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# Click Chemistry reactions: Fundamental mechanisms review of molecular conjugations

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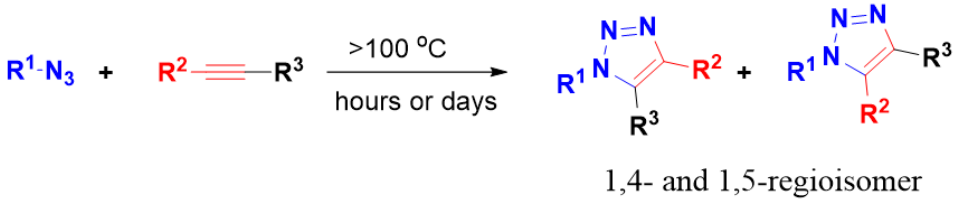
**ABSTRACT**




The click chemistry reactions are the one leading conjugation protocols where two molecules can form the bonds in simple reaction conditions and at faster reaction rate. Understanding of the different methods and catalysts used for the click chemistry reactions provides the platforms for exploration of this reaction in construction of diversity of molecules. In this review, synthesis of triazolyl heterocycles via click chemistry with their in-depth molecular pathway mechanisms have been discussed. The regioselectivity of final products and role of catalysts involved have been present with a number of examples of heterocyclic molecules.

*Keywords: Click Chemistry, Triazoles, Bioorthogonal Chemistry, Reaction Mechanisms, Catalysis.*

## INTRODUCTION

Chemistry, traditionally being the science of synthesis and structural variations of molecules, has gradually undertaken the more challenging task of biology-oriented synthesis.[1,2] The generation of molecules/molecular assemblies possessing well defined biological functions remains an extremely challenging task; immediate refinements in conventional synthetic methodologies are necessary. New and more efficient chemical reactions and methodologies, which may override the laborious protection/deprotection and purification steps in conventional total synthesis, could revolutionize the next-generation chemical and biological research.[3]

In 2009, 94% of the top grossing pharmaceuticals were nitrogen-containing molecules.[4] As pharmaceutical agents containing nitrogen atoms in their structure become increasingly common, growing interest has been generated in the synthesis of molecules that incorporate nitrogen. Therefore, synthetic chemists aim to incorporate nitrogen-containing heterocycles in their target compounds in the most efficient way. In the last decade, triazoles (1,2,3 & 1,2,4), a nitrogen containing heterocycles (**Figure 1**) have received much attention, as their intriguing physical and biological properties, as well as their excellent stability, render them promising drug core structures.[5]

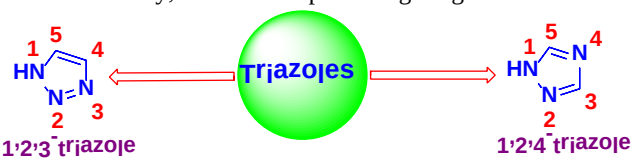



**Figure 1.** Structure of triazoles

In 1960s, Huisgen and his co-workers[6] prepared triazoles *via* 1,3-dipolar cycloaddition reaction between acetylenes and azides which was brought back into focus by Sharpless and others[7] when they established the concept of "click chemistry". This approach (click chemistry) is very popular for the joining of two/more units, mimics the approach used by nature to produce substances. Click reaction has found atremendous number of novel applications[8] after the discovery that it can be efficiently catalyzed by copper(I) (Scheme 1).[9] Moreover, the "click

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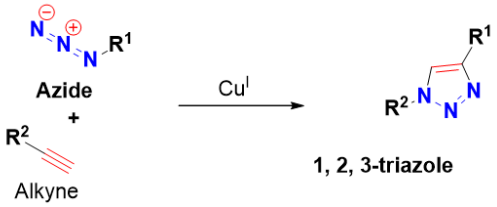
reaction" involve the simple reaction conditions, readily available reactant and reagents, no solvent require, or a benign or simple removable solvent.[9]




**Scheme 1**: Copper catalysed formation of 1,2,3-triazolyl molecule from 'click' of azide and alkyne

At first, the above definition did not true for classical Huisgen 1,3-dipolar cycloaddition, but Meldal in 2002 the first discovery of copper(I) salts catalyzing the reaction and then by Sharpless[7] allowed it to develop from a reaction under harsh conditions that formation a mixture of 1,4- and 1,5- regioisomers to a regioselective reaction that can be completed in a very short reaction time at room temperature (Scheme 2). The above definition fit for the Cu alkyne-azide cycloaddition(CuAAC) reactions that it is almost synonymous of "click chemistry". To developed new synthetic methods to construct chemically modified nucleoside, nucleotide, oligonucleoside and oligonucleotides (ODNs) for biological and nanotechnological applications and the researcher quickly accepted that CuAAC reaction is a great method to synthesized modified nucleoside, nucleotide, oligonucleoside and oligonucleotides. The features of the CuAAC reaction that are potentially useful in such applications are:

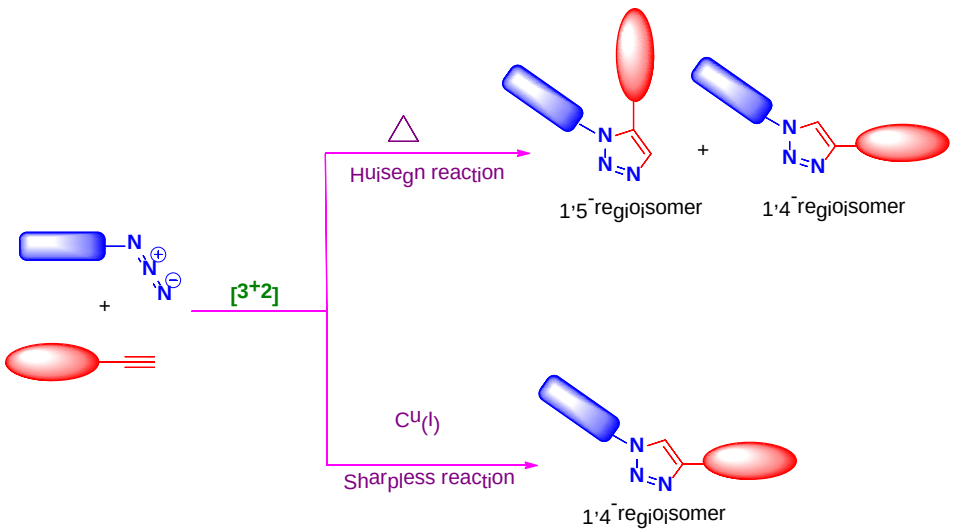
- Azides and alkynes can be attached to nucleic acids without greatly disturbing their biophysical properties.
- Azides and unactivated alkynes are almost entirely unreactive towards the functional groups normally encounteredin nature; they react only with each other.
- The triazole unit is extremely stable, and is not toxic.
- A broad range of biomolecules has been characterized to date, including peptides,[10] proteins,[11] polysaccharides,[12] and even entire viruses[13] and cells.[14]

A set of chemical reactions, known as bio-orthogonal reactions, that are orthogonal to most functional groups in biological systems has so far shown promising applications in biological research.[15] Of these reactions, the Cu(I)-catalyzed version of the Huisen 1,3-dipolar cycloaddition reaction between azides and terminal alkynes for the construction of trizoles, referred to as a "click chemistry reaction", was defined by nobel laureate KB Sharpless and associates in 2001. Click chemistry has recently emerged to become one of the most powerful tools in drug discovery,[16–18] chemical biology, and proteomic applications.[19] In recent years, the design and synthesis of pharmacologically relevant heterocyclic molecules by combinatorial techniques have proven to be a promising strategy in the search for new pharmaceutical lead structures. Click chemistry is one of the powerful reactions for making carbon−heteroatom−carbon bonds in aqueous environment with a wide variety of chemical and biological applications in various fields.[20–22]

In this review we describe the fundamentals of the click chemistry, mechanisms of the click reactions and its uses across synthesis of diverse heterocycles and biological conjugations i.e. biorthogonal chemistry, focusing on synthetic strategies and briefly describing important biological applications. The presented review covers published material since 1893, until the beginning of 2016.

## CLICK CHEMISTRY

1,3-dipolar cycloaddition reactions and Nucleophilic ring opening are the most widely studied click reactions to date. Preparation of potential drug candidates by these reactions utilizes building blocks such as acetylenes and olefins. These starting materials are readily available in Nature[23] or can be accessed through "steam cracking" of alkanes in the petrochemical industry and can be functionalized by oxidative or addition reactions. Several well-known types of reactions have been classified as 'click' reactions (Fig. 2). These include, but are not limited to, cycloadditions of unsaturated species (Diels-Alder cycloadditions and 1,3-dipolar cycloadditions, Fig. 2 Cand D), additions to unsaturated carbon-carbon bonds (epoxidations, sulfenyl halide additions, Fig. 2 A), non-aldol type carbonyl




**Scheme 2**. 1,3-Dipolar Cycloaddition between Azides and Alkynes

chemistry (Fig. 2 D), and nucleophilic substitution chemistry (ring-opening reactions of epoxides, aziridines etc., Fig. 2F). Sequential performance of two different types of 'click' reactions, for instance a Huisgen cycloaddition followed by a Diels-Alder cycloaddition, has been termed a 'double click' reaction.[24–27] Philosophy of 'click' chemistry can be explained by the following statement: "all searches [for new drugs] must be restricted to molecules that are easy to make".

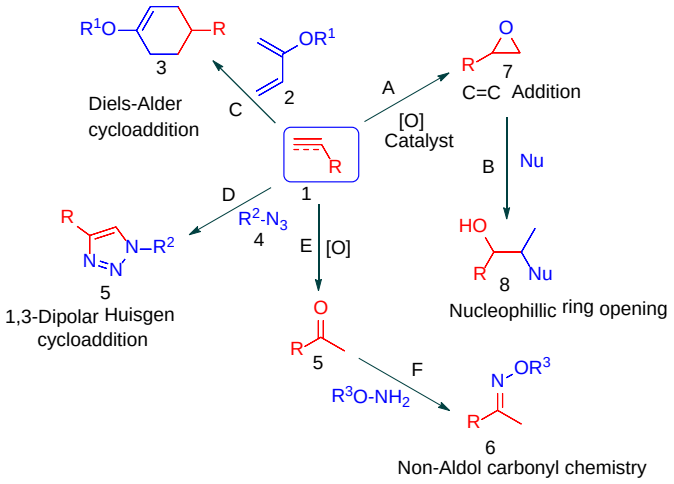
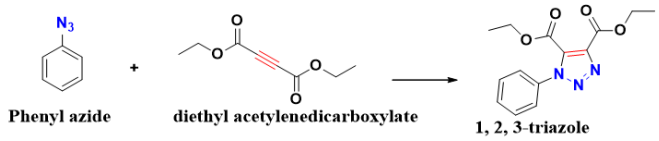



**Figure 2**. 'Click' reactions

## 1,3-Dipolar Huisgen Cycloaddition[3+2] (Triazole) Background

A chemical reaction between a 1,3-dipole and a dipolarophile to form a five-membered ring is known as 1,3-dipolar cycloaddition reaction. Already in 1893, Michael discovered a synthesis of 1,2,3-triazoles(also v-triazole for vicinal)[28] by reacting phenyl azide with acetylene dicarboxylic ester **(Scheme 3)**. Huisgen classified this type of reaction as [3+2] 1,3-dipollar cycloaddition *i.e.* the concerted addition of a 1,3-dipole to a multiple bond.[6,29,30] The 1,3-dipole is characterized by the presence of an electrophilic atom, having an electron sextet and a formal positive charge, as well as a nucleophilic atom, having an electron octet and a formal negative charge, with one in the 1-position and the other one in the 3-position (1c, Fig. 3).




**Scheme 3**: Synthesis of 1,2,3-triazoles

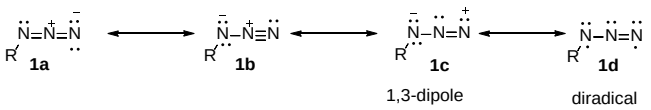



**Figure 3**. Selected contributing structures of an organic azide.

Woodward and Hoffmann in 1969 classified the 1,3 dipolar cycloaddition as an example of pericyclic reactions, which is thermally allowed due to symmetrically and geometrically favorable [$_{\pi}4_s$ +$_{\pi}2_s$] interactions. Nevertheless, rate of reaction and regioselectivity remained unexplained until Sustmann *et al*.[31,32] and Houk *et al*.[33–35] applied a frontier molecular orbital (FMO) model to the reaction.[36,37] FMO model is based upon perturbation theory.[38–41] Concisely, interaction between highest occupied molecular orbital (HOMO) of one reactant (1,3-dipole/dipolarphile) and the lowest unoccupied molecular orbital (LUMO) of the other reactant (1,3-dipole/dipolarphile) with the reaction rate depending on the corresponding energy gap. Therefore, rate of reaction will increase if HOMO-raising electron-donating group (EDG) as well as a LUMO-lowering electron-withdrawing group (EWG). Moreover, EDGs and EWGs will polarize particularly the π system, which influences the regioselectivity because the interaction occurs in such a way that the orbitals with larger orbital coefficients overlap (Fig. 4). Hence, [3+2] cycloaddition reaction of phenyl azide and phenylacetylene yields the 1,4- and 1,5-disubstituted 1,2,3-triazoles (regioisomers) in a 1 : 1 ratio,[42] while electron-deficient and electron excessive alkynes favor the formation of the 1,4-disubstitued triazole(dipole-HOMO control, A) and the 1,5-disubstitued triazole (dipole-LUMO control, B), respectively.[43–46]

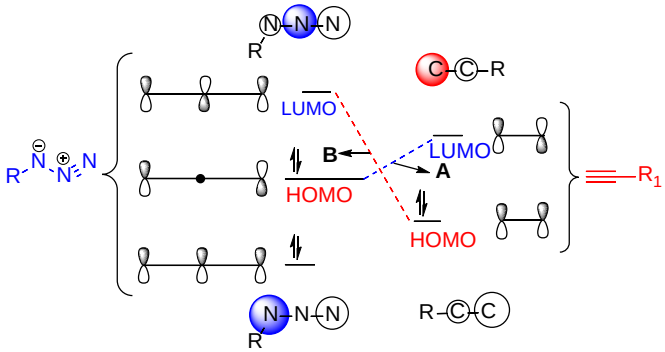
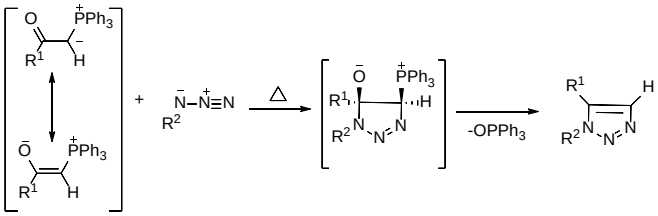



**Figure 4:** FMO interactions between azide and alkyne (R = Ph)

Remarkably, [3+2] cycloaddition reactions between phenyl azidesand α-keto phosphorous ylides as alkyne equivalents followed by elimination of phosphine oxide yields 1,5-disubstituted1,2,3-triazoles exclusively (**Scheme 4**).[47] In cycloaddition reaction, the rate of reaction depends on the solvent, and the reaction is controlled by dipole-LUMO, azides

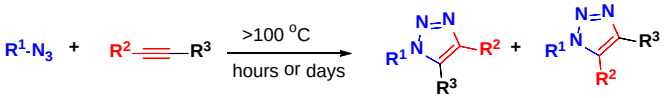



**Scheme 4**. 1,3-Dipolar cycloaddition with a-keto phosphorous ylides.

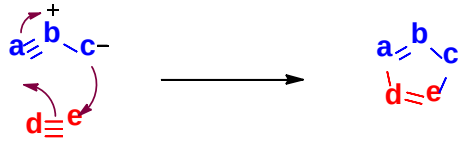
which have electron poor gives shorter reaction time. Importantly, in this reaction substituent have a free choice for the formation of 1,2,3-triazole as they do not control the regioselectivity. Moreover, ynamines were reported to allow the exclusive formation of 1,5-disubstituted 1,2,3-triazoles.

In 1963, Huisgen[48] throughly studied azide alkyne cycloaddition reaction and carried out this reaction using heat source. This reaction suffers a high activation barrier and consequently demands usually elevated temperature and pressure. During the course of his investigation he explored various substituted/unsubstituted alkynes for 1,3-dipolar cycloaddition and observed that a mixture of 1,4- and 1,5-regioisomeric 1,2,3-triazole product was obtained when an alkyne is unsymmetrically substituted or terminal (**Scheme 5A**).[48–50] In true since Huisgen was the first who classified and defined[51] and proposed mechanistic (**Scheme 5B**)[52] of 1,3-dipolar cycloaddition.

A) **Regiochemistry of the 1,3-dipolar cycloaddtion**




B) **Cycloaddition reaction mechanism**




**Scheme 5**: A) Regiochemistry of the 1,3-dipolar cycloaddition, B) Mechanism

Sustman, in 1971 solved the mystery of formation of 1, 4 & 1, 5-regioisomers.[31,53] He proposed the difference between HOMO-LUMO energy level of both azides and alkynes to be responsible for the lack of regioselectivity. The difference between HOMO-LUMO energy levels of both azides and alkynes are very close in magnitude and hence both dipole-HOMO and dipole-LUMO interact simultaneously and subsequently give a mixture of regioisomers (**Figure 2**).

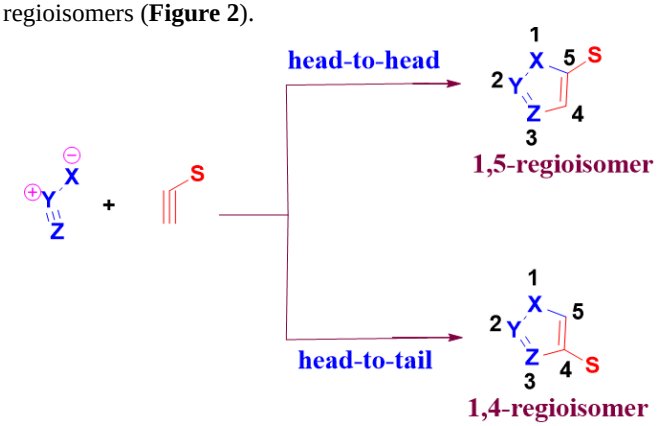



**Figure 5:** Regioisomeric pathways for 1,3-dipolar cycloaddition

Later, it was proposed that the interaction between unsymmetrical reagents in a 1,3-dipolar cycloaddition reaction can give two isomeric adducts depending on the relative position of the substituent in the cyclo adduct. Head-to-head interaction between azide and alkyne produces 1,5-regioisomer while head-to-tail interaction produces 1,4-regioisomer (**Figure 5**).[54,55]

Iso-oxazole is prepared from the alkyne and a nitrile oxide, this reaction is also 1,3-dipolar cycloaddition reaction. A very efficient and practical method has been developed by Fokin and his coworkers that allow to synthesis of 3,5-disubtituted iso-oxazole in a one pot procedure without the formation of regioisomers (**Figure 6**).

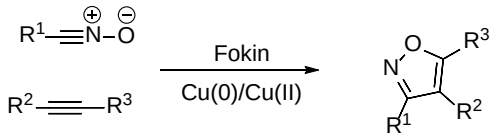



**Figure 6**: Iso-oxazole formation in 1,3-dipolar cycloaddition manner

## TYPE OF TRIAZOLE (1,2,3 AND 1,2,4-TRIAZOLE)

Presence of three nitrogen heteroatoms in five-membered ring systems defines as interesting class of compounds, the triazoles. These may be of two types, the 1,2,3-triazoles or υ-triazoles (I) and the 1,2,4- triazoles or δ-triazoles (II) (Figure 7).

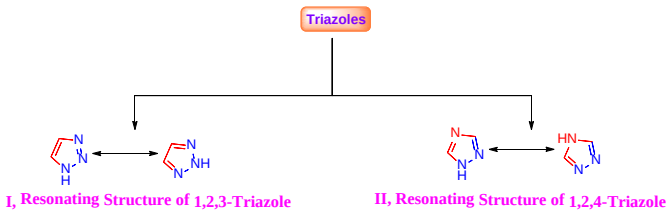
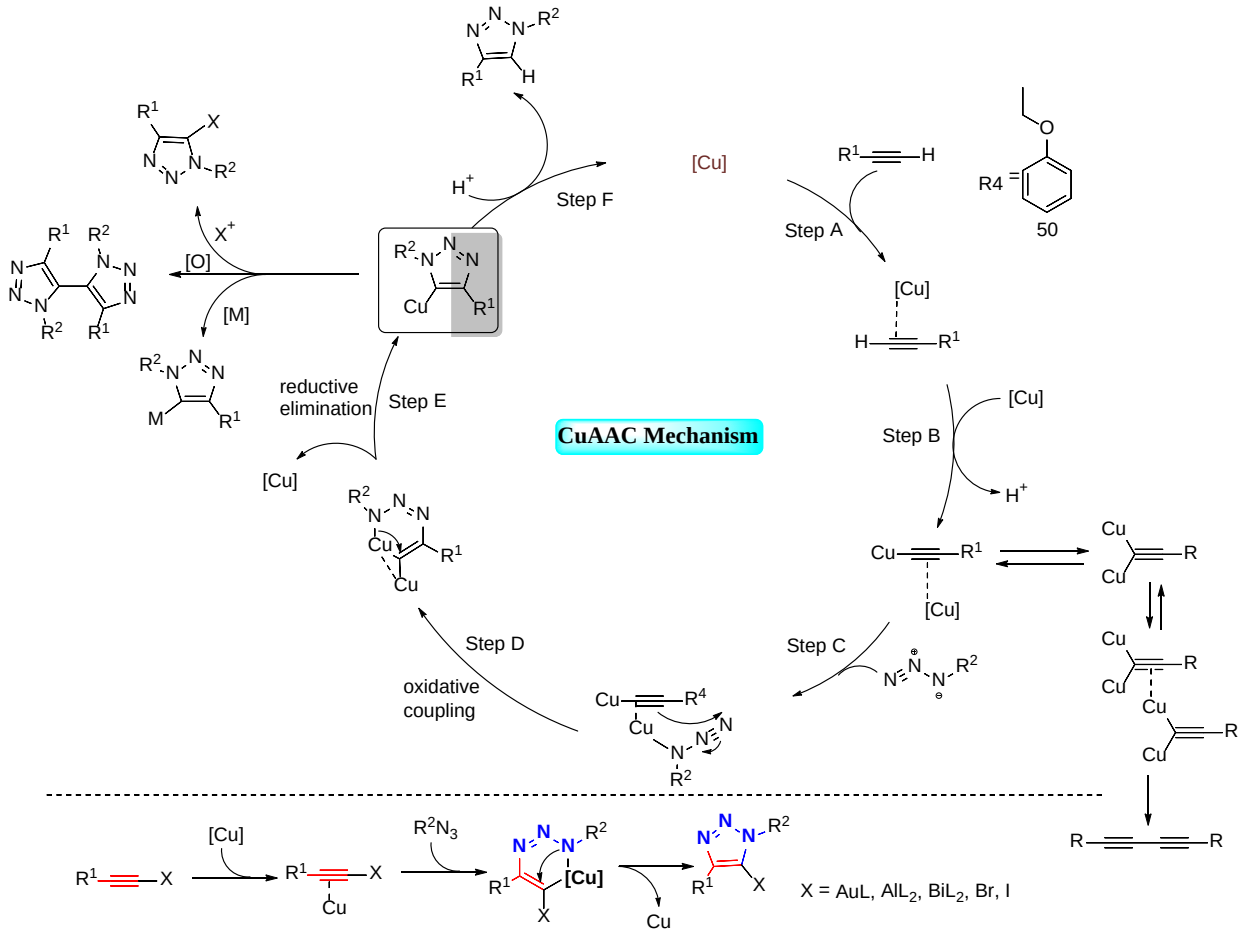



**Figure 7**. Types of triazoles

### Copper-catalyzed azide–alkyne cycloaddition

The Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC) reactions discovered by Meldal et al. and Fokin, Sharpless et al., yields 1,2,3-triazoles most efficiently and with avery high regioselectivity for the 1,4-regioisomer.[56–59] A collection of mechanistic key aspects based on computational[60–62] and experimental studies[63–65] is collected in Scheme 6. Firstly, a Cu(I) species undergoes p coordination of an alkyne (A), which greatly increases the CH-acidity of the terminal alkyne (pKa drops from B25 to B15) and allows the subsequent formation of a s-coordinated Cu(I) acetylide with the activated alkyne (B) in aqueous media even without an additional amine base. DFT calculations suggest that a second Cu(I) remains p-coordinated at the a-carbon of the s-bound acetylide resembling the known m-coordination mode of Cu(I) acetylides.[66] In the next step, coordination of an azide at the p-coordinated Cu(I) center occurs (C). This is corroborated by the absence of the subsequent cycloaddition when using a preformed s-bound Cu(I) acetylide without additional Cu(I). In principle, coordination of the organic

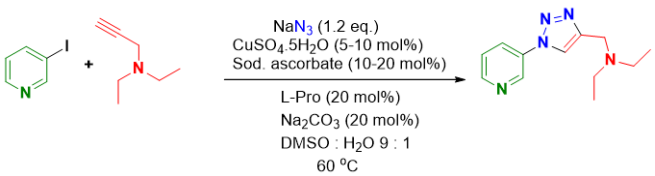



**Scheme 6** Proposed mechanism of the CuAAC (top) and CuAXAC (bottom). ([Cu] denotes a copper fragment that varies in the number of ligands and in the formal oxidation state.)

azide can occur via both the substituted or the terminal nitrogen, but, in contrast to the p-accepting, terminal nitrogen, the p-donating, substituted nitrogen is expected to increase the electron density on the metal center,[67] which would facilitate the subsequent oxidative coupling (D).

The observed selectivity for the 1,4-regioisomer may be explained by the preference for Cu(I) p coordination at the a-carbon of the acetylide, which directs a nucleophilic attack of the b-carbon at the terminal, electrophilic nitrogen of the coordinated azide upon oxidative coupling.[68] As a result of the latter, rate-limiting step, a six-membered metal cycle is formed including a m-alkenylidene. According to computational methods, this intermediate is stabilized by a geminal bimetallic coordination,[69,70] while a potential monometallic cupra-cycle, which was postulated earlier, would represent an unfavorably strained structure possessing excessive electron density. Recently, the transient formation of the bimetallic cupra-cycle was corroborated by a Cu63/Cu65 crossover experiment, which implies that the six-membered ring can isomerize. It should be noted that the formal oxidation states of the two Cu centers are not given as it remains unclear whether Cu(III)[71] is intermediately formed or if both metal centers cooperate in the oxidation step. Furthermore, improved activity has been observed when using a bimetallic, mixed-valent Cu(II)/Cu(I) catalytic system.[72] Ultimately, ring contraction and Cu(I) extrusion via reductive elimination (E) affords the Cu(I)-bound triazolide in a highly exothermic process. In aqueous media, the Cu(I) triazolide then readily undergoes protonolysis (F) liberating the free triazole and allowing the Cu(I) to re-enter the catalytic cycle.

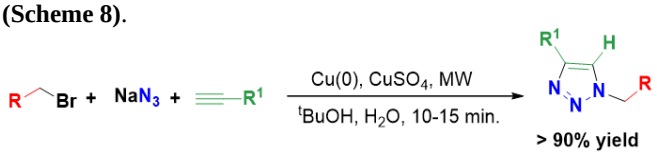
In 2004, Fokin and his coworkers[73] reported one pot synthesis of 1,4-disubstituted 1,2,3-triazole directly from alkyl and aryl halides, sodium azide and terminal alkyne by *in situ* generation of azide. This procedure is safe and efficient for the synthesis of triazoles which does not require isolation of azide intermediate (**Scheme 7**).




**Scheme 7:** One pot synthesis of triazole

## MICROWAVE-ASSISTED COPPER-CATALYZED ONE POT SYNTHESIS OF TRIAZOLES

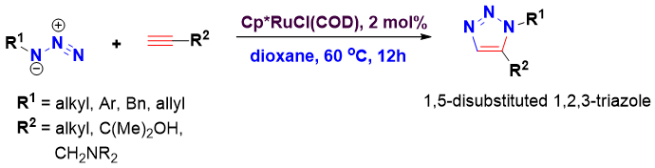
In 2004, Erik Van der Eycken and his co-workers had reported a microwave assisted procedure for the synthesis of various 1,2,3-triazole derivatives using copper (I) catalyst.[74] This synthetic approach only yielded the 1,4-disubstituted triazole isomer but reduces the reaction time tremendously compared to the previous CuAAC approach utilizing conventional heating **(Scheme 8)**.




**Scheme 8.** Microwave assisted synthesis of triazoles

## RUTHENIUM CATALYZED SYNTHESIS OF 1,5-DISUBSTITUTED TRIAZOLES (RUAAC)

In 2005, Fokin and his co-worker introduced ruthenium cyclopentadienyl complexes for the synthesis of triazoles.




**Scheme 9**: Ruthenium catalyzed reaction

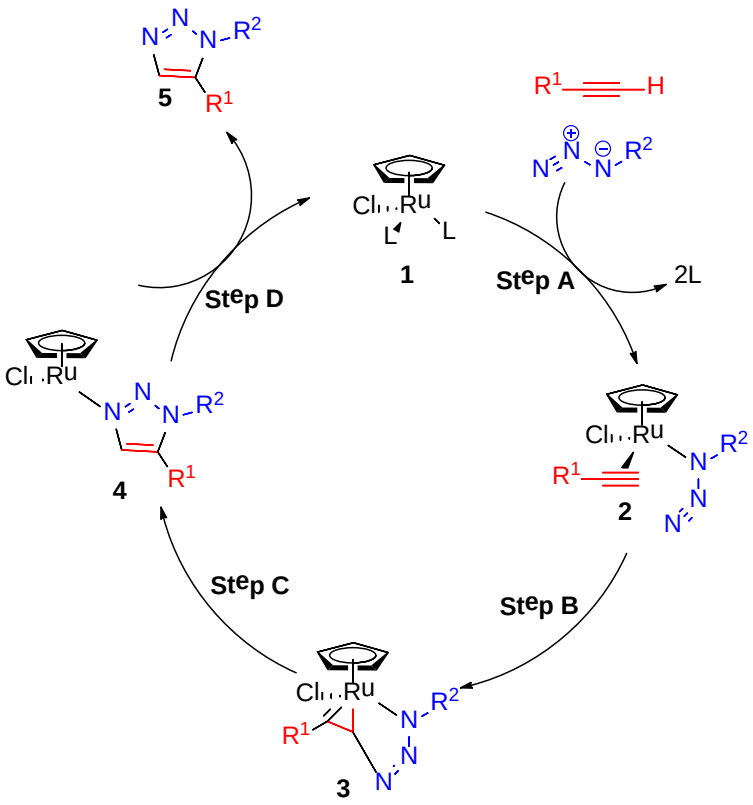



**Figure 7**: Proposed mechanism in the Catalytic Cycle of the RuAAC Reaction

Ruthenium catalyzed reaction however, yielded complimentary regio 1,5-disubstituted isomers from azides and terminal alkynes and internal alkynes (Scheme 9).[75]

This sister process, designated as RuAAC (ruthenium-catalyzed azide–alkyne cycloaddition), is mechanistically quite distinct from its cuprous cousin, although the underlying activation of the alkyne component appears to be fundamentally similar: the nucleophilicity of its $\pi$-system is increased by the back donation from the ruthenium center. While the scope and functional group compatibility of RuAAC are excellent,[76] the reaction is more sensitive to the solvents and the steric demands of the azide substituents than CuAAC (Figure 6). In 2008, Fokin reported the mechanistic detail of RuAAC reaction.

Building on the known ability of the [Ru(Cp)Cl] (Cp = cyclopentadienyl) fragment to catalyze alkyne cyclotrimerization,[77] its catalytic activity in the azide–alkyne cycloaddition was anticipated by Jia, Fokin et al.[75] The strongly electron donating, anionic Cp ligand is required to facilitate the intermediate ruthenium oxidation.[76] Although [Ru(Cp)Cl] only showed modest reactivity and regioselectivity, the use of the pentamethylcyclopentadienyl (Cp*) derivative greatly improved both the activity and, remarkably, the selectivity for the formation of 1,5-disubstituted 1,2,3-triazoles.[78,79] Interestingly, while only a few examples for the conversion of internal alkynes have been reported for the CuAAC,[80,81] both terminal and internal alkynes are in principle equally suited substrates for the RuAAC.[82–85] Based on DFT calculations, a potential RuAAC mechanism was formulated by Lin, Jia, Fokin et al. and further detailed by Nolan et al.[86] (Scheme 9, exemplarily shown for a terminal alkyne). Initially, a coordinatively unsaturated 16-electron species can be used directly or has to be generated by ligand dissociation. Subsequently, ligand substitution via an addition–elimination sequence (G, H) provides the catalytically active species featuring a p-coordinated alkyne. Then, coordination of the azide via the substituted nitrogen (I) is energetically favored in this case and the resulting p donation may facilitate the subsequent oxidative coupling (J). Accordingly, nucleophilic attack of the alkyne at the terminal nitrogen of the azide proceeds with a small activation barrier and affords a six-membered ruthenacycle. Based on the computations, this species involves a metala-cyclopropene,[87] which is in equilibrium with a vinyl complex. The latter is slightly more stable due to reduced strain but not prone to reductive elimination (K) and, therefore, represents a resting state. In the subsequent, rate-limiting step (K), the six-membered ruthenacycle contracts upon reductive elimination with the extruded Ru(II) remaining p-coordinated to the triazole. After isomerization to the N-bound complex (L), the triazole is liberated by substitution with an alkyne (M, N) and the catalytic cycle can start anew. He proposed that the displacement of the spectator

ligands (Fig. 7, Step A) produces the activated complex 2, which is converted, via the oxidative coupling of an alkyne and an azide (Fig. 7, Step B), to the ruthenacycle 3. This step controls the regioselectivity of the overall process. The new C-N bond is formed between the more electronegative and less sterically-demanding carbon of the alkyne and the terminal nitrogen of the azide. The metallacycle intermediate then undergoes reductive elimination (Fig. 7, Step C) releasing the aromatic triazole product and regenerating the catalyst (Fig. 7, Step D) or the activated complex.

## CONCLUSION

In conclusion, the click chemistry reactions are robust and are capable of introducing diversity in the synthesis of heterocyclic molecules. The conjugation of two molecules can be achieved at room temperature or ambient reaction conditions using easily available reagents. The reactions proceed by radical or biradical entities supported by the transition metal catalysts. The copper catalyzed reactions more frequently used in click chemistry. The click chemistry has revolutionized the field of heterocyclic chemistry as well as application in biomolecules conjugations.

## CONFLICT OF INTEREST STATEMENT

Authors do not have any financial or academic conflict of interest for this work.

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