Photoredox Oxo-C(sp³)–H Bond Functionalization via in Situ Cu(I)-Acetylide Catalysis

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terminal alkynes but also serves as a photocatalyst to achieve varieties of 2-vinyl heterocycles in good to excellent yields, even for large scale and late-stage functionalization of natural product.

2-Vinyl heterocycle derivatives are core moieties spread across a multitude of bioactive natural products as well as pharmaceuticals.¹ To achieve this important framework, direct addition of heterocycle radicals to alkynes is particularly attractive because it avoids prefunctionalization of substrates and formation of vast amounts of byproducts.² However, the relatively high bond dissociation energy (BDE = 92.0 kcal/ mol),^{3a} low polarity of oxo-C(sp³)-H bond, and high reductive potential $(E_{1/2}^{red} = +1.75 \text{ V vs SCE for THF})^{3b}$ make the direct activation of the α -C(sp³)–H bond of THF a challenge.⁴ As a result, THF is widely used as a solvent for both academic studies and industrial processes. On the other hand, alkynes, unlike alkenes and enones,⁵ are not so active to react with ether radicals, and the generated vinyl radical intermediate would take part in other pathways instead of C-C bond formation.⁶ Recent advances in visible-light photoredox catalysis have provided a mild way to activate oxo-C-H bonds of ethers, followed by addition to alkynes (Scheme 1).^{7–9} By combining eosin Y^{7a} or $[Ru(bpy)_3]Cl_2^{7b}$ as a photocatalyst and the TBHP/NiCl₂ complex⁸ as an oxidant/

Scheme 1. Photoredox Approaches to 2-Vinyl Heterocycles



catalyst, oxo-C-H bond activation for the synthesis of a 2-vinyl heterocycle has been established.

Herein, we develop a photocatalyzed strategy for synthesis of 2-vinyl heterocycles with both oxo-C(sp³)-H and C(sp)-H activation in the same reaction system. Taking advantage of CuCl to activate the alkyne, the in situ generated Cu(I)-acetylide complex^{10,12} exhibits visible light absorption.^{11,12} Strikingly, the excited Cu(I)-acetylide, with a long lifetime and high reductive potential ($E_{1/2} = -1.77$ V vs SCE),¹¹ is able to deliver an electron^{11c} to *tert*-butyl hydroperoxide (TBHP) for the generation of the ¹BuO[•] radical, which activates the α -C(sp³)-H bond of the heterocycle for the subsequent addition^{7a,14} to afford the desired products. Indeed, terminal alkynes can rapidly be activated by CuCl under visible light irradiation.¹⁰ In comparison with a noble-metal complex (such as Ir and Ru) as a photoredox catalyst, inexpensive Cu(I) salt and a readily available alkyne in situ give Cu(I)-acetylide as a photocatalyst, greatly simplifying the reaction.¹³

Our initial study focused on the direct coupling of phenylacetylene (1a) with THF (2a) as the model substrates. When catalyzed by the simple copper(I) chloride salt using TBHP as an HAT reagent precursor at room temperature, the desired product 2-vinyltetrahydrofuran was obtained in 51% yield with an E/Z ratio of 0.7 (Table 1, entry 1). Other copper(I) halides (halide = bromide, iodide) give slightly lower (Table 1, entries 2–3) yields of 50% and 44%, respectively. Various HAT reagent precursors were tested, identifying TBHP as the best (Table 1, entries 4–6). A different performance was shown when the reaction was performed with a series of bases, such as KOAc, Et_3N , and pyridine, revealing 2-methylpyridine to be the most effective for the formation of the coupling product (3a) in 87% yield



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Table 1. Optimization of the Reaction Conditions^a

$Ph = + \bigcirc conditions$				
		1a 2a	3a	
entry	CuX	oxidant	base	yield (%) ^b
1	CuCl	TBHP	-	51
2	CuBr	TBHP	-	50
3	CuI	TBHP	-	44
4	CuCl	DCP	-	<20
5	CuCl	DTBP	-	<20
6	CuCl	$(NH_4)_2S_2O_8$	_	0
7	CuCl	TBHP	KOAc	32
8	CuCl	TBHP	Et_3N	53
9	CuCl	TBHP	pyridine	58 ^f
10	CuCl	TBHP	2-methylpyridine	87 ^f
11 ^c	CuCl	TBHP	_	0
12 ^d	-	TBHP	-	0
13 ^e	CuCl	TBHP	-	0

^{*a*}Reaction conditions: **1a** (0.2 mmol), **2a** (2.5 mL), MeCN (0.05 mL), CuX (1 mol %), oxidant (1 equiv), base (1 equiv), blue LEDs, argon atmosphere, rt, 24 h. ^{*b*}Isolated yield. ^{*c*}No light. ^{*d*}No CuCl. ^{*c*}In the air. ^{*f*}Yield detected by GC-FID, using mesitylene as an internal standard.

(Table 1, entry 10). Control experiments demonstrated that the conversion of 3a was completely inhibited when CuCl was absent from the reaction system, and no generation of 3a was detected without visible light irradiation (Table 1, entries 11–12). As a result, the visible-light-catalyzed Cu(I) mediated vinylation reaction of THF was able to smoothly proceed under optimized conditions, i.e., CuCl (1 mol %) with TBHP and 2-methylpyridine in 0.05 mL of MeCN, irradiated by blue LEDs at room temperature in an argon atmosphere (Table 1, entry 10).

With the optimized conditions in hand, various aromatic terminal alkynes were examined to explore the scope of photoredox-catalyzed in situ Cu(I) mediated vinylation reaction of heterocycles. As illustrated in Scheme 2, when subjected to the optimal reaction conditions described above, a series of the corresponding vinyl tetrahydrofuran product 3 were afforded smoothly in moderate to good isolated yields, with E/Z isomeric ratios ranging from 0.1 to 4.1. By using THF as both solvent and reactant, unsubstituted phenylacetylene reacted with THF to give 2-styryltetrahydrofuran 3a in a yield of 83% under the optimal reaction conditions. Halogen-containing phenylacetylene showed similar activities to those of phenylacetylene, as ortho-, meta-, and parahalogenophenylacetylene affording corresponding addition products 3b-3j in good yields. The introduction of an electron-withdrawing group such as ester (3k-3m) had only a slight effect on the reaction efficiency, resulting in moderate yields. Phenylacetylenes bearing electron-donating groups including methyl and methoxyl were also good reactants, and the target products 3n-3u were obtained in moderate yields. However, tert-butyl-substituted phenylacetylene (3q) gave the desired product in a low yield of 44%, probably because of the steric hindrance. Therefore, general reactivity could be reached since both electron-withdrawing/-donating properties and the substitution patterns (ortho, meta, para) on the aryl rings seemed to exhibit little influence on the reaction efficiency.

Other aromatic heterocyclic terminal alkynes such as 2ethynylnaphthalene (3v) and 2-ethynylpyridine (3w) could

Scheme 2. Substrate Scope^a



^aReaction conditions: 1 (0.2 mmol), 2 (2.5 mL), MeCN (0.05 mL), CuCl (1 mol %), TBHP (1 equiv), 2-methylpyridine (1 equiv), blue LEDs, argon atmosphere, rt, 24 h. Isolated yield was based on 1.

also tolerate the reaction condition smoothly, giving the corresponding products in moderate yields. Besides THF, oxygen-containing heterocycles including dioxane (3x), dioxolane (3y), and tetrahydropyran (3z) were suitable for this transformation under the optimal conditions. Thus, this visible light photocatalytic C–H functionalization method clearly tolerates a broad spectrum of terminal alkyne partners. To highlight the synthetic application, we developed the functionalization of a natural product derivative. Estrone derivative (1aa) was smoothly transferred into functionalized estrone (3aa) with an E/Z isomeric ratio of 0.6 under the standard reaction conditions. When the substrate loading was scaled up, a yield of 72% was obtained after reaction under optimal conditions, as shown in Scheme 3-1.

Since Cu(I)-phenylacetylide is an important intermediate involved in the reaction process,¹² we directly investigated Cu(I)-phenylacetylide by UV–vis absorption (Figure 1-Left) and luminescence (Figure 1-Right) analysis. CuCl and phenylacetylene in degassed MeCN with irradiation by blue LED soon gave Cu(I)-phenylacetylide as a yellow solid (Figure 1-Left).^{12c} This in situ generated Cu(I) complex showed an absorption peak at 460 nm,^{12c} along with two emission peaks Scheme 3. Scale-up Reaction, Radical Capture and Kinetic Isotope Effect Experiments



Figure 1. (Left) UV–vis absorption spectra of 7.84 × 10⁻⁴ M Cu(I)phenylacetylide in degassed MeCN: preparation of Cu(I)-phenylacetylide, CuCl (2 mg), and phenylacetylene (1 equiv) in degassed MeCN before blue LED irradiation in the left tube and after blue LED irradiation in the right tube. (Right) Luminescence spectra of 7.84 × 10⁻⁴ M Cu(I)-phenylacetylide (labeled by black line); with the addition of 7.84 × 10⁻² M TBHP (labeled by red line) in degassed MeCN with excitation at 460 nm.

at 510 and 574 nm (Figure 1), which was in accordance with other reported values.^{12c} Meanwhile, simple CuCl and phenylacetylene did not show the light absorbing property in this test, respectively. Then, the ratio of Cu(I)-phenylacetylide and TBHP was controlled to be the same as the reaction system. As shown in Figure 1-Right, labeled by the red line, the emission of the Cu(I) complex decreased as TBHP was introduced into the solution, suggesting the single-electron transfer (SET) process from Cu(I)-phenylacetylide to TBHP quenched the emission of Cu(I)-phenylacetylide. When one or more equivalent(s) of 2,2,6,6-tetramethylpiperidin-1-yloxy (TEMPO) or 2,6-ditert-butyl-4-methylphenol (BHT) were added into the reaction system, the reaction had varying degrees of inhibition, as shown in Scheme 3-2. This observation suggested that a radical intermediate might be involved in the reaction pathway. We also investigated the kinetic isotopic effect (KIE) by competition experiments as illustrated in Scheme 3-3. The intermolecular $k_{\rm H}/k_{\rm D}$ was determined to be 3.5 based on ¹H NMR spectroscopic analysis of the isolated products. This isotopic effect implied that α -C-H bond cleavage was probably involved in the ratedetermining step of this reaction. We further performed the on-off light experiment (see Supporting Information) under the optimal conditions. It demonstrated the transformation process was not totally forbidden during the dark condition, indicating that the radical chain reaction mechanism might be involved in this reaction.

Based on the above mechanistic results and previous investigation, a plausible reaction mechanism was proposed and illustrated in Scheme 4. The simple Cu(I) ion activates the





C-H bond of a terminal alkyne to produce the key intermediate Cu(I)-phenylacetylide complex.¹⁰ Visible-light irradiation of this in situ generated Cu(I)-phenylacetylide A affords an excited state of Cu(I)-phenylacetylide $A^{*,11}$ which then undergoes an SET process to deliver an electron to TBHP and generate the intermediate Cu(II)-phenylacetylide B^{11c} and a *tert*-butoxy radical (^tBuO[•]). The ^tBuO[•] radical then abstracts a hydrogen atom from THF to afford an α -oxo-carboncentered radical.⁷ Activated by the copper ion, the C \equiv C bond of Cu(II)-phenylacetylide intermediate B tends to be attacked by an ether radical,¹⁴ to generate carbon-centered intermediate C. The intermediate C accepts the H[•] radical from THF to furnish D. The ligand exchange process between D and the terminal alkyne might give the intermediate A and desired product 3a. The radical chain reaction mechanism might not be excluded since the generated THF radical attacked phenylacetylene directly to give the desired product.⁷

In conclusion, we have introduced in situ Cu(I)-catalysis for the photoredox synthesis of 2-vinyl heterocycle derivatives. A terminal alkyne is activated by CuCl to form a Cu(I)-acetylide complex. Under visible-light irradiation at room temperature, this in situ generated Cu(I)-acetylide complex as a photocatalyst reacts with an HAT precursor to activate the α - $C(sp^3)$ -H bond of a heterocycle. Besides electron-deficient alkynes, direct addition of the generated ether radical to electron-rich/-neutral alkynes has successfully achieved the coupling reaction. The natural product derivative and scale-up reaction perform well under the conditions. With this protocol using readily available starting materials and inexpensive copper salts to form photocatalyst in situ, it is anticipated that this approach would provide a useful design for a variety of carbon/heteroatom-centered radicals addition to alkynes in an economic and environmentally benign way.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04277.

Materials and methods; characterization data for all compounds, ¹H and ¹³C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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