

# Copper-Catalyzed Tandem Cross-Coupling/[2 + 2] Cycloaddition of 1,6-Allenynes with Diazo Compounds to 3-Azabicyclo[5.2.0] Ring Systems

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### **Supporting Information**



**ABSTRACT:** An unprecedented copper-catalyzed tandem cross-coupling/[2 + 2] cycloaddition of 1,6-allenynes with diazo compounds was reported, chemo- and regioselectively providing 3-azabicyclo[5.2.0] frameworks in moderate to excellent yields under mild reaction conditions. Moreover, the products readily convert to highly functionalized quinolines via oxidative radical rearrangement.

ransition-metal-catalyzed intermolecular reactions of different diazo compounds (or their precursor Ntosylhydrazones) with functionalized substrates are powerful tools for the creation of chemical diversity and new chemical entities in organic synthesis.<sup>1</sup> Particularly, the copper-catalyzed reaction of diazo compounds generates a copper-carbene intermediate that undergoes diverse transformations, and the breakthrough has been made in allene synthesis by coppercatalyzed carbene cross-coupling with terminal alkynes.<sup>2</sup> Moreover, the copper-catalyzed cross-coupling reaction of diazo compounds with terminal alkynes generates allene intermediates and offers opportunities for further intramolecular cyclization to afford cyclic scaffolds.<sup>5-7</sup> In 2011, Wang and co-workers reported a copper-catalyzed tandem reaction of N-tosylhydrazones with terminal alkynes to prepare 2-alkylated indoles and benzofurans, in which the formation of the allene intermediate was considered to be the key step (Scheme 1a).<sup>5</sup> In 2015, Sun and co-workers employed this strategy to synthesize five-membered N-heterocycles via a tandem reaction of copper-catalyzed allenoate formation followed by an intramolecular Michael addition (Scheme 1b).<sup>6a</sup> Following this seminal work, Sun and co-workers reported a series of copper-catalyzed tandem annulations of diazo compounds with terminal alkynes to prepare different four- to seven-membered ring systems.<sup>6b-g</sup>

Allenynes were found to possess diverse reactivities and have been utilized in various transition-metal-catalyzed cyclization reactions for the rapid assembly of complex polycyclic skeletons from simple linear substrates with atom economy.

### Scheme 1. Previous Reports and Our Proposal



Since Malacria's seminal work on the cobalt-catalyzed cycloisomerization of allenynes,<sup>8</sup> a variety of metals have been reported to catalyze the cyclization of allenynes.<sup>9</sup>

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However, the use of copper in catalytic reaction of allenynes is quite rare.<sup>10</sup> On the other hand, the development of bisallene chemistry is far behind compared to the advances of allenyne chemistry, presumably because of their high instability and difficulty of synthesis.<sup>11</sup> Thus, we propose that the copper-catalyzed reaction of allenynes bearing a terminal triple bond with diazo compounds could possibly form an in situ bisallene intermediate and then undergo an intramolecular [2 + 2] cycloaddition to form cyclobutane skeletons through the common metallacyclic or radical pathway (Scheme 1c).<sup>11a,12</sup> In this proposal, the control of chemo- and regioselectivity (head-to-head, tail-to-tail, head-to-tail) would be a formidable challenge (Scheme 1d).

Based on the hypothesis and in continuation with our interest in diazo carbene chemistry for developing novel methodologies on polycyclic skeleton synthesis, <sup>13</sup> we initially tested the copper-catalyzed reactions of different readily available allenynes 1a-5a with donor-acceptor diazo compound 6a. To our delight, a bicyclo[5.2.0] structure 7aa was chemo- and regioselectively obtained as the single product when 1,6-allenyne 5a was used in the presence of a catalytic amount of CuCl (Scheme 2). The structure of 7aa was unambiguously confirmed by X-ray diffraction analysis (CCDC 1956559; Figure 1). Herein, we report our preliminary results.<sup>14</sup>



Figure 1. X-ray structure of 7aa.

We first utilized 1,6-allenyne **5a** and phenyl diazoacetate **6a** as model substrates to screen the reaction conditions (Table 1). The reaction was highly dependent upon the catalyst, the reaction medium, and the reaction temperature. When the reaction was performed in methylene dichloride  $(CH_2Cl_2)$  at room temperature without catalyst, the reaction did not occur (entry 1). Then various copper catalysts were examined. The reaction did not work with CuI or CuOTf as catalyst (entries 2–3). Gratifyingly, CuCl and CuBr gave product **7aa** in 50% and 71% yields respectively (entries 4–5). The yield was further increased to 88% when Cu(PPh<sub>3</sub>)<sub>3</sub>Br was employed as catalyst (entry 6). Other metals were totally inert for the

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

N Ts 5a	+ CO <sub>2</sub> Me	catalyst solvent , T	MeO <sub>2</sub> C N Ts 7aa
entry	catalyst	solvent	yield (%) <sup>b</sup>
1	-	$CH_2Cl_2$	-
2	CuI	$CH_2Cl_2$	-
3	CuOTf	$CH_2Cl_2$	_
4	CuCl	$CH_2Cl_2$	50
5	CuBr	$CH_2Cl_2$	71
6	Cu(PPh <sub>3</sub> ) <sub>3</sub> Br	$CH_2Cl_2$	88
7	FeCl <sub>3</sub>	$CH_2Cl_2$	_
8	CoCl <sub>2</sub>	$CH_2Cl_2$	_
9	NiCl <sub>2</sub>	$CH_2Cl_2$	_
10 <sup>c,d</sup>	Ph <sub>3</sub> PAuCl	$CH_2Cl_2$	_
11 <sup>c</sup>	$Rh_2(esp)_2$	$CH_2Cl_2$	_
$12^c$	PtCl <sub>2</sub>	$CH_2Cl_2$	_
13	Cu(PPh <sub>3</sub> ) <sub>3</sub> Br	DCE	65
14	Cu(PPh <sub>3</sub> ) <sub>3</sub> Br	MeCN	_
15	Cu(PPh <sub>3</sub> ) <sub>3</sub> Br	toluene	_
16	Cu(PPh <sub>3</sub> ) <sub>3</sub> Br	1,4-dioxane	_
$17^e$	Cu(PPh <sub>3</sub> ) <sub>3</sub> Br	$CH_2Cl_2$	<10
18 <sup>f</sup>	Cu(PPh <sub>3</sub> ) <sub>3</sub> Br	$CH_2Cl_2$	63
19 <sup>c</sup> ,g	Cu(PPh <sub>3</sub> ) <sub>3</sub> Br	$CH_2Cl_2$	70
20 <sup><i>h</i></sup>	$Cu(PPh_3)_3Br$	$CH_2Cl_2$	_

<sup>*a*</sup>Reaction conditions: **5a** (0.2 mmol), **6a** (0.4 mmol), catalyst (10 mol %), CH<sub>2</sub>Cl<sub>2</sub> (3.0 mL), 12 h, rt. <sup>*b*</sup>Isolated yields. <sup>*c*</sup>Catalyst (5 mol %). <sup>*d*</sup>NaBAr<sub>F</sub> (5 mol %). <sup>*e*</sup>At 0 °C. <sup>*f*</sup>At 60 °C. <sup>*g*</sup>24 h. <sup>*h*</sup>Cs<sub>2</sub>CO<sub>3</sub> (1.0 equiv).

reaction (entries 7–12). Next, different solvents were screened.  $CH_2Cl_2$  was the best choice, and the alternative 1,2-dichloroethane (DCE) gave a moderate yield, whereas other solvents such as acetonitrile (MeCN), toluene, and 1,4-dioxane were not suitable for the reaction (entries 13–16). Moreover, the reaction was sluggish under low temperature (entry 17), while high temperature led to a lower yield due to product decomposition (entry 18). A decrease of the catalyst loading for the reaction gave product 7aa in 70% yield with a longer reaction time (entry 19). Notably, base was detrimental to the reaction. When 1 equiv of  $Cs_2CO_3$  was added, no product was obtained (entry 20).

With the optimal reaction conditions in hand, we next set out to investigate the scope of diazo compounds (Scheme 3). Varying the ester group of diazo compounds did not decrease the yield of the reaction (7aa-ac). Moreover, even the bulky tert-butyl or active allyl group did not inhibit the reaction (7ad-ae). Then, the reaction of 1,6-allenyne 5a with different substituted aryl diazoacetates bearing electron-donating or electron-withdrawing substituents at the aryl moiety all proceeded smoothly to afford the desired products in moderate to excellent yields (7af-as). Additionally, different disubstituted phenyl diazoacetates, bulky naphthyl diazoacetate, and benzofuran-derived diazoacetate were also well tolerated for the reaction (7at-ax). However, the target product 7ay was not obtained from the reaction with thiophene-derived diazoacetate under standard reaction conditions. Gram-scale synthesis was examined under standard reaction conditions and gave product 7aa in 79% yield. The

# Scheme 3. Scope of Diazo Substrates<sup>*a,b*</sup>



"Reaction conditions: **5a** (0.2 mmol), **6** (0.4 mmol),  $Cu(PPh_3)_3Br$  (10 mol %),  $CH_2Cl_2$  (3.0 mL), 12 h, rt. <sup>b</sup>Isolated yields. <sup>c</sup>Gram-scale (5 mmol).

structure of **7ao** was confirmed by X-ray diffraction analysis (CCDC 1960368).

Next, various substituted 1,6-allenynes were subjected to this reaction (Scheme 4). First, changing the  $R^1$  substitution of 1.6allenynes from the p-toluenesulfonyl group (Ts) to other sulfonyl groups had little influence on the reaction and all proceeded well to give the corresponding products in moderate to excellent yields (7ba-ea). Then, the reaction of phenyl diazoacetate 6a with different substituted 1,6-allenynes bearing electron-donating or electron-withdrawing substituents at the 4- or 5-position of the aryl moiety all proceeded smoothly to provide the desired products in good to excellent yields (7fa-pa). However, substitution on the 3- or 6-position of the aryl moiety largely reduced the reaction efficiency (7qara). Furthermore, different disubstituted 1,6-allenynes on the aromatic ring linker of 1,6-allenynes were well tolerated for the reaction (7sa-ua). Gratifyingly, 1,6-allenyne 5v ( $R^2 = Me$ ) furnished the desired product 7va in 68% yield. Unfortunately, pyridine-derived 1,6-allenyne was not suitable for the reaction (7wa).

To further understand the cycloaddition process, radical inhibition experiments were conducted (Scheme 5). When a radical inhibitor (BHT or TEMPO) was present, the reaction went smoothly to give the desired product 7aa in good yield (Scheme 5). This result indicated that the reaction did not proceed via a radical mechanism.



<sup>a</sup>Reaction conditions: **5** (0.2 mmol), **6a** (0.4 mmol),  $Cu(PPh_3)_3Br$  (10 mol %),  $CH_2Cl_2$  (3.0 mL), 12 h, rt. <sup>b</sup>Isolated yields.

Scheme 5. Radical Inhibition Experiments



Although it is premature to discuss the mechanistic details, a tentative mechanistic proposal is depicted in Scheme 6. The reaction of 1,6-allenyne 5a with phenyl diazoacetate 6a in the presence of a copper catalyst generates the copper-carbene intermediate A. Migratory insertion of the carbenic carbon to the alkynyl group affords alkyne intermediate B, which was followed by protonation and demetalation to afford bisallene intermediate C. The reaction of bisallene C with a copper species would regioselectively produce the cupracyclopentane intermediate D by the regioselective coordination of bisallene C followed by C-C bond formation,<sup>15</sup> and cupracycle intermediate D would undergo quick reductive elimination to give cyclobutane product 7aa. The observed high regioselectivity of the reaction could be explained in terms of the regioselective formation of metallacycle **D**, which would be controlled by the electronic and steric effects of the substitution patterns of bisallene C. Diradical intermediates E and F were excluded by radical inhibition experiments (Scheme 5).

The versatility of this copper-catalyzed cross-couping/[2 + 2] cycloaddition reaction can be further exploited in chemoselective transformations to access various quinoline

# Scheme 6. Proposed Reaction Mechanism



derivatives with high degrees of molecular complexity. As outlined in Scheme 7, the products 7 smoothly transformed to



"Reaction conditions: 7 (0.1 mmol), toluene (2.0 mL), 12 h, 80 °C, air. <sup>b</sup>Isolated yields. <sup>c</sup>TEMPO (1.0 equiv).

quinolines (8a-e) in toluene at 80 °C under air with moderate to good yields. A radical inhibition experiment indicated that the reaction proceeded via an oxidative radical rearrangement process. The structure of 8c was confirmed by X-ray diffraction analysis (CCDC 1956565).

In summary, we have developed an unprecedented coppercatalyzed tandem cross-coupling/[2 + 2] cycloaddition reaction of 1,6-allenynes with diazo compounds to chemoand regioselectively construct highly functionalized 3-azabicyclo[5.2.0] frameworks in moderate to excellent yields under mild reaction conditions. Moreover, the products readily transform to functionalized quinolines via oxidative radical rearrangement. It is believed that the continued and renewed investigation on copper-catalyzed intermolecular reactions of allenynes with diazo compounds will not only impact the fields of diazo carbene chemistry and allenyne chemistry but also enrich the synthetic applications to access diverse complex structures attractive for medicinal chemistry. Further studies will be reported in due course.

# ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.9b03727.

Experimental procedures along with characterizing data and copies of NMR spectra (PDF)

# Accession Codes

CCDC 1956559, 1956565, and 1960368 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data\_request/cif, or by emailing data\_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.

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