

Palladium-Catalysed C–C Coupling: Then and Now

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Synthetic procedures for the manufacture of complex drug molecules have changed continually over the years as methodology has improved. However, a step change in efficiency has been achieved by switching from a linear pattern of steps (often more than ten) to a different strategy: the parallel synthesis of key precursor components and then linking them together at a late stage in the process. This has only been possible due to the advances in coupling chemistry that have occurred over the last thirty years, many of them related to the use of palladium catalysis. This article sets out to describe some of the early work in palladium-catalysed C–C bond formation and how the methodologies have changed due to recent developments.

The father of palladium-catalysed coupling chemistry is generally considered to be Professor Richard Heck. Although other reports on organometallic coupling reactions had already been published, it was through his work that the Pd-catalysed reactions became widely known and applied. His initial publication of Pd-catalysed vinylic substitution reactions with aryl halides appeared in 1972 (1), the year following the publication of the same conversion, though under different conditions, by Mizoroki (2). Heck's initial choice of catalyst was Pd(II) acetate, although he noted that Pd/C catalysts were also active, albeit that the reactions were slower and the yields were lower. His conclusion that "in spite of some limitations, the organic halide–olefinic substitution reaction should prove to be a useful synthetic reaction" has been entirely justified by history.

From this point on, throughout the 1970s further examples of Pd catalysis of C–C cross-coupling reactions continued to appear. The related coupling of aryl halides and alkynes rather than alkenes was improved by Sonogashira using copper and Pd catalysts (3). The exploration of tin reagents in coupling chemistry is attributed to Stille. A number of extremely useful transformations can be carried out using this chemistry (4). The coupling of aryl halides with organometallic derivatives of zinc and magnesium was first reported by Negishi (5, 6) and Murahashi (7)

respectively (the latter now being commonly referred to as Kumada coupling due to prior publications on the use of nickel catalysts for this reaction). Pd competes with nickel catalysts for these applications, and its preference must rely on improved selectivity to overcome the cost disadvantages.

Although developed somewhat later than the Heck chemistry, the Suzuki–Miyaura reaction employing boronic acids or esters has found ready acceptance by pharmaceutical chemists for the preparation of biaryl derivatives. The basic reaction was initially published by Miyaura and Suzuki in 1979 (8, 9) using alkenyl boronates and alkenyl halides, but the 'classic' reaction of phenyl boronic acid and aryl halides was reported in 1981 (10). This chemistry has been greatly extended and elaborated over the years (11).

The original publications on Pd-catalysed coupling described the use of aryl bromides and iodides and for a number of years there were no effective catalysts for most aryl chlorides. This relates to the strength of the Ar–X bond, which increases: I < Br < Cl (65, 81 and 96 kcal mol⁻¹ respectively) and makes the oxidative addition step increasingly difficult (12). Aryl chlorides offer significantly greater scope as substrates than do bromides or iodides, and at lower cost. The ability to react these substrates has come about through an improved understanding of the

mechanism and the ways to enhance the rate-determining step. Understanding the properties of the Pd intermediates in the catalytic cycle has allowed the reactions to be applied to a wider range of substrates with improved selectivity under milder conditions.

The mechanism of the Heck reaction and the related cross-couplings has been studied intensively over the years and an outline is shown in Figure 1 (13). The Pd species introduced as the catalyst precursor is believed to be converted to an active species of low coordination number allowing the oxidative addition of the aryl halide. The olefin then binds to a further vacant site on the catalyst. Combination of the aryl and olefinic components and β -hydride elimination forms the product and base-promoted reductive elimination of HX regenerates the catalyst. There has been some debate as to whether Pd(0)/Pd(II) or Pd(II)/Pd(IV) forms the basis for the oxidative

addition/reductive elimination cycle (14–16), with the former believed to be operative in the vast majority of, if not all, cases. The use of strongly stabilising ligands (e.g. in palladacycles) may yield catalysts with very high turnover number (average number of catalytic cycles per molecule of catalyst) and high reactivity, but generally only under vigorous conditions which are believed to be associated with slow reduction/dissociation of the precursor complex (17). The coordination of spectator ligands at Pd is also in question, and as a consequence the charge on the catalytic intermediates may vary under different reaction conditions (16, 18) and the reaction can no longer be adequately described by a simple mechanism such as that given in Figure 1 (12).

Industrial applications were reviewed by de Vries, who also highlighted the importance of economic factors in defining the catalytic precursor (19). Ligandless systems are the most cost

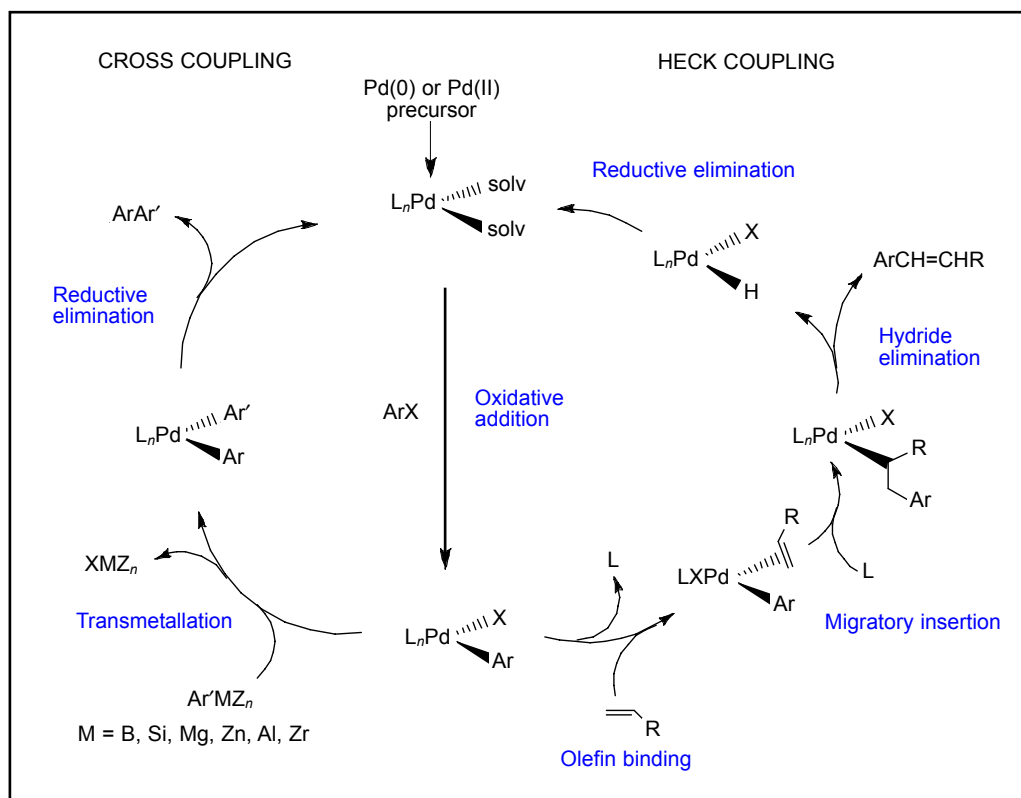


Fig. 1 Outline of mechanisms of Heck and related cross-coupling reactions (L = ligand; $solv$ = solvent; X, Z = halogen (Cl, Br or I))

efficient, but are active for only the more reactive substrates. The application of supported Pd catalysts has continued to generate interest over the years and the performance of these systems can often be enhanced by the addition of phosphines. This suggests that at least some of the activity of these catalysts is due to leached molecular species. A detailed review considering this point has recently been published (17), and further support for the role of leached Pd(0) species has been provided by the work of Jones (20) and Köhler (21). The range of patented cross-coupling technologies has been reviewed by Corbet and Mignani (22).

Regioselectivity in the Heck reaction can be achieved through control of the electronic properties of the alkene. The reaction generally works best with electron-withdrawing substituents on the alkene and gives the β -aryl substituted products in high yield. For electron-donating substituents the α -substituted product can be obtained in good yield under halide-free conditions. This is believed to be associated with shifts in the mechanism related to the charge on the catalytic intermediates. Recently, some progress has been made in regiocontrol of the reactions of aryl halides as well (23, 24). Some control of the *cis* and *trans* stereochemistry of the product can also be achieved through the optimal choice of catalyst and base.

While the mechanisms of all the Pd-catalysed coupling reactions have much in common, the conditions for the cross-coupling reactions are generally milder than those for the Heck reaction and several groups have delighted in achieving the highest turnovers for the reaction under the mildest conditions. Buchwald *et al.* were first to describe catalysts highly active at room temperature for aryl bromides (25). Subsequently, the catalysts have been further developed to allow coupling of aryl chlorides under similarly mild conditions. The use of bulky, strongly electron-donating phosphines has been key to these developments, with many derivatives offering similar performance with standard substrates. More recently, this chemistry has been extended to the coupling of alkyl as well as aryl chlorides

(26), and with application to alkyl boranes (27, 28). Further developments are anticipated.

Heck Reactions

Heck initially noted that ethylene could be coupled with an aryl group in a non-catalytic reaction using the arylmercury halide in 1968. The catalytic reaction of olefins such as styrene using palladium acetate (Pd(OAc)₂) at 1 mol% relative to the aryl halide was reported in 1972 (1). For iodobenzene the reaction was completed by heating at 100°C for typically 1 to 5 hours, but bromobenzene was much less reactive.

Early work on using aryl chlorides revealed that conventional catalytic systems (for example Pd(OAc)₂/PPh₃) were effective for electron-deficient substrates provided forcing conditions (150°C) were used. Pd catalysts stable to these conditions, such as palladacycle (15), pincer (29) and carbene (30) complexes were then shown to be active. Bidentate phosphines, 1,2-bis(diphenylphosphino)ethane (dppe) or 1,4-bis(diisopropylphosphino)butane (dippb), have also been found to be useful in these reactions, although their performance can be very sensitive to both the substituents on phosphorus and the length of the carbon bridge (31). In 1999, Littke and Fu reported the Heck coupling of methyl acrylate or styrene with a variety of unactivated aryl chlorides using tri(*tert*-butyl)phosphine (P(^tBu)₃) as ligand (32), with a similar preference being found by Hartwig in a screening study (33). The initial Fu report indicated the use of Cs₂CO₃ as base with reaction temperatures of 100 to 120°C, but milder conditions were possible when the base was changed to Cy₂NMe (34). Aryl bromides and activated, electron-deficient aryl chlorides could now be reacted at room temperature. Also, the use of different Pd:P ratios suggested a monophosphine species as the active catalyst. This catalyst system also proved to be versatile, allowing a wide choice of electron-rich and hindered aryl chlorides, and of olefinic partners. It is noteworthy that the other triaryl and trialkyl phosphines studied provided ineffective catalysts.

In an industrial context, cost control is important and a variety of ligandless Pd systems have

been developed. As commented above, in his initial studies Heck found Pd/C to have low activity, but in 1973 Julia *et al.* reported some activity for aryl chlorides (35), and interest has revived in the last ten years. Extensive efforts have been made to develop other supported Pd catalysts suitable for recycle, involving both ligandless and anchored ligand systems. Improved conditions have been developed allowing high turnover numbers for aryl bromides and reaction of unactivated aryl chlorides (21). This area of C–C coupling by heterogeneous Pd catalysts has been reviewed recently (36).

Unsupported Pd nanoparticles can also be used (37), and a process whereby these particles are collected on an inexpensive carrier such as Celite[®] (a purified diatomaceous earth product), and then reactivated by oxidation with iodine, has been developed by DSM (19).

The use of alternative solvent media (for example, supercritical fluids or ionic liquids) and reaction conditions (such as microwaves or ultrasound) to optimise the performance of the Heck reaction has also been reviewed (38).

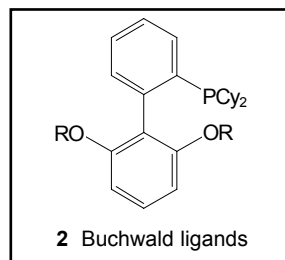
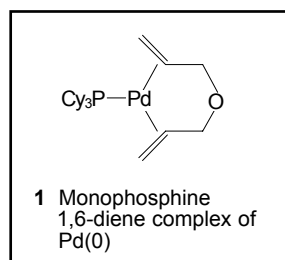
Suzuki-Miyaura Reactions

Initial work on the coupling of alkenyl halides with alkenyl boranes with tetrakis(triphenylphosphine)palladium (Pd(PPh₃)₄) in 1979 identified the key role of the base in achieving high yields (7, 8). In 1981 the ‘classic’ Suzuki-Miyaura reaction of phenyl boronic acid with aryl halides was reported (9). Again, the preferred catalyst was Pd(PPh₃)₄ being used in benzene at reflux. In both these studies aryl chlorides such as chlorobenzene were “quite inert”.

Suzuki-Miyaura coupling of activated aryl chlorides is possible with a wide range of catalysts as these reactions proceed more readily than many other cross-couplings. For example, chloropyridines can be coupled using the original Pd(PPh₃)₄ catalyst. In 1997 Shen reported the use of tricyclohexylphosphine (PCy₃) for the coupling of activated aryl chlorides (39), and the following year Fu reported further work with PCy₃ and P(^tBu)₃ establishing reactivity for a wider range of aryl chlorides (40). Shen proposed that the PCy₃ ligand might promote oxidative addition of the aryl

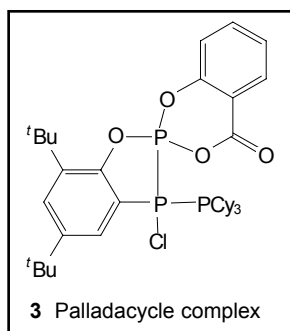
chloride, and that its steric demands might facilitate the formation of a monophosphine complex as the active catalyst and promote reductive elimination. All of these arguments have been subsequently elaborated in further work to design alternative catalysts. Studies conducted on the optimum Pd:PR₃ ratio for *in situ* preparation of the catalysts indicated that this lies in the range 1 to 1.5 suggesting that a monophosphine complex is the most active catalyst (41). Hartwig studied the dimeric complex di- μ -bromobis(tri-*tert*-butylphosphine)dipalladium(I) ([PdBr(P(^tBu)₃)₂]₂) as a precursor suited to the generation of monophosphine species and determined that it is a highly effective catalyst (42). Beller also studied a series of 1,6-diene palladium(0) monophosphine complexes, **1**, and found them to be suitable for aryl chloride couplings (43).

Buchwald has developed a series of ligands based on a 2,2'-biphenyl motif (44, 45). Biphenyldialkylphosphine (alkyl = ^tbutyl or cyclohexyl) reacts with a variety of unactivated aryl chlorides at room temperature with approximately 1 mol% Pd. Further optimisation of these ligands has allowed coupling of aryl, heteroaryl and vinyl boronic acids with extremely hindered aryl chlorides and heteroaryl halides, with the ligand shown as structure **2**, (R = Me) being particularly preferred (45). Interaction between the Pd and C(1) of the second (remote) biphenyl ring is believed to play a key role in the catalytic properties of this group of

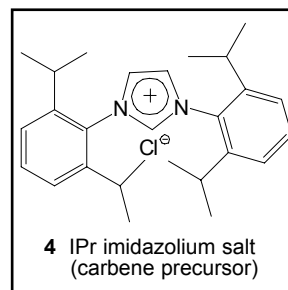


ligands. Fu also demonstrated that PCy_3 catalysts are effective for the coupling of aryl and vinyl triflates, and even simple alkyl bromides and chlorides (albeit with catalyst loading of 10 mol% Pd) (27, 28). In further attempts to optimise the combination of steric and electronic properties of the ligand, a number of other compounds have been introduced recently, e.g. mono- and bis-phosphino ferrocenes (46, 47), methyl-di-*t*-butylphosphine (48), di(adamantyl)-*n*-butylphosphine and other di-adamantylphosphine ligands (49–52).

In developing a series of palladacycle complexes, Bedford found that the combination of PCy_3 with a *P,C*-palladacycle of a phosphite ligand bearing a salicylate group, **3**, showed exceptional longevity and hence could be used at very low loadings (53). Guram, Buchwald and Fu have all reported recently on Suzuki-Miyaura coupling of derivatives of nitrogen heterocycles (chlorides or boronic acids) (54–56).



The recent interest in *N*-heterocyclic carbenes (NHCs) as alternatives to phosphine ligands has included applications in coupling (57). These ligands are strong electron donors and carry bulky substituents so they might be expected to activate aryl chloride substrates. This has been borne out by a number of examples, in the work of Nolan, in particular. Imidazolium salts such as IMes HCl and IPr HCl, **4**, provide an air-stable source of precursor carbene complex when reacted *in situ* with Pd_2dba_3 (dba = dibenzylideneacetone) leading to simplified and more effective experimental procedures. With approximately 2 mol% catalyst good yields were obtained with many aryl chlorides and triflates (30).



Stille Reactions

The synthesis of ketones from acid chlorides and organotin compounds using Pd catalysis was reported by Stille in 1978 (58). The scope and versatility of this chemistry was demonstrated by the mid-1980s (4), although its industrial application has been limited by concerns over tin residues in the product and waste streams. Catalysts employed in the early work on aryl bromides, iodides and triflates included benzyl(chloro)bis(triphenylphosphine)palladium ($\text{PdCl}(\text{CH}_2\text{Ph})(\text{PPh}_3)_2$) and $\text{Pd}(\text{PPh}_3)_4$. Further work demonstrated the advantages of tris-2-furylphosphine or triphenylarsine ligands in this chemistry (59). Stille coupling has been widely studied in reactions of heteroaryl chlorides but there are fewer examples with aryl chlorides. For unactivated aryl chlorides it has been found that $\text{P}(\text{tBu})_3$ yields suitable systems (60). The complex bis(tri-*tert*-butylphosphine)-palladium ($\text{Pd}(\text{P}(\text{tBu})_3)_2$) can also be used as catalyst at loadings down to 0.1 mol% Pd. The combination of $\text{Pd}(\text{OAc})_2$ and the imidazolium salt IPr HCl, **4**, in the presence of ${}^n\text{Bu}_4\text{NF}$ was also effective for coupling aryl bromides and electron-deficient aryl chlorides (61), while Bedford *et al.* reported that simple Pd precursors with PCy_3 gave very effective catalysis (62).

Hiyama Reactions

The reaction with organosilanes is more recently developed than the other cross-couplings, suitable conditions being identified by Hiyama in 1988 (63, 64). The preferred catalyst was bis(allyl)dichlorodipalladium ($[\text{PdCl}(\eta^3\text{-C}_3\text{H}_5)]_2$) at 2.5 mol% under mild conditions, ambient to 50°C giving acceptable yields with aryl iodides and bromides (65). The reaction was extended to selected aryl chlorides in 1996 with the adoption of

dichlorobis(triisopropylphosphine)palladium ($\text{PdCl}_2(\text{P}(\text{Pr})_3)_2$) as catalyst in the presence of KF (66). Fluoride-free reactions of aryl halides (Br and Cl) with aryl and vinyl siloxanes have been achieved through the use of concentrated aqueous sodium hydroxide (50%) at 120°C, with tetrabutylammonium bromide being used as an additive in some cases (67, 68).

Negishi Reactions

Although he studied the coupling of a range of organometallic derivatives (aluminium, magnesium, zinc and zirconium), the name of Negishi is associated with cross-coupling using organozinc derivatives, as reported in 1977 using $\text{PdCl}_2(\text{PPh}_3)_2$ plus $t\text{Bu}_2\text{AlH}$ to generate the Pd(0) catalyst (5, 6). The reactions of heteroaryl chlorides were widely studied using a variety of Pd(0) and Pd(II) catalysts. The first general method applicable to aryl chlorides was developed in 2001 by Fu using as catalyst $\text{Pd}(\text{P}(t\text{Bu})_3)_2$ at 2 mol% and 100°C with 1:1 THF/NMP as solvent (69). Hindered compounds reacted satisfactorily and up to 3000 turnovers were achieved. Buchwald extended his series of biphenyldialkylphosphine ligands to include an example – 2,6-di-isopropoxy-substituted – (see 2) which gave excellent results in a wide variety of Negishi couplings (70). Pd/dppf-based (dppf = diphenylphosphinoferrocene) catalysts have also been found to be useful in this class of reactions (71).

Kumada Reactions

Although the metal-catalysed coupling (particularly Ni and Pd) with organomagnesium reagents (Grignards) has been studied for some time, the applicability of these reactions is limited due to the high reactivity of the Grignard reagents with a variety of functional groups. Early work used $\text{Pd}(\text{PPh}_3)_4$ (7, 72) as catalyst. Studies by Kumada *et al.* of bidentate phosphines suggested that the bite angle is important and that the large value for dppf was particularly suitable – possibly due to the ease of dissociation of one phosphorus donor (71). Initial work on activated aryl chlorides also used $\text{PdCl}_2(\text{dppf})$ (effective down to 0.1 mol% catalyst in THF at 85°C) (73). Other work described the use of palladacycles under more forcing condi-

tions (15) and more recently the application of $\text{Pd}_2(\text{dba})_3/\text{NHCs}$ has been described (74). The preferred ligand was IPr derived from the imidazolium salt 4.

Sonogashira Reactions

Although the coupling of aryl halides and alkynes had been reported previously, the conditions reported by Sonogashira in 1975 greatly improved the attractiveness of this reaction (3). This reaction is often used to convert heteroaryl chlorides to fused-ring heterocycles. The combination of Pd catalyst (typically $\text{PdCl}_2(\text{PPh}_3)_2$) with copper iodide and amine base allowed the coupling to be carried out at room temperature in six hours. It is believed that copper assists the reaction through formation of an acetylide and then this group is transferred to Pd by a transmetalation step. However, the formation of copper acetylides can also lead to homocoupling products, so modification of the conditions, and in particular copper-free conditions, have continued to be investigated. In contrast to many of the reactions above, although different researchers have established some flexibility in the conditions, no general method is yet available for all substrates for this reaction. Aryl chlorides and tosylates can be coupled using $\text{PdCl}_2(\text{PhCN})_2$ and a biphenyldicyclohexylphosphine under copper-free conditions (75) and the addition of tetrabutylammonium fluoride to $\text{PdCl}_2(\text{PPh}_3)_2$ allows a copper-, amine- and solvent-free alkynylation of aryl halides (76). A detailed review of the Sonogashira reaction has recently been published (77).

Conclusion

From the early studies which exemplified these reactions using catalysts based on simple Pd compounds (chloride, acetate) and triphenylphosphine (for example, $\text{Pd}(\text{PPh}_3)_4$, $\text{PdCl}_2(\text{PPh}_3)_2$) these reactions have been extended to cover the full choice of aryl halides with even sterically restricted partners. Changing from aryl to alkyl substituents on phosphorus has reduced the barrier to oxidative addition of the stronger aryl chloride bond and more subtle interactions between the ligand and the Pd atom promote the migratory insertion/reductive

elimination of the products. Thus Fu and Hartwig have shown the wide applicability of PCy_3 and $\text{P}^t(\text{Bu})_3$ systems, while Buchwald has demonstrated the extraordinary versatility of biphenyldialkylphosphine ligands. Many other groups have demonstrated that highly stable precursors such as palladacycle, pincer

and carbene complexes can generate highly active species. It is certain that the remarkable advances in coupling chemistry that have been made in academic laboratories will be increasingly incorporated into industrial fine chemical and pharmaceutical preparations.

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