Review

Azides in the Synthesis of Various Heterocycles

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Abstract: In this review, we focus on some interesting and recent examples of various applications of organic azides such as their intermolecular or intramolecular, under thermal, catalyzed, or non-catalyzed reaction conditions. The aforementioned reactions in the aim to prepare basic five-, six-, organometallic heterocyclic-membered systems and/or their fused analogs. This review article also provides a report on the developed methods describing the synthesis of various heterocycles from organic azides, especially those reported in recent papers (till 2020). At the outset, this review groups the synthetic methods of organic azides into different categories. Secondly, the review deals with the functionality of the azido group in chemical reactions. This is followed by a major section on the following: (1) the synthetic tools of various heterocycles from the corresponding organic azides by one-pot domino reaction; (2) the utility of the chosen catalysts in the chemoselectivity favoring C–H and C-N bonds; (3) one-pot procedures (i.e., Ugi four-component reaction); (4) nucleophilic addition, such as Aza-Michael addition; (5) cycloaddition reactions, such as [3+2] cycloaddition; (6) mixed addition/cyclization/oxygen; and (7) insertion reaction of C-H amination. The review also includes the synthetic procedures of fused heterocycles, such as quinazoline derivatives and organometal heterocycles (i.e., phosphorus-, boron- and aluminum-containing heterocycles). Due to many references that have dealt with the reactions of azides in heterocyclic synthesis (currently more than 32,000), we selected according to generality and timeliness. This is considered a recent review that focuses on selected interesting examples of various heterocycles from the mechanistic aspects of organic azides.

Keywords: organic azides; click reaction; catalysis; five membered rings; six membered rings; organo-metal heterocycles

1. Introduction

Organic azides are organic compounds containing the azide (N₃) functional group. Due to the hazards associated with their use, few azides are commercially used, although...
they display interesting applications in organic chemistry. Organic azides have four mesomorphic structures (1a–1d, Figure 1), and their structure is also described as isoelectronic with carbon dioxide.

\[
\begin{align*}
R-N_3 &= \begin{array}{c}
1 & 2 & 3 \\
R-N-N-N & \leftarrow & R-N=N \leftarrow & R-N-N=N \leftarrow & R-N=N=N
\end{array} \\
1a & \quad 1b & \quad 1c & \quad 1d
\end{align*}
\]

Figure 1. Mesomeric structures of organic azides.

The polar character of the azido group has a remarkable effect on their bond lengths and angles. In methyl azide, as an example, the angles of CH$_2$N$^1$–N$^2$N$^3$ and CH$_3$N$^1$–N$^2$–N$^3$ are approximately 115.28 and 172.58 Å, respectively [1]. Aromatic azides show slightly shorter bond lengths between N$^2$ and N$^3$ [1]. Accordingly, an almost linear azide structure is present, with sp$^2$ hybridization at N$^1$. The polar resonance structures 1b–1d illustrated that strong IR absorption by a band at nearly 2114 cm$^{-1}$ (phenyl azide [2]). Alkyl azides show absorption in the UV region at 287 nm and 216 nm [2]. They also exhibit weak dipole moment (1.44 D for phenyl azide) [2]. Azido group in aromatic substitution reactions directs to ortho- and para-positions.

Organic azides engage in useful organic reactions, as the terminal nitrogen is mildly nucleophilic. Generally, nucleophiles attack the azide at the terminal nitrogen N$_3$, while electrophiles react at the internal atom N$_{\alpha}$ [3]. Azides easily extrude diatomic nitrogen, a tendency that is engaged in many reactions, such as the Staudinger ligation or the Curtius rearrangement [4]. Azides can be reduced to amines by hydrogenolysis [5] or with a phosphine (e.g., triphenylphosphine) in the Staudinger reaction [5]. Organic azides can react with phosphines to give iminophosphoranes, which can be hydrolyzed into primary amines (the Staudinger reaction) [6]. They react with carbonyl compounds to give imines (the aza-Wittig reaction) [7,8] or undergo other transformations. Thermal decomposition of azides gives nitrenes, which participate in various reactions; vinyl azides decompose into 2H-azirines [9].

Since organic azides are highly reactive and have been long established as versatile building blocks in assembling structurally diverse N-containing heterocycles, converting organic azides into high-value compounds, such as heterocycles, would be greatly valued and a subject of enormous current interest. Currently, well over 32,000 total and nearly 1000 in 2021 showed interest in this type of chemistry.

2. Some Synthetic Procedures of Organic Azides

2.1. From Diazonium Salts

The aryl diazonium salts were decomposed readily on reacting with azide ions (NaN$_3$ or Me$_3$SiN$_3$) to the corresponding aryl azide without a catalyst. As an example, the facile conversion of 5-amino-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (1) into 5-azido-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (2) via a two-step reaction involving diazotization followed by azidation using sodium azide as a precursor of azide ion [10] (Scheme 1).
2.2. Via SNAr Reactions (Nucleophilic Aromatic Substitution Reactions)

As an example, synthesis of 2-azido-3-nitropyridines (4) from 2-chloro-3-nitropyridines (3) using NaN₃ as the source of nucleophile (Scheme 2) was established as shown in Scheme 2 [11,12].

\[
\begin{array}{c}
\text{Cl} \\
\text{N} \\
\text{3a-d} \\
\text{R}^1 \\
\text{R}^2 \\
\text{NaN}_3 \\
\text{4a-d} \\
\text{R}^1 = \text{H; R}^2 = \text{H;} \\
\text{c, R}^1 = \text{H; R}^2 = \text{NO}_2; \\
\text{d, R}^1 = \text{R}^2 = \text{NO}_2;
\end{array}
\]

Scheme 2. Synthesis of aryl azides 4a-d via SNAr reaction.

2.3. From Lithium-Reagent

The reaction of aromatic halides 5 with lithium reagent (t-BuLi) followed by the reaction with tosyl azide gave the corresponding aryl azide 6 in 96% yield (Scheme 3) [13].

\[
\begin{array}{c}
\text{Mes} \\
\text{I} \\
\text{5} \\
\text{a) n-BuLi, O°C b) TsN}_3 \\
\text{Mes} = \text{mesityl; Ts = p-toluenesulfonyl.} \\
\text{6 (96%)}
\end{array}
\]

Scheme 3. Synthesis of aryl azide 6 using lithium reagent.

2.4. From Aryl Hydrazines

Kim et al. [14] reported the synthesis of aromatic azide 8 from the reaction of arylhydrazine 7 with nitrosyl ion (Scheme 4).

\[
\begin{array}{c}
\text{O}_2\text{N} \\
\text{NH}_{\text{H}}\text{H}_2 \\
\text{7} \\
\text{N}_2\text{O}_4, \text{CH}_3\text{CN} \\
\text{O}_2\text{N} \\
\text{N}_3 \\
\text{8 (25%)}
\end{array}
\]

Scheme 4. Formation aryl azide 8 from the corresponding hydrazide 7.

3. Chemistry of Azides

3.1. Azide as Aminating Group

3.1.1. Synthesis of 8-Aminoquinoline

The biologically active 8-aminoquinoline 10 was obtained through Ir(III)-catalyzed C8-amination of C2-selenylated quinoline N-oxide 9 with tosyl azide [15] (Scheme 5).

\[
\begin{array}{c}
\text{MeO} \\
\text{N} \\
\text{O} \\
\text{2} \\
\text{H} \\
\text{N} \\
\text{9} \\
\text{MeO} \\
\text{N} \\
\text{O} \\
\text{SePh} \\
\text{10} \\
\text{N} \\
\text{O} \\
\text{Ts}^+ \\
\text{N} \\
\text{O} \\
\text{SePh} \\
\text{(a)}
\end{array}
\]

Scheme 5. Formation of biologically active 8-aminoquinoline 10. Reagents and conditions: (a) [IrCp*Cl₂]₂ (2.0 mol%), AcOH, AgNTf₂, DCE, room temperature.
3.1.2. Synthesis of Amino Furo/Pyrroloindole Derivatives

Zhang and others [16] reported that tryptophols or tryptamines reacted with aryl azides to produce 3a-nitrogenous furoindolines and pyrroloindolines 3a-nitrogenous indole alkaloids. Using a nitrogen source, the reaction proceeded via nitrene transfer/cyclization under copper-catalyzed conditions. Firstly, the reaction was investigated to stand at the optimal reaction conditions indicated in Scheme 6. Starting with tryptophol (2-(1H-indol-3-yl)ethanol) (11a) and 1-azido-4-methoxybenzene, the corresponding furoindole 12a was obtained (Scheme 6). The investigation revealed that the conditions mentioned in entry 14 were chosen to be the optimal reaction conditions for all substrates (CuBH₄(PPh₃)₂ + L₇ (12 mol%), DCE 0.5 h).

| Entry | [Cu]          | Ligand | Solvent | Time (h) | Yield (%) |
|-------|---------------|--------|---------|----------|-----------|
| 1     | CuCl          | L₁     | PhCl    | 48       | 27        |
| 2     | CuCl          | L₂     | PhCl    | 12       | 13        |
| 3     | CuCl          | L₃     | PhCl    | 12       | 17        |
| 4     | CuCl          | L₃     | PhCl    | 12       | 45        |
| 5     | CuOAc         | L₃     | PhCl    | 12       | 45        |
| 6     | CuSCN         | L₃     | PhCl    | 12       | 70        |
| 7     | CuBH₄(PPh₃)₂  | L₃     | PhCl    | 12       | 88        |
| 8     | CuBH₄(PPh₃)₂  | L₄     | PhCl    | 24       | Trace     |
| 9     | CuBH₄(PPh₃)₂  | L₅     | PhCl    | 24       | Trace     |
| 10    | CuBH₄(PPh₃)₂  | L₆     | PhCl    | 12       | 64        |
| 11    | CuBH₄(PPh₃)₂  | L₇     | PhCl    | 0.5      | 92        |
| 12    | CuBH₄(PPh₃)₂  | L₈     | PhCl    | 24       | Trace     |
| 13    | CuBH₄(PPh₃)₂  | L₉     | PhCl    | 24       | Trace     |
| 14    | CuBH₄(PPh₃)₂  | L₇     | DCE     | 0.5      | 95        |
| 15    | CuBH₄(PPh₃)₂  | L₇     | MeCN    | 12       | 77        |
| 16    | CuBH₄(PPh₃)₂  | L₇     | Toluene  | 12       | 56        |
| 17    | CuBH₄(PPh₃)₂  | L₇     | DCE     | 2        | 93        |
| 18    | CuBH₄(PPh₃)₂  | L₇     | DCE     | 2        | 86        |

Scheme 6. Synthesis furoindoline 12a. Reagents and conditions: (a) [Cu] (20 mol%), ligand (24 mol%), solvent, 80 °C, N₂.
Utilizing by the aforementioned optimized condition, a variety of tryptophols (11a–n) and tryptamine substrates (11o–r) were taken to react with 1-azido-4-methoxybenzene, as shown in Scheme 7. According to the electronic nature or positions of the substituents, the reactions proceeded smoothly to give the target products 12a–r in high yields ranging from 72 to 99%. Moreover, different aryl azides were selected to react with tryptophol (2-(5-chlorobenzofuran-3-yl)ethanol) (11e) under the optimized reaction conditions to investigate the effect of substituents on the products’ yields.

Scheme 7. Synthesis of furoindolines 12a–n and pyrroloindolines (120–r). Reagents and conditions: (a) CuBH$_4$(PPh$_3$)$_2$ (12 mol%), L7 (14 mol%), DCE, 80 °C, N$_2$.

Another series of compound 12 was prepared, with azides having electron-donating and -withdrawing groups. The reaction proceeded smoothly to give the corresponding products 12s–f’ in moderate to excellent yields [16] (Scheme 8).
Scheme 8. Synthesis of furoindolines 12s–f` Reagents and conditions: (a) CuBH₄(PPh₃)₂ (12 mol%), L₇ (14 mol%), DCE, 80 °C, N₂.

The suggested mechanism describes the formation of furoindole 12a, as shown in Scheme 9 [16]. Firstly, the azide moiety reacted with copper complex to produce copper nitrene complex A, which abstracts a hydrogen atom from compound 11a to form the copper aminyl species B and imine radical C, which combines to produce the intermediate D. The catalyst moiety was then excluded from the intermediate D to form the imine species E. Finally, E was converted to the desired product 12a via an intramolecular nucleophilic addition [16].
Scheme 9. A plausible mechanism described the formation of compound 12a.

3.2. Azidation
Synthesis of 3-Azido-Tetralins, Chromanes, and -Tetrahydroquinolines

Porter et al. [17] reported the stereoselective synthesis of 3-azido-tetralins, chromanes, and -tetrahydroquinolines via a tandem allylic azide rearrangement/Friedel-Crafts alkylation. The allylic azides 13a–f were cyclized to the corresponding tetralines 14a–f in 58–88% (Scheme 10).

Scheme 10. Azidation by azido group and synthesis of 3-azido-tetralins 14a–f. Reagents and conditions: (a) 10 mol% AgSbF$_6$, CHCl$_3$, 40–60 °C, 24–48 h.
In continuation of the optimized procedure [17], the ethereal allylic azides 15a–i were converted into chromanes 16a–i in 34–97% yields (Scheme 11).

![Scheme 11. Azidation by azido group and synthesis of ethereal allylic azides 15a–i. Reagents and conditions: (a) 10 mol% AgSbF$_6$, CHCl$_3$, 40–60 °C, 24–48 h.](image)

On the other hand, aniline-derived allylic azides 17a–f carrying the N-protecting group were also cyclized using the tandem process to tetrahydroquinolines 18a–f in good yields of 57–81% [17] (Scheme 12).

![Scheme 12. Azidation and cyclization; Synthesis of compounds 18a–f. Reagents and conditions: (a) 10 mol% AgSbF$_6$, CHCl$_3$, 40–60 °C, 24–48 h.](image)
Finally, the tetraline 14a was converted into pyrrolidine 19 [17]. At the same time, the cycloaddition reaction of the tetraline 14a with dimethyl acetylene dicarboxylate gave the triazole 20 (Scheme 13).

Scheme 13. Synthesis of pyrrole 19. Reagents and conditions: (a) HBCy$_2$ (dicyclohexyl borane) (b) DMAD (dimethylacetylene dicarboxylate).

An interest application of previously reported work, was directed towards synthesizing a large family of botanical natural products group named husbanan [17]. Husbanan was synthesized from ethyl 2-phenethylcyclohex-1-enecarboxylate (Scheme 14), which initially underwent reduction followed by partial re-oxidation to the aldehyde 22 (i.e., from ester to alcohol then aldehyde using tetrapropylammonium perruthenate (TPAP), and N-methylmorpholine N-oxide (NMO)). Aldehyde 22 was elaborated by Corey-Chaykovsky epoxidation. Epoxide 23 was isolated after activation with trichloroacetonitrile. Finally, reduction of imidate 25 gave 26 on the presence of dicyclohexyl borane ring closer to the hasubanan product 27 [17] (Scheme 14).

Scheme 14. Synthesis of husbanan 27. Reagents and conditions: (a) (i) LiAlH$_4$; (ii) tetrapropylammonium perruthenate (TPAP, NMO); (b) Me$_3$S$^+$ MeOSO$_3^-$, NaOH; (c) NaN$_3$, acetone/H$_2$O; (d) CCl$_3$CN, DBU; (e) 10 mol% AgSbF$_6$(f) HBCy$_2$ (dicyclohexyl borane).

4. Organic Azides in the Synthesis of Heterocycles

Organic azides have synthesized various heterocycles of the five-member ring with one heteroatom, such as pyrroles. They are also involved in synthesizing heterocycles with two heteroatoms, such as pyrazole and isoazole, oxazole, thiazole, oxazine, and pyrimidine. In addition, heterocycles containing three heteroatoms, such as 1,2,3-triazoles and thiadiazole, are also included. Furthermore, organic azides are used in synthesizing heterocycles of six-membered rings and with one heteroatom, such as pyridine, isoquinoline, and phenanthidine. Heterocycles with four heteroatoms, such as tetrazole, are also discussed.
Synthetic interest applications of organometal heterocycles (i.e., phosphorus-, boron-, and aluminum-containing heterocycles) were also investigated. Figure 2 indicates the contribution of organic azides in heterocyclic synthesis.

**Figure 2.** Contribution of organic azides in heterocyclic synthesis, exemplary cases of the heterocycles.

### 4.1. Synthesis of the Pyrrole Ring

Dong and others [18] reported that dipyrrin-supported nickel catalyst \((\text{AdF}L)\text{Ni(py)}\) \((\text{AdF}L: 1,9\text{-di}(1\text{-adamantyl})-5\text{-perfluorophenyl}dipyrrin; \text{py}: \text{pyridine})\) catalyzed the productive intramolecular C–H bond amination to give N-heterocyclic products 28a–k using aliphatic azide substrates. The catalytic amination conditions were mild, requiring 0.1–2 mol% catalyst, and occurred at room temperature. The amination process occurred using different substrates having multiple activatable C–H bonds (Schemes 15 and 16). The selective catalyst showed high chemoselectivity favoring C–H bonds in ethers, halides, thioethers, esters, etc. (Scheme 17). Sequential cyclization of substrates with ester groups was achieved to provide facile preparation of indolizidine derivatives found in various alkaloids [18].

**Scheme 15.** Synthesis of pyrroles 28a–e. Reagents and conditions: (a) 1 mol% \((\text{AdF}L)\text{Ni(py)}\) \((\text{AdF}L), C_6D_6, 25–80 \, ^\circ\text{C}.$$
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Scheme 15. Synthesis of pyrroles 28a–e. Reagents and conditions: (a) 1 mol% \((\text{AdFL})\text{Ni(py)}\) (AdFL), C\(_6\)D\(_6\), 25–80 °C.

Scheme 16. Synthesis of pyrroles 28f–k. Reagents and conditions: (a) 1 mol% \((\text{AdFL})\text{Ni(py)}\) (AdFL), C\(_6\)D\(_6\), 60 °C.

The amination cyclization reaction mechanism is illustrated in Scheme 18. Benzene (4-azido-4-methyl pentyl), as an example, releases pyridine and N\(_2\) from L to give the corresponding nickel iminyl species A. The next step would be a hydrogen atom abstraction to give radical B, followed by radical recombination to give the cyclized product 28a [18].
Sun et al. [19] have reported the diastereoselective synthesis of Boc-protected 4-methylproline carboxylates 35, starting with the reduction of the azido compound 29. Selective cleavage of the primary TBS-alcohol 30 was performed using NH₄F in MeOH at room temperature for 6 h. Oxidation of the alcohol 30 was achieved using 2-iodoxybenzoic acid (IBX) in DMSO at 30 °C, and the resulting aldehyde 31 was subsequently transformed into the corresponding methyl ester 32 by adding KOH/I₂/MeOH. Deprotection of ester 32 with camphorsulfonic acid (CSA) afforded the corresponding alcohol 33. Tosylation of alcohol 33 with p-toluenesulfonyl chloride in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) as a base, gave compound 34 in high yield (90%). Finally, the two-step azide reduction/intramolecular SN₂ cyclization procedure was performed to obtain the desired Boc-protected (2S,4S)-4-methylproline carboxylate (35) in 90% yield (Scheme 19) [19].

Scheme 18. The postulated reaction mechanism for the formation of pyrroles and C-H amination.

Scheme 19. Synthesis of pyrrole 35. Reagents and conditions: (a) NH₄F (50 eq.), MeOH, room temperature, 6 h (75%); (b) IBX, DMSO, room temperature, 2 h; (c) I₂, KOH, MeOH, 0 °C, 1 h (95%); (d) CSA, MeOH, room temperature, 2 h; (e) TsCl, DABCO, CH₂Cl₂, room temperature, 18 h, (90%); (f) 10% NaHCO₃, H₂, MeOH, room temperature, 2 h, then NaHCO₃, Boc₂O, 12 h (90%).
Using chiral bisoxazoline-copper (BOX-Cu) complexes as catalysts, the cyclization process of asymmetric azide-ynamides via α-imino copper carbene intermediates polycyclic N-heterocycles with high enantioselectivities (up to 98:2 e.r.) was performed [20]. N-Styryl benzyl-tethered(azido)ynamide [N=([2-(azidomethyl)phenyl]ethynyl)-N-cinnamyl-4-methylbenzene sulfonamide] (36a) was selected as the model substrate, and Cu(CH$_3$CN)$_4$BF$_4$ was used as a catalyst to give ((8bR,9R,9aS)-9-phenyl-2-tosyl-2,4,9,9a-tetrahydro-1H-benzo[e]cyclopropa[c]indole) (37a) in 86% yield and N-cinnamyl-4-methyl-N-(naphthalen-2-yl)benzensulfonamide (38) as a side product (Scheme 20). The reaction was applied to various N-(azido)ynamide 36a–z. Firstly, different selected N-protecting groups of the ynamides 36a–e were examined, and the reaction proceeded smoothly when Ts-, Bs-, Ns-, SO$_2$Ph-, and Ms- were used as protecting groups (PG = protecting group, Bs = 4-bromobenzene-sulfonyl, Ns = 4-nitrobenzene-sulfonyl)(azido)ynamides producing the desired tetracyclic heterocycles 37a–e in 63–83% yields. In addition, various aryl-substituted benzyl-tethered (azido)ynamides 36f–m, having either electron-withdrawing and/or electron-donating groups, were also examined, and the corresponding cyclopropanation products 37f–m were obtained in good yields. The reaction was also applied to the thienyl- and furanyl-substituted (azido)ynamides 36n,o to give 37n and 37o in 76% and 67% yields, respectively. Different substituents on the phenyl ring 36p–v (f, Cl, Br, Me, and OMe) were also examined, and products 37p–v were obtained in 63–88% yields. Piperidine fused tetracyclic heterocycle 37w was also obtained in 71% yield. Moreover, methyl-, ethyl-, and even dimethyl-substituted N-allyl (azido)ynamides 36x–z were also suitable substrates for this type of cyclization to give products 37x–z in 69–86% yields (Scheme 21). In addition, the reaction was extended to investigate the copper-catalyzed cyclization for N-propargyl benzyl-tethered (azido)-ynamides 39a–u (Scheme 22) to synthesize 3H-pyrrolo[2,3-c]isoquinolines 40a–u using 10 mol% of Cu(CH$_3$CN)$_4$PF$_6$ as the catalyst and 2 equiv. of DDQ (4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile) as oxidant [20].

| Entry | Catalyst | Conditions | 37a (%) | 38 (%) |
|-------|----------|------------|---------|--------|
| 1     | Cu(OTf)$_2$ | DCE, 80 °C, 4 h | 18      | 54     |
| 2     | CuI      | DCE, 80 °C, 4 h | 21      | 50     |
| 3     | CuCl     | DCE, 80 °C, 4 h | 74      | 8      |
| 4     | Cu(CH$_3$CN)$_4$PF$_6$ | DCE, 80 °C, 4 h | 86      | <5     |
| 5     | Cu(CH$_3$CN)$_4$BF$_6$ | DCE, 80 °C, 4 h | 74      | 8      |
| 6     | Cu(OTf)$_2$ | DCE, 80 °C, 16 h | 32      | 30     |
| 7     | Zn(OTf)$_2$ | DCE, 80 °C, 3 h | <1      | 67     |
| 8     | Sc(OTf)$_3$ | DCE, 80 °C, 3 h | <1      | 77     |
| 9     | CF$_3$CO$_2$H | DCE, 80 °C, 2 h | <1      | 55     |
| 10    | MsOH     | DCE, 80 °C, 2 h | 10      | 78     |
| 11    | Cu(CH$_3$CN)$_4$BF$_6$ | DCE, 60 °C, 27 h | 75      | 7      |
| 12    | Cu(CH$_3$CN)$_4$BF$_6$ | toluene, 80 °C, 6 h | 25      | 35     |
| 13    | Cu(CH$_3$CN)$_4$BF$_6$ | PhCl, 80 °C, 5 h | 41      | 24     |
| 14    | none     | DCE, 80 °C, 5 h | <1      | 62     |

Scheme 20. Synthesis of pyrrole 37a. Reagents and conditions: 36a (0.1 mmol), catalyst (0.01 mmol), solvent (2 mL), 60 °C to 80 °C, 2–27 h, in vials.
Scheme 21. Synthesis of pyrroles 37a–z. Reagents and conditions: Cu(CH$_3$CN)$_4$BF$_4$ (0.02 mmol), DCE (4 mL), 80 °C, 4 h.

Scheme 22. Synthesis of pyrroles 40a–u. Reagents and conditions: DDQ, Cu-(CH$_3$CN)$_4$PF$_6$, DCE, room temperature, 5 h.

**Scheme 21.** Synthesis of pyrroles 37a–z. Reagents and conditions: Cu(CH$_3$CN)$_4$BF$_4$ (0.02 mmol), DCE (4 mL), 80 °C, 4 h.

**Scheme 22.** Synthesis of pyrroles 40a–u. Reagents and conditions: DDQ, Cu-(CH$_3$CN)$_4$PF$_6$, DCE, room temperature, 5 h.
Under thermal and UV light exposure, vinyl azides have been known to decompose into nitrenes and/or 2H-azirines, and they have been widely utilized to synthesize various N-heterocycles [21]. A photocatalyst-free visible light synthesized substituted pyrroles 42a–i from α-keto vinyl azides 41a–i. The optimized reaction condition was determined by applying the reaction on compound 41a, and it was observed that the optimal reaction condition was irradiation of 0.1 M solution of 41a in DCE with a blue LED (7 W) light (Schemes 23 and 24).

| Entry | Energy Source       | Solvent | Time (h) | Yield (%) |
|-------|---------------------|---------|----------|-----------|
| 1     | 7 W blue LED        | DCE     | 24       | 85        |
| 2     | 8 W CFL             | DCE     | 24       | 65        |
| 3     | Heating (60 °C)     | DCE     | 12       | 41        |
| 4     | 7 W blue LED        | DCE     | 24       | 85        |
| 5     | 7 W blue LED        | DCM     | 24       | 82        |
| 6     | 7 W blue LED        | MeOH    | 24       | -         |
| 7     | 7 W blue LED        | CH3CN   | 24       | -         |

Scheme 23. Optimized reaction condition of the decomposition of vinyl azide 41a.

The reaction mechanism was described as a result of the denitrogenative photodecomposition process of α-keto vinyl azides, 1,3-amino group migration, and coupling of intermediates 43–48 with secondary amines, as shown in Scheme 25 [22].

Scheme 24. Synthesis of chromenopyrroles 42a–i. Scope of the photodecomposition of vinyl azides 41 to access substituted pyrroles 42. Reagents and conditions: (a) 7 W blue LED light, DCE, 24 h.
with more than 12:1 1,8-aza-Michael addition/[3+2] cycloaddition between α-Jahn et al. [24] demonstrated the construction of tetrahedropyrrolo-pyrazole 49 followed by transfer of the amide group to the amine decomposition process of intermediates of pendant alkene using iodine in a basic medium as a catalyst. In contrast, Jahn et al. [24] demonstrated the construction of tetrahedropyrrolo-pyrazole 46, 47a–m via Aza-Michael addition/[3+2]cycloaddition between α,β-unsaturated esters 43a–c and amide 43d and allylic amines 44a–f using nonaflyl azides 45 ((F3C(CF2)3SO2N3, NfN3), acting as aza- transfer reagent) in the presence of n-BuLi. The reaction proceeded regioselectively with more than 12:1 1,8-trans/1,8-cis selectivity (Scheme 26) [24].

4.2. Synthesis of the Pyrazole Ring

Quiclet-Sire et al. [23] reported syntheses of tetrahydropyrrolo-pyrazole from hydrazones of pendant alkene using iodine in a basic medium as a catalyst. In contrast, Jahn et al. [24] demonstrated the construction of tetrahydropyrrolo-pyrazole 46, 47a–m via Aza-Michael addition/[3+2]cycloaddition between α,β-unsaturated esters 43a–c and amide 43d and allylic amines 44a–f using nonaflyl azides 45 ((F3C(CF2)3SO2N3, NfN3), acting as aza- transfer reagent) in the presence of n-BuLi. The reaction proceeded regioselectively with more than 12:1 1,8-trans/1,8-cis selectivity (Scheme 26) [24].

\[
\begin{align*}
\text{Scheme 25.} & \text{ Postulated mechanistic steps for the conversion of vinyl azides 41 into chromenopyrroles 42.} \\
\text{4.2. Synthesis of the Pyrazole Ring} \\
\text{Quiclet-Sire et al. [23] reported syntheses of tetrahydropyrrolo-pyrazole from hydrazones of pendant alkene using iodine in a basic medium as a catalyst. In contrast, Jahn et al. [24] demonstrated the construction of tetrahydropyrrolo-pyrazole 46, 47a–m via Aza-Michael addition/[3+2]cycloaddition between α,β-unsaturated esters 43a–c and amide 43d and allylic amines 44a–f using nonaflyl azides 45 ((F3C(CF2)3SO2N3, NfN3), acting as aza- transfer reagent) in the presence of n-BuLi. The reaction proceeded regioselectively with more than 12:1 1,8-trans/1,8-cis selectivity (Scheme 26) [24].} \\
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 26.} & \text{ Synthesis of pyrrolopyrazoles 46a–m and 47am. Reagents and conditions: (a) n-BuLi, THF. –78 °C, then AcOH, –78–25 °C.} \\
\end{align*}
\]

| 46/47 | R1  | R2  | R3  | R4  | R5  | n (%) | Trans/cis |
|-------|-----|-----|-----|-----|-----|-------|-----------|
| a     | Me  | OBu | H   | H   | H   | 1     | 77        | 12:1      |
| b     | Me  | OMe | H   | H   | H   | 1     | 37        | 14:1      |
| c     | Ph  | OBu | H   | H   | H   | 1     | 72        | 15:1      |
| d     | Me  | OMe | Me  | H   | H   | 1     | 95        | 15:1      |
| e     | Me  | OBu | Me  | H   | H   | 1     | 91        | 14:1      |
| f     | Me  | OBu | Me  | Me  | H   | 1     | 58        | 15:1      |
| g     | Me  | OBu | Me  | Me  | Me  | 1     | 85        | 12:1      |
| h     | Me  | OBu | Me  | H   | H   | Me    | 1        | 70        | 50:1      |
| i     | Me  | OBu | Me  | H   | Me  | Me    | 1        | 62        | >20:1     |
| j     | Ph  | OBu | Me  | H   | H   | H     | 1        | 90        | 15:1      |
| k     | Me  | NMe2 | Me  | H   | H   | H     | 1        | 76        | >20:1     |
| l     | Me  | NMe(OMe) | Me  | H   | H   | H     | 1        | 71        | 17:1      |
| m     | Me  | OBu | Me  | H   | H   | 2     | 71        | >20:1     |
The mechanism for this reaction is illustrated in Scheme 27. Initially, lithiation of the amine 44 gave the lithium amide 48, which coordinates to the carbonyl group of 43, followed by transfer of the amide group to the β-position via the formation of intermediate 49. (Z)-Enolate then 49 couples with nonafyl azide (NfN₃) to form the unstable triazenido 50. Protonation 50 would give the intermediate 51, followed by the formation of diazo intermediate 52. Finally, diastereoselective cycloaddition step takes place via transition state 53 and 54 to give the diastereoisomers 46 (1,8-trans) and 47 (1,8-cis) (Scheme 27) [24].

Moreover, Just and others [25] reported the catalytic syntheses of fused tricyclic pyrrolopyrazolines via aza-Michael cycloaddition of cyclic amines 55 as well as (R)-N-benzycycloalkenyl amines 58 with NfN₃ 45; the reaction was catalyzed by lithium chloride (LiCl). Diastereoselective products have been obtained in good yields (68–84%) for the tricyclic products (trans)-56a–f and (cis)-57a–f, while in the case of 5,5,5-tricyclic (trans)-59a–d and (cis)-60a–d, the yield ranged from 72 to 85%. Regarding the optimized reaction conditions (Schemes 28 and 29), it was observed that the diastereomers’ yields depend on the nature of cycloalkenylmethyl amines having five- or six-membered rings and α,β-unsaturated esters bearing alkyl or aryl substituents in β-position. In Scheme 30, the proposed mechanism for forming the tetrahedral-pyrrolo-pyrazole from the reaction of cycloalkenyl amines and α,β-unsaturated esters via intermediates 61–65 was postulated [25].

Previously, a cycloaddition reaction was reported between cinnamyl azide and methyl acrylates to obtain the tetrahydro-pyrrole-pyrazole [26,27]. Recently, Carlson et al. [28] developed the previously mentioned procedure via stereoselective interaction between allylic azides and acrylates in high yields. The development includes (i) secondary and tertiary azides, (ii) the use of an enantioenriched azide, (iii) cinnamyl azides substituted at
the α or β-carbon, (iv) derivatization of the products, and (v) additional Michael acceptors. Interestingly, it was found the following sequences: (A) the reaction was not completed during the reaction with cinnamoyl azide 66a, (B) 1 equivalent of acrylate 43 did not consume the azide at room temperature for three d, and (C) quantitative intermediates 67a–69a were obtained (Scheme 31). Optimization of acrylates 43 with cinnamoyl azides with aryl group of electrons withdrawing character has been investigated in Scheme 32. Re-optimization of reaction conditions such as (i) solvent, (ii) concentration, (iii) temperature, (iv) equivalents of acrylate, (v) time, and (vi) addition of DIPEA. It was found that the reaction proceeds well with a variety of cinnamoyl azides and the yields were improved. When DIPEA was used as a solvent compound, 70b was obtained with a 94% yield (Scheme 33). Optimization of the reaction in the scope of the substrate, incorporating methyl or phenyl group adjacent to the azide, for compound 70a a diastereomer was observed. Furthermore, cyclic azide resulted in the formation of tricyclic compounds 70u–w, as demonstrated in Scheme 34 [28].

\[
\text{R}^1\text{COC}_2\text{H}_4\text{OR}^2 + \text{HN} + \text{C}\quad \text{R}^2 \quad \text{R}^1\text{COC}_2\text{H}_4\text{OR}^2 + \text{HN} + \text{C} \\
\text{trans-56a-k} \quad \text{cis-57a-k} \\
\text{Scheme 28. Synthesis of cis/trans-pyrrolotriazoles 56a–k and 57a–k. Reagents and conditions: (a) BuLi, THF, 1 mol% LiCl, −78 °C, then AcOH, −78 to 25 °C.}
\]

\[
\text{R}^1\text{COC}_2\text{H}_4\text{OR}^2 + \text{HN} + \text{C} \\
\text{trans-59a-k} \quad \text{cis-60a-k} \\
\text{Scheme 29. Synthesis of cis/trans-pyrrolotriazoles 59a–k and 60a–k. Reagents and conditions: (a) BuLi, THF, 1 mol% LiCl, −78 °C, then AcOH, −78 to 25 °C.}
\]
The suggested stereochemical rationale for the formation of tricyclic compounds 56 and 57a–k.

Scheme 30. Synthesis of tetrahydro-pyrrole-pyrazoles 67a–70a. Reagents and conditions: (a) THF 5 mL, r.t 3 d.
Scheme 31. Synthesis of tetrahydro-pyrrole-pyrazoles 67a–70a. Reagents and conditions: (a) THF 5 mL, r.t 3 d.

| Solvent | Additive | 67b (%) | 68b (%) | 69a (%) |
|---------|----------|---------|---------|---------|
| DMSO    | -        | 14      | 77      |
| MeOH    | -        | 95      | -       |
| Hexane  | -        | 54      | 35      |
| THF     | -        | 34      | -       | 46      |
| benzene | -        | 37      | -       | 11      |
| benzene | AcOH     | -       | 67      | -       |
| benzene | HFIP     | -       | 55      | 17      |
| benzene | DMAP     | -       | 8       | 80      |
| benzene | pyridine | 5       | -       | 41      |
| benzene | TEA      | -       | -       | 85      |
| benzene | DIPEA    | -       | -       | 91      |
| toluene | DIPEA    | -       | -       | 83      |
| THF     | TEA      | -       | -       | 72      |
| THF     | DIPEA    | -       | -       | 78      |

Scheme 32. Synthesis of tetrahydro-pyrrole-pyrazoles 67b–69b. Reagent and conditions: (a) Solvent (0.2 mL), additive (0.5 equiv.), 70 °C, 24 h.

Scheme 33. Synthesis of pyrrole-pyrazoles 70a–n. Reagent and conditions: (a) 0.5 equiv. DIPEA, benzene, 70 °C, 24 h.

Scheme 34. Synthesis of pyrrole-pyrazoles 70o–w. Reagents and conditions: (a) (i) 3.5 equiv. acrylate, neat; (ii) 0.5 DIPEA, 70 °C.
4.3. Synthesis of Heterocycles Containing Two Heteroatoms

Vinyl azides 71 reacted with trifluoroacetic anhydride 72 in the presence of NEt₃ to give 5-(trifluoromethyl)isoxazoles 73a–as via denitrogenative cyclization processes (Scheme 35) [29].

Scheme 35. Syntheses of 5-trifluoromethyl isoxazoles 73a–73as. Reagent and conditions: (a) Et₃N, 1,4-dioxane, under N₂ atmosphere.

Vinyl azides 71 reacted with trifluoroacetic anhydride 72 in the presence of NEt₃ to give 5-(trifluoromethyl)isoxazoles 73a–as via denitrogenative cyclization processes (Scheme 35) [29].
4.4. Synthesis of Oxazole, Thiazole, and Oxazine Derivatives

The reaction of substituted vinyl azides 74 with a combination of substoichiometric amounts of iron(II) chloride and Togni's trifluoromethylating reagent 75 resulted in the formation of 2,2,2-trifluoroethyl-substituted 3-oxazolines 76, 3-thiazolines 77, and 5,6-dihydro-2H-1,3-oxazines 78. It was found that the optimal reaction conditions clarified that DCM, DCE, DMF, and 1,4-dioxane were solvents of choice, and the temperature varied from 80°C to ambient temperature (Scheme 36) [30].

Scheme 36. Azides in the synthesis of oxazole, thiazole, and oxazine derivatives. Reagents and conditions: (a) FeCl₂ (20 mol%), DCM, room temperature, 30 min.

The proposed mechanism described the formation of compound 76a. It showed the role of FeII in the reaction steps and its activation of Togni’s reagent via the formation of intermediates A–C; deprotonation was then achieved by the FeIII iodobenzoate complex (D) to give compound 76a and iodobenzoic acid 79 (Scheme 37) [30].
4.5. Synthesis of the Triazole Ring

Reactivity of azides 80 in [3 + 2] cycloaddition with aromatic or aliphatic terminal alkynes 81a–i clarified that 5 mol% of CuMeSal (copper(I) 3-methylsalicylate), with azidotrifluoromethane and other azidoperfluoroalkanes, afforded a range of N-bromo tetrafluoroethyl-substituted 1,2,3-triazoles 82a–i in good to high yields (Scheme 38). Since the reaction gave only one regioisomer, it was described as highly efficient and regiospecific (the reaction exclusively afforded only the 1,4-disubstituted triazole derivatives) at room temperature [31].

![Diagram of triazole synthesis](image)

**Scheme 38.** Synthesis of N-bromotetrafluoroethyl-substituted 4-aryl-1,2,3-triazoles 82a–i. *Reagents and conditions:* (a) THF, CuMeSal (0.05 mmol), r.t. overnight.

Ionic liquid/iron(III) chloride as a homogeneous catalyst was applied in the synthesis of 1,2,3-triazoles 84a–n from the reaction of substituted azides and substituted styrenes 83a–g [32] (Scheme 39).

Regioselective synthesis of 1,4,5-trisubstituted-1,2,3-triazoles 86a–n from the catalyzed reaction between enaminones 85 and aryl azides using 1-methyl pyridinium trifluoromethanesulfonate [mPy]OTf as the ionic liquid in basic medium via 1,3-dipolar cycloaddition (Scheme 40). Herein, the reaction selectively generates only the 1,5-disubstituted triazoles as the only possible product over 1,4-disubstituted triazoles. As illustrated in Scheme 41, the proposed mechanism demonstrated that the formation of triazoles 86a–n from the reaction of the aryl azides and enaminones 85a–g was taken via the formation of intermediate 87a–n [33]. The reaction was described as retro-Michael addition to give two regioisomers. Elimination of aniline from the two regiosomers afforded the corresponding triazoles 86a–n. Moreover, the reaction took place with complete regioselectivity yielding the regioisomer with the electron-deficient group of the enaminone in position 4 and the alkyl substituent in position 5 as the only product of the reaction.
Regioselective synthesis of 1,4, 5-trisubstituted-1,2,3-triazoles... Accordingly, the yields of compounds 89a–u became good compared with the previous method, as shown in Scheme 43.

| 84a–n | R   | R¹    | Yield (%) |
|-------|-----|-------|-----------|
| a     | Bn  | H     | 95        |
| b     | Bn  | 2-Cl  | 85        |
| c     | Bn  | 3-Cl  | 84        |
| d     | Bn  | 4-Cl  | 86        |
| e     | Bn  | 4-MeO | 93        |
| f     | Bn  | 4-Me  | 92        |
| g     | Bn  | 2-NO₂ | 81        |
| h     | Ph  | H     | 91        |
| i     | Ph  | 2-Cl  | 87        |
| j     | Ph  | 3-Cl  | 93        |
| k     | Ph  | 4-Cl  | 92        |
| l     | Ph  | 4-MeO | 92        |
| m     | Ph  | 4-Me  | 96        |
| n     | Ph  | 2-NO₂ | 95        |

Scheme 39. Synthesis of 1,2,3-triazoles 84a–n. Reagents and conditions: (a) FeCl₃ (20%), 100 °C.

Scheme 40. Synthesis of 1,2,3-triazoles 86a–n. Reagents and conditions: (a) [mPy]OTf/H₂O, Et₃N, 100 °C, 4–10 h.

Scheme 41. Reaction mechanism for the reaction between enaminones and azides to form triazoles 86a–n.

Zhang et al. [34] reporoom temperatureed the one-pot multicomponent reaction for the syntheses of 5-thiotriazoles 89a–u, 91a–m, and 5-selenotriazole 92a–l scaffolds using sulfur and selenium elements. Firstly, the reaction was displayed between methyl propiolate, benzyl bromide, S₈, and 4-methoxybenzyl azide (PMBN₃) and was selected to optimize the reaction conditions. It was clear that the optimized condition was achieved for 89a in the following conditions: CuI (1.3 equiv), K₂CO₃ (2.0 equiv), and S₈ (3.0 equiv) in MeCN (or DMF), first at 0 °C for 1 h and then at 50 °C for 10 h (Scheme 42). The yield was increased with an increasing amount of CuI to 1.3 equivalent and at 50 °C using DMF or MeCN as a solvent. Accordingly, the yields of compounds 89a–u became good compared with the previous method, as shown in Scheme 43.
### Scheme 42. The optimization of the multicomponent reaction for the formation of thiotriazoles 88, 89a, and 90.

| Entry | Additive (2.0 Equiv.) | CuI (Equiv) | Solvent | T (°C) | Yield (%) 89a | Yield (%) 90 | Yield (%) 88 |
|-------|-----------------------|-------------|---------|--------|---------------|---------------|---------------|
| 1     | K2CO3                 | 0.5         | DMF     | 0      | 0             | 29            | 40            |
| 2     | K2CO3                 | 0.5         | DMF     | 0–rt   | 22            | 34            | 32            |
| 3     | K2CO3                 | 1.0         | DMF     | 0–rt   | 55            | 16            | 29            |
| 4     | K2CO3                 | 1.3         | DMF     | 0–rt   | 59            | 23            | 0             |
| 5     | K2CO3                 | 1.5         | DMF     | 0–rt   | 51            | 12            | 0             |
| 6     | K2CO3                 | 1.3         | DMF     | 0–50   | 62            | 22            | 0             |
| 7     | -                     | 1.3         | DMF     | 0–rt   | 0             | 0             | 22            |
| 8     | K2CO3                 | 1.3         | DMSO    | 0–50   | 0             | -             | -             |
| 9     | K2CO3                 | 1.3         | THF     | 0–50   | 41            | -             | -             |
| 10    | K2CO3                 | 1.3         | MeCN    | 0–50   | 80            | -             | 0             |
| 11    | Cs2CO3                | 1.3         | MeCN    | 0–50   | 36            | 14            | -             |
| 12    | t-BuOK                | 1.3         | MeCN    | 0–50   | 34            | 12            | -             |
| 13    | DIPEA                 | 1.3         | MeCN    | 0–50   | 20            | -             | -             |

**Scheme 43. Substrate effect on the formation of 5-thiotriazoles 89a–u under the optimal conditions.**
Next, the influence of the alkynes and azides was examined using DMF as the solvent at temperatures ranging from room temperature to 70 °C for the generation of the sulfonylating agent (Scheme 44). Aromatic alkynes with methyl, methoxy, and nitro groups on the benzene ring worked well to produce the corresponding 5-thiotriazoles 91a–i. The efficiency of acylacetylenes was demonstrated by the generation of 91j bearing a reactive hydroxyl group. Aliphatic alkynes also proved to be effective for this process 91l. The excellent availability of this multistep reaction has been well demonstrated by the generation of products 91i and 91k from α-azidoacetate and 2-phenylethyl azide, respectively. Under the previous mild sequential copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) and thiolization reaction conditions, the estrone derivative of an alkyne was easily transformed into the corresponding 5-thiotriazole 91m in 52% yield.

\[
\begin{align*}
\text{Scheme 44. Substrate effect of alkynes and azides in the synthesis triazolothiols 91a–m.}
\end{align*}
\]

5-Selenotriazoles 92a–l were prepared using selenium as a reagent under the standard conditions in DMF or MeCN, as shown in Scheme 45. The examination was extended to synthesize fused bicyclic 5-thiotriazoles 93a–g [34] (Scheme 46).

Copper(I) acetylide VI was formed from a terminal alkyne and CuI under basic conditions. The proposed mechanism for this work is shown in Scheme 47. In the beginning, CuI reacted with sulfur to give copper sulfide I. Subsequently, the oxidative addition with a halide forms II, transformed into copper(II) thiolate IV via reductive organic group transfer and oxidation. The cycloaddition of VI with the azide produced the copper(I) triazolide intermediate VI1. Reaction of copper(II) thiolate IV with the copper(I) triazolide would give the intermediate V. Finally, reductive elimination of V would then lead to the expected 5-thiotriazole 89a–u (Scheme 47) [34].
Scheme 44. Substrate effect of alkynes and azides in the synthesis of triazolothiols.

Scheme 45. Synthesis of selenotriazoles.

Scheme 46. Synthesis of fused bicyclic 5-thiotriazoles. Reagents and conditions: (a) CuI (0.65 mmol), S₈ (1.5 mmol), K₂CO₃ (1.0 mmol), DMF, 0 °C, 30 min, room temperature or 70 °C, 10 h or overnight.

Scheme 47. Synthesis of selenotriazoles.

a, R’ = H, X = Br (80%);
b, R’ = Me, X = Br (77%);
c, R’ = OMe, X = O (53%);
d, R’ = Br, X = Br (82%);
e, r’ = CN, X = Br (85%);
f, R’ = NO₂, X = Br (88%).

h, X = Br (72%)
i, X = Br (22%)  X = OTs (29%)
j, X = Br (68%)
k, X = Br (20%)
l, X = Br (51%)

Scheme 45. Synthesis of selenotriazoles 92a–l.

Scheme 46. Synthesis of fused bicyclic 5-thiotriazoles. Reagents and conditions: (a) Cu(I) acetylide VI was formed from a terminal alkyne and CuI under basic conditions. The proposed mechanism for this work is shown in Scheme 47. In the beginning, CuI reacted with sulfur to give copper sulfide I. Subsequently, the oxidative addition with a halide forms II, transformed into copper(II) thiolate IV via reductive organic group transfer and oxidation. The cycloaddition of VI with the azide produced the copper(I) triazolide intermediate VI₁. Reaction of copper(II) thiolate IV with the copper(I) triazolide would give the intermediate V. Finally, reductive elimination of V would then lead to the expected 5-thiotriazole 89a−u (Scheme 47) [34].
Scheme 47. A plausible mechanism for the formation of thiotriazoles.

Copper catalyzed 1,3-dipolar cycloaddition between azides and 4-allyl-2-methoxy-1-(prop-2-yn-1yloxy)benzene (94) in refluxing acetonitrile afforded the corresponding monocycloadduct 95a–g with regioselectivity in high yields between 78 and 90% (Scheme 48) [35].

Scheme 48. Synthesis of triazoles 95a–g. Reagents and conditions: (a) CuI, MeCN, room temperature, 2 h.

5-Amino-1,2,3-triazoles 98a–k were prepared from the corresponding amidines 97a–k reacting with tosyl azides in a methanolic basic medium (Scheme 49) [36].

Stanciu et al. [37] reported that N,N′-carbonyldiimidazole (CDI) synthesized amphiphilic esters based on dextran via a one-pot procedure based on the reaction between the polysaccharide and different substituted 1,2,3-triazoles-4-carboxylates 102a–f. Firstly, the triazole derivatives 102a–f were obtained through copper alkyne azide cycloaddition (CuAAC) between azide 101a–f and ethyl propiolate. Basic hydrolysis of the triazole ester 102a–f using KOH (aq), MeOH/H2O gave 1,2,3-triazol-4-carboxylic acid derivatives 103a–f [37]. Esterification of the dextran (polysaccharide) with the triazole ester activated in situ with 1,1′-carbonyldiimidazole (CDI) to give the dextran esters 104a–f (Scheme 50).
(DMSO, room temperature, 24 h); (ii) Dex40 (DMSO, 80 °C, 24 h).

14:1:0:0 (Scheme 51) [40].

Figure 3. Structure of the interlocked NHC-CuI complexes 1-TFPB and 2-TFPB [40].

| 98 | R¹ | NR²R³ | R⁴ | RSO₂N₃ (Equiv.) | Yield (%) |
|----|----|------|----|----------------|-----------|
| a  | CN | Azepane | H  | c              | 98        |
| a  | CN | Azepane | H  | a, 2.0         | 91        |
| a  | CN | Azepane | H  | a, 1.4         | 81        |
| b  | CN | 4-benzylpiperidine | H  | c              | 95        |
| b  | CN | 4-benzylpiperidine | H  | a, 1.0         | 98        |
| c  | CN | Morpholine | H  | c              | 93        |
| c  | CN | Morpholine | H  | a, 1.0         | 82        |
| c  | CN | Morpholine | Ph | a, 1.0         | 91        |
| d  | CN | Morpholine | Ph | a, 1.0         | 91        |
| e  | CN | Pyridine  | Ph | a, 1.0         | 87        |
| f  | CN | Pyridine  | H  | a, 1.0         | 85        |
| g  | CN | Pyridine  | H  | a, 1.0         | 92        |
| h  | CN | NH₂      | Bn | c              | 84        |
| h  | CN | NH₂      | Bn | a              | 84        |
| i  | CN | NH₂      | 4-MeOC₆H₄ | a           | 89        |
| j  | CN | NH₂      | 4-MeOC₆H₄ | a           | 86        |
| k  | CO₂Et | NMe₂  | H  | c, 2.0         | 60        |
| k  | CO₂Et | NMe₂  | H  | a, 2.2         | 81        |

Scheme 49. Synthesis of 5-amino-1,2,3-triazoles 98a–k. Reagents and conditions: (a) EtOH, reflux; (b) Et₃N, MeOH, room temperature.

101a–f + CO₂Et → 102a–f (46-84%)

Scheme 50. Synthesis of esters of dextran-triazole esters 104a–f. Reagents and conditions: (a) CuSO₄·5H₂O, sodium ascorbate, t-BuOH/MeOH/H₂O₂; (b) KOH (aq), MeOH/H₂O; (c) (i) CDI (DMSO, room temperature, 24 h); (ii) Dex40 (DMSO, 80 °C, 24 h).
N-Heterocyclic carbene-copper (NHC-Cu) complexes were known as organometallic catalysts that could differentiate the reactivities of simple terminal alkynes and azides through amplified steric discrimination, allowing efficient sequential ligations of a diyne with two different azides under conditions of premixing all of the reaction partners in solution [38,39]. The interlocked NHC-Cul complexes were found as 1-TFPB and 2-TFPB (TFPB: tetrakis[3,5-bis(trifluoromethyl)phenyl] borate) (Figure 3). The rotaxane 1-TFPB catalyzed a competition reaction involving two pairs of individual alkynes and azides. Therefore, a heating mixture of the non-bulky alkyne 105, the bulky alkyne 106, the non-bulky azide 107, and the bulky azide 108 in THF at 323 K for 48 h in the presence of rotaxane 1-TFPB (15 mol%), four possible triazole products were formed 109–112 with good selectivity. The triazole 109 was predominant, with the ratio of the triazoles 109–112 being 14:1:0:0 (Scheme 51) [40].

Figure 3. Structure of the interlocked NHC-CuI complexes 1-TFPB and 2-TFPB [40].

Scheme 51. Synthesis of triazoles 109–112. Reagents and conditions: Method (a) 1-TFPB (15 mol%), THF-d6, 50 °C, 48 h; Method (b) (i)1-TFPB (15 mol%), THF, 50 °C, 48 h; (ii) Cu(MeCN)4PF6/2,6-lutidine.

Moreover, when azides 107 and 108 were reacted with diyne 113, under the same conditions in the presence of rotaxane 1-TFPB (15 mol%) and then adding [Cu(MeCN)4]PF6 and 2,6-lutidine to the intermediate mixture bis-triazole, 114 was isolated in 74% yield (Method A) (Scheme 52). When the last reaction was performed in the presence of 2-TFPB (15 mol%) under the same conditions in the dark for 48 h, the less bulky alkyne and azide had disappeared, while those of the bulky alkyne and azide remained, exhibiting good chemoselectivity toward the coupling of the less bulky parts. Irradiation of this intermediate mixture with light (350 nm, 5 min) cleaved approximately half of the macrocyclic components formed. Heating the resulting mixture (323 K, 12 h) led to the coupling of the bulky pair of alkyne/azide partners and the formation of triazole product 114 in 84% yield (Scheme 52) [40].
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Scheme 52. Synthesis of ethyl 2-(4-(1-(3-((1-(2-methoxy-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methoxy)methyl(benzyl)oxy)-2-methylpropan-2-yl)-1H-1,2,3-triazol-1-yl)-2-methylpropanoate (114). Reagents and conditions: Method A (i) 1-TFPB (15 mol%), THF-\(d_6\), 50 °C, 48 h; (ii) Cu(MeCN)\(_4\)PF\(_6\)/2,6-lutidine. Method B (i) 2-TFPB (15 mol%), THF-\(d_6\), 50 °C, 48 h, dark; (ii) hv, (350 nm), 5 min, room temperature; (iii) hv, 15 min, room temperature, then 50 °C, 12 h.

Syntheses of 2-(4-((1-phenyl-1H-1,2,3-triazol-4-yl)methoxy)phenyl)isoindoline-1,3-dione derivatives 119a–f were involved in three steps. 4-Aminophenol 116 reacted with phthalic anhydride (115) in acetic acid at 100 °C to give compound 117 (Scheme 53). Propargylation of 117 afforded the corresponding 2-(4-(prop-2-yn-1-yloxy)phenyl)isoindoline-1,3-dione (118), which in the presence of potassium carbonate and subsequently treated with various azides via 1,3-dipolar cycloaddition (click reaction) during treatment with 10 mol% of sodium ascorbate and 10 mol% of copper sulfate. Consequently, the reaction afforded 1,2,3-triazolisoindoline-1,3-dione derivatives 119a–e in excellent 70% to 81% yield, as shown in Scheme 53 [41].

Scheme 53. Synthesis of 1,2,3-triazolisoindoline-1,3-dione derivatives 119a–f. Reagents and conditions: (a) Acetic acid, 100 °C, 3 h; (b) \(\mathrm{K}_2\mathrm{CO}_3\), Propargyl bromide, DMF, room temperature, 3 h; (c) Azides, 10 mol% of sodium ascorbate, 10 mol% of CuSO\(_4\)-H\(_2\)O, DMF: Water (1:1), room temperature, 10 to 12 h.

Applying the same procedure mentioned, the synthesis of triazoles 123a–e was also established in the same three steps. Compound 122 was obtained, which in the presence of potassium carbonate and subsequently treated with various azides and 10 mol% of sodium ascorbate and 10 mol% of copper sulfate, afforded the final compounds 123a–e via 1,3-dipolar cycloaddition (Click reaction) (Scheme 54) [41].
phthalic anhydride (115) in acetic acid at 100 °C to give compound 117 (Scheme 53). Propargylation of 117 afforded the corresponding 2-(4-(prop-2-yn-1-yloxy)phenyl)isoindoline-1,3-dione (118), which in the presence of potassium carbonate and subsequently treated with various azides via 1,3-dipolar cycloaddition (click reaction) during treatment with 10 mol% of sodium ascorbate and 10 mol% of copper sulfate. Consequently, the reaction afforded 1,2,3-triazolyisoindoline-1,3-dione derivatives 119a–e in excellent 70% to 81% yield, as shown in Scheme 53 [41].

Scheme 53. Synthesis of 1,2,3-triazolyisoindoline-1,3-dione derivatives 119a–f. Reagents and conditions: (a) Acetic acid, 100 °C, 3 h; (b) K$_2$CO$_3$, propargyl bromide, DMF, room temperature, 3 h; (c) Azides, 10 mol% of sodium ascorbate, 10 mol% of CuSO$_4$·H$_2$O, DMF:H$_2$O (1:1), room temperature, 10 to 12 h.

Applying the same procedure mentioned, the synthesis of triazoles 123a–e was also established in the same three steps. Compound 122 was obtained, which in the presence of potassium carbonate and subsequently treated with various azides and 10 mol% of sodium ascorbate and 10 mol% of copper sulfate, afforded the final compounds 123a–e via 1,3-dipolar cycloaddition (Click reaction) (Scheme 54) [41].

Scheme 54. Synthesis of triazoles 123a–e. Reagents and conditions: (a) acetic acid, 100 °C, 3 h; (b) K$_2$CO$_3$, propargyl bromide, DMF, room temperature, 3 h; (c) Azides, 10 mol% of sodium ascorbate, 10 mol% of CuSO$_4$·5H$_2$O, DMF:H$_2$O (1:1), room temperature, 10 to 12 h.

CuFe$_2$O$_4$@MIL-101(Cr) was used as a catalyst in synthesizing benzodiazepine triazole derivatives during the reaction of chalcones containing the acetylene group in the o or p positions 124a–c with substituted azides containing both electron-withdrawing groups and electron-donating groups (Scheme 55). Firstly, the chalcones 124 reacted with o-phenylenediamine 125 to furnish the corresponding diazepine acetylene derivatives 126, which on click reaction underwent cyclization to give the triazole derivatives 127a–u [42].

Scheme 55. Synthesis of triazoles 127a–v. Reagents and conditions: (a) CuFe$_2$O$_4$@MIL-101(Cr), water reflux; (b) H$_2$O, reflux.
Propargylurea (128) underwent cyclocondensation with methyl trifluoropyruvate benzothiazolylimine (129) in the presence of Et₃N to give 5-alkynyl-substituted trifluoromethyl hydantoin 130 in 67% yield. The alkyne 130 was subjected to CuAAC reaction with 2-azidoacetamides 131 to give the corresponding 1,4-substituted 1,2,3-triazoles 132a–f (Scheme 56) [43].

Azides reacted regioselectivity with alkynes via CuAAC 1,3-dipolar cycloaddition using CuI to form triazoles 133a–g as a major product and triazoles 134a–g as minor products. An exception was the reaction of methyl azide with tert-butyl prop-2-yn-1-ylcarbamate, which resulted in a mixture of triazole 133a with 2-azidoacetamides as minor products.

Furthermore, azide 143 was reacted even with a reactive dipolarophile, such as acetylenedicarboxylate in t-BuOH in the presence of a basic cocatalyst gave triazole 144 (74%) (Scheme 59) [44].

Azides reacted regioselectivity with alkynes via CuAAC 1,3-dipolar cycloaddition using CuI to form triazoles 133a–g as a major product and triazoles 134a–g as minor products. An exception was the reaction of methyl azide with tert-butyl prop-2-yn-1-ylcarbamate, which resulted in a mixture of triazole 133a with 2-azidoacetamides as minor products. Under similar conditions, the longer aliphatic chain azide (3-(azidomethyl)heptane) reacted with phenylacetylene to give triazole 133h in high yield (90%) (Scheme 59). Bis-triazoles 137 and 139 were obtained in high yields with a faster rate of reaction via click reaction of 1,3-diazidopropane (136) and diazide 138 with ethyl propiolate and phenylacetylene, respectively (Scheme 57). Bis-triazoles 137 and 139 were obtained in high yields with a faster rate of reaction via click reaction of 1,3-diazidopropane (136) and diazide 138 with ethyl propiolate and phenylacetylene, respectively (Scheme 57). Bis-triazoles 137 and 139 were obtained in high yields with a faster rate of reaction via click reaction of 1,3-diazidopropane (136) and diazide 138 with ethyl propiolate and phenylacetylene, respectively (Scheme 57). Bis-triazoles 137 and 139 were obtained in high yields with a faster rate of reaction via click reaction of 1,3-diazidopropane (136) and diazide 138 with ethyl propiolate and phenylacetylene, respectively (Scheme 57).

\[ \text{N-Propargylated cinnolinones 145a–c reacted with benzyl azide to afford the corresponding triazole derivatives 146a–c via CuAAC in CHCl}_3. \] It was noted that the complexes of the [(IPr)CuX] series (X = Cl, Br, I) did not exhibit catalytic activity. However, [(IMes)CuX] complexes (X = Cl, Br, I) containing a less sterically hindered ligand showed higher activity under the same reaction conditions; this was attributed to the electronic...
nature of the halides, and the catalytic reactivity increased in the order of Cl\(^-\) < Br\(^-\) \(\approx\) I\(^-\), (Scheme 60) [45].

\[
\begin{align*}
R^1N_3 + & R^2\equiv \quad (a), (b) \quad \begin{array}{c}
\text{133c-g} \\
\text{134a-g}
\end{array} \\
R^1N_3 + & R^2\equiv \quad (c) \quad \begin{array}{c}
\text{133a-g} \\
\text{135 (21%)}
\end{array}
\end{align*}
\]

133a-g: R\(^1\) = H, R\(^2\) = (a, CH\(_2\)NHBoc (49%); b, CH\(_2\)OH (94%); c, COOME (97%));
d, R\(^1\) = CH\(_2\)OH, R\(^2\) = CH\(_2\)NHBoc (52%); e, R\(^1\) = CN, R\(^2\) = CH\(_2\)NHBoc (40%);
f, R\(^1\) = COOEt, R\(^2\) = CH\(_2\)OH (47%); g, R\(^1\) = CONH\(_2\), R\(^2\) = CH\(_2\)NHBoc (55%).

134a-e: a, R\(^1\) = H, R\(^2\) = COOME (9.5%); b, R\(^1\) = CH\(_2\)OH, R\(^2\) = CH\(_2\)NHBoc (37%);
c, R\(^1\) = CN, R\(^2\) = CH\(_2\)NHBoc (36%); d, R\(^1\) = COOEt, R\(^2\) = CH\(_2\)OH (47%);
e, R\(^1\) = CONH\(_2\), R\(^2\) = CH\(_2\)NHBoc (40%).

Scheme 57. Synthesis of various regioisomers of triazoles 133-135. Reagent and conditions: (a): R\(^1\) = H, R\(^2\) = CO\(_2\)Me, PhH, 20 °C to room temperature, 12 h; (b): R1 \(\neq\) H, PhMe, 80–90 °C, 24 h; (c) Cul, PhCOOH, i-PrOH–H\(_2\)O.

\[
\begin{align*}
\text{MeO}_2C & \quad \begin{array}{c}
\text{137 (74%)}
\end{array} \\
\text{Ph} & \quad \begin{array}{c}
\text{139 (70%)}
\end{array}
\end{align*}
\]

Scheme 58. Synthesis of bis-triazoled 137 and 139. Reagent and conditions: (a) CuI (1 mol%), Et\(_3\)N, THF; (b) CuSO\(_4\)·5 H\(_2\)O, NaAsc, DMSO–H\(_2\)O.
Scheme 59. Synthesis of bis-triazole carboxylate derivatives 141, 142 and 144. Reagents and conditions: (a) PhMe; (b) CuI (1 mol%), THF; (c) CuI (10 mol%), Et₃N, THF.

N-propargylated cinnolinones 145a–c reacted with benzyl azide to afford the corresponding triazole derivatives 146a–c via CuAAC in CHCl₃. It was noted that the complexes of the [(IPr)CuX] series (X = Cl, Br, I) did not exhibit catalytic activity. However, [(IMes)CuX] complexes (X = Cl, Br, I) containing a less sterically hindered ligand showed higher activity under the same reaction conditions; this was attributed to the electronic nature of the halides, and the catalytic reactivity increased in the order of Cl⁻ < Br⁻ ≈ I⁻, (Scheme 60) [45].

Scheme 60. Synthesis of 1,2,3-triazoles 146a–c. Reagents and conditions: (a) [(NHC)CuX] (2 mol%), solvent, room temperature, 18 h.

Filimonov et al. [46] reported a one-step, eco-friendly method for synthesizing 1,2,3-thiadiazol-4-carbimidamides 149a–r and 1,2,3-triazole-4-carbothioamides 150a–j, during the reactions of 2-cyanothioacetamides 147a–g with various types of azides 148 in water in the presence of alkali (Scheme 61). Furthermore, N,N'-bis-(2-cyanothiocarbonyl)-pyrazine...
147h was reacted with sulfonyl azides 148 to give the bicyclic 1,2,3-thiadiazoles 151–153, and 1,2,3-triazoles 154a–f connected via a 1,1'-piperazinyl linker (Scheme 62). On the other hand, 2-cyanothioacetamides 155 reacted with aromatic azides in water in the presence of alkali to afford 1-aryl-5-amino-1,2,3-triazole-4-carbothioamides 156a–l (Scheme 63). In contrast to aromatic azides and sulfonyl azides, 6-azidopyrimidine-2,4-diones 157a–c reacted with cyanothioacetamides 147a–e to give N-pyrimidine-6-yl-5-dialkylamino-1,2,3-thiadiazole-4-N-l-carbimidamides 158a–i. Additionally, compounds 158a–i were obtained in two step-reaction starting with 6-chloro-1,3-disubstituted-pyrimidine-2,4-dione 159 (Scheme 64).

Scheme 61. Synthesis of triazoles 147–150. Reagents and conditions: (a) NaOH, H$_2$O, 0 °C; (b) EtONa, EtOH, 23 °C, 1 h.
Scheme 62. Synthesis of bis-triazoles 154a–f. Reagents and conditions: (a) H₂O, NaOH; (b) NaOMe, MeOH; (c) TsN₃, pyridine.

Scheme 63. Synthesis of triazoles 156a–l. Reagents and conditions: (a) NaOH, H₂O, 50–60 °C.
Scheme 64. Synthesis of N-pyrimidin-6-yl-5-dialkylamino-1,2,3-thiadiazole-4-N-l-carbimidamides 158a–i. Reagents and conditions: (a) H$_2$O, NaOH, 0 °C; (b) NaN$_3$, H$_2$O, r.t., 24 h; (c) H$_2$O, 0 °C, 24 h.

Bis(azidomethyl)-5,5-diethylpyrimidinetrione (160) underwent CuAAC 1,3-dipolar cycloaddition with alkyne (prop-2-yn-1-ol) to afford bis((4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)methyl)pyrimidinetrione (161) (Scheme 65) [46].

Scheme 65. Synthesis of bistriazolylpyrimidinetrione 161. Reagents and conditions: (a) CuSO$_4 \cdot 5$H$_2$O, NaAsc, DMF, 50 °C, stirring 15–50 h.

The copper-mediated click reaction using 3-aminophenyl-acetylene (162) and benzyl azide as the starting materials gave the monotriazole 163 using a well-defined copper carbenec complex [CuCl (IPr)] (IPr = 1,3-bis-(2,6-diisopropylphenyl)imidazolin-2-ylidene).
carbene complex [CuCl (IPr)] (IPr = 1,3-bis-(2,6-diisopropylphenyl)imidazolin-2-ylidene) as a catalyst. Compound 163 underwent diazotization and azidation followed by [3 + 2] click reaction to afford the non-symmetrical bis(triazoles) 164. Alkylation of 164 using Meerwein’s salt (CH$_3$)$_3$OBF$_4$ gave the dicationic pro-ligand salt 165. The non-symmetrical triazolium salt 165 and symmetrical 1,2,3-triazolium salts [47–50] 166 and 167 were utilized to synthesize mesoionic carbene-sulfur adducts 168a, 169b, and 170c. Firstly, the triazolium salts 165/166 were reacted with elemental sulfur in a base (KO$_t$Bu and K$_2$CO$_3$) non-symmetrical mesoionic bis (NHT) compound 168 the symmetrical analog 169 in good yields, 76% and 72%, respectively. Complexes 170–173 were formed with the treatment of 167 with elemental sulfur in the presence of K$_2$CO$_3$ as a base (Scheme 66) [51].

Scheme 66. Synthesis of cationic-anionic triazoles. Reagents and conditions: (a) [CuCl(IPr)], EtOH/H$_2$O; (b): NaNO$_2$, HCl, and then NaN$_3$, and then 1-hexyne, [CuCl (IPr)], EtOH/H$_2$O, 82% (two-step combined yield); (c): (CH$_3$)$_3$OBF$_4$, dichloroethane (DCE), 56%; (d) K$_2$CO$_3$, S8, MeCN, 90°C, 24 h.

Yoshida et al. [52] reported that the double-click reaction between aryl azides and the diyne (183) afforded a regioisomeric mixture of bicyclo-adduct 184 (trans/cis) in an excellent yield. It was observed that 1-adamantyl azide was bulky, caused retention to the cycloaddition and gave the bis-cyclo-adduct with 18% for 4 h. The 2,6-diisopropylphenyl
azide gave the bis-cyclo-adduct in quantitative yields, while the unhindered benzyl azide gave the bis-cyclo-adduct in 83% yields for 1 h. The studies were prolonged to cover the effect of the substituent in the aryl azide to clarify that the bulkiness groups enhanced the reaction rate, and the electronic nature of substituted groups in both \( \sigma \) - and \( \pi \)-positions showed a limited effect on the reaction rate. In contrast, 2,6-disubstituted phenyl azides had accelerated reaction rates as the size of substituents became bulkier (the lower click ability of adamantyl azide than that of diisopropylphenyl azide was attributed to the stabilization of the azido group by hyper-conjugation with \( \text{C-H} \) bonds, which decreases the distortion ability of the azido group) (Scheme 67) [52]. The click ability of the alkyl and alkenyl azides with Sondheimer diyne (174) afforded the regioisomeric bicyclo adducts 176 (trans/cis). The studies showed that the reaction rate was faster in the case of alkyl azides than in the alkenyl azides, indicating that resonance retarded the reaction rate and that both the inductive effect and hyper-conjugation increased the reaction rate (Scheme 67) [52,53].

Scheme 67. Cycloaddition of Sondheimer diyne 174 with aryl azides. Reagents and conditions: (a) 2.4 equiv. of azide, MeOH room temperature.

| Compound 176 | R         | Yield (%) | Trans/cis | \( K \) (M^{-1}s^{-1}) |
|--------------|-----------|-----------|-----------|------------------------|
| a            | PhCH=CH... | 99        | 57/43     | 9.6 \times 10^{-2}    |
| b            | PhCH=CH... | 98        | 53/47     | 4.1 \times 10^{-2}    |
| c            | MePhCH...  | 98        | Not determined | 2.1 \times 10^{-2} |
| d            | CH=CHPh    | 98        | 49/51     | 3.9 \times 10^{-3}    |
| e            | CH=CCPh=CHPh | 97       | 54/46     | 6.1 \times 10^{-3}    |
| f            | PhCH=CPh   | Quant.    | 75/52     | 8.9 \times 10^{-2}    |

The synthesis of triazolyl benzoxazine derivatives 179a-n via one-pot reaction (e.g., Ugi reaction [54]) using the so-called Passerini-azide reactions (a method to prepare tetrazoles by substituting hydrazoic acid generated in situ from NaN\(_3\) or TMS-N\(_3\) (177), has been reported [54–56]. The reaction of 2-azidobenzaldehydes 176, 177, and isocyanides 178 gave 4H-3,1-benzoxazine derivatives by the in-situ formation of azide intermediate (Scheme 68) [56].

The proposed mechanism for the formation of compounds 179a-n was started from the Passerini-azide adduct 180, which reacted with the palladium reagent to form the palladium–nitrogen intermediate 181 with the elimination of the nitrogen molecule. Insertion of isocyanide 178 to the formed intermediate 181 gave the three-membered ring intermediate 182. The carbodiimide intermediate 183 was formed via reductive elimination of intermediate 182. Finally, intermolecular cyclization of intermediate 184 resulted in the formation of the benzoxazine derivatives 179a–n, as illustrated in Scheme 69 [56].
tert-butyl ester or diethyl (4-azidobutyl) phosphonate was reacted with 2-propyn-1-ol and 3-butyn-1-ol in the presence of NaH to give the alkynyl derivatives 186. That was followed by the cycloaddition click reaction with phenyl azide, azido acetic acid tert-butyl ester or diethyl (4-azidobutyl) phosphonate at 20 °C in the presence of Cu(I) (Scheme 70) [57].

Regioselective syntheses of functionalized cyclotriphosphazenes linked via 1,2,3-triazole 187a–e. Firstly, 1,3,3,5,5-penta[1-(2,2-dimethy1-1,3-dioxolan-4-yl)methoxy]-1-chlorocyclotriphosphazene (185) reacted with 2-propyn-1-ol and 3-butyn-1-ol in the presence of NaH to give the alkynyl derivatives 186a,b. That was followed by the cycloaddition click reaction with phenyl azide, azido acetic acid tert-butyl ester or diethyl (4-azidobutyl) phosphonate at 20 °C in the presence of Cu(I) (Scheme 70) [57].

**Scheme 68.** Synthesis of 4-triazolylbenzoxazoline derivatives. *Reagents and conditions:* (a) CH$_2$Cl$_2$; (b) R$^3$NC 178, Pd(PPh$_3$)$_4$, THF, 60 °C.

**Scheme 69.** A plausible mechanism for the formation of oxazine derivatives 179a–n.
Another regioselective 1,3-dipolar cycloaddition reaction was established between N-propargyl-substituted-1,8-dioxodecahydroacridines 188a–d with aromatic azides in the presence of CuSO$_4$.5H$_2$O/ascorbic acid as catalyst (Click reaction) in a 2:1 mixture of CH$_2$Cl$_2$:H$_2$O at room temperature gave 1,2,3-triazole-dioxodecahydroacridine hybrids 189a–e in high yields (70–86%). Furthermore, the click reaction was subjected to propargyloxy-benzaldehydes 190a–d to give 1,4-disubstituted 1,2,3-triazolealdehydes 191a–e in 55–88% yields (Scheme 71). The application of the Hantzsch route on the corresponding 1,2,3-triazolealdehydes 191a–e with two molecules of 1,3-cyclohexanedione 192 produced 1,4-disubstituted 1,2,3-triazole-O-acridinedione 193a–e (55–90% yields). Treatment of 1,2,3-triazolealdehydes 191a–e with two molecules of 1,3-cyclohexanedione in triethylamine and acetic acid gave the corresponding 1,2,3-triazole-O-xanthenediones 194a–e in 67–91% yields (Scheme 71) [58].

Scheme 70. Synthesis of 1,2,3-triazoles 187a–e. Reagents and conditions: (i) THF, NaH, 0 °C stirring, then 20 °C, 1 h; (ii) CuSO$_4$.5H$_2$O (0.06 mmol, 20 mol%) of sodium ascorbate (0.12 mmol, 20 mol%).

\[
\begin{align*}
\text{R} & = -CH_2CHO \quad \text{(a)} \\
\text{R} & = -CH_2CHO \quad \text{(b)} \\
\text{R} & = -CH_2CHO \quad \text{(c)} \\
\text{R} & = -CH_2CHO \quad \text{(d)}
\end{align*}
\]

Reagents and conditions:

- (a) CuSO$_4$.5H$_2$O, sodium ascorbate, DCM:H$_2$O (1:1), 12 h
- (b) AcONH$_4$, Et$_3$N, EtOH, 12 h
- (c) Et$_3$N, AcOH, 12 h

Scheme 71. Regioselective synthesis of 1,2,3-triazoles 193a–e and 194a–e. Reagents and conditions:

- (a) CuSO$_4$.5H$_2$O, sodium ascorbate, DCM:H$_2$O (1:1), 12 h
- (b) AcONH$_4$, Et$_3$N, EtOH, 12 h
- (c) Et$_3$N, AcOH, 12 h
Annulation reactions between gem-diamino enaminones 195 and 197 (ketene aminals) and tosyl azide furnished N-heterocycle fused 196a–q and 5-amino side-chain 198a–r functionalized 1,2,3-triazoles under transition metal-free conditions, using NaHCO3 as a catalyst to promote the reaction (Schemes 72–74). The reaction was screened to optimize the reaction conditions. Firstly, the reaction was performed using different solvents, such as water, DMSO, DMF, toluene, and MeCN; it was observed that DMSO is the solvent of choice. Additionally, the reaction was performed under different basic conditions using NaOH, tBuONa, NaHCO3, and DBACO; it was found that using NaHCO3 is favorable for obtaining high yields (Scheme 72) [58].

1,2-Diacetylenic benzenes 199 were cyclized with sodium azide (NaN3) furnished the corresponding [1,2,3]triazolo[5,1-a]isoquinolines 201, but with low regioselectivity for substrates bearing two different alkyne substituents (R1 ≠ R2) [59–61]. Additionally, the same triazoloisoquinolines 201 were obtained via annulation of acetylenes with (2-halo)phenyl-1,2,3-triazoles 200 under transition-metal catalyzed conditions [62–65]. On the other hand, the annulation of 2-azido-3-(2-iodophenyl)acrylates 202 to the corresponding triazolo-isoquinolines 203 was achieved using copper chloride as a transition metal catalyst in these heterocyclization [66,67] (Scheme 75).

Recently, Wu et al. [68] reported that AlCl3 syntheses of triazoloisoquinolines via three-component Henry reaction–triazole formation–intramolecular 6-endo-dig cyclization were successfully achieved. Upon reacting 2-(phenylethynyl)-benzaldehyde 204a, nitromethane, and sodium azide in the presence of Lewis acid in DMF at 100 °C, a mixture of [1,2,3]triazolo[5,1-a]isoquinoline 205a and isoquinoline 206 was obtained. However, triazole 207 was obtained when an excess of AlCl3 was used. Among these studies, it was found that Sc(CF3SO3)3 and AlCl3 were the preferable Lewis acids to promote the formation of triazoloisoquinolones, as shown in Scheme 76.

| Entry | Base     | Solvent | T (°C) | Yield (%) |
|-------|----------|---------|-------|-----------|
| 1     | TMEDA    | H2O     | reflux| 38        |
| 2     | TMEDA    | DMF     | 120   | 42        |
| 3     | TMEDA    | DMSO    | 120   | 44        |
| 4     | TMEDA    | MeCN    | Reflux| 39        |
| 5     | TMEDA    | Toluene | reflux| 20        |
| 6     | NaOH     | DMSO    | 120   | 41        |
| 7     | tBuONa   | DMSO    | 120   | 63        |
| 8     | NaHCO3   | DMSO    | 120   | 74        |
| 9     | DABCO    | DMSO    | 120   | 55        |
| 10    | NaHCO3   | DMSO    | 120   | 77        |
| 11    | NaHCO3   | DMSO    | 120   | 59        |
| 12    | NaHCO3   | DMSO    | 120   | 85        |
| 13    | NaHCO3   | DMSO    | 120   | 66        |
| 14    | NaHCO3   | DMSO    | 130   | 78        |
| 15    | NaHCO3   | DMSO    | 110   | 71        |
| 16    | NaHCO3   | DMSO    | 100   | 66        |

Scheme 72. Screening of the optimized reaction conditions for the reaction of enaminones and tosyl azide.
Scheme 73. Syntheses of fused imidazotriazoles 197a–q. Reagent and conditions: (a) NaHCO₃, DMSO, 120 °C, 12 h.

Scheme 74. Syntheses of 5-amino-1,2,3-triazoles 198a–g. Reagent and conditions: (a) NaHCO₃, DMSO, 120 °C.
of [1,2,3]triazolo[5,1-tromethane, and sodium azide in the presence of Lewis acid in DMF at 100 °C, a mixture azole formation were successfully achieved. Upon reacting 2-(phenylethynyl)-benzaldehyde found that Sc(CF3SO3)3 and AlCl3 were the preferable Lewis acids to promote the for-

Scheme 75. Synthesis of triazoloisquinolines 203.

**Scheme 76.** Synthesis of triazoloisquinoline 205a. Reagent and conditions: (a) CH3NO2 (3.0 equiv.), NaN3 (2.5 equiv.), Lewis acid.

The type of solvent and Lewis acid affected the yield and the regioselectivity of the product, as in 205a. Additionally, the substituted group affected the yield of the target product in which the presence of electron-donating groups gave higher yields than electron-withdrawing groups. On replacing the phenyl ring with pyridine ring (an electron-
and naphthalene (π-electron delocalized group), the triazoloisoquinolones 205h and 205i were synthesized in moderate yields of 32 and 53%, respectively, as shown in Scheme 77 [68].

Scheme 77. Substituent affected the yields of the synthesized triazoloquinolines 205a–v. The plausible mechanism for the formation of compound 205a is illustrated in Scheme 78 [68].
Mn(OAc)$_3$·2H$_2$O were used as catalysts in the syntheses of bicyclic azido alcohol 208 via azide radical addition/cyclization/oxygen insertion reaction of alkyne-tethered cyclohexadienones 208 with TMSN$_3$ under mild conditions. The azido alcohol 209a was led to react with phenylacetylene via Cu-catalyzed click reaction 1,2,3-triazole 210 was obtained in 84% yield (Scheme 79) [69]. The plausible mechanism for forming the azido alcohol 209a is shown in Scheme 80. It was described due to azide radical addition, then radical conjugation, and lastly, oxygen insertion process through the formation of the intermediates A–E [69].

Intramolecular azide–alkene cycloaddition of N-bromoalkyl indole and pyrrole derivatives 211a–v resulted in the formation of polycyclic fused 1,2,3-triazoles 212a–v [70]. As a model example, the reaction progress was investigated to determine the optimized conditions via the reaction of 211a (0.5 mmol) with sodium azide (0.6 mmol) in ethanol at room temperature for 20 h and under catalyst-free conditions. The reaction proceeded smoothly to give (6,7-dihydro-5H-[1,2,3]triazolo[5',1':3,4][1,4]diazepino[1,2-a]indol-1-yl)(phenyl)methanone 212a in 64% yield (Scheme 81). When the reaction was first applied to the seven-membered ring annulated indole by varying substituents (R$^1$) on the benzoyl group. It was observed that electron-donating groups, such as amine, methoxy, hydroxyl, and isobutyl, under the optimal reaction conditions, gave the desired products in 65–91% yields (Scheme 82). Similarly, halogen substituents were also produced the appropriate products (212b–d, 212i, and 212m) in good to high yields (73–81%). However, highly electron-poor substituents, such as CF$_3$, showed lower efficiency (212k, 69% yield), and the reaction of 3,5-ditrifluoromethyl acetophenone failed to give the corresponding product. Additionally, the investigation was extended to prepare six-membered ring annulated indoles by using N-bromoethyl substituent on the indole under the optimized conditions. It was shown that electron-donating and electron-withdrawing groups produced the corresponding fused polycyclic N-heterocycles (212o–t) in slightly lower yields (72–81%). Alkyl groups on the
ketone derivatives led to the desired products 212u and 212v in good yields (77% and 72%, respectively) [70].

Scheme 79. Synthesis of 1,2,3-triazoles 210a–p. Reagents and conditions: (a) Mn(OAc)₃·2H₂O (50 mol%), TMSN₃ (2.1 mmol, 5 eq.), CH₃CN (2 mL), O₂ balloon, room temperature, 6–24 h. (b) CuSO₄·H₂O, Sodium ascorbate, tBuOH:H₂O (1:1), room temperature, 24 h.
Scheme 80. Proposed mechanism for the formation of the azido alcohol 188a.

| Entry | Catalyst          | Solvent                  | Yield (%) |
|-------|-------------------|--------------------------|-----------|
| 1     | None              | Ethanol                  | 64        |
| 2     | None              | DMF                      | 71        |
| 3     | Cu(OtF)$_2$ (5 mol%) | DMF                      | 76        |
| 4     | Sc(OtF)$_3$ (5 mol%) | DMF                      | 78        |
| 5     | AgOAc (5 mol%)    | DMF                      | 48        |
| 6     | CuI (5 mol%)      | DMF                      | 0         |
| 7     | KO-t-Bu (50 mol%) | DMF                      | 0         |
| 8     | None              | Water:Acetone (1:1)      | Trace     |
| 9     | None              | ACN                      | -         |
| 10    | None              | DCM                      | -         |
| 11    | None              | Water:Acetone (1:1)      | 86        |
| 12    | None              | Water:Acetone            | 32        |
| 13    | None              | Water:Acetone            | 15        |

Scheme 81. Optimization of reaction conditions in the synthesis of 1,2,3-triazolo-diazapine 134a.
Scheme 82. Synthesis 1,2,3-triazolo-diazapines 212a–j and 1,2,3-triazolopyrazines 212k–v. Reagents and conditions: (a) NaN₃ (0.6 mmol), solvent (5 mL), room temperature 18–20 h.
Ugi four-component reaction/alkyne–azide cycloaddition reaction was applied to synthesize triazoloquinoxalines. Reacting 2-azidobenzenamines 213, isocyanide 178, aldehydes, and propiolic acids 214 afforded [1,2,3]triazolo[1,5-a]quinoxalin-4(5H)-ones 216a–s via the formation of Ugi adducts 215. The cyclization occurs via an alkyne–azide cycloaddition reaction (Scheme 83) [71].

![Reaction Scheme]

***Scheme 83.*** Synthesis of triazoloisoquinoxalines 216a–s. **Reagents and conditions:** (a) MeOH, r.t., 12–24 h; (b) DMF, 90 °C.

| Entry | Compd. | R¹ | R² | R³ | R⁴ | Yield (%) |
|-------|--------|----|----|----|----|-----------|
| 1     | a      | H  | 4-ClC₆H₄ | Ph | t-Bu | 85        |
| 2     | b      | H  | Ph  | Ph | c-C₆H₁₁| 75        |
| 3     | c      | H  | 2-ClC₆H₄ | Ph | t-Bu | 70        |
| 4     | d      | H  | 4-MeC₆H₄ | Ph | t-Bu | 72        |
| 5     | e      | H  | 4-O₂NC₆H₄ | Ph | t-Bu | 0         |
| 6     | f      | H  | 4-ClC₆H₄ | Ph | c-C₆H₁₁| 83        |
| 7     | g      | H  | 4-ClC₆H₄ | Me | t-Bu | 92        |
| 8     | h      | H  | n-Pr | Ph | t-Bu | 0         |
| 9     | i      | H  | 4-MeC₆H₄ | Ph | c-C₆H₁₁| 73        |
| 10    | j      | 4-Me| 4-ClC₆H₄ | Ph | t-Bu | 90        |
| 11    | k      | 4-Cl| 4-ClC₆H₄ | Ph | t-Bu | 77        |
| 12    | l      | 4-Me| 4-MeC₆H₄ | Me | c-C₆H₁₁| 78        |
| 13    | m      | 4-Cl| 2-ClC₆H₄ | Me | c-C₆H₁₁| 72        |
| 14    | n      | 4-Br| 4-ClC₆H₄ | Ph | t-Bu | 75        |
| 15    | o      | 4-Br| 4-MeC₆H₄ | Me | t-Bu | 75        |
| 16    | p      | 4,6-Me₂| 4-MeC₆H₄ | Ph | t-Bu | 50        |
| 17    | q      | 4-Cl| 2-ClC₆H₄ | Ph | t-Bu | 68        |
| 18    | r      | 4-Br| 2-furyl| Ph | t-Bu | 71        |
| 19    | s      | 4-Br| 2-thiophenyl | Ph | t-Bu | 72        |
Gangaprasad et al. [72] reported the syntheses of 1,2,3-triazole fused benzooxazepine and benzodiazepine analogs 218a–q via one-pot azide substitution and intramolecular azide-olefin 217 oxidative cycloaddition sequence under metal-free conditions (Scheme 84) [72].

Scheme 84. Synthesis of 1,2,3-triazole fused benzooxazepine and benzodiazepines analogs 218a–q.

Reagents and conditions: (a) DMF, 90 °C, 6 h.

Aly et al. [73] reported that copper(I)-catalyzed azide-alkyne [3+2] dipolar cycloaddition reaction (CuAAC) between 219a–d and 220 to afford the target hybrids 221a–d, in good to excellent yields depending on the concentration of catalyst (Scheme 85). Additionally, the target compounds 221a–d were synthesized, in very good yields, via the reaction of 4-[[1-(2-oxo-1,2-dihydroquinolin-4-yl)-1H-1,2,3-triazol-4-yl]methoxy]benzaldehydes 222a–d [73] with acetophenone (Scheme 85).
Similarly, doubly derivatized chalcones were prepared by the interaction between (E)-1,3-bis[4-(prop-2-yn-1-yloxy)phenyl]prop-2-en-1-one (223) and 4-azidoquinolin-2(1H)-ones 219a–d in the presence of CuAAC to obtain 1,2,3-triazoles 224a–d [73]. The 1,2,3-triazoles 224a–d were also synthesized by the reactions of aldehydes 225a–d with 4-{4-[(4-acetylphenoxy)-methyl]-1H-1,2,3-triazol-1-yl}-quinolin-2(1H)-ones 226a–d in basic medium, as shown in Scheme 86.

Aly et al. [74] also reported that the synthesis of hybrids 228a–g through click chemistry which is a powerful tool for a quick, highly selective, and reliable access to a reaction product with high yields. The [3+2] cycloadditions of 4-azidoquinolin-2(1H)-ones 219a–d with 4-(prop-2-yn-1-yloxy)quinolin-2(1H)-ones 227a–c, gave the corresponding 4-[(1-(2-oxo-1,2-dihydroquinolin-4-yl)-1H-1,2,3-triazol-4-yl)methoxy]quinolin-2(1H)-ones 228a–g (Scheme 87). Compounds 228a–c were found to be the most active antiapoptotic hy-
brids with significant measurements for the antioxidant parameters (malondialdehyde (MDA), total antioxidant capacity (TAC), and the apoptotic biomarkers (testicular testosterone, tumor necrosis factor (TNFα) and caspase-3) in comparison to the reference. A preliminary mechanistic study was performed in order to improve the antiapoptotic activity through caspase-3 inhibition. A compound assigned as 6-methoxy-4-(4-(((2-oxo-1,2-dihydroquinolin-4-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)quinolin-2(1H)-one (228c) was selected as a representative of the most active hybrids in comparison to N-acetyl cysteine (NAC). Assay of cytochrome C for 228c revealed a down expression of cytochrome C level by about 3.54 fold, comparable to NAC (4.13 fold). In caspases-3,8,9 assays, 228c was found to exhibit more potency and selectivity toward caspase-3 than other caspases. Testicular histopathological investigation was carried out on all targeted compounds 228a–g, indicating a significant improvement in spermatogenesis process for compounds 228a–c if compare with the reference relative to the control [74].

Scheme 87. Click reactions between 4-azido-quinolin-2(1H)-ones 219a–d and alkynes 227a–c.

4.6. Synthesis of Tetrazole Ring

One-pot syntheses of 5-substituted 1H-tetrazole derivatives 229a–j [75] were achieved using a dimethyl sulfoxide–nitric acid combination in an aldehyde, hydroxylamine combination hydrochloride, and sodium azide under mild conditions (Scheme 88). The proposed mechanism is illustrated in Scheme 89 [75].

| Entry | Ar         | Time (h) | Product | Yield (%) |
|-------|------------|----------|---------|-----------|
| 1     | Ph         | 4.5      | a       | 94        |
| 2     | 4MeOC6H4   | 4        | b       | 97        |
| 3     | 4-O2NC6H4  | 3        | c       | 95        |
| 4     | 4-MeC6H4   | 5        | d       | 79        |
| 5     | 3-O2NC6H4  | 3.5      | e       | 95        |
| 6     | 2-naphthyl | 6        | f       | 85        |
| 7     | 4-ClC6H4   | 3        | g       | 95        |
| 8     | 2-Cl-pyridin-4-yl | 3 | h       | 95        |
| 9     | 4-HOOC6H4  | 4        | i       | 89        |
| 10    | 4-H2NC6H4  | 3.5      | j       | 92        |

Scheme 88. 5-substituted 1H-tetrazole derivatives 229a–j. Reagents and conditions: (a) 20 min, 40 °C; (b) NaN3 (10 mmol), 20 min, H2O, 40 °C; (c) ArCHO (0.05 mmol), NH2OH-HCl (0.05 mmol), DMSO, 40 °C, 3–6 h.
Heterocyclization of 1,2,4-triazol-3-amine 230 and 3-amino-1-tert-butyl-1,2,4-triazole 231 was established via alkylation of 3-amino-1,2,4-triazole 230 using \( t\text{-BuOH-HClO}_4 \) with triethyl orthoformate and sodium azide in absolute ethanol. The reaction gave \( 1\text{-}(1,2,4\text{-triazol-3-yl})\text{-}1H\text{-tetrazole} \) 232 and \( 1\text{-}(1\text{-tert-butyl-1,2,4-triazol-3-yl})\text{-}1H\text{-tetrazole} \) 233, respectively, as depicted in Scheme 90 [76].

Grinding a mixture of Schiff bases: 4-(3-hydroxybenzylideneamino)antipyrine and 4-(4-nitrobenzylideneamino)antipyrine 234a,b with sodium azide (NaN\(_3\)) gave the corresponding tetrazoles 235a,b (Scheme 91) [77].

Cobalt nano-particles, a heterogeneous catalyst, catalyzed the synthesis of tetrazoles 236a-j from a multicomponent reaction of amines, sodium azide, and triethyl orthoformate under solvent-free conditions at 100 °C (Scheme 92). The reaction was screened for the effects of the amount of both catalyst and solvent; it was found that carrying the reaction using 50 mg of the catalyst under solvent-free conditions gave the tetrazole 236a j 96% yield. The proposed mechanism is illustrated in Scheme 93, which involved condensation between the amine and ethyl orthoformate followed by cycloaddition ([1,3]-dipolar cycloaddition) of azide and imine to give the tetrazole product [78].
Scheme 92. Cobalt nano-particles, a heterogeneous catalyst, catalyzed the synthesis of tetrazoles 236a–j. Reagents and conditions: (a) Co-nano-catalyst, Solvent-free.

Scheme 93. Proposed mechanism for the formation of tetrazoles 236a–j.

Reaction of the chloropyrimidine (7-chloro-3-methyl-1-phenyl-1H-pyrazolo[4′,3′:4,5]thieno[3,2-d]pyrimidine) (237) with sodium azide in DMF in presence of NH₄Cl gave the tetrazole derivative 238, which was identified as (7-methyl-9-phenyl-9H-pyrazolo[4′,3′:4,5]thieno[2,3-c]tetrazolo[1,5-c]pyrimidine) (Scheme 94) [79].

Scheme 94. Synthesis of tetrazole derivative 238. Reagents and conditions: (a) NH₄Cl, DMF.
Ag/Fe\(_3\)O\(_4\) nanocomposite catalyzed the synthesis of 5-(3-bromophenyl)amino-1H-
tetrazole\textsuperscript{240} from 3-bromophenyl cyanamide \textsuperscript{239} and sodium azide in DMF at 110 °C \textsuperscript{[78]}. Aminotetrazole–palladium (II) complex \textsuperscript{243} was prepared via the nucleophilic substitution between 5-(3-bromophenyl)amino-1H-
tetrazole \textsuperscript{240} and Fe\(_3\)O\(_4\)@SiO\(_2\)@(CH\(_2\))\(_3\)-Cl \textsuperscript{241}, followed by incorporation of the Pd-ions using PdCl\(_2\)2H\(_2\)O in EtOH under reflux for 24 h \textsuperscript{[80]} (Scheme 95).

\[ \text{Br-N=C-N} + \text{NaN}_3 \rightarrow \text{Br-N} = \text{N-N-N} \]

\[ \text{SiO}_2 \quad \text{Fe}_3\text{O}_4 \quad \text{SiO}_2 \quad \text{Fe}_3\text{O}_4 \]

\[ \text{HN} = \text{N-N-N} \quad \text{HN} = \text{N-N-N} \]

\[ \text{HN} = \text{N-N-N} \quad \text{HN} = \text{N-N-N} \]

Scheme 95. Synthesis of tetrazole \textsuperscript{243}. Reagents and conditions: (a) Ag/Fe\(_3\)O\(_4\) nanocomposite, DMF, 110 °C; (b) DMF, K\(_2\)CO\(_3\); (c) EtOH, reflux, 24 h.

Trose et al. \textsuperscript{[79]} have reported that the reaction of \textit{N}-Heterocyclic carbene (NHC)-based copper azide complex [Cu(N\(_3\))(IPr)] \textsuperscript{244} (IPr = N,N'-bis[2,6-(di-isopropyl)phenyl]-imidazole-2-ylidene) with dimethyl acetylenedicarboxylate (as an activated alkyne), produced triazolate copper complex \textsuperscript{245} (Scheme 96). However, complex \textsuperscript{244} was found that it was reacted with the activated \textit{p}-toluenesulfonyl cyanide \textsuperscript{246} to give the tetrazole complex \textsuperscript{247} in quantitative yield upon mixing (98%). In contrast, the reaction of complex \textsuperscript{244} with the less activated 4-(trifluoromethyl)benzonitrile \textsuperscript{248} needed heating and longer reaction times (50 °C, 16 h) to form the bis tetrazole complex \textsuperscript{249} in high yield (93%) (Scheme 96) \textsuperscript{[81]}.
Scheme 96. Syntheses of triazolate and tetrazolate copper complexes 245, 247, and 249. Reagents and conditions: (a) heating 50 °C, 16 h.

4.7. Synthesis of Thiadiazole

The more reactive thioamide 250 was reacted with tosyl azide in the presence of Et$_3$N at room temperature to afford 1,2,3-thiadiazole 251 (30 and 22% yield) together with compounds 252. At the same time, the thioamide 147c reacted with tosyl azide (R = p-Me-C$_6$H$_4$) to produce thiadiazole 253 (100 and 90% yield) (Scheme 97) [36].

Scheme 97. Synthesis of thiadiazole 253. Reagents and conditions: (a) Et$_3$N, MeOH, room temperature, 100 min; (b) PyH, 55 °C, 4 h.

4.8. Synthesis of Pyridine and Isoquinoline Derivatives

Singam et al. [82] reported the regioselective aryl nicalation of ortho functional diaryl acetylene 254a with Ar(BOH)$_2$ 255a–p to synthesize substituted di-aryl isoquinolines 256a–p (Scheme 98).
Scheme 98. Synthesis of isoquinoline derivatives 256a–p. **Reagents and conditions:** (a) Ni(acac)\(_2\) (10 mol%), PPh\(_3\) (10 mol%), Cs\(_2\)CO\(_3\) (20 mol%), dioxane, 90 °C.

Additionally, *ortho* diarylacetylene derivatives 254b–m were investigated under the same reaction conditions, which on reacting with Ph(BOH)\(_2\) 255a gave the desired product 256q–b’ in high yields, as depicted in Scheme 99.

Scheme 99. Synthesis of isoquinoline derivatives 256q–b’. **Reagents and conditions:** (a) Ni(acac)\(_2\) (10 mol%), PPh\(_3\) (10 mol%), Cs\(_2\)CO\(_3\) (20 mol%), dioxane, 90 °C.

The 5,6-diarylnicotinates 258a–e were performed from enynyl azides 257 with 255a,d,g,h,q under the same standard conditions (Scheme 100) [82].
Pd-PEPSSI-IPr was used as a catalyst to reach the optimal reaction conditions during the reaction of acetophenone-\(N\)-acetylhydrazone (259a) and (1-azidovinyl) benzene (260a) (Scheme 101) [83]. It was concluded that toluene was the best solvent of choice, and heating to 100 °C gave 81% yield of 261a (Scheme 101)
The procedure showed that N-acetyl hydrazones 259 were screened to react with (1-azidovinyl)benzene (260a), as shown in Scheme 102. Variation from alkyl aryl ketones to benzophenone and cycloalkyl aryl ketones hydrazones reacted smoothly with 260a to afford isoquinolines 261a–ab in 60–81% yields (Scheme 102) [83]. The C-H functionalization occurred regioselectively at the less hindered site for meta-substituted substrate (Me, 259k), yielding a mixture of two isomers, 261k (major) and 261l [83]. Either electron-donating (Me, Bu, Ph, OMe, OPh) or electron-withdrawing (F, Br, Cl, CN) group on the para-position of the phenyl ring of acetophenone N-acetylhydrazones were transformed to the desired products in moderate yields.

Scheme 102. Synthesis of isoquinolines 261a–ab. Reagents and conditions: (a) Pd-PFPPSI-IPr (10 mol%), Cu₂O (2.0 equiv.), NaOAc (1.0 equiv), toluene, 100 °C, 12 h.

The reaction of various vinyl azides 260a–p with N-acetyl hydrazone 259a under the standard reaction conditions was examined (Scheme 103). Fused isoquinolines 261ac–ap were obtained via the same previous procedure [83].
Scheme 103. Syntheses of isoquinolines 261ac–ap. Reagents and conditions: (a) Pd-PFPPSI-IPr (10 mol%), Cu_{2}O (2.0 equiv.), NaOAc (1.0 equiv), toluene, 100 °C, 12 h.

The transformations of 1-tetralone, 1-benzosuberone hydrazones 262a–d proceeded smoothly to give the desired polycyclic product 263a,b in moderate yields. Moreover, chroman-4-one and thiochroman-4-one-hydrazone substrates were converted to polyheterocyclic products 263c,d in 88% and 91% yields (Scheme 104).

Scheme 104. Synthesis of fused isoquinolines 263a–d. Reagents and conditions: (a) Pd-PFPPSI-IPr (10 mol%), Cu_{2}O (2.0 equiv.), NaOAc (1.0 equiv), toluene, 100 °C, 12 h.
7-Methoxyflavanone \(264\) was reacted with acetohydrazide \(265\) to hydrazone \(266\), which, when treated with vinyl azide \(260a\), provided the isoquinoline product \(267\) in 51% yield (Scheme 105) [83].

\[
\text{MeO} \quad \text{O} \quad \text{HNNH} \quad \text{Ph} \quad \text{MeO} \quad \text{O} \quad \text{N} \quad \text{HNNH} \quad \text{Ph} \quad \text{MeO} \quad \text{O} \\
\rightarrow \quad \text{O} \quad \text{N} \quad \text{HNNH} \quad \text{Ph} \quad \text{MeO} \quad \text{O} \quad \text{N} \quad \text{HNNH} \quad \text{Ph} \quad \text{MeO} \quad \text{O} \\
\text{264} \quad \text{265} \quad \text{266} \quad \text{N}_3 \quad \text{260a} \quad \text{267} \quad (51\%) \\
\]

**Scheme 105.** Formation of isoquinoline product \(267\). *Reagents and conditions:* (a) EtOH, reflux; (b) Pd-PFPPS-IPr (10 mol%), \(\text{Cu}_2\text{O} \) (2.0 equiv.), \(\text{NaOAc} \) (1.0 equiv), toluene, \(100^\circ\text{C} \), 12 h.

### 4.9. Synthesis of Phenanthridine

Phenanthridines \(269a,b\) were synthesized using the catalytic system of \(\text{FeCl}_2/\text{N}-\text{heterocyclic carbene (NHC) SIPr-HCl} \) from 9-azidofluorenes \(268,b\) via 1,2-aryl migration (Scheme 106) [84].

\[
\begin{align*}
\text{R} & \quad \text{N}_3 \\
\text{268a,b} & \quad \text{269a,b} \\
\text{a}, \text{R} = \text{Me} & \quad (55\%) \\
\text{b}, \text{R} = \text{Et} & \quad (59\%) \\
\text{L} & = \text{dipp} \quad \text{N} \quad \text{N} \quad \text{dipp} \quad \text{Cl}^{-} \\
\end{align*}
\]

**Scheme 106.** Formation of phenanthridines \(269a,b\). *Reagents and conditions:* (a) \(\text{FeCl}_2 \) (10 mol%), ligand (10 mol%), \(\text{PhCl}, \text{Ar,} \ 80^\circ\text{C} \).

### 4.10. Synthesis of Imidazoindoles

Jin and others [85] reported that the multicomponent reaction of sulfonyl azides, alkynes \(270\), and allylamines \(271\) was catalyzed by copper iodide in the presence of triethylamine in DMSO/\(\text{K}_2\text{CO}_3\) and dimethyl ethylenediamine as a ligand (L), affording 2,3-dihydro-\(1\text{H}-\text{imidazo}[1,2-\alpha]\)indoles \(272a-4\) (Scheme 107). Four C–N bonds were formed by way of azide-alkyne cycloaddition (CuAAC) and double Ullmann-type coupling reactions in a one-pot process, as illustrated in the reaction mechanism (Scheme 107) [85].

The proposed mechanistic steps were proposed, as shown in Scheme 108. First, a copper-catalyzed azide-alkyne cycloaddition reaction (CuAAC) takes place to generate intermediate A, which then transforms to ketenimine B by the extrusion of \(\text{N}_2\). Nucleophilic addition of 2-bromoprop-2-en-1-amine \(270a\) to intermediate B affords carboxamidine C and/or its tautomer. Finally, a consecutive copper-catalyzed C–N coupling reactions proceeds to provide 2,3-dihydro-\(1\text{H}-\text{imidazo}[1,2-\alpha]\)indole \(272a\) (Scheme 108) [85].
Scheme 107. Synthesis of 2,3-dihydro-1H-imidazo[1,2-a]indoles 272a-t. Substrate scope of azides and alkynes. Reagents and conditions: (a) CuI (10 mol%), Et$_3$N (1.0 equiv), 270 (0.5 mmol), azide (0.6 mmol), 271a (0.5 mmol), DMSO (3 mL) at r.t. for 1 h; 2) CuI (20 mol%), L (0.3 mmol), K$_2$CO$_3$ (2 equiv) at 80 $^\circ$C for 6 h. Mes = 2,4,6-Trimethylphenyl.

Scheme 108. Proposed mechanism for the formation of imidazoindoles 272a.

4.11. Synthesis of Quinazoline Derivatives

Kumar et al. [86] reported the tandem synthesis of 2-quinazoline carboxylates 275a–m using 2-(azidomethyl)phenyl isocyanides 273a–m along with carbazates 274 in the presence of Mn(OAc)$_3$·2H$_2$O (Scheme 109).
Scheme 109. Synthesis of quinazoline derivatives 275a–m. Reagents and conditions: (a) Mn(OAc)$_3$·2H$_2$O (0.63 mmol), TBHP (1.89 mmol, 5 M in decan), and EtOAc, 12 h at 80 °C.

The postulated mechanism is illustrated in Scheme 110. Initially, the Mn(OAc)$_3$·2H$_2$O-assisted homolysis of tert-butyl hydroperoxide (TBHP) generates the tert-butoxy and the tert-butyl peroxy radicals. Bond cleavage of the C-N in methyl carbazate 274 forms the alkoxycarbonyl radical (B), which loses molecular N$_2$. Radical (B) then attacks the R–NC bond of 2-(azidomethyl)phenyl isocyanide (273a) to form an imidoyl radical intermediate (C). The intermediate C then undergoes intramolecular cyclization with the azido group to give a cyclized aminyl radical (D) by nitrogen loss. Finally, a hydrogen abstraction of the radical intermediate (D) leads to the desired product (275a) (Scheme 110) [86].

Scheme 110. Proposed mechanism for the formation of quinazoline 275a via the radical pathway.
4.12. Synthesis of Borane Containing Heterocycles

4.12.1. Synthesis of Diborylaniline and Diboryl-Fused Pyrimidine

Priesch et al. [87] reported that the c-nitrogen insertion of aryl azides into the B–B bond of electron-rich cyclic l-hydridodiboranes 276 was stabilized by one N-heterocyclic carbene (NHC) ligand leads to the expansion of the central C$_3$B$_2$ ring, yielding unsymmetrical polyheterocyclic 1,1-diboryltetrazaines 278 and 279 via the intermediate 277. The 2-benzyl-bridged analogs undergo further NHC ring expansion and thermally-induced loss of N$_2$ to give polyheterocyclic diborylanilines 280 (Scheme 111) [87].

Scheme 111. Syntheses of diborylfused pyrimidines 279 and diborykanilines 280. Reagents and conditions: (a) benzene, 60 °C; (b) benzene 80 °C; (c) benzene, 80–100 °C, 12–15 d; (d) benzene, room temperature.

4.12.2. Synthesis of Triazaphosphaborolidine

1-(Benzo[d][1,3,2]dioxaborole-2-yl)-2-(diphenylphosphino)-1,2-diphenylhydrazine (280) showed frustrated Lewis pairs (FLPs) reacted with benzyl azide, forming 4′-benzyl-1′,2′,3′,3′-tetraphenylspiro[benzo[d][1,3,2]dioxaborole-2,5′-[1,2,4,3,5]triazaphosphborolidin]-3′-ium-12-uide (281) in 73% yield (Scheme 112) [88].

Scheme 112. Formation of 4′-benzyl-1′,2′,3′,3′-tetraphenylspiro[benzo[d][1,3,2]dioxaborole-2,5′-[1,2,4,3,5]triazaphosphborolidin]-3′-ium-12-uide (281). Reagents and conditions: (a) CH$_2$Cl$_2$, room temperature, 24 h stirring.
4.13. Synthesis of Aluminum-Containing Heterocyclic

Drescher and others [89] reported the ring expansion of alumina cyclopentadienes (alumoles) on treatment with organic azides. Treatment of alumole \( \text{282} \) and trimethylsilyl azide in benzene at 60 °C gave cycloadduct \( \text{283} \) in 61% yield, while mesityl (Mes = 2,4,6-Me\(_3\)C\(_6\)H\(_2\)) or 2,6-diphenylphenyl azide forming the aza-cycloadducts \( \text{284} \) (31%) or \( \text{285} \) (73%), respectively (Scheme 113) [89].

![Scheme 113. Synthesis of aluminum heterocycles 283–285. Reagents and conditions: (a) benzene, 60 °C. (b) room temperature.](image)

4.14. Synthesis of Phosphorus-Containing Heterocycles

4.14.1. Synthesis of Triazaphosphocine

Treatment of 1-(di-tert-butylphosphino)-3-methyl-1,2,3,4-tetrahydroquinazoline (286) with phenyl azide gave benzo[\(\varepsilon\)]1,3,5,2-triazaphosphocine (287) instead of phosphazide derivative ((E)-1-(di-tert-butyl(phenyltriaz-2-en-1-ylidene)phosphorany1)-3-methyl-1,2,3,4-tetrahydroquinazoline) (288). The reaction of compound 286 with phenyl azide takes place on P(III) of compound 286 was believed to give P(V) product phosphazide 288, which underwent ring enlargement to give benzotriazaphosphocine 287. Derivative 289 reacted readily with phenyl azide to give compound 290 in a high yield (Scheme 114) [90].

![Scheme 114. Synthesis of triazaphosphocine 287. Reagents and conditions: (a) Benzene, r.t., 3 h.](image)
4.14.2. Synthesis of Benzothiazaphosphole

The reaction of ortho-phosphinoarenesulfonyl fluorides 291 with trimethylsilyl azide resulted in benzo-1,2,3-thiazaphosphole 292 [91]. To optimize the reaction condition, it was found that a mixture of acetonitrile and 10 equivalents of trimethylsilyl azide at 60 °C was the optimal reaction chosen condition (Scheme 115) [92]. The three possible mechanistic pathways (A), (B) and (C) for forming the benzo-thiazaphosphole 292a are illustrated in Scheme 116 [91].

Scheme 115. Syntheses of benzo-1,2,3-thiazaphospholes 292a–u. Reagents and conditions: (a) MeCN, 10 equiv. Azide, 60 °C, 12 h.

Scheme 116. Mechanistic pathways for the formation of compound 292a.
5. Conclusions

In summary, the azido group in organic substrates are effectively served in the synthesis of various heterocycles through different mechanistic steps, such as one-pot reactions, nucleophilic additions (such as Aza-Michael addition), cycloaddition reactions (such as [3+2] cycloaddition), mixed addition/cyclization/oxygen, and insertion reactions of C-H amination. The selectivity of the chosen catalyst plays an important role in the chemoselectivity favoring C–H and C-N bonds, as it can be seen that organic azides have been used in the synthesis of various types of natural products producing good to excellent yields. Most indicative is the utility of organic azides in the synthetic procedures of fused heterocycles, such as quinazoline derivatives along with organo-metal heterocycles (i.e., phosphorus-, boron-, and aluminum-containing heterocycles). This review focused on synthesizing various heterocycles using azide chemistry and mechanistic aspects.

Author Contributions: A.A.A. Conceptualization, writing, editing, and submitting), A.A.N. (Editing, fund acquisition, and project administration, W.A.A.A., I.M.A., A.I.A.-E., E.M.E.-F. and M.A.A. (Project administration), S.B. (Editing, project administration). H.N.T. (Writing and editing). All authors have read and agreed to the published version of the manuscript.

Funding: This work was funded by the Deanship of Scientific Research at Jouf University under grand No. (DSR-2021–03-0369).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data is contained within the article.

Acknowledgments: This work was funded by the Deanship of Scientific Research at Jouf University under grand No. (DSR-2021–03-0369). We acknowledge support from the KIT-Publication Fund of the Karlsruhe Institute of Technology. Stefan Bräse is grateful for support from the DFG-funded cluster program “3D Matter Made To Order” under Germany’s Excellence Strategy-2082/1-390761711.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

TMS: trimethylsilyl; pmp: pentamethylpiperidines; DCE dichloroethane; Tf: trifluorosulfonyl; Nf: nonafluorobutanesulfonyl; Py: pyridinyl; Ms: mesyl; Bs: brosyl; Ts: tosyl; Ns: nosyl; CuMeSal: copper 3-methylsalicylate; NHC: N-heterocyclic carbene; Boc: ter-butyloxycarbonyl; IBX: 2-Iodoxybenzoic acid; DABCO: diazabicyclooctane; BOX: bisoxazoline; CSA: camphorsulfonic acid; TBS: tribuylsilyl; IMes. 1,3-Bis(2,4,6-trimethylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene; TFPB: tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

Hazardous Information: A qualified scientist with appropriate safety precautions should be mandatory for using azides. The website azide.org should be consulted [92].

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