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Copper(I)-catalyzed interrupted click/radical relay: A four-component modular synthesis of triazole sulfones

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ABSTRACT

A new, four component copper(I)-catalyzed interrupted click/radical relay cascade has been developed. This unprecedented interrupted click reaction provides a rapid modular synthesis of triazole sulfones, important privileged heterocyclic pharmacophores which cannot be accessed by a traditional click reaction. Radical interception of cuprate-triazole, the key reaction intermediate formed *in situ*, is an important feature of this process.

The sulfone group, O=S=O is a basic functional group in organic chemistry and it is found in numerous top-selling drugs such as Celecoxib [1], Tipranavir [2] and Promin [3,4] (Fig. 1). Diaryl or heteroaryl sulfones have shown significant antimicrobial and antioxidant activity [5–11]. A 1,2,3-triazole is a type of privileged heterocyclic pharmacophores widely used in medicinal and biological chemistry. A triazole sulfone(VI) has been shown to have potent antifungal activity against filamentous fungi [12]. Synthesis of such compounds can however be difficult. Heat promoted Huisgen cycloaddition of alkynyl sulfones with azides for example, produces two regioisomers with poor selectivity [13], and copper(I)-catalyzed azide alkyne cycloaddition (CuAAC) reactions are limited to terminal alkynes and are difficult to produce triazole sulfones [14]. Consequently, development of an efficient method to access these sulfones is necessary.

Click reactions are modular, reliable and efficient reactions, which can rapidly join small units together. This type of reaction has important features, including stereospecificity, facile reaction conditions, high yields and easily available starting materials. In 2002, the groups of Sharpless [15,16] and Meldal [17] reported the reaction with CuAAC giving 1,4-disubstituted 1,2,3-triazoles as a single product. In the subsequent 20 years this reaction has been developed as a prime example of "click chemistry" and is now widely used in organic chemistry, medicinal chemistry, chemical biology, and materials science [18–25]. These are typical examples of "two component" click reactions (Scheme 1A) [26–32]. In 2016, we reported the "three component" click reaction by using an active heteroatom electrophile to intercept the key click intermediate, the cuprate triazole (**M^1**) [33]. Diverse 5-hetero-functionalized triazoles could be quickly assembled in one step in high yields with absolute regioselectivity. Since then, diverse functionalized trisubstituted triazoles were constructed with a sequence of C−C or C-heteroatom bond formation reactions (Scheme 1B) [34–51]. Such interrupted click chemistry reactions are important because traditional click reactions using CuAAC cannot produce these core structures. "Four component" click reaction has been rarely reported to date. Herein, we report the first example of construction of triazole sulfones through an interrupted click/sulfone radical relay sequence (Scheme 1C).

Incorporation of sulfur dioxide into organic molecules is still underdeveloped when compared with the reactions of carbon monoxide. In 2010, the Willis group [52] reported the first use of DABCO·$(SO_2)_2$ (DABSO), a crystalline solid, as a convenient source of sulfur dioxide which participates in a palladium-catalyzed three-component coupling of aryl iodides, SO_2 and hydrazines. Subsequently, the groups of Willis, Wu and others have made tremendous progress in the synthesis of molecules containing O=S=O

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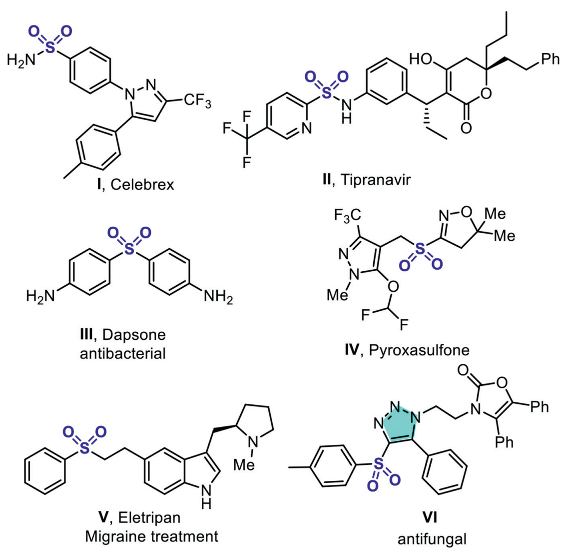
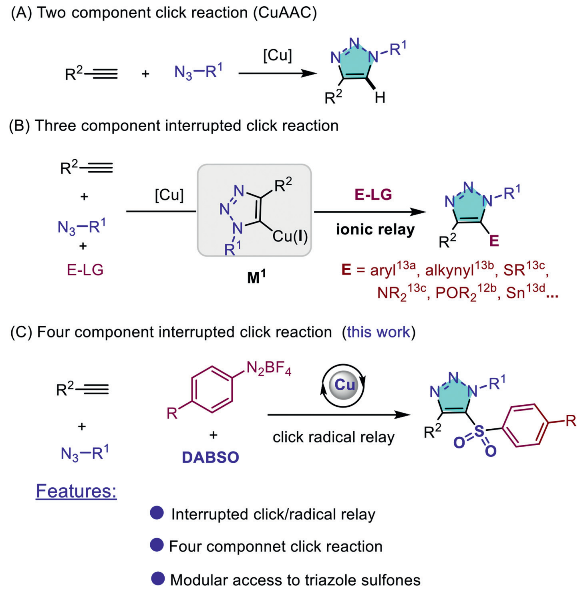


Fig. 1. Representative pharmaceuticals and bioactive products containing a sulfone moiety.



Scheme 1. The click reaction and multicomponent interrupted click reactions.

using DABSO as a convenient and safe source of SO_2 [53–70]. More importantly, this reagent shows ambident reactivity in both transition-metal catalyzed and radical reactions. For instance, Wu *et al.* [71] have demonstrated that aryldiazonium salts combined with DABSO can generate sulfonyl radicals which participate in radical cascade reactions. With our continuing interest in interrupted click reactions, we questioned if this sulfonyl radical formed in situ could intercept click intermediate, triazole copper (**M^1**) to construct triazole sulfones. All previous interrupted click reactions proceed via an ionic electrophilic pathway, and to date, an interrupted click radical relay of this type has not been reported.

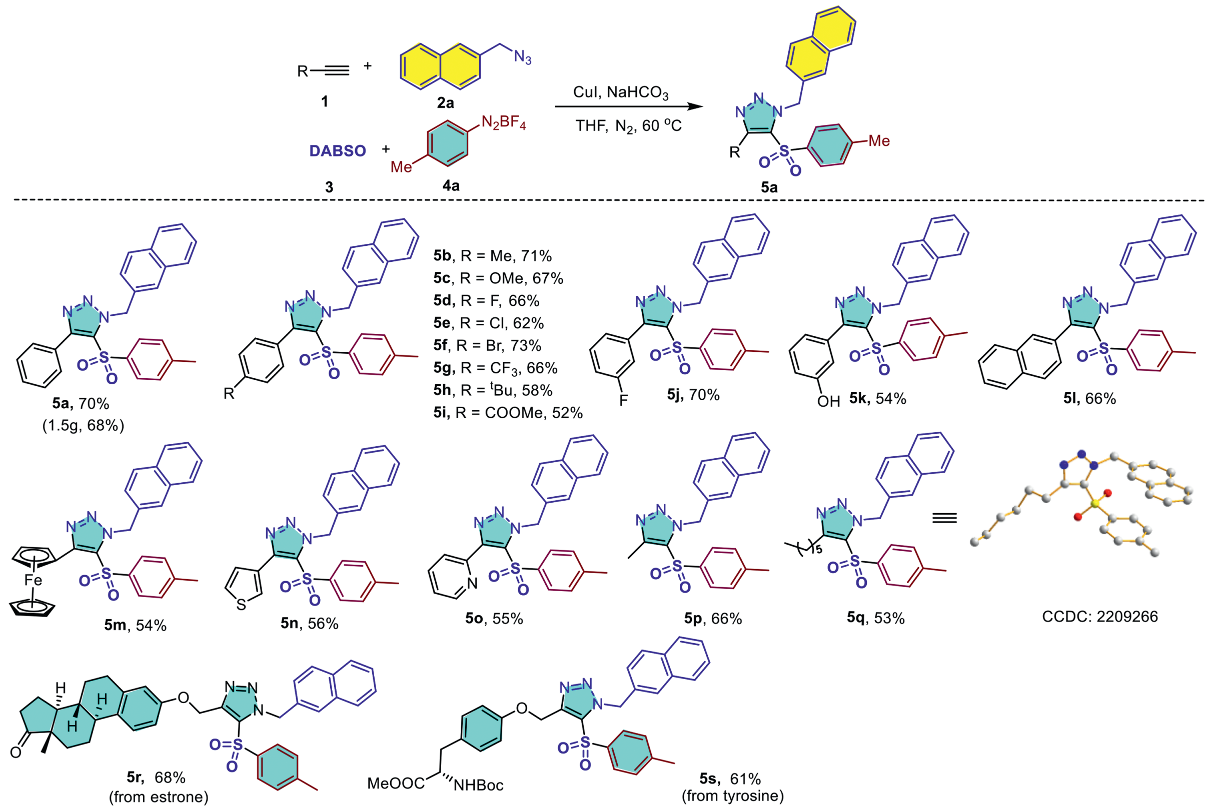
The major challenge of this four-component click reaction lies in ensuring that the four reactants proceed in the proposed programmed cascade and balancing the transition metal catalytic cycle with the high reactivity of radicals, to prevent domination by undesired side reactions. To test our hypothesis, phenylacetylene (**1a**), 2-naphthyl methylene azide (**2a**), DABSO (**3**), and *para*-tolyldiazonium tetrafluoroborate (**4a**) were selected as the model substrates to optimize various copper(I)-catalyzed click reaction conditions (for details, see Table S1 in Supporting information). In addition to the main product, 1-(naphthalen-2-ylmethyl)-4-phenyl-5-tosyl-1*H*-1,2,3-triazole (**5a**), the protonated two-component click product (**6a**) was the major side product of the reaction, and traces of other possible side products such as an alkynyl sulfone (**7a**) or an internal alkyne (**8a**) were observed. After a detailed optimization of various reaction parameters, the proposed four-component coupling product (**5a**) was isolated in 70% yield under quite simple standard conditions, involving a mixture of CuI (10 mol%), $NaHCO_3$ (2 equiv.) in dry THF (2 mL) stirred at 60 °C in a N_2 atmosphere (Table S1, entry 1).

With the optimal conditions established, we investigated the substrate scope of this four-component click reaction. First, the reactivity of various terminal alkynes was examined (Scheme 2). This four-component click reaction is applicable to a wide range of terminal alkynes including aromatic and aliphatic alkynes and delivers the corresponding triazole (**5a-5q**) in moderate to good yields. Aromatic alkynes bearing different electron-withdrawing or electron-donating functional groups at the *para*- or *meta*-position of the phenyl ring all reacted smoothly under standard conditions, giving the desired products in good yields. A series of functional groups such as methoxyl, fluoro, bromo, trifluoromethyl and phenyl are all tolerated, thus allowing further functionalization if necessary. Various other structures, including ferrocene (**5m**), thiophene (**5o**), and pyridine (**5p**) are all successful in this transformation. The structure of a triazole (**5q**) was unambiguously characterized by X-ray diffraction analysis. This method can be further utilized in the late-stage functionalization of complex natural products. Functionalized alkynes derived from estrone (**5r**) and tyrosine (**5s**) reacted smoothly under the standard conditions, affording the corresponding products in good yields. Thus this reaction has good potential in drug discovery and development.

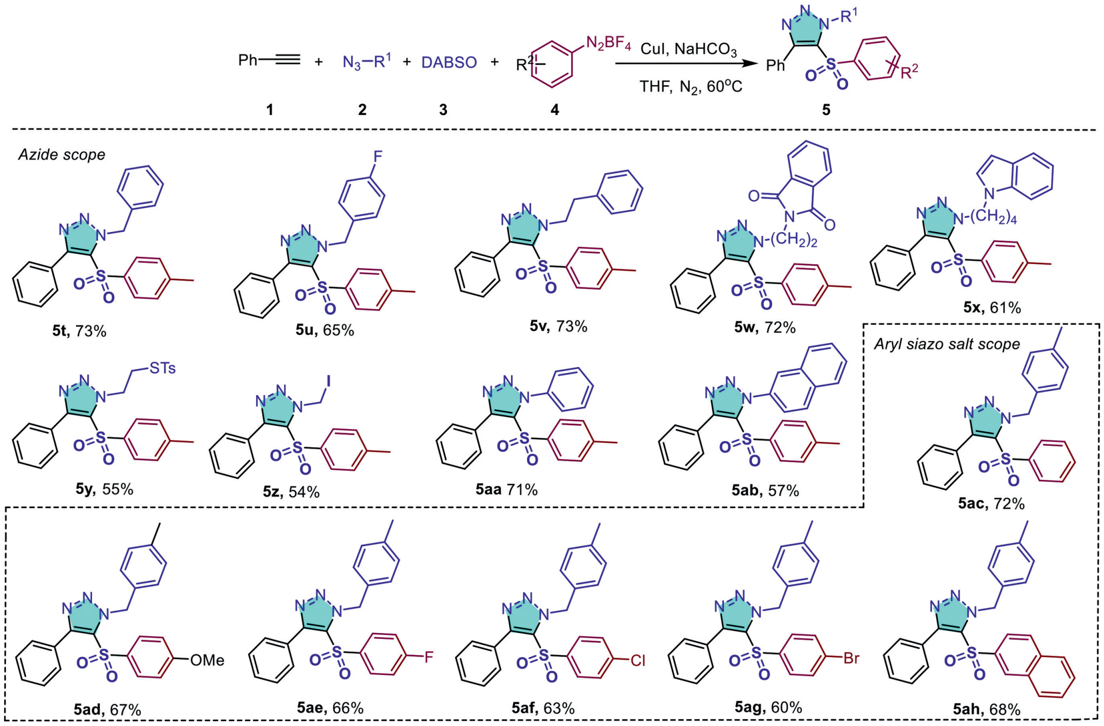
The scope of azides and aryl diazo salts was next examined (Scheme 3). Aliphatic and aromatic azides that were tested reacted smoothly, affording the corresponding four-component adducts in good yields. Phthalimide-protected amine (**5w**), indole skeleton (**5x**) and aliphatic iodide (**5z**) are all tolerated under these mild conditions. Various aryl diazo salts with different electron-withdrawing groups or electron-donating groups are amenable to this transformation, giving the corresponding products (**5ac-5ah**) smoothly.

To gain more insight into the mechanism of the reaction, we conducted several control experiments (Fig. 2). Upon addition of the radical inhibitor 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) into the reaction system, the four-component reaction was totally shut down, and the two-component click product, 1-(naphthalen-2-ylmethyl)-4-phenyl-1*H*-1,2,3-triazole (**6a**) was produced in 92% yield (Fig. 2A). These results indicated the second step involves a radical process while the radical species has little effect on the robust CuAAC catalytic cycles. To trap the radical species, a milder radical scavenger, 1,1-diphenylethylene was used. This prevented the four-component click reaction and led to the isolation of (2-tosylethene-1,1-diyl)dibenzene (**9**) in 45% isolated yield, suggesting formation of a toluenesulfonyl radical in the standard reaction. A further copper(I)-catalyzed three-component reaction of 1,1-diphenylethylene, DABSO, and toluenediazonium tetrafluoroborate (**4a**) produced **10** in 72% yield. These results clearly indicate that copper(I) promotes the reaction between DABSO and **4a** can generate a tolylsulfone radical very efficiently. These experiments clearly indicate a click reaction followed by a sulfone radical relay process.

Two other possible reaction pathways can be considered for this reaction (Path B and C, Fig. 2). The three-component reaction between the alkyne (**1a**), DABSO, and **4a** in the absence of azide, did produce 1-methyl-4-(phenethynesulfonyl)-benzene (**7a**) [72,73], however this internal alkyne is not reactive enough to un-



Scheme 2. Substrate scope of terminal alkynes. Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), **3** (0.3 mmol), **4a** (0.4 mmol), CuI (10 mol%), NaHCO$_3$ (2 equiv.), dry THF 2 mL, 60 °C, under a nitrogen atmosphere for 24 h.



Scheme 3. Substrate scope of azides and aryl diazo salts. Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), **3** (0.3 mmol), **4** (0.4 mmol), CuI (10 mol%), NaHCO$_3$ (2 equiv.), dry THF 2 mL, 60 °C, under a nitrogen atmosphere for 24 h.

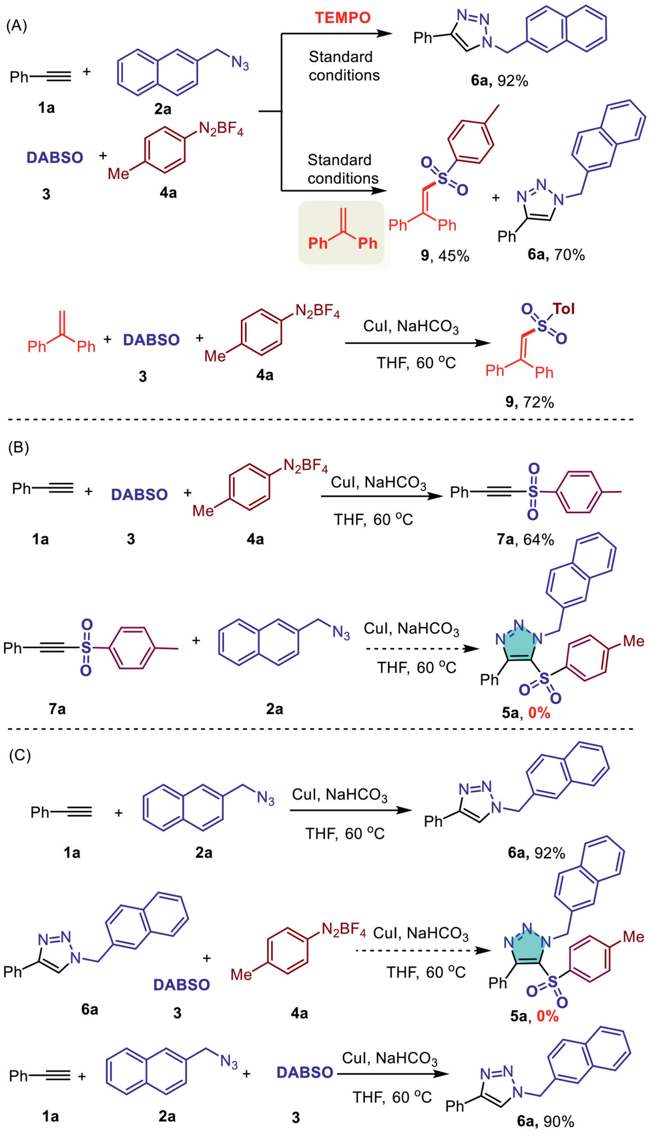


Fig. 2. Control experiments.

dergo a click reaction with an azide to produce **5a**, and it rules out path B. Actually, the ethyne (**7a**) was not observed as a byproduct in the standard reaction system indicating that in the click reaction the reaction of copper(I) acetylide is more dynamically favored than radical coupling. A CuAAC reaction generating a protonated product (**6a**) and a subsequent sulfone radical substitution reaction might also produce **5a** (path C). When compound **6a**, DABSO, and **4a** were subjected to the standard reaction conditions, no reaction was observed and **6a** remained intact in reaction system, showing that the radical relay species is not the protonated CuAAC product (**6a**), but the triazole copper intermediate (**M^1**), and path C is therefore unlikely. The reaction between the alkyne (**1a**), azide (**2a**), and DABSO (**3**) under standard conditions, only **6a** was produced in 90% yield.

According to these data and previous reports, an interrupted click/radical relay mechanism was proposed and is shown in Fig. 3. Copper(I) acetylide undergoes a kinetically favored cycloaddition with the azide, generating the key click intermediate **M^1**. This intermediate can react with toluenediazonium tetrafluoroborate (**4a**) through a single electron transfer (SET) process, generating triazole copper(II) (**M^2**) and a tolyl radical. The tolyl radical reacts with sulfur dioxide to give a tolylsulfone radical, in a process which was shown by Wu *et al.* to be barrierless. This radical then reacts with triazole copper(II) (**M^2**) to form product **5a**, possible through a SET oxidation to Cu(III) and then finally, a reductive elimination sequence. If no DABSO is present, the aryl radical formed in situ would react with triazole copper(II) (**M^2**) to form an 5-arylated triazole product, which could become involved in a three-component click reaction between alkyne, DABSO and a aryldiazonium salt to build trisubstituted triazoles (for details, see Supporting information).

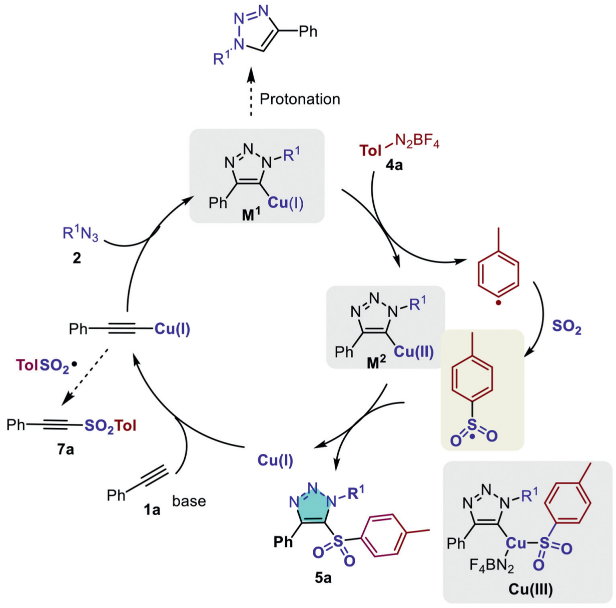


Fig. 3. Proposed mechanism.

In summary, we have developed the first copper(I)-catalyzed four-component click reaction to access triazole sulfones. A new interrupted click reaction and radical relay process was observed for the first time. This method can integrate four simple precursors into complex structures with an inexpensive copper(I) catalyst and there is no requirement for ligands. This strategy has the advantages of high bond-formation efficiency, and modular construction of products with diversity and complexity. We anticipate this new four-component reaction will be useful in combinatorial chemistry, medicinal chemistry, polymer chemistry and other related areas.

Declaration of competing interest

The authors declare no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2023.108478.

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