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Copper-Catalyzed Azide–Alkyne Cycloaddition: Regioselective Synthesis of 1,4,5-Trisubstituted 1,2,3-Triazoles**

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azides · click chemistry · cycloaddition · iodoalkynes · iodotriazoles

Since Kolb, Finn, and Sharpless laid down the foundations of click chemistry in 2001,[1] there has been an explosive growth in this area of chemistry. The emergence of the copper-catalyzed azide–alkyne cycloaddition reaction[2] (CuAAC) as an entry point to 1,4-triazoles **1** raises a challenge for the discovery of new chemical approaches with equal or even greater fidelity. The CuAAC is second order with respect to copper, although increasing the concentration of copper results in less reactive species such as metal aggregates. These results suggest that a family of Cu^I species in dynamic equilibrium may exist in solution.[3] However, whether mono- or dicuprate species are involved, the observed regioselectivity may be neatly explained through a key complex (**5** or **8**) between a copper(I) acetylide with the α-nitrogen atom of the organic azide **4** (Scheme 1).[3] Consequently, the CuAAC is limited to terminal alkynes.

The recent advent of the ruthenium-catalyzed Huisgen reaction makes available the complementary 1,5-disubstituted 1,2,3-triazoles, although efficiency and reliability does not match the parent reaction. Notably, Ru^{II}-catalysis can be extended to internal alkynes, thus giving the corresponding trisubstituted products.[4] However, few reliable methods exist for the synthesis of trisubstituted triazoles with good regiocontrol and functional group tolerance, thus presenting an opportunity for discovery. Several groups have independently taken up this challenge, and sought to discover a general method for the regio-controlled synthesis of substituted 1,2,3-triazoles using metal-catalyzed "cycloaddition" reactions. The first example was reported by Wu et al. in 2005,[5] who investigated the possibility of trapping cuprate–triazole intermediates (e.g. see **7**, Scheme 1)[6] with electrophiles. Optimal results were obtained when ICl was used in conjunction with a stoichiometric quantity of CuI and five equivalents of triethylamine.

The versatility of this protocol was demonstrated by the broad substrate tolerance of the azides, including benzyl, alkyl, and 2,2-dihydropolyfluoroalkyl groups. Meanwhile, the terminal alkyne could carry substituents such as alkyl, ester, amide, and aromatic groups. The corresponding 5-iodo-1,2,3-triazole products were amenable to further functionalization, thus making them attractive synthetic intermediates. Trapping cuprate-triazole intermediates with alternative electrophiles such as allyl bromide, benzoyl chloride, and acetyl chloride resulted in lower yields. Major disadvantages include the requirements for stoichiometric quantities of Cu^I, and prolonged reaction times (20 h).

Later in 2005, Rutjes and co-workers reported a catalytic procedure for the formation of 5-bromo-1,2,3-triazoles.[7] By using bromoalkynes and a combination of CuI and $Cu(OAc)_2$, the reaction with organic azides proceeded readily to form the corresponding 5-bromo-1,2,3-triazole derivatives in high yield and with excellent regioselectivity. Nonetheless, this catalytic system often gave small quantities of 5-iodo-1,2,3-triazoles as the by-product, which could be avoided if a combination of $CuBr/Cu(OAc)_2$ was used. In general, the method was robust and had a wide scope—tolerating electron-withdrawing and electron-donating groups, as well as sterically congested alkynes. Interestingly, the reaction was not amenable to iodoalkynes, which appeared to be unstable under the reaction conditions.

While investigating the effects of amine ligands on the solubility of Cu^I salts in CuAAC related work in 2006, Porco and co-workers observed the unexpected formation of 5-alkynyl-1,2,3-triazoles.[8] Exploiting this discovery, the group found optimal conditions using a 2:1 ratio of Cu^I/*N*-methylmorpholine oxide (NMO) and *N*,*N*,*N′*-trimethylethylenediamine as the ligand under an oxidative atmosphere. 5-Substituted triazoles were obtained within 20 min, albeit in low to moderate yields (31–64 %) as a result of competing Glaser coupling.

In 2007, Hsung and co-workers reported the use of allyl iodides as suitable electrophiles for trapping cuprate–triazole intermediates **7** derived from ynamides, organic azides, and one equivalent of CuBr in CH_3CN.[9] Their plan was to develop a practical entry to 5-allyl-1,2,3-triazoles as substrates

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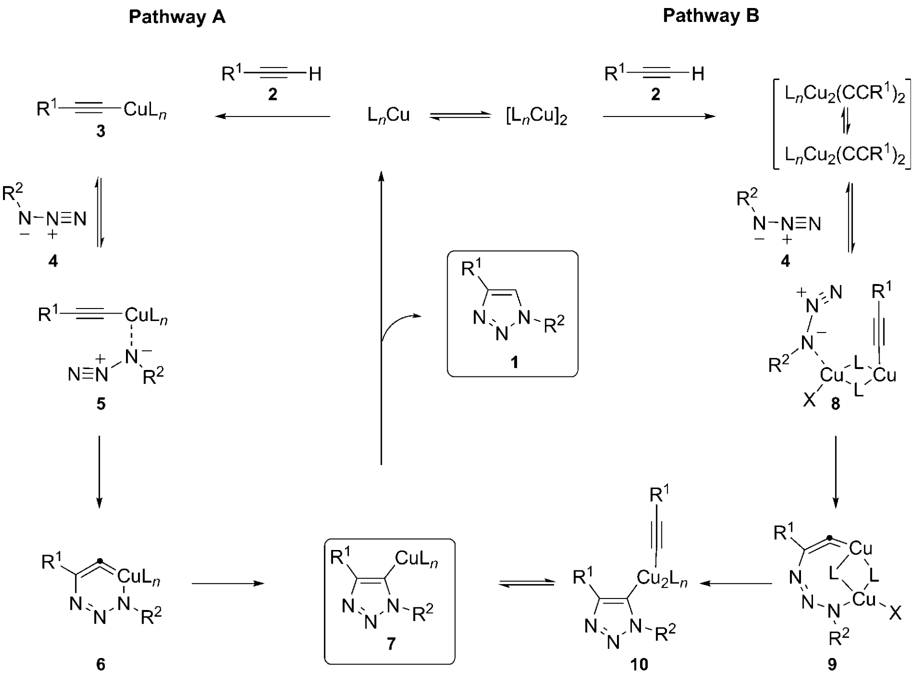


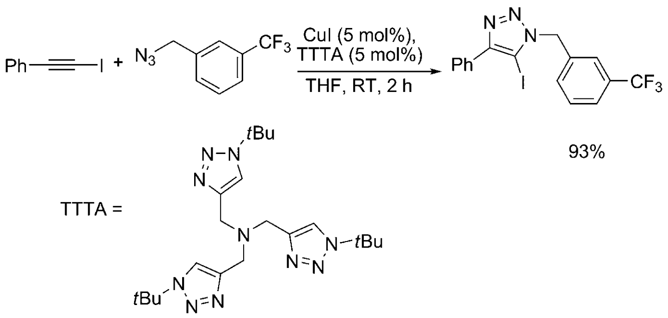
Scheme 1. Proposed mechanism for the copper-catalyzed reaction.

for ring-closing metathesis. Limiting the scope of this reaction was the requirement for strict anhydrous conditions because of the sensitivity of ynamides towards hydrolysis, and a need for stoichiometric quantities of Cu^I salts. Although promising as a basis to build more complicated ring systems, the reactions were generally sluggish (48 h) and the yields were moderate (26–74 %).

More recently (2008), Zhang and co-workers reported an advance on Wu's methodology[5] by developing a one-pot system.[10] A combination of CuI and NBS (*N*-bromosuccinimide) were used to generate in situ, a reactive iodonium ion for trapping the cuprate–triazole intermediate (see **7**, Scheme 1). This improved protocol generally provided higher yields with shorter reaction times, although this reaction still required an equimolar quantity of CuI.

The latest and perhaps most significant advancement in methodology towards the synthesis of trisubstituted 1,2,3-triazoles has very recently emerged from Hein et al.[11] Building upon their pioneering work on the CuAAC reaction, their team has developed a system using stable and readily accessible 1-iodoalkynes for the synthesis of 5-iodo-1,2,3-triazoles using catalytic Cu^I salts (Scheme 2). A series of copper sources and ligands were screened, with the CuI/TTTA complex emerging as the superior system. Unlike the related methods described herein, the optimized reaction worked efficiently with low catalyst loadings and with complete regioselectivity. Reaction times were short, and the conditions were mild with straightforward work-up/purification. This new "click" reaction tolerated a comprehensive number of functional groups, as exemplified by the vast array of simple to sterically congested substituents placed on the azide and alkyne components. The reaction was amenable to scale-up, thus enabling multigram quantities of the target 5-iodo-1,2,3-triazoles to be prepared.

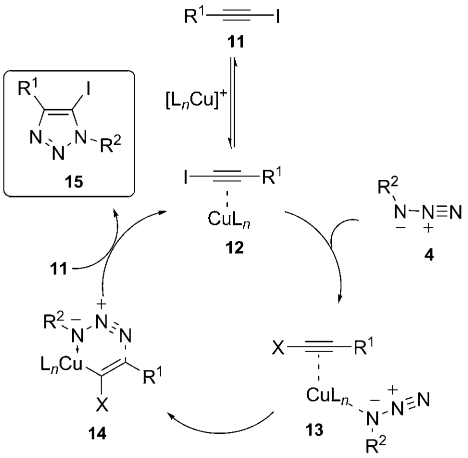
The CuI/TTTA catalyst shares properties with the classic CuAAC system, in that it is compatible with a wide range of protic solvents including water. Sharpless, Fokin, and co-workers also described a simple and efficient entry to the 1-iodoalkyne building blocks from the corresponding terminal acetylenes. The method required treating a terminal alkyne with *N*-iodomorpholine in the presence of CuI, giving the product within 30–60 min in good to excellent yield. The reliability of this iodination protocol was demonstrated in a one-pot, two-step synthesis of the 5-iodo-1,2,3-triazoles in yields comparable to those observed for purified 1-iodoalkynes. This efficient method was extended to a convenient multi-component, one-pot procedure for the synthesis of trisubstituted triazoles. 5-Iodo-1,2,3-triazoles were rapidly assembled and cross-coupled with arylboronic acid using catalytic palladium.



Scheme 2. The Cu^I-catalyzed cycloaddition of organic azides and 1-iodoalkynes developed by Hein et al.

A detailed mechanistic investigation to explain the high fidelity and regiospecificity of this reaction is yet to be provided. Sharpless, Fokin, and co-workers propose two plausible pathways, one of which mirrors that of the standard CuAAC reaction—where the regiochemistry is controlled through coordination of the azide by the proximal nitrogen center of **4** with copper acetylide **3** leading to complex **5**, followed by cycloaddition leading to **7** (Scheme 1). In the presence of electrophiles (e.g. I^+), the cuprate–triazole intermediates (e.g. **7**) are quenched. In such a case, it would be expected that sluggish or in situ generated electrophiles would result in low conversions owing to the formation of 5-*H*-triazoles through proton quenching (see Wu,[5] Porco,[8] and Hsung[9]).

Based on their preliminary studies, Sharpless, Fokin, and co-workers[11] favor the mechanism outlined in Scheme 3 as



Scheme 3. Mechanistic proposal for the copper-catalyzed reaction.

the most plausible pathway. Their reasoning is based mainly on the observation that even when the reaction is conducted in protic solvents, or with substrates containing acidic protons, exclusive formation of the iodotriazole was observed. Otherwise, cuprate **7** could in principle be quenched with other electrophiles, including a proton, thus leading to a mixture of 5-iodo and 5-prototriazoles. The mechanism envisioned begins with formation of a π-complex **12** between Cu^I and the iodoalkyne **11**. Unlike the classic CuAAC mechanism, the activated acetylene does not seem to form an acetylide. Instead, the organic azide engages into a dative interaction with the metal centre **13**, followed by a ring closure via a vinylidene-like transition state **14**, to give 5-iodotriazole **15**.

The same mechanistic features can be ascribed to the protocol developed by Rutjes and co-workers,[7] but this does not explain the formation of 5-iodo-1,2,3-triazoles. In this case, the 5-iodo-1,2,3-triazoles could have formed from in situ generated iodoalkynes through halogen–halogen nucleophilic displacement between bromoalkyne and CuI.[12] The results of Sharpless, Fokin, and co-workers contradict this hypothesis, as there was no observed reactivity between the organic azide and iodoalkyne in the absence of an additive such as TTTA. Rutjes and co-workers claimed that iodoacetylenes were unstable under their reaction conditions. This observation may suggest that 5-halotriazoles are being generated by another route. Notably, traces of iodotriazoles observed in Rutjes protocol might be a consequence of longer reaction times (16–40 h). The traces of iodotriazoles would account for the formation of iodoalkynes and the subsequent sluggish Cu^I-mediated cycloaddition.

In summary, Sharpless, Fokin, and co-workers have described an efficient, robust, and reliable protocol for the synthesis of 5-iodo-1,2,3-triazoles. Although further mechanistic studies are required to fully explain the observed regioselectivity, it is evident that the success of this system may be attributed to the additive effect of TTTA on the catalytic cycle. The ligand appears to enhance the catalytic activity of CuI without compromising the stability of iodoalkynes. As a result, the reaction is amenable to low catalyst loadings compared to related protocols. The method is wide in scope and offers benefits commensurate with the familiar CuAAC, thus proving a welcome addition to the click chemistry toolbox.

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