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Copper(I)-Catalyzed Three-Component Click/Alkynylation: One-Pot Synthesis of 5-Alkynyl-1,2,3-triazoles

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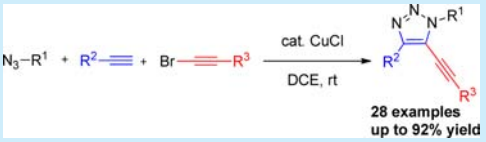
Supporting Information

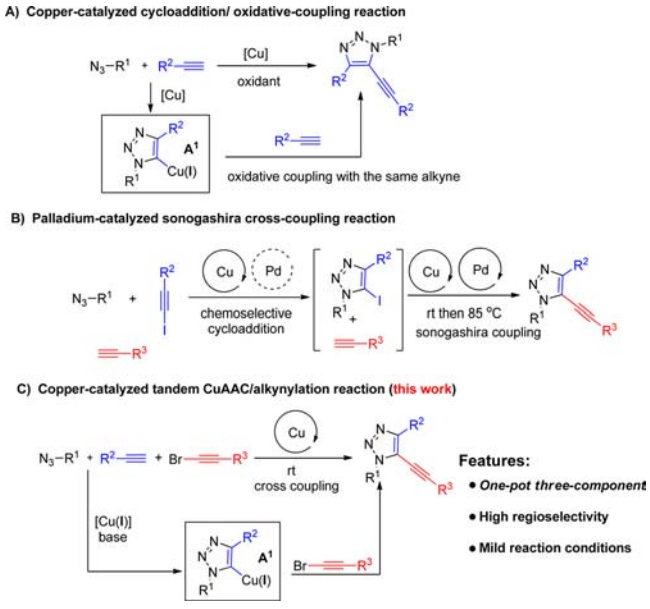
ABSTRACT: A copper(I)-catalyzed tandem CuAAC/alkynylation reaction of various alkynes, organic azides, and bromoalkynes to provide rapid access to 5-alkynyl-1,2,3-triazoles has been developed. The reaction proceeded via a copper-catalyzed alkyne azide cycloaddition followed by interception of the in situ formed cuprate−triazole intermediate with bromoalkyne. This reaction offers a new method to afford fully substituted triazoles in high yields with complete regioselectivity under mild reaction conditions.



The copper-catalyzed azide−alkyne cycloaddition (CuAAC) has received significant attention since its pivotal discovery by the Meldal[1] and Sharpless groups.[2] It also has played a unique role in a variety of disciplines such as organic chemistry,[3] polymer chemistry, materials science,[4] and biological conjugation.[5] In addition, the 1,2,3-triazole products are important nitrogen heterocyclic compounds and have found widespread applications in medicinal chemistry.[6] Recently, they were also widely used as ligands for catalysis[7] and directing groups for transition-metal-catalyzed C−H activation.[8] The classical CuAAC reaction affords only 1,4-disubstituted 1,2,3-triazoles using terminal alkyne as an essential substrate; however, such reactions of internal alkyne affording trisubstituted triazoles are much more difficult because of their low reactivity and difficulty in regiocontrol. Thus, the development of an efficient strategy to access fully substituted triazoles beyond click chemistry is highly desirable.[9,10]

5-Alkynyl-1,2,3-triazoles are an important type of substituted 1,2,3-triazoles, and the alkyne moiety can be converted into other functional groups or heterocycles. Previous methods primarily focus on the oxidative coupling reaction between the in situ formed cuprate-trizaole **A**[1] with the same alkyne, which limits the diversity of the products (Scheme 1A).[11] This method needs to add exogenous oxidizing agents, and it would be difficult to inhibit homocoupling byproducts such as 1,3-diynes and bistriazoles.[12] Recently, Lautens et al. described a Cu/Pd-catalyzed two-step sequence to access 5-alkynyl-1,2,3-triazoles (Scheme 1B).[13a] This reaction involves a copper-catalyzed chemoselective cycloaddition to form the stable 5-iodo-1,2,3-triazoles followed by a palladium-catalyzed Sonogashira cross-coupling reaction with terminal alkynes. This elegant three-component reaction was successful based on the fact that the iodoalkyne is more reactive in the CuAAC reaction than terminal alkyne. However, this reaction requires precious palladium catalyst. Very recently, we developed a copper(I)-catayzed interrupted click reaction for the synthesis of diverse 5-heterofunctionalized triazoles.[14] The essence of this strategy is the use of an active heteroatom electrophile to trap the cuprate−triazole intermediate **A**[1]. Following this concept, we were intrigued by the question of whether an electrophilic alkynyl reagent such as bromoalkyne could intercept the intermediate **A**[1] to construct 5-alkynyl-1,2,3-triazoles (Scheme 1C).

Scheme 1. Methods for Synthesis of the Fully Substituted 5-Alkynyl-1,2,3-triazoles



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Bromoalkyne, as an electrophilic alkynyl agent, has been extensively studied in many synthetic reactions due to its special properties such as higher stability, easier handling, and ready preparation in quantitative yields from terminal alkyne and NBS.[15] However, achieving the desired three-component reaction is challenging, as there are three competing reactions: (1) bromoalkyne may compete with terminal alkyne to undergo cycloaddition with azides forming 5-bromotriazles **6**;[16] (2) reaction of copper(I) acetylide with the bromoalkyne generating diyne, which is unreactive under click reaction conditions; and (3) protonation of the cuprate−triazole intermediate $\mathbf{M}^1$ producing the undesired 1,4-disubstituted triazole **5**. How to inhibit the undesired reaction pathways is the most challenging issue of the proposed three-component reaction.

To test this hypothesis, phenlyacetylene **1a**, benzyl azide **2a**, and bromoalkyne **3a** were selected as model substrates to optimize the reaction conditions (see the Supporting Information for details). We first investigated the influence of solvents (pentane, toluene, MeCN, THF, DCE, and iPrOH) (Table 1, entries 1−6) in the presence of 20 mol % CuCl and

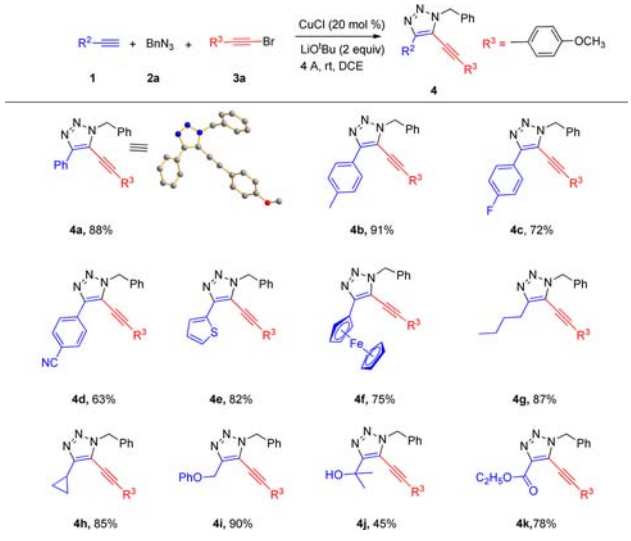
Table 1. Optimization of Reaction Conditions[a]

				yield[b] (%)	
entry	base	temp (°C)	solvent	**4a**	**5a**
1	LiO^{t}Bu	25	pentane	67	25
2	LiO^{t}Bu	25	toluene	52	17
3	LiO^{t}Bu	25	CH_3CN	35	52
4	LiO^{t}Bu	25	THF	63	21
5	**LiO^{t}Bu**	**25**	**DCE**	**88**	**8**
6	LiO^{t}Bu	25	iPrOH	48	33
7	KO^{t}Bu	25	DCE	21	64
8	NaO^{t}Bu	25	DCE	46	18
9	K_2CO_3	25	DCE	51	43
10	Et_3N	25	DCE	40	47
11	NaOMe	25	DCE	62	31
12	LiO^{t}Bu	40	DCE	67	24
13[c]	LiO^{t}Bu	25	DCE	86	6

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), **3a** (0.4 mmol), CuCl (20 mol %), base (0.4 mmol), 4 Å molecular sieves (MS, 150 mg), and solvent (1 mL) were stirred at room temperature under N_2 atmosphere for 12 h. [b]Isolated yield. [c]CuCl (10 mol %).

LiO^{t}Bu as the base. To our delight, the byproduct **6** from the direct cycloaddition of bromoalkyne with azide was not observed under these conditions. DCE was the best solvent, affording the desired product **4a** in 88% isolated yield together with 8% of the click product **5a**, which is the optimial reaction condition (entry 5). The structure of **4a** was confirmed by X-ray crystallographic analysis (Scheme 2). Further optimization of different bases showed that LiO^{t}Bu plays an essential role in this reaction, and other bases tested were found to be less efficient (entries 7−11). When the reaction temperature increased to 40 °C, only 67% yield of **4a** was obtained (entry 12). Interestingly, the reaction proceeded efficiently at room temperature with only 10 mol % of copper catalyst loading

Scheme 2. Scope of the Terminal Alkynes[a]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), **3a** (0.4 mmol), CuCl (20 mol %), LiO^{t}Bu (0.4 mmol), 4 Å molecular sieves (MS, 150 mg), and DCE (1 mL) were stirred at room temperature under N_2 atmosphere for 12 h. Isolated yields are reported.

(entry 13). Screening other copper catalysts or adding nitrogen or phosphine ligands into the reaction system could not increase the yield (see the SI for details).

With the optimized reaction conditions in hand, we initially investigated the scope of various terminal alkynes (Scheme 2). Both aromatic and aliphatic alkynes reacted smoothly with **2a** and **3a**, affording the corresponding 5-alkynyl-1,2,3-triazoles in good to excellent yields as the single regioisomer. It was observed that the electron-withdrawing or electron-donating groups at the *para* position of the aromatic ring were well tolerated to give the desired products (**4a−d**) in 63−91% yields. In addition, thiophene- or ferrocene-substituted acetylenes gave **4e** and **4f** in 82% and 75% yields, respectively. Notably, alkylacetylenes were also applicable in this transformation to afford the corresponding triazoles in good yields (**4g−j**). Sterically hindered alkyne **1j** could also react efficiently to provide triazole **4j** in 45% yield. Electron-deficient ethyl propiolate was also suitable for this three-component reaction, generating trisubstituted triazole **4k** in 78% yield.

We next examined the scope of this transformation with respect to different azides (Scheme 3). All of the aliphatic azides tested can participate in this cross-coupling reaction to give the desired 1,2,3-triazoles derivatives in good to excellent yields under standard conditions. Interestingly, cinnamyl- (**4o**), octyl- (**4q**), and phthalimide-protected amines (**4r**) and the indole skeleton (**4s**) are all tolerated under these mild reaction conditions.

The scope of various bromoalkynes was further investigated (Scheme 3). Various aryl-substituted bromoalkynes and alkyl-substituted bromoalkynes were all amenable to this reaction, providing the corresponding triazoles **4t−y** in mostly very good yields. Notably, the triisopropyl (TIPS)-substituted bromoalkyne could also react with terminal alkyne and azide to form trisubstituted triazole product **4y** in 87% yield. The TIPS of the triple bond can be efficiently removed by TBAF, giving a terminal alkyne substituted triazole **7** in 84% yield (Scheme 4). This terminal alkyne could be further functionalized; for example, another step of click reaction with benzyl azide and *N*-

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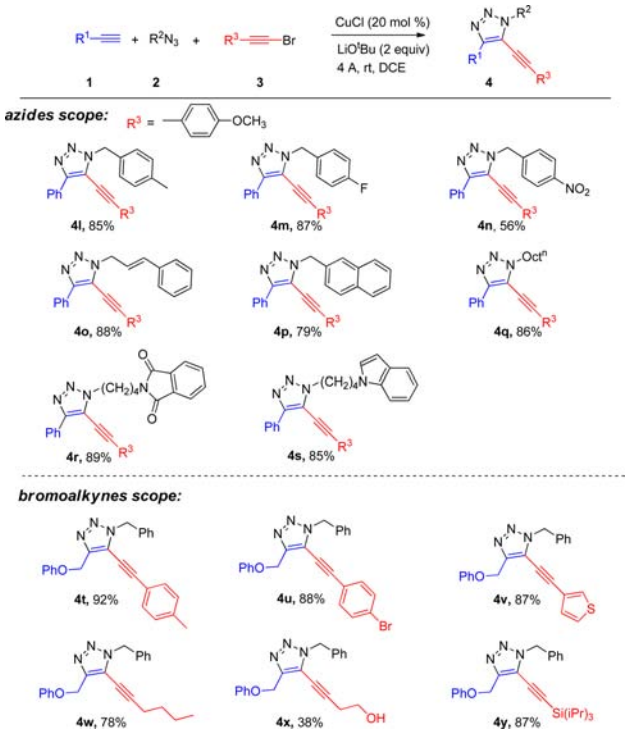
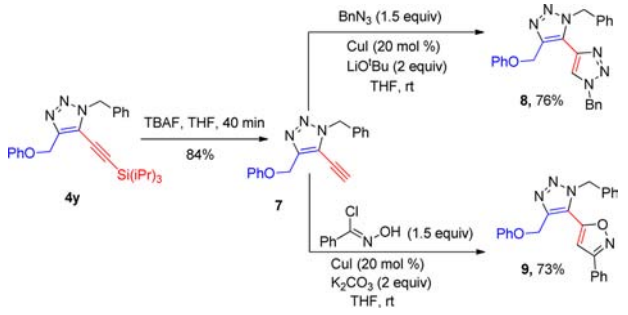
Scheme 3. Substrate Scope of Azides and Bromoalkynes[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), **3** (0.4 mmol), CuCl (20 mol %), LiO^{t}Bu (0.4 mmol), 4 Å molecular sieves (MS, 150 mg), and DCE (1 mL) were stirred at room temperature under N_2 atmosphere for 12 h. Isolated yields are reported.

Scheme 4. Synthesis of Terminal Alkyne-Substituted Triazole and Its Further Functionalization Reactions

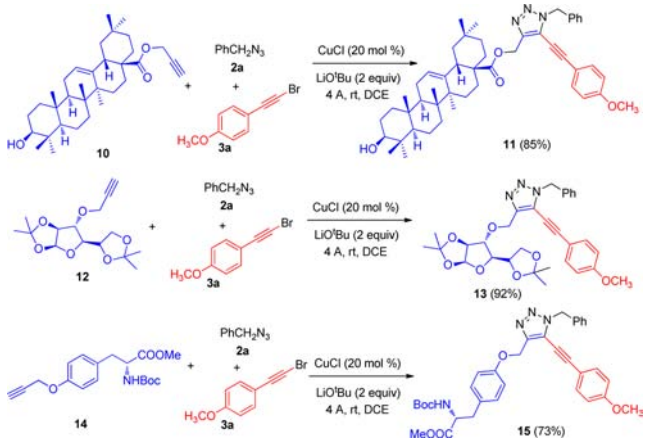


hydroxybenzimidoyl chloride gave the bistriazoles **8** and isoxazole-substituted triazole **9** in 76% and 73% yields, respectively.

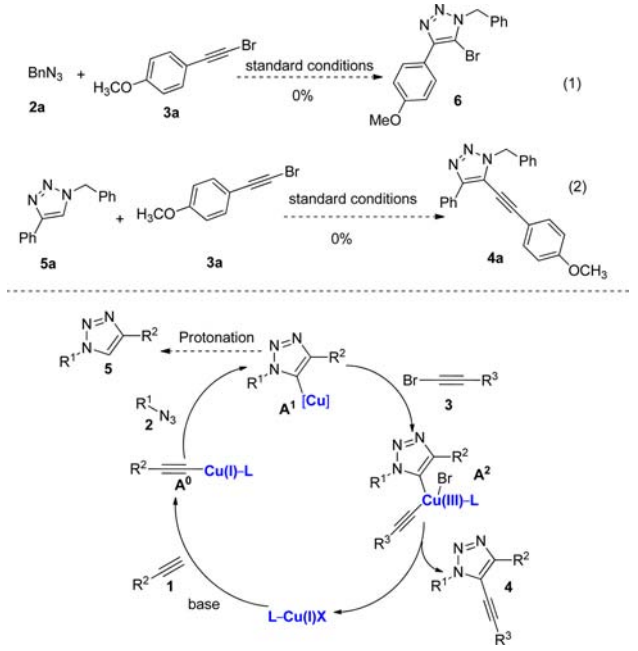
The utility of this chemistry was demonstrated by the late-stage click reaction on bioactive natural compounds, sacchaarides, and amine acid derivatives (Scheme 5). The oleanane-type triterpene-derived alkyne **10** could be transformed into the corresponding triazole **11** in 85% yield. Moreover, the sugar derivative **12** and the amino acid derivative **14** were all suitable substrates and afforded the desired products in good yields. These reactions indicated that this method has great potential in medicinal chemistry.

Control experiments were conducted to explore the reaction mechanism (Scheme 6). First, **2a** failed to react with **3a** to afford the trisubstituted triazole **6** under the standard conditions, which indicated the terminal alkyne is more reactive than bromoalkyne **3a** in this cycloaddition reaction. Disub-

Scheme 5. Late-Stage Functionalization of Biologically Active Molecules



Scheme 6. Control Experiments and Proposed Reaction Mechanism



stituted triazoles (**5a**), the major byproduct of this reaction, were subjected to the reaction with **3a** under the standard conditions.The product **4a** was not detected, which indicated the click reaction and subsequent C−H activation pathway are not possible.

On the basis of these experiments, a reasonable reaction mechanism was proposed (Scheme 6). First, copper(I) acetylide $\mathbf{A^0}$ was generated from the reaction of CuCl and alkyne in the presence of LiO^{t}Bu. Then the cycloaddition of $\mathbf{A^0}$ with the azide formed the cuprate−triazole intermediate $\mathbf{A^1}$. $\mathbf{A^1}$ reacted with the bromoalkyne through an oxidative addition reaction to form intermediate $\mathbf{A^2}$, which undergoes a reductive elimination to furnish the target product **4** along with regeneration of Cu(I) catalyst.

In summary, we have developed a copper(I)-catalyzed three-component reaction to access diverse 5-alkynyl-1,2,3-triazoles from easily available terminal alkynes, organic azides, and bromoalkynes. The reaction has notable features, including inexpensive copper catalyst, mild conditions, and complete

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regioselectivity. This method could also be utilized in the late-stage functionalization of bioactive compounds and amino acids. Further applications of this interrupted click reaction strategy in organic synthesis and medicinal chemistry are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02199.

Experimental details and spectral data for new compounds (PDF)

X-ray data for compound **4a** (CIF)

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Notes

The authors declare no competing financial interest.

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