CHEMISTRY
AN ASIAN JOURNAL
ACES
COMMUNICATION

DOI: 10.1002/asia.201300340

Synthesis of Allyl Allenes through Three-Component Cross-Coupling Reaction of *N*-Tosylhydrazones, Terminal Alkynes, and Allyl Halides

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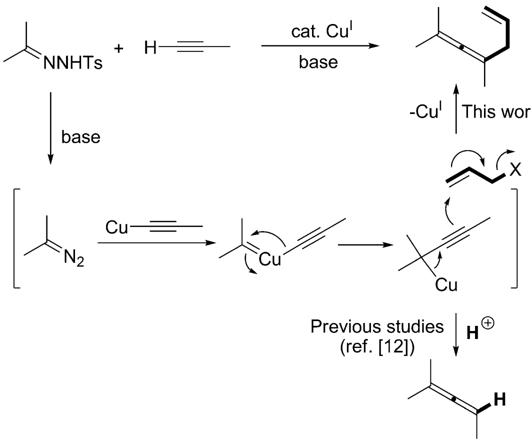
Dedicated to Professor Irina Petrovana Beleskaya

Allenes have attracted considerable attention in recent years due to their unique structural features and chemical properties related to the presence of two perpendicular π bonds. Allenes can undergo diverse transformations, which are highly useful in organic synthesis.[1,2] Allene moieties also exist in many natural products and pharmaceutically relevant compounds.[3] Over the past decades, enormous efforts have been directed to the development of efficient methods for the synthesis of allenes.[4–6] The traditional approach toward allenes is based on S_N2'-type displacement of propargyl alcohol derivatives with organocopper species.[5] More recently, allene synthesis based on direct coupling of two simple fragments has been explored.[7–11] In this context, Crabbé and co-workers in 1979 reported the CuBr-mediated reaction to form terminal allenes from 1-alkynes and formaldehyde in the presence of diisopropylamine.[9] Recently, Ma and co-workers have significantly improved this transformation and expanded the reaction to aldehydes, which constitutes an efficient synthesis of 1,3-disubstituted allenes.[11] Moreover, axially chiral allenes have been successfully synthesized with high enantioselectivity by the same group with their method.[11g]

We recently reported a different method for allene synthesis by Cu^I-catalyzed cross-coupling reaction of *N*-tosylhydrazones with terminal alkynes.[12–14] A mechanism involving a copper carbene migratory insertion process has been proposed to account for these transformations (Scheme 1). In the proposed catalytic cycle of our previous studies, the last step is the protonation of a propargyl copper or allenyl copper intermediate.



Scheme 1. Allene synthesis through Cu^I-catalyzed three-component reaction.

We envisioned that such nucleophilic organocopper species could also be trapped by carbon electrophiles, instead of a proton. Herein, we demonstrate that indeed the nucleophilic organocopper species can be trapped by allyl halides. This leads to the development of a three-component reaction of *N*-tosylhydrazone, terminal alkyne, and allyl halide, which constitutes an efficient synthesis of tri- and tetrasubstituted allenes.[15,16]

At the outset of this investigation, CuI-catalyzed three-component reaction of *N*-tosylhydrazone **1a**, phenylacetylene **2a**, and allyl iodide **3a** was examined (Table 1). With 1,4-dioxane as the solvent at 90 °C, the effect of base was first studied (Table 1, entries 1–3). With NaH as the base, the reaction was found to give the desired product **4a** in 15 % yield, while KO*t*Bu and NaHMDS were less effective.[17] It was also observed that the amount of base slightly affected the reaction (Table 1, entry 4). Carrying out the reaction at 110 °C could further improve the yield (Table 1, entry 5). The effect of solvent was then studied (Table 1, entries 6 and 7). The reaction in toluene afforded **4a** in diminished yield, while in MeCN, **4a** was formed in only trace amount. To our delight, adding 20 mol % tetra-*n*-butylam-

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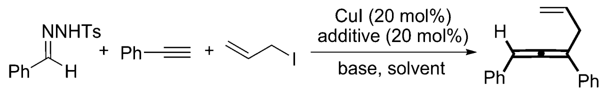
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.201300340.

Table 1. Optimization of reaction conditions.[a]



1a **2a** **3a** **4a**

Entry	Base (equiv)	Solvent	Additive (20 mol %)	Yield [%][b]
1	NaH (3.0)	dioxane	–	15
2	KO*t*Bu (3.0)	dioxane	–	9
3	NaHMDS (3.0)	dioxane	–	trace
4	NaH (4.5)	dioxane	–	22
5[c]	NaH (4.5)	dioxane	–	38
6[c]	NaH (4.5)	toluene	–	18
7[c]	NaH (4.5)	MeCN	–	trace
8	NaH (6.0)	dioxane	TBAB	40
9[d]	NaH (6.0)	dioxine	TBAB	74
10[e]	NaH (6.0)	dioxine	TBAB	82

[a] If not otherwise noted, the reaction conditions are as following: **1a** (0.1 mmol), **2a** (0.1 mmol), **3a** (0.1 mmol), CuI (20 mol %), base, TBAB, solvent (1.5 mL), 90 °C for 1 h. [b] Yield of isolated product. [c] Reaction was carried out at 110 °C. [d] **1a**:**2a**:**3a** = 1.5:1.0:1.2; **2a** (0.4 mmol); dioxane (6 mL). [e] **1a**:**2a**:**3a** = 2.0:1.0:1.5; **2a** (0.4 mmol); dioxane (6 mL).

monium bromide (TBAB) could improve the reaction (Table 1, entry 8). In the investigation of the conditions, we have found that protonation is more facile than nucleophilic attack of the allyl halide by an allenic intermediate. Therefore, excess NaH was used to trap the proton in the reaction system. Finally, we could obtain the allene product in acceptable yields by changing the ratio of substrates (Table 1, entries 9 and 10).

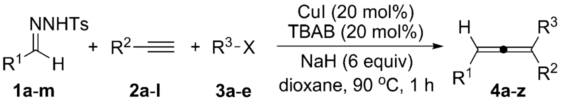
Having the optimized reaction condition in hand, we then proceeded to study the substrate scope of this reaction by using various substituted *N*-tosylhydrazones, terminal alkynes, and allyl halides (Table 2 and Scheme 2). The reaction with allyl bromide and allyl chloride afforded the expected allene products in diminished yields, showing their low reactivity relative to the corresponding allyl iodide (Table 2, entries 1–3).

As for the *N*-tosylhydrazone substrates, it was observed that the coupling proceeded well with these derived from aromatic aldehydes, and the reaction was not significantly affected by the substituents on the aromatic rings. The *N*-tosylhydrazones with both electron-donating and electron-withdrawing groups worked well in this reaction (Table 2, entries 17–24). The reaction also tolerates the *N*-tosylhydrazones bearing naphthyl and furan substituents (Table 2, entries 25 and 26). Moreover, the reaction also worked with the *N*-tosylhydrazones derived from aliphatic aldehydes (Table 2, entries 27 and 28).

Encouraged by the results, we further explored the possibility of the synthesis of tetrasubstituted allenes with this three-component coupling reaction. Under slightly modified reaction conditions with $[Cu(MeCN)_4]PF_6$ as catalyst and 1,10-phenanthroline as the ligand, the *N*-tosylhydrazones derived from ketones furnished the desired tetrasubstituted allene products in moderate to good yields. As summarized in Scheme 2, the reaction is efficient for a series of ketone-derived *N*-tosylhydrazone substrates bearing various substituents, including a cyclopropyl group (**6e**). Notably, the reaction with *N*-tosylhydrazone derived from cyclic ketones also afforded the allene product in moderate yield (**6h**).

To further demonstrate the use of this reaction, a gram-scale experiment has been carried out under standard reaction conditions. The reaction proceeded smoothly, providing the allene product in 74 % yield (1.37 g, Scheme 3).

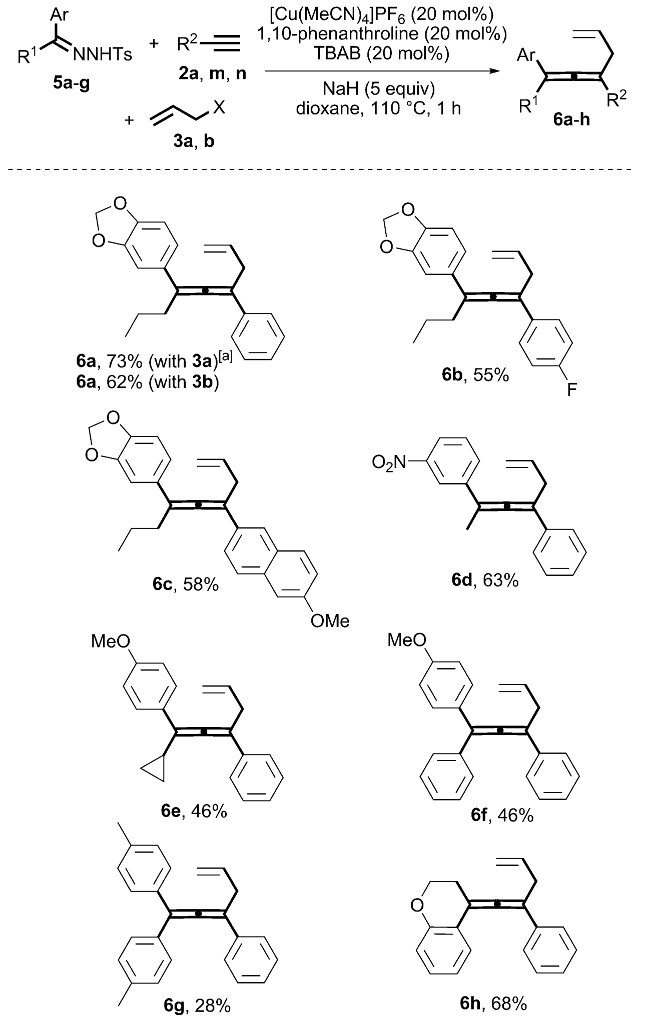
Table 2. Copper-catalyzed three-component coupling of various *N*-tosylhydrazone, terminal alkyne, and allyl halide.[a]



1a-m **2a-l** **3a-e** **4a-z**

Entry	**1**, R^1 =	**2**, R^2 =	**3**, R^3 =	Yield [%][b]
1	Ph	Ph	**3a**, allyl (X = I)	**4a**, 82
2	Ph	Ph	**3b**, allyl (X = Br)	**4a**, 67
3	Ph	Ph	**3c**, allyl (X = Cl)	**4a**, 37
4	Ph	Ph	**3a**, 2-methylallyl (X = Cl)	**4b**, 38
5	Ph	Ph	**3e**, 2-vinylcyclohexyl (X = Br)	**4c**, 34
6	Ph	*p*-MeC_6H_4	**3a**	**4d**, 64
7	Ph	*m*-MeC_6H_4	**3a**	**4e**, 53
8	Ph	*p*-*t*BuC_6H_4	**3a**	**4f**, 71
9	Ph	*p*-$MeOC_6H_4$	**3a**	**4g**, 55
10	Ph	*p*-$F_3CC_6H_4$	**3a**	**4h**, 72
11	Ph	*o*-ClC_6H_4	**3a**	**4i**, 51
12	Ph	3-thienyl	**3a**	**4j**, 72
13	Ph	$PhCH_2CH_2$	**3a**	**4k**, 55
14	Ph	*n*Bu	**3a**	**4l**, 46
15	Ph	$THPOCH_2CH_2$	**3a**	**4m**, 84
16	Ph	*t*Bu	**3a**	**4n**, 28
17	*p*-ClC_6H_4	Ph	**3a**	**4o**, 77
18[c]	*p*-BrC_6H_4	Ph	**3a**	**4p**, 71
19	2-benzo[*d*][1,3]dioxol	Ph	**3a**	**4q**, 60
20	*p*-$Me_2NC_6H_4$	Ph	**3a**	**4r**, 65
21	*p*-MeC_6H_4	Ph	**3a**	**4s**, 63
22	*m*-MeC_6H_4	Ph	**3a**	**4t**, 56
23	*p*-$MeOC_6H_4$	Ph	**3a**	**4u**, 75
24[c]	*o*-$MeOC_6H_4$	Ph	**3a**	**4v**, 62
25[d]	2-naphthyl	Ph	**3a**	**4w**, 56
26	2-furanyl	Ph	**3a**	**4x**, 50
27[e]	$PhCH_2CH_2$	Ph	**3a**	**4y**, 42
28[e]	*t*Bu	Ph	**3a**	**4z**, 50

[a] Unless otherwise noted, all the reactions were carried with *N*-tosylhydrazone (0.8 mmol), terminal alkyne (0.4 mmol), and allyl halide (0.6 mmol), CuI (20 mol %), NaH (2.4 mmol), TBAB (20 mol %) in 1,4-dioxane (6 mL), 90 °C for 1 h. [b] Yield of isolated product. [c] 1,4-dioxane (8 mL). [d] 70 °C. [e] Without adding TBAB.



6a, 73% (with **3a**)[a]
6a, 62% (with **3b**)

6b, 55%

6c, 58%

6d, 63%

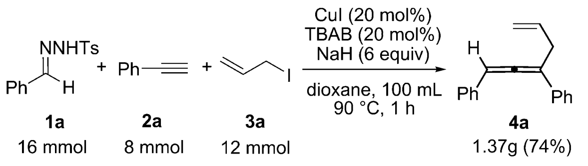
6e, 46%

6f, 46%

6g, 28%

6h, 68%

Scheme 2. Copper-catalyzed three-component coupling with ketone-derived *N*-tosylhydrazones. All the reactions were carried out with *N*-tosylhydrazone (0.64 mmol), terminal alkyne (0.4 mmol), and allyl halide (0.6 mmol), [Cu(MeCN)$_4$]PF$_6$ (20 mol%), NaH (2.0 mmol), 1,10-phenanthroline (20 mol%), TBAB (20 mol%) in 1,4-dioxane (5 mL), 110 °C for 1 h. [a] Yield of isolated product.



Scheme 3. Gram-scale experiment.

In conclusion, we have developed a copper-catalyzed three-component cross-coupling reaction of *N*-tosylhydrazones, terminal alkynes, and allyl halides, leading to the straightforward formation of tri- and tetrasubstituted allyl allenes from easily available starting materials.[18] Moreover, this reaction suggests the possibility of incorporating other electrophiles in this type of copper-catalyzed coupling reactions. The investigations along this line are currently underway and the results will be reported in due course.

Experimental Section

General procedure for the Cu^I-catalyzed cross-coupling

CuI (0.08 mmol, 15.36 mg), NaH (2.0 mmol, 96 mg, 50% purity) and *N*-tosylhydrazone 1 (0.88 mmol) were suspended in dioxane (5 mL) in a 25 mL Schlenk tube under nitrogen. Then terminal alkyne **2** (0.4 mmol) and allyl iodide **3** (0.6 mmol) were added. The resulting solution was stirred at 90 °C for 1 h. After cooling to room temperature, the resulting mixture was filtered through a short pad of silica gel, then eluted with hexane and CH$_2$Cl$_2$. The volatile compounds were removed in vacuo, and the residue was purified by column chromatography (SiO$_2$, hexane).

Acknowledgements

The project is supported by 973 Program (No. 2009CB825300), Natural Science Foundation of China (21272010).

Keywords: allenes • copper • diazo compounds • homogeneous catalysis • multicomponent reactions

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Received: March 14, 2013

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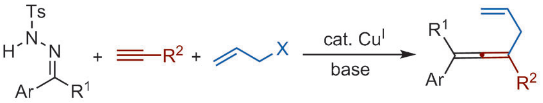

Three's a crowd: Tri- and tetrasubstituted allyl allenes can be easily accessed by this Cu^I-catalyzed three-component coupling reaction of *N*-tosylhydrazones, terminal alkynes, and allyl halides. The reaction proceeds through a mechanism involving copper carbene migratory insertion.

Cross-Coupling Reactions

Fei Ye, Mohammad Lokman Hossain, Yan Xu, Xiaoshen Ma, Qing Xiao, Yan Zhang, Jianbo Wang** . ■■■■–■■■■

Synthesis of Allyl Allenes through Three-Component Cross-Coupling Reaction of *N*-Tosylhydrazones, Terminal Alkynes, and Allyl Halides