

Prospects and Applications of Palladium Nanoparticles in the Cross-coupling of (hetero)aryl Halides and Related Analogues

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Discovering efficient methods for the formation of carbon-carbon bonds is a central ongoing theme in organic synthesis. Cross-coupling reactions catalysed by metal nanoparticles are attractive alternatives to the traditional use of metal counterparts due to the catalytic tunability, selectivity, recyclability and reusability of the nanoparticles. The ongoing search for sustainable processes demands that reusable and environmentally benign catalysts are used. While the advantages of nanoparticles catalysts over bulk catalysts cannot be over-

emphasised, the problem of sintering, agglomeration and leaching are drawbacks to their full industrial applications. Hence, efforts are being made towards advancing the efficiency of the catalytic nanoparticle systems over the years. This review presents the progress, the challenges and the prospects of palladium nanoparticle with focus on Heck, Suzuki, Hiyama and Sonogashira cross-coupling reactions involving (hetero) aryl halides and the analogues.


1. Introduction

The use of nanomaterials for solving critical issues in many scientific fields, including catalysis, has attracted the interest of various research groups.^[1] The large-scale applicability and the outstanding physical and chemical properties of nanomaterials have had a significant impact on recent efforts in the research and development of modern technologies.^[1b,2] It is well established that there are certain limitations to using solid-supported ligand-free metal catalysts in cross-coupling reactions despite their numerous advantages over homogeneous ligated catalysts such as metal leaching, lack of recyclability, product contamination, and recovery as well as economic and environmental issues.^[3] Consequently, the use of highly efficient, economical and recoverable catalysts, with low or null toxicity is essential from a green chemistry and sustainability perspective.^[3b,4] The synthesis of transition metal nanoparticles and their application in C–C bond formations has received considerable attention in the past few dates.^[1a,d,3a,5] Due to their high surface area, they often show remarkable catalytic performance and are considered to be on the borderline between the homogeneous and heterogeneous catalysts. However, in practice, their separation and recovery from the

reaction medium using standard techniques is cumbersome, and this hurdle has been overcome by stabilising metal nanoparticles over a variety of organic and inorganic supports. Several stabilising agents such as thiols,^[6] phosphines^[7] synthetic polymers^[8] and silica derivatives^[9] have been designed and described. Recently, magnetic nanoparticles have been widely applied as solid supports for the catalyst.^[10] Magnetic nanoparticle-supported catalysts can be simply and efficiently separated from the reaction system by a permanent external magnet, thus avoiding the complex operating process.^[11] Organic polymer-coated magnetic nanoparticles can be stabilised in reaction media to prevent nanoparticle aggregation. Moreover, it is easier to functionalise the polymers by introducing various kinds of ligands as well as immobilise the metal catalysts efficiently. Nevertheless, the prevention of sintering^[10b] of nanoparticle in the metal nanoparticle-catalysed reaction is paramount so that the nanoparticles retain their size, structure, and most importantly, their catalytic efficiency. The direct consequence of sintering might be particle growth and coalescence, shape deformation, and change in the composition of the active nanoparticles, which eventually results in altered activity or total deactivation of the nanocatalysts.^[12] However, Pd-leaching probably poses a more significant challenge in the practical application of immobilised palladium nanoparticles in catalysing C–C bond construction than sintering. This is because most recent cross-coupling reactions are conducted in relatively mild temperature conditions. Consequently, an appropriate selection of stabiliser is the most critical parameter for the design of metallic nanoparticles with minimal leaching or sintering effects.^[13] Over the last two decades, the attention of many research groups has been directed towards catalytic activation/functionalisation of aryl and heteroaryl halides using metal nanoparticles catalysis despite the tremendous success recorded in using ligand-supported palladium homogenous catalysts in the transformation due to its econo-

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my, environmental friendliness and industrial application.^[13a,14] This review provided an overview of the application of palladium nanoparticle catalysed cross-coupling over the past two decades with particular focus on Heck, Suzuki, Sonogashira, and Hiyama reactions.

2. Heck Cross-Coupling Reactions

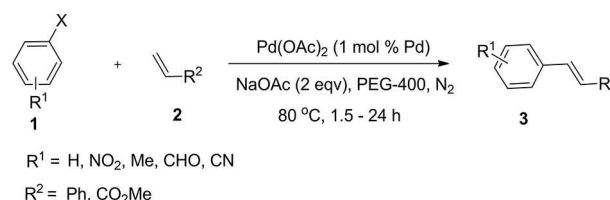
The Mizoroki-Heck reaction, independently discovered by Mizoroki and Heck in the early 1970s, is one of the most efficient methods for alkenylation of aryl, vinyl, and alkyl halides.^[15] It has been implicated in the synthesis of several drugs and intermediates such as naproxen (an anti-inflammatory agent),^[16] prosulfuron (herbicide),^[17] Singulair,^[18–19] Eletriptan,^[18,20,21] BVDU (antiviral),^[22] Axitinib (antitumour),^[23] 2-ethylhexyl-*p*-methoxycinnamate (UV sunscreen B agent),^[24] and comonomers of styrene polymers.^[9a] Due to the recyclability and reusability of catalytic nanoparticle systems; various supported catalytic systems are being developed for Heck reactions.

2.1. Heck Coupling Catalysed by Polymer Stabilised Pd Nanoparticles

Polymers have been widely utilised as a support/stabiliser for nanoparticles.^[11,5c] Their extensive application is attributed to their availability, enhanced stabilisation properties of metal nanoparticles and resistance to particle sintering/agglomeration. Jin and co-workers^[25] reported ligand-free Heck reaction catalysed by in situ generated Pd nanoparticles stabilised by PEG-400 (Figure 1).

The cross-couplings between aryl iodides (1) with electron-withdrawing groups or electron-donating groups and styrene or acrylic acid methyl ester (2) were achieved in good yields using a 1 mol% Pd loading of the catalyst in short times (Scheme 1).

In this reaction, the reactivity of styrene was faster than that of acrylic acid methyl ester when using the same aryl bromide;



Scheme 1. PEG-400/Pd(OAc)₂ catalysed Heck reaction of aryl halides with olefins

However, reaction failed for the reaction of 4-bromobenzaldehyde and acrylic acid methyl ester.

Recently, the use of novel engineered polymers such as polyorganophosphazenes with an inorganic backbone,^[26] polyvinyl pyridines,^[11,27] fibres^[11] and dendrimers^[1a,i,28] as supports has become increasingly popular. In a related development, palladium nanoparticles supported on triazine functionalised mesoporous covalent organic polymers (Pd@MCOP) was used as an effective catalyst for the cross-coupling reaction of various substituted aryl halides (4) with styrenes 5–6 and acrylate 7 respectively (Scheme 2).^[44] The catalyst was effective in cross-coupling aryl bromides containing electron-withdrawing and electron-donating groups aryl bromide as well as hindered substrate coupled readily with styrene to give excellent yields (86–98%).

Yang et al.^[11b] reported a novel heterogeneous Pd catalyst by attaching Pd(II) onto poly(undecylenic acid-co-*N*-isopropylacrylamide-co-potassium 4-acryloyloxylopyridine-2,6-dicarboxylate)-coated Fe₃O₄(Fe₃O₄@PUNP) magnetic microgel. The Fe₃O₄@PUNP–Pd catalyst was used for the cross-coupling reaction between substituted aryl halides (11) with acrylic acid (12) under argon atmosphere. It was found that only 0.1 mol% quantity of the catalyst was sufficient to attain 89–96% yield of the required cinnamic acid derivatives 13 (Scheme 3). Pleasingly, all the catalysts could be used for several cycles with negligible loss of their activities.



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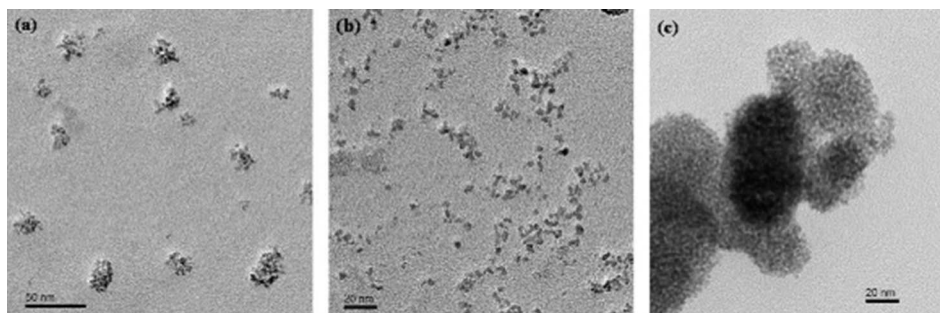
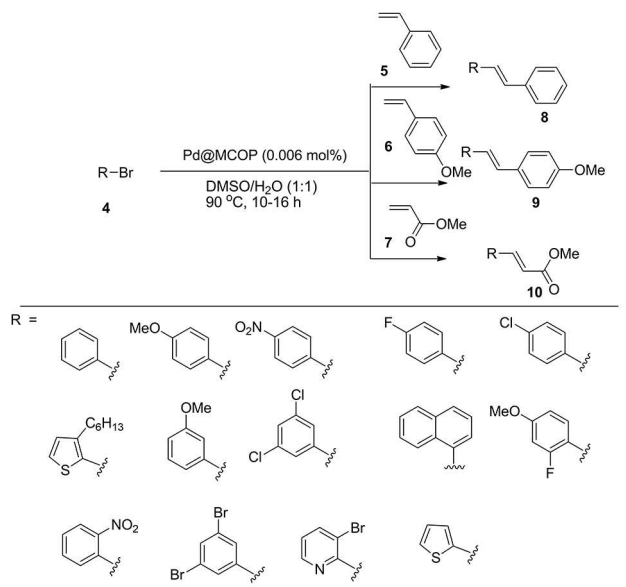


Figure 1. TEM micrographs of Pd nanoparticles (a) 30 min after the reaction, (b) 180 min after the reaction, (c) prepared Pd nanoparticles ($\text{Pd}(\text{OAc})_2$ 1 mol%) in PEG-400 at rt under N_2 . Adapted from Lui et al.^[25] with permission.



Scheme 2. Heck reaction of substituted aryl halides with styrenes and acrylate catalysed by Pd/MCOP.

2.2. Heck Coupling Catalysed by Pd Nanoparticles Supported on Biopolymers

Biopolymers and biomass-related polymers have been recently employed for the preparation of supported metal nanoparticles. Biopolymers have drawn attention for use as supports for catalytic applications due to their several advantages compared to traditional supports including low toxicity and cost as well as high biocompatibility, availability and abundance.^[1a] Keshipour and co-workers^[29] prepared palladium nanoparticles supported

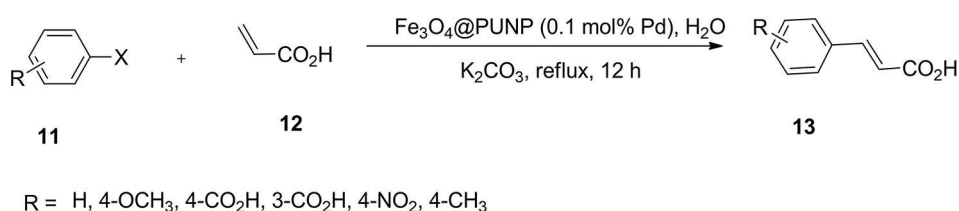
on ethylenediamine-functionalised cellulose as stabilising material (PdNPs@EDACs) for the Heck reaction of styrene (15) and methyl acrylate (18) with several halobenzenes (14 and 15) (Scheme 4). It was observed that NMP and H_2O were the best solvents but the water was used from the green chemistry perspective. By maintaining the temperature at $100\text{ }^\circ\text{C}$, the best-desired cross-coupled products (91–99% yield) were obtained with K_2CO_3 in the presence of the relatively higher catalyst loading (0.30 mol% of Pd(0)) in H_2O at a short time of 8 h.

These remarkable results were comparable to those obtained by Reddy et al.^[30] and Morres *et al.*^[31] using Pd impregnated on cellulose and nano-cellulose in an organic solvent and organic solution, respectively.

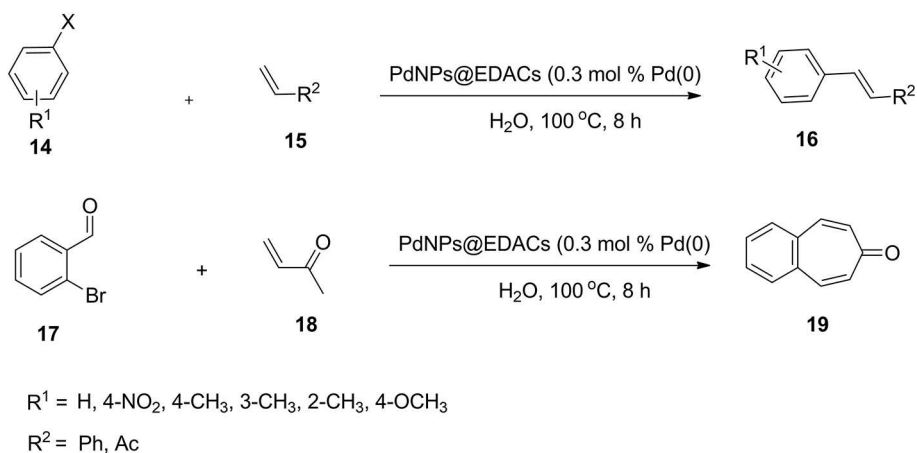
Green synthesis of palladium nanoparticles supported on pectin^[48] was explored in Heck reaction between activated and non-activated aryl halides (20) and *n*-butyl acrylate (21) under solvent-free conditions to obtain the products in good to excellent yields of 57–94% (Scheme 5). Interesting, the Pd_{np}/pectin catalyst was highly stable and insensitive to oxygen that the reaction did not require an inert atmosphere.

In 2015, Shen et al.^[23] reported a novel D-glucosamine-derived pyridyltriazole@palladium catalyst (Figure 2) for solvent-free Heck reactions between different aryl halides (23) and olefins (24) under solvent-free conditions (Scheme 6). Besides finding application in the facile synthesis of the marketed drug Axitinib, the catalyst can retain its activity for at least six times of separation and reuse.

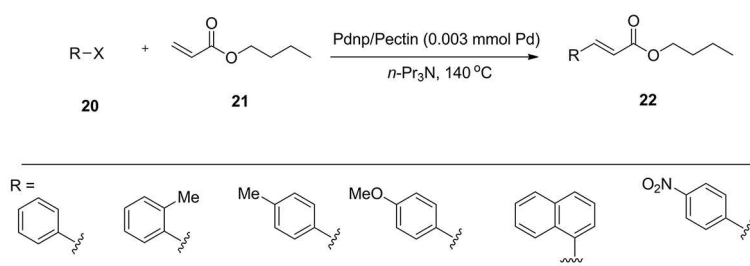
High interest in cyclodextrins in the present era reveals their extensive applications in organic synthesis and stabilization of transition metal nanoparticles for C–C bond formations.^[32,49–52] In this regard, Zhao and coworkers^[33] investigated β -cyclodextrin-capped palladium nanoparticle-catalyst, which provided



Scheme 3. Fe_3O_4 @PUNP–Pd-catalyzed Heck reaction of substituted aryl halides with acrylic acid in water under argon atmosphere.



Scheme 4. Heck reaction of styrene and methyl acrylate with halobenzenes catalysed by PdNPs@EDACs.



Scheme 5. Heck reaction of aryl halides with n-butyl acrylate catalysed by Pd_{np}/pectin.

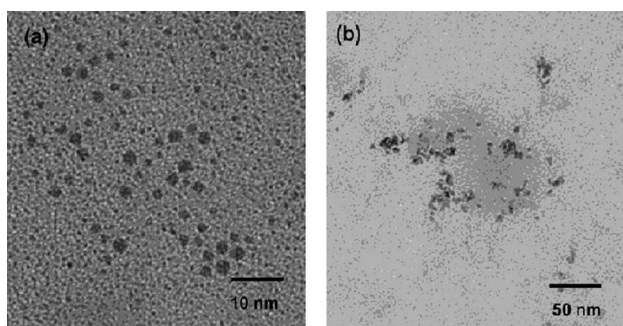
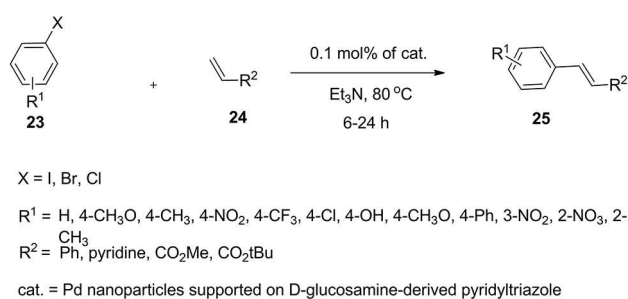
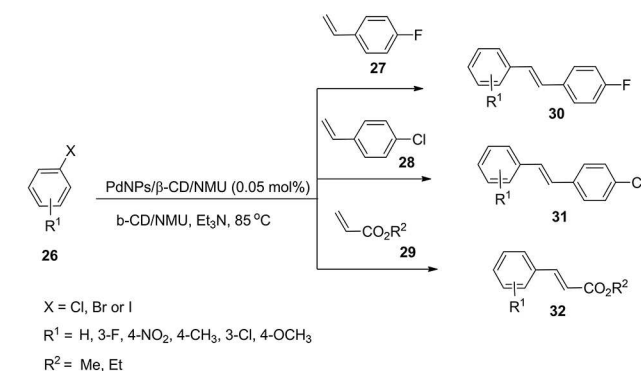


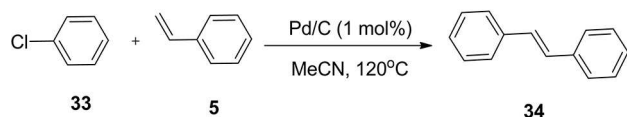
Figure 2. TEM images of (a) D-glucosamine-derived pyridyltriazole@palladium catalyst, and (b) recovered catalyst after the sixth run. Reproduced from Zhang et al.^[23] with permission from The Royal Society of Chemistry.



Scheme 6. Heck reaction of substituted aryl halides with olefins catalysed by D-glucosamine-derived pyridyltriazole@palladium catalyst.



Scheme 7. Heck reactions between substituted aryl halides with styrenes catalysed by PdNPs/β-CD/NMU.



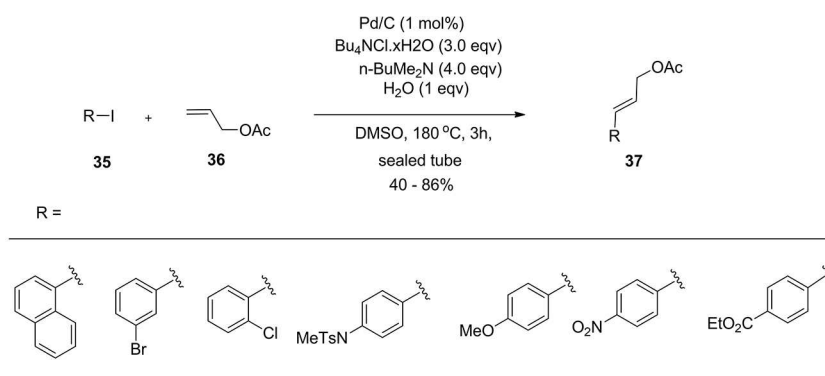
Scheme 8. Pd/C catalysed cross-coupling of chlorobenzene with styrene.

2.3. Heck Coupling Catalysed by Carbon-Supported Nanoparticles

Carbon materials present great merits as supports for the nanoparticle-catalysed cross-coupling. The contemporary advancement in this aspect has allowed the preparation of carbon nanostructures with well-defined porosities and high surface areas. Heck reaction catalysed by palladium supported on carbon was successfully used for the synthesis of stilbene^[34] (Scheme 8). Pleasingly, the relatively high yield of stilbene (34) obtained using autoclave was remarkable,^[34] coupled with high reusability of the catalyst without significant loss of the activity.

In a related study involving allyl acetates (36), Mariampillai et al.^[35] observed that Palladium on carbon gave increased reactant conversion with tetrabutylammonium chloride akin to a discovery made by Jeffery.^[36] The coupling of various aryl iodide partners (35) with allyl acetates (36) proceeded well to give the olefinic products (37) under low catalyst loading (Scheme 9).

Mechanistically, the authors posited that an initial oxidative insertion of palladium into the aryl halide 35 followed by carbopalladation of olefin 36 would give the intermediate that undergoes β -acetoxy elimination leading to the product 37.^[35] Whereas substrates bearing electron-withdrawing groups required a shorter reaction time, those with electron-donating substituents had extended reaction time, probably due to slower oxidative addition.^[37] This procedure gives rapid access to a range of both terminal and internal olefins, which can easily be further functionalized.



Scheme 9. Intramolecular Heck-type coupling of allyl acetate with various aryl iodides catalysed by Pd/C.

2.4. Heck Coupling Catalysed by Graphene Supported Pd Nanoparticles

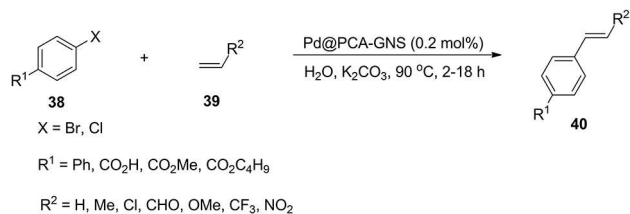
Sharavath and Ghosh^[38] made a novel contribution towards Heck cross-coupling reaction by employing palladium nanoparticles supported on noncovalently functionalised graphene using PCA–GNS–Pd. They coupled several aryl bromides and aryl chlorides (38) containing a wide range of functional groups with styrene and olefin 39 using water as the solvent and with low catalyst loadings (0.2 mol%) in pure water (Scheme 10). By optimising the coupling reaction between p-bromobenzaldehyde and styrene in the presence of TBAB as phase transfer catalyst (PTC), the coupling of various aryl halides (38) with styrenes and olefins 39 was achieved to obtain the coupled products 40 in good to excellent yields (41–92%). Good to excellent yields were afforded with different aryl chlorides having varied substituent groups. Aryl chlorides and bromides with hydrophilic substituents also produced higher yields, whereas chlorides with hydrophilic substituents gave excellent yields due to high solubility of substrates in water.

The incorporation of cyclodextrin (CD) molecules into graphene oxide (GO), before GO is fully reduced results CD–GNS hybrids exhibiting high dispersibility and stability in water, and do not aggregate for a long time.^[39] Because of these versatile properties, CD–GNS supported Pd NPs have been investigated as recyclable heterogeneous Pd catalysts in pure water (Figure 3).

In 2014, Ghosh et al.^[39] described the use of palladium nanoparticle- β -cyclodextrin-graphene nanosheet (Pd@CD–GNS) and used them for Heck reaction in water. The reaction gave 60–95% yield of the related products at 90°C in sodium carbonate, TBAB and 0.05 mol% catalytic mixture.

2.5. Heck Coupling Catalysed by Surfactant (TX-100) Stabilised Palladium Nanoparticles in Ionic Liquid

Research has shown that Imidazolium ionic liquid ([BMIM]PF₆) is an ideal medium for the preparation and stabilisation of transition metal nanoparticles. To illustrate of this property, Kuang and co-workers^[40] investigated the catalytic performance of the greener ionic liquid H₂O/TX-100/[BMIM]PF₆ microemul-



Scheme 10. Heck coupling of aryl halides with styrene catalysed by PCA-GNS-Pd.

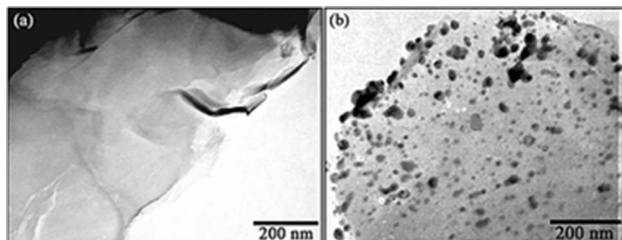
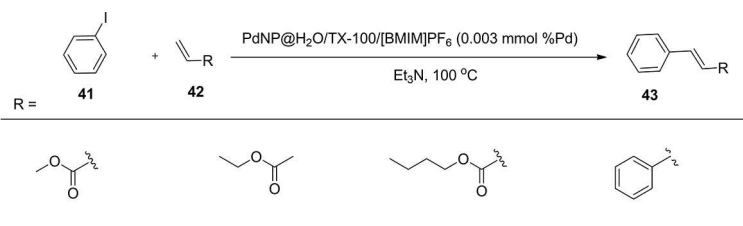


Figure 3. TEM images of CD-GNS (a), fresh Pd@CD-GNS (b), reused catalyst for Suzuki-Miyaura reaction (after 2 runs). Adapted from Ghosh et al.^[39] with permission from the Royal Society of Chemistry.

sion containing the Pd nanoparticles for the reaction of iodobenzene (41) with methyl acrylate, ethyl acrylate and styrene (42) (Scheme 11).

The nanoparticles were prepared by dissolving palladium chloride first in water before mixing with surfactant (TX-100) in the ionic liquid [BMIM]PF₆. On addition of the palladium chloride, reduction of the palladium chloride by the surfactant (TX-100) in the ionic liquid microemulsion occur rapidly *in situ* without any further reducing agents to produce the nanoparticles composite (Figure 4). Interestingly, the H₂O/TX-100/[BMIM]PF₆ microemulsion containing Pd nanoparticles was found to decrease the reaction time for the Heck reaction compared with the conventional solvent system and the catalytic activity of the Pd nanoparticles only decreased after the fourth cycle.^[40] Notably, compared with an organic liquid base (Et₃N), the catalytic activity of the system greatly decreased with the use of an inorganic solid base such as Na₃PO₄, NaOAc and Na₂CO₃. This is because inorganic solid bases destroy the stability of microemulsion and cause the agglomeration of Pd nanoparticles.^[40]



Scheme 11. Product yields for other Heck reactions of aryl iodide with alkenes in H₂O/TX-100/[BMIM]PF₆ microemulsion ionic liquid.

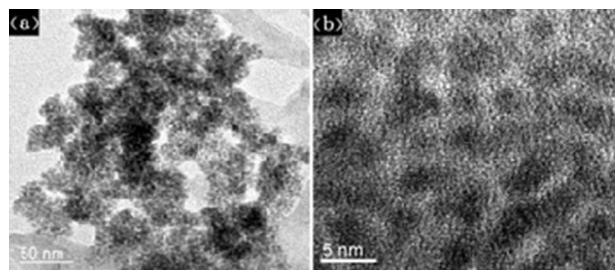
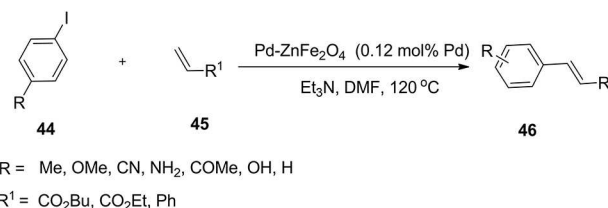


Figure 4. a) TEM image, b) HRTEM image of Pd nanoparticles separated from the [BMIM]PF₆ microemulsion. Adapted from Kuang et al.^[40] with permission from the Royal Society of Chemistry.



Scheme 12. Heck reaction of aryl halides with alkenes catalysed by Pd-Zn/Fe₃O₄ nanoparticle under the ligand-free condition.

2.6. Heck Coupling Catalyzed by Zn/Fe₃O₄ Supported Pd Nanoparticles

Nargakar and co-workers^[37] employed palladium supported on zinc ferrite nanoparticles for the Heck coupling reactions of aryl halides (44) with alkenes (45) under ligand-free condition (Scheme 12).

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 surface stabiliser or capping agent (Figure 5). The advantage of the protocol 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 a significant loss in its activity. The most appealing feature of the strategy is that the materials can be quickly recovered using a permanent magnet in the reactor and can be reused in up to 20 runs without a significant loss in catalytic activity.

In a related reaction, Kim and co-workers^[41] carried out the reaction using Pd-Fe₂O₄ heterodimeric nanocrystal catalytic system at a temperature of 110 °C within 24 h (Scheme 13). The

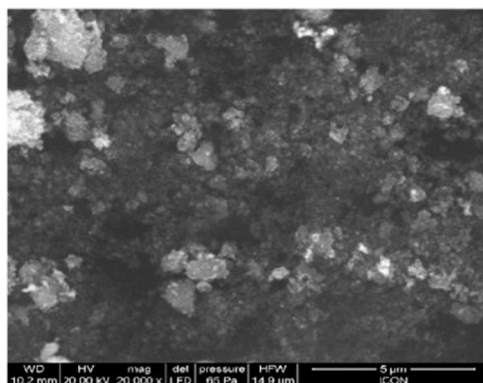
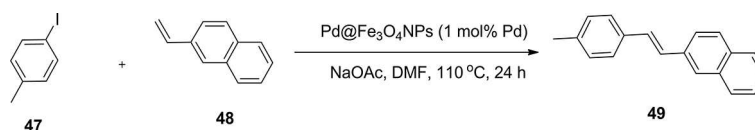


Figure 5. SEM image of Pd–ZnFe₂O₄ MNPs. Adapted from Nagarkaret et al^[37] with permission from the Science Direct.

catalytic system showed good yields (85–94%) of coupled products from the reactions with aryl iodides having electron-rich or electron-poor substituents, except for the case of electron-rich 1-iodonaphthalene that gave 46% yield. Besides, the reactions of styrene with aryl bromides (**47**) gave a very poor yield of a product as a result of the weak conversion of the starting material by the catalyst.

3. Suzuki-Miyaura Cross-Coupling Reactions

Suzuki cross-coupling reaction is one of the highly versatile and utilised reactions for the selective construction of carbon-carbon bonds.^[42] Suzuki reaction is a palladium or nickel-catalysed cross-coupling of an organoboron reagent and an organic halide or pseudohalide in the presence of a base.^[43–44] The success of this reaction can be associated with the generally mild reaction conditions required and the versatility of the boron species as organometallic partners.^[45] Compared to related C–C bond formations, the environmentally benign nature, high functional group tolerance, wide commercial availability of the reactants, and compatibility with aqueous conditions are expedient.^[46] Consequently, it is majorly used in the formation of biaryl compounds, substituted aromatic compounds and alkene derivatives which are structural components several natural products,^[47] nucleosides,^[48] agrochemicals, pharmaceuticals, and advanced materials.^[49] Quite many improvements have been made in recent years.^[1b,50] From a green chemistry perspective, metal nanoparticle catalysis immobilised on solid supports has been adapted for several Suzuki cross-coupling reactions.



Scheme 13. Heck reaction of aryl iodide with alkenes catalysed by Pd–Fe₃O₄ nanocrystals.

3.1. Suzuki-Miyaura Coupling Catalysed by Pd Nanoparticles Supported on MIL-101-NH₂

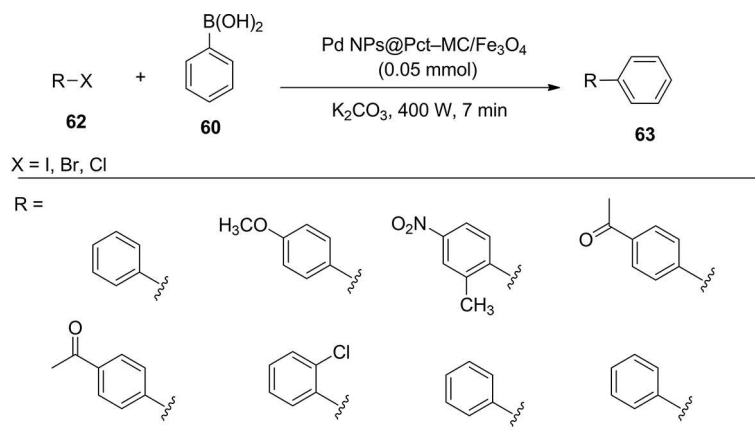
In 2015, Pascanu and co-workers^[51] successfully prepared a diverse set of heteroaromatic and highly functionalised biaryls through the Suzuki-Miyaura cross-coupling reaction catalysed by Pd nanoparticles supported in a functionalised mesoporous MOF (8 wt% Pd@MIL-101(Cr)-NH₂).^[52] They investigated the coupling of boronic acids or pinacolate esters with heteroaryl iodides (**51**) using K₂CO₃ as the base (2 eq) in a mixture of H₂O/EtOH (1:1) (Scheme 14). The majority of the functionalised (hetero)aromatic halides, including hindered aryl iodides, less reactive aryl bromides and lengthy substrate, reacted in excellent yields at mild temperatures (20 or 50 °C) and in short reaction times (0.5–4 h), leading to pharmaceutical relevant intermediate biaryl products despite the presence of one or several heteroatoms.

The coupling of 2-bromobenzonitrile (**53**) with *p*-tolyl boronic acid (**54**) occurred at ambient temperature in only 30 min to afford a quantitative yield of **55**, an intermediate used in the synthesis of the cardiovascular drug Valsartan (Scheme 15).^[53]

Superior results and better tolerance towards multiple co-ordinating heteroatoms were obtained when the heterocyclic moiety was located on the boron transmetallating partners. A large variety of exciting (hetero)aromatic or vinyl boronic acids of pyridines, indoles, furans and thiophenes (**56**) were coupled with aryl iodides and aryl bromides (**57**) and afforded biaryls **58** (Scheme 16).^[51]

3.2. Suzuki Coupling Catalyzed by GO/Fe₃O₄/PAMPS/Pd Nanoparticles

Metal oxides offer high thermal and chemical stabilities combined with a well-developed porous structure and high surface areas (> 100 m² g^{−1}), meeting the requirements for most applications.^[1a] They can also be easily prepared and further functionalised, adding value to their use as support or catalyst. Asadi and co-workers^[54] designed and prepared novel, and recyclable catalytic system based on palladium nanoparticles (Pd-NPs) immobilised onto the surface of graphene oxide (GO) modified by poly 2-acrylamido-2-methyl-1-propane sulfonic acid decorated with magnetic Fe₃O₄ (GO/Fe₃O₄/PAMPS/Pd). They modelled the reaction on bromotoluene and the best conversion of 4-bromotoluene to the corresponding biphenyl occurred with 0.4 mol% of catalyst in 2 h in a mixture of H₂O and EtOH as the solvent (Scheme 17).



Scheme 18. Suzuki-Miyaura reaction of halobenzene with phenylboronic acids catalysed by Pd NPs@Pct-MC/Fe₃O₄.

workup, high reaction yields, easy separability, and excellent reusability.^[57]

In another front, Nehlig and co-workers^[59] used highly efficient and retrievable immobilised Pd on magnetic nanoparticles bearing proline as a catalyst (Figure 6) for Suzuki-Miyaura catalyst in aqueous media (Scheme 19).

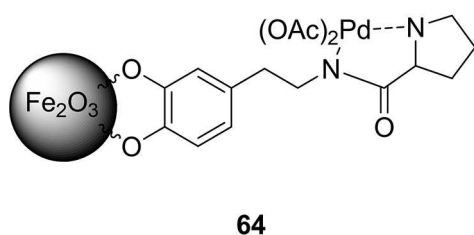
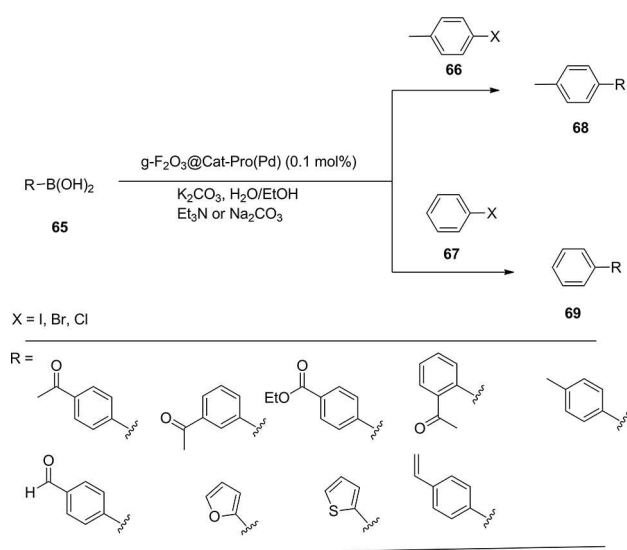


Figure 6. Structure of Pd on Fe₂O₃ nanoparticles bearing proline as a catalyst. Adapted from Nehlig et al.^[59] with permission from The Royal Society of Chemistry.



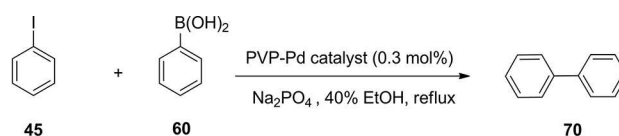
Scheme 19. Suzuki reaction of (hetero)aryl halides with phenylboronic acids catalysed by g-F₂O₃@Cat-Pro(Pd).

The optimised reaction conditions were applied in the cross-coupling of aryl halides with various boronic acids. The excellent catalyst yields and conversions were obtained with low Pd loadings (down to 0.01 mol% Pd), and the catalyst was stable up to 6 months in water under aerobic conditions and efficiency remained unaltered even after 7 repeated cycles.

3.3. Suzuki Coupling Catalyzed by PVP Stabilized Pd Nanoparticles

Li and co-workers^[60] applied palladium nanoparticles stabilised by poly(N-vinyl-2-pyrrolidone) (PVP) as an efficient catalyst for the Suzuki reactions of phenylboronic with iodobenzene in an aqueous medium to give the biaryl in 95% yield (Scheme 20).

It was observed that the Pd metal precipitated during the reaction, thus decreasing the catalytic during the reaction. Therefore, further improvements on the catalyst stability are necessary for practical applications. Narayanan and El-Sayed^[61] on an investigation of the effect of the catalysis and recycling on the stability and catalytic performance of the nanoparticles observed that refluxing the nanoparticles for 12 h during the reaction increases the average size and width of the distribution of the nanoparticles. This was linked to Ostwald ripening in which the small nanoparticles dissolve to form larger nanoparticles. However, the average size of the nanoparticles decreased in size when recycled for the second cycle (Figure 7). This could be due to the large nanoparticles aggregating and participating out of solution which explains the observed loss of the catalytic efficiency of the nanoparticles during the second cycle.



Scheme 20. Suzuki-Miyaura reaction of iodobenzene with phenylboronic acid catalysed by PVP-Pd Catalyst.

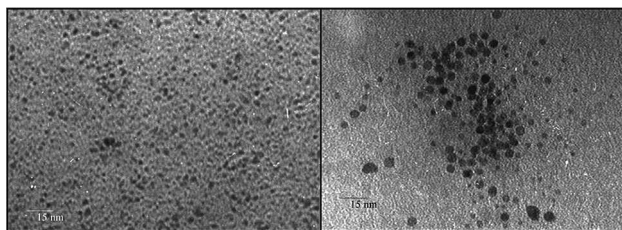


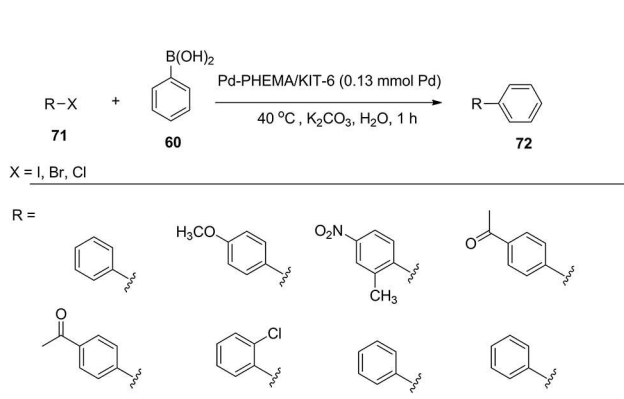
Figure 7. Left: nanoparticle size and distribution before catalysis; Right: nanoparticles size and distribution after the first cycle of catalysis. Reproduced from Narayanan and El-Sayed with permission.^[61] with permission from American Chemical Society.

3.4. Suzuki Coupling Catalyzed by PHEMA/KIT-6 Supported Pd Nanoparticles

Kalbasi and Mosaddegh^[62] investigated the Suzuki reactions of different aryl halides and phenylboronic acid with Pd nanoparticle-poly(2-hydroxyethyl methacrylate)/KIT-6 (Pd-PHEMA/KIT-6) composite as the catalyst (Scheme 21). The reaction condition was optimised with phenylboronic acid and aryl iodide with a satisfactory yield and was extended to other aryl halides.

They observed that the coupling reactions with aryl bromide and aryl chloride required a higher temperature (95 °C) to obtain excellent yields. However, it can be concluded that Pd-PHEMA/KIT-6 exhibits excellent catalytic activities for Suzuki-Miyaura cross-coupling reactions of aryl chloride, bromide and iodides in aqueous medium and under aerobic conditions.^[63] Notably, the catalyst was reused for nine cycles stability and no significant loss of activity/selectivity performance.

In a related development, Calo and co-workers^[64] explored Pd nanoparticles as efficient catalysts for Suzuki and reactions of aryl halides in ionic liquids. The optimised reaction was applied to the substituted chloroarenes to obtain unsymmetrical biphenyls. In this protocol, the ionic liquid, THeptAB is better stabilising agent than TBAB for Pd NPs because it consistently provided better yields of biaryls than TBAB irrespective of the electrophilic substrates used. While excellent yields of biaryls were obtained from the coupling of chloroben-



Scheme 21. Suzuki-Miyaura reaction of aromatic aryl halides and phenylboronic acid-catalysed by Pd-PHEMA/KIT-6.

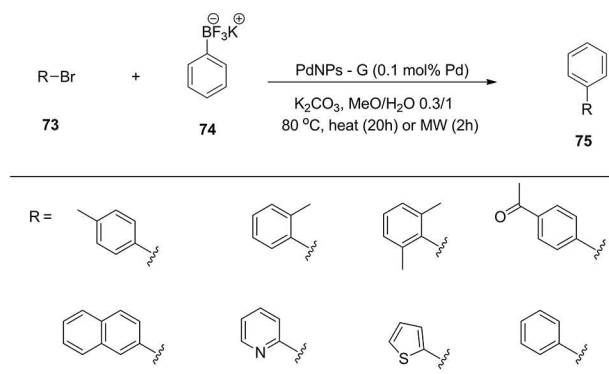
zene with phenylboronic acid, higher temperatures (at least 110 °C) were required in the case of deactivated electron-rich aryl chlorides. Recycling experiments, carried out on *p*-bromotoluene with Na₂CO₃ as a base, showed that the catalytic system could be reused for three runs with a slight decrease in product yields.

3.5. Suzuki Coupling Catalyzed by Graphene Supported Pd Nanoparticles

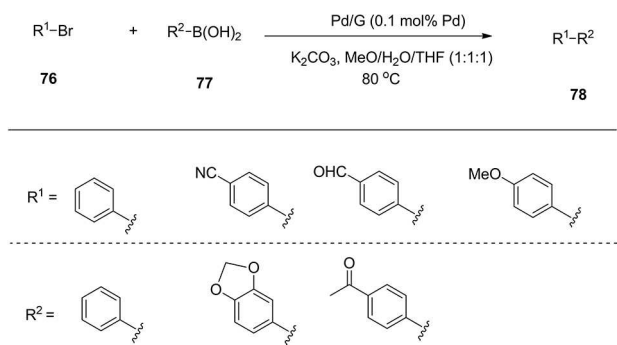
Many researchers have investigated the catalytic activity of the graphene-based nanocatalysts in Suzuki cross-coupling reaction. In 2018, Nasrollahzadeh and co-workers^[65] reported a comprehensive review graphene-based nanocatalysts in Suzuki cross-coupling reaction. García-Suárez et al^[66] efficiently used palladium nanoparticles supported on graphene platelets as a catalyst in the Suzuki-Miyaura coupling between aryl bromides and potassium aryltrifluoroborates using 0.1 mol% of Pd and potassium carbonate as a base in MeOH/H₂O as solvent at 80 °C by Gómez-Martínez and co-workers (Scheme 22). They modelled the reaction between 4-bromoanisole and potassium trifluoroborate to study the catalytic activity of the palladium supported catalysts.

Brinkley and co-workers developed the analogous reaction.^[67] The Pd/G prepared by this strategy was useful in Suzuki-Miyaura cross-coupling reactions with a broad range of substrates (Scheme 23). Reactions were carried out by combining an aryl halide (0.27 mmol), a substituted boronic acid (0.32 mmol), K₂CO₃ (0.9 mmol), and the Pd/G catalyst (2 mol%) in 4 ml of H₂O:EtOH (1:1) and microwave irradiation at 80 °C for 10 min. The carbon-based materials employed as active catalyst supports portray vast promise in organic reactions, which is linked to their structural resemblance with organics, large specific surface area, chemical stability, and photocatalytic properties.^[68]

In 2014, Sharavath and Ghosh^[38] made a novel contribution towards Suzuki cross-coupling reaction by using noncovalently functionalised graphene-supported palladium nanoparticles (PCA-GNS-Pd) (Scheme 24). The reaction between various aryl



Scheme 22. Suzuki reaction between aryl bromide and potassium phenyl trifluoroborate catalyzed by palladium nanoparticles supported on graphene platelets.

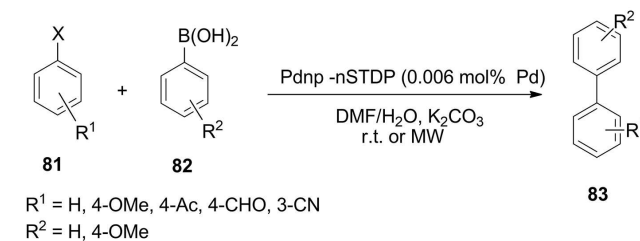


Scheme 23. Suzuki-Miyaura reaction of aromatic aryl halides and phenylboronic acid-catalysed by Pd/G.

halides with phenylboronic acids gave good to excellent yields of the coupled product (65–97%) by using 0.2 mol% PCA–GNS–Pd, Na_2CO_3 and H_2O . Notably, there were no apparent effects on yield when aryl bromides containing electron-donating or electron-withdrawing substituents were used. However, moderate to good yields were afforded when the reaction was carried out with electron-rich and electron-poor aryl chlorides as well as with the sterically hindered aryl halide substrates at longer reaction times. However, it was observed that Pd-reduced graphene oxide and Pd–GO nanocomposites have lower catalytic activity towards chloro- and bromo-arenes in water than the PCA–GNS–Pd nanocomposites.^[69]

3.6. Suzuki Coupling Catalyzed by Nano-Silica Triazine Dendritic Polymer (nSTDP) Supported Pd Nanoparticles

In 2013, Isfahani and co-workers^[70] developed a new thermally stable, oxygen insensitive, phosphine-free, air- and moisture-stable, and reusable palladium nanoparticles immobilised on nano-silica functionalised triazine dendritic polymer (Pd_{np} -nSTDP) catalyst and applied it for the Suzuki-Miyaura cross-coupling under conventional conditions and microwave irradiation. The catalytic system showed high activity in the Suzuki-Miyaura cross-coupling of aryl iodides, bromides and chlorides with aryl boronic acids (Scheme 25). These reactions were best



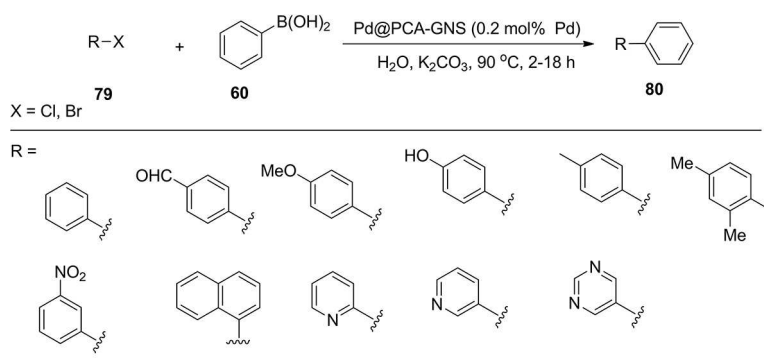
Scheme 25. Suzuki cross-coupling reaction of substituted aryl halides with different substituted phenylboronic acids catalysed by Pd_{np} -nSTDP.

performed in a DMF/water mixture (1:3) in the presence of only 0.006 mol% of the catalyst under prevailing conditions and microwave irradiation to afford the desired coupling products in high yields (80–96%). The Pd_{np} -nSTDP was also utilised as an active catalyst for making a series of a star- and banana-shaped molecule with a benzene, pyridine, pyrimidine or 1,3,5-triazine unit as the central core.

Further in 2014, they reported the preparation of a series of di- and trisulfides with benzene, pyridine, pyrimidine, or 1,3,5-triazine as the central cores by one-pot multi C–S cross-coupling reactions of aryl/heteroaryl halides with aromatic/heteroaromatic thiols in the presence of the Pd_{np} -nSTDP as the reusable catalyst under thermal conditions and microwave irradiation.^[71]

3.7. Suzuki Coupling Catalyzed by Bio-Supported Pd Nanoparticles

Sarkar and co-workers^[3b] prepared waste corn-cob cellulose supported poly(amidoxime) palladium nanoparticles (PdNs@PA) by the surface modification of waste corn-cob cellulose through graft co-polymerization and subsequent amidoximation.^[72] The supported nanoparticles showed high catalytic activity (45–400 mol ppm) towards Suzuki-Miyaura cross-coupling of aryl bromides/chlorides (84) with organoboronic acids (85) and (86) using 0.03 mol% of palladium at 80 °C to give the corresponding biaryl products 87 and 88 up to 99% yield with a high turnover number (TON) 19777 and turnover frequency (TOF) 4944 h^{-1} (Scheme 26). Moreover, the PdNs@PA was easily



Scheme 24. Suzuki-Miyaura coupling of aryl halides with phenylboronic acid by PCA–GNS–Pd.

recovered from the reaction mixture and reused several times without significant loss of its catalytic activity.

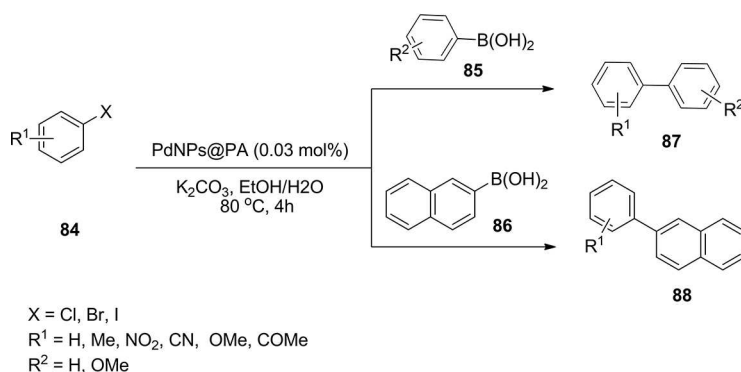
In a related development, Baran and co-workers^[73] designed a green chitosan/starch composite as support material for stabilisation of palladium nanoparticles. They employed it in the synthesis of a series of biphenyl compounds via Suzuki-Miyaura cross-coupling reactions with an unconventional technique. In 2019, Dhara and co-worker^[74] used glucose stabilised palladium nanoparticles (PdNPs) as a catalyst for Suzuki reactions of both electron-rich and electron-deficient aryl halides with a variety of boronic acids to access a wide variety of biaryl compounds and substituted alkenes in good to excellent yields. Contrarily, Baruah *et al*^[75] used nanoparticles supported on cellulose (Scheme 27). The catalyst can be recycled up to ten times without losing its activity significantly.

In another related research, Firouzabadi *et al*^[76] described a newly developed material composed of magnetic Fe₃O₄ nanoparticles modified with agarose-supported palladium nanoparticles (Pd@agarose-Fe₃O₄). They investigated the catalytic properties of Pd@agarose-Fe₃O₄ for Suzuki-Miyaura coupling reaction by modelling the reaction of 4-iodotoluene with phenylboronic acid in the presence of K₂CO₃ for cross-coupling of different aryl halides with organoboron boronates and boronic acids to obtain the coupled product in 67–97% yield.^[76] While it took half of 30 min to record >90% yields of biaryl with aryl iodide substrates, 24 h was needed to obtain biphenyls from both activated and deactivated aryl chloride with lower yields.

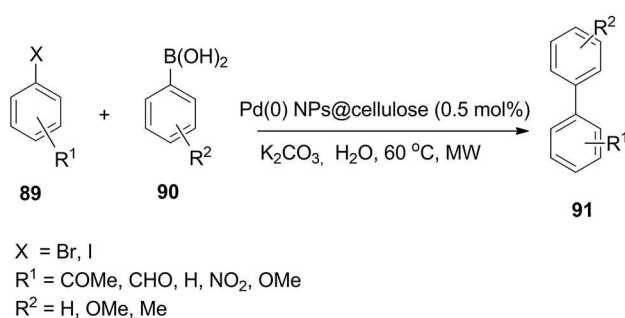
3.8. Suzuki Coupling Catalyzed by Pd Bimetallic Nanoparticles

Several reports have demonstrated the application of two nanoparticulate palladium-based catalysts in cross-coupling including Suzuki reaction.^[77] Kim and co-workers^[78] explored the application of carbon-supported bimetallic Pd–M (M=Ag, Ni, and Cu) nanoparticles made by γ -irradiation in Suzuki cross-coupling. They applied it for cross-coupling of an organohalide (92) with phenylboronic acid (60) in ethanol (Scheme 28).

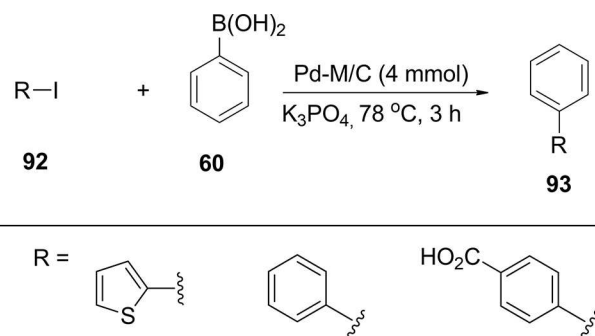
Applying the yield of the reaction to determine catalytic efficiency, it was observed that the carbon-supported Pd–Cu bimetallic system was the most efficient.



Scheme 26. Suzuki reaction of substituted aryl halides with aryl boronic acids catalysed by PdNPs@PA.



Scheme 27. Suzuki reaction of substituted aromatic aryl halides with phenylboronic acids catalysed by glucose stabilised palladium nanoparticles.



Scheme 28. The Suzuki reaction of (hetero)aryl halides with phenylboronic acid catalysed by Pd–Cu bimetallic system supported on carbon.

In another study, Singh and coworkers^[79] prepared Bimetallic Ni–Pd alloy nanoparticles (99:1 or 95:5 Ni to Pd atomic ratios) and explored it for Suzuki C–C coupling reactions under moderate reaction conditions. Expectedly, significantly enhanced catalytic activity was achieved with the studied Ni–Pd nanoparticle catalysts for the C–C coupling reactions and products were obtained in moderate to high yields.

4. Hiyama Cross-Coupling Reactions

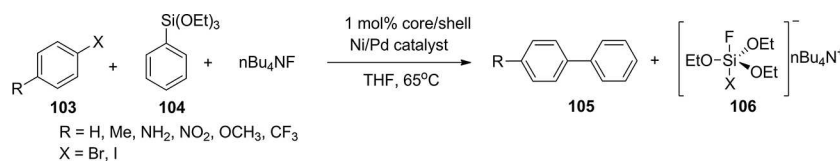
Hiyama cross-coupling reactions have emerged as possible substitutes to the Suzuki-Miyaura cross-couplings.^[80–82] It is a

4.3. Hiyama Coupling Catalysed by Pd Bimetallic Nanoparticles

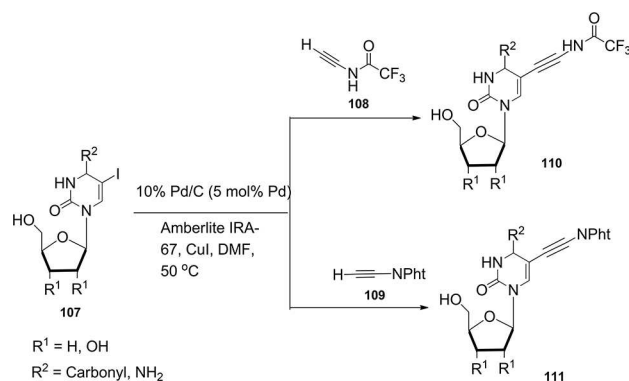
As alloys or core-shell states, bimetallic nanocatalysts are proven to show superior catalytic performance compared to that of its monometallic analogous for many catalytic reactions.^[98] The enriched catalytic performance of bimetallic systems is attributed to the favourable synergistic interactions between the metals, for which strong metal-metal interactions presumably tune the bonding pattern of the reactants and stabilise the vital reaction intermediates on the catalyst surface.^[98a,b] These distinctive features are principally due to their composition and structure, causing specific electronic effects and in particular singular catalytic behaviour, which is distinguished by the synergy between both metals.^[99] Rothenberg and co-workers^[100] reported the application of stable and highly mono-dispersed core-shell bimetallic Ni–Pd nanoparticles in the cross-coupling reaction of different haloaryl (**103**) and phenylmethoxysilane (**104**) (Scheme 32). With a variety of iodo- and bromoaryl, good product yields were obtained; thus acting as a good source of biaryl-containing compounds which are vital intermediates for preparing biologically active molecules, organic semiconductors and liquid crystals.^[101] Further study of the catalytic activity of Ni/Pd core/shell cluster *vis-a-vis* Ni(OAc)₂, Ni(0) clusters, Pd(OAc)₂, Pd (0) cluster, Ni(0)/Pd(0) alloyed cluster in the Hiyama cross-coupling revealed that the activity of the nanoparticle palladium could be increased by combining it with non-reactive metal like Nickel in the following order Pd (0) cluster < alloy Ni–Pd clusters < core-shell Ni–Pd clusters. The substrate scope of the catalyst was not expanded to involve aryl chlorides probably because of the inactivity of the catalyst to convert the substrates.

5. Sonogashira Cross-Coupling Reactions

Sonogashira cross-coupling is the formation of carbon-carbon bonds by cross-coupling of terminal alkynes with aryl halides or vinyl halides.^[15b,102–103] Sonogashira reaction has been applied in the synthesis of alkyne-containing aromatic compounds,^[104–105] natural products,^[106–107] medicinal products,^[108–109] oligomers,^[110–111] and polymers.^[112] The air sensitivity of copper co-catalyst which results in oxidative homocoupling of acetylenes to give diacetylenes as potentially explosive copper acetylides is the major setback of the reaction.^[103] Difficult removal of high boiling point solvents from the reaction mixture increases cost due to low homogeneous Pd catalyst reusability^[113] as well as product contamination by toxic Pd



Scheme 32. Bimetallic Ni–Pd nanoparticles Hiyama cross-coupling reaction of phenyl(triethoxy)silane with various haloaryls catalysed by Ni/Pd core/shell cluster.



Scheme 33. Solid-supported Sonogashira coupling of deoxynucleoside derivatives mediated by Pd/C/Amberlite IRA-67.^[131]

metal during the reaction.^[114–115] However, recent improvements have been made.^[113,116–117] including the development of supported Pd for heterogeneous catalysis which simplifies separation and recyclability of the catalyst. Several catalysts support such as perovskites,^[118] carbon,^[119–120] zeolites,^[121] hydrotalcite,^[121] silica,^[122] celluloses,^[30] and polymers^[123] 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 reducing catalyst leaching is a significant consideration.^[124,125] To date, most of the supported catalysts developed still have ample room for further improvement.^[126] From the green chemistry point of view, using recyclable supported catalysts in aqueous media is desirable.

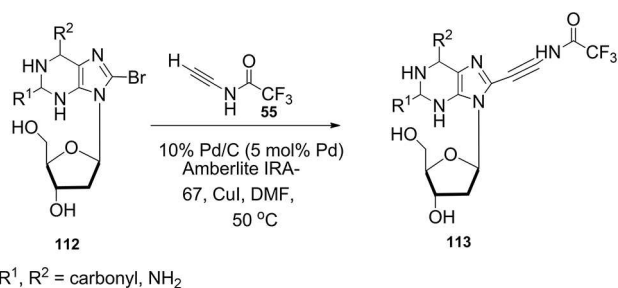
5.1. Sonogashira Coupling Catalysed by Carbon-Supported Pd Nanoparticles

The application of Pd on carbon was also exploited by Stoltz and co-workers.^[127] They explored the Pd/C and Amberlite IRA-67-mediated ligand-free Sonogashira coupling of several deoxynucleoside derivatives **107** with trifluoroacetyl (**108**) and phthalimido reagents **109**. They modelled the strategy employed by the Kotschy and co-workers^[128] replacing the Pd/C for Pd(PPh₃)₄, lowering the catalyst loading to 5% and carrying out the reaction at 50 °C to afford deoxyuridine, uridine, dideoxyuridine and deoxycytidine derivatives **110–111** (Scheme 33). The dideoxyuridine derivatives are particularly crucial as a critical intermediate in the synthesis of conventional Sanger DNA sequencing reagents.^[129] On the other hand, nucleic acids are

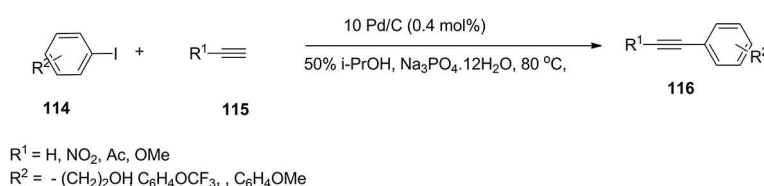
advantageous biomaterials because they are non-toxic, environmentally friendly, readily available and biodegradable; that is why the successful preparation of bio-nano particles such as DNA-NPs has recently emerged.^[130]

The condition was extended to the synthesis of 2-deoxyadenosine and 2-deoxyguanosine derivatives **112** (Scheme 34). Although the coupling of 8-bromo-2-deoxyadenosine and 8-bromo-2-deoxyguanosine derivatives was sluggish under Pd/C-catalysis, the use of Pd(PPh₃)₄/Amberlite IRA-67 system gave good to excellent yields of cross-coupled products **113**.

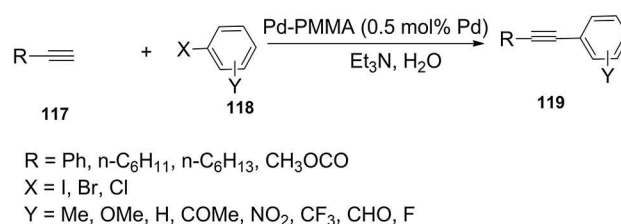
Sajiki and co-workers^[132] reported the cross-coupling of a variety of aryl iodides (**114**) with aromatic and aliphatic terminal alkynes (**115**) to give the corresponding 1,2-disubstituted aromatic alkynes (**116**) in good yields by using only 0.4 mol% of the heterogeneous 10% Pd/C as the catalyst (Scheme 35). They explored the scope and limitations of the substrates under the optimised reaction conditions (10% Pd/C and Na₃PO₄·12H₂O (2.0 eq) in 50% iPrOH at 80 °C). Iodobenzene and the aryl iodides containing an electron-withdrawing group on 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 the wet-type Pd/C to catalysis of Sonogashira coupling reaction, and the reaction proceeded efficiently under argon and aerobic conditions.



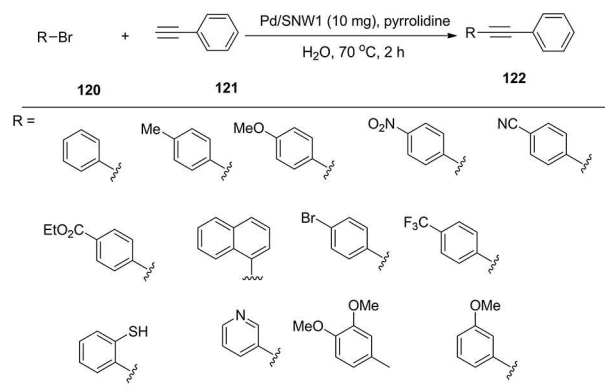
Scheme 34. Solid-supported Sonogashira coupling of deoxynucleoside derivatives mediated by Pd/C/Amberlite IRA-67.^[131]



Scheme 35. Copper-, ligand-, and amine-free Sonogashira coupling reactions of various substituted aryl iodides with aliphatic and aromatic terminal alkynes catalysed by Pd/C.



Scheme 36. Sonogashira cross-coupling of aryl halides with phenylacetylenes catalysed by Pd(0)/PMMA in water.



Scheme 37. Cross-coupling of different substituted aryl halides with phenylacetylenes catalysed by Pd/SNW1 in water.

5.2. Sonogashira Coupling Catalysed by Polymer-Supported Nanoparticles

Zang and co-workers in 2012^[126] employed Pd(0) loaded polymethyl methacrylate (PMMA) microspheres for Sonogashira cross-coupling of a variety of terminal acetylenes (**117**) with different phenyl iodides, bromides and chlorides (**118**) in aqueous media (Scheme 36). The coupling of phenyl iodides with electron-donating or electron-withdrawing groups proceeded readily with phenylacetylene in excellent product yields.

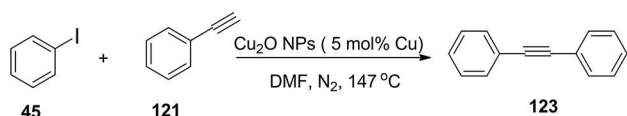
In a related development, Shunmughanathan *et al.*^[133] developed melamine-based microporous network polymer-supported palladium nanoparticles (Pd/SNW1) as a stable and efficient catalyst for the Sonogashira coupling reaction in water (Scheme 37). Preliminary studies were performed using iodobenzene and phenylacetylene as model substrates in the presence of catalysts under various conditions to optimise the reaction yield. The optimised reaction condition was applied in

the coupling of bromobenzene with phenylacetylene to afford various phenylethynyl benzene in good yields.

5.3. Sonogashira Coupling Catalysed by Copper Clusters or Pd Nanoparticles

Rothenberg and co-workers^[134] first reported substituted diphenylalkynes prepared in good isolated yield and high selectivity for Palladium-free and ligand-free Sonogashira cross-coupling of phenylacetylene (121) with various aryl halide (45) under stable Copper cluster catalysis (Scheme 38). Phenylacetylene and aryl halide (1.5:1 eq) were reacted in the presence of the base and the metal clusters at 110 °C. The stable copper cluster was prepared by reducing solutions of the chloride salt precursor with tetraoctylammonium formate (TOAF) in DMF at 65 °C. In this reaction, the nature of the base is critical to obtaining a high yield of the product. TBAA is more effective than TBAF, Et₃N and NaOAc providing 100% conversion.

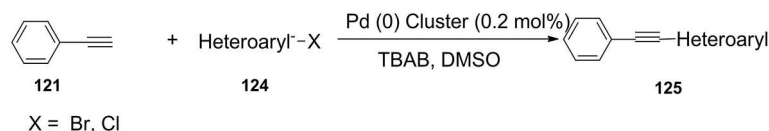
In a related reaction, Wei and co-workers^[135] applied an in situ generated palladium nanoparticles catalyst supported on Al(OH)₃ for the Sonogashira cross-coupling reactions of (hetero) aryl bromides and chlorides. The optimised reaction conditions were harnessed in cross-coupling of various (hetero)aryl halides (45) bearing neutral, electron-withdrawing or electron-donating substituents on the phenyl ring with phenylacetylene (120)



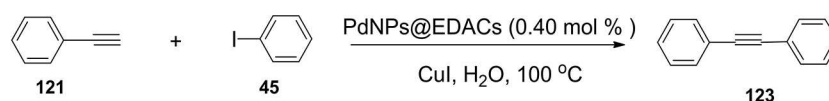
Scheme 38. Cu₂O catalyse cross-coupling of phenylacetylene and iodobenzene.



Scheme 39. Cross-coupling of substituted aryl halides with phenylacetylene catalysed by Pd nanoparticles supported on Al(OH)₃.



Scheme 40. Pd(0)/Al(OH)₃ cross-coupling of (hetero)aryl acetylenes with bromobenzene.



Scheme 41. Sonogashira reaction of iodobenzene with phenylacetylene catalysed by PdNPs@EDACs.

bearing electron-donating and electron-withdrawing groups in the benzene ring to afford the 1,3-diyne products 123 in good to excellent yield (Scheme 39).

Heteroaryl bromides derived from pyridines, thiophenes, quinolines, and pyrimidines (124) were converted to the corresponding cross-coupled products 125 in modest to high yields (Scheme 40). In this reaction, DMSO was the best form of solvent than DMF and H₂O. Also, K₂CO₃, K₃PO₄, KOAc provided lesser yield than NaOAc in the reactions while KOH gave no yield at all.

In another development, Turimala and co-workers^[136] investigated the Sonogashira-type cross-coupling reaction between phenylacetylene and iodobenzene in DMF solvent and K₂CO₃ as a base using Cu₂O nanoparticles (NPs). The Cu₂O nanoparticles (NPs), prepared by a microemulsion synthesis method, successfully catalyse C–C coupling reactions. The catalytic protocol is under ligandless and base-free conditions and it was suggested to follow a truly heterogeneous pathway.

5.4. Sonogashira Cross-Coupling Catalysed by EDACs Supported Nanoparticles

Shaabani et al^[29] synthesized and characterized Pd nanoparticles supported on ethylenediamine-functionalized cellulose as an efficient novel bio-supported heterogeneous catalyst for the Heck and Sonogashira couplings in H₂O at 100 °C. The catalytic activity of PdNPs@EDACs for the Sonogashira coupling reaction was assessed with halobenzene (45) and phenylacetylene (120) in the presence of CuI (Scheme 41). At first, the influence of the solvent, the temperature, amount of catalyst and different kinds of bases on the reaction was studied. The

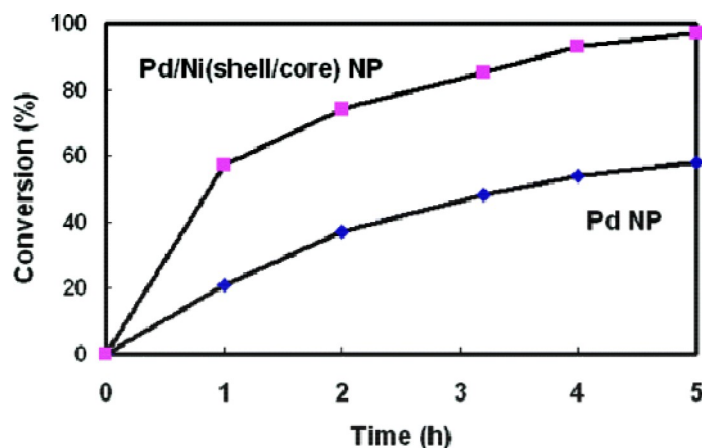


Figure 8. Comparison of Pd/Ni catalytic activity with similarly sized Pd nanoparticles. Reproduced from Hyeon et al.^[139] with permission from the American Chemical Society.

optimal results were obtained in the presence of 0.40 mol% of catalyst and 100 mol% of K_2CO_3 in H_2O after 7 h.

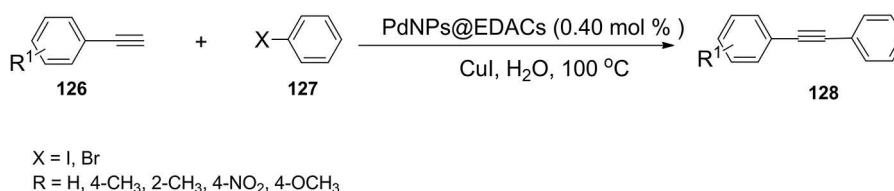
The optimal reaction condition was applied for the coupling of various electron-neutral, electron-rich, or electron-poor aryl halides (**127**) reacted with phenylacetylene (**126**) to generate the corresponding cross-coupling products **128** (Scheme 42). Pleasingly, the catalyst could be easily recovered by simple filtration and reused for at least 4 cycles without losing its activity.

5.5. Sonogashira Coupling Catalysed by Pd Bimetallic Nanoparticles

Increasing interest has been focused recently on bimetallic nanoparticles due to their unique physicochemical properties compared to their corresponding monometallic counterparts. These distinctive features are principally due to their composition and structure, causing specific electronic effects and in particular singular catalytic behaviour, which is distinguished by the synergy between both metals.^[99] A wide variety of Pd bimetallic nanoparticles have been reported and used for Sonogashira and other named-cross-coupling reactions because of their unique advantages over a monometallic one such as catalytic control, selectivity, stability and synergistic effects.^[99d,137] After the pioneering work of Silvert et al. in 1996 on the synthesis of PdAg nanoalloys by polyol methodology using EG as a solvent,^[138] several contributions of palladium bimetallic nanoparticles (BMNPs) have been described in the

literature, mostly involving noble metals, such as gold, platinum and ruthenium, but also BMNPs, including first-row transition metals such as iron, cobalt, nickel, and copper.^[99d] Hyeon and coworker^[139] synthesised Pd–Ni bimetallic nanoparticles with a Ni-rich core and Pd-rich shell structure from thermal decomposition of palladium and nickel salts at a temperature of 205 °C and found out that the catalytic activity of Pd/Ni showed much better catalytic activity than similarly sized Pd nanoparticles (Figure 8). The nanoparticle catalyst was active for bromoaryl but conspicuously showed no activity for chloroaryl.

The catalyst was recycled and reused for at least five times without losing its catalytic activity. It was noted solvent polarity and concentration of the stabilisers are important factors in optimising the stability and activity of nanoparticle clusters; and that the deposition of the Pd shells on Ni cores is driven by variation standard potentials which allowed Ni(0) to reduce Pd(II) to Pd(0).^[100] Similarly, Evangelistic and co-workers^[140] reported a poly-4-vinyl pyridine-supported bimetallic Cu/Pd nanoparticles ($d_m = 2.5$ nm) synthesised by metal vapour synthesis (MVS) technique and supported on poly-4-vinyl pyridine (PVPy) resin that showed significantly higher catalytic activity in Sonogashira-type cross-coupling reactions compared to the related monometallic Cu and Pd systems. While Pd/Ni nanoparticle catalysts provided a synergistic catalytic effect, Gadi and co-workers^[140] observed metal nanocluster prepared by reduction of bimetallic Cu/Pd with tetrabutylammonium acetate (TBAA) in DMF at 65 °C were less active than either monometallic Pd or Cu nanoparticle catalysts in Sonogashira cross-coupling of aryl halides. While in the presence of 5 mol% of Cu



Scheme 42. Cross-coupling of different substituted aryl halides with phenylacetylene catalysed by PdNPs@EDACs.

cluster variety of aryl iodides gave quantitative yields of coupled products, aryl bromides supplied good to moderate yields and no conversion of chloroarenes.

6. Reactions Mechanism

The precise mechanism for metal nanoparticle C–C cross-coupling of aryl halides is controversial as a result of the various hypothesis that been postulated.^[1c,141] It was posited that palladium nanoparticles on a solid support are a reservoir from which active palladium atoms are leached out to involve in the catalytic cycle; and after that, regenerated Pd(0) is redeposited into the palladium cluster.^[1d,142] This is called dissolution-redeposition theory. Whether the mechanism for the nanoparticles cross-coupling reaction is to be regarded as homogeneous or heterogenous has also been debated. However, in 2011 study by Perez-Lorenzo proposes both mechanisms for palladium nanoparticle catalysed Suzuki reactions may be regarded as mutually complementary and depended on the mobilisation degree of the nanoparticles (Figure 9).^[143]

In heterogeneous nanoparticle catalysis, the catalytic transformation (oxidative addition to reductive elimination) of substrates (aryl halides) take place in the surface of the palladium cluster. In another way, the mechanism may become homogenous if the leached out active palladium atoms initiate and complete the catalytic transformation of the substrate in the solution. These heterogeneous and homogenous mechanisms are generally followed by other named palladium nanoparticle catalysed cross-coupling reaction, e.g Heck, Sonogashira, Hiyama etc. Eight years after Prez-Lorenzo study on homogenous/heterogeneous nature of the mechanism of Pd catalysed C–C bond formation, an interfacial surface-enhanced Raman spectroscopic study of the same mechanism unveiled clear evidence of only heterogeneous catalysis which occurs by direct contact of aryl halides with the Pd metallic surface.^[144] Furthermore, increasing the electrical attraction between the nanoparticle surface and the substrate molecules enhanced the turnover frequency (TOF) of the catalyst. Conversely, the inactivity of soluble Pd species that leached out of the cluster

into the solution suggests the exclusion of homogeneous catalysis. Detailed discussion on the status of the mechanism of palladium nanoparticles C–C cross-coupling reaction can be found in the reviews by Knight et al and Friedrich et al.^[1c,145]

7. Conclusions and Outlook

Pd nanoparticles have higher surface to volume ratios than the analogous bulk catalysts. This relatively increased surface area leads to a higher proportion of active surface atoms and, ultimately, to enhanced catalytic performance. The tunability, recyclability and environmentally benign nature of immobilised nanoparticles on solid supports and the ones suspended in colloidal solutions account for their wide acceptability as a heterogeneous and homogeneous catalyst in varieties of named-cross-coupling reactions, unlike the bulk catalyst. However, the major setbacks to the efficient usability catalysing electron-rich and sterically encumbered substrates are rooted in their often agglomeration and leaching. Therefore, a variety of supports and capping agents have been investigated to circumvent these undesirable effects.^[13b] Besides, catalysts involving two (bimetallic) and multimetallic have been introduced because they provide catalytic synergism, selectivity and thermal stability. Though the reviewed articles are limited to Heck, Suzuki, Hiyama and Sonogashira, the observations from applications of palladium nanoparticles to other named cross-coupling reaction are similar to the ones discussed. For example, several bioactive compounds such as allocolchicines, stegnacine and eupomatilones have been prepared from 2-bromo-3,4,5-trimethoxy benzaldehyde^[146] using of Fe₃O₄ supported Pd(0) nanoparticles (Pd/Fe₃O₄) by Stille cross-coupling. The scope of the catalytic strength excluded the unreactive aryl chloride substrate. The efficient adaptability of nanoparticles for the catalytic transformation of aryl halide substrates is still far from being accomplished, particularly, the inefficiency of the catalyst for activation of aryl chlorides like homogeneous bulk Pd(0) complexes containing electron-rich bulky ligands such as phosphine. Hence, the main concern in nanoparticles catalysis is still finding a catalytic system to effectively activate C–Cl and

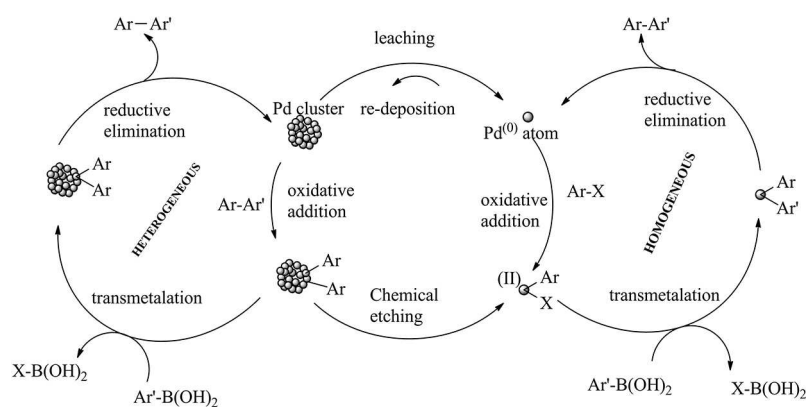


Figure 9. The proposed mechanism for nanoparticles cross-coupling reaction of aryl halides. Adapted from Perez-Lorenzo et al.^[143] with permissions from American Chemical Society.

the development of reusable catalyst with minimal or no loss of activity of variety.

List of Abbreviations

BVDU	bromovinyldeoxyuridine
PEG	polyethylene glycol
MCOP	mesoporous covalent organic polymers
PUNP	poly(undecylenic acid-co-N-isopropylacrylamide-co-potassium 4-acryloxyopyridine-2,6-dicarboxylate)
EDACs	ethylenediamine-functionalised cellulose
NMU	β -cyclodextrin/N-methyl urea
BMIM	1-Butyl-3-methylimidazolium Hexafluorophosphate Microemulsions
PCA	1-pyrene carboxylic acid
CD-GNS	β -cyclodextrin-graphene nanosheet
PAMPS	poly 2-acrylamido-2-methyl-1-propane sulfonic acid
Pct-CMC	pectin-carboxymethyl cellulose
PVP	poly(N-vinyl-2-pyrrolidone)
PHEMA	poly(2-hydroxyethyl methacrylate)
nSTDP	Nano-Silica Triazine Dendritic Polymer
PEMMA	polymethyl methacrylate
Pin	pinacolate
PVPy	poly-4-vinyl pyridine
TOF	turn over frequency
TBAA	tetra-n-butylammonium acetate
TBAF	tetra-n-butylammonium fluoride

Conflict of Interest

The authors declare no conflict of interest.

Keywords: nanoparticles · cross-coupling reactions · Suzuki-Miyaura cross-coupling · Heck reaction · supported catalysts

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