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Metal catalyzed notable organic reactions: Synthesis, mechanistic insights and applications

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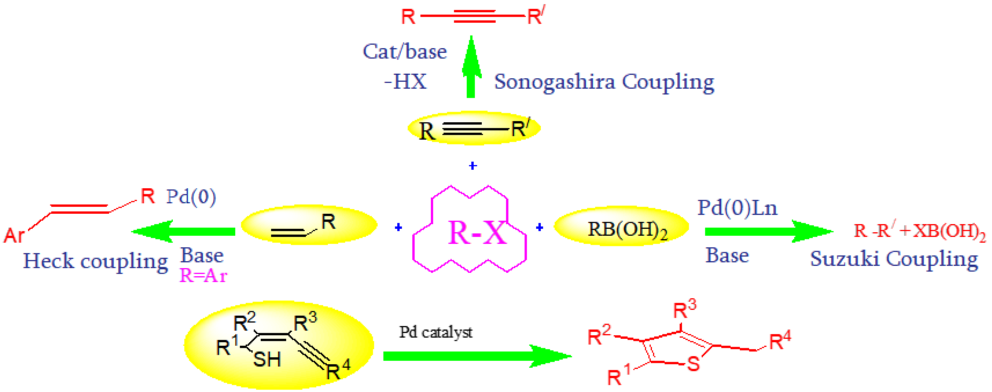
ABSTRACT

Transition metal catalysts have played an important role in forming carbon–carbon and carbon–heteroatom bonds. Formation of these bonds by using various transition metals such as Pd, Ni, Ru, Rh has been extensively investigated and documented in the literature. Recent years have witnessed a tremendous growth in the number of metal-catalyzed highly selective chemical transformations. The catalysis of organic reactions by different metals has been shown to be a powerful tool in organic synthesis. This review focuses on various metal catalyzed notable synthetic strategies adopted for the synthesis of a series of organic molecules and explores the mechanistic insights and applications of selected unique reactions.



Keywords: Catalysts, heteroatom bonds, transformations, organic synthesis

INTRODUCTION

Transition metal catalysts dominate organic synthesis and the fine chemical industry. Specifically, there are numerous procedures in industrial and fine chemical companies that require transition metals as their key catalysts. The oxidation of alcohols to carbonyl-containing compounds[1,2] or their full oxidations[3,4] are among the central reactions in organic chemistry[5,6] and are of interest for the development of environmentally benign processes,[7,8] production of new materials[9,10] and energy sources.[11,12] Due to their significant role in industrial fields and expected further applications,[13] these reactions continue to attract a great attention, disclosing new catalysts,[14,15] substrates, oxidants with peculiar features and applications. More recently, metal catalysts such as Pd,Ni, Pt, Rh, and Ru, have found widespread use due to their better performance under milder conditions.[16] Platinum catalysts are superior with regard to regioselectivity, especially with tin compounds as co-catalysts. During the last two decades, activation of C–H bonds in alkanes has been achieved under mild conditions[17] using several catalysts such as Hg[18] Pd[19] and Pt.[20] For example, Catalytic oxidation of methane to methanol is done using the combination of metallic gold as catalyst and selenic acid (H_2SeO_4) as oxidant in 96% of sulphuric acid (H_2SO_4) as solvent at $180^{\circ}C$.[21] Transition metal-catalyzed stereo and chemoselective oxidations of bis-homoallylic alcohols in THFs have been described and the mechanism of cyclisation developed.[22-24] Several methods for the synthesis of furans using diverse reaction conditions and versatile reagents and substrates have also been reported.[25-28] The synthesis of tri-substituted furans in quantitative yields by cyclisation of 3-alkyne-1,2-diols under heterogeneous catalysis has been demonstrated.[29] Enantioselective or diastereoselective

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synthesis of pyrrolidines has been achieved by copper-catalyzed 1,3-dipolar cycloaddition of azomethine ylides and a vinyl component.[30-31] An environment friendly one-pot synthesis of 3,5-disubstituted isoxazoles starting from diketones in an ionic liquid has also been reported.[32] Solid phase synthesis has also been applied to achieve various substituted isoxazoles.[33-35] Oxadiazole nucleus is one of the most important pharmacological scaffolds.[36-40] A common synthetic method involves the cyclisation of 1-acyl-4-alkyl/aryl semicarbazides/thio semicarbazides to 2-alkyl/arylamino-5-alkyl/aryl-1,3,4-oxadiazoles using special reagents and reaction conditions.[41]

In this review article metal catalyzed selected synthetic transformations of a series of reactions involving C – C, C –H and Carbon- hetero atom bond formations have been discussed. Plausible mechanistic insights along with recent applications have also been explored for a wide range of notable reactions.

GOLD-CATALYZED C–C BOND FORMATIONS

Gold-catalyzed a Grignard-type alkynylation of ortho-alkynylaryl aldehydes in water in the presence of a catalytic amount of a tertiary amine base, i-Pr2Net.[42] Formation of 1-alkynyl-1H-isochromenes has also been reported by the intramolecular cyclisation of the hydroxyl-alkyne intermediate directly by this precious metal catalyst (Figure 1).

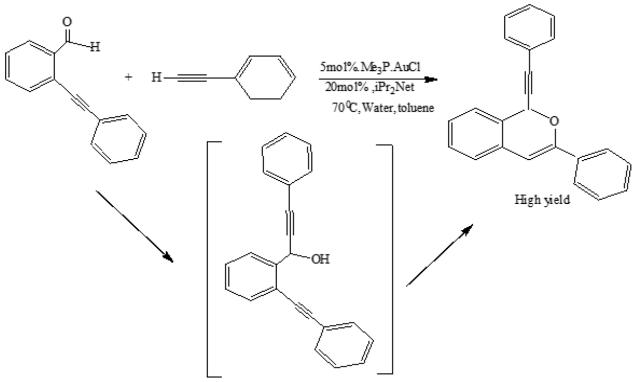
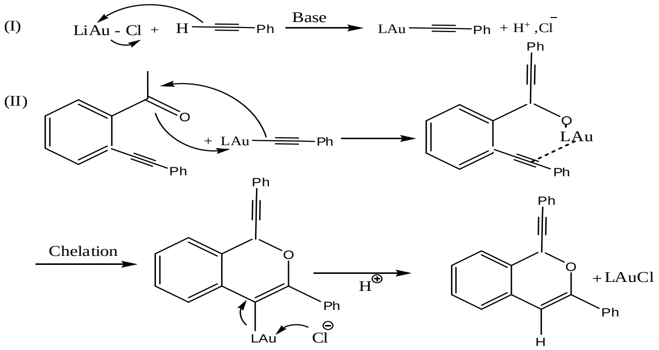


Figure 1. Grignard-type alkynylation of ortho-alkynylaryl aldehydes

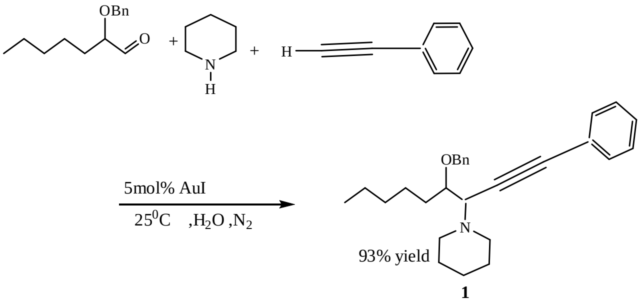
Mechanism developed for the alkynylation of ortho-alkynylaryl aldehydes can be depicted as below (Scheme-1)



Scheme 1. Mechanism developed for Grignard-type alkynylation of ortho-alkynylaryl aldehydes

Au(III) and Au(I) has also been found to catalyze efficiently the direct coupling of aldehyde, alkyne, and a secondary amine.[42a]

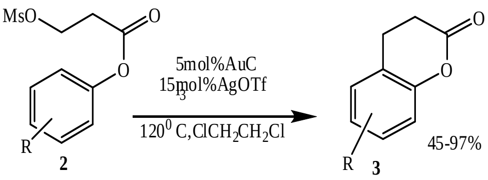
In a three-component coupling reaction of alpha-oxyaldehydes, alkynes, and amines in water by using gold, silver, and copper catalysts, gold(I) was found to be the most effective catalyst to afford propargylamines (1) in good yields and moderate diastereoselectivities.[43] (Scheme 2)



Scheme 2. Formation of propargylamines

Addition of arenes to primary alcohol mesylate

Gold(III)-catalyzed aromatic C–H functionalization with primary alcohol triflate or methanesulfonate esters to construct C–C bonds has been reported.[44] Efficient synthesis of substituted arene products (**3**) has been achieved using 5 mol % of AuOTf in dichloroethane at 120 °C. Mechanistically the aryl gold(III) species acts as a reaction intermediate which then reacted with the sulfonate ester to give the final product (Scheme-3).



Scheme-3: Construction of C-C bond

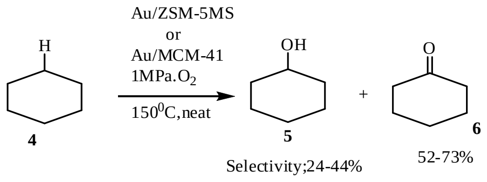
GOLD-CATALYZED C–O BOND FORMATIONS

Catalytic oxidation of methane

C–H bond activation in alkanes has been successfully achieved under mild conditions[45] using several catalysts such as Hg,[46] Pd,[47] and Pt.[48] Catalytic oxidation of methane to methanol using the combination of metallic gold as catalyst and selenic acid (H_2SeO_4) as oxidant in 96% of sulphuric acid (H_2SO_4) as solvent at 180°C has also been reported.[49] This catalytic reaction resulted in a 94% selectivity of CH_3OSO_3H at 28% methane conversion.

Catalytic oxidation of cycloalkanes

The oxidation of cyclic alkanes (**4**) was also explored through the activation of C–H bonds. An efficient oxidation of cyclohexane at 150 ^{0}C using calcined gold supported on nanocrystalline ZSM-5 (Au/ZSM-5) as catalyst with 1 MPa of oxygen as a source of oxidant has been achieved. The oxidation reaction takes place only in presence of atmospheric oxygen. This transformation afforded quantitative oxidation of cyclohexane with 90% selectivity for cyclohexanol (**5**) and cyclohexanone (**6**) under solvent free conditions (Scheme-4).

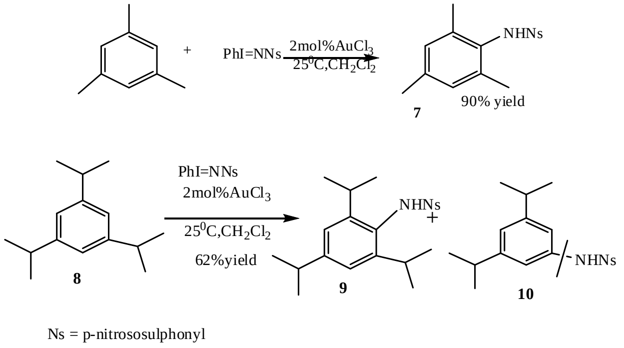


Scheme 4: Selective oxidations of cycloalkanes

C-N BOND FORMATIONS

NITRENE INSERTION

Very recently the use of aryl gold(III)[50-53] to C–N bond formations via the activation of aromatic or benzylic C–H bonds using 2 mol % of $AuCl_3$ in CH_2Cl_2 at room temperature has been reported. The addition of mesitylene to PhI=NNs (8:1) in the presence of $AuCl_3$ as catalyst resulted only the aromatic C–N bond formation product (**7**) in excellent yields. The tri, tetra and penta-methylbenzenes (**8**) yielded the desired aromatic C–N bond formation products in high yields (61–90% yield) (**9,10**), while di- and mono-substituted benzene as well as benzene afforded less than 5% yield of the desired products. However,1,3,5- triisopropylbenzene resulted a mixture of aromatic and aliphatic C–N bond formation products with a ratio of 1:1.5 (Scheme-5)



Scheme-5: Gold Catalyzed C-N bond formation

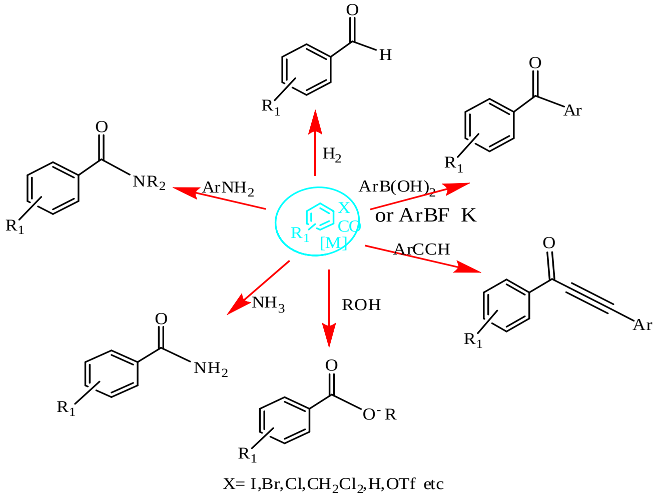
Applications

Gold based catalysts in the form of metal complexes or nanoparticles find a variety of applications in the field of bio-medical science. Gold nanoparticles-modified electrodes are used in the assembly of electrochemical DNA biosensors. They constitute useful analytical tools for sequence-specific DNA diagnosis and detection due to their inherent advantages of low cost, sensitivity and rapidity of response. These nanoparticles have also been used in the assembly of electrochemical and amperometric biosensors for the diagnosis of patients with germ cell tumors and hepatocellular carcinoma. Gold nanoparticles cause local heating when they are irradiated with light (800–1200 nm). The potential use of GNPs in photothermal destruction of tumors has been recently reported.

TRANSITION METAL CATALYZED CARBONYLATION REACTIONS

Carbonylative activation of c–x bonds

The field of Carbonylation research has received much attention during the past decades dueto their distinguishable advantages. Under reaction conditions, the corresponding metal carbonyls or hydridocarbonyls are formed from various catalyst precursors which can be metal salts (halides preferred), complex salts, oxides, or, in some special cases, even fine metal powders. In the case of metal halides, the nature of the anion plays a significant role. The catalytic activity of these co-catalysts increases from chloride over bromide to iodide while fluorides are inactive (Scheme-6)

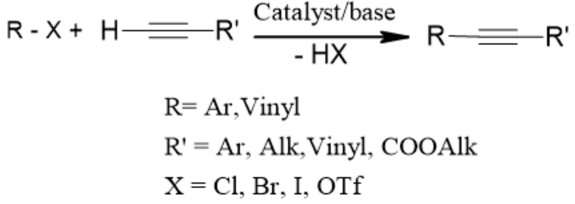


Scheme 6- Transition metal catalyzed carbonylation reactions of C–X bonds

NOTABLE REACTIONS

SONOGASHIRA REACTION

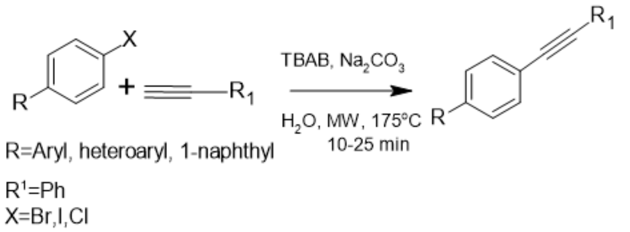
The Sonogashira reaction is a palladium-catalyzed sp^2–sp cross-coupling reaction between a terminal alkyne and an aryl or vinyl halide/triflate performed with or without the presence of a copper (I) co-catalyst [54]. It is now one of the most important methods to prepare aryl alkynes and conjugated enynes, which represent reactive intermediates and a range of natural products (Scheme-7).



Scheme 7. Sonogashira coupling

Microwave assisted transition metal-free Sonogashira type-coupling reaction of aryl halide in water with phenyl acetylene as the coupling partner has been reported in the presence of TBAB The use of

TBAB(1equiv.) and an excess of base Na_2CO_3 (4.0 equiv.) was found to be essential (Scheme-8).

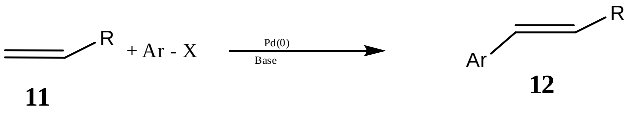


Scheme 8. Transition metal-free Sonogashira type-coupling reaction

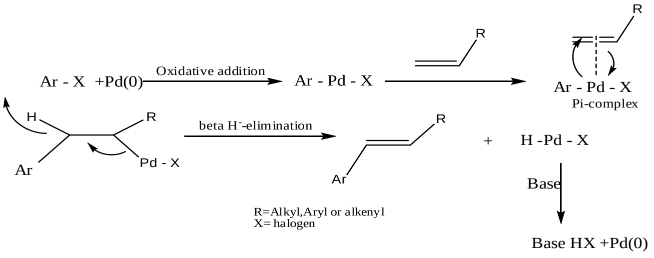
At present the Sonogashira coupling reaction is one of most powerful processes for C–C bond formation, especially for the synthesis of substituted alkynes. If the Sonogashira reaction is carried out in a CO atmosphere, the reactions are called Carbonylative Sonogashira reactions, leading to the formation of alkynone, as an interesting structural motif found in numerous biologically active molecules.

HECK COUPLING

The reaction of alkyl- or aryl-substituted alkenes **(11)** containing at least one hydrogen atom at the C= C bond with aryl, benzyl, and vinyl halides or triflates, forming a new C–C bond and affords a substituted alkene **(12)** is known as the **Heck coupling** (or Mizoroki–Heck reaction). It is generally catalysed by palladium species generated *in situ* from various Pd(II) salts or complexes and requires bases (organic or inorganic) to neutralize the acid HX formed during the reaction.[55]

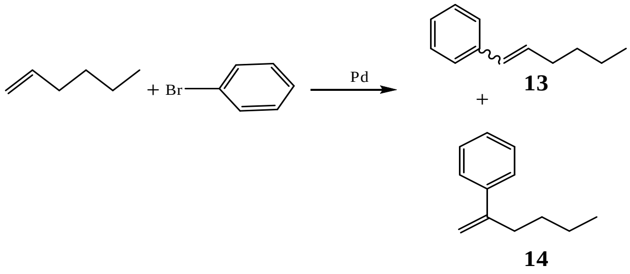


The plausible mechanism proposed for the Heck reaction can be explained on the basis that the coupling of an organopalladium species formed by oxidative addition to an alkene is followed by hydride elimination. The product is an alkene in which vinyl hydrogen on the original alkene is replaced by the organic group on palladium. Thus aryl and alkenes halides can be coupled to alkenes.(Scheme-9).

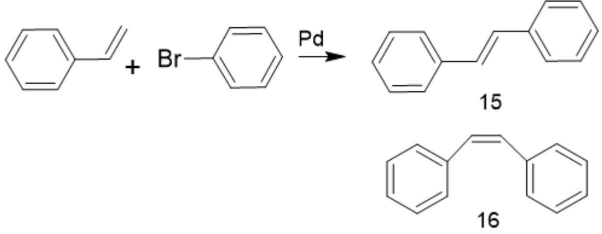


Scheme 9: Proposed Mechanism for Heck Reaction

Heck reaction also leads to the formation of two different products (**13&14**)

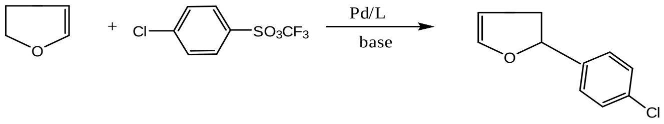


The coupling of bromo- or iodobenzene to styrene yields a regioselective mixture of E- and Z-stilbenes **(15)** and **(16)**. An electron-withdrawing substituent at the olefinic double bond often improves the regioselectivity, while an electron donating substituted alkene leads to the formation of regioisomers-(Scheme-10).



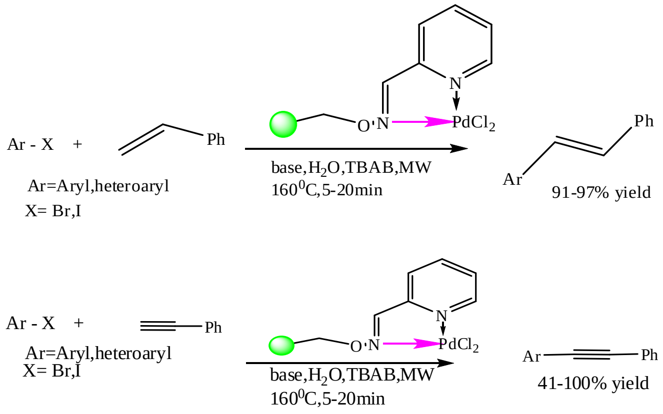
Scheme 10. Formation of E and Z Stilbenes by Heck coupling

A wide range of functional groups, both in the alkene and in the halide, are used in Heck coupling, which render the reaction practically more applicable and synthetically robust(Scheme-11).



Scheme-11- Palladium catalyzed Heck coupling

Heck reactions between aryl halides and alkenes continue to attract attention in the synthesis of pharmaceutical products and polymers. The possibility of carrying out Mizoroki–Heck cross-coupling reaction in water could be of great importance for the development of industrial processes. Microwave assisted Mizoroki–Heck reactions in water using 2-pyridinealdoxime-based Pd(II)-complex as a heterogeneous precatalyst have also been reported. The catalytic activity of the Pd(II) precatalyst has been optimized in the reaction of 4-bromoacetophenone with *tert*- butyl acrylate. Excellent yields have been achieved in water and DMF in the presence of NaOH/iPr_2NH and TBAB. The cross-coupling reaction of aryl and heteroaryl bromides has been highly regio and stereo selective and provided only more stable E-isomer. However, the reaction with less reactive styrene, resulted in the formation of two isomeric products with E-isomer of 1,2-disubstituted alkene as major product.(Scheme-12).



Scheme 12-Microwave assisted Mizoroki-Heck reactions

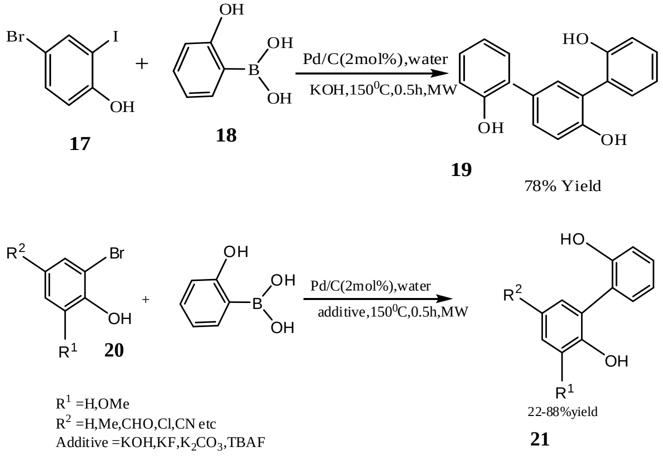
Suzuki Miyaura Reaction

Suzuki–Miyaura reaction is a Pd-catalysed cross coupling reaction between organic boron compounds (usually, boronic acids or boronic esters) and aryl or alkyl halides/ triflates proceeding under relatively mild reaction conditions[56] (Scheme-13)

$$RX + R'B(OH)_2 \xrightarrow[\text{base}]{Pd(0)\,L_n} R-R' + XB(OH)_2$$

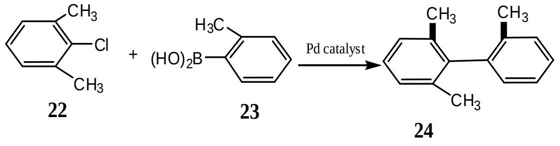
Scheme-13- Suzuki–Miyaura reaction

Suzuki–Miyaura reaction is one of the most useful carbon-carbon bond-forming coupling reactions involving organic electrophiles and organoboron compounds and holds an important place in synthesis of natural products, pharmacy and covalent organic frameworks. This reaction has been conducted in aqueous medium and more eco-friendly ionic liquids, the latter being important due to their low vapour pressure, high dielectric constant, and high thermal stability. The successful application for Suzuki–Miyaura reactions of different halo phenols in aqueous media using Pd/C as catalyst has been discussed wherein various *o*-iodophenols **(17)** with *o*-boronophenol **(18)** resulted high yields of corresponding products **(19)**,however,o-bromophenols (**20**) afforded poor yields-(**21**) (Scheme-14).



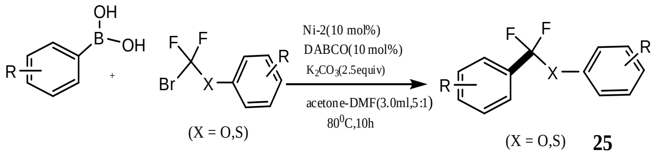
Scheme 14. Microwave assisted Suzuki–Miyaura reaction of o-halo phenols with o-boronophenol

A unique reaction of synthetic importance is the coupling of aryl- and hetaryl halides (or triflates) **(22)** with aryl and hetarylboronic acids **(23)** leading to a convenient synthesis of biphenyls, even sterically demanding derivatives such as **(24)**, bis-hetaryls and hetaryl phenyls (Scheme-15).



Scheme-15- Palladium catalyzed synthesis of Biphenyls

Because of the wide use of mono- or difluoro methyl halides in the transition-metal catalyzed C-C coupling reactions with different partners [57-68] Ni-catalyzed Suzuki cross-coupling reaction, using aryloxydifluoromethyl bromides ($ArOCF_2Br$) as a unique halide species to undergo coupling with arylboronic acids has also been reported leading to highly efficient synthesis of various aryl aryloxy difluoromethyl ethers (**25)**(Scheme-16).



Scheme 16. Ni-catalyzed Suzuki cross-coupling reaction

Stille Coupling Reaction

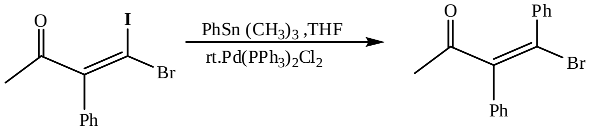
Coupling reaction of organotin compounds with carbon electrophiles-(Scheme-17).

$$\underset{26}{R^1X} + \underset{27}{R^2Sn(R^3)_3} \xrightarrow{Pd(0)Ln} \underset{28}{R_1-R_2} + \underset{29}{(R^3)_3SnX}$$

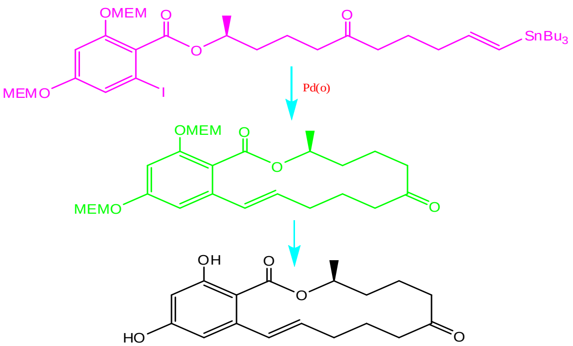
Scheme-17. Stille Coupling Reaction

After Heck and Suzuki reactions, the Stille reaction also belongs to a class of palladium-catalyzed carbon–carbon bond forming reactions. The palladium-catalyzed reaction of an organotin compound (**27**) with a carbon electrophile (**26**) is called Stille coupling.

The palladium component may be added to the reaction mixture as Pd(0) as well as Pd(II)- compound; in the latter case the Pd(II) is reduced first toPd(0) by excess stannane.Different types of substrates can be used in this reaction. Iodide is a better leaving group than bromide; this can be used for a regioselective coupling reaction(Scheme-18).



Scheme 18. Stille coupling



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Scheme 19. 14-membered lactone ring formation by Stille coupling

Applications

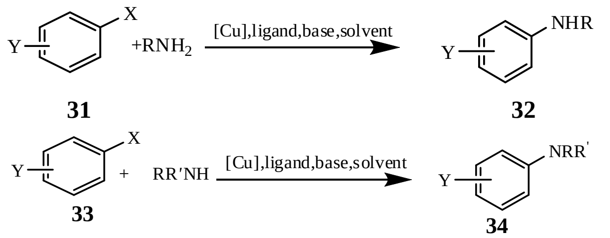
Pd-catalyzed C−N coupling reactions have had the greatest impact in the field of medicinal chemistry. Given the large number of nitrogen-containing biologically active compounds, the integration of N-arylation reactions in the pharmaceutical industry has been rapid. Recently, high-throughput methods for Pd-catalyzed C−N coupling have even been carried out on nanomolar scale to investigate preparative conditions for complex drug like molecules. Pd-catalyzed C−N coupling reactions often involve challenging transformations in total synthesis. In many cases, N-arylations have been used for the construction of heterocycles embedded in the final natural product structure. Due the donor ability of nitrogen-containing functional groups and the prevalence of highly conjugated systems in organic materials, N-arylation reactions are widely employed in materials research. Pd-catalyzed N-arylation reactions have been exploited in the synthesis of ligands to assemble heterocycles or to introduce chelating functional groups into an existing framework.

COPPER CATALYZED COUPLING REACTIONS

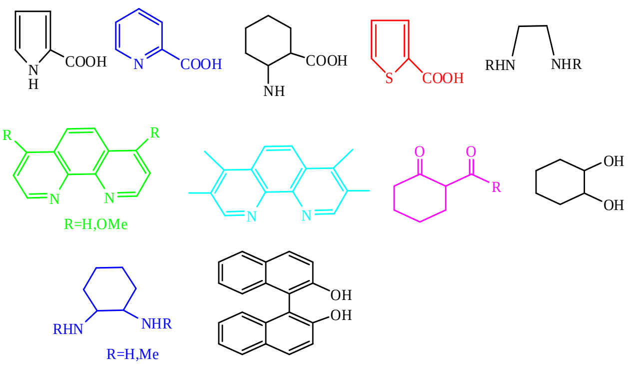
Ullmann type coupling reactions between aryl halides and N - containing reactants, phenols and other related nucleophilic agents are useful methods for the preparation of aromatic amines, biaryl ethers and N - aryl heterocycles with a wide range of applications in pharmaceutical and material sciences. In the recent past, use of special ligands in Ullmann reaction have increased the area of applications in organic synthesis by manifold.

Arylation of aliphatic primary and secondary amines

Copper catalyzed arylation of aliphatic primary amines (**31-34)** now has become a unique reaction for C-N bond formation. A series of ligands have been found effective for this transformation (Scheme-20).

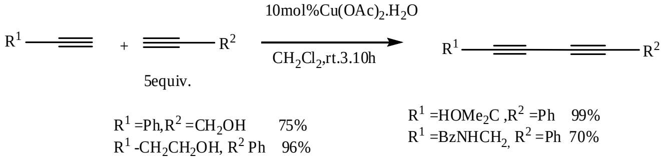


C-N bond formation by Ullmann reaction



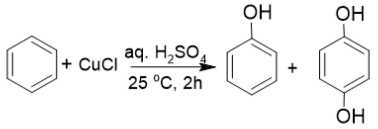
Scheme 20. Newly developed ligands

A general method for the cross-coupling of aryl acetylenes has been recently studied. High yields of the cross-coupled diynes were afforded using Cu(OAc)₂·H₂O, piperidene and air at room temperature[70] (Scheme-21).



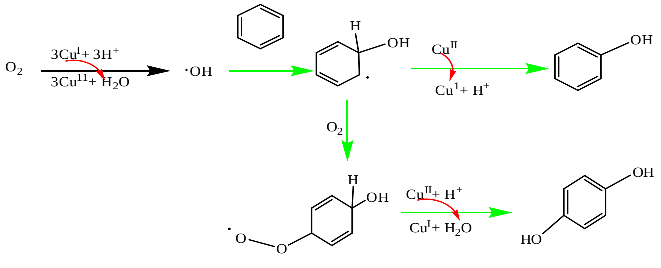
Scheme-21- Cross-Coupling of alkyl and aryl acetylenes

Phenol can be generated from benzene using a copper (I) source under oxygen and acidic conditions in 7.5% yield with respect to Copper.[71] Similar results have been obtained for the formation of phenol with dilute sulphuric acid, CuCl, and oxygen at room temperature.[72] Hydroquinone also forms in excellent yields along with smaller amounts of catechol-(Scheme-22).



Scheme 22. Copper-Mediated Oxygenation of Benzene

Mechanistically, copper reacts with oxygen under acidic conditions and forms hydroxyl radicals. Whereas Copper(II), generated through the process, has been confirmed to be inactive as a catalyst,. Most probably the mechanism proceeds through the attack of hydroxide radical on benzene to afford a hydroxycyclohexadienyl radical followed by one-electron oxidation and rearomatization to form the phenol product (**34)**-(Scheme-23)



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Scheme-23 Proposed Mechanism for the Copper-Mediated Oxygenation of Benzene

Applications

Owing to the high demand for mild and efficient oxidation catalysts, use of copper and its complexes as versatile catalysts in the oxidation of organic compounds has attracted significant attention of researchers. The chemistry of copper catalysis leaps forward when used in combination with molecular oxygen which can act either as a sink for electrons or a source of oxygen atoms that are incorporated into the product or both. Copper nanoparticles catalyzed Biginelli reaction at room temperature to give the product 3,4-dihydopyrimidinone from aldehydes, b-diketoester (ethylacetoacetate) and urea (or thiourea) has been reported. Due to their wide spectrum of biological and therapeutic properties dihydropyrimidinones (DHPMs) and their derivatives are widely used in both natural and synthetic organic chemistry. Copper-catalyzed cross-coupling reactions are one of the most useful reactions in synthetic organic chemistry due to the formation of C– N, C–O, C–S, and C–C bonds. Due to low cost and abundant storage of Cu in the earth, high catalyst activity in C–X coupling reactions and less toxic, copper catalysis opens a new door in field of research in C–X bonds (X = C, N, O, S) formation during coupling reactions.

CONCLUSION

This mini-review summarizes the various metal catalyzed synthetic techniques of a wide range of organic reactions. In comparison to other Transition metal elements such as Pd, Ni, Co, Fe, Pt etc., gold catalysis has demonstrated high efficiency in a variety of different chemical transformations. Au(I) and Au(III) complexes have been found highly useful for generating new C–C, C–O, C–N, and C–S bonds under mild conditions. Gold catalysis has also been used as a powerful tool for cascade or domino reaction processes. Furthermore mechanisms for different reactions like Heck reaction have been discussed here. Recent applications for a range of synthetic developments indicate the relevance of these notable reactions in organic synthetic chemistry.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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