

# Cu(I)-Catalyzed Cross-Coupling of Conjugated Ene-yne-ketones and Terminal Alkynes: Synthesis of Furan-Substituted Allenes

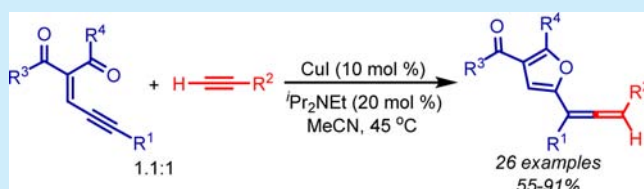
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**S** Supporting Information

**ABSTRACT:** A new method for the synthesis of furan-substituted allenes via Cu(I)-catalyzed coupling of conjugated ene-yne-ketones with terminal alkynes has been developed. A wide range of functional groups are tolerated, and the products are obtained in good to excellent yields under mild conditions. A copper carbene migratory insertion is proposed as the key step in this transformation with conjugated ene-yne-ketones as carbene precursors.

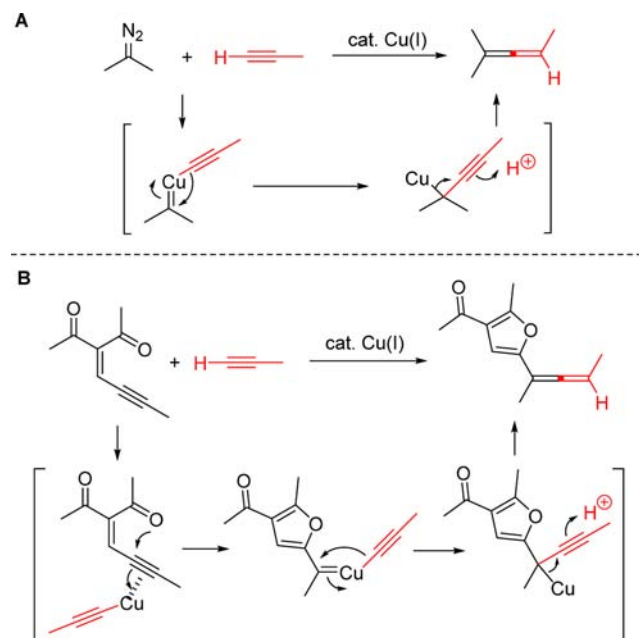


Diazo compounds,<sup>1</sup> either directly used or generated in situ from *N*-tosylhydrazones, have recently emerged as a novel type of cross-coupling partners in transition-metal-catalyzed reactions.<sup>2</sup> In these transformations, diazo compounds serve as metal carbene precursors and carbene migratory insertion is the key step in the carbon–carbon bond formation. On the basis of this general process, we have previously reported a new method for the synthesis of allenes through Cu(I)-catalyzed reaction of diazo compounds with terminal alkynes (Scheme 1, A).<sup>3,4</sup>

To further expand the scope of the this type of coupling reaction that involves the carbene process, we have conceived that a similar coupling reaction may be possible with carbene precursors other than diazo compounds, such as ene-yne-ketones.<sup>5,6</sup> In this context, we have very recently reported a Pd-catalyzed cross-coupling reaction between benzyl, aryl, or allyl bromides and conjugated ene-yne-ketones.<sup>7</sup> The reaction affords 2-alkenyl-substituted furans, which are generated through palladium (2-furyl)carbene migratory insertion. As the continuation of our interests in this field, we report herein the Cu(I)-catalyzed cross-coupling reaction of ene-yne-ketones with terminal alkynes.<sup>8</sup> The reaction uses cheap copper catalyst and affords furan-substituted allenes with high efficiency under mild conditions (Scheme 1, B).

At the outset of this study, we employed conjugated ene-yne-ketone **1a** and phenylacetylene **2a** as the model substrate with CuI as the catalyst to optimize the reaction conditions (Table 1). Upon examining the solvents, MeCN was proved to be most suitable for this transformation, which afforded the desired product **3a** in 69% yield (entry 4). Other solvents, including toluene, dioxane, and dichloroethane (DCE), were less effective (entries 1–3). With MeCN as the solvent, some bases were then investigated, and diisopropylamine and 2,2,6,6-tetramethylpiperidine (TEMP) gave comparable yields of **3a**

## Scheme 1. Allene Formation through Cu Carbene Migratory Insertion

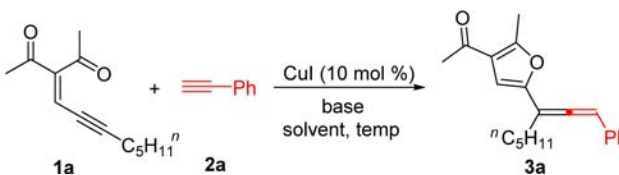


(entries 6 and 7).<sup>9</sup> However, K<sub>2</sub>CO<sub>3</sub> afforded **3a** in only 14% yield (entry 5).

We then turned our attention to the effect of temperature. As illustrated in entries 9–12, we found that the reaction proceeded efficiently at 40–45 °C, while either high or low temperatures gave inferior results. Control experiments confirmed that copper catalyst was essential for the reaction

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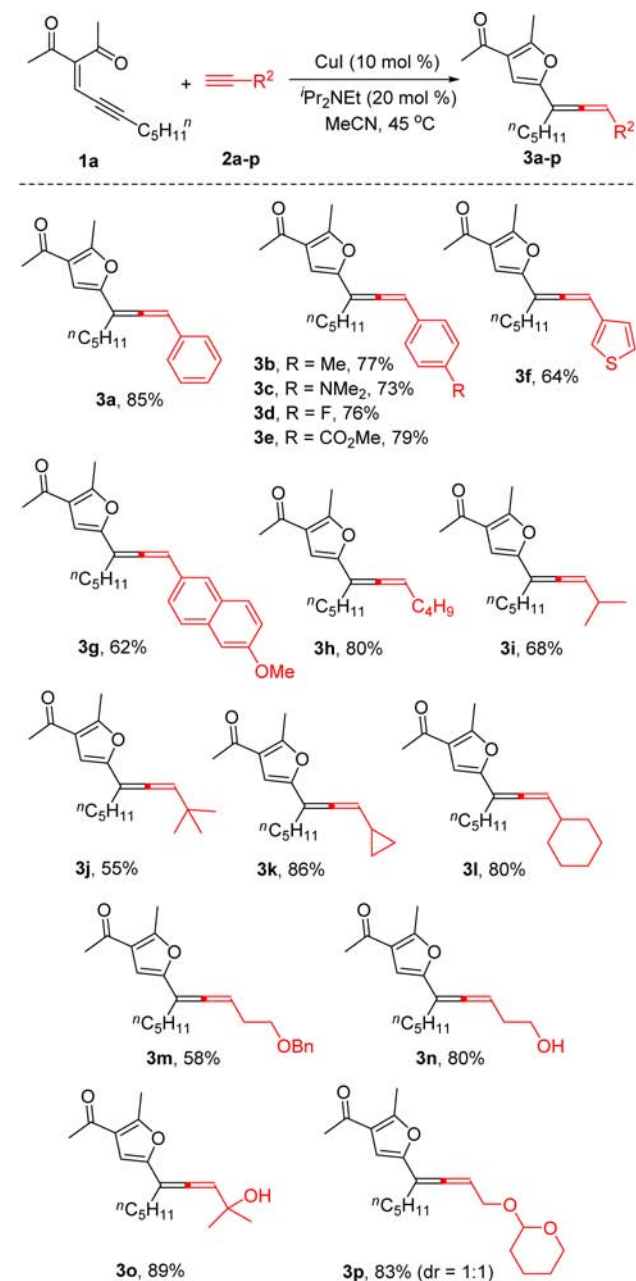
Table 1. Optimization of Reaction Conditions<sup>a</sup>


entry	solvent	base (equiv)	temp, °C	yield, % <sup>b</sup>
1	toluene	<sup>t</sup> Pr <sub>2</sub> NEt (1)	45	<5
2	dioxane	<sup>t</sup> Pr <sub>2</sub> NEt (1)	45	10
3	DCE	<sup>t</sup> Pr <sub>2</sub> NEt (1)	45	<5
4	MeCN	<sup>t</sup> Pr <sub>2</sub> NEt (1)	45	69
5	MeCN	K <sub>2</sub> CO <sub>3</sub> (1)	45	14
6	MeCN	<sup>t</sup> Pr <sub>2</sub> NH (1)	45	60
7	MeCN	TEMP (1)	45	58
8 <sup>c</sup>	MeCN	<sup>t</sup> Pr <sub>2</sub> NEt (1)	45	0
9	MeCN	<sup>t</sup> Pr <sub>2</sub> NEt (1)	30	51
10	MeCN	<sup>t</sup> Pr <sub>2</sub> NEt (1)	40	69
11	MeCN	<sup>t</sup> Pr <sub>2</sub> NEt (1)	50	55
12	MeCN	<sup>t</sup> Pr <sub>2</sub> NEt (1)	60	26
13	MeCN	none	45	58
14 <sup>d</sup>	MeCN	<sup>t</sup> Pr <sub>2</sub> NEt (0.2)	45	82
15 <sup>d,e</sup>	MeCN	<sup>t</sup> Pr <sub>2</sub> NEt (0.2)	45	85
16	MeCN	<sup>t</sup> Pr <sub>2</sub> NEt (0.1)	45	68
17	MeCN	<sup>t</sup> Pr <sub>2</sub> NEt (0.2)	45	73
18	MeCN	<sup>t</sup> Pr <sub>2</sub> NEt (0.4)	45	72

<sup>a</sup>Reaction conditions are the following if not otherwise noted: **1a** (0.20 mmol), **2a** (0.20 mmol), CuI (10 mol %), and base in solvent (2 mL) for 10 h at the indicated temperature. <sup>b</sup>All yields refer to the isolated yields by column chromatography. <sup>c</sup>The reaction was carried out in the absence of Cu catalyst. <sup>d</sup>MeCN (4 mL) was used. <sup>e</sup>**1a** was used in slightly increased amount (0.22 mmol).

(entry 13). Notably, the amount of base could be reduced to a catalytic loading without the sacrifice of the yields (entries 16–18). Additionally, the desired product **3a** was obtained in 82% yield in diluted solution (entry 14). Finally, slightly increasing the amount of ene-yne-ketone **1a** could afford the product in 85% yield (entry 15).

With the optimized conditions in hand, the scope of terminal alkynes was first examined. As shown in Scheme 2, aryl-substituted terminal alkynes were reacted smoothly with conjugated ene-yne-ketone **1a**, affording the corresponding allene products in good to excellent yields (**3a–g**). In these transformations, the electronic nature of substituents has no significant impact on the outcome (**3b–e**). It is notable that heteroaryl and polycyclic aromatic substrates **2f** and **2g** were also tolerated to give the corresponding products **3f** and **3g** in 64% and 62% yields, respectively. Next, a series of alkyl-substituted terminal alkynes were subjected to this reaction. To our delight, the desired products **3h–j** were obtained in acceptable yields when the primary, secondary, and tertiary alkyl-substituted terminal alkynes were used as the substrates. Additionally, terminal alkynes substituted with cyclic alkyl moieties were also suitable components for this reaction, providing the corresponding products **3k** and **3l** in 86% and 80% yields, respectively. 3-Butyn-1-ol **2m** protected by a benzyl group also worked well in the reaction, affording allene **3m**. Notably, a free hydroxyl group tolerates the reaction conditions, as demonstrated by the examples of **3n** and **3o**. It

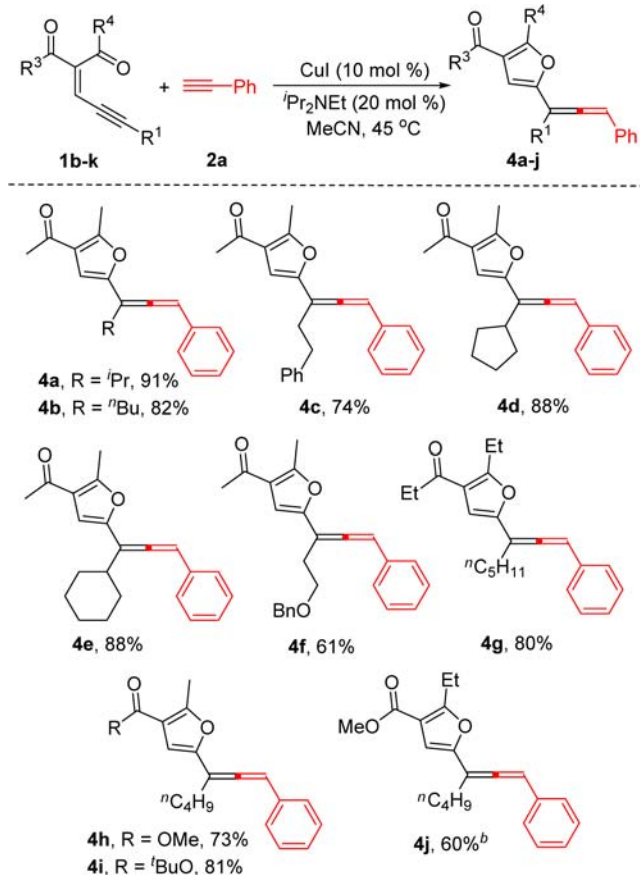
Scheme 2. Scope of Terminal Alkynes<sup>a</sup>

<sup>a</sup>Reaction conditions: **1a** (0.22 mmol), **2a–p** (0.20 mmol), CuI (10 mol %), and <sup>t</sup>Pr<sub>2</sub>NEt (20 mol %) in MeCN (4 mL) at 45 °C for 10 h.

is worth mentioning that the desired product **3p** was obtained in 83% yield as a 1:1 mixture of diastereomers.

Encouraged by these results with various alkynes, we next turned our attention to explore the scope of conjugated ene-yne-ketones in this reaction. As illustrated in Scheme 3, the reaction of ene-yne-ketones with both acyclic and cyclic alkyl substituents adjacent to the alkyne moiety gave the products in excellent yields (**4a–e**). The benzyl-protected hydroxy group could tolerate the reaction conditions (**4f**).

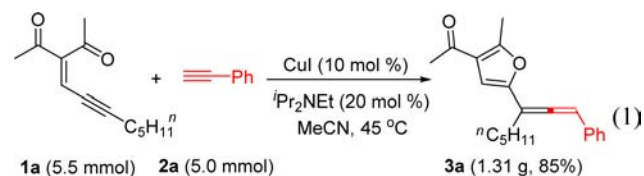
Next, the influence of the nucleophilic carbonyl oxygen was studied (**4g–j**). The reaction proceeded smoothly and afforded the products **4g** in 80% yield when R<sup>3</sup>, R<sup>4</sup> are ethyl groups. It is worth mentioning that the conjugated ene-yne-ketones derived from  $\beta$ -ketoesters are a mixture of *E*- and *Z*-isomers. However,

Scheme 3. Scope of Conjugated Ene-yne-ketones<sup>a</sup>

<sup>a</sup>Reaction conditions are the following if not otherwise noted: **1b–k** (0.22 mmol), **2a** (0.20 mmol), CuI (10 mol %), and  $i\text{Pr}_2\text{NEt}$  (20 mol %) in MeCN (4 mL) at 45 °C for 10 h. <sup>b</sup>2.5 equiv of ene-yne-ketones **1k** was used.

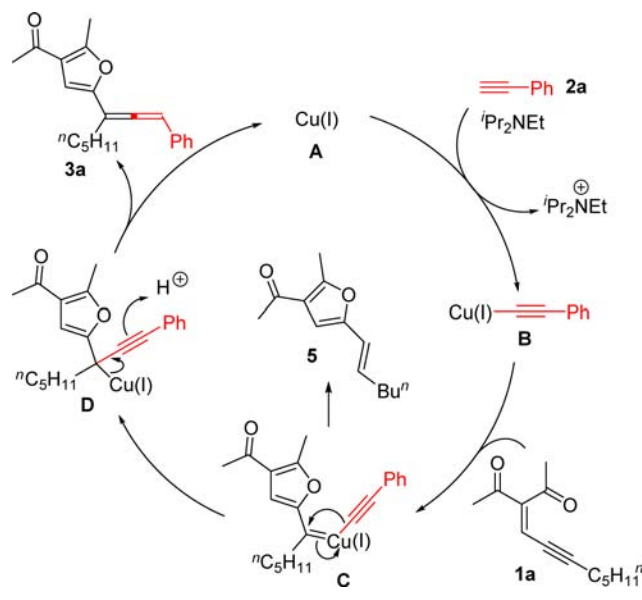
only one isomer of the allene products **4h–j** was observed in diminished yields when the mixture of *E*- and *Z*-isomers was employed in these reactions. This indicates that isomerization of the double bonds in conjugated ene-yne-ketones does not easily occur under the reaction conditions. Notably, only the ketone carbonyl oxygen acts as nucleophile in the cyclization.<sup>6,7</sup> The *E*-isomers could be separated from the mixture by silica gel column chromatography in the cases of **4h** and **4i**. They afforded the allenes **4h** and **4i** in good yields in the Cu(I)-catalyzed reaction with **2a**. In the case of ene-yne-ketones **1k**, the *E*- and *Z*-isomers could not be separated by silica gel column chromatography; therefore 2.5 equiv of ene-yne-ketone was used, and the product **4j** was prepared in 60% yield.

To demonstrate the usefulness of this protocol, a gram-scale experiment was carried out under the standard reaction conditions (eq 1). The reaction proceeded smoothly, providing 1.31 g of product **3a** (85%), which is comparable to the small scale experiment shown in Scheme 2.



A plausible mechanism is proposed in Scheme 4. First, copper acetylide **B** is formed from phenylacetylene in the

Scheme 4. Proposed Reaction Mechanism



presence of the copper(I) salt with the aid of base. Then, the alkyne moiety of ene-yne-ketones **1a** is activated by copper species **B** and subsequently undergoes 5-*exo-dig* cyclization by nucleophilic attack of the carbonyl oxygen atom, leading to copper carbene species **C**. Afterward, the intermediate **D** is produced through a copper carbene migratory insertion process.<sup>10</sup> We could observe trace amount of olefin **5**, which is due to 1,2-H shift from **C**, as the byproduct. Finally, the furan-substituted allene **3a** is formed by protonation of intermediate **D**. The protonation is consistent with a deuterium labeling experiment.<sup>11</sup> It is noteworthy that only allene products are obtained in this reaction. The alkyne products, which may be formed through direct protonation at the carbon atom that is attached to the copper center, are not observed.

In summary, we have developed an efficient approach for the synthesis of furan-substituted allenes via Cu(I)-catalyzed procedure. Allenes have been recognized as versatile intermediates in organic synthesis.<sup>12,13</sup> Owing to their peculiar structural features, allenes undergo diverse transformations that are distinct from those of alkenes and alkynes. In addition, allene motifs are the key structures in biologically active natural products and pharmaceutically related compounds.<sup>14</sup> Since the widespread applications of allenes, numerous methods for the synthesis of allenes have been developed in the past two decades.<sup>15</sup> In the allene synthesis reported in this paper, conjugated ene-yne-ketones are used as the carbene precursors, and copper carbene migratory insertion is proposed as the key step in the reaction mechanism. A wide range of substrates are tolerated in this reaction, and the products are obtained in good to excellent yields under mild conditions. Moreover, this investigation may open up new possibilities for the combination of copper-catalyzed coupling reactions with conjugated ene-yne-ketones.

**■ ASSOCIATED CONTENT****■ Supporting Information**

Experiment details, spectral data, and  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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**Notes**

The authors declare no competing financial interest.

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