

REVIEW ARTICLE

Recent Advances in the Application of Heterogeneous Nanocatalysts for Sonogashira Coupling Reactions

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Abstract: Sonogashira coupling reactions demonstrates an efficient and facile methodology for C(sp)-C(sp²) bond formations *via* transition-metal-catalyzed processes and have found applications in a wide variety of areas including medicinal chemistry, agrochemistry, materials, electronics and synthesis of natural products, biologically active molecules, heterocycles, dendrimers and conjugated polymers or nanostructures. In recent years, nanosized heterogeneous catalysts have been widely studied for the above reactions due to thermal stability, reusability and high catalytic activities. In this review, we present an introduction to the subject of carbon-carbon bond formations and recent efforts in the preparation and application of heterogeneous nanocatalysts for Sonogashira coupling reactions. The scope, limitations, and green aspects of the reactions, convenient methods of preparation of heterogeneous nanocatalysts and their characterization have also been highlighted. These include metal nanoparticles, nanoclusters and nanocrystals, bimetallic, trimetallic and core-shell nanoparticles, polymer-supported metal nanoparticles, carbon- or graphene-supported metal/metal oxide nanohybrids and metal-organic frameworks Pd catalysts. Numerous examples demonstrated the use of effective supports such as silica, SBA-15, MCM-41, BaO, Smopex[®], ZnO, celluloses, montmorillonite, Al₂O₃, chitosan and natural biomaterials in Sonogashira coupling reactions.

This work is dedicated to the 45 years of frankly attempts of Professor Ali Akbar Entezami to the education and development of chemistry in Iran.

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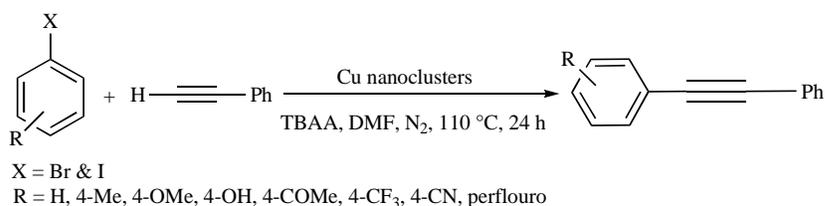
Keywords: Sonogashira coupling reaction, vinyl halides, phosphine ligands.

1. INTRODUCTION

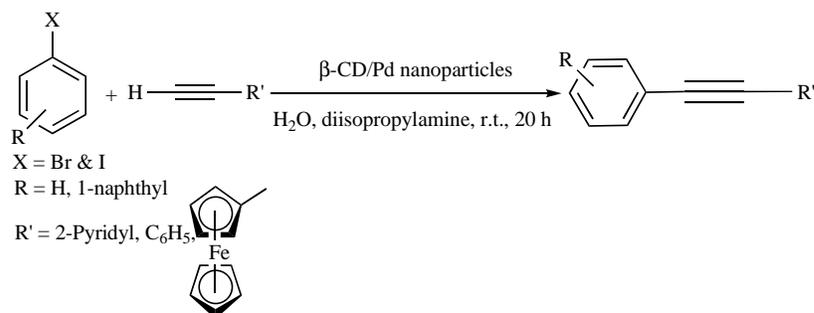
The Sonogashira coupling reaction of terminal alkynes with aryl or vinyl halides is one of the most important, powerful and versatile methods for the formation of C(sp)-C(sp²) bonds introduced by Sonogashira *et al.* in 1975 and has been widely applied in wide fields of science and technology such as heterocycles synthesis, natural products, biologically active molecules, pharmaceuticals and material science [1-6]. Traditionally, the Sonogashira reaction is carried out using a homogeneous palladium catalyst, in conjunction with CuX (X = Cl, Br, I) as a co-catalyst in the presence of toxic phosphine ligands and stoichiometric amount of base in organic solvents such as an amine, benzene, THF or DMF under the inert conditions, which were economically and environmentally malignant. However, most of these methods suffer from certain disadvantages such as employing expensive and air or moisture sensitive phosphine ligands, harsh reaction conditions, inert atmosphere conditions, low yields, long reaction times, environmental pollution caused by formation of diyne side products *via* Glaser-type oxidative dimerization of in situ generated copper acetylide,

tedious work-up, use of non-green solvents and homogeneous catalysts that restrict their usage in practical applications. The problem with homogeneous catalysts is the difficulty to separate the catalyst after the completion of the reaction and impossibility to reuse it in consecutive reactions. Therefore, attempts to finding the useful heterogeneous catalysts for the ligand-, copper- and amine-free Sonogashira reactions is still being continued to remove the drawbacks of its traditional conditions to use the homogeneous catalytic systems [7-11]. In order to avoid these drawbacks, several heterogeneous catalytic systems have also been reported in recent decade. There are several mechanisms for the Sonogashira coupling reaction between aryl halides and terminal alkynes under different conditions [11]. To date, several mechanisms including Pd-free, Cu-free, amine-free, ligand-free and solvent-free conditions and also variations of the ligands, solvents and bases with a view to improve the coupling reactions as more efficiently have been reported [11]. However, the exact mechanism of the Sonogashira coupling reaction is not well understood yet and therefore it still has been remained a topic of debate [11]. In this review and in the course of our researches on the coupling reactions using various catalysts [12-20], the recent progresses for improvement and optimizing the Sonogashira coupling reactions using heterogeneous nanocatalysts such as Pd NPs, metallic and trimetallic NPs, Pd/Fe₃O₄ NPs, Ag NPs, Au NPs, Ru NPs and Cu NPs as efficient and recyclable cata-

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Scheme 1.



Scheme 2.

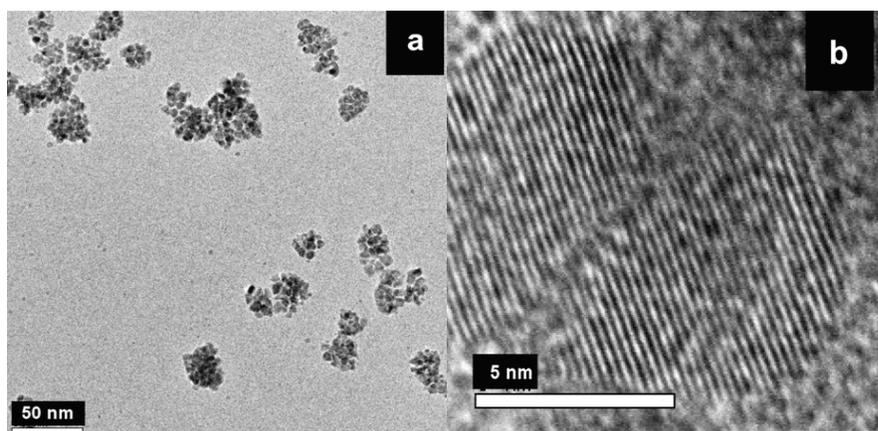


Fig. (1). (a) TEM and (b) HRTEM image of palladium nanoclusters. Reprinted from ref. 24 with permission. Copyright (2008) Sciencedirect.

lytic systems impregnated on the extended range of new generation supports are consciously investigated.

2. THE VARIOUS CATALYTIC SYSTEMS FOR SONOGASHIRA COUPLING REACTIONS

2.1. Metal Nanoparticles, Nanoclusters and Nanocrystals

There are many reports in the field of metal nanoparticles (NPs), nanoclusters and nanocrystals (NCs) that used as effective catalysts for the formation C-C bond *via* Sonogashira coupling reactions.

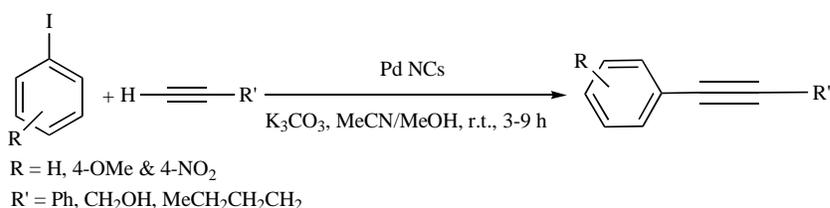
Rothenberg *et al.* reported Cu nanoclusters catalyzed the Sonogashira coupling reactions of aryl halides with phenylacetylene in the presence of tetra-*n*-butylammonium acetate (TBAACl) under ligand- and palladium-free reaction conditions (Scheme 1) [21]. After the completion of the reaction, Cu nanoclusters can be recycled up to three cycles without any loss of activity to give a final turnover number of 73.

The synthesis of TBAB stabilized Pd NPs using counter ions in Sonogashira coupling reaction was investigated by Rothenberg *et al.* [22]. According to their study the activity of ions ordered as NO₃⁻ > Cl⁻ > OAc⁻ that introduce a mechanism in which Pd atoms at the rim of the cluster are involved in an oxidative addition with ArBr and

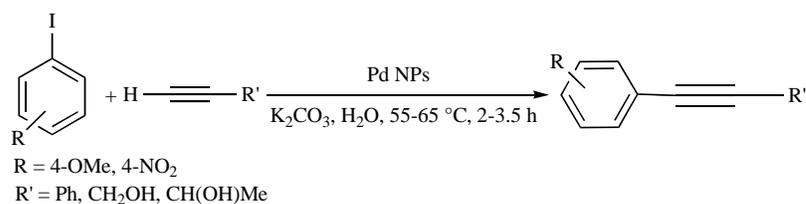
then the soluble species of [PdBr(X)(Ar)(L)]⁻ is separated from the cluster which caused the end of the catalytic cycle of Sonogashira reaction catalyzed by Pd atoms leached from the cluster.

In 2007, Liu and co-workers efficiently developed catalyzed phosphine-free Sonogashira reaction co-catalyzed with CuI in aqueous solution at room temperature through host-guest recognized catalytic process with receptor-modified β cyclodextrin-capped PdNPs (β-CD/Pd) (Scheme 2) [23]. Results showed that the yield of aryl iodides in Sonogashira reaction was better than those reported for the corresponding aryl bromides under the same conditions. Eliminating the organic solvent in the Sonogashira reaction represents a significant advancement in the development of a greener process.

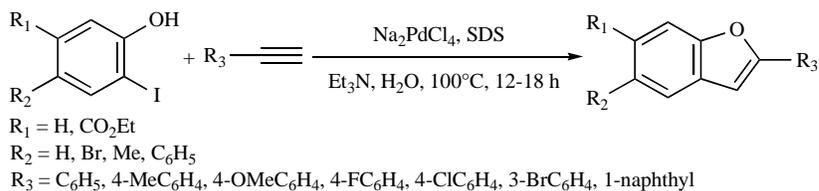
In 2008, Chand *et al.* reported the formation of Pd nanoclusters using a simple method in a 1:1 mixture solvent system of MeCN-MeOH without stabilizer [24]. This catalytic system was applied in the copper-, amine- and ligand-free Sonogashira reactions at open air. However this catalytic system only works for aryl iodides (Scheme 3). TEM and HRTEM image of obtained palladium nanoclusters product are shown in Figure 1. The obtained catalyst at the end of the reaction was recovered and reused for Sonogashira coupling without loss of its activity.



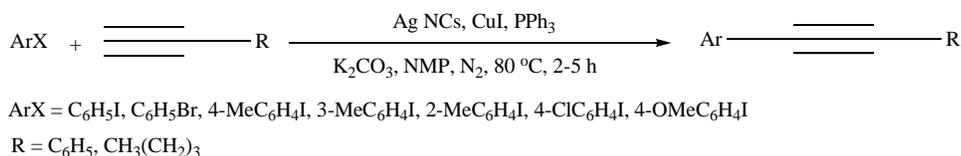
Scheme 3.



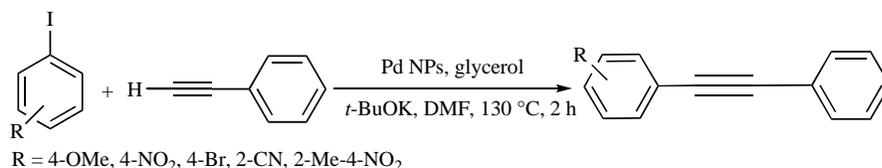
Scheme 4.



Scheme 5.



Scheme 6.



Scheme 7.

In 2009, Sarkar *et al.* synthesized catalytically active Pd NPs in water by a novel reduction of Pd(II) with a Fischer carbene complex using polyethylene glycol (PEG) that act as stabilizer and control size of the generated nanoparticles [25]. This system also well performed in the copper-, amine- and phosphine-free Sonogashira reaction between different aryl halides and alkynes (Scheme 4). Although the reaction proceeded well with aryl iodides, no coupling product was observed with activated bromides even at elevated temperatures under a wide range of conditions.

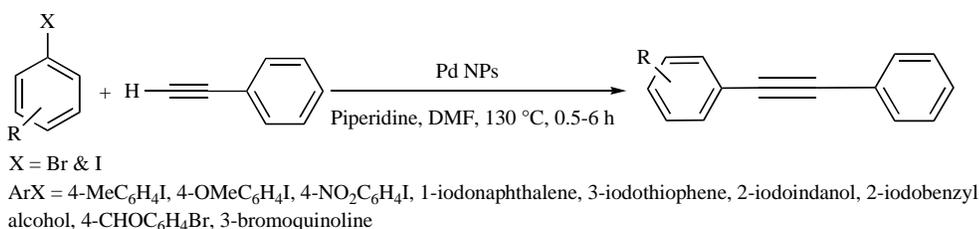
In the same year, Malta and co-workers discovered an efficient methodology for the synthesis of palladium NPs in water from 2-hydroxypropyl- α -cyclodextrin, which acts as both a reductant and stabilizing agent [26]. The Pd NPs catalyst could be used in the Suzuki, Heck and Sonogashira reactions in which various products synthesized in a good yield in aqueous media. The catalyst can be easily recovered and reused four times.

Recently, Ranu *et al.* reported the synthesis of 2-substituted benzo[b]furan derivatives from the reaction of 2-iodophenols with arylacetylenes in water catalyzed by *in situ* generated palladium NPs under aerobic conditions in the absence of ligand or copper co-catalyst (Scheme 5) [27]. The products were obtained in high yields

by this method. The prepared NPs in the presence of amine, which probably acts as stabilizer agent, recycled up to 4 times.

In 2012, Bao and co-workers synthesized Ag nanocrystals (NCs) at gram-scale by thermal reduction of solid AgNO₃ with dodecylamine in 1-octadecene as solvent. This new product can catalyze a series of the Sonogashira reactions in high yield (Scheme 6) [28]. They found that in the presence of PPh₃, CuI and K₂CO₃ both aryl iodides and bromides can react with aromatic or aliphatic terminal alkynes to give the corresponding cross-coupling products with high yields at 80 °C for less than 5 h. However, this method is not applicable for aryl chlorides. Also, the Ag NCs can be recycled and reused three times without loss of catalytic properties.

In 2014, for the first time, Gómez and co-workers prepared Pd NPs in glycerol in the presence of tris(3-sulfophenyl)phosphine trisodium salt (TPPTS) as stabilizer. These nanoparticles dispersed in glycerol were efficiently used in C-X (X = C, N, P, S) bond formation processes and C-C multiple bond hydrogenation reactions [29]. The catalyst was active for the Sonogashira coupling reaction between iodoaryl substrates and phenylacetylene on which the products were obtained in a high yield (Scheme 7). This catalytic system could be recycled more than ten times without loss of activity or selectivity.



Scheme 8.

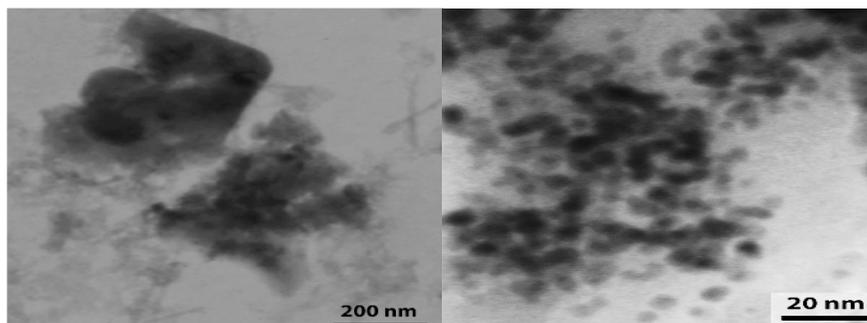
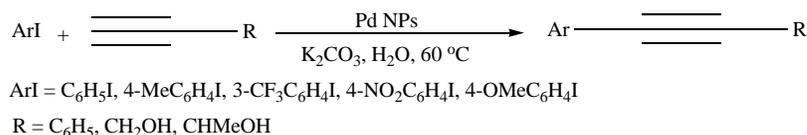


Fig. (2). TEM images of Pd nanoparticles. Reproduced with permission from ref. 31. Copyright (2014) Sciencedirect.



Scheme 9.

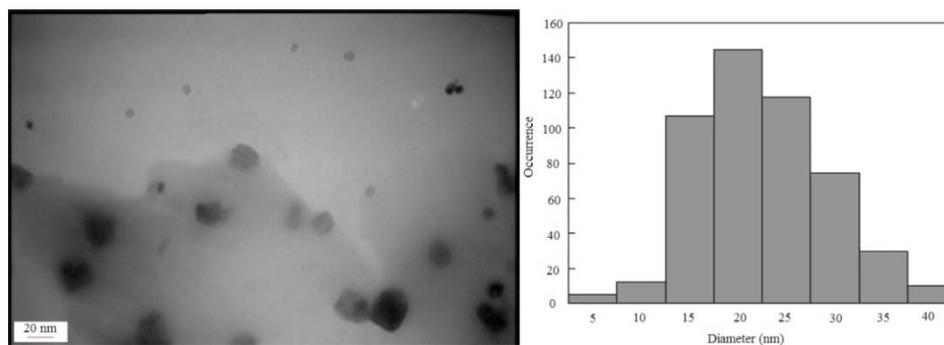


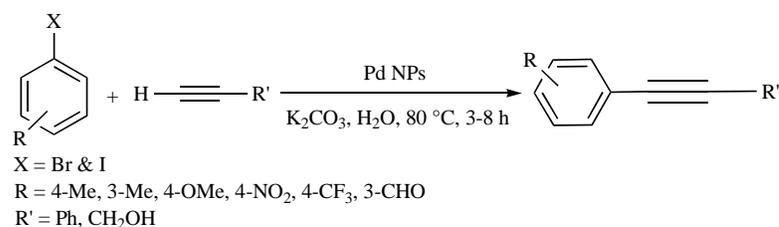
Fig. (3). TEM image and size distributions of Pd NPs. Reprinted from ref. 32 with permission. Copyright (2015) Royal Society of Chemistry.

In the same year, Shafir *et al.* successfully prepared palladium NPs by the hydrogenation of Pd(dba)₂ in the presence of a tris-imidazolium iodide as stabilizer [30]. Then Pd NPs were used as an efficient catalyst for Heck and copper-free Sonogashira reactions with a range of aryl iodides and bromides in the presence of piperidine as base and DMF as solvent at 130 °C (Scheme 8).

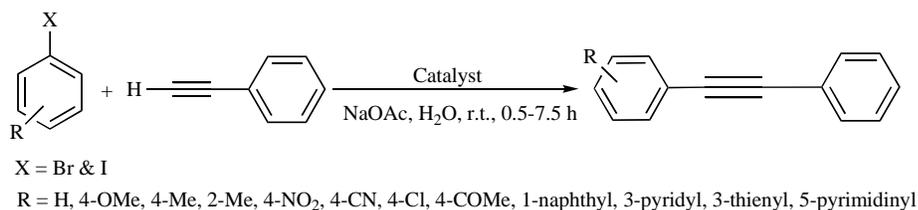
In 2014, the straightforward, high yields and easy workup method for green synthesis of water-dispersible palladium nanoparticles (Fig. 2) by *Sour Cherry* tree gum as reductant presented by Nasrollahzadeh and co-workers. Application of this catalyst in ligand-, amine- and copper-free Sonogashira coupling showed the high performance of Pd NPs under the mild and aerobic conditions (Scheme 9) [31]. The reusability of the catalyst makes it useful for commercial applications. The recycling potential was studied by model Sonogashira coupling reaction for *p*-iodoanisole with phenylacetylene in three consecutive cycles under similar reaction conditions. This test clearly demonstrates the stability of the catalyst over multiple runs and supporting its stability over extended duration.

Recently, we developed green synthesis of Pd NPs (Fig. 3) via the reduction of aqueous Pd^{II} ions using extract of the fruits of *Piper longum* without application of any stabilizer or surfactant for investigation of their catalytic performances in the Sonogashira coupling reaction in water under ligand- and copper-free conditions (Scheme 10) [32]. No obvious decrease of catalytic activity of Pd NPs was detected after five cycles of catalytic reactions which strongly confirms the stability of Pd NPs.

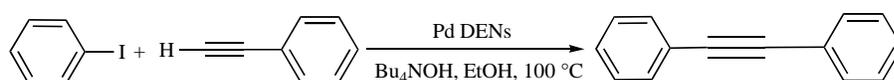
In 2015, Shafiee *et al.* successfully synthesized a highly water-dispersible palladium nanocatalyst through immobilization of Pd onto the surface of PEGylated imidazolium based phosphinite ionic liquid functionalized γ -Fe₂O₃@SiO₂ core-shell nanoparticles. The catalyst [Pd@PEGylated ImIL-OPPh₂- γ -Fe₂O₃@SiO₂] showed high activity for the Mizoroki-Heck and Sonogashira coupling reactions of aryl halides in water under the mild conditions (Scheme 11) [33]. The catalyst could be recycled and reused 10 times without significant loss of activity.



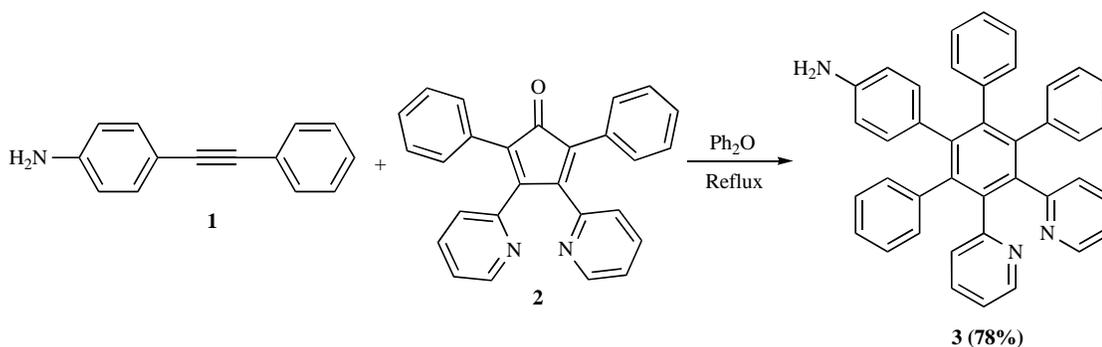
Scheme 10.



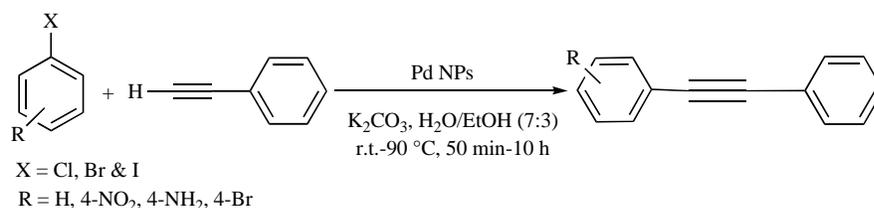
Scheme 11.



Scheme 12.



Scheme 13. Synthesis of derivative 3. Reprinted from ref. 35 with permission. Copyright (2015) Royal Society of Chemistry.



Scheme 14.

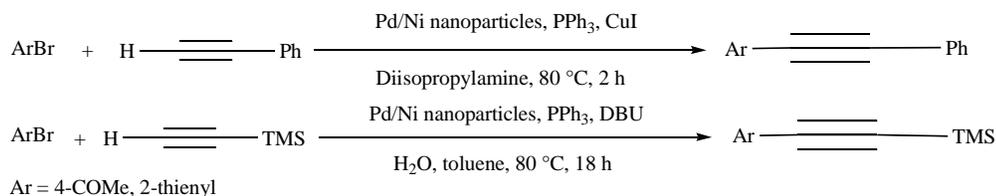
Also, Ricciardi *et al.* described the use of a simple technique for depositing dendrimer-encapsulated Pd nanoparticles (Pd DENs) on the inner walls of glass microreactors. The Pd DEN-microreactors has been employed in the Heck-Cassar (copper-free Sonogashira) and Suzuki-Miyaura (SMC) cross-coupling reactions. The catalyst was used in the Sonogashira coupling of iodobenzene with phenylacetylene with high turnover frequency (TOF) (Scheme 12) [34].

Quite recently, Walia *et al.* designed and synthesized the hetero-oligophenylene derivative **3** on which the aggregates of this derivative served as reactors, stabilizers and shape directing agents for the *in situ* generated spherical Pd NPs. The hetero-oligophenylene derivative **3** was prepared through the Diels-Alder reaction of 4-phenylethynyl-phenylamine with 2,5-diphenyl-3,4-di(pyridin-2-yl)cyclopenta-2,4-dienone in diphenylether at 240 °C in

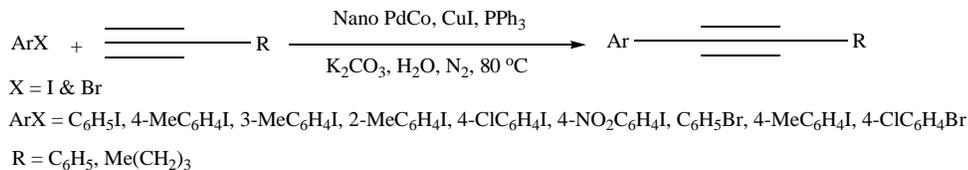
78% yield (Scheme 13). The *in situ* generated Pd NPs showed highly efficiency in the copper and amine free Sonogashira coupling reactions involving activated and unactivated substrates under aerial conditions at room temperature (Scheme 14) [35].

2.2. Bimetallic, Trimetallic and Core-Shell Nanoparticles

In a separate study, Pd/Ni bimetallic nanoparticles were prepared by Hyeon and co-workers through thermal decomposition of metal-surfactant complexes from a mixture of Pd(acac)₂ and Ni(acac)₂ in trioctylphosphine [36]. The material tested for various Sonogashira coupling reactions showed a good catalytic activity (Scheme 15). The catalyst could be recycled and reused at least 5 times without significant loss of activity. The Pd/Ni NPs catalyst was inactive for chloro-aryl substrates.



Scheme 15.



Scheme 16.

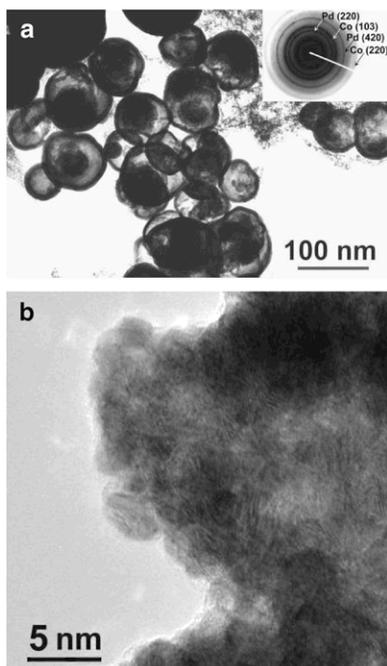
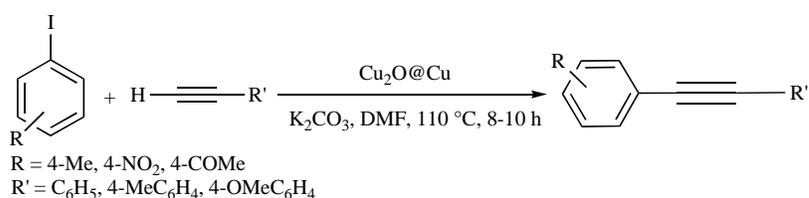


Fig. (4). (a) TEM and (b) high-resolution TEM images of PdCo bimetallic hollow nanospheres. Reprinted from ref. 37 with permission. Copyright (2006) Royal Society of Chemistry.

In 2006, PdCo bimetallic hollow nanospheres for performing in the Sonogashira reaction have been developed (Scheme 16) [37]. This Pd-containing bimetallic hollow nanostructure was prepared by the redox reaction of CoSO_4 and H_2PdCl_4 with NaBH_4 in polyethylene glycol solution (Fig. 4). Under environmentally friendly reaction conditions, coupling a series of aryl halides with terminal alkynes was studied. All products were isolated in good to excellent yields. The catalyst was recovered and reused for three times.

The excellent catalytic ability of the $\text{Cu}_2\text{O@Cu}$ core-shell structure in the Sonogashira coupling reactions was demonstrated by



Scheme 17.

Varma and co-workers in 2012 [38]. The catalyst was prepared through the reduction of Cu^{2+} in the mixture containing ethylene glycol and glucose at near ambient conditions. SEM and TEM images of $\text{Cu}_2\text{O@Cu}$ product are shown in Figure 5. The Sonogashira coupling reaction was carried out in the presence of K_2CO_3 as base in DMF at 110°C (Scheme 17). All products were isolated in good to excellent yields.

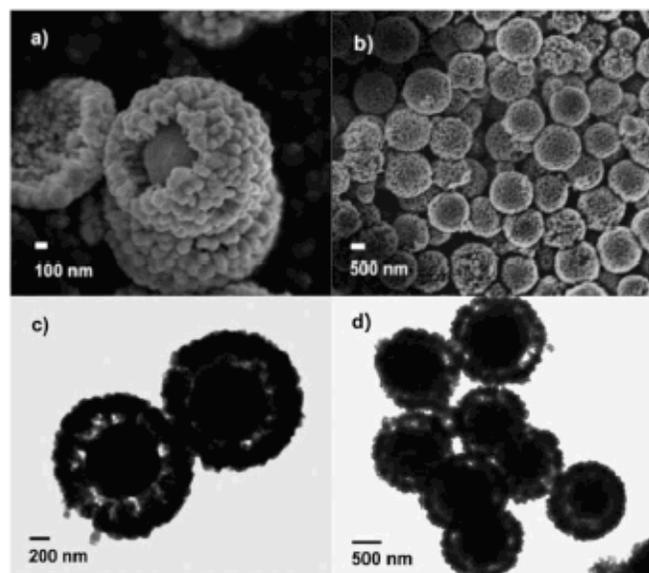
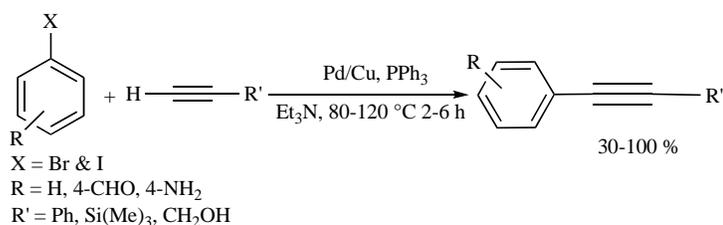
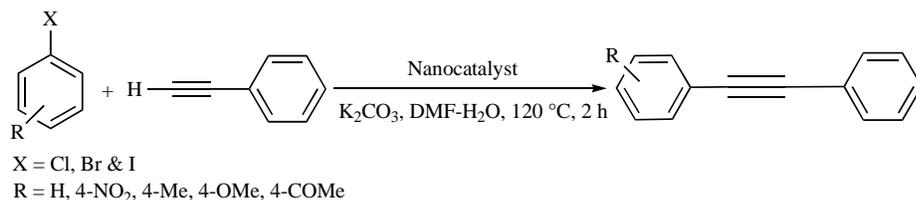


Fig. (5). Images of the typical core-shell $\text{Cu}_2\text{O@Cu}$. (a) High magnification SEM image; (b) low-magnification SEM image; (c) high magnification TEM image; (d) low-magnification TEM image. Reprinted from ref. 38 with permission. Copyright (2012) Royal Society of Chemistry.

In the same year, Polanski and co-workers successfully prepared a copper-supported nano palladium catalyst by an innovative method of nanoparticle transfer from the SiO_2 intermediate carrier to the target Cu carrier [39]. This approach cause to formulate palladium NPs distributed on electrolytic copper. The role of the cop-



Scheme 18.



Scheme 19.

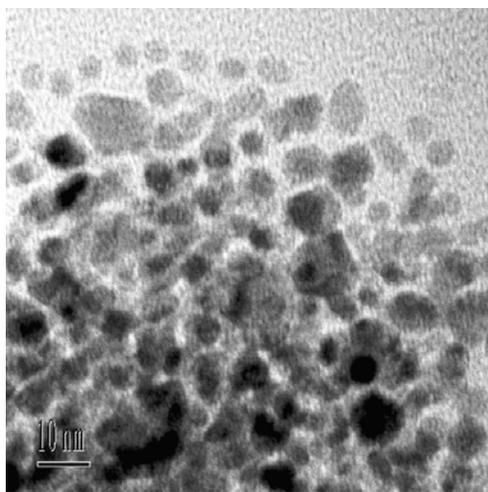


Fig. (6). TEM image of palladium metal colloids on PVP. Reproduced with permission from ref. 41. Copyright (2005) Scienencedirect.

per in the analyzed bimetallic system can be regarded as support for both for the palladium nanoparticles and co-catalyst. The properties of such a bimetallic system and its application as the catalyst in the Sonogashira reactions were investigated. The Sonogashira coupling generally occurs in the presence of a substantial amount of palladium catalyst with copper(I) salt as co-catalyst under an inert atmosphere (Scheme 18). In this work, a tiny amount of Pd oxide performed on the catalyst surface, as an unexpected result. With taking into account of the importance of the aerobic oxygen for high activity of the Pd-catalyzed Sonogashira coupling, they believed that the coexistence of Pd oxide is essential for the observed enhancement in the activity of bimetallic Pd/Cu system. In addition, up to two cycles, the catalyst performance (100% conversion) can

be fully achieved, but a fairly high deactivation in a third cycle (5% conversion) is then observed.

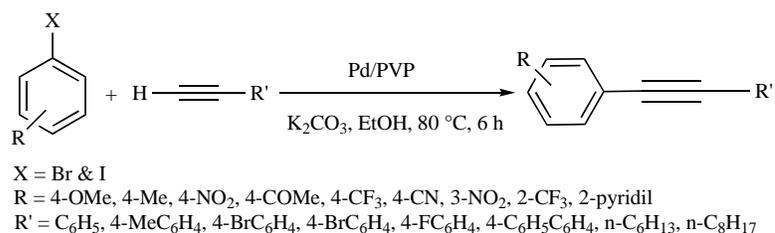
Santhanalakshmi *et al.* reported the formation of Pd NPs, core/shell Au-Ag bimetallic NPs and Au-Ag-Pd trimetallic NPs (tnp) catalysts by chemical method with cetyltrimethylammonium bromide as the capping agent (Scheme 19) [40]. They investigated their catalytic activities in the Sonogashira coupling reactions under aerobic conditions. They observed that Au-Ag-Pd trimetallic NPs catalyzed the Sonogashira coupling reactions better than Pd NPs and Au-Ag bimetallic catalysts due to the sequential electronic effect between elements in a particle. The nanoparticle catalyst can be recycled and reused at least three times without losing the catalytic activity.

2.3. Polymer-supported Metal Nanoparticles

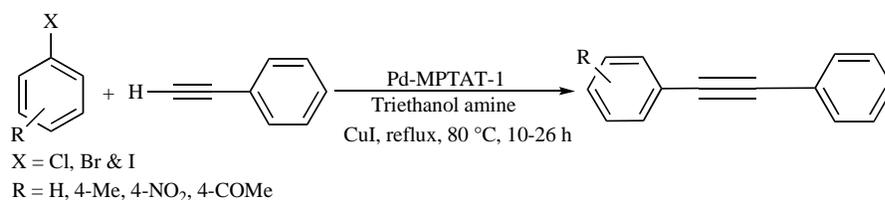
Polymer materials have played an important role as support in C-C coupling reactions.

In 2005, Wang and co-workers described a novel Pd NPs/supported catalyst system based on PVP as a support (Fig. 6) [41]. In this work, the resulted Pd NPs@PVP was able to catalyze the Sonogashira coupling reactions of aryl halides with phenylacetylene under the ligand-, copper-, and amine-free reaction conditions (Scheme 20). This protocol used environmentally benign reagents and solvents. Finally this catalyst can be recycled *via* a simple decantation procedure at least eight times without loss of activity.

In 2011, Bhaumik *et al.* reported the preparation of MPTAT-1 *via* organic-organic radical polymerization of 2,4,6-triallyloxy-1,3,5-triazine (TAT) in aqueous medium in the presence of an anionic surfactant (sodium dodecyl sulfate). Specifically, MPTAT-1 was chosen as a support for immobilizing Pd(II) at its surface to form new catalyst Pd-MPTAT-1 (palladium grafted mesoporous poly-2,4,6-triallyloxy-1,3,5-triazine). The particles are spherical in



Scheme 20.



Scheme 21.

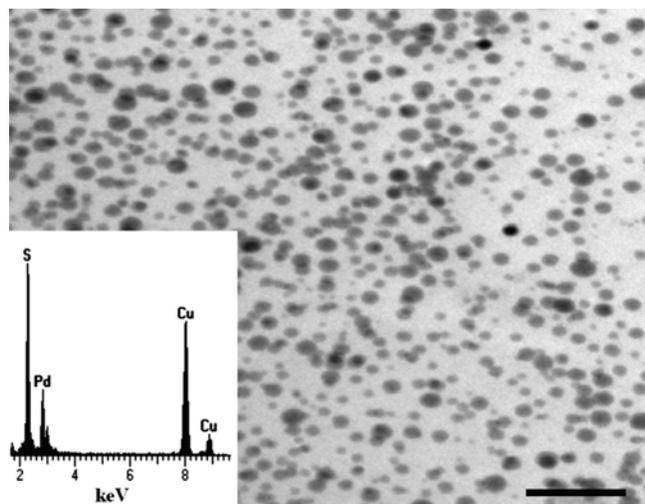


Fig. (7). A TEM image of the PdNPs-PPS recorded on a carbon coated copper grid; scale bar = 50 nm; inset shows the corresponding EDX spectrum of Pd NPs-PPS collected from TEM, confirming the presence of palladium and sulfur. Reprinted from ref. 43 with permission. Copyright (2011) Royal of Society of Chemistry.

nature and have a diameter of *ca.* 50 nm. They have shown that Pd-MPTAT-1 is an efficient catalyst in the Sonogashira reaction under eco-friendly conditions and reflux using CuI as the co-catalyst and also triethanolamine as solvent as well as base at 80 °C for 10 till 26 h. Pd-MPTAT-1 can be recycled several times without much loss in reactivity. (Scheme 21) [42]. Application of CuI dramatically improves conversion for aryl iodides and aryl bromides. However, moderate conversion was found for aryl chlorides.

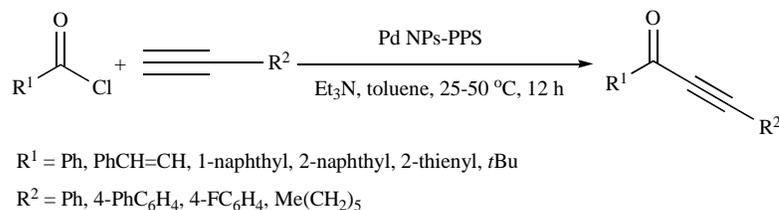
In the same year, Mandal *et al.* have reported a convenient method for the synthesis of palladium nanoparticles (Pd NPs), sta-

bilized in a polymer matrix, PPS [PPS = poly (1,4-phenylene sulfide)], *via* the thermolysis of Pd(OAc)₂. The particles are spherical in nature and have an average diameter of *ca.* 6 nm (Fig. 7). Pd NPs-PPS catalyzed acyl Sonogashira reaction of acid chlorides with a variety of terminal alkynes to give the corresponding alkynones in excellent yields under the mild conditions. The reaction was carried out in the presence of dry toluene, dry triethylamine at a temperature between 25 and 50 °C under a nitrogen atmosphere (Scheme 22) [43]. The Pd NPs-PPS was recycled up to four times with no substantial change in particle size, due to the strong gripping ability of polymer support through sulfur coordination.

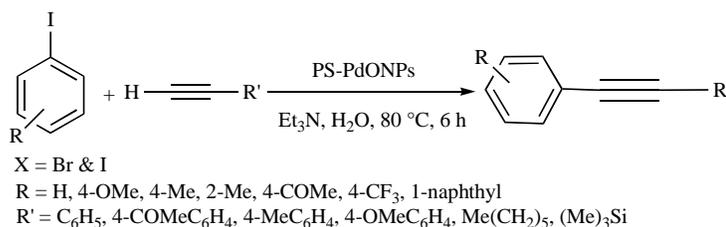
Another approach applying a heterogeneous palladium catalyst was reported by Ohtaka and co-workers [44]. They disclosed the polystyrene-supported PdO nanoparticles (PS-PdONPs) as a heterogeneous catalyst. PS-PdONPs was prepared by thermal decomposition of Pd(OAc)₂ in the presence of polystyrene which exhibited highly catalytic activity for copper-free Sonogashira coupling reactions in water (Scheme 23) that also recycled at least 10 times without loss of activity.

In 2013, a novel and green method for the preparation of palladium NPs supported on pectin, as both reductant and ligand was described by Khazaei and co-workers. Palladium NPs were formed by *in situ* reduction of PdCl₂ in the presence of pectin without addition of external reducing agents. TEM image of obtained palladium nanoparticles supported on pectin is shown in Figure 8. This system also performed well in the copper-amine- and phosphine-free Sonogashira reaction between different aryl halides and alkynes (Scheme 24) [45]. This catalytic system exhibited high catalytic efficiency and air stability in the Sonogashira coupling reactions. The catalyst can be recycled and reused at several times without losing the catalytic activity.

In the same year, Tamami *et al.* prepared palladium nanoparticles supported on polymeric N-heterocyclic carbene grafted silica



Scheme 22.



Scheme 23.

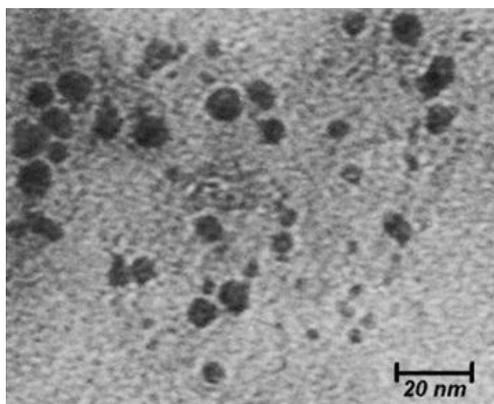


Fig. (8). TEM image of palladium nanoparticles supported on pectin. Reprinted from ref. 45 with permission. Copyright (2013) Sciencedirect.

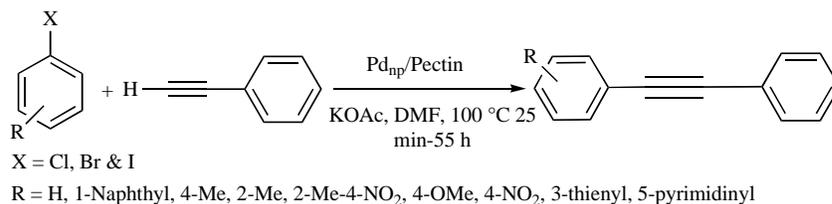
(Si-PNHC-Pd). This catalytic system exhibited excellent activity in Sonogashira coupling reactions of phenylacetylene with various aryl halides. The catalyst was successfully reused up to 12 runs without appreciable change in its properties (Scheme 25) [46]. The thermal stability and highly reusability for around 12 cycles with TON 2130 is the catalyst useful characteristic.

In 2014, Basu *et al.* been synthesized a new class of poly-ionic resin-supported Pd/Cu based bimetallic nanocomposite (Pd/Cu-ARF(II)) through the co-impregnation mode using an equimolar solution of palladium acetate and cupric acetate [47]. The Amber-

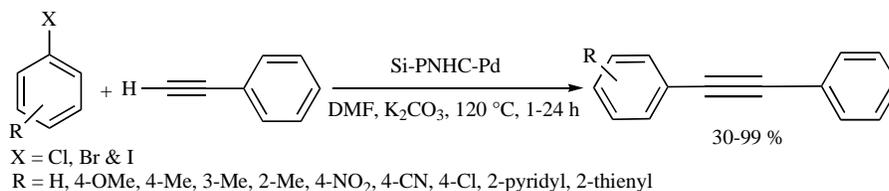
lite resin formate (ARF) was prepared from commercially available Amberlite IRA 900 (chloride form)(source: Acros Organics, Belgium) by rinsing with 10% aqueous formic acid solution until free from chloride ions. The as-synthesized nanocomposite material (Pd/Cu-ARF) applied as highly efficient and recyclable catalyst in the Sonogashira cross-coupling reactions under N_2 and ligand-free conditions in CH_3CN at $80\text{ }^\circ C$ (Scheme 26). The catalyst was recovered and reused for at least five consecutive runs with no obvious decrease of catalytic activity.

Qi *et al.* reported the preparation of a nanoporouspreoxidated-polyacrylonitrile fiber mat supported Pd (Pd/PrePAN fiber mat) by electrospinning and thermal treatment for application as a robust heterogeneous for the Sonogashira coupling reactions of aryl iodides with phenylacetylene (Scheme 27) [48]. The procedure provided products in excellent yields. The catalyst was easily recovered and reused for five consecutive runs without any loss of activity.

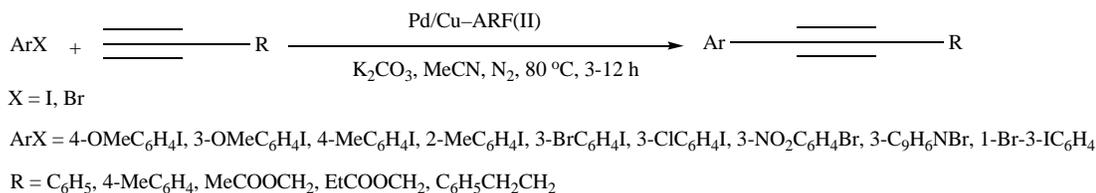
In 2014, another paper was published about the preparation of a nanopolymer-supported palladium(II) complex catalyst [PS-tet-Pd(II), 5], using a simple protocol (Scheme 28 and Fig. 9) [49]. They reported its application as a novel and stable heterogeneous catalyst for the copper- and phosphine-free Sonogashira coupling reaction in water under aerobic conditions (Scheme 29). The catalyst can be recovered from the reaction mixture by simple filtration and reused several times without significant loss of its catalytic activity.



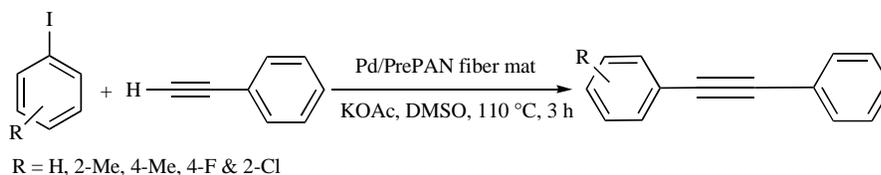
Scheme 24.



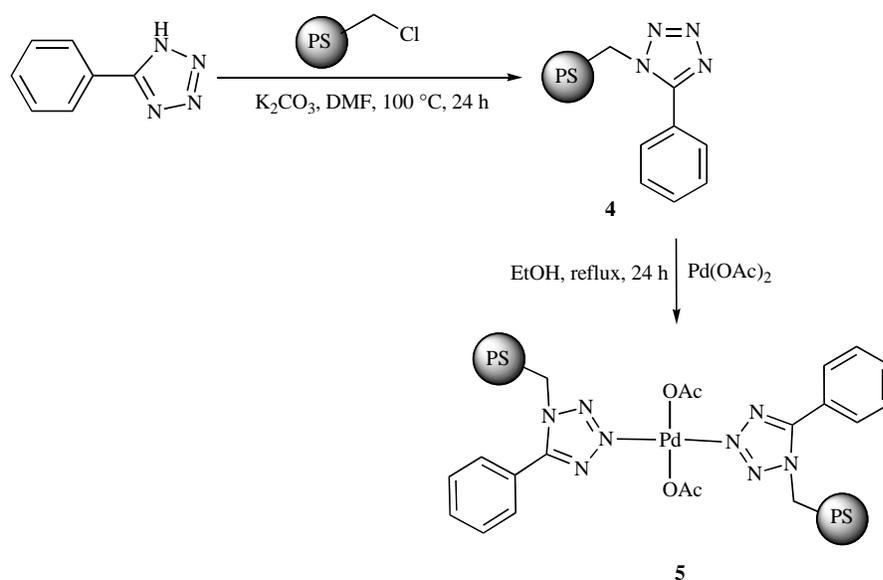
Scheme 25.



Scheme 26.



Scheme 27.



Scheme 28. Preparation of palladium tetrazole-supported complex **5**. Reprinted from ref. 49 with permission. Copyright (2014) Tetrahedron Letters.

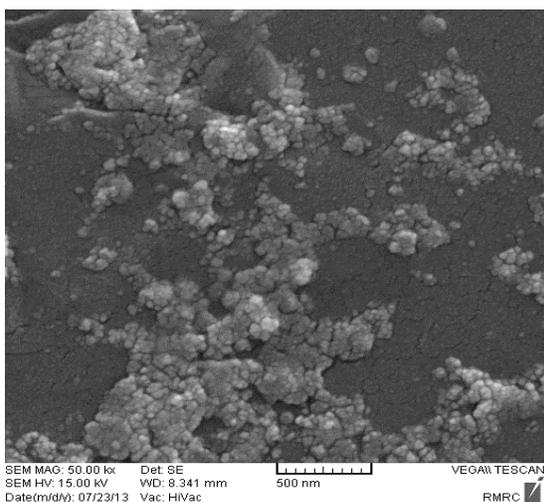


Fig. (9). SEM image of PS-tet-Pd(II). Reproduced with permission from ref. 49. Copyright (2014) Sciencedirect.

In 2014, Sureshbabu and co-workers described the preparation of PVC-supported Pd NPs through the reduction of PdCl₂ by a non-toxic and eco-friendly route, employing sodium formate and NaOH in ethanol-water system [50]. Then the prepared PVC supported Pd NPs (Fig. 10) were employed as catalyst in Heck and Sonogashira coupling reactions in water medium to afford the respective products in good to excellent yields. To avoid drawbacks such as hinders the recovery and reutilization of the expensive Pd catalysts while frequently using of two metals and phosphines in Sonogashira coupling reaction, they are often air-sensitive but not com-

mercially available. Resulted PVC supported Pd NPs were explored for the Sonogashira cross coupling reaction between iodobenzene and phenyl acetylene under copper- and phosphine-free aerobic conditions (Scheme 30).

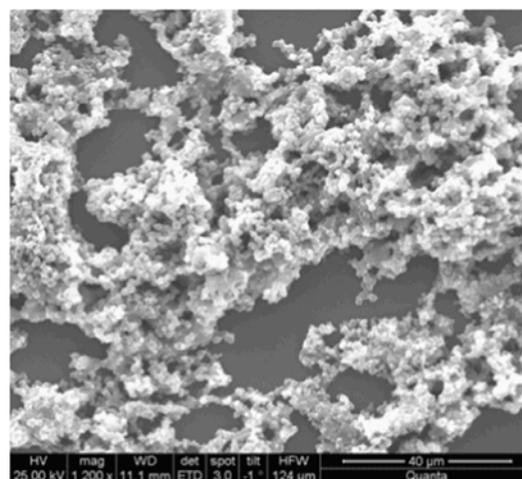
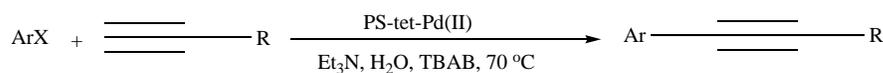


Fig. (10). SEM image of PVC-Pd⁰ nanoparticles. Reproduced with permission from ref. 50. Copyright (2014) Sciencedirect.

In 2014, the possibility to synthesize and evaluation of catalytic activity of the ternary nanocomposites (microgel/nanoclay/metal nanoparticles) have been described by Pich *et al.* [51]. Laponite nanoclay embedded inside microgels acts as cation exchanger. It is the controlled size process because of the nature of the reducing agent or the content in clay component contributes to determine the final metal nanoparticle size. The resulted nanocomposites were

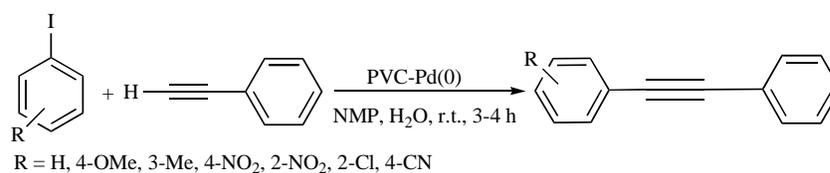


X = I & Br

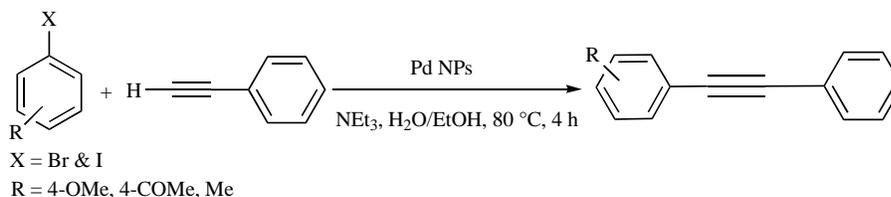
ArX = C₆H₅I, 4-OMeC₆H₄I, 4-MeC₆H₄I, 2-MeC₆H₄I, 4-COMeC₆H₄I, 4-NO₂C₆H₄I, 4-CF₃C₆H₄I, C₆H₅Br, 4-OMeC₆H₄Br, 4-MeC₆H₄Br, 4-NO₂C₆H₄Br, 4-COMeC₆H₄Br, 2-C₅H₄NBr, 1-C₁₀H₇I

R = C₆H₅, 4-C₄H₉

Scheme 29.



Scheme 30.



Scheme 31.

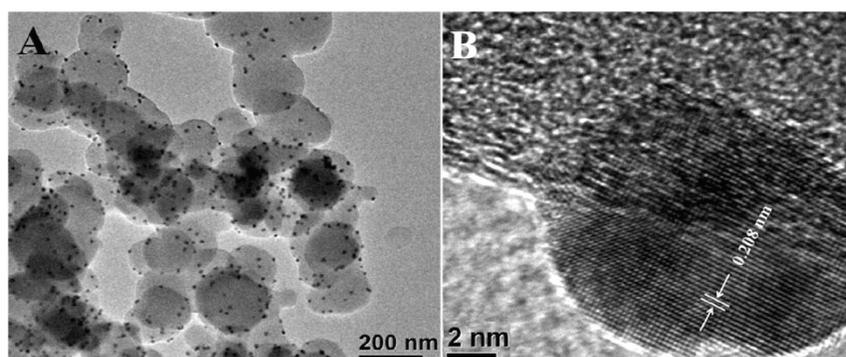
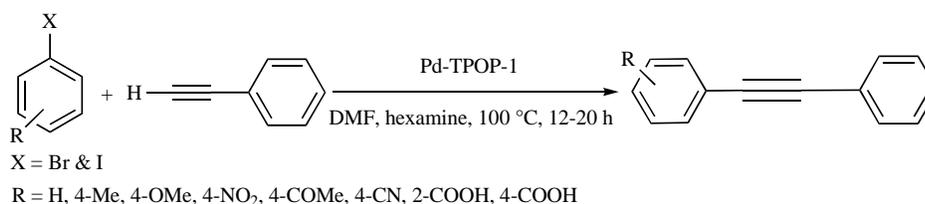
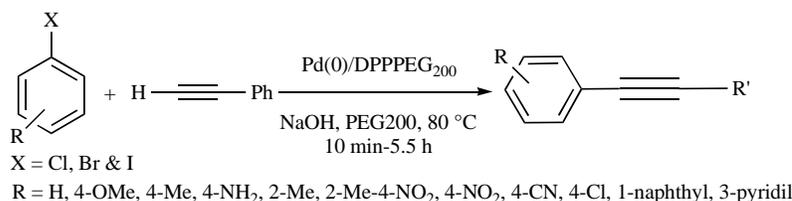


Fig. (11). TEM (A) and HR-TEM (B) images of Pd-TPOP-1. Reproduced with permission from ref. 52. Copyright (2014) Royal Society of Chemistry.



Scheme 32.



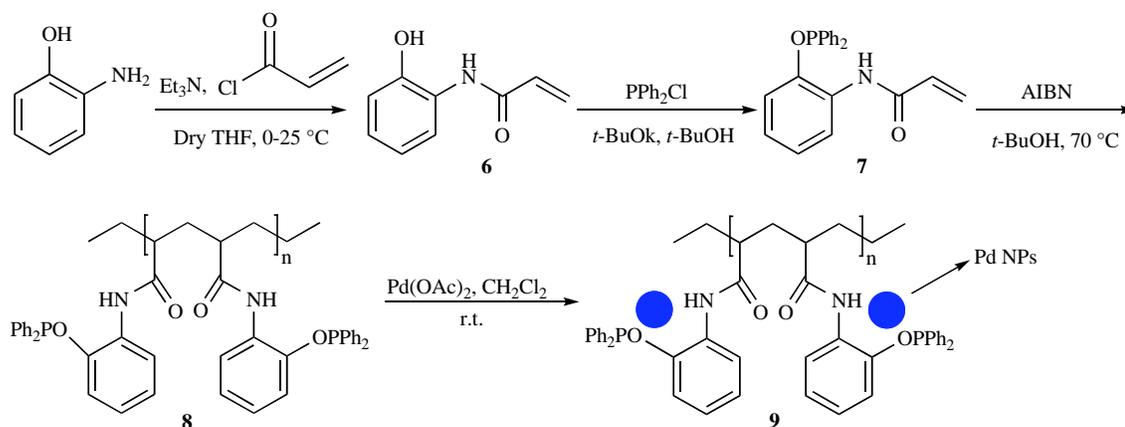
Scheme 33.

tested as catalysts in the Suzuki and Sonogashira cross-coupling reactions (Scheme 31).

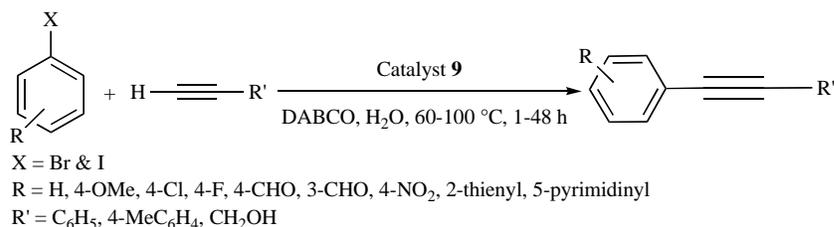
In 2014, Bhaumik and co-workers reported a novel triazine-functionalized porphyrin-based on porous organic polymer (TPOP-1) as support for designing Pd nanocatalyst. The polymer prepared by hydrothermal treatment of 4,4',4''-(1,3,5-triazine-2,4,6-triyl)tris(oxy)tribenzaldehyde and pyrrole in glacial acetic acid in the presence of FeCl₃. TPOP-1 had a highly porous nature and abundance of electron-donating basic N-sites, therefore favors the adsorption of Lewis acid CO₂ molecules and impregnation of palladium nanoparticles at the surface of polymer matrix to form the Pd-TPOP-1. The Pd-TPOP-1 was prepared *via* impregnation of Pd(OAc)₂ in the colloidal suspension of TPOP-1 in acetone (Fig. 11). The Pd-TPOP-1 was found to be efficient, stable against leach-

ing and reusable catalyst in the Sonogashira cross-coupling of aryl halides with phenylacetylene (Scheme 32). Aryl bromides, in contrast to aryl iodides require much longer periods of time for the Sonogashira cross-coupling reactions [52].

Very recently, Iranpoor and co-workers reported the synthesis and application of diphenylphosphorylated PEG200 (DPPPEG200) as a very suitable ligand through the reaction of PEG200 with ClPPh₂. Then, this stable solid ligand was used for the *in situ* generation of nano-Pd(0) particles through its reaction with PdCl₂ as a precatalyst. In the next step, the catalytic activity of Pd(0)/DPPPEG200 was also studied for the Sonogashira cross-coupling reactions of aryl halides using NaOH as base in PEG200 (Scheme 33) [53]. In this method, aryl chlorides, in contrast to aryl iodides and bromides, require much longer periods of time for the



Scheme 34. Preparation of catalyst. Reproduced with permission from ref. 54. Copyright (2015) Royal Society of Chemistry.



Scheme 35.

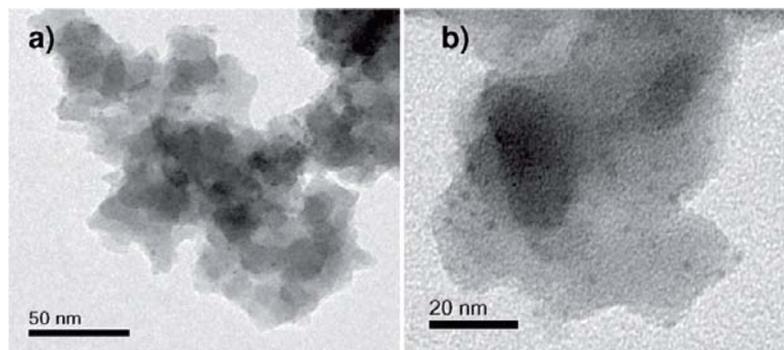


Fig. (12). TEM images of Pd/SNW1. Reprinted from ref. 55 with permission. Copyright (2015) John Wiley & Sons.

Sonogashira cross-coupling reactions. The catalyst could be recycled four times in the corresponding reactions without significant deactivation in the catalytic activity.

In 2015, Gholinejad *et al.* reported the use of novel method for stabilization of Pd nanoparticles on polymer containing phosphorus-nitrogen ligands (**8**) on which palladium nanoparticles have an average diameter of 2-3 nm (Scheme 34). The heterogeneous catalyst was successfully applied in the Suzuki-Miyaura and copper-free Sonogashira-Hagihara coupling reactions of aryl halides under low palladium loading conditions. Results showed that using DABCO [1,4-diazabicyclo(2.2.2)octane] as a base and H₂O as a solvent at 60 °C are the most suitable reaction conditions for the copper-free Sonogashira-Hagihara coupling (Scheme 35) [54]. In comparison with aryl iodides, aryl bromides require much longer periods of time for the Sonogashira cross-coupling reactions. Reactions of aryl bromides were carried out at 100 °C in water in the presence of tetrabutylammonium bromide (TBAB) and DABCO. This system could be recycled 9 times without significant loss of activity. In addition, this method is not applicable for aryl chlorides.

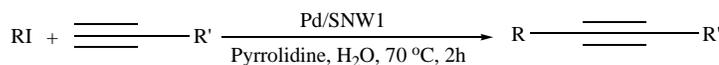
The simple preparation of melamine-based microporous polymer network as solid support to stabilize palladium nanoparticle in

water medium has offered by Shunmughanathan and co-workers [55]. From TEM analysis, the average particle size of the Pd/SNW1 is approximately 2 nm (Fig. 12). The resulting Pd/SNW1 utilized in copper-free Sonogashira coupling of aryl iodides with high performance and good selectivity (Scheme 36). The hot filtration test and recycling experiment clearly demonstrated that Pd/SNW1 is truly heterogeneous in nature. This catalytic system failed with aryl chlorides and aryl bromides, wherein only the homocoupling of the alkynes occurred.

2.4. Carbon- or Graphene-Supported Metal/Metal Oxide Nanohybrids

There are many reports in the field of carbon- or graphene-supported metal/metal oxide nanohybrids that used as heterogeneous catalysts for the Sonogashira coupling reactions, but there are just a few examples about these catalysts.

In 2011, El-Shall *et al.* reported the formation of Pd nanoparticle catalysts supported on partially reduced graphene nanosheets (Pd/PRGO) through pulsed laser irradiation of aqueous solutions of graphene oxide and palladium ions. The strong catalyst-support interaction is essential for the dispersion of Pd NPs and conse-



R = Ph, 4-MeC₆H₄, 4-MeOC₆H₄, 4-MeOCC₆H₄, 4-O₂NC₆H₄, 4-NCC₆H₄, 4-EtO₂CC₆H₄, 4-BrC₆H₄, 4-F₃COC₆H₄, 3-NCC₆H₄, 3-F₃CC₆H₄, 3-MeOC₆H₄, 1-naphthyl, 2-thiophenyl, 3-pyridyl, 3,4-Me₂C₆H₃, 4-IC₆H₄

R' = Ph, 3-MeC₆H₄, 4-Me₂NC₆H₄, 4-BrC₆H₄, 4-MeOC₆H₄, 2-MeOC₆H₄, 4-Me(CH₂)₄C₆H₄

Scheme 36.

quently high catalytic activity and recyclability of the Pd/PRGO catalysts. TEM image of Pd NPs supported on reduced graphene nanosheets is shown in Fig. 13. They investigated their catalytic activities in the Sonogashira coupling reactions of iodobenzene or bromobenzene with phenylacetylene under ligand-free and microwave irradiation conditions (Scheme 37) [56].

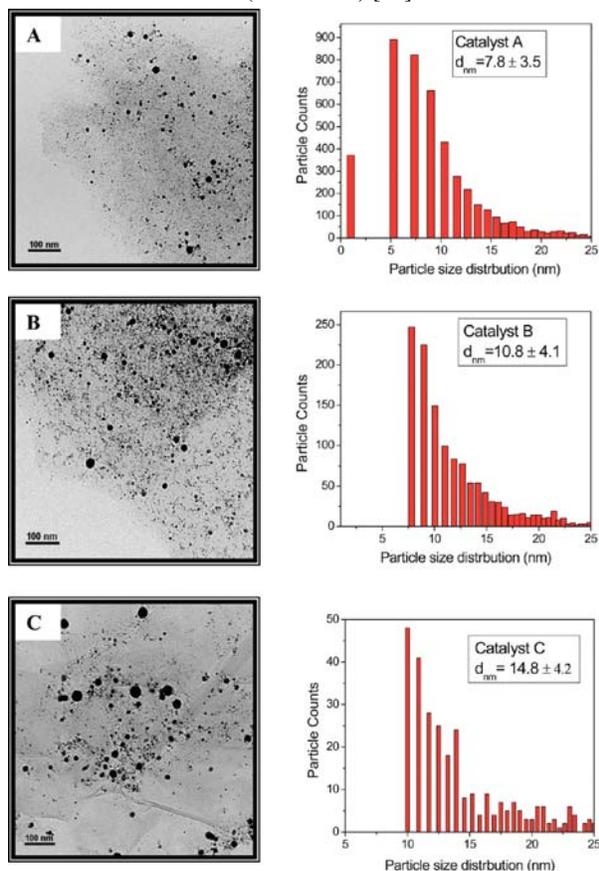


Fig. (13). TEM images and particle size distributions of the Pd/PRGO catalysts. Reprinted from ref. 56 with permission. Copyright (2011) American Chemical Society.

Bannwarth and co-workers presented in situ reduction of Pd²⁺ on graphite oxide (GO) as an active catalyst for ligand-free Suzuki-Miyaura couplings of aryl chlorides and Mizoroki-Heck as well as Sonogashira reactions [57]. This versatile, air-stable system could be readily prepared and easily recovered. The TEM image showed

that the Pd NPs of about 2.9 nm in diameter were well-dispersed on the surface of GO (Fig. 14). The Sonogashira reaction of aryl iodides with phenylacetylene was carried out in the presence of Na₃PO₄·12H₂O in *i*PrOH/H₂O under Ar at 80 °C for 24 h and coupling products were obtained in good to excellent yields (Scheme 38). However, this method was not applicable for aryl bromides and aryl chlorides.

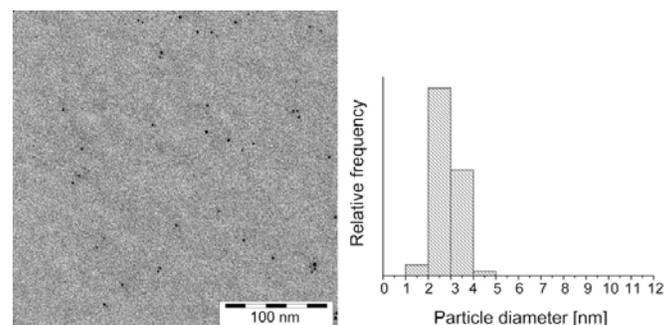
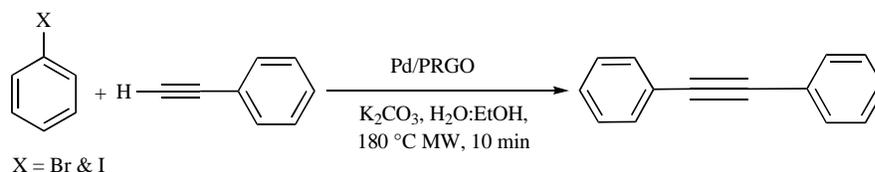


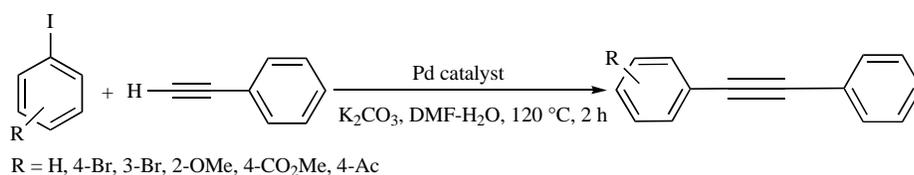
Fig. (14). TEM Picture (left) and size distribution (right) of Pd-nanoparticles on GO generated *in situ* during the Sonogashira coupling. Reprinted from ref. 57 with permission. Copyright (2011) John Wiley & Sons.

In 2013, Shaabani and co-workers prepared a highly active catalyst based on polypropyleniminegrafted graphene (PdCo ANP-PPI-g-graphene hybrid material) [58]. The PPI dendrimers (third generation) were grown on the surface of graphene to obtain the PPI-grafted graphene hybrid material and subsequent loading of palladium and cobalt on the PPI-g-graphene was performed using co-complexation method. The new hybrid material was used as an efficient heterogeneous catalyst for Sonogashira cross-coupling reactions of terminal alkynes and aryl halides under copper- and solvent-free conditions using ultrasound irradiation at room temperature for 1-72 h (Scheme 39). The reaction was carried out under mild and aerobic reaction conditions and products were obtained in high yields. The catalyst was recovered and reused for six times with no obvious decrease of catalytic activity.

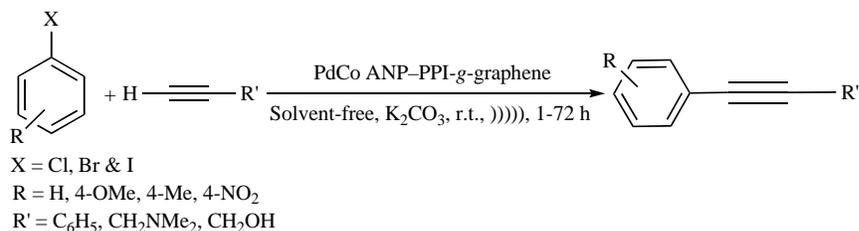
Xu *et al.* have fabricated a series of Pd-Co NPs with different compositions on graphene (G) sheets (Fig. 15) [59]. The catalytic efficiencies of this Pd-Co/G were tested in various Sonogashira-type reactions. Among these different kinds of Pd-Co/G NPs tested, the Pd-Co (1:1) NPs were found to be the most active catalyst for the coupling between phenylacetylene and aryl halide in a tetrahydrofuran/water mixture using triethylamine as a base (Scheme 40). The enhanced reactivity was attributed to both the large surface



Scheme 37.



Scheme 38.



Scheme 39.

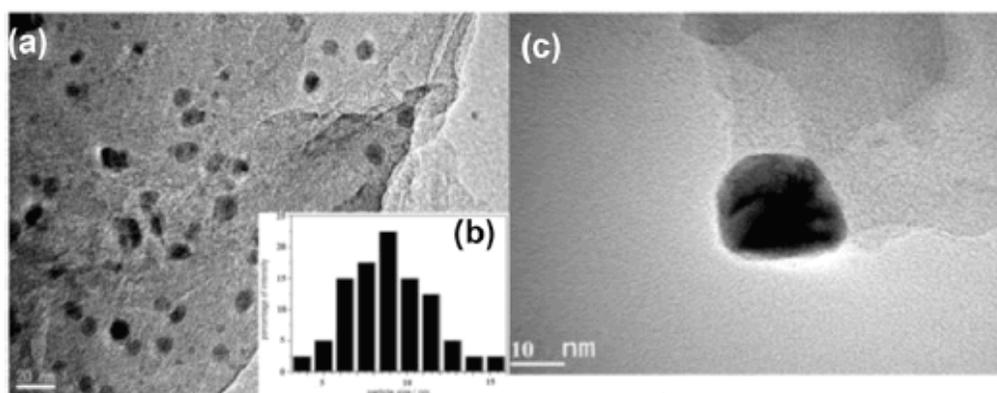
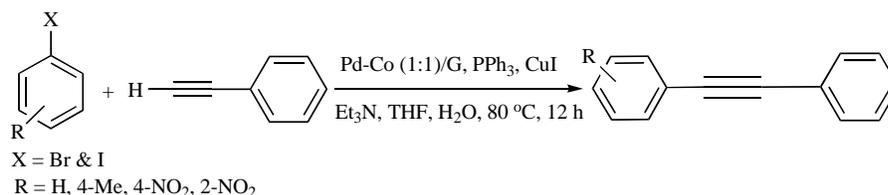
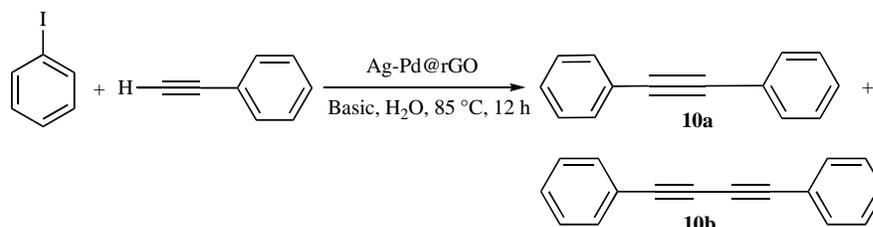


Fig. (15). (a, b) TEM image and the particle size distribution of Pd-Co (1:1)/G catalyst, (c) TEM image of a single Pd-Co (1:1)/G nanoparticle. Reproduced with permission from ref. 59. Copyright (2014) Sciencedirect.



Scheme 40.



Scheme 41.

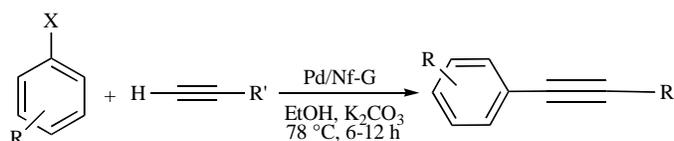
area of G and promotional effect of Co-dopants which provided more Pd active sites for the reactants. Combined both efficiency and durability of a homogeneous catalyst, the Pd-Co/G composites provide great potential for G to support other bimetallic nanoparticles, which offer more opportunities for designing new catalysts.

Gao and colleagues prepared Ag-Pd@reduced graphene oxide bimetallic nanoparticles through a redox reaction between GO, Ag and Pd precursors [60]. The Ag-Pd@rGO had excellent catalytic

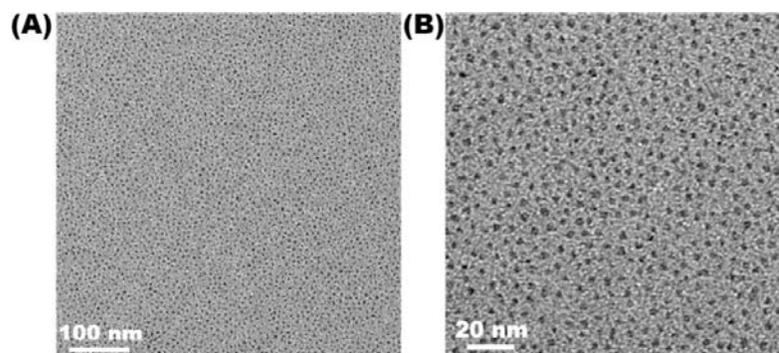
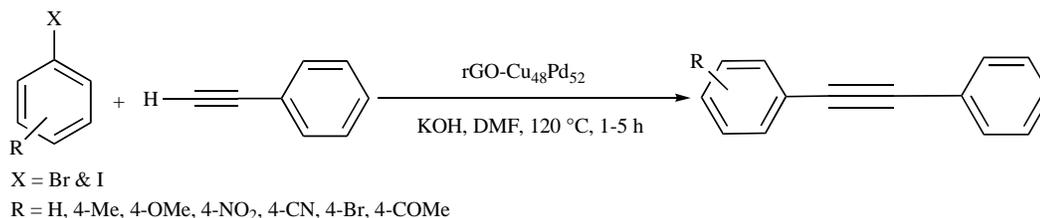
activity in the Sonogashira coupling reaction of iodobenzene and phenylacetylene in the presence of various bases and water as the solvent at 85 °C for 12 h under a nitrogen atmosphere (Scheme 41). Among the various bases (K₂CO₃, Et₃N and NaOH) tested, potassium carbonate led to significant conversion (Table 1). There is an excellent correlation exclusively between the atmosphere controls and major products. For the reaction under the air, the yield of 1,2-diphenylethyne (**10a**, cross-coupling product) was decreased but the

Table 1. Optimization of reaction conditions in the Sonogashira coupling reaction of iodobenzene and with phenylacetylene. Reproduced from Ref. [60], with kind permission.

Entry	Atmosphere	Base	Yield of 2a	Yield of 2b
1	N ₂	K ₂ CO ₃	92%	Trace
2	N ₂	Et ₃ N	81%	Trace
3	N ₂	NaOH	74%	Trace
4	Air	NaOH	12%	Trace
5	Air	K ₂ CO ₃	7%	72%
6	Air	Et ₃ N	Trace	34%
7	O ₂	K ₂ CO ₃	Trace	85%



X = Br & I

R = H, 4-Me, 4-OMe, 4-NO₂, 4-CHO, 4-COMe, 4-CF₃, 4-OH, 4-NH₂, 2-OH, 1-naphthyl, 2-pyridil, 2-thienylR' = C₆H₅, 4-OMeC₆H₄, 4-NO₂**Scheme 42.****Fig. (16).** (A,B) Representative TEM images of as-prepared Cu₄₈Pd₅₂ NPs at different magnifications. Reprinted from ref. 62 with permission. Copyright (2015) American Chemical Society.

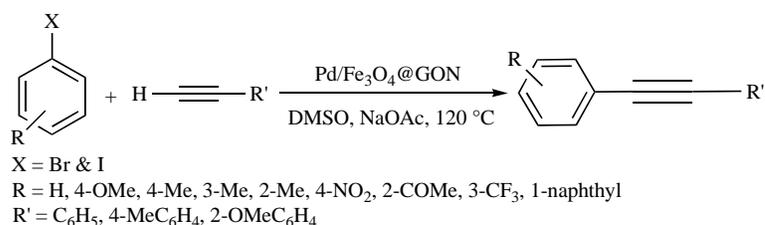
X = Br & I

R = H, 4-Me, 4-OMe, 4-NO₂, 4-CN, 4-Br, 4-COMe**Scheme 43.**

yield of 1,4-diphenylbuta-1,3-diyne (**10b**, homocoupling product) increased, whereas when oxygen was introduced during the reaction, the product contained only **10b**. Moreover, the Ag-Pd@rGO catalyst can be reused for ten times with a negligible drop in activity.

Very recently, Nagarkar and co-workers reported that Sonogashira coupling reaction between aryl halides and phenylacetylenes can be achieved using Pd NPs deposited on nafion-graphene as a heterogeneous recyclable catalyst in ethanol at 78 °C for 6-12 h (Scheme 42) [61]. The catalyst was easily recoverable and reusable for five cycles without loss in the activity.

Later, the efficiency of the rGO-Cu₄₈Pd₅₂ application as heterogeneous catalyst for the Sonogashira reaction of various aryl halides with phenylacetylene was also shown [62]. Using the metal salt reduction by morpholine-borane complex in oleylamine and 1-octadecene solution at 80 °C, they firstly synthesized Cu₄₈Pd₅₂ alloy NPs that were later deposited on rGO by using a liquid self-assembly method to form rGO-Cu₄₈Pd₅₂ catalyst (Fig. 16). The electron-neutral, electron-rich and electron-poor aryl halides reacted with phenylacetylene very well to generate the corresponding coupling products in good to excellent yields in the presence of KOH as base in DMF at 120 °C (Scheme 43). According to the reaction



Scheme 44.

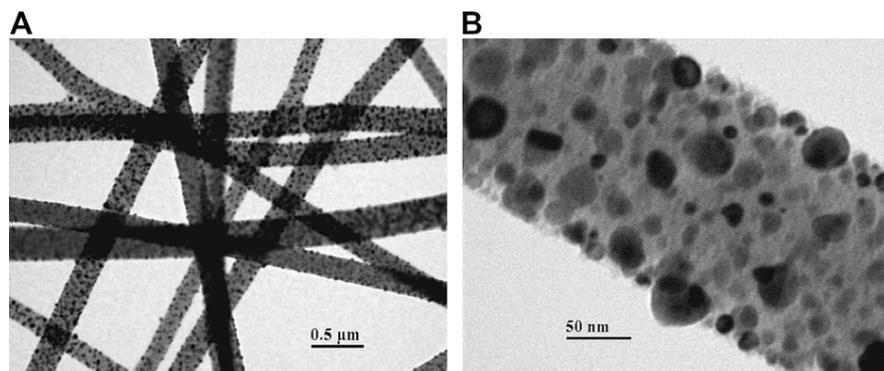
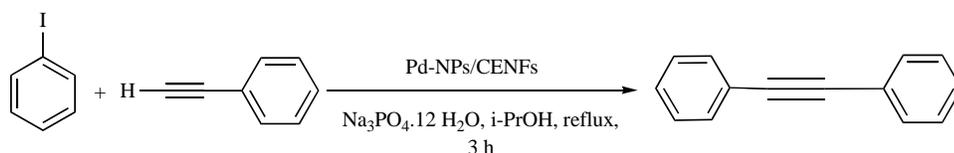


Fig. (17). TEM images of Pd-NP/CENFs: lower magnification (A); higher magnification (B). Reproduced with permission from ref. 64. Copyright (2008) Sciencedirect.



Scheme 45.

results, compared with aryl iodides low efficiency was observed for the coupling reaction of aryl bromides with phenylacetylene. The catalytic system was found to be very active, and could be reused five times before deactivation occurred.

Very recently, preparation of Pd nanoparticles supported on Fe₃O₄@amine-functionalized graphene as a core-shell nanocomposite was done by Kim and co-workers [63]. The amination of graphene shell was occurred through a condensation reaction between GO and a polyamine. Then Pd nanoparticles were immobilized on Fe₃O₄@GON using sonochemical method without additional reducing agents. This catalytic system was used to catalyze the Sonogashira cross-coupling reactions between various aryl halides and terminal acetylenes (Scheme 44). Furthermore, the catalytic activity of this system remained for several cycles.

In 2008, novel Pd-carrying composite carbon nanofibers based on polyacrylonitrile by electrospinning and carbonization process was offered by Houet *et al.* The catalytic activities of this composite nanofiber (Fig. 17) were tested in a copper-, ligand- and amine-free Sonogashira reaction in liquid-phase (Scheme 45) [64]. This process would be of interest for industrial and academic applications.

In 2013, Ganapathy and Sekar described a Pd NPs/supported catalyst system based on C_(binaphthyl) by covalent bonds as a support (Fig. 18). In this work, the resulted Pd(C_(binaphthyl)) was able to catalyze C-C bond forming Heck, Suzuki-Miyaura and Sonogashira cross coupling reactions with high turnover and quantitative recovery (Scheme 46) [65]. The catalyst was quantitatively recovered and reused in which that even after three catalytic cycles had the same reactivity and particle size.

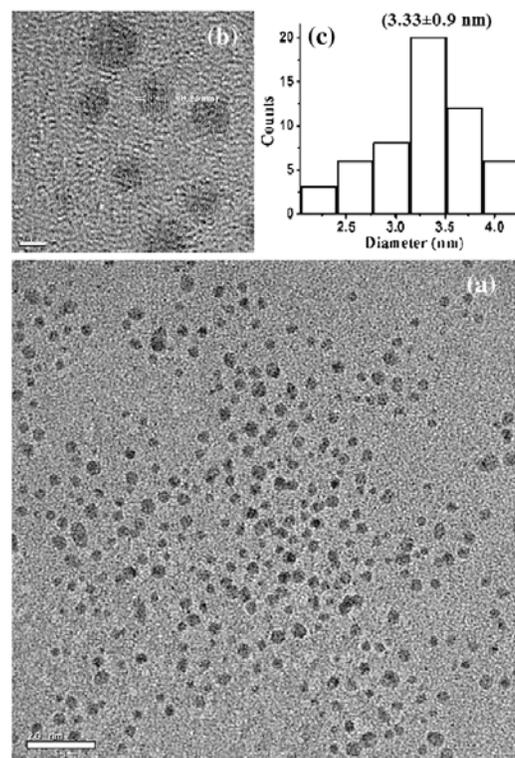
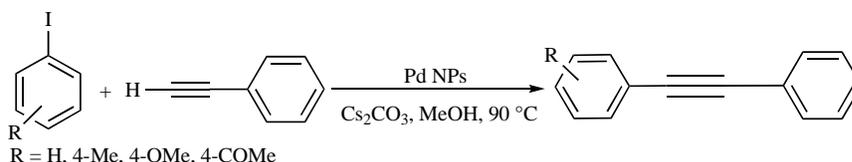
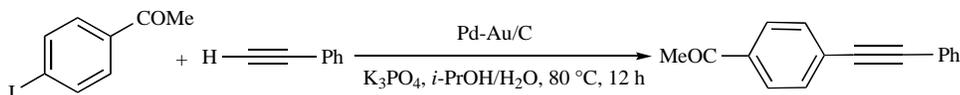


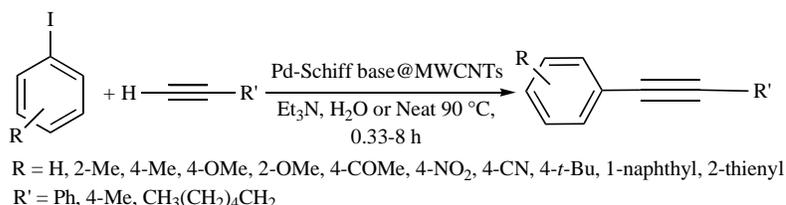
Fig. (18). (a) HRTEM micrographs of Pd-binaphthyl NPs. (b) Lattice fringe image. (c) Particle size distribution. Reproduced with permission from ref. 65. Copyright (2013) Sciencedirect.



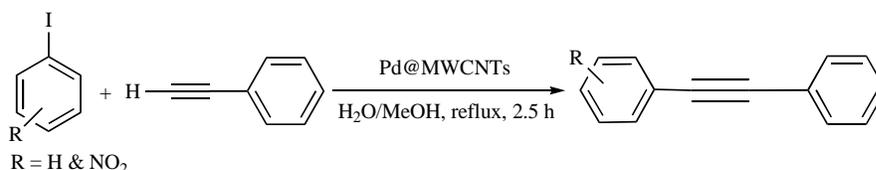
Scheme 46.



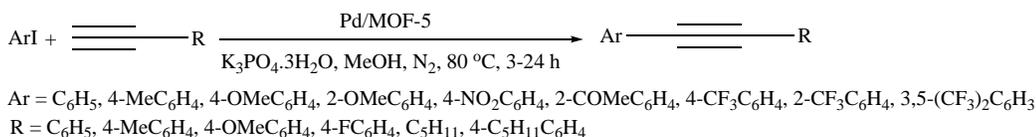
Scheme 47.



Scheme 48.



Scheme 49.



Scheme 50.

In the same year, Felpin *et al.* devised a novel strategy to increase the recyclability of palladium on carbon-based catalysts through the formation of an alloy with gold without altering its initial shape [66]. The heterogeneous Pd-Au/C catalyst was used for the Sonogashira reaction of 4-iodoacetophenone with phenylacetylene in aqueous *i*PrOH under the copper-free conditions at 80 °C (Scheme 47). This catalyst was recycled several times.

Also, Movassagh *et al.* reported the air-moisture stable and recyclable Pd(II)-Schiff base complex anchored to multi-walled carbon nanotubes (Pd-Schiff base@MWCNTs). This catalytic system was applied in the copper- and phosphorous-free Sonogashira reaction of aryl iodides and terminal alkynes in aqueous media under aerobic conditions (Scheme 48) which results demonstrated that this system behaves as a very efficient heterogeneous catalyst. The easy preparation and separation of the catalyst make it as a good heterogeneous system and useful alternative to other heterogeneous palladium catalysts [67]. During the coupling reactions of bromobenzene and chlorobenzene with phenylacetylene under the same reaction conditions, there is trace amount of product after 24 h and no product for mentioned reactions, respectively. For more investigation, the coupling reaction of bromobenzene with phenylacetylene was performed along with CuI as co-catalyst which produced a trace amount of coupling product and a considerable amount of homo coupling product of phenylacetylene. Moreover, introducing the TBAB to the system shows an insignificant change of the reaction output (20% yield).

Very recently, a simple and affordable generation of Pd-carbon nanotube semi-soluble catalyst (Pd@MWCNTs), using electrodeposition method at ambient conditions with simple and convenient recovering has been offered by Ignaszak *et al.* The catalytic performance of this catalyst has investigated in several cross-coupling reactions (Scheme 49) [68]. This catalyst system revealed a very good selectivity for Suzuki-Miyaura and Sonogashira cross-coupling reactions since homo-coupling products were not identified. The recovered catalyst after the reaction was repeatedly used until deactivation due to the partial dissolution of Pd or phase separation in Pd@MWCNTs.

2.5. Metal-organic Frameworks Pd Catalysts

Metal-organic frameworks (MOFs) were used as porous matrices to embed metal nanoparticles (MNPs) and occasionally metal oxide clusters due to their large surface area and porosity compared to other related micro- and mesoporous materials, which are subsequently used as heterogeneous catalysts for organic transformations.

Shu and co-workers supported Pd NPs on MOF-5 by a chemical method at room temperature and studied their catalytic performance in ligand- and copper-free Sonogashira coupling reaction [69]. The Pd NPs were well dispersed on the outside surface and observed as black dots ranging from 3 to 6 nm. Pd/MOF-5 has also shown good catalytic activity and good yield for the reaction of aryl iodides with terminal alkynes having various kinds of substituents giving the corresponding aryl substituted alkynes (Scheme 50). However, this

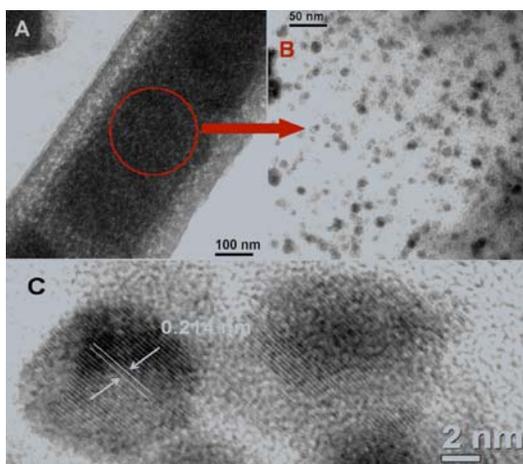
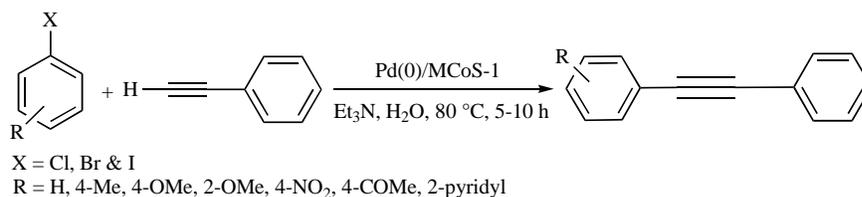


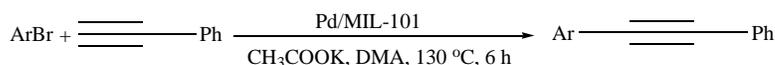
Fig. (19). HR-TEM images of Pd(0)/MCoS-1 catalyst. Reprinted from ref. 70 with permission. Copyright (2014) Sciencedirect.

method is not applicable for aryl bromides and aryl chlorides. Among aryl iodides, *ortho*-substituted iodobenzenes showed lower yield than the *para* isomer. The catalyst can be reused for several times. However, according to XPS studies, the catalyst loses its activity in the third use.

In 2014, Islam *et al.* developed a new class of Pd-NPs grafted at the surface of Co-containing metal-organic framework material MCoS-1 (Pd(0)/MCoS-1) [70]. HR-TEM images of obtained Pd(0)/MCoS-1 catalyst are shown in Figure 19. The Pd(0)/MCoS-1 showed excellent catalytic activities in copper-free Sonogashira cross-coupling between terminal alkynes and aryl halides in water (Scheme 51). The catalyst is easily recoverable by simple filtration and can be reused for six times without appreciable loss of catalytic



Scheme 51.



ArBr = C₆H₅Br, 4-MeC₆H₄Br, 4-OMeC₆H₄Br, 4-NO₂C₆H₄Br, 4-CNC₆H₄Br, 3-CNC₆H₄Br, 4-COMeC₆H₄Br, 4-COEtC₆H₄Br, 4-CF₃C₆H₄Br, 1-Bromonaphthalene, 9-Bromophenanthrene, 2-Bromopyridine, 3-Bromopyridine, 2-Bromoquinoline, 3-Bromoquinoline, 4-Bromoisquinoline, 2-Bromothiophene, 3-Bromothiophene.

Scheme 52.

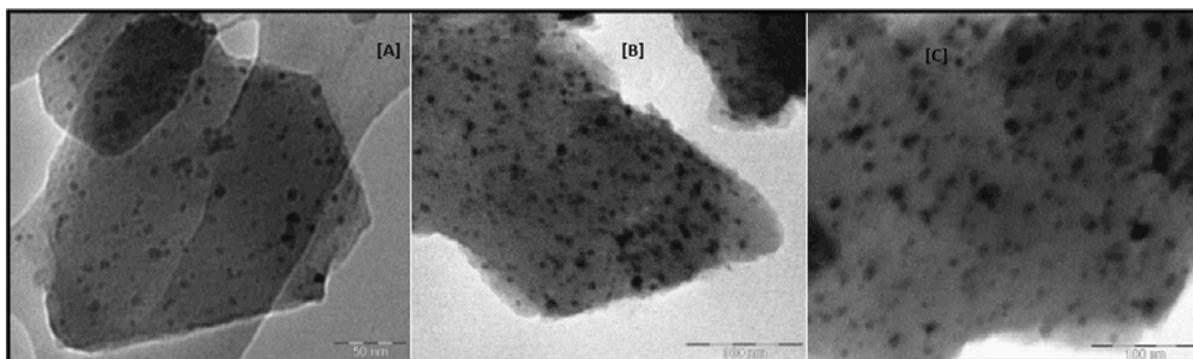


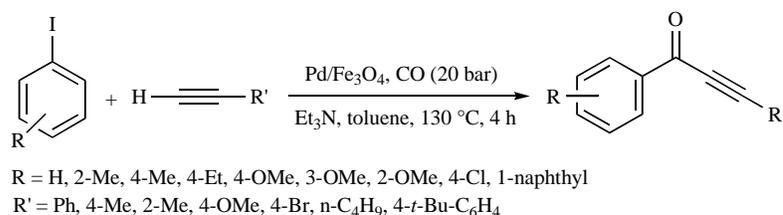
Fig. (20). TEM images of (A, B) fresh Pd/MIL-101 and (C) used Pd/MIL-101. Reprinted from ref. 71 with permission. Copyright (2015) John Wiley & Sons.

activity. The effect of electron withdrawing and donating substituents was tested on the yield of the coupling products which gave an excellent and slightly lower yield, respectively. Furthermore, the results showed that the yield of coupling product using *para*-substituted aryl iodides is more than its *ortho*-substituted ones probably because of the strict effect. Also, the reaction time required for the aryl bromides is more than aryl iodides and the yield using chlorobenzene under the optimized conditions was not desirable. Moreover, the investigation of the reaction yield under severe conditions (*i.e.* 4.0 equivalent of Et₃N, 100 °C and 2 wt% Pd loading) showed that Pd(0)/MCoS-1 catalytic system is not active enough to obtain a considerable yield of product during the coupling reaction of less reactive chlorobenzene and phenylacetylene.

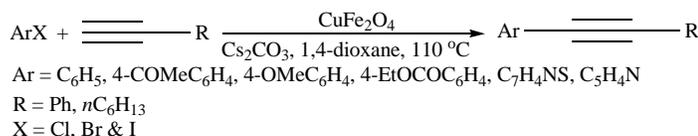
Kantam *et al.* have developed a highly efficient heterogeneous catalyst system, Pd/MIL-101, from metal-organic framework MIL-101 and palladium nanoparticles. The high porosity and surface area of MIL-101 and also high stability of nano-size palladium particles act as an active catalyst for the Sonogashira cross-coupling reaction and does not require external ligands. The coupling reactions of aryl and heteroaryl bromides with various alkynes are performed using low loading of palladium on MIL-101 under copper-free and aerobic conditions in the presence of CH₃COOK in DMA solvent at 130 °C for 6 h (Scheme 52) [71]. This catalyst was easily separated from the reaction mixture and used for other four reaction cycles without further purification (Fig. 20).

2.6. Magnetically Recyclable Nanocatalysts

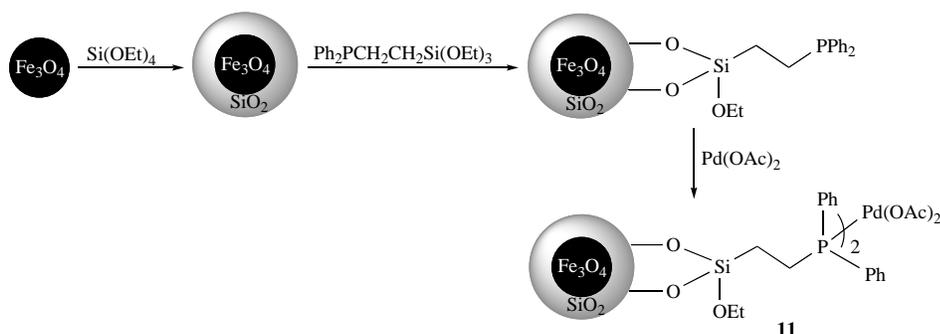
Recent advances in the development of metal and metal oxide based MRNCs (magnetically recyclable nanocatalysts) for catalytic conversion of organic compounds have led to a dramatic expansion of their potential applications.



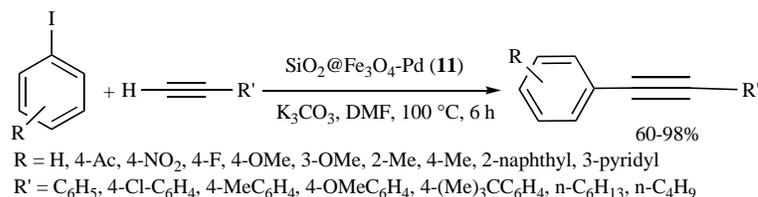
Scheme 53.



Scheme 54.



Scheme 55. Preparation of the magnetic nanoparticle-supported palladium catalyst. Reprinted from ref. 75 with permission. Copyright (2015) John Wiley & Sons.



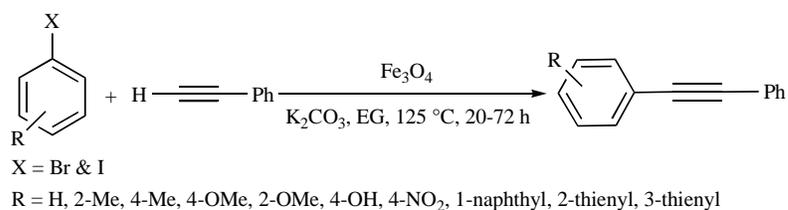
Scheme 56.

In 2008, Xia *et al.* reported a recyclable phosphine-free catalyst system for α,β -alkynyl ketones synthesis. Using palladium nanoparticles on Fe₃O₄ nanoparticles (Pd/Fe₃O₄) and Et₃N, the carbonylative Sonogashira coupling of aryl iodides with alkynes was carried out and the desired products were isolated in moderate to excellent yields under ligand-free conditions (Scheme 53) [72]. The catalyst was prepared through a wet impregnation incorporating palladium nanoparticles and superparamagnetic Fe₃O₄ nanoparticles in a KBH₄ solution. Because of the magnetic behavior of Fe₃O₄, the catalyst was recoverable and could be reused seven times with sustained selectivity and activity.

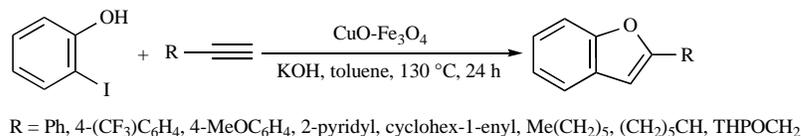
Following the production of micro-pine morphological structure of dendrite nanoferrites and its dopamine functionalization followed by reaction with Na₂PdCl₄ and hydrazine reduction, they leads to the synthesis of amino functionalized micro-pine ferrites Pd NPs for Pd catalyzed coupling reactions [73]. The Sonogashira coupling reaction of aryl iodides and bromides using the aforementioned catalyst in the presence of potassium carbonate and pyridine in DMF at 100 °C under microwave irradiation demonstrated a good yield of coupling products. Leaching and recyclability were analyzed performing Heck couplings under similar reaction conditions which showed the negligible palladium leaching probably due to the well-defined amine binding sites located on the surface of the micro-pine ferrites.

A Pd-free system of magnetite and other ferrite NPs substitutions as MFe₂O₄ (M: Cu⁺², Co⁺² and Ni⁺²) were proposed by Panda *et al.* for Sonogashira reaction. Fe₃O₄, CoFe₂O₄ and NiFe₂O₄ NPs are inactive catalysts whereas CuFe₂O₄ NPs catalyzed the combination of aryl halides and substituted alkynes in an alkylation reaction in 1,4-dioxan at 110 °C and in the presence of 2 eq. of Cs₂CO₃ with a suitable yield (Scheme 54) [74]. In catalyst combination Fe plays a significant role through the reaction of phenylacetylene and iodobenzene in the presence of CuO NPs in which diphenylacetylene was isolated with a low yield (25 %), therefore, the synergistic effects of Fe and Cu in the structure of CuFe₂O₄ NPs was demonstrated to co-catalyze the alkylation reaction. Furthermore, during the studies on mentioned catalyst, it was found that a limit amount of Fe and Cu leached into the reaction media. Also the catalyst could be reused for three reaction cycles with insignificant loss of its activity.

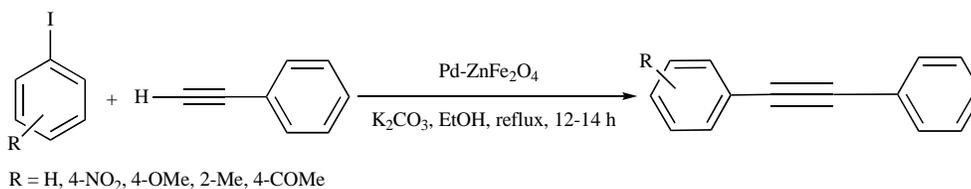
In 2012, Wang and co-workers were synthesized easily recoverable magnetic nanoparticles-supported palladium catalyst (SiO₂@Fe₃O₄-Pd) (Scheme 55) for the C-C coupling reactions. The SiO₂@Fe₃O₄-Pd catalyst was used for Sonogashira reactions of aryl iodides and activated aryl bromides with terminal alkynes in the presence of DMF and K₂CO₃ at 100 °C for 6 h (Scheme 56) [75]. The coupling products were obtained in good to excellent yields whereas a lower yield was observed using an *ortho*-substituted aryl



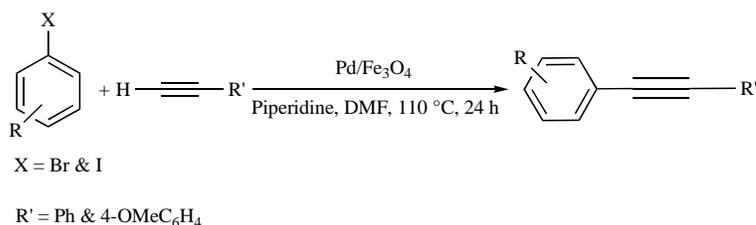
Scheme 57.



Scheme 58.



Scheme 59.



Scheme 60.

iodide, therefore, the introduced catalytic system had not a suitable ability to run the coupling reaction of aryl chloride and terminal alkynes. Also, the reusability and recoverability of mentioned catalyst was at least eight times without significant loss of catalytic activity.

Firouzabadi and co-workers reported the application of magnetite (Fe₃O₄) nanoparticles in the Sonogashira-Hagihara reactions of aryl iodides and activated heteroaryl bromides with alkynes in ethylene glycol under ligand-free conditions (Scheme 57) [76]. The results showed that other solvents such as water, DMF and NMP are not suitable for this reaction. The catalyst was recovered using an external magnet and reused five times without appreciable loss in its catalytic activity.

The Sonogashira cyclization reaction for catalytic synthesis of benzo[*b*]furanes and indoles using Pd/Cu and Cu supported magnetite as catalyst was studied by Cano *et al.* in 2012, (Scheme 58) [77]. The mentioned catalysts required no application of expensive and tedious organic ligands and showed excellent yield under reaction conditions. Also, the catalyst was easily prepared using impregnation of Cu or Pd salts on Fe₃O₄. Furthermore, the selectivity of the reaction was quite important because of using a reagent with two C-C bonds and stopping the reaction after the first cyclization. Also, the electron-rich substituted aromatic rings demonstrated an excellent yield. Moreover, the recyclability of the catalysts through a simple reagent was 10 times with insignificant loss in its activity.

In 2013, the synthesis of super-paramagnetic Pd-ZnFe₂O₄ catalyst was reported by Singh *et al.* [78]. The Sonogashira coupling reaction of terminal alkynes with aryl halides was run using the catalyst in the absence of Cu co-catalyst (Scheme 59). Furthermore,

the catalyst could be reused to three cycles while keeping its activity.

In 2013, Kim and co-workers reported another method for the Sonogashira coupling reaction using Pd/Fe₃O₄ heterodimeric nanocrystals catalyst system (Scheme 60) [79]. TEM image of heterobimetallic nanoparticles obtained are shown in Figure 21. The nanocrystals-catalyzed Sonogashira reaction proceeded smoothly without requiring any additives and offered reaction conditions that are environmentally friendly and atom efficient. The results showed good yields of the Sonogashira products from the reactions with aryl iodides possessing electron-rich or electron-poor positions, regardless the position of substituent. In this process the catalyst was easily separated by an external magnet and recycled six times without losing its catalytic activity.

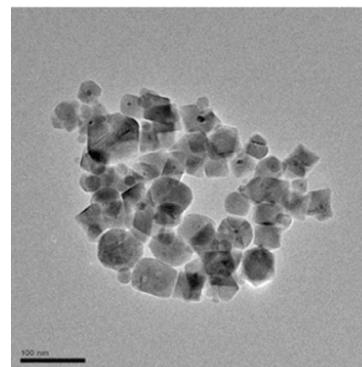


Fig. (21). TEM image of heterobimetallic nanoparticles. Reprinted from ref. 79 with permission. Copyright (2013) Sciencedirect.

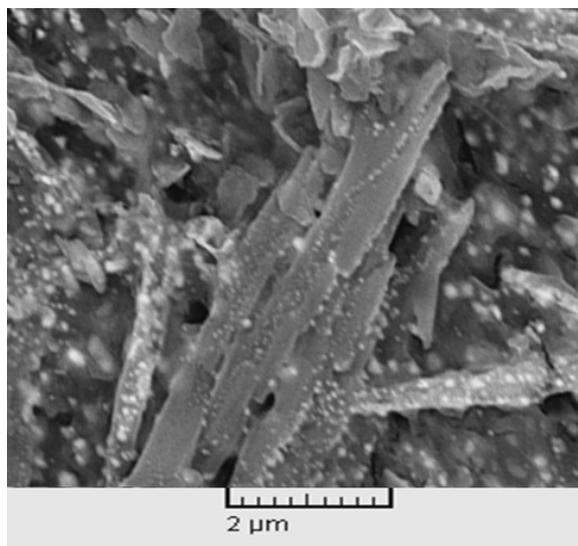


Fig. (22). The Scanning electron microscope image of Pd@Fe₃O₄. Reprinted from ref. 80 with permission. Copyright (2014) Royal Society of Chemistry.

In 2014, Nasrollahzadeh *et al.* published the preparation of Pd@Fe₃O₄ nanowires (Fig. 22) with highly magnetic sensitivity and stability through the arc discharge of Fe in deionized (DI) water and electroless deposition of palladium [80]. The Pd/Fe₃O₄ exhibited highly catalytic activity for the Sonogashira coupling reactions in the presence of piperidine as the base and DMF as solvent at 110 °C for 24 h under the nitrogen atmosphere (Scheme 61). The catalyst exhibited a strong magnetic response which could be rapidly separated by an external magnet and reused six times with no loss of activity.

In 2014, Firouzabadi and co-workers described the preparation of Pd nanoparticles-supported on agarose-functionalized magnetic nanoparticles of Fe₃O₄ using a simple route (Fig. 23). The catalyst used in the Suzuki-Miyaura, Heck-Mizoroki and Sonogashira-Hagihara (Scheme 62) coupling reactions of aryl halides in wet PEG200 showed a good activity and high recyclability without apparent loss of activity over six consecutive runs by simple separation with an external magnet [81].

In 2014, Kumar and his co-workers designed and synthesized hexaphenylbenzene derivative **3** containing azaindole groups which serve as reactors for the preparation of ferromagnetic iron oxide (α -

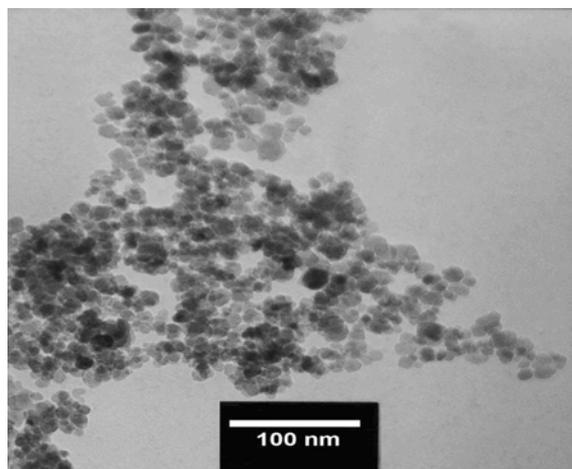
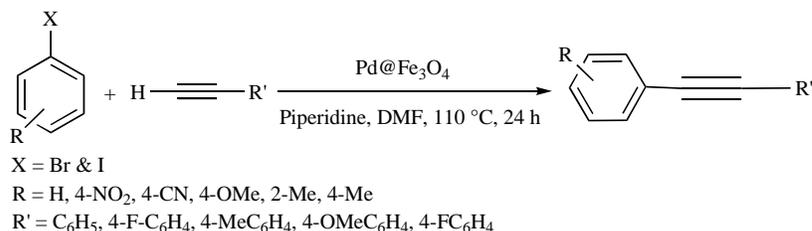


Fig. (23). TEM image of Pd@agarose-Fe₃O₄ with the average spherical particle size 10-15 nm. Reprinted from ref. 81 with permission. Copyright (2014) Royal Society of Chemistry.

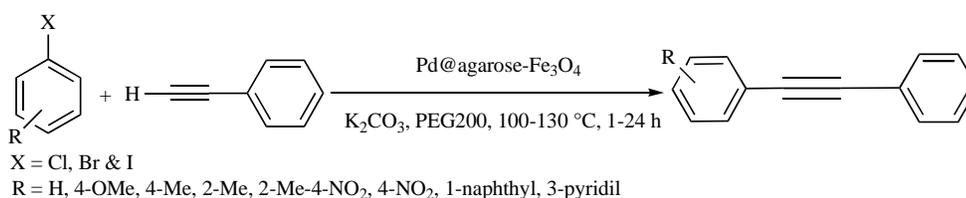
Fe₂O₃) nanoparticles in aqueous medium at room temperature. The hexaphenylbenzene derivative **14** was prepared through the condensation of compound **12** with 7-azaindole-3-carboxaldehyde **13** in THF/under reflux conditions in 85% yield (Scheme 63). The generated α -Fe₂O₃ NPs showed excellent catalytic activity in palladium-, copper- and amine-free Sonogashira coupling reactions (Scheme 64) [82].

In 2015, Phukan and co-workers successfully immobilized Pd NPs onto the CoFe₂O₄ magnetic nanoparticles. Then, the Pd-CoFe₂O₄ was used to catalyze the Sonogashira coupling reaction of aryl halides with various alkynes in ethanol at 70 °C for 4-18 h (Scheme 65) [83]. This palladium catalyst system could be easily separated using an external magnet and reused up to five catalytic cycles without losing its activity.

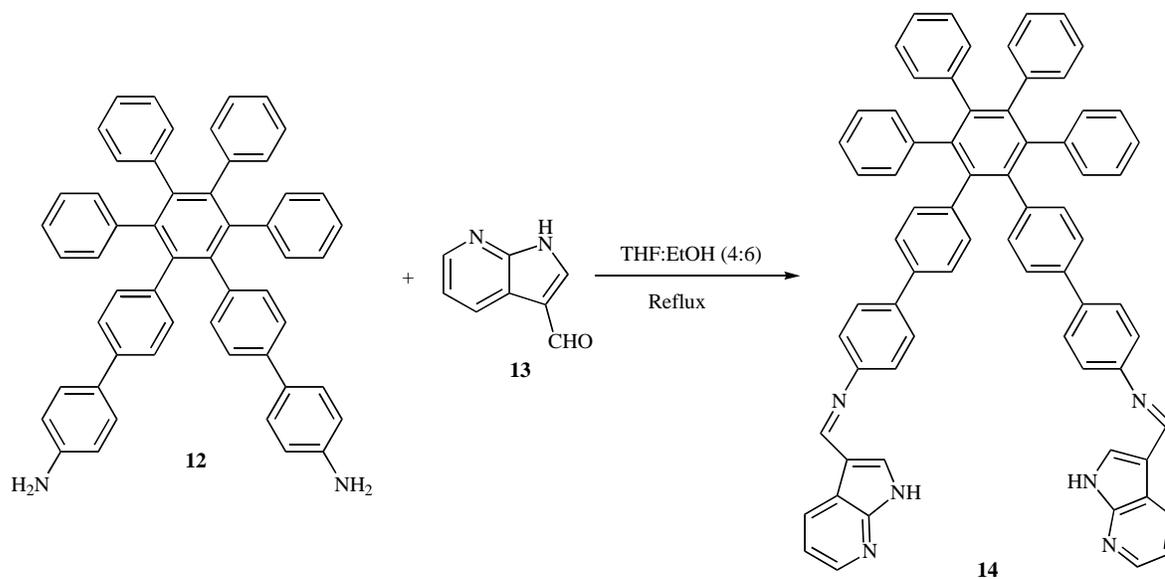
Very recently, Nasrollahzadeh *et al.* offered a green and environmentally friendly synthetic method for synthesis Pd/Fe₃O₄ nanoparticles using *Euphorbia condylocarpa M. bieb* root extract as reducing and stabilizing agent (Fig. 24). Catalytic applications of the resulted catalyst system were investigated in ligand- and copper-free Sonogashira and Suzuki coupling reactions (Scheme 66) [84]. This catalyst can be recovered by using a magnet and reused several times without significant loss of its catalytic activity.



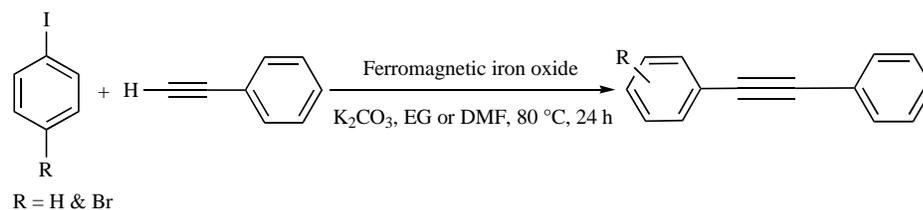
Scheme 61.



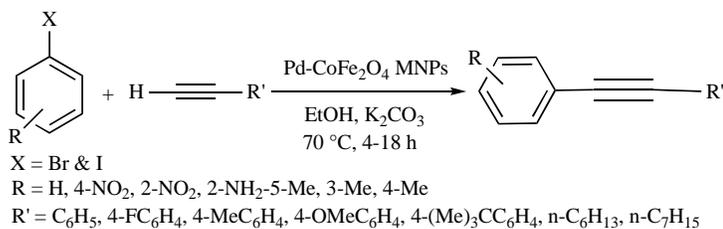
Scheme 62.



Scheme 63. Synthesis of a HPB based derivative 3. Reprinted from ref. 82 with permission. Copyright (2013) Royal Society of Chemistry.



Scheme 64.



Scheme 65.

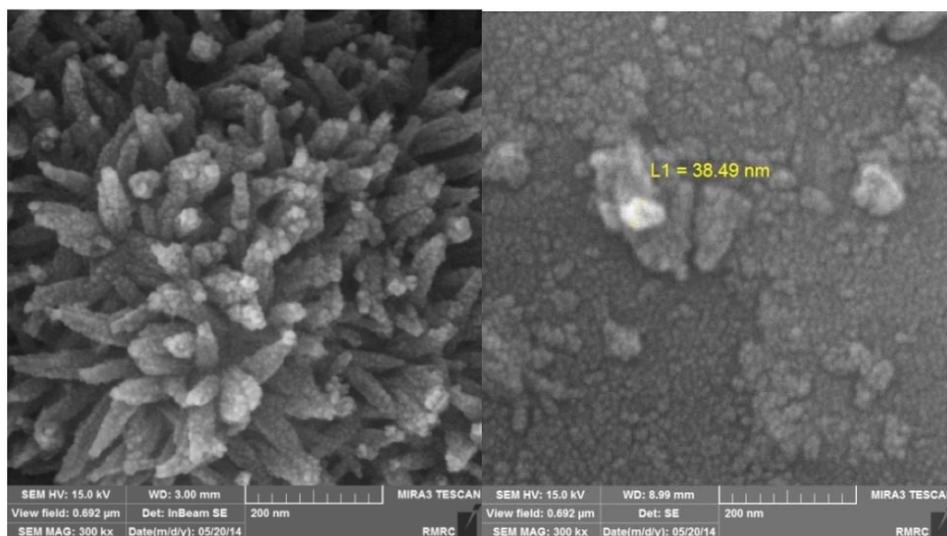
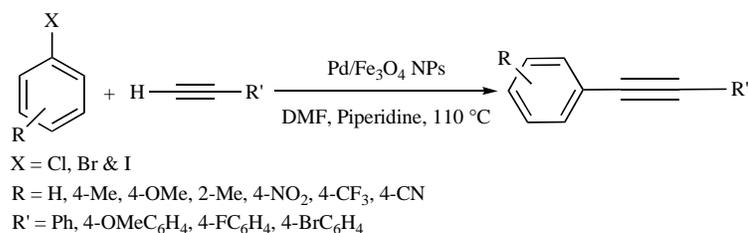
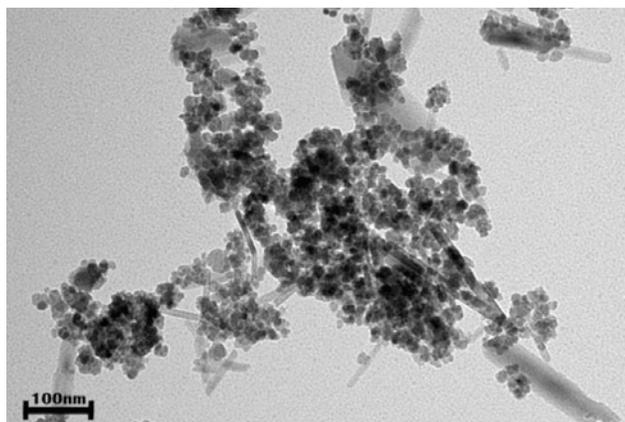
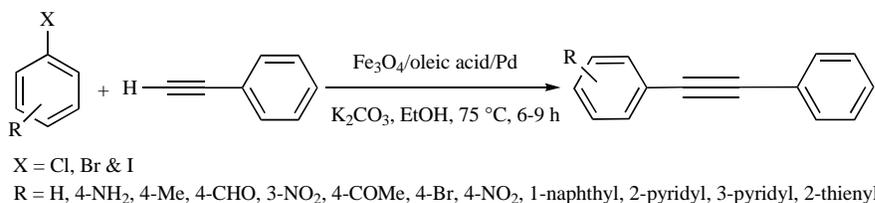


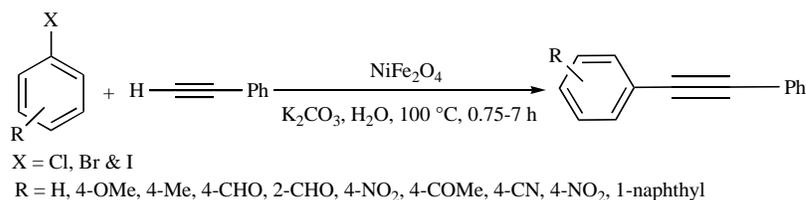
Fig. (24). FE SEM images of Pd/Fe₃O₄ NPs. Reproduced with permission from ref. 84. Copyright (2015) Sciencedirect.



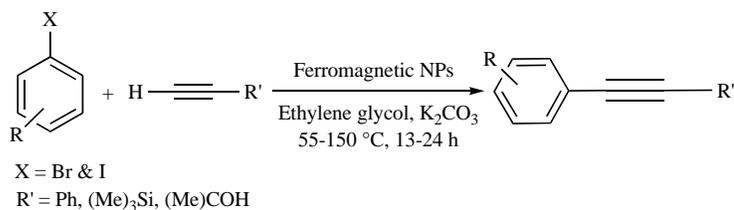
Scheme 66.

Fig. (25). TEM image of Fe₃O₄/oleic acid/Pd. Reproduced with permission from ref. 85. Copyright (2015) Sciencedirect.

Scheme 67.



Scheme 68.



Scheme 69.

Very recently, immobilization an oxime-derived palladacycle on a highly active Fe₃O₄/oleic acid solid support was reported by Karami *et al.* (Fig. 25) [85]. This system acts as a heterogeneous catalyst for the copper-free Sonogashira cross-coupling reactions. By the immobilization of this complex on a Fe₃O₄/oleic acid solid support, it was possible to carrying out the Sonogashira cross-coupling reaction in ethanol and water-organic solvent mixtures (Scheme 67). This heterogeneous catalyst can be separated by an external magnet and reused six times without loss of its activity.

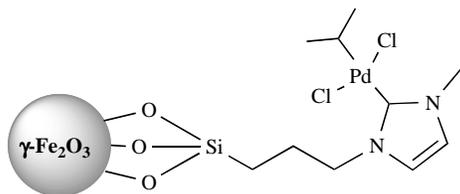
Moghaddam *et al.* has recently published the preparation of nickel ferrite with magnetic sensitivity. The nickel ferrite exhibited

highly catalytic activity for the copper-free Sonogashira reaction in water as a green solvent (Scheme 68) [86]. The catalyst exhibited a magnetic response to separate by an external magnet and several times reusability.

Quite recently, Bhalla *et al.* synthesized *in situ* generated ferromagnetic α -Fe₂O₃ NPs as an efficient and recyclable catalyst for carbon-carbon bond formation *via* Sonogashira-Hagihara coupling reactions (Scheme 69) [87]. In this method, different aryl halides reacted with different alkynes to give products in good to excellent yields. The catalyst could be rapidly separated by an external mag-

netdue to the ferromagnetic nature of α - Fe_2O_3 NPs and reused 13 times with sustained selectivity and activity.

In continuation of study about the Sonogashira coupling reaction, γ - Fe_2O_3 @NHCPd catalyst (Scheme 70) was investigated [88]. During this research, the Sonogashira reaction using the above catalyst was studied for both aryl bromides and iodides with phenylacetylene, which demonstrated an excellent yield (Scheme 71). Also, the mentioned catalyst was recycled over five times with a negligible loss in activity.

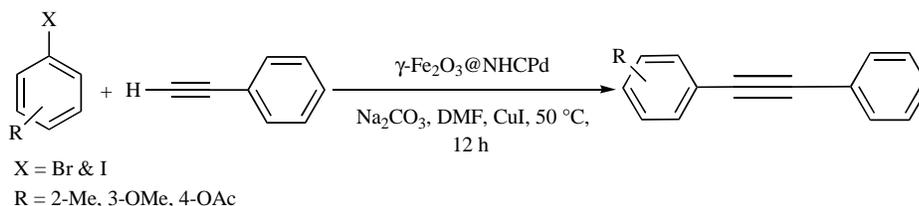


Scheme 70. The structure of the γ - Fe_2O_3 @NHCPd.

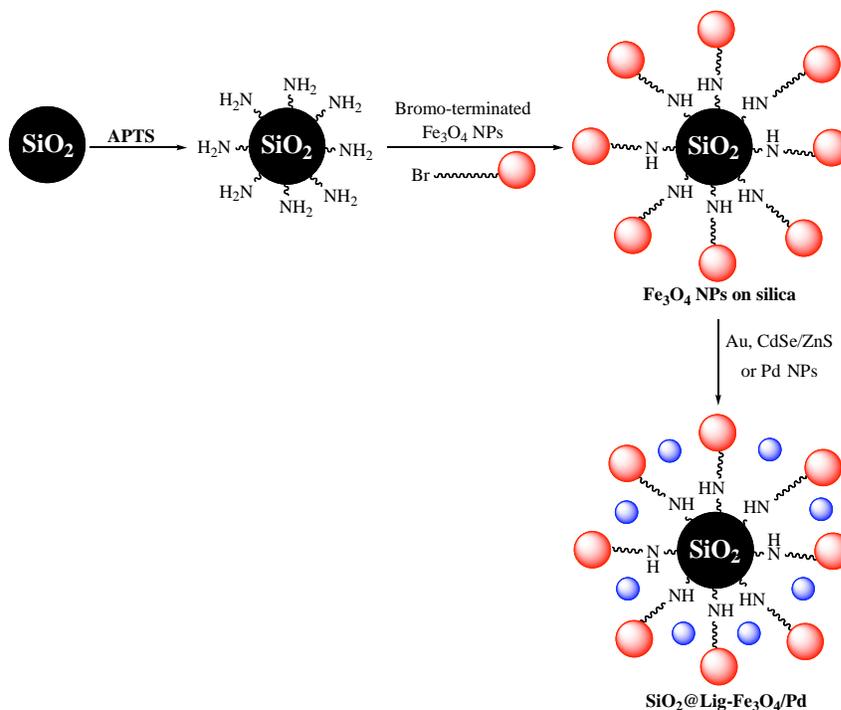
In 2006, Hyeon *et al.* proposed a process for the assembly of multifunctional nanoparticles on silica nanospheres [89]. For synthesis the mentioned NPs, silica spheres were functionalized with

amino groups using aminopropyltrimethoxysilane (Scheme 72), then the capping oleic acid ligands of the Fe_3O_4 NPs exchanged with 2-bromo-2-methylpropionic acid and then coupled with amino groups for production the Fe_3O_4 NPs on the silica spheres. In continuation to the synthesis of multifunctional NPs on silica nanospheres, functional Au, CdSe/ZnS and Pd NPs were assembled on produced magnetite SiO_2 . The ability of assembled multifunctional catalyst for Sonogashira reaction of aryl iodides and bromides (Scheme 73) demonstrated an excellent activity for the first cycle of the reaction but a descending activity (98 to 17% conversion) over four successive recycling process because of the loss of Pd NPs from the silica nanospheres.

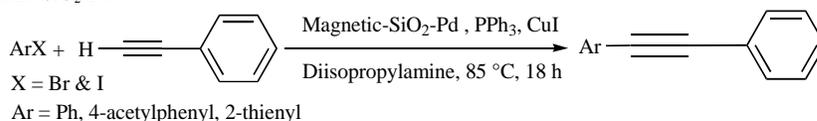
In another study on Sonogashira reaction, Pd immobilized on N-doped magnetite carbon NPs introduced as a reusable catalyst by Jang *et al.* for the mentioned reaction [90]. During this study the coupling process of 4-bromoacetophenone with phenylacetylene in DMSO (20 mL) using Nitrogen-doped magnetic carbon nanoparticles (0.01 g) with Na_2CO_3 in the presence of CuI as co-catalyst at 100°C was investigated (Scheme 74). The synthesized catalyst under the above conditions caused to produce a high yield of product and a suitable reusability for more than three times with insignificant loss of activity.



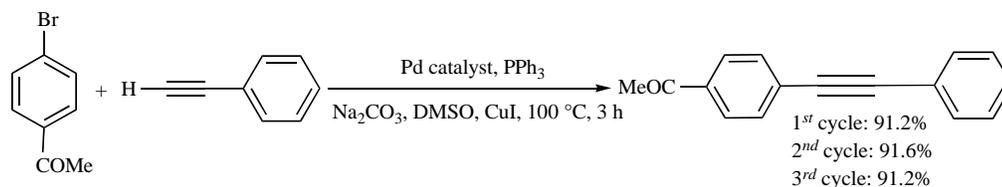
Scheme 71.



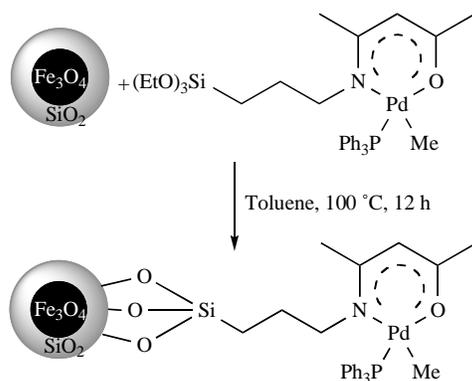
Scheme 72. Synthesis of magnetic- SiO_2 -Pd.



Scheme 73.



Scheme 74.

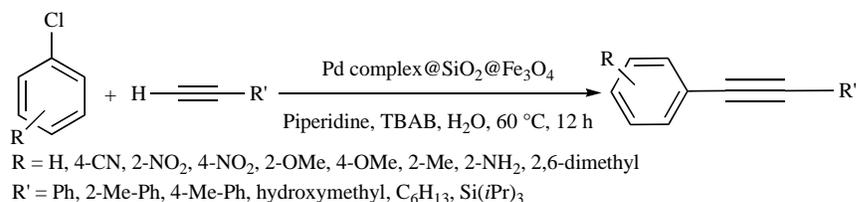
Scheme 75. Synthesis of silylated palladium complex@SiO₂@Fe₃O₄.

For more achievements in this field, In 2010, a silylated palladium complex successfully immobilized on the surface of robust SiO₂@Fe₃O₄ that was coated with a thin layer of silica using sol-gel method (Scheme 75) [91]. Jin and Lee reported the use of Pd@SiO₂@Fe₃O₄ catalyst as a highly active, easily recoverable, and practical heterogeneous catalyst for the Suzuki, Sonogashira (Scheme 76) and Stille coupling reactions of unreactive aryl chlorides.

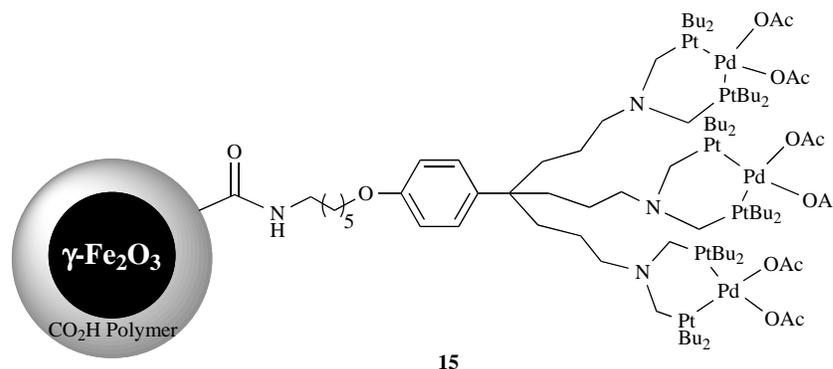
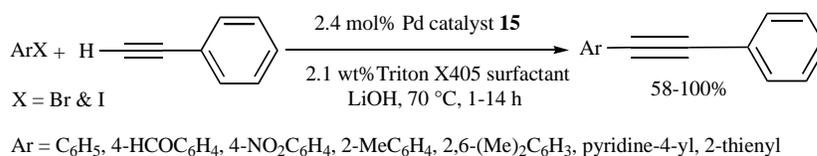
In fact what is important during this reaction was easily separation of catalyst from the reaction media using an external magnetic field and first time application of aqueous media.

In recent studies, a super-paramagnetic NPs (γ -Fe₂O₃/polymer)-supported dendritic catalyst based on a bulky electron-rich phosphine Pd^{II} complex was presented by Rosario-Amorin *et al.* [92]. The catalyst **15** (Scheme 77) was synthesized using the reaction of carboxylic acid groups of the core-shell γ -Fe₂O₃/polymer of super-paramagnetic nanoparticles with the amino groups at the focal point of an amino-terminated Dendron. Then its catalytic activity for the copper-free Sonogashira C-C coupling reaction was investigated (Scheme 78). During the reaction, the effect of surfactant in particles colloidal dispersion demonstrated an important role to achieve the cross-coupling yield. Also the methanol reaction media showed a similar effect to the aqueous media including surfactant.

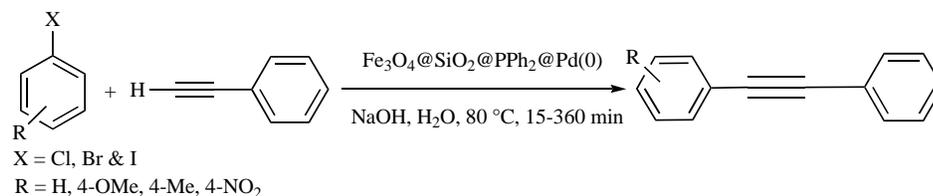
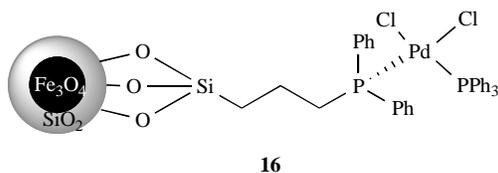
In 2013, Zolfigol *et al.* have reported the design of a novel system for the preparation of the {Fe₃O₄@SiO₂@PPh₂@Pd(0)} as a novel magnetically separable catalyst. {Fe₃O₄@SiO₂@PPh₂@Pd(0)} as a black powder was used for the Sonogashira cross-coupling reactions of aryl halide derivatives with phenylacetylene



Scheme 76.

Scheme 77. Synthesis of (γ -Fe₂O₃/polymer)-supported dendritic catalyst.

Scheme 78.

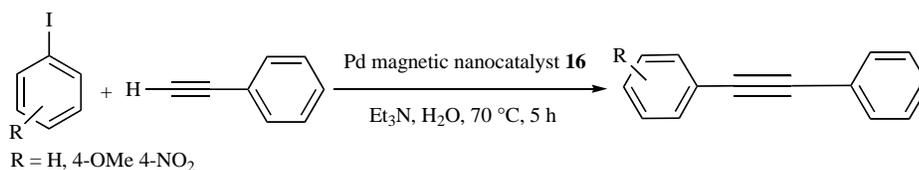
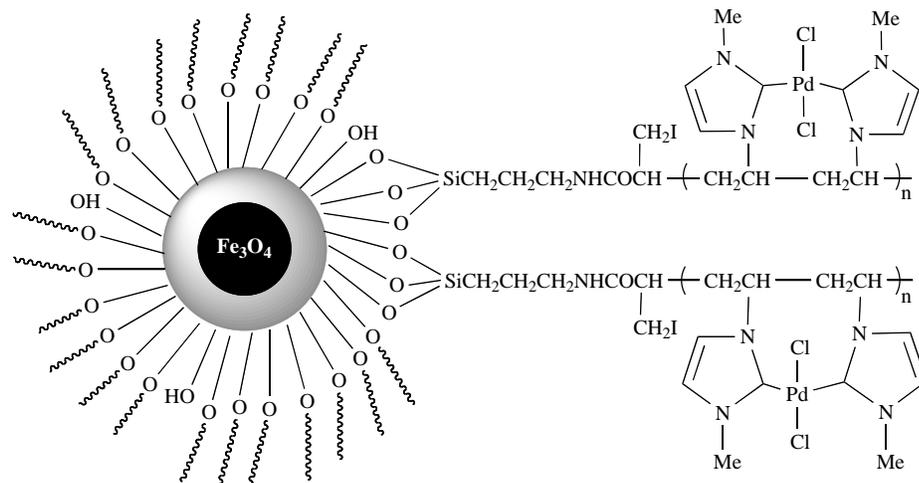
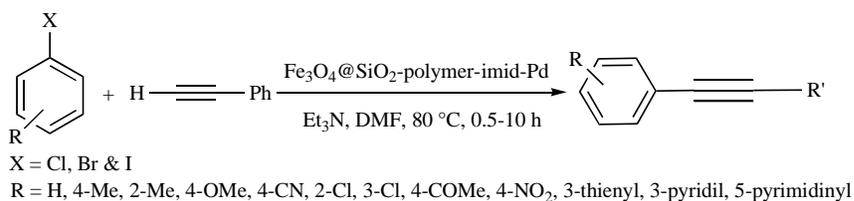
**Scheme 79.****Scheme 80.** Synthesis of palladium magnetic nanocatalyst.

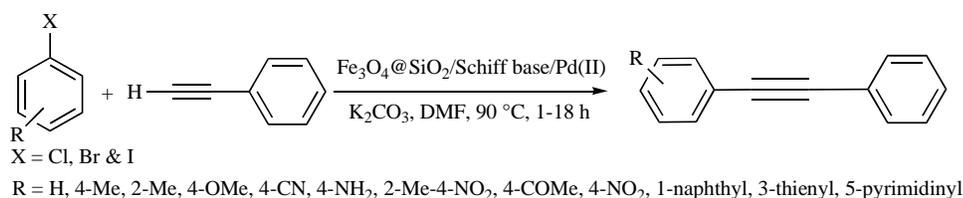
in water and in the presence of NaOH as base (Scheme 79) [93]. A diverse range of coupling products was obtained in a good to high yield. Also the magnetically separable Pd catalyst could be recycled and reused several times (up to 6 times) without losing the catalytic properties.

Further the studies done by Chen, Zhang and Li on catalyst effect in Sonogashira reactions lead to synthesis the PdCl₂(PPh₃)₂ coordinated to the phosphine-functionalized silica core-shell mag-

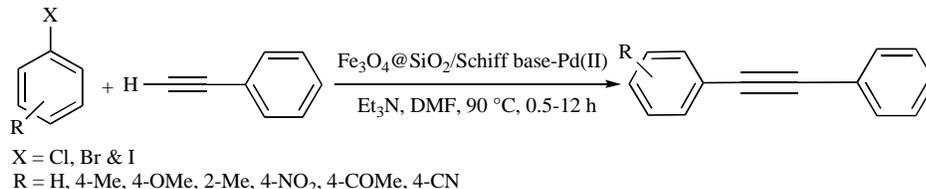
netic NPs (Schemes 80 and 81) [94]. The results of this study demonstrated that the activity and selectivity of synthesized catalyst **16** was similar to the PdCl₂(PPh₃)₂ catalyst for highly dispersion of Pd(II) active sites on the surface of magnetic support during the cross coupling reactions. Furthermore, only the conversion of aryl iodides with phenylacetylene was satisfactory in coupling reaction but the catalyst was not effective for the coupling of aryl bromides with phenylacetylene.

In the next year, other group reported another method for Sonogashira coupling reaction using Fe₃O₄@SiO₂-polymer-imid-Pd magnetic porous nanospheres (Schemes 82 and 83) [95]. Fe₃O₄@SiO₂ nanosphere was synthesized by using prepared Fe₃O₄ magnetite nanoparticles by simple co-precipitation method as the core, tetraethoxysilane (TEOS) as the silica source and polyvinyl alcohol (PVA) as the surfactant. Then Fe₃O₄@SiO₂ was coated with polymeric *N*-heterocyclic carbene/Pd. The catalyst could be sepa-

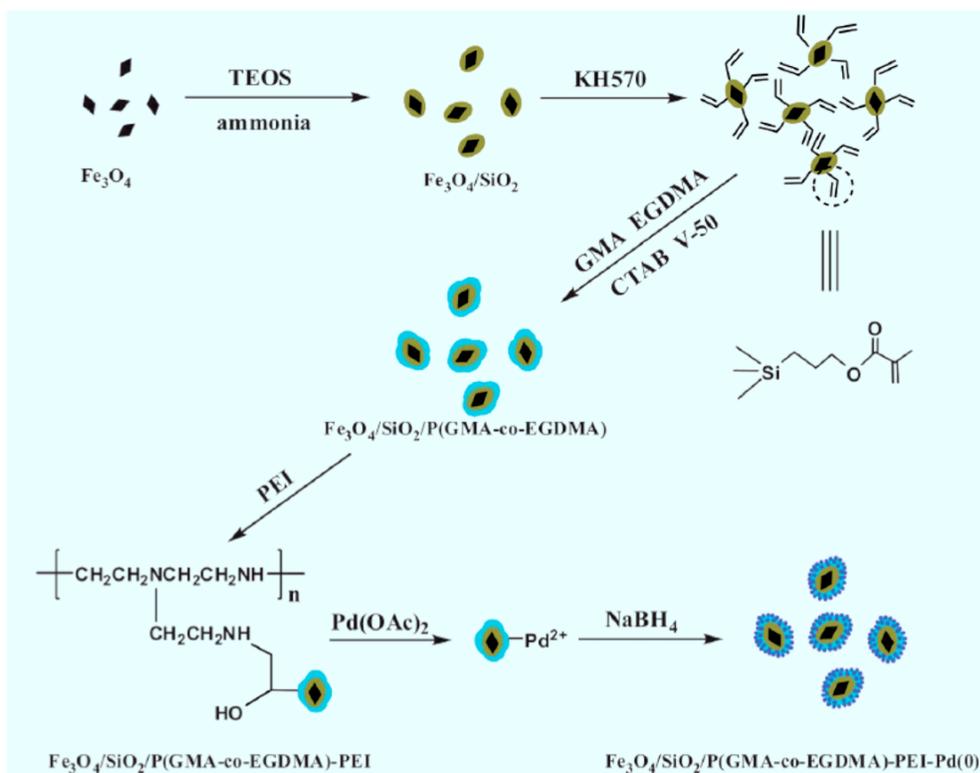
**Scheme 81.****Scheme 82.** The structure of the Fe₃O₄@SiO₂-polymer-imid-Pd magnetic porous nanospheres.**Scheme 83.**



Scheme 84.



Scheme 85.



Scheme 86. Preparation process of the $\text{Fe}_3\text{O}_4/\text{SiO}_2/\text{P}(\text{GMA-co-EGDMA})\text{-PEI-Pd}(0)$ catalyst. Reproduced with permission from ref. 98. Copyright (2015) Royal Society of Chemistry.

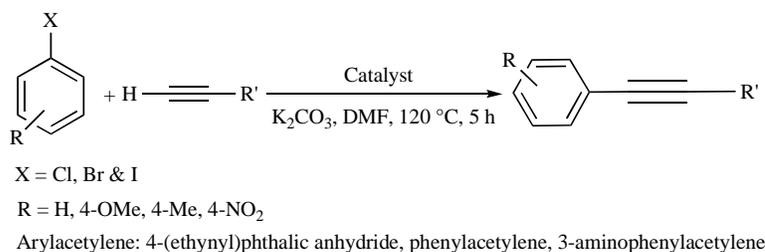
rated using an external magnet and could be reused for six cycles without significant loss of its catalytic activity.

Javidi and co-workers have investigated the use of Schiff base complex of metal ions (Zn, Mn, Cd, Co, Cu, Ni, Fe and Pd) immobilized on superparamagnetic Fe_3O_4 nanoparticles in the copper and phosphine-free Sonogashira coupling reaction of aryl halides with phenylacetylene. Following the catalysts evaluation, $\text{Fe}_3\text{O}_4/\text{SiO}_2/\text{Schiff base-Pd(II)}$ was the best choice, giving the desired products in higher conversion (Scheme 84) [96].

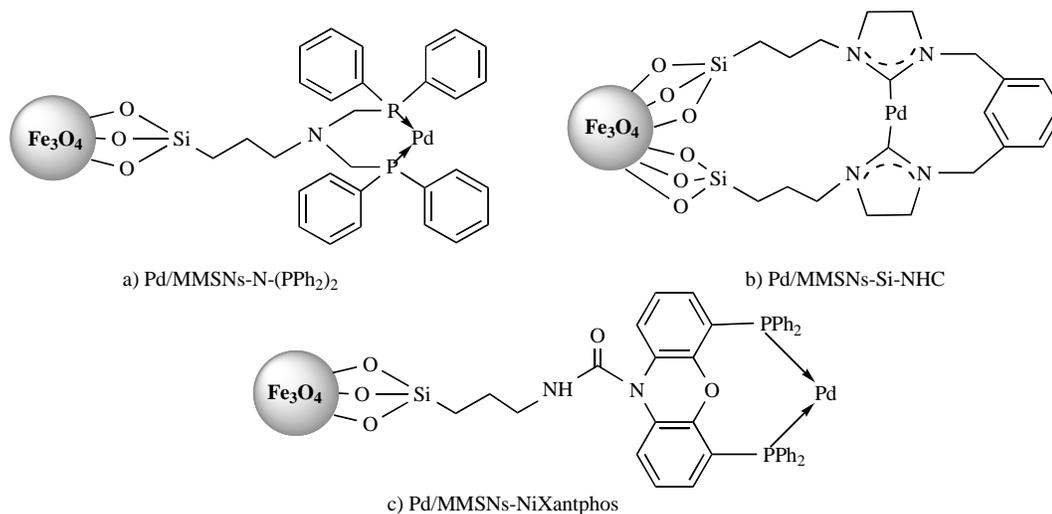
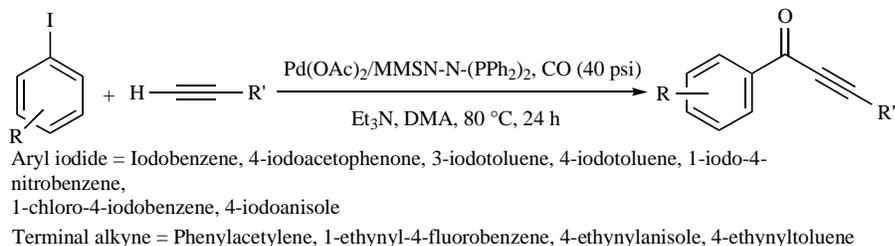
In 2014, Esmailpour and co-worker have offered superparamagnetic nanoparticles functionalized with Schiff base complex of Pd(II) [$\text{Fe}_3\text{O}_4/\text{SiO}_2/\text{Schiff base-Pd(II)}$] as an efficient catalyst for copper-free and phosphine ligand-free Sonogashira reactions of aryl halides (Scheme 85) [97]. Notably, this novel catalyst also gave an excellent yield (79-92%) in coupling with less reactive aryl chlorides.

In addition to facility preparation, high yield and short reaction times, the easy separation by external magnetic field and recovering at least 6 times without loss in activity are the benefits of used catalytic system.

In 2015, Zhang and co-workers were fabricated a novel magnetic $\text{Fe}_3\text{O}_4/\text{SiO}_2/\text{P}(\text{GMA-co-EGDMA})$ composite nanoparticles grafted with hyperbranched/linear polyethylenimine ligands. Then Pd NPs were immobilized on carrier surface through Pd^{2+} ions complexation with multifunctional organic ligands (Scheme 86) [98]. The supported Pd nanoparticle catalyst ($\text{Fe}_3\text{O}_4/\text{SiO}_2/\text{P}(\text{GMA-co-EGDMA})\text{-PEI-Pd}(0)$) was investigated by catalyzing the copper-free Sonogashira cross-coupling reaction between aryl halides and aryl acetylene in the presence of K_2CO_3 as base and DMF as solvent at 120°C for 5 h (Scheme 87). The catalyst can be reused eight times without obvious loss of catalytic activity.



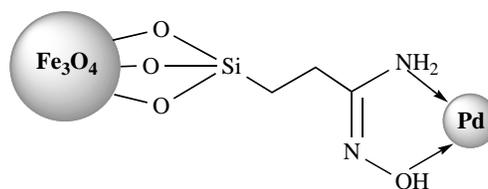
Scheme 87.

Scheme 88. Palladium supported on a) MMSN-N-(PPh₂)₂, b) MMSN-Si-NHC, and c) MMSN-NiXantphos.

Scheme 89.

Abu-Reziq and Natour reported a study on the preparation of functionalized magnetic mesoporous silica nanoparticle-supported palladium catalysts and their application in the copper-free carbonylative Sonogashira coupling reactions of aryl iodides with terminal alkynes [99]. Magnetic mesoporous silica nanoparticles (Fe₃O₄@mSiO₂ or MMSN) with a surface area of 1909 m²g⁻¹ were prepared by a sol-gel route under the basic conditions using tetraethoxysilane (TEOS) as the silane monomer, magnetite nanoparticles (MNP), and cetyltrimethylammonium bromide (CTAB) as both stabilizer and mesostructure-templating surfactant agent. The MMSN were modified with phosphine and N-heterocyclic carbenes (NHCs) ligands and then employed as catalyst nanosupports for the immobilization of palladium species on the surface within the pores of MMSN. Of the various functionalized MMSN (Scheme 88), palladium(II) acetate supported on MMSN-N-(PPh₂)₂ showed high activity in the carbonylative Sonogashira coupling reaction. The reaction was carried out in the presence of 40 psi carbon monoxide, triethylamine as the base and dimethylacetamide as reaction solvent at 80 °C for 24 h which coupling products were obtained in good to excellent yields (Scheme 89).

In 2015, Veisi and co-workers described a new procedure for synthesis of a novel Fe₃O₄/amidoxime(AO)/Pd nanocatalyst through grafting of AO groups on Fe₃O₄ NPs and subsequent deposition of Pd NPs (Scheme 90) [100]. As shown in Figure 26, the diameter of Fe₃O₄ NPs is 15-20 nm and also Pd NPs with average size of 3 nm entrapped in iron oxide. The produced Fe₃O₄/AO/Pd catalyst could catalyze the phosphine-free Sonogashira reactions between aryl halides and terminal alkynes in dimethylformamide and Et₃N catalyzed by Fe₃O₄/AO/Pd as an effective nano catalyst at 80 °C for 0.5 to 12 h (Scheme 91). The highly stable catalyst was recovered in a facile manner by applying an external magnet device and recycled seven times without any significant loss in activity.

Scheme 90. The Structure of the Fe₃O₄/AO/Pd catalyst.

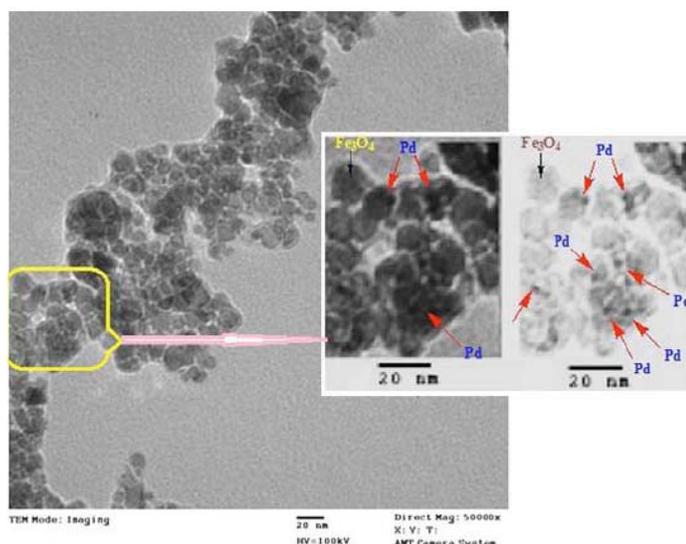
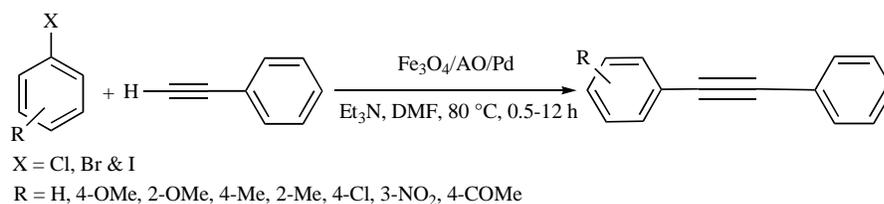
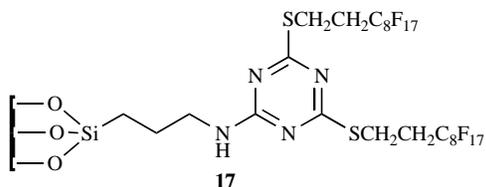


Fig. (26). TEM image of Fe₃O₄/AO/Pd. Reprinted from ref. 100 with permission. Copyright (2015) John Wiley & Sons.



Scheme 91.



Scheme 92.

2.7. Application of Other Supports Such as Silica, SBA-15, MCM-41, BaO, Smopex[®], ZnO, Celluloses, Montmorillonite, Al₂O₃, Chitosan and Natural Biomaterials in the Sonogashira Reaction

Loading of metal and metal oxide NPssupported on the silica, SBA-15, MCM-41, BaO, Smopex[®], ZnO, xylan-type hemicelluloses, montmorillonite, Al₂O₃, chitosan and natural biomaterials is a promising field of research about catalysts.

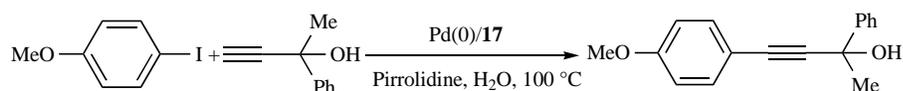
In 2009, Lambert group was prepared Rh nanoparticles supported on an acidic solid (γ -alumina) and on a basic solid (BaO) both in the absence and presence of tetra butyl ammonium acetate as a base. The Sonogashira reaction of iodobenzene with phenylacetylene was carried out in DMF at 120 °C for 24 h under the inert (argon) atmosphere [101]. The Rh NPs/ γ -alumina was better catalyst than Rh NPs/BaO. Moreover, the size of NPs played an important role in the yield of the reaction in which larger catalysts

(8 nm) are better than very tiny ones (2 nm) because of the adversely strict effect of very small NPs.

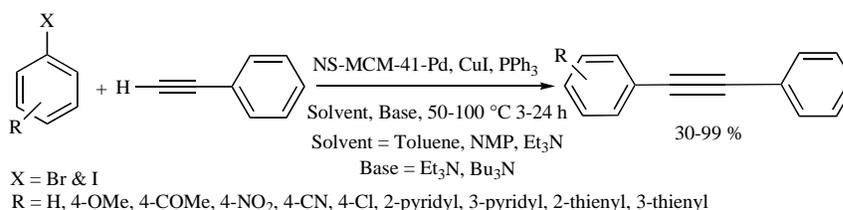
Perfluoro-tagged Pd NPs immobilized on silica gel (Scheme 92) was used as catalyst for the alkynylation coupling of terminal alkynes with aryl iodides and some aryl bromides using pyrrolidine in refluxed water as solvent [102]. It was shown that highly levels of Pd (39-240 nm) were found in the crude products due to the relative weakness of the fluoros-fluoros interactions, therefore, its reusing was limited to four runs but when the fluorinated system linked to the silica gel 17 the reusability of catalyst increased to eleven runs (Scheme 93).

A heterogeneous catalyst of nanosized MCM-41-Pd (NS-MCM-41-Pd), was used to catalyze the Sonogashira coupling of aryl and heteroaryl halides with terminal alkynes in the presence of CuI and triphenylphosphine (Scheme 94) [103]. The coupling products were obtained in high yields using low Pd loadings to 0.01 mol%, and the NS-MCM-41-Pd catalyst was recovered by centrifugation of the reaction solution and also reused in further runs without significant loss of reactivity. Under similar conditions, NS-MCM-41-Pd was used for the Sonogashira coupling of a wide variety of arylhalides with alkynols in the presence of CuI, triphenylphosphine and Et₃N as base and solvent at 90 °C (Scheme 95).

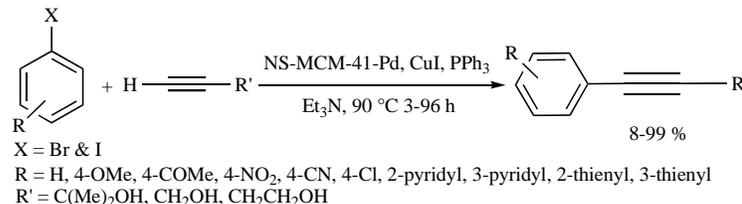
The development of eco-friendly catalytic processes by using Pd-grafted PMO (Organic-inorganic hybrid periodic mesoporous organosilica) material (Scheme 96) as catalyst for a series of C-C cross-coupling reactions, namely Hiyama and Sonogashira cou-



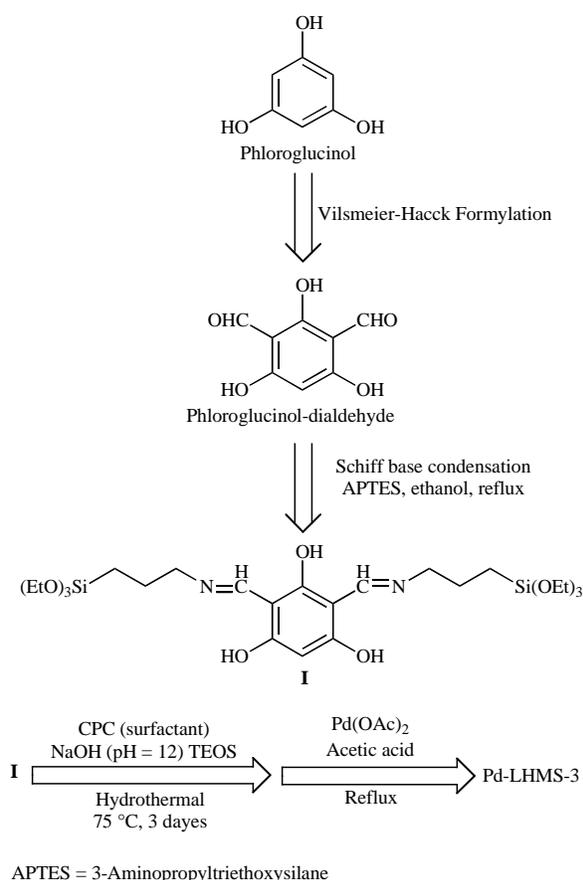
Scheme 93.



Scheme 94.

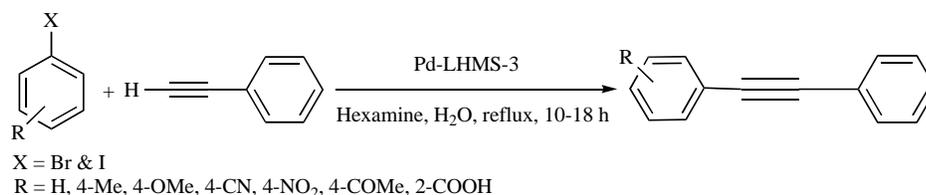


Scheme 95.



Scheme 96. Synthesis of Pd-LHMS-3.

plings, and cyanation reactions was done by Bhaumik and co-workers [104]. The Pd-containing PMO material (Pd-LHMS-3) was used as a unique catalyst for the copper-free Sonogashira coupling



Scheme 97.

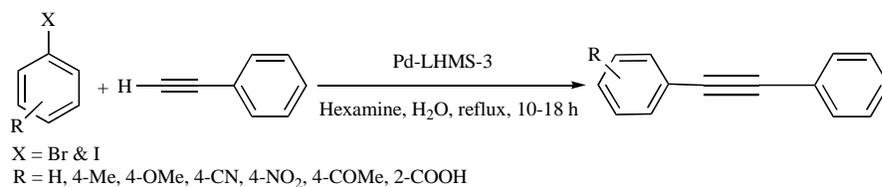
reaction in the presence of water and hexamine under the environmental benign reaction conditions (Scheme 97). The catalyst showed an excellent catalytic activity and recycled simply from the reaction mixture.

In 2004, Chang and co-workers have proposed a novel catalyst system based on ruthenium nanoparticles-supported on alumina [105]. The catalyst was used for copper-free Sonogashira coupling reactions over a wide range of substrates in benign and convenient conditions with high efficiency and selectivity (Scheme 98). In addition, the recovery of the Ruthenium/Alumina catalyst after the completion of the reaction was simply possible in which it didn't undergo any activity decreasing rate even after the second reaction cycle.

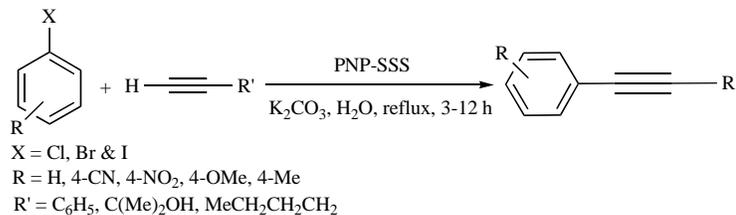
In 2011, Khalafi-Nezhad *et al.* reported the synthesis of a highly effective recyclable catalytic system based on the immobilization of Pd NPs on a silica-starch substrate (PNP-SSS) [106]. The PNP-SSS also performed well in the copper-free Sonogashira reaction between different aryl halides and alkynes in water under reflux conditions (Scheme 99). No observation of the obvious decrease of catalytic activity of PNP-SSS was considered even after five cycles of Sonogashira reaction of bromobenzene with phenylacetylene which confirmed the superior stability of catalyst.

Crudden *et al.* have employed mesoporous silica with high surface area (1000 m²g⁻¹) and large pore size as a support in construction of SBA-15-SH-Pd catalyst [107]. The Pd catalyst showed remarkable catalytic performance in the Suzuki-Miyaura and Sonogashira cross coupling reactions. The Sonogashira reactions of aryl iodides and aryl bromides were carried out using NaOAc as base in DMF/H₂O mixture as solvent at 100 °C for 1-24 h in which the coupling products were obtained in good to excellent yields (Scheme 100). However, this method is not applicable for aryl chlorides.

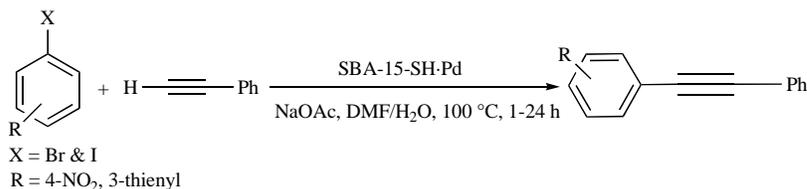
In 2012, Pagliaro and co-workers developed another methodology for the Sonogashira coupling of different aryl halides with



Scheme 98.



Scheme 99.



Scheme 100.

Table 2. Conversion and Leaching of Pd from the *SiliaCat* palladium catalysts used in the Sonogashira coupling reactions of aryl iodides with phenylacetylene. Reproduced with permission from ref. 110. Copyright (2012) ACS.

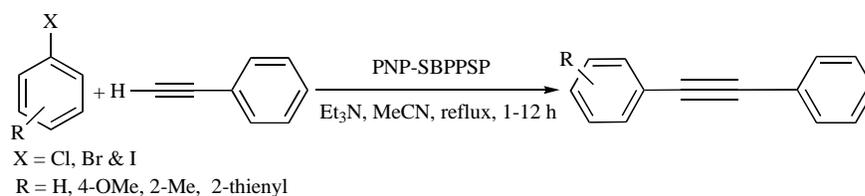
Entry	Substrate	<i>SiliaCat</i> DPP-Pd			<i>SiliaCat</i> S-Pd			<i>SiliaCat</i> Pd ⁰		
		Conv/Select	Pd [ppm]	Si [ppm]	Conv/Select	Pd [ppm]	Si [ppm]	Conv/Select	Pd [ppm]	Si [ppm]
1		100:100	1.5	5	100:100	4	1.4	100:100	1.1	8
2		100:100	11	50	100:100	0.4	7	99:99	0.3	30
3		99:98	9	35	100:100	0.6	8	99:98	0.4	35
4		100:100	8	12	99:100	0.7	4	91:98	0.4	16
5		100:100	6	29	100:100	1.2	4	100:100	0.4	21
6		90:98	18	24	30:90	0.8	9.8	85:94	1.8	6
7		83:98	6	18	80:98	3	4	75:99	5	6
8		55:95	18	33	30:93	3	7	36:97	14	11

Leaching determined by ICP-OES analysis. The solvent was evaporated and replaced by DMF/EtOH (3:1 v/v).

phenylacetylene using *Silia Cat*Pd(0) as a heterogeneous catalyst under various reaction conditions to synthesize the carbon-carbon bonds in moderate to excellent yields [108]. Low Pd content is observed. In all cases, no inert atmosphere is required for carrying out the Sonogashira reaction. The *SiliaCat*Pd(0) as a reusable cata-

lyst can be easily recovered in a facile manner from the reaction mixture.

The same group reported that *SiliaCat*Pd(0) made of a mesoporous organosilica gel doped with ultrasmall (3-5 nm) Pd⁰ nanocrystallites, can catalyze the Sonogashira reaction phenylacety-



Scheme 101.

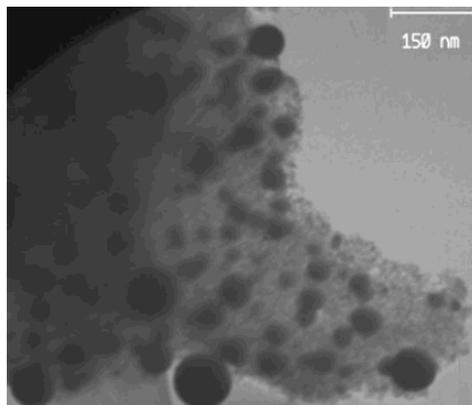


Fig. (27). TEM image reproduced with permission from ref. 111. Copyright (2013) Springer.

lene and 4-iodo-acetophenone in ethanol at reflux [109]. The catalyst can be reused several times without any additional activation treatment.

In order to further understanding on the catalyst effects in coupling reactions, various *SiliaCatPd* catalysts (*SiliaCat* DPP-Pd, *SiliaCat* S-Pd, and *SiliaCatPd*⁰) were applied for the Suzuki, Sonogashira, and Heck coupling reactions [110]. The method enables quick screening with identification of the best reaction conditions and rapid library generation. Also, during the reaction it was found that the minimal leaching values obtained using the *SiliaCatPd*⁰ catalyst (Table 2).

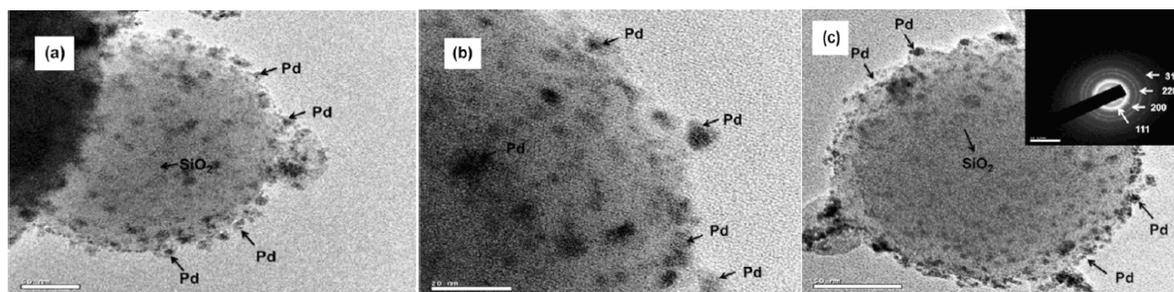
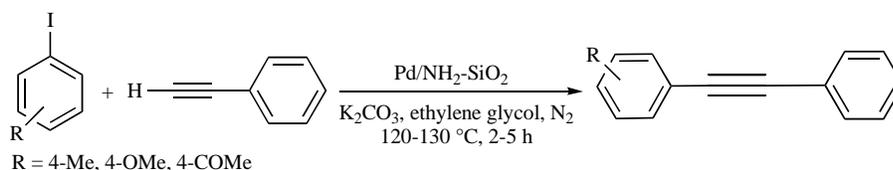
In 2013, Niknam and co-workers discovered a general and efficient methodology for the copper-free Sonogashira cross-coupling

reaction using immobilized palladium nanoparticles on silica functionalized *N*-propylpiperazine sodium *N*-propionate (SBPPSP) as a heterogeneous catalyst (Scheme 101) [111]. The SBPPSP was prepared by simple operation from commercially available and relative cheap starting materials on which the average sizes of the obtained Pd nanoparticles were obtained 21 nm (Fig. 27). The catalyst could also be recovered and reused four times without appreciable loss in catalytic activity.

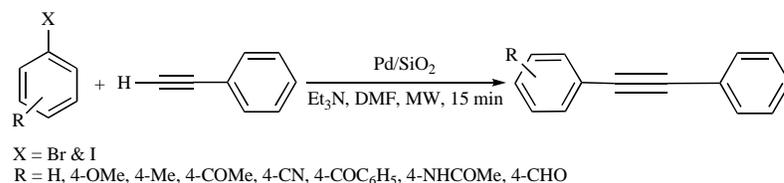
In 2013, Rajagopal and co-workers successfully immobilized Pd nanoparticles onto the amine-functionalized silica (NH₂-SiO₂) through the silica adsorbed palladium precursor (Pd(OAc)₂) and ascorbic acid reduction method (Fig. 28) [112]. Then, the Pd/NH₂-SiO₂ composite was used to catalyze the Suzuki, Heck and Sonogashira coupling reactions. The Sonogashira coupling reaction was conducted in ethylene glycol (Scheme 102). This palladium catalyst system was successfully recycled three times with slight decrease in its catalytic activity.

Soni and co-workers prepared palladium doped silica (Pd/SiO₂) nanoparticles *via* the sol-gel route using the P123 triblock copolymer as a structure directing agent [113]. The Pd/SiO₂ as a reusable catalyst showed highly catalytic activity in the Sonogashira reactions under microwave irradiation which could be rapidly separated from the reaction mixture and reused nine times without a significant loss in its catalytic activity (Scheme 103). All products were isolated in good to excellent yields.

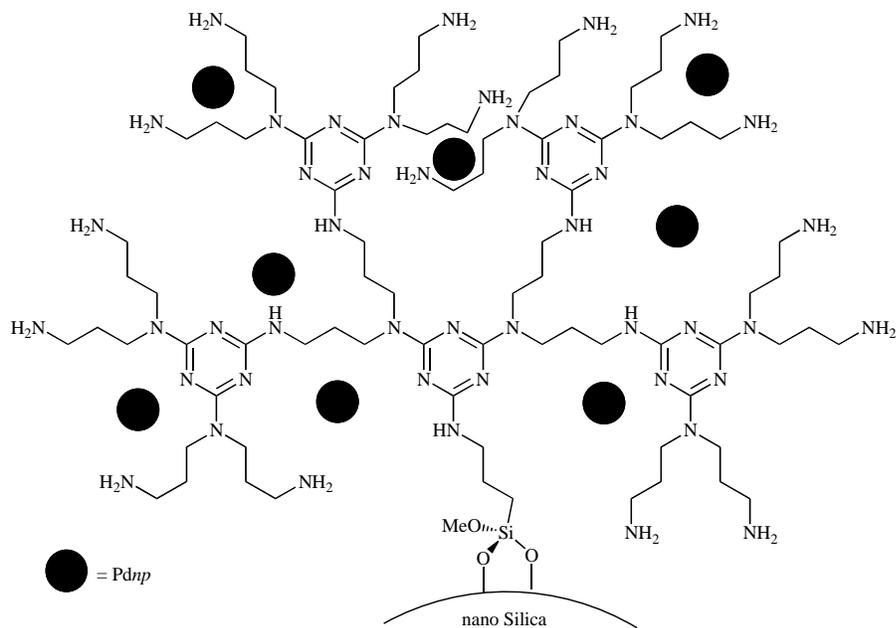
Mohammadpoor-Baltork and co-workers successfully immobilized palladium nanoparticles onto the nano silica triazine dendritic polymer (Pd_{np}-nSTDP) (Scheme 104) [114]. The Pd_{np}-nSTDP was found as a highly effective catalyst for the Sonogashira coupling reactions of aryl halides (iodides, bromides, and chlorides) with

Fig. (28). HRTEM photographs of (a-c) correspond to the different images of the representative Pd/NH₂-SiO₂ and inset of (c) shows SEAD spectrum of Pd/NH₂-SiO₂. Reproduced with permission from ref. 112. Copyright (2013) Sciencedirect.

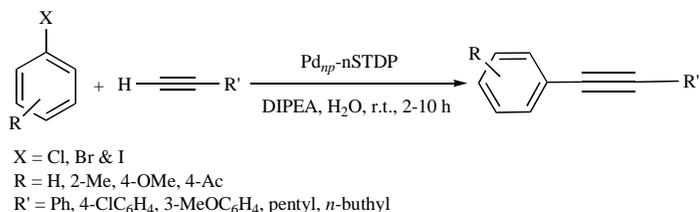
Scheme 102.



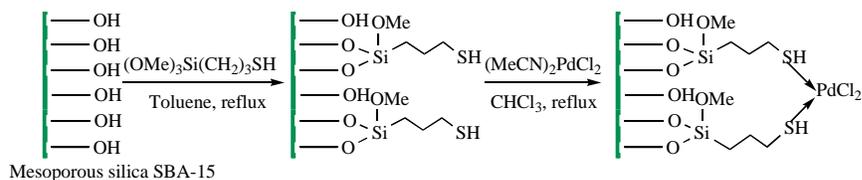
Scheme 103.



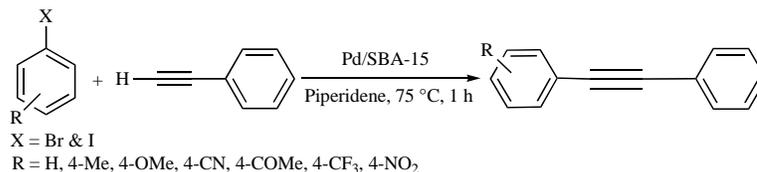
Scheme 104. The structure of the Pdnp-nSTDP catalyst.



Scheme 105.



Scheme 106. Preparation of the SBA-15 supported Pd-catalyst. Reprinted from ref. 115 with permission. Copyright (2015) Royal Society of Chemistry.

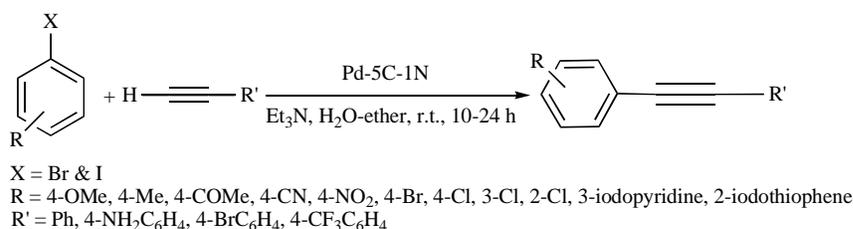


Scheme 107.

aromatic and aliphatic terminal alkynes in water (Scheme 105). This palladium catalyst system was successfully recycled three times with slight decrease in its catalytic activity.

Sarkar and co-workers prepared thiol-functionalized SBA-15 supported palladium catalyst. The nanostructured mesoporous SBA-15 silica supported Pd-catalyst was synthesized in two steps (Scheme 106) [115]. The first step involves the preparation of SBA-

15 supported mercapto precursor by the reaction of SBA-15 silica with (3-mercaptopropyl)triethoxysilane in refluxing toluene for 12 h. In the second step, mercaptopropylated SBA-15 was treated with (CH₃CN)₂PdCl₂ in CHCl₃ at 65 °C for 12 h. A High catalytic activity was observed for nanostructured SBA-15 supported Pd-catalyst in the Sonogashira reactions (Scheme 107). There was almost no change after six cycles of catalytic experiments.



Scheme 108.

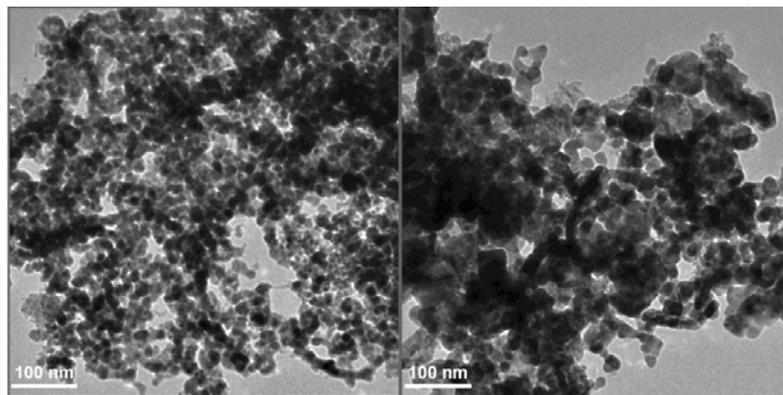
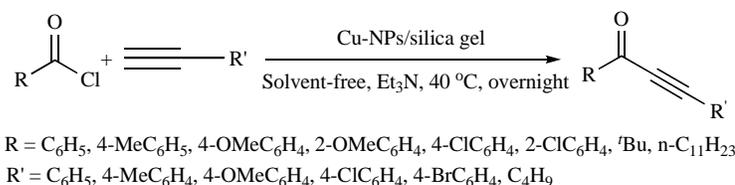
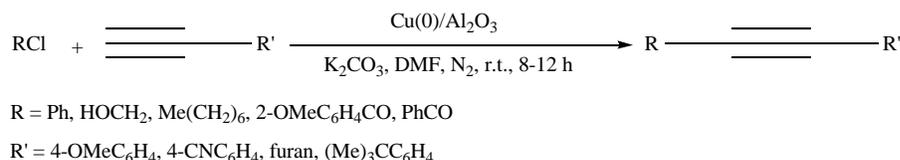


Fig. (29). TEM image of supported copper nanoparticles: Cu-NPs/silica gel (left); Cu-NPs/ γ -Al₂O₃ (right). Reproduced with permission from ref. 117. Copyright (2013) Royal Society of Chemistry.



Scheme 109.



Scheme 110.

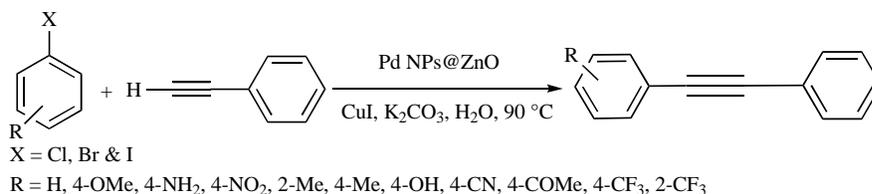
In 2015, Zhao and co-workers successfully immobilized Pd NPs onto improved mesoporous silica as an efficient and reusable pH-responsive catalyst [116]. This catalyst system efficiently promotes the Sonogashira reaction in water-based biphasic systems under the copper-free conditions. The catalyst can be pH-triggered and highly dispersed in organic phase in a pH range from 9 to 10 just like a homogeneous catalyst, and can be recycled and reused like a heterogeneous aqueous medium. The Sonogashira reaction between aryl halides and terminal alkynes in water catalyzed by pH-responsive palladium nanocomposite (Pd-5C-1N) at room temperature for 10 until 24 h (Scheme 108). Among aryl halides, substituted bromobenzenes showed lower yield than the iodobenzenes.

In 2013, Yao *et al.* successfully immobilized copper nanoparticles on the γ -Al₂O₃- and silica gel [117]. TEM images are shown in Figure 29. They had been catalyzed Sonogashira cross-coupling reaction of acyl chlorides and terminal alkynes under palladium-, ligand-, and solvent-free conditions (Scheme 109) which demonstrated the good to excellent yields. The silica gel-supported catalyst showed much better catalytic activity than the Al₂O₃-supported catalyst because silica gel supported Cu-NPs exhibit a smaller size,

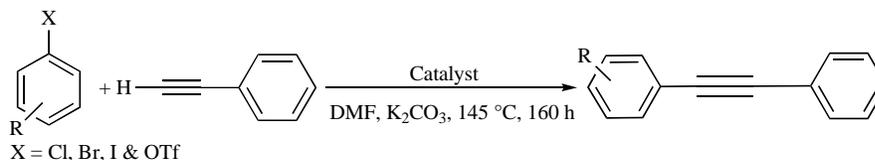
better morphology and more uniform distribution. The catalyst could be simply recovered and reused several times without loss in catalytic properties.

Likhar and co-workers discovered a new one-step approach for the synthesis of highly monodispersed nano copper(0) stabilized on alumina [Cu(0)/Al₂O₃] with thermal reduction of copper-aluminium hydrotalcite (Cu-Al HT) [118]. The efficiency and stability of the Cu(0)/Al₂O₃ catalyst has been proved by activating unreactive aryl chlorides and studying the recovery and reusability properties for coupling reactions (Scheme 110). The easy recovery and reusability with only a minor loss in catalytic activity and selectivity was shown in coupling reactions. This unique catalytic system opened up an attractive alternative to noble metal-based catalysts for the formation of C-C bond.

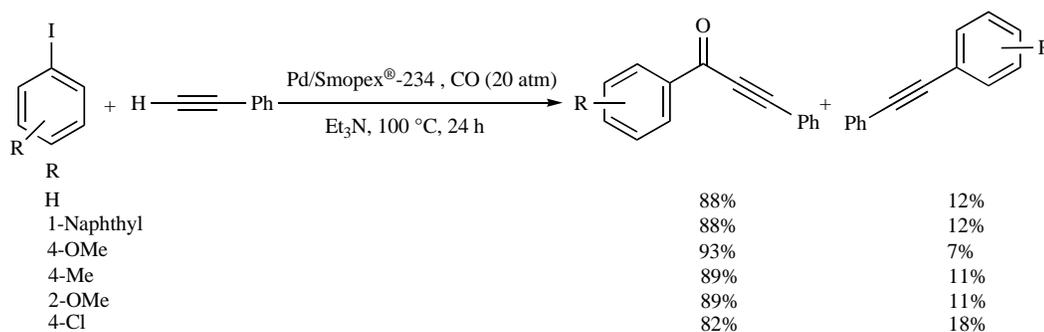
In 2014, Hosseini-Sarvari and colleagues successfully prepared Pd/ZnO nanoparticles by co-precipitation method (palladium loading is 9.8 wt%) [119]. Then, the Pd/ZnO was used to catalyze the ligand-free C-C bond formation through the Mizoroki-Heck and Sonogashira reactions. The Sonogashira reaction was carried out by a mixture of aryl halide, phenylacetylene, CuI, K₂CO₃ and nano



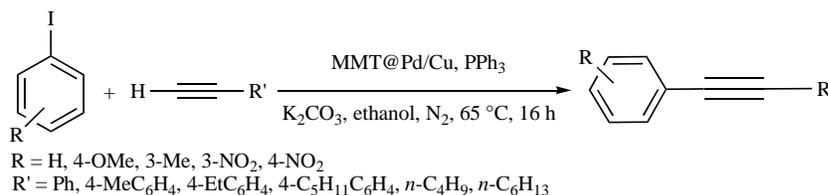
Scheme 111.



Scheme 112.



Scheme 113.



Scheme 114.

Pd/ZnO in H₂O (Scheme 111). This palladium catalyst system could be recovered and recycled several times and the results indicated that only 0.01% wt of the Pd metal is leached out from the catalyst surface after five cycles (for both Heck and Sonogashira reactions).

Very recently, Wendt *et al.* have investigated the impact of supports with different nature (redox: CeO₂, TiO₂ and non-redox: Al₂O₃) and deposition-precipitation (DP) and also incipient wetness impregnation (IMP) routes on the performance of supported gold nanoparticles in the Sonogashira coupling reaction of aryl halides with phenylacetylene (Scheme 112) [120]. The evaluation of catalyst demonstrated that the catalysts performance is negligibly dependent on the specific surface area of the catalysts. Synthesis paths, however, greatly affected the catalytic activity and selectivity. Of the tested catalysts in Sonogashira coupling, catalysts obtained by DP route proceeds with better conversion and cross-coupling selectivity over CeO₂ and TiO₂ supported samples compared to Al₂O₃ supported ones and results clearly showed that smaller gold particles (4-15 nm) supported on redox carrier, such as CeO₂ or TiO₂, are superior as catalyst for the Sonogashira coupling, because they have a large number of active sites.

A novel PdNPs supported on two Smopex[®] metal scavengers was prepared from metal vapour synthesis (MVS) technique and used in carbonylative Sonogashira reactions of aryl iodides with

phenylacetylene without application of phosphine ligands or CuI as co-catalyst (Scheme 113) [121]. This is an appliance method based metal scavengers Smopex[®]-111 and Smopex[®]-234 for the synthesis alkynyl ketones with high chemoselectivity (82-93%). The Pd/Smopex[®]-234 was a truly heterogeneous catalyst and could be recycled from the reaction mixture with no loss of activity.

Gao and co-workers developed a general and efficient methodology for the Sonogashira cross-coupling reaction between aryl iodides and phenylacetylenes in the presence of montmorillonite-supported Pd/Cu nanoalloys (MMT@Pd/Cu). The corresponding coupling products are obtained from various aryl iodides in a straightforward manner in moderate to good yields (Scheme 114) [122].

Sun group took use of xylan-type hemicellulose (XH) as a promising support for the synthesis of Pd NPs. The catalyst (Pd NPs@XH) was obtained by a deposition-precipitation method (Fig. 30) [123]. The supported palladium catalyst was then used as a heterogeneous catalyst for the Suzuki, Heck, and Sonogashira coupling reactions in the presence of Et₃N as the base and CH₃CN as the solvent under thermal and aerobic conditions (Scheme 115). This method is not applicable for aryl chlorides because the corresponding product failed even after 10 h in DMF at 120 °C. The catalyst was recovered and reused for six times without significant loss of its catalytic activity.

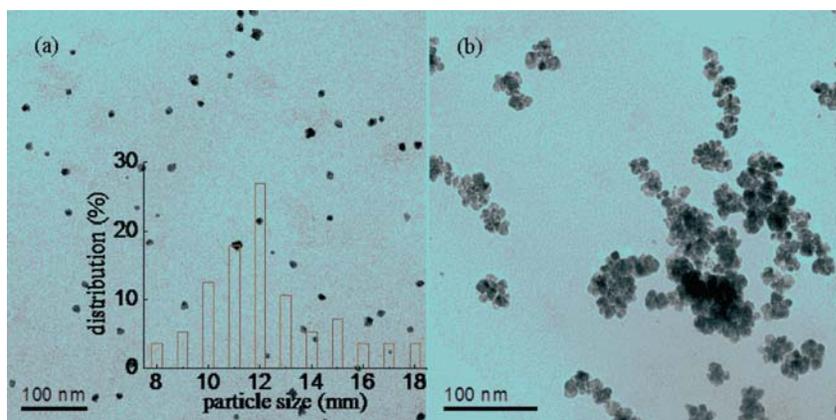
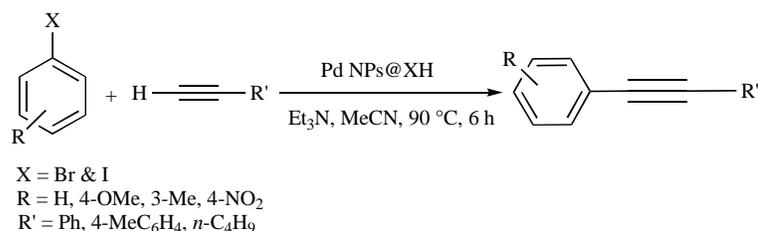


Fig. (30). TEM images: (a) fresh PdNPs@XH and the particle size distribution histogram; (b) PdNPs@XH originated from the Suzuki reaction (reused six times). Reprinted from ref. 123 with permission. Copyright (2014) Royal Society of Chemistry.



Scheme 115.

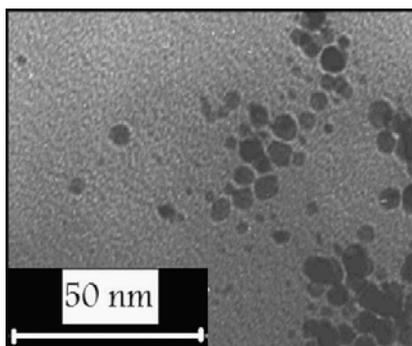
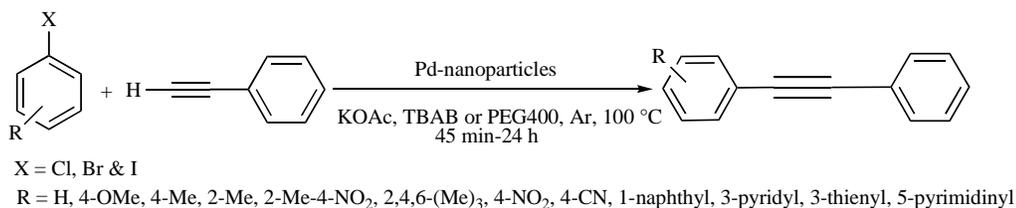


Fig. (31). TEM picture of the supported palladium nanoparticles on gelatin. Reprinted from ref. 124 with permission. Copyright (2011) Royal Society of Chemistry.

In 2011, gelatin-stabilized Pd nanoparticles (4-7 nm) (Fig. 31) were prepared by Firouzabadi and co-workers from a simple method. The catalyst exhibited high catalytic activity in the ligand- and amine-free Sonogashira-Hagihara coupling reactions in molten tetrabutylammonium bromide (TBAB) or polyethylene glycol (PEG400) in the presence of potassium acetate as a base at 100 °C under an argon atmosphere (Scheme 116). The catalyst can be recycled up to 6 times in the reaction [124]. Dimerization of phenylacetylene was carried out under the similar conditions in air.



Scheme 116.

In 2012, Firouzabadi *et al.* applied agarose as a nontoxic, cheap, degradable natural product as a support and ligand for palladium NPs (Fig. 32). High efficiency of the catalyst beside its recycling ability, are the merits of this catalyst system. This catalytic system was successfully applied in Mizoroki-Heck and Sonogashira-Hagihara coupling reactions. This catalytic system also showed high catalytic activity for Sonogashira-Hagihara coupling reaction of various aryl halides (I, Br, Cl) under the copper and ligand-free conditions in polyethylene glycol (PEG400) as an ecofriendly and non-poisonous media (Scheme 117) [125].

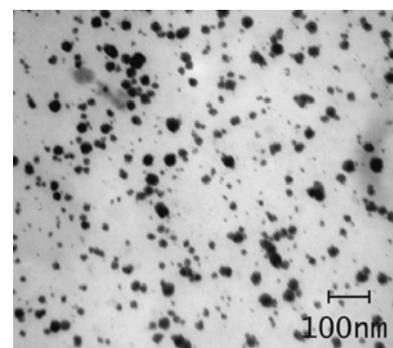
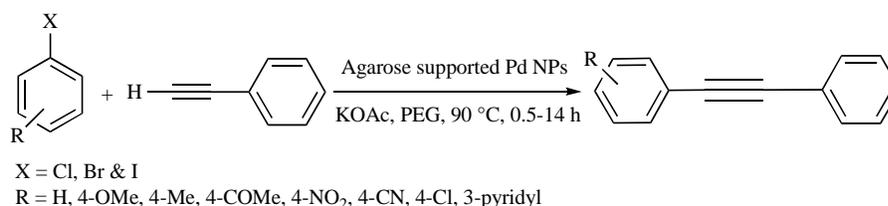
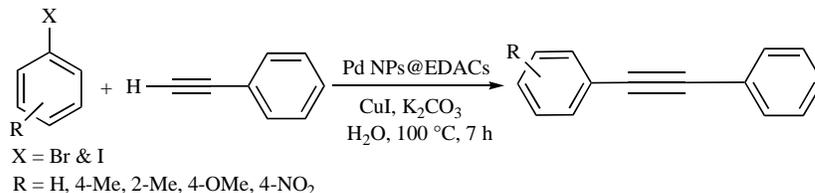


Fig. (32). TEM image of the agarose supported Pd nanoparticles. Reproduced with permission from ref. 125. Copyright (2012) Sciencedirect.



Scheme 117.



Scheme 118.

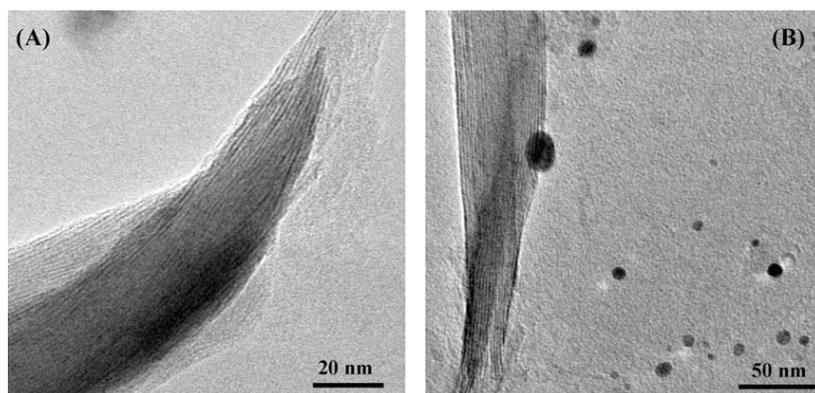
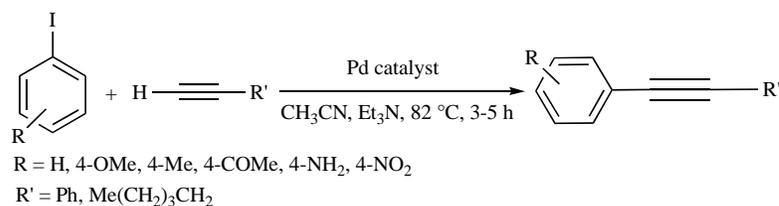
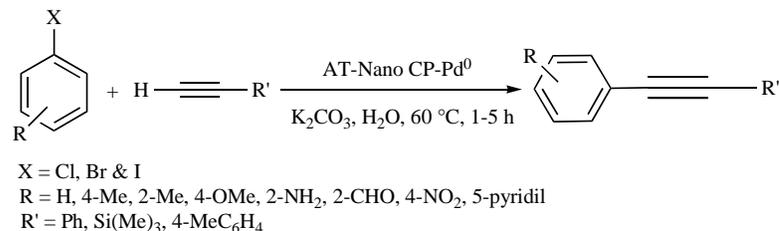


Fig. (33). Typical HRTEM images of AT-Mont. (A) before and (B) after supporting Pd⁰-nanoparticles. Reproduced with permission from ref. 127. Copyright (2013) Sciencedirect.



Scheme 119.



Scheme 120.

Shaabani *et al.* described a novel Pd NPs/supported catalyst system based on ethylenediamine-functionalized cellulose (Pd NPs@EDACs) as a bio-support. In this work, the resulted Pd NPs@EDACs was able to catalyze the Sonogashira coupling reaction of aryl halides with phenylacetylene in the presence of CuI and K₂CO₃ in water at 100 °C (Scheme 118) [126]. This catalyst was successfully recycled for at least 4 cycles without losing its activity.

In situ generation of Pd⁰-nanoparticles into the nanopores of modified montmorillonite by controlled acid activating with H₂SO₄ and their catalytic performance in Heck and Sonogashira reactions

(Scheme 119) [127] have been carried out by Dutta and Borah in 2013. The resulting pores provide the space for nanoparticle formation and control the growth of the particles up to desired nano sized range (Fig. 33). This nanocatalyst was recovered and reused for new batch of reactions without significant loss of activity.

In 2014, Baghbanian *et al.* synthesized palladium NPs supported on natural nanozeolite clinoptilolite and investigated its catalytic performances in Sonogashira reaction of a variety of aryl halides with different alkynes (Scheme 120) [128]. Aryl halides substituted with electron-withdrawing groups, gave the better conversions

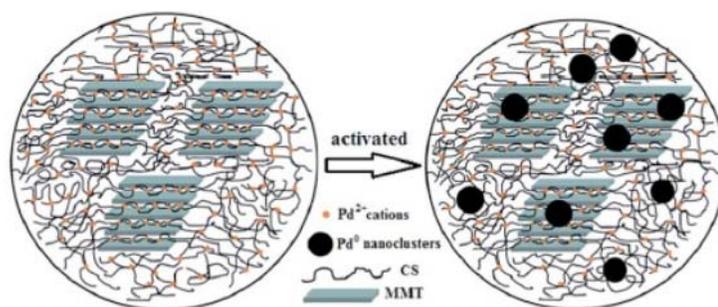
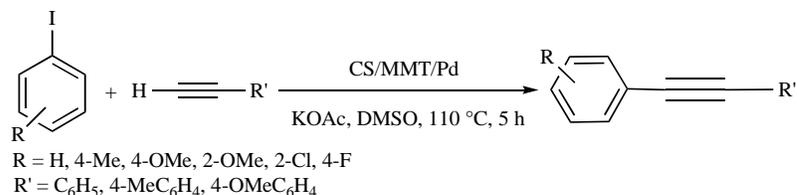
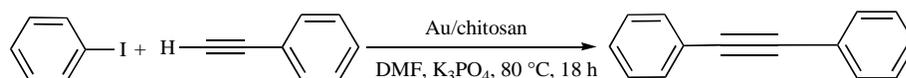


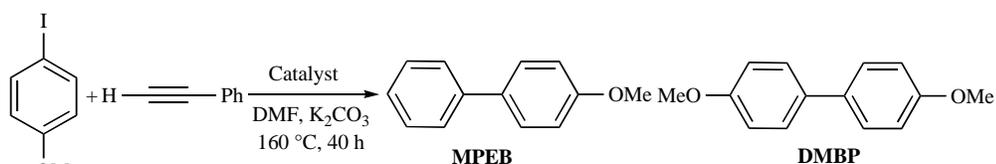
Fig. (34). Phase dispersion diagram of the fresh and activated CS/MMT/Pd hybrid microspheres. Reprinted from ref. 129 with permission. Copyright (2015) Royal Society of Chemistry.



Scheme 121.



Scheme 122.



Catalyst	Conv. (%)	Selectivity (%)	
		MPEB	DMBP
Au ₂₅ (SR) ₁₈ /CeO ₂	96.1	88.1	11.9
Au ₂₅ (SR) ₁₈ /TiO ₂	92.8	82.9	17.1
Au ₂₅ (SR) ₁₈ /SiO ₂	90.8	79.3	20.7
Au ₂₅ (SR) ₁₈ /MgO	93.3	80.6	19.4
2–3 nm AuNC/CeO ₂	65.5	57.2	42.8

Scheme 123.

in shorter reaction times, in comparison with electron-donating substituents. In addition, the Sonogashira reaction of iodobenzene with phenylacetylene was carried out for eight runs without obvious decrease in the yield.

Qi and coworkers synthesized chitosan-based/montmorillonite/palladium (CS/MMT/Pd) hybrid microspheres by simple method through interactions between CS, MMT and Pd species (Fig. 34) [129]. Pd²⁺ cations can be reduced to Pd⁰ nanoclusters about 5 nm in size. They were entrapped in the CS matrix and interlayers of MMT. The CS/MMT/Pd hybrid microspheres are very active in the Sonogashira coupling reaction of various aromatic halides with alkynes and can be recycled 10 times without a significant decrease in product yields (Scheme 121).

In 2010, Primo and Quignard investigated the synthesis of gold nanoparticles immobilized onto chitosan as an efficient porous support [130]. Results showed that chitosan was able to control the growth of the gold nanoparticles and acted as macromolecular ligand for chelating these nanoparticles. The resulted macroporous hybrid, were then treated in carbon-carbon coupling reactions and showed high selectivity of product toward the Sonogashira cross coupling between iodobenzene and phenylacetylene under mild

conditions (Scheme 122). Finally the recyclability of the catalyst was tested and it was found that catalyst can be reused three times without significant loss of activity.

In 2013, Jin and co-workers described the preparation of gold nanocluster catalysts using a simple route (Fig. 23). The catalysts were used in the Sonogashira cross-coupling reaction of phenylacetylene and *p*-iodoanisole (Scheme 123) [131]. To investigate the potential effects of various oxide supports (including acidic and basic oxides), Jin and co-workers have compared CeO₂, TiO₂, MgO, and SiO₂. As shown in Scheme 123, there are some small influences of supports on the catalytic performance of the catalysts. Furthermore, using a combination of DMF (as the solvent) and K₂CO₃ (as the base), the CeO₂-supported Au₂₅(SR)₁₈ nanocluster catalyst gives rise to excellent conversion of *p*-iodoanisole (96.1%) and high selectivity for 1-methoxy-4-(2-phenylethynyl) benzene (MPEB) (88.1%).

3. CONCLUSION

We have summarized the recent advances of Sonogashira coupling reactions of various aromatic halides with alkynes using heterogeneous nanocatalysts. In this review, a wide range of supports such as polymer, carbon, graphene, metal oxides, metal-

such as polymer, carbon, graphene, metal oxides, metal-organic frameworks, SBA-15, SiO₂, Al₂O₃ and magnetic nanoparticles have been introduced in order to preparation of heterogeneous nanocatalysts. The mentioned nanocatalysts showed high catalytic activities in the coupling reactions which could be recycled and reused from the reaction mixture. In addition, in recent years, tendency to the use of nanometals such as Pd, Cu, Ag and Au species have been reported as catalysts in the Sonogashira reaction. Although, most of these catalytic systems or methods are quite effective for aryl iodides or bromides but not applicable for aryl chlorides. Thus, the need for other methods or catalytic systems for the Sonogashira coupling reaction of aryl chlorides is essential in next future.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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