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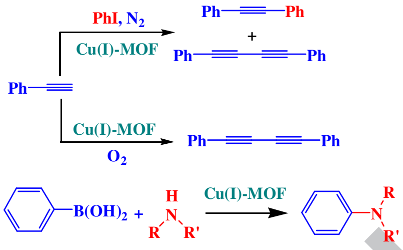
Poonam Rani and Rajendra Srivastava*



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Cu(I) Metal Organic Framework Catalyzed C-C and C-N Coupling Reactions

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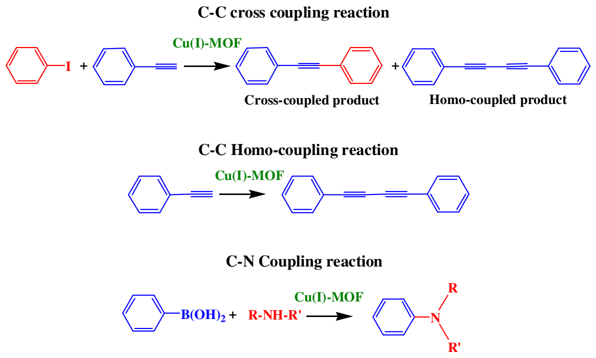
ABSTRACT

DABCO (1,4-diazabicyclo[2.2.2]octane) based Cu(I) metal organic framework (here after represented as Cu(I)-MOF) catalyzed Sonogashira cross-coupling reaction of iodobenzene and phenylacetylene was conducted smoothly to afford diphenylacetylene in excellent yield under N_2 atmosphere. For comparative study, piperidine based Cu(I) clusters were also investigated. Among these catalysts, Cu(I)-MOF exhibited higher activity with good selectivity for the C-C cross-coupled product. Cu(I) catalysts investigated in this study were exhibited similar activity in the C-C homo-coupling reaction of phenylacetylene in O_2 atmosphere. Application of these catalysts was extended in the C-N coupling reactions between phenylboronic acid and aromatic/aliphatic/heterocyclic amines. The Cu(I)-MOF can be readily recovered from the reaction mixture and reused for several cycles without loss in the catalytic activity.

Cross-coupling reactions are important synthetic methodology in organic chemistry and used in the C-C and C-heteroatom bond forming reactions.[1-12] The resultant products are extremely valuable intermediates with respect to organic synthesis, which also serve as important building units found in innumerable compounds of biological, pharmaceutical, and material science interest. In general, cross-coupling reactions are catalyzed by the Pd based catalysts.[1-4] However, the high price of Pd renders commercial processes based on Pd based catalysts less attractive. For this reason, recent attention has been given to develop less expensive transition metal catalysts.[5-8] The application of copper-catalyzed Ullmann-type coupling reaction[9] has received considerable attention in last decade since the breakthrough was achieved by the group of Buchwald and others.[10] Cu catalyzed Suzuki-Miyaura coupling reaction was reported by Rothenberg and co-workers.[7] In the presence of copper or copper-based nanocolloids, a variety of aryl halides were reacted with phenylboronic acid to afford products in moderate to excellent yields.[7] Furthermore, CuI and copper nanoclusters have also emerged as catalysts for the Sonogashira cross-coupling reaction.[8] The first catalytic Sonogashira cross-coupling between aryl iodides and terminal alkynes based on CuI/PPh_3 was reported by Miura and co-workers.[8a] Not only phosphines but also 1,10-phenanthroline was found to be an effective ligand for the copper-catalyzed couplings of aryl iodides and vinyl iodides with terminal alkynes.[8] Later, a wide range of ligands such as ethylenediamine, *N*1,*N*1,*N*2,*N*2-tetramethylethene-1,2-diamine, *N*,*N*-dimethylglycine, 2-aminopyrimidine-4,6-diol etc. were investigated in the Cu mediated cross-coupling reactions.[8] In general, the catalytic systems were formed by the *in-situ* generation of active copper species in the presence of suitable copper precursor and ligand. In these, Cu based catalytic process, the starting copper salts or copper complexes are usually present in various oxidation states including Cu(0), Cu(I), and Cu(II).[11] Several studies revealed that Cu(I) species were the active catalyst in the copper catalyzed cross-coupling reactions. For example, Cu(0) precursor had been demonstrated to be oxidized by aryl halides to afford the active Cu(I) complex in the Ullmann-type reactions by using electrochemical techniques.[11a] Similarly, UV−Vis and NMR spectroscopy revealed that Cu(I) species were the active component in the coupling reaction, which was produced by the reduction of Cu(II) precursor in the presence of alcohols or amines.[11b]



Scheme 1. Cu(I) catalyzed C-C and C-N coupling reactions investigated in this study.

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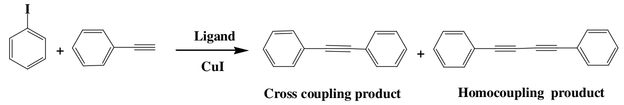
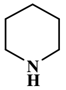
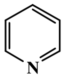
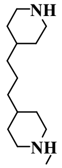
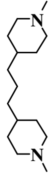
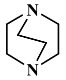
Table 1
CuI/Amine ligand catalyzed Sonogashira cross-coupling reaction between iodobenzene and phenylacetylene.

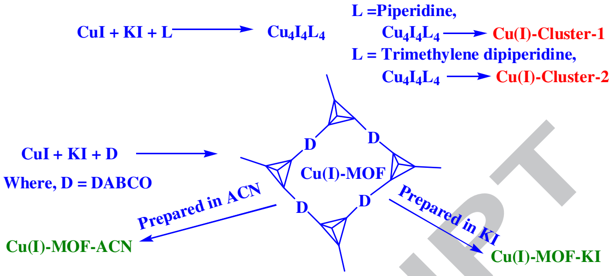


Ligand	Reactions in N_2 atmosphere			Reaction under standard condition		
	Ph-I Conv. (%)	Products yield (%)		Ph-I Conv. (%)	Products yield (%)	
		Cross-couple	Homo-couple		Cross-couple	Homo-couple
	69	80	20	55	48	52
	34.8	72	28	26	56	44
	81.3	90 (70)^{a}	10 (7)^{a}	58	60	40
	56	88 (46)^{a}	12 (5)^{a}	66	69	31
	42	76	24	38	60	40

Reaction condition: Iodobenzene (0.5 mmol), phenylacetylene (0.5 mmol), CuI (0.05 mmol), ligand (0.1 mmol), K_2CO_3 (1 mmol), DMF (3 mL), temperature (140 °C), time (12 h).
^{a}Parenthesis represents the isolated yield.

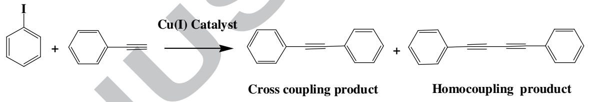
As mentioned above, most of the Cu catalyzed reaction requires Cu salt and a suitable ligand. Therefore, the development of efficient and well-defined copper catalyst for C-C and C-heteroatom coupling reactions still remains an interesting and demanding goal. The objective of this study was to find a suitable and well defined Cu(I) catalysts for C-C and C-N coupling reactions (Scheme 1).

First attempts were made to find Cu(I) catalysts for Sonogashira cross-coupling reaction. Initially, a combination of CuI and amine ligands was investigated and the obtained results are summarized in Table 1. In addition to desired cross-coupled product, homo-coupled product of phenylacetylene was also observed. Control experiments revealed that the reaction atmosphere played important role in obtaining higher selectivity for the desired product. When the reaction was performed in standard condition, homo-coupled product was obtained in significantly large amount. It is known in the literature that O_2 atmosphere favors the formation of homo-coupled product.[12] To obtain the higher selectivity for the cross-coupled product, reactions were performed in N_2 atmosphere (Table 1). Due to the presence of residual oxygen left in the reaction vessel, the homo-coupled product was formed in the small amount. Among the ligands investigated in this study, trimethylene dipiperidine exhibited the highest activity and selectivity towards the formation of cross-coupled product. To the best of our knowledge, this ligand has never been used in C-C coupling reaction. Our group has shown the applicability of trimethylene dipiperidine as precursor for the synthesis of dicationic ionic liquid based structure directing agents for the synthesis of zeolites.[13]



Scheme 2. Cu(I) cluster and Cu(I)-MOF based catalysts investigated in this study.

Table 2
Cu(I) catalyzed Sonogashira cross-coupling reactions between iodobenzene and phenylacetylene.

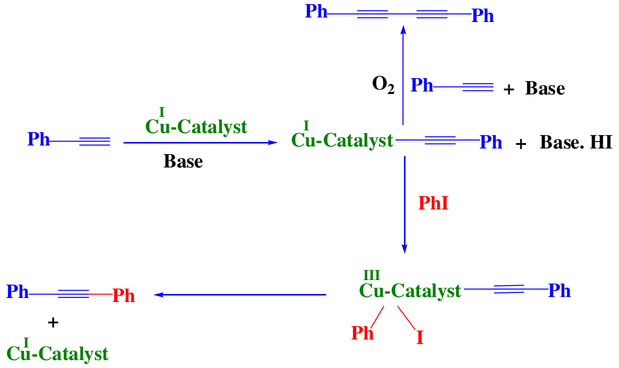


Catalyst	Reactions in N_2 atmosphere			Reaction under standard condition		
	Ph-I Conv. (%)	Products yield (%)		Ph-I Conv. (%)	Products yield (%)	
		Cross-couple	Homo-couple		Cross-couple	Homo-couple
Cu (I)-Cluster-1	55.1	74	26	66	51	49
Cu (I)-Cluster-2	50.5	96 (46)^{a}	4 (2)^{a}	27	78	22
Cu(I)-MOF-ACN	84	87	13	72	61	39
Cu(I)-MOF-KI	92	88 (81)^{a}	12 (9)^{a}	81	59	41

Reaction condition: Iodobenzene (0.5 mmol), phenylacetylene (0.5 mmol), K_2CO_3 (1 mmol) equivalent), catalyst (0.05 mmol), DMF (3 mL), temperature (140 °C), time (12 h).
^{a}Parenthesis represents the isolated yield.

Though, the combination of CuI and trimethylene dipiperidine was found to be a good catalytic system for the Sonogashira cross-coupling reaction, but the aim was to find a well defined Cu(I) catalyst for the Sonogashira cross-coupling reaction. For this, Cu(I)-piperidine (hereafter represented as Cu(I)-Cluster-1) and Cu(I)-trimethylene dipiperidine (hereafter represented as Cu(I)-Cluster-2) based catalysts were prepared (Scheme 2) by following the reported procedure[14] and investigated in the Sonogashira cross-coupling reaction (Table 2). Though the activity of Cu(I)-Cluster-2 was marginally lower than Cu(I)-Cluster-1, but it exhibited higher selectivity towards the desired product. Having found the encouraging results using Cu(I) clusters, DABCO (1,4-diazabicyclo[2.2.2]octane) based Cu(I) metal organic framework $[Cu_4I_4(DABCO)_2]$ was prepared (Scheme 2) by following the reported procedure[15] and investigated in the Sonogashira cross coupling reaction (Table 2). $[Cu_4I_4(DABCO)_2]$ metal organic framework (MOF) was prepared in the acetonitrile medium (represented as Cu(I)-MOF-ACN) and saturated KI medium (represented as Cu(I)-MOF-KI) (Scheme 2). Cu(I)-MOF catalysts exhibited the highest catalytic activity in the Sonogashira cross-coupling reaction under N_2 atmosphere (Table 2). To the best of our knowledge, this is the first report in which Cu(I)-MOF have shown to exhibit such an excellent activity in the Sonogashira cross-coupling reaction. Among the two MOF, catalyst prepared in KI medium was found to exhibit the highest activity and selectivity (Table 2).

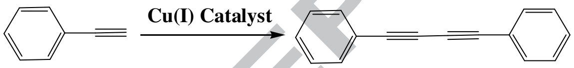
Based on the results obtained from Cu(I) catalysts and (CuI + Lignad) system, it can be said that Cu(I) catalytic species must have formed *in-situ* in the case of (CuI + Lignad) system, which took part in the Sonogashira cross-coupling reaction. It can be suggested that phenylacetylene reacts with the Cu(I) catalyst and form {alkenyl–Cu(I)catalyst}species, which then reacts with the iodobenzene. Subsequently, the product is formed and the catalyst is regenerated (Scheme 3). In the presence of residual O_2,{alkenyl–Cu(I)catalyst}species reacts with phenylacetylene to produce homo-coupled product (Scheme 3).



Scheme 3. Proposed mechanism for the Cu(I) catalyzed Sonogashira C-C coupling reaction.

Applicability of Cu(I)-MOF and Cu(I) clusters were investigated in the homo-coupling of phenylacetylene (Table 3) in O_2 atmosphere. It was found that homo-coupling reaction required comparatively mild reaction condition than Sonogashira cross-coupling reaction. Furthermore, only 2 mol% catalyst was required for homo-coupling reaction. Under this mild condition, Cu(I)-MOF and Cu(I) clusters exhibited almost similar activity.

Table 3
Cu(I) catalyzed, homo-coupling reaction of phenylacetylene in O_2.

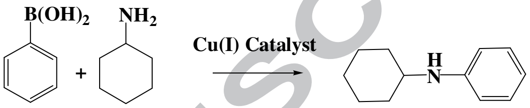


Entry	Catalyst	Product yield (%)
1.	Cu (I)-Cluster-1	92
2.	Cu (I)-Cluster-2	93
3.	Cu(I)-MOF-ACN	91
4.	Cu(I)-MOF-KI	96

Reaction condition: Phenylacetylene (2 mmol), catalyst (0.04 mmol), triethylamine (2 mmol), acetonitrile (10 mL), temperature (27 °C), Time (3 h).

Having shown the applicability of Cu(I)-MOF in the C-C cross-coupling and homo-coupling reactions, the aim was to extend its application in C-N coupling reactions using Cu(I)-MOF catalyst (Table 4). For comparison, other Cu(I) catalysts investigated in this study were also tested for C-N coupling reaction. Among the catalysts investigated, Cu(I)-MOF-KI was found to be the best catalyst. It may be noted that 100% selectivity towards desired product was observed when cyclohexyl amine was the reactant. To define the scope of the Cu(I) catalyzed C-N reaction, this protocol was applied to a series of aliphatic/aromatic/heterocyclic nitrogen containing compounds and phenylboronic acid (Table 5). These reactions afforded the corresponding C-N adducts in good to excellent yields. C-N coupling reaction was found to be substrate dependent. For example, when cyclohexyl amine and imidazole were used as reactants, no other side product was obtained. However, with other amine reactants, by-products were observed. For example, when the reaction was performed with secondary amines such as pyrrolidine, piperidine, and piperazine; in addition to desired product, biphenyl was obtained as by-product. Furthermore, it may be noted that when piperazine was used as a reactant, borate salt was also obtained as by-products. Using benzyl amine as a reactant, more selectivity for dibenzylamine was obtained when compared to desired C-N cross coupled product.

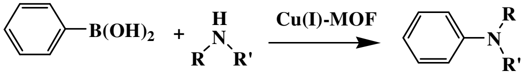
Table 4
Cu(I) catalyst mediated N-arylation of cyclohexyl amine and phenylboronic acid.

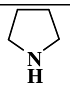
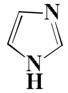
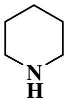
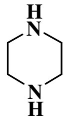
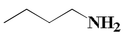
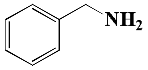


Entry	Catalyst	Product yield (%)
1.	Cu (I)-Cluster-1	78
2.	Cu (I)-Cluster-2	84
3.	Cu(I)-MOF-ACN	97
4.	Cu(I)-MOF-KI	99
5.	Cu(I)-MOF-KI (Third recycled)	99

Reaction condition: Phenylboronic acid (1 mmol), cyclohexyl amine (1.2 mmol), catalyst (0.05 mmol), methanol (3 mL), temperature (27 °C), time (5 h).

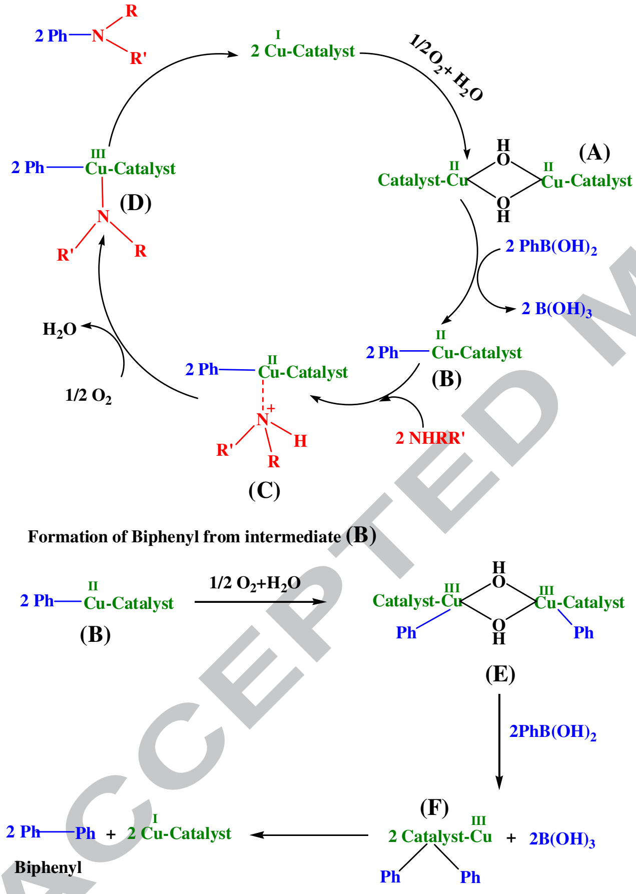
Table 5
Cu(I)-MOF catalyzed N-arylation of amines and phenylboronic acid.



Entry	Amine	^{a}Products yield (%)	
		Desired product	Other products
1.		78 (75)^{b}	5% biphenyl + 17% one unidentified product
2.		100 (100)^{b}	Nil
3.		61 (59)^{b}	32 % biphenyl + 7 % di(piperidin-1-yl)methane
4.		71 (68)^{b}	20% biphenyl + 9% Triphenylboroxin
5.		82 (80)^{b}	18% one unidentified product
6.		32 (29)^{b}	Dibenzylamine (68%)

Reaction condition: Phenylboronic acid (1 mmol), amine (1.2 mmol), catalyst (0.05 mmol), methanol (3 mL), temperature (27 °C), time (5 h).
^{a}Yield was determined from the integration of the GC detector signal.
^{b}Parenthesis represents the isolated yield.

A possible mechanism for C-N cross coupling reaction over Cu(I) catalyst is shown in Scheme 4. Cu(I)-catalyst is converted to bis-hydroxy Cu(II)-species (A). Such type of intermediate species are known in the literature.[14] The transmetalation of phenylboronic acid with bis-hydroxy Cu(II)-species (A) would generate Cu(II) species (represented as (B)). Then amine coordinate to the Cu(II) species to generate another Cu(II) species (represented as (C). In the presence of O_2, the Cu(II) species readily oxidized to Cu(III) species, thereby forming a Cu(III) intermediate (represented as D), which would subsequently undergo reductive elimination to give the C-N coupled product along with the regeneration of Cu(I) catalyst. The formation of biphenyl as a by-product can also be proposed from the reaction intermediate (B). Intermediate (B) is converted to bis-hydroxy Cu(III)-species (E). The transmetalation of phenylboronic acid with bis-hydroxy Cu(III)-species (E) would generate Cu(III) species (represented as (F)), which on reductive elimination produced biphenyl as a by-product.



Scheme 4. Proposed mechanism for the Cu(I) catalyzed C-N coupling reaction between phenylboronic acid and amines.

For practical application, the reusability of Cu(I)-MOF is very important. Though this catalyst was soluble in the C-N cross coupling reaction mixture in methanol medium, it can be easily separated. When toluene was added in the reaction mixture, solid catalyst was separated, which was then filtered by simple filtration, washed with water and dried under vacuum before reuse. Recovered catalyst was used in the fresh reaction and afforded product in the quantitative yield (Table 4). Reused catalysts exhibited consistent activity even after three cycles. To verify the stability of Cu(I)-MOF catalyst, the powder X-ray diffraction pattern of the recovered Cu(I)-MOF catalyst after third recycling experiment was obtained. The diffraction pattern indicated that the framework was very robust and exhibited a very similar diffraction pattern of the fresh catalyst.

Cu(I) cluster prepared by piperidine form cubane structure.[15] In this structure, ligand is attached to Cu site through nitrogen atom of piperidine. No sites are available to join one cubane structure to other cubane structure. Therefore, it forms $Cu_4I_4L_4$ type cluster complex. Whereas, it is reported that four cubane clusters are bridged by the DABCO ligands in Cu(I)-MOF to form a planar four-membered ring in the ab plane and each four-membered ring, in turn, connects to eight adjacent four-membered rings and form MOF.[16] As shown above, for Sonogashira cross-coupling and C-N coupling reactions, Cu(I)-MOF was found to be more active than Cu(I) clusters. It is well known in the literature that metal complex exhibits less activity in solution medium when compared to metal complex encapsulated in zeolite or other solid matrix.[17,18] This is due to the fact that metal complexes tend to aggregate in the solution medium.[17] Upon encapsulation in solid matrix, metal complexes are not aggregated and exist as isolated species.[18] More reactants are accessible to these isolated species and therefore more activity was observed for metal complex encapsulated in solid matrix. In Cu(I)-MOF, structure is highly ordered and Cu sites are more isolated when compared to Cu clusters, which makes Cu(I) sites in Cu(I)-MOF accessible to more number of reactant sites and make them more active than Cu(I) clusters.

In summary, Cu(I) clusters and Cu(I)-MOF were found to exhibit good catalytic activity in Sonogashira C-C cross-coupling reaction, C-C homo-coupling reaction of phenylacetylene, and C-N coupling reactions between amines & phenylboronic acid. Among these catalysts, Cu(I)-MOF-KI exhibited the highest activity in these reactions. Isolated Cu sites present in Cu(I)-MOF is responsible for the high catalytic activity.

Acknowledgments

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18. *Catalytic procedure: Sonogashira C-C coupling reaction:* For the reaction performed at standard condition, iodobenzene, phenylacetylene, K_2CO_3, and catalyst were taken in Teflon-coated stainless-steel autoclave, and the reaction was performed at 140 °C for 12 h. For the reaction performed under N_2 atmosphere, autoclave was thoroughly flushed with N_2 for 10 minutes and then the reaction vessel was kept at 1 bar N_2 pressure at ambient temperature. Temperature of the autoclave was raised to 140 °C and the reaction was carried for 12 h. Progress of the reaction was analyzed by Gas-chromatograph (Younglin YL6100) and products were identified by GC-MS (Shimadzu, QP2010 Ultra). After the reaction, reaction mixture was filtered and evaporated. The crude products were purified by column chromatography on silica gel using hexane/ethyl acetate to afford the corresponding coupled products.

    C-C homo-coupling reaction: Phenylacetylene, triethylamine, catalyst, and acetonitrile were taken in round bottom flask and the reaction was performed under ambient condition. During the reaction, O_2 was bubbled through the reaction mixture. Progress of the reaction was analyzed by Gas-chromatograph and product was identified by GC-MS. After the reaction, reaction mixture was filtered and evaporated. The crude products were purified by column chromatography on silica gel using hexane/ethyl acetate.

    C-N coupling reaction: Phenylboronic acid, amine, catalyst, and methanol were taken in round bottom flask and the reaction was performed at ambient condition under air. Progress of the reaction was analyzed by Gas-chromatograph and products were identified by GC-MS. After the reaction, reaction mixture was filtered and evaporated. The crude products were purified by column chromatography on silica gel using hexane/ethyl acetate.