



MODERN SYNTHETIC METHODS FOR TRANSITION METAL CATALYZED OXIDATIVE COUPLING OF TERMINAL ALKYNES WITH ARYLBORONIC ACIDS

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ABSTRACT

A concise overview is given on the recent advancements in transition metal-catalyzed oxidative cross-coupling between terminal alkynes and arylboronic acids. The oxidative coupling reaction allows for an efficient access towards internal alkynes. The catalysts generally exhibit good tolerance towards organic functionalities and are stable in air and moisture. Progress has been made in expanding the scope and the applications as well as understanding the mechanism of this reaction. The use of the first-row transition metals as catalysts is much more appealing than the precious metals owing to the apparent advantages such as cheapness and earth abundance.

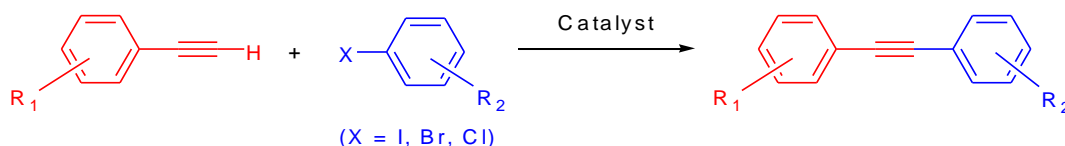
KEYWORDS

Transition metal; Catalysis; Oxidative coupling; Alkynes; Arylboronic acids

1. INTRODUCTION

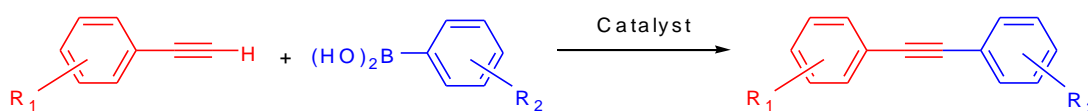
There is high demand for new methods to facilitate the synthesis of alkynes which are prevalent motifs found in numerous dendrimers [1], conjugated oligomers and polymers [2], natural products, pharmaceuticals [3], optical materials [4], etc.. The traditional palladium catalyzed - copper cocatalyzed Sonogashira cross-coupling (alkynylation of aromatics) reaction between an aryl halide and a terminal alkyne to synthesize internal alkynes (Scheme 1) has emerged as one of the most widely used carbon-carbon bond forming reactions in organic chemistry. Since its discovery in 1975, the original procedure [5] has been modified from time to time by varying the transition metal source, ligand, solvent, base, additive, reaction temperature and catalyst loading to enhance the efficiency and generality of this reaction.[6-13] Though the protocol shows high efficiency and tolerance of functional groups, it does not proceed well for electron-poor alkynes. Further in many

cases, harsh reaction conditions (usually temperatures $>80\text{ }^{\circ}\text{C}$) must be employed and many of the phosphine ligands used are expensive and air-sensitive which hamper the applications of the palladium-based catalytic system for the industrial use. So, there is need for the development of an easy and convenient approach for the synthesis of substituted alkynes under mild reaction conditions.



Scheme 1: Transition metal catalyzed Sonogashira cross-coupling reaction

Oxidative coupling reactions, particularly methods that enable the direct functionalization of the C–H bonds, have been the focus of significant research interest [14-20]. In recent years, transition metal catalyzed oxidative coupling of alkynes and arylboronic acids has emerged as an alternative for the traditional Sonogashira reaction. This C–C cross-coupling reaction offers many advantages such as mild reaction conditions, commercial availability or ease of preparation of a large number of air and water stable boronic acid derivatives, easy handling, easy removal of boron residues, the low toxicity of reagents and by-products as well as high functional group tolerance, thus explaining the increasing interest in academic research. In addition, it is economical and environmentally benign to employ molecular oxygen in air as the stoichiometric oxidant. For all these reasons, search for new, efficient and cost effective catalysts for oxidative cross-coupling reactions is very appealing. This review attempts to provide an overview of the status of chemistry of transition metal catalyzed oxidative coupling of alkynes and arylboronic acids (Scheme 2). The literature survey is complete to June 2016.



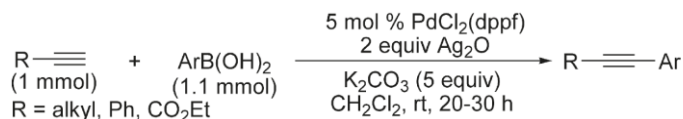
Scheme 2: Transition metal catalyzed oxidative cross-coupling reaction

2. TRANSITION METAL CATALYZED OXIDATIVE COUPLING OF ALKYNES AND ARYLBORONIC ACIDS

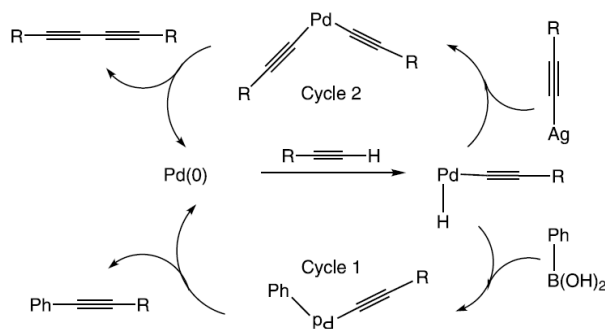
2.1 Pd CATALYZED REACTIONS

Zou and coworkers developed a new procedure for the construction of arylalkynes through the cross-coupling of terminal alkynes with arylboronic acids [21]. The effective cross-coupling was catalyzed by $[\text{Pd}(\text{dppf})\text{Cl}_2]$ (where dppf = 1,1'-bis(diphenylphosphino)ferrocene) and Ag_2O as additive in $\text{CH}_2\text{Cl}_2\text{-K}_2\text{CO}_3$ under aerobic conditions at room temperature. The protocol worked well

for both electron-rich and electron-deficient alkynes (Scheme 3). It was believed that Ag₂O activates carbon-boron bond thereby accelerating the transmetalation between the boronic acid and the palladium species. Other additives gave poor results. A plausible Pd(II)/Pd(0) mechanistic cycle assisted by silver(I) oxide was also proposed (Scheme 4). Electron-donating and electron-withdrawing substituents on the alkyne or boronic acids gave comparable yields of the desired products. However, alkadiynes was also observed in some cases and the palladium-ligand catalytic system used was highly expensive.

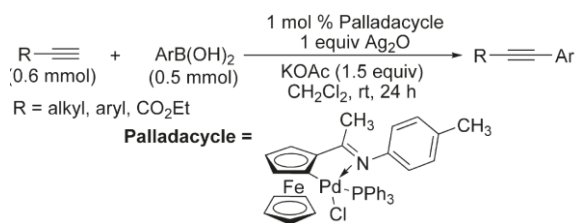


Scheme 3: Reaction conditions designed by Zou and coworkers

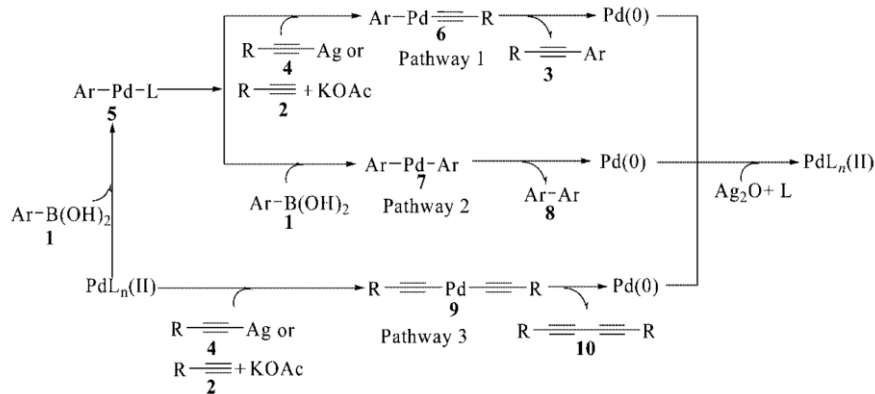


Scheme 4: The mechanistic cycle proposed by Zou and coworkers

Subsequently, Yang and Wu extended the scope of this oxidative coupling reaction using a cyclopalladated ferrocenylimine complex in CH₂Cl₂-KOAc in presence of Ag₂O as additive at room temperature under N₂ atmosphere [22]. This method provided the first example of a palladacycle-catalyzed cross-coupling reaction of arylboronic acids with terminal alkynes and also a facile route for the synthesis of substituted alkynes with a low Pd loading of 1 mol% (Scheme 5). It was observed that electron-donating electron-withdrawing or heterocyclic aromatic groups had little effect on the cross-coupling reaction and moderate to good yields were obtained. The scope of the substrates could be extended to electron-poor alkynes (alkynes with electron donating substituents), for which the traditional Sonogashira reaction does not proceed. A plausible mechanism was also suggested by the group (Scheme 6).

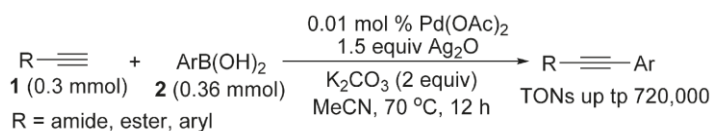


Scheme 5: Reaction conditions for palladacycle-catalyzed cross-coupling reaction

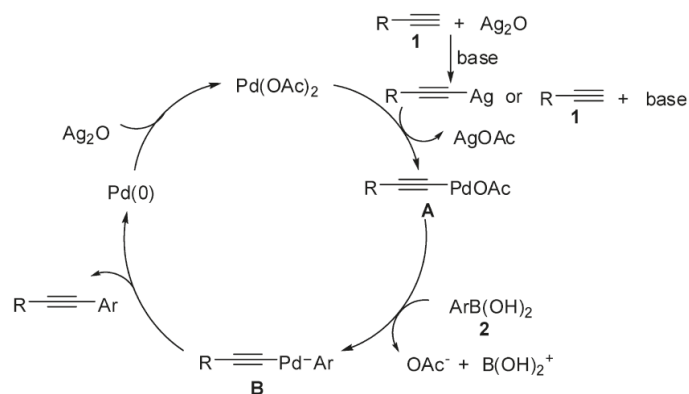


Scheme 6: Mechanism proposed by Wu and coworkers

Zhou et. al., further improvised on the palladium-catalyzed reaction of terminal alkynes with arylboronic acids [23]. In the presence of $\text{Pd}(\text{OAc})_2$ and Ag_2O in $\text{CH}_3\text{CN} - \text{K}_2\text{CO}_3$ at 70°C , a variety of terminal alkynes, including electron poor terminal alkynes, smoothly underwent the reaction with numerous boronic acids to afford the corresponding internal alkynes in moderate to good yields (Scheme 7). It was noteworthy that the reaction proceeds under ligand-free conditions and relative lower Pd loading, and the maximal TONs (turnover numbers) of the reaction were up to 720,000. A Pd(II)/Pd(0) mechanism assisted by silver(I) oxide was also proposed (Scheme 8). Ag_2O was supposed to play four different roles in the reaction: (i) base, (ii) generation of the active alkynylsilver in situ, (iii) promoter for the activation of the alkynylpalladium complex facilitating the transmetalation of aryl group from arylboronic acid, and (iv) oxidant to regenerate the active Pd(II) species. The methodology was extended to the synthesis of 1*H*-isochromenes and diynes.

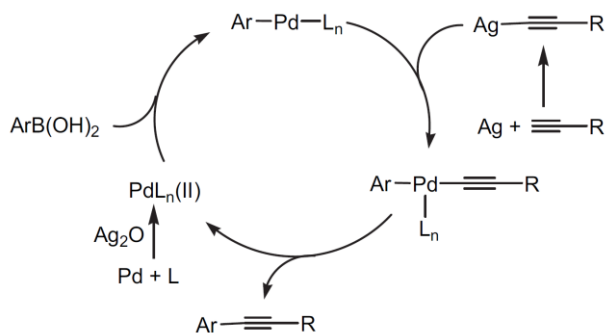


Scheme 7: Reaction conditions developed by Zhou et. al.



Scheme 8: Pd(II)/Pd(0) mechanism assisted by silver(I) oxide as proposed by Zhou et. al.

The research group of Bao offered an alternative protocol for this cross-coupling reaction using porous palladium nanospheres as heterogeneous catalysts in conjunction with Ag_2O , triphenylphosphine and Cs_2CO_3 under N_2 atmosphere in dry dichloromethane [24]. The corresponding arylalkynes were formed with good to excellent yields. There were also other obvious advantages such as broad applicability, high selectivity, simple experimental operation as well as the convenient preparation, high efficiency and reusability of catalyst. It was believed that the reaction proceeded via a Pd(II)/Pd(0) catalytic cycle (Scheme 9).



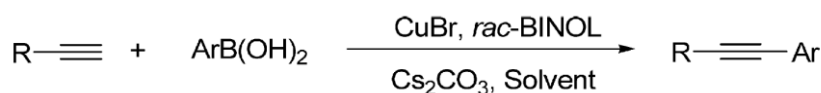
Scheme 9: The possible mechanism for nano-palladium catalyzed oxidative cross-coupling reaction

From Xu's laboratory the synthesis and structural characterization of two new air-stable N-heterocyclic carbene (NHC) adducts of cyclopalladated ferrocenylpyridine containing chloride or iodide anions was reported [25]. These adducts have been successfully applied to the coupling of terminal alkynes with arylboronic acids under atmospheric conditions using Ag_2O and KOAc in 1,2-dichloroethane at $80\text{ }^\circ\text{C}$. The effect of substituents on the alkynes and arylboronic acids were also investigated and the desired products were obtained in moderate to excellent yields. The coupling tolerated a wide range of functional groups and represents a practical alternative for the traditional Sonogashira coupling reaction.

2.2 Cu CATALYZED REACTIONS

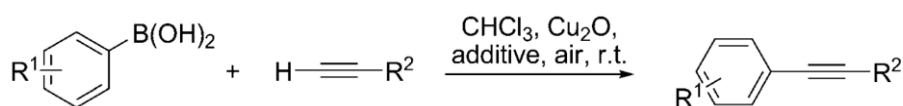
The development of reactions using abundant metals as a replacement for noble metals (such as palladium) has also received attention reflecting supply shortages of several important elements. Copper is an abundant and inexpensive metal, and is widely used in organic synthesis as a reagent or catalyst, thus attracting attention for this oxidative coupling reaction.

CuBr/*rac*-BINOL-catalyzed coupling reaction of arylboronic acids with terminal alkynes in DMF in presence of Cs₂CO₃ was explored by the group of Mao [26]. The desired products were obtained in satisfactory yields under optimized loading of CuBr and *rac*-BINOL (Scheme 10). In comparison the palladium-catalyzed Sonogashira coupling reaction, this protocol is simple and avoids the use of air-sensitive and expensive catalysts or silver(I) oxide as additive. The ease of availability and low price of the catalyst makes this catalytic method useful.



Scheme 10: Copper catalyzed oxidative coupling reaction from Mao's laboratory

The work done by Fu and coworkers revealed the efficacy of the inexpensive copper(I) oxide in mediating this oxidative coupling reaction [27]. They used Cu₂O as the catalyst in chloroform, pyridine – methanol mixture as additive, oxygen in the air as the stoichiometric oxidant, in the absence of ligand or sealed reaction vessels (Scheme 11), and observed remarkable functional group tolerability in the oxidative coupling reaction. The electronic effect of substituent groups on the aromatic boronic acids didn't show any evident difference of reactivity and the target products were obtained in good to excellent yields.



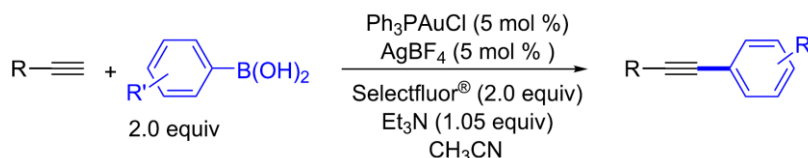
Scheme 11: Copper(I) oxide catalyzed oxidative coupling reaction developed at the group of Fu

Later on, the group of Kobayashi extended the cross-coupling reactions between alkynes and boronic acids using a small amount of a CuBr in methanol and 2,6-lutidine media [28]. This reaction proceeded smoothly in 2,6-lutidine with high selectivity, and the undesired homocoupling reactions were suppressed. Wide substrate generality has been demonstrated. It is noted that lower amounts of the catalyst and lower concentration can improve the yields significantly for some substrates.

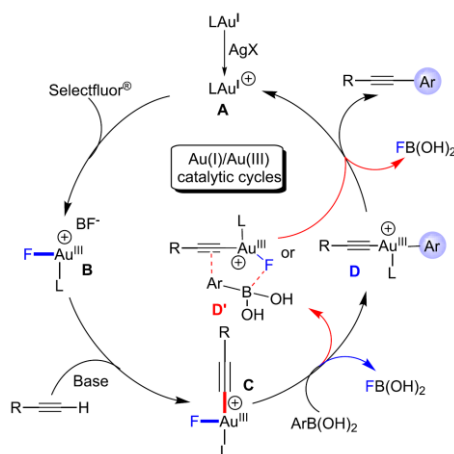
Cubic, rhombic dodecahedral, and octadecahedral Cu₂O nanocrystals (NCs) were selectively synthesized by Peng and coworkers [29]. The ligand-free arylation of phenylacetylene with arylboronic acids catalyzed by as-obtained Cu₂O NCs using dioxane and 2-propanol (4:1) as solvent and *tert*-BuOK as base at 60 °C was also investigated. These heterogeneous catalysts show good to excellent yields, while displaying distinct shape evolution (or stability) during the catalytic reaction. Cu₂O octadecahedra was found to have the best catalytic activity upon recycling. Cu₂O cubes had the lowest stability, with their surfaces etched rough after the first cycle of oxidative arylation.

2.3 Au, Fe AND Ni CATALYZED REACTIONS

Zang and coworkers developed an unprecedented Au-catalyzed cross-coupling reaction of terminal alkynes and arylboronic acids under mild conditions [30]. Selectfluor® and counter ion effects played significant role in the development of an exceptionally mild catalyst system in CH₃CN-Et₃N (Scheme 12). Good tolerance toward many functional groups of substrates was also observed. Au(I)/Au(III) mechanistic cycle was also proposed (Scheme 13).



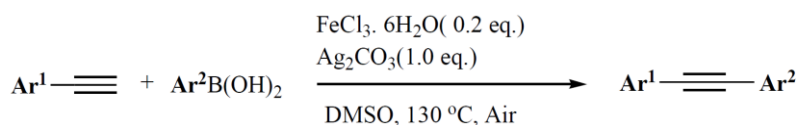
Scheme 12: Au catalyzed oxidative coupling reaction



Scheme 13: Au(I)/Au(III) mechanistic cycle proposed from the laboratory of Zhang

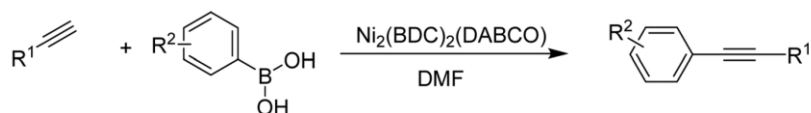
Iron-catalyzed cross-coupling of terminal alkynes with arylboronic acids under mild conditions (Scheme 14) was developed by You et. al. [31]. Silver salts were crucial for the success of the cross-coupling. Electron-rich substituents were beneficial for the transformation, whereas electron-withdrawing substituents slightly decreased yields of the reaction. The reaction tolerated a wide range of functional groups, such as, methyl, methoxy, aldehyde, ester, cyano, carboxyl fluoro

and hydroxy groups. Although the reaction gave only moderate yields, the advantage of this method was its use of convenient and inexpensive iron(III) chloride as catalyst.



Scheme 14: Fe catalyzed oxidative coupling reaction

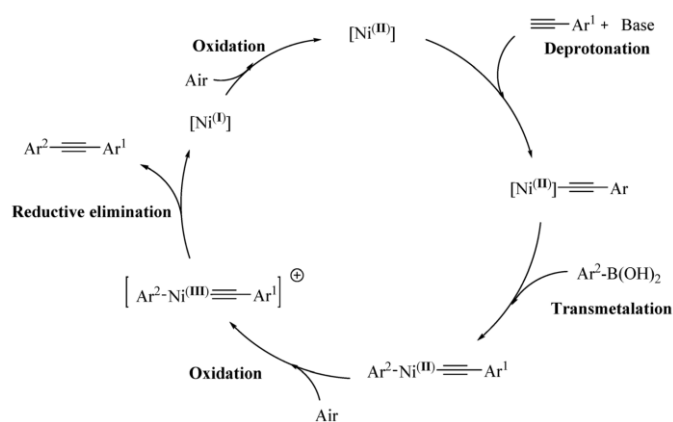
A crystalline porous metal–organic framework $\text{Ni}_2(\text{BDC})_2(\text{DABCO})$ (where $\text{H}_2\text{BDC} = 1,4$ -benzenedicarboxylic acid; $\text{DABCO} = 1,4$ -diazabicyclo[2.2.2]octane) was synthesized and suitably characterized by Phan and coworkers [32]. The nickel complex was found to act as an efficient and recyclable heterogeneous catalyst for the cross-coupling reaction between phenylboronic acids and aryl- as well as alkylacetylenes in the presence of molecular oxygen in air as the stoichiometric oxidant (Scheme 15). Various reaction conditions such as solvent, base, concentration of base, reaction temperature, ligand additives, ligand concentration, substrate ratio, catalyst loading were first optimized. High conversions of the cross-coupling products were achieved in air with no homo-coupling products being detected by GC under optimized reaction conditions. A Ni(II)/Ni(III) reaction mechanism was also proposed (Scheme 16). $\text{Ni}_2(\text{BDC})_2(\text{DABCO})$ exhibited significantly higher catalytic activity in the coupling reaction than that of other nickel metal-organic-frameworks.



R^1 : aryl, alkyl

R^2 : -Cl, F, H, C_2H_5 , OCH_3 , COOH , CHO

Scheme 15: Ni catalyzed oxidative coupling reaction



Scheme 16: Proposed mechanism through Ni(II)/Ni(III) catalytic cycle

3. SUMMARY AND FUTURE OUTLOOK

The review documents the use of transition metal complexes as potential homogeneous and/or heterogeneous catalysts for the oxidative coupling reaction between terminal alkynes and arylboronic acids resulting. Silver(I) salts were found to be crucial for the formation of internal alkynes. The reactions tolerated different functional groups, thereby avoiding the need for protection and deprotection of functional groups during organic synthesis. The electronic effect of substituent groups on the alkynes or the aromatic boronic acids did not show significant difference of reactivity. The oxidative cross-coupling between arylboronic acids and alkynes represents a practical alternative for the traditional Sonogashira reaction, especially for the coupling of electron deficient alkynes with arylboronic acids.

Despite many important contributions and significant progress, many challenges remain. To meet these, proper optimization of the reaction conditions (such as choice of solvent, base, temperature, air / inert atmosphere, catalyst loading, reaction time) must be done to determine the optimal reaction condition and to achieve high turnover number and turnover frequency for this coupling reaction. In addition, detailed mechanistic studies supported by appropriate computational studies have to be performed to shed more light on the transition metal species and other intermediates involved during the cross-coupling reaction. Owing to the increased amount of research work being conducted in this field and the utility of the internal alkynes in various fields, major steps to solve these challenges should emerge in the near future.

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