Bachelor's thesis

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Norwegian University of Science and Technology
Faculty of Natural Sciences
Department of Chemistry

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Regioselective Azide-Alkyne Cycloaddition Towards Functionalized 1,2,3-Triazoles

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Supervisor: Bård Helge Hoff
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Preface

The bachelor project in chemistry presented in this report was conducted during the spring semester of 2024 at the Norwegian University of Science and Technology under the supervision of Professor Bård Helge Hoff. This project is a requirement for the bachelor's degree and part of 180 ECST credits. This is an original, unpublished, and independent work by S. Yasuda.

As a declaration of the use of AI-based aids, the Microsoft Word grammar checker was turned on by default in the creation of the report. No other AI tools were used unless explicitly mentioned otherwise.

Shuhei Yasuda

Trondheim, April 2024

Abstract

This theoretical literature review describes the various azide-alkyne cycloaddition (AAC) reactions and highlights their strengths and limitations. AAC is a straightforward way to prepare 1,2,3-triazole rings and is widely used in many synthesis applications because of its efficiency, versatility, and selectivity. Normally, a selective AAC requires a catalyst, and this review aims to address the important aspects known to date that will help in catalyst selection and will be useful for those who are interested in the synthesis of functionalized 1,2,3-triazoles.

Besides metal-catalyzed AAC, organocatalysts and catalyst-free AAC reactions are also examined. However, these reactions have not been well developed, and further investigation must be needed.

Contents

Symbols and Abbreviations

AAC	Azide-Alkyne Cycloaddition
AgAAC	Silver-catalyzed Azide-Alkyne Cycloaddition
AuAAC	Gold-catalyzed Azide-Alkyne Cycloaddition
BHT	Butylated Hydroxytoluene
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
COD	1,5-Cyclooctadiene
Cp	Cyclopentadiene
Cp*	1,2,3,4,5-Pentamethylcyclopentadiene
CuAAC	Copper-catalyzed Azide-Alkyne Cycloaddition
CuMeSal	Copper(I) 3-Methylsalicylate
CuOAc	Copper(I) Acetate
CuTC	Copper(I) Thiophene-2-Carboxylate
DCA	Dipolar Cycloaddition
DCE	1,2-Dichlroethane
DCM	Dichloromethane
DFT	Density Functional Theory
DIPEA	*N,N*-Diisopropylethylamine
DMA	Dimethylacetamide
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl Sulfoxide
DPPA	Diphenylphosphoryl Azide
EDG	Electron Donating Group
EWG	Electron Withdrawing Group
FDA	The United States Food and Drug Administration
*i*Pr	Isopropyl
IrAAC	Iridium-catalyzed Azide-Alkyne Cycloaddition
MAAC	Metal-catalyzed Azide-Alkyne Cycloaddition
m-CPBA	*meta*-Chloroperoxybenzoic Acid
MS	Methanesulfonyl
MW	Microwave
NBD	Norbornadiene
NHI	N-Heterocyclic Imine/Imino
NiAAC	Nickel-catalyzed Azide-Alkyne Cycloaddition
O/N	Overnight

PdAAC	Palladium-catalyzed Azide-Alkyne Cycloaddition
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
PhSMe	Thioanisole
RhAAC	Rhodium-catalyzed Azide-Alkyne Cycloaddition
RT	Room Temperature
RuAAC	Ruthenium-catalyzed Azide-Alkyne Cycloaddition
RuAtAC	Ruthenium-catalyzed Azide-Thioalkyne Cycloaddition
TBAA	Tetrabutylammonium Azide
TBAF	Tetra-*n*-butylammonium Fluoride
TBTA	Tris([1-benzyl-1H-1,2,3-triazol-4-yl)methyl]amine
Tf	Trifluoromethanesulfonyl
$TMSN_3$	Tetramethylsilyl Azide
Ts	Toluenesulfonyl
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
ZnAAC	Zinc-catalyzed Azide-Alkyne Cycloaddition

1. Introduction

The fact that 59% of FDA-approved unique small molecule drugs contain a nitrogen heterocycle shows that nitrogen heterocycles are the most significant structures in pharmaceuticals.[1] Notably, functionalized 1,2,3-triazoles have attracted much attention over decades due to their simple synthesis, versatility, and wide range of applications.[2] A substituted 1,2,3-triazole ring does not act only as a stable linkage to connect two chemical/biological components[3] but also as an amide bond isostere.[4,5] Moreover, compounds containing 1,2,3-triazole(s) are utilized as anticancer agents,[6] antifungals,[7] anti-inflammatory,[8] antituberculosis,[9] kinase inhibitors,[10] fluorescent chromophores,[11] catalysts,[12] and directing groups for C-H activation.[13,14]

Regioselective synthesis of 1,4- and 1,5-disubstituted triazole via azide-alkyne cycloaddition (AAC) is often referred to as "the cream of the crop" of click chemistry.[15] The term "click chemistry" was introduced by Karl Barry Sharpless in 1999, and the term "click reaction" was defined in 2001:[15]

> *"The reaction must be modular, wide in scope, give very high yields, generate only inoffensive byproducts that can be removed by nonchromatographic methods, and be stereospecific (but not necessarily enantioselective). The required process characteristics include simple reaction conditions (ideally, the process should be insensitive to oxygen and water), readily available starting materials and reagents, the use of no solvent or a solvent that is benign (such as water) or easily removed, and simple product isolation. Purification—if required—must be by nonchromatographic methods, such as crystallization or distillation, and the product must be stable under physiological conditions."*

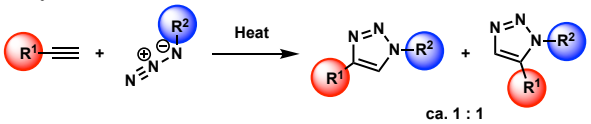
This concept has become an attractive topic, as evidenced by a literature search via Scopus performed on March 31st, 2024, which disclosed that a total of 20152 articles containing the keywords "click chemistry" or "click reaction" were published in 24 years. Click chemistry has been widely used in many research fields due to its effective, eco-friendly, and straightforward synthetic method: among them, AAC is the premier example of click reactions.[16] AAC was first reported by Rolf Huisgen as a 1,3-dipolar cycloaddition (1,3-DCA) also known as Huisgen cycloaddition.[17] In 2001, Meldal and Sharpless independently discovered copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) regioselectively yielding 1,4-disubstituted 1,2,3-triazole.[18,19] In 2005, synthesis of 1,5-disubstituted 1,2,3-triazoles via ruthenium(II)-catalyzed azide-alkyne cycloaddition (RuAAC) was reported.[20] In addition, other transition metal-catalyzed azide-alkyne cycloaddition (MAAC)[21] and metal-free AAC have also been developed.[2223] Although the effective synthesis of the 1,2,3-triazole ring is still being investigated, this review aims to provide important aspects of the various types of AAC and highlight key points for the successful synthesis of the desired regioisomers of 1,2,3-triazoles.

2. Theory

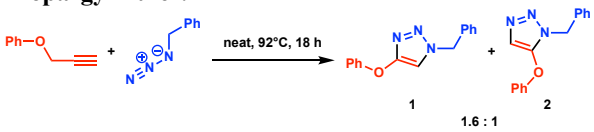
2.1. Huisgen 1,3-Dipolar Cycloaddition: Thermal Azide-Alkyne Cycloaddition Reactions

Even though the theory of 1,3-DCA was interesting, this reaction was formerly not used as this thermal cycloaddition is often very slow due to the high activation energy and requires elevated temperatures. Moreover, the thermal reaction also gives a mixture of the 1,4- and 1,5-regioisomers of 1,2,3-triazole (Scheme 1).[19] The ratio of the mixture is ca. 1:1 depending on functional groups bound to azide/alkyne (Scheme 2).19 A computational study by density functional theory (DFT) showed that the activation barriers for the uncatalyzed thermal AAC giving 1,4- and 1,5-regioisomers were 25.7 and 26.0 kcal/mol, respectively.[24]

Scheme 1. Huisgen 1,3-Dipolar Cycloaddition of Alkyne and Azide.



Scheme 2. Thermal AAC of Benzyl Azide and Phenyl Propargyl Ether.



Although its mechanism is still not fully understood, two possible mechanisms are proposed: a stepwise and a concerted mechanism. Metadynamics computer simulations have shown that when the functional group is relatively small, such as a methyl group, 1,3-DCA has a preference for 1,4-regioisomers in a concerted mechanism and for 1,5-regioisomers in a stepwise mechanism. Changing to larger functional groups might reverse the concerted/stepwise preference for 1,4-regioisomers and eliminate the concerted preference for 1,5-regioisomers.[25]

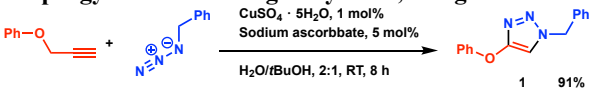
2.2. Copper-Catalyzed Azide-Alkyne Cycloaddition (CuAAC) Reactions

CuAAC reactions allow a significant rate acceleration up to a factor of 7 compared to the thermal AAC,[24] and produce only 1,4-disubstituted 1,2,3-triazoles from azides and terminal alkynes at ambient temperature (Scheme 3).[19] This regioselectivity results from the favorable orientation of the reactants in the transition state: the transition state leading to the 1,4-regioisomer was found to be 8.9 kcal/mol lower in energy than that giving the 1,5-disubstituted 1,2,3-triazole.[26,27] Furthermore, for the formation of the 1,5-isomers, the terminal nitrogen should be complexed with the copper of the acetylides, which is electronically unfavorable.[28]

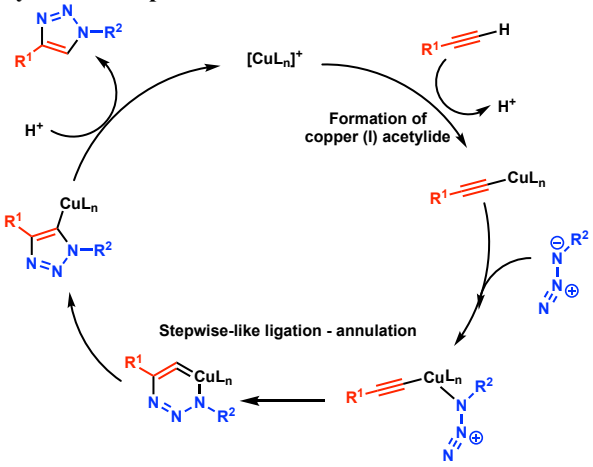
Originally, the mechanism of the CuAAC was assumed to be a stepwise process, involving the formation

of mononuclear copper(I) acetylides (Scheme 4), and the concerted cycloaddition of azide and copper(I) acetylide was disregarded.[19,24] However, recent DFT studies have found that CuAAC occurs in a single concerted step with the formation of a dinuclear copper intermediate.[29,32] Thus, the actual steps consist of: the formation of dinuclear copper acetylide intermediate (Step A), the coordination of the azide to the first intermediate (Step B), the concerted cyclization between the alkynyl and the to create two C-N bonds (Step C), and the proton transfer from the alkyne to the third intermediate (Step D), as outlined in Scheme 6.[32,33]

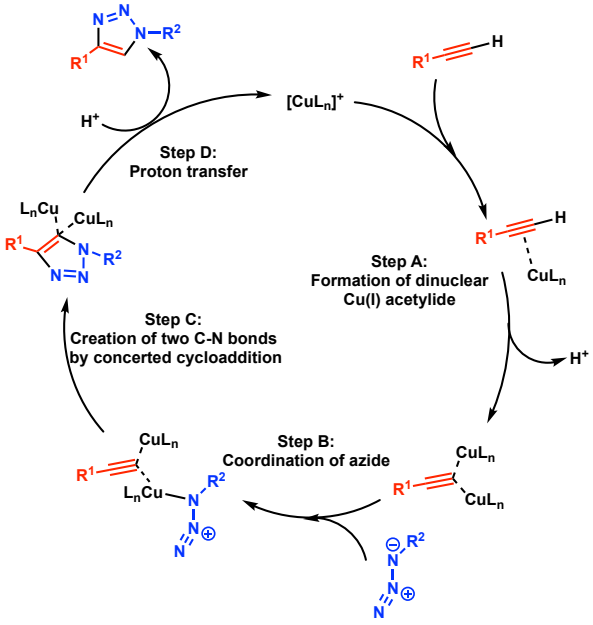
Scheme 3. CuAAC of Benzyl Azide and Phenyl Propargyl Ether Yielding Only the 1,4-Regioisomer.



Scheme 4. Early Proposed Catalytic Cycle of CuAAC by K. B. Sharpless.



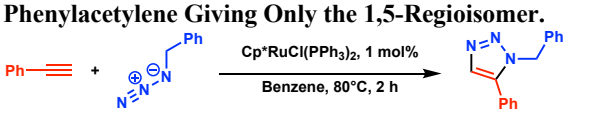
Scheme 5. Recently Suggested Catalytic Cycle of CuAAC.



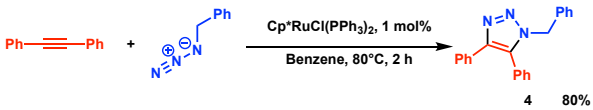
2.3. Ruthenium-Catalyzed Azide-Alkyne Cycloaddition (RuAAC) Reactions

Whereas CuAAC gives only 1,4-regioisomers of 1,2,3-triazole, RuAAC affords mainly 1,5-disubstituted 1,2,3-triazole (Scheme 6).[20] Additionally, in contrast to copper catalysis, ruthenium catalysis allows the cycloaddition of azides and internal alkynes, yielding fully substituted 1,2,3-triazoles (Scheme 7).[34] The involvement of terminal and internal alkynes in ruthenium catalysis proposes that ruthenium acetylides are not involved in the catalytic cycle, as opposed to the mechanism of CuAAC that requires the formation of dinuclear copper acetylide complex.[24,35] Hence, the reason for the 1,5-selectivity is assumed to be that the ruthenium catalyst activates the alkyne through π-interactions, increasing the nucleophilicity of the alkyne and facilitating the nucleophilic attack from its most nucleophilic carbon to the electrophilic terminus of the azide.[35] The currently accepted mechanism of RuAAC is shown in Scheme 8.[35] The mechanism consists of four steps: the formation of the activated Ru-azide-alkyne complex through the replacement of the spectator ligands with azide and alkyne (Step A, ligation), the conversion from the activated complex to the ruthenacyclic intermediate via the oxidative coupling of the alkyne and the azide at which the new C–N bond is formed between the more electronegative carbon of the alkyne (terminal carbon) and the terminal nitrogen of the azide (Step B, regioselectivity-determining step), reductive elimination (Step C, rate-determining step), and releasing the triazole product and regenerating the catalyst (Step D).[35,36] For the formation of the activated complex at Step A, there are four possible structures (Figure 1); **CMP-A** and **CMP-B** give a 1,5-regioisomer while **CMP-C** and **CMP-D** give a 1,4-regioisomer.[35] In addition, DFT calculations have indicated that energetic, steric, and electronic factors favor the pathway starting from the activated complex **CMP-A**, and this is consistent with experimental results, namely, the formation of 1,5-disubstituted triazole.[35,37]

Scheme 6. RuAAC of Benzyl Azide and Phenylacetylene Giving Only the 1,5-Regioisomer.



Scheme 7. RuAAC of Benzyl Azide and Diphenylacetylene Giving the Fully Substituted 1,2,3-Triazole.



Scheme 8. Proposed Catalytic Cycle for RuAAC with [Cp*RuCl] Catalyst.

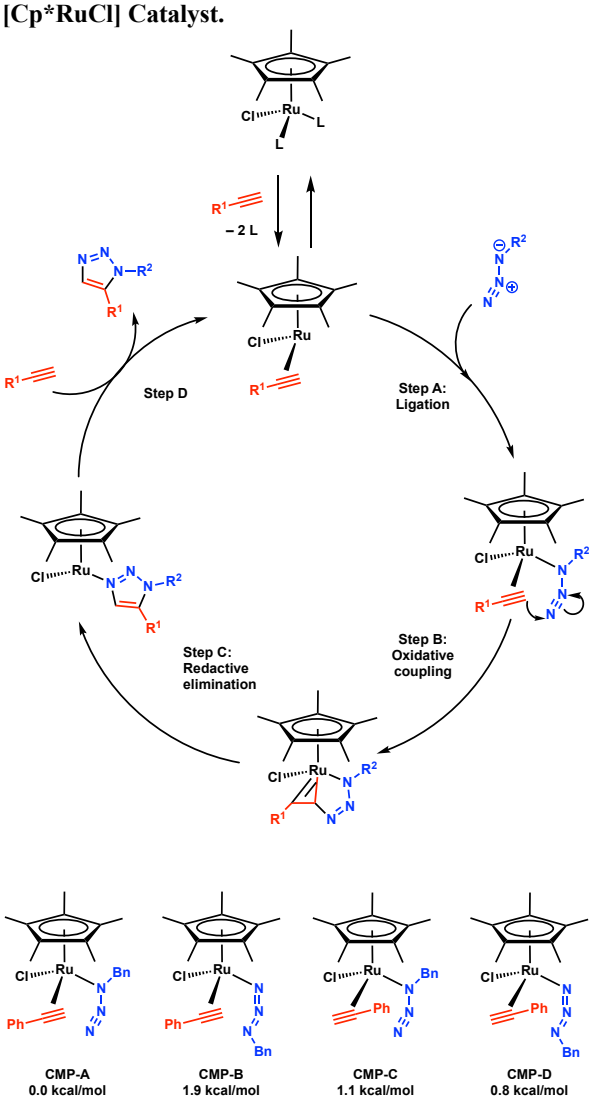
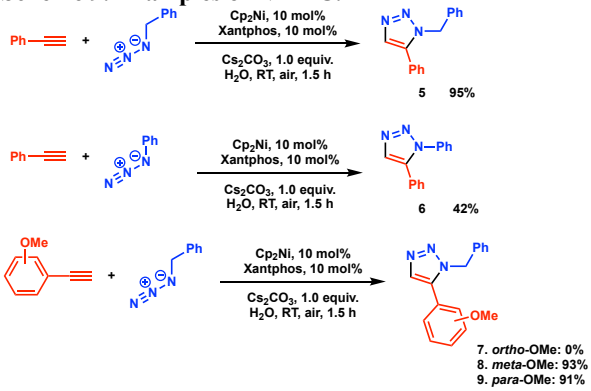


Figure 1. Structures and Computed Energies of Four Possible [Cp*RuCl]-Azide-Alkyne Activated Complexes.

2.4. Other Transition Metal-Catalyzed Azide-Alkyne Cycloaddition (MAAC) Reactions

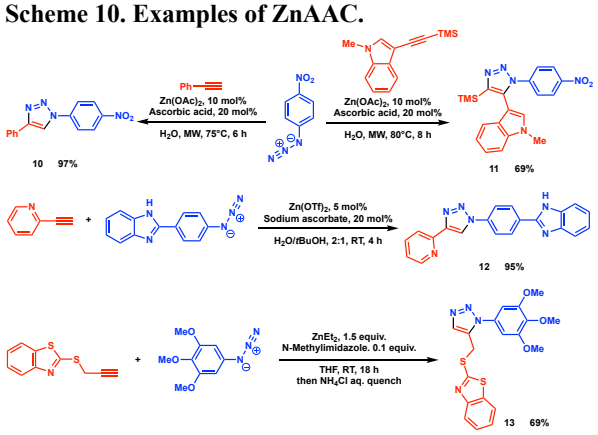
While copper and ruthenium catalysts are most commonly used in AAC reactions to synthesize 1,4- and 1,5-disubstituted 1,2,3-triazoles, other metals have been also investigated to allow AAC reactions under milder/greener conditions. Nickel-catalyzed AAC (NiAAC) reactions regioselectively yield 1,5-regioisomers in water under air at room temperature, as opposed to RuAAC.[38] Especially, Cp_2Ni/Xantphos-catalyzed AAC reactions are robust enough to tolerate both aliphatic and aromatic alkynes with diverse functional groups such as methoxy-, amine-, nitro-, chloro-, and methyl moieties.[38] However, NiAAC is incompatible with 2-ethynylanisole (*ortho*-OMe phenylacetylene) due to its steric demand: NiAAC reactions are favored by lower steric hindrance of substrates (Scheme 9).[38]

Scheme 9. Examples of NiAAC.



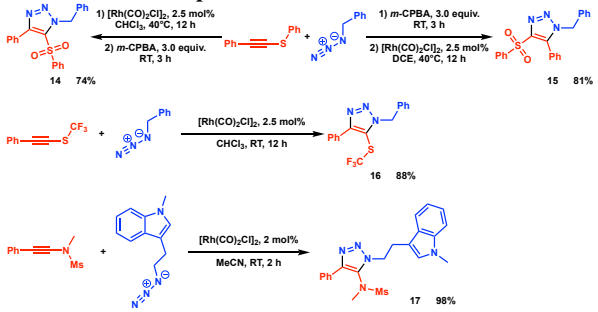
Zinc-catalyzed AAC (ZnAAC) reactions can produce both 1,4-disubstituted, 1,5-disubstituted, and fully substituted 1,2,3-triazoles via the formation of a π-complex between zinc catalyst and alkyne.[39] As a catalyst, $Zn(OAc)_2$ is used for the synthesis of 1,4-disubstituted and fully substituted 1,2,3-triazoles,[39] $Zn(OTf)_2$ for 1,4-regioisomers,[40] and $ZnEt_2$ for 1,5-regioisomers (Scheme 10).[41]

Scheme 10. Examples of ZnAAC.



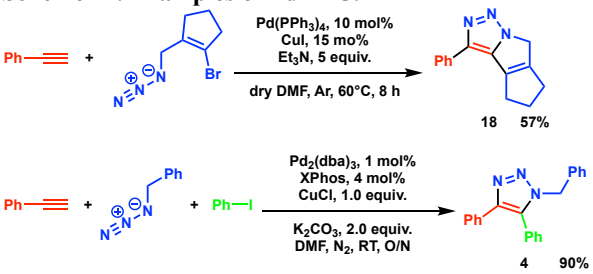
Rhodium-catalyzed AAC (RhAAC) is superior in that it proceeds under mild conditions and is compatible with water and air. RhAAC using $[Rh(CO)_2Cl]_2$ as a catalyst is most known for the synthesis of fully substituted 4- and 5-sulfonyl-1,2,3-triazoles,[42] 1,4-disubstituted 5-trifluoromethylthio-1,2,3-triazoles,[43] and 1,4-disubstituted 5-amino-1,2,3-triazoles under mild condition in one-pot (Scheme 11).[44]

Scheme 11. Examples of RhAAC.



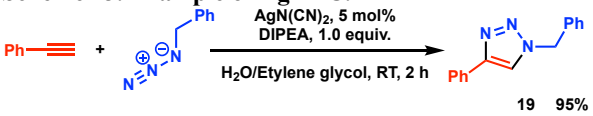
Palladium-catalyzed AAC (PdAAC) is a useful reaction for the synthesis of fused 1,2,3-triazoles via tandem Sonogashira coupling – CuAAC reaction[45] and for the synthesis of fully substituted 1,2,3-triazoles via a one-pot three-component reaction of azides, alkynes, and aryl halides with palladium catalyst and copper(I) co-catalyst (Scheme 12).[46]

Scheme 12. Examples of PdAAC.



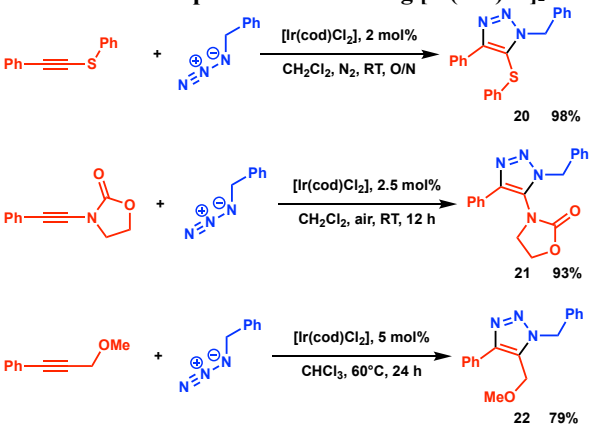
Silver-catalyzed AAC (AgAAC) reactions afford 1,4-disubstituted 1,2,3-triazoles via nucleophilic attack on silver(I) acetylides by azides.[47] McNulty et al.[47] reported AgAAC using a homogeneous silver(I) catalyst accelerated with the aid of a ligand. Silver dicyanamide ($AgN(CN)_2$)-catalyzed AAC with base is also a simple and efficient method to synthesize 1,4-regioisomers at room temperature, and the catalysis tolerates various functional groups of alkynes such as alcohol, aryl, and ester (Scheme 13).[48]

Scheme 13. Example of AgAAC.

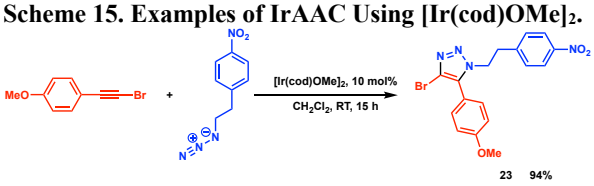


Iridium-catalyzed AAC (IrAAC) is applied to synthesize fully substituted 1,2,3-triazoles. $[Ir(cod)Cl]_2$ (cod = cyclooctadiene) is often used as a catalyst to produce 1,4-disubstituted 5-thio-,[49] 5-amido-,[50] and 5-ether-1,2,3-triazoles[51] from internal electron-rich alkynes and organic azides under mild conditions (Scheme 14). $[Ir(cod)OMe]_2$ catalyst is, on the other hand, used to prepare 1,5-disubstituted 4-bromo-1,2,3-triazoles, but this catalysis is only suitable for electron-donating aryl alkynes (Scheme 15).[52]

Scheme 14. Examples of IrAAC Using $[Ir(cod)Cl]_2$.

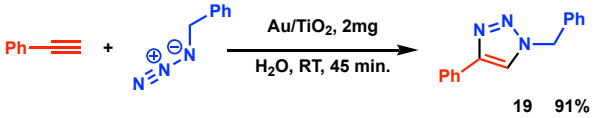


Scheme 15. Examples of IrAAC Using $[Ir(cod)OMe]_2$.



Recyclable gold nanoparticle-catalyzed syntheses of 1,2,3-triazoles are known as gold-catalyzed AAC (AuAAC) reactions. The reaction mechanism is stepwise: formation of metal acetylide, cyclization between nucleophilic nitrogen of azide and electrophilic carbon of alkyne, and generation of 1,4-disubstituted 1,2,3-triazole by the removal of the gold catalyst.[53] Nanoporous titanium dioxide (TiO_2)-supported AuAAC is remarkable as Au/TiO_2 nanoparticles can be reused up to five times without any loss of product yield. This reaction is compatible with water and is suitable for both aliphatic and aromatic alkynes substituted by electron-donating groups (EDGs) as well as electron-withdrawing groups (EWGs) (Scheme 16).[53]

Scheme 16. Example of AuAAC.

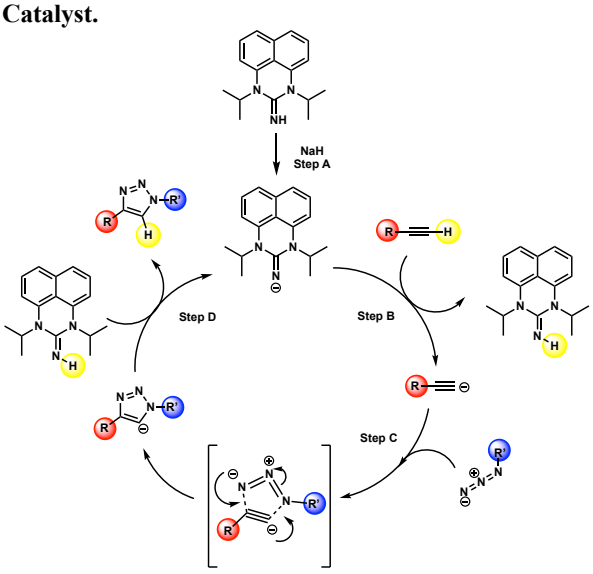


2.5. Metal-Free Azide-Alkyne Cycloaddition Reactions

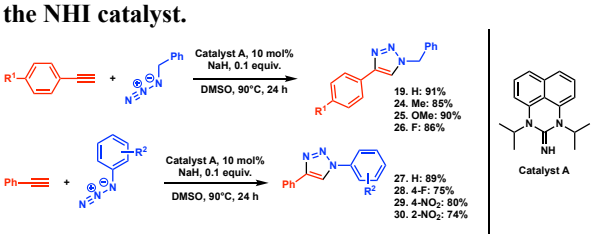
As described, 1,4- and 1,5-disubstituted 1,2,3-triazoles have diverse pharmaceutical applications. Nevertheless, metal-catalyzed synthesis often leads to the presence of trace metal contaminants that negatively affect human health; therefore, metal-free AAC reactions are in significant demand.[54] Not to mention, it has the advantage of being insensitive to air and moisture, lower toxicity and environmentally friendly.[55]

Revathi et al.[56] developed N-heterocyclic imine/imino (NHI) catalysts to access 1,4-disubstituted 1,2,3-triazoles from terminal alkynes and organic azides. The plausible mechanism supported by DFT studies is given in Scheme 17: the formation of the active imino catalyst by treating sodium hydride (NaH) with the imine precatalyst (Step A), the highly basic imino catalyst abstracting a proton from the terminal alkyne to generate the acetylide (Step B), the nucleophilic attack of the terminal nitrogen on the acetylide (Step C), and the formed triazolide anion abstraction a proton from the imine to yield the 1,4-regioisomer (Step D).[56] The outcome of this approach is not affected by the electronic properties of the substituted groups of alkynes, but by the electronic properties of the functional groups of azides: EWG on the azides hinders the product formation (Scheme 18). Despite the various substrates investigated, the substrate scope of this reaction can be limited due to the use of the strong base, NaH, and a potential issue with this procedure is that it may be challenging to scale up the reaction because of the thermal instability hazards of a NaH/DMSO mixture.[57]

Scheme 17. Suggested Mechanism of AAC Using NHI Catalyst.

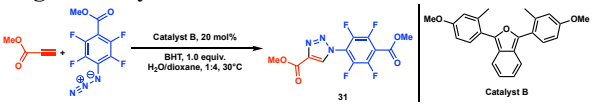


Scheme 18. Examples of Organocatalyzed AAC Using the NHI catalyst.

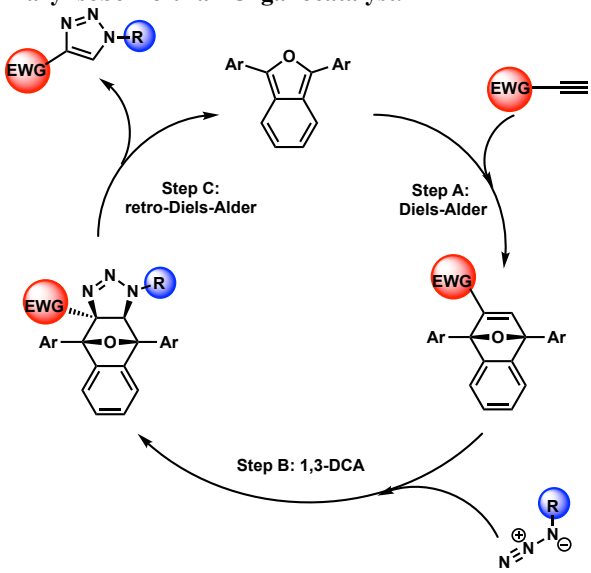


In 2024, Levandowski et al.[23] reported diarylisobenzofuran derivatives as organocatalysts for 1,4-regioselective AAC reactions. The chosen model reaction is the cycloaddition of perfluorophenyl azide and ethyl propialate. Here, perfluorophenyl azide is very activated, and the AAC reaction with this azide proceeds without any catalysts (1,4-/1,5-regioisomer, 87:13).[22] Still, the isobenzofuran organocatalyst increased the rate and regioselectivity of the AAC reaction, resulting in the 1,4- and 1,5-regioisomer ratio of 96:4 (Scheme 19).[23] The catalytic cycle, depicted in Scheme 20, consists of three steps: the formation of a benzooxanorbornadiene adduct by a Diels-Alder reaction of a diarylisobenzofuran with an electron-deficient alkyne (Step A, rate-determining step), 1,3-DCA between the benzooxanorbornadiene adduct and an azide (Step B, regioselectivity-determining step), and releasing a 1,4-disubstituted triazole by a retro-Diels-Alder reaction (Step C).[23] DFT studies also support the formation of 1,4-regioisomer with a 4.1 kcal/mol kinetic preference over the formation of 1,5-regioisomer.[23]

Scheme 19. Example of Organocatalyzed AAC Using Organocatalyst.

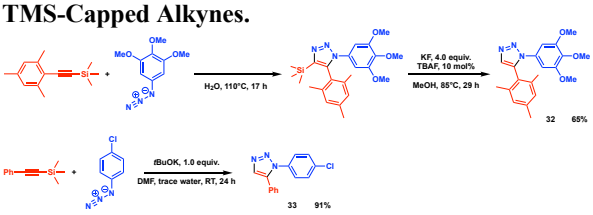


Scheme 20. Proposed Mechanism Using the Diarylisobenzofuran Organocatalyst.



Metal-free 1,5-regioselective synthesis of 1,2,3-triazoles was achieved by the reaction between organic azides and trimethylsilyl-capped (TMS-capped) alkynes.[22] Desilylation can be easily performed with potassium fluoride (KF) and tetrabutylammonium fluoride (TBAF) or potassium *tert*-butoxide (*t*BuOK) after cycloaddition (Scheme 21).[22,58]

Scheme 21. Examples of AAC Between Azides and TMS-Capped Alkynes.



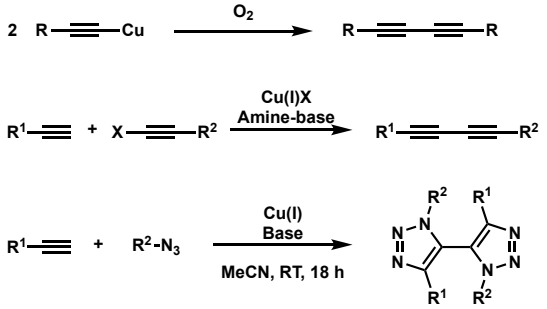
3. Discussion

3.1. The Reaction Scope of CuAAC

A wide range of experimental conditions for CuAAC reactions have proved that almost any source of solvated copper(I) can be used as a catalyst in CuAAC.[18,19] Copper(I) source is usually prepared in three ways: (i) direct use of Cu(I) salts, (ii) oxidation of Cu metal, and (iii) in situ reduction of Cu(II) salts.[59] As a direct source of Cu(I) salts, copper iodide (CuI), copper bromide (CuBr), copper chloride (CuCl), copper acetate (CuOAc), and coordination complexes, such as $[Cu(CH_3CN)_4]PF_6$, are commonly utilized.[59] A key is to maintain a high level of active Cu(I) species during a reaction since Cu(I) is the least thermodynamically stable among the oxidation states of copper (0, +1, +2).[60] The procedure therefore requires an inert atmosphere and anhydrous degassed organic solvents, such as acetonitrile (MeCN) or tetrahydrofuran (THF), to aid solubilization and to prevent oxidation of Cu(I) to Cu(II).[59] It also requires an excess of nitrogen base, such as triethylamine or *N,N*-diisopropylethylamine (DIPEA), to help stabilize the active Cu(I) state and to

promote the deprotonation of alkynes to form the active Cu(I)-acetylide intermediate.[19] However, the presence of the base will lower the yield by facilitating the formation of diacetylenes, bis-triazoles, and 5-hydroxytriazoles (Scheme 22).[19] In some cases, 5,5'-bistriazoles can be formed in up to 95% via oxidative coupling by adding bases.[61] Furthermore, the presence of halide ions, especially iodide ions, in CuAAC can act as inhibitors, leading to the formation of polynuclear acetylide complexes that interfere with the productive catalytic cycles.[6062] Copper(I) iodide may also lead to the formation of 1-iodoalkynes and consequently 5-iodo-1,4-disubstituted triazoles.[63]

Scheme 22. Possible Side Reactions of CuAAC.

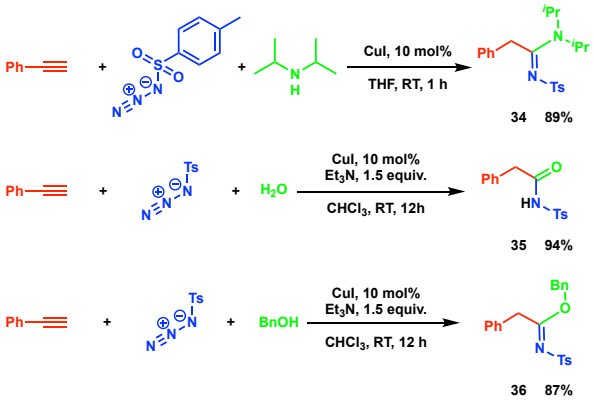


Oxidation of copper metal is another method to generate the Cu(I) catalyst for CuAAC. The cycloaddition between azides and alkynes in water/alcohol mixtures in the presence of excess copper turnings affords the corresponding 1,4-disubstituted 1,2,3-triazoles.[24] The copper metal procedure has the advantage of synthesizing compound libraries for biological screening due to the very low copper contamination in triazole products,[60] While using copper turnings requires a stoichiometric amount of copper and long reaction times, activated Cu(0) nanosize powder provides an alternative method of Cu(I) generation.[64] The benefit of using Cu(0) powder is that it requires only a catalytic amount of the copper powder and shortens the reaction time by enhancing the formation of copper acetylide thanks to its larger surface area than Cu metal.[64] The drawbacks are, however, that the solvation of Cu(0) particles requires a slightly acidic environment (ca. pH 5). Hence, it is necessary to add secondary amine hydrochloride salts to enhance the dissolution of Cu(0), resulting in the generation of the catalytic Cu(I) species.[64] Since the reaction will not proceed without amine hydrochloride salts, this method cannot be applied to substrates containing acid-sensitive functional groups. Further, Cu(0) nanosize powder costs more than seven times as much as other copper sources used in CuAAC.[65]

In situ generation of Cu(I) from Cu(II) salts by reduction is most extensively applied as it is inexpensive, often purer than Cu(I) salts, and compatible with oxygen and water.[19] Particularly, copper(II) sulfate pentahydrate with a three- to ten-fold excess of sodium ascorbate as a reducing agent in a water/alcohol mixture is favored.[65] In some cases, $Cu(OAc)_2$ can be used without any reducing agents in alcoholic media. The plausible explanation is that Cu(II) is reduced to active Cu(I) species either by alcohol oxidation, alkyne oxidative homocoupling, or both, evidenced by spectroscopic observations.[66]

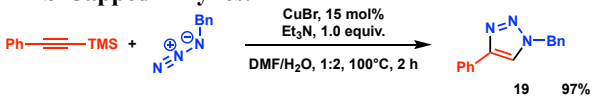
Regarding substrates, CuAAC is not significantly affected by the steric and electronic properties of functional groups attached to azides and alkynes.[60] In general, primary, secondary, and tertiary, electron-deficient and electron-rich, aliphatic, aromatic, and heteroaromatic azides react well with terminal alkynes substituted with alcohols, carboxylic acids, and amines without protecting groups.[60,65] Exceptionally, reactions between terminal alkynes and azides having *N*-sulfonyl or *N*-phosphoryl azides do not usually afford 1,2,3-triazoles but give amidines,[67] amides,[68], or imidates (Scheme 23).[69] In order to produce 1,4-disubstituted sulfonyl triazoles, the reaction needs to be tuned: for example, using CuBr and thioanisole (PhSMe),[70] $Cu(OAc)_2{\cdot}H_2O$ and 2-Aminophenol (Entry 5, Table 1),[71] or copper(I) thiophene-2-carboxylate (CuTC) as a catalytic system (Entry 6).[72]

Scheme 23. Examples of CuAAC Between Terminal Alkynes and *N*-Sulfonyl Azides.



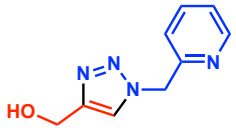
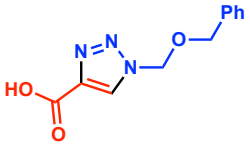
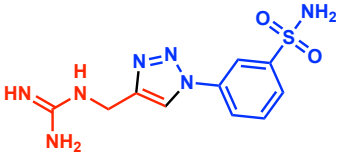
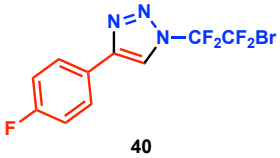
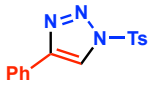
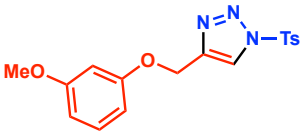
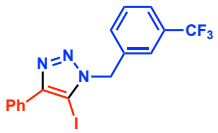
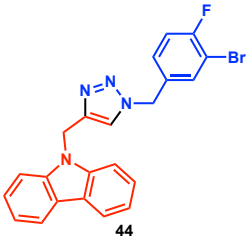
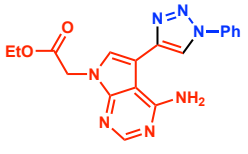
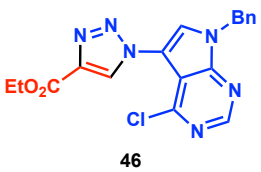
CuAAC reactions do not usually proceed with azides and internal alkynes. Nonetheless, 1-iodoalkynes and TMS-protected alkynes can react with organic azides to give 5-iodo-1,4,5-trisubstituted-1,2,3-triazoles (Entry 7, Table 1)[63] or 1,4-disubstituted 1,2,3-triazoles under certain conditions (Scheme 24).[73,74]

Scheme 24. Example of CuAAC Between Azides and TMS-Capped Alkynes.



Keeping the reactants soluble throughout the reaction is also a key requirement for success, and a water/alcohol mixture is most commonly used solvent because water supports copper acetylides in their reactive states and alcohol facilitates the solvation of lipophilic reactants. Other organic co-solvents, for example, *N,N*-dimethylformamide (DMF) or dimethyl sulfoxide (DMSO) are also employed for more hydrophobic reactants.[75] As expected from CuAAC being the cream of the crop of click chemistry, CuAAC produces 1,4-disubstituted 1,2,3-triazoles in high yields with a simple workup. As for workup, in many cases only filtration is required to collect a pure precipitate when the product is solid; only aqueous extraction is required for non-solid triazoles.[76] The reaction scope of CuAAC is summarized in Table 1.

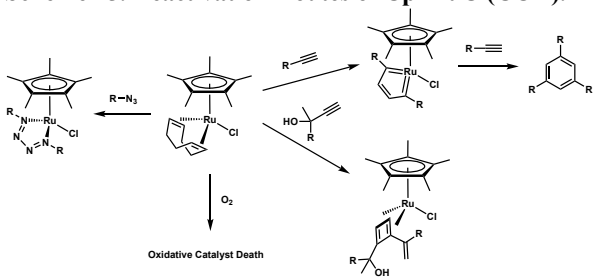
Table 1. Copper-Catalyzed Reactions of Azides with Terminal Alkynes.

Entry	Product	Conditions	Yield, %	Ref.
1	 **37**	Azide, 1.0 equiv. Alkyne, 1.5 equiv. $Cu(OAc)_2$, 5 mol% *t*BuOH, RT, 1 - 2 min.	>95	*66*
2	 **38**	Azide, 1.0 equiv. Alkyne, 1.0 equiv. $CuSO_4 \cdot 5H_2O$, 1 mol% Sodium ascorbate, 10 mol% H_2O/*t*BuOH, 1:1, RT, O/N	91	*19*
3	 **39**	Azide, 1.0 equiv. Alkyne, 1.0 equiv. $CuSO_4 \cdot 5H_2O$, 1 mol% Sodium ascorbate, 10 mol% H_2O/*t*BuOH, 1:1, RT, O/N	88	*19*
4	 **40**	Alkyne, 1.0 equiv. Azide, 1.2 equiv. CuMeSal, 5mol% THF, RT, O/N	98	*77*
5	 **41**	Azide, 1.0 equiv. Alkyne, 1.1 equiv. $Cu(OAc)_2 \cdot H_2O$, 10 mol% 2-Aminophenol, 5 mol% MeCN, RT, 20 min.	95	*71*
6	 **42**	Alkyne, 1.0 equiv. Tosyl azide, 1.1 equiv. CuTC, 10 mol% Toluene, RT, 2h	93	*72*
7	 **43**	Azide, 1.0 equiv. Alkyne, 1.0 equiv. CuI, 5 mol% Et_3N, 2.0 equiv. THF, RT, 6 h	90	*63*
8	 **44**	Alkyne, 1.0 equiv. Azide, 1.0 equiv. $CuSO_4 \cdot 5H_2O$, 20 mol% Sodium ascorbate, 20 mol% H_2O/*t*BuOH, 1:1, RT, 8-10 h	85	*78*
9	 **45**	Alkyne, 1.0 equiv. Corresponding iodide, 1.2 equiv. NaN_3, 1.2 equiv., $NaCO_3$, 20 mol% L-Proline, 20 mol%, Cu/C, 40 mol% $DMSO/H_2O$, MW, 130°C, 30 min.	75	*79*
10	 **46**	1) Heterocyclic iodide, 1.0 equiv. NaN_3 aq., 1.5 equiv. MeCN/DMSO, RT, 1 min. 2) CuCl, 10 mol%, MeCN/DMSO, RT, 30 min. 3) Corresponding alkyne, 1.5 equiv. DIPEA 2 equiv., AcOH, 2 equiv. MeCN/DMSO, RT, 3h	47	*80*

3.2. The Reaction Scope of RuAAC

For 1,5-regioselective RuAAC reactions, only four complexes containing the [Cp*RuCl] (pentamethylcyclopentadienyl ruthenium chloride) are found to be viable, which are $Cp^*RuCl(PPh_3)_2$, $[Cp^*RuCl]_4$, Cp*RuCl(COD), and Cp*RuCl(NBD) (NBD = norbornadiene); otherwise, RuAAC does not proceed or gives 1,4-regioisomers (Entry 1, Table 1).[20,35] These four Ru-catalysts are rather sensitive to atmospheric oxygen. Thus, RuAAC reactions should be carried out under an inert atmosphere.[35] For instance, the conversion of the reaction between benzyl azide and phenylacetylene using 4 mol% Cp*RuCl(COD) is quantitative under argon and only 20% under air.[81] However, degassing solvents has little effect on the reaction rate and yield and is claimed not to be necessary.[81] In addition to oxygen, ruthenium catalysts can also be deactivated by azides and alkynes. For example, Cp*RuCl(COD) reacts with organic azides to give ruthenium tetraazadiene complexes, which can be isolated by column chromatography, appearing as a green band on a silica gel column.[81] Besides, [2+2+2] alkyne cyclotrimerization giving benzene derivatives via ruthenacyclopentatriene and dimerization reaction of propargylic alcohol giving cyclobutadiene ruthenium complex may be observed (Scheme 25).[82,83] These three ruthenium complexes are no longer active, even at an elevated temperature, and, it is therefore important to add the ruthenium catalyst to the system in the presence of both azides and alkynes.[81] RuAAC usually requires excess azides or excess alkynes, and products are often isolated by chromatographic methods, as opposed to CuAAC.[84]

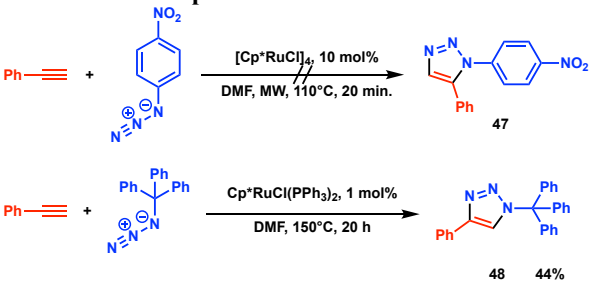
Scheme 25. Deactivation Routes of Cp*RuCl(COD).



RuAAC reactions are often conducted in aprotic solvents such as acetone, THF, toluene, dioxane, dichloromethane (DCM), DMF, and chloroform, and the reaction mixture must be completely homogeneous.[81] Whereas DMF activates and stabilizes ligands by the formation of complexes with ruthenium,[85] reactions in DMSO have been reported to be problematic.[86] In addition to DMSO, water, ethyl acetate, methanol, isopropyl alcohol, hexane, and diethyl ether are reported as detrimental to catalysis. Even though ruthenium catalysts are incompatible with water, the solvents need not be extremely dry as the presence of adventitious water usually does not affect the catalysis.[35] The Reaction temperature varies with substrate and catalyst type from ambient to 110°C; in general, reactions with $[Cp^*RuCl]_4$ and Cp*RuCl(COD) require a lower temperature to achieve full conversion, in contrast to the $Cp^*RuCl(PPh_3)_2$ that requires temperatures exceeding 60°C.[81] Thus, the use of microwave heating is occasionally applied to achieve a high conversion in a short time.[84] The reaction efficiency can be improved by increasing catalyst loading (Entries 3 and 4, Table 2). On the other hand, slight variations in the reaction temperature and extending reaction times do not improve the yield of the reaction (Entries 4, 5, and 6).[84]

RuAAC is not as versatile as CuAAC with respect to substituent tolerance. Specifically, the steric demands of the azide substituent frequently affect the yield of the reaction: RuAAC involving primary azides are most efficient, cycloadditions of secondary azides often react slower and result in slightly lower yields, and tertiary azides, with a few exceptions, hardly participate in catalysis.[35] Furthermore, azides containing diortho substituents or strongly electron-withdrawing groups, such as (4-nitro)azidobenzene, fail to participate in the reaction.[84] Moreover, it is surprisingly reported that the RuAAC reaction of 2,2-diaryl-2-azidoamines and terminal alkynes affords the 1,4-regioisomers because its steric congestion from the geminal diaryl groups of the azide may hinder the preference for 1,5-regioisomer formation (Scheme 26).[87]

Scheme 26. Examples of Steric Demand on RuAAC.



On the contrary, RuAAC is not very sensitive to the substituents on the alkyne: terminal alkynes containing halide, alcohol, ether, acetal, nitrile, ester, amine, sulfonamide, and heterocyclic groups are readily involved in the reaction.[35] However, acidic functionalities such as carboxylic acid and boronic acids can be problematic.[86] Likewise, it is experimentally proven that the electron-rich alkynes are more reactive than the electron-deficient species.[88]

As stated, the unique feature of RuAAC is its ability to produce fully substituted 1,2,3-triazole from internal alkynes and organic azides. Regioselectivity is often high for unsymmetrically substituted internal alkyne but depends on the electronic properties of the substituents, their steric demands, and the ability to form hydrogen bonding.[35] It is known that hydrogen bond donors, such as alcohols and amines, in the propargylic position (next to an alkyne) will always be at the C-5 position of the product, i.e., the new C-N bond is formed between the terminal nitrogen of the azide and the ß-carbon of the alkyne.[35] This directing effect can be ascribed to the formation of a strong hydrogen bond between the hydrogen bond donor group and the chloride ligand on the ruthenium. Without such directing groups, the new C-N bond is formed between the terminal nitrogen and the more nucleophilic carbon of the alkyne: the more electronegative carbon of the alkyne becomes C-4 in the 1,2,3-triazole.[35] Interestingly, adding

Cu(I) salts to the Ru catalysis improves the regioselectivity and the reaction rate of RuAAC of internal alkynes and azides; with any luck, residual Cu can be in alkynes since a majority of alkynes are prepared via Sonogashira coupling reaction.[89] Furthermore, the cycloaddition of azides and internal thioalkynes (RuAtAC) preferentially takes place over the reaction between azides and internal alkynes; sulfur usually ends up at the C-5 position of the triazole product (Scheme 27).[90] The reaction scope of RuAAC is summarized in Table 2.

Scheme 27. Example of RuAtAC.

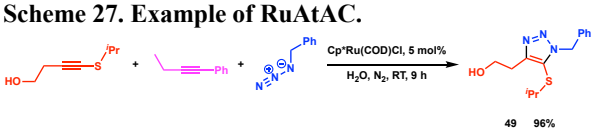
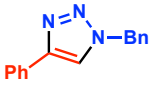
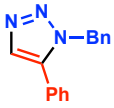
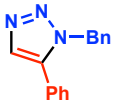
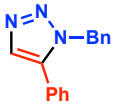
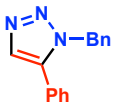
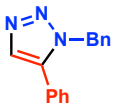
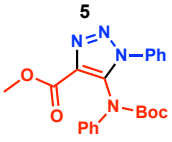
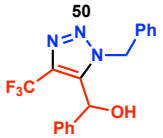
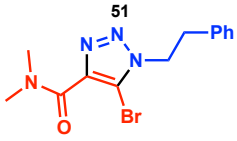
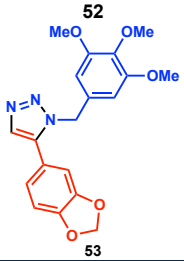


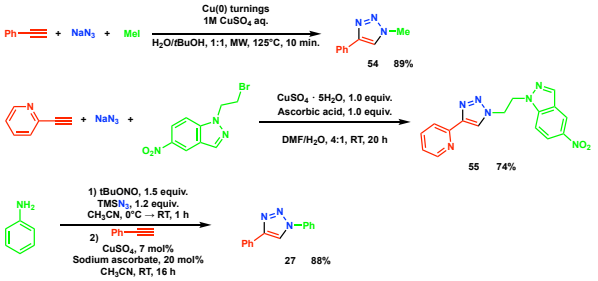
Table 2. Ruthenium-Catalyzed Reactions of Azides and Alkynes.

Entry	Product	Conditions	Yield, %	Ref.
1	 **19**	Azide, 1.0 equiv. Alkyne, 1.5 equiv. $Ru(OAc)_2(PPh_3)_2$, 5 mol% Benzene, 80°C, 4 h	Quantitative conversion	*20*
2	 **5**	Azide, 1.0 equiv. Alkyne, 1.5 equiv. $Cp^*RuCl(PPh_3)_2$, 5 mol% Benzene, 80°C, 2 h	80	*20*
3	 **5**	Alkyne, 1.0 equiv. Azide, 1.1 equiv. $[Cp^*RuCl]_4$, 2 mol% DMF, MW, 110°C, 20 min.	33	*84*
4	 **5**	Alkyne, 1.0 equiv. Azide, 1.1 equiv. $[Cp^*RuCl]_4$, 10 mol% DMF, MW, 110°C, 20 min.	73	*84*
5	 **5**	Alkyne, 1.0 equiv. Azide, 1.1 equiv. $[Cp^*RuCl]_4$, 10 mol% DMF, MW, 90°C, 20 min.	69	*84*
6	 **5**	Alkyne, 1.0 equiv. Azide, 1.1 equiv. $[Cp^*RuCl]_4$, 2 mol% DMF, MW, 110°C, 10 min.	66	*84*
7	 **50**	Azide, 1.0 equiv. Alkyne, 1.0 equiv. $[Cp^*RuCl]_4$, 4.5 mol% DMF, RT, 2 h	86	*91*
8	 **51**	Azide, 1.0 equiv. Alkyne, 1.5 equiv. $[Cp^*RuCl]_4$, 10 mol% THF, 66°C, 5 h	89	*92*
9	 **52**	Alkyne, 1.0 equiv. Azide, 1.25 equiv. CpRu(COD)Cl, 3 mol% MeCN, RT, 1 h	85	*93*
10	 **53**	Azide, 1.0 equiv. Alkyne, 1.7 equiv. $Cp^*RuCl(PPh_3)_2$, 20 mol% Benzene, reflux, 24 h	94	*94*

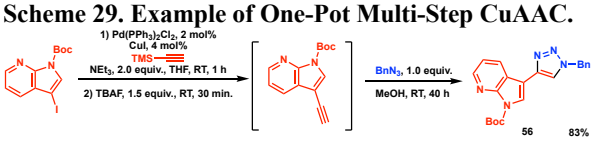
3.3. One-Pot Synthesis of 1,2,3-Triazole Scaffolds

Organic azides are easily prepared by insertion of the N_3 group via nucleophilic substitution of the corresponding halides with azidating agents such as sodium azide (NaN_3), trimethylsilyl azide ($TMSN_3$), diphenylphosphoryl azide (DPPA), and tetrabutylammonium azide (TBAA).[95] Even though organic azides are basically safe compounds, those of low molecular weight can be unstable and explosive.[96] There are some noteworthy points when handling azides. For organic azides to be safe, the "rule of six" or "carbon to nitrogen ratio" is practical: either six carbons per azide or a C/N ratio greater than three is required for a sufficient level of safety. Most organic azides are decomposed to release N_2 gas by certain transition metals, temperatures above 180°C, and strong acids.[96] Additionally, Aryl azides, vinyl azides, acyl azides, and α-azido ketones are less stable and more dangerous than aliphatic azides.[15] While sodium azide is as toxic as sodium cyanide, it is relatively safe in aqueous media.[96,97] As a general rule, contact with metals, acids, and halogenated solvents must be kept away from inorganic azides.[98,99] Owing to these safety criteria for handling azides, a method to avoid isolation of organic azides is convenient; a one-pot, two-step procedure with in situ generation of organic azides has been developed.[100] For CuAAC, reactions are readily accomplished by mixing alkynes, halides (or aromatic amines), NaN_3 (or $TMSN_3$), and copper(I) catalysts simultaneously in a solution (Scheme 28).[100-103] When the nucleophilic substitution of halide is less efficient, the formation of 1H-1,2,3-triazole is a competitive reaction.[100] One important aspect to keep in mind while workup is copper azides are explosive when dry; they must be removed before drying.[100] Moreover, telescoping CuAAC allows for three or more reaction steps in one pot, for instance, sequential Sonogashira coupling – desilylation – CuAAC reaction giving 1,4-disubstituted 1,2,3-triazoles (Scheme 29).[104-106] 1,5-Disubstituted 1,2,3-triazoles can be similarly synthesized by one-pot NiAAC or sequential one-pot RuAAC (Scheme 30).[86,107]

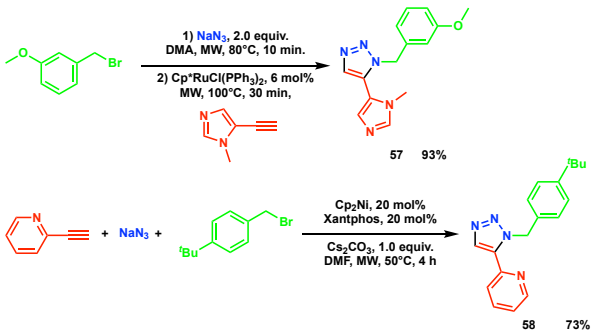
Scheme 28. Examples of CuAAC of Alkynes and In Situ Generated Azides.



Scheme 29. Example of One-Pot Multi-Step CuAAC.



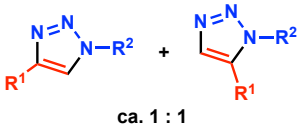
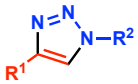
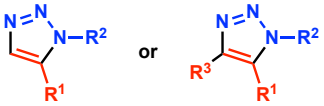
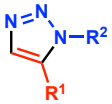
Scheme 30. Examples of One-Pot RuAAC and NiAAC.

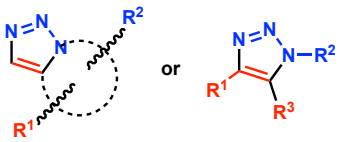
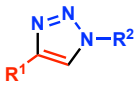
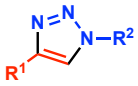
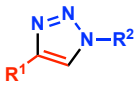


3.4. Other MAAC and Metal-Free AAC Compared to CuAAC and RuAAC

Reaction scopes of MAAC and organocatalyzed AAC including thermal AAC, CuAAC, and RuAAC are summarized in Table 3. Note that azide-alkyne cycloaddition reactions are highly exothermic and should be conducted on a small scale before scale-up.[108]

Table 3. Strengths and Limitations of Various AAC Reactions.

Method	Product	Substrate scope	Strengths	Weaknesses
Thermal	 ca. 1 : 1	Azides and terminal alkynes	Sustainable	High temperature, slow reaction, non-selective
Cu		Azides and terminal alkynes, TMS-alkynes or 1-iodoalkynes	Regioselective, versatile, inexpensive, air-insensitive	Copper toxicity
Ru		Azides and terminal/internal alkynes	Regioselective, internal alkynes tolerance	High temperature, incompatible with oxygen and water
Ni		Azides and non-bulky alkynes	Regioselective, Water- and oxygen-insensitive	Unsuitable for bulky alkynes

Zn		Azides and alkynes	Inexpensive, green conditions	Zinc toxicity
Rh	 **R^1: Alkyl, aryl, sulfonyl** **R^3: SR, SO_2R, SCF_3, NRR'**	Azides and thio-, sulfonyl-, and aminoalkynes	Compatible with water and air	Unsustainable, substrate limitations
Pd		Azides and terminal alkynes	Step economy	Unsustainable and expensive
Ag		Azides and terminal alkynes	Sustainable, various alkynes tolerance	Expensive, ligand or base needed
Ir	 **R^3: thio-, amido-, ether**	Azides and internal electron-rich alkynes	Mild conditions	Expensive, substrate limitations
Au		Azides and terminal alkynes	Sustainable, compatible with water	Expensive
Organocatalyst		Azides and terminal alkynes	Sustainable, inexpensive	Substrate limitations, commercially unavailable catalysts
No catalysts		Azides and TMS-capped alkynes	Sustainable, inexpensive	Possibility of side reactions

4. Conclusion

In summary, azide-alkyne cycloaddition is a fascinating method for the synthesis of 1,2,3-triazole rings because of its efficiency, versatility, and selectivity. This review has provided an overview of commonly used AAC reactions with their strengths, limitations, and examples. CuAAC is simple, robust, reliable, inexpensive, and tolerant towards a wide range of functional groups attached to azides and alkynes, resulting in 1,4-disubstituted 1,2,3-triaozoles. However, copper contamination is highly cytotoxic and should be avoided. RuAAC and NiAAC are right choice for 1,5-regioselective synthesis of 1,2,3-triazoles. The drawback is that RuAAC is strongly affected by the steric properties of the substituent of azides, while NiAAC is mainly influenced by the steric demand of alkynes. RhAAC allows the reaction between azides and thioalkynes, sulfonylalkynes, and aminoalkynes. Likewise, IrAAC involves the reaction of azides with thioalkynes, alkynyl amides, and alkynyl ethers. PdAAC is useful to synthesize fused 1,2,3-triazoles. AgAAC and AuAAC are sustainable as the catalyst can be recovered several times without loss of catalytic activity. Although metal-free AAC is attractive in terms of cost and environmental impact, most metal-free AAC has been performed with simple substrates; further investigation is needed to validate the method's usefulness. Since 1,2,3-triazole derivatives have a wide range of applications from pharmaceuticals to materials science, there is an ever-increasing demand for highly efficient synthesis methods. The selected examples presented in this report will be useful to those planning to prepare 1,2,3-triazole scaffolds via AAC reactions.

References

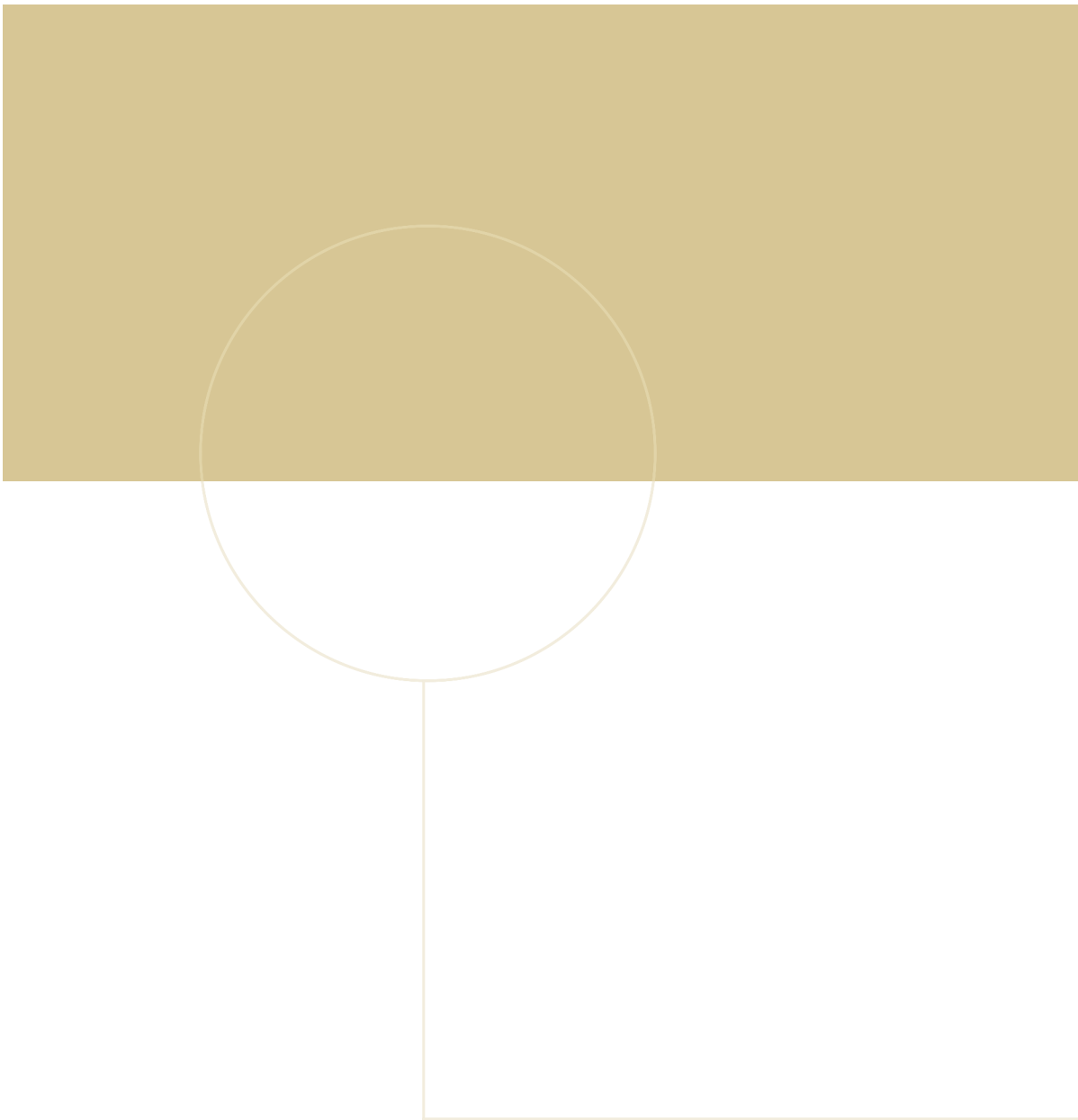
1. Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals: Miniperspective. *J. Med. Chem.* **2014**, *57* (24), 10257–10274. https://doi.org/10.1021/jm501100b.
2. Kumar, L.; Lal, K.; Kumar, A.; Paul, A. K.; Kumar, A. Pyrazoline Tethered 1,2,3-Triazoles: Synthesis, Antimicrobial Evaluation and in Silico Studies. *Journal of Molecular Structure* **2021**, *1246*, 131154. https://doi.org/10.1016/j.molstruc.2021.131154.
3. Struthers, H.; Mindt, T. L.; Schibli, R. Metal Chelating Systems Synthesized Using the Copper(I) Catalyzed Azide-Alkynecycloaddition. *Dalton Trans.* **2010**, *39* (3), 675–696. https://doi.org/10.1039/B912608B.
4. Kumari, S.; Carmona, A. V.; Tiwari, A. K.; Trippier, P. C. Amide Bond Bioisosteres: Strategies, Synthesis, and Successes. *J. Med. Chem.* **2020**, *63* (21), 12290–12358. https://doi.org/10.1021/acs.jmedchem.0c00530.
5. Grob, N. M.; Schibli, R.; Béhé, M.; Valverde, I. E.; Mindt, T. L. 1,5-Disubstituted 1,2,3-Triazoles as Amide Bond Isosteres Yield Novel Tumor-Targeting Minigastrin Analogs. *ACS Med. Chem. Lett.* **2021**, *12* (4), 585–592. https://doi.org/10.1021/acsmedchemlett.0c00636.
6. Zhao, L.; Mao, L.; Hong, G.; Yang, X.; Liu, T. Design, Synthesis and Anticancer Activity of Matrine–1H-1,2,3-Triazole–Chalcone Conjugates. *Bioorganic & Medicinal Chemistry Letters* **2015**, *25* (12), 2540–2544. https://doi.org/10.1016/j.bmcl.2015.04.051.
7. Deswal, S.; Naveen; Tittal, R. K.; Ghule Vikas, D.; Lal, K.; Kumar, A. 5-Fluoro-1H-Indole-2,3-Dione-Triazoles- Synthesis, Biological Activity, Molecular Docking, and DFT Study. *Journal of Molecular Structure* **2020**, *1209*, 127982. https://doi.org/10.1016/j.molstruc.2020.127982.
8. Boshra, A. N.; Abdu-Allah, H. H. M.; Mohammed, A. F.; Hayallah, A. M. Click Chemistry Synthesis, Biological Evaluation and Docking Study of Some Novel 2′-Hydroxychalcone-Triazole Hybrids as Potent Anti-Inflammatory Agents. *Bioorganic Chemistry* **2020**, *95*, 103505. https://doi.org/10.1016/j.bioorg.2019.103505.
9. Tripathi, R. P.; Yadav, A. K.; Ajay, A.; Bisht, S. S.; Chaturvedi, V.; Sinha, S. K. Application of Huisgen (3+2) Cycloaddition Reaction: Synthesis of 1-(2,3-Dihydrobenzofuran-2-Yl-Methyl [1,2,3]-Triazoles and Their Antitubercular Evaluations. *European Journal of Medicinal Chemistry* **2010**, *45* (1), 142–148. https://doi.org/10.1016/j.ejmech.2009.09.036.
10. Kim, W.; Lee, S.-M.; Jeong, P.-H.; Jung, J.-H.; Kim, Y.-C. Synthesis and Structure-Activity Relationship Studies of 1,5-Isomers of Triazole-Pyrrolopyrimidine as Selective Janus Kinase 1 (JAK1) Inhibitors. *Bioorganic & Medicinal Chemistry Letters* **2022**, *55*, 128451. https://doi.org/10.1016/j.bmcl.2021.128451.
11. Namba, K.; Osawa, A.; Ishizaka, S.; Kitamura, N.; Tanino, K. Direct Synthesis of Fluorescent 1,3a,6a-Triazapentalene Derivatives via Click–Cyclization–Aromatization Cascade Reaction. *J. Am. Chem. Soc.* **2011**, *133* (30), 11466–11469. https://doi.org/10.1021/ja203917r.
12. Neel, A. J.; Hehn, J. P.; Tripet, P. F.; Toste, F. D. Asymmetric Cross-Dehydrogenative Coupling Enabled by the Design and Application of Chiral Triazole-Containing Phosphoric Acids. *J. Am. Chem. Soc.* **2013**, *135* (38), 14044–14047. https://doi.org/10.1021/ja407410b.
13. Ye, X.; He, Z.; Ahmed, T.; Weise, K.; Akhmedov, N. G.; Petersen, J. L.; Shi, X. 1,2,3-Triazoles as Versatile Directing Group for Selective Sp2 and Sp3 C–H Activation: Cyclization vs Substitution. *Chem. Sci.* **2013**, *4* (9), 3712. https://doi.org/10.1039/c3sc51211h.
14. Zurro, M.; Mancheño, O. G. 1,2,3-Triazole-Based Catalysts: From Metal- to Supramolecular Organic Catalysis. *Chem. Rec.* **2017**, *17* (5), 485–498. https://doi.org/10.1002/tcr.201600104.
15. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. Click Chemistry: Diverse Chemical Function from a Few Good Reactions. *Angew. Chem. Int. Ed.* **2001**, *40* (11), 2004–2021. https://doi.org/10.1002/1521-3773(20010601)40:11<2004::AID-ANIE2004>3.0.CO;2-5.
16. Kolb, H. C.; Sharpless, K. B. The Growing Impact of Click Chemistry on Drug Discovery. *Drug Discovery Today* **2003**, *8* (24), 1128–1137. https://doi.org/10.1016/S1359-6446(03)02933-7.
17. Huisgen, R. 1,3-Dipolar Cycloadditions. Past and Future. Angew. Chem. Int. Ed. Engl., **1963**, 2, 565-598. https://doi.org/10.1002/anie.196305651
18. Tornøe, C. W.; Christensen, C.; Meldal, M. Peptidotriazoles on Solid Phase: [1,2,3]-Triazoles by Regiospecific Copper(I)-Catalyzed 1,3-Dipolar Cycloadditions of Terminal Alkynes to Azides. *J. Org. Chem.* **2002**, *67* (9), 3057–3064. https://doi.org/10.1021/jo011148j.
19. Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. A Stepwise Huisgen Cycloaddition Process: Copper(I)-Catalyzed Regioselective "Ligation" of Azides and Terminal Alkynes. *Angew. Chem. Int. Ed.* **2002**, *41* (14), 2596–2599. https://doi.org/10.1002/1521-3773(20020715)41:14<2596::AID-ANIE2596>3.0.CO;2-4.
20. Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. Ruthenium-Catalyzed Cycloaddition of Alkynes and Organic Azides. *J. Am. Chem. Soc.* **2005**, *127* (46), 15998–15999. https://doi.org/10.1021/ja054114s.
21. Wang, C.; Ikhlef, D.; Kahlal, S.; Saillard, J.-Y.; Astruc, D. Metal-Catalyzed Azide-Alkyne "Click" Reactions: Mechanistic Overview and Recent Trends. *Coordination Chemistry Reviews* **2016**, *316*, 1–20. https://doi.org/10.1016/j.ccr.2016.02.010.
22. Kloss, F.; Köhn, U.; Jahn, B. O.; Hager, M. D.; Görls, H.; Schubert, U. S. Metal-Free 1,5-Regioselective Azide–Alkyne [3+2]-Cycloaddition. *Chemistry An Asian Journal* **2011**, *6* (10), 2816–2824. https://doi.org/10.1002/asia.201100404.
23. Levandowski, B. J.; Graham, B. J.; Houk, K. N.; Raines, R. T. Click Organocatalysis: Acceleration of Azide–Alkyne Cycloadditions with Mutually

Orthogonal Click Reactions. *J. Org. Chem.* **2024**, *89* (4), 2232–2237. https://doi.org/10.1021/acs.joc.3c02182.
24. Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. Copper(I)-Catalyzed Synthesis of Azoles. DFT Study Predicts Unprecedented Reactivity and Intermediates. *J. Am. Chem. Soc.* **2005**, *127* (1), 210–216. https://doi.org/10.1021/ja0471525.
25. Danese, M.; Bon, M.; Piccini, G.; Passerone, D. The Reaction Mechanism of the Azide–Alkyne Huisgen Cycloaddition. *Phys. Chem. Chem. Phys.* **2019**, *21* (35), 19281–19287. https://doi.org/10.1039/C9CP02386K.
26. Meldal, M.; Tornøe, C. W. Cu-Catalyzed Azide−Alkyne Cycloaddition. *Chem. Rev.* **2008**, *108* (8), 2952–3015. https://doi.org/10.1021/cr0783479.
27. González-Lainez, M.; Gallegos, M.; Munarriz, J.; Azpiroz, R.; Passarelli, V.; Jiménez, M. V.; Pérez-Torrente, J. J. Copper-Catalyzed Azide–Alkyne Cycloaddition (CuAAC) by Functionalized NHC-Based Polynuclear Catalysts: Scope and Mechanistic Insights. *Organometallics* **2022**, *41* (15), 2154–2169. https://doi.org/10.1021/acs.organomet.2c00246.
28. Özen, C.; Tüzün, N. Ş. The Mechanism of Copper-Catalyzed Azide–Alkyne Cycloaddition Reaction: A Quantum Mechanical Investigation. *Journal of Molecular Graphics and Modelling* **2012**, *34*, 101–107. https://doi.org/10.1016/j.jmgm.2011.12.012.
29. Ahlquist, M.; Fokin, V. V. Enhanced Reactivity of Dinuclear Copper(I) Acetylides in Dipolar Cycloadditions. *Organometallics* **2007**, *26* (18), 4389–4391. https://doi.org/10.1021/om700669v.
30. Worrell, B. T.; Malik, J. A.; Fokin, V. V. Direct Evidence of a Dinuclear Copper Intermediate in Cu(I)-Catalyzed Azide-Alkyne Cycloadditions. *Science* **2013**, *340* (6131), 457–460. https://doi.org/10.1126/science.1229506.
31. Zhu, L.; Brassard, C. J.; Zhang, X.; Guha, P. M.; Clark, R. J. On the Mechanism of Copper(I)-Catalyzed Azide-Alkyne Cycloaddition. *The Chemical Record* **2016**, *16* (3), 1501–1517. https://doi.org/10.1002/tcr.201600002.
32. Héron, J.; Balcells, D. Concerted Cycloaddition Mechanism in the CuAAC Reaction Catalyzed by 1,8-Naphthyridine Dicopper Complexes. *ACS Catal.* **2022**, *12* (8), 4744–4753. https://doi.org/10.1021/acscatal.2c00723.
33. Beutick, S. E.; Vermeeren, P.; Hamlin, T. A. The 1,3-Dipolar Cycloaddition: From Conception to Quantum Chemical Design. *Chemistry An Asian Journal* **2022**, *17* (17), e202200553. https://doi.org/10.1002/asia.202200553.
34. Majireck, M. M.; Weinreb, S. M. A Study of the Scope and Regioselectivity of the Ruthenium-Catalyzed [3 + 2]-Cycloaddition of Azides with Internal Alkynes. *J. Org. Chem.* **2006**, *71* (22), 8680–8683. https://doi.org/10.1021/jo061688m.
35. Boren, B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. V. Ruthenium-Catalyzed Azide−Alkyne Cycloaddition: Scope and Mechanism. *J. Am. Chem. Soc.* **2008**, *130* (28), 8923–8930. https://doi.org/10.1021/ja0749993.
36. Lamberti, M.; Fortman, G. C.; Poater, A.; Broggi, J.; Slawin, A. M. Z.; Cavallo, L.; Nolan, S. P. Coordinatively Unsaturated Ruthenium Complexes As Efficient Alkyne–Azide Cycloaddition Catalysts. *Organometallics* **2012**, *31* (2), 756–767. https://doi.org/10.1021/om2012425.
37. Boz, E.; Tüzün, N. Ş. Reaction Mechanism of Ruthenium-Catalyzed Azide–Alkyne Cycloaddition Reaction: A DFT Study. *Journal of Organometallic Chemistry* **2013**, *724*, 167–176. https://doi.org/10.1016/j.jorganchem.2012.11.011.
38. Kim, W. G.; Kang, M. E.; Lee, J. B.; Jeon, M. H.; Lee, S.; Lee, J.; Choi, B.; Cal, P. M. S. D.; Kang, S.; Kee, J.-M.; Bernardes, G. J. L.; Rohde, J.-U.; Choe, W.; Hong, S. Y. Nickel-Catalyzed Azide–Alkyne Cycloaddition To Access 1,5-Disubstituted 1,2,3-Triazoles in Air and Water. *J. Am. Chem. Soc.* **2017**, *139* (35), 12121–12124. https://doi.org/10.1021/jacs.7b06338.
39. Morozova, M. A.; Yusubov, M. S.; Kratochvil, B.; Eigner, V.; Bondarev, A. A.; Yoshimura, A.; Saito, A.; Zhdankin, V. V.; Trusova, M. E.; Postnikov, P. S. Regioselective Zn(OAc) $_2$ -Catalyzed Azide–Alkyne Cycloaddition in Water: The Green Click-Chemistry. *Org. Chem. Front.* **2017**, *4* (6), 978–985. https://doi.org/10.1039/C6QO00787B.
40. Harkala, K. J.; Eppakayala, L.; Maringanti, T. C. Synthesis and Biological Evaluation of Benzimidazole-Linked 1,2,3-Triazole Congeners as Agents. *Org Med Chem Lett* **2014**, *4* (1), 14. https://doi.org/10.1186/s13588-014-0014-x.
41. Smith, C. D.; Greaney, M. F. Zinc Mediated Azide–Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles. *Org. Lett.* **2013**, *15* (18), 4826–4829. https://doi.org/10.1021/ol402225d.
42. Song, W.; Zheng, N.; Li, M.; Dong, K.; Li, J.; Ullah, K.; Zheng, Y. Regiodivergent Rhodium(I)-Catalyzed Azide–Alkyne Cycloaddition (RhAAC) To Access Either Fully Substituted Sulfonyl-1,2,3-Triazoles under Mild Conditions. *Org. Lett.* **2018**, *20* (21), 6705–6709. https://doi.org/10.1021/acs.orglett.8b02794.
43. Song, W.; Zheng, N.; Li, M.; He, J.; Li, J.; Dong, K.; Ullah, K.; Zheng, Y. Rhodium(I)-Catalyzed Regioselective Azide-internal Alkynyl Trifluoromethyl Sulfide Cycloaddition and Azide-internal Thioalkyne Cycloaddition under Mild Conditions. *Adv Synth Catal* **2019**, *361* (3), 469–475. https://doi.org/10.1002/adsc.201801216.
44. Liao, Y.; Lu, Q.; Chen, G.; Yu, Y.; Li, C.; Huang, X. Rhodium-Catalyzed Azide–Alkyne Cycloaddition of Internal Ynamides: Regioselective Assembly of 5-Amino-Triazoles under Mild Conditions. *ACS Catal.* **2017**, *7* (11), 7529–7534. https://doi.org/10.1021/acscatal.7b02558.
45. Rakshit, M.; Kar, G. K.; Chakrabarty, M. A New General Synthesis of Annulated 1,2,3-Triazoles Using Tandem Sonogashira-CuAAC Reaction. *Monatsh Chem* **2015**, *146* (10), 1681–1688. https://doi.org/10.1007/s00706-015-1430-y.
46. Wei, F.; Li, H.; Song, C.; Ma, Y.; Zhou, L.; Tung, C.-H.; Xu, Z. Cu/Pd-Catalyzed, Three-Component Click Reaction of Azide, Alkyne, and Aryl Halide: One-Pot Strategy toward Trisubstituted

Triazoles. *Org. Lett.* **2015**, *17* (11), 2860–2863. https://doi.org/10.1021/acs.orglett.5b01342.
47. McNulty, J.; Keskar, K. Discovery of a Robust and Efficient Homogeneous Silver(I) Catalyst for the Cycloaddition of Azides onto Terminal Alkynes. *Eur J Org Chem* **2012**, *2012* (28), 5462–5470. https://doi.org/10.1002/ejoc.201200930.
48. Ali, A. A.; Chetia, M.; Saikia, B.; Saikia, P. J.; Sarma, D. AgN(CN)2/DIPEA/H2O-EG: A Highly Efficient Catalytic System for Synthesis of 1,4-Disubstituted-1,2,3 Triazoles at Room Temperature. *Tetrahedron Letters* **2015**, *56* (43), 5892–5895. https://doi.org/10.1016/j.tetlet.2015.09.025.
49. Ding, S.; Jia, G.; Sun, J. Iridium-Catalyzed Intermolecular Azide–Alkyne Cycloaddition of Internal Thioalkynes under Mild Conditions. *Angew Chem Int Ed* **2014**, *53* (7), 1877–1880. https://doi.org/10.1002/anie.201309855.
50. Song, W.; Zheng, N. Iridium-Catalyzed Highly Regioselective Azide–Ynamide Cycloaddition to Access 5-Amido Fully Substituted 1,2,3-Triazoles under Mild, Air, Aqueous, and Bioorthogonal Conditions. *Org. Lett.* **2017**, *19* (22), 6200–6203. https://doi.org/10.1021/acs.orglett.7b03123.
51. Duan, X.; Zheng, N.; Li, M.; Sun, X.; Lin, Z.; Qiu, P.; Song, W. Remote Ether Groups-Directed Regioselective and Chemoselective Cycloaddition of Azides and Alkynes. *Chinese Chemical Letters* **2021**, *32* (12), 4019–4023. https://doi.org/10.1016/j.cclet.2021.05.037.
52. Rasolofonjatovo, E.; Theeramunkong, S.; Bouriaud, A.; Kolodych, S.; Chaumontet, M.; Taran, F. Iridium-Catalyzed Cycloaddition of Azides and 1-Bromoalkynes at Room Temperature. *Org. Lett.* **2013**, *15* (18), 4698–4701. https://doi.org/10.1021/ol402008u.
53. Boominathan, M.; Pugazhenthiran, N.; Nagaraj, M.; Muthusubramanian, S.; Murugesan, S.; Bhuvanesh, N. Nanoporous Titania-Supported Gold Nanoparticle-Catalyzed Green Synthesis of 1,2,3-Triazoles in Aqueous Medium. *ACS Sustainable Chem. Eng.* **2013**, *1* (11), 1405–1411. https://doi.org/10.1021/sc400147r.
54. Mehri, A. Trace Elements in Human Nutrition (II)—An Update. *Int. J. Prev. Med.*; **2020**, *11* (2). https://dx.doi.org/10.4103/ijpvm.IJPVM_48_19.
55. MacMillan, D. W. C. The Advent and Development of Organocatalysis. *Nature* **2008**, *455* (7211), 304–308. https://doi.org/10.1038/nature07367.
56. Revathi, S.; Shinde, A. L.; Rajashekhar, M. K.; Mandal, D.; Maity, A. R.; Garai, S.; Ghatak, T. N-Heterocyclic Imino-Catalyzed 1,4-Regioselective Azide–Alkyne Cycloaddition (AAC): A Metal-Free Approach. *Chem. Commun.* **2023**, *59* (85), 12699–12702. https://doi.org/10.1039/D3CC04065H.
57. Yang, Q.; Sheng, M.; Henkelis, J. J.; Tu, S.; Wiensch, E.; Zhang, H.; Zhang, Y.; Tucker, C.; Ejeh, D. E. Explosion Hazards of Sodium Hydride in Dimethyl Sulfoxide, *N*, *N* -Dimethylformamide, and *N*, *N* -Dimethylacetamide. *Org. Process Res. Dev.* **2019**, *23* (10), 2210–2217. https://doi.org/10.1021/acs.oprd.9b00276.
58. Wu, L.; Chen, Y.; Tang, M.; Song, X.; Chen, G.; Song, X.; Lin, Q. Potassium Tert-Butoxide Promoted Cycloaddition Reaction for the Synthesis of 1,5-Disubstituted 1,2,3-Triazoles from Aromatic Azides and Trimethylsilyl-Protected Alkynes. *Synlett* **2012**, *23* (10), 1529–1533. https://doi.org/10.1055/s-0031-1291042.
59. Fantoni, N. Z.; El-Sagheer, A. H.; Brown, T. A Hitchhiker's Guide to Click-Chemistry with Nucleic Acids. *Chem. Rev.* **2021**, *121* (12), 7122–7154. https://doi.org/10.1021/acs.chemrev.0c00928.
60. Hein, J. E.; Fokin, V. V. Copper-Catalyzed Azide–Alkyne Cycloaddition (CuAAC) and beyond: New Reactivity of Copper(i) Acetylides. *Chem. Soc. Rev.* **2010**, *39* (4), 1302. https://doi.org/10.1039/b904091a.
61. Angell, Y.; Burgess, K. Base Dependence in Copper-Catalyzed Huisgen Reactions: Efficient Formation of Bistriazoles. *Angew Chem Int Ed* **2007**, *46* (20), 3649–3651. https://doi.org/10.1002/anie.200700399.
62. Kalra, P.; Kaur, R.; Singh, G.; Singh, H.; Singh, G.; Pawan; Kaur, G.; Singh, J. Metals as "Click" Catalysts for Alkyne-Azide Cycloaddition Reactions: An Overview. *Journal of Organometallic Chemistry* **2021**, *944*, 121846. https://doi.org/10.1016/j.jorganchem.2021.121846.
63. Hein, J. E.; Tripp, J. C.; Krasnova, L. B.; Sharpless, K. B.; Fokin, V. V. Copper(I)-Catalyzed Cycloaddition of Organic Azides and 1-Iodoalkynes. *Angew Chem Int Ed* **2009**, *48* (43), 8018–8021. https://doi.org/10.1002/anie.200903558.
64. Orgueira, H. A.; Fokas, D.; Isome, Y.; Chan, P. C.-M.; Baldino, C. M. Regioselective Synthesis of [1,2,3]-Triazoles Catalyzed by Cu(I) Generated in Situ from Cu(0) Nanosize Activated Powder and Amine Hydrochloride Salts. *Tetrahedron Letters* **2005**, *46* (16), 2911–2914. https://doi.org/10.1016/j.tetlet.2005.02.127.
65. Bock, V. D.; Hiemstra, H.; Van Maarseveen, J. H. Cu^{I} -Catalyzed Alkyne–Azide "Click" Cycloadditions from a Mechanistic and Synthetic Perspective. *Eur J Org Chem* **2006**, *2006* (1), 51–68. https://doi.org/10.1002/ejoc.200500483.
66. Brotherton, W. S.; Michaels, H. A.; Simmons, J. T.; Clark, R. J.; Dalal, N. S.; Zhu, L. Apparent Copper(II)-Accelerated Azide−Alkyne Cycloaddition. *Org. Lett.* **2009**, *11* (21), 4954–4957. https://doi.org/10.1021/ol9021113.
67. Bae, I.; Han, H.; Chang, S. Highly Efficient One-Pot Synthesis of *N* -Sulfonylamidines by Cu-Catalyzed Three-Component Coupling of Sulfonyl Azide, Alkyne, and Amine. *J. Am. Chem. Soc.* **2005**, *127* (7), 2038–2039. https://doi.org/10.1021/ja0432968.
68. Cassidy, M. P.; Raushel, J.; Fokin, V. V. Practical Synthesis of Amides from In Situ Generated Copper(I) Acetylides and Sulfonyl Azides. *Angew Chem Int Ed* **2006**, *45* (19), 3154–3157. https://doi.org/10.1002/anie.200503805.
69. Kim, S. H.; Park, S. H.; Choi, J. H.; Chang, S. Sulfonyl and Phosphoryl Azides: Going Further Beyond the Click Realm of Alkyl and Aryl Azides. *Chemistry An Asian Journal* **2011**, *6* (10), 2618–2634. https://doi.org/10.1002/asia.201100340.
70. Wang, F.; Fu, H.; Jiang, Y.; Zhao, Y. Copper-Catalyzed Cycloaddition of Sulfonyl Azides with Alkynes to Synthesize *N* -Sulfonyltriazoles 'on Water' at

Room Temperature. *Adv Synth Catal* **2008**, *350* (11–12), 1830–1834. https://doi.org/10.1002/adsc.200800291.
71. Liu, Y.; Wang, X.; Xu, J.; Zhang, Q.; Zhao, Y.; Hu, Y. Highly Controlling Selectivity of Copper(I)-Catalyzed Azide/Alkyne Cycloaddition (CuAAC) between Sulfonyl Azids and Normal Alkynes or Propynoates. Tetrahedron 2011, 67 (34), 6294–6299. https://doi.org/10.1016/j.tet.2011.06.017.
72. Raushel, J.; Fokin, V. V. Efficient Synthesis of 1-Sulfonyl-1,2,3-Triazoles. *Org. Lett.* **2010**, *12* (21), 4952–4955. https://doi.org/10.1021/ol102087r.
73. Cuevas, F.; Oliva, A.; Pericàs, M. Direct Copper(I)-Catalyzed Cycloaddition of Organic Azides with TMS-Protected Alkynes. Synlett 2010, 2010 (12), 1873–1877. https://doi.org/10.1055/s-0030-1258120.
74. Xu, H.; Sun, Z. General Cycloaddition Between a Trimethylsilyl-Capped Alkyne and an Azide Catalyzed by an N-Heterocyclic Carbene-Copper Complex and Pyridine-Biscarboxamide. Adv Synth Catal 2016, 358 (11), 1736–1740. https://doi.org/10.1002/adsc.201501171.
75. Haldón, E.; Nicasio, M. C.; Pérez, P. J. Copper-Catalysed Azide–Alkyne Cycloadditions (CuAAC): An Update. *Org. Biomol. Chem.* **2015**, *13* (37), 9528–9550. https://doi.org/10.1039/C5OB01457C.
76. Wu, P.; Feldman, A. K.; Nugent, A. K.; Hawker, C. J.; Scheel, A.; Voit, B.; Pyun, J.; Fréchet, J. M. J.; Sharpless, K. B.; Fokin, V. V. Efficiency and Fidelity in a Click-Chemistry Route to Triazole Dendrimers by the Copper(I)-Catalyzed Ligation of Azides and Alkynes. *Angewandte Chemie* **2004**, *116* (30), 4018–4022. https://doi.org/10.1002/ange.200454078.
77. Tichý, D.; Košťál, V.; Motornov, V.; Klimánková, I.; Beier, P. Preparation of 1-Azido-2-Bromo-1,1,2,2-Tetrafluoroethane and Its Use in the Synthesis of N-Fluoroalkylated Nitrogen Heterocycles. *J. Org. Chem.* **2020**, *85* (17), 11482–11489. https://doi.org/10.1021/acs.joc.0c01610.
78. Surineni, G.; Yogeeswari, P.; Sriram, D.; Kantevari, S. Rational Design, Synthesis and Evaluation of Novel-Substituted 1,2,3-Triazolylmethyl Carbazoles as Potent Inhibitors of Mycobacterium Tuberculosis. *Med Chem Res* **2015**, *24* (3), 1298–1309. https://doi.org/10.1007/s00044-014-1210-y.
79. Lawson, C. P.; Dierckx, A.; Miannay, F.-A.; Wellner, E.; Wilhelmsson, L. M.; Grøtli, M. Synthesis and Photophysical Characterisation of New Fluorescent Triazole Adenine Analogues. *Org. Biomol. Chem.* **2014**, *12* (28), 5158–5167. https://doi.org/10.1039/C4OB00904E.
80. Lubriks, D.; Sokolovs, I.; Suna, E. Indirect C–H Azidation of Heterocycles via Copper-Catalyzed Regioselective Fragmentation of Unsymmetrical λ^3-Iodanes. *J. Am. Chem. Soc.* **2012**, *134* (37), 15436–15442. https://doi.org/10.1021/ja305574k.
81. Oakdale, J. S.; Fokin, V. V. Preparation of 1,5-Disubstituted 1,2,3-Triazoles via Ruthenium-Catalyzed Azide Alkyne Cycloaddition. *Org. Synth.* **2013**, *90*, 96–104. https://doi.org/10.15227/orgsyn.090.0096.
82. Yamamoto, Y.; Kinpara, K.; Saigoku, T.; Takagishi, H.; Okuda, S.; Nishiyama, H.; Itoh, K. Cp*RuCl-Catalyzed [2 + 2 + 2] Cycloadditions of α,ω-Diynes with Electron-Deficient Carbon−Heteroatom Multiple Bonds Leading to Heterocycles. *J. Am. Chem. Soc.* **2005**, *127* (2), 605–613. https://doi.org/10.1021/ja045694g.
83. Le Paih, J.; Dérien, S.; Demerseman, B.; Bruneau, C.; Dixneuf, P. H.; Toupet, L.; Dazinger, G.; Kirchner, K. Ruthenium-Catalyzed Synthesis of Alkylidenecyclobutenes via Head-to-Head Dimerization of Propargylic Alcohols and Cyclobutadiene–Ruthenium Intermediates. *Chemistry A European J* **2005**, *11* (4), 1312–1324. https://doi.org/10.1002/chem.200400899.
84. Rasmussen, L. K.; Boren, B. C.; Fokin, V. V. Ruthenium-Catalyzed Cycloaddition of Aryl Azides and Alkynes. *Org. Lett.* **2007**, *9* (26), 5337–5339. https://doi.org/10.1021/ol701912s.
85. Trost, B. M.; Frederiksen, M. U.; Rudd, M. T. Ruthenium-Catalyzed Reactions—A Treasure Trove of Atom-Economic Transformations. *Angew Chem Int Ed* **2005**, *44* (41), 6630–6666. https://doi.org/10.1002/anie.200500136.
86. Johansson, J. R.; Lincoln, P.; Nordén, B.; Kann, N. Sequential One-Pot Ruthenium-Catalyzed Azide−Alkyne Cycloaddition from Primary Alkyl Halides and Sodium Azide. *J. Org. Chem.* **2011**, *76* (7), 2355–2359. https://doi.org/10.1021/jo200134a.
87. Sadu, V. S.; Sadu, S.; Kim, S.; Hwang, I.-T.; Kong, K.-J.; Lee, K.-I. Influence of Steric Demand on Ruthenium-Catalyzed Cycloaddition of Sterically Hindered Azides. *RSC Adv.* **2017**, *7* (6), 3229–3232. https://doi.org/10.1039/C6RA25403A.
88. Hou, D.-R.; Kuan, T.-C.; Li, Y.-K.; Lee, R.; Huang, K.-W. Electronic Effects of Ruthenium-Catalyzed [3+2]-Cycloaddition of Alkynes and Azides. *Tetrahedron* **2010**, *66* (48), 9415–9420. https://doi.org/10.1016/j.tet.2010.09.099.
89. Ramasamy, S.; Petha, C.; Tendulkar, S.; Maity, P.; Eastgate, M. D.; Vaidyanathan, R. Synergistic Effect of Copper and Ruthenium on Regioselectivity in the Alkyne–Azide Click Reaction of Internal Alkynes. *Org. Process Res. Dev.* **2018**, *22* (7), 880–887. https://doi.org/10.1021/acs.oprd.8b00163.
90. Destito, P.; Couceiro, J. R.; Faustino, H.; López, F.; Mascareñas, J. L. Ruthenium-Catalyzed Azide–Thioalkyne Cycloadditions in Aqueous Media: A Mild, Orthogonal, and Biocompatible Chemical Ligation. *Angew Chem Int Ed* **2017**, *56* (36), 10766–10770. https://doi.org/10.1002/anie.201705006.
91. Ferrini, S.; Chandanshive, J. Z.; Lena, S.; Comes Franchini, M.; Giannini, G.; Tafi, A.; Taddei, M. Ruthenium-Catalyzed Synthesis of 5-Amino-1,2,3-Triazole-4-Carboxylates for Triazole-Based Scaffolds: Beyond the Dimroth Rearrangement. *J. Org. Chem.* **2015**, *80* (5), 2562–2572. https://doi.org/10.1021/jo502577e.
92. Zhang, C.-T.; Zhang, X.; Qing, F.-L. Ruthenium-Catalyzed 1,3-Dipolar Cycloaddition of Trifluoromethylated Propargylic Alcohols with Azides. *Tetrahedron Letters* **2008**, *49* (24), 3927–3930. https://doi.org/10.1016/j.tetlet.2008.04.065.
93. Oakdale, J. S.; Sit, R. K.; Fokin, V. V. Ruthenium-Catalyzed Cycloadditions of 1-Haloalkynes with Nitrile Oxides and Organic Azides: Synthesis of 4-Haloisoxazoles and 5-Halotriazoles. *Chemistry A*

European J **2014**, *20* (35), 11101–11110. https://doi.org/10.1002/chem.201402559.
94. Imperio, D.; Pirali, T.; Galli, U.; Pagliai, F.; Cafici, L.; Canonico, P. L.; Sorba, G.; Genazzani, A. A.; Tron, G. C. Replacement of the Lactone Moiety on Podophyllotoxin and Steganacin Analogues with a 1,5-Disubstituted 1,2,3-Triazole via Ruthenium-Catalyzed Click Chemistry. *Bioorganic & Medicinal Chemistry* **2007**, *15* (21), 6748–6757. https://doi.org/10.1016/j.bmc.2007.08.020.
95. Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. Organic Azides: An Exploding Diversity of a Unique Class of Compounds. *Angew Chem Int Ed* **2005**, *44* (33), 5188–5240. https://doi.org/10.1002/anie.200400657.
96. *New Smart Materials via Metal Mediated Macromolecular Engineering*; Khosravi, E., Yagci, Y., Savelyev, Y., Eds.; NATO Science for Peace and Security Series A: Chemistry and Biology; Springer Netherlands: Dordrecht, 2009. https://doi.org/10.1007/978-90-481-3278-2.
97. Mix, K. A.; Aronoff, M. R.; Raines, R. T. Diazo Compounds: Versatile Tools for Chemical Biology. *ACS Chem. Biol.* **2016**, *11* (12), 3233–3244. https://doi.org/10.1021/acschembio.6b00810.
98. Treitler, D. S.; Leung, S. How Dangerous Is Too Dangerous? A Perspective on Azide Chemistry. *J. Org. Chem.* **2022**, *87* (17), 11293–11295. https://doi.org/10.1021/acs.joc.2c01402.
99. Conrow, R. E.; Dean, W. D. Diazidomethane Explosion. *Org. Process Res. Dev.* **2008**, *12* (6), 1285–1286. https://doi.org/10.1021/op8000977.
100. Feldman, A. K.; Colasson, B.; Fokin, V. V. One-Pot Synthesis of 1,4-Disubstituted 1,2,3-Triazoles from In Situ Generated Azides. *Org. Lett.* **2004**, *6* (22), 3897–3899. https://doi.org/10.1021/ol048859z.
101. Appukkuttan, P.; Dehaen, W.; Fokin, V. V.; Van Der Eycken, E. A Microwave-Assisted Click Chemistry Synthesis of 1,4-Disubstituted 1,2,3-Triazoles via a Copper(I)-Catalyzed Three-Component Reaction. *Org. Lett.* **2004**, *6* (23), 4223–4225. https://doi.org/10.1021/ol048341v.
102. Eddahmi, M.; La Spada, G.; Hafid, A.; Khouili, M.; Catto, M.; Bouissane, L. Towards Alzheimer's Disease-Related Targets: One-Pot Cu(I)-Mediated Synthesis of New Nitroindazolyltriazoles. *Bioorganic Chemistry* **2023**, *130*, 106261. https://doi.org/10.1016/j.bioorg.2022.106261.
103. Barral, K.; Moorhouse, A. D.; Moses, J. E. Efficient Conversion of Aromatic Amines into Azides: A One-Pot Synthesis of Triazole Linkages. *Org. Lett.* **2007**, *9* (9), 1809–1811. https://doi.org/10.1021/ol070527h.
104. Friscourt, F.; Boons, G.-J. One-Pot Three-Step Synthesis of 1,2,3-Triazoles by Copper-Catalyzed Cycloaddition of Azides with Alkynes Formed by a Sonogashira Cross-Coupling and Desilylation. *Org. Lett.* **2010**, *12* (21), 4936–4939. https://doi.org/10.1021/ol1022036.
105. Merkul, E.; Klukas, F.; Dorsch, D.; Grädler, U.; Greiner, H. E.; Müller, T. J. J. Rapid Preparation of Triazolyl Substituted NH-Heterocyclic Kinase Inhibitors via One-Pot Sonogashira Coupling–TMS-Deprotection–CuAAC Sequence. *Org. Biomol. Chem.* **2011**, *9* (14), 5129. https://doi.org/10.1039/c1ob05586k.
106. Zhou, W.; Zhang, M.; Li, H.; Chen, W. One-Pot Three-Component Synthesis of Enamine-Functionalized 1,2,3-Triazoles via Cu-Catalytic Azide–Alkyne Click (CuAAC) and Cu-Catalyzed Vinyl Nitrene Transfer Sequence. *Org. Lett.* **2017**, *19* (1), 10–13. https://doi.org/10.1021/acs.orglett.6b02850.
107. Camberlein, V.; Kraupner, N.; Bou Karroum, N.; Lipka, E.; Deprez-Poulain, R.; Deprez, B.; Bosc, D. Multi-Component Reaction for the Preparation of 1,5-Disubstituted 1,2,3-Triazoles by in-Situ Generation of Azides and Nickel-Catalyzed Azide-Alkyne Cycloaddition. *Tetrahedron Letters* **2021**, *73*, 153131. https://doi.org/10.1016/j.tetlet.2021.153131.
108. González-Bobes, F.; Kopp, N.; Li, L.; Deerberg, J.; Sharma, P.; Leung, S.; Davies, M.; Bush, J.; Hamm, J.; Hrytsak, M. Scale-up of Azide Chemistry: A Case Study. *Org. Process Res. Dev.* **2012**, *16* (12), 2051–2057. https://doi.org/10.1021/op3002646.



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