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Recent advances in transition metal-catalysed cross-coupling of (hetero)aryl halides and analogues under ligand-free conditions

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The formation of new bonds is pivotal in organic chemistry and a prerequisite to life because it allows the construction of complex molecules from simple precursors. This gives credence to the intensive study of metal-catalysed C–C bond formation *via* cross-coupling reactions over the past few decades. However, despite the tremendous success recorded for ligand-supported palladium in the catalytic transformation of (hetero)aryl halides, the challenges in their practical application lie in their cost and difficulty of preparation, sensitivities to air/moisture, toxicity and complete incompatibility with aqueous media, which remarkably limit their industrial applications. Non-ligated or ligand-free metal-catalysed cross-coupling reactions are attractive alternatives to ligand-supported counterparts due to their recyclability, cost-effectiveness, sustainability and full industrial applications. Over the years, various research groups have strived to advance ligand-free catalytic systems for cross-coupling of (hetero)aryl halides because of the aforementioned advantages. This review highlights the progress, challenges and prospects in ligand-free metal-catalysed cross-coupling of (hetero)aryl halides and their analogues.

1. Introduction

The emergence of organic transformations catalysed by transition metals, commonly known as transition metal cross-coupling reactions (Scheme 1),[1] has virtually transformed the trend in organic synthesis and these reactions have remained as simple strategies for rapid construction of C–C, C–N, C–O and other C-heteroatom

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$$\begin{array}{ccccc} R'{-}X & + & R{-}M & \xrightarrow{\text{Catalyst}} & R'{-}R \\ \mathbf{1} & & \mathbf{2} & & \mathbf{3} \\ \text{electrophilic} & & \text{nucleophilic} & & \text{product} \\ \text{coupling partner} & & \text{coupling partner} & & \end{array}$$

Scheme 1 General equation for a transition metal-catalysed cross-coupling reaction.

bonds from readily available appropriately functionalized substrates.[2,3] Palladium metal has emerged as a choice catalyst for a wide range of cross-coupling reactions chiefly because reactions catalysed by palladium are generally mild and compatible with numerous functional groups.[4] In addition, palladium catalysts generally allow selective reactions with high turnover numbers (TONs) and turnover frequencies (TOFs).[5]

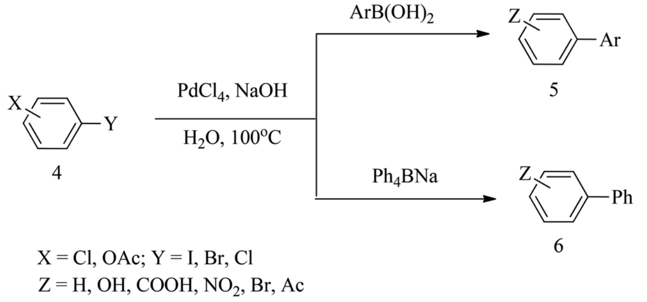
Metal-catalysed methodologies have been proven to be the most powerful and find use in target- or diversity-oriented synthesis which was previously impossible or only possible using multi-step approaches. They have found utility in synthetic routes to biphenyls or substituted aromatic moieties, prochiral ketones, acrylates and other related compounds of interest in pharmaceuticals,[6,7] including but not limited to indanone A, nifedipine, losartan, HIV-1 protease and taxol, which are subunits in many marketed drugs, agrochemicals, fine chemicals, conducting polymers, liquid crystalline materials, *etc.*[8,9]

Transition metal-catalysed cross-coupling reactions have been applied in the construction of C–N bonds[10] including the complementary addition of an alkyl, alkenyl, or aryl group to an amide,[11] breaking of classical inert amide bonds,[12,13] non-conventional installation of an amino group on alkenes and alkynes,[14] *etc.* They have also been adapted to perform intra-cellular bio-orthogonal reactions for the intracellular synthesis of drugs including cytotoxic agents[15] as well as site-selective derivatisation and cyclisation of peptides.[16] Consequently, because of their several advantages over classical reactions,[14] they have been under the spotlight of several academic and industrial research groups leading to significant improvements during the last two decades. They have been applied in the construction of an array of compounds including highly functionalized heteroaromatics[14] which are significant substructures found in various natural or synthetic alkaloids, linear and fused ring-substituted phenothiazine and phenoxazine systems,[17,18] chalcones as well as flavonoids,[19] ynones,[20] and steroids,[21] to mention but a few. Due to the diversity of the structures encountered, as well as their biological and pharmaceutical relevance, several new economic, efficient and selective synthetic strategies to access these compounds are being developed.

The development of a ligand-free approach for aryl, heteroaromatic and vinyl fluorosulfates, halides, or traditional sulfates (triflates, mesylates and tosylates)[22] as electrophilic partners for transition metal-catalysed cross-coupling reactions has attracted increasing attention because the process is more cost-effective and also avoids ligand and metal contaminations in the final product.[23,24] In other words, the phosphine-based ligands used in conventional transition metal-catalysed cross-coupling reactions are expensive compared to the metal catalyst employed; thus the process is cheaper. Ligand-free activation of aryl chloride is one of the most challenging fields in synthetic organic chemistry.[25–27] However, over the past two decades, the attention of many research groups has been directed towards catalytic activation/functionalization of aryl and heteroaryl halides under ligand-free conditions due to its economy and environmental friendliness. This review captures the recent advances in ligand-free transition metal-catalysed Suzuki–Miyaura,[28,29] Sonogashira,[30,31] Hiyama,[32] Mizoroki-Heck,[33,34] Negishi[35] and Stille[36] reactions.

2. Ligand-free Suzuki–Miyaura cross-coupling

The Suzuki cross-coupling reaction is one of the most versatile and utilised reactions for the selective construction of carbon–carbon bonds. It is mainly used in the formation of biaryl compounds, substituted aromatic compounds and alkene derivatives that are structural components of numerous natural products, agrochemicals, pharmaceuticals, and advanced materials, such as organic electroluminescent (EL) materials.[37,38] The Suzuki reaction is a palladium or nickel-catalysed cross-coupling reaction of an organoboron reagent and an organic halide or pseudohalide in the presence of a base.[39,40] Reports on the palladium-mediated Suzuki reaction of aryl boronic acids with aryl iodides or activated bromides in water as a solvent have been demonstrated with only one recent exception.[41–43] The coupling of aryl chlorides has also been reported but involves the use of an oxime-carbapalladacycle as the catalyst.[44] Several reports on the use of water as a co-solvent focusing on the use of aryl iodides or activated bromides have been made,[45,46] and one recent report[47] demonstrated the use of aryl chlorides in a 20 : 1 DMA/water mix. The first reports on microwave-mediated Suzuki reactions came in 1996, using $Pd(PPh_3)_4$ as a catalyst both for homogeneous[48] and solid-phase[49] biaryl syntheses. More recently, microwave heating has been used to facilitate the coupling of aryl boronic acids with poly(ethylene glycol) esters of an aryl iodide, triflate, and bromothiophene in water.[50] Suzuki–Miyaura cross-coupling offers many advantages over other transition metal-catalysed reactions[51] which include easy availability of organoboron compounds, stability to moisture and air, low toxicity, broad functional group tolerance, and relatively milder reaction conditions.[52] Due to economic and environmental concerns, the Suzuki reaction has been adapted to ligand-free conditions. In recent years, a lot of ligand-free Suzuki cross-coupling reactions have been reported for the formation of essential molecules.



Scheme 2 Ligand-free Pd-catalysed Suzuki reaction of aryl boronic acid and sodium tetraphenylborate with a variety of aryl halides.

a. Cross-coupling of aryl boronic acid or sodium tetraphenylborate with aryl halides

In 1997, Bumagin and Bykov[27] reported a ligand-free palladium-catalysed Suzuki cross-coupling reaction between aryl halides **4** and organoboron compounds in which Pd(0) complexes were generated *in situ* from $PdCl_2$ or $Pd(OAc)_2$ in aqueous alkali solution to afford polyfunctional biaryls **5** and **6** in 60–99% yields (Scheme 2).

The best conversion of *p*-chlorobenzoic acid **7** was achieved in the presence of 3 mol% $PdCl_2$ pre-catalyst with NaOH within 3 h to furnish biphenyl **8** in 92% yield (Scheme 3). However, electron-rich chlorophenols reacted with sodium tetraphenylborate (Ph_4BNa) to afford moderate yields of isolated products.

A heterogeneous palladium catalytic system (Pd/C) in a dimethylacetamide–water (DMA–H_2O) mixture cross-coupled phenylboronic acid with a variety of aryl halides without observable homocoupling by-products. Electron-poor aryl halides gave higher yields (79–95%) of biaryls, while neutral and deactivated aryl halides gave moderate yields, but an increase in the amount of catalytic loading improved the yields. The ability of Pd/C to activate the C–Cl bond in aryl chlorides was attributed to the synergistic anchimeric and electronic effect that takes place between the catalyst surface and the aryl chloride.[27]

b. Cross-coupling of 2-halogenopyridines with aryl boronic acids

Liu and co-workers[53] demonstrated a very fast and efficient oxygen-promoted ligand-free Pd-catalysed cross-coupling reaction of substituted 2-halogenopyridines **10**, 2-halogenopyrazines **11** and 5-halogenopyrimidines **12** with various boronic acids **9** for the synthesis of the corresponding 4-aryl substituted pyridine, pyrazine and pyrimidine derivatives **13–15** in aqueous isopropanol (Scheme 4). The cross-coupling reactions gave the biaryl products in 52–99% yields in a couple of hours.

However, heterocyclic compounds are of particular interest to the pharmaceutical industry because of their potential bioactivities,[54,55] but their inclusion in metal-catalysed cross-coupling reactions remains a challenge as a result of the potential chelation of their donor groups such as the heteroatoms to metal centres.[53,56] The binding either slows down the rate of the reaction or results in catalyst inactivity.[57] Therefore, catalytic systems that are compatible with heterocyclic aryl halides will be advantageous in ligand-free cross-coupling reactions.

c. Microwave-assisted cross-coupling of aryl halides and aryl boronic acids

Leadbeater and Marco[58] reported a ligand-free palladium-catalysed Suzuki reaction in water using microwave heating. Their methodology used a low palladium loading (0.4 mol%), was fast (5–10 min reaction time), and was usefully applied for coupling reactions involving aryl iodides, bromides and chlorides **16** with boronic acid **17** (Scheme 5).

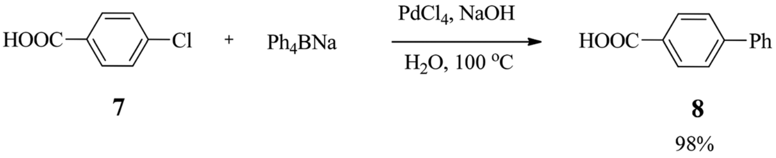
d. Cross-coupling of aryl halides with aryl boronic acids

In 2011, Qiu and co-workers[53] developed a convenient, effective and mild protocol for the palladium-catalysed ligand-free Suzuki reaction of aryl bromides **19** with aryl boronic acids **20** in aqueous *N*,*N*-dimethylformamide (DMF) in the presence of K_2CO_3 in air at room temperature (Scheme 6). The choice of volume ratio of DMF–H_2O as well as the base is critical to the reaction. Hence, at a catalytic loading of 0.0025 mmol and a DMF–H_2O ratio 1 : 1, a model coupling reaction of 4-bromoanisole with phenylboronic acid provided a quantitative yield within 5 min.

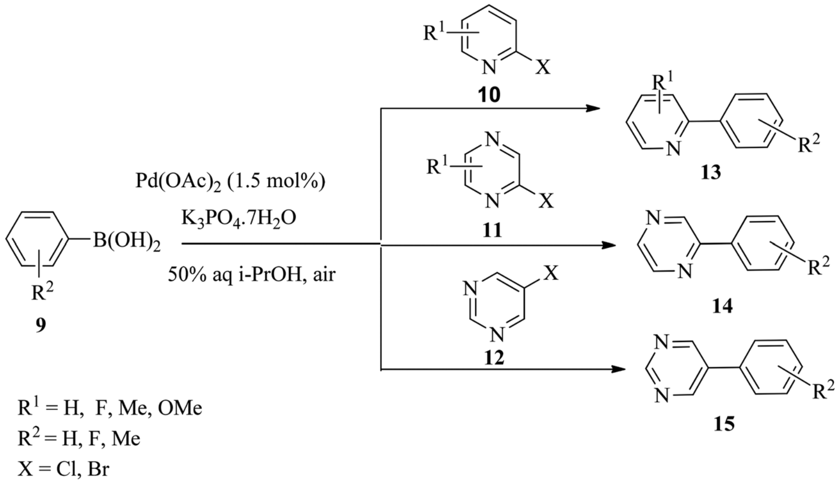
Furthermore, the optimised conditions of the protocol were extended to the cross-coupling reactions of nitrogen-based heteroaryl halides **23–25** with aryl boronic acids **22** in moderate to excellent yields (Scheme 7). A room temperature cross-coupling reaction of 2-chloropyrazine with phenylboronic acid and 4-methyl phenylboronic acid gave 83% and 88% yields of biaryls, respectively, within 24 h.

e. Bio-supported cross-coupling of aryl halides with aryl boronic acids

Tang and co-workers[57] described bio-supported and recyclable palladium nanoparticles as an efficient phosphine-free catalyst for the Suzuki reaction of an aryl halide **29** with



Scheme 3 Ligand-free Pd-catalysed synthesis of biphenyl-4-carboxylic acid.

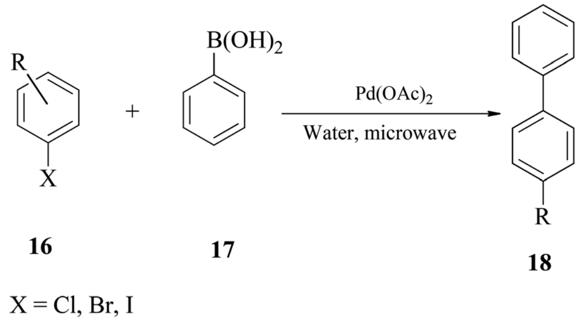


Scheme 4 Oxygen-promoted Suzuki–Miyaura synthesis of 2-phenylpyridines.

substituted aryl boronic acids **30** in water (Scheme 8). The catalyst was highly recyclable, maintaining yields of 86% after five cycles in the coupling of iodobenzene with phenylboronic acids. The reaction conditions resulted in the coupling of chlorobenzene with phenylboronic acid in 89% yield at 95 °C. They also compared the coupling reaction mentioned above in DMF and an organic base. The result indicated that the reaction proceeded in less than 3.5 h at 85 °C, but the coupling gave a lower yield of 78%.[57] This was probably due to a decrease in efficiency of heterogeneous catalysis with the dispersion of reactants into the bacterial cellulose network. With a recycled catalyst and when DMF is used as the reaction solvent, a lower yield was also recorded; so, it was concluded that environmentally friendly processes which employ water remain the best strategy.

f. Bimetal catalysed cross-coupling of (hetero)aryl halides with an arylboronic acid

Kim and co-workers[59] reported the application of carbon-supported bimetallic Pd–M (M = Ag, Ni, and Cu) nanoparticles synthesized by γ-irradiation at room temperature without reducing agents in Suzuki cross-coupling of a halide of thiophene, benzene and benzoic acid with phenylboronic acid in ethanol (Scheme 9). Evaluation of the catalytic efficiency determined by the yield of the reaction showed that the Pd–Cu bimetallic system supported on carbon is the most efficient (Pd–Cu/C > Pd/C > Pd–Ag/C > Pd–Ni/C) in the Suzuki cross-coupling of the halides of thiophene, benzene and benzoic acid with yields of 96.7%, 97.5%, and 88.7%, respectively.



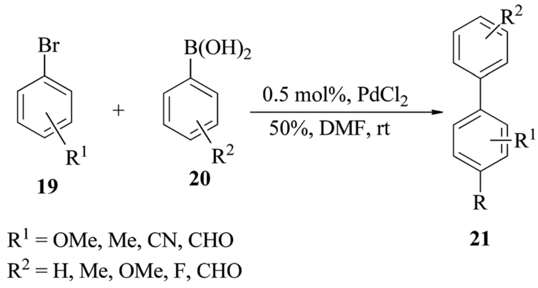
Scheme 5 Microwave-mediated Suzuki coupling of aryl halides with aryl boronic acids in water using Pd(OAc)$_2$.

g. Homeopathic cross-coupling of various aryl halides with boronic acids

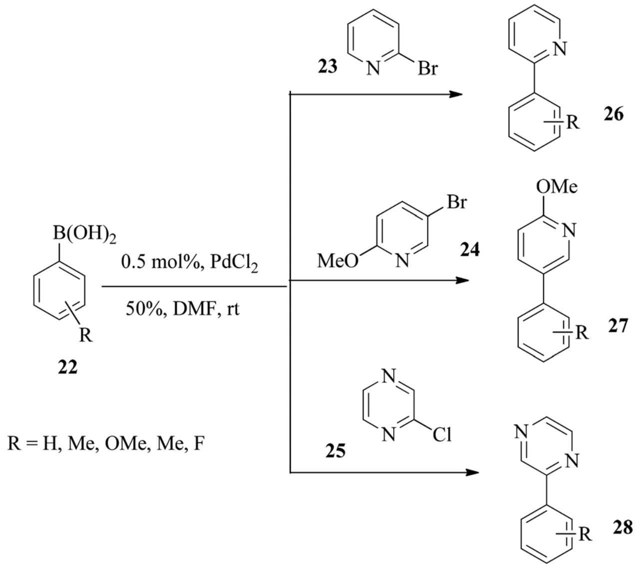
The De Vries group demonstrated the application of a 'homeopathic' ligand-free palladium catalyst in the coupling of aryl bromides and chlorides.[60] The catalyst (Pd(OAc)$_2$) at a loading of 0.02–0.05 mol% generally performed well for both activated aryl bromides and chlorides, but mixed results were obtained with deactivated aryl bromides and chlorides (Scheme 10).

The cross-coupling of 4-chloronitrobenzene **38** with phenylboronic acid **39** in the presence of 0.05% Pd(OAc)$_2$ at 130 °C for 17 h afforded 4-nitrobiphenyl **40** in 94% GC yield (Scheme 11).

Interestingly, at a loading of as small as 0.005 mol%, the 4-nitrobiphenyl product was also obtained in 83% yield, but the reaction protocol failed to convert deactivated electron-



Scheme 6 Suzuki reactions of aryl bromides with aryl boronic acids.

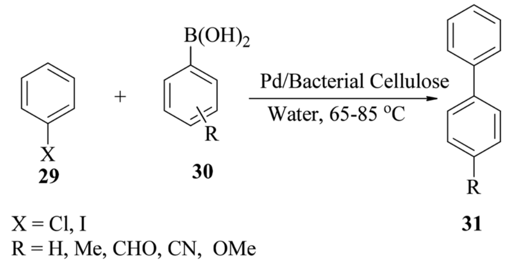


Scheme 7 The Suzuki reaction of *N*-heteroaryl halides with aryl boronic acids.

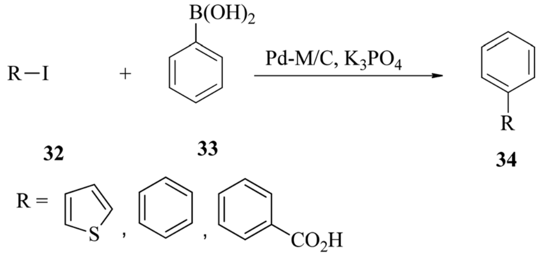
rich aryl chlorides. The failure of the deactivated electron-rich aryl chlorides to react stems from increased C–Cl bond strength probably because of the contribution of both inductive and mesomeric effects.

3. Ligand-free Hiyama cross-coupling reaction

Cross-coupling reactions of organosilicon compounds have emerged as viable alternatives to Suzuki coupling reactions.[43,61,62] The Hiyama cross-coupling reaction[63] is a chemo- and stereoselective cross-coupling reaction of organosilanes with organic halides. It has gained popularity for asymmetric biaryl compound synthesis or construction of multi-substituted alkenes that are components of various functional materials. This is associated with low cost, low toxicity, commercial availability, easy preparation and handling, high tolerance to a variety of functional groups when compared to organomagnesium and organocopper, and high stability of organosilicon reagents to moisture and air compared to other organometallic compounds of zinc, aluminium, boron and zirconium conventionally used in cross-coupling reactions.[32,64] Since the first report of the use of aryl(alkoxy)silanes for Hiyama coupling by Shibata and co-workers,[65] reactive aryl bromides and iodides have been largely used instead of the relatively cheap and commercially available aryl chlorides.[32,66] Several limitations have hampered the use of aryl chlorides in Hiyama coupling.[64,67–71] Below are some of the recent ligand-less Hiyama cross-coupling reactions.



Scheme 8 The Suzuki reaction of aryl halides with aryl boronic acids.



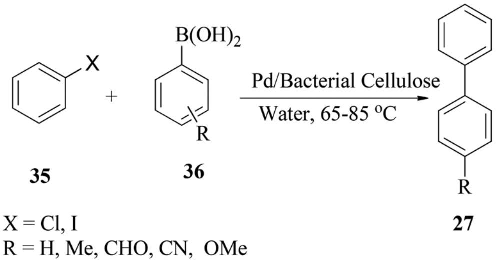
Scheme 9 The Suzuki reaction of (hetero)aryl halides with phenylboronic acid.

a. Cross-coupling of substituted aryl halides with arylalkoxysilanes

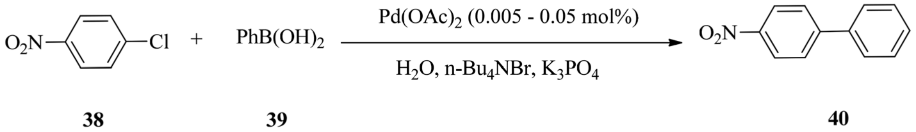
Sajiki and co-workers[72] reported the first active palladium on carbon-catalysed ligand-free Hiyama cross-coupling of a variety of electron-rich and electron-poor aryl halides **41** with aryltriethoxysilanes **42** in good to excellent yields at 0.5 mol% Pd/C catalytic loading in refluxing toluene within 24 h (Scheme 12). The use of fluoride sources such as TBAF·3H$_2$O or metal fluorides is critical for the reaction to proceed. The reaction was also extended to phenytrimethoxysilane derivatives, and good yields were obtained within 48 h.

In the same vein, Ranu and co-workers[73] reported a simple one-pot fluoride-free operation using *in situ* generated palladium(0) nanoparticles for efficient Hiyama cross-coupling of a wide variety of substituted aryl bromides and iodides with aryl silanes in water (Scheme 13). The reaction proceeded very quickly and was performed in air with excellent chemoselectivity and high yields.

A similar reaction was independently reported by Sarkar and co-workers[74] using colloidal palladium nanoparticles (1 mol%) generated from the Fischer carbene complex of tungsten as the reductant and PEG as the capping agent in water.



Scheme 10 The Suzuki reaction of aryl halides with aryl boronic acids.



Scheme 11 Homeopathic Suzuki reaction of aryl chlorides.

b. Cross-coupling of allyl acetates with aryl/vinyl silanes

In 2008, Ranu and co-workers[75] reported a simple and efficient palladium(0) nanoparticle catalysed Hiyama cross-coupling reaction of both activated and unactivated open-chain allylic acetates and organosiloxanes. They demonstrated that several structurally substituted allyl acetates **47** underwent regio- and stereoselective coupling reactions with phenyl, tolyl, and vinyl siloxanes **48** to produce the corresponding allylated products **49** in 65–82% yields over 7–10 h (Scheme 14). The coupling with vinyl siloxanes was a novel method for the synthesis of 1,4-pentadiene.

c. Bimetallic-catalysed cross-coupling of haloaryls with phenylmethoxysilane

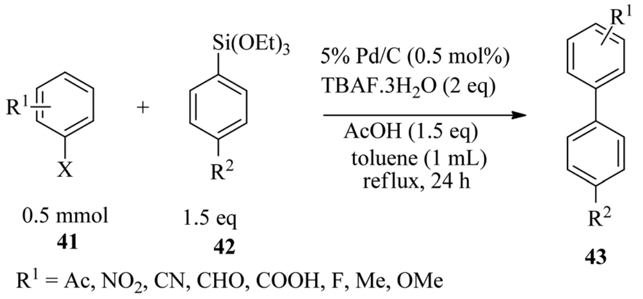
Rothenberg and co-workers[76] reported the application of stable and highly mono-dispersed core–shell bimetallic Ni–Pd nanoparticles in the ligand-free Hiyama cross-coupling reaction of different haloaryls **50** and phenylmethoxysilane **51**. With a variety of iodo- and bromoaryls, good product yields were obtained, thus confirming that they acted as a good source of biaryl-containing compounds which are vital intermediates for preparing biologically active molecules, organic semiconductors and liquid crystals (Scheme 15).[77]

4. Ligand-free Sonogashira cross-coupling

The generation of sp–sp^2 carbon–carbon bonds by cross-coupling of terminal alkynes with aryl halides or vinyl halides is termed Sonogashira cross-coupling.[78,79] A palladium (Pd) catalyst, ligand, copper(I) salt co-catalyst and amine base are requirements for a standard Sonogashira cross-coupling reaction. The Sonogashira reaction has been reported for the synthesis of alkyne-containing aromatic compounds,[80,81] natural products,[82,83] medicinal products,[84,85] oligomers,[86,87] and polymers.[88] The major setbacks of the reaction are the sensitivity of the copper co-catalyst to oxygen, causing oxidative homocoupling of acetylenes to form diacetylenes and copper acetylides which are potentially explosive,[79] difficulty in removal of high boiling point solvents from the reaction mixture, increase in cost due to low reusability of the homogeneous Pd catalyst,[89] and contamination of the product by toxic Pd metal.[90,91] Significant efforts have been directed to improving Sonogashira reactions.[89] Among the developments are ligand-free and copper-free Sonogashira reactions which reduce the cost, simplify the reaction procedures and avoid the formation of oxidative homocoupling by-products. In the same vein, high boiling solvents have been substituted with water and other benign solvents.[92,93] The development of supported Pd for heterogeneous catalysis simplifies the separation and recyclability of the catalyst. Several catalyst supports such as perovskites,[94] carbon,[95,96] zeolites,[97] hydrotalcite,[97] silica,[98] cellulose,[99] and polymers[100] have been employed. In the development of supported catalysts, the use of the right amount of catalyst loading on the supporting material to ensure catalyst reactivity and reduce catalyst leaching is a significant consideration.[101,102] To date, most of the supported catalysts developed still have ample room for further improvement.[103] From the green chemistry point of view, using recyclable supported catalysts in aqueous media is desirable.

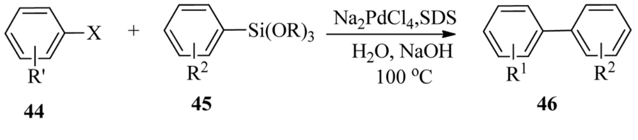
a. Solid-supported coupling of nucleotide derivatives

Stoltz and co-workers[104] explored the Pd/C and Amberlite IRA-67-mediated ligand-free Sonogashira coupling of several deoxynucleoside derivatives **54** with trifluoroacetyl **55** and phthalimido reagents **56**. They modelled the strategy employed by Kotschy and co-workers[105] replacing Pd/C with Pd(PPh$_3$)$_4$, lowering the catalyst loading to 5% and carrying out the reaction at 50 °C to afford deoxyuridine, uridine,



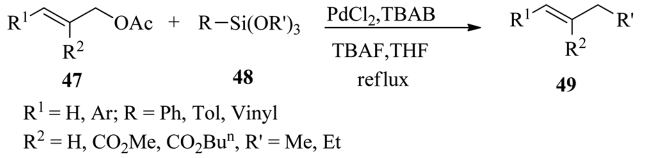
R^1 = Ac, NO_2, CN, CHO, COOH, F, Me, OMe
R^2 = H, Cl, Me, OMe
X = Br, Cl

Scheme 12 The Hiyama cross-coupling of various aryl halides with aryltriethoxysilanes.



R^1 = H, Me, OMe, CHO, COMe, F, Cl, NO_2
R^2 = H, Me
R = Me, Et
X = Br, I

Scheme 13 One-pot fluoride-free palladium(0) nanoparticle catalysed Hiyama coupling of aryl bromides/iodides with arylsiloxane.



Scheme 14 One-pot fluoride-free palladium(0) nanoparticle catalysed Hiyama coupling of allylic acetates with arylsiloxane.

dideoxyuridine and deoxycytidine derivatives **57–58** (Scheme 16). The dideoxyuridine derivatives are particularly crucial as critical intermediates in the synthesis of conventional Sanger DNA sequencing reagents.[106]

The conditions were extended to the synthesis of 2-deoxyadenosine and 2-deoxyguanosine derivatives **59** (Scheme 17). Although the coupling of 8-bromo-2-deoxyadenosine and 8-bromo-2-deoxyguanosine derivatives was sluggish under Pd/C-catalysis, the use of the Pd(PPh$_3$)$_4$/Amberlite IRA-67 system gave 78% and 98% yields of **60a** and **60b** in 11 h and 7 h, respectively.

b. Polymer-supported cross-coupling of aryl halides with phenylacetylene derivatives in water

Ligand-less Pd(0) loaded polymethyl methacrylate (PMMA) microspheres were employed for the Sonogashira cross-coupling reaction in aqueous media by Zhang and co-workers in 2012.[103] A variety of terminal acetylenes **61** were coupled with different phenyl iodides, bromides and chlorides **62** (Scheme 18). Phenyl iodides containing electron-donating or electron-withdrawing groups coupled readily with phenylacetylenes in excellent product yields.

c. Copper nanocluster catalysed cross-coupling of alkynes with aryl halides

Rothenberg and co-workers[107] were the first to obtain substituted diphenylalkynes **66** in good isolated yields and high selectivity from palladium-free and ligand-free Sonogashira cross-coupling of phenylacetylene **64** with various aryl halides **65** under stable copper cluster catalysis in 2004. 1.5 eq. of phenylacetylene and 1 eq. of each of the aryl halides were reacted in the presence of 1.5 eq. of the base and 5 mol% of metal clusters at 110 °C (Scheme 19). The stable metal cluster was prepared by reducing solutions of the chloride salt precursor with tetraoctylammonium formate (TOAF) in DMF at 65 °C.

d. Nanoparticle supported cross-coupling of alkynes and (hetero)aryl halides

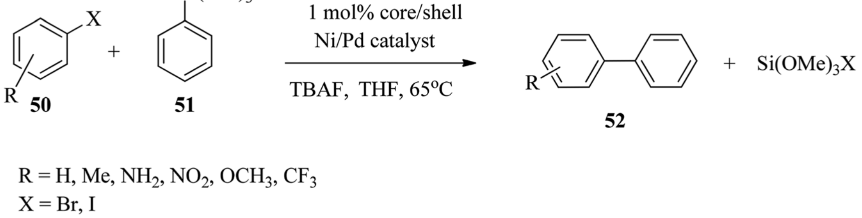
Wei and co-workers[108] reported the application of *in situ* generated palladium nanoparticles as a catalyst supported on Al(OH)$_3$ (Scheme 20) in ligand- and copper-free Sonogashira cross-coupling reactions of (hetero)aryl bromides and chlorides.

The optimised reaction conditions were applied in cross-coupling of various (hetero)aryl halides **69** bearing neutral, electron-withdrawing or electron-donating substituents in the phenyl ring with phenylacetylene **68** bearing electron-donating and electron-withdrawing groups in the benzene ring to afford the 1,3-diyne products in 53–98% yields (Scheme 21).

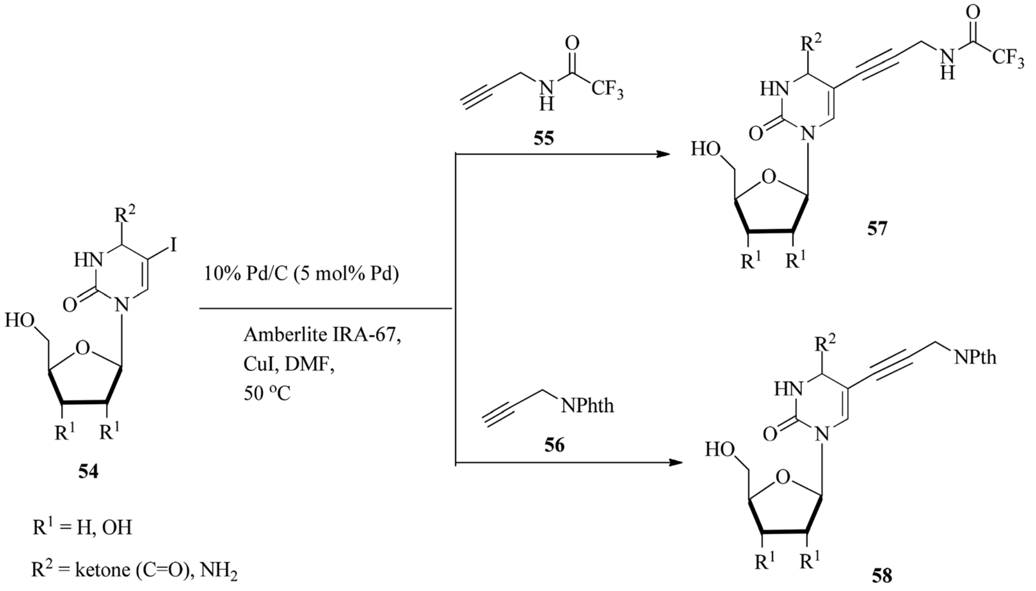
Heteroaryl bromides derived from pyridines, thiophenes, quinolines, and pyrimidines **71** were converted to the corresponding cross-coupled products **72** in moderate to excellent yields (Scheme 22).

e. Cross-coupling of aromatic and aliphatic terminal alkynes with aryl iodides

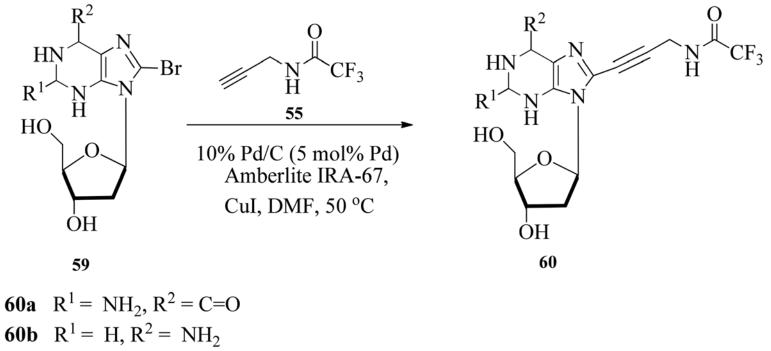
Sajiki and co-workers[109] reported the cross-coupling of a variety of aryl iodides **73** with aromatic and aliphatic terminal alkynes **74** to give the corresponding 1,2-disubstituted aromatic alkynes **75** in good yields by using only 0.4 mol% of the heterogeneous 10% Pd/C as the catalyst without a ligand, copper salt, or amine in an aqueous medium (Scheme 23). They explored the scope and limitations of the substrates under the optimized reaction conditions (10% Pd/C and Na$_3$PO$_4$·12H$_2$O (2.0 eq.) in 50% iPrOH at 80 °C). Iodobenzene and aryl iodides containing an electron-withdrawing group in the aromatic ring, such as nitro and acetyl functionalities and 3-iodopyridine, a π-deficient heteroaryl iodide, were smoothly coupled with a variety of both aliphatic and aromatic terminal alkynes. While the coupling of 4-iodoanisole containing an electron-donating methoxy group produced relatively lower efficiencies (38–72% yields), the coupling products were smoothly obtained. They also demonstrated the application of wet-type Pd/C to catalyze the Sonogashira coupling reaction, and the reaction proceeded efficiently under argon and aerobic conditions.



Scheme 15 Bimetallic Ni–Pd nanoparticle catalysed ligand-free Hiyama cross-coupling reaction of phenylmethoxysilane with various haloaryls.



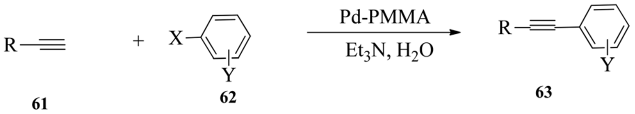
Scheme 16 Solid-supported Sonogashira coupling of deoxynucleoside derivatives.



Scheme 17 Solid-supported Sonogashira coupling of deoxyadenosine and deoxyguanosine derivatives.

5. Ligand-free Heck cross-coupling

The Heck reaction, a powerful method for synthesising several olefinic compounds, involves the carbon–carbon coupling of aryl halides with olefins.[110–137] In the last few years, significant development involving the coupling of various pseudo-halides such as aryl triflates,[111] acid chlorides,[112] aryl anhydrides,[113] aryl sulfonyl chlorides,[114] and aromatic diazonium salts[115] has been made. The synthesis of several drugs and intermediates such as naproxen (an anti-inflammatory agent),[116] prosulfuron (herbicide),[117] Singulair,[118,119] eletriptan[120,121] and 2-ethylhexyl-*p*-methoxycinnamate (UV B sunscreen agent)[122] is carried out using the Heck reaction.[123] It has also found utility in the synthesis of 2- and 4-vinyl toluene which serve as comonomers for styrene polymers.[124] The catalytic system for an efficient Heck reaction consists of a palladium source, ligand, base and solvent. Usually, phosphine-containing ligands are used in the Heck reaction, as they play an essential role in stabilisation and *in situ* generation of Pd(0) species from Pd(II) complexes. Due to the high cost, toxicity and thermal instability of phosphine-containing ligands,[125] various phosphine-free (ligand-less) catalytic systems have been developed.[154–158]

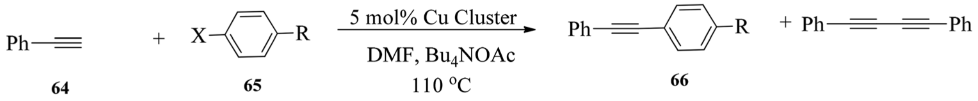


R = Ph, n-C_6H_{11}, n-C_6H_{13}, $CH_3OC(=O)$
X = I, Br, Cl
Y = Me, OMe, H, COMe, NO_2, CF_3, CHO, F

Scheme 18 Polymer-supported cross-coupling of aryl halides with phenylacetylenes in water.

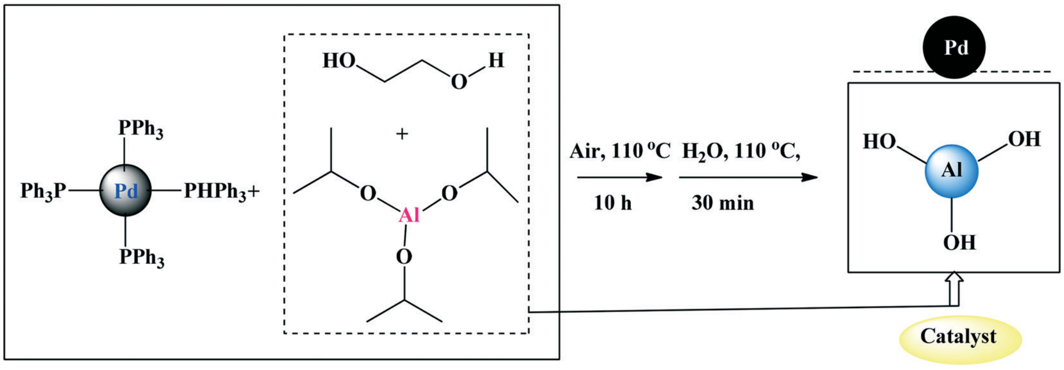
a. Cross-coupling reaction between 5-iodo-2-deoxyuridine and various acrylate derivatives

Len and Hervé[126] reported a palladium-catalysed Heck cross-coupling reaction between 5-iodo-2-deoxyuridine and various acrylate derivatives using ligand-free conditions and

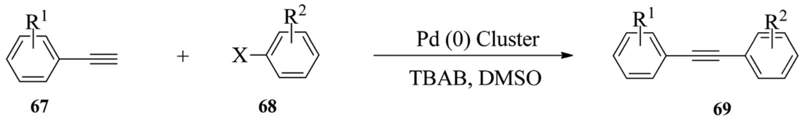


R = H, Me, Perfluoro, CF_3, NO_2, OMe, CN
X = I, Br

Scheme 19 Copper nanocluster catalysed cross-coupling of alkynes and aryl halides.

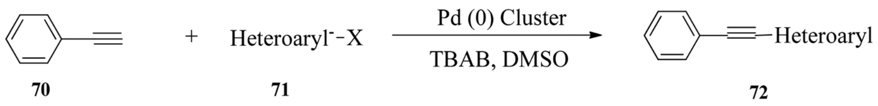


Scheme 20 Preparation of the Pd nanoparticle catalyst.[108]



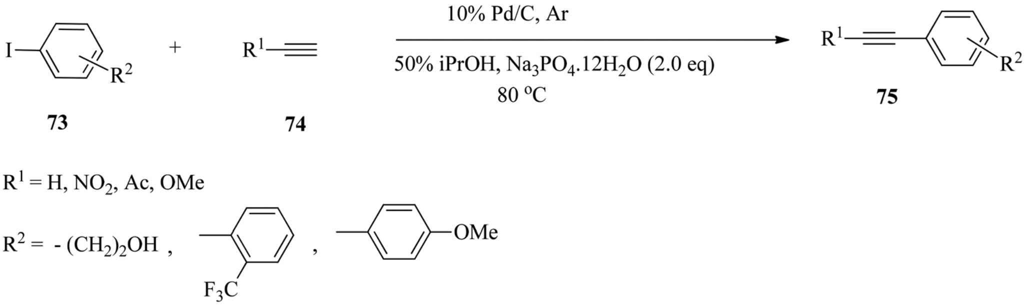
X = Br, Cl
R^1 = H, NO
R^2 = H, NO_2, F, Cl, CHO, Me, OMe

Scheme 21 Cross-coupling of aryl halides with phenylacetylene.



X = Br, Cl

Scheme 22 Cross-coupling of (hetero)aryl acetylenes with bromobenzene.



Scheme 23 Copper-, ligand-, and amine-free Pd/C-catalysed Sonogashira coupling reactions of various aryl iodides with aliphatic and aromatic terminal alkynes.

microwave assistance in pure water. The reaction is particularly important because of its application for the greener total synthesis of antiviral BVDU in higher yield.[126] The initial Heck cross-coupling reaction was performed using deprotected 5-iodo-2-deoxyuridine **76** and methyl acrylate **77** in the presence of Pd(II) and NEt_3 in sole water at 80 °C under microwave irradiation (Scheme 24). NEt_3 was chosen because it is an inexpensive joint base, and Shaughnessy demonstrated that NEt_3 was able to reduce the Pd(II) pre-catalyst to a Pd(0) active species.

They noted that the Heck reaction is affected by the amount of the catalyst and the temperature. The palladium sources were not very efficient at 80 °C as a full reactant conversion was not achieved within 1 h. Side reactions were observed with an increase in temperature to 100 °C; hence, an increase in catalyst loading from 1.5–2 mol% to 10 mol% gave minimal side reactions. The optimal conditions were extended to the synthesis of derivatives (Scheme 25).

b. Cross-coupling of halobenzene with methyl acrylate, ethyl acrylate and styrene

Biffis and co-workers[127] efficiently used palladium on carbon as a catalyst for Heck C–C coupling reactions without a phosphine ligand. One of the most impressive results is the relatively high yield of stilbene **83** from the reaction of chlorobenzene **81** with styrene **82** in pure methanol in an autoclave (Scheme 26).[127] Under these conditions, the added triphenylphosphine ligand acted as an inhibitor rather than a promoter.

In a related reaction, Kuang and co-workers[128] investigated the catalytic performance of the greener ionic liquid H_2O/TX-100/[BMIM]PF_6 microemulsion containing Pd nanoparticles for the ligand-free Heck reaction of iodobenzene **84** with methyl acrylate, ethyl acrylate and styrene **85** (Scheme 27). Palladium chloride is dissolved in water before mixing with TX-100/[BMIM]PF_6.[128] The reduction of palladium chloride by the surfactant (TX-100) in the ionic liquid microemulsion occurs rapidly *in situ* without any further reducing agents.

c. Intermolecular Heck-type cross-coupling of aryl iodides with allylic acetates

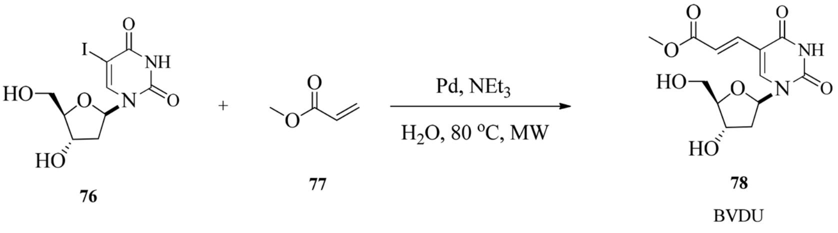
Mariampillai and co-workers[129] studied palladium-catalysed arylation of allylic acetates **88**. They examined the choice of Pd catalyst and tetrabutylammonium salts in the initial coupling experiment. Optimisation of the Pd catalyst showed Pd/C to be the catalyst of choice and tetrabutylammonium chloride resulted in increased reactant conversion. The mechanism proceeds *via* β-acetoxy elimination, instead of β-hydride elimination, to furnish the olefinic products **89**. Optimal reaction conditions were employed for ligand-free palladium on carbon coupling of various aryl iodides **87** with allyl acetate **88** in the presence of a trialkylamine base and water (Scheme 28).

The presence of electron-donating groups on the aryl iodide partner resulted in increased reaction times, probably due to slower oxidative addition of Pd into the aryl iodine bond.[130] While electron-withdrawing substituents required a shorter reaction time, aryl chlorides and bromides were stable under the reaction conditions, providing a useful handle for further functionalization of the products. They further investigated the cross-coupling of 1-iodonaphthalene with various allylic acetates under the same reaction conditions.[131]

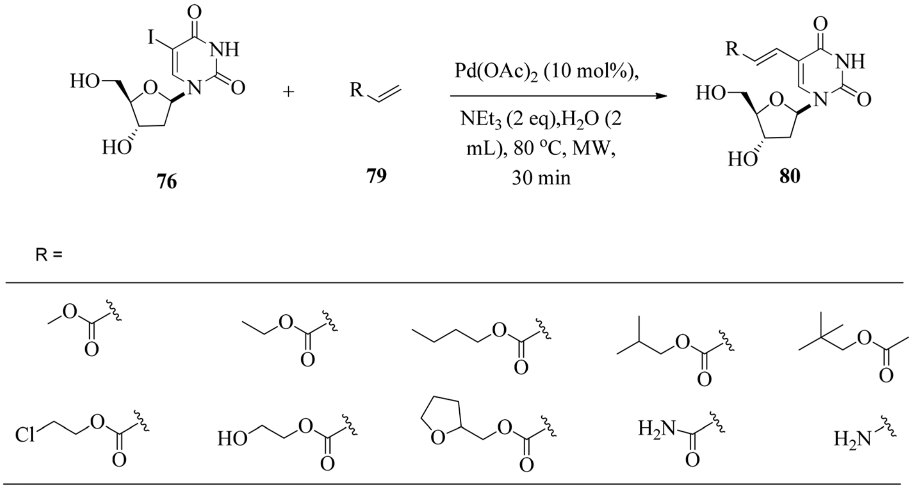
d. Heck reaction of aryl halides with alkenes

Nagarkar and co-workers[130] employed palladium supported on zinc ferrite nanoparticles for Heck coupling reactions of aryl halides **90** with alkenes **91** under ligand-free conditions (Scheme 29). The efficient superparamagnetic solid catalyst was prepared by loading Pd(0) species during the synthesis of zinc ferrite nanoparticles by ultrasound assisted co-precipitation in the absence of a surface stabiliser or capping agent. The advantage of the reaction stems from the fact that an external magnet could quickly separate the nanocrystal catalyst from the reaction mixture, and the catalyst can be recycled six times without losing its activity.

In a related reaction, Kim and co-workers[131] carried out the reaction using a Pd–Fe_2O_4 heterodimeric nanocrystal catalytic system and NaOAc as the base at a temperature of 110 °C for 24 h. They established the scope of the catalytic system by first screening various substituted aryl halide substrates **93** using styrene **94** or tertbutyl acrylate as an olefin counterpart (Scheme 30).[131] Similarly, the heterodimer nanocrystals showed great advantages such as catalyst separation and reuse. The results showed acceptable yields from the reactions with aryl iodides having electron-rich or electron-poor substituents, except for the case of 1-iodonaphthalene which gave 46% yield. Most reactions



Scheme 24 Ligand-free Heck coupling of 5-iodo-2-deoxyuridine with methyl acrylate in water as the sole solvent.



Scheme 25 Ligand-free Heck coupling of 5-iodo-2-deoxyuridine with acrylate derivatives in water as the sole solvent.

using styrene or *tert*-butyl acrylate and aryl iodides gave good yields regardless of the position of the substituent, but the reactions with aryl bromides gave slightly lower yields while leaving some unreacted starting materials.

e. PEG-400 supported cross-coupling of halobenzenes with methyl acrylate and styrene

In a related development, Jin and co-workers[132] reported a ligand-free Heck reaction catalysed by *in situ* generated Pd nanoparticles in PEG-400. A variety of aryl iodides and bromides gave the cross-coupling products with good to excellent isolated yields. The cross-coupling reactions between aryl iodides **96** with electron-withdrawing groups or electron-donating groups and styrene or acrylic acid methyl ester **97** were achieved in good yields using a 1 mol% Pd loading in short times (Scheme 31).

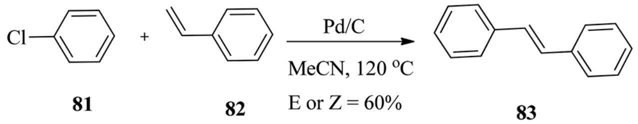
However, cross-coupling of aryl bromides with styrene or acrylic acid methyl ester took a more extended time. The reactivity of styrene was higher than that of acrylic acid methyl ester when using the same aryl bromide. But, no reaction was recorded between 4-bromobenzaldehyde and acrylic acid methyl ester.

f. Cross-coupling of aryldiazonium tetrafluoroborate with acrylates

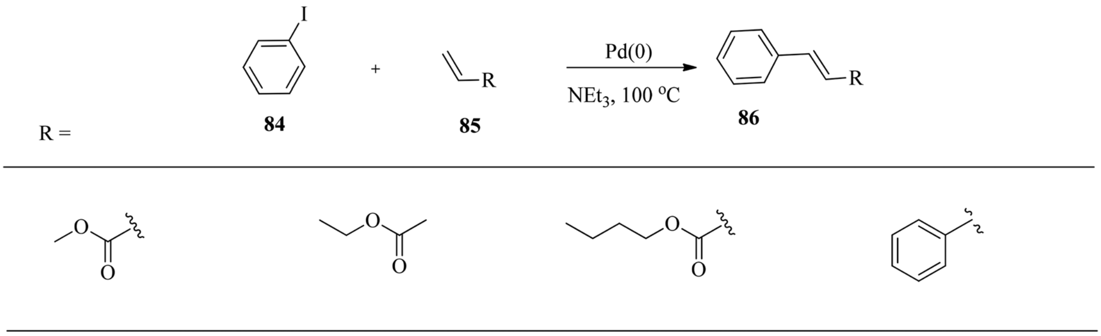
Felpin and co-workers[133] studied various palladium supported on charcoal (Pd/C) catalysts for the Heck reaction of aryldiazonium tetrafluoroborates **99** with acrylates **100** at room temperature in methanol (Scheme 32). Aryldiazonium tetrafluoroborate salts were prepared efficiently by the reaction of the corresponding anilines with sodium nitrite and tetrafluoroboric acid.[134,135] The stable diazonium electrophiles compete favourably with less reactive and more expensive halogenated electrophiles as exemplified by reported industrial applications.[136,137] Nitro-substituted diazonium salts reacted efficiently with methyl acrylate, and a high level of chemoselectivity for the diazonium group was observed with 2-bromobenzenediazonium tetrafluoroborate. While electron-poor diazonium salts reacted smoothly at 25 °C with loading as low as 0.1 mol% Pd, electron-rich substrates required higher Pd loading and eventually moderate heating activation. The use of $CaCO_3$ as an additive proved to be beneficial in terms of yields and kinetics for less reactive arenediazonium salts, and the base could enhance the rate of the reductive elimination step.

In a related reaction, Felpin and co-workers[138] prepared *cis*-stilbenes **103** with good to excellent stereoselectivity by employing a $Pd(OAc)_2$ catalyst for the Heck reaction of aryl diazonium salts **99** with 2-aryl acrylates **102** under the same conditions (Scheme 33). It was observed that the coupling furnished the *cis*-stilbene products with perfect control of the double bond geometry, which is unrelated to the stereoelectronic effect on the acrylates or diazonium salts. The reactions are particularly important because aryl acrylates with a NO_2 group at C2 in the aromatic ring are valuable synthetic intermediates for the preparation of oxindoles and related heterocycles which are biologically active such as tenidap, *etc.*[139,140]

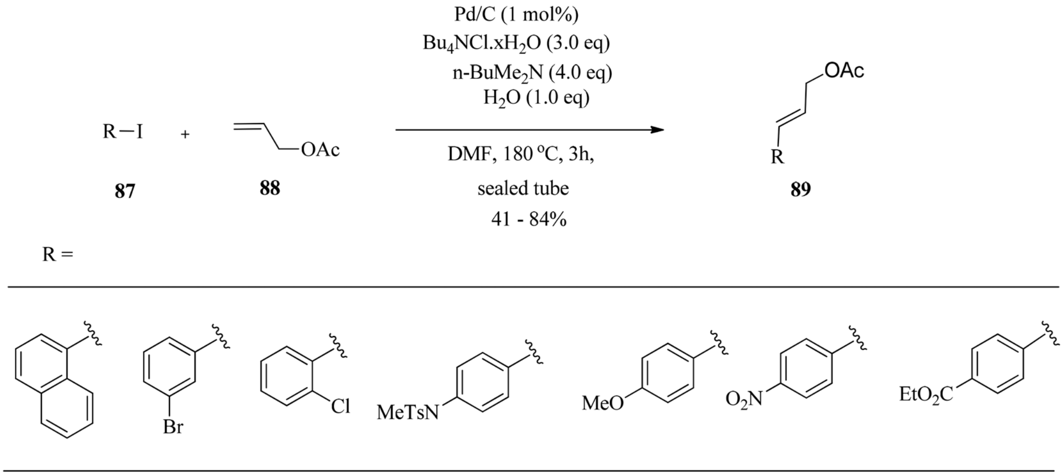
With 2-aryl acrylate without a C2 substituent, an isomeric mixture of the product (*E*/*Z* ratio: 80/20) was obtained. However, 2-chloro-, 2-cyano-, 2-methyl-, and 2,5-dimethoxy-2-phenyl acrylates gave *cis*-stilbenes in high isomeric purity leading to the conclusion that 2-aryl acrylate having at least one substituent in the aromatic ring at C2 reacts with diazonium salts under palladium catalysis to give almost exclusively *cis*-stilbenes.[139]



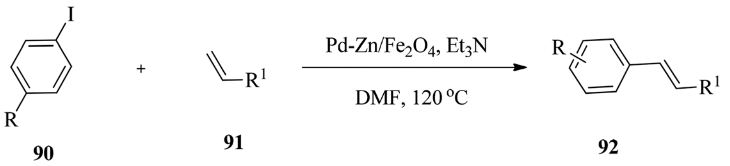
Scheme 26 Pd/C-catalysed cross-coupling of chlorobenzene with styrene to afford stilbene.



Scheme 27 Product yields for other Heck reactions in an ionic liquid microemulsion.



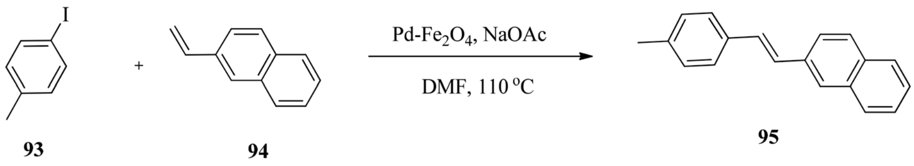
Scheme 28 Heck-type coupling of allyl acetate with various aryl iodides.



R = Me, OMe, CN, NH$_2$, COMe, OH, H

R^1 = CO$_2$Bu, CO$_2$Et, Ph

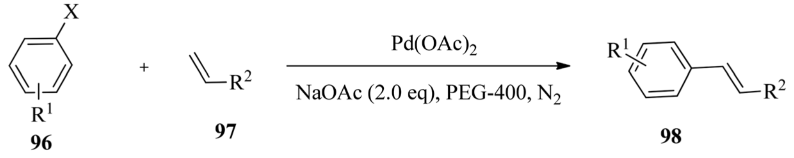
Scheme 29 Pd–Zn/Fe$_3$O$_4$ nanoparticle-catalysed Heck coupling reactions of aryl halides with alkenes under ligand-free conditions.



Scheme 30 Cross-coupling reactions using Pd–Fe$_3$O$_4$ nanocrystals.

g. Cross-coupling of aryl sulfinic acid salts with vinyl substrates

Hu and co-workers[141] investigated the Pd(OAc)$_2$-catalysed cross-coupling of aryl sulfinic acid salts **104** with vinyl substrates **105** under mild reaction conditions (Scheme 34). The high efficiency and reactivity of the aryl sulfinic acid salts could be associated with the formation of active Pd species *via* the release of SO$_2$ during the catalytic cycle. The mild reaction conditions combined with the widely available

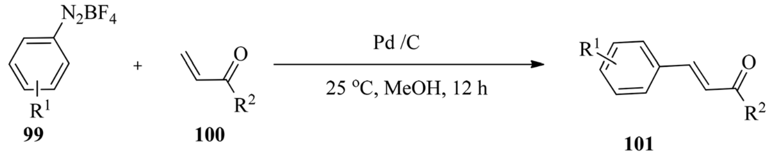


R^1 = H, NO2, Me, CHO, CN

R^2 = Ph, CO_2Me

X = I, Br

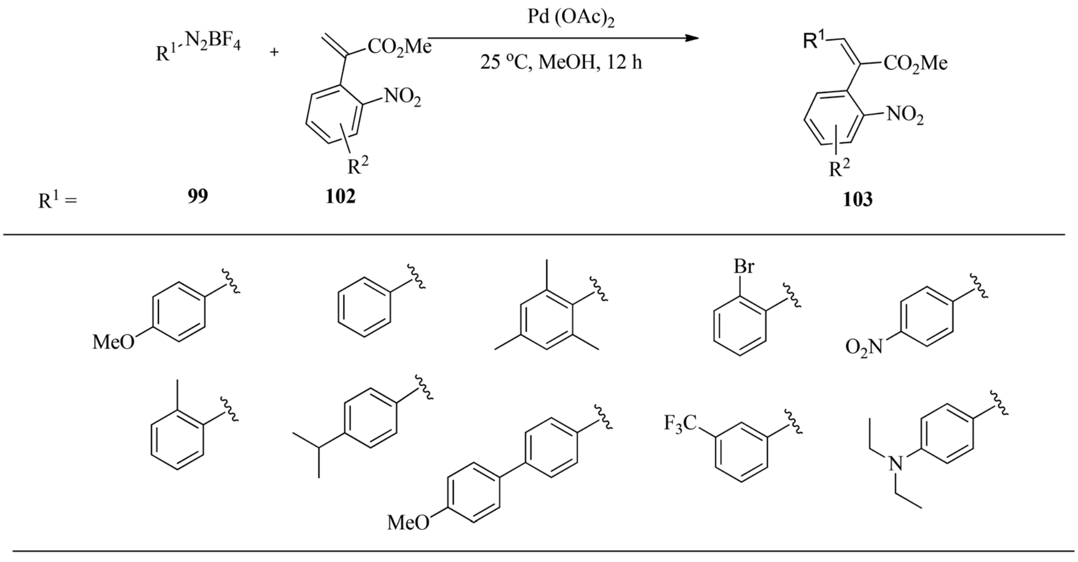
Scheme 31 PEG-400/Pd(OAc)$_2$-catalysed Heck reaction of aryl halides with olefins.



R^1 = NO_2, Br, CO_2 Me, OMe

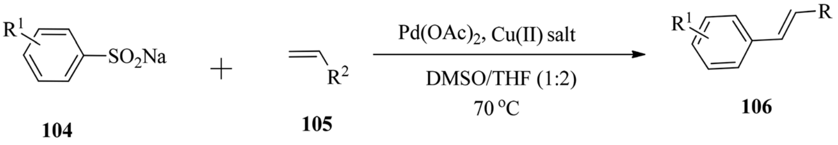
R^2 = OMe, CO_2Me, OEt, O^tBu, $N(CH_3)_2$

Scheme 32 Heck reaction of aryldiazonium tetrafluoroborates with acrylates.



R^2 = H, Me, OMe, Ph

Scheme 33 Preparation of various substituted stilbenes by Heck-type coupling.



R^1 = H, Me, OMe, CL, Br, I, NO_2

R^2 = CO_2Me, CO_2Bu, CN, Ph

Scheme 34 Pd-Catalysed Matsuda–Heck coupling of aryl sulfinic acid salts with a vinyl substrate.

sodium aryl sulfinate enable this transformation to be an attractive alternative to Heck-type cross-coupling.

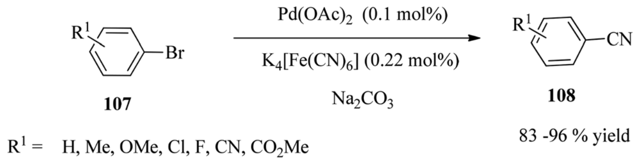
h. Ligand-free palladium-catalysed cyanation of aryl halides

Weissman and co-workers[142] described the ligand-free cyanation of aryl halides **107** using 0.1 mol% $Pd(OAc)_2$ loading in combination with a non-toxic cyanide source, $M_4[Fe(CN)_6]$, (M = K or Na). A series of aryl halides were reacted under standard conditions (Scheme 35).

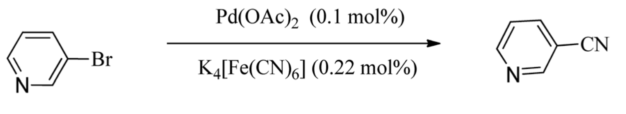
Rapid (≤5 h) and complete reactions were achieved for activated aryl bromides bearing electron-withdrawing groups. Moreover, electron-neutral systems and a mildly electron-rich arene, *p*-bromotoluene, were completely reacted within 5 h with assay yields >90%. The cyanation of an *N*-heteroaryl bromide (3-bromopyridine) **109** gave an 86% assay yield of the product (**110**) after 8 h at 120 °C (Scheme 36). High selectivity was observed for 3-bromochlorobenzene. The reaction is particularly crucial as aromatic nitriles constitute a vital component of numerous commercial compounds, including pharmaceuticals, agrochemicals (herbicides and pesticides), pigments and dyes.[143]

6. Ligand-free Stille cross-coupling reaction

Stille coupling is the palladium-catalysed cross-coupling of aryl halides or pseudohalides with organostannanes. It is one of the most potent strategies for the straightforward construction of carbon–carbon bonds in synthetic chemistry.[144,145] The main advantages of the Stille coupling reaction range from high stability and functional group tolerance, the broad reaction scope of aryl halides and pseudohalides to its chemoselectivity. Therefore, the reaction has been widely applied in the synthesis of natural products[146,147] and biological research.[148] Stille coupling reactions are generally carried out in organic solvents under homogeneous catalysis. The development of a recyclable and reusable catalytic system is highly attractive and valuable from the viewpoints of green chemistry and practical application. Consequently, several new strategies involving heterogenized homogeneous catalysts have been developed for recycling and reusing catalysts, including the use of Pd complexes supported by silica gel,[55,149] polymers,[150,151] nanoparticles,[152,153] porous metal–organic frameworks,[154] and metal nanoparticles.[155,156] Alternative approaches involving the combination of palladium complexes with several green solvents, such as ionic liquids,[157,158] polyethene glycol,[159,160] H_2O,[161–164] or H_2O in the presence of surfactants,[165–167] have also been applied as reusable catalytic systems.



Scheme 35 Ligand-free palladium-catalysed cyanation of aryl halides.



109 **110**

Scheme 36 Ligand-free palladium-catalysed cyanation of 3-bromopyridine.

a. Ligand-free cross-coupling of aryl bromides with organostannanes

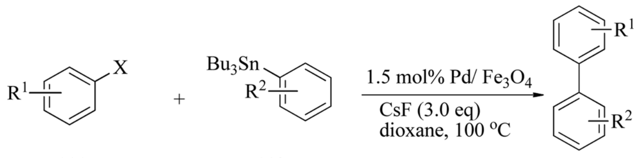
In 2012, Prasad and Satyanarayana[168] investigated the application of Fe_3O_4 supported Pd(0) nanoparticles (Pd/Fe_3O_4) for the Stille cross-coupling of aryl halides **111** with organotin compounds **112** under ligand-free conditions (Scheme 37). The best catalytic system for the cross-coupling was identified by screening the reaction with various bases in combination with different solvents.

CsF and dioxane proved to be the best system for Pd/Fe_3O_4. The scope and generality of the reaction were established, applying different aryl halides **114** and butylarylstannanes **115** to obtain the corresponding biaryls **116** (Scheme 38).

The reaction was extended to a variety of neutral, electron-rich, and electron-poor bromoarenes **117** and substituted tributylphenylstannanes **118**, and the corresponding biaryls **119** were obtained in good to excellent yields (Scheme 39). Several bioactive compounds such as allocolchicines, stegnacine and eupomatilones were prepared from 2-bromo-3,4,5-trimethoxy benzaldehyde as an aryl halide.[168]

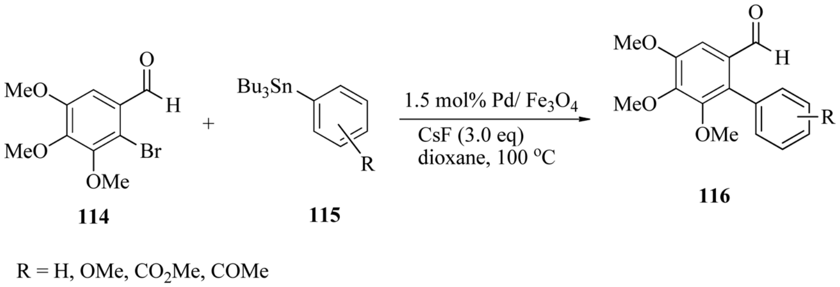
7. Ligand-free Negishi cross-coupling

Among all the coupling reactions, the Negishi reaction has found to be a potent tool for the preparation of many chemical and pharmaceutically active compounds due to its compatibility with various functional groups, high chemoselectivity and excellent stereoselectivity of organozinc reagents, and easy preparation of a wide variety of organozinc halides (RZnX) and organozinc (R2Zn) compounds.[35,169–172] This reaction is usually catalysed by nickel or palladium complexes, and ancillary ligands are traditionally needed to sufficiently enhance the reactivities of the palladium and

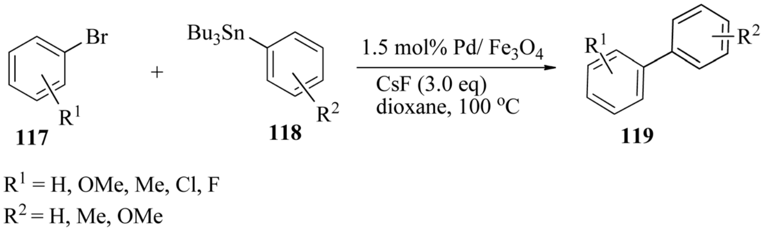


111 **112** **113**

Scheme 37 Pd/Fe_3O_4 nanoparticle-catalyzed cross-coupling of aryl halides under ligand-free conditions.



Scheme 38 Fe_3O_4-Catalysed Stille cross-coupling of 2-bromo-3,4,5-trimethoxybenzaldehyde with different tributylarylstannanes.



Scheme 39 Pd/Fe_3O_4-catalysed Stille cross-coupling of different bromoarenes with different tributylarylstannanes.

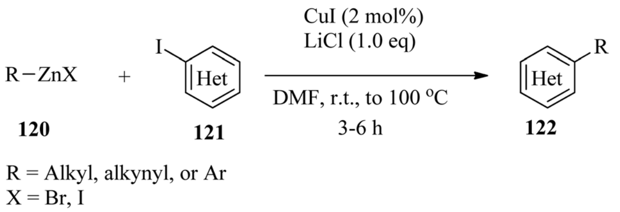
nickel catalysts. Inexpensive nickel has positively received the researcher's attention from the very beginning due to the high cost of palladium precursors. Recently, Negishi cross-coupling reactions employing ligand-free conditions have been adapted for greener and economical synthesis of various products.

a. Cross-coupling of alkyl-, aryl-, and alkynyl zinc reagents with heteroaryl iodides

Recently, Thapa *et al.* in 2015[173] reported a ligand-free, copper-catalysed Negishi cross-coupling reaction of various zinc reagents **120** with heteroaryl iodides **121** (Scheme 40). The reaction proceeds within three hours at room temperature for alkylzinc reagents; however, higher temperatures are required for coupling with aryl- and alkynyl zinc reagents to give the desired coupling products **122** in very high yields.

b. Cross-coupling of 6-chloropurines with organozinc halides

Wang and co-workers[174] developed an efficient method for the synthesis of 6-alkyl or 6-aryl purines (nucleosides) **125** *via* nickel-catalysed Negishi cross-coupling reactions of 6-chloropurines **123** and organozinc halides **124**. The optimised reaction conditions were employed in the cross-coupling reaction of several 6-chloropurines **123** with various substituents at N-9, including alkyl and sugar carbon substituents (Scheme 41).



Scheme 40 Coupling with alkyl, alkynyl or arylzinc reagents with (hetero)aryl halides.

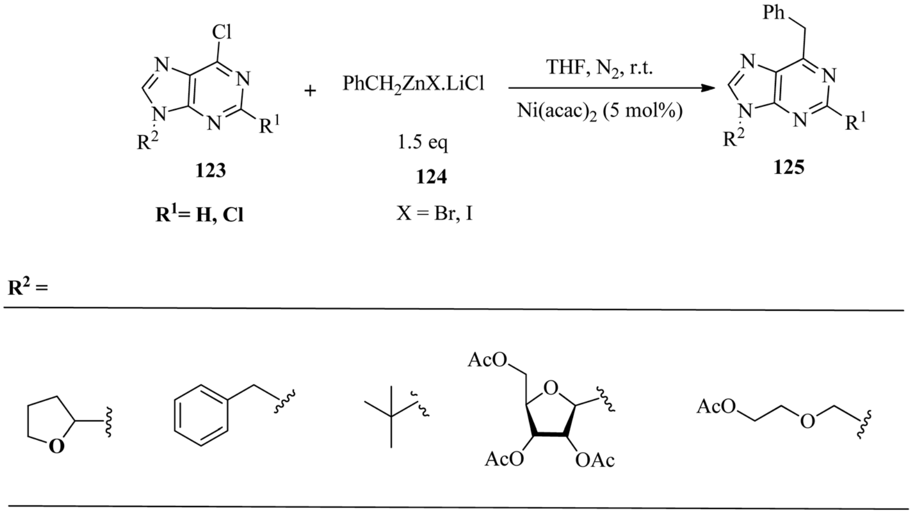
The reaction of N-9 alkyl or tetrahydropyranyl-substituted purines proceeded smoothly in more than 97% yields, whereas 2,3,5-triacetyl-6-chloropurine nucleoside gave the corresponding product in 80% isolated yield which serves as a useful access for the preparation of purine nucleoside analogues. Moreover, the cross-coupling reaction employing acetyl protected 2,6-dichloropurine nucleoside was able to selectively produce 6-benzyl-2-chloropurine nucleoside and 2,6-dibenzylpurine nucleoside by varying the quantity of benzyl zinc bromide. The same result was obtained for acyclovir side-chain protected 2,6-dichloropurine.

Other alkylzinc halides were also subjected to the reaction under the optimised conditions (Scheme 42). The primary alkylzinc halides **126**, such as benzyl zinc, methylzinc, and pentylzinc, produced the corresponding products **127** in good to excellent yields. Cyclic alkyl zinc bromides, cyclopentylzinc and cyclohexylzinc gave the desired products in satisfactory yields. However, isopropyl zinc bromide gave a mixture of products due to rearrangement.[174]

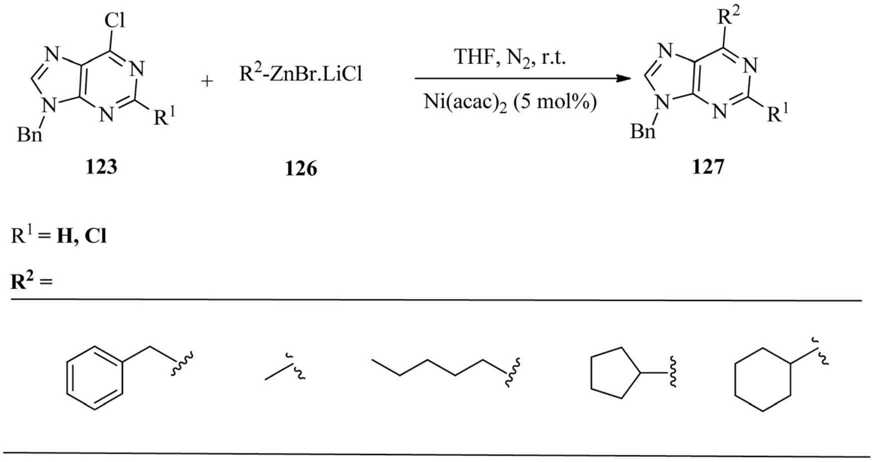
Testing of the optimised reaction conditions on arylzinc chlorides gave low yields; however, satisfactory yields of the aryl and substituted arylpurines **129** were obtained with the corresponding iodides **128** (Scheme 43).

8. Mechanism of ligand-free cross-coupling

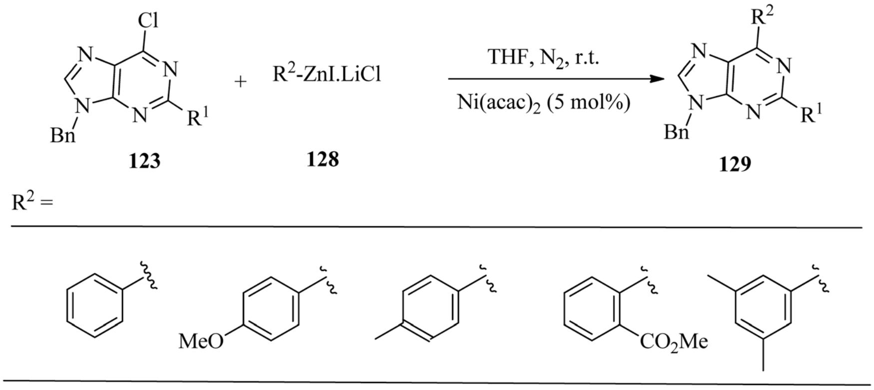
How can a pure ligand-free Pd-catalysed system be understood, given that it is generally believed that phosphine



Scheme 41 The cross-coupling reaction of 6-chloropurines with benzyl zinc bromide.



Scheme 42 The cross-coupling reaction of 9-benzyl-6-chloro-purine with various alkylzinc halides.



Scheme 43 The Negishi cross-coupling reaction of 9-benzyl-6-chloro-purine with arylzinc iodide.

ligands exert stabilising and activating effects? To proffer an answer to this question, Reetz and Westermann reported a mechanistic study supported by transmission electron microscopy (TEM) of three phosphine-free catalytic systems, namely, $Pd(OAc)_2$/DMG, $Pd(OAc)_2/(n\mathrm{Bu})_4N^+Cl^-$ and $Pd(OAc)_2$ for Heck and Suzuki–Miyaura cross-coupling reactions.[175] The result disclosed the presence of an *in situ* generated nano-sized Pd colloid as the active species in the phosphine-free reactions. The authors predicted the active catalyst in other related C–C forming reactions in the presence of Pd salts without a unique ligand to be nanosized Pd colloids. Nano-sized Pd colloids are highly active atoms as a result of their high surface-to-volume ratio compared to molecular Pd catalysts. Several polymers and ionic liquids stabilise these palladium colloids such as polyaniline and tetra-alkylammonium salts. In recent years, numerous investigations have been made to ascertain whether the mechanism of ligand-free/nanoparticle-catalysed cross-coupling reactions is homogenous or heterogeneous.[176–178] Claver *et al.* summarised the two major mechanisms that were proposed.[179] One, palladium nanoparticles are real heterogeneous catalysts while the second says palladium nanoparticles act as a reservoir of molecular species which leached out 'naked palladium atoms'. Lorenzo, in his critical and comprehensive investigation of the two mechanisms in palladium nanoparticle-catalysed Suzuki cross-coupling, stated that 'rather than being mutually exclusive, both mechanisms should be considered as complementary and dependent on the immobilisation degree of the palladium nanoparticles'.[180] More recently, reinvestigation of the transmetalation and reductive steps of ligand-free SMC cross-coupling of aryl halides using first-principles molecular dynamics simulations with an explicit solvent model showed that PdX^- was the active species of the catalyst. The origin of the reduction of catalytic reactivity for aryl halides was attributed to the more substantial activation barrier in the oxidative addition step which causes aggregation of Pd catalysts.[181] While ligand-less Pd-catalysed cross-coupling reactions are often conducted at a relatively faster rate than ligand-supported ones, the aggregation or agglomeration of Pd(0), which results in incomplete conversion of substrates, is a disadvantage to their applications, especially to cross-coupling of aryl chlorides and sterically hindered substrates.[182]

9. Conclusion

Ligand-free metal-catalysed cross-coupling is a cost effective and environmentally benign protocol for functionalization of (hetero)aryl halides and pseudohalides. Though it has achieved relative success in the transformation of aryl iodides and bromides, the cross-coupling of electron-rich/sterically encumbered aryl chlorides and heterocyclic substrates remains a big challenge. There have been steady efforts over the years to apply ligand-free protocols in cross-coupling of low reactivity aryl chlorides; however, the catalytic efficiency cannot be compared with ligand-supported catalysts. This is because the stereochemical requirement needed by the ligand with its electron donor groups to increase the electron density in the metal centre which activates oxidative addition step and the bulkiness of the ligand which facilitates the reductive elimination step conspicuously is lacking in nanoparticles.[183] In various examples of ligand-free Pd-catalysed cross-coupling, electron-deficient aryl halides are more reactive than electron-rich ones under similar conditions but they could benefit tremendously from microwave-assisted heating.[184]

Therefore, the primary concern of ligand-free cross-coupling reactions remains finding suitable catalyst systems with low loading, reduced cost owing to their simple separation and multiple usages, less contamination of the product, least side reactions and environmentally friendly and benign solvents. In conclusion, the extensive applications of ligand-free cross-coupling reactions in Suzuki–Miyaura cross-coupling, Sonogashira cross-coupling, Hiyama cross-coupling, Heck reaction, Stille cross-coupling and Negishi cross-coupling have been highlighted and will remain economical and environmentally friendly protocols for future researchers in functionalization of a wide variety of compounds with industrial and therapeutic applications.

Conflicts of interest

There are no conflicts to declare.

References

1 Y. Chen, W. Lai, L. Xie and W. Huang, Palladium-catalysed cross-couplings in organic synthesis: An introduction to the 2010 Nobel Prize in Chemistry, *Chin. Sci. Bull.*, 2011, **56**(13), 995–1006.
2 H.-F. Zhang, Copper-catalysed ligand-free Suzuki–Miyaura coupling reaction of aryl halides with arylboronic acid, *J. Med. Chem. Sci.*, 2019, 2(1), 1–40, 38–40.
3 L. Rocard and P. Hudhomme, Recent developments in the Suzuki–Miyaura reaction using nitroarenes as electrophilic coupling reagents, *Catalysts*, 2019, **9**(3), 213.
4 E. A. Onoabedje and U. C. Okoro, Ligand-supported palladium-catalysed cross-coupling reactions of (hetero) aryl chlorides, *Synth. Commun.*, 2019, **49**(17), 2117–2146.
5 M. Lamblin, L. Nassar-Hardy, J. C. Hierso, E. Fouquet and F. X. Felpin, Recyclable heterogeneous palladium catalysts in pure water: Sustainable developments in Suzuki, Heck, Sonogashira and Tsuji–Trost reactions, *Adv. Synth. Catal.*, 2010, **352**(1), 33–79.
6 A. O. King and N. Yasuda, Palladium-catalysed cross-coupling reactions in the synthesis of pharmaceuticals, in *Organometallics in Process Chemistry*, Springer, 2004, pp. 205–245.
7 J. Magano, Large-scale applications of transition metal-catalysed couplings for the synthesis of pharmaceuticals, *Chem. Rev.*, 2011, **111**(3), 2177–2250.
8 N. Miyaura, A new stereospecific cross-coupling by the palladium-catalysed reaction of 1-alkenylboranes with 1-alkenyl or 1-alkynyl halides, *Tetrahedron Lett.*, 1979, **20**(36), 3437–3440.
9 R. K. Arvela, A Re-assessment of the transition-metal-free Suzuki-type coupling methodology, *J. Org. Chem.*, 2005, **70**(1), 161–168.
10 P. Ruiz-Castillo and S. L. Buchwald, Applications of palladium-catalysed C–N cross-coupling reactions, *Chem. Rev.*, 2016, **116**(19), 12564–12649.

11 C. L. Allen and J. M. Williams, Metal-catalysed approaches to amide bond formation, *Chem. Soc. Rev.*, 2011, **40**(7), 3405–3415.

12 N. A. Weires, E. L. Baker and N. K. Garg, Nickel-catalysed Suzuki-Miyaura coupling of amides, *Nat. Chem.*, 2016, **8**(1), 75–79.

13 C. Liu and M. Szostak, Twisted amides: From obscurity to broadly useful transition-metal-catalysed reactions by N-C amide bond activation, *Chemistry*, 2017, **23**(30), 7157–7173.

14 S. Guo, J. C. Yang and S. L. Buchwald, A practical electrophilic nitrogen source for the synthesis of chiral primary amines by copper-catalysed hydroamination, *J. Am. Chem. Soc.*, 2018, **140**(46), 15976–15984.

15 Y. Bai, J. Chen and S. C. Zimmerman, Designed transition metal catalysts for intracellular organic synthesis, *Chem. Soc. Rev.*, 2018, **47**(5), 1811–1821.

16 T. Willemse, W. Schepens, H. W. van Vlijmen, B. U. Maes and S. Ballet, The Suzuki–Miyaura cross-coupling as a versatile tool for peptide diversification and cyclization, *Catalysts*, 2017, **7**(3), 74.

17 J. I. Ayogu, B. E. Ezema and C. G. Ezema, Utility of Suzuki-Miyaura cross-coupling reaction in synthesis of benzo[a] phenothiazine and benzo[a]phenoxazine rerivatives and their antimicrobial screening, *Asian J. Chem.*, 2015, **27**(12), 4467–4473.

18 C. Ike, B. Ezema, J. Ayogu, D. Ugwu, C. Ezema, A. Nwasi and E. Adekola, Synthesis and antimicrobial screening of novel benzoxazinophenothiazine derivatives, *Asian J. Chem.*, 2015, **27**(11), 4115–4119.

19 N. Eleya, I. Malik, S. Reimann, K. Wittler, M. Hein, T. Patonay, A. Villinger, R. Ludwig and P. Langer, Efficient synthesis of frylated flavones by site-selective Suzuki–Miyaura cross-coupling reactions of the bis(triflate) of 5,7- and 7,8-dihydroxyflavone, *Eur. J. Org. Chem.*, 2012, **2012**(8), 1639–1652.

20 R. E. Whittaker, A. Dermenci and G. Dong, Synthesis of ynones and recent application in transition-metal-catalysed reactions, *Synthesis*, 2016, **48**(02), 161–183.

21 R. Skoda-Földes and L. Kollár, Transition-metal-catalysed reactions in steroid synthesis, *Chem. Rev.*, 2003, **103**(10), 4095–4130.

22 Q. Liang, P. Xing, Z. Huang, J. Dong, K. B. Sharpless, X. Li and B. Jiang, Palladium-catalysed, ligand-free Suzuki reaction in water using aryl fluorosulfates, *Org. Lett.*, 2015, **17**(8), 1942–1945.

23 J. P. Simeone and J. R. Sowa, Palladium on carbon as a precatalyst for the Suzuki–Miyuara cross-coupling of aryl chlorides, *Tetrahedron*, 2007, **63**(51), 12646–12654.

24 N. Bumagin, P. More and I. Beletskaya, Synthesis of substituted cinnamic acids and cinnamonitriles via palladium catalysed coupling reactions of aryl halides with acrylic acid and acrylonitrile in aqueous media, *J. Organomet. Chem.*, 1989, **371**(3), 397–401.

25 Y. Ben-David, M. Portnoy and D. Milstein, Chelate-assisted, palladium-catalysed efficient carbonylation of aryl chlorides, *J. Am. Chem. Soc.*, 1989, **111**(23), 8742–8744.

26 C. R. LeBlond, A. T. Andrews, Y. Sun and J. R. Sowa, Activation of aryl chlorides for Suzuki cross-coupling by ligandless, heterogeneous palladium, *Org. Lett.*, 2001, **3**(10), 1555–1557.

27 N. A. Bumagin and V. V. Bykov, Ligandless palladium catalysed reactions of arylboronic acids and sodium tetraphenylborate with aryl halides in aqueous media, *Tetrahedron*, 1997, **53**(42), 14437–14450.

28 N. Miyaura and A. Suzuki, Palladium-catalysed cross-coupling reactions of organoboron compounds, *Chem. Rev.*, 1995, **95**(7), 2457–2483.

29 A. Kumbhar, S. Jadhav, S. Kamble, G. Rashinkar and R. Salunkhe, Palladium supported hybrid cellulose–aluminum oxide composite for Suzuki–Miyaura cross coupling reaction, *Tetrahedron Lett.*, 2013, **54**(11), 1331–1337.

30 Y. Feng, X. Jiang and J. K. De Brabander, Studies toward the unique pederin family member psymberin: full structure elucidation, two alternative total syntheses, and analogs, *J. Am. Chem. Soc.*, 2012, **134**(41), 17083–17093.

31 S. N. Jadhav, A. S. Kumbhar, S. S. Mali, C. K. Hong and R. S. Salunkhe, A Merrifield resin supported Pd–NHC complex with a spacer (Pd–NHC@SP–PS) for the Sonogashira coupling reaction under copper-and solvent-free conditions, *New J. Chem.*, 2015, **39**(3), 2333–2341.

32 Y. Nakao and T. Hiyama, Silicon-based cross-coupling reaction: an environmentally benign version, *Chem. Soc. Rev.*, 2011, **40**(10), 4893–4901.

33 J. Williams, *Preparation of alkenes: A practical approach*, Oxford University Press, 1996.

34 S. Jadhav, A. Kumbhar and R. Salunkhe, Palladium supported on silica-chitosan hybrid material (Pd-CS@SiO_2) for Suzuki-Miyaura and Mizoroki-Heck cross-coupling reactions, *Appl. Organomet. Chem.*, 2015, **29**(6), 339–345.

35 C. Han and S. L. Buchwald, Negishi coupling of secondary alkylzinc halides with aryl bromides and chlorides, *J. Am. Chem. Soc.*, 2009, **131**(22), 7532–7533.

36 J. K. Stille, The palladium-catalysed cross-coupling reactions of organotin reagents with organic electrophiles [new synthetic methods (58)], *Angew. Chem., Int. Ed. Engl.*, 1986, **25**(6), 508–524.

37 J. Hassan, M. Sevignon, C. Gozzi, E. Schulz and M. Lemaire, Aryl-aryl bond formation one century after the discovery of the Ullmann reaction, *Chem. Rev.*, 2002, **102**(5), 1359–1470.

38 I. Hussain, Synthesis of biaryls ligand-free Suzuki-Miyaura cross-coupling reactions: A review of homogeneous and heterogeneous catalytic developments, *Adv. Synth. Catal.*, 2016, **358**(21), 3320–3349.

39 N. Miyaura and A. J. C. R. Suzuki, Palladium-catalysed cross-coupling reactions of organoboron compounds, *Chem. Rev.*, 1995, **95**(7), 2457–2483.

40 I. Maluenda and O. Navarro, Recent developments in the Suzuki-Miyaura reaction: 2010–2014, *Molecules*, 2015, **20**(5), 7528–7557.

41 J. P. Genet and M. Savignac, Recent developments of palladium(0) catalysed reactions in aqueous medium, *J. Organomet. Chem.*, 1999, **576**(1–2), 305–317.

42 H. Sakurai, T. Tsukuda and T. Hirao, Pd/C as a reusable catalyst for the coupling reaction of halophenols and arylboronic acids in aqueous media, *J. Org. Chem.*, 2002, **67**(8), 2721–2722.

43 D. Badone, M. Baroni, R. Cardamone, A. Ielmini and U. Guzzi, Highly efficient palladium-catalysed boronic acid coupling reactions in water: scope and limitations, *J. Org. Chem.*, 1997, **62**(21), 7170–7173.

44 L. Botella and C. Nájera, A convenient oxime-carbapalladacycle-catalysed Suzuki cross-coupling of aryl chlorides in water, *Angew. Chem., Int. Ed.*, 2002, **41**(1), 179–181.

45 K. H. Shaughnessy and R. S. Booth, Sterically demanding, water-soluble alkylphosphines as ligands for high activity Suzuki coupling of aryl bromides in aqueous solvents, *Org. Lett.*, 2001, **3**(17), 2757–2759.

46 C. Dupuis, K. Adiey, L. Charruault, V. Michelet, M. Savignac and J.-P. Genêt, Suzuki cross-coupling of arylboronic acids mediated by a hydrosoluble Pd(0)/TPPTS catalyst, *Tetrahedron Lett.*, 2001, **42**(37), 6523–6526.

47 C. R. LeBlond, A. T. Andrews, Y. Sun and J. R. J. O. l. Sowa, Activation of aryl chlorides for Suzuki cross-coupling by ligandless, heterogeneous palladium, *Org. Lett.*, 2001, **3**(10), 1555–1557.

48 M. Larhed and A. Hallberg, Microwave-promoted palladium-catalysed coupling reactions, *J. Org. Chem.*, 1996, **61**(26), 9582–9584.

49 C. G. Blettner, W. A. König, W. Stenzel and T. Schotten, Microwave-assisted aqueous Suzuki cross-coupling reactions, *J. Org. Chem.*, 1999, **64**(11), 3885–3890.

50 C. G. Blettner, W. A. König, W. Stenzel and T. Schotten, Microwave-assisted aqueous Suzuki cross-coupling reactions, *J. Org. Chem.*, 1999, **64**(11), 3885–3890.

51 E.-I. Negishi and A. de Meijere, *Handbook of organopalladium chemistry for organic synthesis*, Wiley-Interscience, 2002, vol. 2.

52 R. Martin and S. L. Buchwald, Palladium-catalysed Suzuki-Miyaura cross-coupling reactions employing dialkylbiaryl phosphine ligands, *Acc. Chem. Res.*, 2008, **41**(11), 1461–1473.

53 C. Liu, Q. Ni, F. Bao and J. Qiu, A simple and efficient protocol for a palladium-catalysed ligand-free Suzuki reaction at room temperature in aqueous DMF, *Green Chem.*, 2011, **13**(5), 1260–1266.

54 A. Thakur, K. Zhang and J. Louie, Suzuki-Miyaura coupling of heteroaryl boronic acids and vinyl chlorides, *Chem. Commun.*, 2012, **48**(2), 203–205.

55 D.-H. Lee, J.-Y. Jung and M.-J. Jin, Highly active and recyclable silica gel-supported palladium catalyst for mild cross-coupling reactions of unactivated heteroaryl chlorides, *Green Chem.*, 2010, **12**(11), 2024–2029.

56 K. L. Billingsley, K. W. Anderson and S. L. Buchwald, A Highly active catalyst for Suzuki–Miyaura cross-coupling reactions of heteroaryl compounds, *Angew. Chem., Int. Ed.*, 2006, **45**(21), 3484–3488.

57 P. Zhou, H. Wang, J. Yang, J. Tang, D. Sun and W. Tang, Bio-supported palladium nanoparticles as a phosphine-free catalyst for the Suzuki reaction in water, *RSC Adv.*, 2012, **2**(5), 1759–1761.

58 N. E. Leadbeater and M. Marco, Ligand-free palladium catalysis of the Suzuki reaction in water using microwave heating, *Org. Lett.*, 2002, **4**(17), 2973–2976.

59 S.-J. Kim, S.-D. Oh, S. Lee and S.-H. Choi, Radiolytic synthesis of Pd-M (M=Ag, Ni, and Cu)/C catalyst and their use in Suzuki-type and Heck-type reaction, *J. Ind. Eng. Chem.*, 2008, **14**(4), 449–456.

60 A. Alimardanov, L. Schmieder-van de Vondervoort, A. H. de Vries and J. G. de Vries, Use of "homeopathic" ligand-free palladium as catalyst for aryl-aryl coupling reactions, *Adv. Synth. Catal.*, 2004, **3346**(13–15), 1812–1817.

61 S. E. Denmark and R. F. Sweis, Organosilicon compounds in cross-coupling reactions, *Metal-catalysed cross-coupling reactions*, 2004, pp. 163–216.

62 A. C. Spivey, C. J. Gripton and J. P. Hannah, Recent advances in group 14 cross-coupling: Si and Ge-based alternatives to the Stille reaction, *Curr. Org. Synth.*, 2004, **1**(3), 211–226.

63 S. E. Denmark and C. S. Regens, Palladium-catalysed cross-coupling reactions of organosilanols and their salts: practical alternatives to boron-and tin-based methods, *Acc. Chem. Res.*, 2008, **41**(11), 1486–1499.

64 O. Y. Yuen, C. M. So, H. W. Man and F. Y. Kwong, A general palladium-catalysed Hiyama cross-coupling reaction of aryl and heteroaryl chlorides, *Chem. – Eur. J.*, 2016, **22**(19), 6471–6476.

65 K. Shibata, K. Miyazawa and Y. Goto, Preparation of functionalised biaryl compounds via cross-coupling reactions of aryltrialkoxysilanes with arylbromides, *Chem. Commun.*, 1997, (14), 1309–1310.

66 H. F. Sore, W. R. Galloway and D. R. Spring, Palladium-catalysed cross-coupling of organosilicon reagents, *Chem. Soc. Rev.*, 2012, **41**(5), 1845–1866.

67 L. Ackermann, C. J. Gschrei, A. Althammer and M. Riederer, Cross-coupling reactions of aryl and vinyl chlorides catalysed by a palladium complex derived from an air-stable H-phosphonate, *Chem. Commun.*, 2006(13), 1419–1421.

68 C. Dash, M. M. Shaikh and P. Ghosh, Fluoride-free Hiyama and copper- and amine-free Sonogashira coupling in air in a mixed aqueous medium by a series of PEPPSI-themed precatalysts, *Eur. J. Inorg. Chem.*, 2009, **2009**(12), 1608–1618.

69 J. Yang and L. Wang, Synthesis and characterization of dinuclear NHC–palladium complexes and their applications in the Hiyama reactions of aryltrialkyoxysilanes with aryl chlorides, *Dalton Trans.*, 2012, **41**(39), 12031–12037.

70 S. Modak, M. K. Gangwar, M. N. Rao, M. Madasu, A. C. Kalita, V. Dorcet, M. A. Shejale, R. J. Butcher and P. Ghosh, Fluoride-free Hiyama coupling by palladium abnormal *N*-heterocyclic carbene complexes, *Dalton Trans.*, 2015, **44**(40), 17617–17628.

71 J.-H. Li, C.-L. Deng, W.-J. Liu and Y.-X. Xie, Pd(OAc)$_2$/DABCO as an inexpensive and efficient catalytic system for Hiyama cross-coupling reactions of aryl halides with

aryltrimethoxysilanes, *Synthesis*, 2005, **2005**(18), 3039–3044.

72 T. Yanase, Y. Monguchi and H. Sajiki, Ligand-free Hiyama cross-coupling reaction catalysed by palladium on carbon, *RSC Adv.*, 2012, **2**(2), 590–594.

73 B. C. Ranu, R. Dey and K. Chattopadhyay, A one-pot efficient and fast Hiyama coupling using palladium nanoparticles in water under fluoride-free conditions, *Tetrahedron Lett.*, 2008, **49**(21), 3430–3432.

74 D. Srimani, S. Sawoo and A. Sarkar, Convenient synthesis of palladium nanoparticles and catalysis of Hiyama coupling reaction in water, *Org. Lett.*, 2007, **9**(18), 3639–3642.

75 R. Dey, K. Chattopadhyay and B. C. Ranu, Palladium(0) nanoparticle catalysed cross-coupling of allyl acetates and aryl and vinyl siloxanes, *J. Org. Chem.*, 2008, **73**(23), 9461–9464.

76 L. D. Pachón, M. B. Thathagar, F. Hartl and G. Rothenberg, Palladium-coated nickel nanoclusters: new Hiyama cross-coupling catalysts, *Phys. Chem. Chem. Phys.*, 2006, **8**(1), 151–157.

77 R. W. Scott, H. Ye, R. R. Henriquez and R. M. Crooks, Synthesis, characterization, and stability of dendrimer-encapsulated palladium nanoparticles, *Chem. Mater.*, 2003, **15**(20), 3873–3878.

78 K. Sonogashira, Y. Tohda and N. Hagihara, A convenient synthesis of acetylenes: catalytic substitutions of acetylenic hydrogen with bromoalkenes, iodoarenes and bromopyridines, *Tetrahedron Lett.*, 1975, **16**(50), 4467–4470.

79 R. Chinchilla and C. Nájera, Recent advances in Sonogashira reactions, *Chem. Soc. Rev.*, 2011, **40**(10), 5084–5121.

80 M. Eckhardt and G. C. Fu, The first applications of carbene ligands in cross-couplings of alkyl electrophiles: Sonogashira reactions of unactivated alkyl bromides and iodides, *J. Am. Chem. Soc.*, 2003, **125**(45), 13642–13643.

81 A. Soheili, J. Albaneze-Walker, J. A. Murry, P. G. Dormer and D. L. Hughes, Efficient and general protocol for the copper-free Sonogashira coupling of aryl bromides at room temperature, *Org. Lett.*, 2003, **5**(22), 4191–4194.

82 J. W. Grissom, G. U. Gunawardena, D. Klingberg and D. Huang, The chemistry of enediynes, enyne allenes and related compounds, *Tetrahedron*, 1996, **52**(19), 6453–6518.

83 A. P. Thankachan, K. Sindhu, K. K. Krishnan and G. Anilkumar, An efficient zinc-catalysed cross-coupling reaction of aryl iodides with terminal aromatic alkynes, *Tetrahedron Lett.*, 2015, **56**(41), 5525–5528.

84 K. Nicolaou and W. M. Dai, Chemistry and biology of the enediyne anticancer antibiotics, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**(11), 1387–1416.

85 M. De Kort, V. Correa, A. R. P. Valentijn, G. A. Van Der Marel, B. V. Potter, C. W. Taylor and J. H. Van Boom, Synthesis of potent agonists of the d-myo-Inositol 1,4,5-trisphosphate receptor based on clustered disaccharide polyphosphate analogues of adenophostin A, *J. Med. Chem.*, 2000, **43**(17), 3295–3303.

86 K. T. Nielsen, *Light harvesting by dye linked conducting polymers*, 2006.

87 S. Huang and J. M. Tour, Rapid bi-directional synthesis of oligo (1,4-phenylene ethynylene) s, *Tetrahedron Lett.*, 1999, **40**(17), 3447–3450.

88 V. Francke, T. Mangel and K. Müllen, Synthesis of α,ω-difunctionalized oligo-and poly (p-phenyleneethynylene)s, *Macromolecules*, 1998, **31**(8), 2447–2453.

89 A. Molnar, Efficient, selective, and recyclable palladium catalysts in carbon-carbon coupling reactions, *Chem. Rev.*, 2011, **111**(3), 2251–2320.

90 A. Thayer, Removing impurities, *Chem. Eng. News*, 2005, **83**(36), 55–58.

91 C. E. Garrett and K. Prasad, The art of meeting palladium specifications in active pharmaceutical ingredients produced by Pd-catalysed reactions, *Adv. Synth. Catal.*, 2004, **346**(8), 889–900.

92 C.-J. Li, Organic reactions in aqueous media with a focus on carbon-carbon bond formations: a decade update, *Chem. Rev.*, 2005, **105**(8), 3095–3166.

93 A. Lubineau and J. Augé, Water as solvent in organic synthesis, in *Modern solvents in organic synthesis*, Springer, 1999, pp. 1–39.

94 S. Lohmann, S. P. Andrews, B. J. Burke, M. D. Smith, J. P. Attfield, H. Tanaka, K. Kaneko and S. V. Ley, Copper-and palladium-containing perovskites: catalysts for the Ullmann and Sonogashira reactions, *Synlett*, 2005, **2005**(08), 1291–1295.

95 A. L. D. Ramos, P. da Silva Alves, D. A. Aranda and M. Schmal, Characterization of carbon supported palladium catalysts: inference of electronic and particle size effects using reaction probes, *Appl. Catal., A*, 2004, **277**(1–2), 71–81.

96 S. Raju, P. R. Kumar, K. Mukkanti, P. Annamalai and M. Pal, Facile synthesis of substituted thiophenes via Pd/C-mediated sonogashira coupling in water, *Bioorg. Med. Chem. Lett.*, 2006, **16**(24), 6185–6189.

97 A. Corma, H. García and A. Primo, Palladium and copper supported on mixed oxides derived from hydrotalcite as reusable solid catalysts for the Sonogashira coupling, *J. Catal.*, 2006, **241**(1), 123–131.

98 C. M. Crudden, M. Sateesh and R. Lewis, Mercaptopropyl-modified mesoporous silica: A remarkable support for the preparation of a reusable, heterogeneous palladium catalyst for coupling reactions, *J. Am. Chem. Soc.*, 2005, **127**(28), 10045–10050.

99 K. R. Reddy, N. S. Kumar, P. S. Reddy, B. Sreedhar and M. L. Kantam, Cellulose supported palladium(0) catalyst for Heck and Sonogashira coupling reactions, *J. Mol. Catal. A: Chem.*, 2006, **252**(1–2), 12–16.

100 A. C. Albéniz and N. Carrera, Polymers for green C–C couplings, *Eur. J. Inorg. Chem.*, 2011, **2011**(15), 2347–2360.

101 N. E. Leadbeater, Fast, easy, clean chemistry by using water as a solvent and microwave heating: the Suzuki coupling as an illustration, *Chem. Commun.*, 2005(23), 2881–2902.

102 B. M. Dioos, I. F. Vankelecom and P. A. Jacobs, Aspects of immobilisation of catalysts on polymeric supports, *Adv. Synth. Catal.*, 2006, **348**(12–13), 1413–1446.

103 W.-B. Yi, X.-L. Shi, C. Cai and W. Zhang, Polymer-supported Pd(0) catalyst for copper-and ligand-free Sonogashira reactions in aqueous media, *Green Processes Synth.*, 2012, **1**(2), 175–180.

104 N. K. Garg, C. C. Woodroofe, C. J. Lacenere, S. R. Quake and B. M. Stoltz, A ligand-free solid-supported system for Sonogashira couplings: applications in nucleoside chemistry, *Chem. Commun.*, 2005(36), 4551–4553, DOI: 10.1039/B505737J.

105 Z. Novák, A. Szabó, J. Répási and A. Kotschy, Sonogashira coupling of aryl halides catalysed by palladium on charcoal, *J. Org. Chem.*, 2003, **68**(8), 3327–3329.

106 J. M. Prober, A system for rapid DNA sequencing with fluorescent chain-terminating dideoxynucleotides, *Science*, 1987, **238**(4825), 336–341.

107 M. B. Thathagar, J. Beckers and G. Rothenberg, Palladium-free and ligand-free Sonogashira cross-coupling, *Green Chem.*, 2004, **6**(4), 215–218.

108 X. Li, X. Gong, Z. Li, H. Chang, W. Gao and W. Wei, Ligand- and copper-free Sonogashira and Heck couplings of (het)aryl chlorides and bromides catalysed by palladium nanoparticles supported on in situ generated $Al(OH)_3$, *RSC Adv.*, 2017, **7**(5), 2475–2479, DOI: 10.1039/C6RA25416K.

109 S. Mori, T. Yanase, S. Aoyagi, Y. Monguchi, T. Maegawa and H. Sajiki, Ligand-free Sonogashira coupling reactions with heterogeneous Pd/C as the catalyst, *Chem. – Eur. J.*, 2008, **14**(23), 6994–6999.

110 I. P. Beletskaya and A. V. Cheprakov, The Heck reaction as a sharpening stone of palladium catalysis, *Chem. Rev.*, 2000, **100**(8), 3009–3066.

111 D. E. Frantz, D. G. Weaver, J. P. Carey, M. H. Kress and U. H. Dolling, Practical synthesis of aryl triflates under aqueous conditions, *Org. Lett.*, 2002, **4**(26), 4717–4718.

112 H.-U. Blaser and A. Spencer, The palladium-catalysed arylation of activated alkenes with aroyl chlorides, *J. Organomet. Chem.*, 1982, **233**(2), 267–274.

113 M. S. Stephan, A. J. Teunissen, G. K. Verzijl and J. G. de Vries, Heck reactions without salt formation: aromatic carboxylic anhydrides as arylating agents, *Angew. Chem., Int. Ed.*, 1998, **37**(5), 662–664.

114 M. Miura, H. Hashimoto, K. Itoh and M. Nomura, Palladium-catalysed desulphonylative vinylation of arenesulphonyl chlorides under solid–liquid phase-transfer conditions, *J. Chem. Soc., Perkin Trans. 1*, 1990(8), 2207–2211.

115 S. Cacchi, G. Fabrizi, A. Goggiamani and A. Sferrazza, Heck reaction of arenediazonium salts with N,N-diprotected allylamines. Synthesis of cinnamylamines and indoles, *Org. Biomol. Chem.*, 2011, **9**(6), 1727–1730.

116 L. S. Hegedus, *Transition metals in the synthesis of complex organic molecules*, University Science Books, 1999.

117 M. Beller, A. Zapf and W. Mägerlein, Efficient synthesis of fine chemicals and organic building blocks applying palladium-catalysed coupling reactions, *Chem. Eng. Technol.*, 2001, **24**(6), 575–582.

118 I. Shinkai, A. King and R. Larsen, A practical asymmetric synthesis of LTD4 antagonist, *Pure Appl. Chem.*, 1994, **66**(7), 1551–1556.

119 J. E. Macor and M. J. Wythes, *Indole derivatives*, 1996.

120 H. C. Shen, Selected Applications of Transition Metal-Catalysed Carbon–Carbon Cross-Coupling Reactions in the Pharmaceutical Industry, in *Application of transition metal catalysis in drug discovery and development*, 2012, pp. 25–95.

121 J. Perkins, *Eur. Pat.*, 1088817, 2001; J. E. Macor and M. J. Wythes, *Int. Pat.*, WO9206973, 1992 to Pfizer Inc.; C. Q. Meng, *Curr. Opin. Cent. Peripher. Nerv. Syst. Invest. Drugs*, 2000, **2**, 186.

122 F. E. Herkes, *Catalysis of organic reactions*, CRC Press, 1998, vol. 75.

123 H. Sigel, *Metal ions in biological systems*, Metal complexes in tumor diagnosis and as anticancer agents, CRC Press, 2004, vol. 42.

124 V. Polshettiwar and T. N. Asefa, *Synthesis and applications*, Wiley Online Library, 2013.

125 C. Yang, H. M. Lee and S. P. Nolan, Highly efficient Heck reactions of aryl bromides with n-butyl acrylate mediated by a palladium/phosphine-imidazolium salt system, *Org. Lett.*, 2001, **3**(10), 1511–1514.

126 G. Hervé and C. Len, First ligand-free, microwave-assisted, Heck cross-coupling reaction in pure water on a nucleoside–Application to the synthesis of antiviral BVDU, *RSC Adv.*, 2014, **4**(87), 46926–46929.

127 A. Biffis, M. Zecca and M. Basato, Palladium metal catalysts in Heck C-C coupling reactions, *J. Mol. Catal. A: Chem.*, 2001, **173**(1), 249–274.

128 G. Zhang, H. Zhou, J. Hu, M. Liu and Y. Kuang, Pd nanoparticles catalysed ligand-free Heck reaction in ionic liquid microemulsion, *Green Chem.*, 2009, **11**(9), 1428–1432.

129 B. Mariampillai, C. Herse and M. Lautens, Intermolecular Heck-type coupling of aryl iodides and allylic acetates, *Org. Lett.*, 2005, **7**(21), 4745–4747.

130 A. S. Singh, U. B. Patil and J. M. Nagarkar, Palladium supported on zinc ferrite: A highly active, magnetically separable catalyst for ligand free Suzuki and Heck coupling, *Catal. Commun.*, 2013, **35**, 11–16.

131 J. Chung, J. Kim, Y. Jang, S. Byun, T. Hyeon and B. M. Kim, Heck and Sonogashira cross-coupling reactions using recyclable $Pd–Fe_3O_4$ heterodimeric nanocrystal catalysts, *Tetrahedron Lett.*, 2013, **54**(38), 5192–5196.

132 W. Han, N. Liu, C. Liu and Z. L. Jin, A ligand-free Heck reaction catalysed by the in situ-generated palladium nanoparticles in PEG-400, *Chin. Chem. Lett.*, 2010, **21**(12), 1411–1414.

133 F. X. Felpin, E. Fouquet and C. Zakri, Heck cross-coupling of aryldiazonium tetrafluoroborate with acrylates catalysed by palladium on charcoal, *Adv. Synth. Catal.*, 2008, **350**(16), 2559–2565.

134 P. Hanson, S. C. Rowell, A. B. Taylor, P. H. Walton and A. W. Timms, Sandmeyer reactions. Part 6. 1 A mechanistic investigation into the reduction and ligand transfer steps of Sandmeyer cyanation, *J. Chem. Soc., Perkin Trans. 2*, 2002(6), 1126–1134.

135 P. Hanson, J. R. Jones, A. B. Taylor, P. H. Walton and A. W. Timms, Sandmeyer reactions. Part 7. 1 An investigation into the reduction steps of Sandmeyer hydroxylation and chlorination reactions, *J. Chem. Soc., Perkin Trans. 2*, 2002(6), 1135–1150.

136 P. Baumeister, W. Meyer, K. Oertle, G. Seifert and H. Steiner, Invention and development of a novel catalytic process for the production of a benzenesulfonic acid-building block, *Chimia*, 1997, **51**(4), 144.

137 U. Siegrist, T. Rapold and H.-U. Blaser, Process development for a herbicide intermediate via catalytic carboxylation of an aromatic diazonium compound, *Org. Process Res. Dev.*, 2003, 7(3), 429–431.

138 F. X. Felpin, K. Miqueu, J. M. Sotiropoulos, E. Fouquet, O. Ibarguren and J. Laudien, Room-temperature, ligand-and base-free Heck reactions of aryl diazonium salts at low palladium loading: Sustainable preparation of substituted stilbene derivatives, *Chem. – Eur. J.*, 2010, **16**(17), 5191–5204.

139 F.-X. Felpin, O. Ibarguren, L. Nassar-Hardy and E. Fouquet, Synthesis of oxindoles by tandem Heck-Reduction-Cyclization (HRC) from a single bifunctional, in situ generated Pd/C catalyst, *J. Org. Chem.*, 2008, **74**(3), 1349–1352.

140 O. Ibarguren, C. Zakri, E. Fouquet and F.-X. Felpin, Heterogeneous palladium multi-task catalyst for sequential Heck-reduction–cyclization (HRC) reactions: influence of the support, *Tetrahedron Lett.*, 2009, **50**(36), 5071–5074.

141 S. Hu, P. Xia, K. Cheng and C. Qi, Pd-catalysed ligand-free desulfitative Heck reaction with arenesulfinic acid salts under air, *Appl. Organomet. Chem.*, 2013, **27**(3), 188–190.

142 S. A. Weissman, D. Zewge and C. Chen, Ligand-free palladium-catalysed cyanation of aryl halides, *J. Org. Chem.*, 2005, **70**(4), 1508–1510.

143 M. J. O'Neil, *The Merck index: an encyclopedia of chemicals, drugs, and biologicals*, RSC Publishing, 2013.

144 J. K. Stille, The Palladium-catalysed cross-coupling reactions of organotin reagents with organic electrophiles[New Synthetic Methods(58)], *Angew. Chem., Int. Ed. Engl.*, 1986, **25**(6), 508–524.

145 C. Cordovilla, The Stille reaction, 38 years later, *ACS Catal.*, 2015, **5**(5), 3040–3053.

146 K. C. Nicolaou, Total synthesis of rapamycin, *J. Am. Chem. Soc.*, 1993, **115**(10), 4419–4420.

147 M. M. Heravi, Recent developments of the Stille reaction as a revolutionized method in total synthesis, *Tetrahedron*, 2014, **70**(1), 7–21.

148 K. C. Nicolaou, Total synthesis of Epothilone E and related side-chain modified analogues via a stille coupling based strategy1This paper is dedicated with admiration and respect to the memory of Sir Derek H. R. Barton.1, *Bioorg. Med. Chem.*, 1999, 7(5), 665–697.

149 S. M. McAfee, J. S. J. McCahill, C. M. Macaulay, A. D. Hendsbee and G. C. Welch, Utility of a heterogeneous palladium catalyst for the synthesis of a molecular semiconductor via Stille, Suzuki, and direct heteroarylation cross-coupling reactions, *RSC Adv.*, 2015, 5(33), 26097–26106.

150 M. M. Dell'Anna, Stille coupling reactions catalysed by a polymer supported palladium complex, *J. Organomet. Chem.*, 2006, **691**(1–2), 131–137.

151 S. Bahari, Diphenylphosphinoethane-functionalized polystyrene resin-supported Pd(0) complex — A highly active and recyclable catalyst for the Stille reaction under aerobic conditions, *Can. J. Chem.*, 2012, **90**(9), 784–789.

152 M.-J. Jin, A Practical heterogeneous catalyst for the Suzuki, Sonogashira, and Stille coupling reactions of unreactive aryl chlorides, *Angew. Chem., Int. Ed.*, 2010, **49**(6), 1119–1122.

153 A. Ghorbani-Choghamarani, Palladium supported on modified magnetic nanoparticles: a phosphine-free and heterogeneous catalyst for Suzuki and Stille reactions Suzuki and Stille reactions catalysed by FeO/SiO-PAP-Pd, *Appl. Organomet. Chem.*, 2016, **30**(3), 140–147.

154 D. Saha, Anchoring of palladium onto surface of porous metal–organic framework through post-synthesis modification and studies on Suzuki and Stille coupling reactions under heterogeneous condition, *Langmuir*, 2013, **29**(9), 3140–3151.

155 B. M. Choudary, Layered double hydroxide supported nanopalladium catalyst for Heck-, Suzuki-, Sonogashira-, and Stille-type coupling reactions of chloroarenes, *J. Am. Chem. Soc.*, 2002, **124**(47), 14127–14136.

156 G. Xu, Y. Zhang, K. Wang, Y. Fu and Z. Du, Microwave-assisted Stille cross-coupling reaction catalysed by in situ formed palladium nanoparticles, *J. Chem. Res.*, 2015, **39**(7), 399–402.

157 S. T. Handy, Organic synthesis in ionic liquids: The Stille coupling, *Org. Lett.*, 2001, 3(2), 233–236.

158 C. Chiappe, G. Imperato, E. Napolitano and D. Pieraccini, Ligandless Stille cross-coupling in ionic liquids, *Green Chem.*, 2004, **6**(1), 33–36.

159 W. J. Zhou, K. H. Wang and J. X. Wang, Atom-efficient, palladium-catalysed Stille coupling reactions of tetraphenylstannane with aryl iodides or aryl bromides in polyethylene glycol 400 (PEG-400), *Adv. Synth. Catal.*, 2009, **351**(9), 1378–1382.

160 A. Ghorbani-Choghamarani, A. Naghipour, F. Heidarizadi, R. Shirkhani and B. Notash, Bis [(2-methylacetatobenzyl) tri(p-tolyl) phosphonium] hexabromodipalladate (II); synthesis, characterization, structural study and application as a retrievable heterogeneous catalyst for the amination of aryl halides and Stille cross-coupling reaction, *Inorg. Chim. Acta*, 2016, **446**, 97–102.

161 A. I. Roshchin, N. A. Bumagin and I. P. Beletskaya, Palladium-catalysed cross-coupling reaction of organostannoates with aryl halides in aqueous medium, *Tetrahedron Lett.*, 1995, **36**(1), 125–128.

162 R. Rai, K. B. Aubrecht and D. B. Collum, Palladium-catalysed stille couplings of aryl-, vinyl-, and alkyltrichlorostannanes in aqueous solution, *Tetrahedron Lett.*, 1995, **36**(18), 3111–3114.

163 C. Wolf and R. Lerebours, Efficient Stille cross-coupling reaction using aryl chlorides or bromides in water, *J. Org. Chem.*, 2003, **68**(19), 7551–7554.

164 S. Ogo, Y. Takebe, K. Uehara, T. Yamazaki, H. Nakai, Y. Watanabe and S. Fukuzumi, pH-dependent C–C coupling reactions catalysed by water-soluble palladacyclic aqua catalysts in water, *Organometallics*, 2006, **25**(2), 331–338.

165 J.-H. Li, X.-C. Hu, Y. Liang and Y.-X. Xie, PEG-400 promoted $Pd(OAc)_2$/DABCO-catalysed cross-coupling reactions in aqueous media, *Tetrahedron*, 2006, **62**(1), 31–38.

166 W. Susanto, C.-Y. Chu, W. J. Ang, T.-C. Chou, L.-C. Lo and Y. Lam, Fluorous oxime palladacycle: a precatalyst for carbon–carbon coupling reactions in aqueous and organic medium, *J. Org. Chem.*, 2012, 77(6), 2729–2742.

167 G.-P. Lu, C. Cai and B. H. Lipshutz, Stille couplings in water at room temperature, *Green Chem.*, 2013, **15**(1), 105–109.

168 A. S. Prasad and B. Satyanarayana, Magnetically recoverable Pd/Fe_3O_4-catalysed Stille cross-coupling reaction of organostannanes with aryl bromides, *Bull. Korean Chem. Soc.*, 2012, **33**(8), 2789–2792.

169 A. Krasovskiy, V. Malakhov, A. Gavryushin and P. Knochel, Efficient synthesis of functionalized organozinc compounds by the direct insertion of zinc into organic iodides and bromides, *Angew. Chem., Int. Ed.*, 2006, **45**(36), 6040–6044.

170 E.-I. Negishi, Transition metal-catalysed organometallic reactions that have revolutionized organic synthesis, *Bull. Chem. Soc. Jpn.*, 2007, **80**(2), 233–257.

171 V. B. Phapale and D. J. Cárdenas, Nickel-catalysed Negishi cross-coupling reactions: scope and mechanisms, *Chem. Soc. Rev.*, 2009, **38**(6), 1598–1607.

172 S. Sase, M. Jaric, A. Metzger, V. Malakhov and P. Knochel, One-pot Negishi cross-coupling reactions of in situ generated zinc reagents with aryl chlorides, bromides, and triflates, *J. Org. Chem.*, 2008, 73(18), 7380–7382.

173 S. Thapa, A. Kafle, S. K. Gurung, A. Montoya, P. Riedel and R. Giri, Ligand-free Copper-catalysed Negishi coupling of alkyl-, aryl-, and alkynylzinc reagents with heteroaryl iodides, *Angew. Chem., Int. Ed.*, 2015, **54**(28), 8236–8240.

174 D.-C. Wang, H.-Y. Niu, G.-R. Qu, L. Liang, X.-J. Wei, Y. Zhang and H.-M. Guo, Nickel-catalysed Negishi cross-couplings of 6-chloropurines with organozinc halides at room temperature, *Org. Biomol. Chem.*, 2011, **9**(22), 7663–7666.

175 M. T. Reetz and E. Westermann, Phosphane-free palladium-catalysed coupling reactions: the decisive role of Pd nanoparticles, *Angew. Chem., Int. Ed.*, 2000, **39**(1), 165–168.

176 K. Köhler, W. Kleist and S. S. Pröckl, Genesis of coordinatively unsaturated palladium complexes dissolved from solid precursors during Heck coupling reactions and their role as catalytically active species, *Inorg. Chem.*, 2007, **46**(6), 1876–1883.

177 N. T. Phan, M. Van Der Sluys and C. W. Jones, On the nature of the active species in palladium catalysed Mizoroki–Heck and Suzuki–Miyaura couplings–homogeneous or heterogeneous catalysis, a critical review, *Adv. Synth. Catal.*, 2006, **348**(6), 609–679.

178 P. Mpungose, Z. Vundla, G. Maguire and H. Friedrich, The current status of heterogeneous palladium catalysed Heck and Suzuki cross-coupling reactions, *Molecules*, 2018, **23**(7), 1676.

179 A. Balanta, C. Godard and C. Claver, Pd nanoparticles for C–C coupling reactions, *Chem. Soc. Rev.*, 2011, **40**(10), 4973–4985, DOI: 10.1039/C1CS15195A.

180 M. Pérez-Lorenzo, Palladium nanoparticles as efficient catalysts for Suzuki cross-coupling reactions, *J. Phys. Chem. Lett.*, 2012, 3(2), 167–174.

181 T. Hirakawa, Y. Uramoto, S. Yanagisawa, T. Ikeda, K. Inagaki and Y. Morikawa, First-principles molecular dynamics analysis of ligand-free Suzuki–Miyaura cross-coupling in water: Transmetalation and reductive elimination, *J. Phys. Chem. C*, 2017, **121**(36), 19904–19914.

182 S. N. Jadhav, A. S. Kumbhar, C. V. Rode and R. S. Salunkhe, Ligand-free Pd catalysed cross-coupling reactions in an aqueous hydrotropic medium, *Green Chem.*, 2016, **18**(7), 1898–1911.

183 D. Astruc, Transition-metal nanoparticles in catalysis: from historical background to the state-of-the art, in *Nanoparticles and Catalysis*, 2008, pp. 1–48.

184 T. Akiyama, T. Taniguchi, N. Saito, R. Doi, T. Honma, Y. Tamenori, Y. Ohki, N. Takahashi, H. Fujioka and Y. Sato, Ligand-free Suzuki–Miyaura coupling using ruthenium(0) nanoparticles and a continuously irradiating microwave system, *Green Chem.*, 2017, **19**(14), 3357–3369.