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Graphical Abstract

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Copper-Catalyzed Regioselective Allylic Leave this area blank for abstract info. **Oxidation of Olefins via C-H Activation** Nengbo Zhu, Bo Qian, Haigen Xiong, and Hongli Bao* Cat. Cu(I) R₁ up to 71% yield



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Copper-Catalyzed Regioselective Allylic Oxidation of Olefins via C-H Activation

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ABSTRACT

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Keywords: Allylic oxidation Olefin Regioselective Diacyl peroxides Copper catalysis Allylic radical A regioselective oxidation of allylic C-H bond to C-O bond catalyzed by copper (I) was developed with diacyl peroxides as oxidants. The oxidation of allylic C-H bond was accomplished with good yield and regioselectivity under mild reaction conditions. This method has a broad substrate scope including cyclic olefins, terminal and internal acyclic olefins and allyl benzene compounds. The reaction proceeds by a radical mechanism as suggested by spin trapping experiments.

The direct functionalization of C-H bond is a key task in modern organic chemistry.¹ Allylic oxidation² of olefins is a typical C-H bond functionalization reaction which could directly convert C-H bond into diverse functional groups.³ Allylic esters⁴ are important intermediates which can be converted into allylic alcohols⁵ and provide facile access to a variety of valuable compounds.⁶ The first copper-catalyzed allylic oxidation⁷ of olefins with perester was published by Kharasch and Sosnovsky in 1959.8 As a useful tool for direct C-H bond functionalization at the allylic position of olefins, Kharasch-Sosnovsky reaction has been further developed by many researchers.⁹ The results for cyclic olefins^{9f} are excellent (Scheme 1a).¹⁰ However, the yields for acyclic olefins are unsatisfying.¹⁰ The best yield for allylic C-H oxidation was 54% using 10 equivalents of acyclic olefin (Scheme 1a).^{10e} In 2005, White and coworkers developed a palladium-catalyzed allylic oxidation system affording branched products with morderate yield (Scheme 1b).^{6d} Very recently, Hartwig and coworkers reported oxidation of hindered alkenes to form linear allylic esters (Scheme 1b).^{6e} Herein, we report a copper-catalyzed regioselective allylic oxidation of olefins with high yield and broad substrate scope including cyclic olefins, terminal and internal acyclic olefins and allyl benzene compounds (Scheme 1c).

We initiated our studies by adopting benzoyl peroxide as the oxidant in the presence of various catalysts for the oxidation of 1octene and the results are summarized in Table 1. During preliminary catalyst screening, CuBr and CuBr₂ were found effective in this system, gave the desired products in 61% and 58% yield, respectively (entries 5 and 6). It was found that 70 °C was the best reaction temperature when different temperatures were investigated using CuBr as catalyst (entries 6-8). At 70 °C using CuBr as the catalyst, the ratio of olefin: oxidant: catalyst was investigated. To our delight, when the ratio of olefin: oxidant: catalyst was 1: 1.5: 0.1, the reaction gave 71% yield and good regioselectivity (B/L is 8.2:1) (entry 12).

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(a) Traditional Kharasch and Sonsnovsky reaction (perester as oxidant)

1.5 equiv.

$$\begin{array}{c} & & & & & \\ & & & & \\ & & & & \\$$

(b) Palladium catalyzed allylic C-H oxidation

1 equiv

 \cap



Scheme 1. Allylic C-H oxidation reactions: (a) Examples of traditional Kharasch and Sosnovsky reactions. (b) Examples of Palladium catalyzed allylic C-H oxidation reactions. (c) This work.

up to 71% yield

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Under the optimized reaction conditions, the scope of oxidants was evaluated with 1-octene (Table 2). In general, the oxidants with the different substituents on the phenyl group can be transformed into the desired products with moderate yields and regioselectivities. The oxidants having 3-methyl and 3,5-dimethyl substituents gave 69% and 62% yields, respectively (entries 2 and 3). The oxidants with 4-fluoro and 4-chloro groups delivered the corresponding products in 62% and 72% yields, respectively (entries 6 and 7). Interestingly, sterically bulky 2-naphthoic peroxyanhydride (**2j**) can also be used as an oxidant for the reaction, although the yield and regioselectivitiy were lower than those of benzoyl peroxides (entry 9).

Table 1. Reaction conditions optimization. ^[a]

| C_5H_{11} + C_5H_{11} OBz + C_5H_{11} OBz | | | | | |
|---|---------------------------|---------------|--------------------|-----------------------------|----------------------|
| 1 | 2a | | 3a | | 4a |
| Entry | Catalyst (mol%) | Temp. (°C) | Olefin/ Oxidant | Yield (%) ^[b] | 3a/4a ^[c] |
| 1 | CuTc (10) | 70 | 1:1 | 7 | 0.6:1 |
| 2 | CuOTf (10) | 70 | 1:1 | ND | |
| 3 | NiCl ₂ (10) | 70 | 1:1 | Trace | |
| 4 | Pd(TFA) ₂ (10) | 70 | 1:1 | 13 | 0.6:1 |
| 5 | CuBr ₂ (10) | 70 | 1:1 | 58 | 8.0:1 |
| 6 | CuBr (10) | 70 | 1:1 | 61 | 7.3:1 |
| 7 | CuBr (10) | 60 | 1:1 | 38 | 7.2:1 |
| 8 | CuBr (10) | 80 | 1:1 | 46 | 7.1:1 |
| 9 | CuBr (5) | 70 | 1:1 | 60 | 6.5:1 |
| 10 | CuBr (15) | 70 | 1:1 | 55 | 8.4:1 |
| 12 | CuBr (10) | 70 | 1:1.5 | 71 ^[d] | 8.2:1 |
| 13 | None | 70 | 1:1.5 | ND | |

[a] The reaction was conducted on a 0.5 mmol scale in 4 mL 1,2diclorobenzene under argon atmosphere. [b] GC yield (1,4-Dimethoxybenzene as internal standard). [c] Determined by GC. [d] Isolated yield.







[a] The reaction was conducted on a 0.5 mmol scale in 4 mL 1,2-dichlorobenzene under argon atmosphere, [b] Isolated yield. [c] Determined by 1 H NMR.

We next examined the scope of olefins (Table 3). A range of acyclic terminal olefins reacted smoothly and afforded the corresponding products in moderate to good yields (entries 1-5). Notably, TBS group is tolerated under the reaction condition. Moreover, the cyclic olefins, such as cyclohexene and 1,3cyclooctadiene delivered allylic oxidation products in 71% and 57% yields, respectively (entries 6 and 7). 1,1-Disubstituted olefin 5h 1-methylenecyclohexane (entry 8) afforded the products in 50% yield with moderate regioselectivity (6h/7h=3.7:1). It is worth noting that the internal olefins worked well in this system. (E)-3-hexene gave 71% yield and 1:1 mixture of two phenyl esters was formed (entry 9). The substrate with two terminal alkenes (1,7-octadiene, entry 10) was studied and gave mono-fuctionalization products in moderate yield (53%, 6j/7j=5:1). Methyl 10-undecenoate (5k) afforded the desired products in 64% yield with B/L=8.7:1. Finally, (but-3envloxy)benzene (51) and (hept-6-envloxy)benzene (5m) were examined and obtained corresponding products in moderate yields and regioselectivities.

Table 3. Scope of alkenes^[a].





[a] The reaction was conducted on a 0.5 mmol scale in 4 mL 1,2-dichlorobenzene under argon atmosphere.[b] Isolated yield. [c] Determined by 1 H NMR. [d] Determined by GC.

To explore the reaction mechanism, several experiments were carried out. Initially, when TEMPO¹¹ was added into the reaction, no desired products were observed. Next, with NHPI¹² (N-hydroxyphthalimide), the anticipated products **3a**, **4a** and a NHPI adduct **8** were isolated in 41%, 3% and 14% yield, respectively (scheme 2). Compound **8** presumably arises from the formation of a nitroxyl radical form NHPI under the reaction conditions.





The previous reports¹³ and the results of mechanistic experiments are consistent with a radical pathway for allylic oxidation and two plausible pathways mechanism are proposed (Scheme 3). The reaction started with the homolysis of benzoyl peroxide under heating conditions (with or without the involvement of the copper catalyst) to afford benzoyloxy radical¹⁴ (I). The Cu(I) species is oxidized by benzoyloxy radical to offer the copper(II) benzoate¹⁵ (intermediate II) and another molecule of benzoyloxy radical abstracts an allylic hydrogen atom to give benzoic acid and allylic radical (III). In path a, Cu(II) benzoate species II transfers benzovloxy group to the allylic radical III to form the desired products and regenerate the Cu(I). An alternative pathway involves copper (III) benzoate species¹⁶ (intermediate IV). The last step is the reductive elimination of the intermediate IV affording allylic ester products and regenerating copper (I) catalyst.



Scheme 3. Proposed catalytic cycle for oxidation of allylic C-H bond.

In conclusion, we have developed a practical method for the allylic C-H oxidation of olefins, including acyclic terminal, acyclic internal and cyclic olefins. This is an atom efficient reaction using one equivalent of alkene and commercially available oxidant (BPO) to deliver the corresponding products in moderate to good yields. Functional groups like TMS, TBS, ester, and ether were tolerated.

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Highlights

(1) It's a convenient and practical protocol for the oxidation of allylic C-H bond.

(2) Acyclic terminal and internal olefins, cyclic olefins work well in this system.

Acception and ether are tolerated.

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