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ARTICLE TYPE

Recent Advancements and Perspectives in Copper-catalyzed Sonogashira Coupling Reactions

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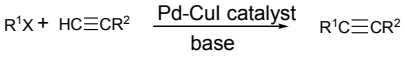
C-C bond formation using transition metal catalyzed Sonogashira coupling reaction is an indispensable tool in synthetic organic chemistry. Initially Pd complexes were used as catalyst; however advances in catalyst design fuelled the development of Cu catalysts, which are cheaper and more environmentally benign than the Pd complexes. This is the first review reported so far dealing exclusively with Cu-catalyzed Sonogashira coupling reaction. This review illustrates the current strategies and potentials of Cu-catalyzed Sonogashira coupling reactions.

1. Introduction

Transition metal catalyzed reactions have evolved as a versatile tool in organic chemistry during the last three decades because of easy carbon-carbon bond formation which were used in the synthesis of many pharmaceuticals and agrochemicals. These reactions have many desirable features like mild reaction conditions, high efficiency and good functional group tolerance. The Pd-catalyzed cross-coupling reactions between sp^2-C halides and terminal alkynes have been reported independently by Heck, Cassar and Sonogashira in 1975.[1, 2] Heck and Cassar relied on Pd catalysts for coupling between sp^2-C halide and terminal alkyne, while Sonogashira utilized a combination of Pd and Cu catalysts. The Sonogashira-Hagihara reaction involves the cross-coupling reaction between an aryl halide (Cl, Br, I, OTf) and a terminal acetylene in presence of catalytic amounts of Pd complex, Cu^I salt and a base to form an aryl acetylene.[3-7] A combination of 1-10 mol% of $Pd(PPh_3)_2Cl_2$ or $Pd(PPh_3)_4$ and CuI as the catalyst system was generally used for the reaction. Owing to the high cost of Pd, the use of Sonogashira reaction in large scale production is restricted and consequently alternative catalyst systems are searched for.[8] Thus replacing Pd with cheaper, more abundant and less toxic Cu has become an area of active research. This review highlights the existing strategies and potentials of Sonogashira coupling reaction using Cu based catalysts as the sole catalyst system (without the use of Pd compounds) and covers literature from 2000-2013.



R^1=aryl,vinyl; R^2=aryl,alkyl

Scheme 1. General representation of Pd/Cu-catalyzed Sonogashira coupling reaction

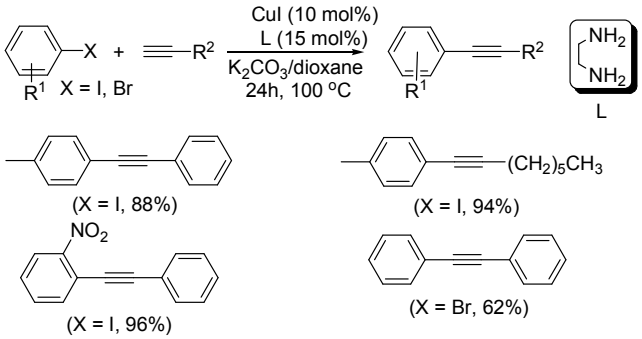
The Sonogashira coupling reactions are carried out in a variety of catalytic systems and reaction conditions.

2. Different catalytic systems for Sonogashira coupling

Depending on the nature of the ligand present in the complex, the catalyst systems are classified as discussed below.

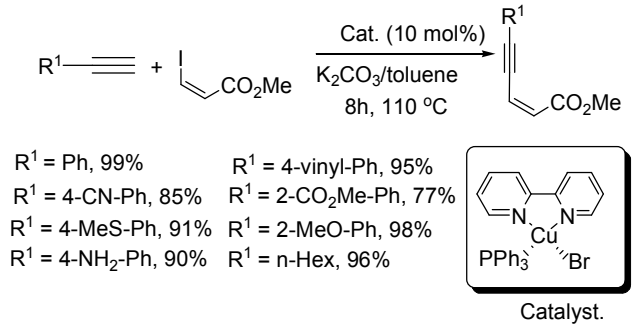
2.1. Cu-Nitrogen complexes

This is the most widely used catalytic system for Sonogashira coupling reaction. Guo *et al*. in 2005 reported CuI-ethylenediamine catalyst system for the Sonogashira coupling of aryl iodides and aryl bromides with aryl and alkyl acetylenes by avoiding the use of toxic PPh_3.[9] In the optimized reaction condition, 10 mol% of CuI, 15 mol% of ethylenediamine and 2 equivalents of K_2CO_3 were used in dioxane at 100 ^oC (scheme 2). Electron-withdrawing and electron-donating groups on the aryl iodides and bromides were tolerated in the reaction affording more than 80% yields for the iodides and 60-70% for the bromides.



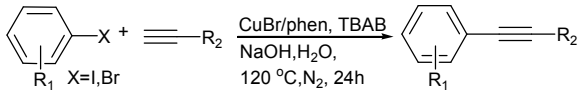
Scheme 2. Cu-catalyzed coupling reaction of aryl halides with terminal alkynes using ethylenediamine as ligand.

Venkataraman *et al*. utilized [Cu(phen)(PPh_3)Br] catalyzed coupling of electron-rich and electron-poor aryl iodides with phenyl acetylene in presence of K_2CO_3 in toluene at 110 °C (scheme 3).[10] They also used the methodology for the coupling of aryl acetylenes and (*Z*)-Methyl-3-iodoacrylate with complete retention of stereochemistry using [Cu(bipy)(PPh_3)Br] as the catalyst.



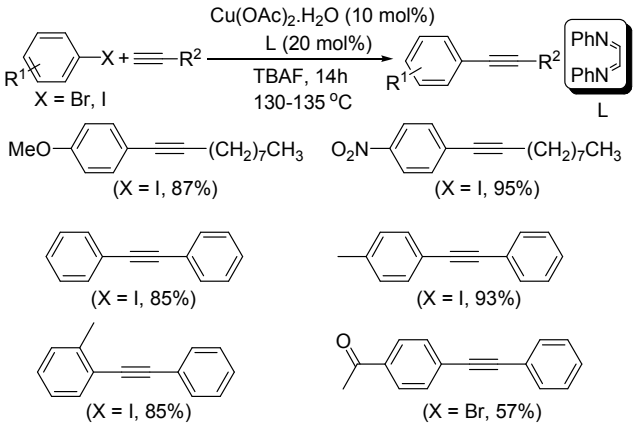
Scheme 3. Cu-catalyzed coupling reaction of terminal alkynes with (Z)-Methyl-3-iodoacrylate.

An inexpensive and environmentally friendly protocol for Sonogashira couplings of aryl halides with terminal alkynes was introduced by Fu *et al*. in the presence of CuBr using 1,10-phenanthroline as the ligand and tetrabutylammonium bromide (TBAB) as the phase-transfer catalyst in water (scheme 4).[11]



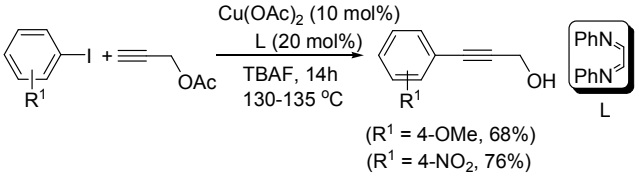
Scheme 4. CuBr/phen catalyzed Sonogashira coupling reaction.

1,4-diphenyl-1,4-diazabuta-1,3-diene was used as a ligand in combination with catalytic $Cu(OAc)_2$ and TBAF for the Sonogashira coupling of aryl iodides and aryl bromides with terminal alkynes without any solvent under aerobic conditions (scheme 5).[12] Good yields of the products were obtained irrespective of the nature of the substituents present in the substrates. Aryl bromides showed low reactivity, and a slight increase in yield was observed when TBAF was replaced with TBAB or by increasing the catalyst loading.



Scheme 5. Cu-catalyzed coupling reaction of aryl halides with terminal alkynes using 1,4-diphenyl-1,4-diazabuta-1,3-diene.

The deprotection of -OAc group in propargylacetate was observed during the coupling reaction (scheme 6). Although Cu^{II} is a popular reagent for Glaser coupling of alkynes, no homo coupling product was observed under the optimized reaction conditions, arguably suppressing the oxidative homocoupling of alkynes.



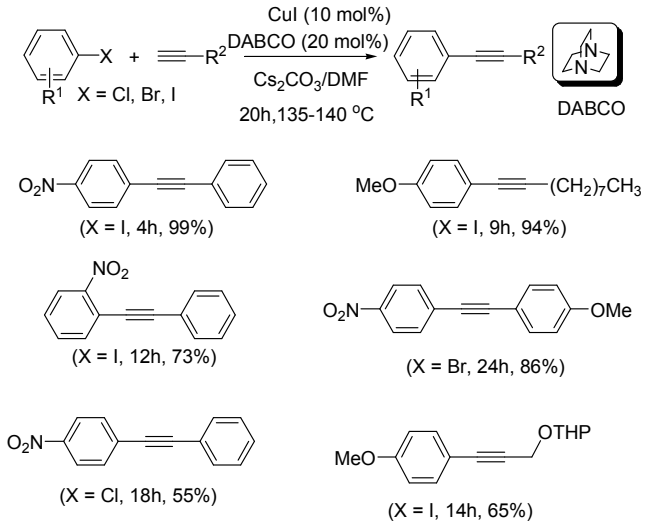
Scheme 6. Deprotection of acetate group during Sonogashira coupling reaction.

Argon suppressed the Cu(II)acetate-catalyzed reaction but favoured the Cu^{I}-catalyzed reaction indicating that oxygen promotes the Cu(II)acetate-catalyzed Sonogashira reaction. The same authors then replaced the 1,4-diphenyl-1,4-diazabuta-1,3-diene ligand with 4,6-dimethoxy-2-aminopyrimidine under essentially the same reaction condition used earlier (10 mol% of $Cu(OAc)_2$, 20 mol% of ligand, TBAF at 125-130 °C without any solvent and in the presence of air) and observed that the coupling occurred in excellent yields for reaction between electron deficient aryl iodides and aryl acetylenes.[13] Aryl bromides and alkyl acetylenes afforded lower yields. The authors assume that the addition of pyrimidine ligand suppresses the oxidative homocoupling of terminal alkynes.

Li and co-workers further modified the catalyst system ($Cu(OAc)_2$) by replacing the ligand with a coordinating solvent (Et_3N) and observed that aryl iodides and aryl bromides reacted with aryl and alkyl acetylenes in presence of 50 mol% of $Cu(OAc)_2$ yielding good to excellent amounts of the cross coupled products.[14] Electron-donating and electron-withdrawing groups in the aryl iodide component were used in the study. The utility of this reaction is impeded by the requirement of 50 mol% of $Cu(OAc)_2$ as the catalyst and the formation of homocoupling products from the terminal acetylene.

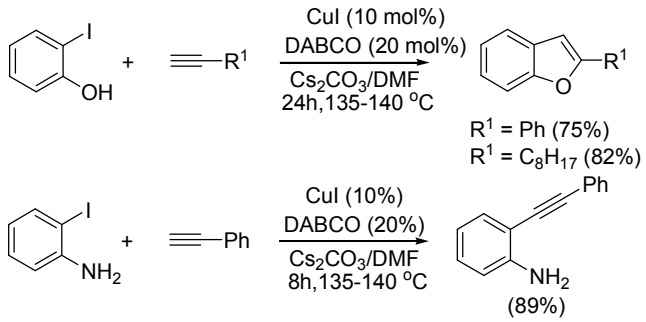
Li and co-workers applied the reaction conditions used by them in the CuI-DABCO catalyzed Suzuki-Miyaura coupling to Sonogashira reaction between aryl halide and a terminal alkyne,

which afforded good to excellent yields of the coupling products.[15] Here 10 mol% of CuI, 20 mol% of DABCO and Cs_2CO_3 were used in DMF at 135-140 ^oC (scheme 7). Substrates containing both electron-donating and electron-withdrawing groups were tolerated in the reaction. The protocol was successfully extended to alkyl acetylenes and vinyl halides.



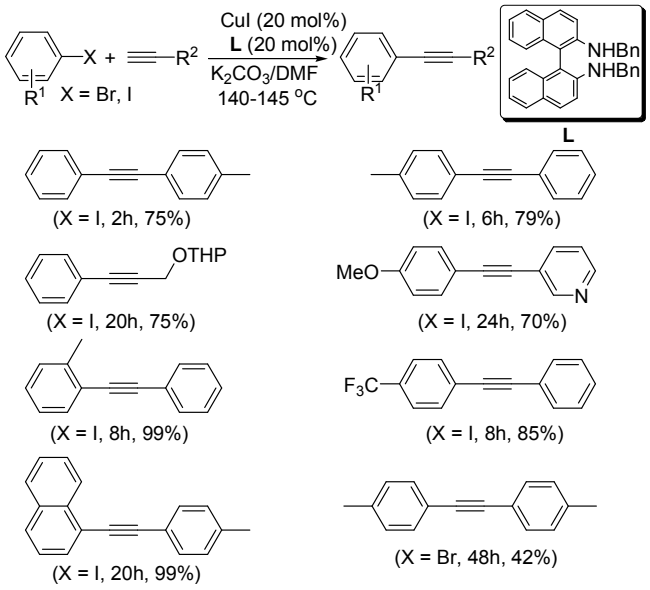
Scheme 7. Cu-catalyzed Sonogashira coupling reaction using DABCO as the ligand.

When the reaction condition was applied to *o*-iodophenol, Sonogashira coupling followed by intramolecular ring closure took place leading to benzofuran (scheme 8). However the corresponding aniline failed to undergo the ring formation and gave only the Sonogashira product.



Scheme 8. Cu-catalyzed tandem Sonogashira-ring closure reaction using DABCO as the ligand.

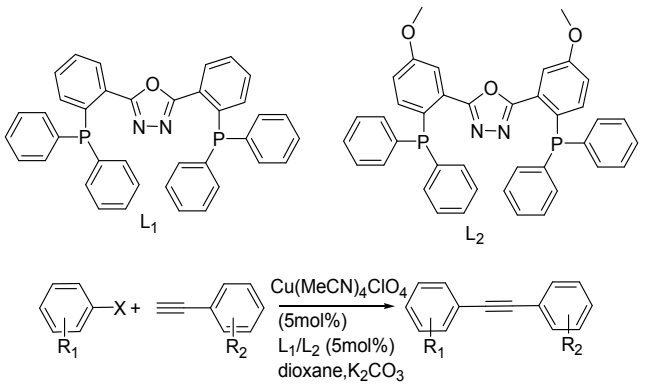
Sonogashira coupling between aryl iodides and terminal alkynes was achieved by Sekar *et al*. using *N,N*'-dibenzyl BINAM-CuI in the presence of K_2CO_3 (scheme 9).[16]



Scheme 9. Cu-catalyzed Sonogashira coupling reaction using *N,N'*-dibenzyl BINAM as the ligand.

Terminal alkynes containing heterocycles and sensitive groups (eg.OTHP) also gave the coupling product in good yields. Aryl bromides also underwent the reaction; but their reactivity was found to be less compared to that of the iodo derivatives.

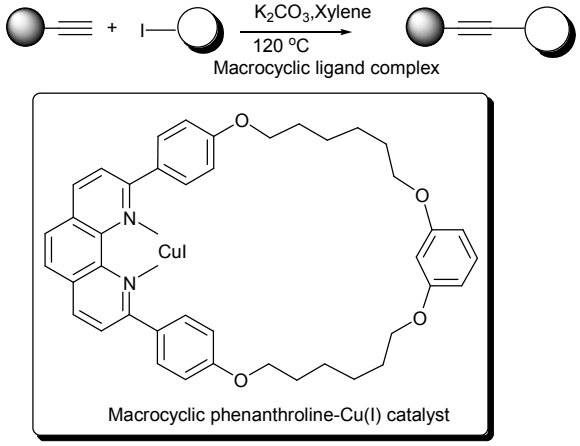
Two diphosphane ligands containing nitrogen donor groups such as 2,5-bis(2-(diphenylphosphino)phenyl)-1,3,4-oxadiazole (L_1) and 2,5-bis(2-(diphenylphosphino)5-methoxyphenyl)-1,3,4-oxadiazole(L_2) were prepared and screened by Xu *et al*. for Cu-catalyzed Sonogashira coupling reactions.[17] They observed that ligands L_1 or L_2 in conjunction with $Cu(MeCN)_4ClO_4$ exihibit better catalytic activity than the corresponding Cu(I) complexes L_1Cu or L_2Cu (scheme 10). The reaction was found to be highly sensitive to the nature of substituents on aryl halides, alkynes and ligands.



Scheme 10. Sonogashira coupling reaction using diphosphane ligands.

Saito *et al*. reported a convenient method for the synthesis of mechanically interlocked [2]rotaxanes by Sonogashira coupling mediated by a macrocyclic phenanthroline-Cu(I) complex (scheme 11).[25] Here the bond formation occurred selectively inside the macrocyclic ring. Phenyl acetylenes and aryl halides

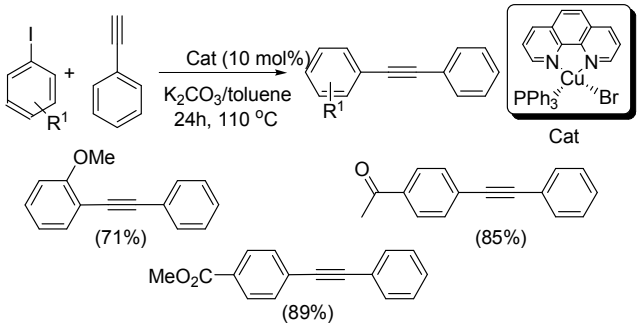
having bulky substituents were used as the substrate for synthesising the rotaxanes



Scheme 11. Sonogashira coupling reaction using Macrocyclic phenanthroline-Cu(I) catalyst.

2.2. Cu-Phosphorus complexes

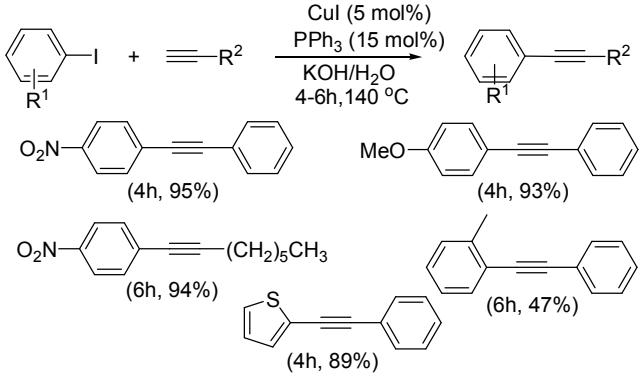
Phosphines are used as efficient ligands in combination with many transition metals and are widely used in C-C bond formation. This is particularly true in the case of Pd-catalyzed coupling reactions.[18] In 1993 Miura *et al*. reported a combination of CuI-PPh_3 system to achieve the coupling between aryl and vinyl iodides with terminal alkynes.[19] Another example where copper catalyst along with phosphorus ligand used in the Sonogashira coupling was reported by Venkataraman *et al*. wherein premade Cu^I complexes of the type Cu(phen)(PPh_3)Br and Cu(neocup)(PPh_3)Br were used for aryl-acetylene coupling reactions to afford excellent yields of the product (scheme 12).[20]



Scheme 12. Cu-catalyzed cross-coupling reaction of aryl iodides and phenyl acetylene using [Cu(phen)(PPh_3)Br].

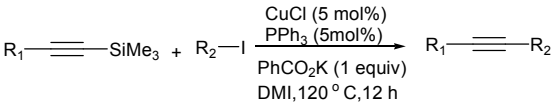
Venkataraman *et al*. further extended the work to *o*-iodophenols and terminal acetylenes using [Cu(phen)(PPh_3)$_2$]NO_3 as the copper source which led to the formation of benzofuran derivatives *via* a tandem Sonogashira-cyclization reaction.[21] The use of Cu(II)-PPh_3 in Sonogashira reaction has also been reported.[22]

Interestingly, simple Sonogashira coupling in water has been reported by Liu *et al*. using CuI and PPh_3 using KOH as the base at 140 °C (scheme 13).[23] This procedure was found to be compatible with both electron-donating and electron-withdrawing groups on the aryl iodide. Aliphatic terminal alkynes were also found to be suitable for this reaction.



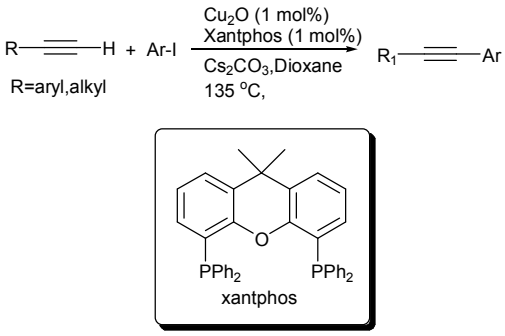
Scheme 13. Cu-catalyzed coupling reaction of aryl halides with terminal alkynes in water.

Nishihara *et al.* introduced a direct method for the cross-coupling reaction of alkynylsilanes with aryl halides using inexpensive and readily available CuCl/PPh_3 catalytic system in the presence of $PhCO_2K$ additive (scheme 14).[24] This protocol was found to be very useful for a broad range of targets including aryl-, heteroaryl-, and alkyl-substituted alkynylsilanes and various electron-rich and electron deficient aryl iodides



Scheme 14. CuCl/PPh_3 catalyzed Sonogashira coupling reaction.

Another unprecedented protocol for Sonogashira coupling reaction was reported by Lee *et al*. employing Cu_2O/xantphos catalytic system which tolerates a broad range of functional groups like enolizable ketones, esters,nitro groups, unprotected amines, halides etc (scheme 15).[40] They have also demonstrated for the first time that di-*ortho*-substituted aryl iodides can be used as a coupling partner in the presence of this catalytic system

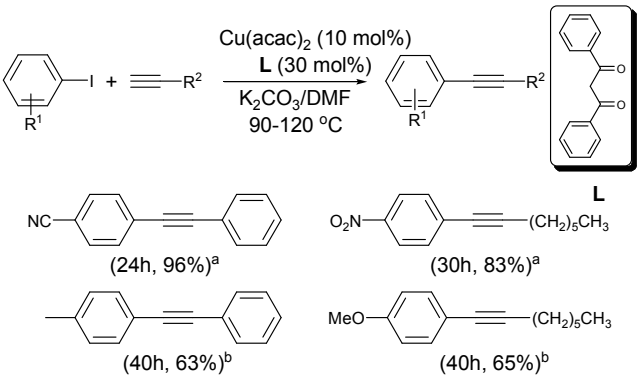


Scheme 15. Sonogashira coupling reaction in the presence of Xantphos ligand

2.3. Cu-Oxygen complexes

Oxygen containing ligands together with transition metals were also used in catalysis for coupling reactions.[26] In particular, Cu-oxygen complexes found application in C-C bond formation.[27] Sonogashira coupling using Cu(acac)$_2$ and 1,3-diphenylpropane-1,3-dione as the ligand in DMF was reported by Taillefer *et al* (scheme 16).[28] Aryl iodides having electron-withdrawing groups on reaction with phenyl acetylene or hexyl

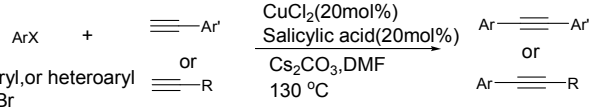
acetylene afforded good to excellent yields of the product at 90 °C while iodobenzene and aryl iodides containing electron-donating substituents required higher temperature (120 °C) to get moderate to excellent yields.



Scheme 16. $Cu(acac)_2$-catalyzed Sonogashira coupling reaction using 1,3-diphenylpropane-1,3-dione as the ligand.

Mao *et al*. reported CuBr-catalyzed Sonogashira cross-coupling reaction of aryl iodides with aryl and alkyl acetylenes in the presence of *rac*-BINOL and Cs_2CO_3 to afford low to moderate yields.[29]

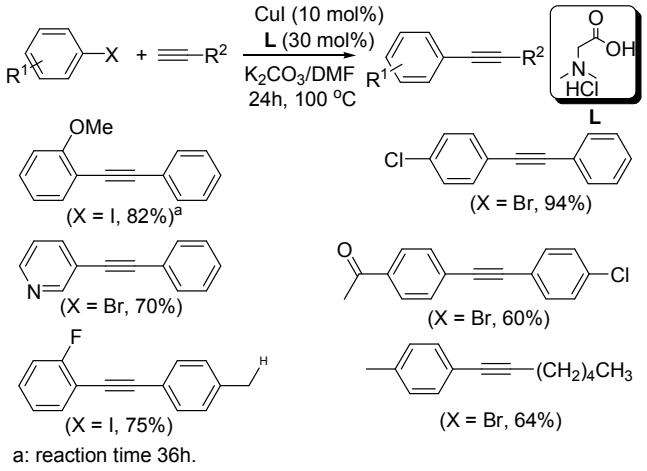
An efficient, and inexpensive $CuCl_2$/salicylic acid catalytic system for Sonogashira coupling reaction was developed by Chen *et al.* for the cross-coupling reaction of haloarenes and iodoheteroarenes with terminal alkynes under mild reaction conditions to products in 18-95% yields (scheme 17).[30] Here, Salicylic acid acts as a bidentate donor ligand to activate the catalytic reactivity of copper chloride in the coupling reaction. Substituted aryl iodides and heteroaryl iodides reacted effectively with terminal alkynes affording the corresponding aryl alkynes in high yields.



Scheme 17. $CuCl_2$/salicylic acid-catalyzed Sonogashira-type cross-coupling reaction.

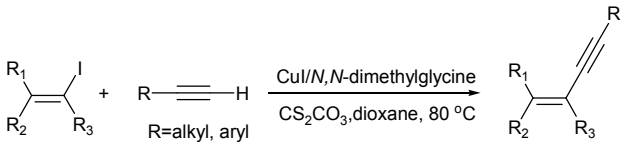
2.4 Cu-N and O bidentate ligand Complexes

The CuI/*N,N*-dimethylglycine catalyst system developed by Ma *et al*. has been successfully applied in the Sonogashira coupling in the absence of palladium and phosphine. [31] Thus a variety of aryl bromides/iodides reacted with terminal alkynes in the presence of CuI, *N,N*-dimethylglycine:hydrochloride and K_2CO_3 affording products with yields ranging from 60-99% (scheme 18). Both electron-rich and electron-deficient aryl iodides gave excellent yields while aryl bromides required a higher catalyst loading (20 mol% of CuI, 60 mol% of *N,N*-dimethylglycine). Functional groups such as –Cl, -F, $-NO_2$, alkoxy, ester, ketone and pyridyl were tolerated on the aryl iodide. Aliphatic alkynes are also suitable substrates for this transformation.



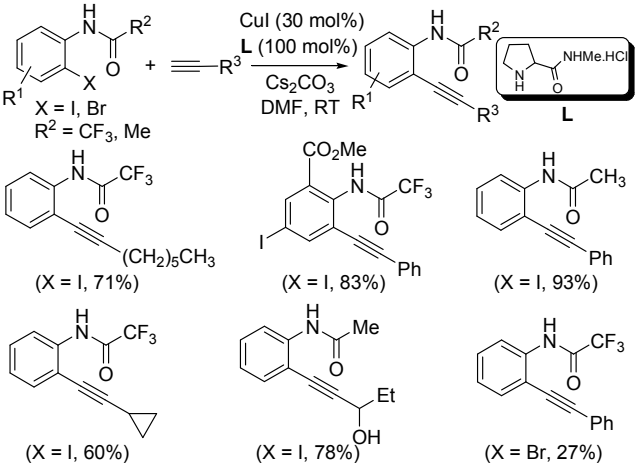
Scheme 18. Cu-catalyzed Sonogashira coupling reaction using *N,N*-dimethylglycine as ligand.

Later the same group succeeded in extending the above protocol to vinyl iodides leading to the synthesis of conjugated enynes at a lower temperature (scheme 19).[32] They also found that the geometry of the olefin part was preserved during coupling.



Scheme 19. Aminoacid catalyzed Sonogashira coupling reaction

Cu-catalyzed Sonogashira reaction of *o*-iodoacetanilide with alkynes at RT was achieved using N-methylpyrrolidine-2-carboxamide ligand. [33] Here 30 mol% of CuI and one equivalent of ligand were used along with 2.5 equivalents of Cs_2CO_3 in DMF at RT (scheme 20).

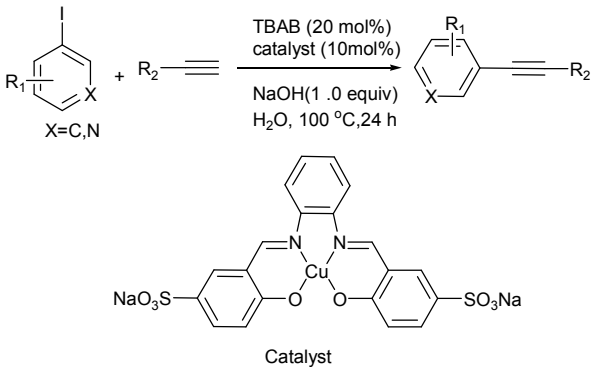


Scheme 20. Cu-catalyzed Sonogashira coupling reaction of *o*-iodoacetanilides using N-methylpyrrolidine-2-carboxamide as ligand.

In the case of *o*-diiodoacetanilide, both the *o*-positions could be

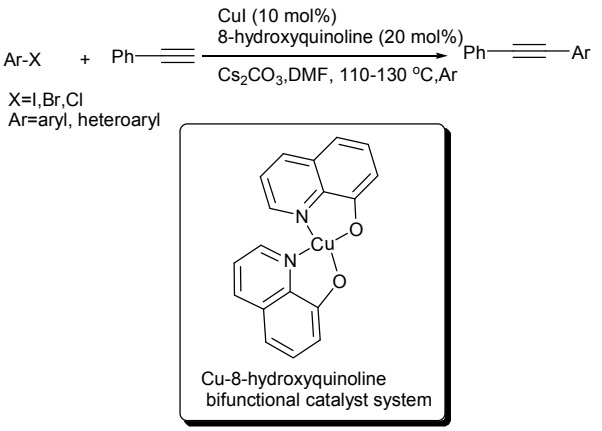
substituted with alkynes. The *o*-bromoacetanilides showed lower reactivity towards coupling with alkynes under this condition.

Reusable sulfonato-Cu(II) (salen) complex was reported as a new catalytic system for the alkynylation of aryl iodides with terminal alkynes in water under aerobic conditions by Zhou *et al* (scheme 21).[34] It was demonstrated that aryl halides with electron-withdrawing groups gave excellent yields of the product compared to electron-rich aryl iodides and the reaction was also found to be sensitive to steric effects.



Scheme 21. Sonogashira coupling catalyzed by reusable sulfonato-Cu(II) (salen) complex.

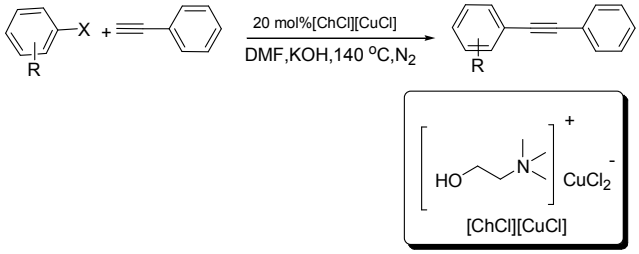
Mao and co-workers developed an interesting bifunctional catalyst systems using 8-hydroxyquinoline which could attach both the electrophilic and nucleophilic substrates through two different parts.[35] They found that this catalytic system is applicable for the coupling of a broad range aryl halides and heteroaryl halides with terminal alkynes (scheme 22). A variety of aryl iodides can be successfully used in this reaction and for aryl bromides a higher reaction temperature and a longer reaction time is required to get satisfactory results. They succeeded in extending the protocol to arylchlorides by adding TBAB as an additive. Furthermore when 1,4-dibromobenzene was used as the substrate only mono substituted product was formed.



Scheme 22. Sonogashira coupling using bifunctional catalyst system

They also designed another bifunctional catalytic system by combining 1,10-phenanthroline with BINOL and applied for the coupling between 4-iodoanisole and phenylacetylene giving good yields of the product.

Very recently Choline Chloride/CuCl has been reported as an inexpensive and moisture stable catalytic system for Sonogashira coupling (scheme 23).[36] Besides acting as an OH functionalised ligand, choline chloride also acted as a tetraalkylammonium salt, that supported and stabilised the Cu(I) species during the reaction. This catalytic system was found to be effective in the reaction of phenylacetylenes with a variety of aryl halides. Very good yields were obtained when aryl halides substituted with electron-withdrawing groups were used.

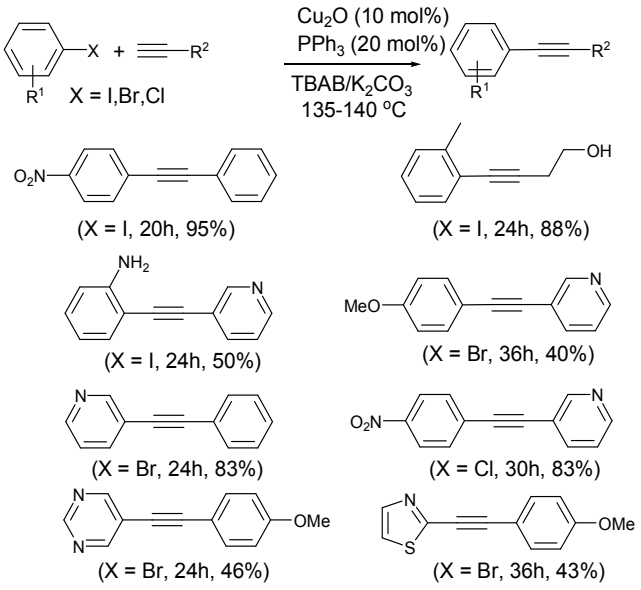


Scheme 23. Choline chloride/CuCl catalyzed Sonogashira coupling.

2.5. Cu nanoparticles

Cu nanoparticles show remarkable catalytic activity due to their high surface to volume ratios. Rothenberg *et al*. utilised heterogeneous copper nanoclusters for the palladium and phosphine free Sonogashira coupling of phenyl acetylene and aryl halides.[37] High yields were obtained when tetrabutylammonium acetate (TBAA) was used as the base in DMF at 110 °C. Electron deficient aryl halides afforded excellent yields.

Li *et al*. developed a reusable Cu_2O/PPh_3/TBAB system for the cross-coupling reaction of aryl and heteroaryl halides with terminal acetylenes under neat conditions (scheme 24).[38] Among the four different types of Cu_2O used, the Cu_2O nanoparticles were found to be the best when used in presence of PPh_3 and TBAB. Both electron-rich and electron-poor aryl halides reacted with alkynes having aryl, hetero aryl and alkyl groups in the presence of octahedral Cu_2O nanoparticles without loss of activity for 4 runs. For aryl bromides and chlorides, octahedral Cu_2O afforded the coupling products; albeit in low yields. Heteroaryl bromides and chlorides also gave moderate yields with alkynes.

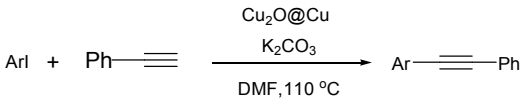


Scheme 24. Cu-catalyzed Sonogashira coupling reaction using Cu_2O nanoparticles

3. Sonogashira coupling under ligandless conditions.

3.1. Inside-out core–shell architectures (Cu_2O@Cu)

Catalytic species with a Cu_2O core and a Cu shell, which are in contrast to the normally reported Cu_2O-outside structure ($Cu@Cu_2O$), were reported by Varma *et al*. in 2012.[39] They successfully employed the Cu_2O@Cu composite in Sonogashira coupling reaction of aryl iodides with phenyl acetylenes and found that biaryl acetylenes could be produced with excellent yields (85–94%) in the absence of Pd and ligand (scheme 25). Moreover, different functional groups such as –COMe, $–NO_2$, and –OMe were found to be compatible with the reaction conditions. The recovered Cu_2O@Cu after reaction still could keep the core–shell structure, implying the good stability of the composition. The recovered catalyst could also be reused.



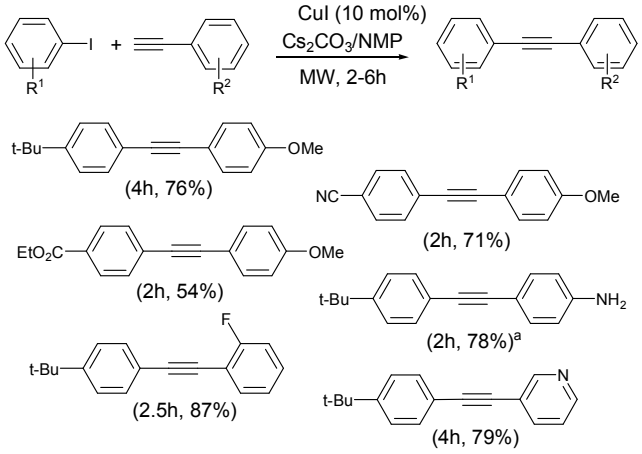
Scheme 25. Sonogashira coupling reaction using Cu_2O@Cu composite

3.2. Supported Cu catalysts

An interesting ligand free supported copper precatalysts for Sonogashira coupling reaction was reported by Biffis *et al*.[41] They developed Cu(II) oxide and Cu metal highly dispersed on alumina, which can be used as a precatalyst for Sonogashira coupling reaction of aryl iodides with electron-rich alkynes like arylacetylenes. Eventhogh the substrate scope of the reaction is limited, it represent a novel class of solid easy to handle catalytic system that allows a simpler product recovery.

4. Sonogashira coupling under microwave irradiation

In recent years, microwave-assisted rate acceleration technology has evolved as a powerful tool in organic synthesis, because of the manifold advantages such as milder reaction conditions, faster reaction and enhanced selectivity. Copper-catalyzed Sonogashira coupling of aryl iodides and aryl acetylenes under microwave irradiation was reported by He *et al*. wherein the substrates were subjected to MW irradiation in presence of Cs_2CO_3 and in the absence of any ligands affording 43-87% yields of the products (scheme 26).[42]



a: N-arylation product was also formed in 10%.

Scheme 26. Cu-catalyzed Sonogashira coupling reaction under microwave irradiation.

No specific influence of electronic effects on the reactivity of acetylenes or aryl iodides was noticed in this reaction. Ester and acetyl groups on the aryl iodide gave lower yields of the coupling product presumably due to decomposition under the basic reaction condition. The reaction was found to be sluggish for aryl bromides. Phenyl acetylene containing an $-NH_2$ group gave in addition to the Sonogashira coupling product, an N-arylated product as well in small amount. Alkyl alkynes are inert to this reaction.

In 2002 Wang *et al*. reported a Cu-catalyzed microwave assisted Sonogashira coupling between electron-rich/electron deficient aryl acetylenes and aryl iodides in presence of CuI, PPh_3 and K_2CO_3 in DMF.[43]

Cu-catalyzed Sonogashira reaction in polyethyleneglycol (PEG) under microwave irradiation has also been reported.[44] PEGs of different molecular weight were studied in presence of CuI to produce low to moderate yields of the products.

Sonogashira cross-coupling reaction catalyzed by Cu salt under microwave irradiation in water was recently reported by Chen and co-workers; however a stoichiometric amount of tetrabutylammonium bromide was required for achieving satisfactory yields.[45] The synergic effect of Fe and Cu salts was utilised by Vogel *et al.* in Sonogashira coupling wherein aryl iodides reacted with terminal alkynes in the presence of $Fe(acac)_3$, CuI and Cs_2CO_3 in DMF or NMP affording good to excellent yields.[46] Microwave irradiation of the reaction mixture reduced the reaction time manifold.

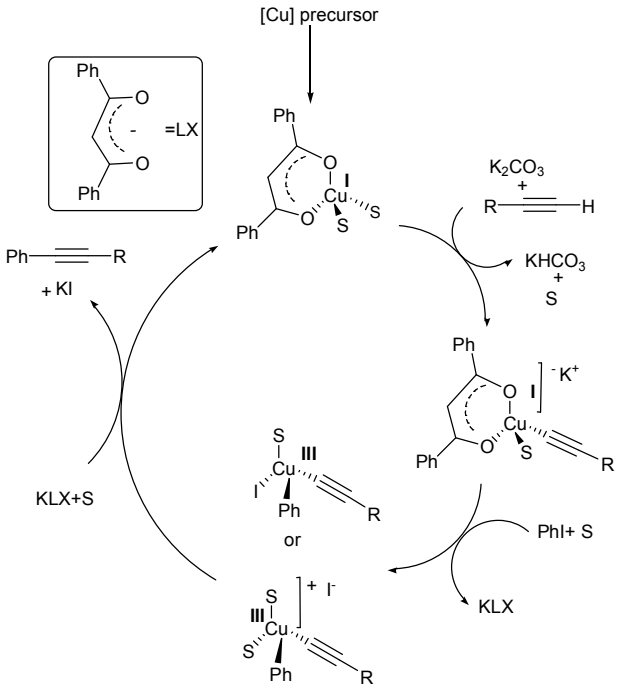
5. Mechanism

Although a great deal of progress has been achieved in improving the reaction conditions and designing ligands for the Cu-catalyzed C-C bond forming reactions, the mechanistic aspects on the intricate details with which the reactants and

catalysts go through still remains elusive and lacks sufficient experimental proof. Based on different mechanistic studies it is assumed that the Cu(I) salts first reacts with terminal alkynes to form a Cu(I) acetylide species which then undergoes oxidative addition with aryl halide followed by decomposition to give the required product.

Wang *et al*. in 2002 put forward a catalytic cycle for Sonogashira coupling reaction under microwave irradiation.[43] In the first step, the terminal acetylene reacts with CuI-PPh_3 in the presence of a base to form the organometallic compound. The highly reactive organometallic compound then enters the cross-coupling reaction with iodoarene to give aryl alkynyl derivative of Cu-PPh_3. This derivative is unstable and can easily regenerate the CuI and PPh_3 through reductive elimination.

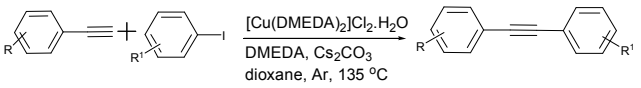
The mechanism of Cu-catalyzed Sonogashira coupling in presence of 1,3-diphenylpropane-1,3-dione ligand was reported by Taillefer *et al.*[28] They proposed that the ligand coordinated to copper salt forms the catalytic species in this reaction (scheme 27). In the first step the deprotonated alkyne reacts with Cu(I)-diketone ligand complex to generate the Cu(I)-acetylide intermediate. This then undergoes oxidative addition with aryl iodide to form a four coordinated Cu^{III} complex, which may exist either as neutral or cationic form. Then reductive elimination occurs expelling the cross coupled product.



Scheme 27. Mechanism of Sonogashira coupling reaction proposed by Taillefer *et al.*

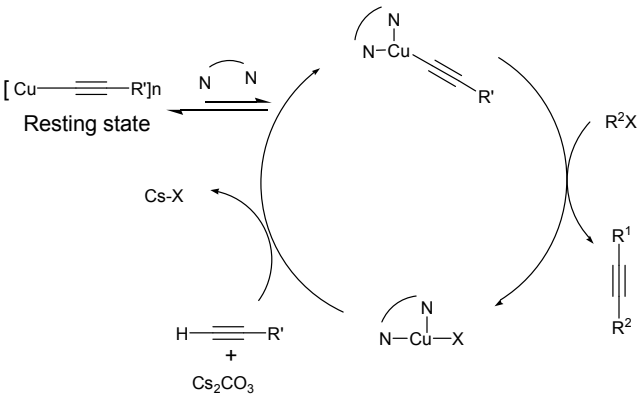
A similar mechanism was suggested by Nishihara *et al*. for the coupling between alkynylsilanes with aryl halides.[24]

Bolm *et al*. reported an efficient catalytic system for Sonogashira-Hagihara type reactions.[47] They were successful in carrying out the coupling reactions between various aryl iodides and terminal aryl alkynes using $[Cu(DMEDA)_2]Cl_2.H_2O$ as a catalyst precursor and Cs_2CO_3 as base in dioxane (scheme 28).



Scheme 28. Sonogashira coupling using Cu-DMEDA complex

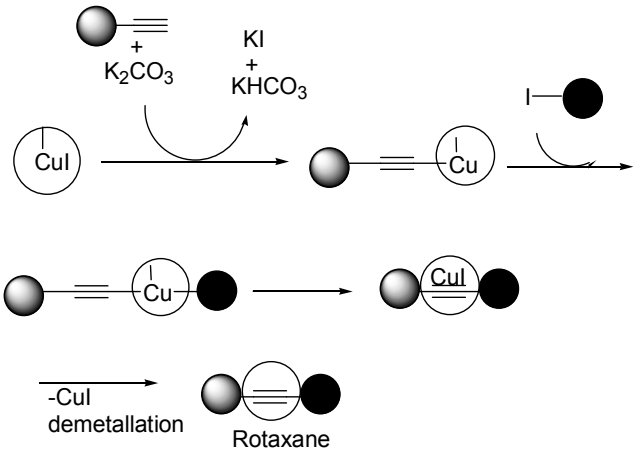
A mechanism was proposed for this reaction based on kinetic measurements and DFT calculations (scheme 29).[48]



Scheme 29. Mechanism proposed by Bolm *et al.* for Cu-catalyzed Sonogashira coupling reaction.

The resting state of the catalyst is assumed to be a polymeric complex $[Cu(phenylacetylene)]_n$ that is in equilibrium with an active monomeric catalyst. The DMEDA ligand activates the resting state by dissolving the $[Cu(phenylacetylene)]_n$ polymer and forming a soluble [Cu-(DMEDA)(phenylacetylene)] complex. This complex reacts with the aryl halide, which results in coupling leading to C-C bond formation and generation of [Cu(DMEDA)(I)] complex. The [Cu(DMEDA)(phenylacetylene)] complex, which is proposed to be the active state of the catalyst, is regenerated through transmetallation with Cesium phenyl-acetylenate.

Saito *et al*. proposed a mechanism for the formation of [2]rotaxanes by Sonogashira coupling [25]. Alkynes in the presence of base form a Cu(I)-acetylide complex upon which aryl iodide gets added oxidatively and forms a Cu(III)-complex (scheme 30). The oxidative addition is accelerated by the presence of a *ortho* carbonyl group. Finally reductive elimination occurs and a new C-C bond is formed.

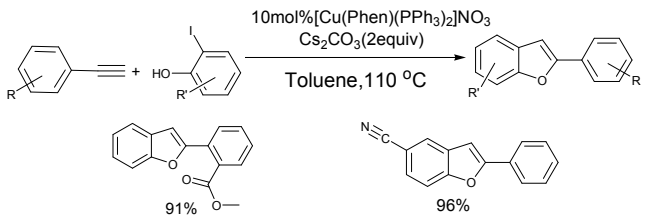


Scheme 30. Mechanism for the synthesis of rotaxane proposed by Saito *et al.*

A mechanism for Cu^{II}-catalyzed Sonogashira coupling under aerobic condition was proposed by Li *et al*.[13] based on Miura[19] and Rothenberg[37] involving a four-centered transition state for active Cu catalyst. Subsequent consecutive oxidative addition and reductive elimination afford the required arylacetylenes as the product.

6. Applications

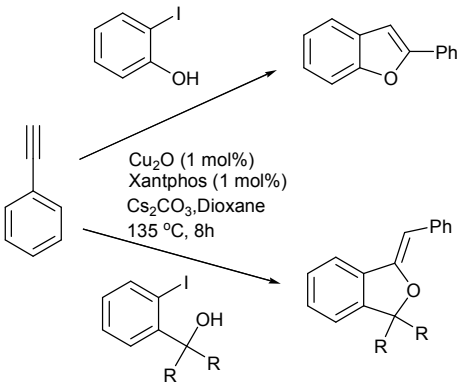
C-C bond formation using transition metal catalysis finds application in a wide variety of areas such as pharmaceuticals, agrochemicals, organic synthesis etc.[49] Most of these coupling reactions were achieved by Pd catalysis. Sonogashira coupling reaction using Pd and Cu catalyst were used for the synthesis of aryl acetylenes. Now a days Sonogashira coupling using Cu catalyst alone is an emerging field. Some cascade reactions combining Sonogashira coupling leading to heterocycles has also been reported. Thus Venkataraman *et.al* reported an interesting one pot synthesis of 2-arylbenzo[*b*]furans[21] ; the core structure is prevalent in some natural products and the compounds show important biological activities,[50] like anticancerous,[51] antifungal[52] etc. The traditional methods for the synthesis of benzo[*b*]furans have limited functional group tolerance and require multistep reactions. In Venkataraman's method benzo[*b*]furan derivatives were prepared from *o*-iodophenols and aryl acetylenes using $[Cu(Phen)(PPh_3)_2]NO_3$ as the catalyst and Cs_2CO_3 as the base in toluene (scheme 31).



Scheme 31. Synthesis of 2-arylbenzofurans using $[Cu(Phen)(PPh_3)_2]NO_3$ as the catalyst.

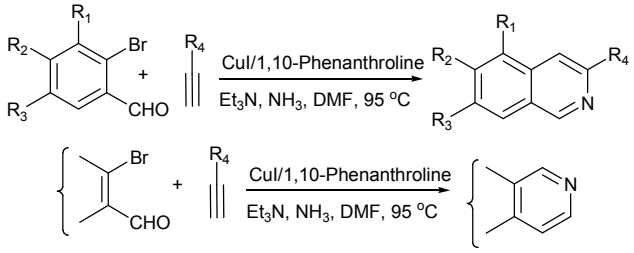
Here both electron-rich and electron-deficient arylacetylenes and *o*-iodophenols reacted effectively affording the corresponding benzo[*b*]furans in excellent yields. This procedure avoids the use of expensive and air sensitive additives. It was also found that arylacetylenes containing alkene as the substituent gave the coupling products in good yields without the formation of Heck coupling products, which would be observed if a Pd catalyst was used. Mao *et al* reported that bifunctional Cu catalyst can also be used for this reaction, but it require slightly higher temperature.[35]

Benzofurans and isobenzofurans can also be synthesized through a 5-*exo*-*dig*-cyclization in one pot method introduced by Lee *et al* (scheme 32).[40]



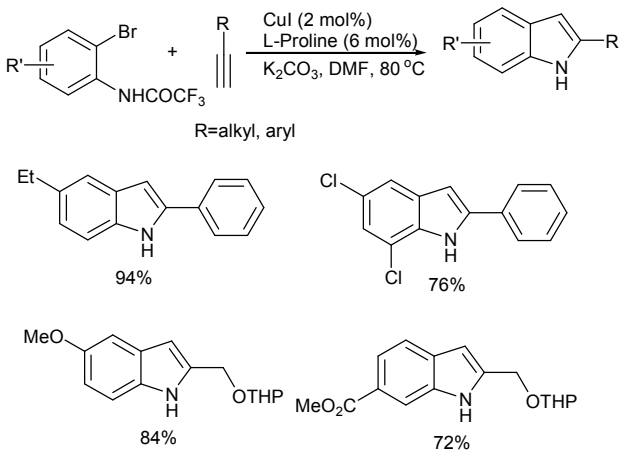
Scheme 32. Synthesis of benzofurans and isobenzofuran derivatives

Another interesting one pot method for the synthesis of biologically active nitrogen heterocycles like isoquinoline and pyridine was developed by Ray *et al.* employing 1,10-phenanthroline as the ligand.[53] Here the reaction between terminal alkyne and substituted aromatic *o*-bromoaldehyde afforded isoquinoline derivatives as the product while the reaction between terminal alkynes and non aromatic *β*-bromoaldehyde gave pyridines and dihydro isoquinoline derivatives (scheme 33).



Scheme 33. Synthesis of isoquinoline and pyridine derivatives.

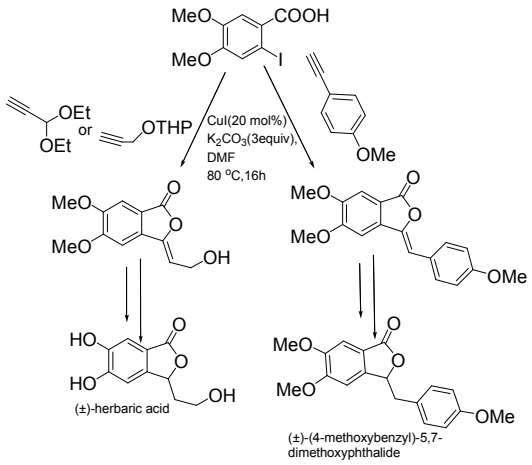
Ma *et al.* utilized CuI/L-Proline catalytic system for the synthesis of indole derivatives which are prevalent in biologically active natural products from 2-bromotrifluoroacetanilides and terminal alkynes.[32] The ortho substituent effect directed by $-NHCOCF_3$ group plays a key role in this transformation (scheme 34). The reaction was applied to substrates having both electron-rich and electron-deficient functional groups and aromatic and aliphatic alkynes; however with simple aliphatic alkynes, only low yields were obtained.



Scheme 34. Synthesis of indole derivatives via Sonogashira coupling reaction

The catalyst system developed by Zhou *et al.*[34] was successfully applied in the synthesis of biologically active 2 –aryl indoles by a cascade process with 2-iodoanilines and terminal alkynes.The recycled catalyst was reused giving excellent yields of the product.

Sonogashira coupling has also been used for the total synthesis of naturally occurring phthalides (±)-herbaric acid and (±)-(4-methoxybenzyl)-5,7-dimethoxyphthalide from terminal alkynes and 2-iodobenzoic acid derivatives *via* 5-*exo*-dig cyclisation with high stereo-, regio- and chemoselectivities (scheme 35).[54]



Scheme 35. Application of Sonogashira coupling in natural product synthesis

7. Summary and Outlook

Sonogashira coupling reaction is an important transformation in organic synthesis for the production of important compounds including heterocycles, natural products and pharmaceuticals. Since its discovery in 1975, significant improvements have been made in the reaction conditions. The pioneering work used Pd as catalyst, which is toxic and expensive, and consequently initiated the search for an alternative catalytic system. In this context Cu emerged as a new catalyst, which is abundant and cheap. Today Cu-catalyzed Sonogashira coupling reaction is an indispensible tool in synthetic organic chemistry. The recent advances discussed herein illustrate the potential of this chemistry. The common catalytic system uses Cu^{I} in the presence of P, N and O ligands. However scant reports are available using Cu^{II} salts and reactions in solvent-free, ligand-free and in aerobic conditions. Limited reports are available dealing with the mechanistic aspects of this reaction. Further efforts to study the mechanism and to extend the application of this protocol are still going on.

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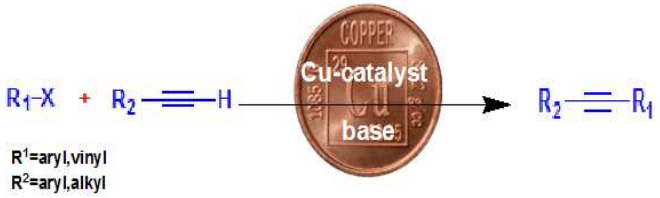
Recent Advancements and Perspectives in Copper-catalyzed Sonogashira Coupling Reactions

Anns Maria Thomas, Asha Sujatha and Gopinathan Anilkumar*



The review highlights the orgin, development, mechanistic insights and recent applications of Cu-catalyzed Sonogashira coupling reactions.