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Copper-nicotinamide complex: sustainable applications in coupling and cycloaddition reactions

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Abstract:

Crystalline copper (II)-nicotinamide complex, synthesized via simple mixing of copper chloride and nicotinamide solution at room temperature, catalyzes the C-S, C-N bond forming and cycloaddition reactions under a variety of sustainable reaction conditions.

Carbon-hetero atom cross-coupling and cycloaddition reactions play a seminal role in organic synthesis[1-5] and they constitute a key step in accomplishing the synthesis of biologically and industrially significant materials. These reactions have been utilized in the synthesis of therapeutics for the treatment of inflammation, diabetes, alzheimer's, HIV and cancer.[6-12] Traditionally, C-S and C-N couplings have been achieved under harsh reaction conditions with the use of toxic and high boiling polar solvents such as DMF, quinoline, *N*,*N*-dimethylacetamide or HMPA in presence of a base and expensive palladium complexes. Alternatively, aryl disulfides could be prepared from aryl sulfones or aryl sulfoxides by reducing them using air sensitive $LiAlH_4$ and DIBAL-H.[13-14] Similarly, the Buchwald-Hartwig amination reaction using palladium complexes has been well explored.[15-16] However, these methods require highly expensive *N*-heterocyclic carbenes, phosphine and any other complex organic ligand as an additive.[15] Many of these ligands are air-sensitive and require longer reaction times for completion of the reaction. On the other hand, Co and Ni catalysis is associated with toxicity.[17-22] Recently, there has been significant progress in the discovery of copper-catalyzed coupling reaction of aryl halides with

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amines and thiols.[15,23-29] Majority of these reactions are highly dependent on the use of organic ligands which play an important role in accelerating copper-catalyzed coupling of aryl halides with amines and thiols. However, none of them have displayed general reactivity for promoting these coupling reactions. On the other hand, copper-catalyzed azide alkyne cycloaddition requires Cu(I) or Cu(II) catalyst in the presence of suitable additives such as sodium ascorbate.

The void of expensive transition metals and ligands in modern organic synthesis has become difficult because it allows many impossible reactions to proceed under mild reaction conditions. Due to the environmental concerns, however, the focus has shifted to the development of inexpensive, easily available, active, multi-tasking and benign catalysts. Engaged in the development of sustainable methods for efficacious organic synthesis,[30-34] herein, we report a mild, versatile and biomaterial-derived, copper-nicotinamide complex, which serves as efficient catalyst for aryl C-S, C-N coupling and cycloaddition reactions.

The copper (II)-nicotinamide complex was simply prepared by addition of copper chloride to aqueous solution of nicotinamide. Immediately after the addition, crystals of copper (II)-nicotinamide complex started appearing with a beautiful morphology (Figure 1). The application of this complex were studied in some common but important organic transformations.

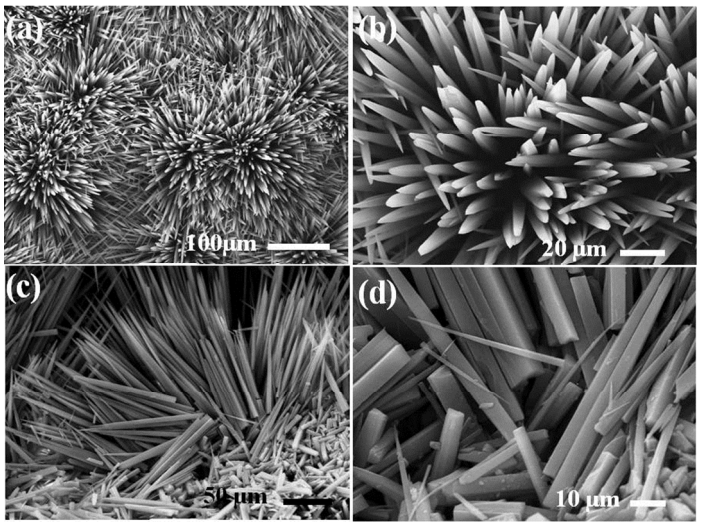
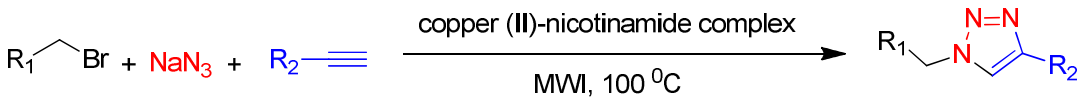


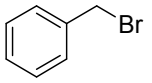
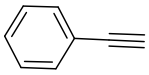
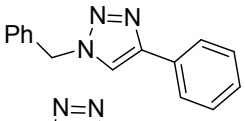
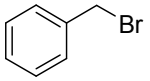
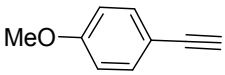
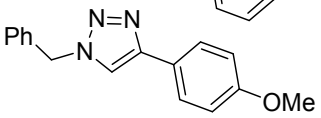
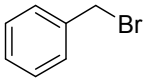
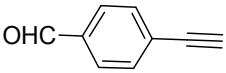
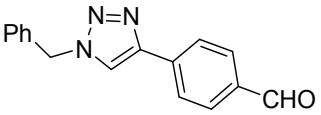
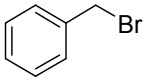
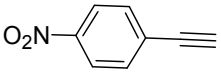
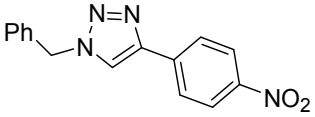
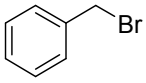
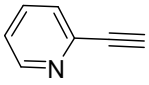
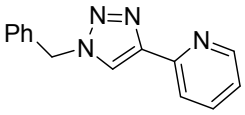
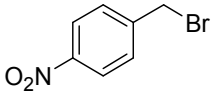
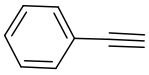
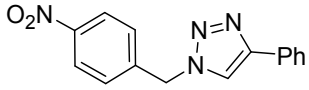
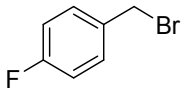
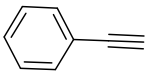
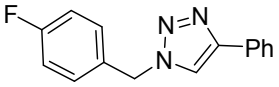
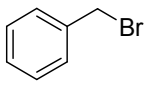
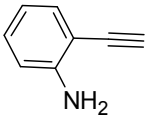
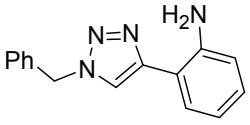
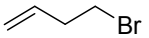
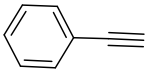
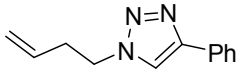
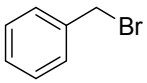
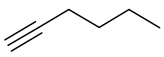
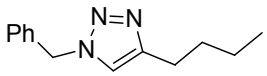
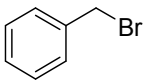
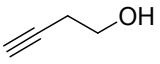
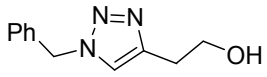
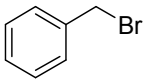
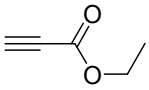
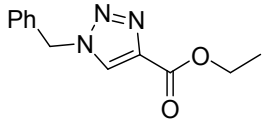
Figure 1. SEM image of copper (II)-nicotinamide

To demonstrate the efficacious use of copper (II)-nicotinamide complex in cycloaddition reactions, a mixture of benzyl bromide, sodium azide, aliphatic alkyne and catalyst complex was irradiated with microwaves under solvent-free conditions (Scheme 1). This protocol was studied for an array of substrates and in all the cases (Table 1, entries 1-11), reactions proceeded smoothly at 100 ^{o}C to afford the desired 1,2,3-triazoles in 8-15 min. with the exception of ethyl propionate (Table 1, entry 12), where the reaction gave a mixture of products. To counter this problem and to minimize the formation of undesired products due to possible decomposition of ethyl propionate, the reaction temperature was reduced to 60 ^{o}C which led to an increase in the reaction time to 30 min (require, Table 1, entry 12) to furnish the corresponding triazole in 82 % yield.



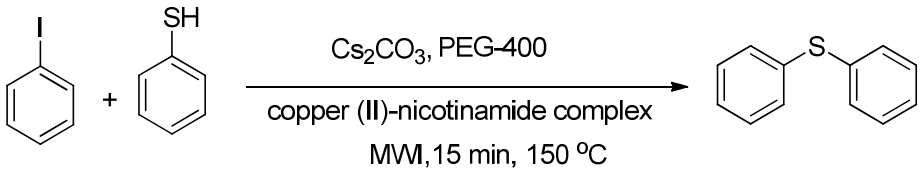
Scheme 1. Copper (II)-nicotinamide catalyzed synthesis of 1,2,3-triazoles under solvent-free conditions

Table 1. Azide-Alkyne Cycloaddition using copper(II) nicotinamide complex

Entry	Alkyl halide	Alkyne	Times	Product	Yield
1			8 min		97%
2			8 min		98%
3			8 min		97%
4			10 min		88%
5			8 min		95%
6			8 min		93%
7			13 min		95%
8			10 min		85%[b]
9			15 min		94%
10			15 min		95%
11			15 min		88%
12			30 min		82% [c]

a) Reaction conditions: 1.2 mmol of alkyl halides, 1.5 mmol of NaN_3, 1.0 mmol of alkyne, 10 mg (0.025 mol%) of catalyst. MW, 100 ^oC, Power: 100 W. b) (i)1.2 mmol of alkyl halides, 1.5 mmol of NaN_3, MW, 100 ^oC, Power: 100 W, 5 min; (ii)1.0 mmol of alkyne, 10 mg (0.025 mol %) of catalyst. MW, 100 ^oC, Power: 100 W, 8 min.c) Reaction was performed at 60^oC

The copper-nicotinamide catalyst was then employed for the expeditious C-S cross-coupling of aryl iodides and aryl thiols under microwave (MW) irradiation conditions. The initial experiments were optimized for the C-S coupling reactions using the reaction of iodobenzene and thiophenol as a model (Scheme 2). The reactants up on MW heating at 100 ^{o}C for 30 minutes in presence of copper (II)-nicotinamide catalyst (10 mg) and K_2CO_3 (2 equiv) afforded the product in moderate yields. The transformation was studied in various solvents, such as water, polyethylene glycol-400 (PEG-400), DMF, THF, toluene and bases such as K_2CO_3, Cs_2CO_3, and KOH. The optimum yield (91%) of the corresponding thiol (Table 2, entry 1) was obtained in PEG-400 using Cs_2CO_3 as the base at 150 ^{o}C for 15 minutes under MW heating conditions. It was observed that during the reaction process, the copper-nicotinamide catalyst forms a homogeneous mixture with the reaction solvent. The optimized protocol was then extended to other aryl iodides and aryl thiols (Table 2, entries 1-12).



Scheme 2. C-S cross-coupling of aryl iodides and thiophenol

In almost all the cases, reaction progressed effectively to offer the corresponding diaryl sulfides in high yields (Table 2. Entries 1-12). The gas chromatography-mass spectrometer (GC-MS) profiles of the crude reaction mixtures show the smooth reaction progress (Figure 2); the presence of the slightly excess reactant, aryl iodide (1.1 eq.), over aryl thiols (1.0 eq.) was apparent from the GC profiles (Figure 2).

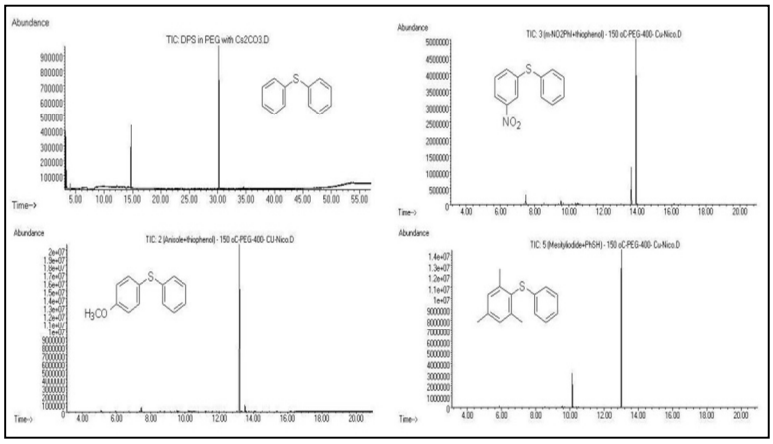
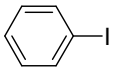
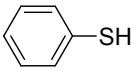
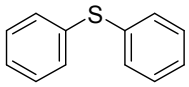
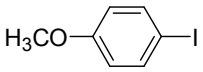
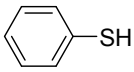
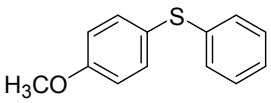
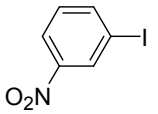
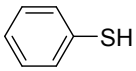
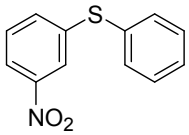
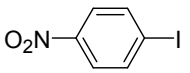
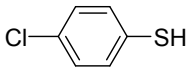
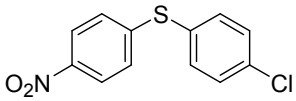
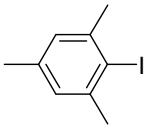
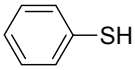
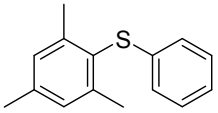
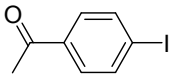
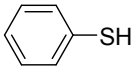
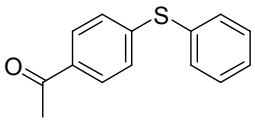
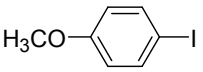
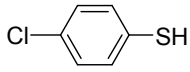
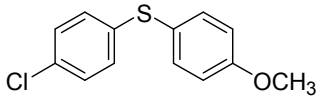
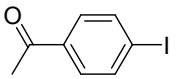
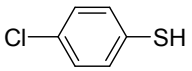
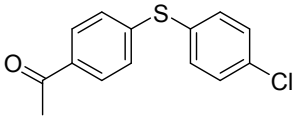
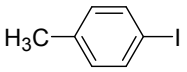
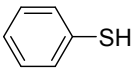
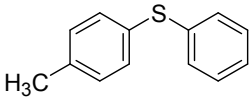
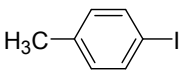
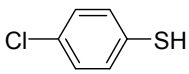
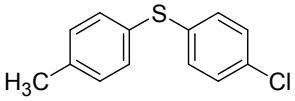
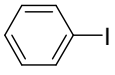
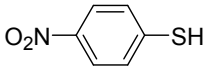
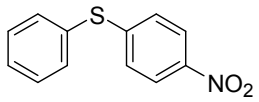
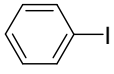
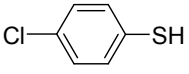
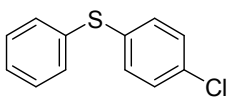


Figure 2. GC-MS profiles of some of the crude reaction mixtures.

The presence of nitro (-NO_2) or chloro (-Cl) substituent on thiophenol counterpart did not affect the reaction outcome delivering the corresponding products (Table 2, entries 11 and 12) in high yields. Aryl iodides containing electron donating (-OMe, -Me; Table 2, entries 2, 5, 7, 9, and 10) as well as electron withdrawing groups (-NO_2, -COMe; Table 2, entries 3, 4, 6, and 8) participated smoothly in the reactions that delivered the corresponding product in high yields. The sterically hindered mesityl iodide also underwent cross-coupling efficiently to afford diaryl sulfides (Table 2, entry 5) in 84% yield.

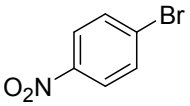
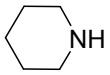
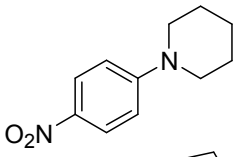
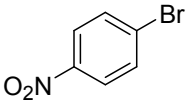
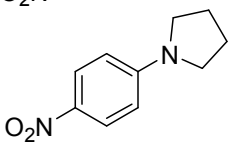
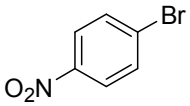
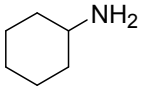
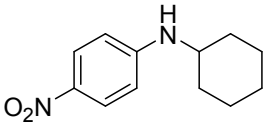
With the aforementioned encouraging results, we further explored the amination of aryl halides, a reaction that has been explored predominantly using palladium as a catalyst. However, many of these methods involve the use of air-sensitive and expensive organic ligands and require longer reaction times and excess amount of bases which could complicate the reaction especially where base sensitive substrates are employed. Interestingly, we observed a unique reactivity of copper-nicotinamide catalyst which allows amination of aryl halides to proceed under solvent-free and base-free conditions (Table 3).

Table 2 Synthesized diaryl sulfides from aryl iodides and thiophenols

Entry	Aryl iodide	Thiophenol	Product	Yield (%)
1				95%
2				92%
3				88%
4				90%
5				84%
6				88%
7				86%
8				85%
9				90%
10				95%
11				91%
12				89%

[a] Reaction conditions: 1.0 mmol of aryl iodide, 1.2 mmol thiophenol, 10 mg (0.025 mol %) of copper-nicotinamide catalyst, Cs_2CO_3 (1.0 mmol), PEG-400 (2 mL), MWI, 150 ^{o}C, 15 min.

Table 3. Copper (II)-nicotinamide catalyzed amination of aryl halides [a]

Entry	Aryl halides	Amines	Time	Prodcut	Yield
1			60 min		97%
2			60 min		99%
3			60 min		99%

a) Reaction conditions: 1 mmol aryl halides, 1.2 mmol amines, 10 mg (0.025 mol %) copper (II)-nicotinamide catalyst, Neat, MWI, 100 W, 100 ^{o}C, 60 min

Conclusion

In conclusion, a simple and morphologically appealing copper-nicotinamide complex has been employed in the synthesis of aryl coupling and cycloaddition reactions. The attractive features of this approach include the use of benign solvent or solventless conditions, MW-accelerated transformations, simple, and high yielding sustainable protocols thus demonstrating the versatility of the catalyst for a variety of reactions.

Experimental section

Synthesis of Copper (II)-nicotinamide complex.

Copper chloride (0.1N) and nicotinamide (0.1N) solutions were mixed in a 2:5 ratio. The crystals of Copper(II)-nicotinamide complex, Cu(nicotinamide)$_2$Cl$_2$ start growing immediately after mixing. The supernatant liquid was filtered off and dried under vacuum at 40 ^{o}C and characterized using CHN (C, 36.32%; H, 3.54%; and N, 14.13%) and TGA (ESI, Fig S1) analysis and stored at ambient conditions.

Synthesis of diaryl sulfides

Aryl iodide (1.0 mmol), thiophenol (1.2 mmol), Cs_2CO_3 (1.0 mmol), 10 mg (0.025 mol %) of Copper (II)-nicotinamide complex and PEG-400 (2 mL) were added to a crimp-sealed thick-walled glass tube. The reaction tube was placed inside the cavity of a CEM Discover focused microwave synthesis system equipped with a pressure sensor and a magnetic stirrer. The reaction conditions were set at 150 ^{o}C, 100 Watts for 15 min. After completion of the reaction, the products were extracted using ethyl acetate, washed with water and dried over sodium sulfate followed by concentration under vacuum and purification using column chromatography.

Synthesis of 1,2,3-triazoles

1.2 mmol of alkyl halide, 1.5 mmol of NaN_3, 1.0 mmol of alkyne, and 10 mg (0.025 mol %) of catalyst were placed in a crimp-sealed thick-walled glass tube. The reaction tube was placed inside the cavity of a CEM Discover focused microwave synthesis system equipped with a pressure sensor and a magnetic stirrer. The reaction temperature was set at 100 ^{o}C (temperature monitored by a built-in infrared sensor), a power level of 100 W, and pressure 10–60 psi for a duration of 8-30 min (Table 1). After completion of the reaction, the crude product was extracted with ethyl acetate followed by recrystallization or purification by column chromatography.

Amination of 4-bromonitrobenzene

4-Bromonitrobenzene (1.0 mmol), aliphatic amine (1.2 mmol), and 10 mg (0.025 mol %) of copper(II)-nicotinamide complex were placed in a crimp-sealed thick-walled glass tube. The reaction tube was placed inside the cavity of a CEM Discover focused microwave synthesis system equipped with a pressure sensor and a magnetic stirrer, operated at 100 ^{o}C (temperature monitored by a built-in infrared sensor) and a power level of 100 W for 60 min. After completion of the reaction, the products were extracted using ethyl acetate, dried over sodium sulfate, concentrated under reduced pressure and purified by column chromatography.

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Disclaimer

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Graphical Abstract

Copper-nicotinamide complex: sustainable applications in coupling and cycloaddition reactions

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Copper (II)-nicotinamide complex catalyzes the C-S, C-N bond forming and cycloaddition reactions under a variety of sustainable reaction conditions.