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COMMUNICATION

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

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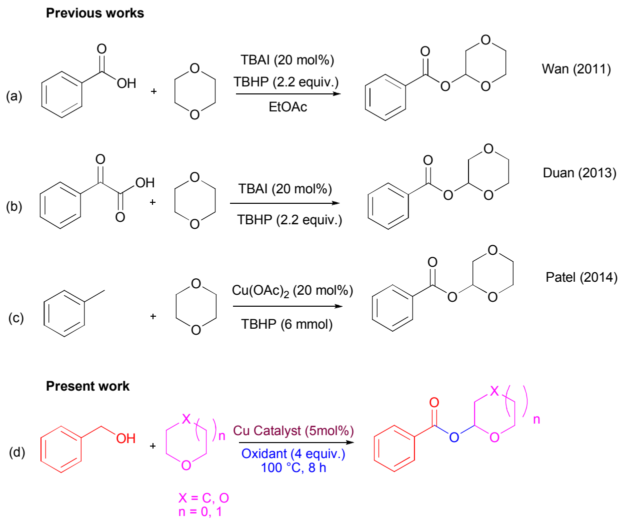
Acyloxylation of C(sp^3)-H bond adjacent to oxygen by adopting copper catalyzed dehydrogenative cross-coupling reaction between simple ethers and benzyl alcohols has been disclosed. The advantages of dehydrogenative cross-coupling reaction are adoption of unactivated ethers as a substrates and good tolerance 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 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 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 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 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 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 Bu$_4$NI-catalyzed C–O bond formation by adopting CDC reaction between carboxylic acids and unactivated simple ethers using *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 copper catalyzed synthesis of α–acyloxy ethers from alkylbenzenes and simple ethers (Scheme 1, c).

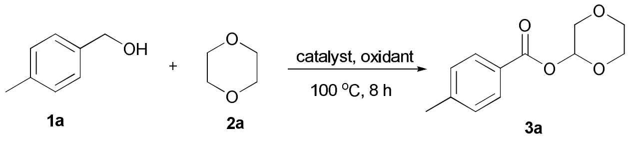


Scheme 1: CDC approach for C–O bond forming reaction *via* C–H bond functionalization

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 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 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 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)$_2$, CuCl$_2$, CuBr$_2$, CuCl, CuI and Cu(OAc)$_2$.H$_2$O. However, the expected product was not observed in all the cases (Table 1, entries 3-6) except Cu(OAc)$_2$.H$_2$O

Table 1 Optimization of reaction conditions.[a]

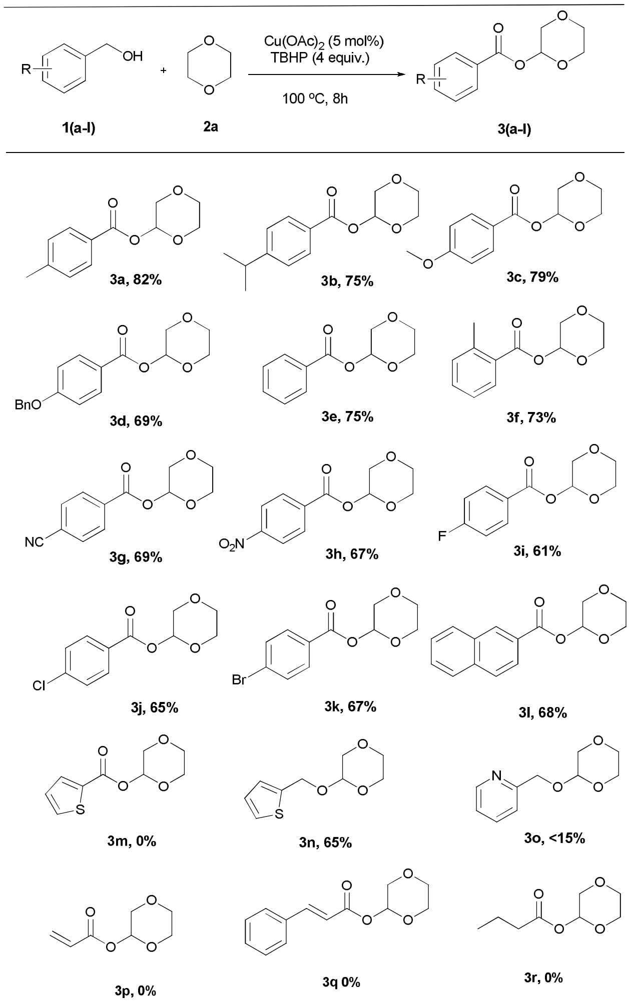


Entry	Catalyst (mol%)	Oxidant (equiv.)	T [°C]	Yields **3a** [%][c]
1	Cu(OAc)$_2$(10)	TBHP in H$_2$O (2)	80	15
2	Cu(acac)$_2$(10)	TBHP in H$_2$O (2)	80	–[d]
3	CuCl$_2$(10)	TBHP in H$_2$O (2)	80	–[d]
4	CuBr$_2$(10)	TBHP in H$_2$O (2)	80	–[d]
5	CuCl(10)	TBHP in H$_2$O (2)	80	–[d]
6	CuI(10)	TBHP in H$_2$O (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 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.



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.

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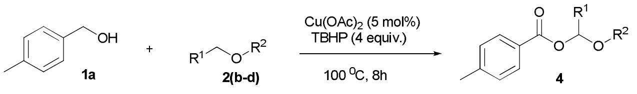
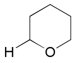
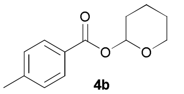
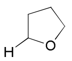
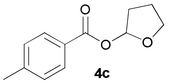
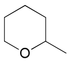
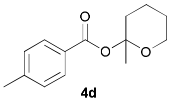
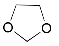
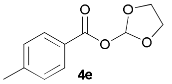
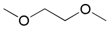
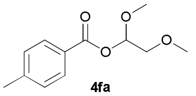
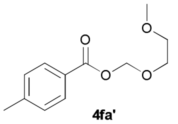
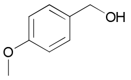
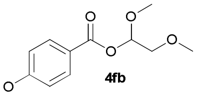
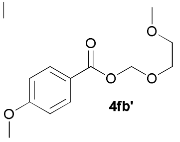
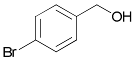
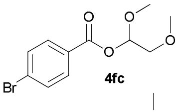
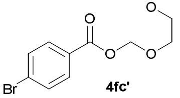
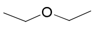
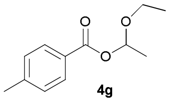
To evaluate the role of ethers we carried out the reactions with cyclic (**2b**-**2e**) and acyclic (**2f**, **2g**) (Table 2) ethers under standard reaction conditions. Cyclic ethers like THP (**2b**) and THF (**2c**) reacted smoothly with benzyl substituted alcohol to provide the corresponding products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

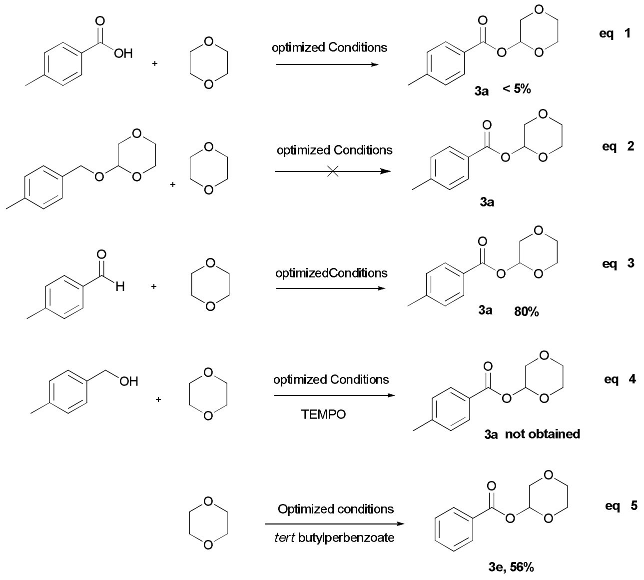
Table 2 Reaction of Benzyl alcohols with ethers [a]



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	 4fb	43%
			 4fb'	30%
7		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 °C, 8 h. [b]Yield of isolated product.

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 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 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 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 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 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 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 conditions afforded the coupling product **3e** in moderate yields (Scheme 3, equation 5).[6i] From this we can predict, the plausible

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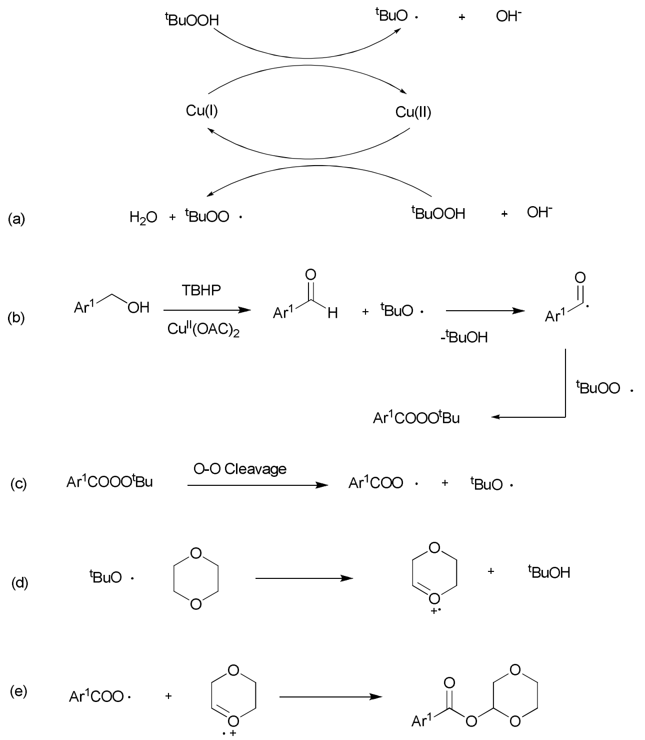

Scheme 4 Plausible pathway for the reaction

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(sp^3)–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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Notes and references

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† Electronic Supplementary Information (ESI) available: See DOI: 10.1039/b000000x/

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10) To our knowledge, the increased yield can be explained as follows. In presence of aqueous TBHP water may acts as a nucleophile and it attacks at oxonium ion which leads to lactol or lactone (e.g 1,4-dioxan-2-one). But in case of TBHP in decane, decane is not a nucleophile, so attack of only acyloxy radical/nucleophile to the oxonium ion and forms the coupling product. From this we can conclude that a reaction enhancement using water-free variant).

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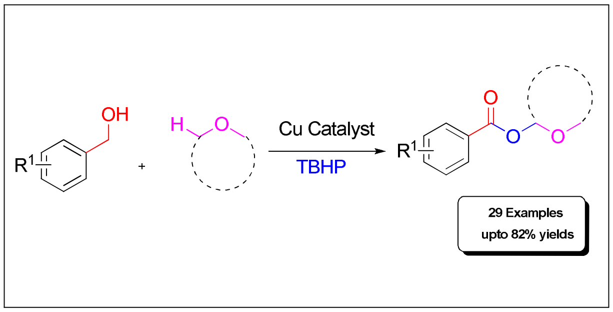
Graphical Abstract



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.