Letter

Dioxygen Activation via Cu-Catalyzed Cascade Radical Reaction: An Approach to Isoxazoline/Cyclic Nitrone-Featured #-Ketols

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Dioxygen Activation via Cu-Catalyzed Cascade Radical Reaction: An Approach to Isoxazoline/Cyclic Nitrone-Featured *α*-Ketols

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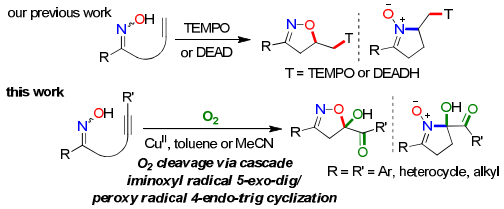
Supporting Information Placeholder

ABSTRACT: A facile, mild and efficient dioxygen activation for the synthesis of isoxazoline/cyclic nitrone-featured *α*-ketols has been achieved by Cu-catalyzed trifunctionalization of internal unactivated alkynes of unsaturated ketoximes at room temperature. ^{18}O isotope tracing and DFT calculation disclose that a cascade iminoxyl radical dichotomous 5-*exo*-dig cyclization/oxygen activation/peroxy radical 4-*endo*-trig cyclization process was involved in the reaction.

KEYWORDS: alkyne, copper catalysis, dioxygen activation, DFT calculation, iminoxyl radical, radical cyclization

Scheme 1. Iminoxyl Radical 5-exo-dig Cyclization and Dioxygen Activation.



Radical cyclization is one of most versatile and powerful methods for the construction of mono- and polycyclic systems.[1] Among them, the alkyne-involved cyclization is an important subtype that has been of long-standing interest to organic chemists.[2] Although the carbon-centered radical cyclizations of alkynes have been well studied,[2a,3] those involving O-/N-atom-centered radicals are rarely reported[4] because the precursors of these hetero-centered species tend to react via an ionic addition rather than a radical process[2,5]. Therefore, the development of general method for O-/N-atom-centered radical cyclization onto alkynes is strongly desired.

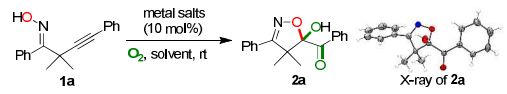
Iminoxyl radicals are classical *σ*-radicals with the single electron spin delocalized on both the O and N atoms.[6] Iminoxyl radicals can be conveniently generated from the oxidation of oximes. Our recent studies demonstrate that the readily prepared *β,γ*- and *γ,δ*-unsaturated ketoximes can be converted to the corresponding iminoxyl radicals, which would undergo dichotomous O- and N-atom 5-*exo*-trig patterns to realize the difuctionalization of alkenes depending on the position of the tethered alkenes[7] (Scheme 1, top). However, the cyclization of iminoxyl radicals onto alkynes has not been reported yet. Owing to our continuous interest in iminoxyl radical cyclizations, herein, we wish to report a Cu-catalyzed iminoxyl radical dichotomous O-/N-atom 5-*exo*-dig cyclization of internal alkynes. This reaction took place via a tandem process which involves a cascade oxygen activation/ peroxy radical 4-*endo*-trig cyclization. In this way, the trifuctionalization of alkynes can be realized by using dioxygen as the oxidant as well as the oxygen source (Scheme 1, down).

As we know, dioxygen is not only an environmentally benign and abundant oxidant but also an ideal oxygen source for the oxygenation of organic substrates.[8] Thus, dioxygen activation has drawn great interest of organic chemists due to its enormous importance in chemistry and biochemistry.[9] Over the past several decades, aerobic functionalization of alkynes has been achieved through transition-metal-catalyzed or metal-free reactions[10], but there are few studies on aerobic radical cyclization of alkynes. In this context, this study not only provides the first example of iminoxyl radical cyclization onto alkynes, but also realizes dioxygen activation and cleavage at room temperature via the in situ generated peroxy radical 4-*endo*-trig cyclization.

Initially, we commenced our study by stirring *β,γ*-alkyne tethered oxime **1a** in toluene under O_2 (1 atm) atmosphere at room temperature for 72 h. To our delight, the alkyne trifunctionalized product isoxazoline-featured *α*-ketol **2a** was obtained in 23% yield (Table 1, entry 1). The structure of **2a** was confirmed by X-ray single-crystal analysis. Apparently, dioxygen served as the iminoxyl raical initiator as well as the oxygen source in the reaction. To improve the reaction efficiency and yield, copper salts were then employed as the catalyst. Our previous study revealed that copper salts could promote the formation of iminoxyl radical.[7d] Indeed, when CuCl was used as the catalyst, the reaction was greatly accelerated and completed in 0.3 h. Meanwhile, the yield of **2a** was improved to 60% (Table1, entry 2). Other copper salts such as CuBr, CuI, $CuCl_2$, $CuBr_2$, $Cu(OAc)_2$, $Cu(stearate)_2$, $Cu(acac)_2$ and $Cu(OTf)_2$ also exhibited beneficial effect on the reaction, among which $CuBr_2$ was found to be the most efficient, with the yield of **2a** being improved to 81% (Table 1, entries 3−10). When ligands such as 2,2'-dipyridyl and phenanthroline were introduced in the reaction, however, the yield of **2a** was decreased (Table 1, entries 11 and 12). In addition, other solvents such as MeCN, DCE, DMSO and DMA were also investigated but no better result was obtained (Table 1, entries 13-16). Other transition metal salts[3a,11] such as $FeBr_2$, $Co(acac)_2$, $NiCl_2$ and $MnBr_2$, which have proven to be efficient catalyst for radical reaction, were also explored, but no better catalytic effect was observed (Table 1, entries 17-20).

With the optimum conditions in hand, the scope of *β,γ*-alkyne tethered ketoximes **1** were explored and the results are summarized in Scheme 2. First, ketoximes bearing a variety of electronic properties on the phenyl of the oxime moiety transformed

Table 1. Optimization of the Reaction.[a]



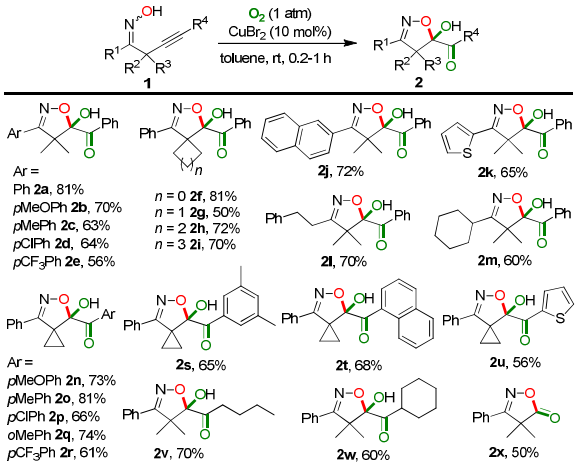
entry	metal salts	solvent	time (h)	yield[b] (%)
1	-	toluene	72	23(57)[c]
2	CuCl	toluene	0.3	60
3	CuBr	toluene	0.3	66
4	CuI	toluene	0.3	75
5	$CuCl_2$	toluene	0.3	63
6	**$CuBr_2$**	**toluene**	**0.3**	**81**
7	$Cu(OAc)_2$	toluene	0.3	73
8	$Cu(stearate)_2$	toluene	0.3	63
9	$Cu(acac)_2$	toluene	0.5	69
10	$Cu(OTf)_2$	toluene	0.3	63
11[d]	$CuBr_2$	toluene	12	54
12[e]	$CuBr_2$	toluene	12	52
13	$CuBr_2$	MeCN	0.3	66
14	$CuBr_2$	DCE	0.3	47
15	$CuBr_2$	DMSO	1	trace
16	$CuBr_2$	DMA	1	trace
17	$FeBr_2$	toluene	24	trace
18	$Co(acac)_2$	toluene	2	33
19	$NiCl_2$	toluene	18	54
20	$MnBr_2$	toluene	2	43

[a]Conditions: **1a** (1 equiv, 0.3 mmol), metal salts (0.1 equiv, 0.03 mmol), O_2 (1 atm), solvent (3 mL), room temperature. [b] Isolated Yields. [c] Yield in parentheses is recovered **1a**. [d]2,2'-Dipyridyl (0.1 equiv) was used. [e]1,10-Phenanthroline (0.1 equiv) was used.

smoothly to the desired products **2a-2e** in good yields. When cyclopropyl,cyclobutyl, cyclopentyl, and cyclohexyl groups were merged in the ketoxime at *α*-position instead of *gem*-dimethyl group, the reaction gave the corresponding *spiro*-compounds **2f-2i** in good yields. Naphthyl substituted ketoxime **1j** was also suitable for the process and afforded the corresponding product **2j** in 72% yield. In addition, ketoxime bearing thienyl ring was also compatible under the reaction conditions, giving rise to the expected product **2k** in 65% yield. Moreover, alkyl group such as phenethyl and cyclohexyl substituted ketoximes were also well tolerated with this protocol, as demonstrated in the cases of **2l** and **2m**. Next, we explored the tolerance of the alkynyl moiety of ketoxime in the reaction. A series of phenylacetylenes bearing both electron-donating and electron-withdrawing groups reacted very well in the reaction, delivering the desired products **2n-2s** in good yields. In addition, naphthyl and thiophene-incorporated alkynes were transformed easily as well, producing the desired products **2t** and **2u** in 68% and 56% yields, respectively. It is noteworthy that the *n*-hexynyl and cyclohexylacetylene substituted ketoxmies were also suitable in the reaction, affording the corresponding products **2v** and **2w** in good yields. However, when the terminal alkyne-tethered ketoxime **1x** was used, the desired isoxazoline featured α-hydroxyl aldehyde was not obtained; instead, the product isoaxazo-5(4H)-one **2x** without a formyl group was obtained in 50% yield, indicating that the formyl group was further oxidized under the circumstance.

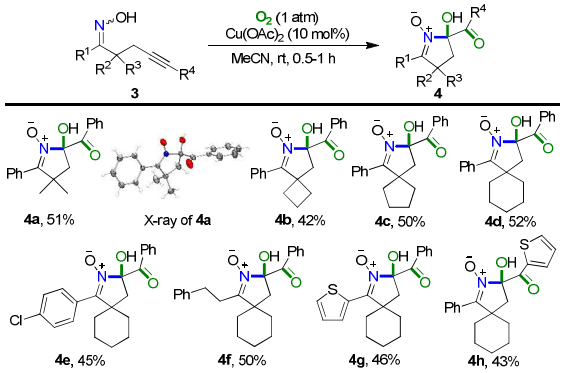
To further extend the scope of this protocol to the synthesis of cyclic nitrone-featured *α*-ketols, *γ,δ*-alkyne tethered ketoxime **3a** was subjected to the standard conditions to see if the N-atom 5-*exo*-dig cyclization[12] could also take place. However, the reaction only gave a trace amount of the desired product **4a** due to the poor solubility of **3a** in toluene. Remarkably, when the $Cu(OAc)_2$/MeCN system was used in the reaction, the product **4a** was obtained in 51% yield. The structure of **4a** was also confirmed by a X-ray single-crystal study. Next, some representative *γ,δ*-alkyne tethered ketoximes **3** were conducted in the reaction, and the correspoding cyclic nitrone-featured *α*-ketols **4** were obtained in moderate yields as shown in Scheme 3.

Scheme 2. Scope of *β,γ*-Alkyne Tethered Ketoximes



[a]All reactions run in 0.1 M toluene using oximes **1** (0.3 mmol) and $CuBr_2$ (0.1 equiv) at rt under O_2. [b] Isolated yields.

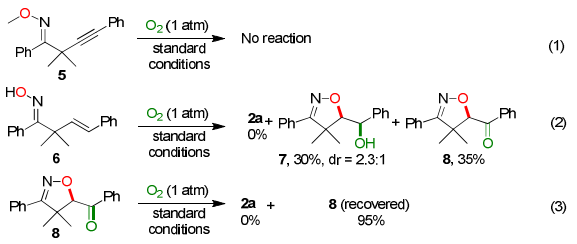
Scheme 3. Scope of *γ,δ*-Alkyne Tethered Ketoximes



[a]All reactions run in 0.05 M MeCN using oximes **3** (0.3 mmol) and $Cu(OAc)_2$ (0.1 equiv) at rt under O_2 (1 atm). [b]Isolated yields.

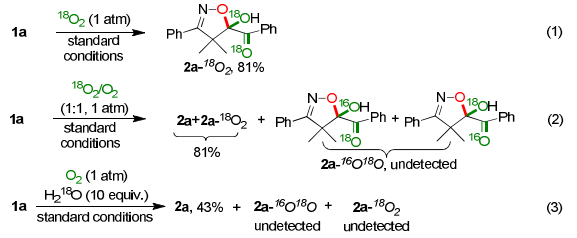
To gain insight into the reaction mechanism, control experiments were conducted as shown in Scheme 4. First, oxime ether **5** was synthesized and tested in the standard conditions but no reaction took place, demonstrating that free oxime as an iminoxyl radical precursor is essential to trigger an efficient trifunctionalization of alkynes (Scheme 4, eq 1). When styrene tethered oxime **6** was tested, the reaction gave the dioxygenation products alcohol **7** and ketone **8** in 30% and 35% yields, respectively, with the desired product **2a** undetected (Scheme 4, eq 2). In addition, when ketone **8** was subjected to the standard conditions, no reaction was found to take place (Scheme 4, eq 3). These results clearly exclude the possibility that the formation of **2a** involved a pathway with **8** as an intermediate, and the alkyne moiety is necessary for the formation of *α*-ketol. On the other hand, although the radical addition onto alkynes under dioxygen atmosphere generally produced ketones through the trapping of the in situ generated alkenyl radicals by dioxygen,[10a] *α*-ketols were formed

Scheme 4. Control Experiments.



in place of the normal ketones in our study, indicating that the in situ formed alkenyl peroxy radicals possibly experience a subsequent 4-*endo*-trig cyclization. ^{18}O isotopic labelling experiment indicates that the O-atoms of both the hydroxyl and carbonyl were derived from the same dioxygen molecule (Scheme 5, using high-resolution ESI-MS, see Support Information). When $^{18}O_2$

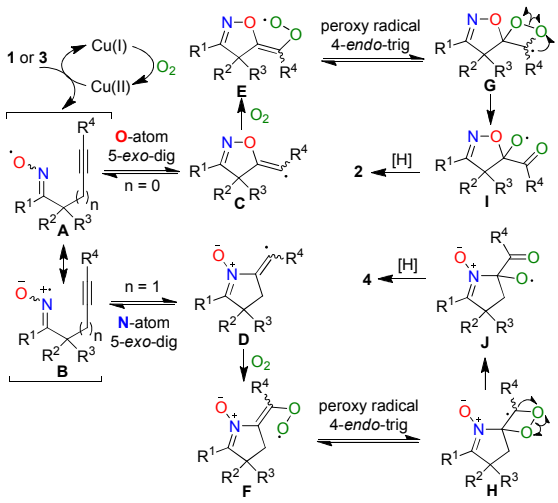
Scheme 5. ^{18}O Isotopic Tracing.



was used as the oxidant, the ^{18}O oxygenated product **2a**-$^{18}O_2$ was obtained in 81% yield (Scheme 5, eq 1). When a mixture of $^{16}O_2/^{18}O_2$ (in a 1:1 ratio of volume) was applied to the reaction, the products **2a** and **2a**-$^{18}O_2$ were obtained in a combined yield of 81% with the products **2a**-$^{16}O^{18}O$ undetected (Scheme 5, eq 2). In addition, when $H_2{}^{18}O$ (10 equiv.) was added in the sample reaction under standard conditions, only **2a** was obtained without the detection of **2a**-$^{16}O^{18}O$ and **2a**-$^{18}O_2$, confirming that the O-atoms of both the hydroxyl and carbonyl came from dioxygen rather than water (Scheme 5, eq 3). These consequences further suggest that the formation of α-ketol involves an alkenyl peroxy radical 4-endo-trig cyclization process.

On the basis of the above results, a proposed mechanism was drawn in Scheme 6. A electron transfer process occurs firstly between Cu(II) and oxime **1** or **3** to produce Cu(I) and the iminoxyl radical. This iminoxyl radical, which possesses an

Scheme 6. Proposed Mechanism



electronic structure with single-electron spin density delocalized on both the O-atom and N-atom (resonance structures **A** and **B**),[7a] then undergoes favorable O-/N-atom 5-*exo*-dig radical cyclization[3h] depending on the position of the tethered alkyne, yielding alkenyl radicals **C** and **D**, respectively. Meanwhile, Cu(I) is oxidized spontaneously by O_2 to Cu (II). The formed alkenyl radicals **C** and **D** are trapped immediately by dioxygen to generate the alkenyl peroxy radicals **E** and **F**, which subsequently undergo peroxy radical 4-*endo*-trig cyclization to give the corresponding carbon radical **G** and **H**. Further O−O bond cleavage in these intermediates yields the alkoxy radicals **I** and **J**, from which **2** and **4** are formed finally via hydrogen abstraction.

To confirm the proposed reaction mechanism, the density functional theory (DFT) caculation[13] was implemented (Figure 1). The energy profiles reveal that the initiation of iminoxyl radical **INT3** is the rate-determining step, the free energy of activation in the absence of the copper catalyst is 31 kcal/mol (through **TS1'**), whereas it is reduced to 23.3 kcal/mol by the addition of $CuBr_2$ with the corresponding transition state being **TS1**. This energy difference explains well the catalytic effect of $CuBr_2$. **INT3** then undergoes 5-*exo*-dig cyclization through **TS2** (7.9 kcal/mol) to deliver the alkenyl radical **INT4**,[3h] which is immediately trapped by O_2 to yield the alkenyl peroxy radical **INT5-E** barrierlessly.[14] **INT5-E** undergoes O-atom 4-*endo*-trig cyclization to form **INT6** through **TS3-E** by an activation energy of 20.1 kcal/mol. Although 4-*endo*-trig cyclization is unfavored according to the

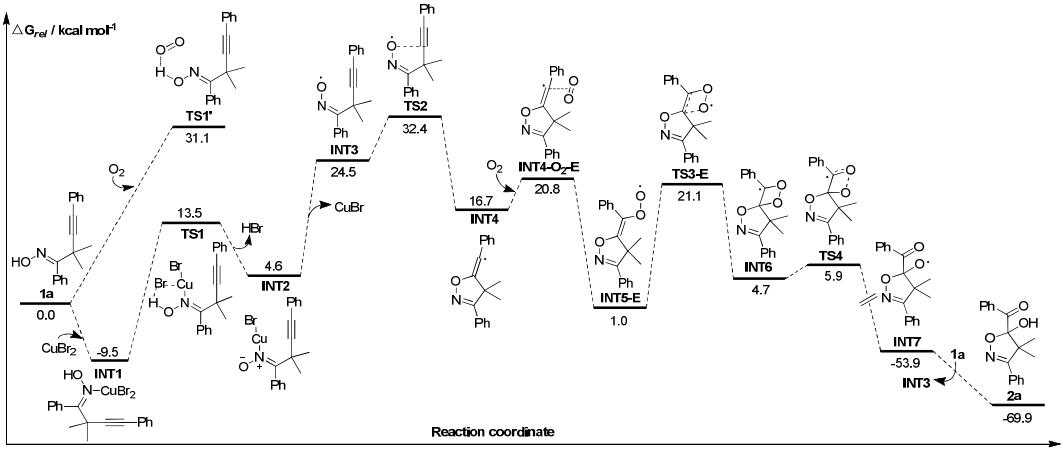


Figure 1. DFT-computed energy profiles for $CuBr_2$-catalyzed iminoxyl radical-triggered cascade reaction.

Baldwin's rule,[15] the caculated result suggests that it is reasonable in our reaction. Such a result can be attributed to the stabilizing anomeric effect in both **TS3-E** and **INT6**, which originates from the interaction between the lone pair of the endocyclic oxygen atom in the isoxazoline ring and the forming $\sigma^*_{C\text{-}O}$ (with the peroxy group) at the attack point.[16] Subsequently, **INT6** undergoes peroxy bond cleavage readily through **TS4** to form the alkoxy radical **INT7** which immediately abstracts a hydrogen atom from **1a** (or from the solvent) to produce **2a**.

In conclusion, we have developed a facile, efficient and environmental friendly Cu-catalyzed trifunctionalization of internal alkynes of unsaturated ketoximes through a tandem iminoxyl radical 5-*exo*-dig cyclization/dioxygen activation/peroxy radical 4-*endo*-trig cyclization process. By using this protocol, structurely important isoxazoline/cyclic nitrone-featured *α*-ketols have been successively achieved. Moreover, this study not only engenders the cyclization of iminoxyl radical onto alkynes for the first time but also realizes dioxygen activation and cleavege at room temperature. Further studies on synthetically useful iminoxyl radical-involved reactions are underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental details and characterization data (PDF). NMR spectra (PDF). X-ray crystallographic data for **2a**, **2x** and **4a** (CIF)

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Notes

The authors declare no competing financial interest.

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(13) Geometries and energies were calculated with B3LYP/(LANL2DZ: Cu; 6-31+G(d,p): others). All calculations were performed with Gaussian 09. See SI for more computational details.

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(16) The calculated NBO energies of anomeric interactions in **TS3-E** and **INT6** are 26.8 and 19.6 kcal/mol, respectively, see SI for detail. For the similar stabilization originates from strong anomeric $n_O \rightarrow \sigma^*_{CO}$ interactions in peroxides, see: Gomes, G.; Vil', V.; Terent'ev, V.; Alabugin, I. V. *Chem. Sci.* **2015**, 6, 6783–6791.

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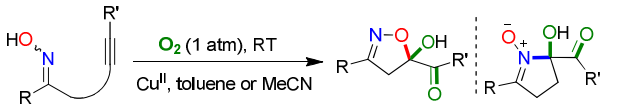

dioxygen cleavage via cascade iminoxyl radical 5-exo-dig/peroxy radical 4-endo-trig cyclization

R = R' = aryl, heterocycle, alkyl
31 examples, up to 81% yield