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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.

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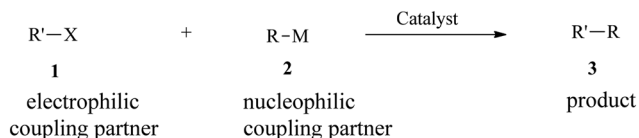
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Scheme 1 General equation for a transition metal-catalysed cross-coupling reaction.

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 bonds¹⁰ 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 agents¹⁵ 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 heteroaromatics¹⁴ 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.

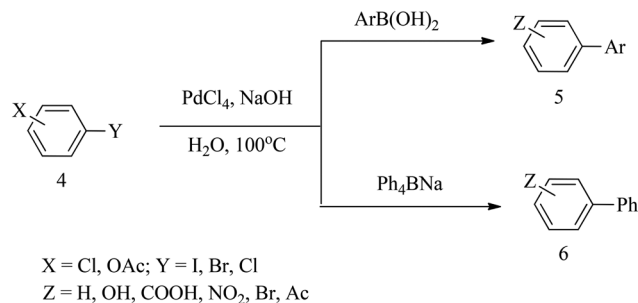
The development of a ligand-free approach for aryl, heteroaromatic and vinyl fluorosulfates, halides, or traditional sulfates (triflates, mesylates and tosylates)²² as electrophilic partners for transition metal-catalysed cross-coupling reactions has attracted increasing attention because

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} Negishi³⁵ and Stille³⁶ 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 report⁴⁷ 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(PPh₃)₄ as a catalyst both for homogeneous⁴⁸ and solid-phase⁴⁹ 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 reactions⁵¹ 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 Bykov²⁷ 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 PdCl₂ 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% PdCl₂ pre-catalyst with NaOH within 3 h to furnish biphenyl **8** in 92% yield (Scheme 3). However, electron-rich chlorophenols reacted with sodium tetraphenylborate (Ph₄BNa) to afford moderate yields of isolated products.

A heterogeneous palladium catalytic system (Pd/C) in a dimethylacetamide–water (DMA–H₂O) 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-workers⁵³ 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 Marco⁵⁸ 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).

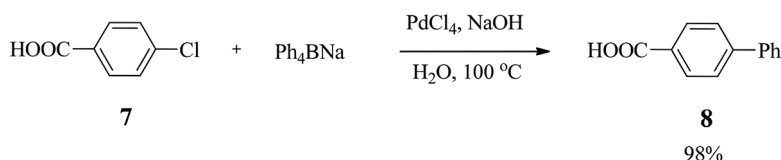
d. Cross-coupling of aryl halides with aryl boronic acids

In 2011, Qiu and co-workers⁵³ 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 K₂CO₃ in air at room temperature (Scheme 6). The choice of volume ratio of DMF–H₂O as well as the base is critical to the reaction. Hence, at a catalytic loading of 0.0025 mmol and a DMF–H₂O 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.

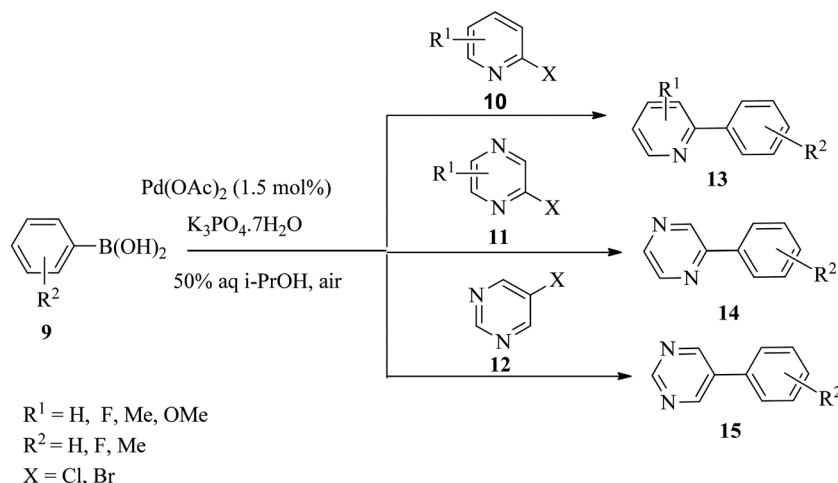
e. Bio-supported cross-coupling of aryl halides with aryl boronic acids

Tang and co-workers⁵⁷ 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-workers⁵⁹ 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

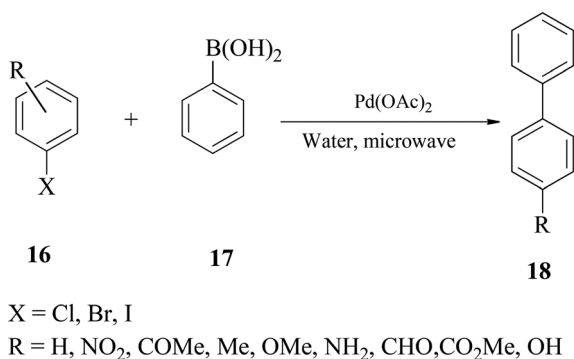
of thiophene, benzene and benzoic acid with phenylboronic acid in ethanol (Scheme 9). Evaluation of the catalytic efficiency determined by the yield of the reaction showed that the Pd-Cu bimetallic system supported on carbon is the most efficient (Pd-Cu/C > Pd/C > Pd-Ag/C > Pd-Ni/C) in the Suzuki cross-coupling of the halides of thiophene, benzene and benzoic acid with yields of 96.7%, 97.5%, and 88.7%, respectively.

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

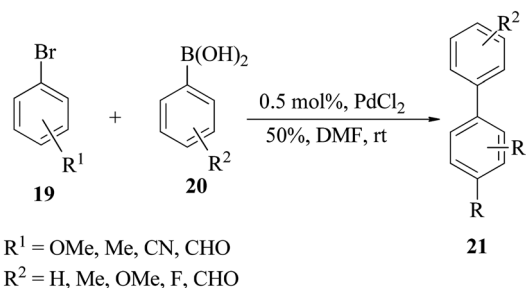
The De Vries group demonstrated the application of a 'homeopathic' ligand-free palladium catalyst in the coupling of aryl bromides and chlorides.⁶⁰ The catalyst (Pd(OAc)₂) at a loading of 0.02–0.05 mol% generally performed well for both activated aryl bromides and chlorides, but mixed results were obtained 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-

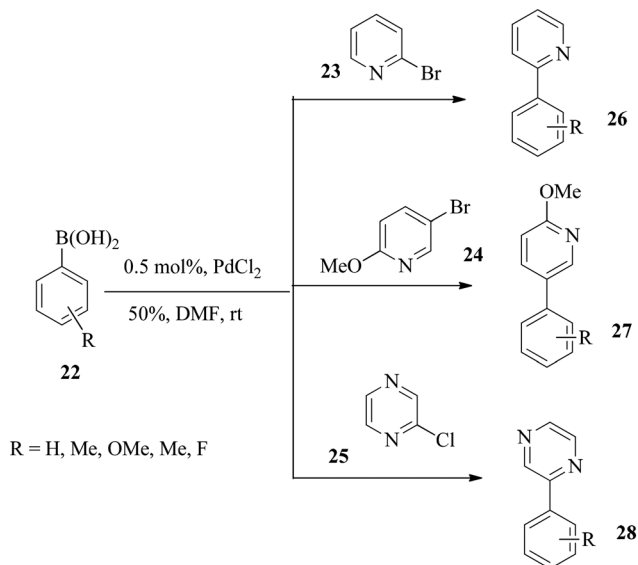


Scheme 5 Microwave-mediated Suzuki coupling of aryl halides with aryl boronic acids in water using Pd(OAc)₂.



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



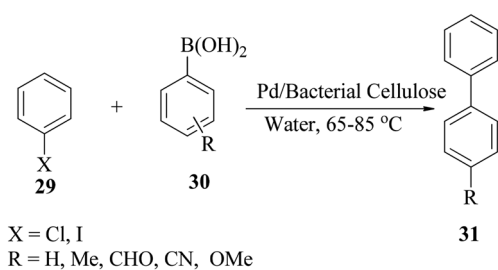


Scheme 7 The Suzuki reaction of *N*-heteroaryl halides with aryl boronic acids.

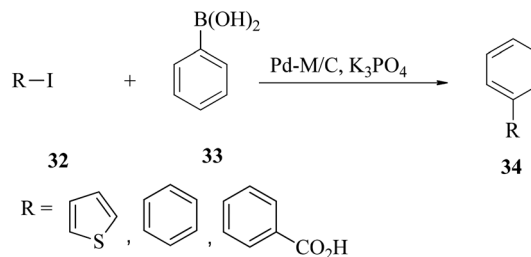
rich aryl chlorides. The failure of the deactivated electron-rich aryl chlorides to react stems from increased C–Cl bond strength probably because of the contribution of both inductive and mesomeric effects.

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 reaction⁶³ 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



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



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

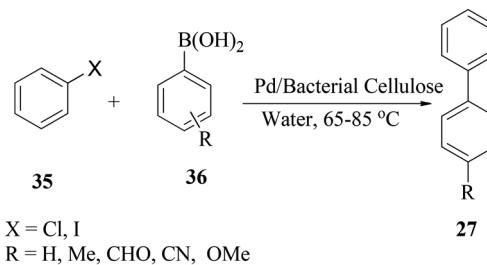
of aryl(alkoxy)silanes for Hiyama coupling by Shibata and co-workers,⁶⁵ reactive aryl bromides and iodides have been largely used instead of the relatively cheap and commercially available aryl chlorides.^{32,66} Several limitations have hampered the use of aryl chlorides in Hiyama coupling.^{64,67–71} Below are some of the recent ligand-less Hiyama cross-coupling reactions.

a. Cross-coupling of substituted aryl halides with arylalkoxysilanes

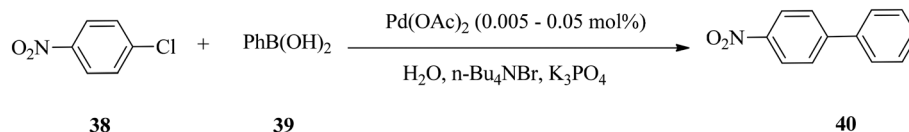
Sajiki and co-workers⁷² reported the first active palladium on carbon-catalysed ligand-free Hiyama cross-coupling of a variety of electron-rich and electron-poor aryl halides **41** with aryltriethoxysilanes **42** in good to excellent yields at 0.5 mol\% Pd/C catalytic loading in refluxing toluene within 24 h (Scheme 12). The use of fluoride sources such as $\text{TBAF} \cdot 3\text{H}_2\text{O}$ or metal fluorides is critical for the reaction to proceed. The reaction was also extended to phenyltrimethoxysilane derivatives, and good yields were obtained within 48 h.

In the same vein, Ranu and co-workers⁷³ 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-workers⁷⁴ 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-workers⁷⁵ 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-workers⁷⁶ 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

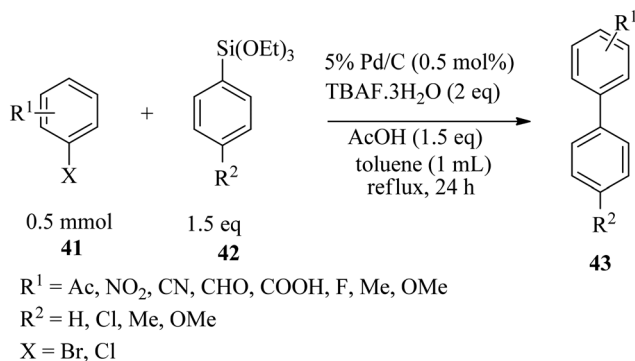
4. Ligand-free Sonogashira cross-coupling

The generation of sp^2 - 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 syn-

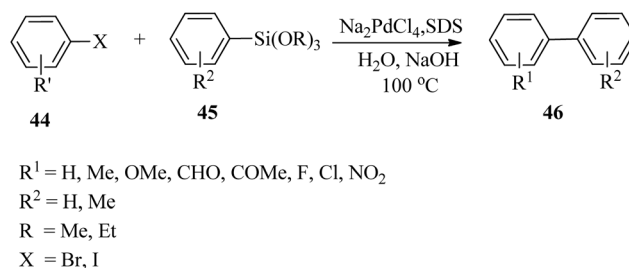
thesis of alkyne-containing aromatic compounds,^{80,81} natural products,^{82,83} medicinal products,^{84,85} oligomers,^{86,87} and polymers.⁸⁸ The major setbacks of the reaction are the sensitivity of the copper co-catalyst to oxygen, causing oxidative homocoupling of acetylenes to form diacetylenes 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 hydro-talcite,⁹⁷ silica,⁹⁸ cellulose,⁹⁹ and polymers¹⁰⁰ 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-workers¹⁰⁴ 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-workers¹⁰⁵ replacing Pd/C with Pd(PPh₃)₄, lowering the catalyst loading to 5% and carrying out the reaction at 50 °C to afford deoxyuridine, uridine,

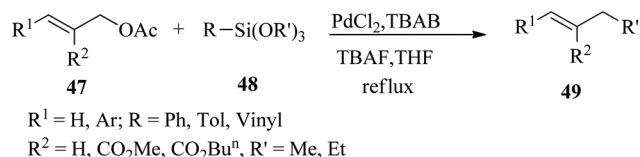


Scheme 12 The Hiyama cross-coupling of various aryl halides with aryltriethoxysilanes.



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(PPh₃)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-workers¹⁰⁷ 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

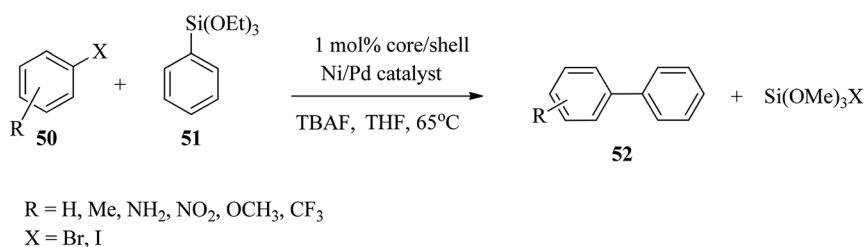
Wei and co-workers¹⁰⁸ reported the application of *in situ* generated palladium nanoparticles as a catalyst supported on Al(OH)₃ (Scheme 20) in ligand- and copper-free Sonogashira cross-coupling reactions of (hetero)aryl bromides and chlorides.

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).

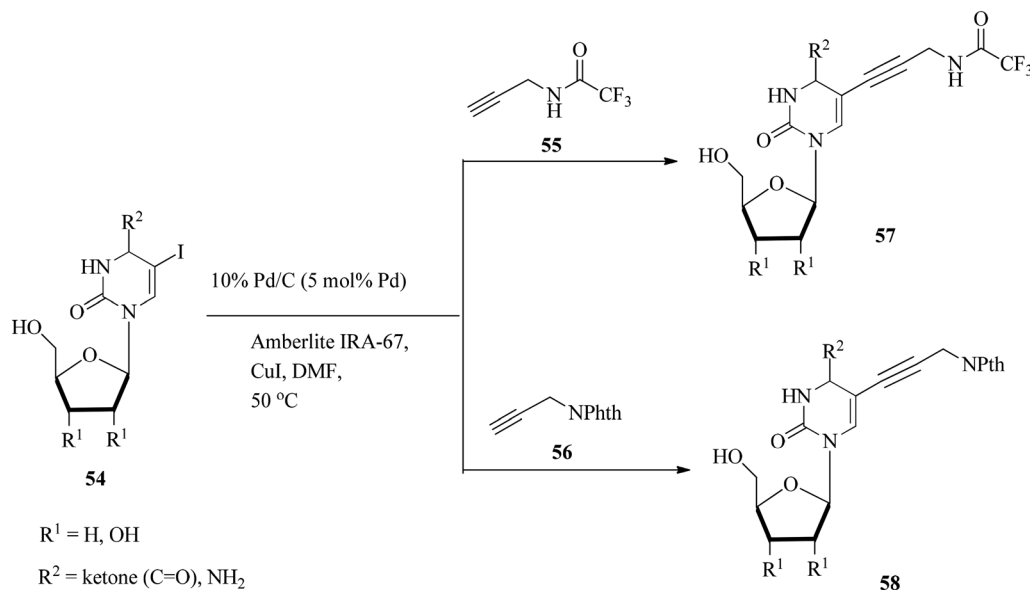
e. Cross-coupling of aromatic and aliphatic terminal alkynes with aryl iodides

Sajiki and co-workers¹⁰⁹ 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 Na₃PO₄ · 12H₂O (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.

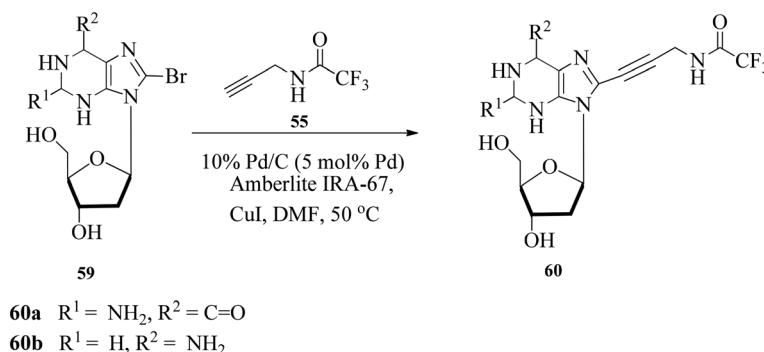


Scheme 15 Bimetallic Ni-Pd nanoparticle catalysed ligand-free Hiyama cross-coupling reaction of phenylmethoxysilane with various haloaryls.





Scheme 16 Solid-supported Sonogashira coupling of deoxynucleoside derivatives.

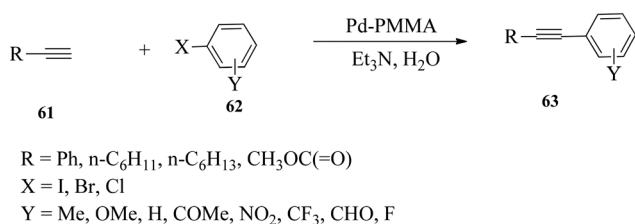


Scheme 17 Solid-supported Sonogashira coupling of deoxyadenosine and deoxyguanosine derivatives.

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 salts¹¹⁵ 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}

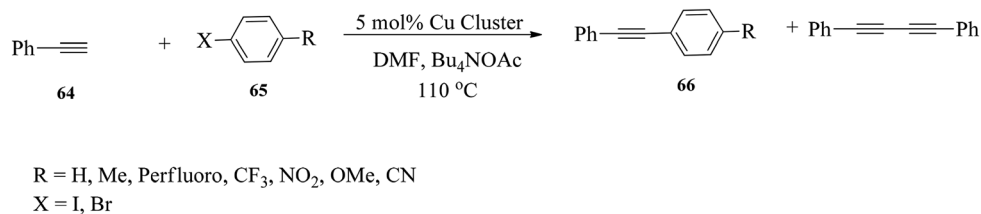


Scheme 18 Polymer-supported cross-coupling of aryl halides with phenylacetylenes in water.

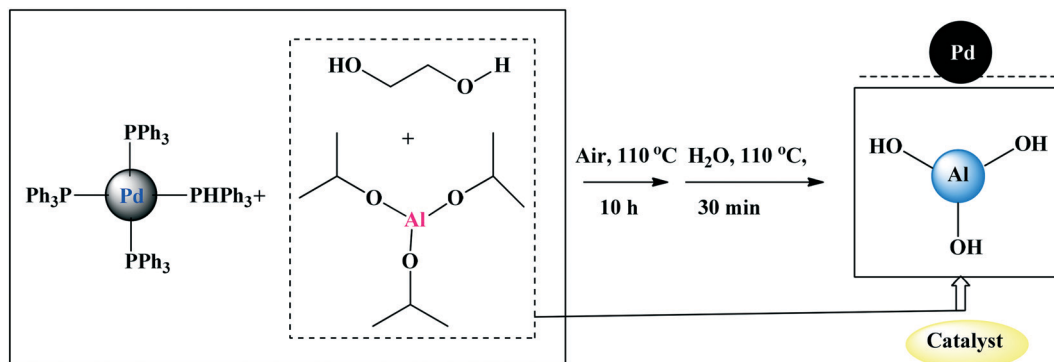
a. Cross-coupling reaction between 5-iodo-2-deoxyuridine and various acrylate derivatives

Len and Hervé¹²⁶ reported a palladium-catalysed Heck cross-coupling reaction between 5-iodo-2-deoxyuridine and various acrylate derivatives using ligand-free conditions and

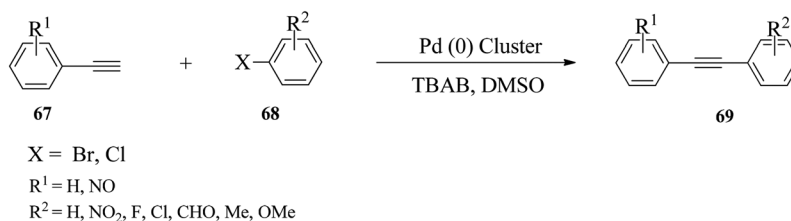




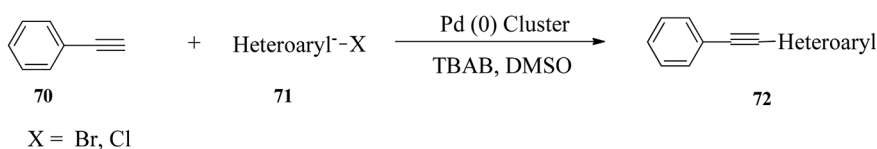
Scheme 19 Copper nanocluster catalysed cross-coupling of alkynes and aryl halides.



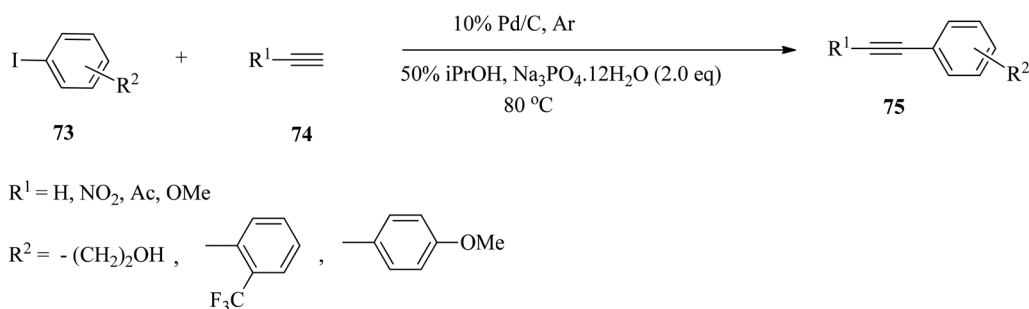
Scheme 20 Preparation of the Pd nanoparticle catalyst.¹⁰⁸



Scheme 21 Cross-coupling of aryl halides with phenylacetylene.



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 NEt₃ in sole water at 80 °C under microwave irradiation (Scheme 24). NEt₃ was chosen because it is an inexpensive joint base, and Shaughnessy demonstrated that NEt₃ 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-workers¹²⁷ 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-workers¹²⁸ investigated the catalytic performance of the greener ionic liquid H₂O/TX-100/[BMIM]PF₆ 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]PF₆.¹²⁸ 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-workers¹²⁹ studied palladium-catalysed arylation of allylic acetates **88**. They examined the choice of Pd catalyst and tetrabutylammonium salts in the initial

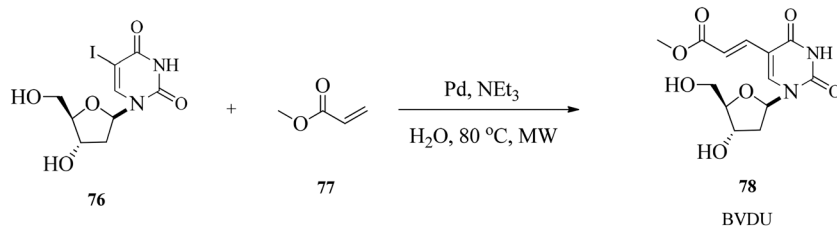
coupling experiment. Optimisation of the Pd catalyst showed Pd/C to be the catalyst of choice and tetrabutylammonium chloride resulted in increased reactant conversion. The mechanism proceeds *via* β-acetoxy elimination, instead of β-hydride elimination, to furnish the olefinic products **89**. Optimal 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

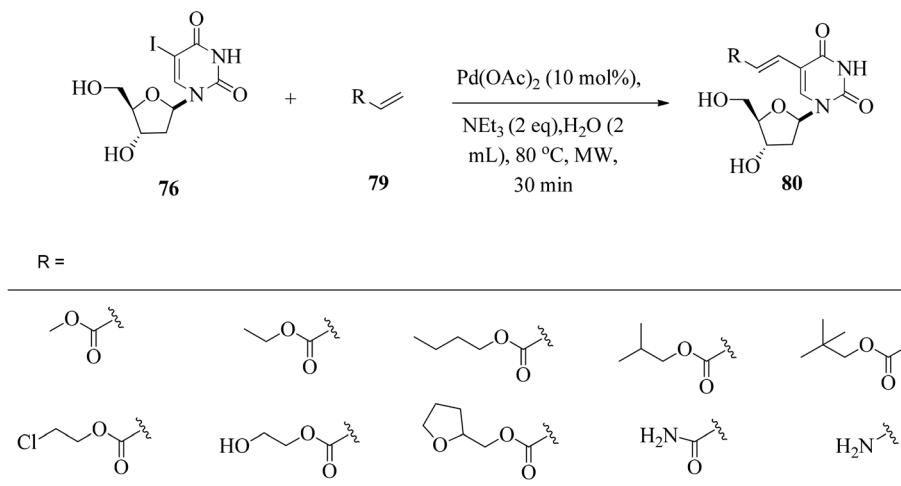
Nagarkar and co-workers¹³⁰ employed palladium supported on zinc ferrite nanoparticles for Heck coupling reactions of aryl halides **90** with alkenes **91** under ligand-free conditions (Scheme 29). The efficient superparamagnetic solid catalyst was prepared by loading Pd(0) species during the synthesis 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-workers¹³¹ carried out the reaction using a Pd–Fe₂O₄ 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-workers¹³² 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.

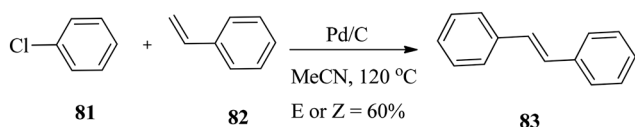
f. Cross-coupling of aryldiazonium tetrafluoroborate with acrylates

Felpin and co-workers¹³³ 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 CaCO₃ 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.

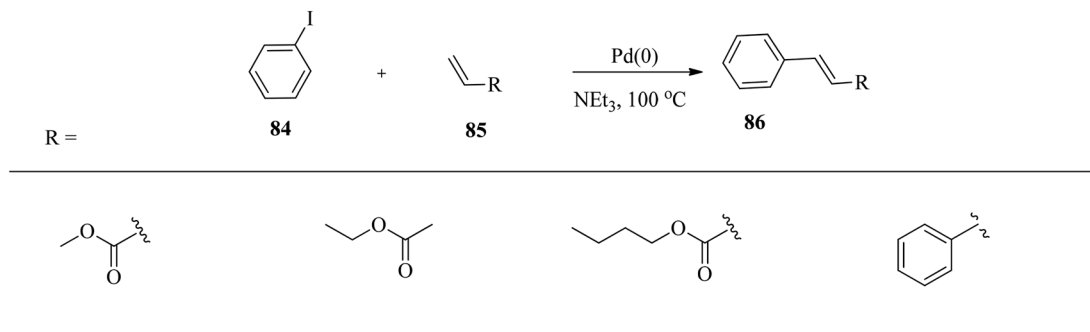
In a related reaction, Felpin and co-workers¹³⁸ prepared *cis*-stilbenes **103** with good to excellent stereoselectivity by employing a Pd(OAc)₂ catalyst for the Heck reaction of aryl diazonium salts **99** with 2-aryl acrylates **102** under the same conditions (Scheme 33). It was observed that the coupling furnished the *cis*-stilbene products with perfect control of the double bond geometry, which is unrelated to the stereo-electronic effect on the acrylates or diazonium salts. The reactions are particularly important because aryl acrylates with a NO₂ 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

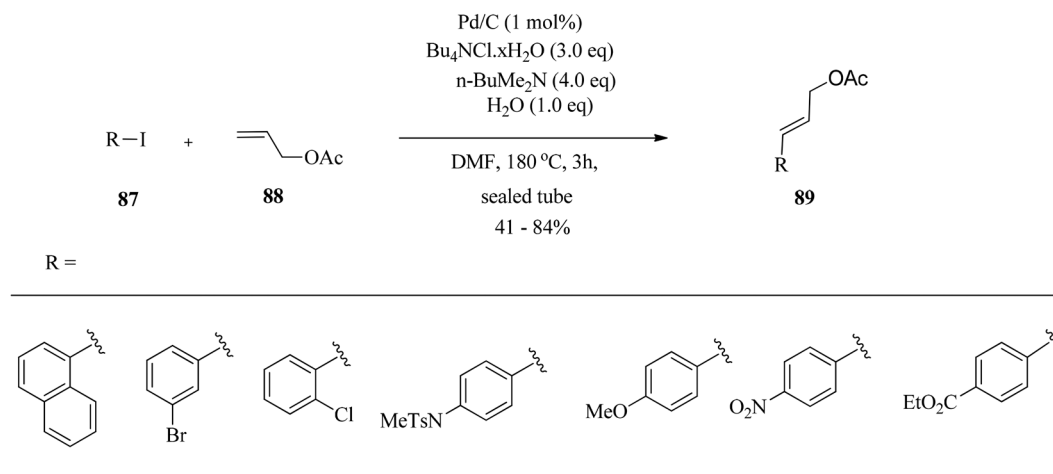


Scheme 26 Pd/C-catalysed cross-coupling of chlorobenzene with styrene to afford stilbene.

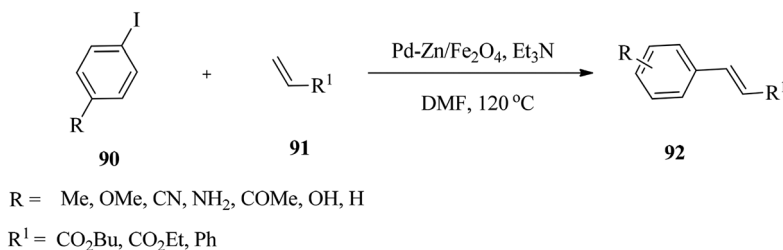




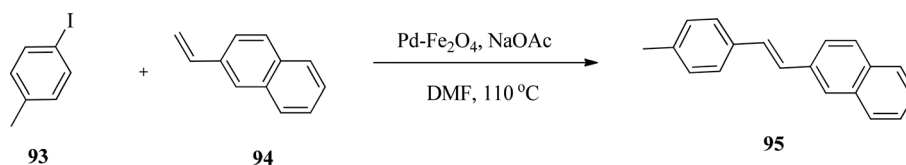
Scheme 27 Product yields for other Heck reactions in an ionic liquid microemulsion.



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



Scheme 29 Pd-Zn/Fe₃O₄ nanoparticle-catalysed Heck coupling reactions of aryl halides with alkenes under ligand-free conditions.



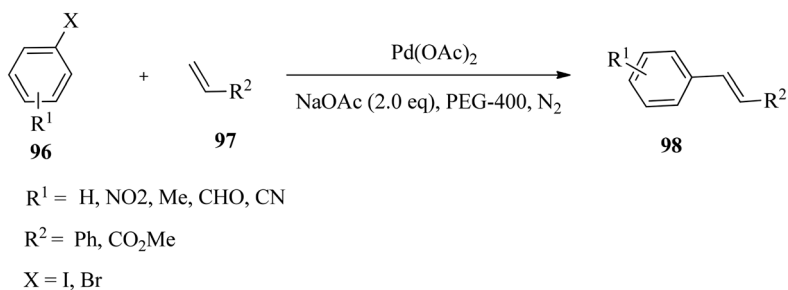
Scheme 30 Cross-coupling reactions using Pd-Fe₃O₄ nanocrystals.

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

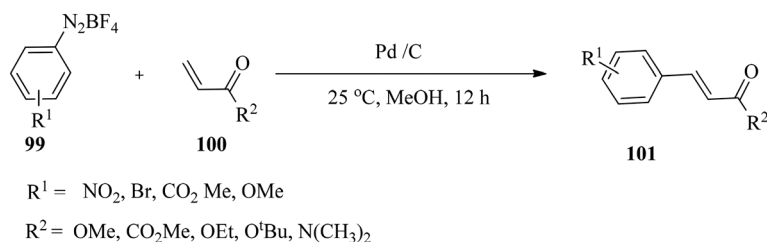
Hu and co-workers¹⁴¹ investigated the Pd(OAc)₂-catalysed cross-coupling of aryl sulfinic acid salts **104** with vinyl sub-

strates **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 SO₂ during the catalytic cycle. The mild reaction conditions combined with the widely available

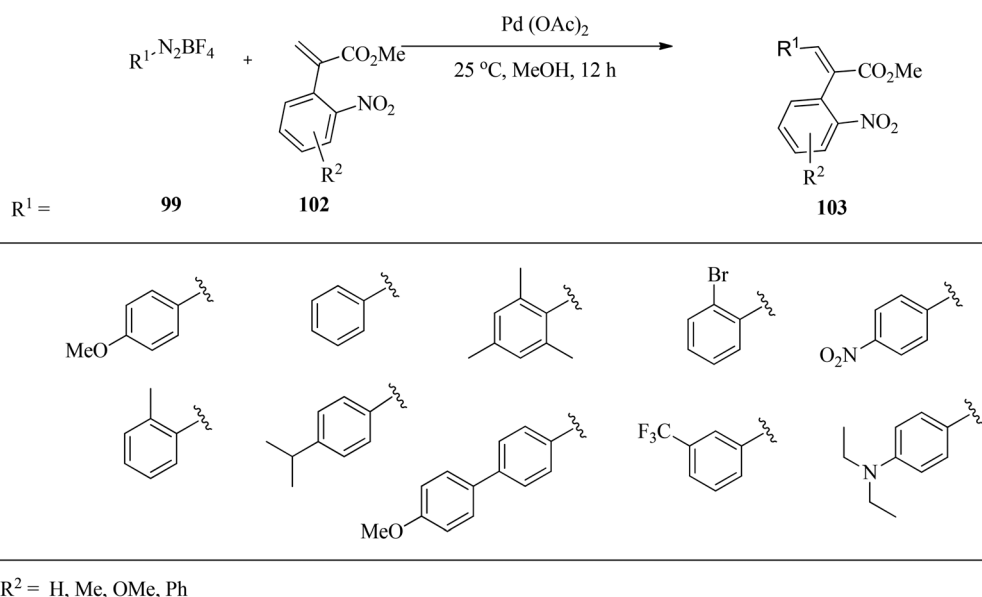




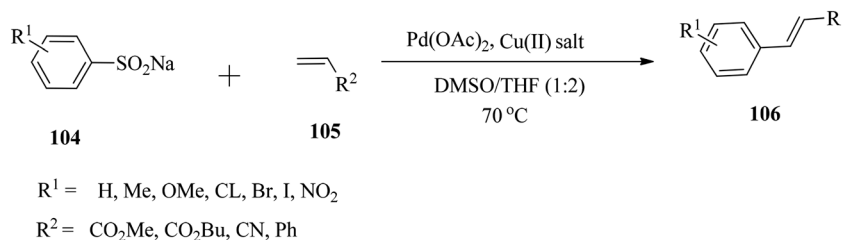
Scheme 31 PEG-400/ $\text{Pd}(\text{OAc})_2$ -catalysed Heck reaction of aryl halides with olefins.



Scheme 32 Heck reaction of aryldiazonium tetrafluoroborates with acrylates.



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



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.

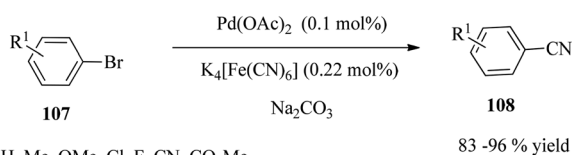
h. Ligand-free palladium-catalysed cyanation of aryl halides

Weissman and co-workers¹⁴² 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, M₄[Fe(CN)₆] (M = K or Na). A series of aryl halides were reacted under standard conditions (Scheme 35).

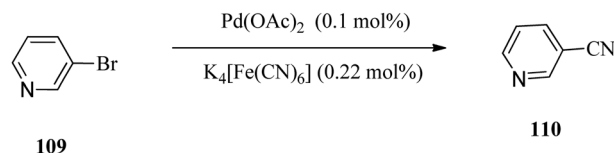
Rapid (≤ 5 h) and complete reactions were achieved for activated aryl bromides bearing electron-withdrawing groups. Moreover, electron-neutral systems and a mildly electron-rich arene, *p*-bromotoluene, were completely reacted within 5 h with assay yields $>90\%$. The cyanation of an *N*-heteroaryl bromide (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} polyethylene glycol,^{159,160} H₂O,^{161–164} or H₂O in



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



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

the presence of surfactants,^{165–167} have also been applied as reusable catalytic systems.

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

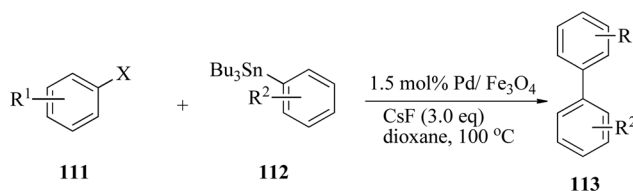
In 2012, Prasad and Satyanarayana¹⁶⁸ investigated the application of Fe₃O₄ supported Pd(0) nanoparticles (Pd/Fe₃O₄) for the Stille cross-coupling of aryl halides **111** with organotin compounds **112** under ligand-free conditions (Scheme 37). The best catalytic system for the cross-coupling was identified by screening the reaction with various bases in combination with different solvents.

CsF and dioxane proved to be the best system for Pd/Fe₃O₄. 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

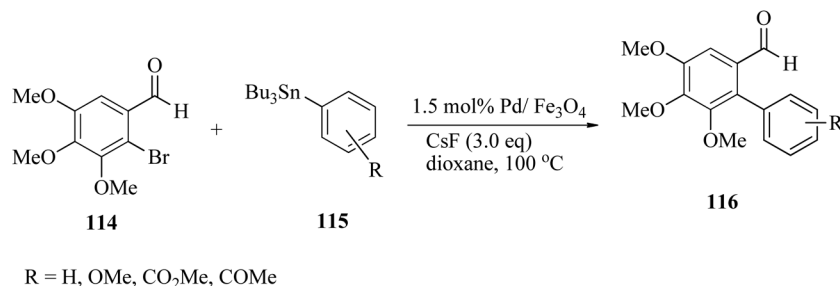
7. Ligand-free Negishi cross-coupling

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

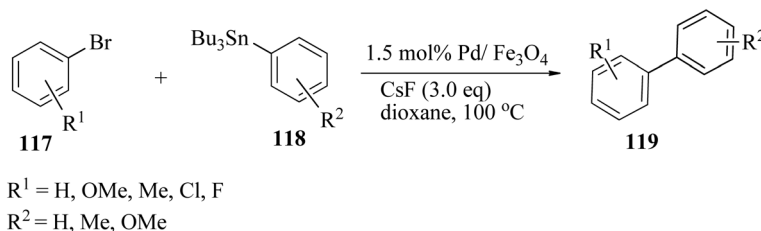


Scheme 37 Pd/Fe₃O₄ nanoparticle-catalyzed cross-coupling of aryl halides under ligand-free conditions.





Scheme 38 Fe₃O₄-Catalysed Stille cross-coupling of 2-bromo-3,4,5-trimethoxybenzaldehyde with different tributylarylstannanes.



Scheme 39 Pd/Fe₃O₄-catalysed Stille cross-coupling of different bromoarenes with different tributylarylstannanes.

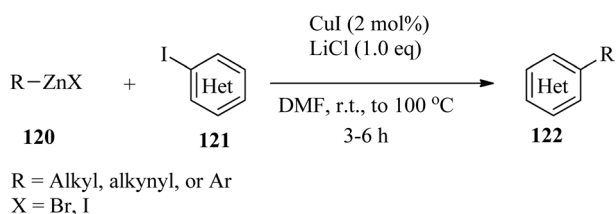
nickel catalysts. Inexpensive nickel has positively received the researcher's attention from the very beginning due to the high cost of palladium precursors. Recently, Negishi cross-coupling reactions employing ligand-free conditions have been adapted for greener and economical synthesis of various products.

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

Recently, Thapa *et al.* in 2015¹⁷³ 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-workers¹⁷⁴ 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 reac-



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

tion 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).

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.

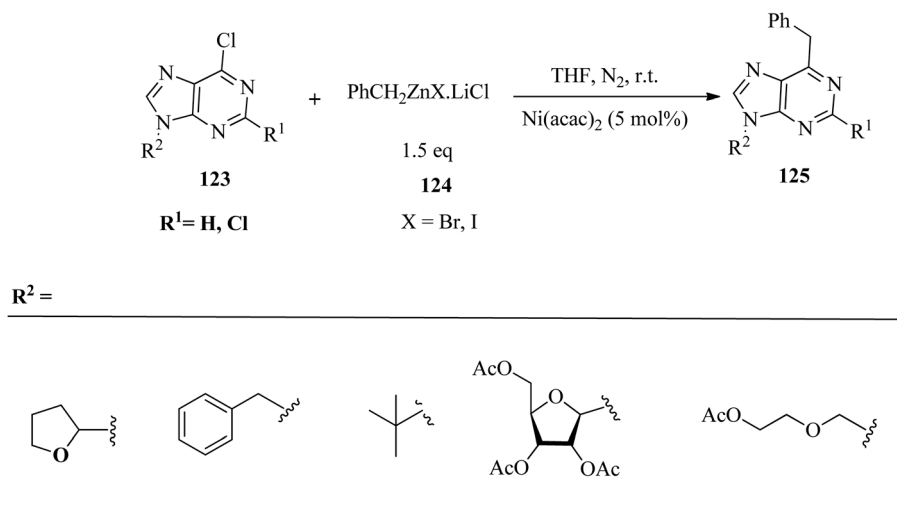
Other alkylzinc halides were also subjected to the reaction under the optimised conditions (Scheme 42). The primary alkylzinc halides 126, such as benzyl zinc, methylzinc, and pentylzinc, produced the corresponding products 127 in good to excellent yields. Cyclic alkyl zinc bromides, cyclopentylzinc 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).

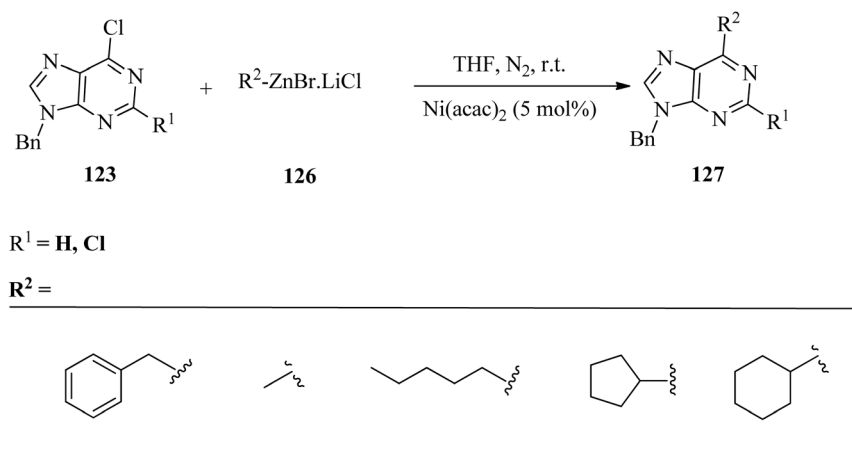
8. Mechanism of ligand-free cross-coupling

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

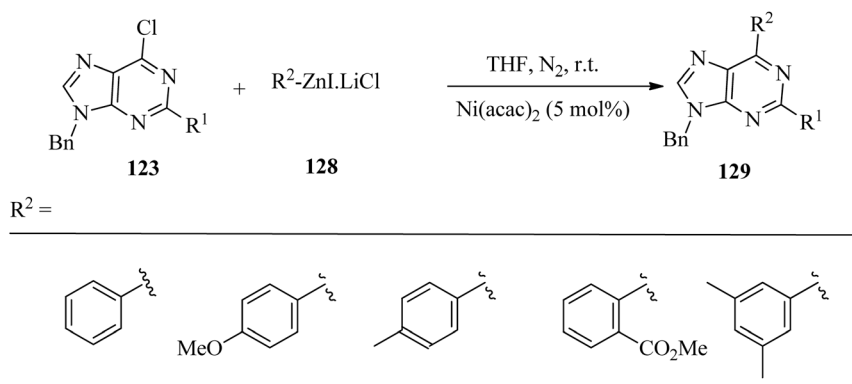




Scheme 41 The cross-coupling reaction of 6-chloropurines with benzyl zinc bromide.



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, $\text{Pd}(\text{OAc})_2/\text{DMG}$, $\text{Pd}(\text{OAc})_2/(\text{nBu})_4\text{N}^+\text{Cl}^-$ and $\text{Pd}(\text{OAc})_2$ 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.

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