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Copper-/Cobalt-Catalyzed Highly Selective Radical Dioxygenation of Alkenes

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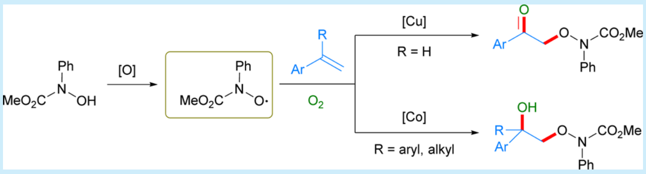
Supporting Information

ABSTRACT: A highly selective radical dioxygenation of alkenes using hydroxamic acid and O_2 was developed, and copper/cobalt was used as the catalyst without assistance of any additional ligands or bases. Mechanistic investigation disclosed that copper salt and O_2 work in concert to activate hydroxamic acid, with Cu(I) and Cu(II) concurrently existing in this reaction.

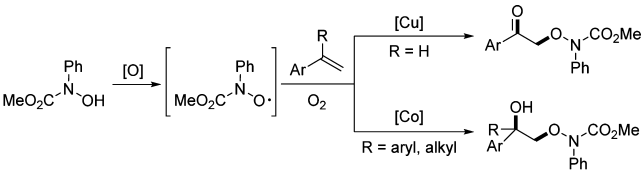


As a classic arsenal in synthetic chemistry, radical chemistry has experienced a renaissance with the upsurge of interest in transition-metal catalysis and photocatalysis.[1] To date, one of the most important challenges for chemists in radical chemistry is to develop new methods to control the reaction selectivity more effectively.[2] However, high reactivity as well as the instability of the radical intermediates makes this target especially challenging.[1,2] In this regard, abundant metal catalysis employing molecular oxygen as the terminal oxidant is particularly valuable due to its availibility, minimal toxicity, and mild conditions.[3] This type of catalysis exhibits intriguing catalytic activities and represents a promising way to tune selectivity in radical chemistry.

Radical reactions of hydrocarbons, especially for the radical "oxygenase-type" reactions, have attracted increasing attention since prefunctionalization of the reactive site is unnecessary and oxygen can be directly incorporated into the desired molecules.[4] In just the past few years, various hydrocarbons have been successfully utilized in cascade oxygenation of alkenes.[5] However, the chemical selectivity of these transformations is generally limited to the comparatively stable radical precursors with assistance from numerous additives. Successful examples for the reactions using O-nucleophiles are quite limited.[6,7] For reactive radical precursors, the final product is often difficult to predict, and a mixture of hydroperoxides, alcohols, and ketones is usually obtained.[5] Until now, strategies aimed at controlling cascade oxygenation of alkenes have been rudimentary. Moreover, in-depth mechanistic understanding of these processes remains poor, limiting further design of new reactions.

Recently, vicinal dioxygenation of alkenes by capitalizing on the vigorous reactivity of hydroxamic acid has been demonstrated by Alexanian and co-workers,[8] in which various alcohols could be typically furnished after reductant workup. Owning to our continuous interests in O_2 activation and abundant metal catalysis,[9] we present herein our recent progress in radical dioxygenation of alkenes using copper or cobalt as the catalyst, in which versatile α-oxyketones and α-oxo tertiary alcohols can be synthesized in a single process (Scheme 1).

Scheme 1. Radical Dioxygenation of Alkenes



Initially, we chose styrene (**1a**) and methyl *N*-hydroxy-*N*-phenylcarbamate (**2a**) as the reactants to investigate the effect of metal catalysts. Not surprisingly, only 7% yield of ketone (**3a**) was formed, while secondary alcohol (**4a**) was observed as the major product in the absence of any catalyst (Table 1, entry 1).[8] Subsequently, we added copper salts as the catalyst precursor to tune the reaction selectivity. It was found that the chemical selectivity of this reaction was switched as expected. A 65% yield of ketone (**3a**) was produced, while only a trace amount of secondary alcohol was detected (entry 2). Further screening showed that CuCl was the best catalyst precursor, and a similar

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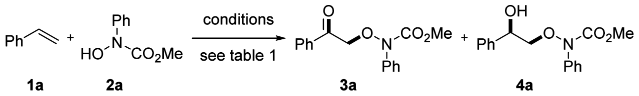
Table 1. Survey of the Reaction Conditions[a]

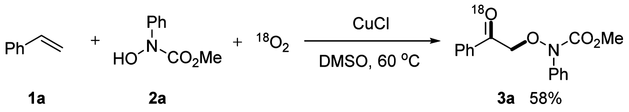


entry	catalyst	temp (°C)	yield of **3a** (%)	yield of **4a** (%)
1[b]		70	7	28
2	CuCl	70	65	trace
3	Cu_2O	70	34	23
4	$CuCl_2$	70	53	trace
5	$Cu(TFA)_2$	70	44	trace
6[c]	$CuCl/Cu(TFA)_2$	70	46	trace
7	**CuCl**	**60**	**67 (65)**	**trace**
8[d]	CuCl	60	46	trace
9[e]	CuCl	60	0	0

[a] Unless otherwise specified, all reactions were carried out using **1a** (0.2 mmol), **2a** (0.3 mmol), and catalyst (0.02 mmol) in DMSO (2.0 mL) for 4 h under O_2 (balloon); yield was determined by HPLC; isolated yield in parentheses. [b] Yield was determined after workup with PPh_3. [c] CuCl (5% mol) and $Cu(TFA)_2$ (5% mol). [d] Under air. [e] Under N_2.

yield was obtained by performing the reaction at 60 °C without any loss of reaction selectivity (entries 3–7). It is notable that 46% yield of **3a** was obtained when the reaction was conducted under air, while no product was formed under N_2. The sharp difference between these two reactions demonstrated the importance of O_2 in this process (entries 8 and 9). To further probe the role of O_2, the reaction between **1a** and **2a** under $^{18}O_2$ was carried out (Scheme 2), and ^{18}O-labeled product **3a** was isolated in 58% with 85% isotopic purity, indicating the carbonyl oxygen atom of the ketone came from O_2.

Scheme 2. $^{18}O_2$ Isotope Labeling Experiment



To gain insight into the reaction mechanism, electron paramagnetic resonance (EPR) experiments were next conducted. As shown in Figure 1, no obvious signal of amidoxyl radical was observed when **2a** was treated only with O_2 (Figure 1A), $CuCl_2$ (Figure 1B), or CuCl (Figure 1C), respectively. On the contrary, the distinct EPR signal of amidoxyl radical was detected when **2a** was treated with O_2 and CuCl (Figure 1D). These results revealed that copper salt and O_2 work synergistically to activate hydroxamic acid, initiating the radical cascade reaction.

To acquire further understanding of the reaction mechanism, we attempted to use operando IR to monitor the reaction between **1a** and **2a** in the presence of $CuCl_2$ or CuCl, respectively. The kinetic profiles of relative absorbance (ConcIRT) versus time for **1a** are shown in Figure 2. Clearly, an inductive period was observed when copper(I) was used as the catalyst precursor.[10]

Furthermore, X-ray absorption near-edge structure (XANES) spectroscopy was also applied to investigate the reaction between **1a** and **2a**. The XANES spectrum of the reaction mixture gave a typical signal for Cu(I) with an edge energy at 8981.6 eV (Figure 3A).[11] Cu(II) with the pre-edge at 8977.4 eV was also observed when the first derivation was calculated (Figure 3B). Moreover,

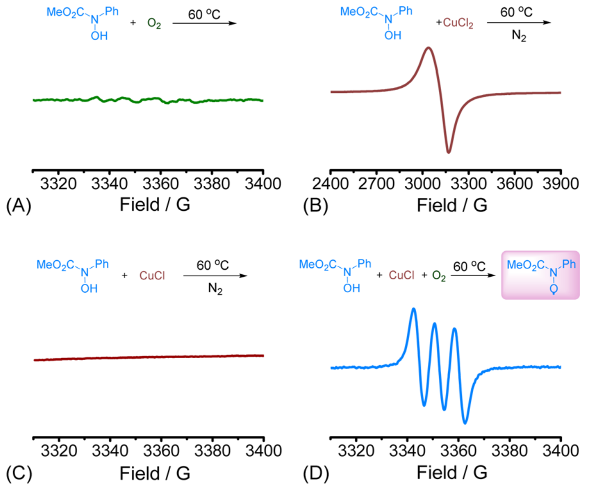


Figure 1. EPR spectra for **2a** (0.3 mmol) in DMSO (2.0 mL) at 60 °C for 10 min under different conditions: (A) under O_2; (B) $CuCl_2$ (0.3 mmol) under N_2; (C) CuCl (0.3 mmol) under N_2; (D) CuCl (0.03 mmol) under O_2.

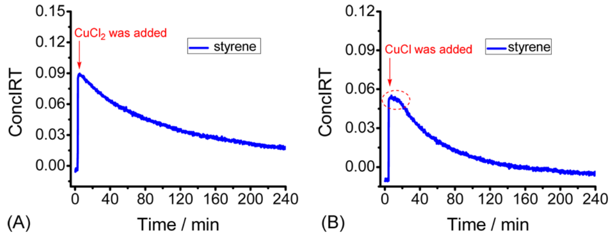


Figure 2. Kinetic profiles for the reaction of styrene **1a** (0.4 mmol), **2a** (0.6 mmol), and different copper salt (0.04 mmol) in DMSO (4.0 mL) at 60 °C for 4 h under O_2 (balloon). (A) $CuCl_2$. (B) CuCl.

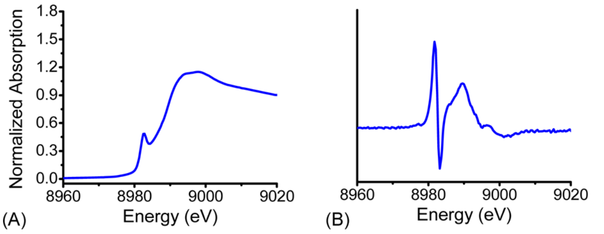


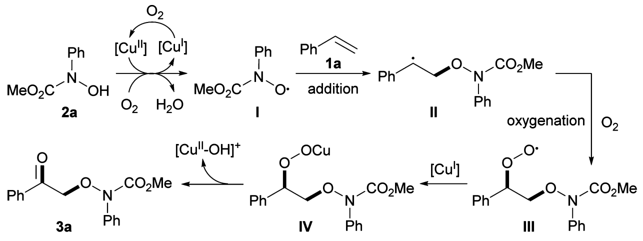
Figure 3. XANES spectra of **1a** (4.0 mmol), **2a** (6.0 mmol), and CuCl (0.4 mmol) in DMF (4.0 mL) at 60 °C under air for 15 min (A) and its first derivation (B).

the existence of Cu(II) in this transformation was also confirmed by EPR. The classic Cu(II) signal can be obviously observed (for details, see the Supporting Infomation). These results indicate that Cu(I) and Cu(II) existed concurrently in this reaction.

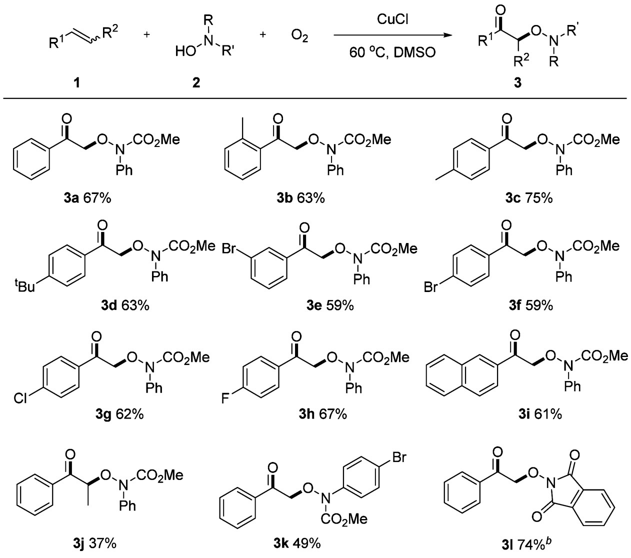
On the basis of the aforementioned results and previous studies,[5] a plausible mechanistic pathway is proposed in Scheme 3. Initially, copper(I) can be oxidized to copper(II) by O_2. Then, copper(II)/copper(I) works in conjunction with O_2 to activate hydroxamic acid **2a**, generating amidoxyl radical **I**. Subsequent radical addition of **I** to styrene (**1a**) produces carbon-centered radical **II**, which could further couple with O_2 and copper(I) to form intermediate **IV**.[12] Finally, **IV** experiences fragmentation to give the desired product **3a** through elimination of $[CuOH]^+$.

Furthermore, the scope of this aerobic dioxygenation of alkenes was explored, and the results were summarized in Scheme 4. Aromatic alkenes showed broad tolerance for both

Scheme 3. Proposed Mechanism

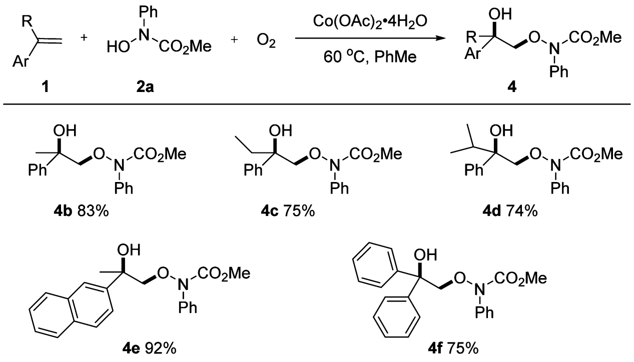


Scheme 4. Copper-Catalyzed Radical Dioxygenation of Alkenes[a]



[a]Unless otherwise specified, all reactions were carried out using **1** (0.20 mmol), **2** (0.30 mmol), and CuCl (0.02 mmol) in DMSO (2.0 mL) under O_2 for 4 h at 60 °C; isolated yields. [b]NMR yield using CH_2Br_2 as internal standard.

Scheme 5. Cobalt-Catalyzed Radical Dioxygenation of 1,1-Disubstituted Alkenes[a]



[a]All reactions were carried out using **1** (0.20 mmol), **2a** (0.30 mmol), and $Co(OAc)_2·4H_2O$ (0.02 mmol) in toluene (2.0 mL) under O_2 for 4 h at 60 °C; isolated yields.

electron-donating substituents (**3b–d**) and electron-withdrawing substituents (**3e–h**), furnishing the corresponding α-oxyketones in good yields.[13] The reaction of 2-vinylnapthalene also proceeded well, giving the product **3i** in 61% yield. Notably, β-methylstyrene was amenable to this protocol as well and afforded the desired product **3j** in 37% yield.[14] In addition, other carbonyl nitroxides were also evaluated. Introduction of a bromine to the phenyl ring of hydroxamic acid had a negative effect on the reaction efficiency (**3k**). It is worth noting that benzoyl nitroxide, as exemplified by NHPI (*N*-hydroxyphthalimide), was also applicable to this protocol, affording the expected product (**3l**) in 74% yield.

Spurred by these encouraging results, we further extended this protocol to synthesize α-oxo-tertiary alcohols (Scheme 5). Intriguingly, when $Co(OAc)_2·4H_2O$ was used to replace the copper catalyst precursor,[15] hydroxamic acid **2a** could facilely react with various 1,1-disubstituted alkenes, furnishing the corresponding tertiary alcohols **4b–f** in 74–92% yields in a single process.

In conclusion, a radical dioxygenation of alkenes via O_2 activation has been achieved in which abundant catalyst and O_2 work synergistically to trigger the radical casade reaction. This transformation features high chemical selectivity and simple conditions without the assistance of any additional ligands or bases. Various important structural motifs such as α-oxyketones and α-oxo tertiary alcohols were synthesized under mild conditions. We believe that these results provide useful insight into abundant metal chemistry and may inspire more efforts toward further synthetic applications.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full experimental details and characterization data for all products. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01223.

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Notes

The authors declare no competing financial interest.

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(10) The inductive period might be due to the transformation from Cu(I) to Cu(II), but other reasons cannot be excluded at current stage.

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(12) According to one of the reviewers, the initial interaction between Cu(I) and O_2 may produce Cu(II) and superoxide radical anion. The superoxide radical anion could be also possibly coupled with intermediate **II** and Cu(II) to give intermediate **IV**.

(13) Some difunctionalization byproducts generated from one molecular alkenes reacted with two molecular hydroxamic acid were detected. In addition, secondary amine generated from the decomposition of the hydroxamic acid was also detected.

(14) Only a trace amount of the desired product was detected when (*E*)-1,2-diphenylethene was employed. For nonaromatic ring substituted alkenes, as exemplified by acrylic acid butyl ester and allylbenzene, no desired product was obtained under the standard conditions.

(15) A 46% yield of **4b** was obtained when CuCl (10% mol) was used as the catalyst precursor.