Review Article

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Advancements in transition metal-catalyzed 1,2,3-triazole synthesis via azide–alkyne cycloaddition

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Abstract: 1,2,3-triazoles have emerged as important structural motifs in chemical biology, attracting increasing focus in recent years because of their wide range of uses. These compounds can be efficiently synthesized using click reactions. Its versatility makes it valuable in drug discovery and materials science. Significant advancements have been made in recent years in the process of making 1,2,3-triazoles, reflecting the growing curiosity and investment in the area of research. The catalytic performance of transition metals Cu, Ir, Rh, Ru, Ni, Pd, Au, Ag, and Zn, which were used as ligands and salts in the azide–alkyne cycloaddition method of 1,2,3-triazole synthesis, has been covered in this review. Cu-complexes and salts were found to be more effective for selective synthesis among all transition metals. Furthermore, it is determined that some azide–alkyne reactions are entirely catalytic in nature and cannot be carried out as such by switching transition metals.

Keywords: f-block; d-block; Ru-catalyzed reactions; Cu-catalyzed reactions

Correction note: Correction added [November 22, 2024] after online publication November 13, 2024: The e-mail address of Shahab Khan – shahabkhan262@gmail.com – was misspelled as shahabkhan262@gamil.com. In the section heading Cycloaddition of azide–alkyne catalyzed by Nickel the name of the chemical element was misspelled as Nikal.

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1 Introduction

1,2,3-triazole is an important structure synthesis that has undergone a profound transformation,[1–6] principally motivated by the CuAAC's adaptability, or cycle of azide–alkyne addition, reaction.[7–9] This synthetic route or transition-metal-catalyzed cross-coupling reactions has become essential to the synthesis of these heterocyclic molecules, owing to its wide substrate applicability, regioselectivity, and broad utility across multidisciplinary scientific realms, including materials science, chemical biology, and medicinal chemistry. Over the past several years, a concerted research effort has been dedicated to advancing transition metal-catalyzed CuAAC reactions, with a specific focus on expanding the repertoire of catalytic systems, refining reaction conditions, and integrating sustainable practices.[10–14] The exploration of catalytic systems beyond the traditional copper-based catalysts has been a transformative endeavor in recent research, encompassing the utilization of ruthenium, palladium, and iron.[15–17] This catalytic chemical process not only broadens the scope of applicable substrates but also offers the promise of milder reaction conditions, thus enhancing the overall effectiveness and usefulness of the synthetic procedure. The strategic design of ligands and the optimization of reaction parameters have been crucial in achieving not only heightened yields but also improved regioselectivity in diverse CuAAC transformations.[18–20]

Prominent initiatives include the exploration of alternative reaction media, such as water, and the design of recyclable catalytic systems. These strides toward sustainability

not only address the imperative of reducing environmental impact but also respond to the global call for more resource-efficient and ecologically mindful chemical processes.[20–22] Furthermore, the significant applications of CuAAC in the synthesis of bioactive molecules, pharmaceuticals, and advanced materials underscores the method's versatility and its indispensable role in contemporary research.[7,23,24] This study also examines the synergistic integration of computational methods, providing a predictive dimension to the field by offering insights into reactivity patterns and elucidating complex reaction mechanisms. The marriage of experimental and computational approaches facilitates a deeper understanding of the CuAAC process, guiding the rational design of catalysts and the fine-tuning of reaction conditions for heightened precision and efficiency.

In organic catalytic synthesis, transition metals like palladium, platinum, and nickel take part through their partially filled *d*-orbitals in the preparation of products. These orbitals enable the metals to form complex interactions with organic molecules, stabilizing reaction intermediates and lowering activation energies, which significantly accelerate reaction rates. In processes such as hydrogenation and cross-coupling reactions (e.g., Suzuki and Heck), the *d*-orbitals facilitate the formation and breaking of bonds by alternating between oxidation states, allowing smooth electron transfer. By stabilizing transition states, these *d*-orbitals reduce the energy required for chemical transformations, making transition metals indispensable in catalytic reactions, including industrial applications like the Haber process for nitrogen fixation.[25]

Here, we examine the developments in the synthesis of 1,2,3-triazoles using catalysts made of transition metals. Our aim extends beyond mere cataloging of recent findings; we aspire to offer an accessible and comprehensive resource for scientists at all levels, from seasoned researchers to those just entering the field. Through insightful analyses of the current state of the discipline and by charting a course for future investigations, this review contributes to the ongoing narrative of synthetic chemistry's evolution (Figure 1).

2 The synthesis of significant 1,2,3-triazoles is accomplished through the cycloaddition of azides and alkynes.

Researching physiologically active heterocyclic molecules with nitrogen atoms is one of the most significant areas of medical chemistry.[26,27] Azole is a nitrogen-containing heterocycle with five members. It is a structural component of several naturally occurring compounds that are biologically active.[28] A range of biological activities, including antibacterial activity, are displayed by azoles and their derivatives.[29] With several uses, the 1,2,3-triazole scaffold is a useful scaffold for heterocycles containing nitrogen.[30] The aromatic feature of 1,2,3-triazole comes from its 6π delocalized electron ring structure, which is not soaked, π-excess heterocycle with five members. Two carbons and three nitrogens' make up 1,2,3-triazoles. Every atom in the five is sp^2 hybridized. N atoms come in two varieties: pyridine and pyrrole. Monocyclic 1,2,3-triazoles are further subdivided into three subclasses according to the placement of the NH proton. 1H- and 2H-1,2,3-triazoles are aromatic and equilibrate each other in solution and gas phase, however, 4H-1,2,3-triazole is non-aromatic by nature[31] among the monocyclic 1,2,3-triazoles in all possible isomers, 1H-1,2,3-triazoles are powerful scaffolds that are widely found in therapeutic, agrochemicals, and materials science have received more attention.[31–33]

Triazole rings may function as crucial transitions in a variety of significant organic reactions.[34,35] These five-membered N-heterocycles' many uses stem from their simple synthesis and ring functionalization processes.[36–38] Significant emphasis has also been given in the last few years to the identification of synthetic procedures centered upon ecological sustainability. Numerous strategies in this respect make use of cutting-edge Lewis catalysts, unusual solvents, and eco-friendly components.[39,40] Much emphasis has been paid to 1,3-dipolar cycloaddition (1,3-DPCA), the most important step in the synthesis of heterocycles.[41] This method has proven to be especially helpful in adding chemical features of a species, like nitrone, which has been demonstrated to function as a radical scavenger and is an essential property of medications, that the relevant precursors usually already carry (i.e., 1,3-dipoles).[42] They serve as helpful dipole partners in the synthesis of new bioactive substances.[42] Moreover, it has been demonstrated that the 1,3-DPCA reaction is especially compatible with the application of cutting-edge green chemistry methods, like microwave-assisted reactions,[43,44] Ultrasound-assisted responses[44] as well as non-traditional reaction solvents.[45]

The steric and electronic properties of the substrate significantly influence the regioselectivity of this method. However, due to the elevated reaction temperatures, low yields, and the formation of two regioisomers when using unsymmetrical alkynes, this technique has seen limited application in synthetic chemistry. In response, several strategies have been developed to improve control over regioselectivity. Among these, ruthenium catalysts were found to selectively produce 1,5-disubstituted compounds, thereby they enhance significance of this method (Scheme 1).[46,47]

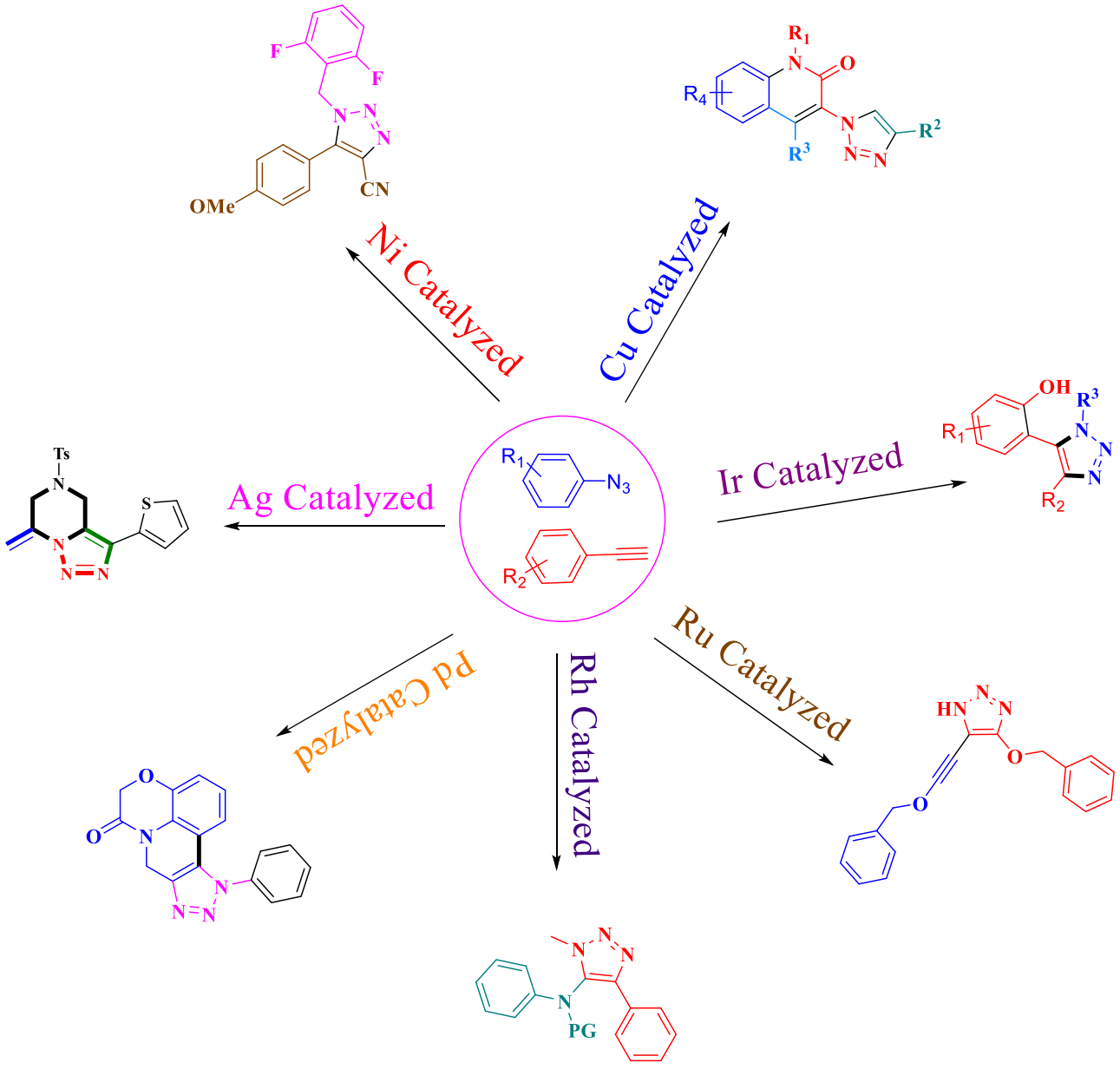
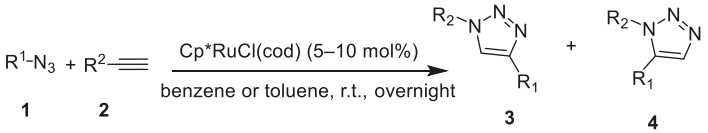
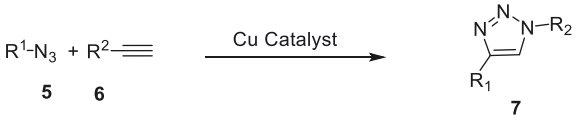


Figure 1: A few significant 1, 2, and 3 triazoles that transition metals catalyze.



Scheme 1: Synthesis of 3 and 4 using Huisgen 1,3-dipolar cycloaddition method.



Scheme 2: Cu-catalyzed reaction of 7.

3 Copper catalyzes the azide–alkyne cycloaddition (CuAAC)

In 2002, Sharpless and Folkin,[48] along with Meldal and colleagues, independently discovered the CuAAC reaction,

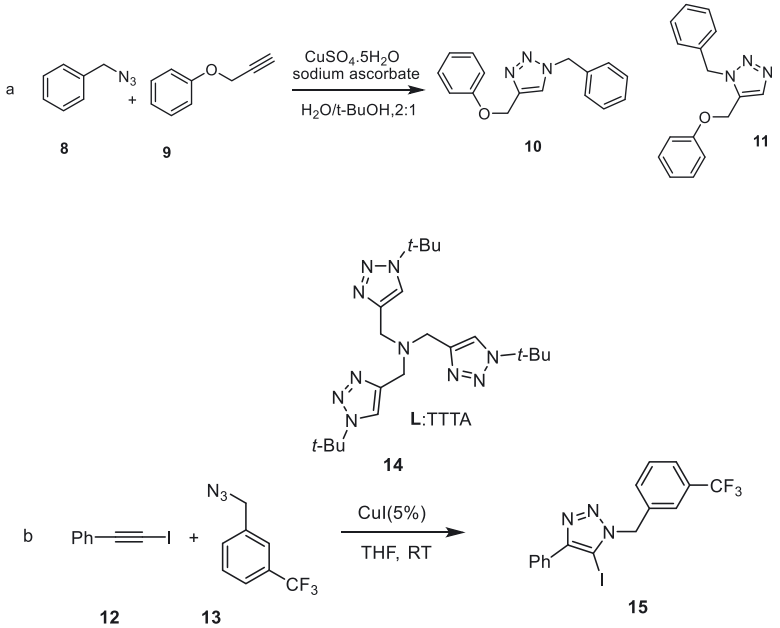
where alkyne 6 and azide 5 serve as primary constituents. In organic synthesis, the CuAAC reaction stands out, although recent click chemistry approaches have been reported, none fully meet the criteria set by Sharpless and colleagues for the ideal click response. The copper-catalyzed reaction between alkynes and organic azides exemplifies click chemistry (Scheme 2).[49]

In the 1970s, Huisgen et al. reported in the 1,3-dipolar cycloaddition procedure, organic azides, and alkynes as well as the successfully generated 1,2,3-triazole compounds.[50] The Sharpless and Fokin group reported a Cu(I)-catalyzed reaction in 2002. [3 + 2] benzylic azides and alkynes undergo cycloaddition to produce 1,2,3-triazoles.[48] (Scheme 3). Using this method, $CuSO_4$(II) was reduced to Cu(I), which shows significant regioselectivity in a 2:1 mixture of water and tert-butanol. Finally, rather than 1,5-disubstituted triazole compound 11, a series of 1,4-disubstituted 1,2,3-triazole were generated. The same Sharpless and Fokin group reported the cycloaddition reaction of organic azides and 1-iodoalkynes catalyzed by Cu(I) in 2009[20] (Scheme 3). CuI catalyzed the reaction between organic azide and iodoalkyne in the presence of an amine ligand (TTTA) **(14)** to successfully synthesize 5-iodo-1,4,5-trisubstituted-1,2,3-triazole **(15)**, use a cycloaddition procedure. Furthermore, the pace and chemical selectivity of the reaction is mostly determined by the presence of amine ligands.

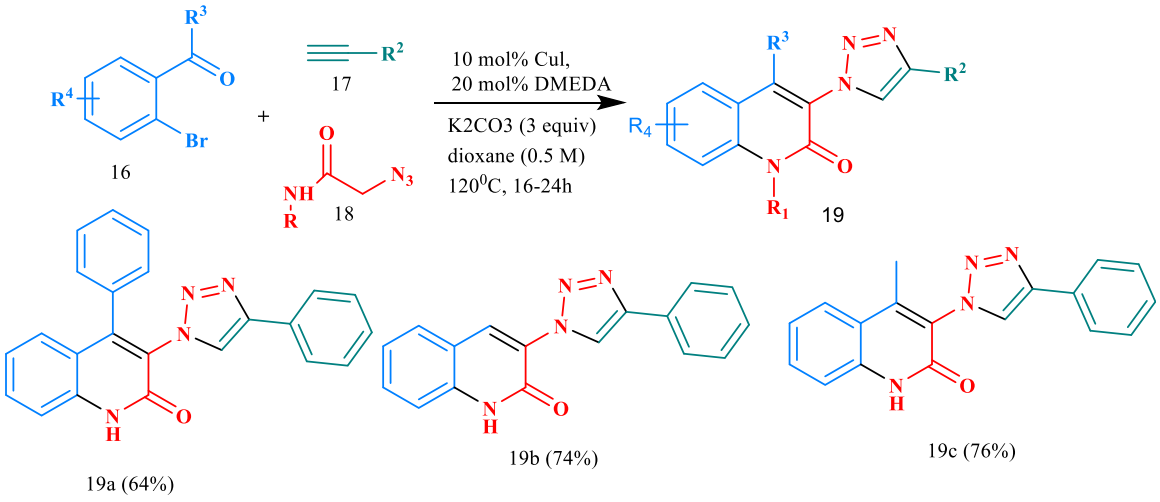
The trio of components[51] cascade response, which is catalyzed by copper, is the sophisticated synthetic strategy employed by the authors to create nitrogen poly heterocycles. They integrate direct C–H arylation, azide–acetylene cycloaddition, and Ullmann-type coupling reactions into a single-pot process. The main breakthrough is the ability to quickly assemble intricate polyheterocyclic systems by using 2-azidoacetamides as flexible building blocks. With this method, the versatility of copper catalysis in forming multiple bonds and rings within a single cascade reaction is demonstrated, highlighting its potential to coordinate a variety of transformations. The study underscores the efficacy and synthetic utility of the proposed methodology through a comprehensive evaluation of its diverse applications (Scheme 4).

Using 1-azido-2-isocyanoarenes[52] in combination with terminal acetylenes or substituted acetaldehydes, a highly effective procedure has been developed for synthesizing 1,2,3-triazolo[1,5-a] scaffolds made of quinoxaline. The four chemical linkages are made up of two C–C and two C–N bonds, which can be formed sequentially without isolating the triazole intermediate, thanks to the trifluoromethylation-triggered cyclization process. Moreover, rhodium-catalyzed carbenoid insertion reactions can easily convert these triazo-fused products into a variety of quinoxaline derivatives (Scheme 5).

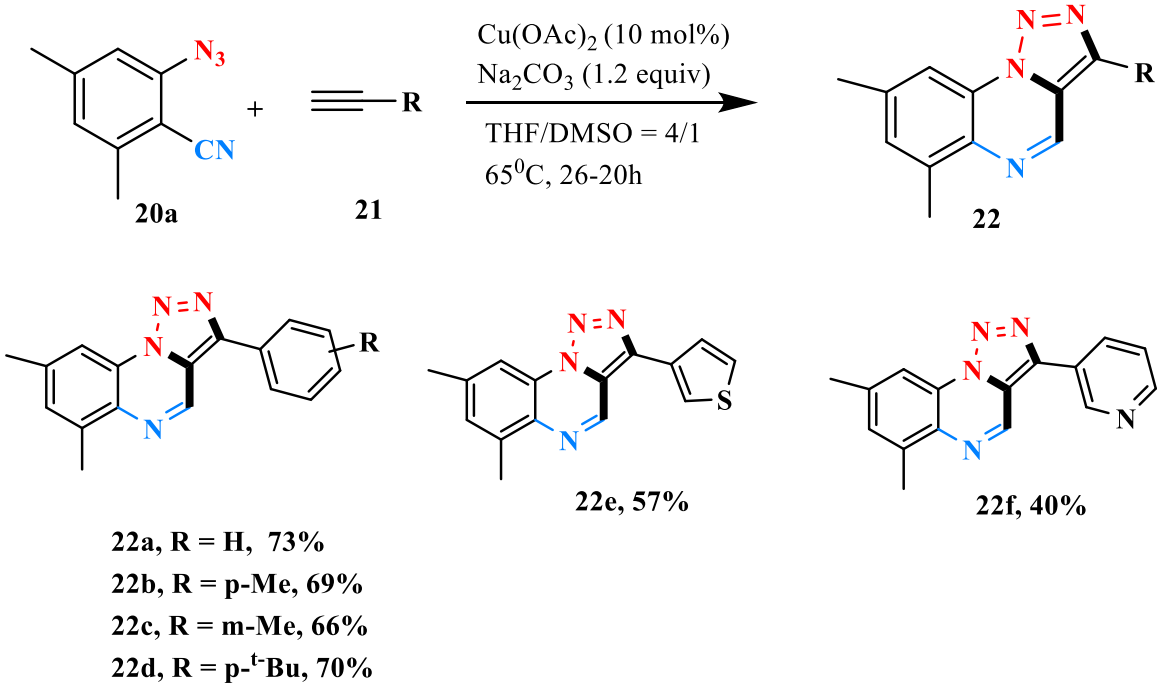
This work establishes a[53] simultaneous response involving intramolecular direct arylation, Ullmann-type C–N coupling and Azide–alkyne cycloaddition (CuAAC), that is catalyzed by an unbound ligand and copper. The developed approach makes it possible to synthesize a novel azaheterocycle framework with triazole fused in one step with efficiency. A noteworthy outcome of the reaction is the production of Triazole-1,2,3-fused imidazole [1,2-a] pyridines, with favorable yields between 59 % and 77 %. This method uses a series of copper-catalyzed transformations to create a logical and efficient pathway to complex azaheterocyclic structures. The copper catalyst's ligand-free state makes the synthetic protocol more straightforward and effective (Scheme 6).



Scheme 3: 3 + 2 cycloaddition process catalyzed by Cu(I).



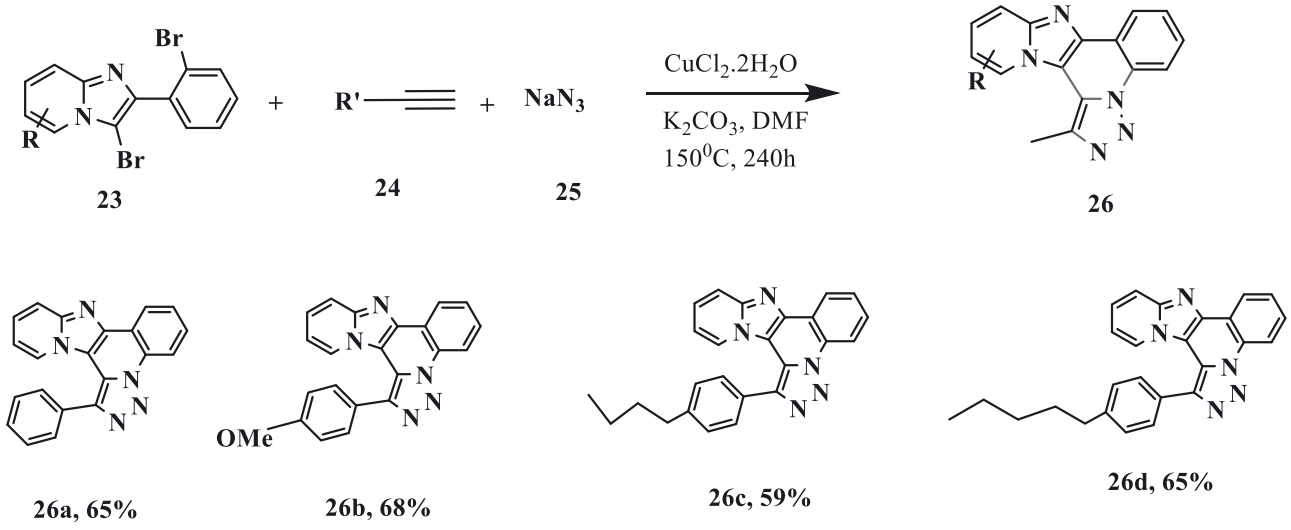
Scheme 4: Nitrogen poly heterocycles can be synthesized in three steps using copper as a catalyst via cyclization, C–N coupling, domino cycloaddition, or (C–H arylation).



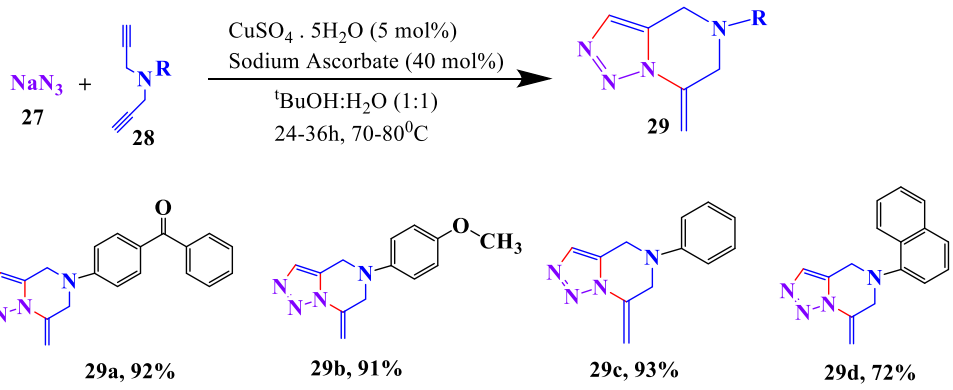
Scheme 5: With good bond-forming efficiency, 1-azido-2-isocyanoarenes are synthesized in a single pot to yield triazolo[1,5-a] quinoxalines [1,2,3].

To produce[54] the medicinal significant Tetrahydro-[1,2,3] hexagonal triazole pyrazine pattern, a tandem synthetic approach has been developed in this study. The technique is applied in mixed aqueous–organic media and involves a concise tandem sequence that combines a "click" reaction with a 6-exo-dig cyclization. This approach shows its adaptability by taking into account a range of substrates that are based on amino acids. The pharmaceutical significance of synthesizing the tetrahydro-[1,2,3]triazolopyrazine scaffold makes it an especially significant process. For the tandem process, the mixed aqueous–organic conditions offer a comfortable and effective environment. The paper provides a thorough discussion of the method's applicability and limitations, providing insights into the range of substrates that can be used and potential difficulties that may arise (Scheme 7).

In this study, overlooked[55] potential cyclic diaryl iodoniums, in contrast to their widely utilized linear counterparts, have been explored for their ability to start two arylations, offering additional atoms and a step-by-step synthesis pathway. The researchers successfully conducted a cascade reaction with



Scheme 6: Intramolecular direct arylation, tandem azide–alkyne cycloaddition catalyzed by copper and ullmann type C–N coupling.



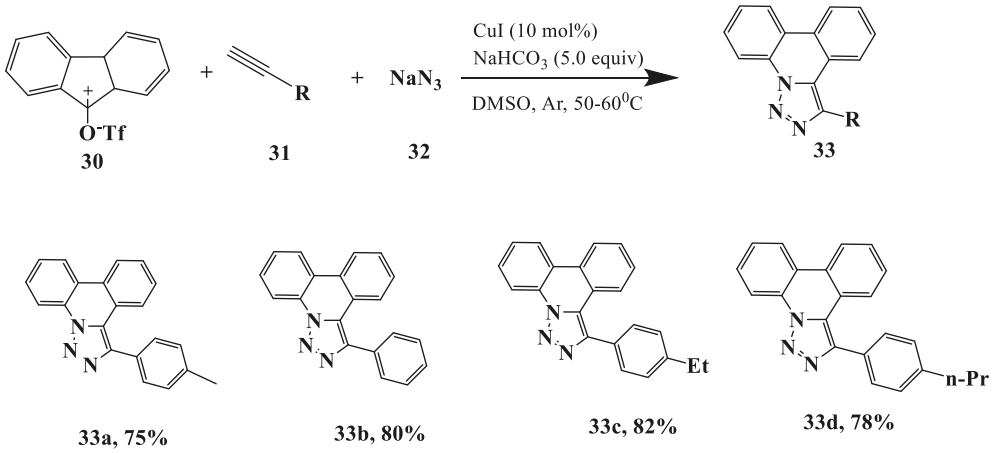
Scheme 7: A highly effective method for creating triazole fused pyrazines is the tandem cycloaddition/6-exo-cyclization [3 + 2] "click".

three components that uses cyclic diaryliodoniums, Alkynes, and sodium azide in mild circumstances, employing cost-effective copper species as catalysts. With unsymmetrical iodonium in particular, the regioselectivity of the reaction was increased by carefully adding two methyl groups, ortho, and para, to the iodine core. This reaction produces a wide variety of intricate compounds quickly, specifically triazole phenanthridine derivatives. This work highlights the efficiency and versatility of cyclic diaryl iodoniums in accessing intricate molecular architectures through a streamlined cascade process (Scheme 8).

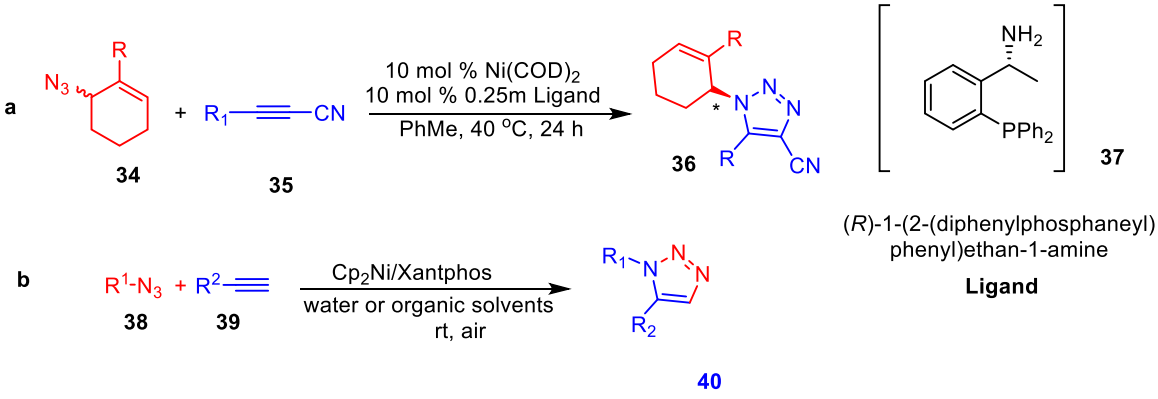
4 Cycloaddition of azide–alkyne catalyzed by Nikal

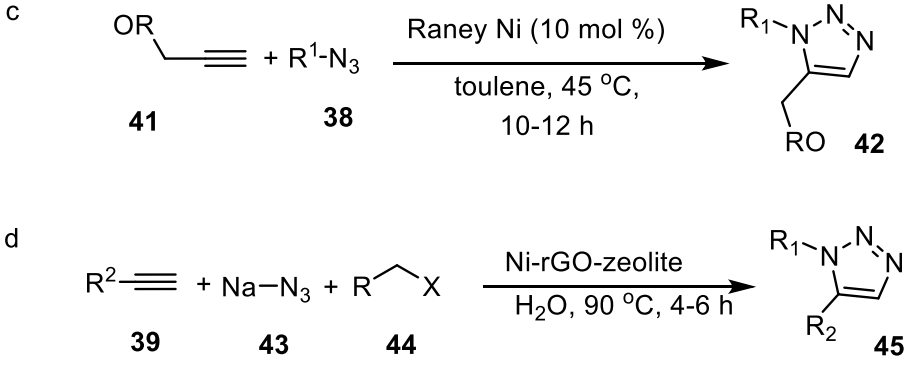
Apart from Cu, other metals can also be used to catalyze the reaction of 1,3-dipolar cycloaddition between alkynes and organic azides, such as Ru, Rh, Ni, and Pd.[56–61] The E-NiAAC reaction's azide scope revealed that while electron-rich and electron-poor groups do not significantly impact the scope of allyl azides, acyclic allyl azide can change the cyclohexyl moiety, resulting in the observation of (E) – and (Z) – olefin isomers (7:1 E/Z). But just one isomer of the intended derivative was isolated. Hong and colleagues[62] revealed that **38** and **39** could be easily and efficiently cycloaddition by nickel utilizing Cp_2Ni/xanthous as a catalyst in either water or an organic solvent (toluene). With a wide range of substrates and strong regioselectivity, product **40** was produced in 42–95 % yield (Scheme 9b).

Basu et al. developed a one-pot[63] method (working at 90 °C for four to 6 h) to synthesis 1,4-disubstituted triazoles 45 with high regioselectivity from halides 44, NaN_3 43, and 39. Ni-rGO-zeolite, a stable ternary nanocomposite catalyst, was present to aid in this reaction (Scheme 9d). To create effective nanocatalysts for this procedure, they combined 2D GO (graphene oxide) with NaY zeolites to create hybrid GO zeolites. The GO-zeolite composite is made by mixing an



Scheme 8: A Cu(I)-catalyzed cascade reaction with calciodoniums, alkynes, and sodium azide efficiently produces triazolophenanthridines.





Scheme 9: Nickel-catalyzed NiAAC, or azide–alkyne cycloaddition.

aqueous suspension of NaY zeolite with protons to acidify the mixture's pH to roughly 7. By lowering the negative charges on the zeolite composite corresponding to the transition point, this process aids in the formation of Al–OH–Si bridges. After giving the mixture a very gentle stir, it is heated for about 16 h at 60 °C. The water is then evaporated, and the entire mass is emptied in order to dry it out. After hydrothermally reducing this GO/zeolite composite with $Ni(OAc)_2{\cdot}4H_2O$ and $NaBH_4$, ternary Ni-rGO-zeolite nanocomposite is produced. The catalyst becomes more active during the final step.

To obtain disubstituted 1,4- or 1,5-azide–alkyne[64] cycloadditions with transition metal catalysis or those without can be used to 1,2,3-triazoles. In aqueous and ambient conditions, azaide-alkyne cycloaddition fails to provide entry to the complementary 1,5-regioisomers due to its narrow substrate scope or the use of catalysts that are insensitive to moisture or air. Nevertheless,

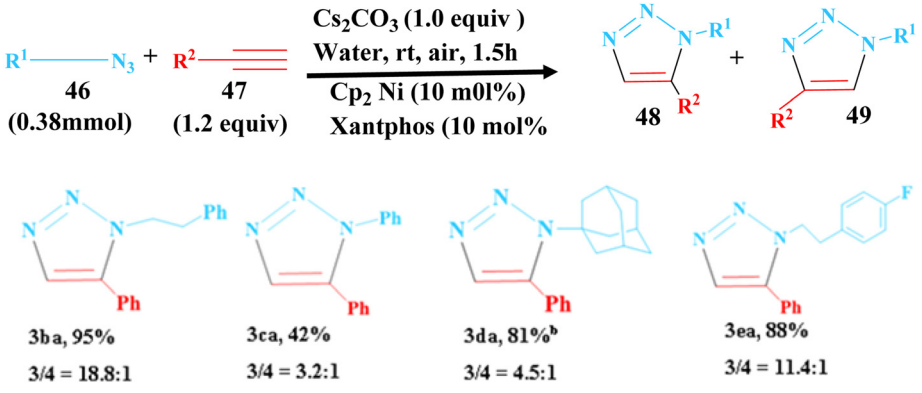
copper-catalyzed cycloaddition is effective in obtaining 1,4-disubstituted products in biomolecular reaction systems. We present a catalytic system employing Xantphos and Cp_2Ni for synthesizing 1,5-disubstituted 1,2,3-triazoles. The reaction occurs in both water and organic solvents at room temperature. This method is straightforward and scalable, accommodating a wide range of substrates, including aromatic and aliphatic compounds. Moreover, it enables the preparation of triazoles linked to carbohydrates or amino acids via cycloaddition (Scheme 10).

Production of 1,5-disubstituted[65] 1,2,3-triazoles can be accomplished efficiently in a single pot using an effective method that combines the conversion of bromide into azide and NiAAC. The use of isolated azides, which are not easily found on the market and may be unstable and challenging to handle, is prohibited by this method. Alcohol, carbamate, and ester are just a few of the functional moieties that this one-pot method can tolerate. Utilizing functionalized aryl and alkyl alkynes along with bromides, a range of 1,5-disubstituted 1,2,3-triazoles can be synthesized with moderate to good yields and regioselectivities. This approach facilitates the generation of diverse libraries of functionalizable 1,5-disubstituted 1,2,3-triazoles, offering valuable prospects for medicinal chemistry and chemical biology applications, among others (Scheme 11).

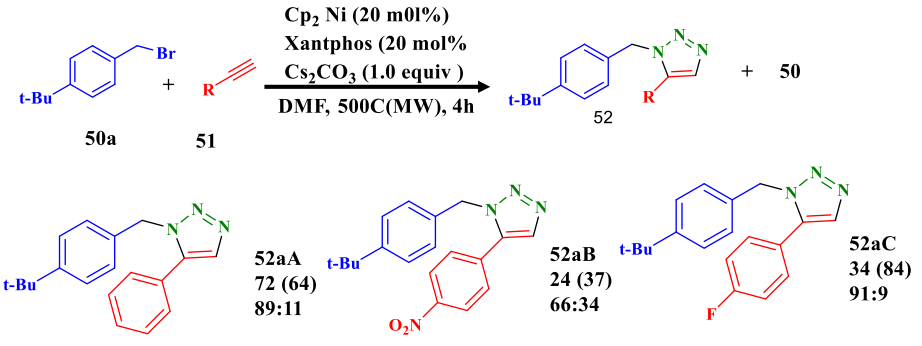
Heterocyclic functionalized frameworks[66] can be synthesized quickly via cycloaddition catalyzed by metals. Conducting azide–alkyne cycloadditions involving competing internal alkynes under reactivity-controlled and metal-catalyzed conditions has posed significant challenges. Here, we introduce a [3 + 2] cycloaddition approach using asymmetrical alkynes and organic azides. Employing nickel as a catalyst leads to the formation of functionalized 1,2,3-triazoles with enhanced control over chemoselectivity and regioselectivity. Specifically, cyano alkynes bearing a 4-cyano substituent and terminal alkynes yield 1,4,5-trisubstituted and 1,5-disubstituted triazoles, respectively. Inverse regioselectivity is seen when the alkynes and ynamides are compared to terminal alkynes and cyano alkynes, respectively. As a result, 1,4,5-trisubstituted triazoles with substituents of 5 amides and 5 thiols are produced. Through calculations using density functional theory, the reaction mechanism was made clear. The alkyne substrate is added oxidatively to the Ni(0)-Xantphos catalyst in order to form the nickel lacyclopropene intermediate, as per the suggested mechanism (Scheme 12).

5 Azide–alkyne cycloaddition catalyzed by iridium (IrAAc)

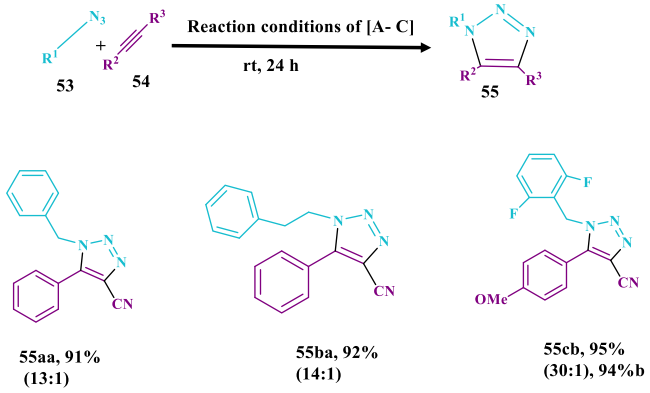
Regarding the complete synthesis[67] in place of 5-amino-triazole 58, Song and associates devised a highly selective,



Scheme 10: To get access to air and water-based 1,5-disubstituted 1,2,3-triazoles, azide–alkyne cycloaddition catalyzed by nickel.



Scheme 11: A multi-component reaction that generates azides *in situ* and produces 1,5-disubstituted 1,2,3-triazoles through azide–alkyne cycloaddition mediated by nickel.

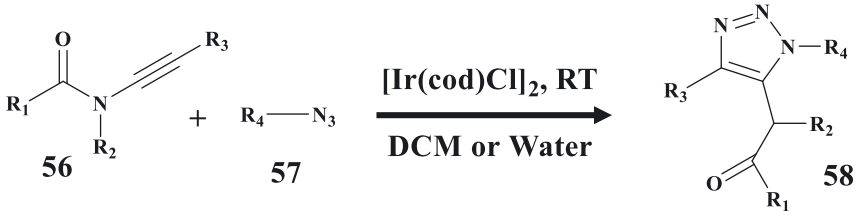


Scheme 12: Click reactions with chemo- and regioselectivity via nickel-catalyzed azide–alkyne cycloaddition.

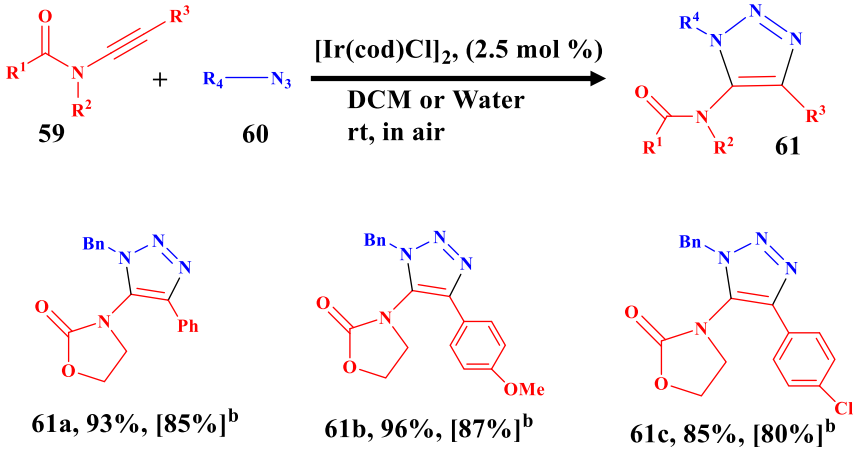
mild, and bioorthogonal approach (Scheme 14). For this technique, cyclic ynamides as well as acyclic ynamides work well; cyclic ynamides yields that are marginally higher than those of electron-poor groupings. If the nearby position of ynamide were to be replaced with a bulky group, the reaction's yield would be decreased (–R2) (Scheme 13).

A technique of obtaining[68] 5-amido completely replaced highly selective 1,2,3-triazoles is described. It involves the gentle, airy, watery, and bioorthogonal azide-ynamide cycloaddition process, which is catalyzed by iridium. Ynamide's strong regioselectivities may be related to the strong interaction between π-acidic iridium and carbonyl oxygen. In chemical and biological contexts, the iridium ion can efficiently catalyze this reaction due to its low cytotoxicity and insensitivity to oxygen and water. The gram-scale production of carbohydrates using this method (Scheme 14).

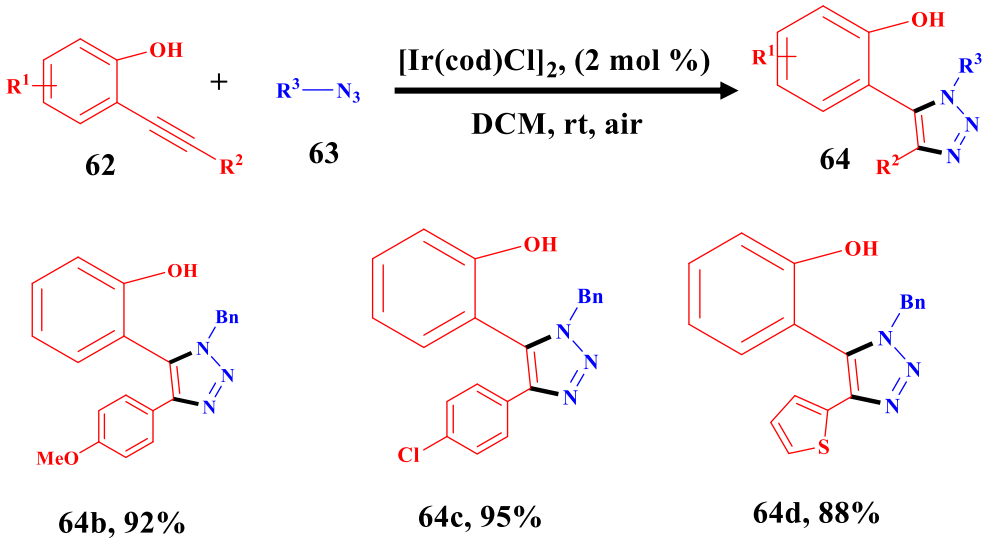
It has been possible to create[69] a novel cycloaddition of azides and alkynes with hydroxyl support, employing iridium as the catalyst. The 2-alkynyl phenols would rapidly access a range of triazoles through a regioselective cycloaddition with distinct azides when 2 mol% of $[Ir(cod)Cl]_2$ is present. This process is aided by the hydroxyl group, which acts as a directing group. The process yields succinctness, diversity, and mild, biocompatible reaction conditions. Moreover, the likelihood of the products undergoing late-stage divergent transformations is increased by the presence of the hydroxyl group (Scheme 15).



Scheme 13: Azide–alkyne cycloaddition catalyzed by iridium (IrAAC).



Scheme 14: Under mild circumstances, iridium catalyzes the complete substitution of 5-amido in 1,2,3-triazoles via azide-ynamide cycloaddition.



Scheme 15: Iridium-catalyzed hydroxyl-enabled cycloaddition of azides and alkynes.

6 Ruthenium-catalyzed azide–alkyne cycloaddition

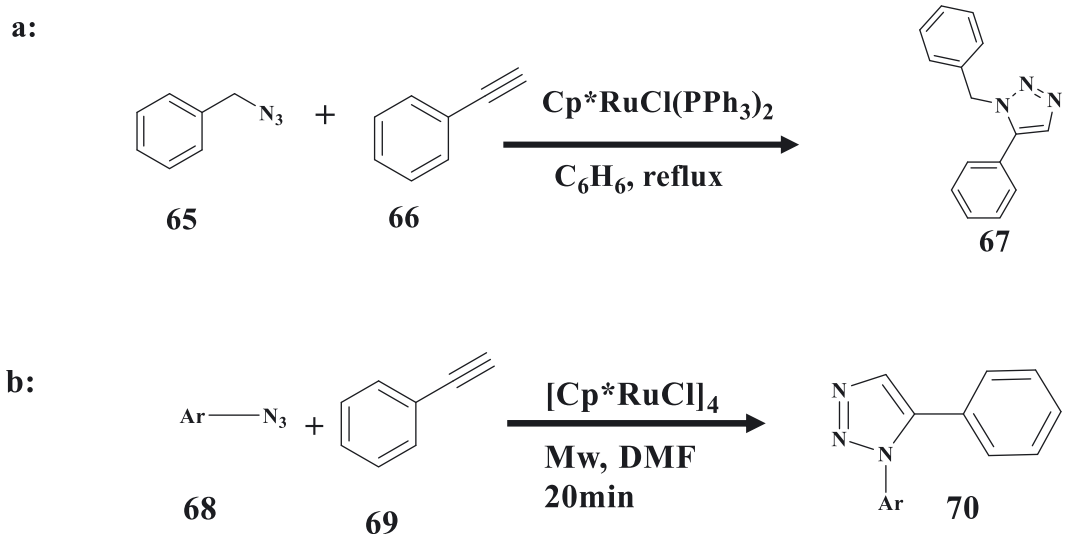
The first one was done by Jia and co-workers in 2005 where they described the selective fashion manner preparation of terminal and internal alkynes and the second was Ru(II) catalyzed transformation of 1,4,5-trisubstituted and 1,5-disubstituted organic azides.[70] These reactions coupled with CuAAC make it possible to obtain both regioisomers of 1,2,3-triazole which is a heterocycle that has been recently reviewed in medicinal chemistry/organic synthesis and material science.[71] These reactions coupled with CuAAC make it possible to obtain both regioisomers of 1,2,3-triazole which is a heterocycle that has been recently reviewed in medicinal chemistry/organic synthesis and material science. Sometime later in 2007, Fokin created a new catalytic system for the Ru(II) mediated cycloaddition of azides and alkynes; the presented process is useful for the formation of 1-arylated 1,2,3-triazoles from aryl azides. Regarding the substrate scope much freedom is possible in this reaction as both aryl and aliphatic azides are compatible with alkynes. When the described reaction is conducted under the microwave condition, it takes only 20 min, and the yield of new 1,2,3-triazole compounds is much higher (Scheme 16).

This reaction occurs efficiently under mild conditions and typically occurs at room temperature.[71] Through the reduction of activation energy, the catalyst facilitates the formation of products. DMF ensures the good solubility of the reactants by acting as a suitable solvent. Microwave irradiation further improves the reaction by raising the yield of the product and accelerating it. This is due to the fact that rapid and uniform heating minimizes adverse effects. Taking everything into account, this method offers a useful way to synthesize 1,5-disubstituted 1,2,3-triazoles, with the reaction products being maximized by microwave irradiation (Scheme 17).

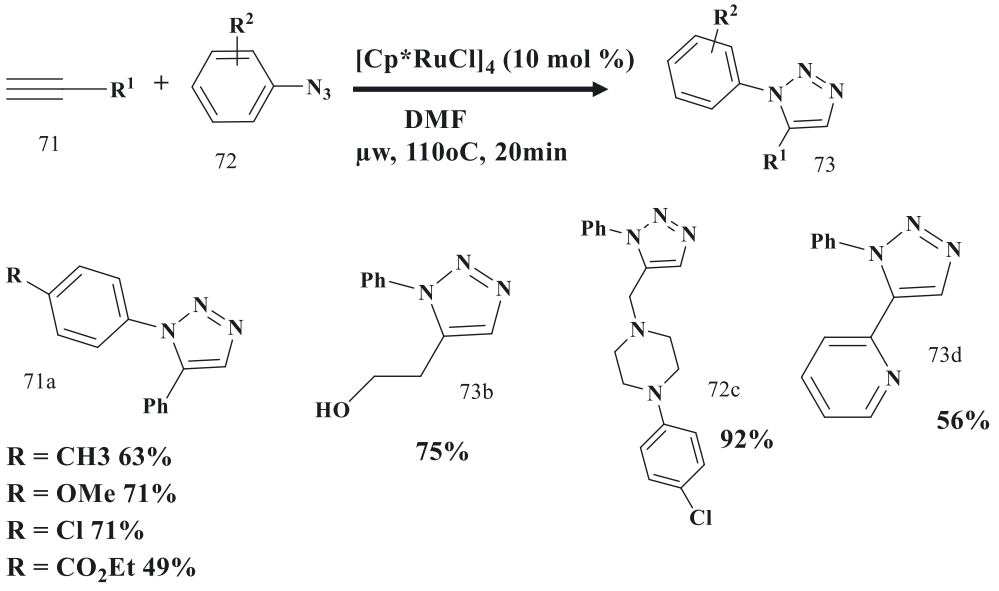
Starting with $Ru(PPh_3)_3Cl_2$ complex,[72] a complex of $[Ru(dppp)_2(CH_3CN)Cl][BPh_4]$ can thus be obtained. According to structural analysis, this complex primarily uses silver salts to act as a catalyst in the homocoupling of alkynes. Furthermore, it mediates the subsequent alkyne-azide click reaction as well as the alkyne homocoupling. The structural details of two catalytically active species, a new complex $[Ru(dip)_2Cl][BPh_4]$ (2) and an intermediate complex $[Ru(dip)_2(CCPh)_2]$ (6), have been obtained through synthesis and characterization (Scheme 18).

Huisgen cycloaddition, a regioselective[73] intramolecular process, generated macrocyclic triazole rings from several azido alkyne substrates. With the aid of catalyst control, two structurally different macrocycles with a 1,5- or 1,4-triazole and a n or $n + 1$ ring size have been produced from a common intermediate. This is the first instance of ruthenium catalyzing an intramolecular Huisgen cycloaddition (Scheme 19).

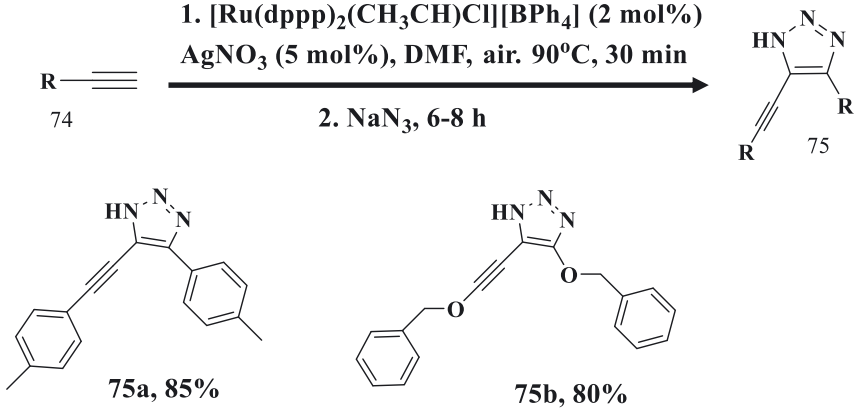
Formation for Numbers n and $n + 1$.The Huisgen [3 + 2] cycloaddition,[74] an important synthetic process that produces 1-protected, Azide–ynamide cycloaddition process catalyzed by ruthenium is known as 5-amido 1,2,3-triazoles. During this reaction, ruthenium acts as a catalyst to combine ynamides – which are compounds with an amide group and a triple bond – with azides. First, by coordination, the catalyst activates the azide and the ynamide. A five-membered ring intermediate is formed when the azide nitrogen atom nucleophilically attacks the activated ynamide. After that,



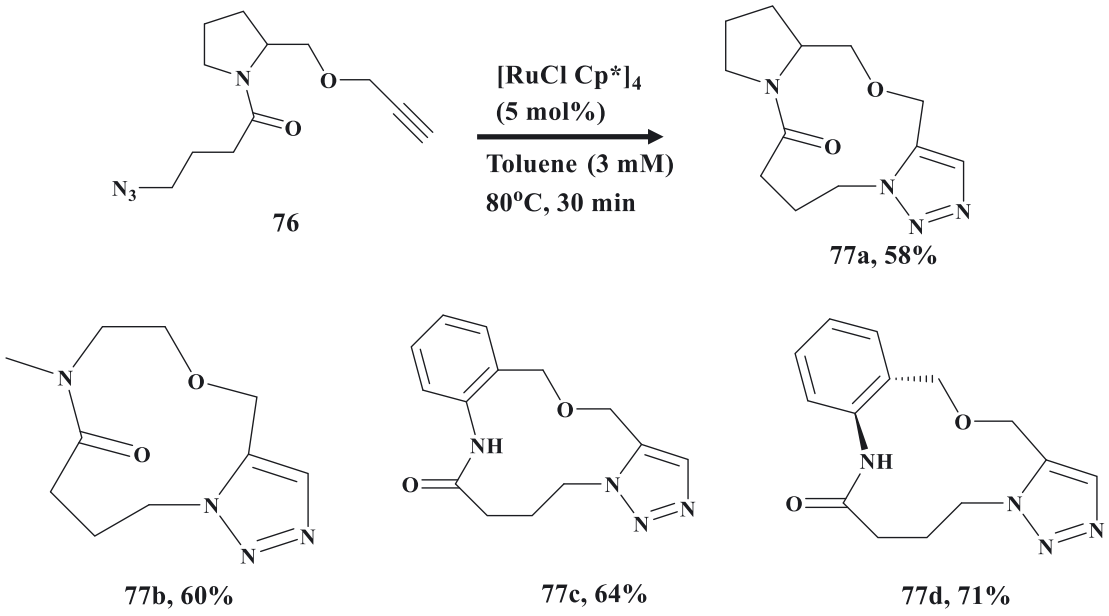
Scheme 16: Azide–alkyne cycloaddition catalyzed by ruthenium (RuAAC).



Scheme 17: Cycloaddition of alkynes and aryl azides is catalyzed by ruthenium.



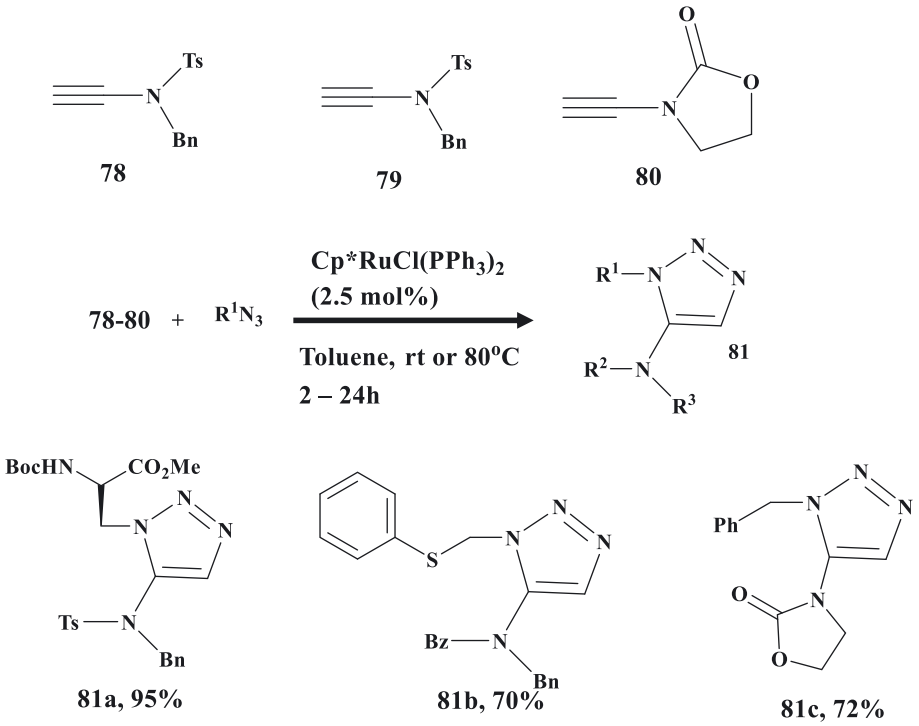
Scheme 18: $[Ru(dip)_2Cl][BPh_4]$ and $[Ru(dip)_2(CH_3CN)Cl][BPh_4]$ are synthesized through ruthenium-catalyzed alkyne reactions.



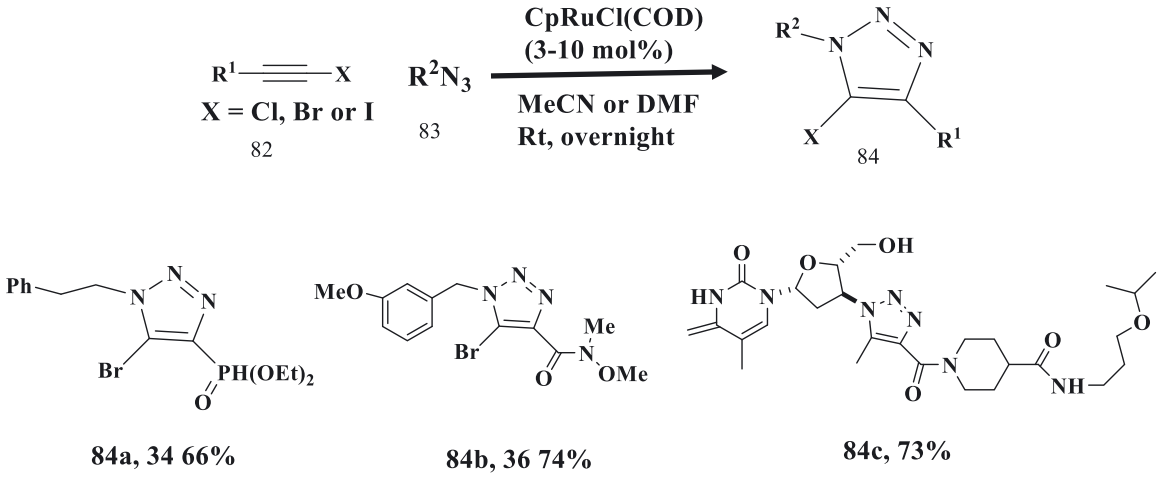
Scheme 19: Using catalyst control to access skeletal diversity: macrocyclic triazole ring.

this intermediate goes through tautomerization and rearrangement, which causes the intended 1,2,3-triazole product to develop. A common modification to the triazole product is 1 protection, which is achieved by employing different protecting groups such as tert-butyl or benzyl to shield the nitrogen atom at position 1 (Scheme 20).

The ease of preparation of the title compounds by the catalytic action of Ruthenium(II) azide (cyclooctadiene) chloride and[75] zynamide cyclopentadienyl involving 4-haloisoxazoles is achievable by the reaction of electron-deficient 1-chloro-, 1-bromo-, and 1-iodoalkynes with nitrile oxides. Organic azides are good 1,3-dipoles that create 5-halo-



Scheme 20: Ruthenium was used for [3 + 2] catalysis in order to protect 1, protected 5-amido 1,2,3-triazoles.



Scheme 21: 2. Cycloaddition catalyzes haloalkynes to generate nitrile oxides and organic azides halotriazoles, fourth and fifth.

1,2,3-triazoles using air-stable transformations under the direction of alkyne-substrate 1. Twenty five equivalents of the corresponding 1,3-dipole compared to the alkyne partner at 30 °C. Reactive 1-haloalkynes are propionic amides and ketones, esters and phosphonates. More so, the halogenated azole products can be further subjected to palladium catalyzed cross coupling reactions and reactive amide group transformations. Given that [CpRuCl(cod)] has no catalytic activity, the steric hindrance of the Cp(η5-C_5Me_5) fragment in this complex is proposed to be greater than that which is found with the Cp (η5-C_5H_5) moiety (Scheme 21).

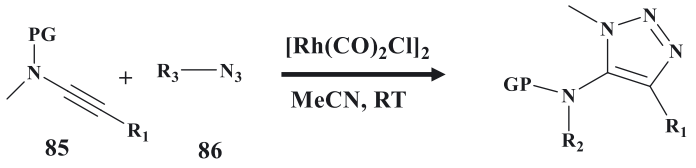
7 Azide–alkyne cycloaddition catalyzed by rhodium (RhAAC)

Li and colleagues[76] described the first open flask technique utilizing rhodium(I) catalyst to synthesize 5-aminotriazoles from lactams **85** and **86** at room temperature. The catalyst used was $[Rh(CO)_2Cl]_2$, and the solvent used was MeCN (Scheme 22). They further state that since the reaction was still as effective in the open flask, there was no need to exclude air or moisture. Numerous solvents could be used with this technique without significantly altering the reaction yield. Different protective group ynamides did not affect the reaction outcomes. It's interesting to note that ynamides and noisy groups had a successful reaction that produced an isolated yield of 84 % triazole. Most likely, the strong electron-withdrawing group characteristics of nasal acyl groups are the cause of the extended reaction time. The reactions to para-methyl, methoxy, trifluoromethyl, and chloroynamides produce the necessary triazoles in excellent yields in contrast to ordinary ynamides, regardless of their electronic nature. Additionally accepted were ortho and meta-alterations on the benzene ring. It was discovered that alkyne amides or ynamides with extra alkenyl moieties or heteroaryl rings are suitable RhAAC reaction substrates (Scheme 22).

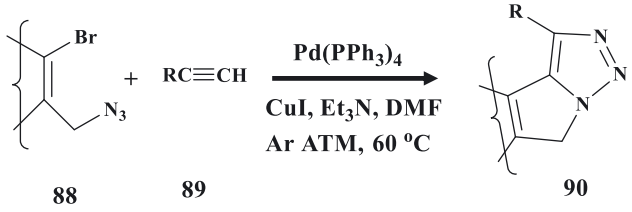
8 Cycloaddition of azide and alkyne catalyzed by palladium

A two-step Sonogashira coupling-CuAAC reaction was developed by Kar et al. to produce cycloolefins and 1,2,3-triazolopolyhydroaromatics.[77] The catalyst for the reaction was $Pd(PPh_3)_4$, the base was Et3N, and the co-catalyst was CuI. The starting materials for the reaction were 2- or 1-azidomethyl-1- or 2-bromodihydronaphthalenes, arenes, or cycloalkenes. The desired compound was obtained as the product of this process, which also aided in intramolecular hetero-annulation. The method yielded moderate to good amounts, up to 59 % yields when the reaction was conducted at 60 °C in a N_2 atmosphere with DMF solvent, and an 8–10 h reaction time (Scheme 23).

A sophisticated synthetic technique[78] involving palladium–copper catalyzed reactions in a single pot has yielded a mixture of 1,2,3-triazoles fused with benzoheterocycles of varying ring sizes, including five, six, seven, and eight-membered rings such as isoindoline, tetrahydroisoquinoline, benzoazepine, and benzoazocine. This method showcases the synthesis of biologically significant uracil derivatives, highlights the impact of bis-hetero-annulations, and demonstrates the versatility of utilizing acetylene gas as a cost-effective substrate. By employing readily available substrates, these reactions offer a broad range of applications and are amenable to experimental manipulation (Scheme 24).



Scheme 22: Azide alkyne cycloaddition catalyzed by rhodium (RhAAC).

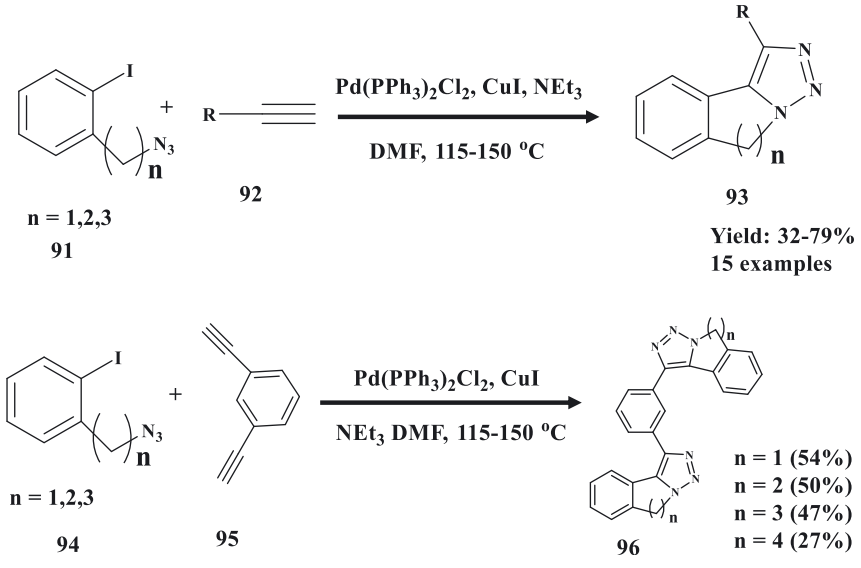


Scheme 23: Azide–alkyne cycloaddition catalyzed by palladium (PdAAC).

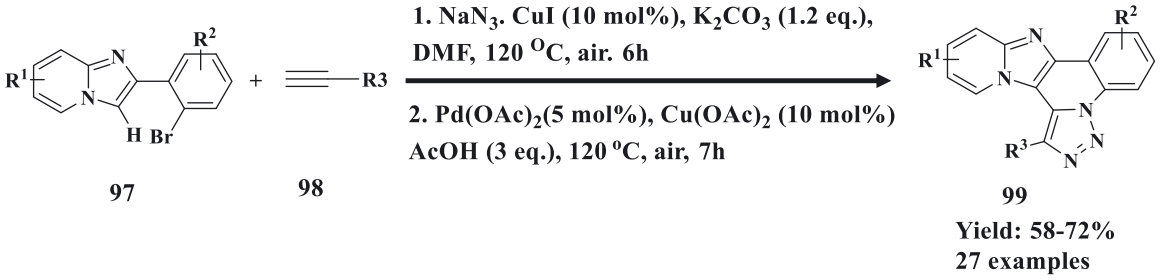
Here, we present an efficient one-pot synthesis[79] method for producing 2-(2-bromophenyl)imidazo[1,2-a]pyridines, incorporating sodium azide and alkynes to yield 1,2,3-triazole/quinoline-fused imidazo[1,2-a]pyridines. This innovative technique combines intramolecular cross dehydrogenative C–C coupling between 1,2,3–triazole and imidazo [1,2-a]pyridine, azide–alkyne cycloaddition, and C–N coupling between 1,2,3–triazole and aryl bromide. Catalyzed by a one-pot bimetallic relay, this cascade process stands out for its simplicity in starting materials, minimal synthetic steps, high efficiency, and utilization of renewable oxidants, rendering it a unique method (Scheme 25).

Fused benzoxazino[1,2,3]Quinolinone[80] 4a–4k triazolyl [4,5–c] derivatives 49 can be made in a single pot using the 5-iodo-4-(prop-2–yn–1–yl) reaction-2H-benzo[b][1,4] Oxazin-3(4H)-one (3) is synthesized in ligand-free conditions using a range of aryl azides and copper and palladium catalysis. The intended fused triazoles were produced in good to exceptional yields by the process. The synthetic derivatives' *in vitro* cytotoxic potential against the cancer cell lines MCF-7, A-549, and HeLa was assessed using the MTT assay. The outcomes demonstrated that compound 4d's cytotoxic activity against MCF-7 and A-549 demonstrated a wide range of activity. The IC50 values of cisplatin, the recommended drug, are similar at 11.18 ± 0.8 and 17.81 ± 0.6 μM (Scheme 26).

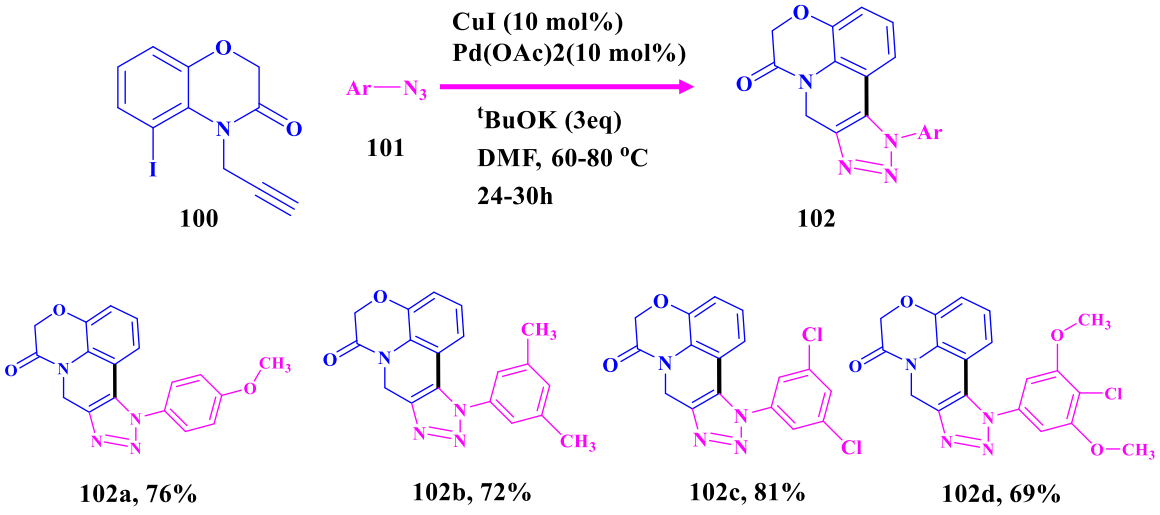
A quick method for[81] Palladium catalysis has been successfully employed to create a variety of fused triazoles with different functionalities under ligand-free conditions. The palladium-catalyzed cyclization that yields the hitherto unattainable fused triazolo[4,5-d]quinoline/chromene/thiochromene derivatives is significantly aided by the addition of TBAI, it was discovered. This technique offers a quick and easy way to get good to outstanding yields of fused triazoles. Compounds 2a and 2f exhibit inhibitory effects against a certain non-small cell lung cancer cell line, as demonstrated by the screening of the produced compounds against several cancer cell lines (Scheme 27).



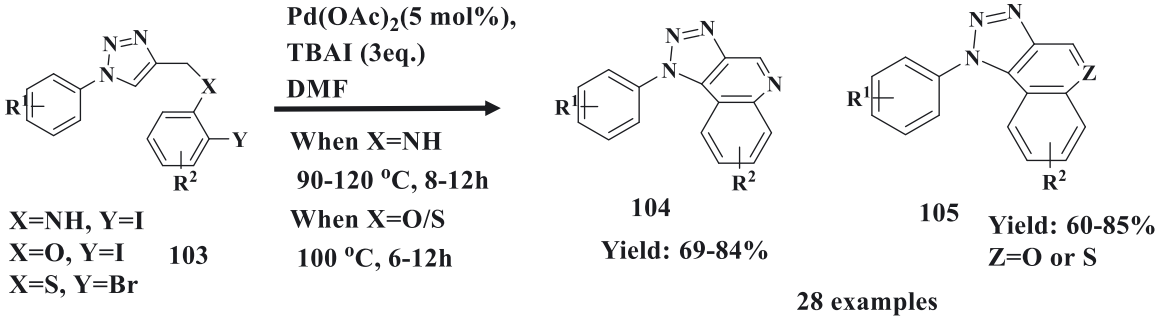
Scheme 24: Benzoheterocycles are efficiently synthesized [1, 2, 3] through Pd–Cu catalyzed heterocyclization.



Scheme 25: Through single-pot cascade reactions, bimetallic relay catalysis yields [1,2,3]triazolo[1,5-a]quinolines.



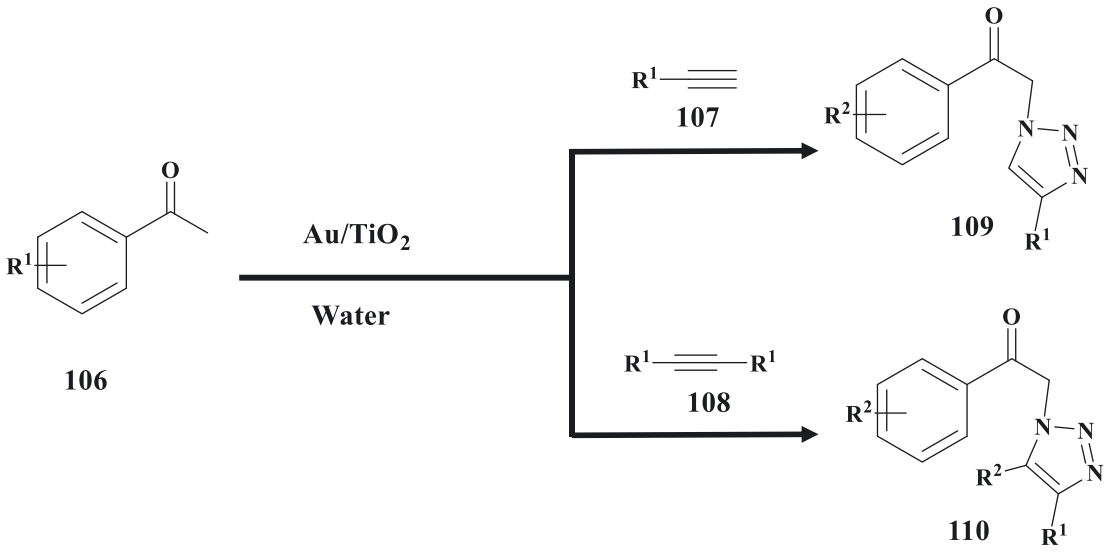
Scheme 26: Anticancer characteristics of fused benzoxazino [1, 2, 3] triazolyl [4, 5-c] quinolinone derivatives synthesized in a single pot.



Scheme 27: Fusion of fused triazolo[4,5-d]quinoline derivatives is catalyzed by Pd and requires tetrabutylammonium iodide.

9 Azide–alkyne cycloaddition catalyzed by gold (AuAAC)

Muthusubramanian and associates in 2013[82] revealed the synthesis of 1,4-disubstituted triazoles 109 and 110 from substituted benzoyl azides 108 and terminal/internal alkynes 1/200 RT in water utilizing porous Au/TiO_2 nanoparticles for 20–30/45 min, respectively. This process was green, efficient, and regioselective (Scheme 28). They also stated that while p-xylene, 1,2-dichloroethane, acetonitrile, and toluene offered extremely low yields, solvents like THF, DMSO, and ethanol gave intermediate yields while water or tBuOH/water gave substantial yields as single regioisomers. After more research, the scientists discovered that a stepwise method utilizing azide 108, benzoyl/alkyl bromide, and 107 produced triazoles with a 75 % yield in 30 min, outperforming one-pot MCR. With no appreciable yield loss, the catalyst was created utilizing a deposition-precipitation technique in up to five cycles. They discovered that aliphatic



Scheme 28: Azide–alkyne cycloaddition catalyzed by gold (AuAAC).

and aromatic alkynes with electron-donating and electron-withdrawing groups were appropriate for this technique, given the range of alkynes used as substrates (Scheme 28).

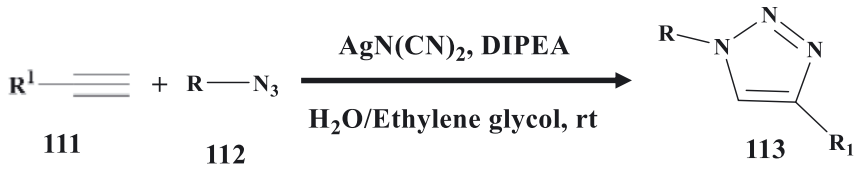
10 Azide–alkyne cycloaddition catalyzed by silver (AgAAC)

Sarma and associates[83] revealed a unique, robust, and extremely effective method for the regioselective synthesis of 113 from 112 and 11 utilizing water and ethylene glycol at room temperature for 2–6 h, which was catalyzed by very efficient silver dicyanamide/DIPEA (Scheme 29). In terms of alkyne substrate scope, they discovered that aromatic alkynes produced a yield that was somewhat higher (90–97 %) than that of aliphatic alkynes (90–94 %). Alcohol and ester, among other functional groups with alkynes, were also appropriate substrates for this methodology (Scheme 29).

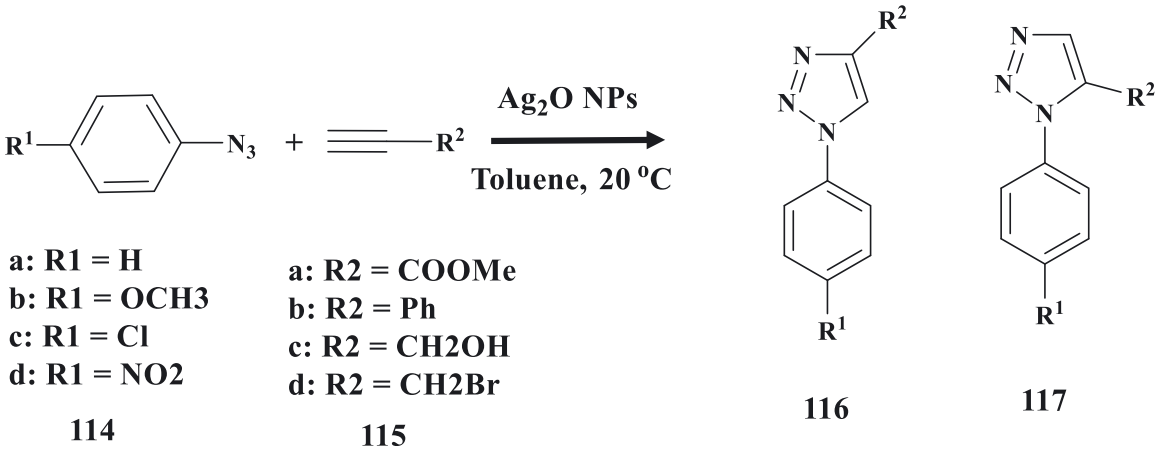
Even though they have[84] Vinyl-1,2,3-triazole synthesis and polymerization have long been known, but only recently have they drawn attention due to the remarkable advancements in the most common application of the "click" chemical theory, the copper-catalyzed azide–alkyne cycloaddition. It is true that up to this point, a substantial library of monomers and polymers based on vinyl-1,2,3-triazoles with aromatic, aliphatic, heterocyclic, or functional groups has been described. Their polymerization hasn't, however, received much media attention, though this is anticipated to change soon. This review discusses the synthesis and polymerization of vinyl-1,2,3-triazole regioisomers, the properties of the resultant materials, and their possible uses in the creation of macromolecular objects that are intelligent and stimuli-responsive (Scheme 30).

A novel, reliable, and effective technique[83] for silver-mediated azide–alkyne cycloaddition (AgAAC) reactions in H_2O/Ethylene Glycol at room temperature has been created. The method states that under mild conditions, 1,4-disubstituted-1,2,3 triazoles can be formed regioselectively using silver dicyanamide/DIPEA, a highly effective catalyst system (Scheme 31).

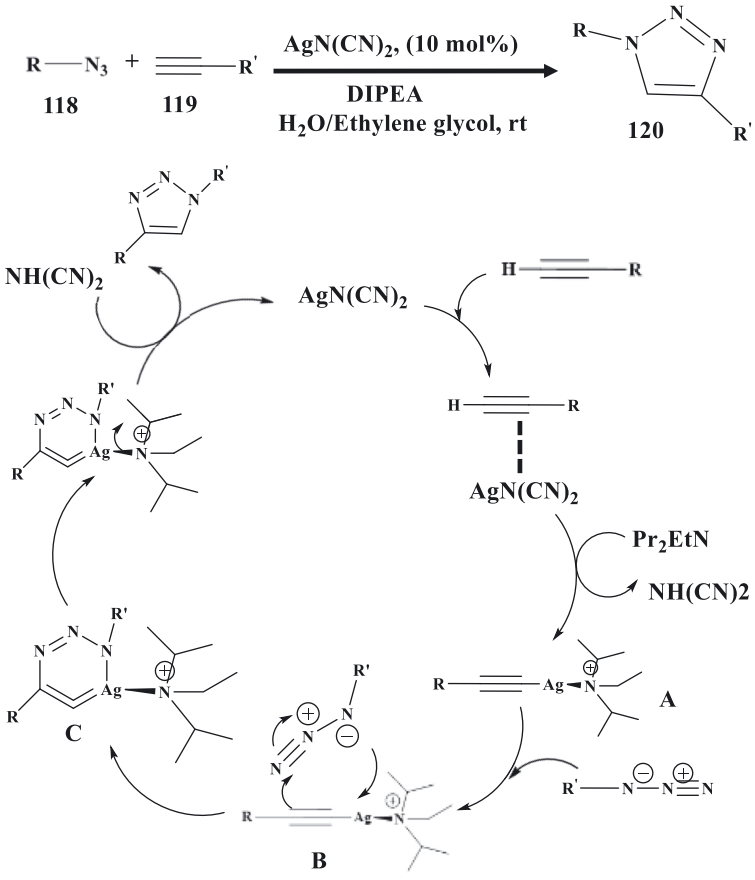
The term "click reaction" describes the dipolar cycloaddition reaction that is catalyzed by copper and involves azides and alkynes. This reaction forms a triazole ring by integrating nitrogens into a cyclic hydrocarbon scaffold. This reaction and its byproducts, triazole-containing heterocycles, are highly important in medicinal chemistry due to their efficiency and versatility. The only metal that can catalyze this process is copper, though its exact mechanism is still a mystery. Here we show that silver halides can also



Scheme 29: Azide–alkyne cycloaddition catalyzed by silver (AgAAC).



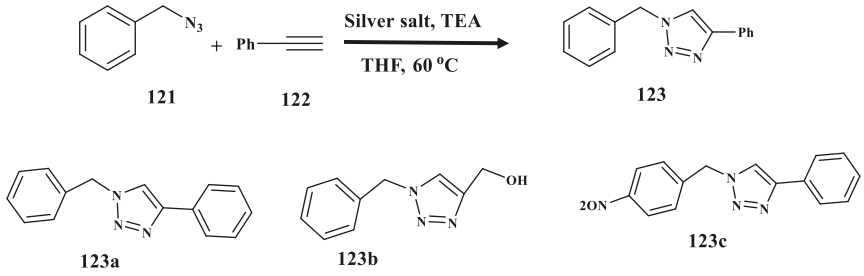
Scheme 30: Polymerization and N- and C-vinyl-1,2,3-triazole synthesis.



Scheme 31: A room temperature catalytic method that is very successful for synthesizing 1,4-disubstituted-1,2,3 triazoles.

catalyze "click reactions" in non-aqueous media. It serves as a substitute for the widely recognized CuAAC click reaction. The kind of counter ion in the silver salt determines the reaction's yield. Numerous notable characteristics of this reaction include strong regioselectivity, mild reaction conditions, easy availability of substrate, and reasonably high yields. This correspondence aims to shed light on the reaction's still-mysterious mechanism by showcasing the effects of solvent and counter ions and presenting the outcomes of a novel catalyst (Scheme 32).

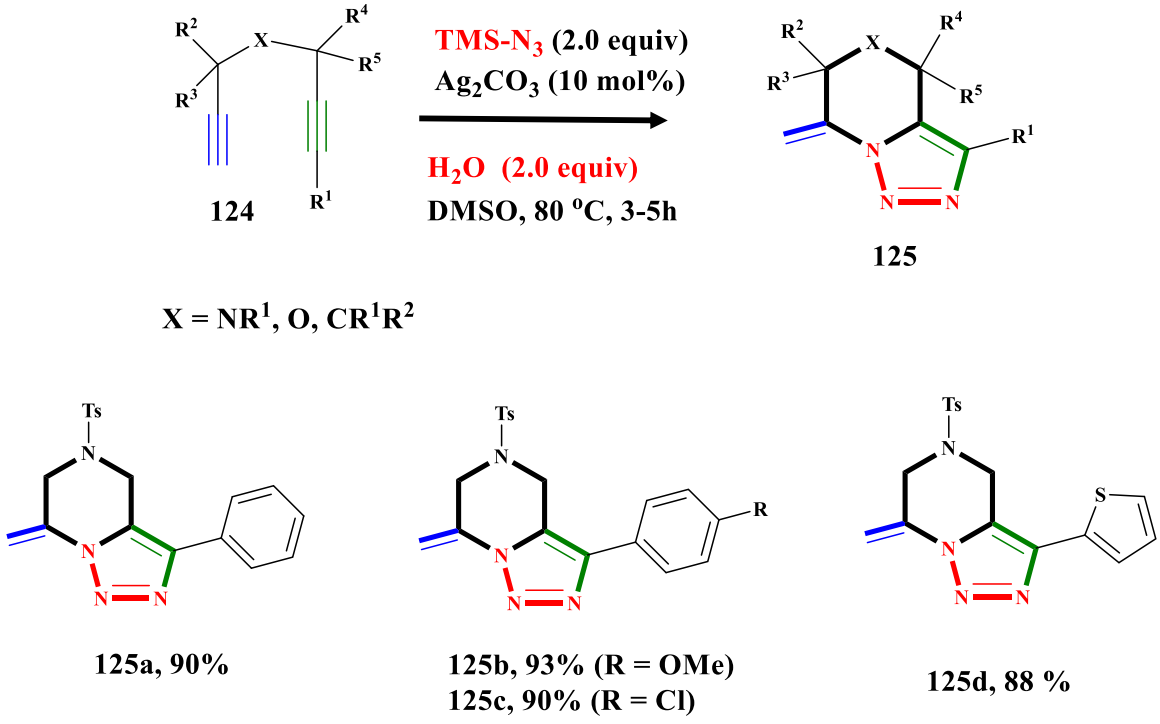
There is a report on an all-purpose[85] hydroazidation cascade and the alkyne-azide 1,3-dipolar cycloaddition of diynes using silver catalysis. Matching 1,5-fused-1,2,3-triazoles were produced in good to exceptional yields when trimethylsilyl azide (TMS-N_3) was reacted with a variety of diynes in the presence of H_2O. This novel technique



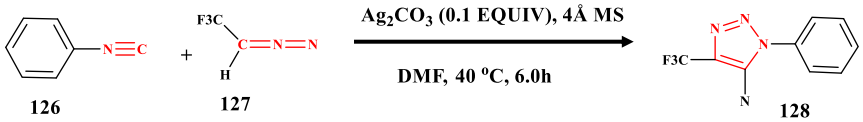
Scheme 32: Azide–alkyne cycloaddition (AgAAC) catalyzed by silver: evaluating the mechanism through calculations using density functional theory.

provides convenient access to a range of fused 1,2,3-triazoles and is easy to operate, thanks to its broad substrate scope, good functional group tolerance, and high reaction efficiency (Scheme 33).

The cycloaddition catalyzed by silver[86] Density functional theory (DFT) simulations were used to study the synthesis of 1,4-disubstituted-1,2,3-triazoles. We present computational investigations of the primary reaction mechanism, two side reaction processes that have been postulated, and the contribution of silver(I) to the understanding of the key characteristics of the transformation in this paper. The investigation of the mechanism suggests that the [3 + 2]-cycloaddition is more likely to be the step that determines the primary reaction's rate, whereas the two competitive side reaction paths are kinetically unfavorable and have comparatively high barriers. Frontier Molecular Orbital (FMO) study suggests that the properties of the isocyanide FMO and how FMO overlap occurs in the cycloaddition are altered when silver(I) is coordinated with isocyanides. According to Natural Population Analysis (NPA) charge analysis, the electron-withdrawing characteristic of silver(I) causes the –NC group's charge density to drop, improving the substituent tolerance and reactivity of isocyanides. Furthermore, in comparison to the substantial electron-withdrawing impact of silver(I) on isocyanides, the effect of substituents on the aryl rings on –NC groups is essentially insignificant. Therefore, it is believed that the superior aryl-substituted tolerance and strong regioselectivity of the technique are due to the catalyst, silver(I) (Scheme 34).



Scheme 33: Silver-catalyzed diynes 1,5-fused 1,2,3-triazole frameworks are produced with TMS-N_3.



Scheme 34: To provide mechanistic insight into the cycloaddition synthesis of 1,4-disubstituted-1,2,3-triazoles, silver is an essential component of the process.

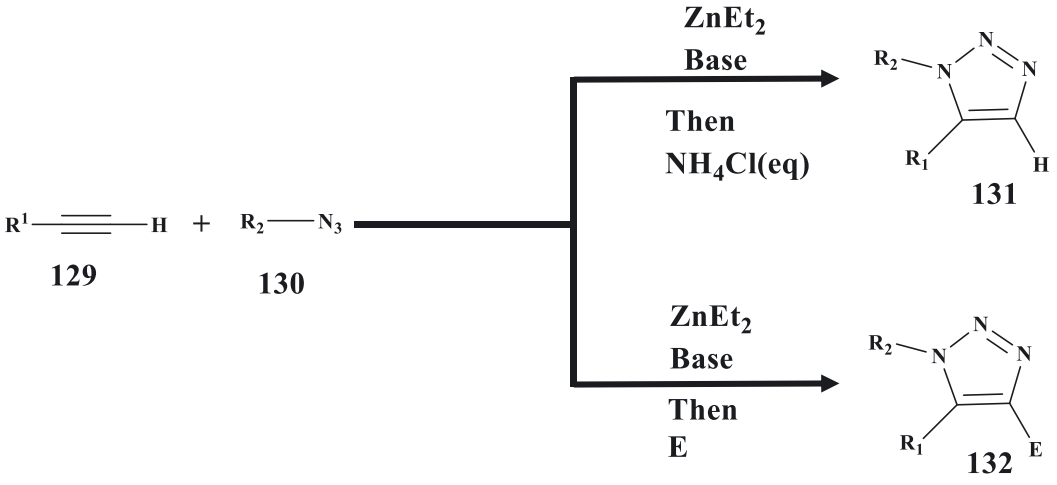
11 Azide–alkyne cycloaddition catalyzed by zinc (ZnAAC)

Greaney and coworkers[87] revealed how to create 131 regioselectively from 129 and 130 by utilizing NH_4Cl and $ZnEt_2$ as catalysts for 72 h at room temperature (Scheme 35). Because of the reactants' breakdown at high temperatures, the reaction's yield is reduced. Esters, thioethers, propargyl ethers, 1,2-diphenylacetylene, and (iodoethynyl)benzene were found to be suitable for the alkyne substrate range, however, tosyl azide compounds and alkyl azides were found to be unsuitable for this approach for the azide range. Nevertheless, 1,4,5-trisubstituted triazoles were also produced by substituting D_2O/D_3CCO_2D for NH_4Cl via a 3-MCR coupling process, demonstrating substitution at the 4-position. The aforementioned procedure takes 18 h to finish at room temperature (Scheme 35).

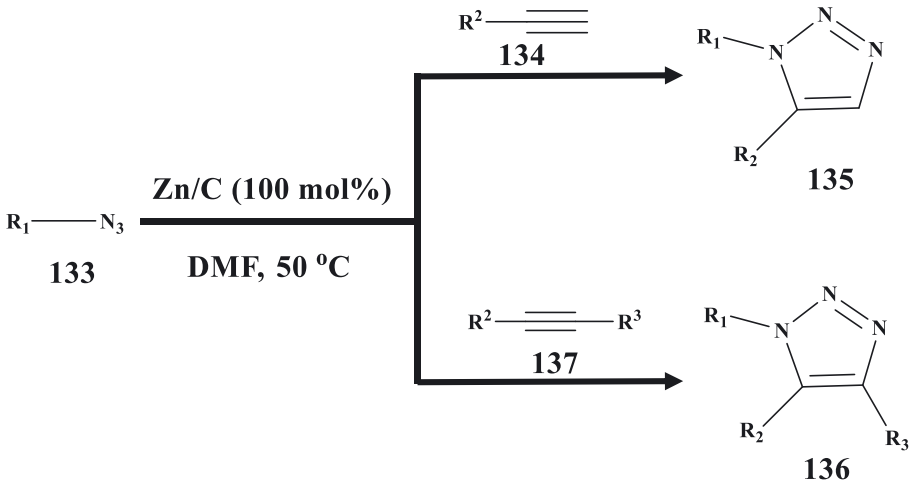
Chen and coworkers[70] developed a novel, mild, heterogeneous method for Zn/C (zinc on carbon) catalysis to synthesize 135 and 136 from 134 with aryl alkynes 133 and 137, respectively. This enabled them to overcome the problem of homogeneous catalyst-product separation and the fact that relatively little progress has been made on heterogeneous solid catalysts (Scheme 36). Additionally, they discovered that 50 °C was the ideal temperature for the procedure and that the aprotic and polar solvent DMF was the appropriate solvent. While charcoal may convert Cu(II) to Cu(I), zinc dust frequently contains Cu(II) impurities. Despite the lack of cycloaddition products, they thought that a tiny amount of CuI, rather than Zn/C, caused an *in situ* catalyzed cycloaddition reaction. This suggests that the reaction might be catalyzed by Zn/C. Additionally, they discovered that aliphatic alkynes did not initiate a reaction and that aryl alkynes with low electron counts were formed in lower yields than those with high electron counts. Lower yields were obtained when the same procedure was used in a one-pot, three-component reaction. The catalyst's efficiency drops after the fifth cycle, and the reaction takes 15–20 h to complete (Scheme 36).

12 Synthesis of 1,4-disubstituted 1,2,3-trizole without metal

Furthermore, there has been a lot of interest lately in the organocatalysis-based synthesis of triazoles from azides.[88–91] Organocatalysis does not yield as many difficult-to-handle intractable metal salt by-products as metal catalysis does. A three-component one-pot technique for the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles was created in 2012 by Cao's research group (Scheme 37a)[92] The activated primary alcohol 137 reacts with N-(p-toluenesulfonyl)imidazole (Tslm) to generate alkyl tosylate (R_1OTs) in this method, which does not require the use of a metal catalyst. The azide



Scheme 35: Azide–alkyne cycloaddition catalyzed by zinc (ZnAAC).

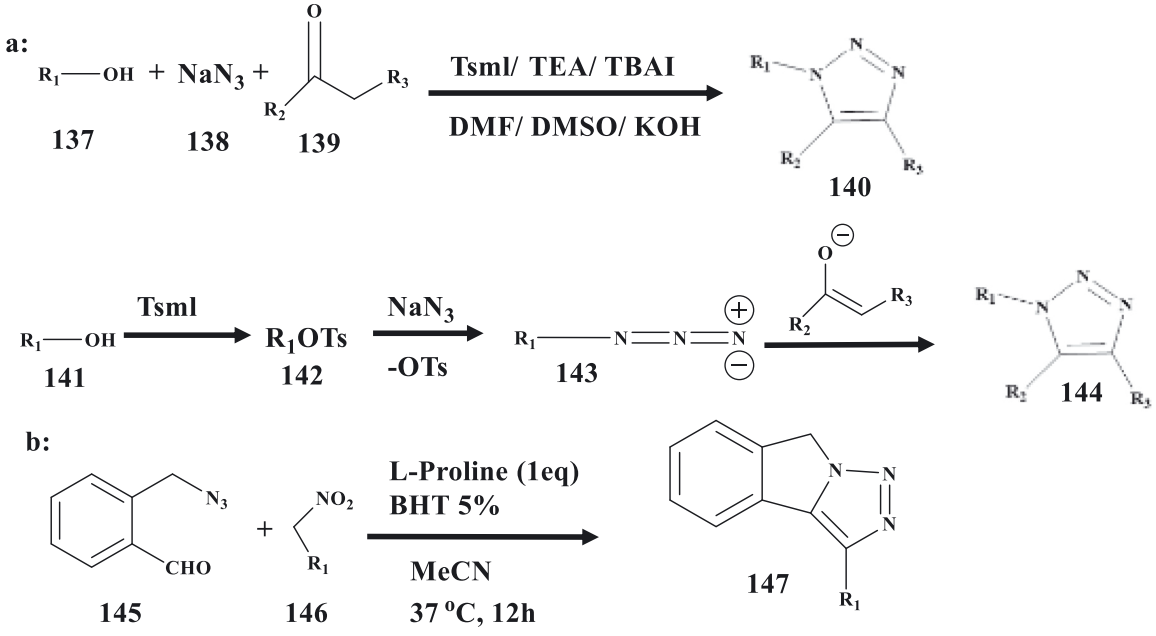


Scheme 36: Intramolecular Schmidt reaction to prepare amides.

ion then combines with the R_1OTs through a nucleophilic substitution reaction to produce an azido alkyl group (R_1N_3). A series of 1,2,3-triazole compounds 140 were produced by dehydration and the cycloaddition process between azido alkyl and enolate. A metal-free three-component process for the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles was also described by Professor Dehaen in 2014 (Scheme 37b)[93] L-proline catalyzes the following reactions: 1,3-dipolar cycloaddition of azide and activated alkenes yields trisubstituted 1,2,3-triazole 147 this reaction is then followed by the Knoevenagel condensation reaction of formyl group with nitro compound 145. A number of triazole moieties and fused triazole heterocycles can be synthesized using this process, which also offers the benefits of good regioselectivity, high yield, and compatibility with functional groups.

13 Conclusions

Advances in the synthesis of 1,2,3-triazoles via azide–alkyne cycloaddition, catalyzed by transition metals, have increased the importance of these molecules in chemical biology, drug development, and materials science. Click chemistry offers a strong platform for their efficient synthesis, underscoring their versatility and potential in various applications. In this review, we have discussed catalytic



Scheme 37: Organocatalyzed azide to triazole.

performance of transition metals Cu, Ir, Rh, Ru, Ni, Pd, Au, Ag, and Zn, which were applied in the form ligands and salts in 1,2,3-triazole synthesis via azide–alkyne cycloaddition. Among all transition metals the Cu-complexes and salts were found more efficient for selective synthesis. It is also concluded that there are certain azide–alkyne reactions which completely catalytic specific, and cannot be perform as such by changing transition metal. Through this review, we have outlined the growing interest and recent advancements in this area with particular focus on reaction conditions, and mechanistic insights.

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