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Copper-Catalyzed TEMPO Addition to Propargyl Alcohols for the Synthesis of Vinylic Alkoxyamines

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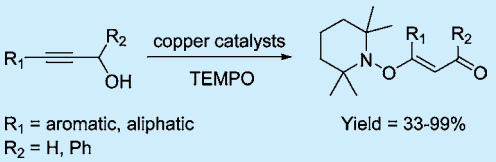
Supporting Information

ABSTRACT: A variety of vinylic alkoxyamines derived from propargyl alcohols and 2,2,6,6-tetramethylpiperidine *N*-oxyl (TEMPO) were synthesized in good yields under copper-catalyzed aerobic conditions. A reaction mechanism was proposed, involving the isomerization of propargyl radicals to allenic radicals, and related mechanistic studies were performed. The kinetic isotope effect on the propargyl C−H bond cleavage (α-deprotonation) reaction was observed (k_H/k_D = 3.76).



Alkoxyamines are widely used to initiate the controlled radical polymerization and radical-mediated addition/cyclization of alkenes; therefore, the efficient and selective syntheses of various alkoxyamines have been investigated.[1] Commonly used synthetic methods for alkoxyamines are (1) reactions of nitroxide radicals with carbon-centered radicals, which are derived from alkyl halides, activated alkanes, carbanions, alkyl hydrazines, and alkylboranes in the presence of appropriate oxidants, peroxides, and metal catalysts;[2] (2) α-oxyamination of carbonyl compounds;[3,4] (3) oxoammonium addition to alkenes;[5] and (4) Meisenheimer rearrangement of allyl *N*-oxides.[6]

Our research group has been interested in the synthesis of alkoxyamines via metal-catalyzed oxyamination of aldehydes using 2,2,6,6-tetramethylpiperidine *N*-oxyl (TEMPO).[4] To expand the scope of the alkoxyamine synthesis, propargyl alcohols were subjected to the copper-catalyzed TEMPO addition reaction, to afford TEMPO-incorporated α,β-unsaturated carbonyl compounds (Scheme 1). Previously reported TEMPO additions to π-systems were limited to the reactions with alkenes in the presence of in situ generated carbon-centered radicals, and with enamines generated from carbonyl groups (Scheme 1).[1,3,4,7] Compared to the previous reactions of TEMPO with alkenes and enamines, the alkyne of propargyl alcohols participated in the reaction with TEMPO to afford vinylic alkoxyamines. In this work, we are pleased to present the first example of copper-catalyzed TEMPO addition to propargyl alcohols to form β-oxyaminated-α,β-unsaturated aldehydes and ketones (vinylic alkoxyamines).

The optimization began with the reaction of phenyl propargyl alcohol **1a** (see Table 1) in the presence of $CuCl_2$ (5 mol %) and TEMPO (2 equiv) at 100 °C under air. Compound **1a** completely disappeared within 3 h, but the yield of **1b** was modest (68%, Table 1, entry 1). The stereochemistry of **1b** was confirmed by ^{1}H NOE measurement.[8] At a lower temperature (50 °C), the yield of **1b** increased to 93% after 18 h (Table 1, entry 2). When the reaction of **1a** was conducted under nitrogen instead of air, **1b** was obtained in 56% yield, implying that oxygen in the air is required to obtain a good yield (Table 1, entry 2). Next, the relative quantities of the catalyst and TEMPO were reduced, independently. As shown in entries 3 and 4, the reduced amounts of the catalysts and TEMPO lowered the yield of **1b**, in both cases. Instead of copper(II) complexes, CuCl was tested to afford **1b** in 63% yield (Table 1, entry 5). Similar copper(II) complexes, $Cu(OTf)_2$ and $Cu(OAc)_2$, catalyzed the reaction to provide **1b** in 91% and 99% yield, respectively (Table 1, entries 6 and 7). Other than copper complexes, $FeCl_3{\cdot}6H_2O$, which is known to react with TEMPO, was used as a catalyst, to form **1b** in 31% yield (Table 1, entry 8). In the absence of any metal catalysts, **1b** was formed in 5% yield (Table 1, entry 9).

Scheme 1. Addition of TEMPO to π-Systems

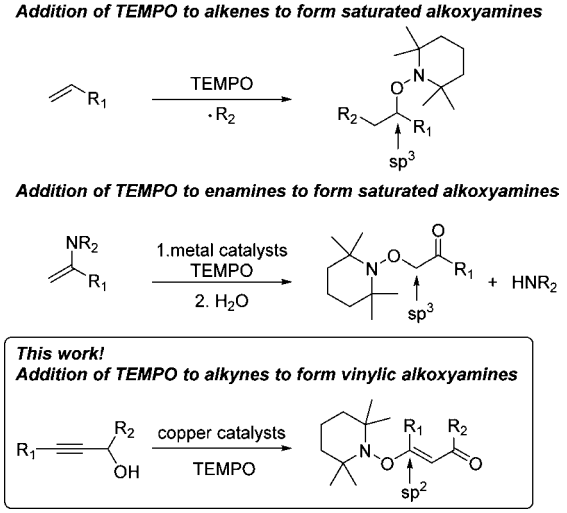


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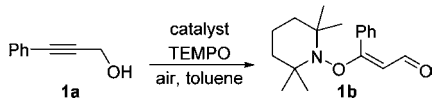
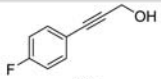
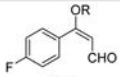
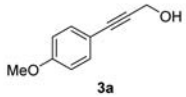
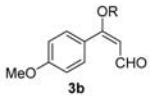
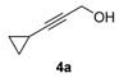
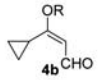
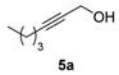
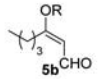
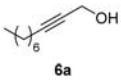
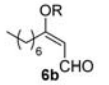
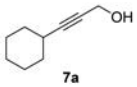
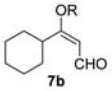
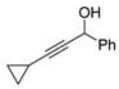
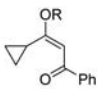
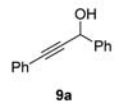
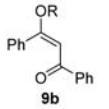
Table 1. Optimization of the Conversion of 1a to 1b

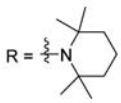


entry	catalyst (mol %)	TEMPO (equiv)	temp	time	yield
1	$CuCl_2$ (5)	2	100 °C	3 h	68%
2	$CuCl_2$ (5)	2	50 °C	18 h	93% (56%[a])
3	$CuCl_2$ (2.5)	2	50 °C	18 h	59%
4	$CuCl_2$ (5)	1.5	50 °C	18 h	55%
5	CuCl (5)	2	50 °C	18 h	63%
6	$Cu(OTf)_2$ (5)	2	50 °C	18 h	91%
7	$Cu(OAc)_2$ (5)	2	50 °C	18 h	99%
8	$FeCl_3 \cdot 6H_2O$ (5)	2	50 °C	18 h	31%
9	–	2	50 °C	18 h	5%

[a] N_2.

Table 2. Substrate Scope

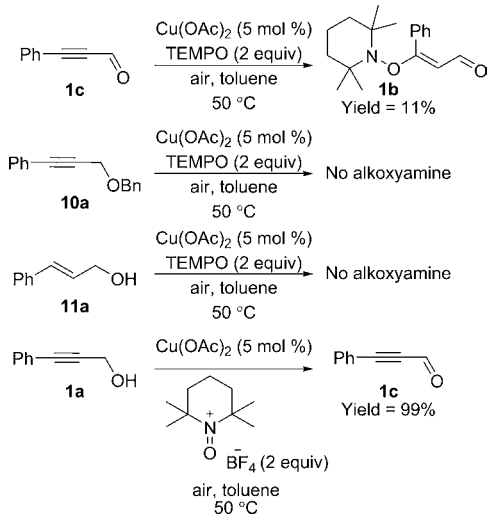
entry	reactant	product	yield
1	 2a	 2b	81%
2	 3a	 3b	90%
3	 4a	 4b	33%
4	 5a	 5b	97%
5	 6a	 6b	91%
6	 7a	 7b	91%
7	 8a	 8b	86%
8	 9a	 9b	87%



Next, the scope of the reaction was examined (see Table 2). Electron-deficient and electron-rich phenyl propargyl alcohols (**2a** and **3a**) were converted to the desired vinylalkoxyamines **2b** and **3b** in 81% and 90% yield, respectively (entries 1 and 2). In the case of cyclopropyl-substituted propargyl alcohol **4a**, the yield was low (33%, entry). The ring-opened product was not isolated in the reaction of **4a**. In contrast to **4a**, aliphatic propargyl alcohols **5a**, **6a**, and **7a** were efficiently transformed to **5b**, **6b**, and **7b** in 97%, 91%, and 91% yield, respectively (entries 4–6). In addition to the 1° propargyl alcohol derivatives, 2° propargyl alcohols were tested (entries 7 and 8). Cyclopropyl-substituted 2° propargyl alcohol **8a** and phenyl-substituted 2° propargyl alcohol **9a** showed yields comparable with those of the reactions of the 1° propargyl alcohol. In contrast to **4a**, cyclopropyl-substituted alcohol **8a** was converted to the desired product in good yield.

To investigate the reaction mechanism, the following control experiments were performed (see Scheme 2). First, the effect of

Scheme 2. Control Experiments



the free hydroxyl group was investigated by using **1c** and **10a**. Conjugated alkynal **1c** was subjected to the reaction conditions to afford **1b** in 11% yield, which is significantly lower than the yield for the reaction of **1a**. This result implies that the conversion of **1a** to **1b** does not proceed via aldehyde **1c**. When the benzyl group was introduced to **1a** as an alcohol protecting group, no alkoxyamine was observed. Based on the reactions of **1c** and **10a**, a free alcohol is required to complete this reaction in high yield. Next, the reactivity of alkyne and alkene was compared by using cinnamyl alcohol **11a**. The addition of TEMPO to alkene was not successful under our copper-catalyzed aerobic conditions. Instead, **11a** was converted to cinnamaldehyde in part and remained as an alcohol. Finally, instead of the TEMPO radical, oxoammonium was tested for alkoxyamine formation from propargyl alcohols. Because the oxoammonium addition to alkenes to form allylic alkoxyamines has been reported by Bailey,[5] we speculated that our reaction would also proceed via the addition of the alkyne to oxoammonium, derived from TEMPO under aerobic conditions; however, only alcohol oxidation to form **1c** was observed, and no alkoxyamine was observed. Based on the above-mentioned control experiments, it is presumed that TEMPO radicals are added to the alkyne possessing a neighboring free alcohol group.

In Scheme 3, a reaction mechanism for the conversion of **1a** to **1b** is proposed. At the beginning of the reaction, a three-centered two-electron Cu(II)–TEMPO radical adduct **I** is formed from $Cu(OAc)_2$, **1a**, and TEMPO.[9−11] An acetate ligand of $Cu(OAc)_2$ was displaced by **1a**. The oxygen radical of intermediate **I** may abstract an α-proton of propargyl alcohol **1a** to afford intermediates **II** and **II′**. The reaction of *deuterio*-**1a** showed a significant kinetic isotope effect (k_H/k_D = 3.76) on α-deprotonation (see Scheme 4). The addition of the TEMPO

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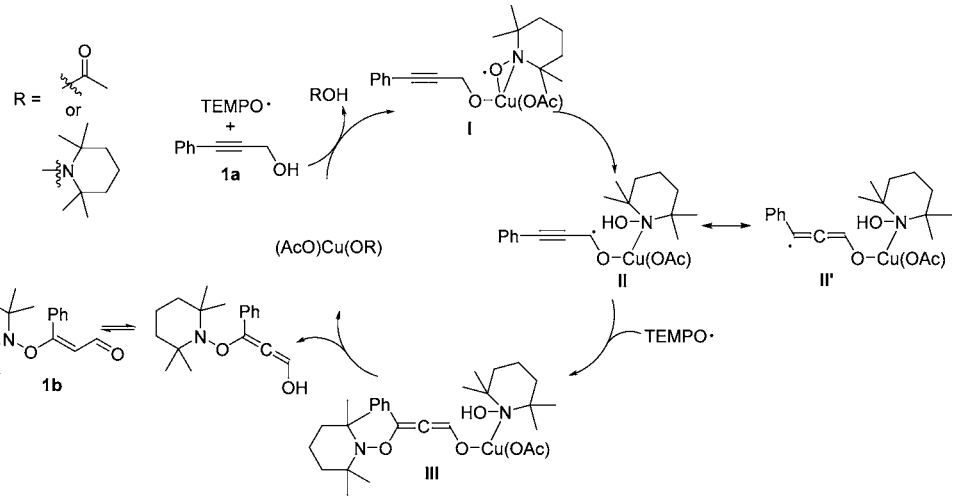
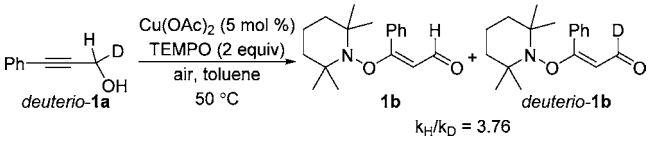
Scheme 3. Proposed Reaction Mechanism



radical to the allenic radical affords **III**,[12] which collapses to allenols and (AcO)Cu(TEMPO). During the tautomerization of allenols to **1b**, the oxyamine group might have an interaction with a proton to rationalize the indicated stereochemistry. In the catalytic cycle, oxygen was not involved, which explained the product formation in the absence of oxygen (Table 1, entry 2). However, oxygen might promote the reoxidation of TEMPOH to the TEMPO radical, to increase the concentration of TEMPO starting materials.[11c]

Scheme 4. Results of the Intramolecular KIE Experiment



In conclusion, we have presented the $Cu(OAc)_2$-catalyzed reaction of propargyl alcohols and TEMPO to afford a range of vinylic alkoxyamines. Regardless of the nature of alkyne substituents (aromatic and aliphatic groups) and the alcohol type (1° and 2°), the desired vinylic alkoxyamines were obtained in good yields except for the cyclopropyl-substituted 1° propargyl alcohol. Based on the control experiments, the reaction mechanism involving a propargyl alcohol bound Cu(II)–TEMPO radical intermediate was proposed, and the isomerization of propargyl radicals to allenic radicals afforded the desired products.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectra of alkoxyamines. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(8) The ^{1}H NOE spectra are attached in the Supporting Information. The irradiation of the olefin proton at 6.5 ppm caused signal enhancements of protons of TEMPO. No signal enhancement of phenyl protons was observed.

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