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Selective C-O bond formation: highly efficient radical dioxygenation of alkenes initiated by catalytic amount of tert-butyl hydroperoxide

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ABSTRACT

A highly selective radical dioxygenation of alkenes using hydroxamic acid and O_2 with 5-10 mol% of *tert*-butyl hydroperoxide as a catalyst was developed. On the basis of this newly developed strategy, a wide range of phenylethanol derivatives with a variety of functional groups can be effectively synthesized.

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1. Introduction

Selective oxidation and oxidative functionalization of organic molecules under mild reaction conditions to construct various oxygenated compounds would be the most important strategy and considered to be an essential area of research in modern organic synthesis.¹ Molecular oxygen is a perfect source to incorporate into organic molecules because of environmentally safe and abundantly available in nature.² A variety of transition-metal catalyzed oxygen incorporation in organic molecules have been developed, however, limited reports talk about such activation of molecular oxygen under metal-free conditions.³ Alkenes are abundant simple chemical feedstocks and organic molecules, which have been used widely in organic synthesis, and methods for their concise, selective oxidative functionalization are attractive to assemble substituted and ketones.^{2c} A number of transition-metalalcohols⁴ catalyzed reactions have been developed for the incorporation of oxygen in alkenes by the activation of molecular oxygen.^{2c} For instance, in 2010, Jiang group reported a palladium-catalyzed dihydroxylation of olefins with oxygen as sole oxidant, but 8 atm of molecular oxygen was needed, which limited the utility of this reaction.⁵ In 2015, a copper-/cobalt-catalyzed highly selective radical

dioxygenation of alkenes was achieved by Lei group.⁶ However, a metal-free conditions for this transformation have not been widely studied up to now,⁷ and thus the search for alternatives which allows to control the selectivity of the alkene dioxygenation, particularly involving environmental friendly pathway, still remains challenging. (a) Previous work:

$$Ph \longrightarrow + ROH \xrightarrow{Co} Ph \xrightarrow{OH} OR by Lei, Ref. 6$$

$$Ph \longrightarrow + ROH \xrightarrow{Ph(OAc)_2} Ph \xrightarrow{O} OR by Adimurthy, Ref. 7a$$

$$Ph \longrightarrow + ROH \xrightarrow{Cu} Ph \xrightarrow{O} OR by Weerpel and Punniyamurthy Ref. 8$$

$$Ph \longrightarrow + ROH \xrightarrow{H^+} Ph \xrightarrow{OH} OR by our group, Ref. 10$$

(b) Present work:

Ph + ROH
$$\xrightarrow{5-10\% \text{ TBHP}}_{O_2}$$
 Ph OF
R= $N \stackrel{N}{\leftarrow}$ or $N \stackrel{N}{\leftarrow}$ N

Scheme 1. Dioxygenation of Alkenes.

Recently, N-hydroxyphthalimide (NHPI) and Nhydroxybenzotriazole were used as hydroxylamine reagent *via* an radical pathway to synthesize α -oxygenated ketones

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by the Lei,⁶ Adimurthy,^{7a} Punniyamurthy,⁸ Woerpel,⁹ and our group.¹⁰ In our previous work, we successfully realized 1-phenylethanol derivatives synthesis using TsOH as catalyst, 4 equivalent tert-butyl hydroperoxide (TBHP) as the oxidant. Lei group also discovered the same reaction using cobalt as the catalyst.⁶ Considering the importance of these phenylethanols, the development of metal-free and acid-free conditions is desirable to avoid the possible contamination of metals and acid to environment. In 2015, Zou group reported an air oxidative radical hydroxysulfurization of styrenes initiated by 0.5 mol % of TBHP.¹¹ Inspired by this work and in continuation of our efforts on the difunctionalization of alkenes,¹² we envisaged whether 1-phenylethanol derivatives can be obtained via an radical addition, when catalysis loading of TBHP was used under oxygen atmosphere (Scheme 1-b).

2. Results/Discussion

In order to screen the suitable reaction condition according to our assumptions, first, omission of the catalyst was carried out, and an 80% yield of product was separated but for a longer reaction time (22h, Table 1, entry 2). Decreasing the oxidant loading to 2.0 equivalents, the yield was decreased to 61% in the air. Interestingly, using 1 atm oxygen as the co-oxidant, 1.2 equivalents of TBHP can give an 89% yield (12h). Then, the loading of TBHP was further decreased to 0.1 equivalents, and a 90% yield of 3a was detected under 1 atm oxygen conditions (entry 9, 24h). A 95% yield of product was also obtained using 0.05 equivalents of TBHP and 1 atm oxygen as the oxidant but for about 48 h (entry 10). Only using oxygen as the oxidant, no target product was observed at room temperature (entry 11), and only 40% yield was obtained at 60 °C, indicating the importance of TBHP. In addition, only using 0.1 equivalents of TBHP as the oxidant under argon atmosphere, no reaction occurred. It was noteworthy that using 3.0 equivalents of TBHP as oxidant under argon atmosphere, no product was achieved. These phenomenon meant the oxygen was very significant for this transformation (entries 13 and 14).

Table 1. Initial studies for the reaction of dioxygenation of alkenes.^a

la	+ N-OH Condition	ons	OH ON O 3a	°
Entry	Oxidative Condition	Solvent	Time	Yield ^b
1	4.0 equiv. TBHP (5-6 M in decane)+ air	CH₃CN	76h	80%
2	4.0 equiv. TBHP (5-6 M in decane)+air	DCE	22h	80%
3	3.0 equiv. TBHP (5-6 M in decane)+air	DCE	22h	93%

ANUS	SCRIPT			
4	2.0 equiv. TBHP (5-6 M in decane)+air	DCE	22h	61%
	, ,			
5	2.0 equiv. TBHP (5-6 M in decane) ± 1 atm Ω_2	DCE	12h	69%
	decale) + 1 ann 02			
6	1.2 equiv. TBHP (5-6 M in	DCE	12h	89%
	decane) + 1 atm O_2			
7	0.4 equiv. TBHP (5-6 M in	DCE	24h	84%
	decane) + 1 atm O_2			
8	0.2 equiv. TBHP (5-6 M in	DCE	24h	98%
	decane) + 1 atm O_2	У		
9	0.1 eauiv. TBHP (5-6 M in	DCE	24h	90%
	decane) + 1 atm O_2			
10	0.05 aquin TPHP (5.6 M in	DCE	19h	0.5%
10	decane) + 1 atm O_2	DCE	4011	9570
11	1 atm O_2	DCE	48h	N.R.
12	1 atm O ₂	DCE	48h	40% ^c
Y				
13	0.1 equiv. TBHP (5-6 M in decane) + 1 atm Ar	DCE	24h	N.R.
14	3.0 equiv. TBHP (5-6 M in decane)+ 1 atm Ar	DCE	24h	N.R.

^{*a*} Reaction conditions: **1a** (2.0 equiv., 0.6 mmol), NHPI (0.3 mmol), oxidant, and solvent (3.0 mL), at room temperature.

^b Isolated yield.

^c The reaction was carried out at 60 °C.

Under the optimized conditions (Table 1, entry 9), the alkene substrate scope was proved to be quite general with activated terminal alkenes and disubstituted alkenes participating in the dioxygenation reaction effectively (Scheme 2). A wide range of substrates and functional groups are tolerated including fluoro, chloro, bromo, methoxy, cyano, tertiary butyl and ester substituents at the different positions of styrenes. Cyclic alkenes such as 1,2dihydronaphthalene can provide the dioxygenation product **3i** in 80% yield. α -Methylstyrene and corresponding substituents can participate in this transformation in a short time (3j and 3k). Notably, 1,1-diphenylethylene proved to be an effective alkene substrate, yielding tertiary alcohol 3n in 63% yield. Phenyl substituted conjugated diene such as (1E,3E)-1,4-diphenylbuta-1,3-diene was tolerated to deliver a isomer **30** (dr=1:1) in a high yield only for 6h. Unactivated alkenes such as norbornene can also produce the target product 3q, and only the major isomer was separated, but

3.0 equivalents of TBHP was needed, and the same for the

product synthesis of **3**p. In addition. Nhydroxybenzotriazole also suitable was for this transformation, and the corresponding products 4a-4e were obtained in good to high yields under optimized conditions (Scheme 3).



Scheme 2. The scope of the activated alkenes. ^{*a*}3.0 equivalents of TBHP was added in the systems.



Scheme 3. The reaction of styrenes with Nhydroxybenzotriazole.

When (1-bromovinyl)benzene was subjected to the standard reaction conditions, a ketone product 5a was yielded via elimination HBr from the intermediate (Scheme 4). In addition, interestingly, when 1-methyl-4-vinylbenzene was carried out in this condition, a mixed product 5b (major:minor=3:1)was obtained.



Scheme 4. Ketone synthesis under standard condition.

Gratifyingly, the reaction could be readily scaled up without loss of its efficiency. When 5 mmol scale was carried out, 1.24g (88%) 3a was obtained implying its potential synthetic utility (Scheme 5).



Scheme 5. Scaled-up Reaction.

To gain insight into the reaction mechanism, the control experiments were carried out (Scheme 6). First, a mixture of styrene and 4-vinylbenzonitrile with NHPI was subjected to the standard conditions in order to elucidate the electronic preference of the reacting alkenes (eq 1). Under the competitive conditions, a 3.4:1 ratio of products was obtained, which means that electron-rich alkenes are inclined to radical addition. Then, when 2.0 equivalents of 2.2.6.6-tetramethyl-1-piperidinyloxy (TEMPO) was added in the reaction system, no target product was observed, but a 60% yield of TEMPO-captured product 6 was separated, which meant that a radical addition mechanism may be involved in this transformation (eq 2). In addition, omission of styrene under the standard conditions, the NHPI can be recovered after reacting with 2.0 equivalents of D₂O. The hydrogen atom of OH in NHPI was partly substituted by deuterium atom (H/D= 7:3), which indicated that NHPI can be easily activated in this reaction conditions (eq 3). Last, when 2.0 equivalents of $H_2^{18}O$ was added to the reaction systems, no ¹⁸O-labeled product **3a** was isolated, indicating the hydroxyl oxygen atom of the alcohols came from O2 (see supporting information).





On the basis of these results and previous studies,^{10,11}a possible mechanism was proposed in scheme 7. Firstly, PINO radical initiated by TBHP selectively adds to **1a** to form intermediate alkyl radical **I**. The molecular oxygen was captured by intermediate **I** to form peroxy radical **II**, following by grabing a hydrogen atom from TBHP to form hydroperoxide **III**. Intermediate **III** reacts with NHPI to give radical **IV**, which then obtains a hydrogen atom to afford product **3a**.



3. Conclusions

In conclusion, we have developed a concise and efficient selectively radical dioxygenation of styrenes initiated by 5-10 mol % of tert-butyl hydroperoxide with N-hydroxyphthalimide or N-hydroxybenzotriazole under oxygen atmosphere. This strategy is straightforward, requires no additives, and involves simple manipulations. In addition, the reaction can be effectively scaled up.

4. Experimental section

4.1 General information

Column chromatography was carried out on silica gel. Unless noted ¹H NMR spectra were recorded on 400 MHz in CDCl₃ or CD₃COCD₃, ¹³C NMR spectra were recorded on 100 MHz in CDCl₃ or CD₃COCD₃. IR spectra were recorded on an FT-IR spectrometer and only major peaks are reported in cm⁻¹. Melting points were determined on a microscopic apparatus and were uncorrected. All new products were further characterized by HRMS (high resolution mass spectra), high resolution mass spectrometry (HRMS) spectra was obtained on a Thermo Scientific LTQ Orbitrap XL instrument equipped with an ESI source; copies of their ¹H NMR and ¹³C NMR spectra are provided.

4.2 Typical procedure for the synthesis of product 3

To a solution of N-hydroxyphthalimide (2, 0.3 mmol, 48.9 mg) in DCE (3.0 mL) was added styrene (1a, 0.6 mmol), 10% TBHP (5-6 M in decane). The flask was evacuated and backfilled with O_2 for 3 times. The reaction mixture was then stirred for 24 h at room temperature. After the reaction, the resulting mixture was quenched with water and extracted twice with EtOAc. The combined organic extracts were washed with brine, dried over Na₂SO₄ and concentrated. Purification of the crude product by flash column chromatography afforded the product **3a** (petroleum ether/ethyl acetate as eluent (6:1)).

2-(2-hydroxy-2-phenylethoxy)isoindoline-1,3-dione, **3a**, ¹H NMR (400 M H_z, CDCl₃): 9.57 (s, 1 H, OH), 7.78-7.84 (m, 2 H), 7.75-7.77 (m, 2 H), 7.32-7.41 (m, 5 H), 5.41 (dd, J = 4.0, 4.0 Hz, 1 H), 4.49-4.51 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃): 163.8, 135.8, 134.8, 127.1, 123.8, 85.5, 78.9;

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