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# Ligand-Free, Copper-Catalyzed Aerobic Benzylic sp<sup>3</sup> C–H Oxygenation

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**Abstract** A ligand-free and operationally simple copper-catalyzed aerobic benzylic sp<sup>3</sup> C–H oxygenation was developed. The addition of *tert*butyl hydroperoxide, either in a catalytic or stoichiometric amount, was key for activating stable C–H bonds under mild conditions to furnish the corresponding ketones or esters in moderate to excellent yield.

Key words sp<sup>3</sup> C–H oxygenation, copper, oxygen, ligand-free, benzylic oxidation

Direct sp<sup>3</sup> C-H functionalization is an important reaction for realizing efficient synthetic routes toward complex molecules.<sup>1</sup> Among them, base-metal-catalyzed,<sup>2</sup> ligandfree<sup>3</sup> aerobic sp<sup>3</sup> C-H oxidations that directly introduce oxvgen functionalities to stable organic molecules using dioxygen  $(O_2)$  as a terminal oxidant are especially advantageous in view of atom economy, low cost of earth-abundant elements, simple operation (especially beneficial to small scale), environmental friendliness, and minimal generation of toxic byproducts. Reports of such reactions without the use of directing groups, however, are still rare.<sup>4</sup> Although there are a few examples of ligand-free, copper-catalyzed aerobic sp<sup>3</sup> C–H oxygenation, the substrate scope of those reactions is quite limited.<sup>5</sup> Herein, we report a ligand-free copper-catalyzed aerobic oxygenation of benzylic sp<sup>3</sup> C-H bonds in the presence of *tert*-butyl hydroperoxide (TBHP), with a comparatively broad substrate scope.

We began our studies by surveying catalytic metal sources for the direct aerobic sp<sup>3</sup> C–H oxygenation of isochroman (**1a**) under ligand-free conditions (Table 1). When the oxygenation was conducted using 10 mol% CuCl in *tert*butanol (*t*-BuOH, 0.1 M) at 50 °C for 12 h under open air conditions, the desired isochromanone (**2a**) was obtained in low yield (5%, entry 1). We then investigated external ini-



tiators and found that adding TBHP (3 equiv) promoted the C–H oxygenation in quantitative yield (entry 2). Reducing the amount of TBHP revealed that even a substoichiometric amount of TBHP was sufficient to promote the reaction (entries 3–5), suggesting that  $O_2$  was the actual terminal oxidant. We determined that the conditions shown in entry 3 using 0.3 equiv TBHP were optimal for the oxygenation of isochromans (see Table 2, entries 1 and 14–19). Catalyst loading could be reduced to 1 mol%, although the yield was slightly decreased compared with the yield produced when TBHP was used in the same amounts (Table 1, entries 6 and 7 vs. entries 4 and 2, respectively).

The indispensable role of O<sub>2</sub> was also supported when the reaction was performed under argon (Ar) atmosphere with the solvent deoxygenated by freeze-pump-thaw cycling. Product **2a** was obtained in only 16% yield and 1-tertbutylperoxyisochromane (3) was detected in 44% yield (Table 1, entry 8). When the reaction was conducted without the copper catalyst, **3** was again formed as the major product (34%) and **2a** was produced in 2% yield (entry 9). When the reaction was carried out with other copper sources, 2a was generally obtained in almost quantitative yield, except when a Cu(II) source was used (entries 10–14). Metal salts containing other elements such as Ni, Fe, Sn, Zn, and In, gave **2a** in low yield (entries 15-20). Pd(OAc)<sub>2</sub> was a good catalyst (entry 21). When 1 mol% IrCl<sub>3</sub> was used as catalyst, the reaction did not proceed (entry 22), but the yield was dramatically improved in the presence of ligands (entries 23-25). Overall, CuCl was the most favorable choice in view of reactivity and cost (Sigma-Aldrich, \$64.8/500 g).

We investigated<sup>6,7</sup> the substrate generality under the optimized conditions of 10 mol% CuCl and 3 equiv TBHP (0.3 equiv when isochromans were used as substrates) in *t*-BuOH under open air at 50 °C for 12 h (Table 2). Fluorene (**1b**) was a good substrate for the oxygenation to give 9-fluo-

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#### Table 1 Optimization of Reaction Conditions



Entry	Metal (mol%)	TBHP (X equiv)	Yield (%)ª
1	CuCl (10)	0	5
2	CuCl (10)	3	100
3	CuCl (10)	1	100
4	CuCl (10)	0.3	99
5	CuCl (10)	0.1	61
6	CuCl (1)	0.3	83
7	CuCl (1)	3	92
8 <sup>b</sup>	CuCl (1)	3	16
9	none	3	2
10	CuBr (10)	3	100
11	Cul (10)	3	96
12	$CuCl_2 \cdot H_2O(10)$	3	62
13	CuOAc (10)	3	100
14	Cu <sub>2</sub> O (10)	3	100
15	NiCl <sub>2</sub> (10)	3	8
16	FeCl <sub>2</sub> (10)	3	33
17	FeCl <sub>3</sub> (10)	3	30
18	SnCl <sub>2</sub> ·2H <sub>2</sub> O (10)	3	3
19	$ZnCl_2$ (10)	3	30
20	In(OTf) <sub>3</sub> (10)	3	0
21	$Pd(OAc)_2(10)$	3	87
22	$IrCl_3(1)$	3	0
23	lr(cod)(acac) (1)	3	79
24	$[Cp^*IrCl_2]_2(1)$	3	88
25	$[lr(cod)Cl]_2(1)$	3	82

<sup>a</sup> Yield based <sup>1</sup>H NMR spectroscopic analysis with 1,1,2,2-tetrachloroethane as internal standard.

<sup>b</sup> The reaction was performed under Ar with deoxygenated solvent.

renone (**2b**) in 83% isolated yield (entry 3). Diphenylmethane (**1c**) was also oxidized in moderate yield (entry 4). Indan (**1d**) and 1,2,3,4-tetrahydronaphthalene (**1e**), which each have two reaction sites, were selectively oxidized to the corresponding mono-ketones **2d** and **2e**, respectively, in moderate to high yield (entries 5 and 6). Butylbenzene (**1f**), possessing an acyclic aliphatic chain at the benzylic position, showed poor reactivity (entry 7). On the other hand, oxygenation of *p*-ethylanisole (**1g**) produced *p*-methoxyacetophonone (**2g**) in 53% yield due to activation by an electron-donating methoxy group (entry 9). Dibenzyl ether (**1h**) and (4-methoxybenzyl) methyl ether (**1i**) were also good substrates, producing the corresponding esters **2h** and **2i** in 70 and 96% yield, respectively (entries 11 and 13). These results demonstrated the applicability of the current method as a mild, oxidative deprotection method of *O*-benzyl- or *O*-*p*-methoxylbenzyl-protected alcohols after conversion into the corresponding esters and hydrolysis. Iso-chroman derivatives possessing various substituents **1j**-**o** could be oxidized with 0.3 equiv TBHP (entries 14–19). Although the yields were slightly decreased, both electron-donating and electron-withdrawing groups were compatible. Both benzylic methyl and methine groups are susceptible to the current oxidation conditions, but difficulties associated with controlling the oxidation state led to lower

yields (entries 20 and 21). Oxygenation of an allylic position was also difficult under our reaction conditions (see the



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Table 2 (continued)





To gain insight into the reaction mechanism, several control experiments were conducted (Scheme 1). Compound 1a reacted with 3 equiv TBHP under open air conditions without CuCl for 12 h to give 64% recovered 1a. 2% 2a. and 34% 3a (Scheme 1, eq. 1, left arrow, and Table 1, entry 9). The result suggests that thermally generated tert-butyl peroxy radical (*t*-BuOO<sup>·</sup>)<sup>8</sup> cleaves the benzylic C–H bond of 1a, and that subsequent trapping of the thus-generated benzylic carbon radical with *t*-BuOO<sup>·</sup> should produce **3a**. The addition of 1 mol% CuCl to the resulting mixture with stirring for an additional 12 h resulted in the complete consumption of 1a and the production of 2a in 83% yield (Scheme 1, eq. 1, right arrow). These findings demonstrated the important role of CuCl for accelerating both the C-H activation and conversion of **3** into **2a**. Although  $O_2$  had little effect on the reaction under CuCl-free conditions (Scheme 1, eq. 1, left arrow vs. eq. 2, left arrow), O<sub>2</sub> significantly accelerated the consumption of **1a** as well as the production of **2a**, but not consumption of **3**, by the addition of CuCl (Scheme 1, eq. 1, right arrow vs. eq. 2, right arrow).

A possible mechanism for the present catalytic cycle exemplified by oxygenation of **1a** is proposed in Scheme 2. First, TBHP is activated through a thermal route (to form *t*-BuOO<sup>•</sup>) or Fenton type mechanism (to form *t*-BuOO<sup>•</sup> or *t*-BuO'). The thus-generated peroxy or alkoxyl radical abstracts a benzylic hydrogen atom from **1a**, affording carbon radical A.<sup>8</sup> Radical A reacts with  $O_2$  to form B, which abstracts a hydrogen atom from 1a to produce hydroperoxide **C** and regenerates **A** (path a). Peroxide **C** is dehydrated to give 2a. Alternatively, radical A reacts with t-BuOO<sup>•</sup> to form 3 (path b),<sup>9</sup> which can also be converted into 2a. Both pathways either from C or 3 to 2a are accelerated in the presence of a copper species,<sup>10,11</sup> perhaps in a mode similar to a Fenton type mechanism.

In summary, we have developed a facile copper-catalyzed, ligand-free benzylic sp<sup>3</sup> C-H oxygenation reaction with TBHP and O<sub>2</sub> under mild reaction conditions. This ligand-free, earth-abundant copper-catalyst system is bene-

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ficial in terms of low cost, benign environmental effects, ease of operation, and avoidance of toxic byproducts. The present method will be a useful tool for benzylic sp<sup>3</sup> C-H functionalization chemistry.

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# **Supporting Information**

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588969.

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- (6) **Cu-Catalyzed Aerobic C–H Oxygenation of 1a; Typical Procedure:** To a test tube charged with CuCl (2.0 mg, 0.02 mmol) and isochroman (**1a**; 251  $\mu$ L, 2.0 mmol) in *t*-BuOH (20 mL) was added TBHP (5.0–6.0 M in decane, 10.9  $\mu$ L, 0.6 mmol) and the mixture was stirred and heated at 50 °C for 12 h under open air. After cooling to room temperature, the reaction was quenched with 25% aqueous ammonia solution and water then the mixture was extracted with EtOAc. The separated organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and products were concentrated after filtration. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give isochromanone (**2a**) as a colorless oil in 83% yield.
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