1,2,3-Triazole and its derivatives are an important class of nitrogen containing aromatic heterocyclic compounds and have attracted a great deal of interest due to their diverse biological activities. 1,2,3-Triazoles as attractive linker units which could connect two pharmacophores to give an innovative bifunctional drug, have become increasingly useful and important in constructing bioactive and functional molecules. Triazoles are stable to acidic/basic hydrolysis and also reduce/oxidative conditions, indicative of a high aromatic stabilization. This moiety is relatively resistant to metabolic degradation [1].

The Cu(I) catalyzed 1,2,3-triazole forming reaction between azides and terminal alkynes has become the gold standard of click chemistry due to its reliability, specificity and biocompatibility. The Cu(I) catalyzed reaction is a mild and very efficient, without protecting groups and purification in many cases. The Cu(I) catalyzed azide alkyne cycloaddition (CuAAC) reaction has successfully fulfilled the requirement of click chemistry as prescribed by Sharpless [3] and within the past few years has become a premier component of synthetic organic chemistry [4]. Since there has been an enormous growth in this area, we restrict this editorial to the methods of synthesis of triazoles, which has been the subject of our attention.

The Cu(I) catalyzed azide-alkyne cycloaddition (CuAAC) reaction is regarded as the jewel in the crown of click chemistry for 1,2,3-triazole synthesis. Sharpless [3] and Meldal [5] groups have reported the dramatic rate enhancement (up to 10^6 times) and improved regioselectivity of the Huisgen 1,3-dipolar cycloaddition reaction of an organic azide and terminal acetylene to afford, regiospecifically, the 1,4-disubstituted-1,2,3-triazole in the presence of CuI catalyst.

In click chemistry, standard catalytic system uses Cu (II) salts (e.g., copper sulfate pentahydrate, copper acetate etc.) in the presence of a reducing agent, such as sodium ascorbate. For maintaining significantly high levels of the catalytic species, this reducing agent reduces Cu(II) to Cu(I). A mixture of tert-butanol and water is used as solvent, under these conditions it is not necessary to use a base to generate the copper acetylidy species. It is important to stress this solvent can also be used for lipophilic compounds. Organic solvents like THF, toluene, DCM, acetonitrile in the presence of stoichiometric amount of copper(I) salts (e.g., CuI, Cu(CH\textsubscript{3})CN\textsubscript{2}, CuBr (PPh\textsubscript{3}), or CuI/P(OEt\textsubscript{3})) and an excess of a base, usually a tertiary amine (e.g., TEA, DIPEA) can be used. There are number of additives that might increase the efficiency of the reaction, such as the tris(benzyltriazolylmethyl)amine (TBTA), triethylamine hydrochloride and the water soluble sulfonated baphenantroline [6]. The success of the CuAAC highlights the need for selective access to the complementary regioisomers, the 1,5-disubstituted triazoles. 1,5-Disubstituted triazoles can be obtained by a ruthenium catalyzed “fusion” of organic azides with alkynes. The click-chemistry reaction using Cu/ RuCl(PPh\textsubscript{3})\textsubscript{2} as catalyst in benzene to give the 1,5-disubstituted triazoles in good to excellent yields [7]. Boren and co-workers reported a study of [Cu/RuCl(PPh\textsubscript{3})\textsubscript{2}] and [Cu/RuCl(cyclooctadiene)] catalysts in the RuAAC of 1,4-disubstituted-1,2,3-triazoles in toulene at 100 °C [8] and Ru(OAc, (PPh\textsubscript{3})\textsubscript{2} catalyzed 1,4-disubstituted-1,2,3-triazole synthesis [9].

Synthesis of 1,2,3-triazole derivatives using catalytic amount of CuSO\textsubscript{4} and sodium ascorbate in THF:H\textsubscript{2}O [10] has been reported. Copper acetate and sodium ascorbate in CH\textsubscript{3}Cl:H\textsubscript{2}O also used for the synthesis of 1,4-disubstituted-1,2,3-triazole [11]. Similarly, CuI/DBU in toulene [12], NET\textsubscript{3}, CuI, THF and CuI, NET\textsubscript{3} in DMSO gave 1,4-disubstituted-1,2,3-triazole derivatives [13]. The CuAAC accelerated by using tris(triazolylmethyl)amine-based ligands. The two new ligands in 3-[4-[(bis[1-tert-butyl-1H-1,2,3-triazol-4-yl]methyl)amino]methyl]-1H-1,2,3-triazol-1-yl]propanol (BTTP) and the corresponding sulfated ligand 3-[4-[(bis[1-tert-butyl-1H-1,2,3-triazol-4-yl]methyl)amino]methyl]-1H-1,2,3-triazol-1-yl]propyl sulfonic acid (BTTPS) used for the synthesis of 1,4-disubstituted-1,2,3-triazole [14]. Instead of copper sulphate and reducing agent ascorbic acid, another copper complex [CuBr(PPh\textsubscript{3})\textsubscript{2}] used in CuAAC reaction at near or in presence of water at room temperature [15].

At room temperature, the complex [Tpm\textsubscript{2},BrCu(NCMe)\textsubscript{2}]BF\textsubscript{4}, provided the best selectivity in chloroform as the solvent for the synthesis of 1,2,3-triazole [16]. A structurally well-defined copper(I) isonitrile complex is shown to be an efficient, heterogeneous catalyst for the Huisgen azide-alkyne 1,3-dipolar cycloaddition under mild conditions in water [17]. Sulfamoyl azides were subjected to the copper catalyzed azide-alkyne cycloaddition reaction utilizing copper(I) thiophene-2-carboxylate (Cu(TC)) in dry toluene [18], nonbasic anhydrous and aqueous conditions [19]. Synthesis of bistriazoles has been achieved by using tris(benzyltriazolylmethyl)amine (TBTA), Cu, EnT(i-Pr), in acetonitrile [20].

In addition to Cu(I) catalysts and heterogeneous Cu catalysts, heterogeneous copper catalysts e.g. Cu/Cu\textsubscript{2}O nanoparticles, copper in charcoal and copper nanostructures, CuOAc\textsubscript{2}, was reported as a catalyst for the cycloaddition of azides and acetylens in the absence of sodium ascorbate. CuO(II) nanoparticles in the absence of reductant shows good catalytic activity to form 1,4-disubstituted 1,2,3-triazoles even in wet THF as well as water [21].
The cyclodaddition of a sugar azide with a sugar acetylene (Cul, i-Pr,EtN) was carried out in various ILs as well as in standard molecular solvents (toluene and DMF) to give the 1,4-disubstituted triazole-linked C-disaccharide [22]. In the presence of Cul and i-Pr,EtN in three different ionic liquids, [C₅dabco][Ni(CN)₂], [C₅dabco][Br] and Ammoeong 110 by thermal and microwave dielectric heating also reported [23]. Efficient and rapid synthesis of 1,2,3-triazole derivatives has been achieved via Huisgen’s 1,3-dipolar cyclodaddition between alkyl/arylazides and diethyl/dimethyl acetylenedicarboxylate in excellent yields under solvent-free conditions [24]. The 1,2,3-triazoles were obtained by the Cul catalyzed 1,3-dipolar Huisgen cyclodaddition reaction using t-BuOH/H₂O as reaction solvents and CuSO₄·5H₂O/sodium ascorbate as the catalyst in ultrasound irradiation [25], Synthesis of 1,2,3-triazoles by 1,3-dipolar cyclodaddition using flow chemistry also reported [26].

References