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Copper-Catalyzed Acyloxylation of C(sp[3])-H bond Adjacent to Oxygen by Cross-Dehydrogenative Coupling Approach

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Acyloxylation of C(sp[3])-H bond adjacent to oxygen by adopting copper catalyzed dehydrogenative cross-coupling reaction between simple ethers and benzyl alcohols has been disclosed. The advantages of dehydrogenative cross-coupling 10 reaction are adoption of unactivated ethers as a substrates and good tolerance of many functional groups.

The construction of carbon–carbon (C–C) and carbon-heteroatom (C–O & C–N) bond using transition-metal catalyzed C–H bond functionalization has emerged as an attractive and powerful tool 15 in modern organic chemistry.[1,2] In particular, functionalization of C(sp[3]) –H bonds under oxidative condition has fascinated much attention among synthetic chemists, since it eliminates the prefunctionalization step and thus make synthetic schemes more shorter and straight forward. In recent years, tremendous efforts 20 have been made for the formation of these bonds through oxidative C–H bond functionalization adjacent to heteroatoms by cross dehydrogenative coupling approach (CDC).[3,4,6] Moreover, the majority of reported methods have focused on functionalization of C(sp[3])–H bond (via reactive iminium ion) 25 intermediates) adjacent to nitrogen atom under oxidative conditions with various pro-nucleophiles.[4] However, the functionalization of C(sp[3])–H bond (via reactive oxonium ion intermediates) adjacent to oxygen atom is relatively inert due to its higher oxidation potential and required strong hydrogen 30 acceptor. In this regard, most of the reported methods were devoted to allylic and benzylic C–H bonds α-position to the oxygen with different carbon based pro-nucleophiles.[5]

In contrast, to our knowledge, there have been scarce reports exist on α-C–H bond functionalization on simple alkyl 35 ethers for construction of C–O, C–N and C–S bond using oxygen, nitrogen and sulphur based pro–nucleophiles via CDC reaction.[6] For example, Wan and co-workers[6c] first described a Bu4NI-catalyzed C–O bond formation by adopting CDC reaction between carboxylic acids and unactivated simple ethers using 40 tert-Butyl hydrogen peroxide as an oxidant (scheme 1, a). Recently, Duan's[6e] group also described a decarboxylative acyloxylation of C(sp[3])–H bond adjacent to oxygen atom with α-oxocarboxylic acids in the presence of TBAI and TBHP as an oxidant (scheme 1, b). Most recently, Patel et al.,[6i] developed a 45 copper catalyzed synthesis of α–acyloxy ethers from
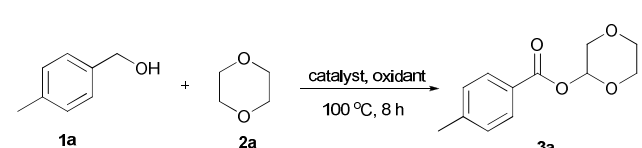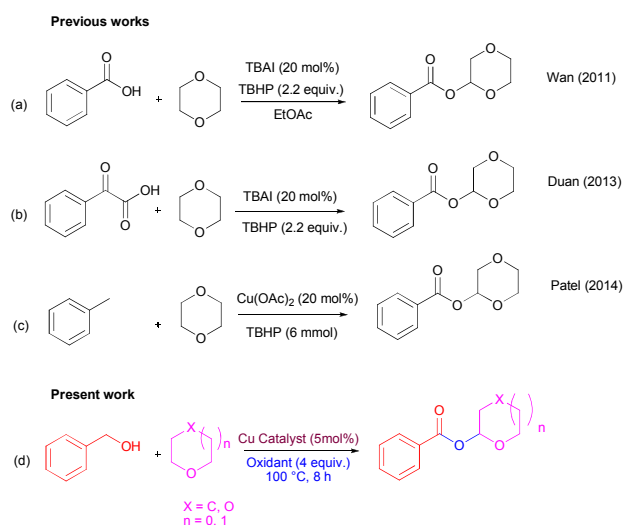

Scheme 1: CDC approach for C–O bond forming reaction via C–H bond functionalization

alkylbenzenes and simple ethers (Scheme 1, c).

50 Traditionally, benzyl alcohols are known to be acylation[7] and acyloxylation reagents.[8] Since benzyl alcohols are naturally abundant, stable, and easy to handle and readily oxidized into aldehydes, acids and thus can be likely to be used as ideal acyl and acyloxylating sources. α-Acyloxy ethers appear as 55 structural motif in biologically active, pharmaceutical and natural products compounds.[9] Herein, we report a copper–catalyzed oxidative CDC reaction between benzyl alcohols and simple cyclic and acyclic ethers in the presence of tert-Butyl hydrogen peroxide (TBHP) as an oxidant (scheme 1, d), affording the 60 acyloxylated products in moderate to good yields.

At the outset of our study, copper catalyzed oxidative C(sp[3])–H bond acyloxylation was investigated with 4–methylbenzyl alcohol (1a) and 1,4–dioxane (2a) as the model substrates (Table 1). The initial reaction was carried out with 10 65 mol % Cu(OAc)2 in presence of 70% aqueous solution of TBHP (2 equiv) at 80 °C for 8 h and we perceived the desired product 3a in 15% yield (Table 1, entry 1). Next we examined with different Cu sources like Cu(acac)2, CuCl2, CuBr2, CuCl, CuI and Cu(OAc)2.H2O. However, the expected product was not observed 70 in all the cases (Table 1, entries 3-6) except Cu(OAc)2.H2O

Table 1 Optimization of reaction conditions.[a]

Entry	Catalyst (mol%)	Oxidant (equiv.)	T [°C]	Yields 3a [%][c]
1	Cu(OAc)$_2$(10)	TBHP in H$_2$O (2)	80	15
2	Cu(acac)$_2$(10)	TBHP in H$_2$O (2)	80	–[d]
3	CuCl$_2$(10)	TBHP in H$_2$O (2)	80	–[d]
4	CuBr$_2$(10)	TBHP in H$_2$O (2)	80	–[d]
5	CuCl(10)	TBHP in H$_2$O (2)	80	–[d]
6	CuI(10)	TBHP in H$_2$O (2)	80	–[d]
7	Cu(OAc)$_2$H$_2$O	TBHP in H$_2$O (2)	80	12
8	Cu(OAc)$_2$(10)	TBHP in H$_2$O (3)	100	35
9	Cu(OAc)$_2$(10)	O$_2$	100	–[d]
10	Cu(OAc)$_2$(10)	H$_2$O$_2$ [e](3)	100	–[d]
11	Cu(OAc)$_2$(10)	DTBP[e]	100	–[d]
12	Cu(OAc)$_2$(10)	TBHP in decane (3)	100	57
13	Cu(OAc)$_2$(5)	TBHP in decane (3)	100	68
14	**Cu(OAc)$_2$(5)**	**TBHP in decane (4)**	**100**	**82**
15	Cu(OAc)$_2$(2)	TBHP in decane (4)	100	80[b]
16	–	TBHP in decane (4)	100	–[d]
17	Cu(OAc)$_2$(5)	–	100	–[d]
18	Cu(OAc)$_2$(5)	TBHP in decane (4)	100	12[f]

[a] *Reaction conditions:* Unless specified, the reaction was carried out with: **1a** (1 mmol), **2a** (2 mL), Cu catalyst (5 mol%), oxidant (4 equiv), T [°C], 8 h. [b] Reaction time was 18 h. [c] Yield of isolated product. [d] Product not observed by TLC [e]H$_2$O$_2$ = hydrogen peroxide, [e]DTBP = Di-*tert*-butyl peroxide. [f] **2a** (1mmol)

catalyst, which gave only 12% yield (Table 1, entry 7). Then, it is necessary to check the quantity of TBHP and temperature role. Accordingly, the aq. TBHP amount was raised to 3 equiv and temperature from 80 °C to 100 °C (Table 1, entry 8) then, the product yield was increased from 15% to 35%. We have evaluated the role of oxidant by screening different oxidants such as O$_2$, H$_2$O$_2$, Di-tert-butyl peroxide (DTBP). However, we could not able to see the required product (Table 1, entries 9–11). Moving from aqueous TBHP to a commercially available TBHP in decane solution, the product yield could be increased from 35% to 57% (Table 1, entry 12).[10] By decreasing the Cu(OAc)$_2$ quantity from 10 mol% to 5 mol% (Table 1, entry 13), the yield was further enhanced from 57% to 68%. Further optimization studies revealed that, the product yield was increased to 82% (Table 1, entry 14), when the reaction has carried out with 5 mol% Cu(OAc)$_2$ and 4 equiv. of TBHP. No significant improvement in the product yield was observed with a loading of 2 mol% of Cu(OAc)$_2$ and prolonging the reaction time (Table 1, entry 15). The lack of product formation in control experiments in the absence of metal or oxidant clearly showed the significance of both metal catalyst and oxidant for this transformation (entry 16, 17).

Having the optimized reaction conditions in our hand (Table 1, entry 14), we screened different benzyl alcohol

substrates **1** for the C(sp^3)–H bond acyloxylation with different unactivated ethers **2**. For example, substrates bearing electron–rich groups like a methyl, isopropyl, methoxy, benzyloxy on aromatic ring showed good active with 1,4-dioxane to offered the desired products (**3a–e**) in good yields. *Ortho*-substituted benzyl alcohol did not affect the reaction and undergoes efficient coupling with 1,4–dioxane and gave the desired product **3f** in 73% yield. The electron–poor groups containing benzyl alcohols such as CN, NO$_2$ and F are worked well under the optimized
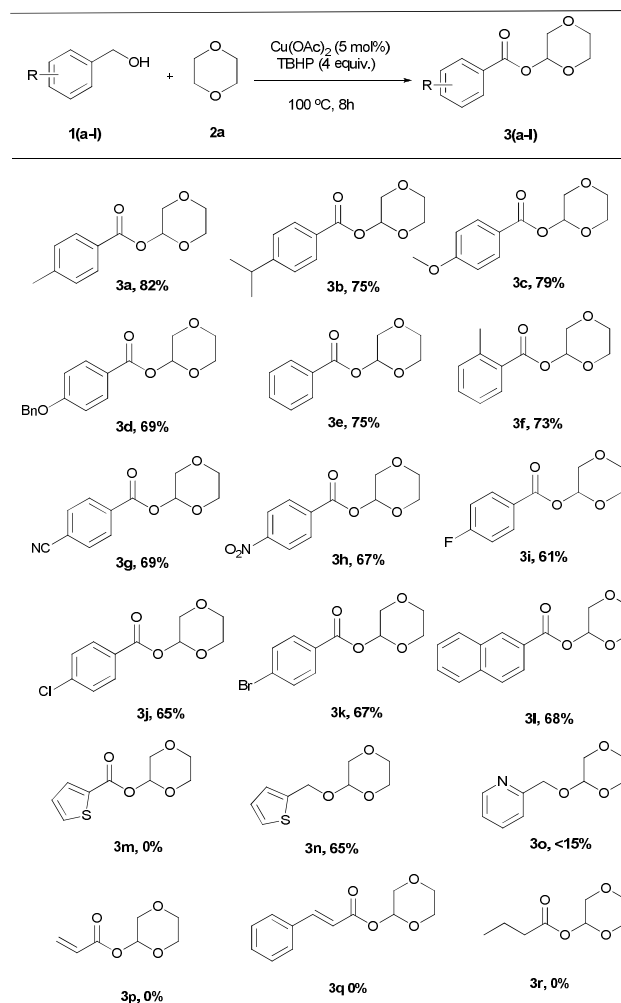
Scheme 2 Cu(OAc)$_2$–catalyzed coupling of 1,4–dioxane with variety of benzyl alcohols.

[a] *Reaction conditions*: benzyl alcohol (1 mmol), 1,4–dioxane (2 mL), Cu(OAc)$_2$ (5 mol%), TBHP in decane (4 equiv), 100 ^{0}C, 8 h.

reaction conditions (**3g–3i**). The present protocol well tolerated for the halogen bearing benzyl alcohols (Cl & Br) without any difficulties (**3j & 3k**). The catalytic system showed good activity in the case of fused ring (naphthalene) containing benzyl alcohol and the product (**3l**) yield was obtained in 68%. Our efforts to activate hetero aromatic benzyl alcohols were not successful; instead of the acyloxylation product (**3m**) we observed the alcohol attack at carbon atom (adjacent to oxygen) (**3n, 3o**) (see Supporting Information). In addition, the acyloxylation of 1,4-dioxane **2a** was also unsuccessful with allyl alcohol and aliphatic alcohol (**3p**, **3q**, **3r**) (Scheme 2) under optimized reaction conditions.

To evaluate the role of ethers we carried out the reactions with cyclic (**2b-2e**) and acyclic (**2f**, **2g**) (Table 2) ethers under standard reaction conditions. Cyclic ethers like THP (**2b**) and THF (**2c**) reacted smoothly with benzyl substituted alcohol to
5 provide the corresponding products (**4b**, **4c**) in 68% &63% good

**Table 2** Reaction of Benzyl alcohols with ethers ^{a}

Entry	Reactant	Ether	Product	Yield ^{b}
1	1a	2b	4b	68%
2	1a	2c	4c	63%
3	1a	2d	4d	–
4	1a	2e	4e	–
5	1a	2f	4fa	46%
			4fa'	31%
6	2f	2f	4fb	43%
			4fb'	30%
7	2f	2f	4fc	36 %
			4fc'	30%
8	1a	2g	4g	–

^{a} *Reaction conditions*: Benzyl alcohol **1a** (1 mmol), **2b–2g** (2 ml), Cu(OAc)$_2$ (5 mol%), TBHP in decane (4 equiv.), 100 ^{0}C, 8 h. ^{b}Yield of isolated product.

10 yields. But 2-methyl THP (**2d**) and 1,3-dioxolane (**2e**) were both inactive for coupling reaction with benzyl alcohols. To compare the reactivity between internal methylene and terminal methyl

carbons, we have carried out the reaction with 1,2–dimethoxyethane (**2f**) under standard conditions and we observed
15 the two products (**4fa–4fc'**) with their respective combined good yields. In the entire cases acyloxylation products at internal methylene carbon were slightly higher. Next, we carried out the reaction of **1a** with diethylether (b.p 35 °C) (**2g**) but we couldn't scrutinize the acyloxy ether (**4g**) under standard reaction
20 conditions.

To explore the mechanism of the reaction several control experiments were performed. In this process, we observed that, the coupling product **3a** was obtained in <5% yield[7a,c] when 4–methylbenzoic acid was used instead of benzyl alcohol under
25 the optimum reaction conditions (scheme 3, equation 1) from this it is apparent that the transformation did not proceed *via* an acid intermediate.[11] Surprisingly, no product observed when reaction was carried out between 2–(4–methylbenzyloxy)–1,4–dioxane (i.e, protected alcohol) and **2a** (scheme 3, equation 2) in our
30 catalytic system. The acyloxylated product **3a** was obtained in 80% yield when the reaction was performed with 4-methyl benzaldehyde (scheme 3, equation 3). Additionally, 2,2,6,6-Tetramethylpiperidinyloxy (TEMPO), a radical scavenger, added to the reaction mixture of **1a** and 1,4–dioxane(**2a**) under
35 optimized reaction conditions, no coupling product **3a** was observed (Scheme 3, equation 4). On the basis of these observations and in line with earlier reports[6b,12] it suggests that, mechanism of the dehydrogenative cross–coupling reaction may undergo a radical pathway in presence of Cu(OAc)$_2$ and TBHP in
40 decane as an oxidant, which is depicted in scheme 3.
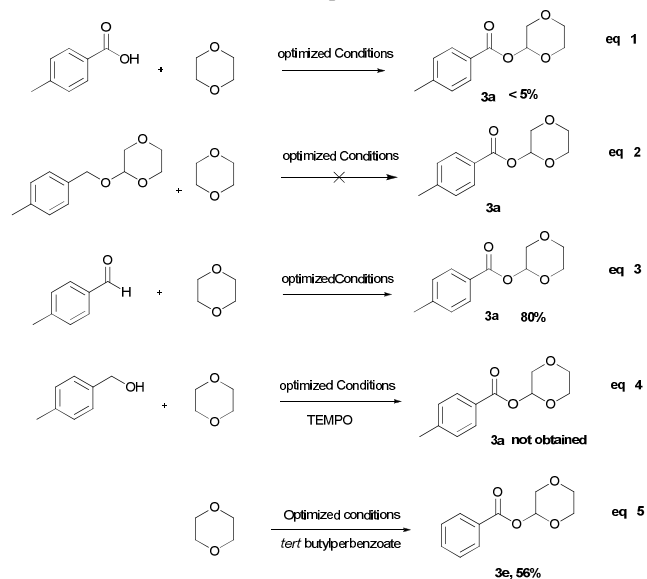
Scheme 3 Investigation of reaction mechanism

The mechanism involve five steps: Initially, tert–butoxyl and tert–butyl peroxyl radicals which are formed through
45 interaction of TBHP with the Cu (II)–Cu (I) redox couple (Scheme 4, step a).[13] Next activate the C–H bonds adjacent to oxygen atom of benzyl alcohol to produce aldehyde. Subsequently, this aldehyde undergoes a similar hydrogen abstraction to form acyl radical, which is coupled with tert butyl
50 peroxy radical provides per ester intermediate (Scheme 4, step b).[14] The intermediacy of *tert*-butyl perbenzoate in this transformation (step b) has been supported by a control experiment, where the treatment of commercially available *tert*-butyl perbenzoate with 1,4–dioxane **2a** under optimized reaction
55 conditions afforded the coupling product **3e** in moderate yields (Scheme 3, equation 5).[6i] From this we can predict, the plausible
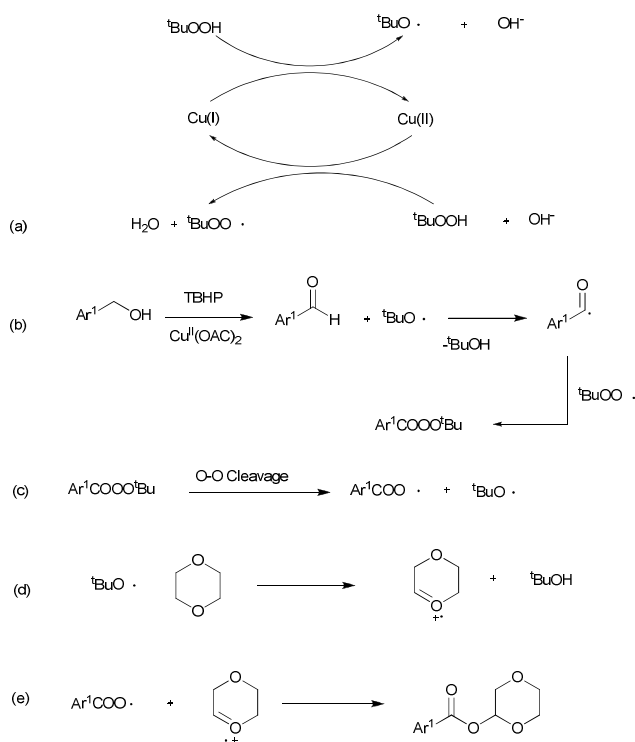
Scheme 4 Plausible pathway for the reaction

mechanism of the reaction as described in scheme 4. This per ester intermediate undergo a homolytic cleavage to acyloxy radical (Scheme 4, step c) which acts as a pro-nucleophile. Tert–butoxyl radical generated by the dissociation of t–BuOOH may abstract α–hydrogen of 1, 4–dioxane to form radical and go through a single electron transfer[15] leads to oxonium species (Scheme 4, step d). Then, finally acyloxylated product **3a** was formed by the coupling of α–oxy radical with oxonium species (Scheme 4, step e).

Conclusions

In summary, we disclosed a Cu–catalyzed oxidative C(sp³)–H bond acyloxylation of unactivated cyclic and acyclic ethers with different substrates of benzyl alcohols by adopting TBHP as an oxidant. *Ortho*-substituted, halogen bearing and fused ring aromatic substrates are well tolerated under the optimized reaction conditions. This novel strategy provides a simple, efficient, and direct access to acyloxylated products. Further investigation towards the scope, mechanism, and synthetic applications of this reaction are expedited in due course.

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Graphical Abstract
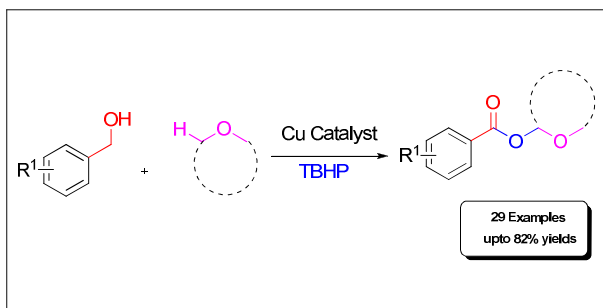
We demonstrated an efficient, unprecedented oxidative dehydrogenative cross coupling between a benzyl alcohol and $C(sp^3)$–H bond adjacent to oxygen atom for the construction of C–O bond, in which benzyl alcohol used as pronucleophile. Significantly, this method reveals a new strategy for the direct use of benzyl alcohols in the synthesis of acyloxylated products in moderate to good yields with the use of inexpensive copper as a catalyst and TBHP as an oxidant.