SCIENCE CHINA
Chemistry

• ARTICLES •

doi: 10.1007/s11426-017-9142-1

C(sp^3)–H bond functionalization of non-cyclic ethers by decarboxylative oxidative coupling with α,β-unsaturated carboxylic acids

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Received August 1, 2017; accepted September 13, 2017; published online November 17, 2017

A copper-catalyzed decarboxylative oxidative coupling of α,β-unsaturated carboxylic acids with non-cyclic ethers is developed. This method provides a new approach for C(sp^3)–H bond functionalization of non-cyclic ethers. Mechanism study shows the reaction involves a radical process.

C(sp^3)–H bond functionalization, non-cyclic ethers, decarboxylative, oxidative coupling, α,β-unsaturated carboxylic acids

Citation: Zhang T, Lan XW, Zhou YQ, Wang NX, Wu YH, Xing Y, Wen JL. C(sp^3)–H bond functionalization of non-cyclic ethers by decarboxylative oxidative coupling with α,β-unsaturated carboxylic acids. *Sci China Chem*, 2017, 60, 10.1007/s11426-017-9142-1

1 Introduction

C(sp^3)–H bond functionalization has always been a dynamic topic of organic chemistry. As one of the powerful methods for C–H bond functionalization, decarboxylative coupling has attracted much attention [1–3].

In recent decades, coupling reactions have gained considerable progress [4]. Due to high yields and mild reaction conditions, coupling reactions have been widely used in organic synthesis. However, conventional coupling reactions normally use organometallic reagents and halides as coupling components, which are expensive and toxic. In 2002, Myers *et al*. [5] reported a Heck-type decarboxylative cross-coupling reaction. Instead of aryl halides, this work used inexpensive, stable, non-toxic and readily available carboxylic acid derivatives as coupling components. In the presence of transition metal catalysts and bases, carboxylic acid derivatives can release CO_2 and generate desired reactive intermediates *in situ* without producing large amounts of byproducts. Since then, lots of remarkable progress has been made in this field including Pd-catalyzed decarboxylative arylation of aryl carboxylic acids and cinnamic acids with aryl halids by Goossen *et al*. [6,7], Pd-catalyzed decarboxylative acylation of α-oxocarboxylic acids with 2-arylpyridine by Ge *et al*. [8], Ru-catalyzed decarboxylative condensation of α-oxocarboxylic acids with amine by Lei *et al*. [9], and Cu-catalyzed decarboxylative coupling reaction of potassium polyfluorobenzoates with aryl iodides and bromides by Liu *et al*. [10]. In addition, oxidative coupling reactions catalyzed by Cu, Fe and Ni salts have also been of interest [11–14].

Many reactions of functionalization of C–H bond adjacent to a heteroatom have been explored [15–26]. In our previous work, Ni- and Mn-catalyzed decarboxylative coupling of cinnamic acids with cyclic ethers, such as tetrahydrofuran, tetrahydropyran and 1,4-dioxane, has been reported [15].

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In this study, we would like to describe a new copper-catalyzed decarboxylative oxidative coupling of α,β-unsaturated carboxylic acids with non-cyclic ethers (Scheme 1). This method provides a new approach for C(sp^3)–H bond functionalization of non-cyclic ethers under mild conditions.

2 Experimental

2.1 General considerations

All reagents were commercially available and used without further purification. ^{1}H and ^{13}C NMR spectra (400 or 100 MHz, respectively) were measured in $CDCl_3$ with TMS as internal standard at room temperature. High resolution mass spectrometer (HRMS) were shown in Supporting Information online.

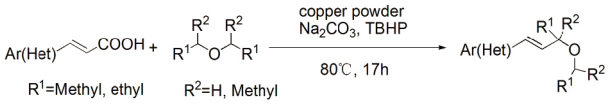
2.2 General procedure

Taking the synthesis of (*E*)-1-(3-ethoxybut-1-enyl)-4-methylbenzene (**3a**) as an example. Copper powder (0.03 mmol), Na_2CO_3 (0.03 mmol), *tert*-butyl hydroperoxide (0.9 mmol, 70% in water) was added successively into a mixture of 4-methylcinnamic acid (0.3 mmol) and ethyl ether (3 mL) at room temperature in sealed tube. The mixture reacted at 80 °C for 17 h. After the reaction was completed, the resulting mixture was concentrated by a rotary evaporator and then separated by column chromatography on silica gel by using petroleum ether and ethyl acetate as eluent.

3a: Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J=7.68 Hz, 2H), 7.11 (d, J=7.72 Hz, 2H), 6.47 (d, J=15.92 Hz, 1H), 6.06 (dd, J_1=15.90 Hz, J_2=7.64 Hz, 1H), 4.01–3.95 (m, 1H), 3.60–3.52 (m, 1H), 3.43–3.36 (m, 1H), 2.32 (s, 3H), 1.32 (d, J=6.28 Hz, 3H), 1.20 (t, J=6.80 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.38, 134.01, 131.15, 130.73, 129.27, 126.37, 76.42, 63.54, 21.80, 21.18, 15.46. HRMS (EI-TOF): *m*/*z* calcd. for $[C_{13}H_{18}O+H]^+$ 190.1358; found 190.1356.

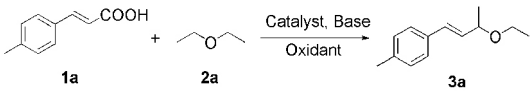
3 Results and discussion

We began our investigation using cinnamic acid **1a** (1 equiv., 0.3 mmol) and diethyl ether **2a** (1 mL, both as reagent and solvent) as model coupling partners, and the results were shown in Table 1. After screening transition metal catalysts (entries 1–7), a 64% yield of the desired product **3a** was achieved by using Cu powder in the presence of Na_2CO_3 and *tert*-butyl hydroperoxide (TBHP). The effect of different bases in the coupling reaction was also tested. It was found that Na_2CO_3 as a base gave the best results (entries 8–11). When other oxidizing reagents such as di-*tert*-butyl peroxide (DTBP), $K_2S_2O_8$ and benzoyl peroxide (BPO) were used instead of TBHP, the yields were lower (entries 12–14). In view of the coordination for copper salts, typical ligands, 1,10-phenanthroline and triphenylphosphine, were added into the optimal condition as additives, but the yields were not improved (entries 15 and 16). Notably, when reaction was carried out at 60 °C, the yield was dramatically decreased (entry 17), indicating the temperature is crucial for the transformation. But considering the nature of low boiling point of diethyl ether, we finally chose 80 °C for the synthesis of unsaturated oxygenous derivates. A controlled experiment without any catalysts were carried on, but no desired product was observed. We also tried some Cu(I)-catalysts like CuI, and the reaction could proceed at room temperature. However, esterification reaction happened instead of decarboxylative coupling reaction. No desired decarboxylative product was observed.



Scheme 1 Coupling of α,β-unsaturated carboxylic acids with non-cyclic ethers.

Table 1 Reaction condition optimization [a]



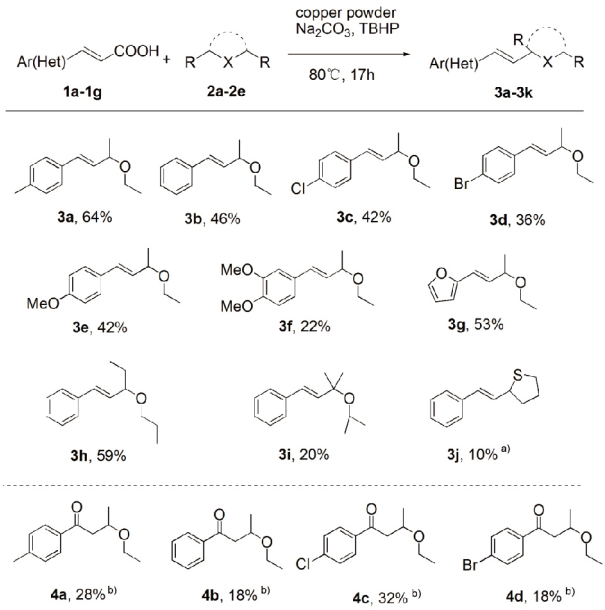
1a **2a** **3a**

Entry	Catalyst	Base	Oxidant	Yield (%) [b]
1	$Mn(OAc)_2$	Na_2CO_3	TBHP	21
2	$Ni(OAc)_2$	Na_2CO_3	TBHP	23
3	$Co(OAc)_2$	Na_2CO_3	TBHP	19
4	$Zn(OAc)_2$	Na_2CO_3	TBHP	<10
5	$MnCl_2$	Na_2CO_3	TBHP	<10
6	$Cu(OAc)_2$	Na_2CO_3	TBHP	47
7	Cu	Na_2CO_3	TBHP	64
8	Cu	NaOAc	TBHP	42
9	Cu	K_2CO_3	TBHP	58
10	Cu	DBU	TBHP	51
11	Cu	DABCO	TBHP	53
12	Cu	Na_2CO_3	DTBP	0
13	Cu	Na_2CO_3	$K_2S_2O_8$	0
14	Cu	Na_2CO_3	BPO	47
15 [c]	Cu	Na_2CO_3	TBHP	37
16 [d]	Cu	Na_2CO_3	TBHP	49
17 [e]	Cu	Na_2CO_3	TBHP	22
18	Cu	–	TBHP	55
19	Cu	Na_2CO_3	–	0
20	–	Na_2CO_3	TBHP	0
21 [f]	Cu	Na_2CO_3	TBHP	23
22 [g]	Cu	Na_2CO_3	TBHP	0

a) Reaction condition: cinnamic acid (1 equiv., 0.3 mmol), diethyl ether as solvent, metal catalyst (0.1 equiv.), base (0.1 equiv.), TBHP (70% in water, 3 equiv.) in sealed tube at 80 °C for 17 h, unless otherwise noted; b) isolated yields; c) 1,10-phenanthroline (0.2 equiv.); d) PPh_3 (0.2 equiv.); e) 60 °C; f) BHT (1 equiv.); g) TEMPO (1 equiv.).

To confirm that the reaction involves a radical process, we designed and performed some mechanistic studies. When 1 equiv. of radical inhibitor 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) were added as additive, no product was obtained.

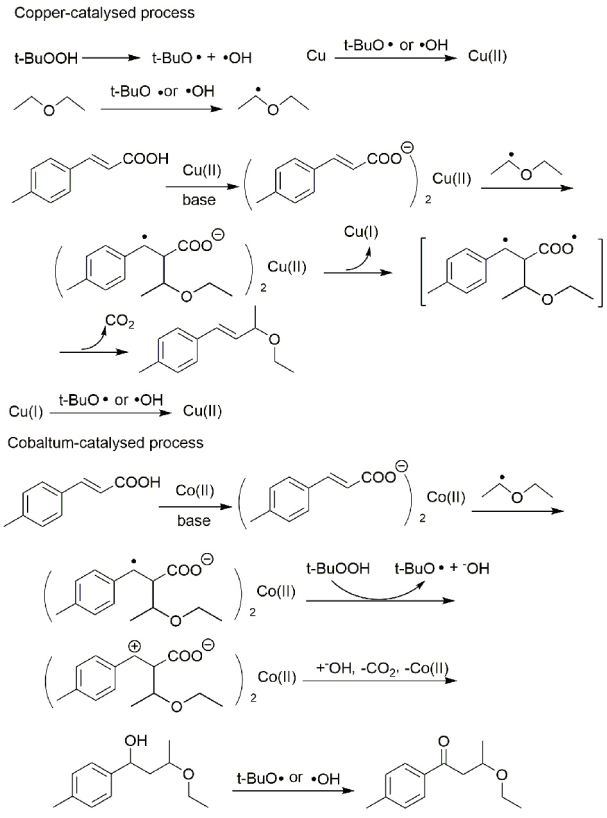
With the optimal conditions in hand, the substrate scope of this coupling reaction was investigated by testing various α, β-unsaturated carboxylic acids **1** and ethers **2** (Scheme 2). Firstly, a series of cinnamic acids containing electron-withdrawing and electron-donating substituents were explored to react with diethyl ether in sealed tubes as shown in Scheme 2. It was found that these reactions can take place smoothly and the desired products were generated in moderate yields. Notably, when (*E*)-3-(furan-2-yl)acrylic acid was used as a substrate, a 53% yield of the desired product **3g** was achieved. We also tried cinnamic acid with strong electron-withdrawing substituent like nitro, however, 3-(4-nitrophenyl)acrylic acid did not work with this method. It was almost impossible to obtain pure products since the yield was very low and too many byproducts were generated. Subsequently, several ethers were investigated as coupling partners with cinnamic acid **1b**. In addition, diethylsulfane and tetrahydrothiophene were used instead of ethers, but only trace amount of desired product **3j** was generated. We also tried coupling reaction of carboxylic acids **1** and some nitrogen aliphatic heterocyclic compounds like 1-phenylpyrrolidine and 1-methylpyrrolidine, but no reaction was observed. In the process of exploring conditions, we found an interesting result that carbonyl compounds were generated when employing $Co(OAc)_2$ as the catalyst, but unfortunately, only poor yields of the carbonyl products **4a**–**4d** were given comparing with the unsaturated compounds using Cu as catalyst.



Scheme 2 Substrate scope for the reaction of α,β-unsaturated carboxylic acids and ethers. Reaction condition: **1** (1 equiv., 0.2 mmol), **2** (3 mL) as solvent, Cu (0.1 equiv.), Na_2CO_3 (0.1 equiv.), TBHP (70% in water, 3 equiv.) in sealed tube at 80 °C for 17 h, unless otherwise noted. a) 120 °C; b) $Co(OAc)_2$ as catalyst.

Notably in ^{1}H NMR spectra, we found an interesting phenomenon. The signal of two protons in methylene at the β-position of chiral carbon atom was split into two peaks. Actually two protons in methylene adjacent to the chiral center are magnetic nonequivalent and chemically nonequivalent, no matter optical purity or racemation of these compounds. Two protons in the same carbon atom have been affected by asymmetric microenvironment of chiral center. Herein, protons in methylene are at the β-position of chiral center, an oxygen atom is in the middle of chiral center and methylene, but herein the two protons in methylene are still chemical shift inequivalence, $-CH_2-$ group actually is $-CH_aH_b-$ structure in these products.

On the base of our previous report [15,25,26], a possible reaction mechanism of the Cu-catalyzed decarboxylative oxidative coupling is proposed in Scheme 3. TBHP produced tert-butoxy radical and hydroxyl radical, which oxidized copper powder to Cu(II) and generated ether radical. Cu(II) catalyst reacted with cinnamic acid to produce a salt of Cu(II) carboxylate, and then ether radical and hydroxyl radical added to salt of Cu(II) carboxylate. Then Cu(I) catalyst and CO_2 eliminated and desired product was generated, and Cu(I) would be oxidized to Cu(II) by *tert*-butoxy radical and hydroxyl radical.



Scheme 3 Proposed possible reaction mechanism.

The mechanism of Co-catalyzed process is different. Ether radical added to salt of Co(II) carboxylate, and then TBHP oxidized the radical adduct to a benzyl carbocation and generated OH anion, which would attack the benzyl carbocation. Finally CO_2 and Co(II) catalyst eliminated and the ketone product was generated.

4 Conclusions

In summary, we have developed a copper-catalyzed decarboxylative oxidative coupling of α,β-unsaturated carboxylic acids with non-cyclic ethers. This method provides a new approach for C(sp^3)–H bond functionalization of non-cyclic ethers. Further study is ongoing in our group.

Acknowledgments This work was supported by the National Natural Science Foundation of China (21572240).

Conflict of interest The authors declare that they have no conflict of interest.

Supporting information The supporting information is available online at http://chem.scichina.com and http://link.springer.com/journal/11426. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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