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Copper-Catalyzed Carbon-Carbon Bond Cleavage of Primary Propargyl Alcohols: β-Carbon Elimination of Hemiaminal Intermediates

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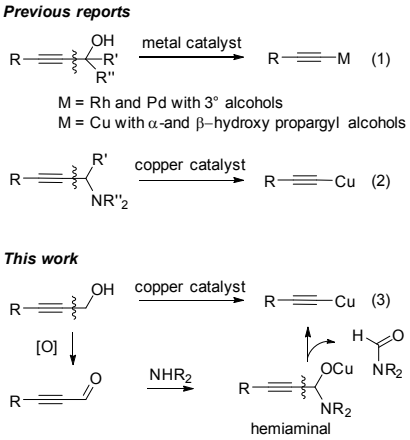
The copper-catalyzed cleavage of carbon-carbon bonds in primary propargyl alcohols under oxygen was investigated. This process involves the formation and fragmentation of hemiaminals from aldehydes (oxidized alcohols) and amines. This reaction mechanism was supported by the formation of *N*-formyl amines and GC experimental results.

The transition-metal-catalyzed cleavage of the σ C-C bond is a challenging subject in organic chemistry due to the inertness of species. Current protocols include ring-opening of strained C-C bonds, C-C bond cleavage of ketones, and β-carbon elimination of tertiary alcohols and propargyl amines.[1,2,3,4] In particular, transition-metal-catalyzed C(sp)-C(sp^3) bond breaking of *tert*-propargyl alcohols via β-alkynyl elimination has proven favorable given the facile release of corresponding ketone. Rhodium and palladium complexes are commonly used to activate these species, allowing the resulting alkynyl-metal species to be used in subsequent reactions like alkene/alkyne couplings and rearrangements (Scheme 1, eq 1).[3] In addition, copper complexes have shown catalytic activity in the dealkynylation of propargyl amines and α- and β-hydroxy propargyl alcohols (Scheme 1, eq 1 and 2).[2] However, aside from this one amine case, this class of reaction is restricted to the aforementioned alcohols. To the best of our knowledge, metal-catalyzed β-alkynyl elimination of primary propargyl alcohols has not been reported.[5]

The transition-metal-catalyzed formation of amides through the oxidation or dehydrogenation of alcohols or aldehydes with amines is generally thought to proceed through hemiaminal intermediates.[6,7] These metal-bound hemiaminals usually undergo β-hydrogen elimination to afford the target. While we were studying the copper-catalyzed oxidation of alcohols,[8] we observed a new catalytic property of copper salts which allow them to promote β-carbon elimination of propargyl alcohols via these intermediates. In this study, we present this new fragmentation mechanism, which favors cleavage of the relatively robust C-C bond over β-hydrogen elimination or C-N bond cleavage (Scheme 1, eq 3).[9] The resulting alkynyl copper species were isolated as triazoles via cycloaddition with azides.[10]



Scheme 1 Metal-catalyzed β-alkynyl elimination.

Testing began with the reaction of phenyl propargyl alcohol **1a** in the presence of $Cu(OAc)_2$ (5 mol%) and 2,2,6,6-tetramethylpiperidinyloxy (TEMPO, 5 mol%) at 100 °C under 1 atm of oxygen (see Table 1). Compound **1a** afforded **1b** in 83% yield after 18 h (Table 1, entry 1). When TEMPO was not included, **1b** was obtained in 13% yield; this suggests that oxidation to the aldehyde was incomplete, and that TEMPO is required to ensure that this important process with respect to dealkynylation proceeds under these conditions (Table 1, entry 2).[11,12] Similarly, in the absence of O_2, **1b** was not formed and **1a** remained mostly unoxidized. The common ligands 1,10-phenanthroline and 2,2'-bipyridine showed no increase in yield (Table 1, entries 3 and 4). Meanwhile, replacing the catalyst with the copper salts $CuCl_2$, $Cu(OTf)_2$ and $Cu(acac)_2$ gave yields of 50, 36, and 7%, respectively (Table 1, entries 5-7). Morpholine was also replaced with methyl

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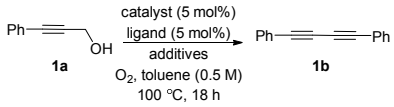
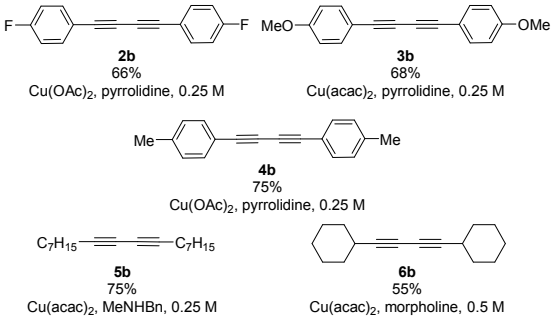
benzyl amine, piperidine, and pyrrolidine which afforded **1b** in 19, 52, and 42% yield, respectively (Table 1, entries 8-10). In the absence of copper catalysts, **1b** did not form (Table 1, entry 11). After obtaining **1b** in a good yield, other propargyl alcohols including aromatic and aliphatic groups were checked. Depending on the substituent of propargyl alcohols, different copper salts, additives, and the solvent were required (supporting information).

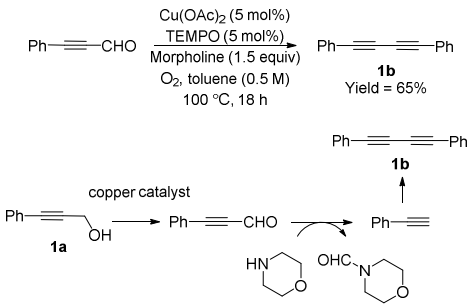
Table 1 Optimization of the conversion of **1a** to **1b** and examples of dimers



entry	catalyst	ligand	additives (equiv)	Yield
1	$Cu(OAc)_2$	TEMPO	morpholine (1.5)	83%
2	$Cu(OAc)_2$	--	morpholine (1.5)	13%
3	$Cu(OAc)_2$	phenanthroline	morpholine (1.5)	56%
4	$Cu(OAc)_2$	bipyridine	morpholine (1.5)	23%
5	$CuCl_2$	TEMPO	morpholine (1.5)	50%
6	$Cu(OTf)_2$	TEMPO	morpholine (1.5)	36%
7	$Cu(acac)_2$	TEMPO	morpholine (1.5)	7%
8	$Cu(OAc)_2$	TEMPO	MeNHBn (1.5)	19%
9	$Cu(OAc)_2$	TEMPO	piperidine (1.5)	52%
10	$Cu(OAc)_2$	TEMPO	pyrrolidine (1.5)	42%
11	--	TEMPO	morpholine (1.5)	--



Presumably, **1b** was formed by the copper-catalyzed Glase-Hay coupling of phenylacetylene which is formed by the β-alkynyl elimination of **1a**. To confirm this hypothesis, the reaction of **1a** was monitored by gas chromatography (supporting information), and a control experiment using phenylpropiolaldehyde was carried out; during GC analysis, phenylacetylene, phenylpropiolaldehyde, **1b**, and *N*-formyl morpholine were all observed, and phenylpropiolaldehyde was converted to **1b** in 65% yield (Scheme 2). Compound **1a** was completely oxidized to phenylpropiolaldehyde within 2 h. Concurrently, it undergoes β-alkynyl elimination, in which the formyl group is transferred to morpholine to afford *N*-formyl morpholine. The resulting phenylacetylene then undergoes oxidative dimerization to afford **1b** through copper-catalyzed oxidation.

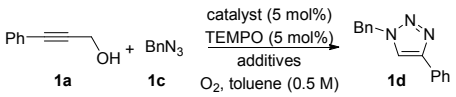


Scheme 2 The control experiment and proposed mechanism for the formation of **1b** from **1a**.

The dimerization yield varied significantly depending on the copper salt and amine additive used (Table 1). It is possible that the yield of **1b** might not accurately reflect dealkynylation efficiently; therefore, the cycloaddition of alkynes and azides was tested, since this cycloaddition occurs even in the absence of catalysts.

β-Alkynyl elimination of **1a** was followed by cycloaddition with benzylazide **1c** under the optimized conditions. As shown in Table 2, triazole **1d** was formed in 73, 50, 50, 83%, using $Cu(OAc)_2$, $CuCl_2$, $Cu(OTf)_2$, $Cu(acac)_2$, respectively (Table 2, entries 1-4). Triazole **1d** was obtained as the major product, showing that this reaction proceeds even in the presence of oxidant.[13] Additionally, unlike the oxidative dimerization results, the cycloaddition yields were not greatly affected by changing amines (Table 2, entries 4-7). The best yield was obtained using $Cu(acac)_2$ and methyl benzyl amine (Table 2, entry 5).

Table 2 Optimization of the conversion of **1a** to **1d**



entry	catalyst	additives (equiv)	Yield
1	$Cu(OAc)_2$	morpholine (1.5)	73%
2	$CuCl_2$	morpholine (1.5)	50%
3	$Cu(OTf)_2$	morpholine (1.5)	50%
4	$Cu(acac)_2$	morpholine (1.5)	83%
5	$Cu(acac)_2$	MeNHBn (1.5)	85%
6	$Cu(acac)_2$	piperidine (1.5)	80%
7	$Cu(acac)_2$	pyrrolidine (1.5)	77%

To better understand the β-alkynyl elimination mechanism, we performed several control experiments (Scheme 3). Frist, we tested the β-alkynyl elimination of **1a** in the absence of amines (eq 1). The desired product **1d** was isolated in 52% yield, suggesting that β-alkynyl elimination occurs but is less efficient. Presumably, a part of **1a** functions as an alcohol nucleophile to form the hemiacetal intermediate, which can undergo dealkylation, but at a lower yield. Phenylpropiolaldehyde and **1c** were also tested in the absence of amines and alcohols, and formed only regioisomer mixtures of **1e** (eq 2). The reaction of phenylpropiolaldehyde with **1c** in the presence of amine provided **1d** in 50% yield (eq 3). After the

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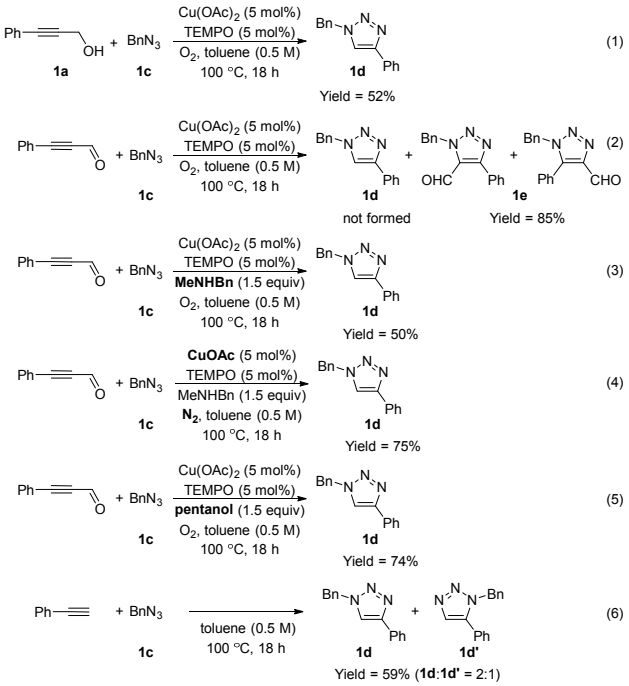
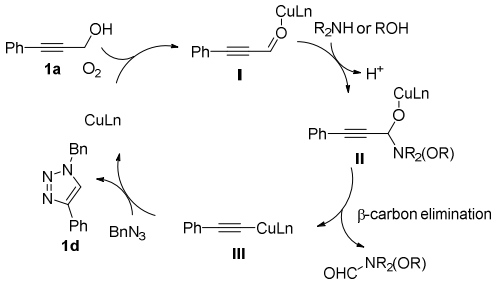
oxidation of **1a** by $Cu(OAc)_2$ and O_2, reduced copper salts become the active species in the second step (non-oxidative reaction); therefore, the CuOAc-catalyzed reaction in the absence of oxygen was carried out to form **1d** in 75% yield (eq 4). The reaction of phenylpropiolaldehyde with **1c** in the presence of pentanol affords **1d** in 74% yield (eq 5). Based on these results, it appears that both amines and alcohols facilitate the β-alkynyl elimination via hemiaminal or hemiacetal intermediates. In the absence of copper catalysts, the reaction of phenylacetylene and **1c** afforded a regioisomer mixture of **1d** and **1d'** in 59% yield. The formation of **1d** as a single regioisomer under our reaction conditions implies that copper catalysts are involved in both dealkynylation and cycloaddition.



Scheme 3 Control experiments.

A reaction mechanism for the dealkynylation of **1a** is proposed in Scheme 4. Propargyl alcohol **1a** undergoes oxidation to form intermediate **I**, which reacts with morpholine (or alcohols) to afford the key hemiaminal (hemiacetal) intermediate **II**. At this stage, dealkynylation occurs to afford intermediate **III** and formamide (formacetate). This intermediate then undergoes cycloaddition with benzylazide to form the corresponding triazoles.



Scheme 4 Proposed reaction mechanism for triazole formation.

Next, the scope of the reaction was examined (Figure 1). Since the dealkynylation yield could not be directly measured under the standard conditions, the yield for acetylene cycloaddition was used to provide an estimate. Halogen-substituted phenyl propargyl alcohols were converted to triazoles **2d** and **3d** in 77 and 85% yield, respectively. Meanwhile, *para*-, *meta*-, and *ortho*-substituted phenyl propargyl alcohols afforded **4d**, **5d**, and **6d** in 78, 85, and 78% yield, respectively. Cyclohexene-substituted propargyl alcohols also participated in the reaction to form **7d** in 57% yield. Overall, cyclohexyl, cyclopropyl, and pentyl propargyl alcohols underwent dealkynylation smoothly. Trimethylsilyl propargyl alcohol also showed good conversion, giving a yield of 81% with benzylazide. In addition to benzylazide **1c**, octylazide was tested to form **12d** in 93% yield.

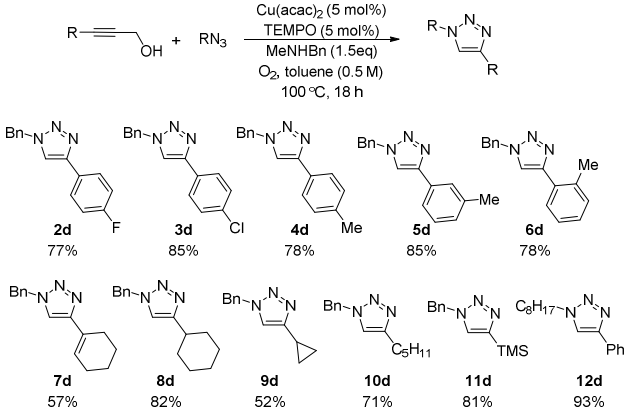


Figure 1 Substrate Scope.

Conclusions

We have presented the copper-catalyzed C-C bond cleavage of primary propargyl alcohols under mild aerobic oxidative conditions. This reaction proceeds through hemiaminal intermediates that form through the oxidation of propargyl alcohols and the subsequent nucleophilic addition of amines to aldehydes. Hemiaminals are known to undergo both β-hydrogen elimination and the C-N bond cleavage; however, in this case, the less polar C-C bond was cleaved to generate the

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alkyne-copper intermediate and the *N*-formyl amine. To assess the extent of conversion of C-C bond cleavage, azides were added to the reaction mixture to elicit cycloaddition; this demonstrated good dealkynylation conversion efficiencies for aromatic, aliphatic, and silyl-substituted propargyl alcohols.

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