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Copper catalyzed C-O bond formation via oxidative cross-coupling reaction of aldehydes and ethers

Quan Wang, Hao Zheng, Wen Chai, Dianyu Chen, Xiaojun Zeng, Renzhong Fu, and Rongxin Yuan*

A practical and efficient construction of C-O bonds via oxidative cross-coupling reaction of aldehydes and ethers has been realized under open air. When 2 mol % copper was used as the catalyst, various α-acyloxy ethers were obtained with up to 93% isolated yield.

In the past decades, the direct activation and cleavage of C–H bonds has been a very intense research field in synthetic organic chemistry.1 Traditional formation of C-C bonds usually needs the prefunctionalization of the reactants. By comparison, the direct activation of C-H bonds and subsequent coupling reaction avoids this laborious process and can be a more atom-economical and potent strategy.2 Most of the researches reported have concentrated on the activation of C-H bond adjacent to an amine nitrogen atom.3 However, only relatively few studies involved the activation of C-H bond adjacent to an ethereal oxygen atom.4

α-Acyloxy ethers are ubiquitous structural unit in many natural products and functional molecules, such as antimalarial drug artemisinin (a), heterocyclic cage compound (b) and the ellagitannin natural product sanguiin H-5 (c) (Scheme 1).5 The C-O bonds in these important building blocks were usually produced by the methods of the esterification of a hemiacetal,6 the nucleophilic substitution of a carboxylic acid and an α-halo substituted ether,7a, 7b or the addition of a carboxylic acid to an alkenyl ether.7c

Besides the traditional methods (Scheme 2a), very few effective synthesis method for it has been reported.8 Recently, wan and co-workers reported a Bu4NI catalyzed oxidative esterification reaction between acids and ethers for the construction of various α-acyloxy ethers with Bu4NI (20 mol %) as the catalyst (Scheme 2b).8a Although metal-free catalysts have many advantages such as higher activity and excellent selectivity, the search for more effective and inexpensive catalyst remains a considerable challenging task.

As an inexpensive and easily obtainable catalyst, copper has been increasingly applied in many oxidative reactions and showed high catalytic activity.9 In 2004, Li and co-worker reported an efficient CuBr catalyzed CDC reaction of tertiary aliphatic amines and terminal alkynes for the formation of C-C bonds.3a Recently, Nicholas and co-worker developed a Cu(OAc)2 catalyzed amidation of 2-phenylpyridine for the formation of C-N bonds with molecular oxygen as the oxidant.10 However, there is no precedent of effective C-O bond formation from aldehydes and ethers catalyzed by metal catalyst has been reported to date. We herein present an
efficient copper catalyzed C-O bond formation for the synthesis of α-acyloxy ethers (Scheme 2c). The reactions proceeded through double C-H activations of ethers and aldehydes, and subsequent cross-coupling reactions.

We began our investigation by the reaction of benzaldehyde (1 equiv) with 1,4-dioxane (20 equiv) catalyzed by Cu(OAc)\(_2\)·2H\(_2\)O (20 mol %) and used aqueous TBHP (4 equiv) as the oxidant. This approach gave the expected product (1a), but the yield was very poor (18%, entry 1, Table 1). At the same time a great deal of benzoic acid as the byproduct was also detected. When the 1,4-dioxane quantity was increased to 40 equiv, a complete disappearance of benzaldehyde and the byproduct benzoic acid was observed with an isolated 92% yield (entry 2). In addition we found that Cu(OAc)\(_2\)·2H\(_2\)O was not completely dissolved in the reaction solvent, and perhaps, a small amount of catalyst worked with the same result. When we decreased catalyst amount to 2 mol %, the solution of reactants became transparently blue and up to 91% yield was obtained in the end (entry 3). When the experiments were carried out with either a copper catalyst or TBHP alone, no desired product could be detected (entry 12 and 13). Other divergent copper(II) salts such as CuBr\(_2\), CuCl\(_2\), CuSO\(_4\), and Cu(ClO\(_4\))\(_2\) were also tried, but led to relatively low yields of (1a) (34-65%, entry 5-8). In particular, no desired product was obtained when copper(I) salts such as CuBr, CuCl was used as catalyst (entry 9 and 10). This result indicated that the use of Cu(II) salts seems to be critical for efficient transformation. When H\(_2\)O\(_2\) was used in place of TBHP as the oxidant, no expected product was detected (entry 11). If the aqueous TBHP quantity was further decreased, the product yield declined dramatically. All the reactions were conducted under open air. Contrary to most traditional transition-metal-catalyzed reactions, the approach was unaffected by the presence of moisture.

### Table 1 Optimization of the reaction conditions\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Oxidant</th>
<th>Yield (%)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^a)</td>
<td>Cu(OAc)(_2)·2H(_2)O</td>
<td>TBHP</td>
<td>18</td>
</tr>
<tr>
<td>2(^a)</td>
<td>Cu(OAc)(_2)·2H(_2)O</td>
<td>TBHP</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>Cu(OAc)(_2)·2H(_2)O</td>
<td>TBHP</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OAc)(_2)</td>
<td>TBHP</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>CuCl(_2)</td>
<td>TBHP</td>
<td>36</td>
</tr>
<tr>
<td>6</td>
<td>CuBr(_2)</td>
<td>TBHP</td>
<td>34</td>
</tr>
<tr>
<td>7</td>
<td>CuSO(_4)</td>
<td>TBHP</td>
<td>51</td>
</tr>
<tr>
<td>8</td>
<td>Cu(ClO(_4))(_2)</td>
<td>TBHP</td>
<td>65</td>
</tr>
<tr>
<td>9</td>
<td>CuBr</td>
<td>TBHP</td>
<td>nd</td>
</tr>
<tr>
<td>10</td>
<td>CuCl</td>
<td>TBHP</td>
<td>nd</td>
</tr>
<tr>
<td>11</td>
<td>Cu(OAc)(_2)·2H(_2)O</td>
<td>H(_2)O(_2)</td>
<td>nd</td>
</tr>
<tr>
<td>12</td>
<td>Cu(OAc)(_2)·2H(_2)O</td>
<td>TBHP</td>
<td>nd</td>
</tr>
<tr>
<td>13</td>
<td>Cu(OAc)(_2)·2H(_2)O</td>
<td>TBHP</td>
<td>nd</td>
</tr>
<tr>
<td>14(^d)</td>
<td>Cu(OAc)(_2)·2H(_2)O</td>
<td>TBHP</td>
<td>90</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: benzaldehyde (1 mmol), 1,4-dioxane (40 mmol), catalyst (2 mol %), and TBHP (4 equiv, 70% aqueous solution) at 80°C for 24 h unless otherwise noted. \(^b\) Catalyst (20 mol %), 1,4-dioxane (20 mmol). \(^c\) Catalyst (20 mol %), 1,4-dioxane (40 mmol). \(^d\) 100 mmol of benzaldehyde was used. \(^e\) Yield of isolated product.

After screening different solvents and temperature we got the optimal reaction conditions (entry 3, Table 1). Then a variety of aldehydes and ethers were subjected to the optimal conditions to explore the applicability of this protocol. Gratifyingly, 1,4-dioxane smoothly underwent reactions with most of aldehydes to give the corresponding α-acyloxy ethers in satisfactory yields (63-93%, 1a-15a, Scheme 3). Among them, 4-methylbenzaldehyde gave the best yield (93%, 1b, Scheme 3). The aldehydes with electron-donating substituents provided higher yields of the α-acyloxy ethers (2a, 8a, 9a and 10a, Scheme 3) than those with electron-withdrawing substituents (5a, 6a, 7a and 13a, Scheme 3). We suspected that the electron-donating substituents in the aryl ring enhanced the stability of the radical intermediates and easily led to homolytic cleavage reaction than electron-withdrawing substituents. The sterically hindered effect of the substituents in benzaldehydes hardly affected the product yields. No matter what substitution positions, ortho-, meta-, and para-methoxy substituted benzaldehydes reacted with 1,4-dioxane to give the similar good results (8a, 9a and 10a, Scheme 3). Aliphatic aldehydes were also examined and moderate yields of 63-70% were obtained (15a, 16a and 17a, Scheme 3). In addition, this methodology was also applicable to the reactions of heteroarenes, such as furan and thiophene with 78-80% yields (11a, 12a, Scheme 3).

To further determine the scope of application, other specific aldehydes were also explored. Most others underwent coupling reactions easily to offer the desired products (1b-10e, Scheme 3) in 58-89% yields. However, tetrahydrofuran (1c, 2c, 10c, Scheme 3) showed slightly lower activity than other ethers, which may be attributed to the instability of five-membered ring radical intermediate. Notably, when acyclic ether, such as 1-butoxybutane(\(d\)) or 1-(2-chloroethoxy)-2-chloroethane(\(e\)) was used as a substrate, ortho-methoxybenzaldehyde showed quite negligible activity compared to meta or para-methoxybenzalde under the same reaction conditions. The phenomenon can be ascribed to the larger steric effect of ortho-methoxy group on benzaldehyde when acyclic ethers were used as coupling partners.
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To further understand these coupling reactions, we carried out several elementary experiments to probe the reaction mechanism. The yield of (1a) declined sharply to 6% when 2,6-di-tert-butyl-4-methylphenol (BHT) was introduced into the reaction solution (Scheme 4a). This result suggested that the reaction may proceed through a radical intermediate. Then benzoic acid instead of benzaldehyde was used directly as the coupling partner and the identical product (1a) was obtained in 92% yield (Scheme 4b). No expected product was found when sodium benzoate was brought into the reaction system (Scheme 4c).

We suspected that the coupling reaction proceeded via an acyloxy radical intermediate, generated in situ from benzaldehyde or benzoic acid. We employed benzoyl peroxide which can offer acyloxy radicals to react with 1,4-dioxane. This reaction afforded the anticipated product (1a) in 33% yield (Scheme 4a). Besides we found trace tert-butylo peroxy ester by LC-MS in the template reaction, which may be provided by the reaction of the acyl radical with the tert-butylo peroxy radical (Scheme 5b). Moreover, deuterated 1,4-dioxane was employed to test the kinetic isotopic effect (KIE) of the experiment under the optimized conditions (Scheme 5c). A significant $k_H/k_D$ of 9.0 was detected, implying that the rate determining step of this conversion should be the cleavage of C-H bond adjacent to an ethereal oxygen atom.

In consideration of these control experiments, we proposed a plausible reaction pathway as shown in Scheme 6. Initially, both tert-butoxyl radical A and tert-butyloxiperoxoy radical B were generated in the catalytic cycle by the aid of copper (Scheme 6a). Then A extracts H from the C-H bond adjacent to an oxygen atom to produce the intermediate C (Scheme 6b). On the aldehyde, A traps H to form the acyloxy radical D. Subsequently D bonds with B to afford the tert-butyloxiperoxoy radical E (Scheme 6c). E decomposes to the acyloxy radical F and tert-butoxy radical A (Scheme 6d). Finally the coupling of F and C affords the expected product (Scheme 6e). A similar radical pathway can be applied to explain the reaction of carboxylic acid with 1,4-dioxane (Scheme 4b). The acyloxy radical F was formed by the reaction of tert-butoxyl radical A and benzoic acid (Scheme 6f).

Conclusions
In conclusion, we have disclosed a convenient and efficient construction of C-O bonds via oxidative cross-coupling reaction of aldehydes and ethers. When 2 mol % copper catalyst was used, the expected product α-acyloxy ether was obtained with up to 93% yield. Moreover, these reactions proceeded smoothly under open air and the presence of moisture did not affect the yields. This is very different from traditional transition-metal-catalyzed reactions. Ongoing investigations focus on the extension of substrate scopes and asymmetric versions of the reaction in our laboratory.

Acknowledgements
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Notes and references

2 For representative examples on C-C or C-X bond formation by using a KJA150001 and KJB150001).


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