# Coupling of *N*-Tosylhydrazones with Terminal Alkynes Catalyzed by Copper(I): Synthesis of Trisubstituted Allenes**

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Allenes are uniquely versatile intermediates in organic synthesis because of their structural and reactive properties that, in many cases, complement the chemistry of alkenes and alkynes.[1,2] Allene moieties have also been found in many natural products as well as pharmaceutically related compounds.[3] Because of the growing importance of this type of compound, synthetic methods that can rapidly lead to substituted allenes from simple and readily available starting materials are highly desirable. Over the past decades, enormous efforts have been devoted to the development of highly efficient allene synthesis.[4] Among the various methods hitherto developed, the most generally useful one is based on S_N2'-type displacement of propargyl alcohol derivatives with organocopper species.[4–6]

With respect to efficiency and versatility, the direct coupling of two fragments mediated by a transition-metal catalyst is obviously more attractive to construct the core structure made of three carbon atoms (Scheme 1). However, the allene synthesis based on direct coupling is much less developed and to the best of our knowledge, up until now there are only three known catalytic methods reported in the literature. These methods include allene cross-metathesis (Scheme 1a), carbene/vinylidene cross-coupling (Scheme 1b), and the Crabbé homologation and its modification (Scheme 1c). For the cross-metathesis, so far there is only one report. Barrett and co-workers employed Grubbs catalyst to demonstrate that it was possible for one of the terminal carbon units of allene substrates to be exchanged, thus affording new symmetrically substituted allenes. A considerable amount of polymer was also formed as side product.[7] Bertrand and co-workers have recently developed an efficient Au^I complex that catalyzes the coupling of enamines and terminal alkynes to afford allene derivatives in good yields.[8] In 1979, Crabbé and co-workers reported an allene synthesis based on a three-component reaction of a terminal alkyne,
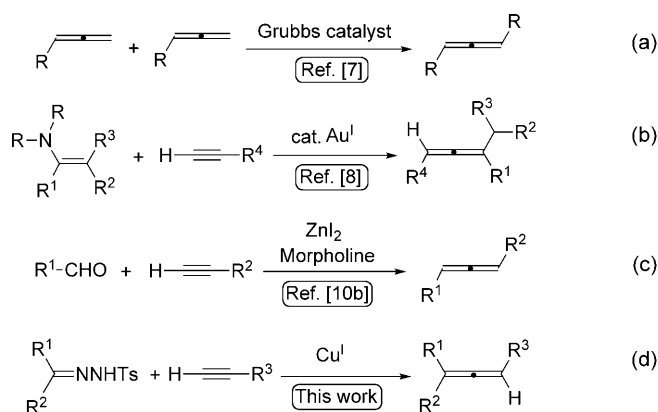
Scheme 1. Allene synthesis by direct coupling of two fragments. Ts = 4-toluenesulfonyl.

formaldehyde, and diisopropylamine mediated by CuBr.[9a–e] This reaction, now recognized as Crabbé homologation, results in low yields in many cases.[9] Recently, Kuang and Ma have significantly improved the Crabbé homologation by replacing CuBr and diisopropylamine with CuI and dicyclohexylamine.[10a]

A severe limitation of the Crabbé homologation is that the reaction only works with formaldehyde, and as a consequence only monosubstituted allenes can be synthesized by this method. Very recently, Kuang and Ma disclosed a breakthrough, which was based on the reaction of aldehydes, morpholine, and terminal alkynes mediated by ZnI$_2$.[10b] This new method can be employed to synthesize 1,3-disubstituted allenes. However, ketones cannot be used as a substrate in place of aldehydes.

Although significant progress has been made in allene synthesis based on the catalytic cross-coupling approach, the reactions hitherto developed still suffer from severe limitations, such as high reaction temperature, high catalyst loading, expensive catalyst, and relative instability of the substrates (such as enamines in Bertrand's system). Furthermore, except in Bertrand's system, trisubstituted allenes cannot be synthesized. Consequently, further development of a catalytic system that can circumvent these limitations is highly demanded.

Investigations over the past few years have demonstrated that the palladium-catalyzed cross-coupling of *N*-tosylhydrazone with a halide is highly efficient, and that the reaction mechanism involves the generation of Pd carbene and a subsequent migratory insertion.[11] Very recently, a palladium-catalyzed three-component coupling of *N*-tosylhydrazone, aryl bromide, and terminal alkyne has been developed in our

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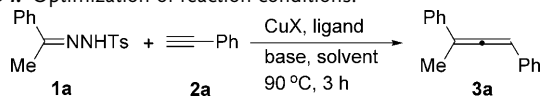Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201005741.

research group.[11g] On the other hand, we have noted that Suárez and Fu have reported a coupling of terminal alkynes with diazoesters or diazoamides catalyzed by CuI to afford 3-alkynoates.[12] Notably, cyclopropenation of the alkyne, which may be expected for such catalytic system,[13] was not observed. Instead, allene was detected as a minor by-product (up to 8% yield). Inspired by this report, and also as an extension of our recent interest in palladium-catalyzed cross-coupling of *N*-tosylhydrazone, we have conceived that a novel method for allene synthesis may be developed based on copper(I)-catalyzed cross-coupling of *N*-tosylhydrazone and terminal alkyne by selecting the appropriate catalytic system. Herein we report such a copper(I)-catalyzed cross-coupling reaction, which affords trisubstituted allenes with high efficiency (Scheme 1d).

At the outset of this investigation, we employed *N*-tosylhydrazone **1a** and phenylacetylene **2a** as the substrates (Table 1). After some initial experiments (Table 1,

entries 1–5), we found that in the presence of Cs_2CO_3 the coupling of **1a** and **2a** catalyzed by CuI could afford allene **3a** in 21% yield (Table 1, entry 4). Encouraged by these initial results, we proceeded to optimize the reaction. We were delighted to find that a combination of Cu^I and ligand could significantly affect the reaction (Table 1, entries 5–18). Thus, a series of nitrogen ligands was examined, and it was identified that the combination of ligand **I** and Cu(MeCN)$_4$PF$_6$ provided the optimal result (Table 1, entry 14). We then went on to screen other reaction parameters and observed that the reaction was subjected to notable concentration effects. After careful experimentation, it was concluded that the reaction carried out with **1a** at a concentration of 0.1 M provided the optimal yield (Table 1, entry 15). Furthermore, the ratio of substrates was examined, and it was found that a **1a/2a** ratio of 1.3:1.0 led to the highest yield of **3a** (Table 1, entry 16). Notably, without ligand the coupling product could only be identified in trace amount (Table 1, entry 5). Finally, a control experiment showed that in the absence of copper catalysts product **3a** was not detected under the otherwise identical reaction conditions (Table 1, entry 19).

With the optimized reaction conditions in hand, the scope of this transformation was studied by using various terminal alkynes and *N*-tosylhydrazones. Treatment of *N*-tosylhydrazone **1a** with a series of terminal alkynes **2a–l** furnished the corresponding products **3a–l** in moderate to good yields (Table 2). The reaction was not significantly affected by the substituents on the aromatic ring of the terminal alkyne. Both electron-rich (Table 2, entries 2, 5, and 6) and electron-deficient aryl-substituted alkynes (Table 2, entries 3 and 4) were effective, although a slightly lower yield was observed when the substituent was *p*-CF$_3$ (Table 2, entry 4). Notably, alkoxyl, acetyl, chloro, and trifluoromethyl groups are all tolerated under the given reaction conditions. The reaction also worked well with naphthyl alkynes (Table 2, entries 9 and

Table 1: Optimization of reaction conditions.[a]

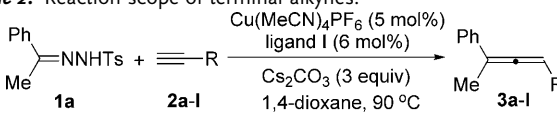| Entry	Base/Solvent	CuX (mol%)/Ligand (mol%)	Yield [%][b]
1	LiO*t*Bu/toluene	CuI(5)/none	trace
2	LiO*t*Bu/DCE	CuI(5)/none	7
3	K$_2$CO$_3$/dioxane	CuI(5)/none	15
4	Cs$_2$CO$_3$/dioxane	CuI(5)/none	21
5	Cs$_2$CO$_3$/dioxane	Cu(MeCN)$_4$PF$_6$(5)/none	trace
6	Cs$_2$CO$_3$/dioxane	Cu(MeCN)$_4$PF$_6$(5)/**A**(6)	37
7	Cs$_2$CO$_3$/dioxane	Cu(MeCN)$_4$PF$_6$(5)/**B**(6)	35
8	Cs$_2$CO$_3$/dioxane	Cu(MeCN)$_4$PF$_6$(5)/**C**(6)	21
9	Cs$_2$CO$_3$/dioxane	Cu(MeCN)$_4$PF$_6$(5)/**D**(6)	23
10	Cs$_2$CO$_3$/dioxane	Cu(MeCN)$_4$PF$_6$(5)/**E**(6)	27
11	Cs$_2$CO$_3$/dioxane	Cu(MeCN)$_4$PF$_6$(5)/**F**(6)	42
12	Cs$_2$CO$_3$/dioxane	Cu(MeCN)$_4$PF$_6$(5)/**G**(6)	37
13	Cs$_2$CO$_3$/dioxane	Cu(MeCN)$_4$PF$_6$(5)/**H**(6)	39
14	Cs$_2$CO$_3$/dioxane	Cu(MeCN)$_4$PF$_6$(5)/**I**(6)	55
15[c]	Cs$_2$CO$_3$/dioxane	Cu(MeCN)$_4$PF$_6$(5)/**I**(6)	73
16[d]	**Cs$_2$CO$_3$/dioxane**	**Cu(MeCN)$_4$PF$_6$(5)/I(6)**	**87**
17	Cs$_2$CO$_3$/dioxane	catalyst ***a*** (5)	21
18	Cs$_2$CO$_3$/dioxane	catalyst ***b*** (5)	27
19	Cs$_2$CO$_3$/dioxane	none	none

[a] All the reactions were carried out with 1a (0.50 mmol), 2a (0.50 mmol) in 3.0 mL of dioxane for 3 h if not otherwise indicated. [b] Yield of the isolated product. [c] 5.0 mL of dioxane as solvent. [d] The ratio of 1a/2a is 1.3:1.0 and in 5.0 mL of dioxane.
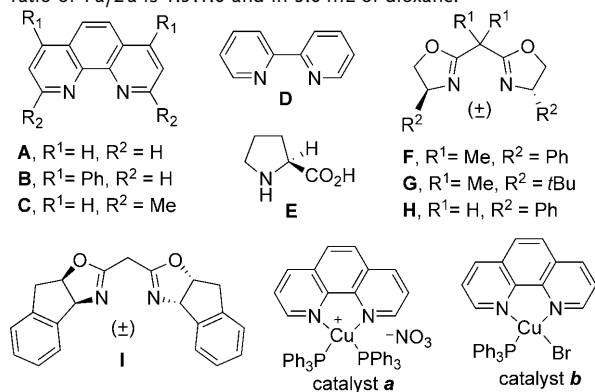
Table 2: Reaction scope of terminal alkynes.[a]

Entry	**2**, R	**3**, Yield [%][b]
1	**2a**, C$_6$H$_5$	**3a**, 87
2	**2b**, *p*-MeC$_6$H$_4$	**3b**, 73
3	**2c**, *p*-ClC$_6$H$_4$	**3c**, 62
4	**2d**, *p*-CF$_3$C$_6$H$_4$	**3d**, 50
5[c]	**2e**, *p*-MeOC$_6$H$_4$	**3e**, 64
6	**2f**, *p*-*t*BuC$_6$H$_4$	**3f**, 87
7	**2g**, *m*-CH$_3$C(O)C$_6$H$_4$	**3g**, 69
8	**2h**, *m*-MeOC$_6$H$_4$	**3h**, 86
9	**2i**, 2-naphthyl	**3i**, 75
10	**2j**, 2-(6-MeO-naphthyl)	**3j**, 75
11	**2k**, 2-thienyl	**3k**, 71
12[d]	**2l**, *n*-C$_5$H$_{11}$	**3l**, 54

[a] All the reactions were carried out with *N*-tosylhydrazones (0.65 mmol), terminal alkynes (0.50 mmol) in 5.0 mL of dioxane for 5 h if not otherwise indicated. [b] Yield of the isolated product. [c] The reaction was carried out at 80°C for 8 h. [d] The reaction was carried out in 3.0 mL of dioxane for 8 h.

10), alkynes bearing a heteroaromatic substituent (Table 2, entry 11), and an alkyl substituent (Table 2, entry 12).

Next, the reaction scope of *N*-tosylhydrazone was studied. The reaction was examined with a series of *N*-tosylhydrazones **1b–l**, which were treated with phenylacetylene **2a** under the optimized reaction conditions (Table 3). The cross-coupling

Table 3: Reaction scope of *N*-tosylhydrazones.[a]

$$R^1\text{-}C(R^2)=NNHTs + \text{≡}\text{—}Ph \xrightarrow[\substack{Cs_2CO_3 \text{ (3 equiv)} \\ 1,4\text{-dioxane, 90 °C}}]{\substack{Cu(MeCN)_4PF_6 \text{ (5 mol%)} \\ ligand\ I\ (6\ mol\%)}} R^1(R^2)C=C=CH\text{—}Ph$$

Entry	1, R^1, R^2	4, Yield [%][b]
1	**1b**, *p*-MeC$_6$H$_4$, Me	**4b**, 75
2	**1c**, *p*-MeOC$_6$H$_4$, Me	**4c**, 64
3	**1d**, *p*-ClC$_6$H$_4$, Me	**4d**, 73
4	**1e**, *m*-O$_2$NC$_6$H$_4$, Me	**4e**, 40
5	**1f**, *m*-MeOC$_6$H$_4$, Me	**4f**, 67
6[c]	**1g**, *o*-MeC$_6$H$_4$, Me	**4g**, 41
7	**1h**, 2-naphthyl, Me	**4h**, 76
8[d]	**1i**, C$_6$H$_5$, C$_6$H$_5$	**4i**, 40
9[d]	**1j**, C$_6$H$_5$, H	**4j**, 50
10[e]	**1k**, C$_6$H$_5$, *n*Pr	**4k**, 69
11	**1l**, PhCH$_2$CH$_2$, H	**4l**, 35
12	**1m**, -(CH$_2$)$_5$-	**4m**, 21

[a] All the reactions were carried out with *N*-tosylhydrazones (0.65 mmol), terminal alkynes (0.50 mmol) in 5.0 mL of dioxane for 5 h if not otherwise indicated. [b] Yield of the isolated product. [c] The reaction was carried out for 8 h. [d] The reaction was carried out in 3.0 mL of dioxane with 5 equiv of Cs$_2$CO$_3$ for 3 h. [e] The reaction was carried out for 11 h.

worked smoothly with *N*-tosylhydrazone substrates that were easily derived from aryl alkyl ketones (Table 3, entries 1–7, 10), diaryl ketones (Table 3, entry 8), and aryl aldehydes (Table 3, entry 9), thus leading to the formation of trisubstituted or disubstituted allene products. However, when R^1 is an aryl group bearing an electron-withdrawing substituent (Table 3, entry 4), the yield is markedly diminished. Besides, the coupling with *ortho*-substituted aryl alkyl tosylhydrazone took place over a longer reaction time (Table 3, entry 6). Finally, the reaction also worked for the *N*-tosylhydrazone derived from aliphatic aldehyde and ketones, albeit in low yields (Table 3, entries 11 and 12).

Based on our understanding of the palladium-catalyzed cross-coupling reaction of *N*-tosylhydrazones,[11] we proposed a plausible mechanism to account for the current copper(I)-catalyzed coupling (Scheme 2). In the presence of base and copper(I) salt, copper acetylide **A** is formed from phenylacetylene. The reaction of copper acetylide **A** with diazo substrate **B**, which is generated in situ from *N*-tosylhydrazone in the presence of a base, leads to the formation of copper–carbene species **C**. Migratory insertion of alkynyl group to the carbenic carbon atom gives intermediate **D**. The allene product is formed by protonation of intermediate **D**, in conjunction with the regeneration of the Cu^I catalyst. It is noteworthy that in this pathway the protonation occurs regioselectively at a triple bond carbon atom. Alternatively, if the protonation occurs at the carbon atom attached to copper, the alkyne product **5** will be formed, which may
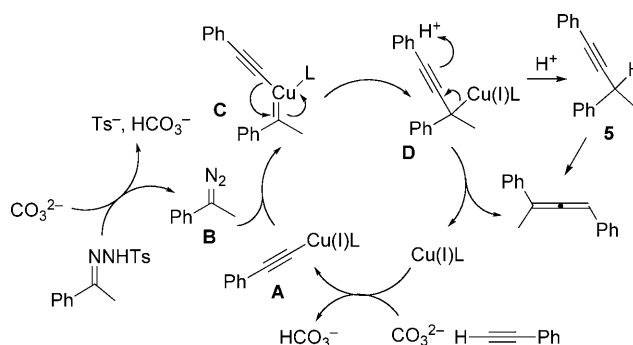
Scheme 2. Mechanistic rationale. L = ligand.

undergo rearrangement to afford the allene product. It is worth mentioning that in the copper(I)-catalyzed coupling of terminal alkynes with diazoesters or diazoamides previously reported by Suárez and Fu, 3-alkynoates, which correspond to **5**, are the main products.[12] Although the reaction mechanism has not been mentioned in Fu's paper, we conjecture that a similar migratory insertion of a copper–carbene intermediate may also be involved, followed by the protonation at the carbon atom attached to the copper center.[14]

In conclusion, we have developed a novel synthesis of substituted allenes from terminal alkynes and tosylhydrazones through the copper(I)-catalyzed alkynyl migratory insertion. This approach can also be viewed as the cross-coupling between the "masked" carbenic carbon atom and vinylidene.[8] Trisubstituted allenes can be directly synthesized through a transition-metal-catalyzed cross-coupling of two fragments. The reaction is operationally simple and the conditions are mild with low catalyst loading and at moderately high temperature. Since the ligands have a significant effect on the reaction, asymmetric catalysis should also be possible. Mechanistically, an unprecedented copper–carbene migratory insertion process is most likely involved,[11,15,16] and is distinctly different from classic copper(I)-catalyzed reactions of diazo compounds. This may open up new possibility to incorporate copper-catalyzed coupling reactions with diazo chemistry.

Experimental Section

Typical procedure for the copper(I)-catalyzed cross-coupling of *N*-tosylhydrazones and terminal alkynes: Under a nitrogen atmosphere, ethynylbenzene **2a** (51 mg, 0.5 mmol) was added to a mixture of Cu(MeCN)$_4$PF$_6$ (9 mg, 0.025 mmol), ligand **I** (10 mg, 0.030 mmol), Cs$_2$CO$_3$ (489 mg, 1.5 mmol), and *N'*-(1-phenylethylidene)tosylhydrazine **1a** (187 mg, 0.65 mmol) in 1,4-dioxane (5 mL). The mixture was stirred at 90 °C for 5 h and was monitored by TLC. The solvent was then removed in vacuo to provide a crude mixture, which was purified by column chromatography on silica gel to afford pure **3a** as a colorless oil (90 mg, 87 %).

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