Copper(II)-Catalyzed Direct Dioxygenation of Alkenes with Air and *N*-Hydroxyphthalimide: Synthesis of *β*-Keto-*N*-alkoxyphthalimides

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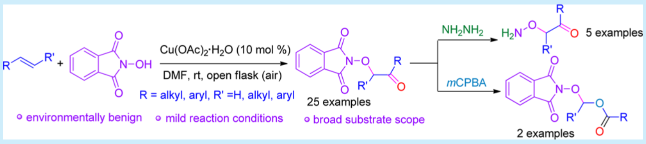
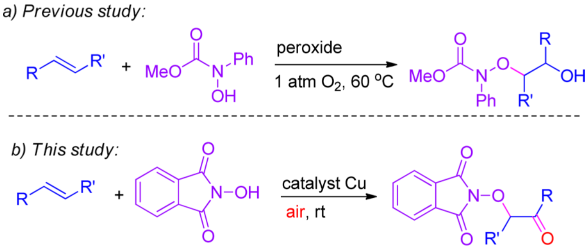
Supporting Information

ABSTRACT: Copper(II)-catalyzed direct dioxygenation of alkenes using air and a simple *N*-hydroxyphthalimide leading to *β*-keto-*N*-alkoxyphthalimides has been developed. The reaction system is mild, efficient, and effective at room temperature with broad substrate scope and substantial steric hindrance. The radical-trapping and ^{18}O-labeling experiments have been demonstrated.



The selective and sustainable dioxygenation of alkenes is critical to the pharmaceutical, petrochemical, and agricultural industries.[1−3] Ideally, the use of oxygen (from air) as the terminal oxidant would be the most attractive as it is cheap and environmentally benign. Although considerable efforts have been made on the aerobic oxidation of organic substrates during the past several decades,[4] the direct incorporation of oxygen from air into substrates is still synthetically challenging.[5] Recently, the direct dioxygenation of alkenes with 1 atm of oxygen and methyl *N*-hydroxy-*N*-phenylcarbamate has been accomplished utilizing peroxide as a radical initiator at moderate temperature (Scheme 1a).[6] Herein, we report a room-temperature copper(II)-catalyzed direct dioxygenation of alkenes with air and *N*-hydroxyphthalimide[7] to give *β*-keto-*N*-hydroxyphthalimides that can lead to widespread utilities in medicinal and biological sciences (Scheme 1b).[8,9] The mild reaction conditions, greater reactivity, and the use of the inexpensive copper salt as the catalyst are the significant practical advantages.

Scheme 1. Aerobic Direct Dioxygenation of Alkenes



First, the reaction conditions were optimized with 4-methylstyrene **1a** as a model substrate in the presence of *N*-hydroxyphthalimide (NHPI) **2** at room temperature under air (Table 1). Gratifyingly, the reaction occurred to produce *β*-keto-*N*-alkoxyphthalimide **3a** in 54% yield when the substrates were stirred with 10 mol % of $Cu(OAc)_2·H_2O$ in 1,2-dichloroethane (DCE) under air (entry 1). Similar results were observed using oxygen, while TBHP, $K_2S_2O_8$, and 30% H_2O_2 produced inferior results (entries 2−5). Under N_2 balloon, **3a** was obtained in trace amounts (entry 6). Subsequent screening of the solvents led to an increase in the yield to 70% using DMF, while toluene, CH_3CN, THF, EtOH, and DMSO furnished the target product in 28−45% yields (entries 7−11). No reaction was observed using H_2O, and the starting material was recovered intact (entry 12). In a set of copper sources screened, CuI, $CuCl_2$, $CuBr_2$, CuO nanoparticle, $Cu(OTf)_2$, and $Cu(OAc)_2·H_2O$, the latter gave the best results (entries 14−18). Decreasing the amount of the catalyst (5 mol %) or alkene (2 equiv) led to the formation of **3a** in <66% yield (entries 19−20). A control experiment confirmed that without the copper source no reaction was observed and the starting material was recovered intact (entry 21).

Having the optimal conditions in hand, the scope of the procedure was explored (Scheme 2). A series of reactions with various alkenes readily proceeded with good yields. The reaction of styrene **1b** gave the oxygenated compound **3b** in 65% yield. Substituted styrene **1c** at the 2-position with a methyl group oxidized to provide **3c** in 80% yield. The reactions of the styrenes **1d−g** bearing substituents at the 3-position with bromo, chloro, methoxy, and methyl groups produced the corresponding dioxygenated compounds **3d−g** in 62−82% yields. In addition, styrenes **1h−n** containing acetoxy, bromo, chloro, chloromethyl, fluoro, methoxy, and phenyl groups at the 4-position oxidized to furnish **3h−n** in 36−68% yields. Di- and trisubstituted styrenes **1o−q** with methyl or methoxy groups at the 2,4- or 3,4,5-, or 2,4,6-positions oxidized to give the target products **3o−q** in 60−68% yields. The oxidation of *trans*-*β*-methylstyrene **1r** produced the desired **3r** in 61% yield, while *cis*-stilbene **1s** and *trans*-stilbene **1t** underwent reaction to afford **3s** in 15% and 45% yields, respectively. Furthermore, 1- and 2-naphthylalkenes **1u−v** could be oxidized to **3t** and **3u** in 55% and 57% yields, respectively. In contrast, alkyl alkene **1w** failed to react, and the starting material was recovered intact. Recrystallization of **3d** in dichloromethane produced single crystals whose structure was

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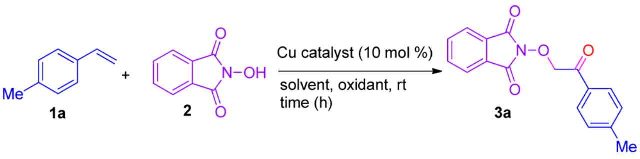
Table 1. Optimization of the Reaction Conditions[a]



entry	copper source	solvent	yield[b,c] (%)
1	$Cu(OAc)_2·H_2O$	DCE	54
2	$Cu(OAc)_2·H_2O$	DCE	52[d]
3	$Cu(OAc)_2·H_2O$	DCE	23[e]
4	$Cu(OAc)_2·H_2O$	DCE	16[f]
5	$Cu(OAc)_2·H_2O$	DCE	39[g]
6	$Cu(OAc)_2·H_2O$	DCE	trace[h]
7	$Cu(OAc)_2·H_2O$	toluene	28
8	$Cu(OAc)_2·H_2O$	CH_3CN	36
9	$Cu(OAc)_2·H_2O$	THF	37
10	$Cu(OAc)_2·H_2O$	EtOH	45
11	$Cu(OAc)_2·H_2O$	DMSO	32
12	$Cu(OAc)_2·H_2O$	H_2O	n.d.
13	**$Cu(OAc)_2·H_2O$**	**DMF**	**70**
14	CuI	DMF	15
15	$CuCl_2$	DMF	54
16	$CuBr_2$	DMF	35
17	CuO nano	DMF	27
18	$Cu(OTf)_2$	DMF	18
19	$Cu(OAc)_2·H_2O$	DMF	53[i]
20	$Cu(OAc)_2·H_2O$	DMF	66[j]
21		DMF	n.d.

[a] Alkene **1a** (1.5 mmol), NHPI **2** (0.5 mmol), $Cu(OAc)_2·H_2O$ (10 mol %), solvent (2.5 mL), rt, air, 5 h. [b] Isolated yield. [c] Trace of *p*-tolualdehyde obtained as a byproduct due to oxidative cleavage of the double bond. [d] O_2 balloon used. [e] TBHP (0.5 mmol) used. [f] $K_2S_2O_8$ (0.5 mmol) used. [g] H_2O_2 (0.5 mmol) used. [h] N_2 balloon used. [i] $Cu(OAc)_2·H_2O$ (5 mol %) used. [j] Alkene **1a** (1 mmol) used. n.d. = not detected.

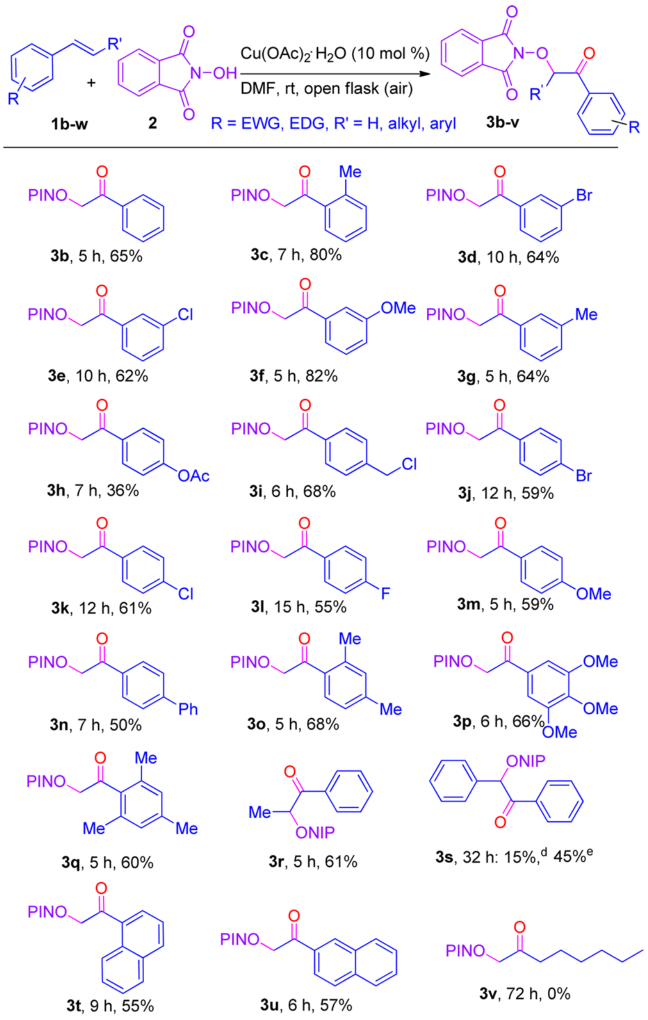
confirmed by X-ray analysis (see the Supporting Information). These results suggest that the substrates bearing electron-donating groups in the aryl ring exhibit slightly greater reactivity compared to those having electron-withdrawing groups.

The utility of the protocol was further extended to the reaction of cyclic alkenes (Scheme 3). These substrates exhibited lower reactivity compared to that of the acyclic alkenes. 1,3-Cyclohexadiene **1x** oxidized to furnish **3w** in 55% yield, and no further oxidation was observed with the conjugated double bond, while the oxidation of indene **1y** produced **3x** in 34% yield. In addition, 1,2-dihydronaphthalene **1z** underwent reaction to produce **3y** in 55% yield. These results suggest that the procedure is general, and a broad range of substrates could be dioxygenated in moderate to high yields.

The protocol was further explored for the gram scale oxidation of 4-methylstyrene **1a** as a representative example (Scheme 4). As above, the reaction smoothly occurred with 62% yield. In addition, *β*-keto-*N*-alkoxyphthalimides can be readily oxidized using *m*-chloroperbenzoic acid to afford the corresponding esters in high yields (Scheme 5).[10] For example, the oxidation of **3a** and **3s** produced the ester derivatives **4a** and **4b** in 85% and 87% yields, respectively.

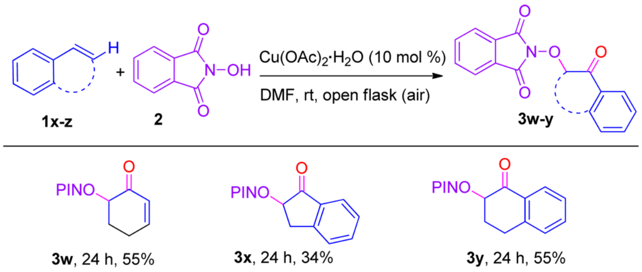
Finally, the reaction of the *β*-keto-*N*-alkoxyphthalimides with hydrazine was explored (Scheme 6).[9] The reactions readily proceeded with good yields. The reaction of **3k** produced alkoxyamine **5a** in 62% yield, while **3i** underwent reaction to

Scheme 2. Reaction of Acyclic Alkenes[a−c]



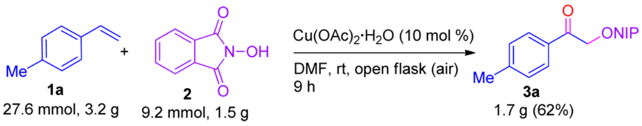
[a] Alkene **1b−w** (3 mmol), NHPI **2** (1 mmol), $Cu(OAc)_2·H_2O$ (10 mol %), DMF (3 mL), rt, air. [b] Isolated yield. [c] Aldehyde obtained as a byproduct in trace due to oxidative cleavage of the double bond. [d] Using *cis*-stilbene. [e] Using *trans*-stilbene.

Scheme 3. Reactions of Cyclic Alkenes[a,b]

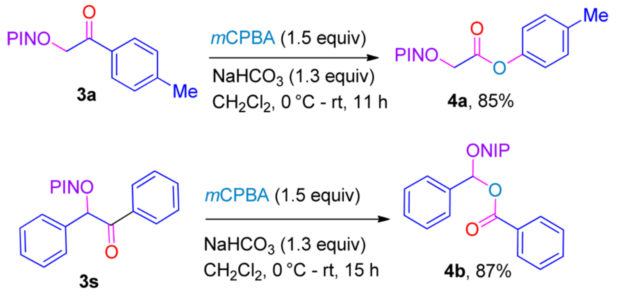


[a] Alkene **1x−z** (3 mmol), NHPI (1 mmol), $Cu(OAc)_2·H_2O$ (10 mol %), DMF (3 mL), rt, air. [b] Isolated yield.

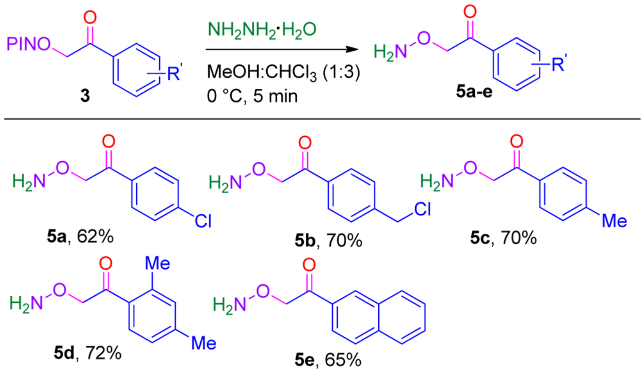
Scheme 4. Gram-Scale Synthesis



Scheme 5. Oxidation to Esters



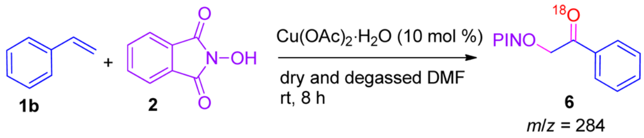
Scheme 6. Synthesis of β-Ketoalkoxyamines



afford **5b** in 70% yield. Similar results were observed with **3a**, **3o**, and **3u**, furnishing the corresponding alkoxyamines **5c**−**e** in 65−72% yields.

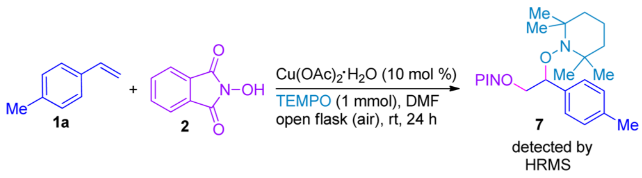
To gain insight in the reaction pathway, isotopic labeling of **1b** was performed as a representative example (Scheme 7). The reaction using ^{18}O incorporated ^{18}O in the target product (see the Supporting Information).[11] In contrast, $H_2{}^{18}O$ failed to react, which suggests that the oxygen source may be the air and not H_2O that could be generated during the reaction. In addition, the radical trapping experiment using TEMPO produced **7**, which reveals that the reaction may take place via a radical pathway (Scheme 8).[12] Thus, NHPI may react with $Cu(OAc)_2$ to produce PINO radical,[7] which can undergo addition with alkene to yield the more stable secondary radical intermediate ***a*** (Scheme 9).

Scheme 7. Isotope Labeling Studies

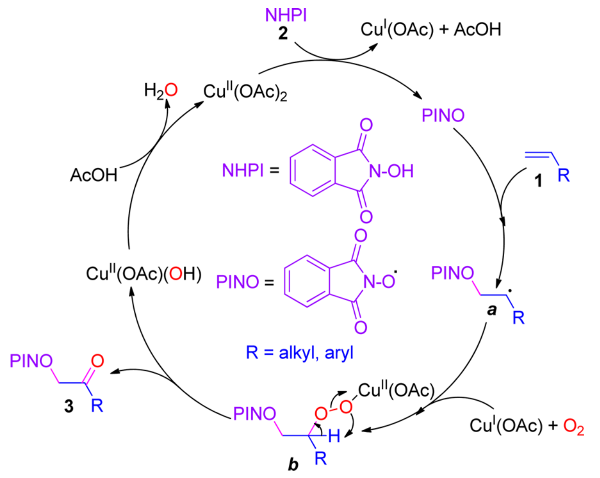


oxygen	solvent	observation
$^{18}O_2$	DMF	^{18}O- incorporated
O_2	DMF + H_2O^{18}(5 μL)	no isotope labeling

Scheme 8. Trapping of Styrenyl Radical by TEMPO



Scheme 9. Proposed Catalytic Cycle



The latter with Cu(OAc) and air can produce the peroxo intermediate ***b***, which can rearrange to furnish the target product **3** and Cu(OAc)(OH) that reacts with AcOH to regenerate the catalyst to complete the catalytic cycle, with water being formed as byproduct.

In summary, a copper(II)-catalyzed direct aerobic dioxygenation of alkenes has been accomplished using air and NHPI at room temperature. The products can be further oxidized into esters using *m*-CPBA, which can serve as useful building blocks in synthetic chemistry. In addition, the reaction of β-keto-*N*-hydroxyphthalimide using hydrazine produces acyl alkoxyamines that can lead to a broad range of applications in pharmaceutical industries. The mild reaction conditions, broad substrate scope and use of copper(II) salts as the catalyst would make this process attractive.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedure, labeling experiments for **6**, single-crystal X-ray data of **3d**, HRMS spectra of **7**, characterization data and NMR spectra (^1H and ^{13}C) of the products **3a**−**v**,**w**−**y**, **4a**,**b**, and **5a**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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