had been used before in coupling reactions,[441,475,476] they recently have been re-examined as supports with potentially unique properties. In the first study, Choudary et al. carried out a tandem Heck reaction–asymmetric dihydroxylation of olefins using a silica material loaded with both Pd nanoparticles on a thiolated surface and a chiral osmium complex attached to the same surface (e.g., **120** in Scheme 36).[524] Because the nature of the Heck catalyst was not a focus of the work, there were few details about the nature of the active species presented.

Later, Shimizu and co-workers presented a very detailed, careful study of Pd(II) species immobilized on a variety of supports, including mercaptopropyl-functionalized mesoporous silica, similarly functionalized amorphous silica, unfunctionalized mesoporous silica and zeolite NaY.[515] Alongside these freshly prepared catalysts, a commercial sample of Pd/C was also studied. In their comprehensive study, the authors characterized the state of the Pd in the solid both before and after reaction using multiple spectroscopic techniques, they characterized the kinetics of the reaction, and they studied the recyclability of the used precatalysts. For the thiol-supported Pd precatalysts, an S:Pd ratio of 1:0.36 was used, insuring the presence of excess ligand on the surface. Characterization of the precatalysts by X-ray absorption spectroscopy (both EXAFS and XANES) UV-vis spectroscopy and X-ray diffraction, showed that the mesoporous thiol-containing support, FSM-SH-Pd, was composed of Pd(II) species bound to two or more thiol groups. The amorphous silica loaded with thiol groups and Pd(II), (SiO_2-SH-Pd), appeared similar. Silica-supported $Pd(OAc)_2$, denoted SiO_2–Pd, had a structure not unlike that of $Pd(OAc)_2$, and Pd/C contained mostly oxidized Pd(II) in the form of PdO. After use in the Suzuki reaction of 4-bromoanisole and phenylboronic acid, each catalyst was again characterized by each technique. The Pd(II) species in the zeolite Y–Pd, SiO_2–Pd, and Pd/C samples were reduced to Pd(0) nearly fully in the reaction. In contrast, on SiO_2-SH-Pd and FSM-SH-Pd, the vast majority of the Pd remained in a Pd(II) state, ligated to sulfur ligands. In both these samples, small amounts of Pd nanoparticles were formed, but unlike the other samples, these were the minor species. All the catalysts were determined to have leached Pd, but the amounts varied, with zeolite Y–Pd losing ~6% of its palladium showing the highest leaching, and FSM-SH-Pd losing the least, 0.05%. The SiO_2-SH-Pd sample leached a similar amount. The fresh catalysts were also used in the Heck reaction of 4-bromoacetophenone and ethyl acrylate and then characterized by the same battery of techniques. The results mirrored those from the Suzuki test, with FSM-SH-Pd leaching 0.01% of the Pd and remaining largely stable over the course of the reaction. Again, a minor amount of Pd(0) formed on the support. A hot filtration test was used in the Heck reaction to check for leached, active species. Using FSM-SH-Pd, the authors found that the solution did not promote the reaction further after the solid precatalyst was removed. Both thiol-containing precatalysts were successfully used in five consecutive reactions, with the FSM catalyst giving slightly higher yields. However, no indication was given concerning the relative rates in each recycled reaction. Nonetheless, the FSM-SH-Pd precatalyst was found to give a highly active system, with the fresh precatalyst giving TONs of 73,000 and initial TOFs of 36,000 h^{-1}. Unfortunately, the precatalysts were found to be less active for the activation of more deactivated aryl halides, moderately converting 4-bromoanisole and bromobenzene and poorly converting 4-chloroacetophenone. The authors assigned the high activity of the thiol-containing precatalysts to immobilized Pd complexes, and they argued that dispersing Pd species on a thiol-laden support was a good way to create heterogeneous catalysts that have long-term stability. An alternate interpretation is that trace amounts of leached species carried out the reaction and that the thiol groups prevented large amounts of Pd from desorbing and aggregating as reduced Pd(0) clusters. The authors assigned the moderate activity of Pd/C on recycle to the moderate activity of Pd(0) nanoclusters that were deposited on the support after one use.

After Shimizu's work, Crudden et al. published another report of thiol-treated silica as a support for Pd precatalysts, this time studying the Heck and Suzuki couplings of chloroarenes and bromoarenes.[514] The materials used had an S:Pd ratio of 4:1 and could effectively be used in Suzuki couplings in both water, DMF, and a mixture of the two solvents, using potassium carbonate as base. Leaching of Pd into solution, as determined by elemental analysis, was extremely low, with concentrations of only 0.003 to 1.3 ppm detected. The mesoporous silica-supported, thiol-coordinated palladium materials proved to be recyclable with almost imperceptible decreases in yield (rates were not provided). In the Heck reaction, leaching was also found to be low, although it was markedly higher when aminosilica materials were used instead of mercaptopropyl materials (35 ppm or 10% of the Pd). Analysis of the level of Pd in solution at various points of the reaction showed that it was unchanging, indicating that a dissolution-redeposition process was unlikely. Application of a filtration test in a Suzuki coupling reaction indicated that only small amounts of active, soluble species were present, with the reaction proceeding very slowly after removal of the solid catalyst. Finally a three-phase test was carried out by immobilization of the aryl halide (bromide or chloride) onto a solid phase. A second solid phase containing the precatalyst was added, as was a solution of aryl halide and boronic acid and the reaction was conducted in the usual manner. To the liquid phase, 0.25 mmol of the soluble halide and 0.37 mmol of the arylboronic acid were added along with potassium carbonate as base. After the reaction, the solid phases were hydrolyzed using aqueous base. The organic products were recovered *via* a standard work-up and the ratio of products derived from soluble aryl halide (ketone)

Table 1. Summary of results obtained using thiol-modified silica materials as supports for Pd(II) precatalysts in Heck couplings.

Support material	Shimizu et al. mercaptopropyl-functionalized FSM-16	Crudden et al. mercaptopropyl-functionalized SBA-15	Davis et al. mercaptopropyl-functionalized SBA-15
Palladium source	$Pd(OAc)_2$	$Pd(OAc)_2$	$Pd(OAc)_2$
Ligand to metal ratio	2.8:1	4:1	1.6:1
Solvent	NMP	DMF	DMF
Halide	4-bromoacetophenone	4-bromoacetophenone	iodobenzene
Olefin	ethyl acrylate	styrene	*n*-butyl acrylate
Base	KOAc	NaOAc	triethylamine
Degree of leaching	0.01%	0.23 ppm	12 ppm
Proposed active species	immobilized Pd	immobilized Pd	leached Pd

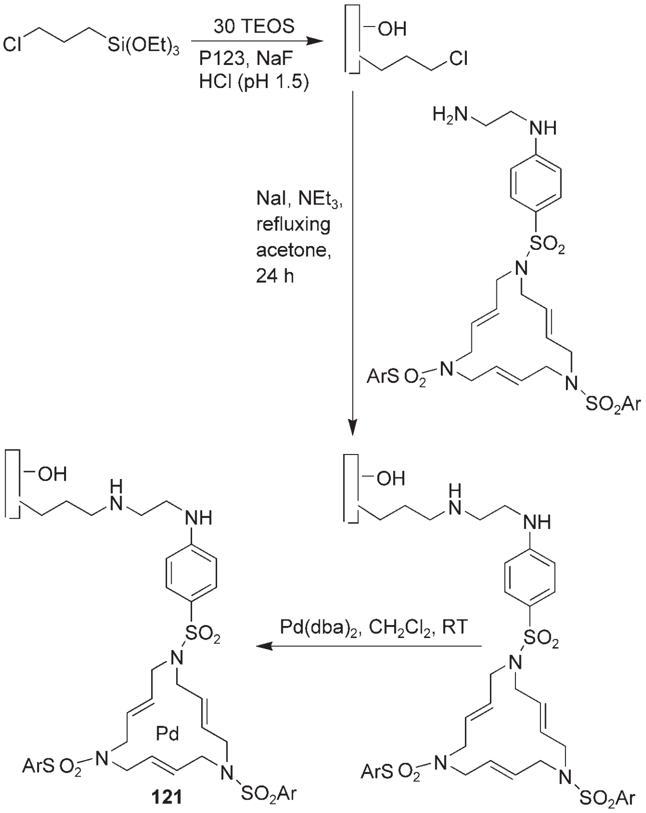
and supported aryl halide (acid) was determined by ^{1}H NMR. In all cases, the soluble aryl halide was completely or nearly completely converted, whereas the solid-bound halide was converted only to a limited extent (3–7% for the bromide and 0% for the chloride). The authors also illustrated an important, yet subtle point about using the three phase test as a test for soluble catalytic species. They argue, as Davies[379] did, that when an aryl halide was chosen as the tethered reactant, soluble aryl halide must also be added to the reactor as well in order to properly mimic the conditions whereby solid palladium is leached. While this is true in many cases, especially in the case of Pd/C, which Davies studied and which leaches primarily *via* oxidative addition of aryl halide, it is not necessarily the case in all circumstances. For instance, one could chose to immobilize the boronic acid for Suzuki couplings or an olefin for Heck couplings and use soluble aryl halide if it was hypothesized that the aryl halide was needed to induce leaching. Overall, the author's 3-phase test results, coupled with the leaching data based on elemental analysis and the filtration test results provided a compelling set of data that allowed the authors to conclude that the vast majority of the catalysis was occurring with Pd species on the solid, thiol-laden silica support.

The most recent study of thiol-supported mesoporous silica and amorphous silica-supported Pd in the Heck reaction resulted in exactly the opposite conclusion to those of Shimizu and Crudden, illustrating the subtleties of these coupling reactions. Davis and co-workers studied a variety of solid catalysts, including thiol-functionalized silicas loaded with $Pd(OAc)_2$, and concluded that they all leached active, soluble Pd species in the Heck coupling of *n*-butyl acrylate and iodobenzene, and that there was effectively no conclusive evidence for catalysis by any solid species in their case.[387] By combining batch reactor tests with flow reactor studies, poisoning studies, hot filtration tests and ICP analysis of the liquid media, a convincing body of evidence was assembled that showed that effectively all catalytic activity was likely associated with leached species. The authors show that the aryl halide is important in the leaching of reduced Pd(0), as was shown by Biffis,[363] and that base was necessary to leach Pd present in elevated oxidation states [e.g., Pd(II)]. This effect of base-induced leaching of Pd(II) was similar to what had been observed in leaching studies with immobilized, well-defined, Pd(II) complexes.[270] The work of Davis et al. is markedly different from that of Shimizu and Crudden in the halide used, the base used, as well as the ratio of S:Pd. This may contribute to the different results that each group reported (Table 1). In particular, the high solubility of the triethylammonium-stabilized palladium species that are likely formed in the reaction may lead to more leaching and/or stabilization of palladium (*vide supra*).

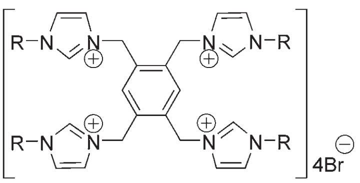
Mehdi, Pleixats and co-workers immobilized a cyclic, triolefin ligand onto silica supports (Scheme 37)[525] in a manner akin to their immobilization on polymeric supports (*vide supra*). The supported Pd(0) complexes (e.g., **121**) were used in Suzuki coupling reactions of aryl bromides and iodides. It was observed that catalysis by leached Pd species was not evident after a room temperature filtration test, whereas it was readily apparent after application of a hot filtration test, indicating that leached catalyst was responsible for at least some of the activity. Pd loss from the solid was found to be between 0.07 and 0.7% after use.

A unique ligand that contains two binding sites for Pd with two bidentate NHC ligands (e.g., **122a**, **122b**, **122c** in Figure 19) was used to complex Pd, and the resulting complexes were physically immobilized on oxide supports.[526] The resulting solids were used in the Suzuki coupling of aryl chlorides and bromides with phenylboronic acid. The authors reported that the precatalysts could be used 2–3 times in refluxing water. In the absence of the support, palladium black formed during the reaction.

Kosslick and Paetzold et al. reported a multifunctional "support" for water-soluble Pd(II) complexes of bidentate phosphines.[521,527] Mesoporous aluminosilicate or mesoporous alumina was first functionalized with a propylsulfonic acid containing silane, creating a solid



Scheme 37. Tethering of a cyclic triolefin ligand onto solid supports followed by metalation with Pd(0) to give precatalyst **121**.



122a R = 2,6-diisopropylphenyl
122b R = mesityl
122c R = *tert*-butyl

Figure 19. Molecules containing two bidentate NHC ligands built of a single phenyl core.

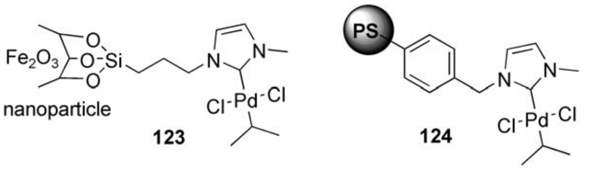


Figure 20. Pd-NHC complexes tethered on magnetic nanoparticles **123**, and polymer resin **124**.

material with cation exchange sites on the surface (two sites in the case of the aluminosilicate, one associated with anionic Al–O species and one with the sulfonic acid). The authors then proceed to "immobilize" a water-soluble palladium complex, $PdCl_2[Ph_2P(CH_2)_2S(CH_2)_3SO_3Na]_2$, on the solid "support." It is not clear how this is done, as the complex is an exchangeable anion but the solid is a cation exchange support. Perhaps the supported sulfonic acid acted as an electron donor ligand for Pd(0) and Pd(II) species, or perhaps the complex was simply physisorbed on the solid. Cationic surfactant was also exchanged with the solid support in some cases. Nonetheless, the authors used the precatalysts in Suzuki reactions in aqueous media, and activity was displayed with a noticeable induction period. Precatalysts that contained sulfonic acid groups allowed for much higher activity than those that lacked such oxide-bound groups. The precatalysts were also reported to be recoverable and reusable, although upon reuse the induction period was absent, providing evidence for the formation of Pd(0) in the first use. Pd(0) was indeed detected *via* XPS in the used catalyst, although the samples had to be milled to detect the reduced palladium. This was evidence that the Pd(0) was formed within the pores of the solid, not near the external surface. Filtration tests indicated that the solid free solution had some activity.

Most recently, Gao and co-workers reported on magnetic nanoparticle-tethered Pd-NHC complexes **123** (Figure 20) for use as recoverable precatalysts in Heck, Suzuki and Sonogashira reactions.[528,529] The precatalysts had improved reaction rates when compared to tethered catalysts on more traditional supports such as polymer resins (e.g. **124**), with the improved reactivity associated with the increased accessibility of the Pd sites. They showed that the majority of the precatalyst can be magnetically recovered (97%) and the solids could be reused in subsequent reactions. However, they did not provide any evidence that the NHC complexes remain intact during or after reaction, nor did they study whether any Pd leaching occurs, potentially resulting in homogeneous catalysis.

Supported aqueous phase or supported liquid phase methods have also been used to support palladium ligand complexes in an effort to facilitate catalyst recovery and recycle. Williams and co-workers immobilized a thin film of a polar solvent such as ethylene glycol on porous glass beads, loaded the liquid film with palladium complexes based on sulfonated phosphines, and added the solids to organic solutions bearing the Heck reaction reagents.[530] The system was effective in promoting the Heck reaction of iodobenzene with methyl acrylate with only limited leaching of Pd into the organic phase (0.2–8.4 ppm). Non-sulfonated phosphine complexes could also readily be used, with the authors reporting the use of guanidinium-phosphine complexes for Heck and Sonogashira couplings.[531] Williams later reported the reverse system, whereby the silica solid was made hydrophobic by organosilane treatment and was then loaded with $Pd(OAc)_2$ and triphenylphosphine or tri-*o*-tolylphosphine in cyclohexane as solvent.[532] Heck reactions were then run in water as solvent, with both aryl iodides and bromides used as reagents. In aqueous systems, Pd leaching was notable (~0.2% of added palladium leached), whereas in methanol or with no solvent, leaching was limited. In both the above reports, leaching was measured at the end of the reaction. In a more detailed report, Williams et al. described some interesting behavior regarding palladium leaching in supported liquid phase systems[533] that was akin to what was seen with the supported palladium metal catalysts described by Köhler and Arai (*vide supra*). As with traditional supported catalysts such as Pd/C, significant leaching of palladium occurred during the reaction (in this case from the supported polar phase into the non-polar organic phase), with the authors reporting that up to 85% of the activity could be associated with palladium species in the non-polar phase. After the reaction, however, the palladium redeposited onto the support leaving very low levels of palladium in the final product-containing organic phase. Furthermore, the organic phase was found to be inactive in converting additional aliquots of reagents after the reaction, indicating that essentially all of the active palladium had redeposited back onto the surface. It should be noted that Williams' report of this redeposition process[533] actually predates the reports of similar phenomena on traditional solid catalysts.[350–352,355–359] The authors also reported on the importance of the iodoarene in drawing the palladium off the support and into solution as well.

Arai and co-workers reported supported liquid phase catalysts as well. In their case, they loaded the solids with Pd(II)-triphenylphosphinetrisulfonate sodium salt complexes and studied their use in the Heck reaction of iodobenzene and olefins in toluene.[534–536] They found that the precatalysts were recoverable and recyclable, with minimal to moderate leaching of palladium into the organic phase. Leaching was as low as 1.8% of the palladium added when ethylene glycol was used as the polar phase, to ~20% when water was used. Reaction rates were enhanced upon reuse, and this was been attributed to reduction of some of the Pd(II) to Pd(0) and *in-situ* formation of quaternary ammonium compounds by trialkylamine plus HI created in the first reaction.

In an interesting twist on supported liquid phase systems, Hagiwara and co-workers added a hydrophobic ionic liquid to a reverse-phase silica gel and immobilized $Pd(OAc)_2$ on the support for use in aqueous Heck reactions.[537]

As for polymeric supports, a huge variety of oxide-ligated metal ligand complexes has been reported for Heck and Suzuki couplings. As most of these supports were insoluble, the leaching of active palladium could be assessed to a greater extent *via* application of a filtration test, although as noted, this test alone is not a conclusive way to characterize leaching (*vide infra*). In most cases, some supported palladium could be recovered after reaction and often used subsequently in another reaction. Only in rare cases was strong evidence for the presence of truly supported, active palladium species reported, with this being more common for Suzuki couplings, and a few systems here appear promising as nearly leaching-free supports for palladium in Heck and Suzuki couplings. In particular, the use of thiols[387,514,515] for palladium immobilization and the utility of Clark/Macqaurrie's extensive solvent treatment steps[471] in the immobilization of stable metal-ligand complexes on solids warrant further investigation to gauge their broader utility.

4.4 Soluble or Polymer Nanosphere-Supported Pd Nanoparticle Precatalysts

Beller first reported the use of preformed colloids as precatalysts in Heck couplings.[331,538] The colloid system effectively promoted the Heck coupling of aryl bromides at high temperatures, although the colloids were found to be unstable under the reaction conditions, leading eventually to palladium black formation. Reetz reported independently early in 1996 that Pd nanoparticles stabilized in solution by propylene carbonate[539] were effective catalysts for conversion of bromoarenes, with the hypothesis at the time being that the surface of the colloids catalyzed the reaction in a heterogeneous manner. The colloidal system was also found to be active for aryl chloride-olefin couplings in the Heck reaction. Relatively high temperatures and high loadings were used. That same year, Reetz et al. reported the use of soluble palladium clusters in Heck and Suzuki reactions of iodo-, bromo- and activated chloroarenes when combined with tetraalkylammonium salts or poly(vinylpyrrolidone) (PVP).[540] Again, in that work, it was suggested that the metal surface of the palladium colloid was the active site in the reaction. In 1998, Reetz showed that the combination of palladium clusters with tetraphenylphosphonium salts yielded an excellent system for the activation of chlorobenzene in the Heck reaction.[541] In that case, the authors noted that there was practically no undesired Pd precipitate, even at relatively high temperatures.

Antonietti utilized poly(styrene)-co(vinylpyridine) block copolymer micelles to stabilize Pd nanoparticles produced *via* reduction of $Pd(OAc)_2$. The supported nanoparticle materials, which were soluble under the reaction conditions in toluene, were applied in the coupling of olefins and aryl bromides under Heck conditions.[542] The precatalysts displayed about the same reactivity as low molecular weight Pd complexes classically used in the Heck reaction, although they displayed higher stability. Under optimized conditions, no noticeable change in the size of the nanoparticles occurred during reaction and palladium black was not observed to form. In testing different size colloids, a strong inverse correlation between activity and particle size was observed.[331] The authors attributed the reactivity to a Pd nanoparticle surface-catalyzed reaction occurring within the block copolymer micelles. The solids were claimed to be reusable without loss of activity, although no details were given about the recycling.[331]

Bradley, Blackmond and co-workers prepared PVP-stabilized Pd nanoparticles of different sizes and used them in the Heck reaction of *p*-bromobenzaldehyde and butyl acrylate.[543] Interestingly, the authors found that the initial rates increased with decreasing particle size, but no direct correlation with the metal surface area was noted.[331] Although it was not possible to ascertain the precise structure of the nanoparticles, the authors found that they were equidimensional and thus were able to apply surface defect site statistics to characterize their hypothesized surface structure. Utilizing the knowledge that the relative population of highly coordinated sites and low coordinated defect sites on the surface varied with particle size, the authors used TOFs derived from reaction calorimetry at 10% conversion coupled with knowledge about the particle sizes of the colloids to characterize the reactions. The authors found that the observed reaction rate correlated most closely with the number of surface defect sites, and that there was a poor correlation with the total number of exposed surface sites. The authors ruled out catalysis by non-nanoparticle solution phase species, despite the fact that the size of the nanoparticles changed during the reaction, based on the observation in a control reaction that the reaction kinetics when using $Pd(dba)_2$ as a naked homogeneous catalyst were different. An alternate interpretation of their work is that defect sites are important as the authors noted, but that these are the sites that leach from the surface to form active, soluble molecular species and that the oxidative addition of the aryl halide at these sites, liberating a molecular species, was an important step in the reaction.

Poly(vinylpyridine) nanospheres were employed as polymeric supports for 1–4 nm Pd(0) nanoparticles by Prakash et al. in the study of Suzuki and Heck coupling reactions of aryl bromides and standard olefinic or boronic acid substrates.[544] Although it is often reported that the nature of the stabilizing groups on the nanoparticles strongly effects catalysis by them [e.g., citrate, poly(pyrrolidone), poly(vinyl alcohol)], no effect was observed in this study. The authors surmised that the polymer-loaded nanoparticles were stable under reaction conditions, although only relatively macroscopic TEM images were utilized to support this hypothesis. Given the small amount of Pd species that need to leach in order to allow for significant catalytic activity in Heck and Suzuki couplings, it is not surprising that no major changes in nanoparticle size or shape were observed.

El Sayed and co-workers began a long-term study of polymer-capped colloidal Pd and Pt nanoparticles as precatalysts in aqueous Suzuki couplings. Beginning in 2000, they reported their studies of iodoarene couplings with arylboronic acids using PVP as a nanoparticle capping agent.[545] They reported that the initial rate depended linearly on the concentration of palladium in the system, and interpreted this as evidence for the catalysis occurring on the nanoparticle surface. Catalyst deactivation occurred during the reaction and in some cases they observed precipitation of palladium black, indicating that some Pd restructuring was occurring during the course of the reaction. Subsequently, a variety of different stabilizers were studied, including hydroxy-terminated poly(amidoamine) (PAMAM) dendrimers of various generations, block copolymer poly(styrene)-b-poly(sodium acrylate) and PVP.[546] Both bromo- and iodoarenes were studied, with some homocoupling of bromoarenes being observed. The authors found that catalytic activity and nanoparticle stability were inversely correlated, with capping agents that gave good nanoparticle stability yielding slow reaction rates. G4 dendrimers gave good stability and poor rates, while G2 dendrimers gave better coupling rates with relatively poor nanoparticle stability. These results were interpreted as consistent with the nanoparticle surface acting as the active site. An alternative interpretation not espoused in the work would be that capping prevented solublization of a small amount of molecular Pd species that might serve as the true, active catalyst. Pd black precipitation was found to vary with reaction conditions such as the base used, pH and other factors. Later, the role of nanoparticle size on the catalytic properties was investigated.[547] Studying Pd nanoparticles of four different sizes stabilized by PVP, the authors discovered that the reactivity did not scale perfectly with nanoparticle size. Rather, assuming the surface reaction model previously described was correct, they provided data that indicated that the catalytic activity best correlated with the number of low coordination edge and vertex atoms. Similar results were reported previously for PVP-stabilized Pd nanoparticles in Heck couplings by other authors.[543] El Sayed and Narayanan studied the stability of PVP-capped nanoparticles under such reaction conditions and monitored the distribution of nanoparticles sizes as a function of different treatment conditions.[548] They found that most treatment conditions (solvent, solvent plus reagent, catalytic reaction, etc.) resulted in an increase in the breadth of the nanoparticle size distribution as well as an increase in the mean nanoparticle size. They attributed this to an Otswald ripening process. When the nanoparticles were recycled and used in a second reaction, they observed that the average particle size decreased, which they attributed to the aggregation and precipitation of larger nanoparticles. Regardless, their data make it clear that some solublization of Pd occurs under the reaction conditions. In line with this, they observed that addition of excess PVP inhibits both the catalytic activity of the system as well as the Otswald ripening process. This observation is consistent with both the authors' hypothesis that catalysis occurs at specific sites on the palladium nanoparticle surface and with the alternate hypothesis that PVP may act as a soluble catalyst poison, removing leached species from solution, as has been espoused in other studies (*vide infra*).[249,250] In a later paper, they showed that excess PAMAM dendrimer has an even more significant effect on the activity.[549] Interestingly, the authors observed that the boronic acid strongly adsorbed onto the surface of the nanoparticles, effectively capping them and reducing the extent of size redistribution. In contrast, iodobenzene did not have this effect. These observations led to the proposal that the catalytic reaction mechanism involved an Eley Rideal process whereby the deprotonated boronic acid adsorbed onto the nanoparticle surface and reacted with aryl halide that was in solution.[548–551] The authors reported detailed FT-IR studies that showed that the boronic acid did adsorb whereas the aryl iodide did not, which they suggested confirmed their proposed mechanism.[551] Pt nanoparticles were also studied in the same reaction and they were observed to display the same nanoparticle size redistribution effects as the Pd systems, although with lower catalytic activity.[550]

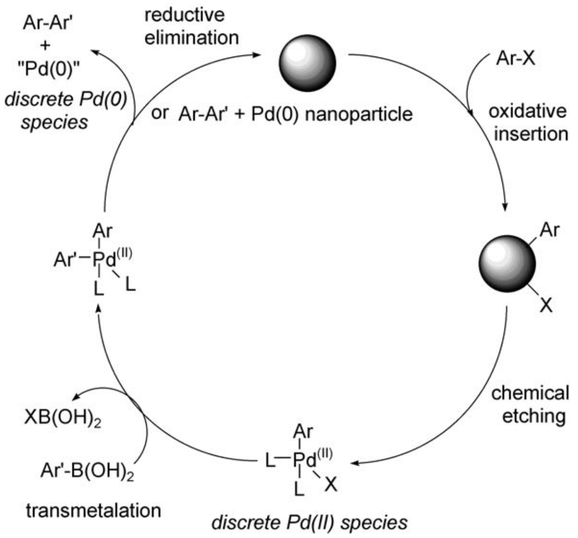
Crooks et al. demonstrated in 2001 that Pd nanoparticles of about 2 nm in diameter stabilized by poly(amidoamine) dendrimers could be used to promote the Heck reaction of aryl iodides and bromides.[552] Significant decomposition of the nanoparticles and Pd leaching were not detected and the polymer-stabilized nanoparticles could be recycled under some conditions. Catalyst activity generally decreased with recycle. The precatalysts could be used without external base, with the hypothesis being that the amidoamine groups of the dendrimer served as base sites in this case. Under these conditions, the catalyst was inactive upon recycle. The same group studied Stille reactions in aqueous media using dendrimer-stabilized Pd(0) nanoparticles.[553] At high temperatures, significant Pd aggregation was observed and Pd black was formed. At lower temperatures, the catalyst appeared stable and the authors attributed the reaction to catalysis by metal nanoparticles.

Dendrimer encapsulated Pd nanoparticles were also studied in the Heck reaction by Christensen et al. who found that Pd leached from the polymer-stabilized nanoparticles when DMF was used as solvent with triethylamine as base.[554] In a later report, they studied the Suzuki coupling of aryl iodides and bromides with *p*-tolylboronic acid, and saw recyclability hampered by slow formation of Pd black.[555]

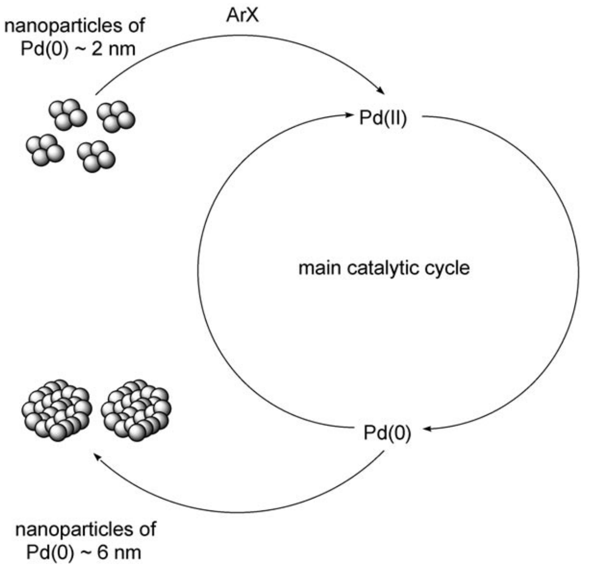
Fox, Whitesell and co-workers reported Pd(0) nanoparticles of about 2 nm in diameter that were stabilized by growing a polymeric dendrimer off them, giving a Pd nanoparticle-cored dendrimer.[556] The dendrimers were used as precatalysts under both homogeneous and heterogeneous conditions in Heck and Suzuki couplings of aryl iodides and bromides. The precatalysts were claimed to be stable and recoverable, although no data concerning recycle or Pd leaching were reported.

Kim and co-workers assembled hollow palladium shells and used them as precatalysts in the Suzuki coupling of iodoarenes and phenylboronic acid.[557] The authors described the materials as recyclable catalysts, with no apparent leaching. Unfortunately, leaching was only probed by elemental analysis, and recycling was only probed *via* measuring reaction yields at prolonged times. In contrast, Biffis and Sperotto studied polymer microgel-supported Pd nanoparticles in the Suzuki coupling of aryl bromides with phenylboronic acid and ascribed the activity to leached Pd species, with the particle-laden microgels acting as a reservoir for molecular catalytic species.[558]

Recently, Hu and Liu studied the Suzuki coupling of aryl bromides or iodides and arylboronic acids using polymer-Pd nanoparticle composites as precatalysts under conventional conditions and microwave heating.[559,560] Careful study of the recycle and reuse of the precatalysts in tandem with TEM analysis of the structure of the nanoparticles gave evidence for significant changes in nanoparticle size and shape. This observation, coupled with the lack of homocoupling using the solid precatalysts, prompted the authors to hypothesize that the catalysis involved a discrete soluble Pd(II) species in solution. Following elimination of the coupled product from the discrete Pd(II) species, the resulting Pd(0) species could oxidatively add another aryl halide to re-enter the catalytic cycle or it could cluster to reform Pd nanoparticles or palladium black. The proposed mechanism (Scheme 38) is similar to those espoused by DuPont[203] for nanoparticle catalysts in ionic liquids and by de Vries[184] for catalysis by homoeopathic, "naked" palladium (Scheme 7), although the intermediate species are likely more accurately represented as anionic entities.



Scheme 38. Nanoparticle etching process whereby discrete molecular palladium species promote the Suzuki coupling reaction in solution.



Scheme 39. Nanoparticle dissolution process to liberate soluble, active molecular palladium species.

Calò and co-workers reported the use of palladium nanoparticles in quaternary ammonium salts as solvents in the Suzuki coupling of aryl bromides and chlorides with phenylboronic acid.[561] The precatalysts could be reused for three runs, although in each run a slight decrease in product yield was observed.

In an interesting work, Rothenberg and co-workers studied the Suzuki coupling of aryl halides and phenylboronic acid using soluble Cu, Pd and mixed metal nanoclusters.[562] Catalytic results were found to be consistent with catalysis by the nanoclusters or leached molecular species that come from the nanoclusters. Distinguishing between the two possible cases could not be achieved with the data given in the paper. Others have reported PVP-supported nanoparticles as recyclable catalysts in Sonogashira reactions, although kinetics were not reported and the yields decreased in each run.[563]

Trezciak and co-workers recently published an interesting study of Pd nanoparticles supported on PVP polymers in $(Bu_4N)^+Br^-$ media as Heck coupling precatalysts using bromobenzene and *n*-butyl acrylate.[564] The nanoparticles were observed to decrease in size and become rounder after exposure to aryl halides or Heck reaction conditions. A larger decrease in size was observed as tetrabutylammonium halides were added to the system, supporting the hypothesis in the literature by Reetz and others that these agents promote the redispersion of the Pd. XPS analysis, which only analyzes for surface species, supports the complete oxidation of Pd(0) species to Pd(II) species following exposure to iodobenzene. Furthermore, in the presence of TBA cations, the authors interpreted their XPS data as consistent with formation of solvated Pd species such as $[Pd(Ph)Br_3]^{2-}$ and $[PdBr_4]^{2-}$, again providing evidence for Pd nanoparticle dissolution. Thus, the authors show that oxidative addition of aryl halides can liberate Pd species from the nanoparticle and interpret this as consistent with catalysis by soluble Pd species, especially under Jeffery conditions.

Dupont et al. presented a careful study of Pd nanoparticles dispersed in ionic liquids as Heck reaction catalysts in 2005.[203] Nanoparticles about 1.7 nm in diameter were used in the two phase ionic liquid/organic Heck reaction and the ionic liquid phase was re-examined by TEM after reaction. They found substantial changes in the size of the nanoparticles after reaction, with an average diameter of 6.1 nm diameter. In addition, they found that the organic phase contained significant amounts of Pd, with the amounts changing as a function of conversion. However, the recovered organic phase after reaction was found to be inactive for further Heck conversion. The authors proposed a nanoparticle dissolution process, akin to the process put forth by de Vries and co-workers for homeopathic Pd, whereby solublized molecular Pd from a larger Pd source is the active catalytic species (Scheme 39). Others have also reported Pd nanoparticles in ionic liquids as recyclable Heck precatalysts, such as the work of Calò on chitosan-supported Pd nanoparticles in TBAB-based ionic liquids.[565]

Zhang et al. studied the Heck reaction of various aryl halides using Pd nanoparticles supported by poly(ethylene glycol) (PEG).[566] The precatalysts were found to convert aryl iodides and activated aryl bromides and the polymer-stabilized Pd could be reused in multiple reactions, although yields decreased with time. The precatalysts were found to leach small amounts of Pd in each cycle, although choice of certain solvents kept the amount small. A cold filtration test did not reveal any activity due to leached species, and thus the authors concluded that the reaction occurred on the surface of the nanoparticles.

Consideration of the large body of work on soluble nanoparticle precatalysts for Heck and Suzuki reactions gives an overall picture that is consistent with the catalytic mechanism espoused by de Vries,[188] Reetz[204], DuPont[203] and others, whereby under most conditions the nanoparticles serve as reservoirs for solvated molecular palladium species that are active catalytic species. In the Heck reaction, there is strong evidence for dissolution of the nanoparticles *via* the oxidative addition of the aryl halide to the surface to liberate the soluble palladium species. However, it is less clear whether Pd(II) species that might remain present on the solid surface after the addition of the aryl halide can react with an incoming olefin to give catalytic turnover on the nanoparticle surface. If this were to occur, two catalytic sites would be apparently operable, one a molecular species in solution and one on the nanoparticle surface. For Suzuki reactions, there is conflicting evidence about the reaction mechanism, with some authors supporting the addition of the boronic acid to the surface followed by a surface-mediated reaction with an incoming aryl halide,[548] while others espouse a leaching mechanism[560] whereby molecular palladium is leached into solution, which acts as the true catalytic species. Overall, as in the use of supported precatalysts such as Pd/C, there is no definitive evidence that complete catalytic turnovers can occur on the metal surface in Heck or Suzuki coupling reactions, although circumstantial evidence continues to be used to support this hypothesis.

4.5 Polymer or Oxide "Encapsulated" Precatalysts

Although related to the precatalysts of Section 4.4, palladium sources encapsulated in polymer or oxide supports now represent a further subclass of catalysts that are increasingly being reported for Heck and Suzuki couplings. An early example includes the work of Gin and Ding, who reported the immobilization of Pd(0) nanoparticles within the mesopores of a lyotropic liquid crystalline polymer which was utilized as a supported palladium precatalyst in Heck coupling reactions.[567] Pd(II) cations were added to the anionic head groups of the polymer *via* ion exchange and the resulting polymer was reduced in hydrogen to generate Pd(0) nanoparticles of approximately 4–7 nm in diameter. As this size was larger than the pore size, some restructuring of the polymer had to take place upon reduction. The material was capable of activating aryl iodides and activated bromides and they reported that this activity was maintained after two recycles.

In 2001, Biffis introduced microgel-stabilized Pd colloids as a new type of catalyst for coupling reactions, demonstrating their applicability in the Heck coupling of aryl halides with *n*-butyl acrylate.[568] In the application of this new precatalyst, it was noted that no palladium black formation was observed and the microgel appeared to be stable, although the overall reactivity was lower than other reported Pd colloid precatalysts.

Ley and co-workers developed $Pd(OAc)_2$ encapsulated by poly(urea) as a new reusable precatalyst for cross-coupling reactions.[569–571] The precatalysts have been demonstrated in both Heck and Suzuki coupling chemistries with various aryl halides as reactants, including iodides, bromides and chlorides. Tetrabutylammonium bromides was used as a base, and there was only limited leaching detected with the precatalysts (ranging from 13–60 ppm). It was not originally established whether the reaction occurred with leached Pd species, although there certainly may be enough leached palladium to function as a good catalyst, as ppb levels of Pd are sufficient for good conversions in some cases.[124,572] Recent studies support the notion that all of the catalysis occurs outside the polymers, as insoluble poisons completely shut down the reactivity, an observation that is not consistent with the reaction occurring inside the polymer particles.[573] In most cases, reaction rates under conditions where leaching was low were also much lower than when using homeopathic palladium.

Kobayashi and co-workers developed a route to encapsulate phosphine-free Pd(0) inside micelles of novel copolymers.[574,575] The "polymer-incarcerated" Pd was successfully used in both Suzuki[574] and Heck[575] couplings of aryl bromides and aryl iodides, respectively. In the Suzuki coupling, leaching of Pd from the polymer was largely dependent on the solvent used, with undetectable amounts of leaching in water/toluene and water/ethanol systems. Utilization of the solid-free filtrate after a reaction in a subsequent homogeneous reaction resulted in no conversion of substrate, which the authors interpreted as an indication of the reaction occurring within the polymer micelles. Addition of an external phosphine ligand such as Buchwald's 2-(dicyclohexylphosphino)biphenyl, **4**, resulted in enhanced reactivity and decreased leaching. This interesting result indicated that either the ligand could infiltrate the polymer and activate the Pd nanoparticles inside or that traces of leached species were supported by the phosphine and promoted the reaction in the liquid phase. In the more detailed study of the Heck reaction, the Pd(0) clusters were characterized by EXAFS and were shown to be approximately 0.7 nm in size. The nature of the polymer used to encapsulate the Pd was shown to have a significant impact on the catalytic properties, especially the leaching behavior of the materials. The best systems had undetectable levels of soluble Pd (<5 ppm), could be used at very low concentrations, and could be recycled. A hot filtration test showed that the filtrate could not convert the reactants, although it should be noted that a short induction period was observed and the kinetics appeared similar to the case of homeopathic Pd described by de Vries.[184] A three phase test showed that there was little or no soluble catalytic species leached from the polymer, as the immobilized aryl iodide was barely converted (although a soluble iodide might be necessary to induce leaching,[514] *vide supra*). Surprisingly, almost no conversion was also observed using Pd/C in the three phase test, yet it is known that this system is composed of entirely soluble catalytic species under most conditions studied. This casts some doubt on the validity of the test or conditions used. TEM analysis of the precatalyst before and after reaction showed no signs of changes in the Pd particle size-formation of large Pd clusters was not detected. Thus, the authors concluded that the reaction occurred within the polymer micelles, with the material acting as a nanoreactor. Improved performance could be obtained by using a polymer that contained $P(aryl)_3$ groups as part of the backbone.[576]

McQuade and Price recently reported the use of cross-linked reverse micelles as hosts for Pd(0) nanoparticles in Heck coupling reactions.[577] Using cross-linked micelles, the authors showed that the precatalysts could be recovered and reused, although the catalytic performance in subsequent reactions degraded. The precatalysts were observed to perform better at very low loadings, an observation in line with those of de Vries,[184] who argued that this was consistent with catalysis by molecular Pd species. Thus, the catalysis in this work may not be associated with heterogeneous Pd sites. The catalyst was reported to be inactive in bromo- and chloroarene conversions. Other encapsulated precatalysts, for example, polymer/silica encapsulated precatalysts, have also recently been reported by other authors.[578]

It is anticipated that the observations about the nature of the "true" catalyst for the above section concerning soluble Pd(0) nanoparticles should be similar for the nanoparticle encapsulated catalysts. Indeed, if the surface of the nanoparticle is in fact not able to promote the coupling reactions, it is likely that these materials simply serve as vehicles for the slow release of active palladium species into solution. As these materials are still relatively new, their ability to prevent palladium leaching and to facilitate true, heterogeneous catalysis is at this point unclear.

5 Distinguishing Between Soluble *vs.* Insoluble, Molecular *vs.* Nanoparticle Catalysts

Determining the nature of the true active species using homogeneous organometallic complexes or mixtures of ligands with metal salts is a science that has been systematically developed over the last several decades. Similarly, understanding the structure and performance of solid, heterogeneous catalysts such as metal oxides or supported metal particles, especially in gas-phase reactions, is a well-developed area of science as well. However, understanding the nature of the true active species using solid catalysts in liquid media remains a relatively less studied, although quite important area. Indeed, in many cases, solids act as truly heterogeneous catalysts, with the reaction occurring on the metal particle surface, whereas in others, it is increasingly found that leached, soluble species are the true catalytic entities. Indeed, in palladium-catalyzed coupling reactions, this increasingly appears to be the case in many well-characterized systems. As this review brings to light, the nature of the true catalytic species in many systems is exceedingly hard to assess. Indeed, we can see why if we consider Leadbeater's recent careful work.

Leadbeater and co-workers carried out an interesting set of studies that serve as an excellent cautionary tale for investigations aimed at determining the homogeneity/heterogeneity of catalysts and the nature of the true active species. In 2003, Leadbetter et al. reported an intriguing study whereby they were able to achieve the Suzuki coupling of 4-bromoacetophenone and other aryl bromides and phenylboronic acid in the absence of any added transition metal.[579,580] As transition metal costs and contamination are a significant problem in applying coupling chemistries commercially, this was a major advance. Subsequently, the authors reported transition metal-free Sonogashira couplings as well.[581] However, later, careful studies by Leadbeater's group along with Singer and Granados of the University of Connecticut showed that the reactions were actually catalyzed by trace amounts of Pd in commercial sodium carbonate reagents.[572] Indeed, even at levels of 50 ppb, the traces of Pd were able to catalyze the reaction. Similar results were reported by Dupont and co-workers, who showed that ppt amounts of residual Pd in previously used reaction glassware are sometimes sufficient to catalyze the Heck reaction.[124] Biffis, Zecca and Basoto also note that only a very small amount of leaching was necessary to give excellent catalytic rates in their review of palladium metal catalysts in Heck couplings.[331] Thus, assessing *what is* the active catalyst and *where is* the active catalyst (support *vs.* solution) can be extraordinarily difficult. Indeed, if ppt levels of palladium are capable of easily catalyzing some reactions, probing the nature of the true catalyst by most spectroscopic or other techniques may be currently impossible. In the paragraphs below, we outline a variety of metrics (and their associated subtleties) that have been used to judge the heterogeneity/homogeneity of the catalytic species in Heck and Suzuki coupling reactions.

5.1 Aryl Iodides *vs.* Bromides *vs.* Chlorides

The first critical choice in any fundamental catalytic study is the reactants that will be used. The fact that trace amounts of palladium are able to rapidly catalyze some coupling reactions makes the choice of test reactions critical in the characterization of new precatalysts. In particular, Suzuki coupling reactions of aryl iodides and bromides are *very efficiently* catalyzed by a myriad of different precatalysts with ultra-low palladium loadings. Similarly, low loadings of many palladium precatalysts can catalyze the Heck coupling of aryl iodides and activated aryl bromides. To this end, it is strongly recommended that deactivated aryl bromides and aryl chlorides be used as reactants in the characterization of new catalysts.

5.2 Filtration or Split Tests

A commonly cited work on the issue of homogeneous *vs.* heterogeneous catalysis is the nice paper by Sheldon and coworkers.[582] This work highlights efforts at the elucidation of the nature of the true transition metal species that are responsible for oxidation catalysis when starting with silicalite-based microporous materials. They applied the hot filtration technique or spilt test to effectively probe whether leached transition metal species were responsible for the observed catalysis and suggested that such a test can provide rigorous proof for catalysis by leached *vs.* truly heterogeneous species. Indeed, in a huge variety of chemistries, this technique works extremely well and can provide valuable information about the nature of the true catalyst. Unfortunately, this test, when applied alone, cannot be rigorously used to assess catalysis by leached species during Heck and Suzuki reactions due to the speed at which leached palladium species can redeposit back onto the support.[350–352] In related chemistries, Lipshutz has suggested that the leached metal can deposit so quickly it may not be detected by a filtration test.[346] Furthermore, as noted above, the amount of leached palladium that need be present in solution for catalysis can be so small, that it might not be detected by many techniques such as rudimentary elemental analysis. Finally, as noted in this review, active species can deactivate quickly in solution in the absence of stabilizers such as TBAB, and especially in the absence of substrate. Thus the filtration test is an excellent test to judge heterogeneity, although it *alone* cannot be used to prove catalysis by supported palladium.

5.3 Kinetic Studies *vs.* Catalyst Recycle with Consistent Yield

Gladysz nicely summarized the concept of an ideal catalyst, pointing out that ultimately, a high TON is more important than recyclability for practical applications.[583] This is especially important in Heck and Suzuki couplings, where palladium leaching from solid precatalysts may negate the utility of having a supported, "recoverable" catalyst. In many cases, very low loadings of homeopathic palladium may turn out to be the most cost-effective way of carrying out coupling reactions, especially since potentially viable recycle strategies for homeopathic palladium are now known.[183] In particular, a key point that is made in Gladysz's work is the proper way of characterizing recyclability of catalysts. Unfortunately, with regard to coupling chemistry, most authors simply report product yields as a function of cycle. In most cases, this information is almost useless, and Gladysz clearly points out why such data are essentially inconsequential, especially when long reaction times are used. Instead, Gladysz suggests that average TOF in each cycle is a more meaningful data set, as it takes into account the kinetics of the reaction. Indeed, TOF *vs.* cycle data are more useful than yield *vs.* cycle data, although an added subtlety comes into play for coupling reactions. Unfortunately, many palladium-catalyzed coupling reactions have significant induction periods that change as a function of cycle. In this case, TOF *vs.* cycle data can be misleading. In such a case, Beletskaya et al. argue for abandonment of the practice of averaging TOFs by measuring a TON after a specific time, noting that such data can give inaccurate results.[221] Instead, they argue for measuring the slope of a tangent line after the induction period to report more representative rates. At the very least, good comparisons should include plots of actual kinetic data along with quantitative initial rates or average TOFs, whereby the initial rates and induction periods can be shared visually with the reader. Ideally, the experimental kinetics can be fit by a theoretical kinetic model as described by Finke in his recent review.[396]

5.4 Reaction Selectivity

For many Heck and Suzuki couplings, reaction selectivity can be a useful diagnostic for comparing different catalysts. For example, common side reactions in Heck and Suzuki reactions are dehalogenation and deboronation of the aryl species, respectively. In addition, in Heck couplings, often different product isomers can be prepared, and the distribution of isomers can give a useful insight into the type of catalyst produced from the starting precatalyst. Certainly, the fact that homogeneous systems based on $Pd(OAc)_2$, palladacycles, or $Pd_2(dba)_3$ and supported systems such as Pd/C or Pd/TiO_2 gave similar product distributions in Heck couplings is consistent with the notion that they produce similar (homogeneous) catalytic species *in situ*.[243] Although selectivity alone is not a conclusive diagnostic, it can be used effectively as a piece of the puzzle that uncovers the true catalytic species in Heck couplings.

5.5 Correlation of Reaction Rate with Concentration of Palladium in Solution

Köhler[358,359] and Arai[350] independently and convincingly showed that the reaction rate when using various supported palladium precatalysts nicely correlates with the content of dissolved palladium. Such an agreement provides powerful kinetic evidence that the true active species under these conditions is a soluble form of palladium. Many authors check for metal leaching only *after* a reaction has been completed, and substantial evidence shows that soluble catalytic species can redeposit on the support fast enough so that leaching may be entirely missed if this is the only test for soluble species.

5.6 "Quantitative" Catalyst Recovery

"Quantitative" catalyst recovery also is a way to measure the recyclability of a system. While this methodology has real bearing on practical reuse of the catalysts, it does not provide strong evidence for a truly heterogeneous palladium coupling catalyst when solid catalysts are used. This is because, as was noted above, palladium catalysts in coupling reactions are often so active that only ppb levels of soluble species are necessary to promote the reaction. It is highly unlikely, in any case, that such levels of leaching would be noted. Thus, while gross loss of palladium from a solid "catalyst" is clear evidence of leaching, recovery of a solid catalyst with "the same amount" of palladium as measured by typical elemental analysis techniques cannot by itself be used to justify a truly heterogeneous catalyst.

The most convincing studies that address the nature of the truly active palladium species are those that utilize an array of techniques to elucidate its homogeneity or heterogeneity. Indeed, Finke's excellent review on distinguishing between soluble homogeneous catalysis and nanoparticle catalysis using reducible transition metals compiles an array of reaction tests, poisons, and experimental procedures that are useful in characterizing the identity of the true catalyst.[396] However, one must carefully think about the validity of any test that has been used for a specific catalyst and reaction type before blindly applying it to any system of interest.

5.7 Mercury Test

For example, we can consider the ubiquitous mercury test, whereby Hg(0) is added to a reaction. Historically, researchers have used the observation of Hg(0) quenching a reaction as evidence for catalysis by heterogeneous metal particles, both in coupling reactions and other types of reactions. Perhaps this is because the historic literature is interpreted as saying that the mercury test distinguishes between homogeneous and heterogeneous catalysis. This is often the case *in the context of the original studies*. Indeed, the historic literature[584,585] with the Hg(0) test focuses on hydrogenation reactions with metal complexes in elevated formal oxidation states bound by protective ligands. Certainly, these catalysts are not affected by Hg(0), as they are not M(0) species and they are protected by strong ligands. Indeed, Weck and Jones have shown that Pd(II) pincers are also unaffected by Hg(0) when carrying out stoichiometric reactions where the ligand remains intact and the complex is in a Pd(II) state.[249] However, Hg(0) does quench the activity of Pd(II) pincer precatalysts in Heck, Suzuki and related coupling reactions.[249–251,270,271,586] Others have interpreted this as "proof of catalysis" by soluble Pd(0) nanoparticles. However, instead we suggest that this can only be interpreted as "catalysis *via* a cycle with a Pd(0) intermediate." de Vries suggests that soluble, molecular palladium species are the true catalysts in Heck coupling reactions promoted by nanoparticle precatalysts as well as by palladacycle or $Pd(OAc)_2$ "naked" precatalysts.[184] Indeed, subsequently, Dupont also has suggested this possibility based on studies of ionic liquids containing palladium nanoparticles as C–C coupling media.[248] In the case of base-stabilized, "naked" molecular Pd(0) species, no logical, chemical reason has been put forth concerning why Hg(0) should not also extinguish activity associated with these species. Thus, it is suggested that "naked" molecular palladium species are examples of *homogeneous catalysts that should be affected by Hg(0)*, as a consequence of their lack of strong protecting ligands and their M(0) state.

5.8 Selective Poisons for Solid Catalysts

The mercury test is often applied as a selective poison for heterogeneous catalysts. However, as noted in the above section, as well as in the work of Whitesides[587] and DuPont,[248] interpretation of a mercury test can be problematic. DuPont suggests that a mercury test can "confirm a homogeneous catalytic system but not a heterogeneous one". We argue that in the context of the coupling reactions described here, this can be better stated as, "the observation that Hg(0) does not affect the catalysis can confirm a mechanism that does not involve unprotected Pd(0) (soluble or supported), whereas an observation that Hg(0) quenches the activity may be consistent with a Pd(0) intermediate." Complications arise from the fact that mercury must be well-dispersed in the organic media, making mixing complications a factor in reproducibility. Also, mercury can sometimes change the nature of the reactivity, or even improve hydrogenation rates.[248,588]

5.9 Selective Poisons for Soluble Catalysts

A variety of small molecules has been espoused as useful poisons that can used as markers for homogeneous catalysis. For example, in Finke's review of distinguishing between homogeneous and heterogeneous catalysis under reducing conditions,[396] PPh_3, CS_2, thiophene, and DCT[585] are suggested as catalyst poisons. Furthermore, it is suggested that the stoichiometry at which the poison completely inhibits the reaction can give insights into the nature of the catalyst, with <1 equivalent relative to metal suggesting heterogeneous catalysis. This interpretation is complicated in Heck and Suzuki coupling reactions by the fact that rarely do we know the true number of active species present, and therefore, establishing the stoichiometry is quite difficult. Indeed, many of the best catalysts are thought to slowly release active palladium which can deactivate with time, making the total active species count dynamic. For this reason, use of small molecule poisons has rarely been useful in giving conclusive proof of homogeneous *vs.* heterogeneous mechanisms in Heck and Suzuki coupling chemistry.

We have employed an alternate approach to the development of selective, homogeneous catalyst poisons. By addition of an insoluble solid material to a reaction that is filled with binding sites, we suggest that soluble reactive palladium species can be pulled out of solution and ligated to the point where their reactivity is extinguished. To that end, we employed cross-linked poly(vinylpyridine) in our studies of supported pincer complexes and showed that addition of this poison effectively shut down catalytic activity.[249,250,270] This was interpreted as evidence for catalysis by soluble species only. It was argued that the poisoning effect of this cross-linked polymer was most consistent with catalysis by naked, molecular palladium species, as it was difficult to envision the cross-linked polymer extinguishing catalysis on the surface of soluble metal nanoparticles. It is suggested that the wide array of transition metal scavengers that are now sold might also be effective poisons for soluble catalytic species.[573]

5.10 3-Phase Test

Davies recently revived the use of the 3-phase test, or Collman test,[589] first proposed by Rebek[590–592] as a clear test for the discrimination of homogeneous catalysis, in the determination of heterogeneity in Pd-catalyzed coupling reactions. Davies et al. were able to conclusively show that both a Heck and Suzuki coupling reaction proceeded by a solution phase mechanism using polymer beads immobilized with one of the two reagents, in this case an aryl iodide.[379] Using this test, one reagent is immobilized on a solid support and the catalyst is immobilized on a second, different solid support. The rest of the reagents are then added to the solution. Ideally, if there is no background reaction in the absence of catalyst, the immobilized reagent should only be converted if there is catalyst or substrate leaching. This is a very useful test to assess homogeneous catalysis and it is an excellent complimentary technique for use in conjunction with filtration tests. There are subtleties involved, however. For example, it must be insured that the species needed to induce leaching are present in the solution phase. Thus, if leaching proceeds *via* oxidative addition of aryl halide to immobilized Pd(0), the aryl halide or another free aryl halide must be present in the reaction solution. In this case, the olefin would be an excellent target for immobilization, in the case of Heck reactions. Another issue concerns the relative rates of conversion of the tethered *vs.* the soluble reactants. For example, if an easy to convert aryl halide is used in solution (e.g., an aryl iodide) but a slow reacting aryl halide is tethered (e.g., a deactivated aryl bromide), the halide in solution might be converted completely before any hypothetical leached palladium species has time to diffuse to and convert the surface-bound reagent. Thus, if the surface-bound reagent is slow reacting, the soluble palladium may deactivate before it can convert much or any of the bound substrate. Nonetheless, the 3-phase test can be a powerful tool in the arsenal of the catalysis scientist in elucidating the nature of the true catalytic species if these subtleties are considered.

A combination of the control experiments described above is suggested to be the best way to probe the nature of the catalytic species when starting with solid precatalysts.[396] An array of such experiments, when coupled with traditional kinetic studies can go a long way in helping to establish the forms of palladium that are truly active in these coupling reactions.

6 Summary and Conclusions

Each year, more applications of palladium-catalyzed Heck and Suzuki reactions are reported. For example, in 2001, de Vries described a number of commercial applications of the Heck reaction,[593] and a recent review of Suzuki couplings in organic syntheses highlights the applicability of this transformation to prepare a wide array of products.[594] More recently, two detailed accounts of processes that utilize Suzuki[595] and Heck[596] couplings as important steps were described. Undoubtedly, these types of reports will increasingly appear in the future.

As the field moves forward, a significant task will be the elucidation of the nature of the true catalytic species when using the myriad precatalysts described above. A lot can be inferred about the nature of the active catalyst when considering the temperature at which the system operates, especially in Heck couplings. There is considerable evidence that added donor ligands such as phosphines, phosphites, NHCs and others can be a component of truly active, soluble palladium complexes in Heck or Suzuki coupling reactions. In considering the discrete soluble transition metal catalysts that have recently been studied, it is clear that an emerging trend is the design of bulky monodentate ligands that can stabilize active monoligated Pd(0) species. It should be noted, however, that the conditions where these ligands seem to influence the catalysis is usually at relatively low temperatures ($<\sim 80\,^{\circ}$C). In contrast, at higher reaction temperatures ($>\sim 120\,^{\circ}$C), it is likely that many preformed metal ligand complexes or mixtures of palladium sources and ligands decompose to generate Pd(0) nanoparticles.[188] These nanoparticles are then precursors to soluble molecular or dimeric palladium species that may act as catalysts in an anionic Amatore/Jutand[17] catalytic cycle (Scheme 3). This is true of palladacycle precatalysts in particular, with the majority of the palladacycles studied (NC, PC, SC, SCS, PCP, etc.) being shown to decompose to liberate soluble, likely homeopathic palladium species that operate *via* a Pd(0)–Pd(II) cycle. Indeed, de Vries nicely summarizes how multitudes of Heck coupling data from many different authors can all be explained by a single mechanistic picture at high temperatures involving anionic intermediates and his recent perspective is highly recommended reading.[188]

Palladium nanoparticles have also been used directly in organic, aqueous and ionic liquid media, and they have been immobilized in polymeric supports or stabilized by oligomers and dendrimers. The collected data clearly show that some aryl halides can oxidatively add to the surface of the nanoparticles and it has been suggested that the resulting Pd(II) species may leach from the nanoparticle to create discrete molecular palladium species. It has been suggested that these soluble species can then participate in the solution phase Heck or Suzuki cycle. It is not clear if complete catalytic turnovers can occur on the surface of the nanoparticles, although this has been suggested by many authors with relatively limited supporting data. At this stage, the possibility of this occurring cannot be conclusively ruled out, although no definitive or even strongly suggestive proof of this phenomenon has thus far been presented.

When solid-supported Pd(0) particles were used as precatalysts, many authors have reported that the activity was associated with soluble, leached palladium species derived from the metal particles. In this regard, supported forms of Pd(0) or even supported PdO are precatalysts that create soluble palladium species that follow the homeopathic catalytic cycle outlined above.[188] After reaction, the soluble palladium was often observed to redeposit on the solid support. In contrast, in some cases, it has been suggested that the catalytic turnovers occur on the palladium metal surface. As noted above in the nanoparticle discussion, no compelling evidence has been presented that shows that palladium macro- or nanoparticle surfaces can act as true catalytic sites giving complete turnovers.

Ligand-functionalized solids will continue to be studied as novel supports for Pd(0) or Pd(II) species in Heck and Suzuki coupling reactions. In essentially all cases where these precatalysts have been studied, some leaching of palladium occurs, although in many cases it is claimed that the leached palladium is inactive (or it deactivates quickly). Several ligands appear to strongly bind palladium and therefore may be promising for immobilization of molecular palladium species to create effective coupling catalysts. These include simple thiols as well as NHC-based ligand systems. It is anticipated that lower temperatures will be needed to prevent palladium agglomeration and catalysis *via* the soluble homeopathic path as discussed above.

There still are no proven examples of catalysts that operate by a Pd(II)-Pd(IV) catalytic cycle in Heck or Suzuki coupling reactions.[597–599] Over the years, the various candidates that potentially could operate by this mechanism have been consistently shown to operate by a traditional Pd(0)–Pd(II) cycle. Indeed, NC, SC, PC, SCS and PCP palladacycles have all been shown to operate by a Pd(0)–Pd(II) mechanism, with the SCS and PCP pincers being conclusively shown to not operate, even to a small extent, by a Pd(II)–Pd(IV) cycle.

Regardless of what palladium precatalyst is used, it is critical for researchers to attempt to understand the nature of the true catalytic species in their studies. This obviously is a very arduous task in many cases, as (i) the fact that ppb levels of palladium may be active in some cases, coupled with (ii) the fact that active palladium species in solution can quickly deactivate *via* clustering of Pd(0), coupled with the prevalence of (iii) leaching/redeposition processes that makes characterization of the possibility of soluble active palladium when using solid precatalysts very difficult. It is equally difficult to prove catalysis occurs on a solid surface given the above difficulties (i–iii). It is suggested that increased use of poisons that are specific for soluble palladium species may help shed light on this issue and that new catalyst poisons be developed to aid in this task. Clearly, the study of palladium-based coupling catalysts will continue and potential breakthroughs in the elucidation of the dynamics of palladium under such reaction conditions and the determination of the type(s) of palladium species that are truly catalytically active will aid in the rational design of future generations of catalysts.

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