2. LITERATURE REVIEW

2.1 INTRODUCTION

This chapter presents a panoramic view on various synthetic methods available in the literature to access the 1,2,3-triazole moieties. The content of this chapter encapsulates synthetic methods categorically arranged under the titles such as azide-alkyne cycloaddition, azide-olefin cycloaddition and their intramolecular versions. Initially this chapter elaborates the general synthetic routes available to prepare the starting materials such as azides, alkynes and olefins. In the azide-alkyne cycloaddition, starting from Huisgen thermal cycloaddition, other cycloadditions such as metal catalyzed regioselective cycloaddition and strain promoted cycloaddition and their mechanistic aspects are discussed in detail. In the case of azide-olefin cycloaddition, the details are furnished as two parts. First part is oxidative azide-olefin cycloaddition and the second one is eliminative azide olefin cycloaddition. In the eliminative azide-olefin cycloaddition, another interesting part is narrated. It is ‘organo-click reactions’. In addition, the methods other than azide-alkyne cycloaddition and azide-olefin cycloaddition are also discussed in the later part of this chapter.

2.2 SYNTHESIS OF BUILDING BLOCKS

The 1,2,3-triazoles synthesized through click reaction has gain much attention due to its widespread applications in various fields. It fact the required starting materials such as alkynes, activated olefins (chalcones, β-nitrostyrenes, etc.) and azides can easily be incorporated into a wide range of compounds by several common methods.

2.2.1 Methods for synthesis of azides

The most common route especially to synthesize alkyl azides from nucleophilic displacement of halides, acetates sulfonates and epoxides by azide ion. The modified Mitsunobu reaction (PPh₃, DEAD, HN₃) transforms alcohols
into alkyl azides with inversion of configuration. The alkyl/aryl azides are synthesized from alkyl/aryl amines via diazotization and nucleophilic displacement with azide ion. CuI/L-proline catalyzed coupling of aryl halides or vinyl iodide with sodium azide affords aryl azides or vinyl azides [33-36].

Scheme 2.1 Methods of preparation of azides.

2.2.2 Methods for synthesis of alkynes

Generally terminal alkynes are synthesized by propargylation of alcohols, amines and amides with propargyl bromide in the presence of base. Another

Scheme 2.2 Methods of preparation of alkynes.
convenient way to synthesize terminal alkynes is with Bestmann-Ohira reaction of aldehydes and dimethyl diazomethylphosphonate in the presence of K₂CO₃. The Sonogashira cross-coupling reaction is well-known as being one of the most important reactions for the construction of carbon-carbon bonds, especially for the synthesis of terminal and internal alkynes through palladium-catalyzed coupling of terminal alkynes with aryl or vinyl halides [37-39].

2.2.3 Methods of preparation of chalcones and β-nitrostyrenes

There are mainly two routes for synthesis of chalcones:

A) Aldol condensation of acetophenones with benzaldehydes
B) Friedel-Crafts acylation of phenols with cinnamoyl chloride

A) Chalcones can be synthesized by aldol condensation of acetophenones with benzaldehydes in the presence of either basic or acidic catalysts. Substituted chalcones were also synthesized by piperidine-catalyzed aldol condensation to avoid side reactions such as multiple condensations, rearrangements, and polymerizations, etc [40-46].

![Scheme 2.3 Methods of preparation of chalcones via aldol condensation.](attachment:image)

B) Chalcones can be synthesized by the Friedel-Crafts acylation of phenols with cinnamoyl chloride in the presence of anhydrous AlCl₃ [47].

![Scheme 2.4 Methods of preparation of chalcones via Friedel-Crafts acylation.](attachment:image)
\(\beta\)-Nitrostyrenes were mainly synthesized through Henry reaction by condensation of nitro-alkanes with benzaldehydes in the presence of bases such as NaOH, KOH, methylamine and ammonium acetate, etc [48-49].

\[
\begin{align*}
\text{R}^1\text{H} + \text{O}_2\text{N}^\ominus\text{R}^2 & \xrightarrow{\text{Base}} \text{R}^1\text{H} + \text{O}_2\text{N}^\ominus\text{R}^2 \\
\text{Base} = \text{NaOH, NH}_4\text{OAc, CH}_3\text{NH}_2, \text{etc.}
\end{align*}
\]

**Scheme 2.5** Methods of preparation of \(\beta\)-nitrostyrenes via Henry reaction.

### 2.3 HUISGEN 1,3-DIPOLAR CYCLOADDITION

A 1,3-dipolar cycloaddition reaction is one of the most important synthetic methods for the construction of five membered heterocyclic systems. Azide-alkyne cycloaddition has been known since 1893 when Michael reported the first synthesis of 1,2,3-triazoles from diethyl acetylenedicarboxylate and phenyl azide [50]. In 1960’s, Huisgen systematically studied the family of 1,3-dipolar cycloaddition (Scheme 2.6) reactions of 1,3-dipoles (azides [51-52], diazo compounds [53], nitrones [54] and nitrile oxides [55], etc.) and dipolarophiles.

1,3-dipolar cycloaddition of a diazo compound

\[
\begin{align*}
\text{Ph} + \text{N}_2\text{O}^\ominus & \xrightarrow{\text{R}^1\text{R}^2} \text{Ph} + \text{N}_2\text{O}^\ominus \\
\text{Isoxazoline}
\end{align*}
\]

1,3-dipolar cycloaddition of a nitrones

**Scheme 2.6** Some examples of the 1,3-dipolar cycloaddition.
Huisgen established mechanism that the 1,3-dipolar cycloadditions proceed in a step-wise fashion rather than a concerted fashion [52] and henceforth the reaction was known as Huisgen cycloaddition (this term is often used to mainly illustrate the 1,3-dipolar cycloaddition of organic azide with alkyne to give 1,2,3-triazole). However, the non-catalyzed Huisgen cycloaddition of azide-alkyne produces a mixture of 1,4- and 1,5-disubstituted-1,2,3-triazoles (Scheme 2.7) [56-57]. In addition, this reaction requires high temperature and long reaction times.

Scheme 2.7 Lack of regioselectivity in the Huisgen 1,3-dipolar cycloaddition.

The significance of such undesirable features is evident by the lack of literature examples of 1,2,3-triazoles earlier to 2002 [58] when the Copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) was first reported.

2.4 COPPER(I)-CATALYZED AZIDE-ALKYNE CYCLOADDITION

The true synthetic utility of the azide-alkyne cycloaddition is realized in the copper(I)-catalyzed version. In 2002, the groups of Meldal [59] and Sharpless [60] independently reported discovery of the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC), which immediately drew attention from researchers all over the world. In the presence of copper(I), this cycloaddition affords exclusively 1,4-disubstituted-1,2,3-triazole and proceeds under very mild conditions (Scheme 2.8). The term “click chemistry” [61] was defined by Nobel laureate K. B. Sharpless in 2001 to explain reactions that are high yielding, wide in scope, generating only inoffensive byproducts that can be removed without chromatographic methods, stereospecific, and can be performed in easily removable or benign solvents.
To date, copper sets out as the only metal catalyst of the azide-alkyne cycloaddition with facile, dependable and 1,4-regiospecificity. Indeed, other metals Ag(I), Pd(0/II), Pt(II), Au(I/III), and Hg(II), etc known to catalyze various transformations of alkynes have all unsuccessful to generate triazoles in good yields. The unique catalytic role of Cu(I) may be revealed by the unexpected combination of its ability to attract terminal alkynes in both $\sigma$- and $\pi$-interactions, and the quick exchange of ligands in its coordination sphere, particularly in aqueous conditions. The synergistic nucleophilic activation of the alkyne and electrophilic activation of the azide induces the development of the first carbon-nitrogen bond [62].

The CuAAC carried out by Meldal using CuI, DIPEA, acetonitrile at RT gives moderate yield of 1,4-triazole and oxidative coupling byproducts resulting from presence of dissolved oxygen. The most convenient and practical procedure to synthesize 1,4-triazoles was introduced by Sharpless using copper(II) sulfate pentahydrate or copper(II) acetate in the presence of sodium ascorbate a mild reductant in $H_2O/t-BuOH$ mixture at RT with >90% purity, without use of ligands or additives. Certainly, Cu(I) salts can also be employed in combination with sodium ascorbate, in which it transforms any oxidized Cu(II) species back to the catalytically active Cu(I).

Since 2002, the CuAAC is a subject in numerous papers and reviews devoted to general aspects [1], mechanism [63] drug discovery [64-66], modification of sugars [37], polymer and material sciences [68-69]. In addition, CuAAC have been utilized in bioconjugation [70-71], bioorthogonal chemical reporters [72-73], cell imaging [74-75], as mitochondrial regulators [76],
combinatorial chemistry [77-78], proton transport facilitators [79], glycoside cluster arrays [80], spacers to dendrimers [81], in the preparation of HPLC packing [82], etc. Regrettably, the mandatory copper is toxic to both bacterial [83] and mammalian cells [84], thus prohibiting applications wherein the cells must remain viable.

Similar to the mechanism of the Huisgen cycloaddition, the Cu(I)-catalyzed variant proceeds in a step-wise fashion that involves a series of exchanging Cu-acetylide complexes. Initially, mono-copper complexes were thought to be the active catalysts, even though more recently, the involvement of dinuclear-copper complexes has been recommended on the basis of kinetic experiments [85] and computational analysis [86-87]. In 2013, Fokin reported a sophisticated mechanistic work and declared that “mononuclear copper-acetylide complexes (1,Cu) are inactive towards organic azides except an exogenous copper catalyst is added” [63]. Finally in 2015 the mechanistic conclusions of CuAAC was reported by Bertrand in continuation of formerly established mechanism is the initiation of the cationic π, σ-bis(copper) acetylide complexes of type (1,Cu2) as the “catalytically active complex,” alternative of 1,Cu (Figure 2.1). It is supported by the isolation of key intermediates 1,Cu2 and 2,Cu2 from the CuAAC reaction. And it is observed that although mono- and dinuclear-copper complexes boost the reaction and bring clear confirmation that the latter is actually kinetically favored [88].

![Figure 2.1](image)

**Figure 2.1** Mechanistic conclusions of CuAAC reaction.
In this CuAAC, 5-copper(I)-triazolide (2Cu) is the key reactive intermediate. Therefore the synthesis of different metalotriazoles and their further synthetic applications have been considered as significantly important to triazole chemistry. Micouin, Gray and Fokin reported the synthesis of 5-metallo-triazoles via Cu(I)-catalyzed reaction between metal acetylides and azides. Xu reported synthesis of bench-stable 5-stannyl triazoles via Cu(I)-catalyzed interrupted click reaction from easily available terminal alkynes. These metalotriazoles were further functionalized (Scheme 2.9) by reacting with active electrophiles and also undergo palladium-catalyzed cross-coupling reactions [89-92].

\[
\begin{align*}
A) & \quad \text{Cu(I)-catalyzed synthesis of metalotriazoles from metal acetylides} \\
R^1 \equiv M + R^2N_3 & \xrightarrow{Cu(I)} N^2N^1-N^1-R^2 \\
M = Cu, Al, Au, Bi, etc. & 5-\text{metallo-triazole}
\end{align*}
\]

\[
\begin{align*}
B) & \quad \text{Cu(I)-catalyzed interrupted click reaction to 5-stannyl-triazoles} \\
R^1 \equiv H + R^2N_3 + Bu_3SnOMe & \xrightarrow{Cu(I)} N^2N^1-N^1-R^2 \\
& \quad \xrightarrow{E^+} N^2N^1-N^1-R^2 \\
& \quad \xrightarrow{Bu_3SnOMe} N^2N^1-N^1-R^2 \\
& \quad \xrightarrow{[Pd]} N^2N^1-N^1-R^2 \\
& 5-\text{Stannyli-triazole}
\end{align*}
\]

**Scheme 2.9** Synthesis of metalotriazole intermediates and their further functionalization.

### 2.5 RUTHENIUM-CATALYZED AZIDE-ALKYNE CYCLOADITION

While the original Huisgen 1,3-dipolar cycloaddition afforded mixtures of 1,4- and 1,5-disubstituted-1,2,3-triazoles, CuAAC selectively produced the 1,4-isomer. However there was a lack of robust methods for the exclusive formation of 1,5-disubstituted-1,2,3-triazoles. In 2005, the ruthenium(II) catalyzed azide alkyn cycloaddition (RuAAC) was discovered by Fokin and Jia resulted in nearly complete regioselective formation 1,5-isomer when terminal alkynes were employed [93]. Additionally, this method worked with internal alkynes as
well this resulted in the synthesis of fully substituted 1,2,3-triazoles with high regioselectivity when they are terminated with a directing group. The origin of this regioselectivity is evident when the proposed mechanism is considered. Unlike the CuAAC, RuAAC works with both internal and terminal alkynes, and providing key mechanistic insight (Scheme 2.10). Ruthenium-acetylides are not formed at all or if they do form, they are not part of the catalytic cycle.

Scheme 2.10 Synthesis of 1,5-disubstituted- and 1,4,5-trisubstituted-1,2,3-triazoles via RuAAC.

The proposed mechanism (Figure 2.2) indicates that the spectator ligands undergo displacement in the first step to generate an activated complex (Step

Figure 2.2 Proposed mechanism of RuAAC by Fokin.
A). It is then transformed into the Ruthenacycle \textit{via} oxidative coupling of azide-alkyne (Step B). The Ruthenacycle intermediate then undergoes ring contraction (Step C) and reductive elimination (Step D) releasing the 1,5-disubstituted-1,2,3-triazole and the catalyst is regenerated. The pentamethylcyclopentadienyl ruthenium chloride catalyst ([Cp*RuCl]) was found to be most reactive and its reactivity was attributed to the Cp* ligand’s ability to stabilize the higher oxidation states of ruthenium.

Still in its infancy, the applicability of the RuAAC has not yet been achieved. However, it has been realized in several applications. For example, the synthesis of vancomycin mimics \textit{via} CuAAC and RuAAC of tripeptides was reported by Liskamp \textit{et al.}, [94] to achieve the desired outcome (Scheme 2.11).

\begin{center}
\includegraphics[width=\textwidth]{image.png}
\end{center}

\textbf{Scheme 2.11} Synthesis of vancomycin mimics \textit{via} Cu(I)- and Ru(II)-catalyzed click reaction.

\section*{2.6 STRAIN-PROMOTED AZIDE-ALKYNE CYCLOADDITION (SPAAC)}

The CuAAC is a model for many applications, but Cu(I) has the adverse effect of being toxic at low concentrations. [3+2] Cycloaddition between azides and strained cyclooctynes reduces that burden by readily giving a triazole product without a toxic catalyst. An emerging field of chemical biology attempts to study the biomolecules in living systems by using bioorthogonal chemical
reactions (that is, reactions that do not interfere with biological processes). Regarding this in 2004 Bertozzi first reported a method to increase the reactivity of the azide-alkyne cycloaddition at room temperature without copper or other metals [95-96]. Utilizing cyclooctynes, has an advantage of its inherent strain to promote the cycloaddition (Scheme 2.12). The substituted analogue of 3,3-difluorocyclooctyne was shown to further increase the reactivity of the SPAAC by lowering the LUMO of the alkyne [97]. The inherent strain in the cyclooctynes has also been increased by introducing the substituents adjacent to the triple bond [98]. Ultimately, the method provided a very booming way to functionalize biomolecules in vitro and in vivo [99] and even in live mice [100].

\[
\begin{align*}
\text{R}_1\text{N}_3 + \text{Cyclooctyne} & \xrightarrow{\text{Strain-promoted}} \text{1,2,3-Triazole} \\
\text{R}_1\text{N}_3 + \text{F-Cyclooctyne} & \xrightarrow{\text{Strain-promoted}} \text{Several functionalized cyclooctynes}
\end{align*}
\]

**Scheme 2.12** Strain promoted, metal free azide-cyclooctyne cycloaddition by Bertozzi.

Although the synthesis of 1,2,3-triazoles from the strained alkynes were fast and efficient, but it results mixtures of regioisomers. This problem is evident when substituted cyclooctynes are desired. Both the CuAAC and RuAAC addressed the problem of regioselectivity.

1,3-Dipolar cycloaddition between azides and haloalkynes in the presence of copper(I) and ruthenium(II)-catalyst, gives regioselective route to 5-
halo-triazoles. Whereas in the presence of iridium(I)-catalyst it gives regioselective route to 4-bromo-triazoles. Post synthetic functionalization (such as arylolation, alkenylation, alkynylation and intramolecular cyclization) of halo-triazoles [101-104] smoothly affords fully substituted 1,2,3-triazoles (Scheme 2.13).

\[
\begin{align*}
&X = \text{Br}, \text{I} \\
&\begin{array}{c}
\text{R}^1_N N N \text{R}^2 \\
\text{X} \\
\end{array} + \begin{array}{c}
\text{R}^2 \equiv \text{X} + \text{R}^1_N \text{N} \\
\end{array} \xrightarrow{[\text{Ir}]} \begin{array}{c}
\text{R}^1_N N N \text{R}^2 \\
\text{Br} \quad \text{X} = \text{Br} \\
\end{array}
\end{align*}
\]

Scheme 2.13 Metal-catalyzed routes to halo-triazoles.

In 2014, Jia and Sun [105] first reported iridium-catalyzed [3+2] cycloaddition between azide and thioalkyne (electron-rich internal alkyne) under mild condition. Recently Lopez and Mascarenas [106] reported ruthenium-catalyzed orthogonal chemical reaction to synthesize 5-thio-1,2,3-triazoles (Scheme 2.14).

\[
\begin{align*}
&\text{R}^3_S \equiv \text{R}^2 + \text{R}^1_N \text{N} \\
&\xrightarrow{\text{Cp}^* \text{Ru} \text{(cod)} \text{Cl} \text{water, rt, 24h (or)}} \xrightarrow{[\text{Ir} \text{(cod)} \text{Cl}_2] \text{2 mol} \%} \text{C} \text{H}_2 \text{Cl}_2, \text{N}_2, \text{rt} \text{Overnight}} \\
\end{align*}
\]

Scheme 2.14 Metal catalyzed azide-thioalkyne cycloaddition.

2.7 AZIDE-OLEFIN CYCLOADITION

Traditional routes to prepare 1,2,3-triazoles via metal-catalyzed/ strain promoted azide-alkyne cycloaddition frequently suffered from poor regioselectivity, a rather tedious reaction procedure. However, the cytotoxicity of copper(I) catalyst, economic and synthetic viabilities of ruthenium catalyst and alkynes insist the need of alternative methods to produce these privileged
molecules. Regarding this, electron-deficient olefins have been prudently chosen as suitable alternatives to alkynes to synthesize 1,2,3-triazoles.

This type of azide-olefin cycloaddition (AOC) between azides and electron-deficient olefins to afford triazolines was established by Huisgen [108] and Labbe [109]. These triazolines are usually unstable and they often fragment into different products based on the reaction conditions [110-116]. At this stage, numerous methods were sought out to convert this unstable triazoline into the stable triazole (Scheme 2.15). In this regard, two inventive approaches have been reported in the literature: 1) oxidative azide-olefin cycloaddition and 2) eliminative azide-olefin cycloaddition.

**Scheme 2.15** Synthesis of triazolines and their further transformations.

2.7.1 Oxidative azide-olefin cycloaddition

In this strategy azide and olefin undergo [3+2] cycloaddition to afford the unstable triazoline and concomitantly it will be oxidized into the 1,2,3-triazoles (Scheme 2.16).

**Scheme 2.16** Background of oxidative azide-olefin cycloaddition.
A few research groups have actively involved in the area of oxidative azide-olefin cycloaddition (OAOC) under mild conditions in the presence and absence of catalysts, such as TBAHS, CuO, nano-Fe₂O₃, Cul, Ce(OTf)₃, ZrO₂-Cu₂-β-CD, nano-Bi₂WO₆, t-BuONa, and Zn(OAc)₂- t-BuOOH or ZnO nanoparticles etc.

In 2007, Nebois reported the catalyst-free oxidative azide-olefin cycloaddition of benzyl azide with 1,4-benzoquinone to afford mixture of benzotriazole-4,7-diones [117].

Chang and Tripathi reported the synthesis of 1-benzyl-1H-naphtho[2,3-d][1,2,3]triazole-4,9-dione by catalyst-free OAOC of benzyl azide with 1,4-naphthoquinone [118-119].

Ampapathi and Tripathi reported a new approach to synthesize macrocyclic glycoconjugates resulting from tetrabutylammonium hydrogen sulfate (TBAHS) catalyzed azide-enone intramolecular cycloaddition [120].

Chen reported one-pot, two step synthesis of N-2-aryl-substituted-1,2,3-triazoles under mild conditions in excellent yields with high regioselectivity via bulk CuO catalyzed azide-chalcone oxidative cycloaddition and post-triazole arylation with 2-nitroarylhalides [121].
Kamal reported tandem three-component reaction to the synthesis of $N$-2-aryl-substituted-1,2,3-triazoles through nano-$\text{Fe}_2\text{O}_3$ catalyzed oxidative cycloaddition of azide and chalcone and consequent regioselective $N$-2-arylation [122].

Chen reported the synthesis of 2,4,5-trisubstituted-1,2,3-triazoles via one-pot, four component reaction with benzaldehydes, acetophenones, sodium azide and aryl halides [123].

Yao reported copper(I)-promoted oxidative azide-olefin cycloaddition for the regioselective synthesis of 1,4-disubstituted/ 1,4,5-trisubstituted-1,2,3-triazoles in the presence of base under oxygen atmosphere [124].

Wang and Pan reported Ce(OTf)$_3$ catalyzed regioselective synthesis of $Z$-β-aryl enaminones and 1,4,5-trisubstituted 1,2,3-triazoles. In toluene chalcones and benzyl azides undergo Ce(OTf)$_3$-catalyzed cycloaddition and subsequent oxidation of triazoline to form 1,2,3-triazole, whereas in DMF the unstable triazoline underwent decomposition and 1,2-H migration, leads to $Z$-β-aryl-
Rangappa and Shasikanth developed an efficient one-pot multi component reaction for the preparation of N-2-substituted-1,2,3-triazoles through oxidative cycloaddition of chalcones and sodium azide using heterogeneous ZrO$_2$ nanoparticle-supported Cu(II)-β-cyclodextrin catalyst and post-triazole alkylation using alkyl benzoates [126].

Kashinath reported aqueous mediated, Bi$_2$WO$_6$ nanoparticles catalyzed regioselective production of Z-β-aryl enaminones and 1,4,5-trisubstituted-1,2,3-triazoles resulting from OAOC [127].

Wan reported the t-BuONa catalyzed domino reactions between secondary enaminones and tosyl azide to synthesize N-substituted-1,2,3-triazoles. This proceeds through oxidative cycloaddition and Regitz diazo-transfer process with tosyl azide at room temperature [128].
Recently Kashinath reported regioselective synthesis of functionalized 1,2,3-triazoles via oxidative cycloaddition of azides with β-nitrostyrenes and chalcones using Zn(OAc)₂-t-BuOOH or ZnO nanoparticles in aqueous medium [129].

Zhou and Chen reported copper-catalyzed synthesis of 4-acyl-1,2,3-triazoles in good yields from three-component reaction of methyl ketones, organic azides and DMF through oxidative cross-dehydrogenative coupling followed by an oxidative cycloaddition [130].

Wang and Pan reported catalyst-free, intramolecular cascade OAOC of benzyl bromides bearing ortho-substituted α, β-unsaturated ketones with sodium azide to furnish fused 1,2,3-triazoles in DMF at room temperature, whereas under thermal condition isoindoline derivatives were produced [131].

### 2.7.2 Eliminative azide-olefin cycloaddition

In this strategy [3+2] cycloaddition of azide and olefin having a leaving group afford unstable triazoline which undergo subsequent elimination reaction to give the 1,4/1,5-disubstituted-1,2,3-triazole (Scheme 2.17).

**Scheme 2.17** Background of eliminative azide-olefin cycloaddition.
In this area, olefins bearing leaving groups such as acetate, sulfone, nitro, alkoxy, amino, etc., have been demonstrated for eliminative azide-olefin cycloaddition (EAOC) using catalysts such as TBAF, Ce(OTf)$_3$, Bi$_2$WO$_6$, diethylamine, pyrrolidine, piperidine, L-proline, DBU, etc. In 2003, Zhu et al., reported the regiospecific synthesis of 5-fluoroalkylated-1,2,3-triazoles in good yield resulting from EAOC of (Z)-ethyl 3-fluoroalkyl-3-pyrrolidino-acrylates with organic azides under thermal condition [132].

Stevens et al., reported the preparation of 1,4-disubstituted-1,2,3-triazoles through cycloaddition of azides with enol ethers and subsequent elimination of alcohol under thermal condition [133]. This reaction is capable to produce triazoles that are inaccessible by traditional azide-alkyne cycloaddition.

Fringuelli and Vaccaro reported TBAF-catalyzed eliminative cycloaddition of 2-aryl-1-cyano- or 2-aryl-1-carbethoxy-1-nitroethenes with TMSN$_3$ under solvent-free condition (SFC) to prepare 4-aryl-5-cyano- (or) 4-aryl-5-carbethoxy-NH-1,2,3-triazoles in good to excellent yields [134].

Shi et al., reported L-proline catalyzed multicomponent cascade reaction for the production of 4-vinyl-substituted-NH-1,2,3-triazoles. It involves the Henry reaction between nitro-alkene with aryl aldehyde to form the 1-aryl-2-nitrodiene followed by eliminative cycloaddition with NaN$_3$ to give NH-triazole. The availability of the C-4 vinyl group allows easy derivatization of triazoles [135].
Jensen et al., reported EAOC of vinyl acetate and organic azides to synthesize unsubstituted $N$-linked-1,2,3-triazoles under microwave irradiation. Additionally, one-pot, three component reaction reported from halides, vinyl acetate and azide under microwave irradiation [136].

$$\text{R-N}_3 + \text{OAc} \xrightarrow{\text{MW,120 °C}} \text{R-N}_3\text{N}_3$$

Pathak and Ganguly et al., reported preparation of 1,4/1,5-disubstituted 1,2,3-triazoles and 1,5-triazolylated monosaccharides and disaccharides under metal-free, thermal condition via eliminative cycloaddition of organic azides with vinyl sulfones [137-138].

Wang et al., described the first example of rare earth metal-catalyzed EAOC which involves Ce(OTf)$_3$ catalyzed [3+2] cycloaddition of organic azides with nitro-olefins and subsequent elimination of nitro group to give 1,5-disubstituted-1,2,3-triazoles with good to excellent yields [139].

Kashinath et al., reported aqueous mediated, nano-$\text{Bi}_2\text{WO}_6$ catalyzed regioselective synthesis of 1,5-disubstituted-1,2,3-triazoles resulting from EAOC of $\beta$-nitrostyrenes and azides [127].
Dehaen et al., described domino reactions between readily available starting materials such as ketones, DMF acetal, and organic azides to synthesize 4-acyl-1,2,3-triazoles (α-ketotriazoles). This reaction is facilitated by the in situ formation of an enaminone intermediate followed by its eliminative cycloaddition with azide. This strategy involves the derivatization of various heterocycles and natural products [140].

![Chemical reaction diagram]

**2.7.3 Organo click reaction**

It is another interesting class of reaction where enamines, iminium ions and enolates generated in situ from various carbonyl compounds would undergo eliminative cycloaddition with aromatic azides in the presence of organocatalysts (amine bases) to achieve the 1,2,3-triazoles [141].

Organocatalytic formation of enamine intermediates from carbonyl compounds with active methylene group would undergo eliminative cycloaddition with aryl azides to achieve the 1,2,3-triazoles (Scheme 2.17).

![Organocatalytic formation of enamine intermediates diagram]

**Scheme 2.18** Synthesis of substituted-1,2,3-triazoles via an enamine intermediate.

Ramachary, Bressy and Wang groups individually reported synthesis of 1,2,3-triazoles by eliminative cycloaddition between carbonyl compounds with active methylene group and aryl azides through enamine catalysis [142-147].
Wang et al., reported regioselective preparation of $\alpha$-keto triazoles via organocatalytic eliminative cycloaddition of allyl ketones with organic azides [148].

Wang et al., reported synthesis of triazole-olefins through an organocatalytic inverse-electron-demand eliminative cycloaddition of organic azides with unsaturated aldehydes in the presence of diethylamine [149].

Wang et al., reported regioselective synthesis of 1,4,5-trisubstituted 1,2,3-triazoles by eliminative cycloaddition between $\alpha,\beta$-unsaturated ketones and organic azides through iminium catalysis [150].

**Scheme 2.19** Synthesis of substituted-1,2,3-triazoles *via* iminium intermediate.
Ramachary et al., reported regioselective synthesis of 1,4-disubstituted-1,2,3-triazoles through an organocatalyzed eliminative azide-aldehyde cycloaddition (organo-click) of enolizable aldehydes with aryl azide in the presence of DBU [151].

\[
\text{Scheme 2.20 Synthesis of substituted-1,2,3-triazoles via enolate intermediate.}
\]

2.7.4 Miscellaneous reactions towards substituted 1,2,3-triazoles

Dehaen et al., reported regioselective synthesis of 1,4,5-trisubstituted 1,2,3-triazoles and 1,2,3-triazole-fused heterocycles through one-pot, three-component reaction of aldehydes, nitroalkanes and organic azides. It is facilitated by an organocatalyzed Knoevenagel condensation between aldehydes and nitro-alkanes, which is followed by the eliminative cycloaddition with azide [152].

\[
\text{Guan et al., reported NH}_4\text{OAc catalyzed one-pot, three-component reaction of aldehydes, nitro-alkanes and sodium azide for the synthesis of 4-aryl-NH-1,2,3-triazoles via eliminative cycloaddition [153].}
\]

\[
\text{Liang and Sun reported synthesis of 5-aryl-NH-1,2,3-triazoles through acid-base catalyzed three-component reaction of aldehydes, nitro-alkanes and sodium azide [154].}
\]
Paixao et al., reported DBU catalyzed regioselective synthesis of 1,4-disubstituted-1,2,3-triazoles by applying a novel inverse-electron-demand eliminative [3+2] cycloaddition strategy from aldehydes, malononitriles and aromatic azides in one-pot, metal-free condition [155].

\[
\text{Condition A: } \text{Fe}_3\text{O}_4@\text{SiO}_2-\text{SO}_3\text{H@MS-NHAc} \\
\text{DMF/CH}_3\text{OH, } 140 \degree \text{C.,} \\
\text{Condition B: } \text{NH}_4\text{OAc/AcOH}
\]

2.8 SYNTHESIS OF 1,2,3-TRIAZOLE-FUSED HETEROCYCLES

Functionalized 1,2,3-triazoles further derivatized into the 1,2,3-triazole-fused heterocycles through intramolecular cycloaddition, metal catalyzed cyclization and reductive cyclization, etc.

Kumara Swamy et al., reported synthesis of [6,6]-, [6,7]-, [6,8]-, and [6,9] ring-fused triazoles, fused pentacyclic and biphenyl-fused, tricyclic derivatives via one-pot, Cu(I)-catalyzed azide-alkyne cycloaddition and followed by intramolecular direct arylation in the presence of t-BuOK [156].

Mani et al., described the intramolecular [3+2] cycloaddition between diazo compound and nitrile to afford triazole-fused chromenes without resort to the conventional CuAAC. This strategy involves in situ generation of
diazomethanes which then undergoes intramolecular [3+2] cycloaddition with a cyano group [157].

Livi et al., reported synthesis of 1,2,3-triazolo[1,5-a]quinoxalin-4-one derivatives via 1,3-dipolar cycloaddition of 2-nitrophenyl azides with carbonyl compounds followed by Pd/C catalyzed hydrogenation and N-alkylation. The prepared compounds act as receptors for benzodiazepine and adenosine A and A2A [158].

Kundu et al., described synthesis of 1,2,3-triazolo[1,5-a]quinoxalin-4-one derivatives through one-pot [3+2] cycloaddition, reduction of nitro group and Pictet-Spengler cyclization with aromatic aldehydes [159].

Cai and Gong reported Cu(I)-catalyzed cascade reactions of 1,1,1-trifluoro-N-(2-iodophenyl)but-3-yn-2-ines and N-(2-iodophenyl) propiolamides with sodium azide to achieve tricyclic 4-(trifluoromethyl)-[1,2,3]triazolo [1,5-a]quinoxalines and 1,2,3-triazolo[1,5- a]quinoxalin-4(5H)-ones through cycloaddition and intramolecular Ullmann coupling [160-161].

Huang and Zhu reported efficient Cu(I)-catalyzed tandem cyclization of 1-azido-2-isocyanocycloarenes and terminal acetylenes to prepare the 1,2,3-triazolo[1,5-
a]quinoxalines. In addition, these fused triazoles are diversified to quinoxaline derivatives via Rh(II)-catalyzed carbenoid insertion [162].

Wang et al., described synthesis of 1,2,3-triazole-fused quinolines/ chromenes/thiochromenes through CuAAC and palladium catalyzed cyclization mediated by tetrabutylammonium iodide (TBAI) in multi step process [163].

Tiwari et al., described the propargylation of hydroxyl group of sugar derived 1,2-azido alcohols, and the in situ generated azido-alkyne undergo metal free intramolecular [3+2] cycloaddition gives C- and O-glycosyl morpholine fused [5,1-c] triazoles [164].

2.9 OBJECTIVES OF THE PRESENT WORK

The above studies encapsulate the conventional synthesis of substituted-1,2,3-triazoles via metal-catalyzed azide-alkyne cycloaddition and strain promoted azide-alkyne cycloaddition. Nevertheless they suffer frequently from poor regioselectivity and tedious reaction procedure. Moreover, the cytotoxicity of copper(I) catalyst, economic and synthetic viability of ruthenium catalyst and alkynes pose the need of alternative methods to synthesize these
privileged molecules. In response to this need, electron-deficient olefins have been judiciously chosen as suitable alternatives to alkynes to access functionalized-1,2,3-triazoles.

The major objectives of the current research are:

- Applying the green synthetic methodologies to synthesize functionalized-1,2,3-triazoles through azide-olefin cycloaddition of electron-deficient olefins using homogeneous and heterogeneous catalysts.
- To synthesize 1,4-disubstituted- and 1,4,5-trisubstituted-1,2,3-triazoles through oxidative azide-olefin cycloaddition using homogeneous and heterogeneous catalyst.
- To synthesize 1,5-disubstituted-4-nitro-1,2,3-triazoles and 1,5-disubstituted-1,2,3-triazoles via oxidative and eliminative [3+2] cycloaddition of nitro-olefins (β-nitrostyrenes) with organic azides in the presence and absence of commercially available CuO nanoparticles under solvent-free condition.
- To synthesize 1,2,3-triazole-fused chromene/quinoline scaffolds via one pot oxidative [3+2] cycloaddition, followed by an intramolecular reductive cyclization.
- To characterize the 1,2,3-triazoles using spectral techniques such as FT-IR, NMR, Mass spectroscopy and Single crystal X-ray diffraction.

2.10 FRAMEWORK OF THE THESIS

The thesis consists of 9 chapters along with references. **Chapter-I** presents a brief literature survey of the paramount importance of substituted-1,2,3-triazoles and their versatile applications in various fields. **Chapter-II** elaborates the synthetic methods reported in the literature to access 1,2,3-triazoles. The methods such as azide-alkyne cycloaddition, azide-olefin cycloaddition and other methods are discussed along with the mechanistic
details of a few landmark reactions. Besides that, it includes the aim and objectives of the current research.

**Chapter-III** deals with the regioselective synthesis of 1,4-disubstituted and 1,4,5-trisubstituted-1,2,3-triazoles via oxidative azide-olefin cycloaddition (OAOC) of organic azides and activated olefins using the commercially available heterogeneous CuO nanoparticles (NPs) under aerobic condition. A diverse array of 1,4-disubstituted- and 1,4,5-trisubstituted-1,2,3-triazoles were obtained in moderate to excellent yields.

**Chapter-IV** describes the regioselective synthesis of functionalized-1,2,3-triazoles via homogenous TEMPO-promoted oxidative azide-olefin cycloaddition of organic azides and activated olefins in aqueous medium under oxygen.

**Chapter-V** deals with a regioselective and tunable synthesis of 1,5-disubstituted-4-nitro-1,2,3-triazoles and 1,5-disubstituted-1,2,3-triazoles via oxidative and eliminative [3+2] cycloaddition of organic azides with nitro-olefins (β-nitrostyrenes) in the presence and absence of commercially available CuO NPs under solvent-free condition.

**Chapter-VI** explains an easy and efficient one-pot synthesis of 1,2,3-triazole-fused chromenes/quinolines via oxidative [3+2] cycloaddition using CuO NPs, followed by an intramolecular reductive cyclization

**Chapter-VII** discusses the summary and conclusion drawn from the present study.

**Chapter-VIII** discloses the scope of future work.

**Chapter-IX** presented the references sited in this research work for the successful interpretation.