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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

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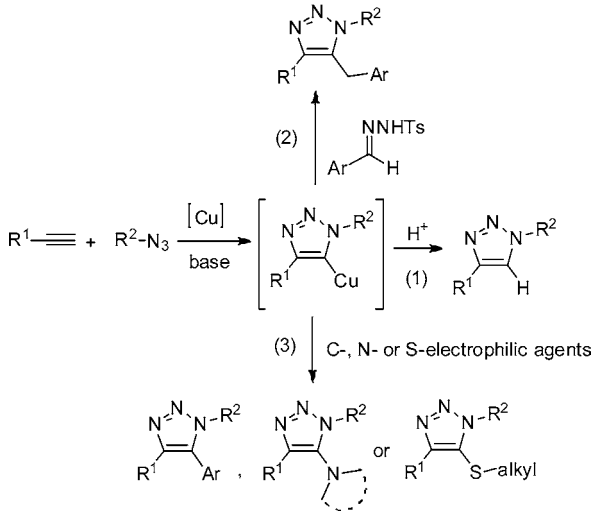
Supporting Information

ABSTRACT: A number of enamine-functionalized 1,2,3-triazole derivatives have been prepared via the Cu-catalyzed three-component reaction of terminal alkyne, azide, and 2*H*-azirine. The reaction proceeds through insertion of vinyl nitrene into the C–Cu bond of the triazolyl-Cu species, providing an efficient and step- and atom-economic approach to the enamine-bearing polysubstituted 1,2,3-triazoles. The resulting triazoles were easily transformed to trisubstituted pyrazoles in the presence of a Rh catalyst.

In recent decades, 1,2,3-triazoles have emerged as an important class of *N*-heterocycles because of their employment in the construction of other heterocycles via metal carbenoids chemistry,[1] and application in medicinal chemistry.[2] Substituted 1,2,3-triazoles are generally obtained through Cu-catalytic azide–alkyne click (CuAAC) reactions[3] and organocatalytic azide–aldehyde/ketone 1,3-dipolar cycloaddition reactions.[4] The CuAAC reaction represents one of the most powerful tools for the furnishment of 1,4-disubstituted 1,2,3-triazoles (Scheme 1, eq 1).[3] The so-called "Cu-catalyzed interrupted click reaction", in which the triazolyl-Cu intermediate was captured by a carbene or an electrophilic partner rather than a proton giving 5-functionalized 1,2,3-triazole has recently been developed.[5−7] The strategy has been applied to the synthesis of trisubstituted 1,2,3-triazoles through copper-catalyzed three-component coupling of alkynes, azides, and *N*-tosylhydrazones (Scheme 1, eq 2).[6] Similarly, the reactions of the triazolyl-Cu species with *C*-, *N*-, or *S*-electrophilic agents led to various trisubstituted 1,2,3-triazoles in high yields (Scheme 1, eq 3).[7] Although these methods provide convenient synthetic ways to polysubstituted 1,2,3-triazoles, the development of novel and efficient approaches to 1,2,3-triazoles, especially in an atom- and step-economic manner, is still highly required.

2*H*-Azirines are a class of highly strained three-membered *N*-heterocyclic compounds.[8] 2*H*-Azirines can form reactive vinyl nitrenes or nitrile ylides under thermal or photolytic conditions. Transition metal species have been shown to accelerate the generation of these intermediates, enabling a wide range of chemistry under milder conditions which are impossible in uncatalyzed processes.[8b] Transition-metal-catalyzed vinyl nitrene transfer reactions using 2*H*-azirines as precursors have attracted much attention. Transition metals such as $PdCl_2(PhCN)_2$,[9] $Rh_2(TFA)_4$,[10] and $FeCl_2$[11] have shown to be effective in rearrangement of 2-aryl-2*H*-azirines to indoles. The mechanism was supposed to be an intramolecular vinyl nitrene transfer process, involving the formation of the reactive metal-vinyl nitrene species (Scheme 2, eq 1). Polysubstituted pyrroles

Scheme 1. Cu-Catalyzed Click Reaction (1) and Interrupted Click Reactions (2) and (3)



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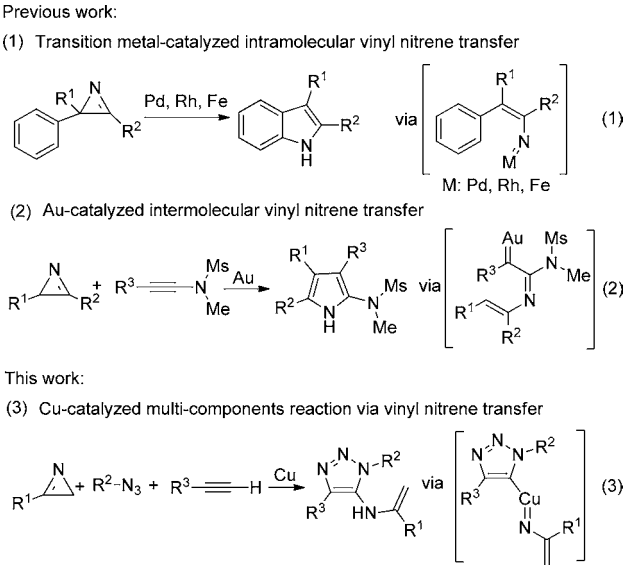
Scheme 2. Transition-Metal Catalyzed Vinyl Nitrene Transfer Strategy

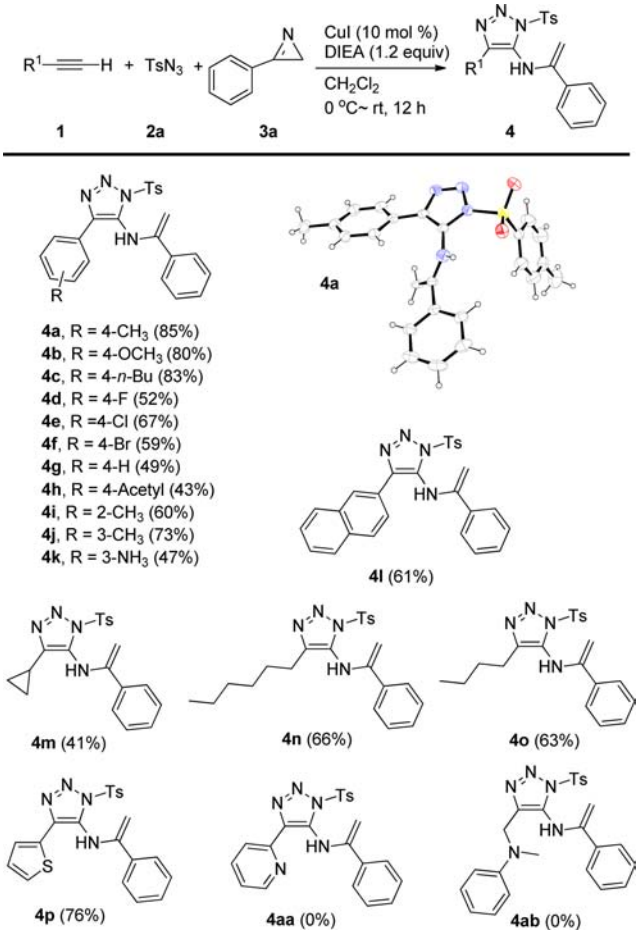


can be obtained from 2*H*-azirines and ynamides via gold-catalyzed intermolecular vinyl nitrene transfer,[12] and a reactive Au-carbenoid intermediate might be involved (Scheme 2, eq 2). Although the intra- and intermolecular vinyl nitrene transfer reactions have been successfully achieved for the construction of *N*-heterocycles, multicomponent reactions of vinyl nitrene transfer have not been reported. We envisioned that 2*H*-azirines could act as vinyl nitrene precursors and furnish the enamine-substituted 1,2,3-triazole derivatives via a nitrene transfer process (Scheme 2, eq 3). As a continuation of our recent work on 1,2,3-triazole chemistry[13] and a Cu-catalyzed nitrene-transfer strategy,[14] herein, we report the multicomponent synthesis of trisubstituted 1,2,3-triazoles via a Cu-catalyzed vinyl nitrene transfer reaction.[15]

We started our work by taking 4-methylphenylacetylene **1a**, TsN_3 **2a**, and 3-phenyl-2*H*-azirine as the model substrates for the optimization of the reaction conditions. As listed in Table S1, when CuI, *N*,*N*-diisopropylethylamine (DIEA), and CH_2Cl_2 were used as the catalyst, base, and solvent, respectively, the three-component reaction proceeded smoothly at room temperature, and the desired product **4a** was isolated in 47% yield. The structure of **4a** was undoubtedly determined by X-ray diffraction analysis (Scheme 3).[16] After a further screening of the reaction conditions, we found that the yield of **4a** could be increased to 85% when the temperature was controlled to 0 °C−rt (the details are given in Supporting Information (SI)).

We then started to investigate the scope of alkynes under the optimized conditions. As illustrated in Scheme 3, a variety of alkynes **1** bearing different substituents on the aromatic rings reacted smoothly with **2a** and **3a**, affording the corresponding triazoles **4a**−**4p** in moderate to excellent yields. Alkynes containing an electron-donating group such as methyl, methoxyl, and *n*-butyl on the aromatic rings gave triazoles (**4a**−**4c** and **4j**) in much higher yields. In contrast, alkynes containing an electron-withdrawing group on aromatic rings led to lower yields of **4d** and **4h**. However, triazole **4k** was afforded only in a moderate yield of 47% in the reaction of 3-ethynylaniline, TsN_3, and 3-phenyl-2*H*-azirine, indicating that the $-NH_2$ group in phenylacetylene may suppress the cycloaddition reaction. To our delight, the bromo-substituent

Scheme 3. Scope of Alkynes[a]



[a]Reaction conditions: **1** (0.65 mmol), **2a** (0.6 mmol), **3a** (0.5 mmol), CuI (10 mol %), DIEA (1.2 equiv), CH_2Cl_2 (1 mL), 0 °C−rt, 12 h, under N_2.

was compatible with the cycloaddition reaction and subsequent nitrene transfer. Triazoles **4d**, **4e**, and **4f** bearing a halogen substituent could be obtained in 52−67% yields, offering the possibility of further functionalization. The effect of the steric hindrance of the substituents on the phenyl ring was found. The reaction of 4-methylphenylacetylene afforded **4a** in 85% yield, whereas the reaction of 2-methylphenylacetylene led to **4i** in 60% yield. Aliphatic alkynes were also suitable for this transformation under the same reaction conditions. The reactions of cyclopropylacetylene, *n*-hexyne, and *n*-octyne with TsN_3 and 3-phenyl-2*H*-azirine readily gave **4m**, **4n**, and **4o** in yields of 41%, 66%, and 63%, respectively. However, we failed to obtain the desired product **4ab** from the reaction of *N*-methyl-*N*-propargylaniline. An aromatic heterocyclic alkyne such as 2-ethynylthiophene was also compatible with the reaction, and the corresponding product **4p** was afforded in 76% yield. Unfortunately, reaction of 2-ethynylpyridine, TsN_3, and 3-phenyl-2*H*-azirine gave a complex reaction mixture, and no desired product **4aa** was isolated.

The scope of 2*H*-azirines and azides was further investigated (Scheme 4). 3-Phenyl-2*H*-azirines bearing an alkyl group gave the desired products **4q** and **4r** in good yields. Various 3-phenyl-2*H*-azirines with halogen substituents were very compatible with the reaction conditions, and the corresponding products **4s**−**4v** were obtained in excellent yields. It is notable

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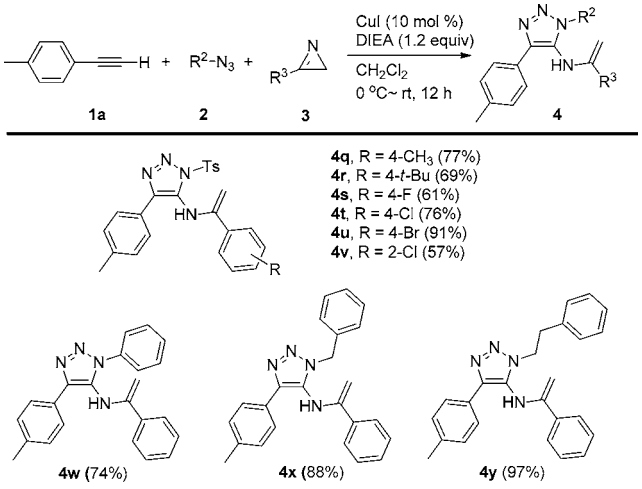
Scheme 4. Scope of Azides and 2*H*-Azirines[a]

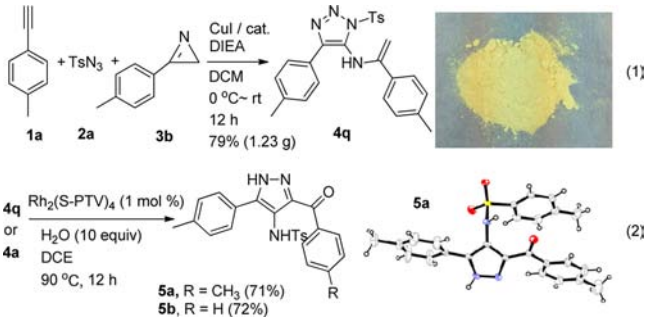


[a]Reaction conditions: **1a** (0.65 mmol), **2** (0.6 mmol), **3** (0.5 mmol), CuI (10 mol %), DIEA (1.2 equiv), CH_2Cl_2 (1 mL), 0 °C−rt, 12 h, under N_2.

that 3-(4-bromophenyl)-2*H*-azirine gave the bromo-remaining product **4u** in an excellent yield, indicating aromatic bromide groups are inert to the reaction conditions and thus enable further functionalization through classical coupling reactions. Reaction of 2,3-diphenyl-2*H*-azirine **3h** gave a complex reaction mixture, and we were not able to isolate the desired product. The reactions of aryl and alkyl azides other than TsN_3 were also tested. As shown in Scheme 4, the desired products **4w**−**4y** derived from the corresponding phenyl, benzyl, and phenylethyl azides were isolated in good to excellent yields.

To explore the potential application of the reaction, the scale-up synthesis and further transformation experiments were conducted. Product **4q** was readily obtained in 79% yield at gram scale (Scheme 5). Interestingly, it was found that **4q** was

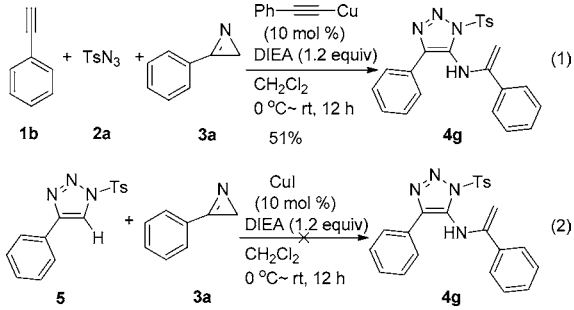
Scheme 5. Scale-up Synthesis and Further Transformation Experiments



smoothly converted to an unexpected pyrazole derivative **5a** in the presence of a rhodium catalyst in DCE. The structure of **5a** was determined by X-ray diffraction.[16] Preliminary studies showed that $Rh_2(S\text{-}PTV)_4$ was more effective than $Rh_2(OAc)_4$ and $Rh_2(Oct)_4$ (see SI), giving **5a** in 71% yield, when 10 equiv of H_2O were added. Without rhodium catalysts, **5a** was given in quite low yield. Similarly, when **4a** was subjected to the $Rh_2(S\text{-}PTV)_4$ catalyst, **5b** was obtained in 72% yield. Further studies are needed to extend the application and clarify the mechanism.

To gain insight into the mechanism of the reaction, several control experiments were performed. When copper(I) phenylacetylide was used as the catalyst instead of CuI, the desired product **4g** was obtained in 51% yield (Scheme 6, eq 1), a

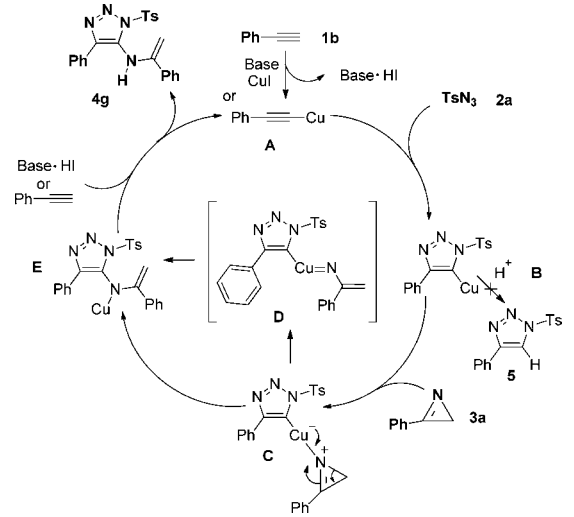
Scheme 6. Control Experiments



slightly increased yield over that with CuI (49%, **4g**) (Scheme 3). It implied that the copper(I) phenylacetylide may act as the catalytically active species in this reaction. On the other hand, when 5-unsubstituted 1,2,3-triazole **5** derived from the click reaction of **1b** and **2a** was subjected to 2*H*-azirine under the standard conditions, the desired product **4g** was not detected (Scheme 6, eq 2). Obviously, it excluded the possibility that product **4g** was formed through a C−H bonding activation/functionalization mechanism, or through a direct insertion of vinyl nitrenenoids into the C−H bond of 1,2,3-triazole **5**.

Based on previous related works[5−7] and the control experiments, a proposed catalytic pathway for the formation of **4g** is outlined in Scheme 7. First, reaction of alkyne **1b** with

Scheme 7. Proposed Catalytic Pathway to 4



CuI in the presence of a base generated copper(I) phenylacetylide species **A**, and a subsequent reaction with TsN_3 **2a** gave intermediate **B** via a 1,3-dipolar cycloaddition reaction. The triazolyl-Cu(I) species **B** was rapidly captured by 2*H*-azirine **3a**, leading to a triazolyl-Cu(I)/2*H*-azirine complex **C**. The rearrangement of **C** would generate Cu(III)-vinyl nitrene species **D**. Further insertion of the vinyl nitrene into the C−Cu bond would yield Cu−NR_1R_2 complex **E**. Finally, protonation of **E** by alkyne afforded the desired product **4g**, and copper(I) phenylacetylide was regenerated to finish the whole catalytic cycle.

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In conclusion, we have described a facile route to synthesize enamine-functionalized 1,2,3-triazoles from terminal alkynes, azides, and 2*H*-azirines. This methodology was characterized by a Cu-catalyzed interrupted click reaction, in which the triazolyl-Cu species was captured by 2*H*-azirine and thus furnished the enamine group on the C5 position of 1,2,3-triazole via vinyl nitrene transfer. To the best of our knowledge, this is the first example involving the insertion of 2*H*-azirine-derived vinyl nitrene into the sp^2 C−Cu bond. In addition, the resulting triazolamines could be converted to pyrazole derivatives. It provides an efficient and step- and atom-economic approach to polysubstituted 1,2,3-triazoles and pyrazoles, which are not easily accessible by other conventional methods. We believe that this vinyl nitrene transfer strategy will have wide applications in building various biologically interesting *N*-heterocycles, and related research is being conducted 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.6b02850.

Full experimental details and characterization data for all products (PDF)
X-ray crystallographic data for **4a** (CIF)
X-ray crystallographic data for **5a** (CIF)

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Notes

The authors declare no competing financial interest.

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(16) CCDC 1469919 (**4a**) and CCDC 1519964 (**5a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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