Synthetic Methods

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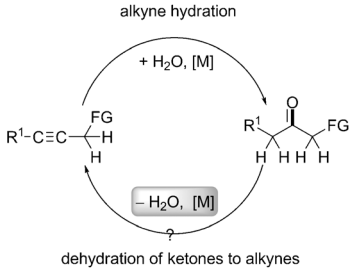
Copper-Catalyzed Aerobic Oxidative Transformation of Ketone-Derived *N*-Tosyl Hydrazones: An Entry to Alkynes**

*Xianwei Li, Xiaohang Liu, Huoji Chen, Wanqing Wu, Chaorong Qi, and Huanfeng Jiang**

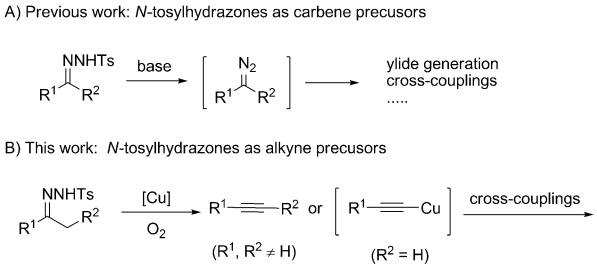
Abstract: *A novel strategy involving Cu-catalyzed oxidative transformation of ketone-derived hydrazone moiety to various synthetic valuable internal alkynes and diynes has been developed. This method features inexpensive metal catalyst, green oxidant, good functional group tolerance, high regioselectivity and readily available starting materials. Oxidative deprotonation reactions were carried out to form internal alkynes and symmetrical diynes. Cross-coupling reactions of hydrazones with halides and terminal alkynes were performed to afford functionalized alkynes and unsymmetrical conjugated diynes. A mechanism proceeding through a Cu-carbene intermediate is proposed for the C–C triple bond formation.*

The hydration reaction of alkynes is a well-studied subject in organic chemistry. However, the retrohydration reaction, namely the conversion of ketones into alkynes, still remains underdeveloped (Scheme 1). Previous synthetic protocols[1] typically involved the enolization of the carbonyl group and subsequent induced enol elimination induced by a sterically hindered base to give the C≡C bond. These known methods have drawbacks, such as low efficiency, requiring stepwise a procedure, and harsh reaction conditions, which limit their applicability in synthetic chemistry. Another challenge faced in ketone-to-alkyne transformations includes the selective deprotonation of proximal hydrogen atoms.



Scheme 1. Retro alkyne hydration strategy: from ketones to alkynes.

In contrast, *N*-tosylhydrazones derived from simple ketones, which were utilized as the precursors of diazo compounds, have been widely exploited in modern synthetic chemistry, especially in transition-metal-catalyzed reactions.[2] Barluenga, Wang and others have demonstrated the synthetic utility of metal/carbene species (derived from *N*-tosylhydrazones) in cross-coupling reactions. Such a methodology has emerged as a powerful strategy for the construction of structurally diverse molecules which might be difficult to access by other cross-couplings.[3]



Scheme 2. Catalytic transformations of *N*-tosylhydrazones.

Despite these excellent developments, the cross-coupling reactions involving *N*-tosylhydrazones as coupling partners are still limited. Thus, developing new strategies combining the chemistry of *N*-tosylhydrazones with other concepts, such as aerobic oxidative transformations, might be one exciting and desirable direction. However, the troublesome compatibility of the stoichiometric amount of oxidant and harsh reaction conditions in these processes might be the major challenges.[4] During our search for more selective aerobic oxidative transformations,[5] we reasoned that a copper/carbene species could be a versatile precursor in such conversions. Herein, we would like to present an example of ketone-to-alkyne (via hydrazones) transformation by selective deprotonation in the presence of O_2.[3,6]

This copper-catalyzed selective oxidation of *N*-tosylhydrazones occurs under an atmosphere of oxygen, thus generating the corresponding internal alkynes or copper acetylide intermediates in situ (Scheme 2), which could subsequently participate in oxidative homocouplings, cross-couplings with halides, and oxidative cross-couplings with terminal alkynes to afford various symmetrical diynes, internal alkynes, and unsymmetrical diynes. We speculate

[*] X. Li, X. Liu, H. Chen, Dr. W. Wu, Dr. C. Qi, Prof. Dr. H. Jiang
School of Chemistry and Chemical Engineering, South China University of Technology
Guangzhou 510640 (P.R. China)
E-mail: jianghf@scut.edu.cn

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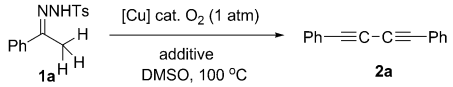
that the key to the success of this transformation might be the judicious choice of the base and oxidant molecular oxygen.

Based on the retro alkyne hydration strategy, the *N*-tosylhydrazone of acetophenone **1a**, a copper carbene precursor[3] was employed to test ketone-to-alkyne transformation. When $Cu(OAc)_2$ was used as the catalyst, we found the additives were quite important (Table 1, entries 1–4). The base additives such as K_2CO_3 and LiO*t*Bu, which are widely used in metal-mediated carbene transformations, afforded (*E*)-but-2-ene-2,3-diyldibenzene, the major byproduct derived from dimerization of the corresponding carbene cuperate. It is delightful that the desired diyne product **2a** was obtained when DABCO was added to the reaction mixture. Compared with other organic bases, DABCO displayed the best efficiency (entry 6 versus entries 7–9). We suspected that DABCO in our catalytic reaction system served both as base and ligand to facilitate this reaction (see the Supporting Information for more experimental recognition). Catalyst investigation demonstrated that CuCl was the most efficient (entries 4–6). Polar solvents were found to be critical for the product formation (entries 10 and 11). Interestingly, other oxidants such as BQ, DDQ, and $PhI(OAc)_2$ could not afford the desired 1,3-diynes, while molecular oxygen (1 atm) gave the best result. Neither the diyne product nor phenylacetylene (the monomer) could be obtained when the reaction was performed under an N_2 atmosphere (entry 15). The copper catalyst was found to be essential for this transformation, with (*E*)-but-2-ene-2,3-diyldibenzene detected as the side product, which indicated that *N*-tosylhydrazones (**1**) could act as the carbene precursors in this oxidative transformation (entry 16).

Table 1: Optimization of the reaction conditions.[a]

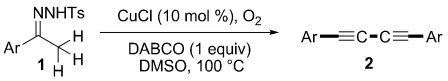


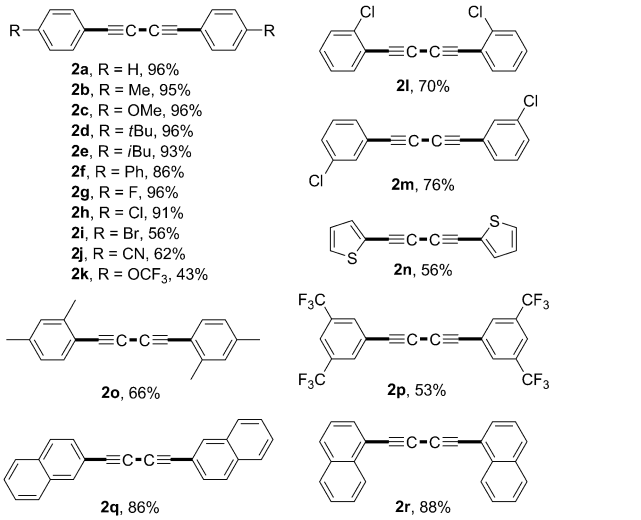
Entry	[Cu]	Additive	Oxidant	Yield [%][b]
1	$Cu(OAc)_2$	–	O_2	–
2	$Cu(OAc)_2$	K_2CO_3	O_2	–
3	$Cu(OAc)_2$	LiO*t*Bu	O_2	–
4	$Cu(OAc)_2$	DABCO	O_2	78
5	$Cu(OTf)_2$	DABCO	O_2	83
6	CuCl	DABCO	O_2	98 (96)
7	CuCl	NEt_3	O_2	< 10
8	CuCl	Pyridine	O_2	< 10
9	CuCl	DBU	O_2	12
10[c]	CuCl	DABCO	O_2	81
11[d]	CuCl	DABCO	O_2	10
12	CuCl	DABCO	BQ	–
13	CuCl	DABCO	DDQ	–
14	CuCl	DABCO	PIDA	–
15	CuCl	DABCO	N_2	–
16	–	DABCO	O_2	–

[a] Reaction conditions: **1a** (0.25 mmol), [Cu] (0.025 mmol), additive (0.25 mmol) in solvent (2 mL), 100 °C, 12 h. [b] Yield was determined by GC analysis. Number in parentheses is isolated yield. [c] DMF as the solvent. [d] Toluene as the solvent.

After optimal reaction conditions were established (Table 1, entry 6), we investigated the scope of this oxidative C≡C bond formation. As depicted in Table 2, substrates with electron-donating substituents on the phenyl ring showed higher reactivity than those with electron-withdrawing ones. Functional groups such as ethers (OMe, OCF_3), halogens (F, Cl, Br), nitriles, arenes, and CF_3 on the benzene ring could be compatible with this transformation. Sterically demanding substituents (**2o**, **2p**) were also tolerated. Notably, thienyl (**2n**) and 1- and 2-naphthyl (**2q**, **2r**) substituted 1,3-diynes, which are potential monomers in luminescent materials, could also be obtained in good yields.

Table 2: Substrate scope of copper-catalyzed aerobic oxidation for diyne formation.[a]



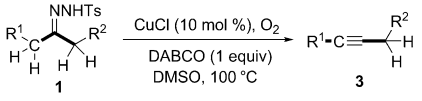


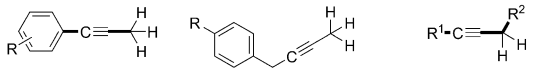
[a] Reaction conditions: hydrazone (**1**; 0.25 mmol), CuCl (10 mol%), DABCO (0.25 mmol) in DMSO (2 mL), 100 °C, O_2 (1 atm), 12 h. [b] Number within the parentheses is the yield of the isolated product on a 1 mmol scale.

N-Tosylhydrazones of ketones bearing two kinds of hydrogen atoms available for deprotonation for C≡C bond formation were also compatible with these reaction conditions, thus affording the corresponding internal alkynes[7] instead of diynes (Table 3). The formation of the desired products was observed with great regioselectivty in moderate to good yields using *N*-tosyl hydrazones of 1-aryl- or 1-alkyl-substituted acetones (**1**). The exclusive formation of internal alkyne products (**3a**–**h**) may be attributed to the lower bond-dissociation energy of secondary C–H groups than its primary counterpart. And the transformation was prone to giving the conjugated products (**3i**–**k**) because of their stability when the substrates have only secondary C–H.

Interestingly, *N*-tosylhydrazones of 1-phenyl-1-ones **1′** could be also converted into **3**, albeit with lower efficiency (**3a**, **3b**) [Eq. (1)]. Moreover, when *N*-tosylhydrazone of 1,2-diphenylethanone **1″** was used as the substrate, the trans-

Table 3: Copper-catalyzed aerobic oxidation for the internal alkyne formation.[a]





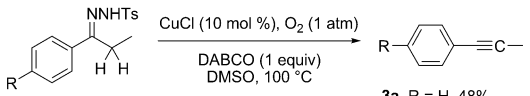
3a, R = H, 85%
3b, R = *p*-MeO, 88%
3c, R = *o*-MeO, 82%
3d, R = *p*-Cl, 78%
3e, R = *p*-F, 72%

3f, R = H, 58%
3g R = Me 62%
3h, R = F, 42%

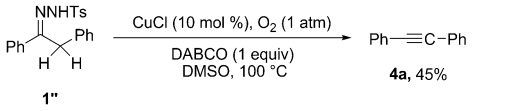
3i, R^1 = Ph, R^2 = Me, 52%
3j, R^1 = Ph, R^2 = Cl, 42%
3k, R^1 = Ph, R^2 = Ph, 58%
3l, R^1 = Ph, R^2 = Et, 45%
3m, R^1 = *p*-CNC_6H_4, Ph, R^2 = *n*Pr, 34%
3n, R^1 = *p*-$MeOC_6H_4$, R^2 = *n*Bu, 43%

[a] Reaction conditions: hydrazone (**1**; 0.25 mmol), CuCl (10 mol%), DABCO (0.25 mmol) in DMSO (2 mL), 100°C, O_2 (1 atm), 12 h.

formation afforded 1,2-diphenylethyne (**4a**) in moderate yield [Eq. (2)].



(1)

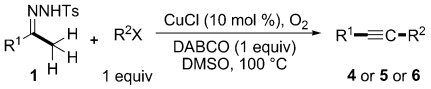


(2)

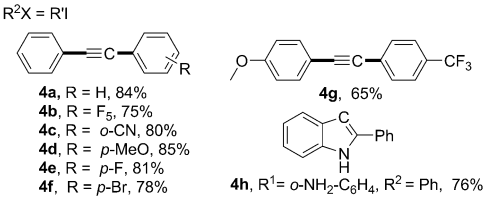
The results above are reminiscent of Glaser–Hay coupling reactions.[8] To investigate whether acetylene cuprates were generated in situ during this transformation, we performed a Castro–Stephens coupling reaction[9] by adding another equivalent of R^2I into the standard reaction system. To our delight, disubstituted acetylenes were obtained with excellent efficiency. The scope of oxidative cross-coupling of the hydrazones **1** with RX affording various functionalized acetylenes, enynes, and ynones is depicted in Table 4. Notably, when using 2-iodoaniline as the coupling partner, a cascade reaction involving cross-coupling and cyclization took place under the optimal reaction conditions to afford the corresponding indole product **4h**.[10] These observations indicated that cuprous acetylides species might be generated in situ during the process, and more importantly, cross-coupling of cuprous acetylides with RX proceeded much faster than oxidative dimerization of acetylene cuprates under these reaction conditions.

Our next target is to provide a complementary protocol for the synthesis of unsymmetrical conjugated diynes by introducing another terminal alkyne using the oxidative cross-coupling strategy.[11] It should be noted that significant challenges are still present in the cross-coupling reactions employing terminal alkynes as the coupling partners.[12] Indeed, the unsymmetrical alkynes **7** were formed in moderate yields by introducing another terminal alkyne (1.5 equiv)

Table 4: Oxidative cross-couplings of **1** with RX to afford alkyne derivatives.[a]



R^2X = R'I

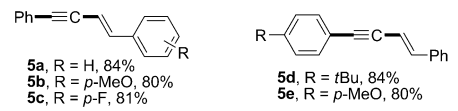


4a, R = H, 84%
4b, R = F_5, 75%
4c, R = *o*-CN, 80%
4d, R = *p*-MeO, 85%
4e, R = *p*-F, 81%
4f, R = *p*-Br, 78%

4g, 65%

4h, R^1= *o*-NH_2-C_6H_4, R^2 = Ph, 76%

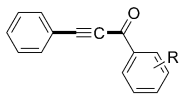
R^2X = R'CH = CHBr



5a, R = H, 84%
5b, R = *p*-MeO, 80%
5c, R = *p*-F, 81%

5d, R = *t*Bu, 84%
5e, R = *p*-MeO, 80%

R^2X = R'COCl

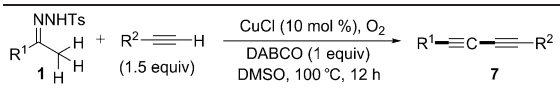


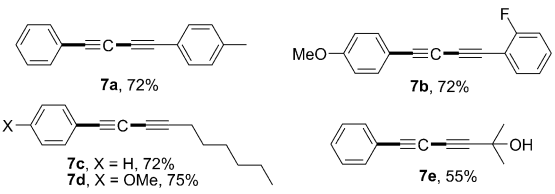
6a, R = H, 78%
6b, R = *m*-MeO, 82%
6c, R = *p*-OMe, 84%
6d, R = *m*-F, 81%
6e, R = *p*-CF_3, 71%

[a] Reaction conditions: **1** (0.25 mmol), RX (0.25 mmol), CuCl (10 mol%), DABCO (0.25 mmol), DMSO (2 mL) at 100°C under O_2 (1 atm), 12 h.

as the nucleophile into the optimal reaction system. As summarized in Table 5, both aromatic and aliphatic terminal alkynes could serve as the proper C–H nucleophile to undergo aerobic oxidative cross-coupling reactions. In general, this method provides an alternative to the Cadiot–Chodkiewicz coupling.[13] Intriguingly, a related copper(I)-catalyzed cross coupling between **1** and terminal alkynes afforded internal alkynes (versus the diyne species in current system),[14] thus highlighting the critical role of molecular oxygen in our reaction system.[15]

Table 5: Copper-catalyzed oxidative cross-coupling of **1** with terminal alkynes.[a]





7a, 72%

7b, 72%

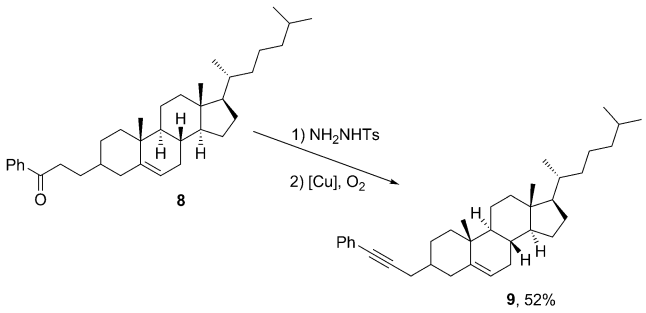
7c, X = H, 72%
7d, X = OMe, 75%

7e, 55%

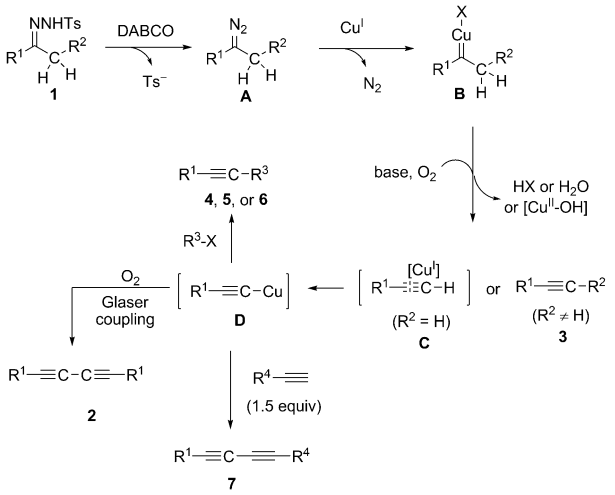
[a] Reaction conditions: **1** (0.25 mmol), terminal alkynes (0.375 mmol), CuCl (10 mol%), DABCO (0.25 mmol), DMSO (2 mL) at 100°C under O_2 (1 atm), 12 h.

We then applied the present protocol to the functionalization of cholesteryl derivatives.[7f,16] The steroid **8**, which was derived from biologically active cholesteryl bromide (see the

Supporting Information), could undergo further modification smoothly and the C≡C-containing alkylated cholesteryl **9** was successfully constructed (Scheme 3).



Scheme 3. Further modification on drug derivatives. Reaction conditions: 1) NH_2NHTs (1 equiv), MeOH, 60 °C, 2 h. (ii) CuCl (10 mol%), DABCO (1 equiv) in DMSO (2 mL), 100 °C under O_2 (1 atm), 12 h.



Scheme 4. A tentative pathway to rationalize the oxidative C≡C bond formation.

To gain more insight to this transformation, we conducted radical capture reactions by adding a radical inhibitor (BHT) or a radical-trapping reagent (TEMPO) to the reaction system, and the formation of the product **2a** was completely inhibited. When diallyl ether was subjected to the standard reaction conditions, the corresponding cyclization product was detected (see the Supporting Information). These observations supported a radical pathway in this reaction.

Meanwhile, styrene could not afford **2a** under the standard reaction conditions, and means that Shapiro reaction[17] might not be involved in this process. Thus, these results were in accordance with the formation of a carbene cuprate. Furthermore, as mentioned above (Table 1, entry 15), molecular oxygen might not only contribute to the homocoupling of in situ generated phenylacetyenes to the corresponding diynes, but also play a vital role in the aerobic oxidation of copper carbene into acetylene cuprate.

Taking into account the experimental results, we propose the following rationale for the mechanism of this copper(I)-catalyzed aerobic oxidative C≡C formation in Scheme 4.[18] Initially, the diazo substrate **A** is generated in situ from the *N*-tosylhydrazone in the presence of DABCO, which reacted with Cu^I to give the copper carbene species **B**. Subsequent oxidation and dehydrogenation of **B** with the assistance of O_2 and base[19] to generate the internal alkynes **3** (when $R^2 \neq H$) or the terminal alkynes in situ ($R^2 = H$), together with the release of HX, H_2O, or [Cu^{II}-OH].[19] We suspect that the in situ formed terminal alkyne can be readily deprotonated by the coordinating copper (an alkyne-coordinated copper species was proposed as an intermediate in the Glaser reaction),[6d,20] thus promoting the selectivity for cross-coupling in the reactions, such as the heteroselective cross-couplings with terminal alkynes to deliver the unsymmetrical diynes **7**. In contrast, internal alkynes can be released upon the formation of the copper-coordinated alkyne. Upon the in situ formation of terminal alkynes, Glaser coupling proceeds to give the corresponding conjugated diynes **2** with the assistance of DABCO as the base and/or ligand.[21] Furthermore, a Castro–Stephens-type coupling product internal alkynes **4**, **5** and **6** were obtained using R′I as the coupling partners. Comparative experiments using phenylacetylene as the substrate to perform the cross-coupling reactions in Table 4 (see the Supporting Information for details) led to lower reactivity and selectivity, which highlighted the potential synthetic utility of the in situ generated copper acetylide derived from *N*-tosylhydrazones under this Cu/O_2 catalytic system.

In summary, copper-catalyzed selectively oxidative transformation of ketone-derived *N*-tosyl hydrazones to alkynes and diynes was developed. The significant features of this chemistry are as follows: 1) inexpensive metal catalyst, green oxidant, readily available starting materials and good functional group tolerance; 2) good reactivity towards $C(sp^3)$–H bond of *N*-tosylhydrazones of ketones under this Cu/O_2 catalytic system, and great regioselectivity towards the substrates bearing more than one available C–H bond for aerobic oxidation; 3) a variety of alkynes and diynes obtained conveniently by selective oxidative deprotonations as well as cross-coupling reactions of in situ generated copper acetylides with halides or terminal alkynes. We anticipate this work could provide some synthetic applications and insight to copper and alkyne chemistry, specifically, in selective aerobic oxidations. Further studies to expand the synthetic scope of this reaction and address further mechanistic details will be reported in due course.

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Keywords: aerobic oxidation · alkynes · copper-catalyzed · cross-coupling · ketones

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