

Chapter 2

Literature Review

In 1893 Michael A first reported the synthesis of 1,2,3-triazole from phenyl azide and diethyl acetylene dicarboxylate in the absence of catalyst.¹ After seven decades Husigen studied the thermal reaction² and found that the reaction is largely exothermic. Its low reaction rate at elevated temperature indicates its high activation barrier. Major drawback of this reaction is the thermodynamic instability, the formation of undesired alkyne- alkyne coupling product and lack of regioselectivity. In 2002, Sharpless and Meldal independently made a mile stone in Husigen 1, 3-dipolar cycloaddition reaction by introducing Cu (I) catalyst by the *in situ* reduction of Cu (II) salt with sodium ascorbate which improves the regioselectivity, rate of the reaction and provides high yield under mild reaction condition.^{3,4} Synthesis of 1,4-disubstituted 1,2,3-triazole from terminal alkyne and an aliphatic azide in presence of copper was termed as Copper catalyzed azide- alkyne cycloaddition reaction (abbreviated to CuAAC). This method provides good functional group tolerance and can be carried out in aqueous media as well as in aqueous with organic co-solvents. Azides which are 1,3-dipolar compound represented by zwitterionic all-octet resonance structures are ambivalent in the 1- and 3-positions, thus displaying electrophilic as well as nucleophilic activity. The dipolarophile can be any double or triple bond (**Fig 1**).

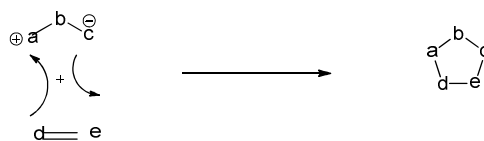
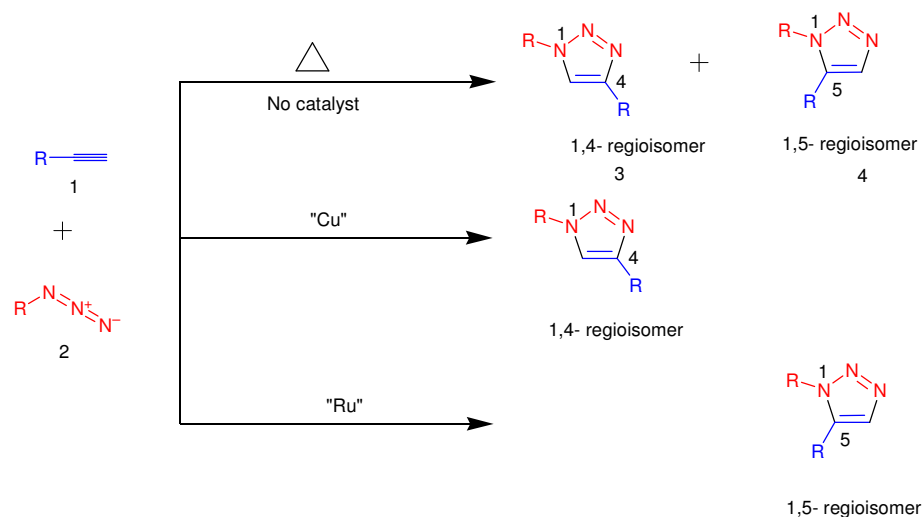


Fig 1

Introducing transition metal provides regioselectivity; copper provides 1,4-disubstituted 1,2,3- triazole where as ruthenium gives 1,5- disubstituted 1,2,3-triazole.^{5,6} (**Scheme 1**) Similarly transition metals like Silver,⁷⁻¹³ Gold,^{14,15} Iridium,¹⁶⁻¹⁸ Nickel,¹⁹ Zinc,²⁰⁻²² and Lanthanides^{23,24} also catalyze the cycloaddition reaction.



Scheme 1

Triazole compounds have made its role in different field like synthetic, pharmaceutical and biological.²⁵ Triazole ring system have attractive features which attracts both coordination and organometallic researchers (**Fig.2**).

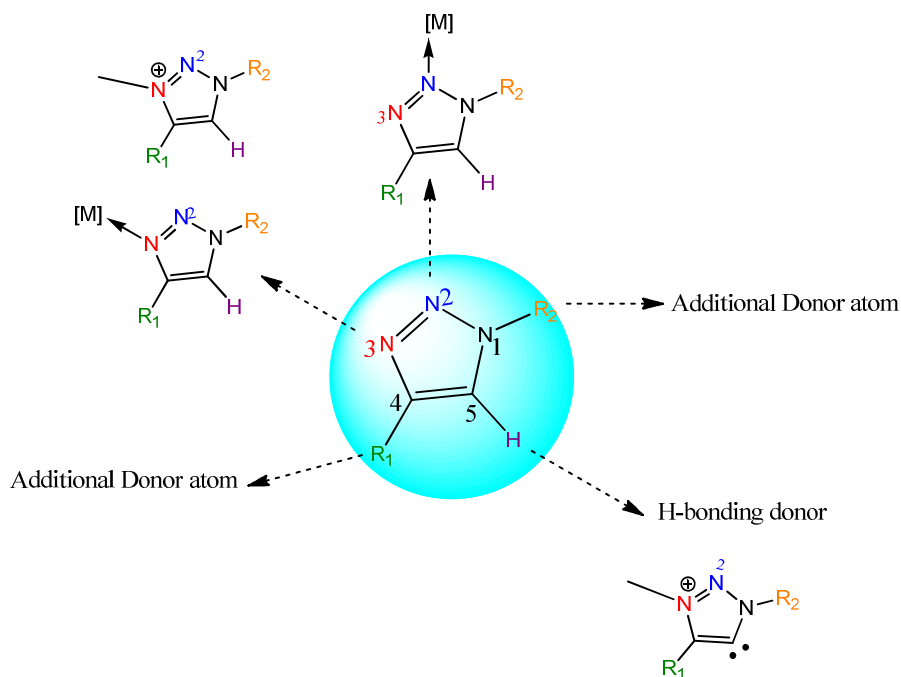


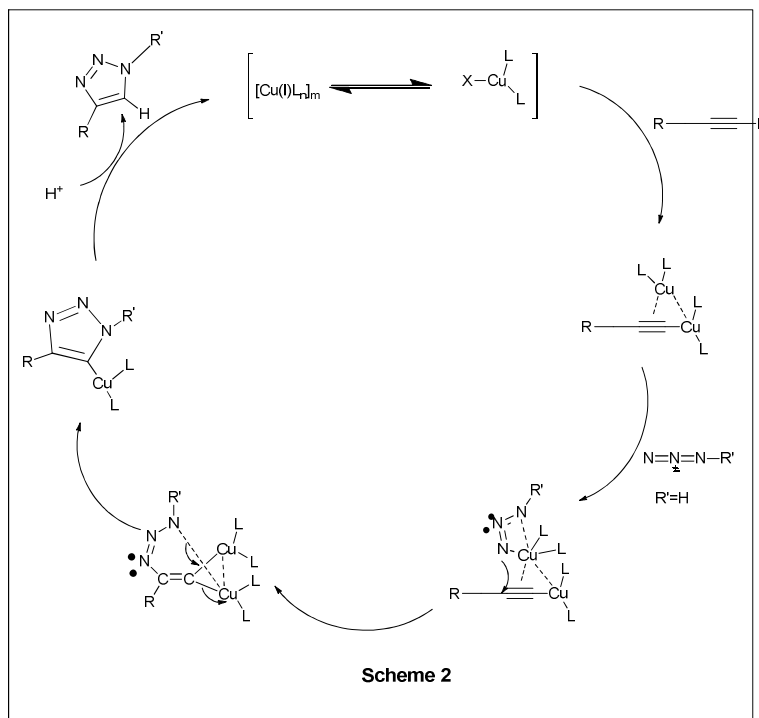
Fig 2 Attractive features of triazole ring system

In the triazole system, N3 is the basic donor atom through which it can act as monodentate ligand. The presence of additional donor groups made the system as a

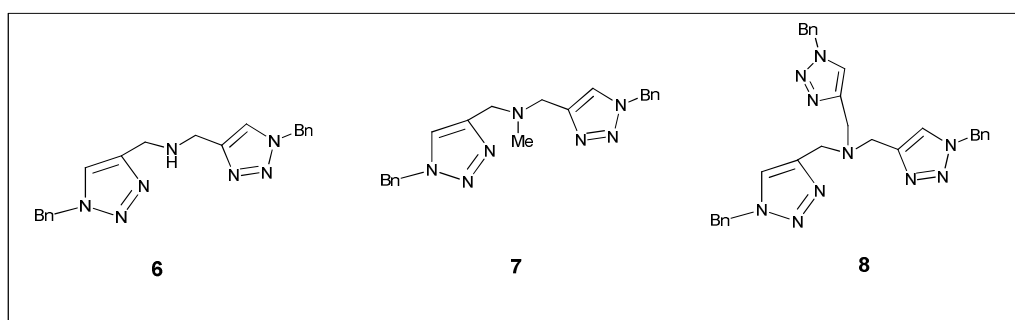
chelate ligand which allows the incorporation of multi triazole ligands within the backbone and thereby generating multi-dentate triazole ligand systems. The alkylation of N3 followed by the deprotonation of triazole C-H leads to the generation of 1,2,3-triazol-5-ylidene which belongs to abnormal *N*-heterocyclic carbene ligand. The deprotonation of ring hydrogen results the formation of carbanion which also allows the triazole system to act as monodentate ligand. The presence of substituent at N1 which contain donor atom compel the metal to bind through N2 rather than N3 because of the chelate effect.

Mechanism

CuAAC proceeds through a step-wise mechanism which includes i) abstraction of a proton to form highly polarized acetylene to yield Cu(I)-acetylide complex, ii) interaction of Cu(I) acetylide with azide and activate it for the nucleophilic addition of acetylide carbon to the 'end' nitrogen of the azide forming copper(III) metallacycle, iii) ring contraction of metallacycle to a triazolyl- copper derivative followed by protonation yields triazole (**Scheme 2**).

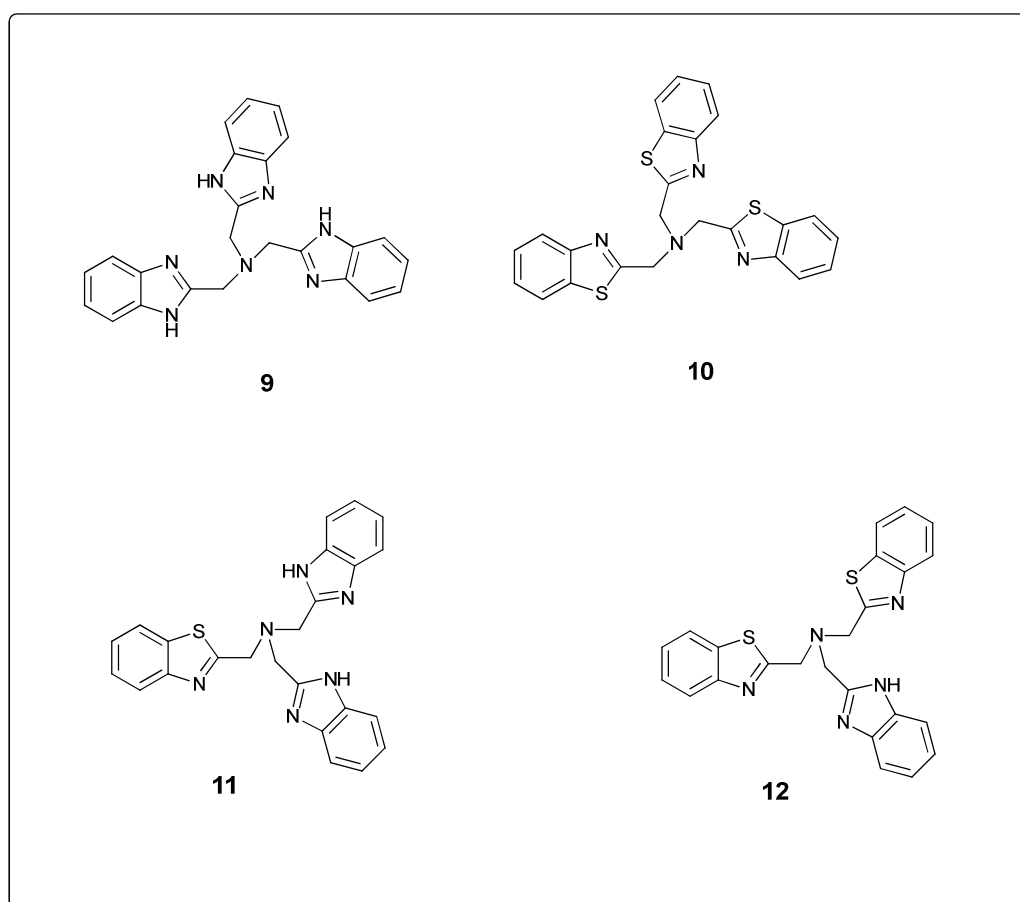


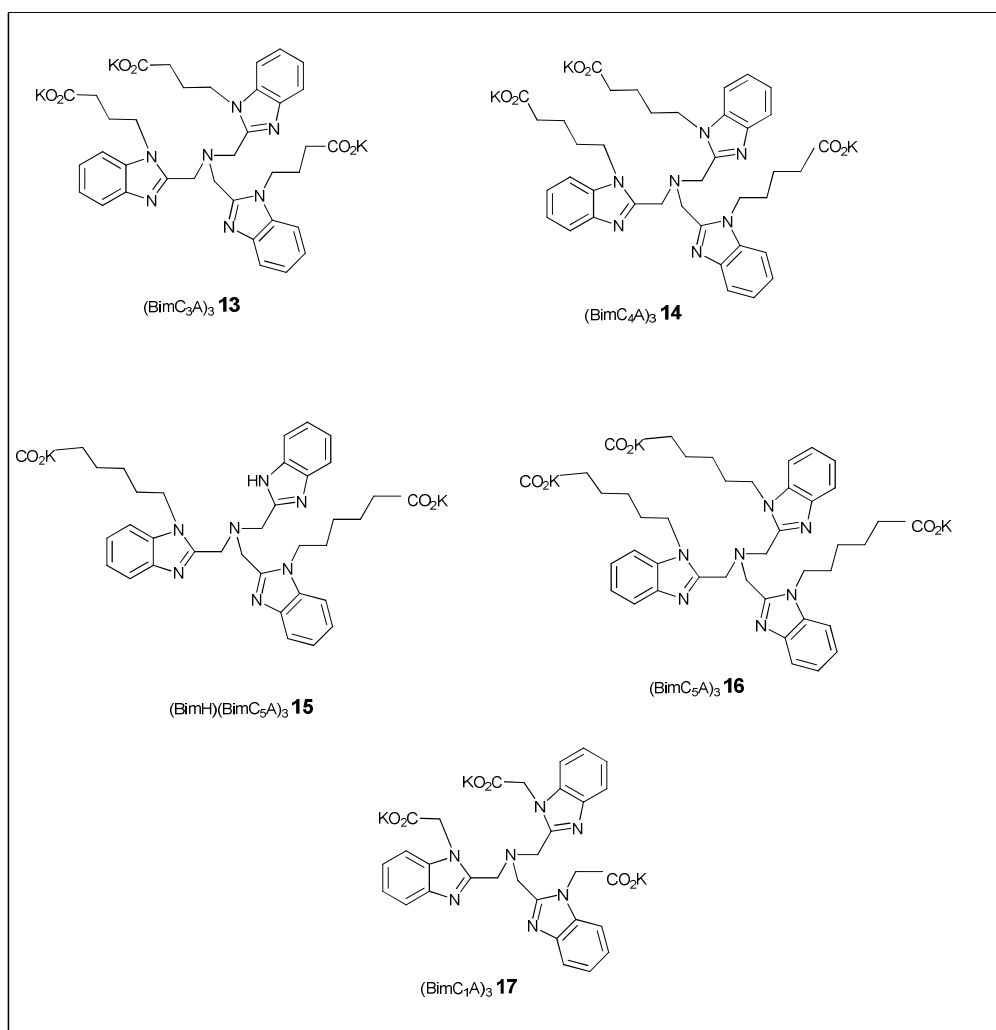
Here copper (I) is the actual catalyst for this cycloaddition reaction. In order to maintain its concentration copper (II) source and a reducing agent is required. Sharpless and Fokin developed a catalytic system of CuSO_4 with sodium ascorbate in water/alcohol mixture.²⁶ Polytriazoles was found to be good ligands which will protect Cu(I) under aerobic and aqueous conditions. They tightly bound to the metal to maintain the oxidation state. Bistriazoles **6** and **7** gives excellent performance of about 94% and 98% yield with $[\text{Cu}(\text{CH}_3\text{CN})_4] \text{PF}_6$ when compared to tris-triazole TBTA **8** with 84% yield. But when reducing the amount of copper catalyst to 0.25 mol% bistriazoles are not as potent in protecting Cu(I) oxidation state whereas TBTA withstands all conditions.²⁷



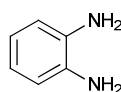
Highly nitrogenated ligands tend to accelerate the reaction by stabilizing and protecting copper(I) species from further oxidation.²⁸

Acceleration of catalyst in the presence of ligand was studied by Finn and coworkers in 2007.²⁹ They synthesized a central tertiary amine surrounded by three benzimidazole heterocycles **9-12** and its derivatives **13-17**. The reaction rate depends on the nature of heterocycle and the substituents on the benzimidazole ring. The catalytic efficiency will remain as such when there is one benzimidazole side arm is present. The rate of CuAAC increases in the order $(\text{Bth})_3 \ll (\text{Bth})(\text{BimH})_2 < (\text{BimH})_3 \ll (\text{Bth})_2(\text{BimH})$. Carboxylic acid or ester group attached to the benzimidazole rings via $(\text{CH}_2)_4$ and $(\text{CH}_2)_5$ were found to be an excellent catalyst. On the other hand, $(\text{BimC}_1\text{A})_3$ **17** produced one of the worst performing catalysts as the acid group is directly attached to the benzimidazole by a CH_2 -linker.



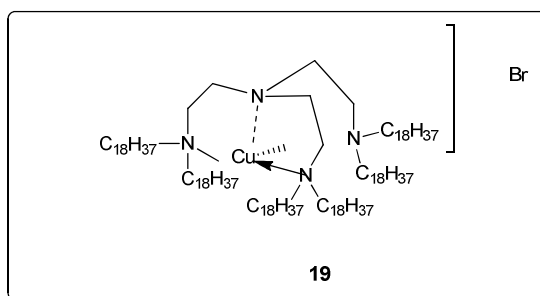


Cycloaddition of different alkynes with glucosyl azide was done in water by using CuSO₄ and sodium ascorbate in presence of *o*-phenylenediamine **18**.³⁰

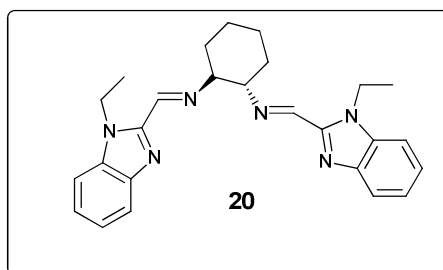


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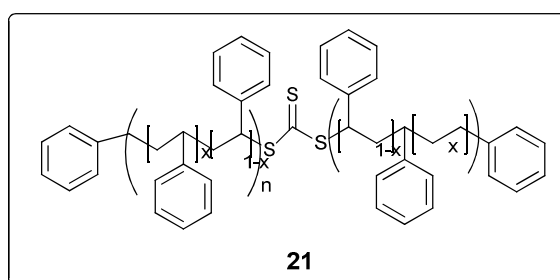
The use of complex **19** as catalyst effectively protects copper from oxidation. Less polar nature of the catalyst allows its separation from hydrocarbon solvents by simple filtration and can be reused two times with no decrease in the yield of triazole.³¹



Nitrogen tetradentate ligand **20** was also reported for CuAAC reaction.³² The reaction proceeds at room temperature using 2mol% Cu(I) salt for 10h. The reaction was successful using different substrates having electron rich, electron poor, and hindered alkyl halides in acetonitrile-water solvent mixture.



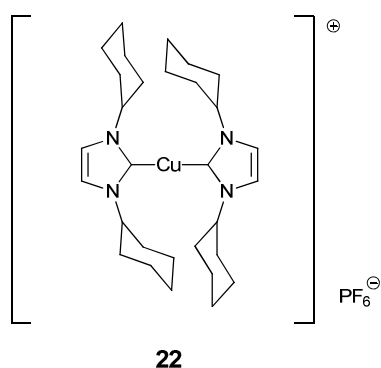
In 2010 Prez and coworkers developed TBTA functionalized styrenic monomer which on RAFT copolymerization with styrene followed by complexation with copper fabricate a good catalyst **21** for CuAAC. The catalyst can be reused 6 times, with minimum loss of activity.³³



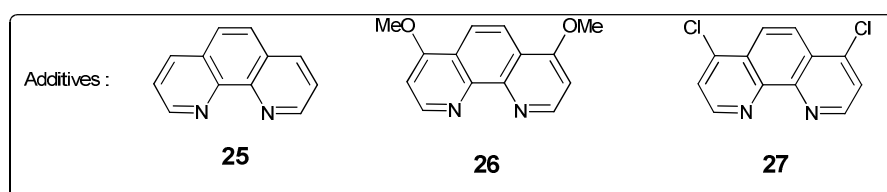
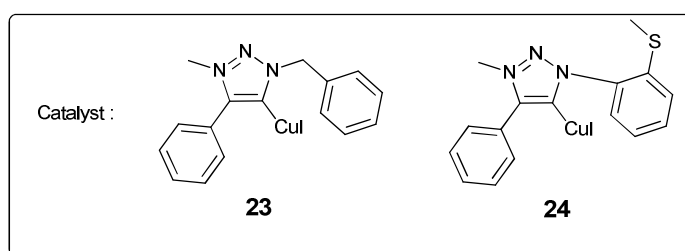
Nolan *et al* reported the catalytic activity of *N*-Heterocyclic carbene complex in CuAAC. They tested the catalytic efficiency of [(IPr)CuCl] and [SIMesCuBr].³⁴ Latter only gives better yield while the former led to partial conversion. It is to be noted that the yield became high and also the reaction time get reduced using water as solvent. They also tested its activity with internal alkynes; the reaction of benzyl

azide, 3-hexyne in presence of catalyst and under copper free condition. Yield of product found to be >5% under copper free condition.

In 2008 Nolen *et al.* again reported the catalytic activity of 2mol% of [(NHC)₂Cu]X at room temperature using water as solvent.³⁵ The catalytic activities of different complexes were studied in which **24** was found to give better result within 90min. Using **24** optimization of solvents was done. The reaction could be better using acetonitrile as solvent as well as in neat condition. Surprisingly, catalyst loading can be reduced to 0.5mol% under neat condition.



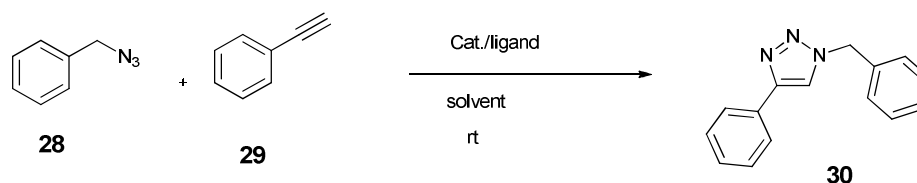
Gautier and Sarkar reported Cu(I) mesoionic carbene with nitrogen additives can be used for cycloaddition reaction.³⁶ The nitrogen additives tend to increase the solubility of catalyst, while decrease in the bond strength of Copper-chlorine bond, thereby hydrolysis leads to catalytically active species.



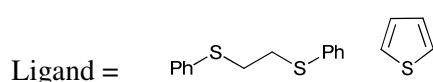
Without the use of additives, catalysts only give 20% and 5% yields respectively even after 24 h. The reaction time was reduced by adding additives and good yield of the product was observed. Additive containing electron donating methoxy group tends to

the oxidation of copper as identified by the color change from yellow orange to green due to the formation of copper(I) additive. Electron withdrawing chloride ion also facilitates the reaction.

Sulfur base ligands for CuAAC reaction was first reported by Fu and coworkers in 2008.³⁷ They developed cycloaddition reaction of water insoluble substrates at room temperature. They used inexpensive chemicals like CuBr/PhSMe. However, they attempted different sulfur containing compounds in cycloaddition reaction like thioanisole, dimethyl sulfoxide, thiophene etc. Among the copper salts they used CuBr because of weak dissolving power of CuI in water. They initially tested using simple reaction of benzyl azide with phenylacetylene (**Scheme 3**). Mixed solvents had given better results and pointed to the choice of water as solvent. They varied the amount of copper as well as ligands, the use of more copper and ligand provided not only the best result but also shortened the reaction time. On increasing ligand concentration from 30 to 50 mol% and catalyst concentration from 5 to 10%, they observed an increase in the yield from 93 to 98 % within 5min reaction time.



Scheme 3

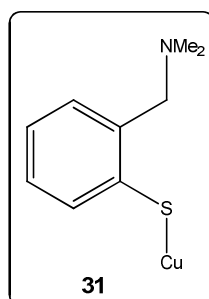


MeSMe, PhSMe, DMSO

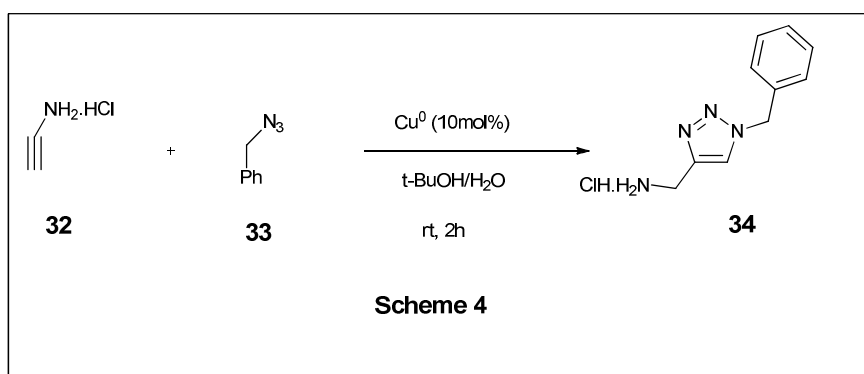
They also carried out cycloaddition of aliphatic and aryl azides with alkynes. Substrates having good solubility in water had given higher reaction rate than one having low solubility. There is no significant difference in reactivity when using electron rich, electron deficient and sterically demanding substrates etc. They summarized that CuBr/thioanisole catalytic system was highly efficient in the cycloaddition reaction.

Catalytic efficiency of (2-aminoarenethiolato)copper(I) was tested in 2009.³⁸ Efficiency was tested by using in three different azide using classical catalyst and by

{[2-(Dimethylamino)methyl]thiophenolato}copper(I) complex **31**. Both acetonitrile and dichloromethane were suitable for the reaction.

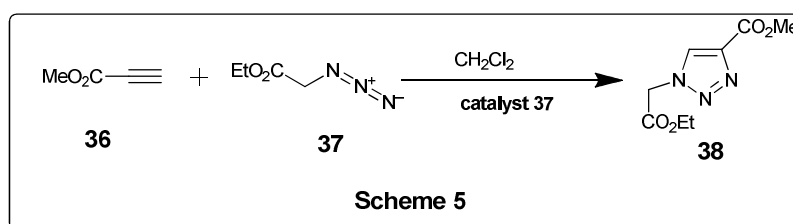
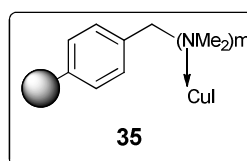


Orgueira *et al.* developed an effective protocol for CuAAC cycloaddition reaction.³⁹ They assumed that the presence of an amine hydrochloride salt would lead to produce catalytically active Cu(I) species from Cu(0) nanosize activated powder, which have large surface area that could enhance acetylide copper complex formation followed by cycloaddition reaction (**Scheme 4**). They got high yield in each reaction by using 10mol% Cu(0) and 1 eqv amine hydrochloride salt in *t*-BuOH/H₂O mixture for 2 h room temperature stirring.

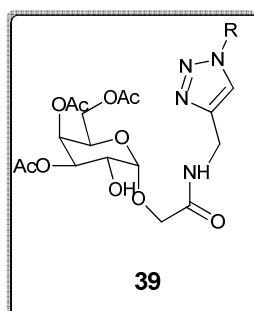


Heterogeneous Catalyst for CuAAC

Girard and coworkers used polymer supported copper iodide as catalyst.⁴⁰ Amberlyst A-21 containing dimethyl-aminomethyl functionality which acts as both base and chelating agent was taken as polymer support in acetonitrile as solvent. This copper immobilized catalyst **35**, AAC reaction provide 1,4-disubstituted triazole **38** in excellent yields. Recyclability and stability of the catalyst was studied using the click reaction between propiolic acid methyl ester **36** and ethyl azidoacetate **37** (Scheme 5). The catalyst can be reused for 4 times without any loss in catalytic activity.



Complex glycoside molecules **39** with antimicrobial activity synthesized by CuAAC reaction using copper(I) iodide supported on Amberlyst A-21 resin and dichloromethane as solvent.⁴¹

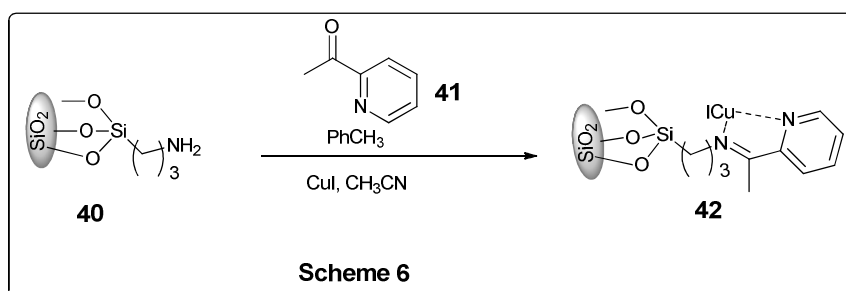


Impregnation of activated wood charcoal with aqueous solution of copper nitrate under sonication was reported by Lipshutz.⁴² Using 10 mol% catalyst, a model reaction was carried out by using benzyl azide and phenylacetylene in dioxane at room temperature for 10 h. Addition of triethylamine or heating the reaction mixture will reduce the reaction time. The catalyst can be reused 3 times.

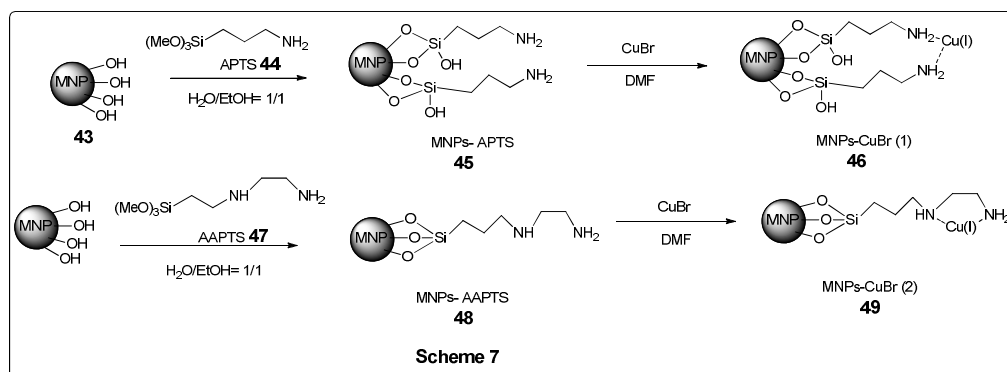
Cuprous oxide immobilized on charcoal with 0.89wt% of copper catalyzes CuAAC reaction.⁴³ The catalyst was found to be effective in aqueous isopropyl alcohol with 5% catalyst loading in the presence of triethylamine as base.

Xiong reported the CuAAC reaction catalyzed by CuBr supported on graphene oxide (GO)/Fe₃O₄.⁴⁴ The catalyst was prepared by two step process; i) coprecipitation method in which GO/Fe₃O₄ was prepared from graphene oxide. ii) refluxing GO/Fe₃O₄ in ethanolic solution of CuBr under nitrogen atmosphere. The CuAAC reaction was carried out in water either using conventional heating or under microwave irradiation using model reaction of sodium azide, phenylacetylene and benzyl chloride. The catalyst GO/Fe₃O₄-CuBr provides excellent result compared to copper acetate. Using optimized reaction conditions CuAAC reaction of different halide and alkynes were conducted in water using 5 mol% of catalyst at 80°C.

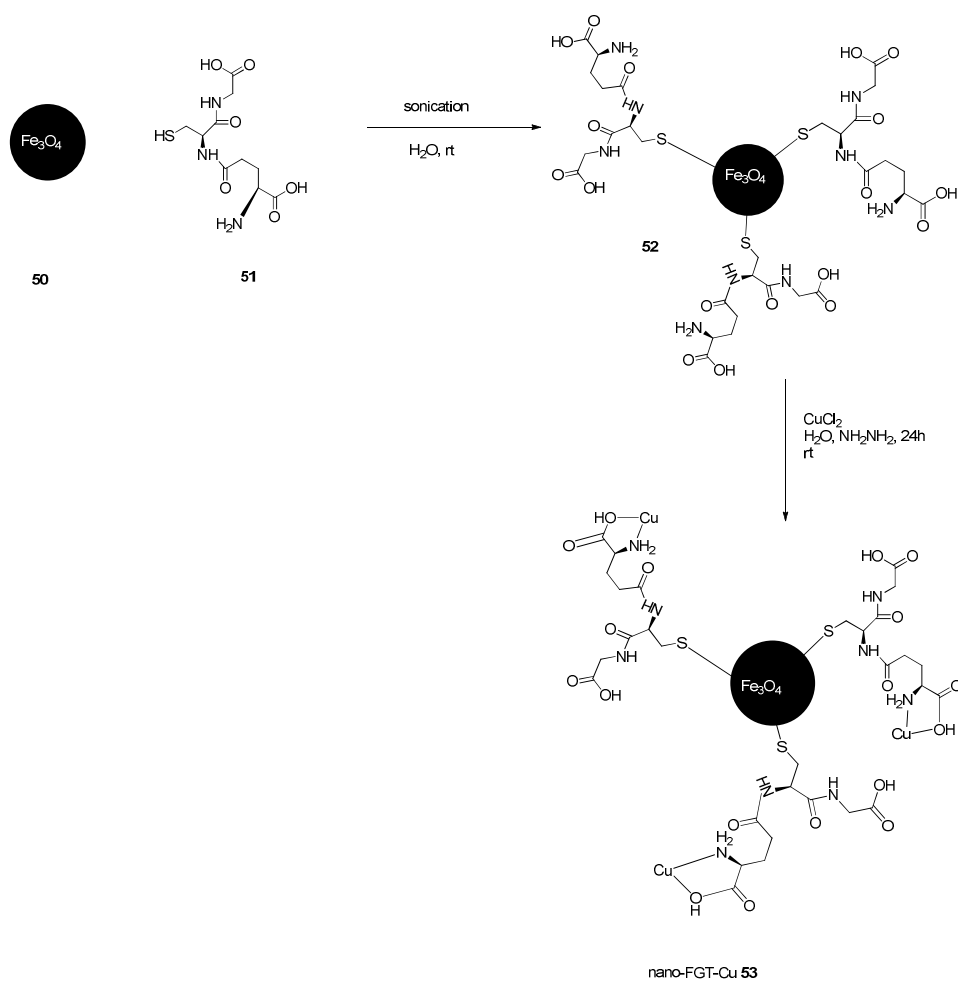
Imine functionalized silica was prepared by Paul in 2010⁴⁵ by refluxing 3-aminopropyl silica with 2-acetylpyridine in toluene (**Scheme 6**). Impregnation of Cu (I) was done at room temperature by stirring imine grafted silica with CuI in acetonitrile. Copper linked silica was found to be a good catalyst for Huisgen cycloaddition reaction between benzyl halide and allyl chlorides with 5 mol% Cu loading. The catalytic efficiency remains unaltered even after seven cycles.



Amino modified magnetic nanoparticles containing copper was synthesized by Xiong in 2013.⁴⁶ Magnetic nanoparticles were prepared conventional procedure, which was modified either with 3-aminopropyltrimethoxysilane (APTS) or [3-(2-aminoethylamino)propyl]trimethoxysilane (AAPTS) by using with a molar ratio of 2:1 in ethanol: water system (v/v = 1/1). The obtained MNP's were treated with CuBr in DMF at room temperature for 6 h. TEM analysis revealed that average diameter around 10-20 nm with quasi spherical shape.



Varma reported the synthesis and catalytic activity of copper nano particles on glutathione functionalized nano ferrite particles (**nano-FGT-Cu**).⁴⁷ Initially they functionalized the nano ferrite particles by sonicating nano ferrite with glutathione in water for 2 h. Copper was incorporated into the NP's by the addition of copper chloride $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ in alkaline medium. TEM results confirm the size which is in the range of 10-25 nm. Weight percentage of copper in catalyst was found out using ICP-AES analysis [1.57%]. Optimization of the reaction conditions were carried out using benzyl azide and phenyl acetylene using microwave irradiation at 120 °C in water as medium. They studied the catalytic activity of **nano-FGT-Cu 53** by performing the reaction between benzyl azide and different alkynes. They didn't observe 1,5- regioisomer in the product. The recovery of the catalyst can be carried out by magnetic separation.



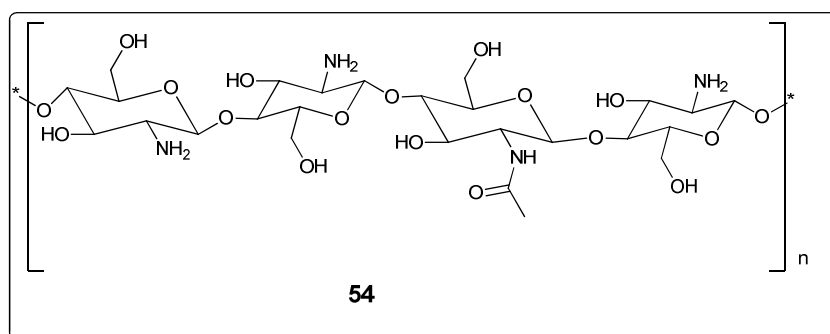
Scheme 8

Alumina supported copper nanoparticles were prepared by Kantham in 2006 using aerogel method.⁴⁸ For this, copper(II) acetylacetonate in methanol was mixed with toluene and then aluminium isopropoxide was added followed by stirring for 2 h. To the above mixture stoichiometric amount of deionized water was added and stirring continued for 18h, followed by autoclaving at 10 kg/cm² and 265 °C for 10 min. Drying of the aerogel material at 120 °C gives a fine powder of Cu-Al₂O₃ nanoparticle. The XRD pattern reveals the presence of both metallic copper and cuprous oxide nanoparticles. Presence of cuprous oxide is due to the oxidation of copper during drying of nanoparticles at 120 °C. The surface area of nanoparticle was found to be 250 m²/g with an average pore diameter of 64.2 Å. From the optimization studies, water was found to be the best solvent to obtain higher yield. One pot synthesis of 1,2,3-triazoles from sodium azide, terminal alkynes and alkyl/allyl halides in water was effectively catalyzed by Cu-Al₂O₃ nanoparticles. The products were recovered by simple extraction with ethyl acetate. The catalyst could be reused

for 3 times without any loss in catalytic activity. Using ICP AES analysis copper content of recovered catalyst after fourth cycle, was found to be the same as fresh.

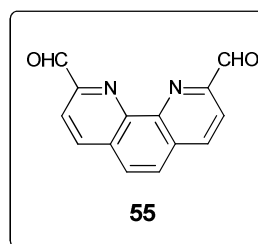
1,2,3-triazole derivatives obtained by the click reaction catalyzed by Cu/Al₂O₃ under ball milling without using any solvent and additives was studied by Ranu *et. al.*⁴⁹ Catalyst was prepared by adding alumina to aqueous solution of CuSO₄ aged for 2h at 25°C. The product obtained is having a copper content of 18.8 mg/g. Triazole derivatives were obtained with excellent yields within 1h.

Biopolymers have gained enormous importance for various applications. Chitosan, a polysaccharide which is derived from chitin have gained much attention in catalysis due to its insolubility in organic solvents, the presence of amino group which anchor transition metal ion or it can be converted to Schiff base which act as ligand.



When Chitosan microspheres dried in supercritical CO₂, it provides stable aerogel porous support with large surface area having pore size >10nm and using this technique amine groups makes more visible towards reactants.^{50,51}

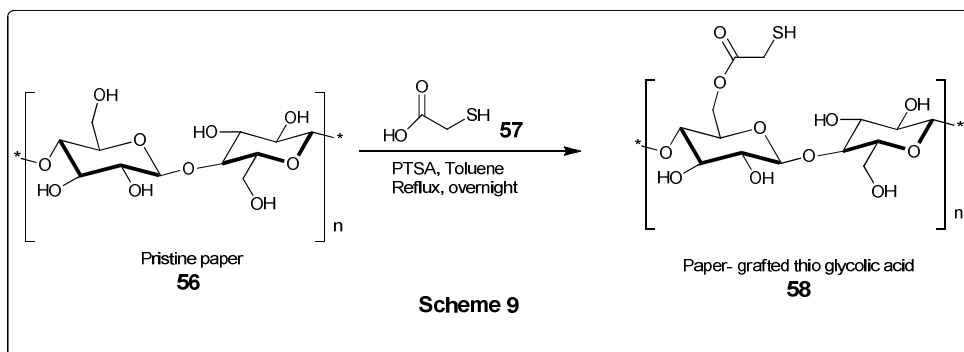
Copper was loaded to the chitosan aerogels in acetonitrile aqueous solution of copper triflate and sodium ascorbate at room temperature with repeated washing followed by metal loading at different concentrations from 0.5 to 2.1 mmol of Cu(I) per gram of catalyst.⁵² For the synthesis of Schiff base, they selected both mono and dialdehydes which forms cross linking throughout the chitosan network. Among these, 2,9-diformylphenanthroline **57** was found to be the best ligand. Optimization of reaction conditions were carried out and most polar solvents provides better result. Using the catalyst, cycloaddition reaction was carried out in EtOH at 70 °C which converts the reactants to 1,4-triazole after 12 h. Reusability of the catalyst was checked using the model reaction between phenylacetylene and benzyl azide and the catalyst could be reused for four times without copper leaching.



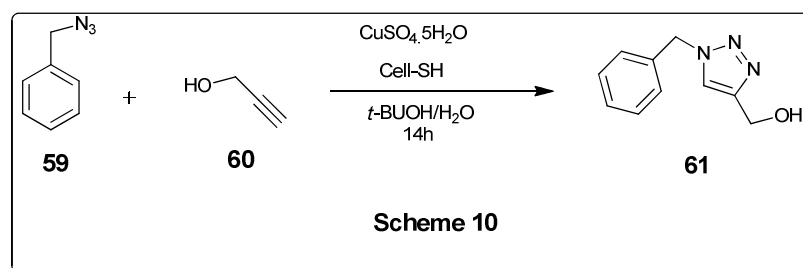
Copper immobilized on chitosan was prepared by Varma⁵³ which was done by suspending Chitosan in an aqueous solution of copper sulfate for 3 h. The product was centrifuged and dried under vacuum. Amount of copper in catalyst found to be 5.1 wt% using ICP-AES. Initially the cycloaddition reaction was carried out to optimize the reaction condition in water at room temperature which provides excellent result within 4h. Expected triazole product obtained in excellent yield (93-99%) within 4-12 h. Reusability of the catalyst was studied using benzyl azide and phenylacetylene and the product was extracted using ethyl acetate. The catalyst was recovered by decanting and dried at 50 °C which can be further used for 5 cycles. Copper leaching was studied using ICP- AES. Before the reaction copper content was 5.1wt % and after 5th cycle copper content was found to be 5.02%.

Agarose supported copper catalyst was reported by Gholinejad⁵⁴ in which catalyst was prepared by mixing CuBr solution in water with agarose hydrogel suspension followed by the addition of NaBH₄ to reduce copper(I) to copper nanoparticle which was indicated by the color change from gray to dark green. After cooling to room temperature the reaction mixture was centrifuged and dried in oven at 80 °C for 24 h. They conducted different CuAAC reactions by introducing arenediazonium salt from aniline. For the catalytic studies 0.05 mol% of the catalyst was added to a mixture of alkyl halide, sodium azide and an alkyne in water and stirring at 40 °C for 8 h leads to the formation of products. The catalyst can be reused for other 5 successive runs.

Felgin *et.al* reported a low cost and simple method for the reduction of Cu(II) to Cu(I) using functionalized cellulose paper.⁵⁵ To break the hydrogen bonds pristine cellulose paper was soaked in aqueous solution of 10% NaOH at 25 °C for 24 h which also enhance reactivity of hydroxyl group, followed by the esterification using *p*-toluene sulfonic acid (PTSA) and they assumed that functionalization mainly took place on the primary hydroxyl functional groups (**Scheme 9**).



The paper cell-SH **60** can act as a sensor and detect the presence of Cu(II) by producing colorimetric change which can be identified using naked eyes. As the concentration of Cu(II) decreases the color of paper strip changes from black to pale brownish. They recorded UV diffuse reflectance spectrum of paper strip dipped in both copper free water sample and aqueous solution of Cu(II) with different concentration. In copper free sample they observed absorbance at 257 nm corresponds to carbonyl groups of ester function whereas the samples containing copper ions shows two $S \rightarrow Cu$ charge transfer bands at 506 and 665 nm respectively. They assumed that there is a thiol-mediated reduction of Cu(II) to Cu(I) which results in the formation of Cu(I)-SCH₂R complexes and leads to $S \rightarrow Cu$ charge transfer. This was confirmed by dipping the paper strip into an aqueous solution of CuCl₂ which turns black within seconds and the paper was characterized using SEM and XPS which confirms the presence of copper thiol complexes. Using this paper strip based reduction of Cu(II) to Cu(I) they investigated its catalytic efficiency in CuAAC reaction.⁵⁶ Initially they carried out a model reaction using propargyl alcohol and benzyl azide in presence of CuSO₄ · 5H₂O using *t*-BuOH/H₂O (1:1) solvent for 14 h at different temperature (**Scheme 10**). At room temperature with 16 mol% SH loading provides sluggish results. As temperature increases with 16 mol% SH loading and 2 mol% Cu loading provides better results. The scope of the catalyst was studied using various azides and alkynes.



They investigated the reusability of the catalyst using the same model reaction. The catalyst provides a comparatively normal yield in the second cycle without further addition of copper whereas a sharp decrease in yield was observed in third cycle.

Cellulose supported CuI nanoparticle was reported as heterogeneous catalyst for 1,2,3-triazole synthesis by Desai.⁵⁷ The catalyst was prepared by adding microcrystalline cellulose to a suspension of CuI in methanol which was then stirred overnight. Residue obtained by filtration which was washed with methanol and acetone and dried under vacuum at 50 °C. For the catalytic studies, they carried out model reaction using benzyl bromide, phenyl acetylene and sodium azide under neat condition at room temperature but the result obtained was not good. Then they tried different solvents, reaction temperature and amount of catalyst optimizing the reaction conditions to 100 mg of Cell-CuI catalyst in aqueous medium at 70 °C. The catalyst can be recovered by filtration followed by washing with ethyl acetate followed by acetone dried in air. This can be reused for 5 successive runs without any loss in catalytic activity. They investigated the reusability of the catalyst using the same model reaction. The catalyst provides a comparatively normal yield in the second cycle without further addition of copper whereas a sharp decrease in yield was observed in the third cycle.

Copper nanoparticles were generated by the chemical reduction of copper (II) acetate monohydrate using hydrazine hydrate in ionic liquid in which PVP was added as a stabilizing agent. Using the above generated copper nanoparticle Salunkhe developed a new catalyst for CuAAC reaction.⁵⁸ The model reaction was carried out by using phenyl azide and phenyl acetylene afforded solid product within 20 min. Cycloadduct from other reaction was separated by extraction using diethyl ether followed by evaporation resulted in good yield of the product. They also tested the recyclability of catalyst, the brown color of solution indicates the presence of Cu(0) even after running five consecutive run.

Using copper wire as catalyst and supercritical carbon dioxide (scCO_2) as organic media Xu and coworkers proposed a reusable and effective catalyst for CuAAC reaction.⁵⁹ The reactions were carried out at different temperatures, in the presence and absence of metallic copper. Higher yield obtained in the presence of catalyst at high temperature. For a model reaction they used copper wire of length 10 cm, as the length increases catalytic efficiency increased. The recovered catalyst can be reused further.

Phase transfer catalyst β -cyclodextrin discovered >100 years ago are cyclic oligosaccharides having the ability to form complex using their lipophilic inner cavities and hydrophilic outer surfaces. They contain α -D glucopyranose linked by α -(1,4) glycosidic bonds.⁶⁰ This phase transfer catalyst was found to be effective catalyst for CuAAC reaction.⁶¹ The relevance of using cyclodextrin as catalyst lies under the fact that it can include water-insoluble organic materials into the cavity in aqueous solution. Model reaction was carried out using benzyl azide and phenylacetylene with different mol% of cyclodextrin in water. Using 1 mol% of catalyst, the reaction was completed within 30 min with 97% isolated yield. Scope of the reaction was studied using various azides and alkynes, providing excellent yield of 1,4-disubstituted triazoles.

Oyster shell powder supported copper(I) used as catalyst for cycloaddition reaction.⁶² OSPs-supported CuBr proved as effective catalyst under microwave irradiation using water as solvent within short time of 15 min. The catalyst could be reused without any loss in activity even after eight cycles.

Xiong reported Cu-FBP (fish bone powder) catalyzed synthesis of 1,2,3-triazole by one pot three component coupling reaction using propargyl bromide, organic azide and organic amine under microwave irradiation using water as a solvent.⁶³ For this they cleaned fish bones under ultrasonic irradiation using hot deionised water which was then kept in ethanol to soak and dried. Crushed into powder and sieved to 100 mesh. Introduction of copper was done by adding CuBr into FBPs in DMF under N_2 atmosphere. Solvent was evaporated under vacuum, the solid product was then washed using distilled water. The presence of copper in FBPs was identified using absorption decrease in FTIR peaks due to metal-ligand bond formation. Comparison of XRD peaks indicates the presence of copper in FBPs. The catalyst was stable up to

250 °C. XPS spectrum of Cu-FBP displays characteristic peaks at 932.4 and 952.6 eV correspond to Cu2p_{3/2} and Cu2p_{1/2}, respectively. The scope of the catalyst was studied using various organic amines, propargyl bromide and benzyl azide in water triethyl amine mixture and stirred at 80 °C under microwave irradiation providing excellent yield of 1,2,3- triazole. The catalyst separated by filtration from the reaction mixture was reused and provide almost 79% yield even after 7 cycles of experiment. The copper percentage in the catalyst after 7th cycle was determined by ICP-AES and found out to be 0.71wt% which was lesser compared to fresh catalyst.

Cuttlebone@CuCl₂ was reported as heterogeneous catalyst for 1,2,3-triazole synthesis via three component reaction between terminal alkynes, organic bromides and sodium azide.⁶⁴ For the preparation of catalyst cuttlebone was powdered washed and dried at 100 °C which was then stirred with CuCl₂ in deionized water at room temperature for 10 h. In order to remove excess copper the catalyst washed with ethanol and dried at 50 °C for 12 h. For the catalytic application, the catalyst was added to a solution of phenyl acetylene, benzyl bromide and sodium azide in water which was then stirred at 40 °C. The total conversion of reactants to product, monitored by TLC, the catalyst was filtered by simple filtration and the reaction mixture was extracted using ethyl acetate and dried under vacuum.

CuAAC reaction became very popular because of its easiness in handling, wide application in different fields and good functional group tolerance. The reaction can be carried out by any Cu(I) source and in solvents including aqueous. Heterogenisation of CuAAC reaction is well accepted by grafting or depositing active copper(I) species on polymers, carbon based materials, silica etc.

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