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Review

Versatile Synthetic Platform for 1,2,3-Triazole Chemistry

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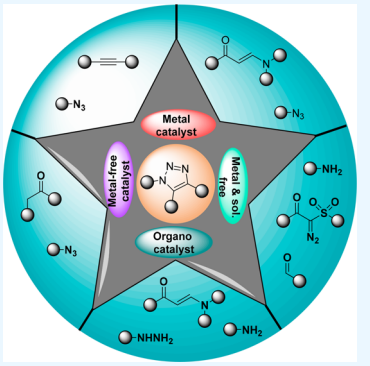
ABSTRACT: 1,2,3-Triazole scaffolds are not obtained in nature, but they are still intensely investigated by synthetic chemists in various fields due to their excellent properties and green synthetic routes. This review will provide a library of all synthetic routes used in the past 21 years to synthesize 1,2,3-triazoles and their derivatives using various metal catalysts (such as Cu, Ni, Ru, Ir, Rh, Pd, Au, Ag, Zn, and Sm), organocatalysts, metal-free as well as solvent- and catalyst-free neat syntheses, along with their mechanistic cycles, recyclability studies, solvent systems, and reaction condition effects on regioselectivity. Constant developments indicate that 1,2,3-triazoles will help lead to future organic synthesis and are useful for creating molecular libraries of various functionalized 1,2,3-triazoles.



1. INTRODUCTION

Heterocyclic chemistry is wide, important and most studied discipline of medicinal chemistry. Heterocyclic bioactive molecules have various heteroatoms such as nitrogen,[1,2] oxygen,[3,4] sulfur,[5−8] and other[9] atoms which have significant biological applications. The study of heterocyclic bioactive molecules containing nitrogen atoms is one of the most important disciplines of medicinal chemistry.[10,11] Among nitrogen-containing heterocycles, azoles are five-membered heterocyclic moieties which are essential structural parts in diverse biologically active natural products.[12] Azoles and their derivatives display various biological effects including capable antibacterial activity.[13] A 1,2,3-triazole scaffold is a potent nitrogen-bearing heterocyclic scaffold which has found wide applications.[14,15] 1,2,3-triazole is an unsaturated, π-excessive, five-membered heterocycle with a 6π delocalized electron ring system which gives it an aromatic character. 1,2,3-triazole is made up of three nitrogens and two carbons. All five atoms are sp^2-hybridized. One N atom is pyrrole kind, and the other two atoms are pyridine kind. Monocyclic 1,2,3-triazole, 1,2,3-triazolium salt, and benzotriazoles are primary classes of 1,2,3-triazoles. Depending on the location of the NH proton, monocyclic 1,2,3-triazoles are further categorized into three subclasses (Figure 1).

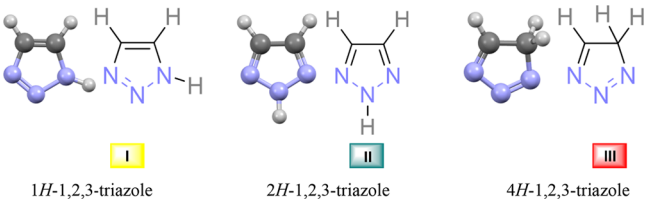


Figure 1. Isomers of monocyclic 1,2,3-triazole.

The 1*H*- and 2*H*-1,2,3-triazoles are aromatic and in equilibrium with each other in solution as well as a gas phase, while 4*H*-1,2,3-triazole is nonaromatic in nature.[16] Among all possible isomers of monocyclic 1,2,3-triazoles, 1*H*-1,2,3-triazole is a powerful scaffold and widely present in therapeutic agents and has gained more interest due to its medicinal chemistry applications, agrochemicals and material science.[17−21] Some synthetic biologically active drugs are mentioned below (Figure 2).

Rufinamide (1-[2,6-difluorobenzyl]-1*H*-1,2,3-triazole-4-carboxamide) **IV** is a novel 1,2,3-triazole bearing antiepileptic drug known by the trade name Inovelon and Xilep, which was discovered by Novartis Pharmaceutical.[22] 1,2,3-Triazole thioether **V** (IC_{50}: 10 nM) is more potent than the original lead molecule RN-18 (IC_{50}: 6 μM) against HIV-1 strain.[23,24] 1,2,3-Triazole-tethered sulfonamide−berberine hybrid compounds **VI** showed an antimalarial activity with IC_{50} = 0.142−28.006 μM in which the R = *p*-chlorophenylamino substituent was the most potent (IC_{50} = 0.142 μM).[25] Imidazole-bearing triazole **VII** showed antibacterial activity comparable to or better than that of linezolid and vancomycin against *Enterococcus faecium* (MIC = 0.5 μg/mL).[26] Cefatrizine showed β-

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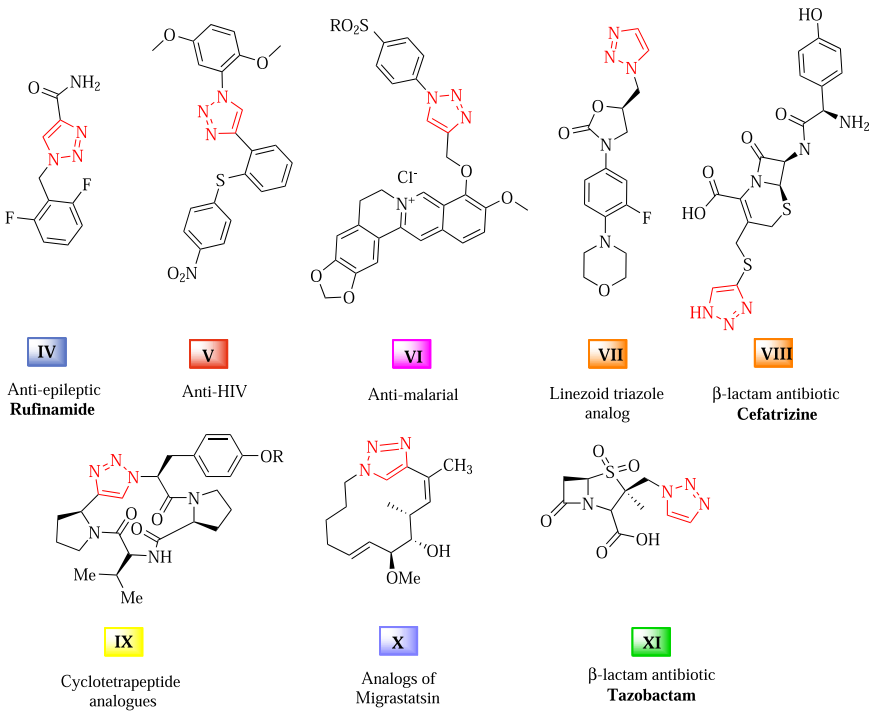

Figure 2. Synthetic bioactive compound containing a 1,2,3-triazole ring.

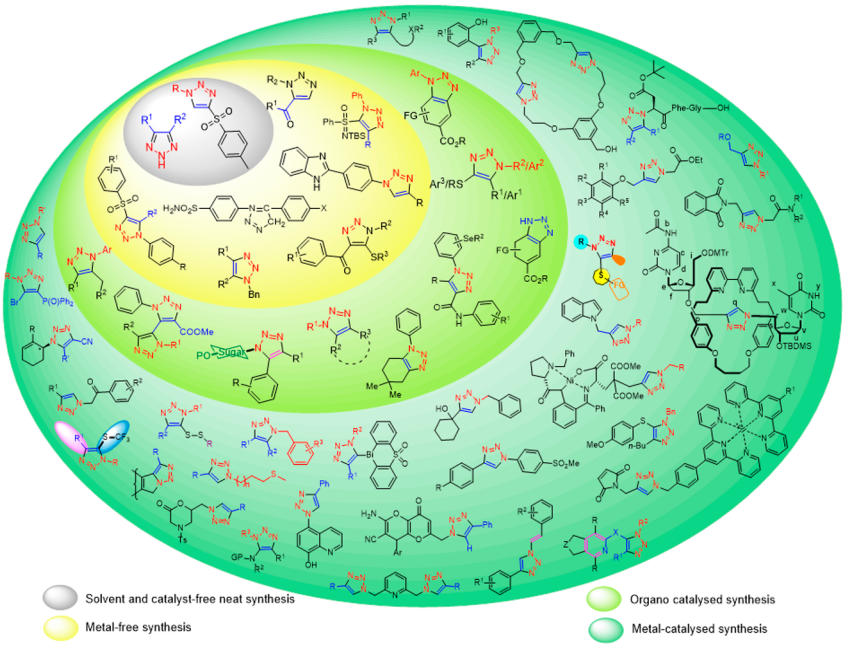

Figure 3. Some privileged triazole-bearing scaffolds covered in this review.

lactam antibiotic activity against *Serratia marcescens* (MIC: >400 μg/mL).[27] Cyclotetrapeptide analogues **IX** showed a 3-fold increase in tyrosinase activity (IC_{50} = 0.5 mM) compared to that of naturally occurring *cyclo*-[Pro-Tyr-Pro-Val] (IC_{50} = 1.5 mM).[28] Macrotriazoles (analogous to Migrastatin) **X** are active against the MDA-MB-361 cell line.[29] Tazobactam is also a 1,2,3-triazole-containing β-lactam antibiotic that shows MIC values of 1.56, 0.1, and 3.13 mg/L against *Escherichia coli*, *Staphylococcus aureus*, and *Klebsiella pneumoniae*, respectively.[30] 1,2,3-Triazole is used as an isostere of carboxylic acid, amide, and ester in the synthesis of many drugs.[31] Several review articles covered the synthetic strategy of 1,2,3-triazole derivatives using only transition-metal-catalyzed cycloaddition. Ding and co-workers[32] covered the literature on metal-catalyzed cycloaddition of azide and internal alkyne only, whereas da Silva Júnior and co-workers[33] presented a review beyond the use of copper-based catalysts due to selective access to 1,5-disubstituted triazole, which involves other transition metal scopes except for copper. In 2020, Ramachary and co-workers[34] reviewed the synthesis of vinyl-functionalized 1,2,3-triazole molecules. Sahu and co-workers[35] reported an advanced synthetic approach for synthesizing a 1,2,3-triazole

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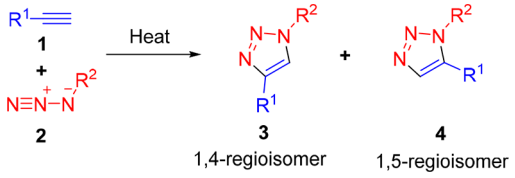
scaffold. In 2013, Schubert and co-workers[36] reported the coordination and supramolecular chemistry of triazole. Moses and Moorhouse[37] gave a detailed application of the click approach. Kappe and Van der Eycken[38] discussed nonclassical methods (such as microwave, heating, or continuous flow processing) for the click reaction. Jozwiak and co-workers[39] reviewed the role of click reaction in drug development. As copper is cytotoxic, Koo and co-workers[40] reported a copper-free click approach as a valuable tool in the biomedical field. So, there are relatively few systematic and recent reviews on 1,2,3-triazole and its derivatives. The present review focuses on the systematic, readable, and researched synthesis of monocyclic 1,2,3-triazoles and their derivatives with their mechanism. The main goal of this review is to present and analyze various methodologies for the synthesis of titled compounds via metal catalysts, organocatalysts, solvent-promoted, catalyst- and solvent-free neat routes which are useful in the future advancement in the synthesis of heterocyclic compounds incorporated with 1,2,3-triazoles (triazole) and their derivatives. Some privileged triazole-bearing scaffolds are shown in Figure 3.

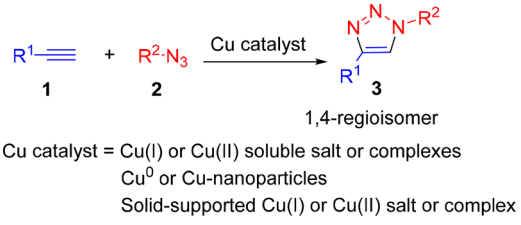
2. SYNTHESIS OF 1,2,3-TRIAZOLE VIA METAL-CATALYZED AZIDE−ALKYNE CYCLOADDITION

1,2,3-Triazole derivatives were first synthesized in 1960 through a Huisgen 1,3-dipolar cycloaddition (Scheme 1)

Scheme 1. Synthesis of 3 and 4 through Huisgen 1,3-Dipolar Cycloaddition



Scheme 2. Cu Catalyzed Synthesis of 3



using azide **2** and alkyne **1** under thermal conditions to produce a mixture of 1,4- and 1,5-disubstituted triazoles **3** and **4**.[41]

The regioselectivity of the approach is controlled by the electronic as well as steric factors of substrates. This approach has not been widely used in synthetic chemistry due to its elevated temperature, low yield, and generation of two regioisomers when using asymmetric alkynes. Later, various strategies were developed to control regioselectivity. With the introduction of a click reaction, traditional 1,3-dipolar cycloaddition failed. Sharpless and co-workers[42] gave criteria for "click chemistry" in 2001. Using a copper catalyst, the click approach generates only 1,4-disubstituted 1,2,3-triazole **3** at ambient temperature in an aqueous medium.[43] It was later found that the ruthenium catalyst produced only 1,5-disubstituted products **4**.[44,45] Metal-catalyzed azide−alkyne cycloaddition (MAAC) reactions are discussed below.

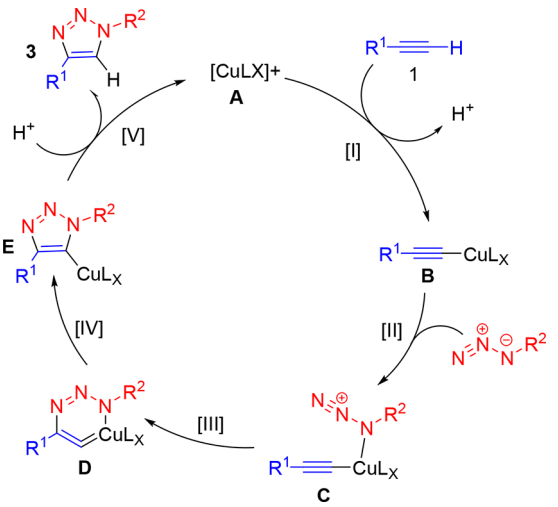
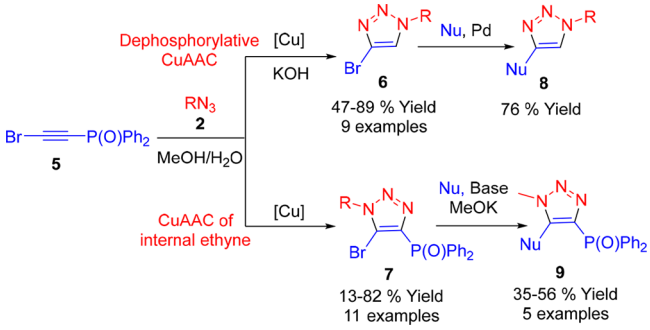
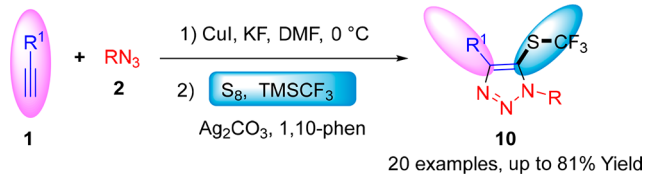


Figure 4. Fokin and co-workers proposed a catalytic cycle for the CuAAC reaction. Reprinted from ref 50. Copyright 2005 American Chemical Society.

Scheme 3. Cu-Catalyzed Synthesis of 8 and 9 without and with the Phosphorylation Approach, Respectively



Scheme 4. Synthesis of 10 from Alkyne, Azide, S_8, and $TMSCF_3$ Using CuI as the Catalyst



2.1. Copper-Catalyzed Azide−Alkyne Cycloaddition (CuAAC). The CuAAC reaction was discovered independently by two research groups of Sharpless−Folkin[46] and Meldal and co-workers[47] in 2002. The CuAAC reaction is often quite slow because of the kinetic stability of starting materials, azide **2** and alkynes **1**. In addition, the CuAAC reaction required high pressure or temperature, as well as a long time to complete. The Huisgen reaction produces a combination of 1,4- and 1,5-products **3** and **4**, whereas with a CuI catalyst or precursors of the CuI catalyst, the reaction of terminal alkynes is selective in the synthesis of 1,4-disubstituted triazoles **3**[47,48] (Scheme 2). Using this catalyst, the reaction rate increased up to 10^7 times in comparison to the catalyst-free reaction. The CuAAC reaction becomes an excellent reaction for organic synthesis. Many click reactions have been reported recently, but none of

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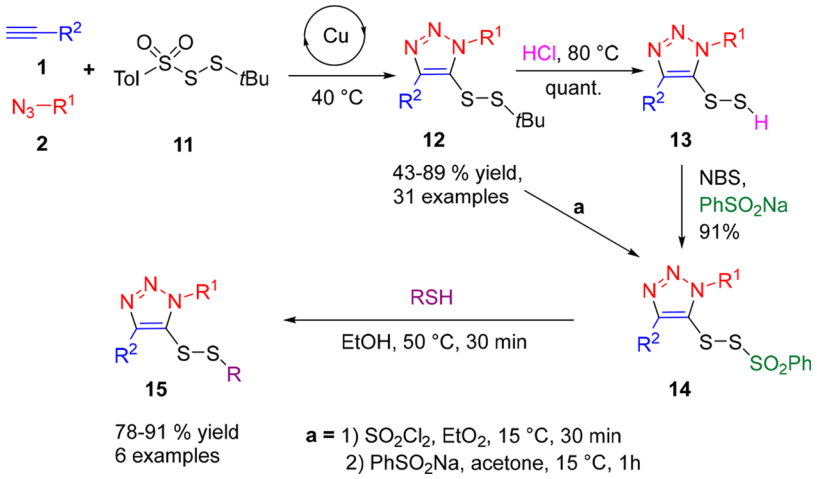
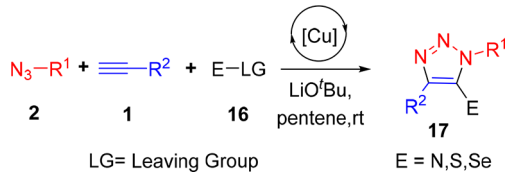
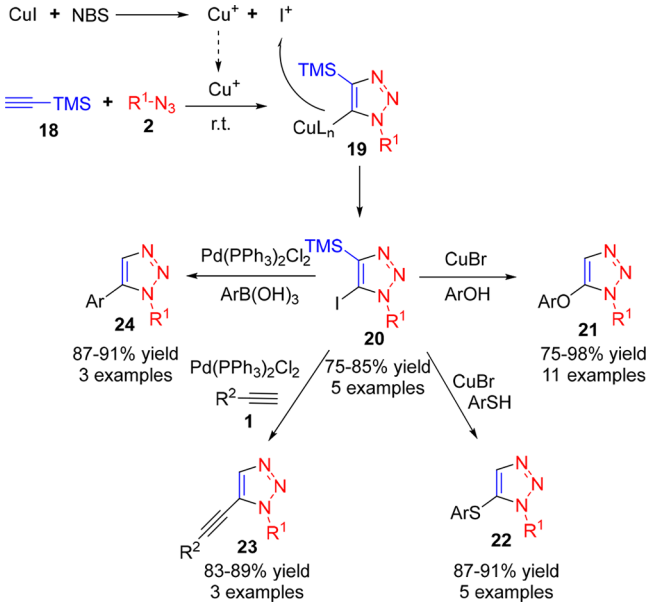
Scheme 5. Synthesis of Derivatives of 10 Using a Persulfuration Reaction via CuI and ^{t}BuOLi



Scheme 6. Use of Click Reaction for the Synthesis of Derivatives of 17 Using CuI as a Catalyst



Scheme 7. Synthesis of Key Precursor 20 and Further Synthesis of Triazole Analogues



them can meet all of the standards of the ideal click reaction given by Sharpless and co-workers.[48]

However, the CuAAC reaction has been regarded as the most suitable reaction for click reactions since it fits with the majority of the criteria for a perfect click reaction. Copper-catalyzed reaction of alkynes with organic azides represents the classic example of click chemistry.[49]

Fokin and co-workers proposed the mononuclear mechanism of the CuAAC catalytical cycle first. The generation of the alkynes Cu(I) complex **A** initiates the reaction process, and the formation of copper(I) acetylide **B** occurs. The formation of Cu(I) with a terminal alkyne reduces the pK_a of the acetylene proton up to pH 9.8,[46,51] providing deprotonation in the aqueous system without the use of the strong base. By coordinating to the metal center, azide is activated. This results in an intermediate between two species—azide and acetylene. The next stage is the generation of the C−N bond, which goes through a strained six-membered copper-containing intermediate. Second, C−N bond formation along with reductive elimination results in the formation of the desired 1,4-disubstituted 1,2,3-triazole **3** byproduct isolation, and catalyst regeneration takes place[51] (Figure 4). Fokin and co-workers[52] presented a common binuclear mechanism for the CuAAC reaction in which copper(I) acetylide is activated through a second copper center via a fragile interaction to form the binuclear copper intermediate **D**.[50]

2.1.1. Cu(I)-Catalyzed Azide−Alkyne Cycloaddition. 2.1.1.1. CuI-Catalyzed Synthesis. Orita and co-workers[53] reported a process-controlled regiodivergent copper-catalyzed process for the synthesis of 4-bromo- and 5-bromotriazoles **6** and **7** through cycloaddition between bromo(phosphoryl)-ethyne **5** and azide **2** using CuI as a catalyst and MeOH/H_2O as a proton source for regeneration of the copper catalyst (Scheme 3). KOH-promoted one-shot dephosphorylation of **5** with azide resulted in 4-bromo-1,2,3-triazole **6**. CuAAC reaction of **5** with azide **2** formed 5-bromo-1,2,3-triazole **7** instead of **6** because the 4-position was occupied by the sterically bulky $Ph_2P(O)$ group. Pd-catalyzed and MeOK-promoted nucleophilic substitution converted products **6** and **7** to 4- and 5-functionalized triazoles **8** and **9**, respectively.

Wu and co-workers[54] reported a one-pot synthesis of 5-trifluoromethylthiotriazole **10** from **1** and **2** with sulfur powder (S_8) and trifluoromethyltrimethylsilane ($TMSCF_3$) using a CuI catalyst (Scheme 4). A terminal alkyne with the electron-donating group (EDG) on aryl alkyne favored this multi-component reaction, while the electron-withdrawing group (EWG) led to poor yield. In addition, a moderate yield was obtained for alkyl alkyne. An electron-withdrawing group on azide also decreases the yield; heterocyclic azide is also a suitable substrate for this reaction.

Xu and co-workers[55] reported a CuAAC/persulfuration reaction with a wide substrate scope, complete regioselectivity, and excellent functional group tolerability for the synthesis of asymmetric triazole disulfides **12** from **1**, **2**, and electrophilic

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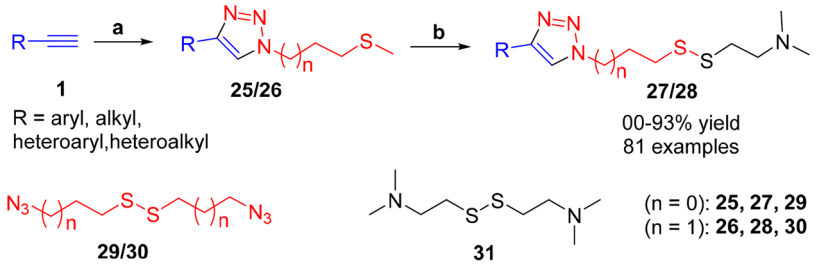
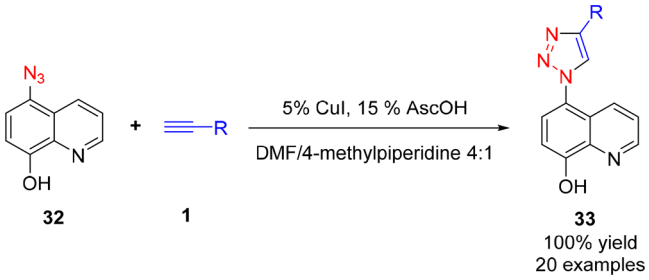
Scheme 8. Synthesis of 27/28 via Cu-Catalyzed Cycloaddition Reaction of Terminal Alkyne and Diazide



Scheme 9. Synthesis of Analogues of 33 Using CuI Catalyst and Ascorbic Acid at RT



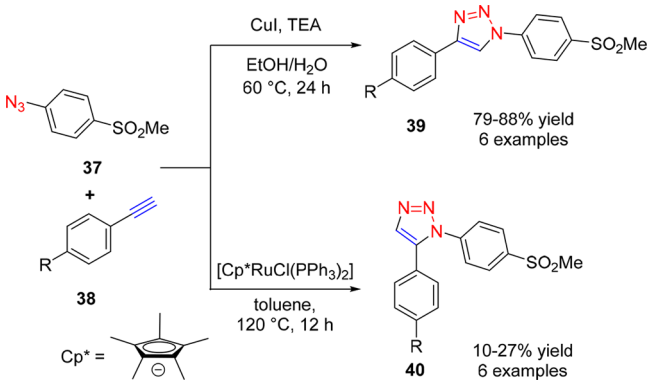
persulfur reagent **11** (*SS*-*t*-butyl *p*-toluenesulfono) in the presence of the CuI catalyst and LiO^{t}Bu as a base (Scheme 5). They evaluated a wide range of 5-persulfur-functionalized triazoles in moderate to good yield and produced single regioisomers. The scope of the reaction was investigated with various azides and alkynes. Under the standard circumstances, all of the aliphatic azides and alkynes reacted easily, giving the appropriate disulfides in good to outstanding yields.

Under the standard conditions, functionalized alkynes obtained from various carbohydrates, vitamins, and proteins can be simply converted to the corresponding triazole disulfides in good to excellent yields. These reactions indicate that this modification has great potential for generating novel physiologically active compounds.

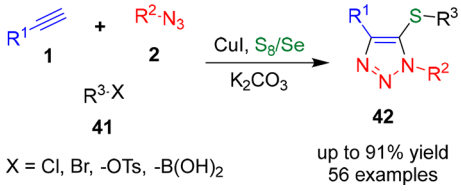
To access a wide range of 5-functionalized triazoles **17**, Xu and co-workers[56] reported a copper-catalyzed interrupted click reaction from **1**, **2**, and different heteroatom electrophiles **16** using much less catalytic quantities of CuI catalyst and LiO^{t}Bu (act as a base) under relatively mild conditions (Scheme 6). This approach has a very broad scope and no required ligands for alkynes, azide, and other heteroatom electrophiles. This intramolecular reaction can be used to construct a bicyclic triazole with various ring sizes.

Zhang and co-workers[57] developed a direct route to synthesize bifunctional trimethylsilyl-5-iodotriazoles

Scheme 11. Synthesis of 39 and 40 through CuI and Ru(II) Catalysts



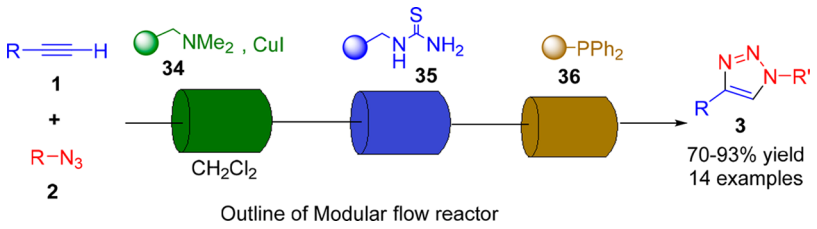
Scheme 12. CuI promoted synthesis of 42 and analogous under mild reaction condition



(TMSIT) **20** from TMS-alkyne **18**, **2**, and iodide followed by copper/palladium-catalyzed nucleophile coupling reaction and desilylation, resulting in a novel approach for the synthesis of structurally diverse 1,5-disubstituted triazoles **21**, **22**, **23**, and **24** via a one-pot reaction, respectively, in high to excellent yields (Scheme 7). This route gave a great alternative for the synthesis of structurally diverse 1,5-disubstituted triazoles due to its short synthetic route and stability of the key precursors 5-iodo-4-TMS-triazoles.

Renslo and co-workers[58] reported a one-pot two-step procedure of copper-catalyzed cycloaddition of terminal alkyne

Scheme 10. Triazole 3 Synthesized from 1 and 2 in the Presence of CuI Catalyst Using a Flow Reactor



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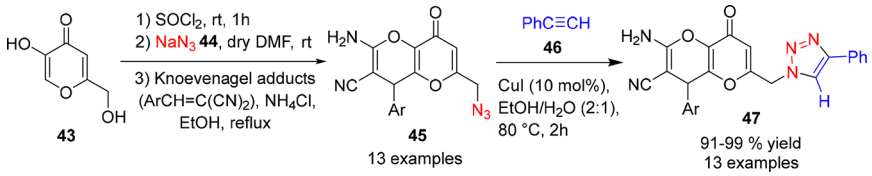
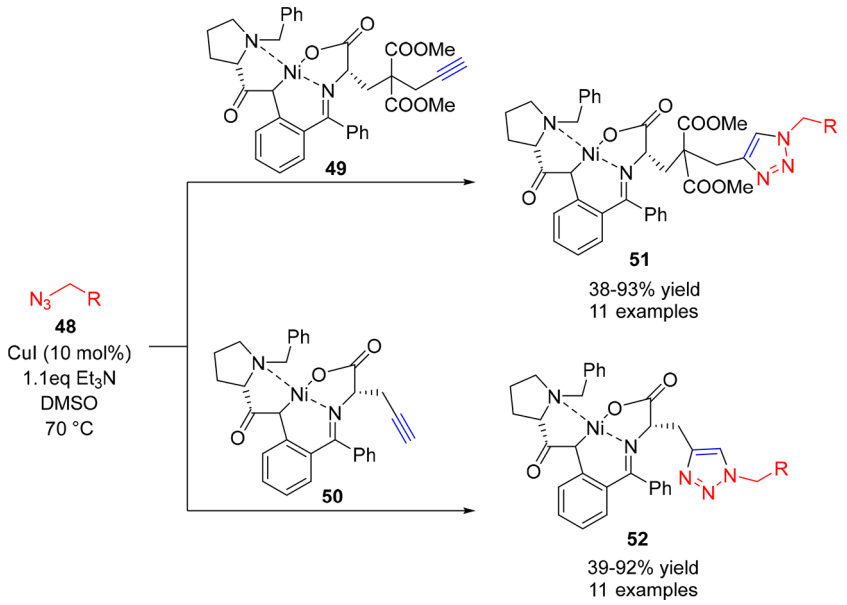
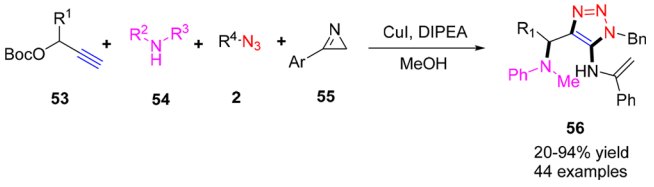
Scheme 13. Synthesis of 47 and Derivatives from 45 Using CuI as the Promoter



Scheme 14. CuI-Promoted Synthesis of 51 and 52



Scheme 15. Synthesis of Polyfunctionalized Triazole 56

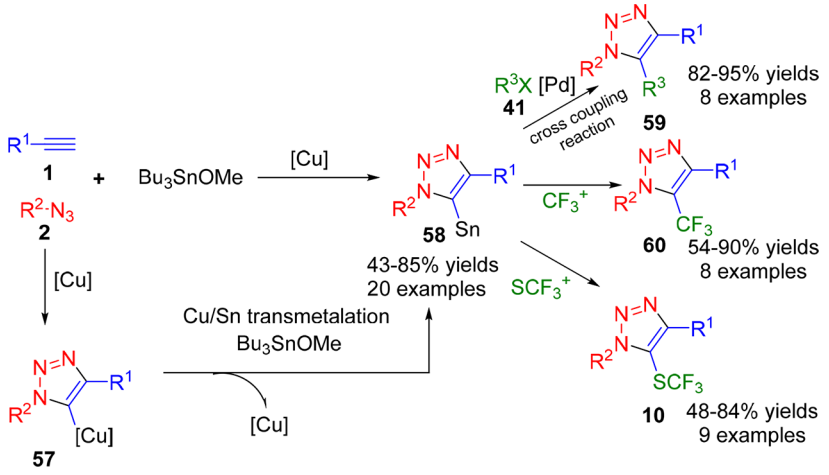


1, diazide **29/30**, and CuI in DMSO for the synthesis of disulfide-bearing triazole **25/26** (Scheme 8).

They found that heating the triazoles to 60 °C during the exchange action maintained the homogeneity of the reaction mixtures. The exchange reaction gave a mixture of thermodynamic products which favored the asymmetrical disulfide products **27/28** and decreased the reversible reaction which formed the symmetrical starting material **25/26**.

Imperiali and co-workers[59] suggested a synthesis of red-shifted 5(4-substituted-1*H*-1,2,3-triazol-1-yl)quinoline-8-ol **33** from 5-azidoquinoline-8-ol **32** and **1** in the presence of a catalytic amount of CuI, ascorbic acid, DMF/4-methylpiperidine (8:2) at RT. The intended product was obtained with 100% yield within 12 h (Scheme 9). Because of the electron-

Scheme 16. Synthesis of 59, 60, and 10 Using Divergent Routes



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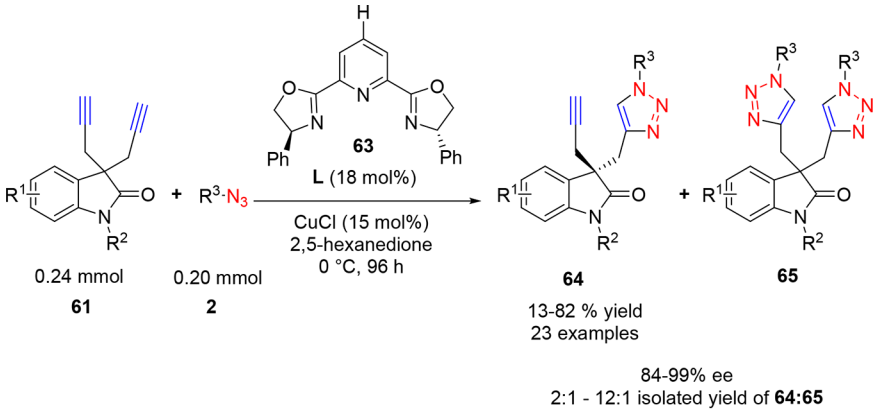
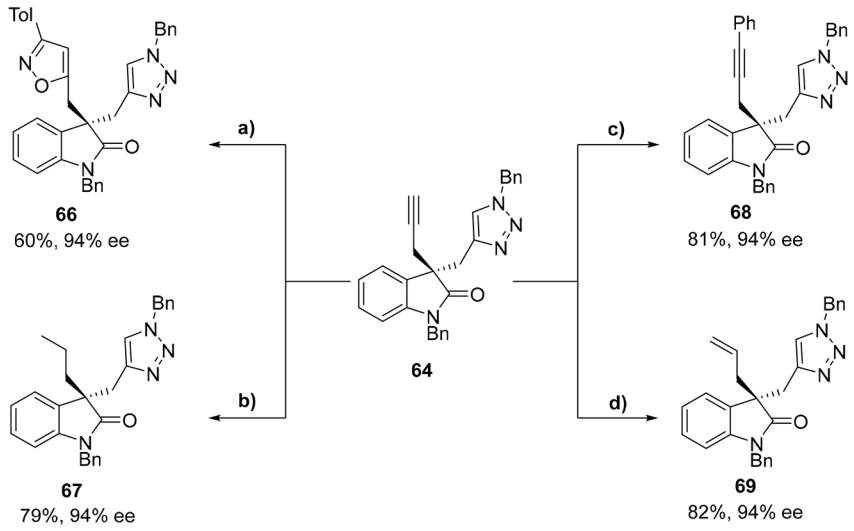
Scheme 17a. Asymmetric Desymmetrization of Oxindole Derivatives 61

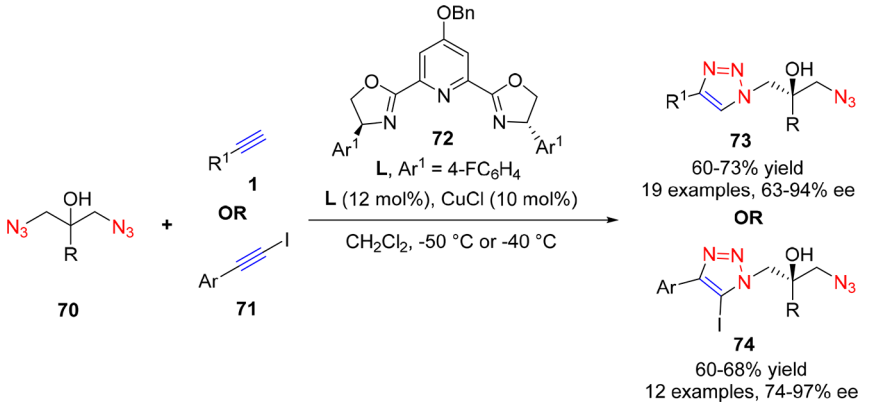


Scheme 17b. Synthetic Elaboration of 64



a) *N*-Hydroxy-4-methylbenzimidoyl chloride, Et_3N, CH_2Cl_2, 10 h. **b)** PhI, $Pd(PPh_3)_4$, CuI, Et_3N, DMF, 4 h. **c)** Raney Ni, MeOH, H_2, 4 h. **d)** Lindlar's catalyst, quinine,MeOH, H_2, 5 h.

Scheme 18. Highly Enantioselective Synthesis of Alcohol-Containing Triazoles 73 and 74



rich azido group's quenching action, **32** displayed no fluorescence. Due to the removal of azide quenching following synthesis of the triazole, **33** showed fluorescence in the presence of 10 mM $MgCl_2$ (λ_{ex} = 371 nm and λ_{em} = 522 nm). Because of these derivative fluorescent properties, they employed them as chelation-sensitive fluorophores to make peptide-based probes for the MAPK-activated protein kinase-2 (MK2) and sarcoma kinase (Src), which are both MAPK-activated protein kinases.

Ley and co-workers[60] reported a flow-based process for the synthesis of **3** from **1** and **2** via the CuI catalyst and DCM as a base. The starting material is introduced into the flow stream and pumped through the column containing amberlyst A-21 ($PS\text{-}NMe_2$) **34**, quadrapure TU (QP-TU) **35**, and phosphine

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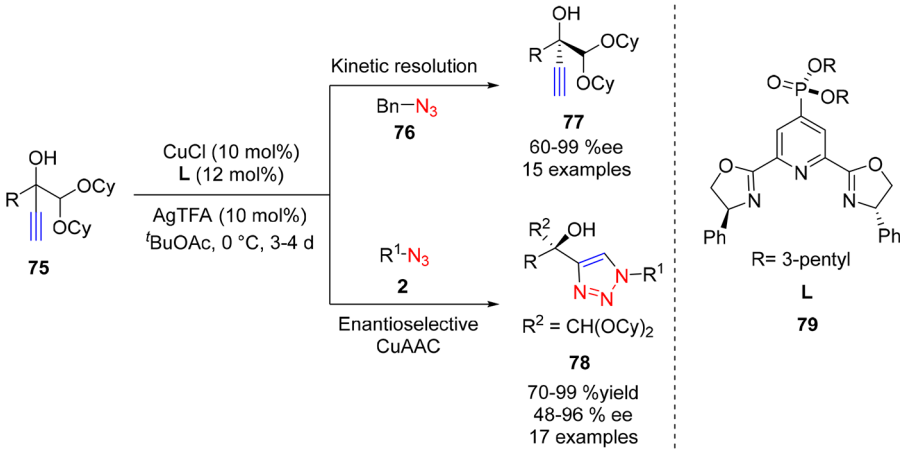
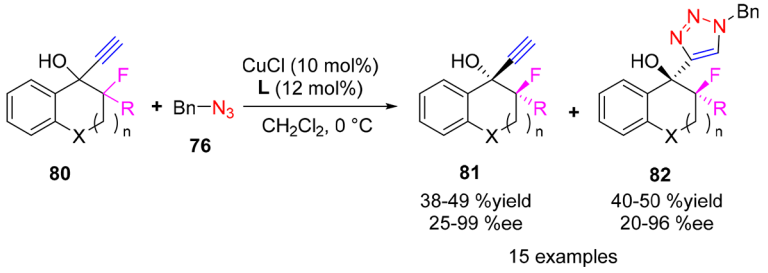
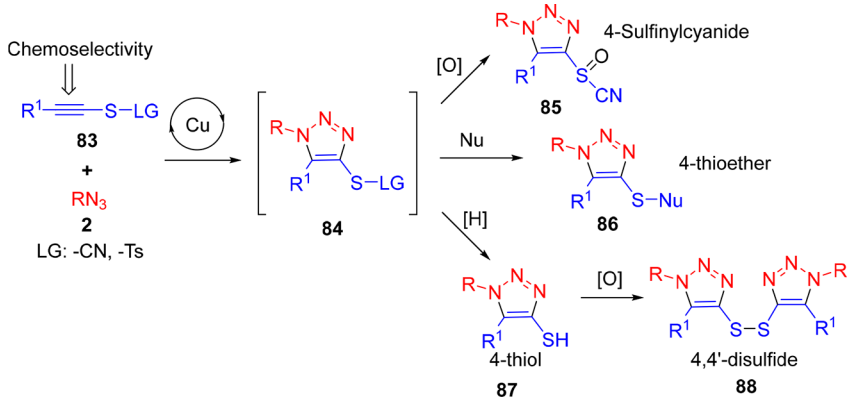
Scheme 19a. Synthesis of 77 and 78



Scheme 19b. Kinetic Resolution of 80



Scheme 20. Synthesis of Analogues Promoted by Cu(I) Catalyst with High Regioselectivity



resin (PS-PPh$_2$) **36** placed in a series. The process required 3 h to give the product in 70−93% yield with >95% purity (Scheme 10).

Suresh and co-workers[61] reported CuI(I)-catalyzed and Ru(II)-catalyzed 1,3-dipolar cycloaddition of aryl azide 1-azido-4-(methanesulfonyl)benzene **37** and various phenyl acetylenes **38** for the synthesis of 1,4- and 1,5-diaryl-substituted triazoles **39** and **40**, respectively (Scheme 11).

Wu and co-workers[62] reported the synthesis of 5-thio- or 5-selenotriazole **42** from **1**, **2**, organohalides/arylboronic acids/tosylates **41**, and elemental sulfur or selenium using CuI as a catalyst and K_2CO_3 under mild conditions with good subtract scope and excellent yields (Scheme 12).

Noroozi Pesyan and co-workers[63] developed a mild, clean, and effective process for the synthesis of 1,4-disubstituted triazole **47** from 2-amino-6-(azidomethyl)-8-oxo-4-aryl-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile **45** and phenylacetylene **46** in the presence of copper iodide (CuI) and green solvent EtOH/H_2O (2:1) at 80 °C for 2 h (Scheme 13). **45** was synthesized from Knoevenagel adducts and **43** using NaN_3**44**, $SOCl_2$, dry DMF, and EtOH. A wide range of azides gave a reaction with phenylacetylene and gave excellent yields of **47**.

Belokon and co-workers[64] reported an efficient reaction for the asymmetric synthesis of amino-acid-containing 1,4-disubstituted triazoles **51** and **52** from azides **48** and Schiff bases of (*S*)- or (*R*)-BPB chiral Ni(II) complexes **49** and **50**, respectively, using copper(I) iodide catalyst, Et_3N, and DMSO at 70 °C with excellent enantioselectivities (>99% ee) (Scheme 14). Complex **50** was prepared using (*S*)-BPB Ni-Gly followed by propargyl bromide alkylation.[65] For the substrate scope of azides, they found that most of all azides gave good to excellent yields (68−93%) except 1-(azidomethyl)-3-fluorobenzene, 4-(azidomethyl)benzonitrile, and 9-(azidomethyl)anthracene,

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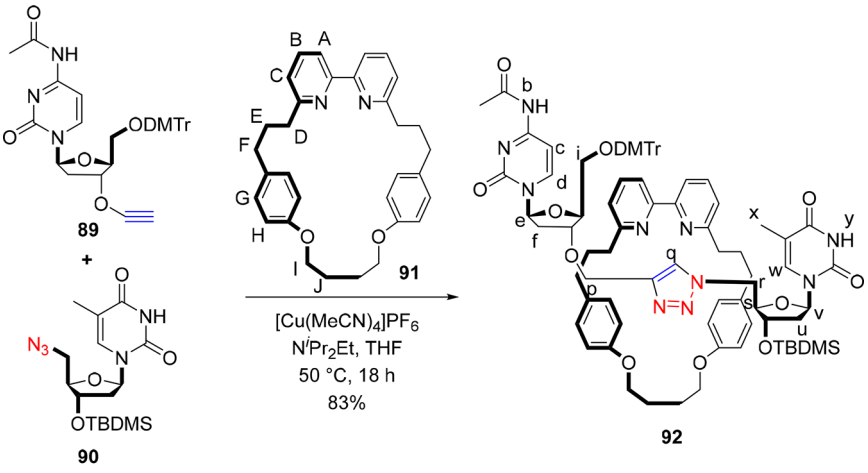
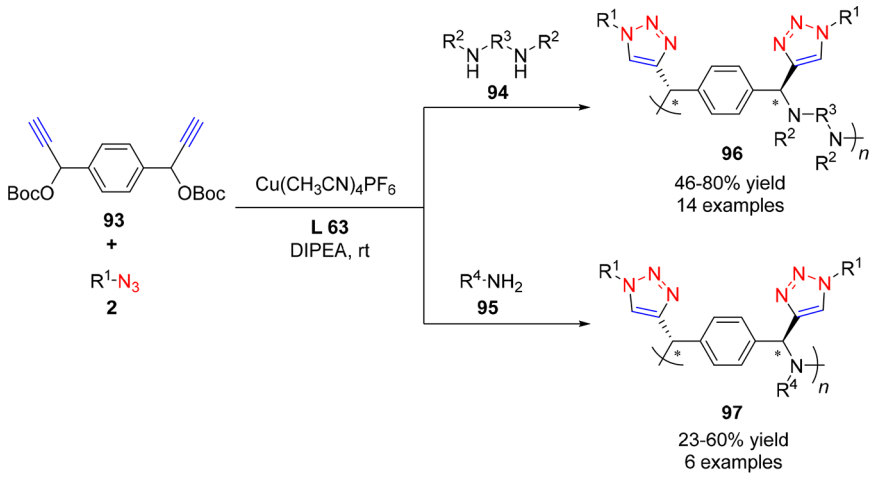
Scheme 21. $[Cu(MeCN)_4]PF_6$-Promoted Synthesis of Rotaxane 92

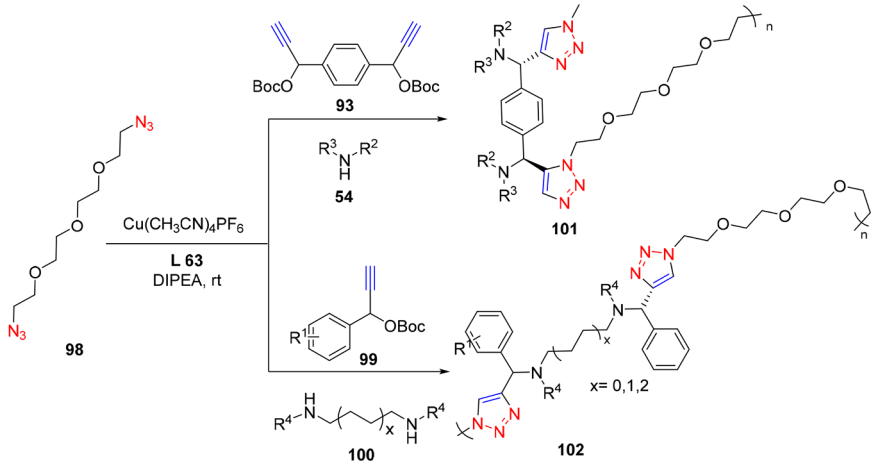


DMTr = C(Ph)(4-(OMe)-$C_6H_4)_2$, TBDMS = ^{t}BuMe$_2$Si

Scheme 22a. Synthesis of 96 and 97 via 3-CAP



Scheme 22b. Synthesis of Diverse Polymers



which gave comparatively fewer yields of 53, 38, and 42%, respectively.

Zheng and co-workers[66] reported novel, one-pot, efficient multicomponent reactions (MCRs) of OBoc-alkynes **53**, azides **2**, amines **54**, and 2*H*-azirines **55** for the synthesis of fully substituted 1,2,3-triazole **56** using copper iodide, DIPEA, and MeOH (Scheme 15). Here, 2*H*-azirines are readily disclosed for the C−N bond formation. Electron-donating and electron-withdrawing alkynes had a good transformation, but alkyl-substituted OBoc-alkyne does not transform into the desired product. For **55**, alkyl 2*H*-azirines did not provide the desired product. This approach is very useful for polyfunctionalized

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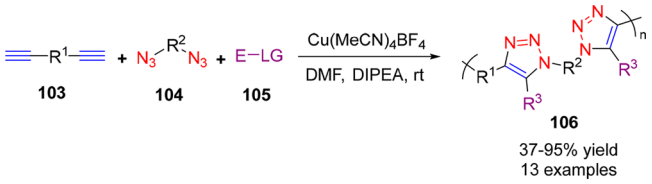
Scheme 23. MCP Reaction of Diynes 103, Diazides 104, and Electrophiles 105



triazole with a wide substrate scope, mild conditions, and good yield.

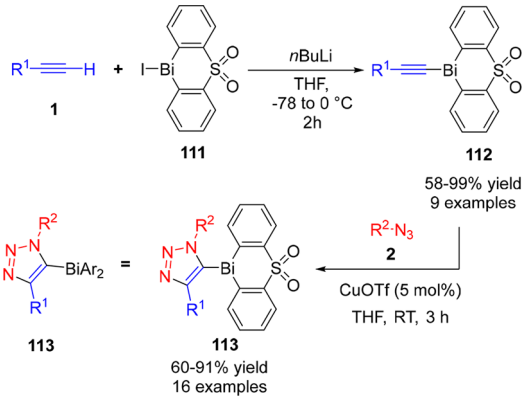
2.1.1.2. CuCl-Catalyzed Synthesis. Xu and co-workers[67] reported a three-component interrupted click approach for a bench-stable 5-stannyl triazole **58** from easily available **1**, **2**, and Bu_3SnOMe using CuCl as a catalyst (Scheme 16). Through a Sn/Cu transmetalation, 5-stanyl triazole **58** was produced which can be used as a potent nucleophilic reagent. This mutual Sn/Cu transmetalation is crucial for future progress in tin chemistry and useful for the synthesis of fully functionalized triazole **59**, trifluoromethylthiolated triazole **10**, and trifluoromethylated triazole **60**.

Zhou and co-workers in 2013[68] reported the first highly enantioselective asymmetric desymmetrization for the synthesis of quaternary oxindoles bearing 1,2,3-triazole **64** from oxindole-based 1,6-heptadiynes **61** and azide **2** using CuCl (18 mol %), PyBOX ligand (15 mol %) **63**, and 2,5-hexanedione at 0 °C for 96 h (Scheme 17a). The N-protecting group of oxindole favors most of the alkyl and acetyl groups but is less favorable for the electron-withdrawing acetyl protecting group, which leads to the formation of undesired ditriazole **65**.

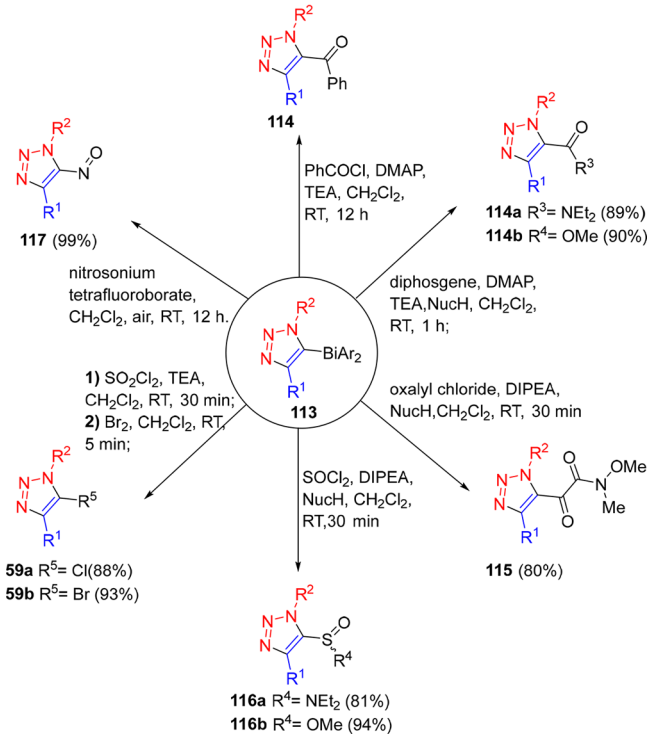
Here, **64** with the alkyne group uses as a versatile synthetic tool for further modification such as [3 + 2] cycloaddition (a), full or partial hydrogenation (b,d), and Sonogashira reaction (c) (Scheme 17b).

Zhou and co-workers[69] first reported a highly enantioselective desymmetric CuCl-catalyzed reaction of terminal alkynes **1** or 1-iodoalkynes **71** with diazides **70** using PyBOX ligands **72** and DCM at −50 to −40 °C for the synthesis of tertiary alcohols containing 1,2,3-triazoles **73** and **74** with excellent yield (Scheme 18). For the PyBOX ligand study, they found that different C4 shielding groups showed a different result. The OBn group increased the % ee ratio of **73** but led to poor yield. Increasing the steric hindrance of the shielding

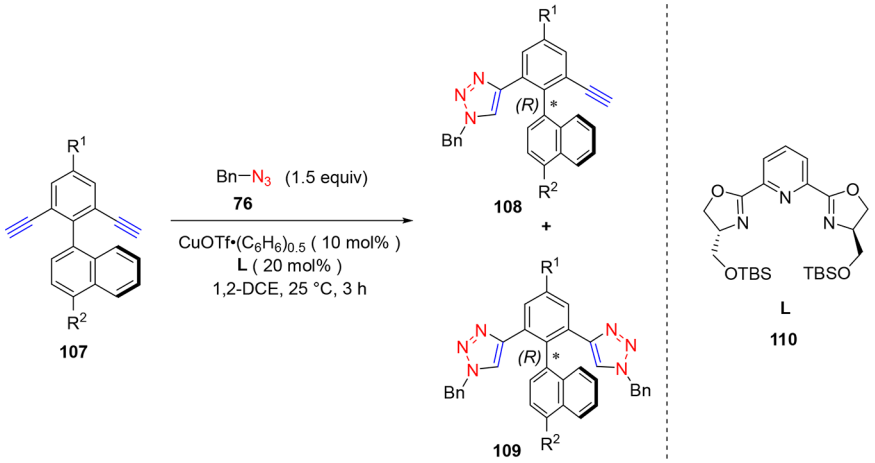
Scheme 25a. CuOTf-Promoted Synthesis of 113



Scheme 25b. Electrophilic Substitution Reactions of 113



Scheme 24. Synthesis of Chiral Biaryl-Bearing Triazoles 108 and 109



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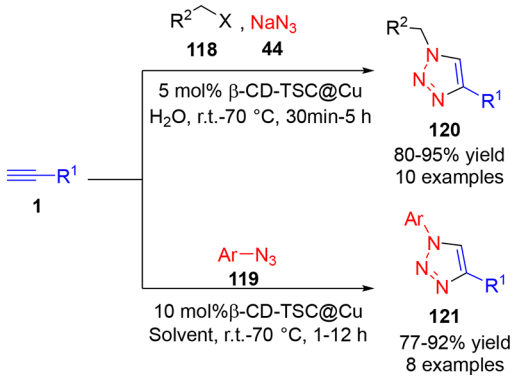
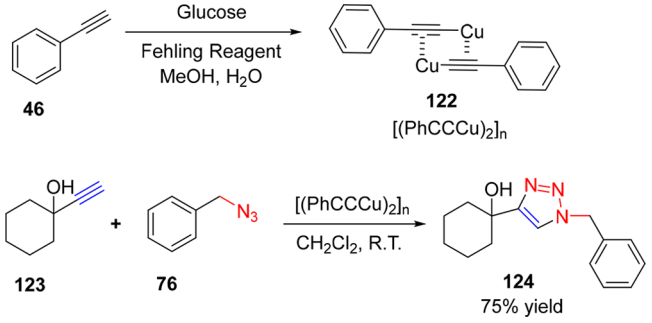
Scheme 26. Synthesis of 120 and 121 Catalyzed by a Nanocatalyst β-CD-TSC@Cu



Scheme 27. Phenylethynylcopper(I)-Promoted Synthesis of 124



group using −1-naphthyl and −2-MeO-3,5-^{t}Bu$_2$-C$_6$H$_2$ also gave poor results. When the phenyl group (−Ar) group was replaced by the 4-fluorophenyl group, the reaction led to a higher % ee ratio and good yield with DCM solvent. Irrespective of the electronic effect of substituents *meta*-substituted diazo alcohol gave a slightly higher % ee in comparison to that at the *para*-position. Based on the study of the reaction mechanism, this approach showed that % ee increased with time and decreased the chiral/achiral ratio, which indicates that enantioselectivity increased by the formation of an achiral ditriazole.

Zhou and co-workers in 2021[70] reported a highly enantioselective asymmetric CuAAC synthesis of a tertiary alcohol functional group bearing 1,2,3-triazole **78** from azides **2** and highly functionalized tertiary alcohol containing ethynyl **75** using CuCl, 3-pentyl-containing PyBOX-phosphonate ligand **L79**, AgTFA additive, and ^{t}BuOAc at °0 C for 3−4 days (Scheme 19a). The 3-pentyl group at the C4 position increase the s-factor. Kinetic resolution (KR) of racemic α-ethynyl alcohol **75** gave a good yield with 87−99% ee and 39−50% yield of **77**. α-Alkyl alcohol such as α-isopropyl alcohol did not give good results (60% ee and 34% yield). The E-CuAAC reaction of this tertiary alcohol containing ethynyl **75** with azide **2** gave chiral α-1,2,3-triazole bearing tertiary alcohol **79** in 70−99% yield with 48−96% ee. This approach is useful for the synthesis of bioactive compounds such as indomethacin, fenbufen, and celecobix.

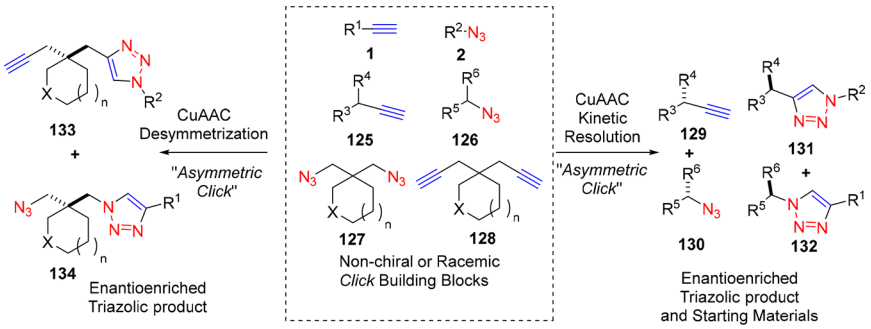
This approach is also suitable for the kinetic resolution of α-monofluorinated α-ethynyl alcohol **80** and benzyl azide **76** for the synthesis of monofluorinated α-triazole-substituted alcohol **82** in 40−50% yield with 20−96% ee and gave chiral alcohol **81** (Scheme 19b).

2.1.1.3. Cu(MeCN)$_4$PF$_6$-Catalyzed Synthesis. Song and co-workers[71] reported an efficient synthesis of 4-heterofunctionalized triazolyl−organosulfur **84** with high regioselectivity and wide substrate scope (33 examples) such as **85**−**88** from internal thiocynatoalkynes **83** and **2**; they used (CuOTf)$_2$PhMe and Cu(MeCN)$_4$PF$_6$ (tetrakisacetonitrile)-copper(I)hexafluorophosphate) as a catalyst (Scheme 20). The electronic effect was not influenced by electron-rich and electron-deficient substituents as they gave the same yield, but for the azide scope of the reaction, the yield for electron-rich azide was slightly lower than that of the electron-deficient azide. The reaction could also occur for a secondary azide.

Goldup and co-workers[72] reported an active template Cu-catalyzed alkyne−azide cycloaddition (AT-CuAAC) reaction of propargyl cytosine **89** and azido thymine **90** for the preparation of rotaxane **92** in the presence of macrocycle **91** using [Cu(MeCN)$_4$]PF$_6$ as a catalyst, N^{i}Pr$_2$Et, and THF at 50 °C for 18 h (Scheme 21). At 32 °C, no amplification was observed when oligonucleotide rotaxane was utilized as the forward primer in PCR amplification. According to the findings, the mechanical link in rotaxanes efficiently limits the interlocked oligonucleotide's capacity to act as a primer for the T7 polymerase. This method utilized in click DNA ligation may be easily extended to the active template manifold for the synthesis of biocompatible triazole-linked oligonucleotides based on rotaxanes.

Zheng and co-workers[73] reported a 3-CAP (three-component asymmetric polymerization) synthesis of chiral polytriazole-methanamines **96** and **97** from OBoc-alkynes **93**, azides **2**, and various types of amines **94** and **95** using Cu(CH$_3$CN)$_4$PF$_6$, ligand (**L**) **63**, and DIPEA at room temperature (Scheme 22a). For 3-CAP, the secondary and

Scheme 28. CuAAC Desymmetrization and CuAAC Kinetic Resolution



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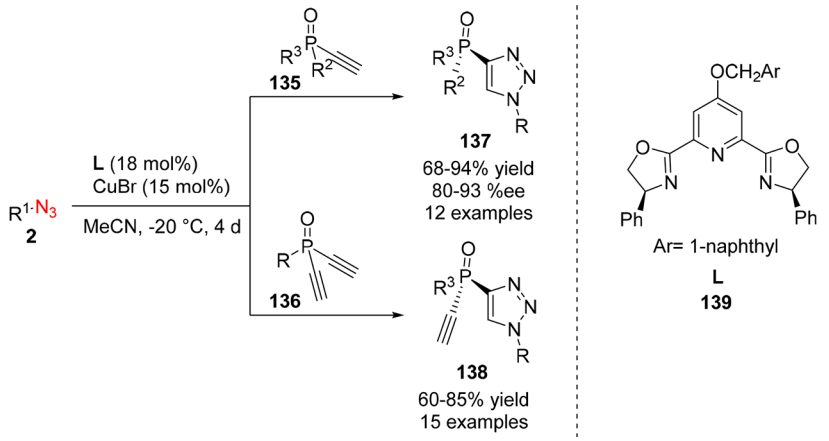
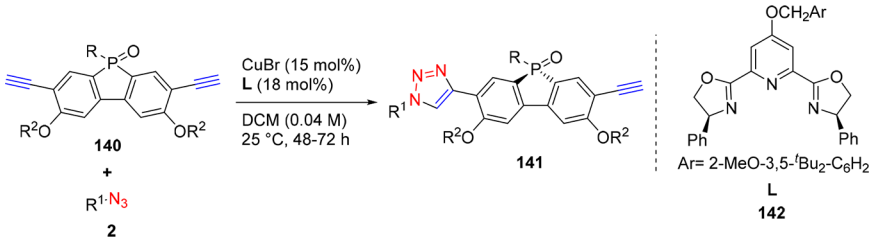
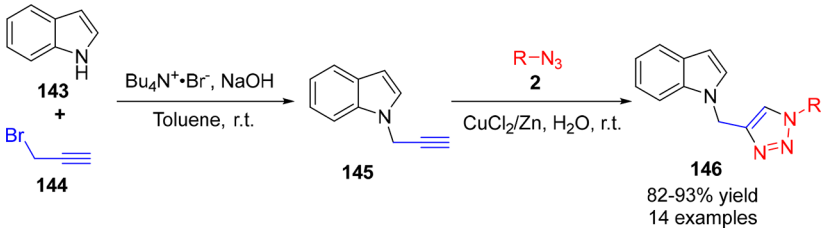
Scheme 29a. Synthesis of 137 and 138 via Kinetic Resolution and Desymmetrization



Scheme 29b. Synthesis of Monoethynylphosphine Oxide 141



Scheme 30. Synthesis of Derivatives of 146 Using $CuCl_2$/Zn Powder in Water at RT



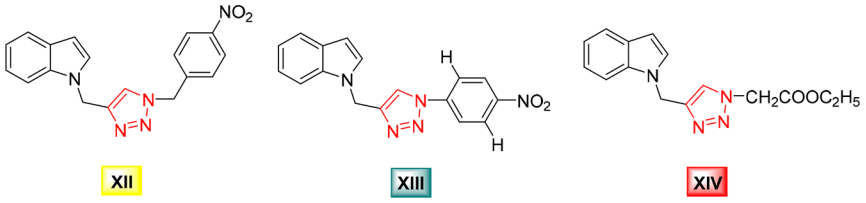
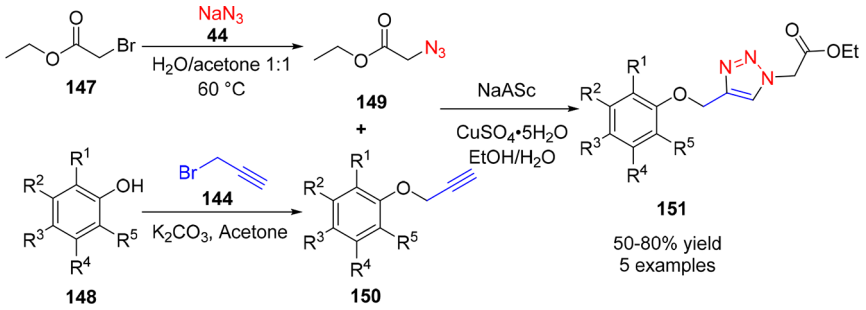


Figure 5. Typical triazole derivatives that show antifungal activity.

Scheme 31. $CuSO_4 \cdot 5H_2O$-Promoted Synthesis of Derivative of 151



primary amine gave good yield and gave M_n up to 46 700 g/mol.

This approach is also useful for the synthesis of structurally diverse polymers **101** and **102**. With diazide **98**, secondary

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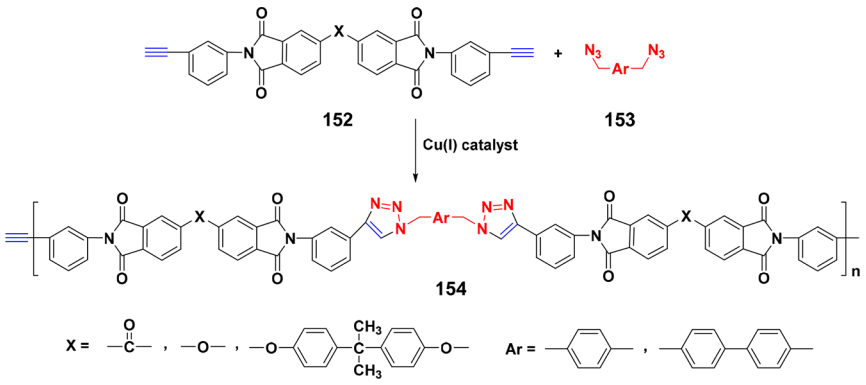
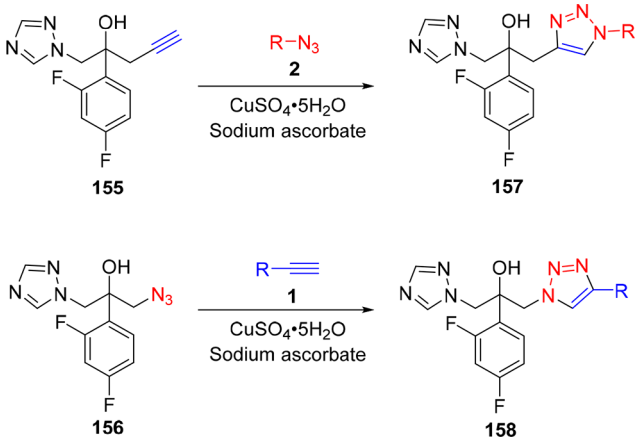
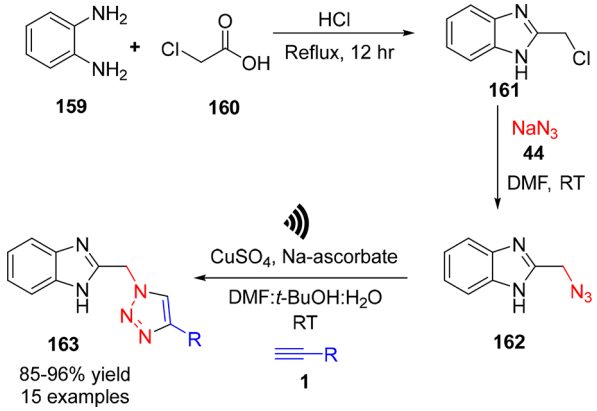
Scheme 32. Synthesis of 154 Using Cu(I) Catalyst



Scheme 33. Synthesis of 157 and 158 Using $CuSO_4 \cdot 5H_2O$



Scheme 34. $CuSO_4$-Assisted Synthesis of 163 and Its Derivatives



amines **54** and **100** and OBoc-alkynes **93** and **99** were used as a substrate and yielded excellent M_n up to 10 200 g/mol (Scheme 22b).

Zheng and co-workers[74] reported MCP (multicomponent polymerization) and interrupted click synthesis of 1,4,5-polytriazoles (1,4,5-PTAs) **106** from diynes **103**, diazides **104**, and electrophile **105** using $Cu(MeCN)_4BF_4$ catalyst, DIPEA (*N*,*N*-diisopropylethylamine) base, and DMF as a solvent at room temperature with high yields, M_n values, and excellent modification efficiency (Scheme 23). Poor solubility of inorganic CuI does not catalyze this polymerization.

2.1.1.4. CuOTf-Catalyzed Synthesis. Fokin and co-workers[75] reported the first asymmetric CuAAC reaction via kinetic resolution of α-chiral azide and desymmetrization of *gem*-diazide. They also discussed the importance and the role of this new PyBOX ligand in the enantioselective synthesis of 1,2,3-triazole.

Uozumi and co-workers[76] reported a highly enantioposition-selective CuAAC approach for the synthesis of axially chiral biaryl groups bearing 1,2,3-triazoles **108** and **109** from prochiral biaryl-bearing dialkynes **107** and benzyl azide **76** using $CuOTf \cdot (C_6H_6)_{0.5}$ (10 mol %), a *tert*-butyl(dimethyl)silyl (TBS) group containing PyBOX ligand **L** (20 mol %) **110**, and 1,2-DCE at 60 °C for 24 h (Scheme 24). Increasing the load of azide up to 1.5 equiv enhanced the % ee to 91% with 64% yield. X-ray crystallographic analysis proved that the absolute configuration of triazole was *R*.

Fokin and co-workers[77] reported the synthesis of 5-bismuth(III) triazolides **113** from a bench-stable, readily available, as well as a nontoxic group of σ-acetylides, 1-bismuth(III) acetylides **111** and **2**, in the presence of CuOTf (Tf = trifluoromethanesulfonyl) and THF as a solvent for 3 h at RT (Scheme 25a).

Further reaction of **113** with various electrophiles enabled the synthesis of fully substituted 1,2,3-triazoles **59**, and **114**–**117** (Scheme 25b).

2.1.1.5. β-Cyclodextrin-TSC@Cu-Catalyzed Synthesis. Naimi-Jamal and co-workers[78] reported a synthesis of 1,4-disubstituted triazoles **120** and **121** from **1**, azides **44**/**119**, and alkyl halides **118** using novel, stable, water-soluble, as well as homogeneous catalyst β-CD-TSC@Cu (copper(I) ions supported on functionalized β-cyclodextrin) as a supramolecular moiety in an aqueous medium with excellent regioselectivity and high yield (Scheme 26). The catalyst was utilized up to 7 times without a remarkable loss of its activity. After the third cycle, very low (≤2 ppm) copper leaching was observed by ICP-OES.

The substrate scope of this reaction reported that 2-bromoacetophenone derivatives minutely decreased the product yield and expanded the reaction time. The hydrophobic internal cavity of β-CD provided a favorable environment for copper ions and organic substrates to interact more effectively.

2.1.1.6. Phenylethynylcopper(I)-Catalyzed Synthesis. Varela-Palma and co-workers[79] developed a synthesis of 1-(1-benzyl-1,2,3-triazol-4-yl)cyclohexanol **124** from 1-ethynylcyclohexanol **123** and benzyl azide **76** using phenylethynylcopper(I) **122** catalyst and CH_2Cl_2 as a solvent

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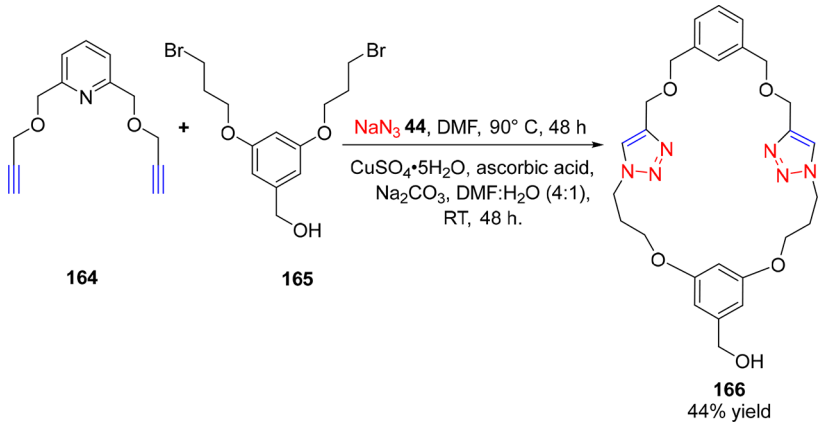
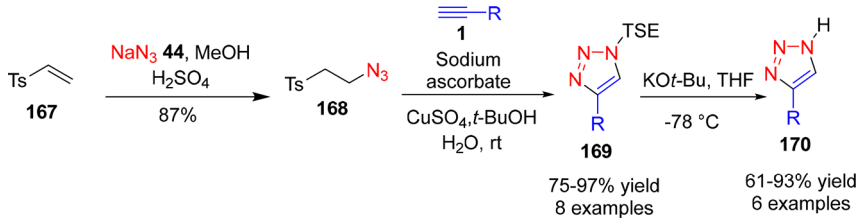
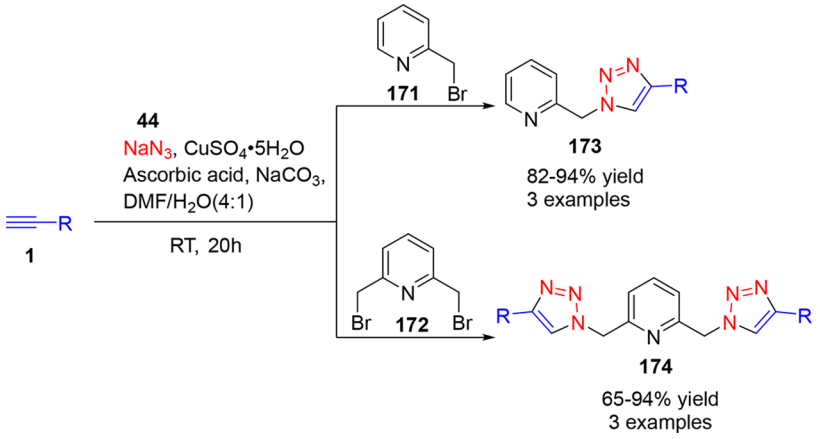
Scheme 35. Synthesis of 166 Using $CuSO_4·5H_2O$ Catalyst in DMF/Water Solvent



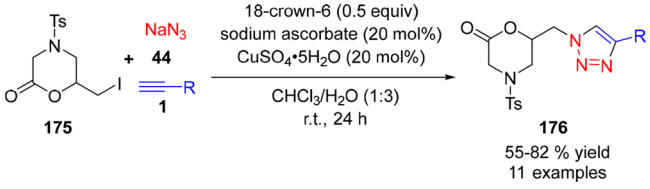
Scheme 36. Synthesis of 169 and Its Derivative 170



Scheme 37. $CuSO_4·5H_2O$-Catalyzed Synthesis of 173 and 174 and Their Derivatives



Scheme 38. Synthesizing 176 via Utilization of 18-Crown-6, Sodium Ascorbate, and $CuSO_4$ in Chloroform/Water



at RT for 24 h. Adding a Fehling A and B solution to the glucose−phenylacetylene **46** mixture resulted in yellow particles such as phenylethynylcopper(I). The 1,3-bis(1,2,3-triazol-1-yl)-propan-2-ol core containing a triazole (10 examples) was synthesized by this protocol with 80−92% yields (Scheme 27).

2.1.1.7. Miscellaneous CuAAC-Catalyzed Reaction. Fossey and co-workers[80] reported a short review on asymmetric CuAAC′ (chiral Click) reaction (Scheme 28). Taking advantage of the difference in the rate of reaction kinetic resolution through CuAAC gave the formation of new enantioenriched material or product. A racemic mixture (50:50) also converts into either *R* or *S* and becomes enantioenriched. Using this approach, kinetically resolved triazoles **131** and **132** are produced from an α-benzylic azide and phenylacetylene.[75] Desymmetrization leads to the loss of one or more symmetry elements and results in a prochiral molecule from the chiral molecule. This approach is useful for producing a single enantiomer from a nonchiral reactant.[81] Desymmetrization is very useful for the synthesis of some biologically active chiral compounds[82] such as (−)-podophyllotoxin and (−)-picropodophyllin.[83]

Zhou and co-workers[84] reported the synthesis of 1,2,3-triazoles **137** and **138** using desymmetrization and an enantioselective CuAAC approach. The newly synthesized chiral PyBOX ligand shows excellent enantioselectivity in

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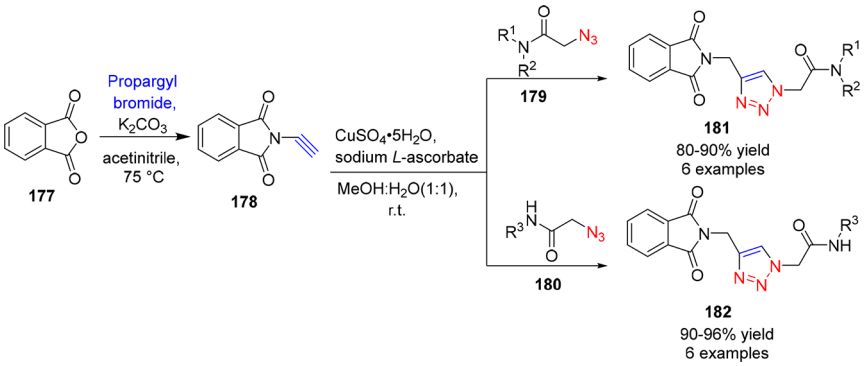
Scheme 39. $CuSO_4·5H_2O$ and Sodium-Ascorbate-Promoted Synthesis of 181 and 182 and Their Derivatives in Aqueous Methanol



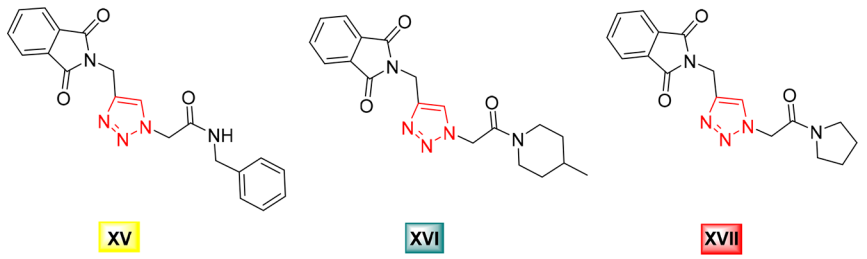


Figure 6. Compounds **XV**, **XVI**, and **XVII**.

1,2,3-triazole. Enantioselective CuBr-catalyzed cycloaddition of azide **2** and alkynylphosphine oxide (P-chiral and P-substituted) **135** using 1-naphthyl-bearing PyBOX ligand **L139** and MeCN at −20 °C for 4 days yielded P-chiral phosphine oxides bearing a 1,2,3-triazole scaffold **137** in excellent yield and high enantioselectivity (Scheme 29a). Desymmetrization of dialkynylphosphine **136** with azide **2** under the CuAAC approach yielded monotriazole **138** with excellent results. This ethynyl-containing triazole is useful for further functionalization.

For the desymmetric CuAAC approach for phosphole diynes **140**, the reaction of **140** with azide **2** yielded chiral monotriazole **141** with good enantioselectivity (Scheme 29b). This versatility of monoethynylphosphine oxide **141** was used as a chiral building block for various reactions.

2.1.2. Cu(II)-Catalyzed Azide–Alkyne Cycloaddition. 2.1.2.1. $CuCl_2$-Catalyzed Synthesis. Xu and co-workers[85] reported a copper-catalyzed synthesis of indole–triazole **146** from 1-(prop-2-ynyl)-1*H*-indole **146** and **2** using $CuCl_2$/Zn powder in water at RT. At RT, the H atom linked to the N atom of indole **143** was replaced by pro-2-ynyl **144** using $Bu_4N^+·Br^-$, NaOH, and toluene, resulting in **145** (Scheme 30).

Most compounds show moderate to good antifungal activity against *Colletotrichum capsica* and cotton *Physalospora* pathogens, using flutriafol and hexaconazole as positive controls. The activity of compounds **XII** and **XIII** was unaffected by the distance between the phenyl ring and the triazole moiety.

The findings revealed that the *ortho*-substituents of the phenyl ring are helpful toward the activity; however, when R is an electron-withdrawing group or hydrogen at the *meta*-position is replaced, the impact is unfavorable. Compound **XIV** has no substituted phenyl ring and was shown to be the most efficient against *Colletotrichum capsica*, with an inhibition ratio of up to 83.33% (Figure 5).

2.1.2.2. $CuSO_4$-Catalyzed Synthesis. Cunha Lima and co-workers[86] described a synthesis of 1,4-disubstituted triazoles **151** from ethyl 2-azidoacetate **149** and terminal alkyne **150** in the presence of $CuSO_4·5H_2O$, sodium ascorbate (NaASc), and EtOH/H_2O (1:1) at RT (Scheme 31). **149** was synthesized by azidation of ethyl 2-bromoacetates **147** and **150** synthesized from a natural product by a propargylation reaction. All synthesized compounds showed moderate antioxidant activity with an EC_{50} value above 75.5 μg/mL in the DPPH assay and 101.1 μg/mL in the ABTS assay. In the CuAAC reaction, the formation of copper(I)acetylide is an important step from the deprotonation of a terminal alkyne. Electron-withdrawing groups raised the reactivity and acidity of the terminal alkyne hydrogen, so reaction times were decreased and yields were increased.

Huang and co-workers[87] developed a step-growth polymerization of diazide **153** and phthalimide dialkyne **152** using the copper catalyst for the synthesis of polytriazoleimide **154** under mild conditions (Scheme 32). IR, NMR, wide-angle XRD, differential scanning calorimetry, thermogravimetric analysis, and intrinsic viscosity are used for characterization. The polytriazoleimides have high solubility in polar solvents and could be readily cast into clear, robust, and flexible films with intrinsic viscosities of 0.39–0.58 dL g^{-1}. The thermal stability and mechanical qualities of these new polytriazoleimide films were impressive.

Cuevas-Yañez and co-workers[88] reported a copper-catalyzed synthesis of 2-aryl-1-(1,2,4-triazolyl)-3-(1,2,3-triazolyl)propan-2-ol derivatives **157** and **158** from 2-(2,4-difluorophenyl)-1-[1,2,4]triazol-1-yl-pent-4-yn-2-ol **155** with various azides **2** and 1-azido-2-(2,4-difluorophenyl)-3-[1,2,4]triazol-1-yl-propan-2-ol **156** with different alkynes **1** using $CuSO_4$ and sodium ascorbate, respectively (Scheme 33). These fluconazole analogues showed good antifungal activity.

Joshi and co-workers[89] reported a facile, greener, and ultrasound-promoted synthesis of triazole **163** in the presence

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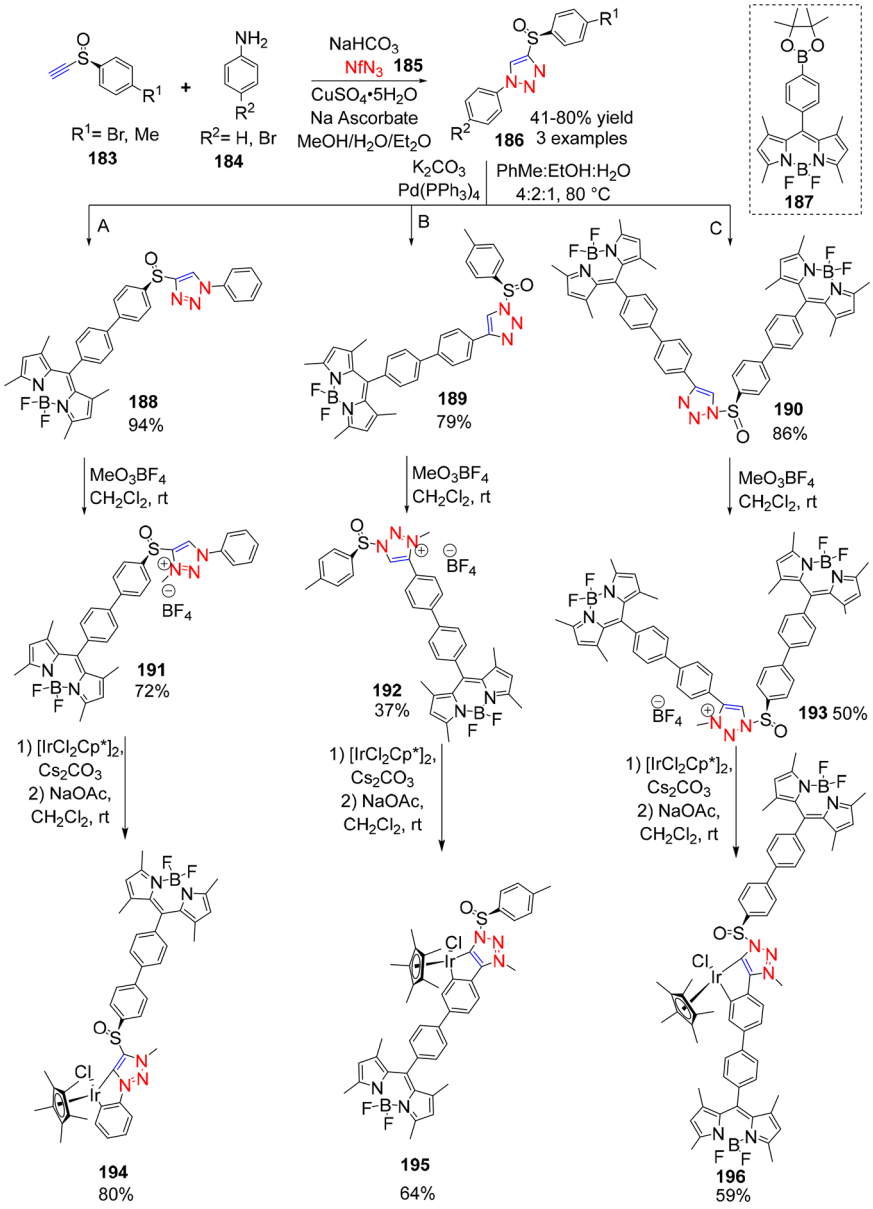
Scheme 40. Synthesis of Ir-Containing Complexes 194−196 Containing Luminescence Properties



of $CuSO_4$, sodium ascorbate, and DMF/*t*-BuOH/H_2O (1:1:1) by reaction between 2-(azidomethyl)-1*H*-benzo[*d*]imidazole **162** and **1** with good yields. The enhanced product formation was observed due to the greater solubility of copper sulfate in this aqueous medium (Scheme 34). *O*-Phenylenediamine **160** reacted with chloroacetic acid in HCl and resulted in 2-(chloromethyl)-1*H*-benzo[*d*]imidazole **161**, which was treated with sodium azide **44** in DMF at RT to yield **162**. An in vitro antimicrobial study reported that all of the synthesized molecules showed moderate activity compared to that of standard drugs. According to the findings, all synthesized molecules were more active against Gram −*ve* bacteria in comparison to Gram +*ve* bacteria.

Crowley and co-workers[90] performed a safe, one-pot CuAAC approach of an exofunctionalized pyridyl-triazole **166** from dialkyne **164**, dibromide **165**, and sodium azide **44** using $CuSO_4{\cdot}5H_2O$ and DMF/H_2O (4:1) for 48 h, resultin in a 44% isolated yield (Scheme 35).

Weinreb and co-workers[91] reported a synthesis of N-protected 4-substituted triazole **169** from *β*-tosylethylazide **168** and **1** using sodium ascorbate/$CuSO_4$ as a catalyst in aqueous *tert*-butanol at RT. With a further reaction of **169** with KO*t*-Bu in THF at −78 °C, the mixture was gently warmed to 0 °C to produce unprotected 4-substituted 1,2,3-triazole **170**. **168** was synthesized from *p*-tolyl vinyl sulfone **167**, sodium azide **44**, and sulfuric acid in MeOH at 0 °C to RT with good yield (Scheme 36). This cycloaddition was also favored for acetylene dicarboxylic acid and dimethyl acetylenecarboxylate with azide. They also reported an efficient ruthenium-catalyzed cycloaddition of alkyl azide with terminal and asymmetric internal alkynes using Cp*Ru(PPh_3)$_2$ and PhH to produce 1,2,3-triazole.

Crowley and co-workers[92] reported a synthesis of various bi- and tridentate pyridyl-triazole ligands with Cu(II) and Ag(I) **173** and **174** from halides (2-(bromomethyl)pyridine **171** and 2,6-(bis-9-bromomethyl)pyridine **172**) with sodium azide **44**

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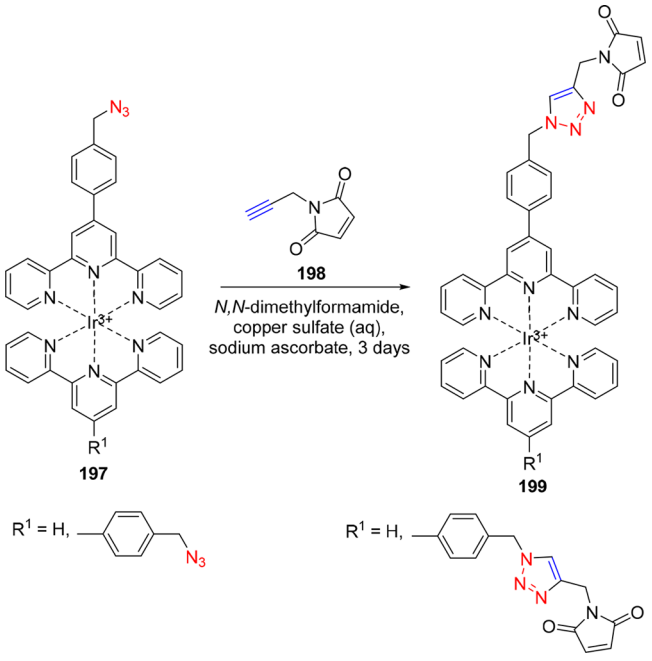
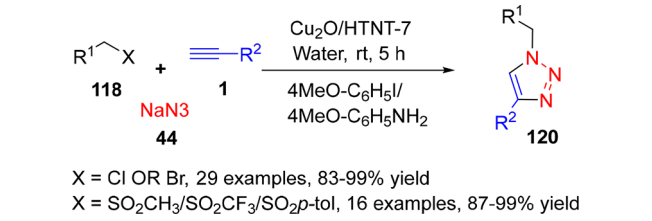
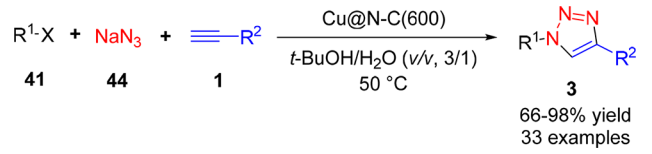
Scheme 41. Synthesis of 199 in the Presence of Aqueous $CuSO_4$ with NaASc in DMF



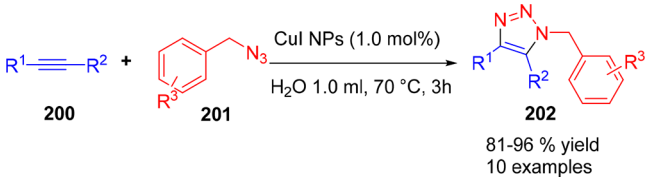
Scheme 42. Utilizing Cu_2O/HTNT-7 as a Catalyst to Synthesize 120 at RT



Scheme 43. Cu@N−C(600)-Promoted Synthesis of 3 in Aqueous ^{t}BuOH



Scheme 44. CuI NP-Promoted Synthesis of 202 and Its Derivatives



and **1** using $CuSO_4{\cdot}5H_2O$, ascorbic acid, DMF/H_2O at RT for 20 h, respectively (Scheme 37).

Thibonnet and co-workers[93] performed the one-pot method of 1,2,3-triazole-containing morpholine scaffold **176** in the presence of 18-crown-6, NaASc, $CuSO_4{\cdot}5H_2O$, and $CHCl_3$/H_2O from **1**, iodomorpholinone **175**, and sodium azide **44** at RT for 24 h using the CuAAC approach (Scheme 38). This

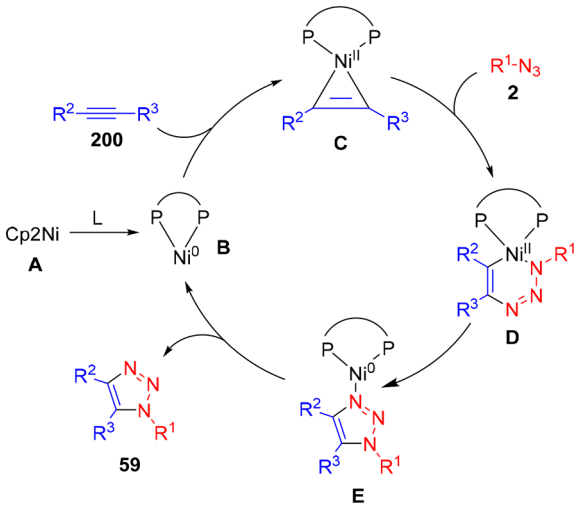


Figure 7. Conceivable mechanism for NiAAC. Reprinted with permission from ref 32. Copyright 2020 John Wiley and Sons.

synthetic approach was carried out under an argon atmosphere.

Tan and co-workers[94] reported a synthesis of novel hybrid phthalimide analogues containing a triazole **181** and **182** via CuAAC reaction of 2-ethynylisoindoline-1,3-dione **178** with various organic azides (2-azido-*N*,*N*-disubstituted acetamide **179** and 2-azido-N-substituted acetamide **180**) in the presence of $CuSO_4{\cdot}5H_2O$, sodium L-ascorbate, and MeOH/H_2O (1:1) at RT (Scheme 39). Compound **178** was synthesized from phthalimide **177** and propargyl bromide using K_2CO_3 in acetonitrile at 75 °C.

The molecular docking of compounds **XV**, **XVI**, and **XVII** (Figure 6) with molecular dynamic simulation studies showed interaction of PPI with ACE2-S1, the best binding energy of **XV** with a value of −9.70 kcal/mol, and the best approximated K_i value of **XV** (0.077 μM). In the interaction with the Mpro protein, compound **XVI** exhibited the best binding energy (−8.76 kcal/mol) and approximate K_i value (0.315 μM), while in the interaction with the PLpro, compound **XVII** showed the best binding energy (−8.87 kcal/mol) and estimated K_i value (0.315 μM). Based on an in silico study, these derivatives may block the entry of SARS-CoV-2 into the host cell.

Sierra and co-workers[95] developed a synthesis for 1,2,3-triazole-BODIPY scaffold **186** from anilines **184** and alkynyl sulfoxides **183** using NfN_3**185**, $NaHCO_3$, and $CuSO_4{\cdot}5H_2O$/sodium ascorbate in MeOH/H_2O/Et_2O with 41−80% yield (Scheme 40). Further substitution on this moiety led to chiral-at-metal BODIPY-based iridium(III) complexes **194**−**196**, which showed excellent luminescence properties.

Thordarson and co-workers[96] reported a step process for the synthesis of iridium(III)azides **199** and further reaction of **199** with 1-(prop-2-ynyl)-1*H*-pyrrole-2,5-dione **198** using DMF, $CuSO_4$, and NaASc for the synthesis of Ir(III)-containing triazole-bisterpyridine **199** for 3 days (Scheme 41). This complex showed photophysical activity which is important for the modification of the polymer and the surface.

2.1.3. Heterogeneous Cu-Catalyzed Azide−Alkyne Cycloaddition. 2.1.3.1. Cu_2O/HTNT-7-Nanocatalyzed Synthesis. Peddiahgari and co-workers[97] developed a novel approach for the CuAAC reaction from organic halides **118**, sodium azide **44**, and **1** using Cu_2O/HTNT-7 nanoparticles (Cu_2O nanoparticles supported on hydrogen trititanate nanotubes)

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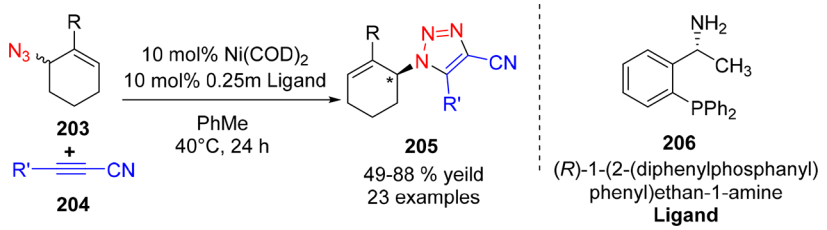
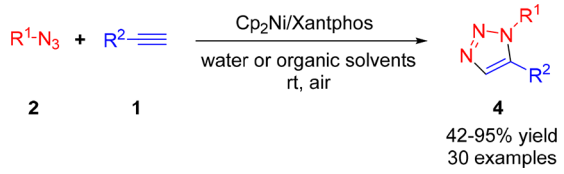
Scheme 45. Preparation of 205 and Its Derivatives Using $Ni(COD)_2$ as a Promoter



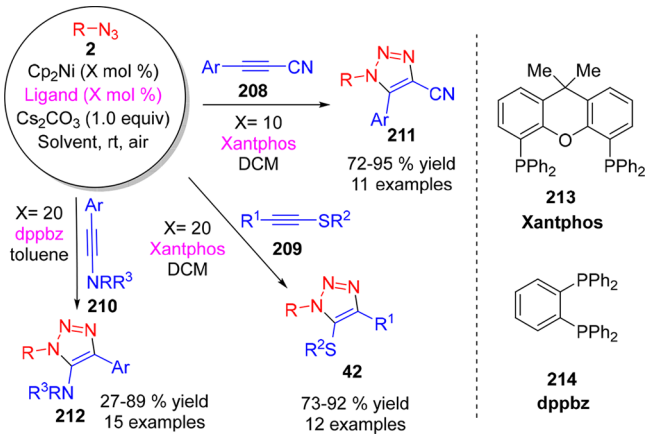
Scheme 46. Synthesis of Derivatives of 4 at RT Using the $NiCp_2$/Xantphos Catalyst



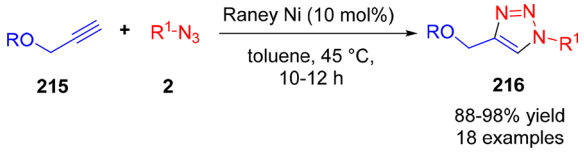
as a catalyst and 4-MeO-C_6H_5I/4-MeO-$C_6H_5NH_2$ as an azide precursor in water mediated at RT with excellent yield for the synthesis of 1,4-disubstituted triazole **120** (Scheme 42). Using different halides and alkynes, they investigated the extent of the CuAAC reaction, in which they found 3-(bromomethyl)-thiophene, 2-(bromomethyl)thiophene, and 2-(bromomethyl)-pyridine immediately produced a complex mixture of by-products, turning the reaction mass dark and viscous. The reusability of the catalyst was tested under optimal conditions and recovered using centrifugation. The retrieved catalyst was reused seven times with no discernible difference in yield. ICP-MS investigation revealed that very low (≤1 ppm) copper leaching was observed.

2.1.3.2. Cu@N−C-Catalyzed Synthesis. Xie and co-workers[98] reported a one-pot synthesis of **3** from **1**, aryl halides **41**, and sodium azide **44** using a novel, efficient, recyclable heterogeneous catalyst Cu@N−C (copper supported on nitrogen-doped carbon) and *t*-BuOH/H_2O (3:1) at 50 °C with high yield and broad substrate scope (Scheme 43). Under an argon flow, the powder $Cu(im)_2$ (copper(II) bisimidazolate) was deposited in a tube furnace and calcined to 600 °C at a heating rate of 5 °C·min^{-1} for 5 h. The resultant solid was cooled to RT to afford the Cu@N−C(600). The retrieved catalyst was used up to 4 times without a discernible change under the standard conditions. Benzyl chloride required a longer time for completion because of its low activity for nucleophilic substitution reaction with sodium azide. Aliphatic alkynes required high temperatures and long reaction times due to their lower reactivity compared to aryl alkynes. The *para*-substituted compounds containing electron-deficient

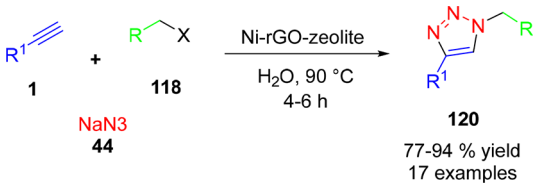
Scheme 48. Synthesis of 42, 211, and 212 Using a Ni Catalyst



Scheme 49. Raney-Nickel-Promoted Synthesis of 216 and Its Derivatives

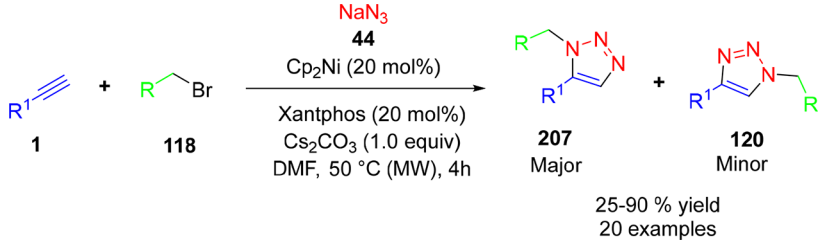


Scheme 50. Ni-rGO-Zeolite NP-Promoted Synthesis of 120 and Its Derivatives



groups resulted in lower yield compared to that with *ortho*- and *meta*-substituted compounds. This approach was also used for the synthesis of ethisterone and zidovudine.

Scheme 47. Regioselective Synthesis of 207 and 120 by Utilizing Nickelocene-Catalyzed Cycloaddition via Microwave Irradiation



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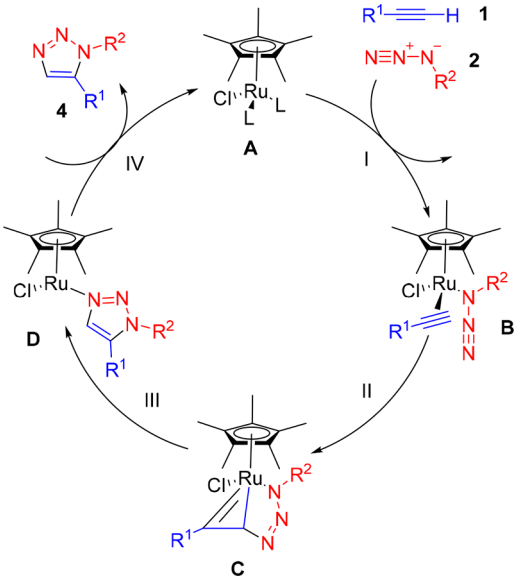


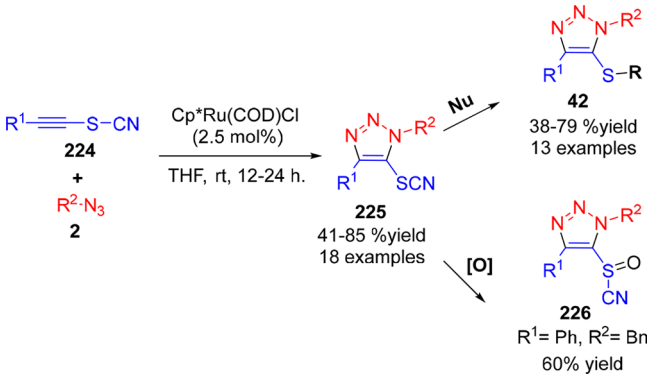
Figure 8. Proposed catalytic cycle of the RuAAC reaction.[106−108] Reprinted from ref 106. Copyright 2008 American Chemical Society.

2.1.3.3. CuI Nanoparticle Synthesis. Maurya and coworkers[99] developed an effective copper-catalyzed protocol using heterogeneous CuI nanoparticles to synthesize 1,4,5-trisubstituted triazole **202** derivatives by reacting alkynes **200** and benzyl azides **201** in a water medium at 70 °C for 3 h (Scheme 44). CuI NPs displayed a significant activity and recyclability (up to 6 cycles) for this reaction, and the intended product was formed in 81−96% yields.

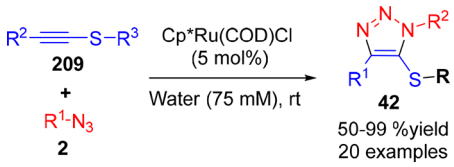
2.2. Nickel-Catalyzed Azide−Alkyne Cycloaddition (NiAAC). A possible catalytic path for NiAAC reaction is shown in Figure 7. First, intermediate **A** is produced from Ni(0) and internal alkyne. In the following cycloaddition process, intermediate **A** acts as a Nu, which allows electron-rich C to attack the terminal N of azide, resulting in nickelacycle intermediate **B**, which further leads to intermediate **C**. After removal of a metal atom, the desired triazole product is obtained and regeneration of the catalyst occurs.

2.2.1. Ni(COD)$_2$-Catalyzed Synthesis. Topczewski and Liu[100] reported the synthesis of N-chiral triazole derivative

Scheme 52. Utilizing (Cp*)Ru(COD)Cl as a Promoter for the Synthesis of 225 and Its Derivatives 42 and 226

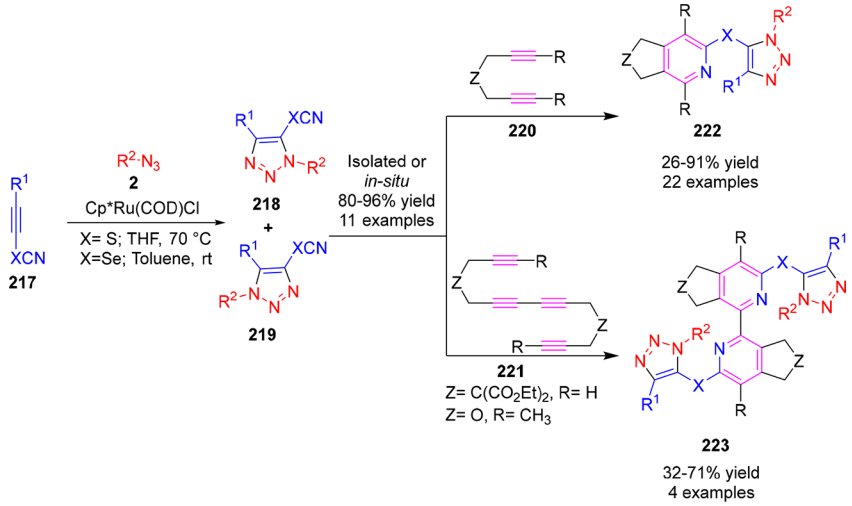


Scheme 53. Synthesis of 42 and Derivatives Using Ru(Cp*)(COD)Cl Catalyst in Water at RT



205 that proceeds via the NiAAC reaction by dynamic kinetic resolution (DKR) between allylic azide **203** and alkynes **204** using Ni(COD)$_2$ as a catalyst and (*R*)-1-(2-(diphenylphosphanyl)phenyl)ethan-1-amine **206** as a ligand in PhMe at 50 °C for 24 h (Scheme 45). This DKR is enabled by a spontaneous [3,3]-sigmatropic rearrangement of the allylic azide. For the alkyne scope of E-NiAAC (enantioselective NiAAC), the reaction with a neutral and electron-deficient substituent on the aryl group had less effect on enantioselectivity, while a strong EWG decreased regioselectivity. The azide scope of the E-NiAAC reaction reported that the scope of allylic azide was not much affected by electron-rich and electron-deficient groups, but when the cyclohexyl part was changed by acyclic allylic azide, both (*E*)- and (*Z*)-alkene isomers were observed (7:1 *E*/*Z*). However, the desired derivative was separated as a single isomer.

Scheme 51. Synthesis of 218 and 219 and Their Derivatives Using Ru(Cp*)(COD)Cl Catalyst



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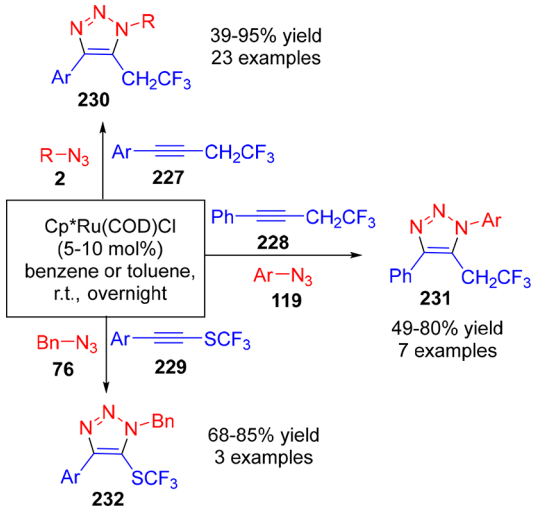
Scheme 54. Synthesis of 230−232 and Their Respective Derivatives by Utilizing a Ru Catalyst



2.2.2. Cp_2Ni/Xantphos-Catalyzed Synthesis. Hong and co-workers[101] reported an efficient and simple nickel-catalyzed cycloaddition reaction of **1** with **2** in water or organic solvent (toluene) using Cp_2Ni/xantphos as a catalyst. Product **4** was obtained in 42−95% yield with broad substrate scope and high regioselectivity (Scheme 46). They also reported that *ortho*-OMe-substituted alkyne gave no reaction due to a steric effect, whereas *meta*- and *para*-OMe-substituted alkynes gave 93 and 91% yield, respectively. So, a lower steric hindrance of substituted alkynes strongly favored the NiAAC reaction. This approach was further explored for biomolecules such as carbohydrates and amino acids. The xantphos ligand and Cp_2Ni precatalyst were essential in achieving the catalytic manifold, which was insensitive to molecular oxygen and water.

Bosc and co-workers[102] reported an effective synthesis of various 1,5-disubstituted-triazole **207** via nickel catalyzed (nickelocene) cycloaddition reaction of **1**, bromide **118** and sodium azide **44** using xantphos, Cs_2CO_3 and DMF. They heated the reaction mixture for 4 h at 50 °C in a microwave which showed excellent yield and regioselectivity (Scheme 47). This approach is very useful when the low-molecular-weight azide is added as a reactant for the synthesis of triazoles. Due to steric hindrance, the *ortho*-substituted phenyl ring containing bromide provided less yield compared to that with the *meta*-/*para*-substituted bromide.

Hong and co-workers[103] reported a synthesis of various fully substituted triazoles **42**, **211**, and **212** from **2** and various alkynes **209**, **208**, and **210**, respectively. They used Cp_2Ni as a catalyst, Xanthos **213**/dppbz **214** as a ligand, and Cs_2CO_3 and DCM or toluene as a solvent at RT (Scheme 48).

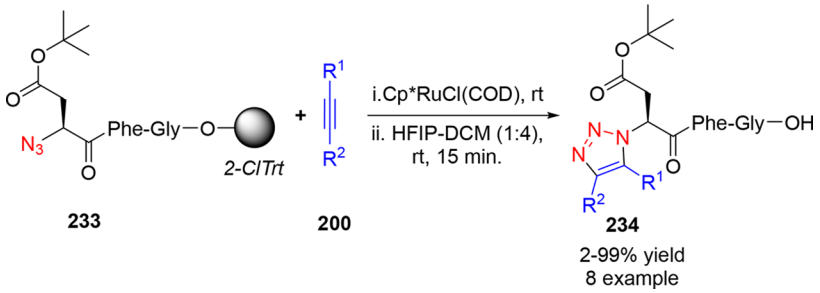
2.2.3. Raney-Nickel-Catalyzed Synthesis. Surya Prakash Rao and co-workers[104] developed a regioselective method of 1,4-disubstituted triazole **216** at 45 °C using a Raney nickel catalyst and toluene solvent from **2** and propargylic ether **215** with excellent yield (Scheme 49). An additional reducing agent was not needed in this reaction with Raney nickel. Here, alkyl and aryl acetylene gave a good yield. However, the NiAAC reaction of propargyl alcohol and phenyl azide yielded the 1,4- and 1,5-regioisomers in a 3:2 ratio with a 93% yield. Without any catalyst, this reaction also produced the 1,4- and 1,5-regioisomeric adducts in a 3:2 ratio; however, it needed 2 min of microwave heating to 140 °C in PEG-200 (polyethylene glycol-200). Per the mechanistic study, Raney Ni serves as a coordinating species in azide and alkyne cycloaddition reactions, and the method does not proceed through Ni acetylides.

2.2.4. Ni-rGO-Zeolite Nanocatalyzed Synthesis. Basu and co-workers[105] performed a one-pot method of 1,4-disubstituted triazole **120** with good regioselectivity in water from **1**, halides **118**, and NaN_3**44** in the presence of the stable catalyst ternary nanocomposite substance, Ni-rGO-zeolite, for 4−6 h at 90 °C (Scheme 50). For the synthesis of the nanocatalyst, they prepared hybrid GO-zeolite from 2D GO (graphene oxide) and NaY zeolite. Synthesis of the GO-zeolite complex involved the addition of NaY zeolite to an aqueous suspension of GO and increasing its pH near 7 due to protonation. The negative charge on zeolite balanced due to protonation, resulting in Al−OH−Si bridging. The reaction mass was heated at 60 °C for 16 h under gentle stirring with subsequent evaporation of H_2O and drying under vacuum. This GO-zeolite was then treated with $Ni(OAc)_2{\cdot}4H_2O$ in the presence of $NaBH_4$ under hydrothermal conditions, and the ternary nanocomposite material, Ni-rGO-zeolite, resulted. The catalyst performed up to four cycles without loss of activity.

2.3. Ruthenium-Catalyzed Azide−Alkyne Cycloaddition (RuAAC). Based on density functional theory (DFT), Boren, Lin, and Fokin described the RuAAC cycle (Figure 8) based on the computational study.[106]

*2.3.1. Cp*Ru(COD)Cl-Catalyzed Synthesis.* Goswami and co-workers[109] reported a one-pot [3 + 2]/[2 + 2 + 2], facile, and atom-economical approach for the synthesis of 2-triazolyl thio-/selenopyridines **218** and **219** from 1-alkynyl thio-/selenocyanates **217** and alkyl/aryl azides **2** using Cp*Ru(COD)Cl catalyst in THF/toluene as a solvent at 70 °C/RT conditions. Further reaction of **218** with diyne **220** in the presence of Cp*Ru(COD)Cl in EtOH yielded **222** with 26−91% yield, whereas the reaction of **217** and **2** with tetraynes

Scheme 55. Synthesis of Derivatives of 234 Using the RuCl(COD)(Cp*) Catalyst at RT



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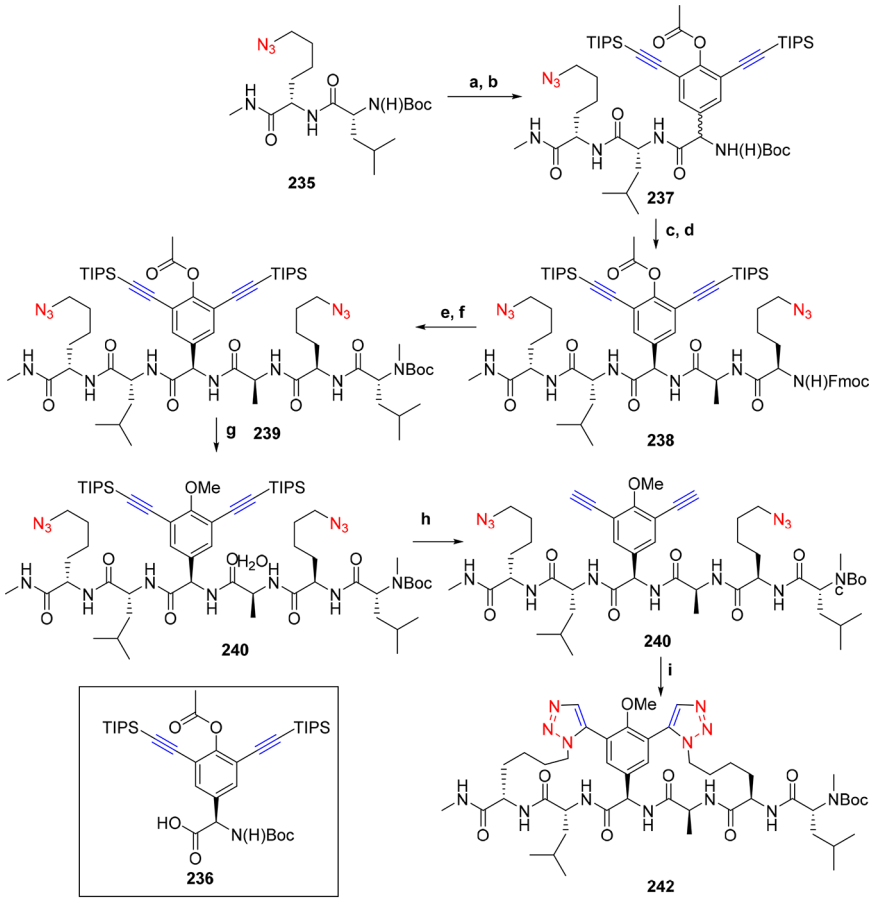
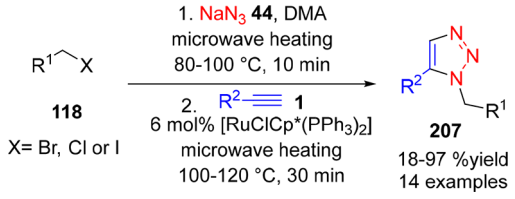
Scheme 56. $[RuCl(Cp^*)]_4$-Promoted Synthesis of 242



a) TFA/DCM, 1 h, quant.; **(b) 236**, BOP, DIPEA, DCM, 3 h; **(c)** TFA/DCM, 1 h, quant.; **(d) 237**, EDCI, HOBt, DIPEA, DCM, 4 h; **(e)** $(CH_3)_2NH$/THF, 1 h; **(f)** Boc-*N*-Me-D-Leu-OH, EDCI, HOBt (Hydroxybenzotriazole), DIPEA, DCM, 3 h; **(g)** MeI, K_2CO_3, acetone, 24 h; **(h)** TBAF/THF, MeOH, 3h; **(i)** $[Cp^*RuCl]_4$, THF/MeOH, 50 °C, 24 h.

Scheme 57. $[RuCl(PPh_3)_2(Cp^*)$ Impulsive Synthesis of 207



221 using Cp*Ru(COD)Cl in ethanol gave **223** with moderate to good yield (Scheme 51).

Song and co-workers[110] reported a regioselective synthesis of fully substituted 5-thiocyanatotriazoles **225** from thiocyanato alkynes **224** and **2** using Cp*Ru(COD)Cl catalyst in THF at RT for 12−24 h (Scheme 52). Further functionalization of **225** using TFAA (trifluoroacetic acid) and H_2O_2 at 80 °C for 24 h yielded **226**. The AAC/nucleophilic substitution cascade three-component reaction of **224** and **2** and alkyl/aryl magnesium bromide using Ru(Cp*)(COD)Cl gave **42** with moderate to good yield. This route is also fit for the synthesis of non-natural carbohydrates.

Mascareñas and co-workers[45] reported an orthogonal reaction for the synthesis of thio-functionalized triazole **42** using thioalkynes **209** and **2** using (Cp*)Ru(COD)Cl as a catalyst in water at RT (Scheme 53). Aliphatic azides are also suitable for this approach and gave a good yield. Also, water is replaced by some biomolecular additives, which also gave good results with this methodology.

Guo and co-workers[44] reported a mild and convenient method for the synthesis of CF_3CH_2- and CF_3S-containing 1,4,5-trisubstituted triazoles **230**−**232** from (trifluoromethyl)-thiolated alkynes **227** and **228** and trifluoromethylated alkynes **229** with various alkyl **2** and aryl azides **119** and **76** using (Cp*)Ru(COD)Cl catalyst at RT in benzene or toluene (Scheme 54). Also, this methodology is suitable for aryl halides, hydroxyl groups, ester, and N-, S-, and O-containing heterocyclic molecules. Regioselectivity of the reaction affords CF_3CH_2 or CF_3S at the 5-position of triazole.

Blixt and co-workers[111] developed solid-phase peptide synthesis (SPPS) of triazole peptide **234** from peptide-terminated (*S*)-(−)-4-*tert*-butyl 2-azidopeptide **233** and internal alkynes **200** using (Cp*)Ru(COD)Cl and HFIP (1,1,1,3,3,3-hexafluoroisopropanol)-DCM (1:4) at RT for 15 min. For the alkyne scope, dimethyl acetylene dicarboxylate gave <2% yield (Scheme 55).

*2.3.2. [Cp*RuCl]$_4$-Catalyzed Synthesis.* Liskamp and co-workers[112] reported a first Ru-catalyzed macrocyclization for the production of a bicyclic 1,5-triazole-bridged vancomycin CDE ring **242** from amino-acid-containing azides **235** and pentapeptide-containing alkynes **237** using $[RuCl(Cp^*)]_4$ catalysts (Scheme 56). In this method, the two ether bridges of bicyclic vancomycin CDE ring were replaced by 1,5-disubstituted triazole.

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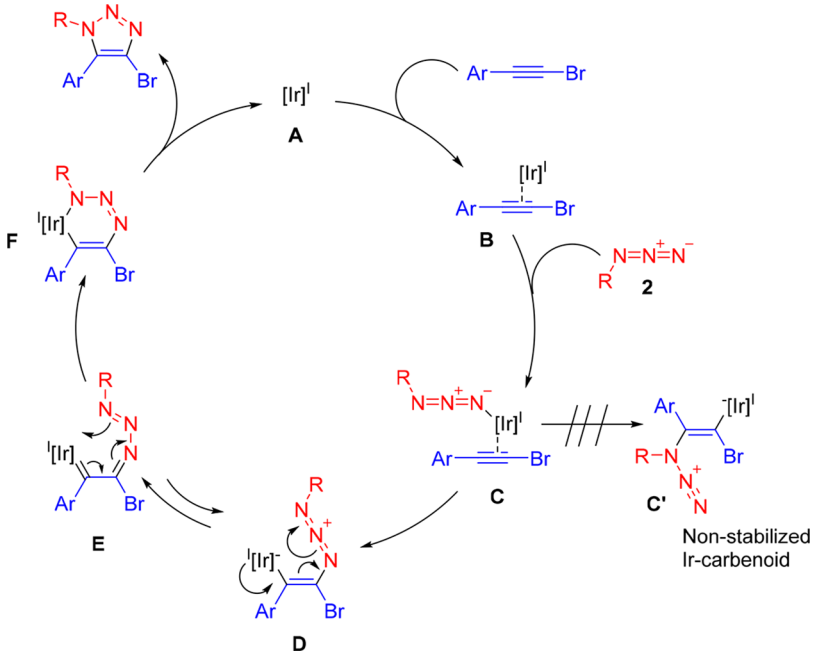
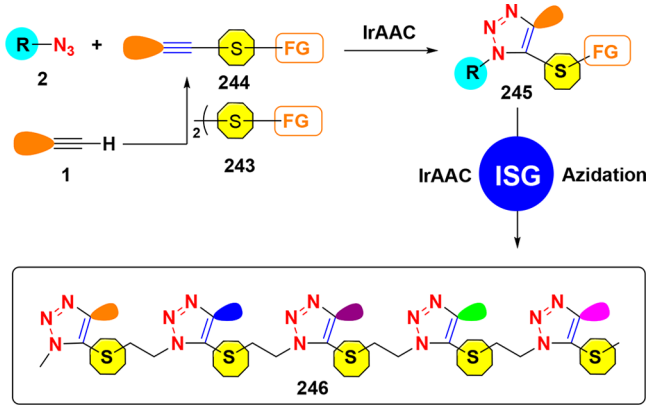
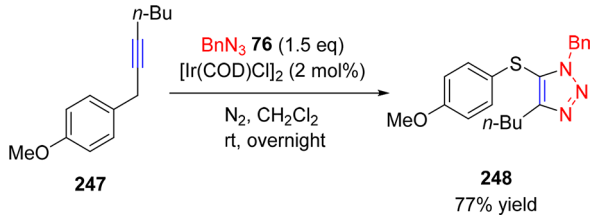


Figure 9. Postulated mechanism of IrAAC. Reprinted from ref 114. Copyright 2013 American Chemical Society.

Scheme 58. $[Ir(COD)Cl]_2$-Catalyzed Synthesis of 246



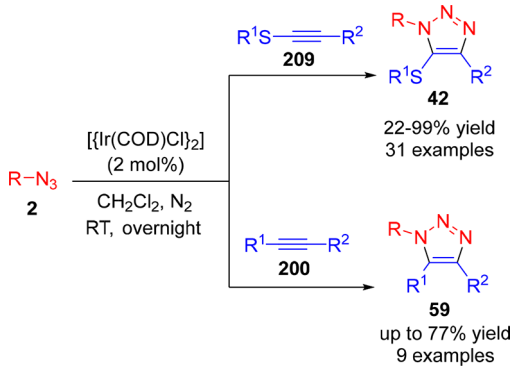
Scheme 59. Iridium-Catalyzed Synthesis of 248 in DCM at RT under a N_2 Atmosphere



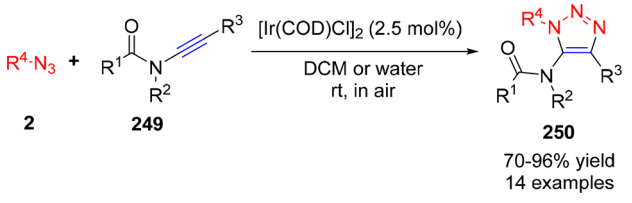
2.3.3. [RuClCp(PPh$_3$)$_2$]-Catalyzed Synthesis.* Johansson and co-workers[113] developed a one-pot two-step methodology for the synthesis of 1,5-disubstituted-1*H*-1,2,3-triazole **207** from **1**, alkyl halide **118**, and NaN_3**44** using [RhClCp*-(PPh_3)$_2$] under MW heating at 100 °C for 30 min (Scheme 57). The secondary alkyl halide did not give any reaction even at a high temperature. An acidic-group-containing alkyl halide is not a suitable substrate for this methodology.

2.4. Iridium-Catalyzed Azide−Alkyne Cycloaddition (IrAAC). A proposed mechanism for IrAAC reaction of alkyne **196** and azide **2** shown in Figure 9. First, Ir(I) complex **A**

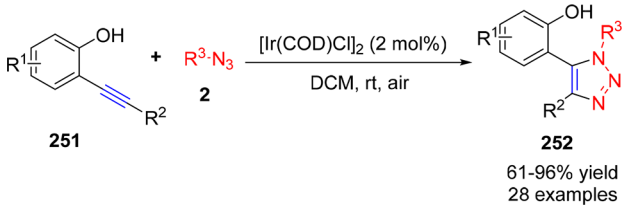
Scheme 60. Synthesis of 42 and 59 and Their Derivatives through an Ir Catalyst



Scheme 61. Preparation of 250 and Its Derivatives Using $[Ir(COD)Cl]_2$ as a Catalyst



Scheme 62. Synthesis of 252 and Its Derivatives Using Ir-Based Azide−Alkyne Cycloaddition



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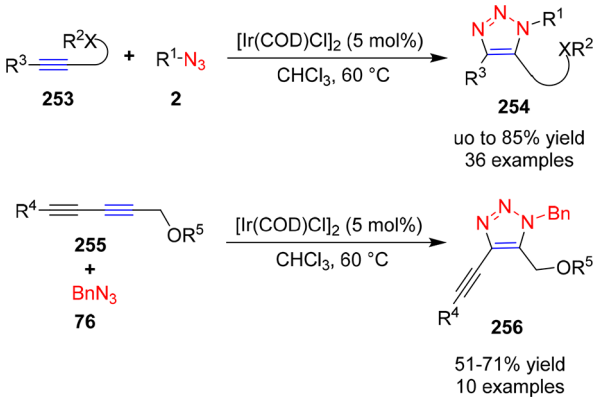
Scheme 63. Synthesis of 254 and 256 by Utilizing $[Ir(COD)Cl]_2$ as a Catalyst



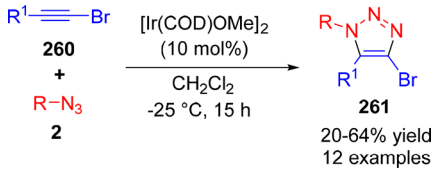
triggered the alkyne, which led to the generation of the alkynyl complex **B** as the CuAAC mechanism.[115] Then the terminal nitrogen of azide had an electrophilic center after coordination with metal, which led to the formation of stabilized Ir carbenoids **C** and **C′**. Subsequent Ir [3 + 2] cycloaddition underwent "Cope-like" cyclization, and **D** and **E** yielded metallacycle **F**,[114] which finally led to the production of the titled product **197**.

2.4.1. [Ir(COD)Cl]$_2$-Catalyzed Synthesis. Ding and co-workers[116] reported a novel, simple, efficient, and sequence-defined polytriazole **246**. First, **1** converted into internal thoialkynes **244** by reacting with **243**. **244** reacted with **2** in the presence of an Ir catalyst to give 5-thio-functionalized 1,2,3-triazole **245**. **245** further underwent an iterative sequential growth (ISG) method for the formation of polytriazole **246** (Scheme 58). Various functional groups were incorporated at the C4 position of the triazole scaffold. The C−S bond is easily detected by tandem mass spectrometry analysis due to the cleavage of a relatively weak C−S bond.[117−119]

Gao and co-workers[120] reported a synthesis of fully substituted 5-thiotriazoles **248** from alkynyl thioether **247** and benzyl azide **76** using $[Ir(COD)Cl]_2$ catalyst and CH_2Cl_2 overnight in a N_2 atmosphere at RT to give 81% yield (Scheme 59). **247** can be easily synthesized from bench-stable, rapidly prepared, and easily activated *N*-alkynylthiophthalimide and 4-methoxyphenylmagnesium bromide via thioester, which under subsequent acid hydrolysis yielded the desired compound **247**.

Sun and co-workers[121] reported a first electron-rich internal alkyne for the synthesis of 5-thiotriazole **42** and fully substituted triazoles **59** using **2** and internal thoialkynes **209** as well as internal alkynes **200** using $[Ir(COD)Cl]_2$ catalysts and dichloromethane at RT, respectively (Scheme 60). Diverse

Scheme 65. Synthesis of Analogues of 261 Using $[Ir(COD)OMe]_2$ Catalysts in DCM



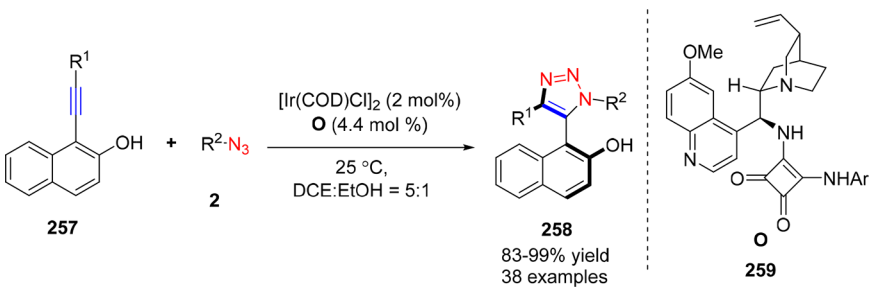
aryl and alkyl azides are suitable for the approach as well as for enhancing steric hindrance on internal thoialkynes **209**, which also did not affect the reaction efficiency. Due to mild reaction conditions, alcohol, ester, aryl halides, ethers, THP-, and silyl-protected alcohols and phthalimide- and Boc-protected amines were also tolerated in this approach. For internal alkynes, they reported that electron-donating and neutral alkynes gave poor yield with greater regioselectivity. Also, prop-1-yn-1-ylbenzene, 1,2-diphenylethyne, and 1,2-diphenylethyne gave a trace amount of yield (<5%), whereas hex-3-yne showed very low conversion.

Song and co-workers[122] developed a highly regioselective, mild, bioorthogonal strategy for the synthesis of fully substituted 5-amidotriazole **250** from ynamides **249** and **2** using $[Ir(COD)Cl]_2$ catalysts with DCM or aqueous conditions at RT (Scheme 61). Cyclic and acyclic ynamide work well with the approach; the electron-rich cyclic ynamide gave a slightly higher yield, while the electron-deficient group gave a slightly low yield. If the adjacent position of ynamide ($-R^2$) was substituted by a bulky group, the reaction yield decreases.

Cui and co-workers[123] reported a mild, efficient, and hydroxyl group synthesis of fully substituted triazole **252** from alkynes **251** and **2** using $[Ir(COD)Cl]_2$ catalysts in DCM at RT (Scheme 62). With the achievement of the cycloaddition of **252** with **2**, they predicted that a hydroxyl group of internal alkynes would work as a directing group.[124−128] For the substrate scope of alkynes, they found that alkyl alkynes gave a yield comparatively less than that of aryl alkynes. Aliphatic alcohol-containing alkynes did not give any reaction,[128] whereas the *meta*-substituted phenolic group gave a very low yield.

Song and co-workers[129] reported excellent regio- and chemoselective synthesis of 5-ether triazoles **254** and **256** from internal alkynes **253** and **255** with azides **2** and **76** using $[Ir(COD)Cl_2]_2$ catalysts in chloroform at 60 °C for 12−24 h (Scheme 63). Upon further investigation, they found that the yield dramatically decreases with an increase in the steric hindrance.

Scheme 64. Synthesis of 258 Using an Ir Catalyst



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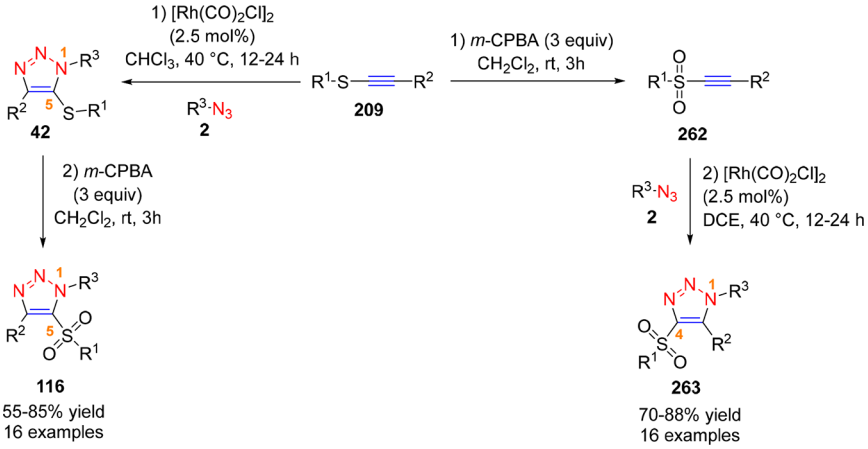
Scheme 66. Regiodivergent Synthesis of 116 and 263



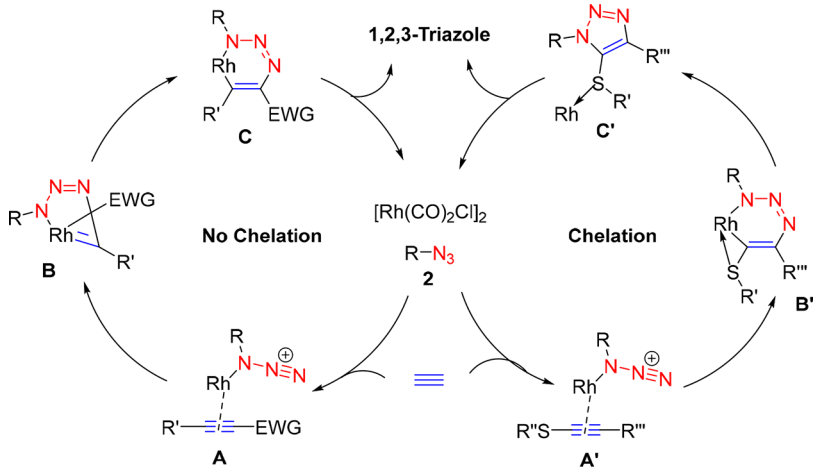
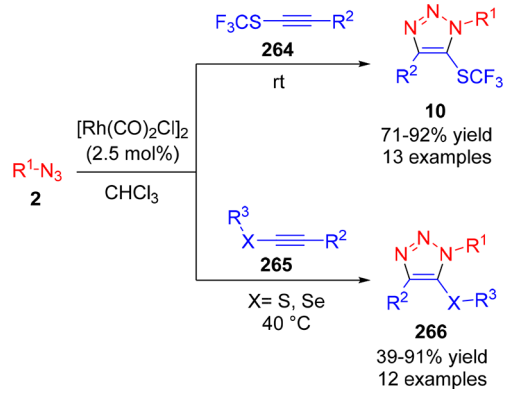
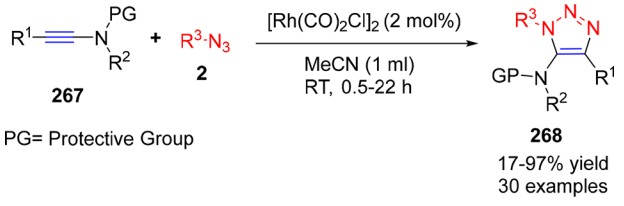


Figure 10. Mechanistic cycle of the Rh catalyst.[32,132] Reprinted with permission from ref 32. Copyright 2020 John Wiley and Sons.

Scheme 67. $[Rh(CO)_2Cl]_2$-Promoted Synthesis of 10 and 266 and Their Derivatives



Scheme 68. Open Flask Approach to Synthesize 268 and Its Derivatives Using RhAAC



Xu and co-workers[130] reported a first atroposelective approach for the synthesis of axially chiral aryl triazole **258** from internal alkynes **257** and azides **2** using Ir(I)/squaramide (**O**) **259** and DCE/EtOH (5:1) at 25 °C (Scheme 64). The optimum asymmetric induction was achieved with quinidine squaramide (**O**) and Ir(I). Other metals such as Cu(I) and Pd(II) are not suitable metal catalysts for this reaction, and organocatalysts (**O**) by themselves did not generate any product. The result suggested that both organocatalysts and metal catalysts are a necessity for the reaction. When the epimer of **O** (quinine-derived squaramide **O′**) was applied with the Ir(I)/squaramide (**O**) catalyst, the configuration-reversed product (*aR*) was formed in excellent yield with 3:97 er in standard conditions. Sterically hindered mesityl azide is also a suitable substrate for this approach that results in great enantioselectivity. The reaction was completely stopped when the −OH group of alkynes was protected, suggesting that the VQM (vinylidene *ortho*-quinone methide) intermediate was probably formed by the organocatalyst. Here, the VQM bifunctional ligands provide hydrogen bonding interactions with ketone. Therefore, the C−N bond determines the stereoselectivity of the approach.[131]

2.4.2. [Ir(COD)OMe]$_2$-Catalyzed Synthesis. Taran and co-workers[114] reported a synthesis of 4-bromo-1,5-substituted triazoles **261** using bromoalkynes **260** and **2** using [Ir(COD)-

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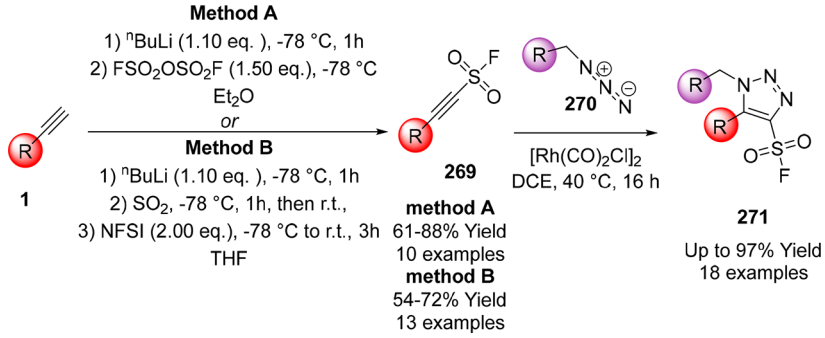
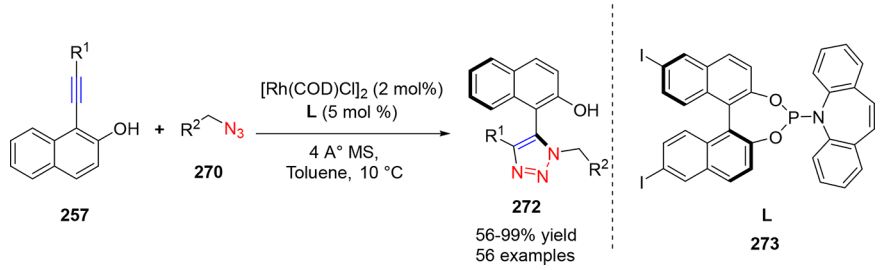
Scheme 69. Use of $[Rh(CO)_2Cl]_2$ as a Promoted Synthesis of 271



Scheme 70. Synthesis of Axially Chiral Triazole 272



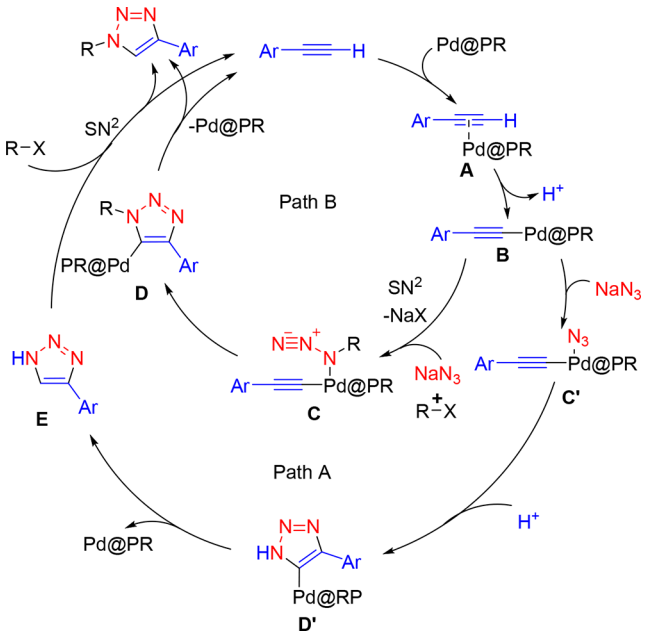
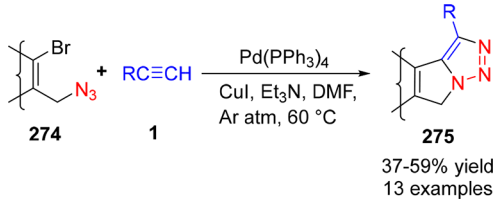


Figure 11. Mechanistic cycle for the Pd catalyst.[137,138] Reprinted with permission from ref 137. Copyright 2015 Royal Society of Chemistry.

Scheme 71. Synthesis of 275 with Its Derivatives through Sonogashira Coupling Using $Pd(PPh_3)_4$



OMe]$_2$ catalysts in dichloromethane at −25 °C for 15 h (Scheme 65). For the substrate scope of the reaction, they found that electron-donating aryl alkynes gave a good yield compared to that with an electron-withdrawing group, and this approach is also suitable for sulfur-containing scaffolds but is affected by the steric effect.

2.5. Rhodium-Catalyzed Azide−Alkyne Cycloaddition (RhAAC). *2.5.1. $[Rh(CO)_2Cl]_2$-Catalyzed Synthesis.* Zheng and co-workers[132] reported a one-pot and regiodivergent synthesis of fully substituted 4-sulfonyl-1,2,3-triazole **263** and 5-sulfonyl-1,2,3-triazole **116** using the RhAAC reaction. Here, the regioselectivity of the reaction is controlled by nonmetallic sulfur(II) and sulfur(VI), giving 4- and 5-sulfonyl-functionalized products, respectively (Scheme 66).[106] For the synthesis of **263**, internal thioalkynes **209** oxidized using *m*-CPBA gave internal sulfonyl alkyne **262**, which further reacts with azide using $[Rh(CO)_2Cl]_2$ and DCE at 40 °C for 12−24 h. The electronic effect of aryl substituents does not affect the regioselectivity and yield, but *p*-nitrophenyl-substituted derivatives gave a slightly lower yield (73%). For the synthesis of **116**, the first internal thioalkyne **116** undergoes the RhAAC reaction to yield 5-sulfur-1,2,3-triazole **42**, which further oxidized into 5-sulfonyl-1,2,3-triazole **116**. Here, **263** followed the nonchelation path, while **116** followed the chelation path (Figure 10).

Song and co-workers[133] reported a regioselective approach for the synthesis of fully substituted 5-thiotriazoles **266** and fully substituted 5-trifluoromethylthiotriazoles **10** from internal thioalkynes **265** and internal alkynyl trifluoromethyl sulfides **264** with **2** at 40 °C and RT, respectively (Scheme 67). They used $[Rh(CO)_2Cl]_2$ as a catalyst and $CHCl_3$ as a solvent. They investigated the substrate scope of the reaction between **264** and **2** in which they found that various fully substituted 5-trifluoromethylthiotriazoles **10** were synthesized at RT without an inert gas medium in good yield and excellent regioselectivity. Yields were similar, and no significant electronic effects were observed. However, the yield of the corresponding compound was lower when *p*-nitrophenylethynyl(trifluoromethyl)sulfane was used as the

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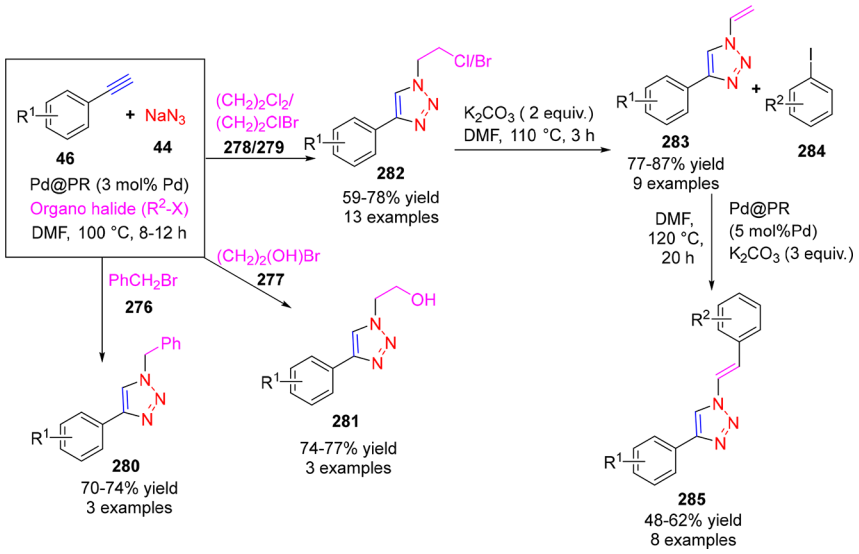
Scheme 72. Synthesis of 280−283 and Their Derivatives Using Polystyrene Resin-Supported Pd(0) Nanocomposites



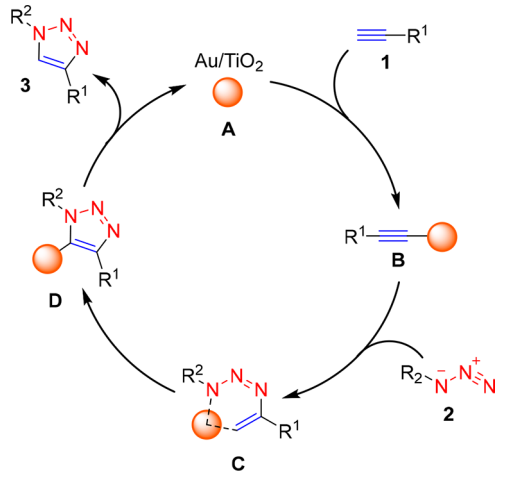


Figure 12. Au/TiO_2-catalyzed cycloaddition.[140,141] Reprinted from ref 140. Copyright 2013 American Chemical Society.

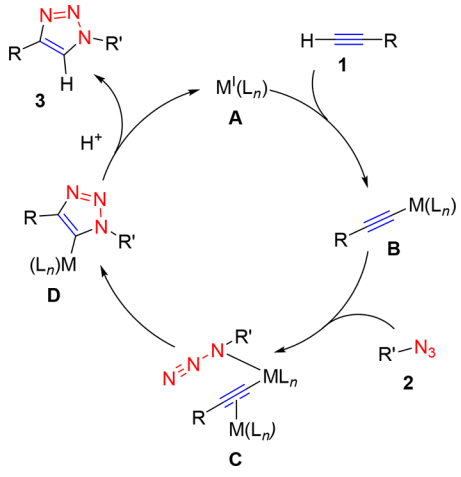
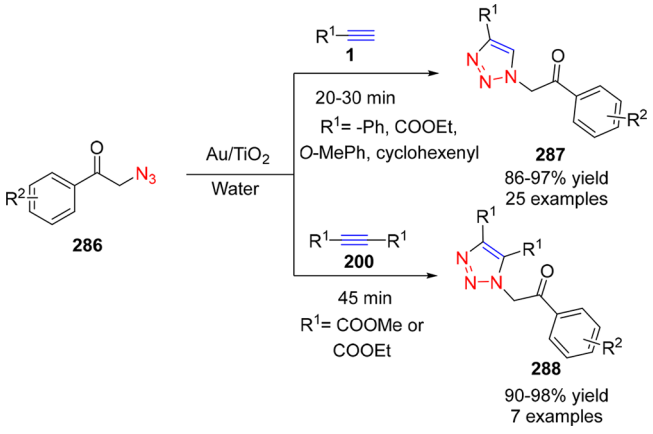
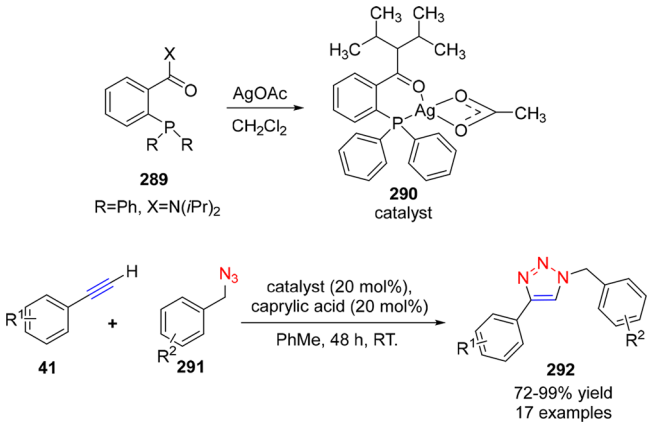


Figure 13. Mechanistic cycle of AgAAC. Reprinted with permission from ref 144. Copyright 2011 John Wiley and Sons.

Scheme 73. Utilizing Gold-Titania Nanocomposites to Prepare 287 and 288



Scheme 74. Silver-Catalyzed Azide−Alkyne Cycloaddition to Form 292



reactant, but the regioselectivity was excellent. The RhAAC reaction could also be carried out with good yields using *ortho*- and *meta*-substituted phenylacetylenes. Due to a combination of unfavorable electronic as well as steric effects with a prolonged reaction time and higher temperature, the reaction for alkyl-substituted **264** did not occur. The expected compound could be produced with good yield and high regioselectivities when alkyl or aryl azides were used as

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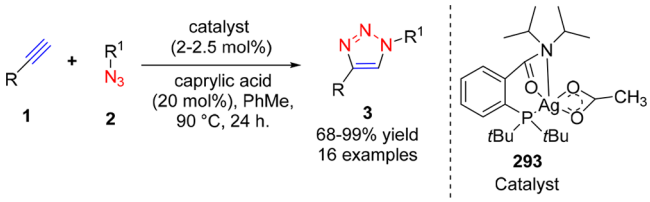
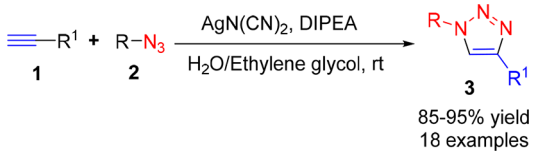
Scheme 75. Formation of 3 Using the Homogeneous Silver(I) Catalyst 293



Scheme 76. $AgN(CN)_2$, DIPEA-Catalyzed Synthesis of 3 in Aqueous Glycol at RT



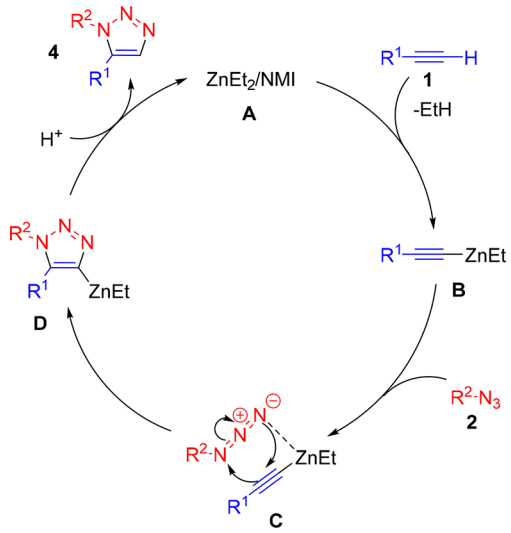
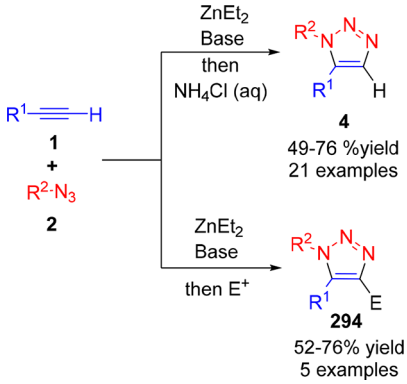


Figure 14. Proposed mechanistic for ZnAAC. Reprinted from ref 147. Copyright 2013 American Chemical Society.

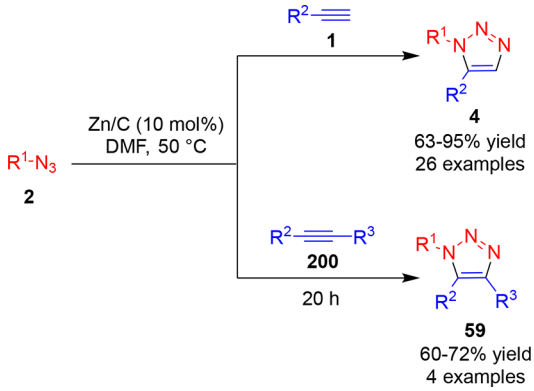
Scheme 77. Regioselective Synthesis of 4 and 294 Using $ZnEt_2$



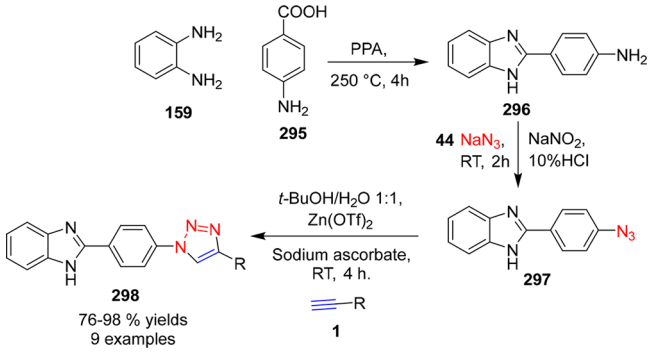
substrates. This approach tolerated a broad range of functional groups, including halogen, ester, and carbonyl groups. The yield was drastically reduced when aryl azides were employed instead of alkyl azides.

Li and co-workers[134] reported the first rhodium(I)-catalyzed open flask approach for the synthesis of 5-aminotriazoles **268**

Scheme 78. Use of Zn/C as a Heterogeneous Catalyst to Synthesize 4 and 59



Scheme 79. Synthesis of 298 Using $Zn(OTf)_2$ Catalyst



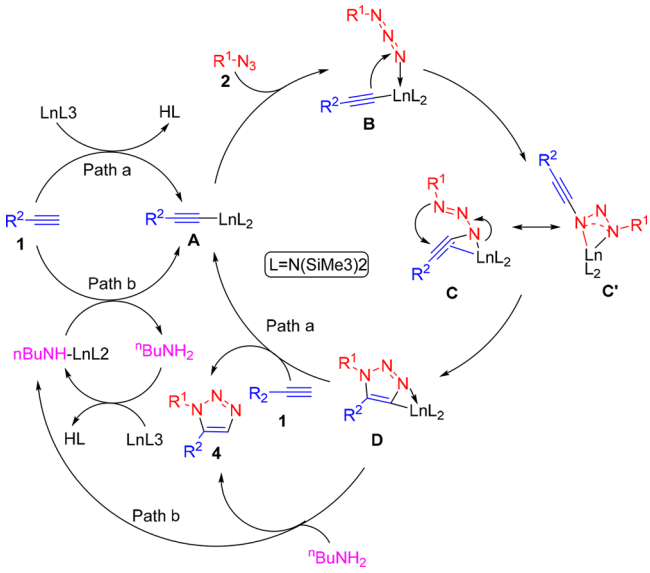
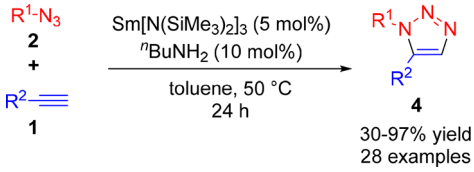


Figure 15. Proposed mechanism for SmAAC reaction[153,154] Reprinted with permission from ref 153. Copyright 2013 Royal Society of Chemistry.

Scheme 80. $[Sm[N(SiMe_3)_2]_3$-Promoted Synthesis of 4



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from internal ynamides **267** and **2** using $[Rh(CO)_2Cl]_2$ catalysts and MeCN as a solvent at RT for 0.5−22 h (Scheme 68). They also reported that exclusion of air and moisture was not necessary because the reaction maintains similar efficiency with an open flask. This approach was also carried out with a variety of solvents without any discernible change in the reaction yield. The reaction outcomes were unaffected by ynamides with different protective groups. Interestingly, the reaction of ynamides with the nosyl group proceeded successfully, producing a triazole with an 84% isolated yield. The prolonged reaction time is most likely due to the nosyl group's strong electron-withdrawing group properties. Regardless of the electronic nature, the reaction of *para*-methyl, methoxy, trifluoromethyl, and chloro-substituted ynamides produced the appropriate triazoles in excellent yields when compared to those with the standard ynamide. The *meta*- and *ortho*-substitution on the phenyl ring was also tolerated. The ynamides with a heteroaromatic ring or an extra alkenyl moiety were found to be good substrates for the RhAAC reaction.

Moses and co-workers[135] reported 2-substituted alkynyl-1-sulfonyl fluorides (SASFs) **269** as a new class of connective hubs. Stereoselective DOC (diversity-oriented clicking) of SASFs **269** with azide **270** showed various 1,5-substituted 1*H*-1,2,3-triazole-4-sulfonyl fluorides **271** in the presence of $[Rh(CO)_2Cl]_2$ catalysts and DCE solvent for 16 h at 40 °C (Scheme 69). Method A was effective with the electron-poor substrate but ineffective for electron-rich substrate caused by separation problems, while method B is effective for electron-rich reactants.

2.5.2. $[Rh(COD)Cl]_2$-Catalyzed Synthesis. Li and co-workers[136] reported an unprecedented and challenging approach for five-membered atropisomerism of 1,2,3-triazole **272** as chiral units. Axially chiral 1,4,5-substituted 1,2,3-triazole **272** was synthesized from internal alkyne **257** and azides **270** using enantioselective Rh catalyst, ligand (**L**) **273**, and 4 Å MS (molecular sieves) in toluene at 10 °C for 10 h (Scheme 70). Here, employment of 4 Å MS enhanced the enantioselectivity and efficiency of E-RhAAC. This approach showed excellent functional group tolerance, as well as electronic properties of the substituent of the aryl rings, but does not affect the enantioselectivity and efficiency of E-RhAAC. Based on a DFT study and experimental observation, it was found that the hydroxy group plays an important role in regioselectivity.

2.6. Palladium-Catalyzed Azide−Alkyne Cycloaddition (PdAAC). Mechanistically, there are two paths A and B for this PdAAC reaction. Both paths A and B are expected to lead to the title product. Surface-bound Pd-alkyne complex **A** collapses to produce complex **B**, which might lead through either pathway A or pathway B. These pathways are characterized by the earlier (path A) and later (path B) substitution reaction step using organohalide. Meanwhile, treatment of commercially available 4-phenyl-1*H*-1,2,3-triazole with 1,2-dichloroethane under the same condition did not yield 1-(2-chloroethyl)-4-phenyl-1*H*-1,2,3-triazole, ruling out pathway A (Figure 11).[137,138]

2.6.1. $Pd(PPh_3)_4$-Catalyzed Synthesis. Kar and co-workers[139] reported the synthesis of 1,2,3-triazolopolyhydroarenes/cycloalkenes **203** class using tandem Sonogashira coupling−CuAAC reaction. **275** was synthesized by Pd(0)−Cu(I)-catalyzed intramolecular heteroannulation of 2-/1-azidomethyl-1-/2-bromodihydronaphthalenes/arene/cycloalkenes **274** and **1** using catalyst $Pd(PPh_3)_4$, cocatalyst CuI, and Et_3N as the base at 60 °C using DMF as a solvent in an inert atmosphere (Scheme 71). This efficient method gave moderate to good yields of up to 59% and required 8−10 h for completion. This approach is very helpful for the synthesis of potential bioactive fused triazoloarenes.

2.6.2. Pd@PR Nanocatalyzed Synthesis. Das and co-workers[137] developed an efficient method for synthesizing 4-aryl-1-alkyl-1*H*-1,2,3-triazoles **280, 281** and **282** from selective monoazidation of 1,2-dihaloethane **278**/**279**, 2-bromoethanol **277** and benzyl bromide **276** with sodium azide **44** and terminal aryl alkynes **46** using Pd@PR (polystyrene resin-supported palladium[0]) nanocomposite and DMF as a solvent for 8−12 h at 100 °C, respectively. **282** further reacted with K_2CO_3 and DMF at 110 °C for 3 h, giving the corresponding *N*-vinyl derivatives **283**. Pd@PR-catalyzed Heck coupling reaction of **283** with aryl iodide **284** in the presence of K_2CO_3 and DMF at 120 °C for 20 h gave 4-aryl-1-(2-arylalkenyl)-1*H*-1,2,3-triazoles **285**. In addition, Pd@PR-catalyzed MW-assisted dehydrohalogenative Heck coupling expanded the scope of *N*-vinyl-1*H*-1,2,3-triazole **283** (Scheme 72). The aryl alkynes with electron-releasing and electron-withdrawing functional groups produced the same yields comparatively. Both heteroaromatic and polyaromatic alkynes were suitable for this phenomenon. Under identical reaction conditions, 1-bromo-2-chloroethane in place of DCE generated an indivisible mixture of corresponding Cl and Br derivatives in moderate yield. Due to more prevalent SN^2 at the C−Br center, a higher percentage of chloro derivatives was produced. This novel phenomenon can provide outstanding examples of Pd@PR nanocomposite catalytic efficiency and selectivity as well as industrial interest.

2.7. Gold-Catalyzed Azide−Alkyne Cycloaddition (AuAAC). Au cycloaddition followed a stepwise mechanism as in the previous report[141] in which due to Au(I) active metal ion **A**, the electron density of alkynes is decreased. So, azide undergoes nucleophilic attack on **B**,[142,143] which leads to the formation of six-membered intermediate **C**. Finally, **3** was derived by the removal of gold from **D** (Figure 12).[141]

2.7.1. Au/TiO_2 Nanocatalyzed Synthesis. Muthusubramanian and co-workers[140] reported the green, efficient, and regioselective synthesis of 1,4-disubstituted triazoles **287** and **288** from substituted phenacyl azide **286** with terminal/internal alkynes **1**/**200** using porous Au/TiO_2 nanoparticles in water at RT for 20−30/45 min, respectively (Scheme 73). They also reported that solvents such as THF, DMSO, and ethanol showed moderate yields, and water or ^{t}BuOH/water resulted in remarkable yields as a single regioisomer, whereas *p*-xylene, 1,2-dichloroethane, acetonitrile, and toluene offered poor yields. Researchers further investigated that a stepwise technique for the synthesis of triazoles performed better than a one-pot MCR using azide **286**, phenacyl/alkyl bromide, and **1** in 75% yield for 30 min. The catalyst was synthesized using the deposition−precipitation method and used up to five cycles without remarkable loss in the yield. For the substrate scope of alkynes, they found that aliphatic and aromatic alkynes with electron-withdrawing and electron-donating groups were suitable for this approach.

2.8. Silver-Catalyzed Azide−Alkyne Cycloaddition (AgAAC). A mechanistic cycle of the AgAAC reaction is discussed below (Figure 13). The active catalyst **A** is formed by losing electrons from $18e^-$ molecules, which generates ligated silver(I) acetylide **B**. Nucleophilic interaction of azide **2** with **B** produces intermediate **C**, which is indicated as a $16e^-$ system, in which nitrogen migrates to carbon, carrying both

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electrons to produce metalated triazole **D**,[145] which leads to targeted molecule **3** on protonation and regenerates the active catalyst.

2.8.1. Ag(I)-Complex-Catalyzed Synthesis. McNulty and co-workers[144] reported a novel, mild, regioselective, and the first purely silver-catalyzed azide−alkynes cycloaddition (AgAAC) reaction for the synthesis of 1,4-disubstituted triazoles **292** from azides **291** and alkynes **41** using a 2-diphenylphosphino-*N*,*N*-diisopropylcarboxamide-ligated silver-(I)acetate complex as catalyst **290**, caprylic acid, and PhMe at RT for 48 h (Scheme 74). Catalyst **290** was synthesized using silver(I)acetate with the amide of the tunable 2-diphenylphosphinobenzoic acid ligand **289** and CH_2Cl_2. They found that the hemilabile nature of the P,O-type ligand may play an important role in cycloaddition because Ag(I) salts alone did not give cyclization products. This hemilabile nature of the ligand may contribute to opening coordination sites for azide complex formation and provide electron density to the alkyl bond via metal to achieve cyclization.

McNulty and co-workers[145] developed a well-defined, chemically stable, highly effective homogeneous silver(I) **293** catalyst for the regioselective synthesis of 1,4-disubstituted triazole **3** from **2** and **1** using caprylic acid and PhMe at 90 °C. The reaction required 24 h for completion (Scheme 75). This approach provides a broad substrate scope as well as a catalyst that can be reused three times without noteworthy loss in product.

Sarma and co-workers[146] reported a highly efficient, robust, as well as novel approach for the regioselective synthesis of **3** from **2** and **1** catalyzed by highly efficient silver dicyanamide/DIPEA using H_2O/ethylene glycol at RT for 2−6 h (Scheme 76). For the substrate scope of alkynes, they found that aromatic alkyne gave slightly more yield (90−97%) compared to aliphatic alkyne (90−94%). Various functional groups containing alkynes such as alcohol and ester are also suitable substrates for this approach.

2.9. Zinc-Catalyzed Azide−Alkyne Cycloaddition (ZnAAC). Based on a deuterated study[148] and according to the proposed mechanistic study of the ZnAAC reaction, transformation initially metalizes the alkyne C−H due to amine base, and formation of zinc acetylide **B** occurs.[149,150] Azide **2** attack on acetylide accelerated the generation of a six-membered intermediate **C**. After a subsequent reaction of **D** with an electrophile, desired product **4** was obtained (Figure 14).[147]

2.9.1. $ZnEt_2$-Catalyzed Synthesis. Greaney and co-workers[147] reported a regioselective synthesis of **4** from **1** and **2** using $ZnEt_2$ as a catalyst and NH_4Cl at RT for 72 h (Scheme 77). At high temperatures, the reaction gave less yield due to the decomposition of the reactant. For the alkyne substrate scope, they found that ester, thioether, propargylic ether, 1,2-diphenyl acetylene, and (iodoethynyl)benzene were suitable, whereas for the azide scope, tosyl azide and alkyl azide were not suitable for this approach. However, substitution at the 4-position was also observed by replacing NH_4Cl with D_2O/D_3CCO_2D through a 3-MCR coupling reaction to afford 1,4,5-trisubstituted triazole. The above approach takes 18 h for completion at ambient temperature.

2.9.2. Zn/C-Catalyzed Synthesis. To overcome the problem of separation of homogeneous catalysts from products and relatively few advancements done on heterogeneous solid catalysts, Chen and co-workers[151] develop a novel, mild, and heterogeneous Zn/C (zinc on charcoal)-catalyzed approach for the synthesis of **4** and **59** from **2** with aryl alkynes **1** and **200**, respectively (Scheme 78). They also found that aprotic and polar solvent DMF was a suitable solvent, and 50 °C was the suitable temperature for this approach. Zn dust typically contains Cu(II) impurities, whereas charcoal might be reduced from Cu(II) to Cu(I). They thought that a trace amount of CuI produced in situ catalyzed cycloaddition instead of Zn/C, but no cycloaddition products were observed. It is suggested that Zn/C could catalyze the reaction. They also reported that electron-deficient aryl alkynes gave less yield than electron-rich substituents, and that aliphatic alkynes did not cause a reaction. This approach was also performed under a one-pot, three-component reaction that produced less yield. The reaction required 15−20 h, and the efficiency of the catalyst decreased after the fifth cycle.

2.9.3. $Zn(OTf)_2$-Catalyzed Synthesis. Eppakayala and co-workers[152] developed a simple and efficient synthesis of novel benzimidazole-linked triazoles **298** from 2-(4-azidophenyl)1*H*-benzo[*d*]imidazole **297** and alkynes **1** using *t*-BuOH/H_2O, $Zn(OTf)_2$, and NaASc at RT. For the synthesis of compound **297**, *o*-phenylenediamine **159** and 4-aminobenzoic acid were reacted in the presence of PPA at 250 °C for 4 h, yielding compound **296**, which further reacted with sodium azide **44** to obtain desired **297** azides (Scheme 79).

2.10. Lanthanide-Catalyzed Azide−Alkyne Cycloaddition (LnAAC). A possible chemical path for the $Ln[N(SiMe_3)_2]_3$-catalyzed cycloaddition of **1** with azide is shown in Figure 15.[153] Activation of the C−H bond of **1** proceeds through the generation of lanthanide acetylide **A** and release of $HN(SiMe_3)_2$. The important intermediates (**C** and **C′**) are formed by the coordination and subsequent 1,1-insertion of azide into the Ln−C bond of **A**.[155] Following that, the distant N atom's intramolecular anti-nucleophilic interaction on a *p*-coordinated alkyne moiety would result in the generation of triazole complex (**D**). Then protonation of **D** with another alkyne results in triazole **4** and the regeneration of lanthanide acetylide **A**. On the other hand, path b might be used to complete the catalytic cycle.

2.10.1. $Sm[N(SiMe_3)_2]_3$-Catalyzed Synthesis. Zhou and co-workers[153] reported a first organolanthanide-/rare-earth-metal-catalyzed cycloaddition with broad substrate scope, mild conditions, and easily available catalyst. They synthesized **4** from **2** and **1** using $Sm[N(SiMe_3)_2]_3$, $^nBuNH_2$, and toluene at 50 °C for 24 h with good to excellent yield (Scheme 80). This catalytic approach differentiates internal and terminal alkynes. It also exhibits novel mechanistic characteristics such as a tandem anionic cascade cyclization reaction and antiaddition across the C≡C triple bond. For the substrate scope, they found that aryl azides are more reactive than alkyl azides because the aryl ring promotes the delocalization of negative charge to its neighboring N atom via conjugation, leading to an increased nucleophilicity of the N atom during the cyclization process. Noncoordinated substituents at the *para*-position of aromatic azides had little effect on the reaction. *o*-Methoxyphenyl azide formed in moderate yield, which might be due to the chelating coordination capable of increasing the bond between the Ln−N kinetic inertness and thermodynamic stability. Furthermore, the competitive coordination of nitro to the metal caused a decrease in yield. Moreover, the reactivity of alkyne is lowered by the strong chelating coordination of the pyridyl group. They also observed that 1-azido-4-(azidomethyl)benzene formed mono- and dicyclized com-

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pounds, depending on the stoichiometric amount of alkyne, while hexa-1,5-diyne gave only monocyclization product.

3. ORGANOCATALYTIC SYNTHESIS OF 1,2,3-TRIAZOLE

Heavy metals in biological systems have been linked to cellular toxicity, oxidative damage, and metabolic instability.[156] To

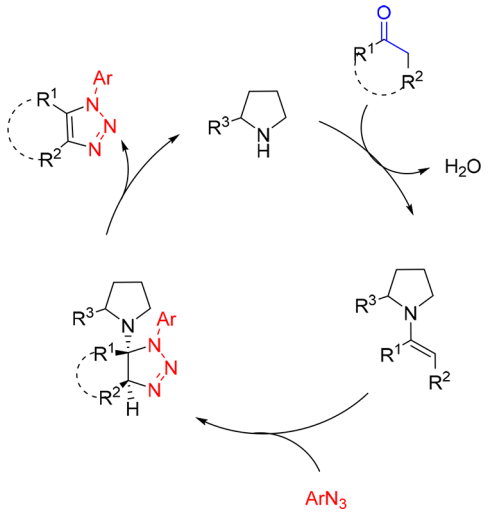
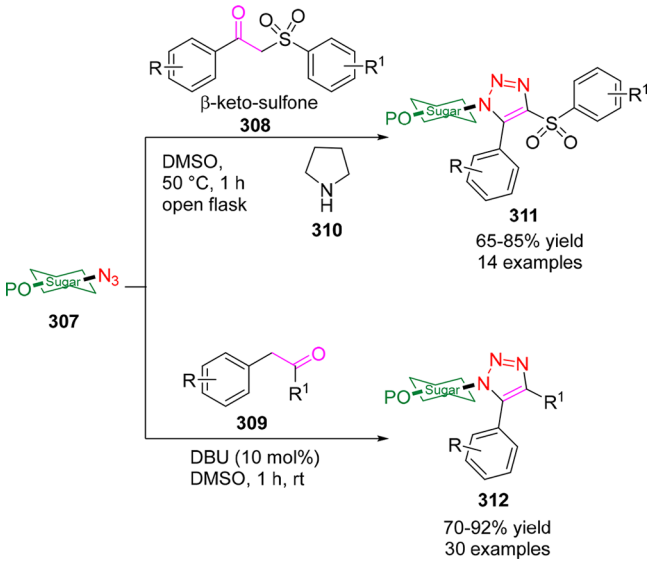


Figure 16. Organocatalytic synthesis of 1,2,3-triazole.[160,161] Reprinted with permission from ref 160. Copyright 2011 John Wiley and Sons.

date, several metal-free (3 + 2) cycloaddition methods have been reported to synthesize numerous functionalized 1,2,3-triazoles. As a result, considerable scientific efforts have been put toward the evolution of a metal-free approach for the synthesis of triazoles in mild conditions. Organocatalysts have recently received a lot of interest in comparison with metal catalysts.[157,158] To accelerate the chemical reaction, organocatalysis employs a small organic moiety mostly consisting of C, P, N, O, H, and S. So, if we compared it with transition metal catalysts, the benefits of organocatalysis include their lack of sensitivity toward moisture and oxygen, their inexpensive, lower toxicity, and ready availability.[159] In 2008, Ramachary and co-workers[167] reported the first organocatalyzed method for the synthesis of triazole. Later on, Bressy

Scheme 82. DBU and Pyrrolidine-Catalyzed Synthesis of 311 and 312

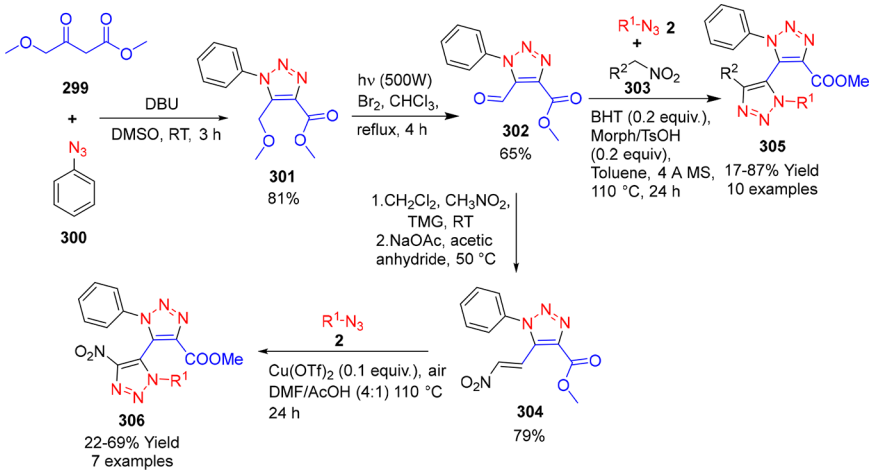


and co-workers[160] reported a synthesis of triazole using unactivated ketones, which becomes a solution for avoiding even trace amounts of metal residues in the final product. Here, we covered DBU, L-proline, diethylamine, pyrrolidine, and prolinamide-catalyzed approaches for the synthesis of 1,2,3-triazole.

Organocatalyzed synthesis is useful for metal-free as well as a one-pot combination of MCRs. Here, ketones are used as a surrogate of alkyne for enamine formation and various fully functionalized 1,2,3-triazoles, which are only obtained intermediately (Figure 16).[160,162,163] According to the catalyst screening done by Wang and co-workers,[161] in addition to a secondary amine, primary and tertiary amines do not show significant catalytic activity and gave very low yields of 26 and <5%, respectively.

3.1. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)-Catalyzed Synthesis. Dehaen and co-workers[164] describe a novel approach for the synthesis of nonsymmetrical 5,5′-*C*,*C*-linked bi-1,2,3-triazoles **305** and **306** from 5-formyl-1,2,3-triazole **302**. 5-Methoxybenzyl analogue **301** was easily synthesized from methyl 4-methoxyacetoacetate **299** and phenyl azide **300**

Scheme 81. DBU-Catalyzed Synthesis of Triazoles 305 and 306



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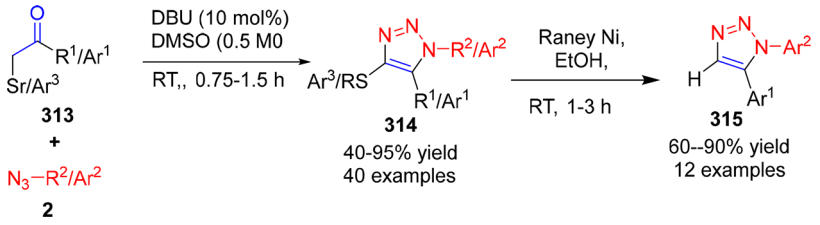
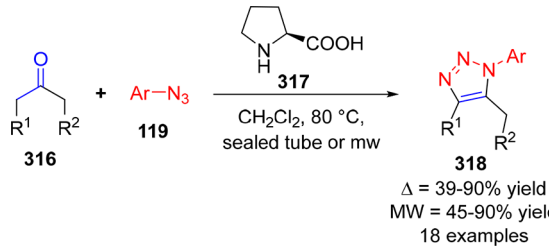
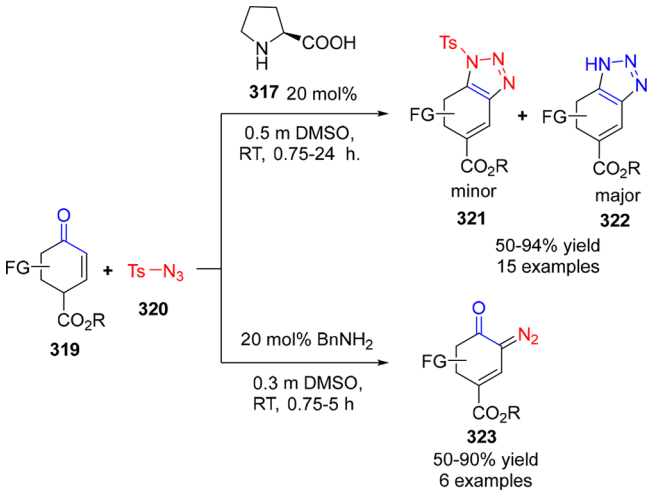
Scheme 83. DBU-Promoted Synthesis of 314 and 315



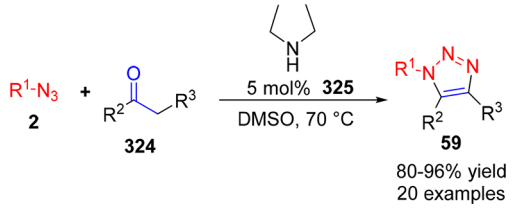
Scheme 84. L-Proline-Catalyzed Synthesis of 318



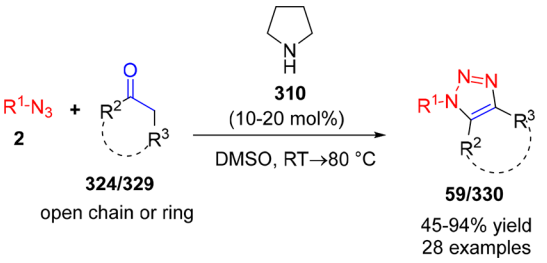
Scheme 85. Synthesis of 322 via L-Proline



Scheme 86. Synthesis of 59 and Its Derivatives Using Et_3N Catalyst in DMSO



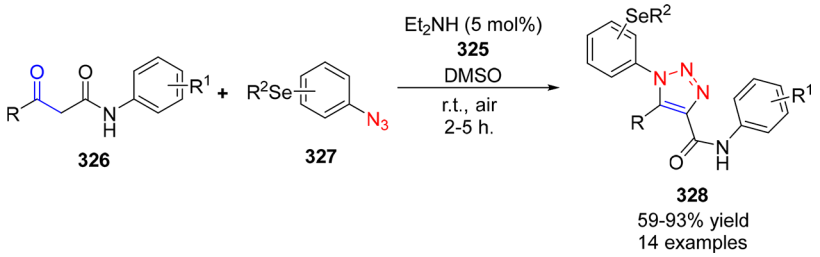
Scheme 88. Pyrrolidine-Mediated Synthesis of 59/330



using DBU and DMSO at ambient temperature for 3 h (Scheme 81). A subsequent photochemical conversion of **301** with bromine yielded **302** with a 65% yield. Aldehyde **302** was further transformed into nitroalkene derivatives **304** via oxidative [3 + 2] cycloaddition reaction. This aldehyde **302** and nitroalkene **304** are used as a reactant for the synthesis of axially chiral unsymmetrical tetra-*ortho*-substituted 5,5′-bi-1,2,3-triazoles **305** and **306**, respectively. More steric hindered *ortho*-substituents prevent atropisomerism. Both approaches showed a broad scope for alkyl and aryl azide with various functional groups.

Mandal and co-workers[165] developed a regioselective, efficient, straightforward, as well as environmentally friendly protocol for the synthesis of sulfonyl-1,2,3-triazolyl glycoconjugates **311** and completely substituted 1,2,3-triazolyl glycoconjugates **312** from glycosyl azides **307**, *β*-keto sulfone **308**, and substituted phenyl aldehyde **309** using DMSO in an open flask at 50 °C for 1 h and DBU and DMSO for 1 h at RT, respectively (Scheme 82). For the DBU-promoted reaction, they found that aprotic polar solvents such as DMSO and DMF gave a good result compared to that with MeOH and CH_3CN (30% yield). They also reported that DMF with DBU gave 85% yield, whereas DMSO with DBU resulted in 92% yield. These results clearly showed that the formation of reactive enolates occurs, and DABCO, benzylamine-like less basic tertiary amine, gave moderate yield compared to that with DBU, while Et_3N in DMSO did not have a reaction after 24 h at RT.

Scheme 87. Development of Analogues of 328 Using Diethyl Amine Catalyst in DMSO at RT



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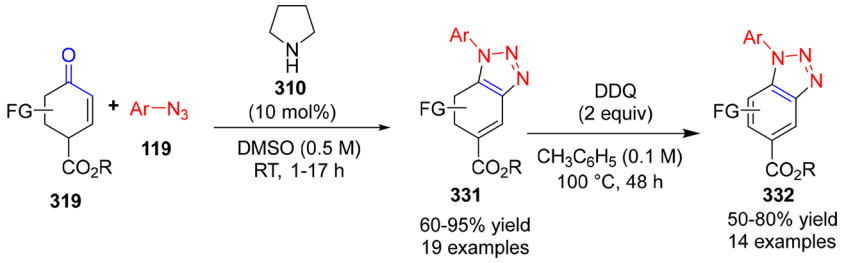
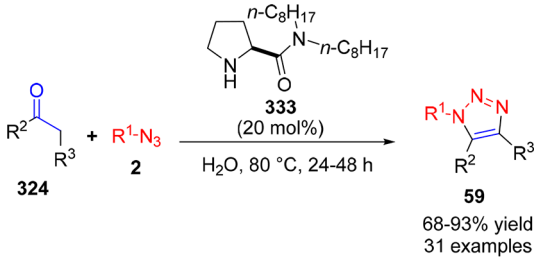
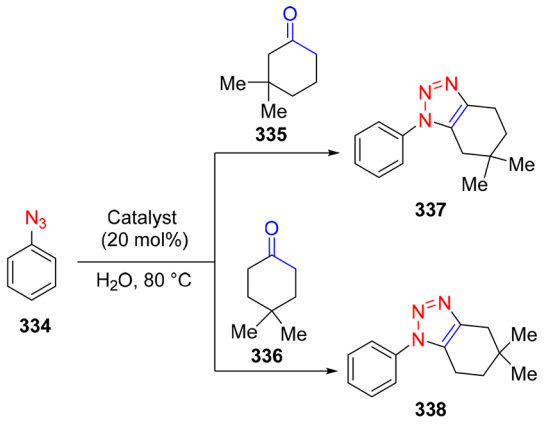
Scheme 89. Synthesis of Derivatives of 332 through the Use of Pyrrolidine Catalyst



Scheme 90a. Use of Proline Amide as a Catalyst to Synthesize 59 and Its Derivatives



Scheme 90b. Prolinamide-Catalyzed Synthesis of 337 and 338



Ramachary and co-workers[166] reported a regiospecific and mild DBU-catalyzed synthesis of **314** and its derivative **315**. Ketones **313** and azides **2** reacted with DBU and DMSO at RT for 0.75−1.5 h to synthesize **314**, which further reacted with Raney Ni and EtOH at RT for 1−3 h to obtain **315** (Scheme 83).

3.2. L-Proline-Catalyzed Synthesis. Bressy and co-workers[160] reported a highly substituted triazole **318** from unactivated ketone **316** and aryl azides **119** using L-proline **317** as an organocatalyst and dichloromethane at 80 °C under thermal conditions (Scheme 84). All cyclic ketones gave good yields. Among all the cyclic ketones cyclooctane gave a higher yield, and the dissymmetrical cyclic ketone showed excellent regioselectivity. They also reported that 4-(NO_2)PhN_3 as well as acetophenone did not react through this approach. Here, the reaction's regioselectivity depends on a combination of two factors. First, regioselectivity results from the preferred form from two enamine intermediates, and second, the regioselectivity is caused by the addition of azide to the enamine.

Ramachary and co-workers[167] reported the first *N*H-1,2,3-triazoles **321** and **322** from Hagemann's ester **319** and *p*-toluenesulfonyl azide **320** using amino acid (L-proline) catalyst **317** and DMSO as a solvent at RT for 0.75−24 h (Scheme 85). This approach gave **322** as a major product. If the reaction proceeds with $BnNH_2$ and DMSO, it yields diazo compound **323** as a major product.

3.3. Diethylamine-Catalyzed Synthesis. Wang and co-workers[162] reported the first metal-free, regioselective, and organocatalyst-promoted enamide−azide cycloaddition reaction using diethylamine **325** as a catalyst. 1,4,5-Trisubstituted 1,2,3-triazole **59** was synthesized from *β*-ketoester **324** and azides **2** using DMSO as a solvent at 70 °C with 80−96% yields (Scheme 86). Also, this approach is useful for various functional groups like ester, ketone, and nitrile for further synthetic applications. Without affecting the yields, the electron-donating group required a longer time compared to the electron-withdrawing group. However, alkyl azide is also a suitable substrate for this approach but required 10 mol % catalyst loading.

Alves and co-workers[168] reported a mild, efficient, and novel approach for a wide range syntheses of (arylselanyl)-phenyl-1*H*-1,2,3-triazole-4-carboxamides **328** from *β*-oxo-amides **326** and aryl azidophenyl selenides **327** using diethylamine **325** catalyst and DMSO at RT for 2−5 h (Scheme 87). For the substrate scope of *β*-oxo-amides, they reported that the electron-deficient group nearer to the oxo position (−R) decreased the yield, while the EWG or EDG group on the amide aromatic ring ($-R^1$) gave a good isolated product. However, when they performed a reaction with a strong electron-withdrawing group such as R^1 = $-NO_2$, only 59% desired product was obtained. For the aryl azidophenyl selenide scope of this reaction, they found that the electron-EWG-containing aromatic ring ($-R^3$) gave good yields compared to those with the EDG. This approach may be useful in the future for the synthesis of novel selenium-containing triazole scaffolds.

3.4. Miscellaneous Organocatalysts. *3.4.1. Pyrrolidine-Catalyzed Synthesis.* Wang and co-workers[161] reported a Huisgen [3 + 2] cycloaddition-promoted enamine-catalyzed method for the synthesis of highly substituted triazoles **59**/**330** using **2** and acyclic/cyclic carbonyl compounds **324**/**329** using pyrrolidine **310** as a catalyst and DMSO at up to 80 °C with complete regioselectivity (Scheme 88). This approach gave moderate to good yield with a very vast substrate scope (28 examples) and was useful for further sophisticated heterocyclic scaffolds. Both cyclic and acyclic ketone compounds gave a good yield with this approach; however, the acyclic ketone gave a good yield compared to that with the cyclic ketone. They also reported that the reaction of TsN_3 with cyclohexanone in the presence of L-proline did not react, while the pyrrolidine-catalyzed reaction gave an 85% yield.

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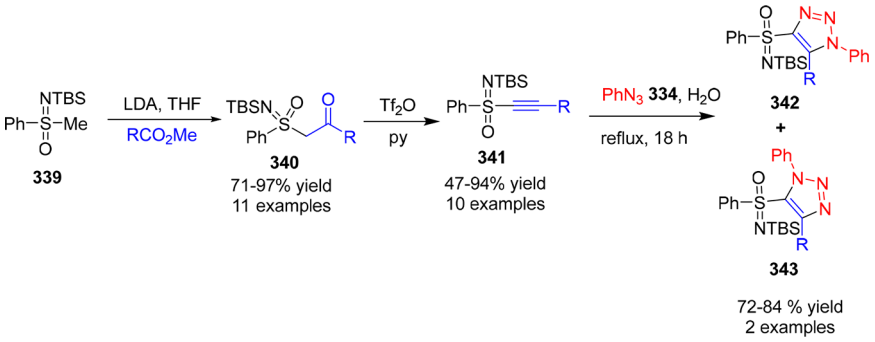
Scheme 91. Regioselective Synthesis of Triazoles 341 and 343 Using LDA Base



Ramachary and co-workers[163] developed a one-pot combination of MCR pyrrolidine **310** catalyzed functionalized bicyclic *N*-aryltriazole **332** from activated cyclic enone **319** and aryl azides **119** using DMSO as a solvent at RT for 1−6 h (Scheme 89). For the azide scope of the method, they found that the electron-withdrawing group and neutral azides resulted in good to excellent yields. However, 4-MeOC$_6$H$_4$N$_3$ did not react even at a higher temperature. The predicted bicyclic *N*-aryltriazole was obtained in good to excellent yields from aliphatic and aromatic unmodified cyclic enones. The aryl substitution at the C6 position of cyclic enone enhanced the yield, while aliphatic substitution lowered the yield and increased the reaction time.

3.4.2. Prolinamide-Catalyzed Synthesis. Wang and co-workers[169] reported a green, enamine-catalyzed, and more feasible method for the synthesis of triazole **59** from cycloaddition of ketones **324** and **2** using water as a solvent. To access a vast library of 1,2,3-triazoles, a longer aliphatic chain-tolerated prolinamide **333** was used as an effective organocatalyst to fully drive the Huisgen 1,3-dipolar cycloaddition (Scheme 90a). This catalyst is effective as a broad substrate scope for the reaction.

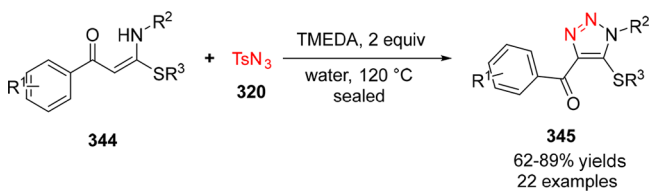
Cyclic ketones with six- to eight-membered rings are suitable substrates for this approach, and naphthalene is a suitable substrate for the azide scope of this reaction.

They also reported that dissymmetrical cyclic ketone has a high level of regioselectivity (Scheme 90b). For example, 3,3-dimethylcyclohexanone **335** resulted in a single regioisomer **337** because the heterocycle is sterically separated from the *gem*-dimethyl group, while the isomer of **335**, which is 4,4-dimethylcyclohexanone **336**, yielded **338**, which is also an isomer of **337** because cycloaddition occurs with the most stable enamine to explain the regioselectivity.

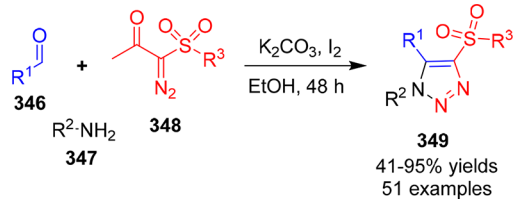
4. METAL-FREE SYNTHESIS OF 1,2,3-TRIAZOLE

Apart from this organocatalysis method, some simple, green, general, efficient, and convenient metal-free approaches are developed for the various types of functionalized triazole derivatives. Some of the reactions are important for the

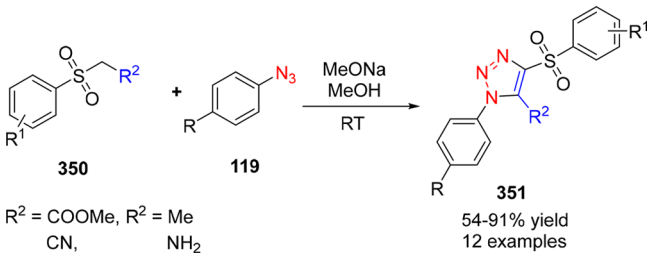
Scheme 92. Green Synthesis of 345 Using TMEDA



Scheme 93. Synthesis of 349 under Metal-Free Conditions



Scheme 94. Synthesis of 351 Using a Base Catalyst



synthesis of thiolated and sulfone-functionalized-1,2,3-triazoles. For example, Wan and co-workers[170] reported a metal-free, organic solvent-free, and easy synthesis of 5-thiolated 1,2,3-triazole. Mohanan and co-workers[171] reported mild as well as metal-free synthesis of a sulfone-functionalized triazole scaffold. These methods involve some base, solvent, ionic liquid, and molecular iodine.

Harmata and co-workers[172] reported an experimentally convenient synthesis of *N*-TBS-*S*-alkynyl sulfoximines **341** from sulfoximines **339** and methyl ester (RCO$_2$Me) using LDA as a base, THF, Tf$_2$O, and pyridine with good to excellent yield. Further utilization of **341** with **334** in H$_2$O at reflux for 18 h gave a mixture of regioisomers of 1,4,5-trisubstituted triazoles **342** and **343** with a good yield (Scheme 91). They also reported that the steric influence controls the regioselectivity of the reaction.

Wan and co-workers[170] reported a metal-free synthesis of sulfur-containing triazole **272** from easily available tosyl azide **320** and *β*-thiolated enaminones **344** using TMEDA as a base and water in a sealed tube at 120 °C (Scheme 92). This approach has broad substrate scope with excellent yield. The use of water as the only medium[173−176] provided a greener route without interfering with any trace amount of metal toxicity.

Mohanan and co-workers[171] reported a metal-free, mild reaction for the synthesis of fully substituted sulfonyl triazole **349** from benzaldehyde **346**, primary amine **347**, and *α*-diazo-*β*-keto sulfone **348** using K$_2$CO$_3$, I$_2$, and EtOH at RT for 48 h

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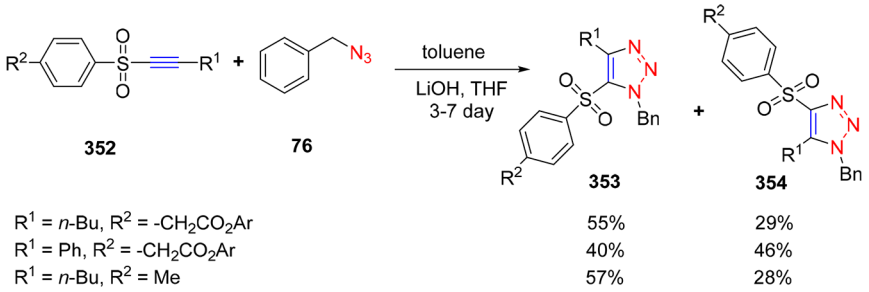
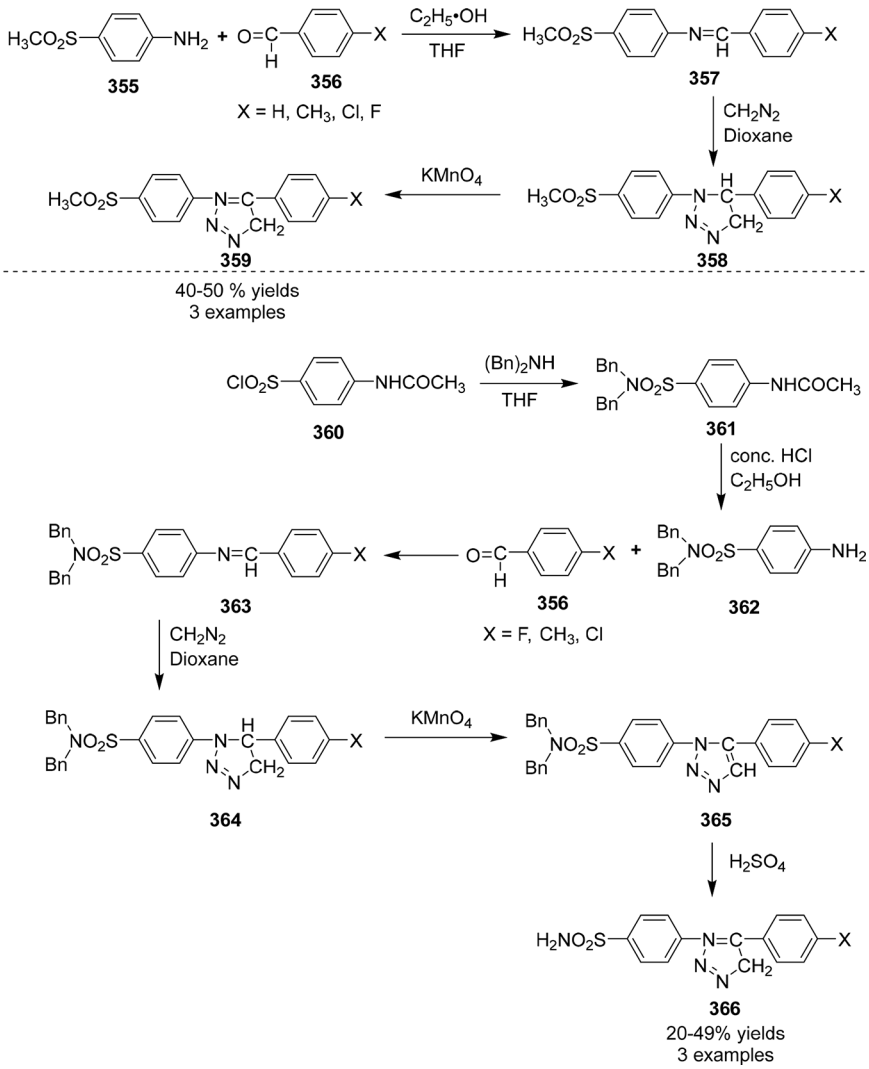
Scheme 95. Synthesis of 353 and 354 from Acetylenic Sulfones



Scheme 96. Synthesis of 359 and 366



(Scheme 93). For the substrate scope of the approach, they determined that aryl aldehyde containing and electron-deficient group did not react because of rapid hydrolysis of imine, and heteroaryl and bi- and trisubstituted aryl aldehyde were also suitable for this approach. Aliphatic, aromatic, as well as sterically crowded primary amine are suitable for this reaction and gave moderate to good yield.

Pokhodylo and co-workers[177] reported a base-catalyzed cycloaddition of β-keto sulfone/β-nitrile sulfones **350** and aryl azides **119** using MeONa and MeOH at RT to synthesize 1*H*-1,2,3-triazol-4-yl sulfones **351** with moderate to good yield for 2−5 h (Scheme 94). These molecular libraries are very useful for biological activity testing. The internal electrophile in β-keto sulfone or β-nitrile sulfone might be a carbonyl or cyano group. Also, sulfonyl azides were employed for diazo transfer to the CH-acid moiety, specifically for activated β-keto ester and β-keto sulfones.[178,179] In this approach, enolate or enol attacks the **119**, and the formation of triazene occurs, which combines with the diazo moiety and sulfonamide after tautomerization.

Back and co-workers[180] reported a cycloaddition reaction of acetylenic sulfones **352** and benzyl azide **76** using toluene,

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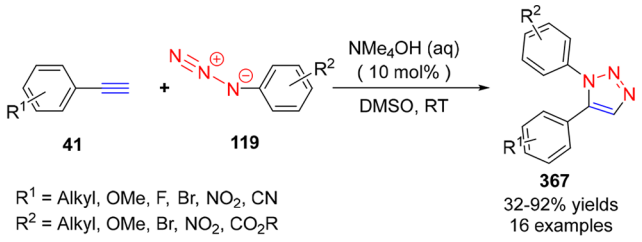
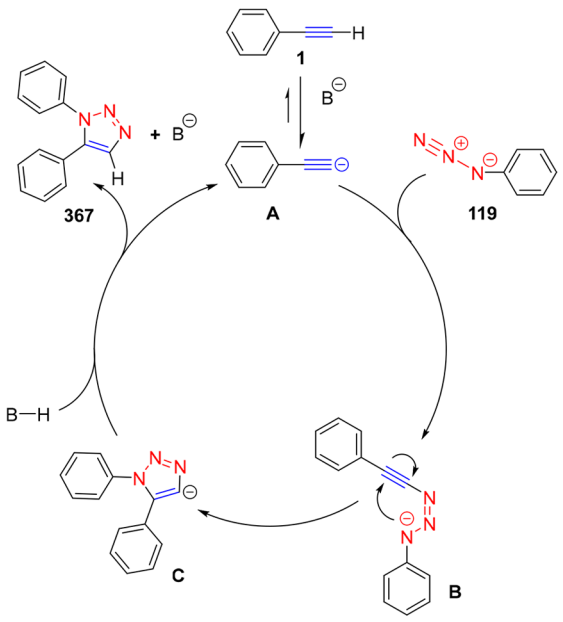
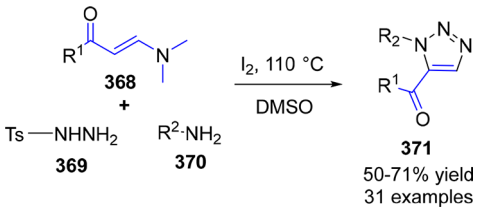
Scheme 97. Regioselective Synthesis of 367 by NMe_4OH and DMSO

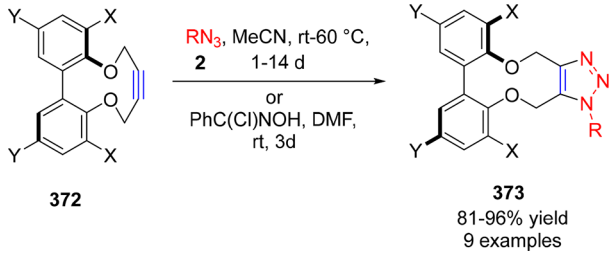




Scheme 98. Synthesis of 371 Using Molecular Iodine



Scheme 99. Strain-Promoted Synthesis of 1,2,3-Triazole 373



LiOH, and THF for 3−7 days for the synthesis of 1,4,5-trisubstituted triazole isomers **353** and **354** (Scheme 95).

Shafii and co-workers[181] reported the synthesis of 1-(4-aminosulfonylphenyl)-5-aryltriazoles and 1-(4-methylsulfonylphenyl)-5-aryltriazoles **359** as COX-2 inhibitors. First, they prepared an imino compound **357** by the reported method,[182] but it did not work. So they performed this reaction in a mixture of ethanol/THF from 4-methylsulfonylaniline **355** and substituted benzaldehyde **356** to afford compound **357** with a good yield (Scheme 96). According to the literature, subsequent 1,3-cycloaddition of **357** with diazomethane in ether also did not provide a cyclization product.[183] Ultimately, cycloaddition was achieved with diazomethane in dioxane/water[184] to obtain 1-(4-methylsulfonylphenyl)-5-aryl-4,5-dihydro-1*H*-1,2,3-triazoles **358**. Subsequent oxidation of **358** with potassium permanganate in acetone gave a low yield[185] of product of **359** but achieved moderate yield (40−52%) with a phase transfer catalyst (tetrabutylammonium chloride).[186] For the synthesis of 1-(4-aminosulfonylphenyl)-5-aryltriazoles, the $-NH_2$ bearing imino compound did not undergo cycloaddition with diazomethane in dioxane. Therefore, 4-acetamidobenzenesulfonyl chloride was reacted with dibenzyl amine in THF followed by acid hydrolysis to obtain compound **362**, which further reacted with substituted benzaldehyde in *p*-toluenesulfonic acid to give imino compound **363**. Further reaction of **363** gave **364**, which further oxidized in the presence of $KMnO_4$ to give compound **365**. Deprotonation of compound **365** yielded the desired product 1-(4-aminosulfonylphenyl)-5-aryltriazoles **366** with 20−49% yield.

Fokin and co-workers[187] reported a mild, transition-metal-free approach for the synthesis of 1,5-disubstituted triazole **367** from terminal aryl alkynes **41** and aryl azides **119** using tetraalkylammonium hydroxide in DMSO at RT (Scheme 97). For the substrate scope, it was found that aryl, heteroaryl, terminal alkynes, and base-labile functional groups are suitable for the reaction. Due to the low acidity, alkyl acetylene did not provide any yield under this condition.[188] Electron-deficient azides and alkyne both gave lower yields due to ineffective triazenide cyclization and a decrease in nucleophilicity.

The aryl acetylide **A** formed by reversible deprotonation of the **41** reacts as a Nu^- for an attack on the terminal nitrogen of aryl azide **119** and forms triazenide intermediate **B**, which undergoes 6π-electrocyclization or 5-endo-dig cyclization to generate the 1,5-disubstituted triazolyl anion **C** and achieves the catalytic cycle by deprotonation of DMSO, water, or a terminal alkyne to form **367**.

Wan and co-workers[189] developed a novel, regioselective, metal- and azide-free 3-MCR approach for the synthesis of 1,5-disubstituted triazole **371** using enaminones **368**, tosyl hydrazine **369**, and primary amines **370** using molecular iodine and DMSO at 110 °C (Scheme 98). For enaminones, they found that the electron-donating group containing the aryl ring gave a good yield compared to that with the electron-withdrawing group, and heteroaryl-based (thiophene) enaminones are also a suitable substrate for this reaction. Primary alkyl amine is not a suitable substrate for this reaction due to the inactive key intermediate.[190]

4.1. Strain-Promoted Azide−Alkyne Cycloaddition (SPAAC). Bioorthogonal synthesis of such chemically modified biomolecules is an emerging field of chemistry as well as biology. Besides these, the CuAAC reaction is important for such synthesis, but the cytotoxicity of the copper catalyst is still a disadvantage for bioorthogonal chemistry. To reduce this restriction, Bertozzi and co-workers[191,192] performed the bioorthogonal, copper-free, and strain-promoted azide−alkyne cycloaddition (SPAAC).

Wills and co-workers[193] reported a catalyst-free and strain-promoted azide−alkyne cycloaddition of strained alkynes **372** with azide **2** using MeCN at room temperature to 60 °C for 1−14 days or using PhC(Cl)NOH and DMF at room

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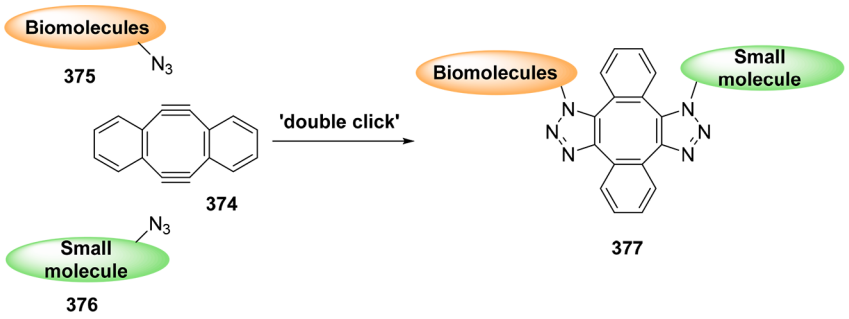
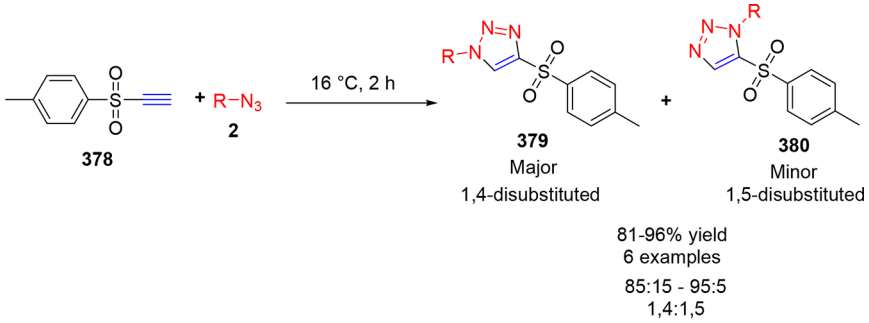
Scheme 100. Synthesis of Functionalized Triazole 377 via SPDC



Scheme 101. Solvent-Free and Catalyst-Free Synthesis of 379 and 380



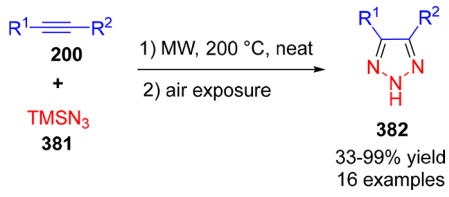
temperature for 3 days for the synthesis of functionalized triazole **373** with 81−96% yield (Scheme 99). These strained alkynes **372** were synthesized from biaryl diols and 1,4-ditosylbut-2-yne.[194]

For the versatile use of the SPAAC reaction, Kii and co-workers[195] reported a catalyst-free strain-promoted "double-click" (SPDC) reaction of Sondheimer (*sym*-dibenzo-1,5-cyclooctadiene-3,7-diyne) **374**, which has two highly strained alkyne bonds with two azido molecules, **375** and **376**, which gave the desired 1,2,3-triazole product **377** (Scheme 100). Here, they use these azido groups which are azido biomolecules (such as proteins, sugars, lipids, and nucleotides) **375** and small azido compounds (fluorescent dyes, photoreactive group, chemical ligands) **376**.

5. SOLVENT- AND CATALYST-FREE NEAT SYNTHESIS OF 1,2,3-TRIAZOLE

For utilization of greener and more simple routes for the synthesis of the titled compound, some metal-/metal-additive-free, catalyst-free, and solvent-free reactions are important because these routes do not require any purification step.

Scheme 102. Microwave-Assisted Synthesis of 382



Gouin and co-workers[196] reported a metal-free, green, and regioselective generation of 4-sulfonyl-functionalized triazoles **379** and **380** from *p*-toluene sulfonyl alkyne **378** and azides **2** at ambient temperature (Scheme 101). The strong withdrawing action of the sulfonyl group lowers the activation energy barrier for the [3 + 2] cycloaddition and allows for direct incorporation of a chemical group onto the aromatic ring for structuring the titled compound. First, the reaction mixture was dissolved in a minimum amount of dichloromethane, and then the mixture was evaporated at 16 °C under reduced pressure for 5 min and then took 2 h under MW conditions to complete the reaction with high regioselectivity. Steric hindrance does not affect the reaction time and product yield.

Surya Prakash and co-workers[197] reported a solvent- and catalyst-free microwave-assisted synthesis of 4,5-disubstituted triazoles **382** using alkynes **200** and trimethylsilyl azide ($TMSN_3$) **381** at a constant temperature of 200 °C for 1−7 h under inert conditions (Ar/N_2). After MW irradiation, the reaction vessels were introduced to air for 30 min (Scheme 102). For the alkyne substrate scope, they found that electron-deficient aromatic, electron-rich aromatic, halogenated, allylic, as well as symmetric and asymmetric substrates are also suitable for this approach. Because the polar moiety selectively absorbs MW irradiation, and nonpolar moieties are inert to it, the presence of polar moieties is necessary to attain more effective heating across the reaction, and as a result, a shorter reaction time can be expected as several polar moieties on the substrate increase. Because of the presence of the trimethylsilyl group, steric hindrance and electron-rich moieties also interfere with the reaction. This approach also provides a safe, atom-economical, as well as a more convenient route for the synthesis of the title compound.

6. CONCLUSION

This review paper analyzed the synthesis recorded in the past 21 years (2002−2022) for 1,2,3-triazole. The CuAAC reaction is the most efficient and often used bioorthogonal reaction because it possesses the majority of criteria for the click reaction and has huge applications in various fields. However, cytotoxicity is also a severe problem that has been detected in

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various types of cells. Ruthenium is a good choice for 1,5-regioisomers and has a broad substrate scope. This approach is influenced by the steric and electronic factors of the substrate. Zn and Sm are also suitable catalysts for the synthesis of 1,5-disubstituted triazole. IrAAC and RhAAC reactions have broad substrate scope as well as the same steric and electronic effect as that in the RuAAC reaction. Some other MAAC reactions have not been explored yet. Recently, organocatalysis synthesis is dominant for the title compound. Nowadays, some green and click-chemistry-based metal- and solvent-free reactions are developed. The majority of this research has been done using simple substances. A few efficient approaches for the manufacture of triazole-scaffold-containing pharmaceuticals have been recently discovered. A constant invention of new developments indicates that 1,2,3-triazoles will help lead to future organic synthesis and are useful for creating molecular libraries of various functionalized 1,2,3-triazoles.

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Author Contributions

D.P.V. and H.M.P. designed a review article collection. All authors contributed equally to the drafting.

Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

MAAC :metal-catalyzed azide−alkyne cycloaddition
CuAAC :copper-catalyzed azide−alkyne cycloaddition
NiAAC :nickel-catalyzed azide−alkyne cycloaddition
RuAAC :ruthenium-catalyzed azide−alkyne cycloaddition
IrAAC :iridium-catalyzed azide−alkyne cycloaddition
RhAAC :rhodium-catalyzed azide−alkyne cycloaddition
PdAAC :palladium-catalyzed azide−alkyne cycloaddition
AuAAC :gold-catalyzed azide−alkyne cycloaddition
AgAAC :silver-catalyzed azide−alkyne cycloaddition
ZnAAC :zinc-catalyzed azide−alkyne cycloaddition
SmAAC :samarium-catalyzed azide−alkyne cycloaddition
SPAAC :strain-promoted azide−alkyne cycloaddition
$TMSCF_3$:trifluoromethyltrimethylsilane
NPs :nanoparticles
TMSIT :trimethylsilyl-5-iodo-triazoles
TMS :trimethylsilyl
DMSO :dimethyl sulfoxide
DMF :dimethylformamide
RT :room temperature
DCM :dichloromethane
BPB :*N*-benzyl proline benzophenone
AT-CuAAC :active template Cu-catalyzed alkyne−azide cycloaddition
PCR :polymerase chain reaction
Tf :trifluoromethanesulfonyl
THF :tetrahydrofuran
β-CD-TSC@Cu :copper(I)-ion-supported thiosemicarbazide-functionalized *β*-cyclodextrin
ICP-OES :inductively coupled plasma optical emission spectroscopy
PPI :protein−protein interactions
NfN_3 :nonafluorobutanesulfonyl or nonaflyl azide
NaASc :sodium ascorbate
Cu_2O/HTNT-7 :Cu_2O nanoparticles supported on hydrogen trititanate nanotubes
ICP-MS :inductively coupled plasma mass spectroscopy
DKR :dynamic kinetic resolution
PEG-200 :polyethylene glycol-200
GO :graphene oxide
DFT :density functional theory
COD :1,5-cyclooctadiene
TFAA :trifluoroacetic acid
SPPS :solid-phase peptide synthesis
HFIP :1,1,1,3,3,3-hexafluoroisopropanol
MW :microwave
ISG :iterative sequential growth
THP :tetrahydropyranyl
Boc :*tert*-butyloxycarbonyl
SASFs :2-substituted alkynyl-1-sulfonyl fluorides
DOC :diversity-oriented clicking
ET_3N :triethyl amine
Pd@PR :polystyrene resin supported palladium[0]
DIPEA :*N*,*N*-diisopropylethylamine
$Zn(OTf)_2$:bis(trifluoromethanesulfonato)zinc
PPA :polyphosphoric acid
Ln :lanthanum
DBU :1,8-diazabicyclo[5.4.0]undec-7-ene
DABCO :1,4-diazabicyclo[2.2.2]octane
TsN_3 :tosyl azide
LDA :lithium diisopropylamide
N-TBS :*N*-*tert*-butyldimethylsilyl
Tf_2O :triflic anhydride
TMEDA :tetramethylethylenediamine
COX-2 :cyclooxygenase-2
MCRs :multicomponent reactions
$TMSN_3$:trimethylsilyl azide

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