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Metal-Free Three-Component Oxyalkynylation of Alkenes

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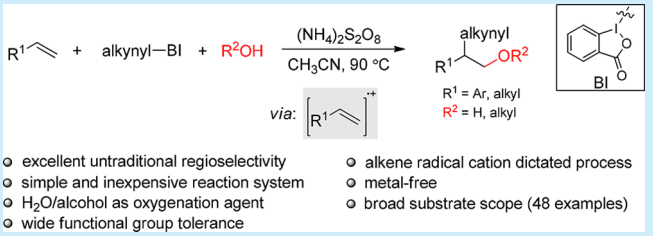
Supporting Information

ABSTRACT: An unprecedented $(NH_4)_2S_2O_8$ mediated metal-free three-component alkene oxyalkynylation using H_2O or alcohol as oxygenation agent is described. Mechanistic studies suggested that the reversed regioselectivity should be dictated by an alkene radical cation intermediate.



Due to their prevalence, selective difunctionalization of alkenes to prepare value-added building blocks of medicinal relevance is a broad goal in chemistry.[1] In this context, three-component carbooxygenation of alkenes is particularly attractive as it allows a one-step introduction of a C−C bond and a C−O bond. Impressive advances have been achieved in this area during the past decade either through a radical-mediated[2] or through a cationic metal species-catalyzed process (Figure 1a).[3] Because of the innate alkene polarization,

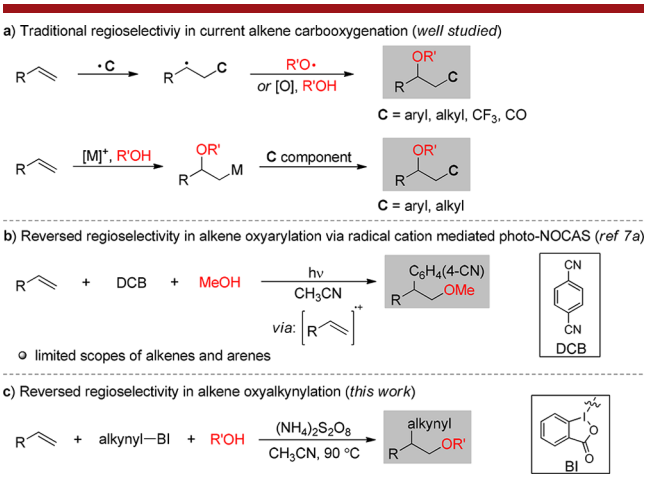


Figure 1. Overview of the regioselectivity in three-component carbooxygenation of alkenes.

the carbooxygenation outcome follows Markovnikov's rule, in which the oxygen bonds to more substituted olefinic carbon. In contrast, direct three-component carbooxygenation to achieve the opposite regioisomer by reversing the alkene polarity has remained a formidable challenge.[4] Known methods, each including only isolated examples, suffer from significantly limited scope and require either stoichiometric palladium species or a large excess of alkenes (up to 80 equiv).[5] Instead, such adducts are customarily accessed by indirect one-pot oxyalkylation of alkenes, which often requires an excess of metal reagents such as trialkylaluminum, organotin, and Grignard reagents.[6] Therefore, developing a general and practical protocol for direct three-component alkene carbooxygenation with reversed regioselectivity is highly desirable.

In seminal work, Arnold disclosed isolated examples of direct three-component oxyarylation of alkenes with reversed regioselectivity through an alkene radical cation-mediated photochemical nucleophile-olefin combination, aromatic substitution (photo-NOCAS) reaction (Figure 1b).[7] Despite the extremely limited scopes of both alkenes and arenes, reversed regioselectivity was observed in modest efficiency. We envisioned that a general and practical carbooxygenation protocol with such regioselectivity might be enabled by a single-electron chemical oxidant promoted generation of the alkene radical cation intermediate. Herein, we report an unprecedented $(NH_4)_2S_2O_8$-mediated metal-free three-component oxyalkynylation of alkenes using H_2O or alcohols as the oxygenation agent (Figure 1c).

Alkynes are common structural elements pervading the realms of biology, chemistry, material science, and medicine and serve as valuable building blocks due to their versatile chemical reactivities. An efficient hydroxyalkynylation to synchronously introduce both alkyne and hydroxyl groups into alkene moieties would be highly desirable. However, to our knowledge, direct three-component oxyalkynylation of alkenes has not been reported to date.[8,9] Therefore, the three-component hydroxyalkynylation of styrene **1a** with phenylethynylbenziodoxolone **2a** and H_2O was initially investigation (Scheme 1a; also see the Supporting Information (SI)).[10] Common single electron chemical oxidants such as $(NH_4)_2Ce(NO_3)_6$ and $Mn(OAc)_3$ did not give any expected **3a**. Delightedly, peroxydisulfate salts promoted the reaction, and $(NH_4)_2S_2O_8$ was identified to be optimal. Other electrophilic alkynylating agents such as phenyl phenylethynyl sulfone and

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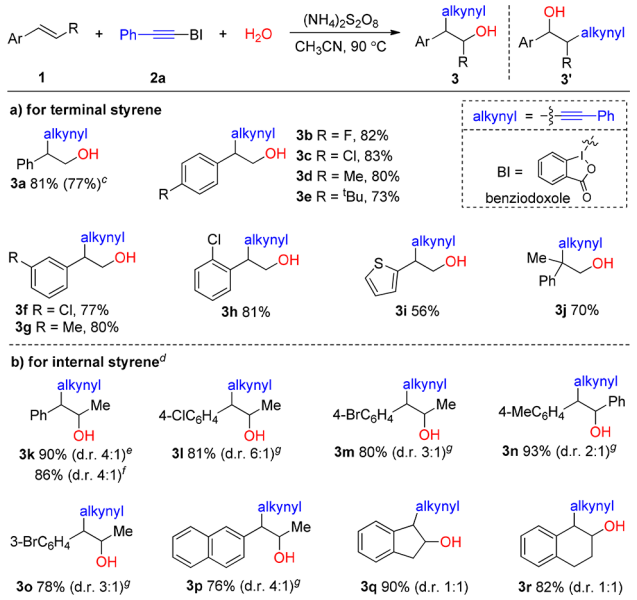
Scheme 1. Scope of Styrenes[a,b,c]



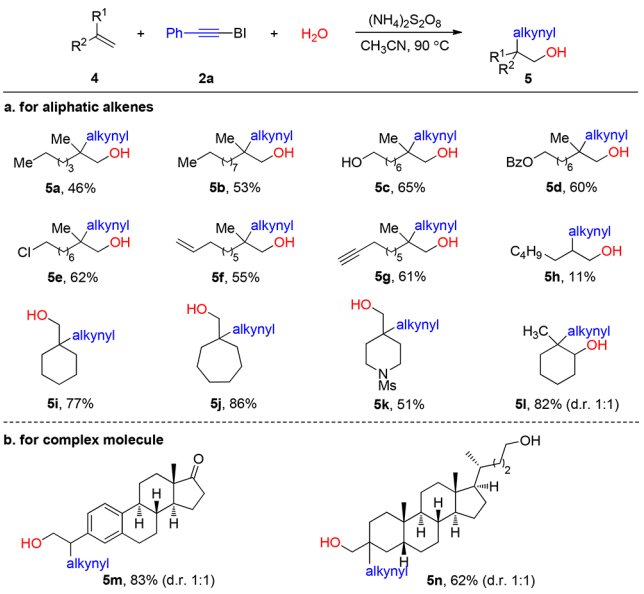
[a]Reaction condition: **1** (0.3 mmol), **2a** (0.1 mmol), and $(NH_4)_2S_2O_8$ (0.2 mmol) in CH_3CN/H_2O (1.0 mL, v:v = 1:1) at 90 °C in 1 h. [b]Yield of isolated product. [c]5.0 mmol scale. [d]d.r. was determined by ^1H NMR spectroscopy. [e](*E*)-**1k** used. [f](*Z*)-**1k** used. [g]Mixture of (*E*)- and (*Z*)-alkenes used.

phenylethynyl phenyliodonium triflate were ineffective components. The optimized procedure is very simple: **1a** (3.0 equiv) and **2a** (1.0 equiv) in H_2O/CH_3CN (1:1 v:v) were treated with $(NH_4)_2S_2O_8$ (2.0 equiv) at 90 °C for 1 h, predominantly delivering *β*-hydroxyalkyne **3a** in 81% yield. No regioisomeric **3a′** was detected. The operationally simple protocol does not require an inert atmosphere, is scalable (entry 1, Scheme 1a), and is affordable due to the incredibly low cost of the sole reagent $(NH_4)_2S_2O_8$ (< $0.04 per gram).

The reaction proved fairly general for a wide range of electronically varied terminal styrenes with different substituent patterns, providing *β*-hydroxyalkynes **3a**–**3i** in high efficiency (Scheme 1a). 1,1-Disubstituted styrene **1j** was tolerated, delivering **3j** bearing a quaternary carbon center in 70% yield. The reactions of electronically varied internal styrenes (**3k**–**3p**) also proceeded smoothly, exhibiting complete regioselectivity in high efficiency (Scheme 1b). The configuration of internal styrenes proved to have trivial influence on the reaction as (*E*)-**1k** and (*Z*)-**1k** were converted to **3k** with comparable d.r. and efficiency. Cyclic styrenes **1q** and **1r** were also competent substrates.

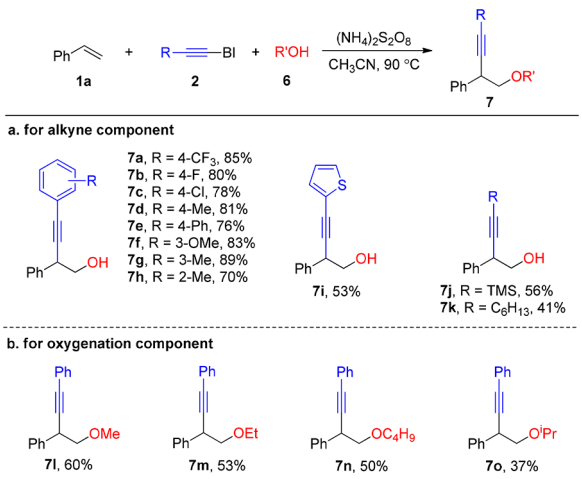
Simple acyclic 1,1-dialkyl substituted alkenes bearing diverse functional groups were suitable substrates for the reaction, affording **5a**–**5g** bearing a quaternary carbon center in moderate to good yields (Scheme 2a). Monoalkyl-substituted **4h** was also tolerated, albeit in a diminished yield. Cyclic 1,1-dialkyl substituted alkenes such as **4i** and **4j** together with piperidine-based **4k** were suitable substrates. Cyclic trialkyl substituted **4l** also exhibited the expected selectivity in 82% yield. The potential capacity of the method in late-stage functionalization of complex molecules of biological interest was further demonstrated (Scheme 2b). The reaction of estrone-based styrene **4m** proceeded, providing **5m** in 83% yield. Lithocholic acid-derived **4n** was also tolerated, affording **5n** bearing a quaternary carbon center in 62% yield.

Scheme 2. Scope of Aliphatic Alkenes and Complex Molecules



The scope of alkyne moieties was next explored (Scheme 3a). A variety of electronically varied aryl and heteroaryl

Scheme 3. Scope of Alkyne and Oxygenation Components



acetylenes with different substituent patterns were well tolerated, affording expected **7a**–**7i** in high efficiency. Trimethylsilyl-substituted **7j** and simple alkyl-substituted **7k** were suitable components. The scope of oxygenation agents also proved to be expansive (Scheme 3b). Aside from H_2O for hydroxylation reaction, common primary methanol, ethanol, and *n*-butanol together with secondary isopropanol were found to be suitable components for respective ether formation (**7l**–**7o**), though the more sterically encumbered *tert*-butyl alcohol and acetic acid did not give any of the expected product.

The synthetic utilities of three-component oxyalkynylation of alkenes were then examined (Scheme 4). Alkyne in **3a** was selectively reduced, furnishing respective *β*-oxyalkane **8a** and *β*-oxyalkenes **8b** and **8c** (Scheme 4a). Hydroxyl motif can be readily converted to other synthetically valuable groups, such as azide **8d**, chloride **8e**, and cyanide **8f**. The versatility of hydroxyl and alkyne groups also allowed alkenes to function as a latent "linker" by quickly integrating multiple scaffolds of

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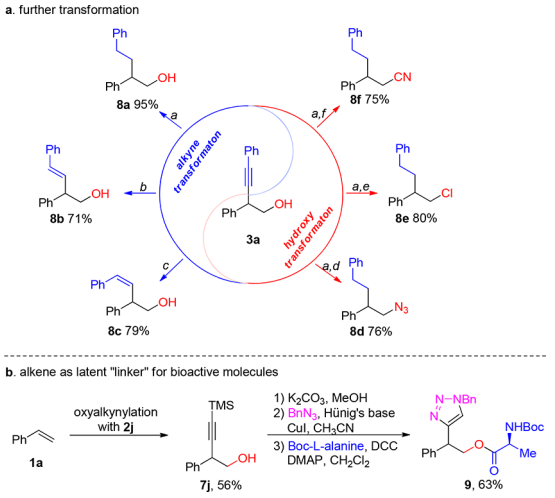
Scheme 4. Synthetic Applications



[a]Pd/C in MeOH under H_2. [b]$LiAlH_4$, THF, 60 °C. [c]Lindlar catalyst, MeOH, rt. [d]TsCl, Et_3N then NaN_3, DMF, 75 °C. [e]Triphosgene, pyridine. [f]TsCl, Et_3N, then NaCN.

biological importance together in the late-stage functionalization (Scheme 4b). For example, 1,2,3-triazole and Boc-L-analine moieties were regioselectively integrated into **1a**, giving **9** in 35% yield over four steps involving alkene oxyalkynylation, desilylation, click reaction, and acylation.

Mechanistic studies by electron paramagnetic resonance (EPR) spectroscopy were performed (Figure 2). When free

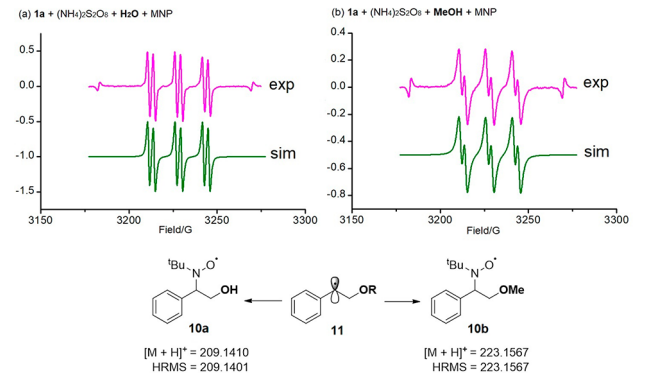


Figure 2. Identification of β-oxyl radical via EPR spectra (X band, 9.1 GHz, room temperature) and mass spectrometry analysis.

radical spin trapping agent 2-methyl-2-nitrosopropane (MNP) was added to the reaction of **1a** and $Na_2S_2O_8$ with H_2O or MeOH, a respective EPR signal with a triplet of doublets pattern was observed.[11] The EPR spectra suggest the generation of two similar nitroxide radicals containing one β-hydrogen.[12] The mass spectrometry analysis of two reaction mixtures indicates that the two nitroxide radicals might be **10a** and **10b**, thus implying the generation of β-oxyl radical **11**. Comparison of the simulation (green line) with the experimental data (purple line) indicated good agreement of the overall line shape, hyperfine peak positions, and intensities of the simulated spectra.

Control experiments were conducted to understand how β-oxyl radical **11** is generated (Figure 3). First, $H_2{}^{18}O$ isotopic labeling experiments suggested that the hydroxyl moiety should originate from H_2O (eq 1, Figure 3a). Accordingly,

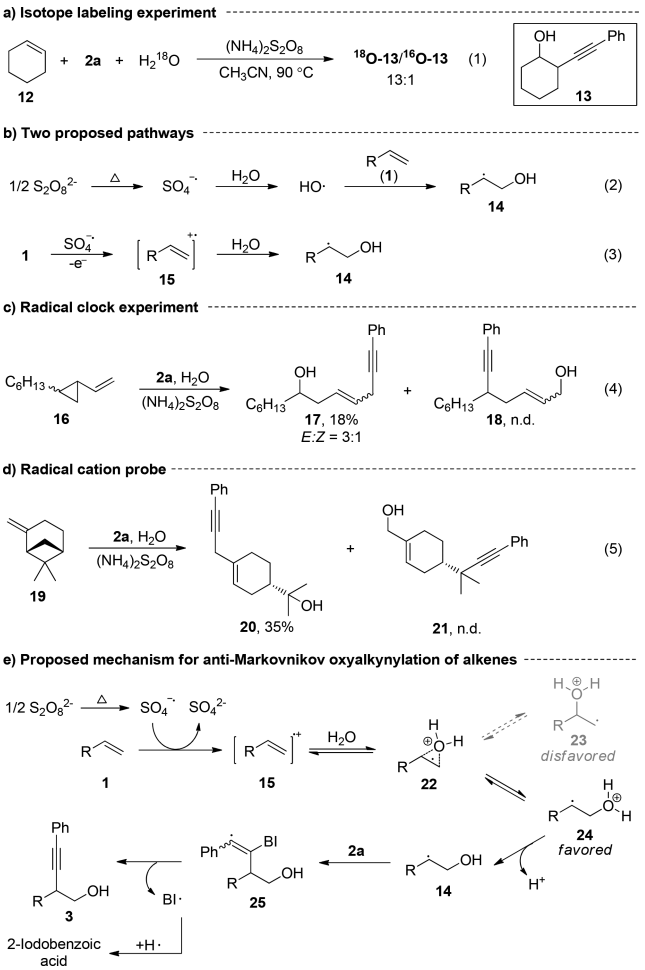


Figure 3. Mechanistic studies.

two pathways were proposed for the generation of β-oxyl radical **11**: (1) hydrogen atom abstraction from H_2O to sulfate radical anion ($SO_4^{-\bullet}$) giving a hydroxyl radical that adds onto alkene **1** (eq 2, Figure 3b); (2) oxidation of **1** by $SO_4^{-\bullet}$ affording alkene radical cation **15** followed by attack of H_2O (eq 3).[13] Second, radical clock experiments were performed to differentiate the two possibilities (Figure 3c). The reaction of cyclopropyl alkene **16** gave hydroxyalkyne **17**, and its regioisomer **18** was not detected, suggesting that the hydroxyl radical addition pathway might not be viable (eq 4, Figure 3c).[14] The observed regioselectivity, however, could be well explained by the alkene radical cation -mediated nucleophilic substitution by H_2O.[15] The radical cation probe β-pinene **19** was applied to further verify the hypothesis (eq 5, Figure 3d).[7a] The reaction exhibited the same regioselectivity as radical cation-mediated photo-NOCAS process, giving **20** in 35% yield, and the opposite regioisomer **21** was likewise not detected, further implying the intermediacy of alkene radical cation. Third, the reduction potential of $S_2O_8{}^{2-}$ and $SO_4^{-\bullet}$ are 2.01 and 2.44 V, respectively;[13] one-electron oxidation potentials of alkenes in this work ranges from 1.8 to 2.2 V vs SCE.[16] Accordingly, $SO_4^{-\bullet}$ might be the species oxidizing alkenes **1** to give radical cation **15** (Figure 3e). According to the DFT calculations by Arnold, H_2O might react with **15** affording a nonclassical, bridged radical cation complex **22**.[4b−e,7c] The regiochemistry was dictated by the relative stabilities of two possible distonic radical cations **23** and **24**.

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The more stable **22** undergoes deprotonation giving radical **14**. The addition of **14** to **2a** followed by a β-elimination, providing β-hydroxyalkyne **3** along with a benziodoxolonyl radical.[10]

In summary, a practical $(NH_4)_2S_2O_8$-mediated metal-free, direct three-component oxyalkynylation of alkenes with reversed regioselectivity to current studies using H_2O or alcohol as the oxygenation agent has been reported. The operationally simple and practical protocol features excellent regiospecificity, a broad substrate scope, inexpensive system, and good functional group tolerance. Mechanistic studies suggested that the regioselectivity was dictated by an alkene radical cation intermediate generated through a single electron oxidation of alkenes by $SO_4^{-\bullet}$. We envision that the method would provide a platform to design other anti-Markovnikov oxygenation reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02954.

Experimental details and spectral data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(16) One electron oxidation potentials of olefins in this work were measured using cyclic voltammetry (see the SI for details).

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