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# Recent Advances in the development of Suzuki Miyaura Coupling Reactions

**Braham Dutt Arya, Neetu Malik, Rahul Sharma**

**Braham Dutt Arya**
Department of Chemistry, Pt. N.R.S. College, M.D. University, Rohtak (HR.) India

**Neetu Malik**
Department of Chemistry, Pt. N.R.S. College, M.D. University, Rohtak (HR.) India

**Rahul Sharma**
MSc Student, Department of Chemistry, University of Delhi, Delhi, India

**Abstract**

For the coupling of carbon –carbon bond, Suzuki Miyura Coupling (SMC) reactions which involves the coupling of an organoboron reagent and an organic halide in the presence of transition metal catalyst and a base, has emerged as most powerful tool for the synthetic transformation. This review collects the recent advances in the development of the catalytic systems, new generation ligands and various reaction mediums to allow the synthetic transformations in high yields.

**Keywords:** Suzuki Coupling reaction, Transition metals, organo catalysts

## Introduction

Synthetic organic chemistry provides a gateway to synthesize molecules which can mimic many important physiological functions that are characteristic of various naturally occurring molecules. Carbon-based organic chemistry is the basis of life and is responsible fornumerous fascinating natural phenomena: color in flowers, snake poison and bacteria killing substances such as penicillin. Organic chemistry has allowed man to build on nature's chemistry; making use of carbon’s ability to provide a stable skeleton for functional molecules. This has given mankind new medicines and revolutionary materials such as plastics. In order to synthesis various organic compounds the most important part is to connect carbon with carbon. Consequently, C-C bond formation is among the most explored area in the synthesis of organic chemistry. Disciplined efforts by many research groups enable us to provide various synthetic tools like Suzuki Miyura [1], Heck [2], Negishi [3] and Sonogashira [4] coupling reactions for the C-C bond formation. These methods provides extensive application in various academic areas including natural products synthesis, materials science, medicinal functional group transformations,agricultural activity products, biological as well as supramolecular chemistry[5-7]. Moreover, some recent applications include coordination chemistry, catalysis studies, and pharmaceutical beneficiary molecules and fine chemical industries. Among these powerful transformations, Suzuki Miyura coupling reactions has attracted the greatest interest of scientific community towards its application over a wide range. Over the past two decades, for the synthetic transformations of biaryl or substituted aromatic moieties and for their further applications in various arenas like polymer synthesis, natural products synthesis and biologically active molecules, SMC becomes one of the most efficient method [8- 10]. Use of milder conditions, ease of handling and separation of boron containing byproducts from reaction mixtures, commercial availability and stability of boronic acids to heat, water and air makes this the most efficient tool for synthetic chemical transformations.

In general, Suzuki reaction is the coupling of an aryl or vinyl boronic acid with an aryl or vinyl halide or triflate using a palladium catalyst. It is a powerful cross coupling method that allows for the synthesis of conjugated olefins, styrene, and biphenyls [11]. However, with the recent advances in synthetic protocols along with ease of purification as well as separation techniques of various organic catalyst, various transition metals in different solvents has been employed for carrying out SMC has been reported.The primary focus of various studies is to understand the mechanism details, factor effecting various elementary steps involved like oxidative addition, transmetallation, reductive elimination and reprocessing the catalyst for further use. Moreover, use of various catalytic systems plays crucial role in determining the yield, specificity and employment of the reaction. Homogenous systems and heterogeneous

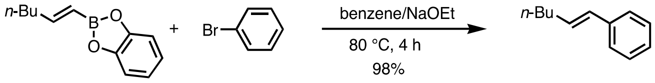
**Correspondence**:
**Braham Dutt Arya**
Department of Chemistry, Pt. N.R.S. College, M.D. University, Rohtak (HR.) India

based systems are considered for defining various catalytic parameters.

Homogenous system primilarly involves Pd based systems, Ni based systems, Fe based systems and other transition metal based systems [12-15]. The catalytic cycle of the palladium-catalyzed SMC is thought to follow a sequence involving the oxidative-addition of an aryl halide to a Pd (0) complex to form an arylpalladium(II) halide intermediate. Transmetallation with a boronic acid and reductive-elimination from the resulting diarylpalladium complex affords the corresponding biaryl and regenerates the Pd0) complex. The most common bases employed for SMC reactions are $K_3PO_4$, $K_2CO_3$, KOH and KF. The role of the base in these reactions is to facilitate the otherwise slow transmetallation of the boronic acid by forming a more reactive boronate species that can interact with the Pd center and transmetallate in an intramolecular fashion.Alternatively, it has also been proposed that the base replaces the halide in thecoordination sphere of the palladium complex and facilitates an intramoleculartransmetallation. However, the role of other ligands can never be denied for carrying out the SMC reactions.During the last ten years, the application of new ligands has dramatically improved the efficiency and selectivity attainable in such cross-coupling reactions. Other factors include choice of organo borane moieties and choice of solvents. In this present review we focus on the SMC reactions as well on the elementary steps involved in the mechanism of the reaction. Furthermore, dependence of these reaction on various catalytic systems, use of other transition metals other than palladium and performance of these reactions in various solvents.

**Suzuki reaction**

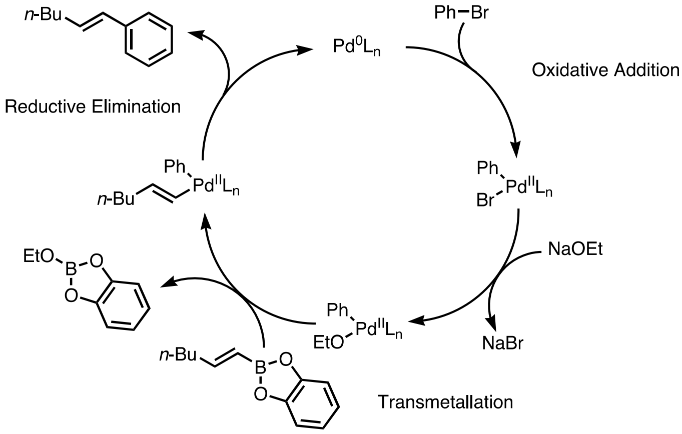
Suzuki reaction is the coupling of an aryl or vinyl boronic acid with an aryl or vinyl halide or triflate using a palladium catalyst. It is a powerful cross coupling method that allows synthesis of conjugated olefins, styrenes, and biphenyls:



Onto the surface of Pd catalyst adsorption of the organic moieties takes place which in turn reduce the required activation energy barrier and allows formingof new C-C bond. Homogenous, heterogeneous and use of other transition metals improves the capabilities of the reaction

**Mechanism**

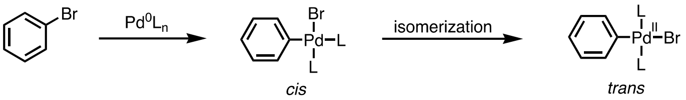
The mechanism of Suzuki miyura coupling reaction involves is best understood by exploring the chemistry of the Pd catalyst. First step is the oxidative addition of the palladium to the organohalide to form the organopalladium species. The coordination number of the central Pd increased by two with addition of organohalide.Further, reaction with base gives an intermediate product by the loss of halide ion, which via transmetalation with the boron ate complexes (produced by reaction of the boronic acid with base) forms the organopalladium species.Reductive elimination of the desired product restores the original palladium catalyst which completes the catalytic cycle.The Suzuki coupling takes place in the presence of a base and for a long time the role of the base was never fully understood. The base was first believed to form a trialkyl borate ($R_3B$-OR), in the case of a reaction of a trialkylborane ($BR_3$) and alkoxide ($^-$OR); this species could be considered as being more nucleophilic and then more reactive towards the palladium complex present in the transmetalation step. Duc and coworkers investigated the role of the base in the reaction mechanism for the Suzuki coupling and they found that the base has three roles: Formation of the palladium complex [ArPd(OR)$L_2$], formation of the trialkyl borate and the acceleration of the reductive elimination step by reaction of the alkoxide with the palladium complex.



As the mechanism of Suzuki reaction involves the three major steps viz oxidative addition, transmetallation and reductive elimination.

**Oxidative Addition**

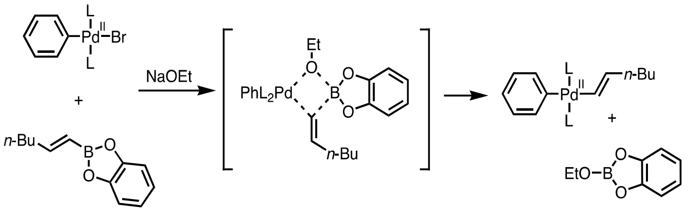
This step involves the oxidation of the Pd (0) to Pd (2) by the loss of two electrons and addition of organohalide on the central metal to form tetra coordinated complex (as shown below). Firstly, addition of the organohalide takes place to give *cis* complex than by isomerization it will rearrange its constituent's atoms to form *trans*complex. This rapid isomerization of *cis* complex to *trans* can be correlated by relative removal of steric hindranceby attained trans configuration.This isomerization is selective for the case of oxidative addition step. It proceeds with retention of stereochemistry with vinyl halides and with inversion with allylic and benzylic halides.



Also the order of reactivity of the leaving groups is as follows: I – >OTf – > Br – >> Cl –.

**Transmetallation**

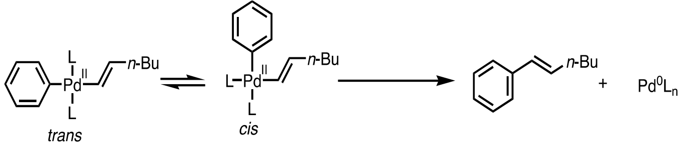
Such reactions involve the transfer of ligands from one metal to another. During the Suzuki reaction it is the step responsible for substitution of the ligand from organoboron compounds to Pd catalytic system via formation of cyclic intermediate.



Yet, the role of the base in the transmetallation process is unresolved, but formation of Boron "ate" complexes via quaternization of the boron with a negatively charged base, are frequently invoked. However, in the presence of base, final outcome is the removal of halide ion from central metal of the palladium catalyst and substitution of alkenyl functionality from the organoborane to Pd metal.

## Reductive Elimination

Herefirst, isomerisation of *trans*product into *cis* isomer occurs and then the elimination product formed with the regeneration of the catalyst. As proposed by Ridgway *et al.* by using deuterium labelling the reductive elimination proceeds with retention of stereochemistry.



The relative rates of elimination from Pd (II) complexes follows the order:aryl–aryl > alkyl–aryl > n-propyl–n-propyl > ethyl–ethyl > methyl–methyl.

## Factors affecting Suzuki Reaction

As the Suzuki reaction is carried out in different catalytic system under controlled conditions of temperature, pressure and solvent. However, the dependence of product formation upon catalytic system is most acknowledged.

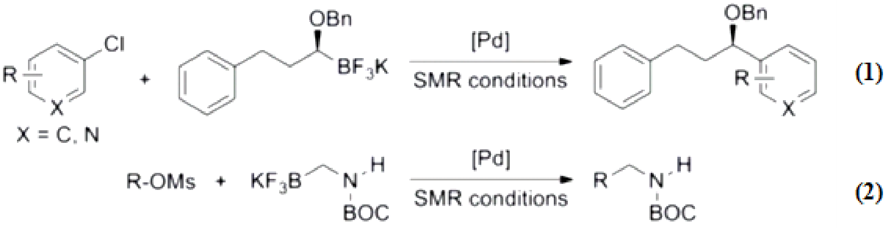
## Catalytic systems

Suzuki miyura reactions mainly involve complexes of transition metals as their catalytic systems. They can be further categorized as homogenous and heterogeneous systems.

## Homogenous systems

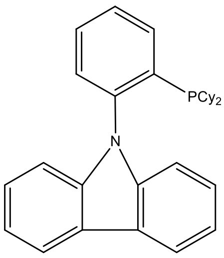
Recently, Thakur et al, 2012 have reported the protocol for the coupling of heteroaryl boronic acids and vinyl chlorides using $Pd(OAc)_2$ and SPhos at 85 °C. They observedthat with increase or decrease of the temperature there was a decrease in the yield of the product [16]. Glasspoole et al 2012, have developed a catalytic system without adding base and under mild conditions. They reported the coupling of allylic carbonates with arylboronicacuds using racemic BINAP as ligand and achieving a high regioselectivity and stereospecific product formation [17]. Recently, Chausset-Boissaire et al 2013, have reported the use of $Pd(dba)_3$, $PPh_3$and $Ag_2O$ as the catalytic systems and suggesting the method for attaining the high yields of region isomers using enantioselective chiral and enantioriched secondary boronic esters as precursors [18].

However, some research groups also demonstrated the use of different oranoboranes other than boronic acids and esters to signifying the dependence of the boronic moiety on the final product. Molanderet al 2012, have reported the coupling of potassium 1-(benzyloxy)alkyltrifluoroborates with aryl and heteroaryl chlorides [19], potassium Boc-protected aminomethyltrifluoroborateswith aryl and heteroarylmesylates with benzyl chlorides. They have used commercially available phosphines like RuPhos or SPho [20]. (Scheme 1)



**Scheme 1: Organoboranes coupling partners reported by Molander et al 2012.**

One of the major problem with the above methods is to use them for sterically challenged substrates. To overcome this situation a number of research has also been made by combined use of palladium based ligands with palladium based complexes. To et al 2011 have reported the synthesis of ligand 1, used in combination $Pd(OAc)_2$ for the synthesis of tri-*ortho*-substituted biaryls [21]. However, to synthesize Di- and tri-*ortho*-substituted biarylsRaders et al 2013 have demonstrated the synthesis of trineopentylphosphine **2** [22]. Moreover, to attain coupling of aryl halides with boronic acids in excellent yields Zao eta al 2013 fabricated the synthesis of tetra-*ortho*-substituted biaryls with ligand 3 and 4 [23].



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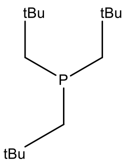

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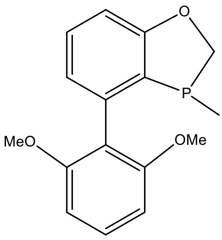

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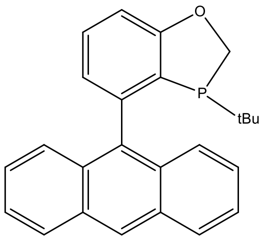
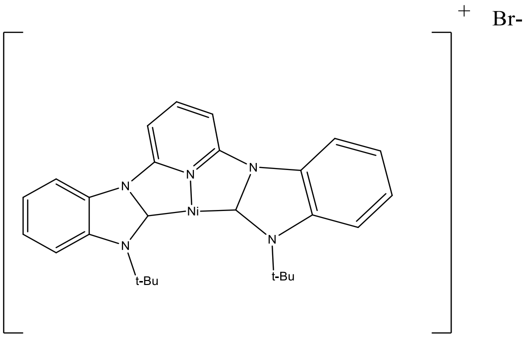


**4**

Further the use of Ni and other transition metal based catalytic systems has completely revolutionize the SMC reactions. The most significant feature is the variety of protocols that have been developed to couple otherelectrophiles than the classic aryl iodides, bromides or chlorides. Phenols [24,25] carbamates and sulfamates [26,27], fluorides [28], phosphates [29]. andheteroaryl ethers [30] have been successfully coupled with organoboron reagents with excellent results. In Table 1, we summarize recent advance catalytic systems developed by various groups.



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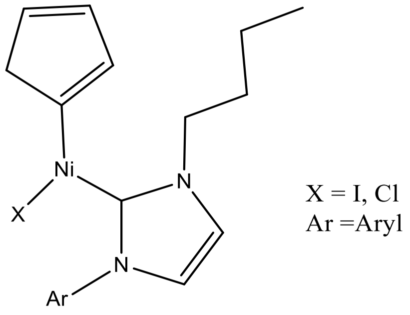

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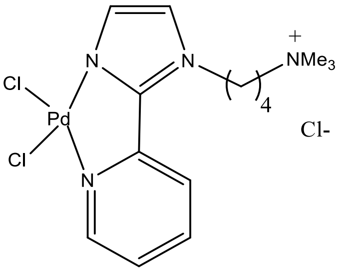

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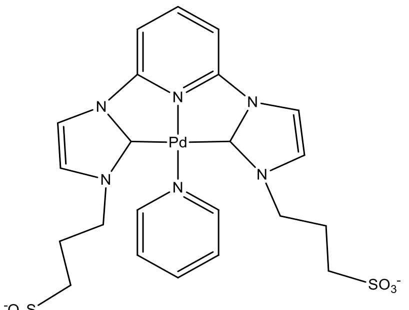

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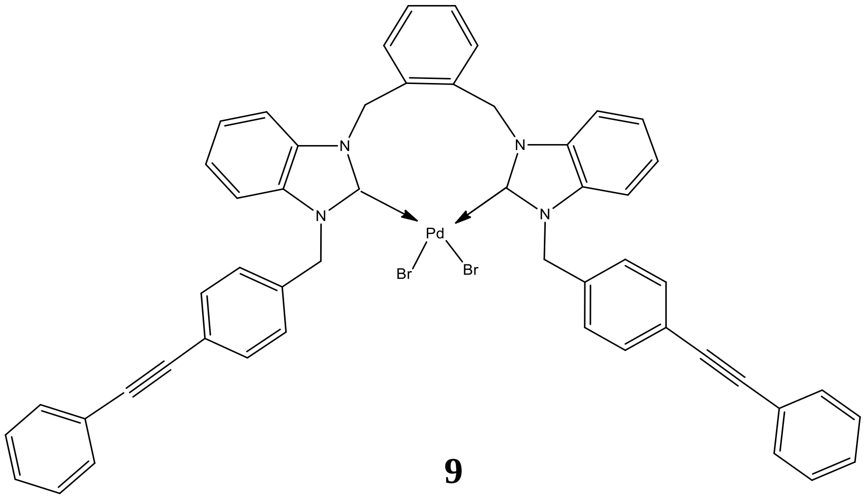

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**Table 1:** List of catalytic systems with various ligand assemblies for employing SMC reactions with various parameters

| Catalytic System | Group | Ligand assembly | R-X | Reference |
|---|---|---|---|---|
| 5 | Tu and co worker | $PPh_3$ | Aryl bromide/chloride/Tosylate | 31 |
| 6 | Chetcuti&Ritleng | $PPh_3$ | Bromo and chloroarenes | 32 |
| 7 | Wang | $PPh_3$/ $Pd(OAc)_2$ | Aryl chloride and bromide | 33 |
| 8 | Godoy &Peris | $Pd(OAc)_2$; Green condition | Aryl chloride and bromide | 34 |
| 9 | Schmitzer | $Pd(OAc)_2$; Green condition | Aryl chloride and bromide | 35 |

## Conclusion

From over four decades, SMC reactions have completely transform the fate of carbon-carbon bond synthesis. Using, various reactions parameters and catalytic systems of desired functionality SMC reactions emerges as a powerful tool for synthetic organic transformation. Finding numerous applications in natural product synthesis and medical chemistry, SMC reactions are the need of today and future prospective. Ligand and catalytic systems of desired shape, size and specific medium are the requirement of future to obtain transformation reaction in high yields. Hence, developments in the catalytic systems for desired reactions transformations need to be more explored.

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