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**Click Chemistry: copper, ruthenium catalyzed and photoinduced  
azide-alkyne cycloaddition**

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**Abstract**

Click chemistry is an extremely powerful method for covalent conjugation of molecular entities quickly and efficiently. Click chemistry knitted the threads between two different molecular entities that have created interesting structures for more than 15 years with a wide range of applications, including in interesting fields such as synthetic chemistry, medicinal science, biochemistry, material science, pharmacology and catalysis. Due to the schematic modification and incorporation of azide and alkyne groups within biological scaffolds, azide-alkyne cycloaddition (AAC) is still the leading methodology among click chemistry. This review focuses on the mechanism, scope, and applications of the CuAAC reaction, RuAAC reaction, and the recent development of photo-click reactions, and their applications cover the literature from the last ten years.

**Keywords:** Click chemistry, Azide-alkyne cycloaddition (AAC), medicinal chemistry, synthetic chemistry.

**1. Introduction**

Huisgen's 1,3-dipolar cycloaddition reaction of organic alkynes and azides yields covalently connected compounds through a 1,2,3-triazole is one of the most important transformations in synthetic organic chemistry shown by the wide range of targets that this technology allows (Huisgen, 1963a). Though the reaction was found in the early twentieth century, it did

not get much attention until the 1960s, when a small group of scientists investigated it and completed detailed research to determine the reaction's mechanism (Huisgen, 1963b, 1989; Huisgen et al., 1967; Tornøe et al., 2002). Azide and alkyne functions may be readily inserted into the scaffold of big organic structures with biological significance. Furthermore, most functional moieties of

other biological substrates (such as proteins, lipids, and nucleic acids) are chemically inert to these groups, allowing them to be viewed as bio-orthogonal and biocompatible. For more than four decades, however, the reaction's applicability was limited by the need for lengthy reaction durations, high temperatures, and low regioselectivity (both the 1,4- and 1,5-isomeric adducts are formed). The strong chemical stability of canonical alkynes accounts for the slow reaction rate. While not bio orthogonal, only electron-deficient alkynes may be used as substrates for free non-catalyzed cycloaddition reaction by conjugate addition processes. The Meldal (Torne et al., 2002) and Sharpless (Rostovtsev et al., 2002) laboratories independently demonstrated the ability of copper(I) salts to accelerate this cycloaddition at room temperature or with moderate heating, enhancing exclusively the 1, 4-regioisomer with minimal workup and purification, in 2002.

Sharpless et al., (2001) coined the phrase "click chemistry" in 2001 and it quickly became a popular discussion subject. Sharpless outlined a set of strict criteria for determining whether or not a response is a "click" reaction. The reaction must be reciprocal and wide in scope, with good to excellent yields, appropriate byproducts that may be eliminated using non-chromatographic techniques, and stereo specificity (but not necessarily enantioselective). There are four major categories of click reactions, which include (a) cycloadditions (e.g., 1,3-dipolar or Huisgen's cycloadditions, Diels-Alder cycloadditions, and so on), (b) nucleophilic substitutions (e.g., nucleophilic opening of spring-loaded rings), (c) additions to the carbon-carbon multiple bonds (e.g., epoxidation, aziridination, dihydroxylation/aminohydroxylation, Michael addition,

etc.) and (d) carbonyl chemistry of non-aldol type transformations.

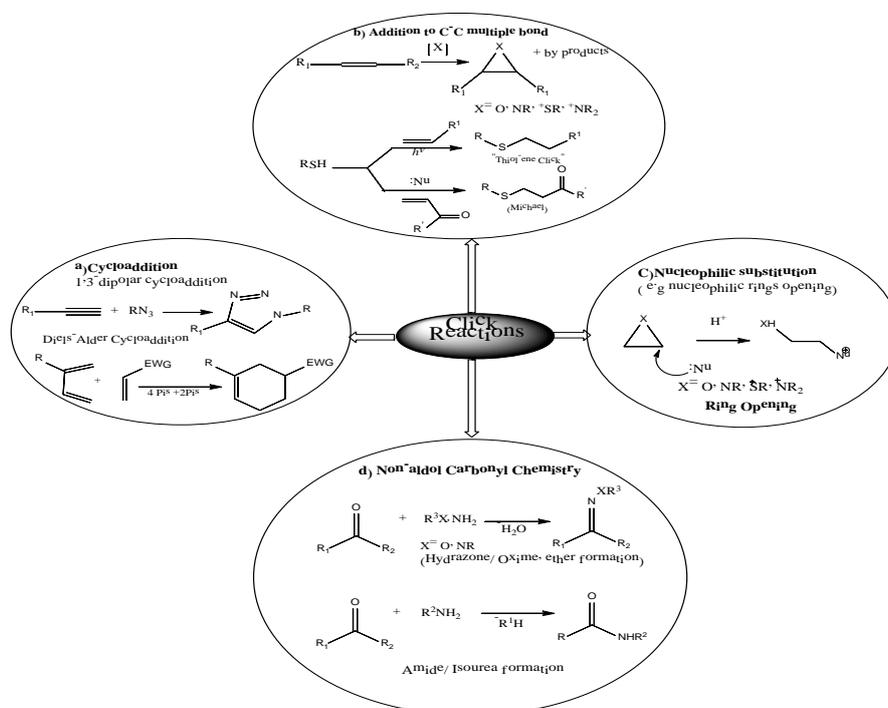
Because it is simple to perform, broad in scope, high yielding, highly efficient, and regioselective, and requires readily available alkynes and azides as starting materials and reagents such as copper catalysts, the copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction meets all of the stringent criteria of the Sharpless click chemistry concept. It generates no inoffensive byproducts and is conducted in easily removable or benign solvent (e.g., H<sub>2</sub>O). Therefore, this reaction is classified as an ideal click reaction and is often called Cu-catalyzed click chemistry (CuAAC or click chemistry). It is undoubtedly believed to have several uses. CuAAC combines organic azides and terminal alkynes in a regioselective way to afford the corresponding 1,4-disubstituted 1,2,3-triazoles exclusively, under relatively moderate conditions, unlike the uncatalyzed cycloaddition of azides and alkynes, which results in a mixture of 1,4- and 1,5- triazole regioisomers at higher temperatures. The Cu(I)-catalyzed azide-alkyne cyclo-addition has been widely used in biology, biochemistry, and biotechnology (Pickens et al., 2018). Researchers have used azide-alkyne cycloadditions on a variety of biological substrates, developed high-efficiency and diverse reactivity catalysts (Wang et al., 2016), discovered that some metal complexes favour the formation of the 1,5-disubstituted adduct, and investigated "activated" alkyne groups for rapid triazole formation in the absence of metal catalysts (Agard et al., 2004; Wang et al., 2016).

The ruthenium-catalyzed 1,3-dipolar azide-alkyne cycloaddition (RuAAC) reaction yielded a regioisomer of the CuAAC product only, namely 1 5-disubstituted triazole, was another breakthrough in the realm of click

reactions in 2005. Furthermore, RuAAC supported a broad range of functional categories. Although the usage of ruthenium-catalyzed azide-alkyne cyclo-addition (RuAAC) is not as common as the CuAAC reaction, reports of its application are fast increasing. The main publications of the ruthenium-catalyzed azide-alkyne cyclo-addition [RuAAC] from 2005 (Li-Zhang et al., 2005) and 2008 (Boren et al., 2008), as well as the synthetic development, mechanistic research, and application of the RuAAC reaction up to September 2016 are included in this review.

Many basic life processes, such as photosynthesis, utilise sunlight as energy to fuel complicated biochemical cascade reactions in nature (Stowell et al., 1997). Chemists have successfully used light to induce important chemical transformations in their attempts to synthesise complex compounds and biomolecular conjugates to create complex molecules and biomolecular conjugates inspired by nature (Hoffmann, 2008).

The combination of benign photochemical processes and click chemistry has ushered in a new era of light-triggered click reactions, also known as photo click chemistry, which allows for the spatiotemporally controlled synthesis of a wide range of molecular structures, conjugates, and networks in complex systems. In the last decade, there has been an increase in the number of photoclick reaction described in the literature. Photo-induced tetrazole-alkene cycloadditions (Herner et al., 2016), light-triggered hetero-Diels-Alder reactions (Arumugam et al., 2011), light-triggered azide-alkyne cycloadditions (Poloukhine et al., 2009), photoinduced sydnone-alkene/ alkyne cycloadditions (Zhang et al., 2018), and light-triggered oxime ligation reactions (Pauloehrl et al., 2012). This review emphasises the historical background and mechanistic research of cycloaddition-based light-triggered click reactions and their many applications in chemical biology and materials sciences.



**Scheme 1. General Classification of Click Reactions.**

## **2. Generalities on click chemistry**

### **2.1 Solvents and additives Catalysts**

The uncatalyzed alkyne-azide cycloaddition requires extended reaction durations and high temperatures to create a mixture of triazoles' 1, 4- and 1,5-regioisomers. Click-inspired CuAAC, on the other hand, provides one regioisomer, namely 1,4-disubstituted triazole, with an associate at an exceedingly fast rate of reaction,  $10^7$  times faster than the reaction permitted in the absence of a catalyst.

The three most typical simple click conjugation procedures are (i) direct use of a copper(I) supply, (ii) varied formation of copper(I) by reduction of a copper(II) supply, and (iii) eventually oxidation of Cu(I) from the basic type. All three techniques are widely utilised to produce a broad range of different triazoles for a wide range of applications. Water is connected with an appropriate solvent choice for the CuSO<sub>4</sub>/ sodium ascorbate catalysed click procedure, which produces a click galvanised triazole product in high yields and with excellent regio-selectivity. However, adding copper(I) ions to the reaction media without reducing agents may induce the azide-alkyne cycloaddition. In essence, the protocol calls for deoxygenated conditions in the presence of mixed aprotic organic solvents such as THF, CH<sub>3</sub>CN, and CH<sub>2</sub>Cl<sub>2</sub>, as well as dissolving agents and comparable alternative solvents. The use of Cu(acac)<sub>2</sub> as a catalyst for forming 1,4-disubstituted triazole-containing disaccharides and trisaccharides from their corresponding glycosyl azides and terminal alkynes was recently reported. In addition, some common bases, such as triethylamine (NEt<sub>3</sub>), 2,6-lutidine, diisopropylethylamine (DIPEA), and base have been used to boost the reaction potency with these reagents. Curiosity aside, it has been found that PhCOOH may aid in the protonation of the

copper triazolide intermediate. As a result, it has been acknowledged as a suitable addition for the click purpose (Shao et al., 2010, 2011) due to different catalysts. However, to develop a catalyst that is both economical and selective, as well as applicable in some applications, it is necessary to look for one that has a variety of advantages, including adequate stability, heterogeneous nature, low cost, recyclability, reduced latent period, and, most importantly, low economic loading. Furthermore, keeping the catalyst concentration constant during the reaction is required since the reaction medium lacks suitable catalyst stability. Instead, some ligands that stabilize the chemical change system are used for additional rate acceleration.

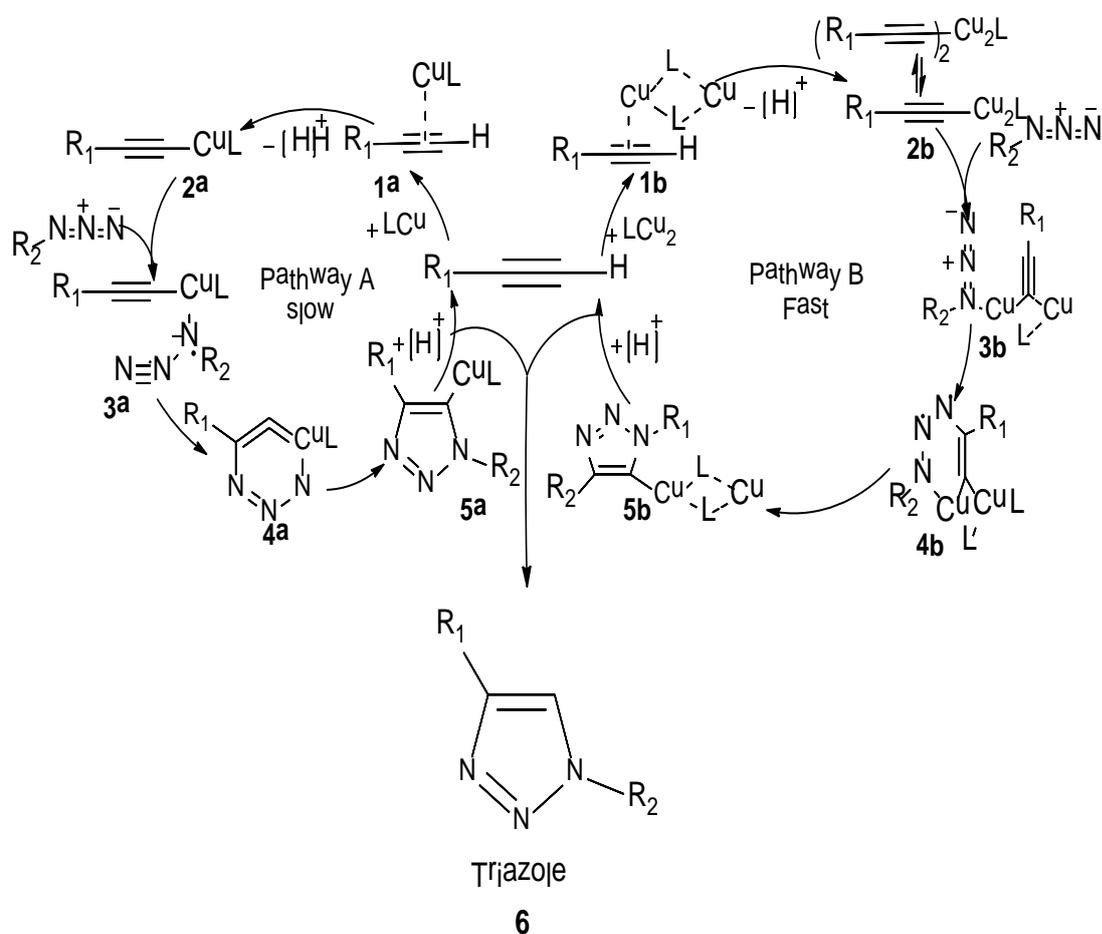
## **3. Copper catalysed azide-alkyne cycloaddition (CuAAC)**

### **3.1 Mechanism of the CuAAC Reaction**

The copper-catalyzed azide-alkyne cycloaddition (CuAAC) is the most researched and well-known metal particle catalysed Huisgen reaction, and it is also the easiest to perform. In contrast to the non-catalyzed version, where the choice between a stepwise or contrasting process is determined by the intentional cluster attached to the reactive moiety, the mixed route is removed in CuAAC, favouring the stepwise technique. Due to the combination of DFT calculations and kinetic studies, it has been discovered that there are two plausible competitor mechanisms in CuAAC for triazole formation: a slow method catalysed by a mononuclear Cu species and an additional kinetically favourable route promoted by the formation of a dinuclear Cu catalyst (Scheme 2) (Himo et al., 2005; Jin et al., 2015). The energy distinction may strengthen the experimental evidence that CuAAC reactions move more quickly in

liquid circumstances. As a result of the metal-alkyne adduct formation, acetylene's acidity is reduced by about 10 units, resulting in deprotonation, which allows the Cu-acetylide adducts (2a and 2b) to be accessible under liquid circumstances. During the last phase, the ring contracts, resulting in the formation of the triazolyl-copper by-product, which then undergoes protolysis, resulting in the formation of the triazole product and the completion of the

chemical change cycle (5a and 5b) (Scheme 2). Therefore, CuAAC is expected to have a variety of reaction mechanisms. However, a small variation of the dinuclear catalyzed pathway, pioneered by Fokin et al., has recently been demonstrated by uninflected a key dinuclear intermediate from the cycloaddition between Cu-phenylacetylide and benzylazide, as previously reported (Jin et al., 2015).



**Scheme 2.** Both of the following competitive pathways for the Cu(I) Catalyzed Azide-Alkyne Cycloaddition (CuAAC) have been identified: Processes using a Mononuclear Cu Species (Pathway A) and the formation of a Dinuclear Cu Catalyst (Pathway B) are both slow and involve the formation of a dinuclear Cu catalyst.

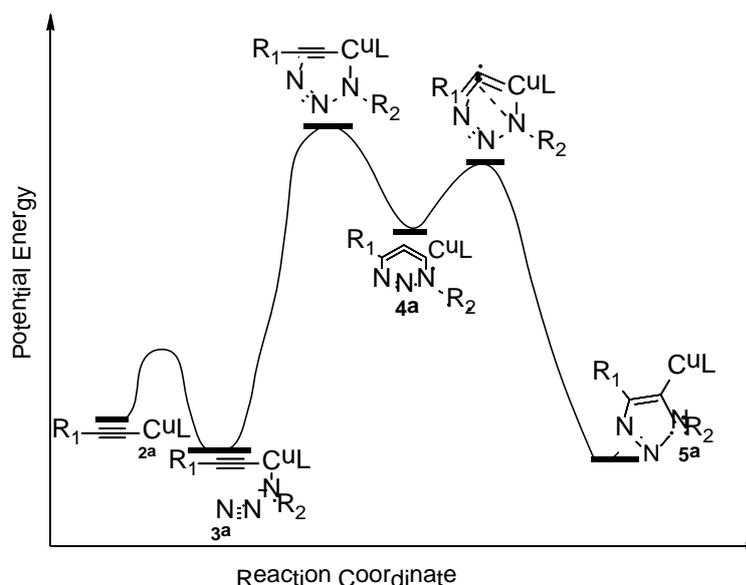


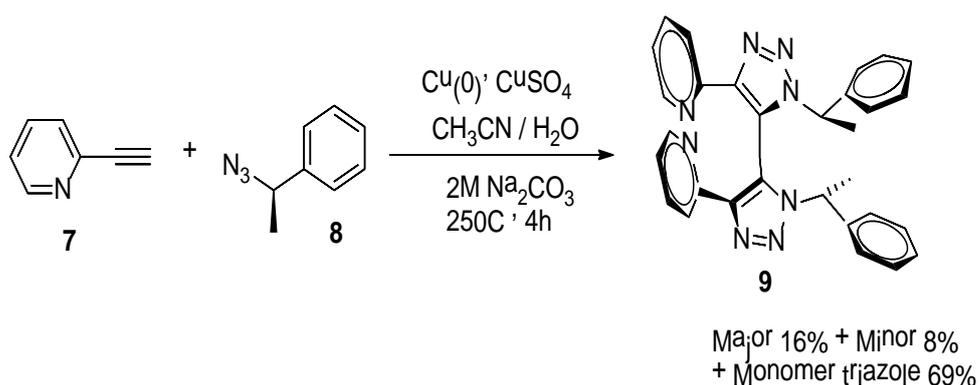
Fig. 1. K. B. Sharpless suggested an energy profile for the reaction of copper(I) acetylides with organic azide based on DFT investigations (L is CH<sub>3</sub>CN or H<sub>2</sub>O).

#### 4. Cu(I) catalysed triazole synthesis side reactions

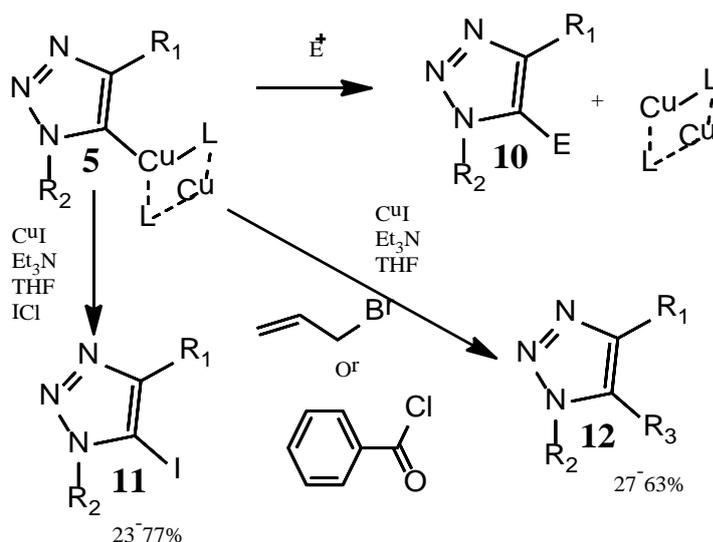
##### 4.1 Cu(I) Triazole Complexes: Side Reactions and Oxidative Couplings

The hydrolytic cleavage of the Cu(I)- a bound end product of the catalytic cycle to renew active catalyst and release the triazole is usually used to assure the

quantitative production of the 1,4-disubstituted triazole. However, during the development of the liquid CuSO<sub>4</sub>/ascorbate version of the reaction, Rostovtsev et al., (2002) detected small quantities of a by-product found to be the bistriazole produced by oxidative coupling.



Scheme 3. Inorganic bases and air may stimulate oxidative coupling to yield up to 90% bis-triazoles.

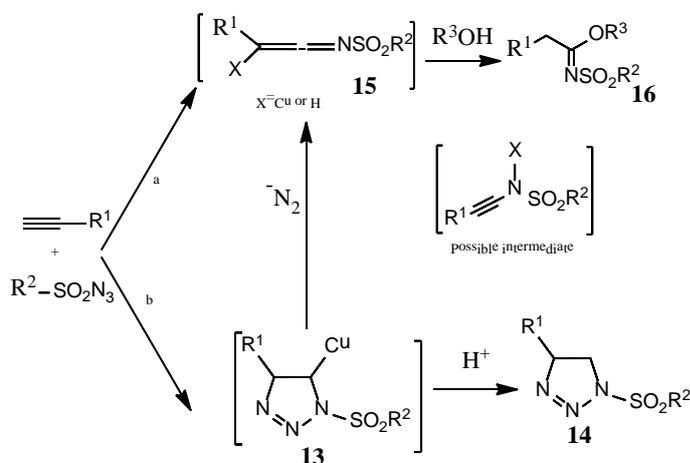


Scheme 4. Reaction of Electrophiles with Copper-Triazole Adduct.

#### 4.2 Competing Electrophiles in Copper-Triazole Demetallization

When electrophiles other than protons are present, large yields of 1,4,5-trisubstituted 1,2,3-triazoles arise. Therefore, to obtain a replacement with iodide inside the five positions for any derivatization, ICl has been utilised frequently to add to the CuI catalysed process (Kuijpers et al., 2005; Wu et al., 2006). Direct 1, 3-cycloaddition with terminal alkyne halide may also provide the 5-substituted halide. Alkyl and acyl

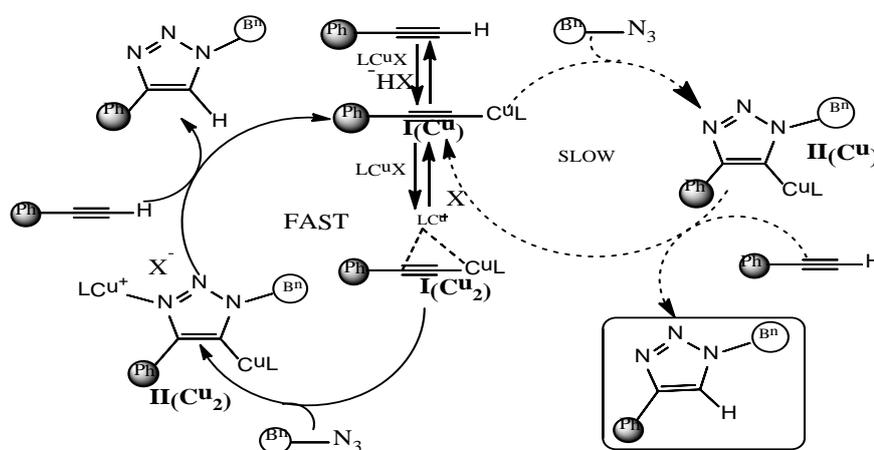
halides may also function as electrophiles, resulting in 27-63% yield of 5-alkylated or 5-acylated triazoles. Terminal bromoalkynes may also enter the CuI or CuBr catalysed process, resulting in a 5-bromo-substituted triazole. In this scenario, CuBr catalysis is preferable over CuI catalysis due to the small quantity of iodide-substituted analogue produced when CuI is utilised. Preparatively, demetallization in the presence of excess acetylene is also employed to get the 5-alkyne substituted triazole (Liu et al., 2019).



Scheme 5. CuAAC in the presence of Sulfonyl Azides may cause the Cu-Triazole 1 to break down, resulting in the formation of the Sulfonylketimine 3.

According to the findings of this research, an interesting examination was conducted into the acceptance of biscopper acetylide I(Cu<sub>2</sub>) as a catalytically active complex rather than mononuclear I(Cu) as a catalytically active complex in the presence of copper (Cu). As previously stated, the exceptional stability of I(Cu<sub>2</sub>) and II(Cu<sub>2</sub>) demonstrates unequivocally that the biscopper route is kinetically more

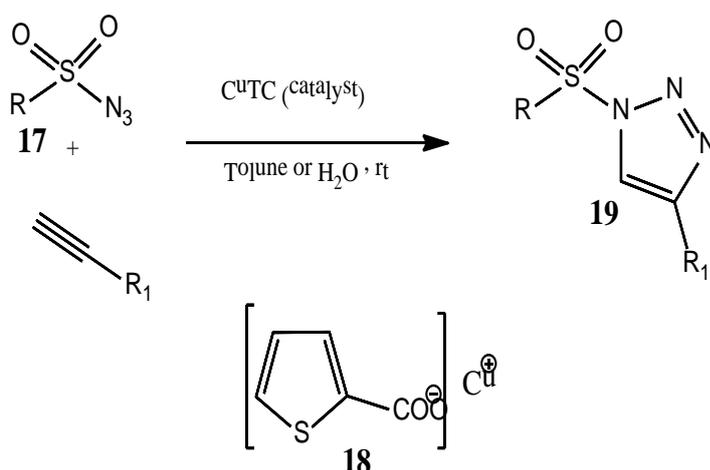
favourable than the mono-copper pathway. In vitro and in vivo studies of the Cu-catalyzed reaction of phenylacetylene with benzyl azide revealed that the dinuclear complexes I(Cu<sub>2</sub>) and II(Cu<sub>2</sub>) are significantly more catalytically active than their mononuclear counterparts I(Cu) and II(Cu). The (CuAAC)CuOTf complex adopts the dinuclear pathway following initiation.



**Scheme 6. Bertrand discovered the convincing mechanism of CuAAC in the reaction between phenylacetylene and benzyl Azide.**

Because of the poor bond strength between N-1 and N-2, click-inspired triazoles' high stability and inactivity, particularly sulfonlated triazoles, is labile. Due to ring chain isomerization during the cycloaddition process, these triazoles give rise to the equivalent N-acylated sulfonamides, complicating the click technique (Cassidy et al., 2006; Cho et al., 2005). A thiophene-2-carboxylate (CuTC)-based copper catalyst 18 has been

developed to click the sulfonyl azides 17 with diverse alkynes and provide the necessary sulfonlated triazoles 19 in high yields under moderate reaction conditions (Scheme 7) to address this problem (Raushel et al., 2010). The CuTC catalyst's considerable stability, very high reaction yield, ease of handling, and efficacy in both aqueous and anhydrous environments, among other things, make it appealing for a wider range of applications.



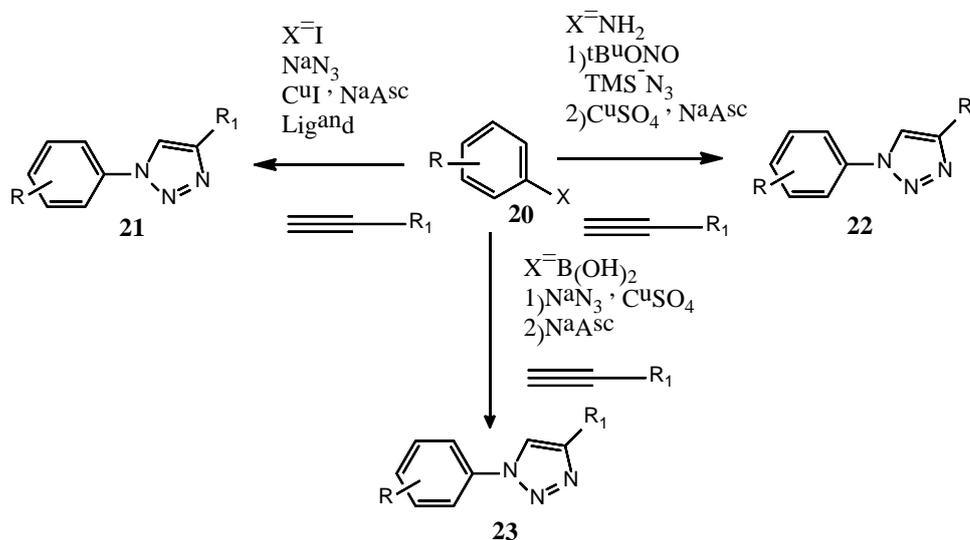
Scheme 7. CuTC-catalysed Alkynes react with sulfonyl azides in this reaction.

## 5. CuAAC is used in "Click Chemistry" and has a variety of applications

### 5.1 Cu(I) in 1,4-Substituted Triazole Preparative Organic Synthesis

Cu(I) catalysed triazole production is a selective transformation that has enabled a variety of multi-component or one-pot

processes in which the azide and alkyne precursors are produced in situ before 1,3-cycloaddition. The synthesis of azide from an alkyl halide and sodium azide under triazole formation conditions is the most prominent precursor reaction (Andersen et al., 2005; Han, 2007; Sreedhar et al., 2007)



Scheme 8. CuAAC and Azide Formation in a Single Pot.

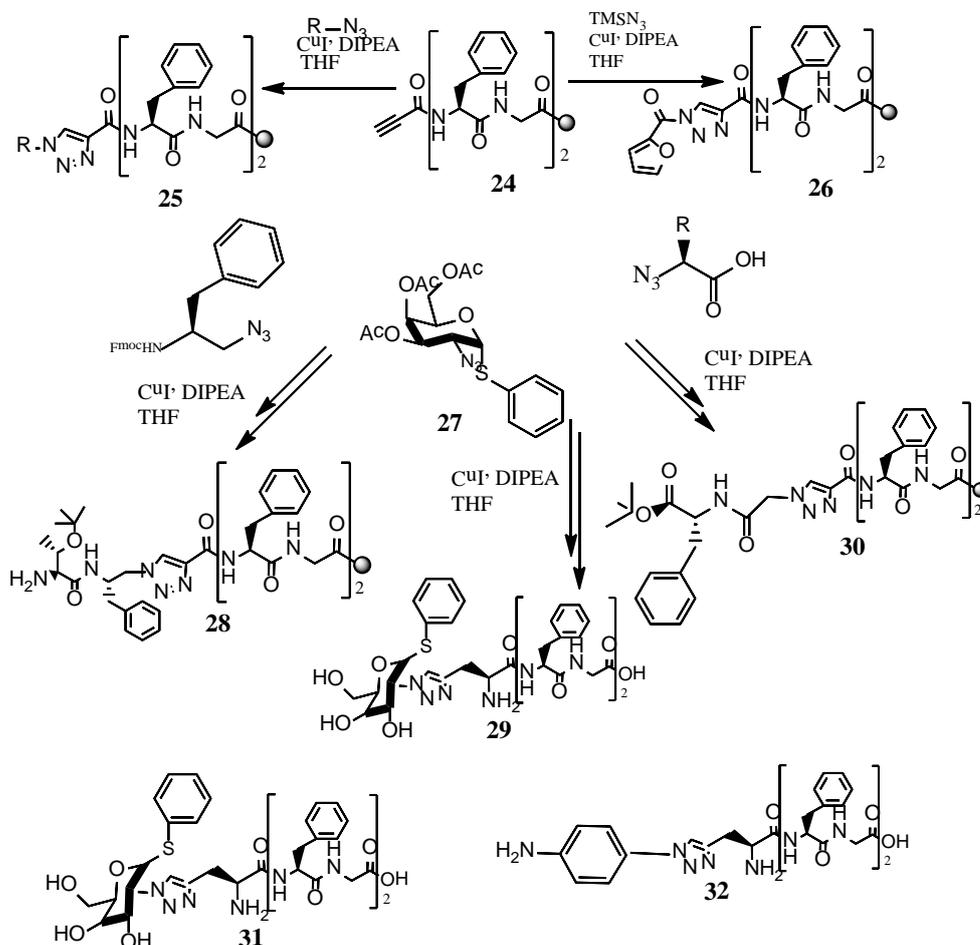
### 5.2 Synthesis of Triazoles in the Solid Phase

It was on solid support that the first report on Cu(I) catalysed triazole synthesis

was published, which included the synthesis of peptidotriazoles and triazole-linked neo-glycopeptides (Tornøe et al., 2001). The alkyne numbers 31 and 32 were

the first to be connected to resin-bound peptides, either as an N-terminal propionyl

group or as an internal propargyl glycine group, respectively.

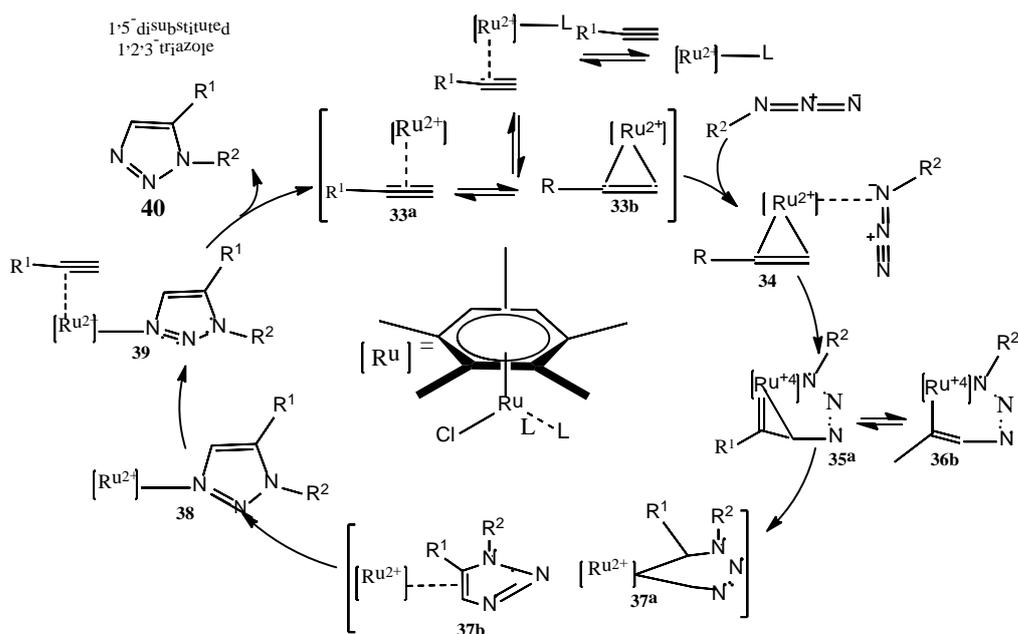


**Scheme 9.** By synthesising a large variety of differently linked peptidic triazoles, for example, 26, 28, and 32, on the solid support in almost quantitative yield, the CuAAC's versatility was established.

## 6. Ruthenium catalyzed azide-alkyne cycloaddition (RuAAC)

The ruthenium-catalyzed azide-alkyne cycloaddition (RuAAC) was a more convenient method for forming 1,5-disubstituted triazoles than metal acetylides. Furthermore, the widespread use of Ru(II) complexes as catalysts in various alkyne processes (Murahashi et al., 2008) sparked interest in using these

compounds in the cycloaddition reaction. Although certain Ru-derivatives [e.g.,  $\text{Ru}(\text{OAc})_2(\text{PPh}_3)_2$ ,  $\text{RuCl}_2(\text{PPh}_3)_3$ , and  $\text{RuHCl}(\text{CO})(\text{PPh}_3)_3$  favour the creation of the 1,4-disubstituted triazole through a process similar to CuAAC (Liu et al., 2012), provide full conversion to the 1,5-regioisomer and are routinely utilised in RuAAC (Johansson et al., 2016).



Scheme 10. The Ru-catalyzed azide-alkyne cycloaddition mechanism is proposed (RuAAC).

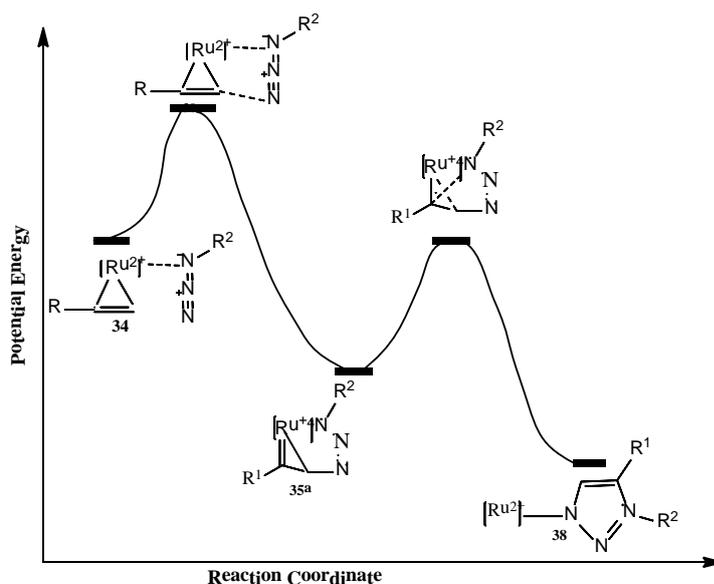


Fig. 2. Based on DFT research, the energy profile of the lowest-energy RuAAC route.

### 7. Advantages of RAAC reaction over CuAAC reaction

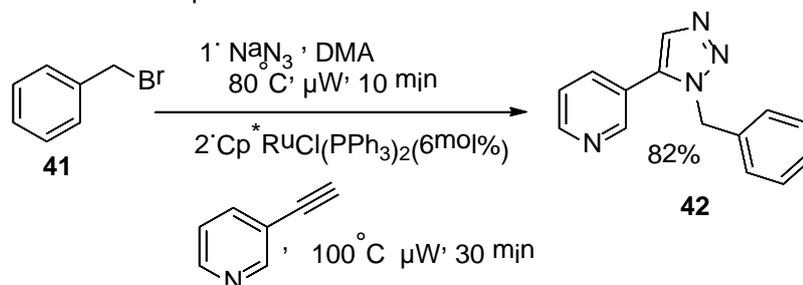
In most RuAAC reactions, organic azide is added to an alkyne in the presence of catalytic quantities of ruthenium (II) complexes containing a [Cp\*RuCl] unit in an aprotic solvent. Most reported RuAAC reactions use either Cp\*RuCl(COD) or Cp\*RuCl(PPh<sub>3</sub>)<sub>2</sub> as the catalyst, with 1 to 5 mol% catalyst, and both of these

complexes are readily accessible commercially. Although heating is usually used to decrease reaction durations, reactions may also be carried out at room temperature, particularly when utilising a high-reactivity catalyst like Cp\*RuCl(COD) (Boren et al., 2008).

Johansson et al. reported a one-pot, sequential microwave-assisted procedure to make triazoles using readily accessible

alkyl halides rather than alkyl azides. Although there are straightforward one-pot procedures for CuAAC accessible in the literature, a solution of benzyl bromide, sodium azide, 3-ethynylpyridine, and  $\text{Cp}^*\text{RuCl}(\text{PPh}_3)_2$  in DMA was microwave heated at  $100^\circ\text{C}$  for 30 minutes, only trace quantities of the desired product were

obtained. The most probable reason is catalyst deactivation or competing reactions (Risse et al., 2011; Taqui Khan et al., 1994). In addition, acidic functionalities in the alkyne or alkyl halide were not acceptable. Thus alkyl chlorides and alkyl iodides were employed instead.



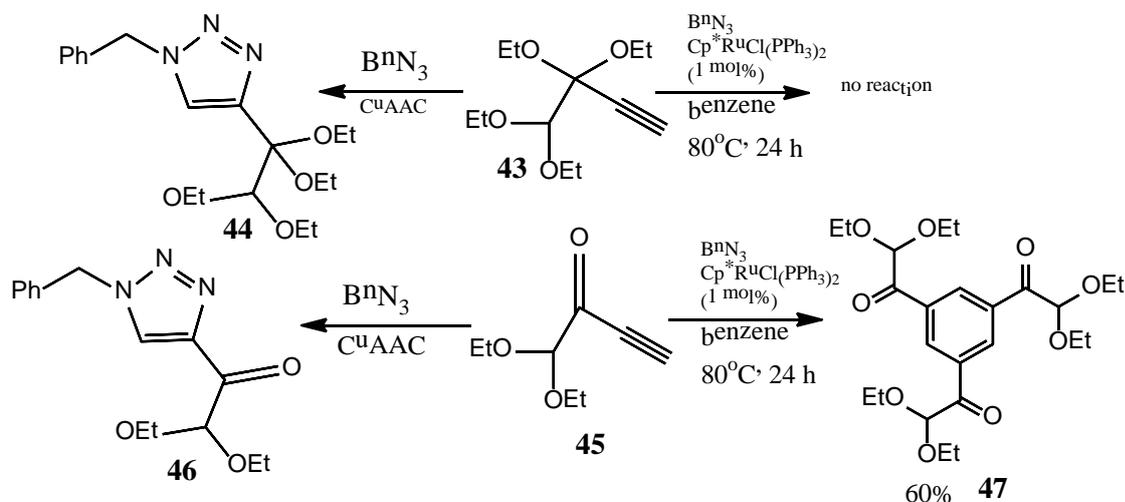
**Scheme 11. Sequential one-pot reaction aided by microwave heating and employing alkyl halides as precursors.**

## 8. Alkynes

### 8.1 Terminal Alkynes with Added Functions

Farooq and colleagues (Farooq et al., 2012) experimented with terminal alkynes with oxygen-containing functional groups at the  $\alpha$  and  $\beta$  carbons in both CuAAC and RuAAC, to produce 1,2,3-triazoles with polar functionalities for use in peptidomimetics. CuAAC was used to produce triazoles 44 and 46 by reacting

ketal 43 and ketone 45 with benzyl azide in the presence of  $\text{CuSO}_4$  (Scheme 12). Instead of a triazole, ketone 45 interacted with  $\text{Cp}^*\text{RuCl}(\text{PPh}_3)_2$  to form the aromatic compound 47. They also experimented with debenzoylation of N-benzylated 1,4- and 1,5-disubstituted 1,2,3-triazoles under hydrogenation conditions, resulting in both isomers yielding the identical 1H-1,2,3-triazole through tautomerization (Farooq et al., 2012).

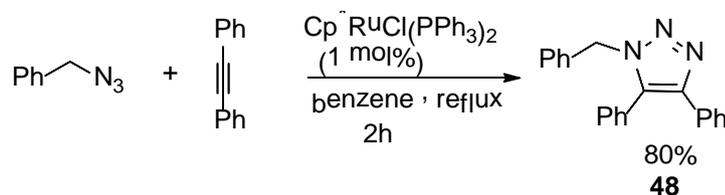


**Scheme 12. CuAAC and RuAAC were tried with highly functionalized alkynes.**

## 8.2 Internal Alkynes

One example of a symmetrical internal alkyne with benzyl azide has been published by Fokin, Jia, and co-workers (Fokin et al., 2005). The key benefit of the RuAAC reaction is that it yielded an 80%

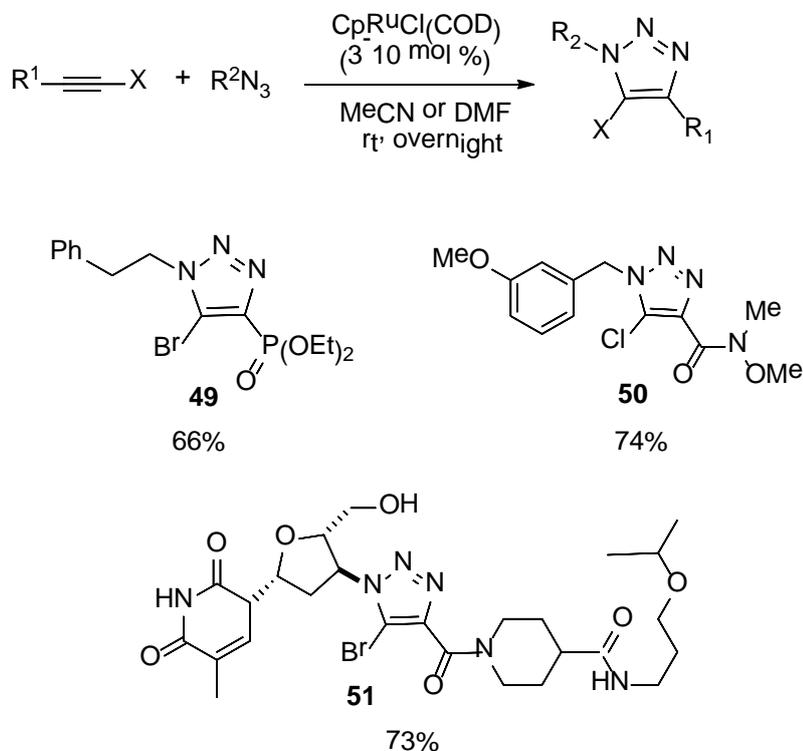
yield of 1,4,5-substituted triazole after 2 hours of reflux in benzene, while the uncatalyzed reaction yields just negligible quantities of product even after 24 hours (Scheme 13).



**Scheme 13.** The discovery of an internal alkyne in RuAAC is the first report of its kind.

Fokin and colleagues explored the interaction of halogenated internal alkynes with palladium-catalyzed cross-coupling reactions, which resulted in the formation of 5-halo-1,2,3-triazoles in the process. Cp\*RuCl(COD) is a typical catalyst for room-temperature RuAAC reactions, although it was shown to be inefficient for

reactions involving halogen-substituted internal alkynes in the reaction mixture. However, this difficulty was resolved by substituting Cp\* with a Cp-ligand that was much less bulky. Consequently, several alkyl azides interacted with Bromo, chloro, or iodo substituted internal alkynes (Scheme 14).



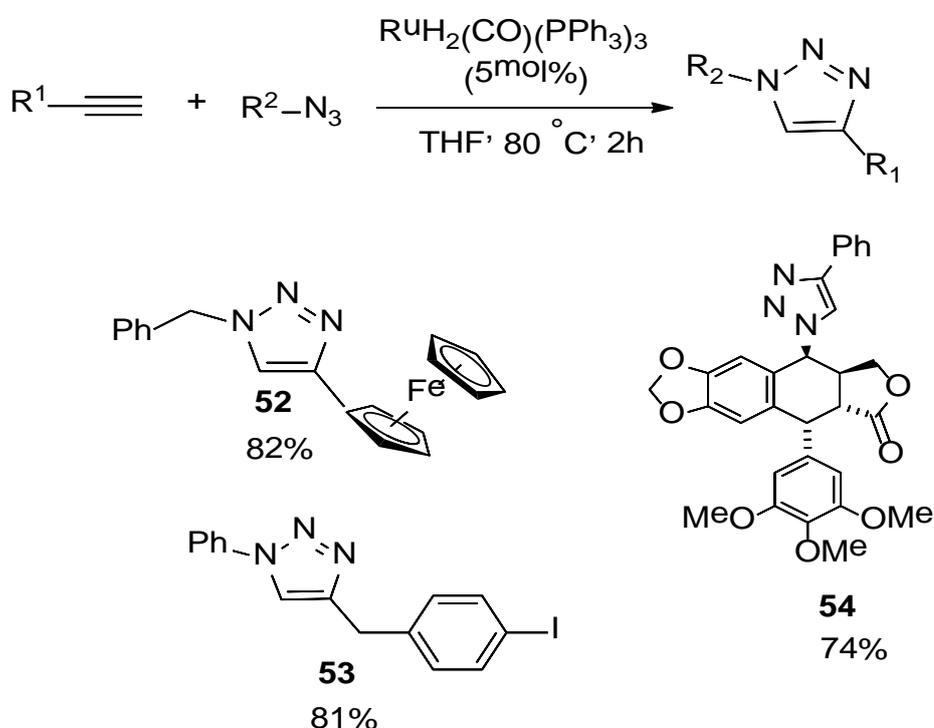
**Scheme 14.** RuAAC reaction of 1-Haloalkynes.

### 9. Catalysts containing ruthenium that produce the 1,4-disubstituted 1,2,3-triazole

Jia, Fokin, and coworkers (Jia et al., 2008; Fokin et al., 2005) claimed that ruthenium catalysts without a cyclopentadienyl ligand produce the 1,4-disubstituted isomer instead of the 1,5, disubstituted 1,2,3-triazole in their initial publications (Boren et al., 2008; Li Zhang et al., 2005). Even though CuAAC may obtain such compounds, it was interesting to assess the range of ruthenium catalysts that could

be utilised in this variation of the cycloaddition and the substrates employed.

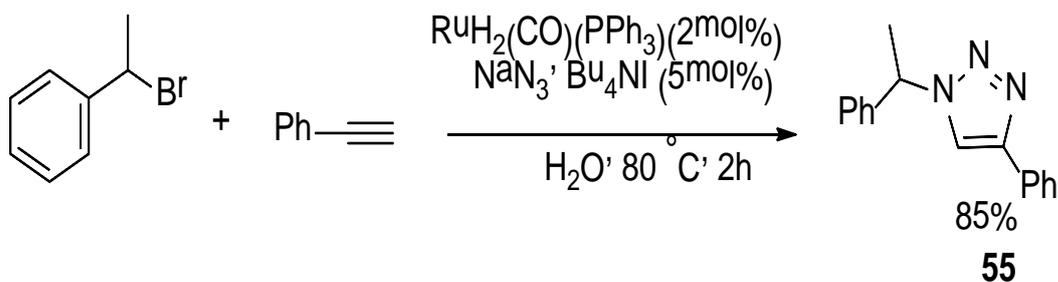
Liu, Jia, and colleagues (Liu et al., 2012) focused on  $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ , the most active of the previously examined catalysts. A broad range of 1,4-disubstituted triazole compounds might be generated employing a 5 mol% catalyst in THF at  $80^\circ\text{C}$ . The production of podophyllotoxin derivatives is of particular interest (Scheme 15).



**Scheme 15.**  $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$  is used to make 1,4-disubstituted 1,2,3-triazoles.

The same catalyst was used in a one-pot cycloaddition/transfer hydrogenation for both processes. Liu and colleagues have shown that the ruthenium-catalyzed cycloaddition (RuAAC) may be carried out in the water with the same catalyst at a lower catalyst loading (0.2%) than in an

organic solvent (Siyang et al., 2015). This work also featured a handy one-pot approach for directly obtaining the 1,4-disubstituted triazoles through in situ azide production from the appropriate bromide (Scheme 16).



**Scheme 16.** An alkyl bromide is used to do a one-pot cycloaddition process on water.

### 10. RuAAC's medicinal and biological uses

Numerous applications in medicinal chemistry, biochemistry, and drug discovery have been identified since RuAAC-compatible catalysts became commercially accessible. This section aims to provide an overview of diverse methods employed in various sectors with the features of 1, 5-triazoles in mind. The strategies are divided into three categories:

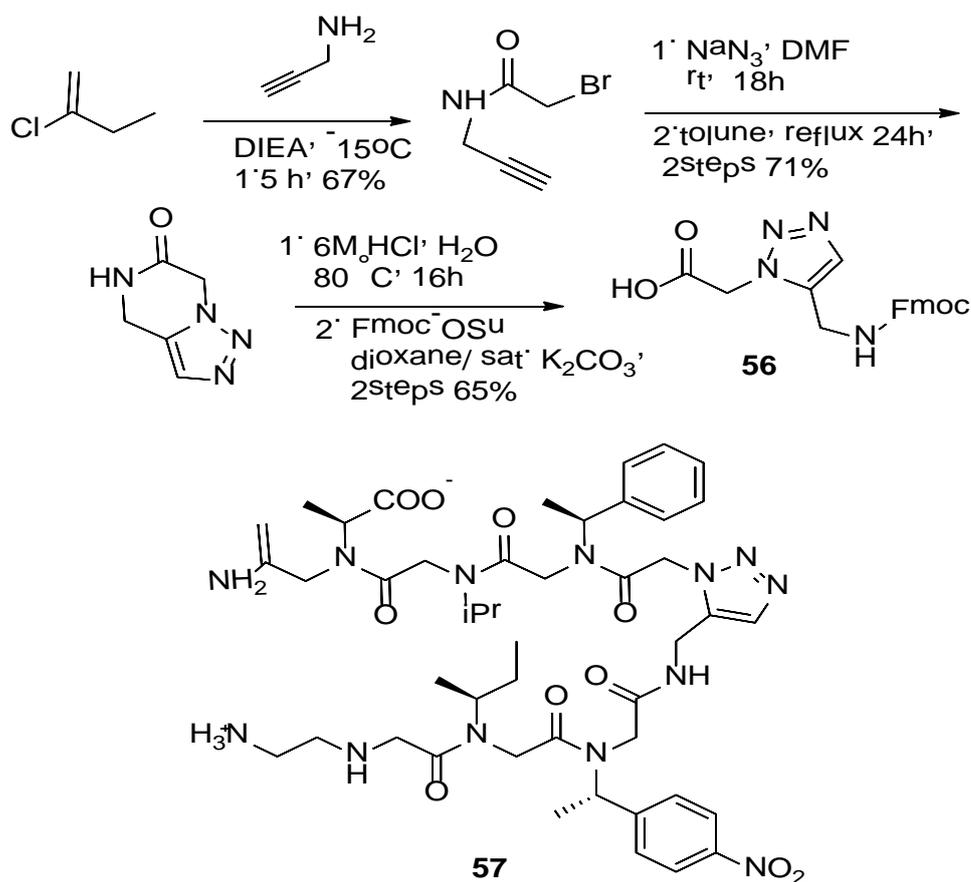
#### 10.1 Peptidomimetics

Peptidomimetics are compounds with secondary structures and biological effects similar to peptides but also have other favourable qualities such as better proteolytic stability or improved affinity to the chosen target region. Peptidomimetics have been created in various ways, and their usage has now become a regular technique in medicinal chemistry and drug development (Scott et al., 2016). The field may be divided into scaffold-based peptidomimetics, local and global changes of the original peptide, and hybrid peptidomimetics. The goal of

peptidomimetic design is to preserve or enhance biological activity, selectivity, and, most crucially, proteolytic stability. The characteristics and uses of the RuAAC reaction as a tool for peptidomimetic applications will be discussed in this section.

Appella and colleagues (Appella et al., 2007) were the first to describe the synthesis of a 1,5-disubstituted 1,2,3-triazole amino acid 56 (Scheme 17) for use as a cis-amide bond mimic to promote turn formation in a synthetic peptide in an aqueous solution, but without the use of RuAAC.

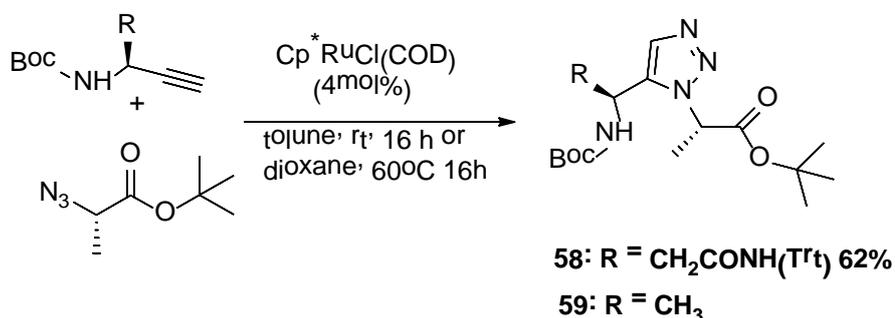
Using solid-phase peptide synthesis (SPPS), triazole 56 is inserted into an artificial peptide sequence to produce peptoid 57 (Scheme 17), which adopts a hairpin-like turn structure as the predominant conformer in 10 mM sodium phosphate buffer (pH 7.0), as demonstrated by thorough NMR measurements.



**Scheme 17. Amino acid synthesis and insertion into the peptoid.**

Raines and colleagues (Raines et al., 2007) investigated the production and use of 1,5-disubstituted 1,2,3-triazoles as cisprolyl peptide bond mimics and discovered that the Xaa-1,5-triazole-Ala unit closely resembles a Xaa-cis-Pro

dipeptide. Some protected Xaa-1,5-triazole-Ala building blocks, such as 58 and 59, were synthesised in moderate-to-high yields utilising the RuAAC process (Scheme 18).



**Scheme 18. The RuAAC Reaction is used to synthesise Xaa-1,5-triazole-Ala building blocks.**

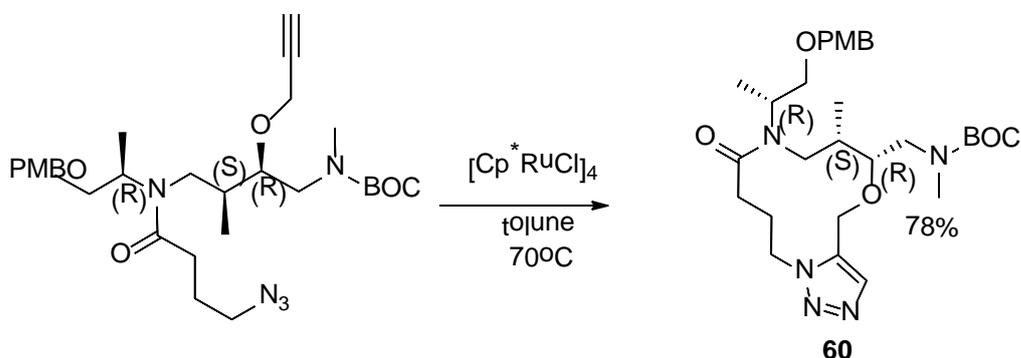
## 10.2 Macrocycles

Due to their usually more favourable features, such as better metabolic stability and permeability, which promote their

usage as oral drug candidates, interest in macrocycles as drug leads has developed in the last decade (Majumdar et al., 2011). This is particularly true for nonpeptidic

macrocycles. For example, the RuAAC macrocyclization processes were repeatable and yielded 50 to 80% of the

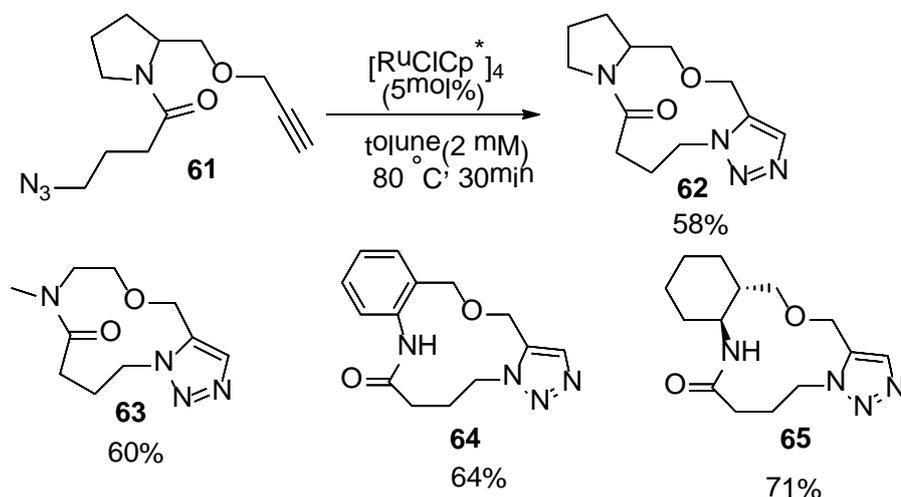
time on a 510g scale. Scheme 19 provides an example.



**Scheme 19.** RuAAC macrocyclization results in the formation of 12-membered triazole macrocycles.

On azido alkyne 34, the RuAAC conditions were improved, and certain 11-, 12-, and 13-membered macrocycles (Kelly et al., 2009; Marcaurrelle et al., 2010) were

synthesised in excellent yields using the optimised conditions. Scheme 20 depicts a few representative cases.



**Scheme 20.** The macrocyclization stage in the synthesis of triazole macrocycles is RuAAC.

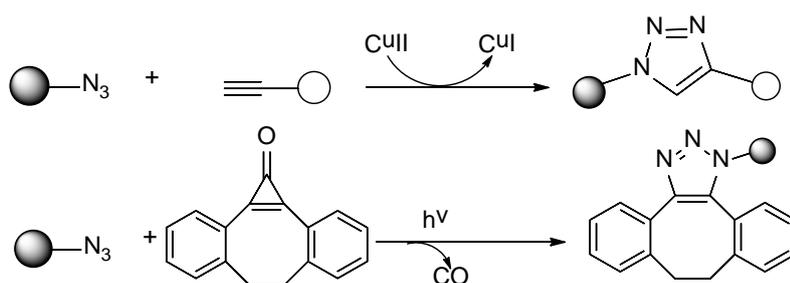
### 11. Light-Triggered Click Chemistry

The combination of click chemistry and benign photochemical processes has ushered in a new era of light-triggered click reactions, also known as photo click

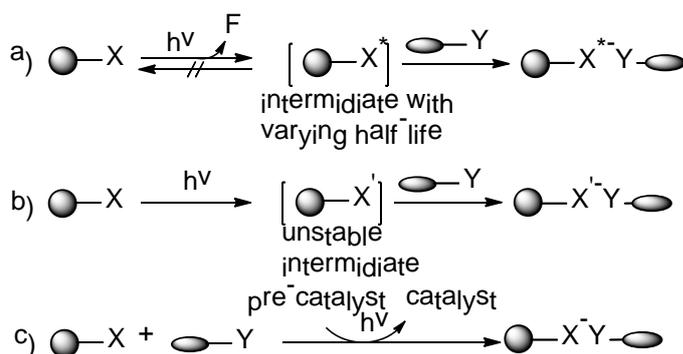
chemistry, which allows for the spatiotemporally controlled synthesis of a wide range of molecular structures, conjugates, and networks in complex systems. Over the last decade, several

picture click responses have been documented in the literature. Photoinduced tetrazole-alkene cycloaddition is one of the most well-known instances (Herner et al., 2016), light-triggered hetero-Diels-Alder reactions (Arumugam et al., 2011), light-triggered azide-alkyne cycloadditions (Poloukhine et al., 2009), photoinduced sydnone-

alkene/alkyne cycloaddition (Linmeng Zhang et al., 2018), photoinduced azirine-alkene cycloaddition (Lim et al., 2010), and light-triggered oxime ligation reactions (Pauloehrl et al., 2012). The photo click reactions start with photon absorption, which produces reactive species. There are three different kinds of photo click chemistry (Scheme 22).



**Scheme 21. Light-triggered azide-alkyne cycloadditions.**



**Scheme 22. There are three different sorts of photo click reactions: (a) Type I; (b) Type II; (c) Type III.**

## 12. Cycloadditions of Azide and Alkyne Triggered by Light

### 12.1 Cu(I)-Catalyzed Azide-Alkyne Cycloadditions are a kind of cycloaddition

An important click reaction in synthetic chemistry, the Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC), is commonly recognised as the prototypic click reaction (Kenry et al., 2019; Meldal et al., 2008). Researchers from the Meldal and Sharpless research groups separately reported the

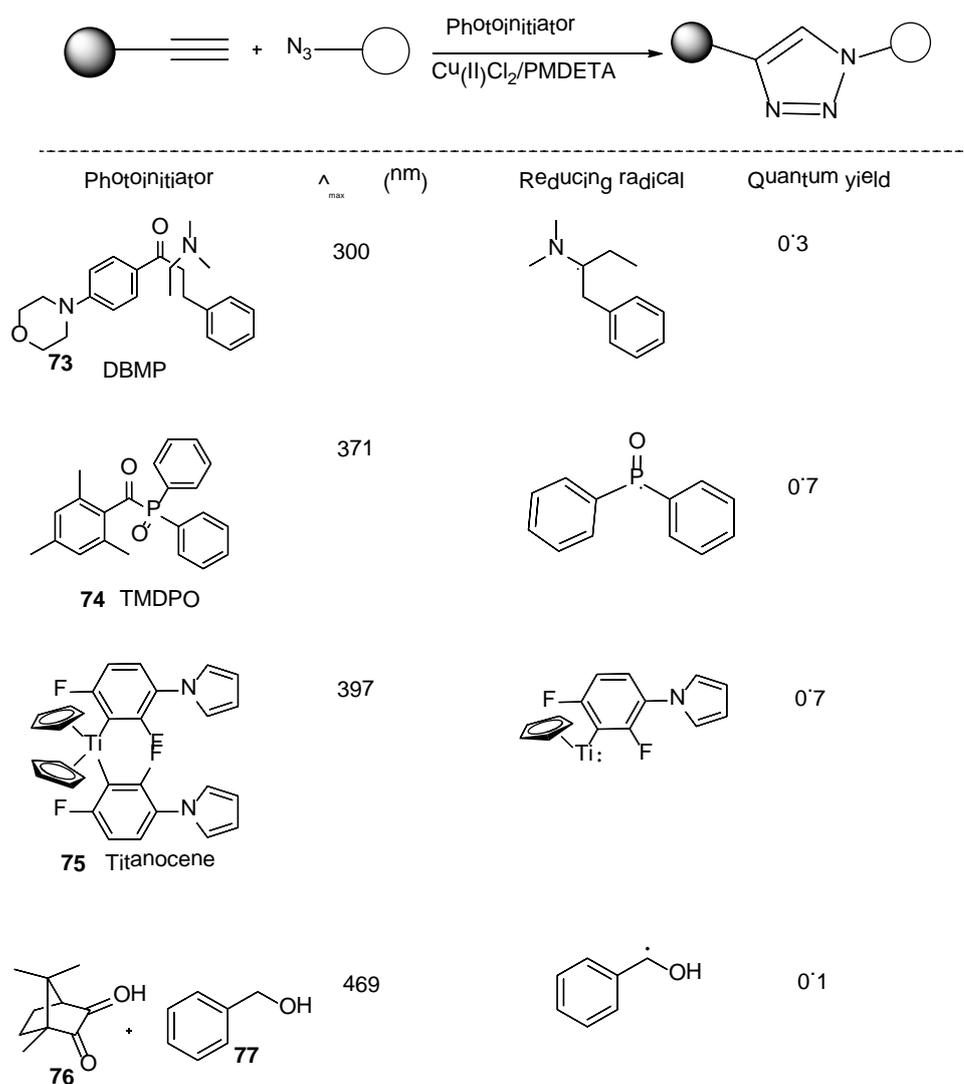
reactions between alkynes and azides to form 1,2,3-triazoles with high regioselectivity and good yields (Scheme 23) (Rostovtsev et al., 2002; Torne et al., 2002; Sharpless and Sharpless, 2002). Because of its durability and adaptability have been widely used in biomolecular ligation, combinatorial synthesis, medicinal chemistry, surface functionalization, and polymer synthesis, among other applications. Through a variety of methods,

including (i) the use of a reducing agent, (ii) electrochemical generation (Devaraj et al., 2006; Hong et al., 2008) of Cu(I), (iii) photochemical approaches (Ritter et al., 2006), and (iv) copper-containing nanoparticles (Pachón et al., 2005). In general, reducing agents such as sodium ascorbate, quinone, and hydroquinone are used in the course of these procedures to reduce oxidative stress. Furthermore, because the photochemical production of Cu(I) catalysts allows for geographical and temporal control of the process, it is particularly useful in several biological and material science applications. In order to do this, König and colleagues reported the first example of a CuAAC reaction induced by light, which was achieved by photoirradiation riboflavin tetraacetate 66 in the presence of Et<sub>3</sub>N (Scheme 23) (Tasdelen et al., 2010). Because of the reduction of Cu(II) to Cu(I), the resultant flavin catalyses the reaction between the azide 69 and the alkyne 70. The photolysis of the Cu(II) catalytic system may result in the generation of Cu(I) species when exposed to light directly or indirectly, respectively. The direct photolysis of Cu(II) complexes includes the absorption of ultraviolet light by a ligand of Cu(II), which results in a ligand metal charge transfer and the reduction of Cu(II) complexes (Scheme 23). This was accomplished by irradiating CuCl<sub>2</sub> with UV/vis in the presence of the PMDETA ligand (Scheme

23), as described by Yagci and colleagues (Sandmann et al., 2013). Bowman and co-workers (Bowman et al., 2011) also described a photo-induced CuAAC reaction based on copper(II) acetate salt in a similar vein. Amine ligands are essential in the light-induced CuAAC processes for direct reduction, which are initiated by the presence of light. In addition to stabilising Cu(I) species, Ligands also increase the solubility of catalytic systems in organic solvents, as seen in the figure. The most efficient ligands were tertiary amines such as triethylamine, PMDETA, tetramethylethylenediamine, and hexamethylenetetramine in this study. Instead, indirect photolysis includes the absorption of UV/visible light by a photoinitiator agent, which results in the generation of reactive radical intermediates, which in turn converts copper(II) oxide (CuO) to copper(I) oxide (Cu<sub>2</sub>O) (Scheme 23).

In most cases, indirect reduction procedures to forming Cu(I) species are quicker than direct irradiation of Cu(II) complexes. Bowman and colleagues (Bowman et al., 2011) demonstrated light-induced CuAAC by photoinitiated Cu(II) reduction employing a CuSO<sub>4</sub>•5H<sub>2</sub>O catalyst and a cleavage type photoinitiator Irgacure for hydrogel production (Scheme 23). The photoinitiator creates the radical species upon light irradiation (400–500 nm), which effectively lowers Cu(II) to Cu (I).





**Scheme 24.** The CuAAC click reaction may be produced by light using free radical photoinitiators.

### 12.3. Photo-Triggered Benzyne Click Reaction

Additionally, Schnarr and colleagues (Schnarr et al., 2008) described a photoinitiated benzyne click reaction using 2-(3-acetyl-3-methyltriaz-1-en-1-yl)benzoic acid 78 as a precursor for the benzyne click reaction (Scheme 25a). A four-step procedure is required to manufacture the benzyne photo precursor 78, which is stable under ambient conditions. In addition, the reaction was compatible with a variety of functional groups and finished in less than 5 minutes.

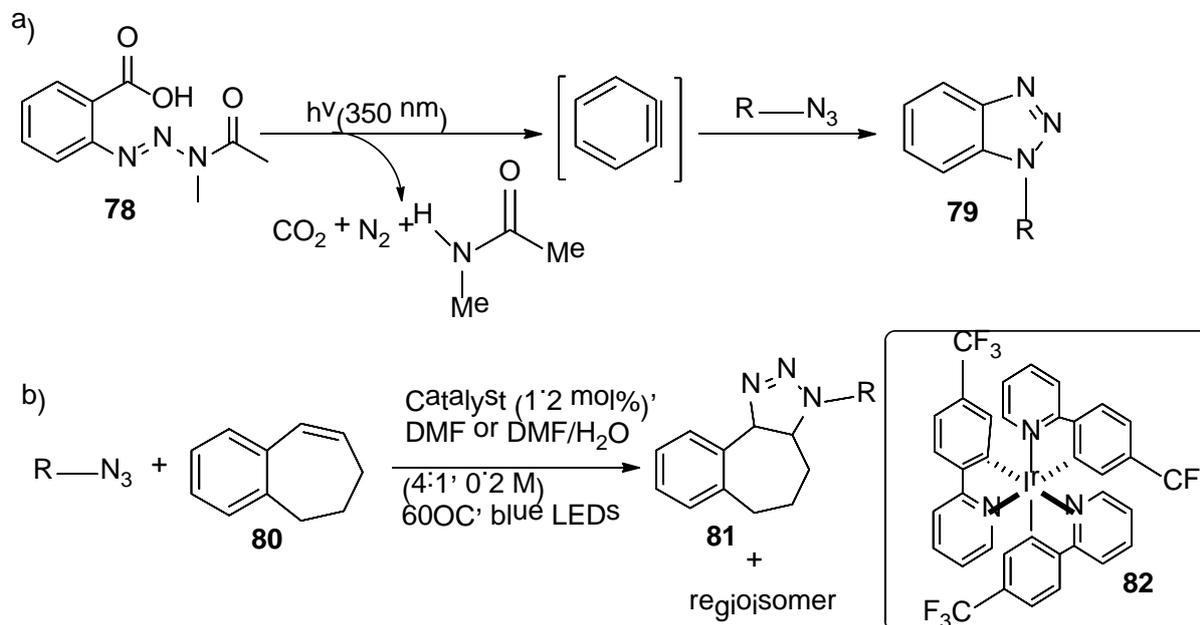
According to theoretical investigations on the reaction of stretched alkenes with azides at room temperature, trans-

cyclooctene is the only one that can take part in the reaction quickly (Schoenebeck et al., 2009). Boosted by these findings, Weaver and colleagues (Weaver et al., 2018) harnessed photochemical energy and produced an alkyl azide cycloaddition using benzo fused cycloheptene 80 that was driven by visible light (Scheme 25b) (Singh et al., 2018).

The process includes the photocatalyzed isomerization of benzocycloheptene to the strained trans-cycloalkene, which reacts quickly with the azides. The reaction between the azide and benzocycloheptene happens only in the presence of light and the photocatalyst 82, giving the reaction a temporal control. This transformation has

a wide functional group tolerance and was used to bioconjugate azide-functionalized insulin quickly. However, the reaction's drawbacks include photocatalyst

precipitation at higher aqueous concentrations and a lengthy irradiation duration, both of which restrict its applicability in biological systems.



**Scheme 25. (a) Photo triggered Benzyne Click Reaction; (b) In the presence of visible light, the [3+2]-cycloaddition of Azides with Alkenes may be accomplished.**

### 13. Conclusion

Several chemical reactions may be utilised to "click" pieces together like "molecular LEGOs" to build complex molecular structures, including the CuAAC reaction. This reaction has been used in practically every branch of chemistry and biology because of its simplicity and durability. The 1, 4-isomer is always formed in this reaction, which is dependable and predictable. Cu(I) clusters and ligands are thought to be involved in the complicated reaction. Through simple transition states involving two Cu(I) atoms on a Cu-cluster, the high specificity of 1,4-triazole synthesis may be explained.

An essential necessity for the evolution of the CuAAC reaction is the continued creation of novel ligands and reaction conditions continuously. Furthermore, the CuAAC has a one-of-a-kind feature in that a

quantitative ligation reaction is assisted by the high  $\Delta G$  of reaction and the considerable decrease in  $\Delta G^\ddagger$  in the presence of Cu (I). Furthermore, due to the production of Cu-acetylide, which produces high polarisation of the triple bond in conjunction with coordination of the azide on the Cu(I) cluster, the Cu(I) cluster becomes very polarised. These characteristics and chemical selectivity seem to be critical success factors in the hunt for novel ligation reactions.

The ruthenium-catalyzed azide-alkyne cycloaddition (RuAAC) directly approaches 1,5-disubstituted 1,2,3-triazoles and serves as a counterpart to the copper-catalyzed "click" reaction, which results in the formation of the triazole's 1,4-isomer. Mechanistic studies imply that the RuAAC reaction follows a different route than the

CuAAC reaction. This is further supported by the fact that internal alkynes may be used in the Ru-catalyzed process, but this is not the case for the CuAAC reaction. Another benefit of the RuAAC reaction is the 1,5-disubstitution pattern, which can be used for many things, including making macrocycles. This is because the regiochemistry in the RuAAC reaction is better suited for smaller rings than the regiochemistry in the CuAAC reaction. The CuAAC reaction, on the other hand, has the advantage of using a less costly catalyst and can often be carried out at a lower temperature than the RuAAC process. Furthermore, both reactions are compatible with a wide variety of functional groups, while RuAAC might be difficult when used with substrates that include acidic functional groups, as previously stated.

The field of light-triggered click chemistry has continued to grow over the past decade, as evidenced by the increasing number of photo click reactions based on the photochemical generation of reactive species that do not require the use of toxic metal catalysts or reagents that have been discovered and reported. However, since most photo click reactions are caused by ultraviolet (UV) light, which may limit their application in biological systems, significant work has been committed to creating photo-triggered click reactions triggered by visible and near-infrared (NIR) light. In addition, because of the availability of a large photo click reaction repertoire that operates at a variety of distinct wavelengths, it is now feasible to execute tandem orthogonal photo click reactions in materials science, which was previously impossible.

Multiplexed manipulation of biomolecules in their native cellular environments will be possible in the future with additional photoactivation modalities,

with the advancements mentioned here and continuing expansion of this field, that the powerful tools obtained from the union of light with click chemistry will fuel a new era of molecular exploration in the chemosphere.

#### 14. Acknowledgements

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