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Copper-catalyzed 1,1-difunctionalization of terminal alkynes: a three-component reaction for the construction of vinyl sulfones

Qi Sun, Linge Li, Liyan Liu, Yu Yang, Zhenggen Zha & Zhiyong Wang*

Hefei National Laboratory for Physical Sciences at Microscale, CAS Key Laboratory of Soft Matter Chemistry & Center for Excellence in Molecular Synthesis of Chinese Academy of Sciences, Collaborative Innovation Center of Suzhou Nano Science and Technology & School of Chemistry and Materials Science in University of Science and Technology of China, Hefei 230026, China

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A copper-catalyzed 1,1-difunctionalization of terminal alkynes was achieved via a three-component reaction, providing a variety of vinyl sulfones with good yields and excellent chemo- and stereoselectivity. Preliminary mechanistic studies indicated that the reaction probably underwent a Cu-catalyzed formal C–H insertion to produce an allene intermediate, which was then trapped by a sulfonyl anion to give the corresponding product.

copper, terminal alkynes, germinal difunctionalization, multicomponent reaction, vinyl sulfones

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1 Introduction

Difunctionalization of terminal alkynes has been playing a significant role in many processes for the synthesis of multisubstituted olefins [1–3]. The most of the previous methods for difunctionalization of terminal alkynes involved radical additions or electrophilic additions, and the multi-functionalization of terminal alkynes typically required several steps under different conditions. Despite the difference in their synthetic routes, these methods are almost general reaction patterns of C–C multiple bonds, resulting in 1,2-difunctionalization [4–15]. By contrast, only a few reports are related to the 1,1-difunctionalization of terminal alkynes [16,17]. To the best of our knowledge, the 1,1-difunctionalization of the terminal alkynes by one-step process is still of great challenge although Sawamura *et al.* [18] and Chirik *et al.* [19] made notable progress in the 1,1-diboration of alkynes recently (Scheme 1). Therefore we assumed that we can overcome this dilemma by virtue of a multicomponent reaction, in which a carbene chemistry is involved.

As a typical one-pot reaction, multicomponent reactions (MCRs) were widely investigated and applied in the rapid construction of complex molecules due to their diversity, efficiency, and environmental amiability [20]. For instance, Strecker [21], Biginelli [22] and Ugi [23] reactions are well employed in the construction of some complex skeletons. The difunctionalization of the terminal alkynes by using MCRs is rare, especially for those involving 1,1-difunctionalization. Recently, a copper-catalyzed three-component reaction for the preparation of β-enamino esters was developed by Huang's group [24] (Scheme 2). Another nickel-catalyzed MCR for the carbosulfonylation of terminal alkynes was reported by Nevado's group [25] (Scheme 2). These use of MCRs provided a new perspective for the synthesis of some important molecular skeletons. On the other hand, due to the particular physiological characteristics and biological activities of vinyl sulfones [26–32], the sulfonylation of the terminal alkyne has attracted attention of the synthetic chemists over the last decade [33–37]. However, most of these synthetic strategies involved tedious steps

*Corresponding author (email: zwang3@ustc.edu.cn)

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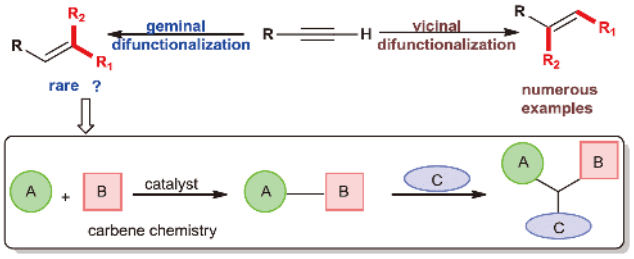
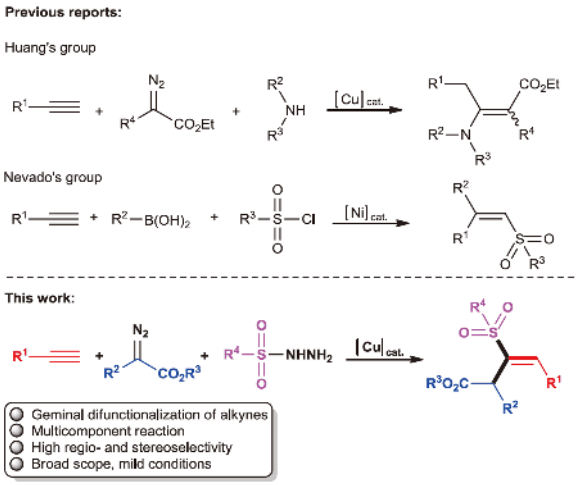


Scheme 1 Designed strategy for multi-component reaction of terminal alkynes 1,1-difunctionalization (color online).



Scheme 2 MCRs involving terminal alkynes (color online).

and strict operation condition. In view of the above, we devised a novel and efficient method for both of the sulfonylation and the 1,1-difunctionalization of the terminal alkynes by virtue of a Cu(I)-catalyzed three-component reaction. Even though any two components of these three reactants (diazo esters, terminal alkynes and sulfonyl hydrazides) can react separately [38–40], this reaction can still proceed smoothly with good chemo- and regioselectivity. By using this developed reaction, a series of substituted vinyl sulfones can be obtained rapidly with good functional-group tolerance and excellent stereoselectivity under mild conditions.

2 Experimental

To a mixture of **1** (0.2 mmol), **2** (2.0 equiv.), **3** (2.0 equiv.), catalyst (0.02 mmol, 10 mol%), and base (3.0 equiv.), 1.0 mL of solvent were added. The reaction mixture was stirred at room temperature until **1** was consumed. Then the reaction mixture was purified directly by column chromatography (silica gel, petroleum ether/EtOAc) to afford the desired product.

3 Results and discussion

We began our studies with phenylacetylene **1a**, diazo ester **2a** and 4-methylbenzenesulfonhydrazide **3a** as the model substrates (Table 1). Initially, various copper catalysts were examined in the reaction. To our delight, the reaction catalyzed by CuBr in the presence of TEA could afford the desired product **4a** in 10% yield (entry 5). After screening of the catalysts, it was found that CuI should be the ideal catalyst for this reaction, affording the desired product **4a** with a yield of 88% while other copper salts gave low yields even no catalytic reactivity for this reaction (entries 1–10).

On the other hand, the base TEA was necessary for this reaction, otherwise the reaction did not work. Therefore a variety of bases were optimized. When DABCO, K_2CO_3 and LiO^tBu were employed in this reaction, no any desired product can be observed while the starting materials were recovered (entries 15–17). After base screening, TEA should be the best base for this reaction. Subsequently different kinds of solvent were examined in the reaction. When acetonitrile was employed as the solvent, the desired product can be obtained with a yield of 34%, and chloroform was employed as the solvent, the yield was 78% (entries 11–14). Moreover, when the reaction was carried out in the DCM, the desired product can be obtained with a yield of 88% (entry 6). This indicated that DCM was the best solvent for this

Table 1 Reaction condition optimization[a)]

Entry	Catalyst	Solvent	Base	Yield (%)[b)]
1	$Cu(MeCN)_4PF_6$	DCM	TEA	trace
2	CuOTf	DCM	TEA	trace
3	CuOAc	DCM	TEA	n.d
4	CuCl	DCM	TEA	trace
5	CuBr	DCM	TEA	10
6	CuI	DCM	TEA	88
7	$CuCl_2$	DCM	TEA	n.d
8	$CuBr_2$	DCM	TEA	n.d
9	$Pd(OAc)_2$	DCM	TEA	n.d
10	AgOAc	DCM	TEA	n.d
11	CuI	MeCN	TEA	34
12	CuI	Toluene	TEA	n.d
13	CuI	MeOH	TEA	n.d
14	CuI	$CHCl_3$	TEA	78
15	CuI	DCM	K_2CO_3	n.d
16	CuI	DCM	LiO^tBu	n.d
17	CuI	DCM	DABCO	n.d
18[c)]	CuI	DCM	TEA	73
19[d)]	CuI	DCM	TEA	40
20[e)]	CuI	DCM	TEA	87
21[f)]	CuI	DCM	TEA	86

a) The reaction was carried out with **1a** (0.2 mmol), **2a** (2.0 equiv.), **3a** (2.0 equiv.), catalyst (10 mol%), base (3.0 equiv.) in solvent (1 mL) at room temperature (25 °C) for 14 h. DCM=dichloromethane, TEA=triethylamine, DABCO=triethylenediamine; b) isolated yields; c) 10 °C; d) 0 °C; e) 50 °C; f) 100 °C.

reaction. Afterwards, the effect of the reaction temperature was also investigated. The experimental result showed that the temperature had an influence on the reaction. When we decreased the temperature from the room temperature to 10 °C, the reaction yield was decreased to 73% (entry 18) while the reaction yield lessened a lot when the temperature decreased to 0 °C (entry 19). When the temperature increase to 50 °C even 100 °C, the reaction yields were reduced a little (entries 20, 21). After optimization, the room temperature should be the best reaction temperature for this reaction. Finally, the optimal condition was identified as below: copper iodide as the catalyst, TEA as the base, DCM as the solvent.

We then conducted an in-depth study of the scope of the reaction substrates under the optimal conditions (Table 1, entry 6). As shown in Figure 1, a variety of sulfonyl hydrazines with different functional groups, reacted readily with phenylacetylene **1a** and ethyl diazoacetate **2a** to give the desired products with good yields. Normally, an electron-donating group (**4a**–**4e**) had a positive effect on this conversion while an electron-withdrawing group negatively affected this transformation (**4f**–**4j**). The naphthalenesulfonyl hydrazide was also tested as a substrate, and the desired product was obtained with a yield of 85% (**4k**). Gratifyingly, phenylmethanesulfonyl hydrazide can also be employed to give the corresponding product with 70% yield (**4l**). Next, the scope of the alkynes and diazo esters was screened. A variety of terminal alkynes (**5a**–**5i**) were used to react with **2a** and **3a** under the optimized condition. Aromatic alkynes could afford the desired products in moderate to good yields regardless of the electron-donating substitution or electron-withdrawing substitution on the phenyl ring (**5a**–**5k**). In addition, phenylacetylenes with *ortho*- or *meta*-substituent groups reacted smoothly in this reaction and the corresponding products were obtained with good yields (**5h**–**5i**). All aromatic alkynes showed good adaptability in this transformation to give the desired products. Furthermore, the positions of the substituents on the phenyl ring had little influence on the chem- and regioselectivity of the reaction. Gratifyingly, when the hydrogen of diazo-esters was varied into methyl group, the reaction could also carried out smoothly, affording the corresponding products efficiently (**5j**–**5k**).

Encouraged by the reaction features, such as high efficiency, simple operation and broad scope, a scaled-up experiment was explored to test the practicality. When 5.0 mmol of phenylacetylene **1a** was reacted with 2.0 equiv. of diazo ester **2a** and 2.0 equiv. of 4-methylbenzenesulfonhydrazide **3a**, the desired product **4a** can be obtained with a yield of 78%, showing a significant potential in organic synthesis (Scheme 3).

Moreover, compound **6** can be synthesized and employed in this reaction to give a modified natural product with a yield of 77% (Scheme 4). This indicates that this developed method can be applied to the modification of steroid drugs to change their biological activity [41].

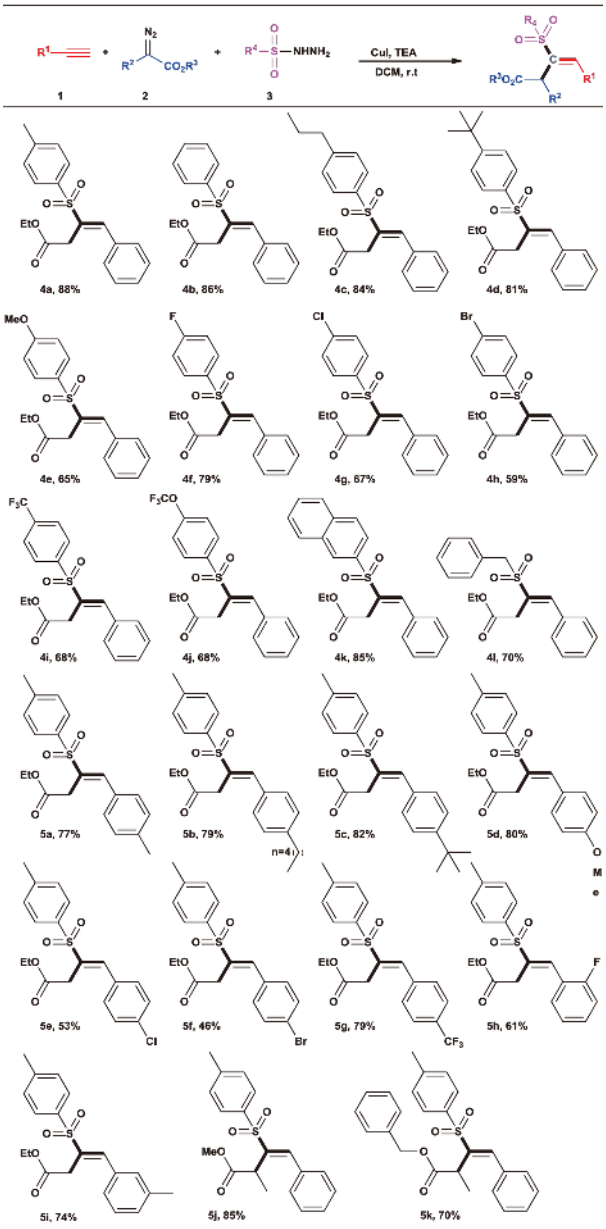
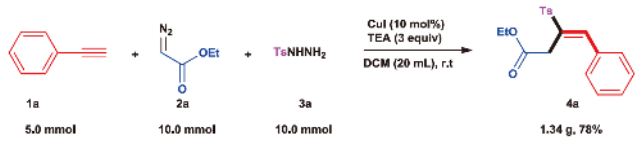
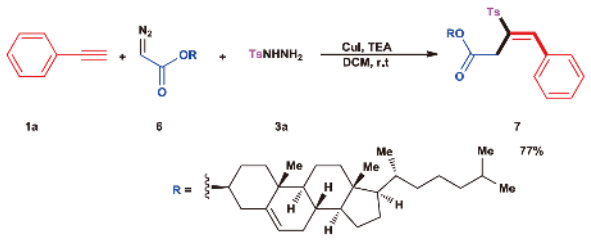


Figure 1 Reaction scope. The reaction was carried out with **1** (0.2 mmol), **2** (2.0 equiv.), **3** (2.0 equiv.), CuI (10 mol%), TEA (3.0 equiv.) in dichloromethane (1 mL) at room temperature for 14 h; isolated yields of all products; the temperature of the reactions involving 4-chlorophenylacetylene and 4-bromophenylacetylene was 100 °C (color online).

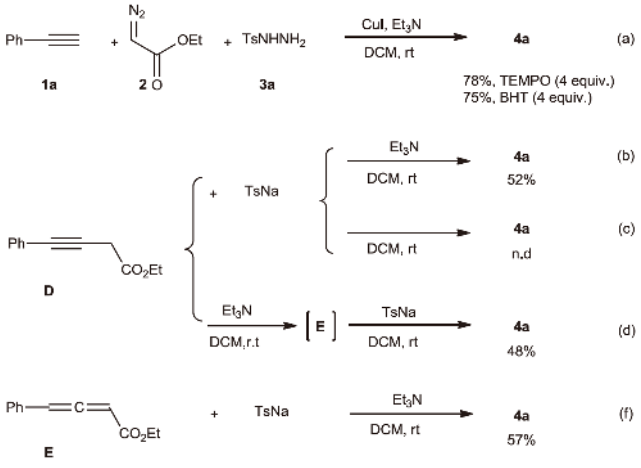
To understand the reaction mechanism, we performed some control experiments. Firstly, 4 equiv. of different radical scavengers (TEMPO or BHT) were added respectively into the reaction mixture, the yield of **4a** did not decrease obviously (Scheme 5(a)). The result almost excluded a radical process in this reaction. Then, compounds **D** was synthesized and reacted with TsNa in the presence of TEA, affording the desired product **4a** with a yield of 52%



Scheme 3 Gram-scale synthesis (color online).



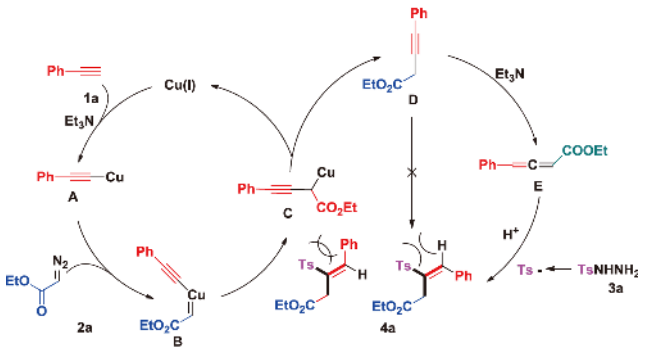
Scheme 4 Product modifcation. The reaction was carried out with **1a** (0.2 mmol), **6** (2.0 equiv.), **3a** (2.0 equiv.), CuI (10 mol%), TEA (3.0 equiv.) in DCM (1 mL) under room temperature (color online).



Scheme 5 Control experiments. TsNa=sodium *p*-toluenesulfinate; TEMPO=2,2,6,6-tetramethylpiperidine-1-oxyl; BHT=tert-butylhydroxy-toluene.

(Scheme 5(b)) while compound **E** gave **4a** with a yield of 57% under the same condition (Scheme 5(e)). In the absence of TEA, however, the reaction did not work (Scheme 5(c)). In order to detect the possible intermediate in this reaction, we employed **D** to react with TEA for 2 h, and then TsNa was added to this mixture. It was found that the product **4a** can be obtained with a yield of 48% (Scheme 5(d)). This implied that **D** should be converted to **E** instantly in the presence of TEA. Subsequently **E** was consumed with the time going to afford the desired product. Finally, **E** was identified as the real intermediate in the reaction based on the above experiment results.

According to the above-mentioned and previous reports [24, 41–48], a possible mechanism was proposed and depicted in Scheme 6. First, copper iodide reacts with phenylacetylene **1a** to form the copper acetylide **A**. Then diazo **2a** reacts with **A** to afford the copper carbenoid **B**, and the intermediate **C** is formed from the subsequent migration in-



Scheme 6 Proposed mechanism (color online).

sertion of alkynyl group. After protonation of **C**, the compound **D** is formed and the catalyst Cu(I) can be generated for the next catalytic round. In the presence of TEA, **D** can be converted into the intermediate **E**, which reacts with the sulfonyl anion generated from **3a**, affording the desired product **4a**. It is noted that the excellent stereoselectivity of the vinyl sulfones can be obtained in the reaction perhaps due to the steric effect between the sulfonyl group and the phenyl group of the alkyne, which was also supported by the NOE spectrum of **5f**, as shown in Supporting Information online. In order to confirm this advantage, methyl 2-diazopropanoate and benzyl 2-diazopropanoate were employed in the reaction. Both **5j** and **5k** can be obtained with *E*-configuration. This stereoselctivity only was dependent to the structures of the sulfonyl hydrazide and the alkyne regardless of the reaction conditions.

4 Conclusions

In summary, a copper-catalyzed three-component reaction was developed to realize 1,1-difunctionalization of the terminal alkynes under mild condition. A series of *α*, *β*-disubstituted vinyl sulfones can be obtained with good yields and excellent chem- and stereoselectivity. This developed method features the tolerance of various functional groups, mild conditions and gram-scale operation. The investigation of the mechanism revealed that the reaction involved the copper carbene migration insertion to the terminal alkynes and the sulfonyl anion addition to the allenyl compound **E**. Moreover, the modification of steroidal drugs presents a great potential in pharmaceutical industry. Further investigation on mechanistic details and synthetic applications is ongoing in our laboratory.

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Conflict of interest The authors declare that they have no conflict of interest.

Supporting information The supporting information is available online at http://chem.scichina.com and http://link.springer.com/journal/. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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