

Visible-Light-Induced Alkoxy Radical Generation Enables Selective C(sp³)–C(sp³) Bond Cleavage and Functionalizations

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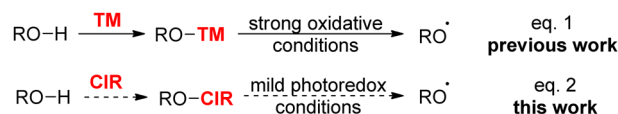
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S Supporting Information

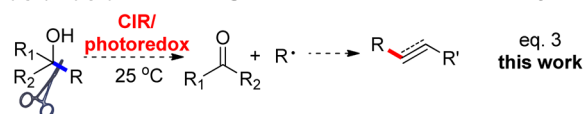
ABSTRACT: The alkoxy radical is an important reactive intermediate in mechanistic studies and organic synthesis; however, its current generation from alcohol oxidation heavily relies on transition metal activation under strong oxidative conditions. Here we report the first visible-light-induced alcohol oxidation to generate alkoxy radicals by cyclic iodine(III) reagent catalysis under mild reaction conditions. The β -fragmentation of alkoxy radicals enables selective C(sp³)–C(sp³) bond cleavage and alkylation/alkenylation reactions with various strained cycloalkanols, and for the first time with linear alcohols.

The alkoxy radical is an important reactive intermediate that not only is useful in mechanistic investigations of many important biological processes but also serves as a versatile reaction intermediate in various useful organic transformations.¹ While it is desirable to use alcohols as alkoxy radical precursors, the homolytic breakage of the oxygen–hydrogen bond in alcohols is thermodynamically and synthetically difficult.² To this end, the oxidation of alcohols to generate alkoxy radicals has been developed employing transition metal activation under strong oxidative conditions, such as silver salts, persulfates, or manganese acetates (eq 1).^{1b,3} While current

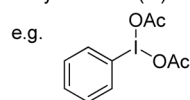
Alkoxy radical generation from alcohol oxidation



C(sp³)–C(sp³) bond cleavage and functionalizations via alkoxy radical

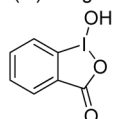


TM = Transition Metals
Noncyclic Iodine(III) Reagents



CIR = Cyclic Iodine(III) Reagents

e.g. BI–OH
(hydroxybenziodoxole)



studies, which are increasingly important for modern organic synthesis and chemical biology studies.⁴

Hypervalent iodine reagents are widely used in organic synthesis, among which the non-cyclic iodine(III) reagents (such as PhI(OAc)₂) are well known for their strong oxidative reactivity.⁵ In contrast, the cyclic iodine(III) reagents (CIR, such as hydroxybenziodoxoles) show unique transition-metal-like reactivity and excellent chemoselectivity.⁶ For example, the CIR-bound carboxylates demonstrate reactivity similar to that of transition metal-bound carboxylates, and CIR-bound alkynes have been used for biomolecule studies.⁷ Visible light catalysis has recently been shown to initiate radical reactions under mild conditions;⁸ however, visible-light-induced alcohol oxidation to generate alkoxy radicals is unknown. We speculate that while the CIR is not known to activate alcohols, its hypothetical coordination to the hydroxyl group may enable the challenging alkoxy radical generation under mild photoredox conditions (eq 2).

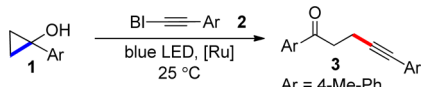
The cleavage of the C(sp³)–C(sp³) bond is useful in planning and implementation of organic synthesis; however, it is challenging to do so in a regioselective and chemoselective manner.⁹ The alkoxy radical is known to selectively cleave the C–C bond via β -fragmentation to yield stable ketones and alkyl radicals (eq 3).¹⁰ However, most current alkoxy radical β -fragmentation reactions only apply to strained cycloalkanols under strong oxidative conditions, and the use of unstrained linear alcohols is elusive due to the difficult C(sp³)–C(sp³) bond cleavage.¹¹ In this Communication, we report the first visible-light-induced alkoxy radical generation from alcohol oxidation, for which both strained cycloalkanols and linear alcohols undergo selective C(sp³)–C(sp³) bond cleavage and alkylation/alkenylation reactions.

We chose cyclopropanol **1** as the model substrate and alkynyl benziodoxole **2** (BI-alkyne) as the radical acceptor.^{7b,d,12} After extensive screening, we were gratified to find that the cyclic iodine(III) reagent acetoxybenziodoxole (BI-OAc) gives alkynylative adduct **3** in 49% yield under blue LED ($\lambda_{\text{max}} = 468 \pm 25$ nm) irradiation using [Ru(bpy)₃](PF₆)₂ as the photocatalyst (entry 1 in Table 1). The use of dichloroethane (DCE) as solvent improves the reaction, and the mixed solvent DCE/H₂O gives 83% yield (77% isolated yield, entries 2 and 3). Other CIRs such as methoxybenziodoxole (BI-OMe) and hydroxybenziodoxole (BI-OH) are also effective, with BI-OH

alcohol oxidation methods are widely used, their limited substrate scope and functional group compatibility make them not suitable for chemoselective synthesis and biomolecule

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Table 1. Optimization of the Alkoxy Radical Generation and Alkynylation


entry	conditions ^a	conversion ^b (%)	yield ^b (%)
1	BI-OAc, DCM	74	49
2	BI-OAc, DCE	80	73
3	BI-OAc, DCE/H ₂ O	>95	83 (77)
4	BI-OMe, DCE/H ₂ O	>95	84 (79)
5	BI-OH, DCE/H ₂ O	>95	86 (83)
6	PhIO, DCE/H ₂ O	74	<5
7	PhI(OAc) ₂ , DCE/H ₂ O	11	<5
8	PhI(OCOFCF ₃) ₂ , DCE/H ₂ O	9	<5
9	entry 5, no [Ru]	<5	<5
10	entry 5, no <i>hν</i>	<5	<5

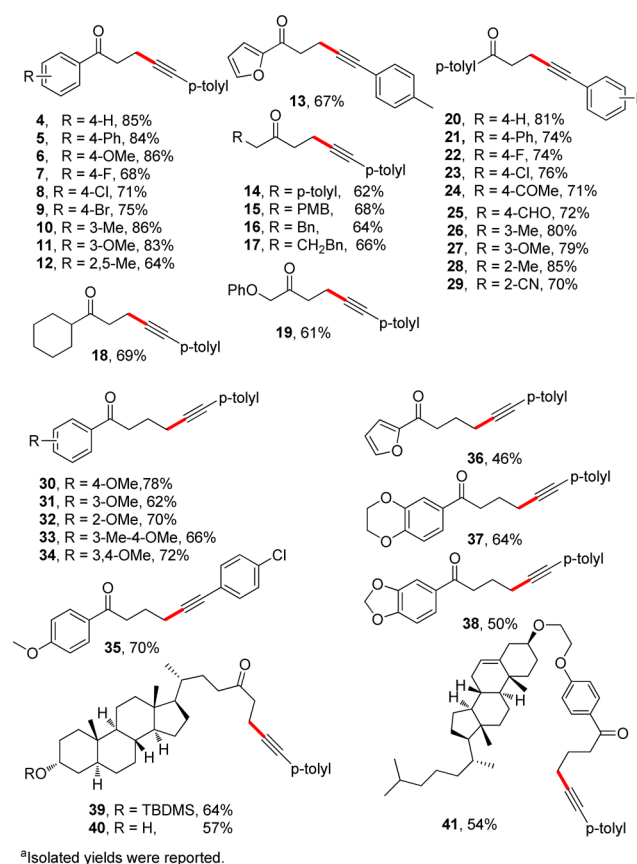
^aReaction conditions: **1** (0.15 mmol, 1.5 equiv), **2** (0.10 mmol, 1 equiv), and Ru(bpy)₃(PF₆)₂ (0.002 mmol, 0.02 equiv) in 2.0 mL of 1:1 dichloroethane/H₂O under nitrogen with 4 W blue LED irradiation at 25 °C for 15 h, unless otherwise noted. ^bConversions and yields were determined by ¹H NMR analysis, and isolated yields are given in parentheses. BI = benziodoxole.

giving optimal 86% yield (83% isolated yield, entries 4 and 5). In contrast, the non-cyclic iodine(III) reagents PhIO, PhI(OAc)₂, and PhI(OCOFCF₃)₂ give none of the desired product for the reaction (entries 6–8). The photocatalyst and light irradiation are both critical for the reaction (entries 9 and 10).

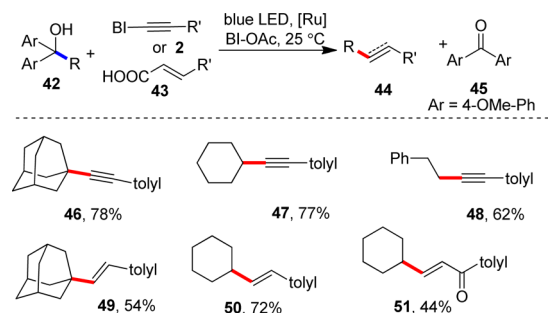
We then tested various cyclopropanol derivatives with this CIR/photoredox dual-catalytic system (Scheme 1). Cyclopropanols substituted with electron-rich or electron-deficient groups at the aryl *para* position both react well to give χ -alkynyl ketones **4–9** in 68–86% yields, and cyclopropanols substituted at the *meta* or *ortho* positions of arenes give products **10–12** smoothly in 64–86% yields. The heterocycle furan-substituted cyclopropanol affords **13** in 67% yield. The alkyl-substituted cyclopropanols react to give **14–19** in 61–69% yields, including unactivated alkyl substitutions and heteroatom substitutions. Various aryl substituents appended to BI-alkynes are compatible, including electron-rich phenyl, methyl, or methoxy groups as well as electron-deficient fluorides, chlorides, ketones, aldehydes, or nitriles (products **20–29**). It is worth noting that functional groups sensitive to transition metal or strong oxidative conditions such as aryl bromides and aldehydes are well tolerated.

For less-strained cyclobutanols, this reaction works well for those with *o*-, *m*-, or *p*-methoxyl aryl substitutions to produce δ -alkynyl ketones **30–35** in 62–78% yields without over-oxidation.¹³ Other electron-rich heterocycles, including furans and acetals, selectively react to give **36–38** in 46–64% yields. This reaction also works well on structurally complex steroidal cycloalkanols, with which χ -alkynyl ketones **39** and **40** are obtained smoothly. It is worth noting that only the cycloalkanol moiety selectively generates the alkoxy radical, while the other free hydroxyl group is left intact (product **40**). A cyclobutanol steroid derivative also selectively gives δ -alkynyl ketone **41** in 54% yield.

With success being obtained using strained cycloalkanols, we next elected to determine whether linear alcohols can undergo visible-light-induced C–C bond cleavage via the alkoxy radical, which have been elusive under traditional transition metal catalysis/strong oxidative conditions.¹¹ Based on the above-

Scheme 1. Substrates Scope of Strained Cycloalkanols and Complexed Molecules

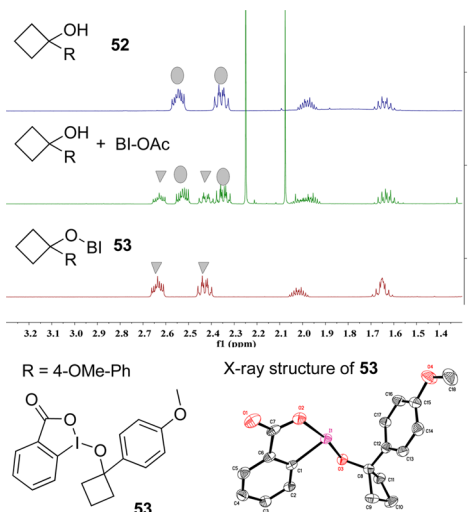
mentioned results that electron-donating aryl substitution is favorable for alkoxy radical generation, we screened linear alcohols with different aryl substitutions and found that alcohol **42** could be effectively transformed to obtain di-*p*-methoxyphenyl ketone **45** after cleaving the C–C bond (Scheme 2).¹⁴

Scheme 2. Substrates Scope of Linear Alcohols

Under optimized reaction conditions, tertiary, secondary, and primary alkyl alkynylation adducts are obtained with linear di-*p*-methoxyphenyl-substituted alcohol substrates in 78%, 77%, and 62% yields, respectively (products **46–48**). The alkyl radicals resulting from C–C bond-cleavage can also be used for effective alkenylation reactions. Using the vinyl carboxylates,^{7a} the alkenylation adducts **49–51** are obtained in 44–72% yields as styrene and vinyl ketone derivatives, which is the first alkenylation reaction reported following alkoxy radical-induced C–C bond cleavage.

To gain mechanistic insights into this CIR/photoredox catalytic system, we first mixed the tertiary cyclobutanol **52** (circles in Scheme 3) with BI-OAc and found a new set of

Scheme 3. Discovery of the Cyclic Iodine(III) Reagent/Alcohol Complex

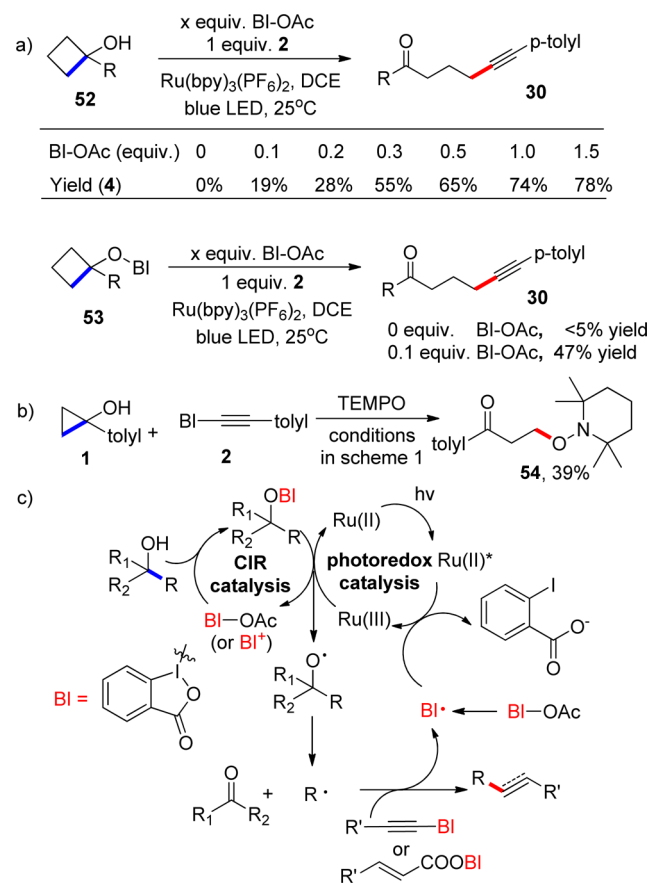


signals (triangles in Scheme 3) in the ^1H NMR spectrum. This unprecedented cyclobutanol/benziodoxole complex **53** can be isolated as a white solid and is stable in the air. X-ray crystallography of **53** shows a short iodine–oxygen bond ($\text{I}-\text{O}_3 = 2.02 \text{ \AA}$) connecting the benziodoxole and the cyclobutanol moiety, and a long iodine–oxygen bond within the benziodoxole moiety ($\text{I}-\text{O}_2 = 2.21 \text{ \AA}$) (see CIF file in the Supporting Information).^{15,16} We also measured the oxidation potential of the complex **53** ($E_{1/2}^0 = 0.84 \text{ V}$ vs SCE in MeCN) by cyclic voltammetry and found it is lower than that of $\text{Ru}(\text{bpy})_3^{3+}$ ($E_{1/2}^{0 \text{ III/II}} = 1.26 \text{ V}$ vs SCE in MeCN). In addition, the oxidation potential of complex **53** is significantly decreased compared to that of cyclobutanol **52** ($E_{1/2}^0 = 1.39 \text{ V}$ vs SCE in MeCN), which further explains the CIR activation on the alcohol.¹⁴

We next performed luminescence quenching experiments and found that BI-OAc (or BI-OH) quenches $\text{Ru}(\text{bpy})_3^{2+*}$ luminescence effectively, while the cyclobutanol **52** or BI-cyclobutanol complex **53** is less effective.¹⁷ We further discovered that cyclobutanol **52** remains unchanged in the absence of BI-OAc, while 0.1 equiv of BI-OAc is effective to initiate the reaction with 19% yield (Scheme 4a). When the cyclobutanol/benziodoxole complex **53** was used, similar results were obtained: very little conversion is observed without BI-OAc, and 0.1 equiv of BI-OAc results in 47% yield of **30**. These collectively suggest that the cyclobutanol/benziodoxole complex **53** acts as the reaction intermediate and the additional BI-OAc is required for the reaction initiation. We also carried out the TEMPO radical quenching experiment with the cyclopropanol **1**: no ring-opening alkylation was observed, and only the ring-opening TEMPO adduct **54** was obtained amid low conversions (Scheme 4b).¹⁸

Based on the mechanistic investigations described above, we propose that the reaction is initiated by oxidation of the photoexcited $\text{Ru}(\text{bpy})_3^{2+*}$ to $\text{Ru}(\text{bpy})_3^{3+}$ with BI-OAc or its decomposing benziodoxole radical adduct (Scheme 4c).^{7d} The $\text{Ru}(\text{bpy})_3^{3+}$ then oxidizes the benziodoxole/alcohol complex formed *in situ* and releases BI-OAc (or the benziodoxole cation

Scheme 4. Mechanistic Investigations and Proposals



BI⁺) for a new CIR catalytic cycle. The alkoxy radical undergoes β -fragmentation to yield the C–C bond-cleaving alkyl radical, which then undergoes radical addition to the alkyne or vinyl carboxylate-bound benziodoxole.^{7a} Finally, the alkylation or alkenylation adducts are yielded, and the benziodoxole radical is released for further $\text{Ru}(\text{bpy})_3^{2+*}$ oxidation.

In conclusion, we have developed the first visible-light-induced alcohol oxidation to generate alkoxy radicals using cyclic iodine(III) reagent catalysis. Both strained cycloalkanol and linear alcohols undergo selective $\text{C}(\text{sp}^3)-\text{C}(\text{sp}^3)$ bond cleavage reactions and yield alkylation/alkenylation products. We envision this dual CIR/photoredox catalytic system will find further applications in chemoselective synthesis and biomolecule studies, and efforts in that direction are under way in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b13066.

Complete mechanistic experiments, optimization tables, experimental methods, and additional experimental data (PDF)

NMR spectra of new compounds (PDF)

X-ray crystallographic data for **53** (CIF)

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Notes

The authors declare no competing financial interest.

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- (13) For cyclobutanols without electron-rich aryl substituents such as the *p*-methyl substitution, only 12% yield was obtained amid low conversions.
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- (17) When a stoichiometric amount of Ru(bpy)₃(PF₆)₂ was incubated with BI-OAc (or BI-OH) upon light irradiation, 24% yield of *o*-iodobenzoic acid was observed as the reduction adducts of benziodoxoles, while **52** or **53** gave very little conversion; see [Supporting Information](#) for details.
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