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Copper-Catalyzed Formation of C–O Bonds by Oxidative Coupling of Benzylic Alcohols with Ethers

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The copper-catalyzed formation of C–O bonds by oxidative coupling of benzylic alcohols with ethers was realized in

open air. A series of α -acyloxy ethers were obtained in good yields with aqueous *tert*-butyl hydroperoxide as the oxidant.

Introduction

Over the past decades, the use of cross-dehydrogenative couplings and oxidative cross-couplings has become a powerful synthetic strategy in organic chemistry.^[1] These couplings avoid the prefunctionalization of the substrates and are more atom and step economical than other traditional cross-coupling reactions. Recently, a number of metal-catalyzed cross-dehydrogenative coupling reactions were developed for the formation of C–C bonds;^[2] however, only relatively few studies have involved the formation of C–O bonds.

 α -Acyloxy ethers are widely appearing substructures occurring in various pharmaceuticals such as the antimalarial drug Artemisinin and Sanguiin H-5.^[3] Classical methods (Scheme 1, a) for preparing this important functional group include the esterification of a carboxylic acid and a hemiacetal,^[4] the nucleophilic substitution of a carboxylic acid

(a)
$$R^{1} + Y + HO + R^{2}$$
 esterification
(Y = OCOR⁴, OH, CI, Br)
 $R^{1} + OH + X + R^{2}$
(X = CI, Br)
 $R^{1} + OH + R^{2} + CO + R^{3}$ addition
(b) $R^{1} + H + H + R^{2} + Cu \text{ catalyst}$
(c) $R^{1} + OH + H + R^{2} + Cu \text{ catalyst}$
 $R^{1} + OH + R^{2} + H + R^{2} +$

Scheme 1. Different pathways for the synthesis of α -acyloxy ethers.

and an α -halo-substituted ether,^[5] and the addition of a carboxylic acid to an alkenyl ether.^[6] The starting materials used in these reactions usually have the same high oxidation state as the product. In recent years, looking at synthetic potential and green chemistry aspects, several research groups have focused on the synthesis of the α -acyloxy ether functionality by an oxidative coupling approach.^[7] Lately,

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our group reported a copper-catalyzed oxidative coupling reaction between aldehydes and ethers for the construction of various α -acyloxy ethers (Scheme 1, b).^[8]

Considering the stability and the availability of alcohols, the direct conversion of alcohols into amides and esters has attracted a great deal of attention over the last few years.^[9] In contrast, the direct synthesis of α -acyloxy ethers from alcohols and ethers is less explored. With these considerations in mind, we expect to design a more environmentally mild and straightforward method for the formation of α -acyloxy ethers. Herein, we wish to disclose the efficient copper-catalyzed oxidative cross-coupling of benzylic alcohols with ethers (Scheme 1, c). A series of α -acyloxy ethers were obtained through C–O bond formation.

Results and Discussion

Initially, benzyl alcohol (1) and 1,4-dioxane (a) were first chosen as the substrates for the model reaction by using $Cu(OAc)_2 \cdot H_2O$ (10 mol-%) as the catalyst and aqueous *tert*butyl hydroperoxide (TBHP) as the oxidant at 80 °C in open air. Target cross-coupling product 1a was obtained in 51% yield (Table 1, entry 1). Then, various metal catalysts, such as FeCl₃, Mn(OAc)₂, Zn(OAc)₂, CuBr, and Cu(ClO₄)₂· 6H₂O, were screened, but they all led to lower yields of 1a (Table 1, entries 2–6). Upon decreasing the amount of Cu(OAc)₂·H₂O to 5 mol-%, product 1a was obtained in 46% yield (Table 1, entry 7). It was found that the oxidant played a crucial role in this reaction. Other common oxidants such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

Table 1. Optimization of the reaction conditions.^[a]

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Entry	Catalyst	Oxidant	Alcohol/TBHP/ 1,4-dioxane ^[b]	Yield ^[c] [%]
1	Cu(OAc) ₂ ·H ₂ O	TBHP	1:3:30	51
2	FeCl ₃	TBHP	1:3:30	31
3	$Mn(OAc)_2$	TBHP	1:3:30	27
4	$Zn(OAc)_2$	TBHP	1:3:30	17
5	CuBr	TBHP	1:3:30	<5
6	$Cu(ClO_4)_2 \cdot 6H_2O$	TBHP	1:3:30	45
7 ^[d]	$Cu(OAc)_2 \cdot H_2O$	TBHP	1:3:30	46
8	$Cu(OAc)_2 \cdot H_2O$	DDQ	1:3:30	<5
9	$Cu(OAc)_2 \cdot H_2O$	NaClO	1:3:30	<5
10	$Cu(OAc)_2 \cdot H_2O$	H_2O_2	1:3:30	<5
11	$Cu(OAc)_2 \cdot H_2O$	O_2	1:3:30	<5
12	$Cu(OAc)_2 \cdot H_2O$	<i>m</i> CPBA	1:3:30	<5
13	$Cu(OAc)_2 \cdot H_2O$	TBHP	1:4:40	59
14	$Cu(OAc)_2 \cdot H_2O$	TBHP	1:5:50	65
15	Cu(OAc) ₂ ·H ₂ O	TBHP	1:6:60	72
16 ^[e]	$Cu(OAc)_2 \cdot H_2O$	TBHP	1:6:60	77
17 ^[e,f]	$Cu(OAc)_2 \cdot H_2O$	TBHP	1:6:60	77

[a] Reaction conditions (unless otherwise noted): Benzyl alcohol (1 mmol), catalyst (10 mol-%), TBHP (70% aqueous solution), 80 °C, 24 h. [b] Molar ratio. [d] Cu(OAc)₂·H₂O (5 mol-%) was used. [e] Temperature of 90 °C. [c] Yield of isolated product. [f] Under an argon atmosphere.

(DDQ), NaClO, H_2O_2 , O_2 , and *m*-chloroperbenzoic acid (*mCPBA*) were also tested under the same reaction conditions and showed negligible activity (Table 1, entries 8–12).

Further investigation demonstrated that different molar ratios of benzyl alcohol/TBHP/1,4-dioxane also played an important role in the reaction. The results in Table 1 indicate that increasing the amount of TBHP or 1,4-dioxane clearly enhanced the yield of the transformation (Table 1, entries 13–15). Upon using 6.0 equiv. TBHP and 60 equiv. 1,4-dioxane, **1a** was isolated in 72% yield (Table 1, entry 15). Upon conducting the reaction at a temperature of 90 °C, the product was obtained in 77% yield (Table 1, entry 16). A higher temperature, however, did not result in any improvement in the yield.

With the optimized reaction conditions in hand (Table 1, entry 16), the generality of this novel process was explored, and the results are summarized in Scheme 2. Initially, the reactions of various substituted aryl alcohols with 1,4-dioxane were examined. In general, the corresponding α -acyloxy ethers were obtained in good to high yields regardless of the different substitution patterns on the aryl ring. The electronic effects of the substituent in the aryl ring played a role in controlling the product yields. Aryl alcohols with electron-donating substituents (see compounds 2a, 6a, 7a, and 8a; Scheme 2) were more reactive than those with electron-withdrawing substituents (see compounds 3a, 4a, 5a, and 11a; Scheme 2). Upon examining heteroarenes such as thiophene and furan, corresponding products 9a and 10a were also obtained in high yields. This protocol worked well for an α , β -unsaturated aryl alcohol, and desired product 12a was obtained in satisfactory yield (Scheme 2). However, an aliphatic alcohol was a poor substrate and delivered product 13a in a low yield (23%, Scheme 2).

To further expand the substrate scope, a series of other specific ethers, including cyclic and acyclic ethers, were also tested (see compounds **1b–8e**, Scheme 2). Most ethers were found to be good coupling partners and offered the desired products in 63-78% yields. However, the reactions of *ortho*-methoxybenzyl alcohol with the acyclic ethers *n*Bu₂O (**d**) and 2-chloro-1-(2-chloroethoxy)ethane (**e**) showed quite negligible activity owing to the larger steric effect of the *ortho*-methoxy group on the benzyl alcohol (see compounds **6d** and **6e**, Scheme 2). In the reaction of unsymmetrical 1,2-dimethoxyethane, two regioisomers (see compounds **1fa** and **1fb**, Scheme 2) were obtained in a good combined yield.

The persistent radical effect played a role in this reaction.^[10] We found a trace amount of 2-(1,4-dioxan-2-yl)-1,4-dioxane by LC–MS in the template reaction (Table 1, entry 16), which may have resulted from dimerization of the ether-derived radical (Scheme 3, d). On the basis of the literature^[8,11] and the results of our experiments, a plausible mechanism is proposed (Scheme 3). Initially, both *tert*-butoxyl radical **A** and *tert*-butylperoxy radical **B** are generated in the catalytic cycle by the aid of copper (Scheme 3, a). Then **A** extracts a proton from 1,4-dioxane to produce intermediate **C** (Scheme 3, b). On the other hand, benzyl alcohol is oxidized to benzaldehyde or benzoic acid by





Scheme 2. Substrate scope for the α -acyloxy ethers. *Reaction conditions:* Alcohol (1 mmol), ether (60 mmol), Cu(OAc)₂·H₂O (10 mol-%), TBHP (6.0 equiv., 70% aqueous solution), 90 °C, 24 h.



Scheme 3. Proposed reaction mechanism.

TBHP and then produces acyloxy radical **D** with the aid of copper (Scheme 3, c). Finally, coupling of **C** and **D** affords expected product **E** (Scheme 3, d).

Conclusions

In summary, the practical and efficient copper-catalyzed construction of C–O bonds through oxidative cross-coupling of benzylic alcohols with ethers was developed. A series of α -acyloxy ethers were obtained in good yields. This approach is more atom economical and environmentally friendly than existing methods. Investigation into an asymmetric version, the detailed mechanism, and synthetic applications of this reaction are underway in our laboratory.

Experimental Section

General: All manipulations were performed in open air. All reagents were commercial grade and were purified according to the established procedures. Column chromatography was generally performed on silica gel (300–400 mesh), and reactions were monitored by thin-layer chromatography (TLC) by using UV light to visualize the course of the reactions. The ¹H NMR (400 MHz) and ¹³C NMR (100 MHz) data were recorded with Varian spectrometers by using CDCl₃ as the solvent at room temperature. ¹H NMR spectra were recorded with tetramethylsilane as the internal reference. ¹³C NMR spectra were recorded with CDCl₃ as the internal reference. MS (ESI) were obtained by using an Agilent 1260–6120 instrument. IR spectra were recorded as KBr pellets or neat with a Nicolet Impact 410 spectrophotometer.

General Procedure for the Synthesis of α -Acyloxy Ether 1a: Benzyl alcohol (1.0 mmol), Cu(OAc)₂·H₂O (10 mol-%), 1,4-dioxane

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(60 mmol), and TBHP (6.0 equiv., 70% aqueous solution) were added to a tube in open air. The mixture was heated in an oil bath at 90 °C. During this period complete disappearance of benzyl alcohol was observed, as judged by TLC. After cooling to room temperature, the mixture was quenched with saturated Na₂SO₃ solution, extracted repeatedly with ethyl acetate, and dried with Na₂SO₄. Then, the organic solvent was removed under vacuum. The crude product was purified by column chromatography (silica gel; hexane/ethyl acetate, 20:1) to give **1a** (160 mg, 77% yield) as a pale yellow oil.

Supporting Information (see footnote on the first page of this article): Product characterization and copies of the ¹H NMR and ¹³C NMR spectra.

Acknowledgments

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Oxidative Coupling

The copper-catalyzed formation of C–O bonds by oxidative coupling of benzylic alcohols with ethers is realized in open air. A series of α -acyloxy ethers were obtained in good yields with aqueous *tert*-butyl hydroperoxide as the oxidant.



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