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Copper-catalyzed oxidative esterification of *ortho*-formyl phenols without affecting labile formyl group

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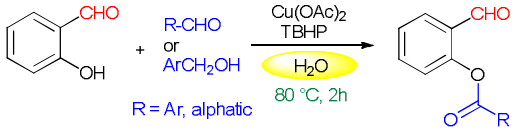
Abstract

A copper-catalyzed oxidative esterification of *ortho*-formyl phenols with aldehydes using TBHP as oxidant in water is developed. Besides aromatic and aliphatic aldehydes, benzylic alcohols are also suitable for this reaction. The sensitive formyl group remains intact under oxidative conditions. This method provides an alternative protocol for classical esterification reactions.



Key Words:
Copper-catalyzed, Esterification, Formyl, TBHP, Saliylaldehyde

Esters are not only prevalent structural motifs in natural products and pharmaceutical drugs, but are also used as protecting groups in synthesis.[1,2] As a result, the synthesis of esters has attracted considerable interest and a number of methods have been devised. Conventionally, ester groups were synthesized by the nucleophilic addition of an alcohol to activated carboxylic acid derivatives such as acid anhydrides or chlorides in the presence of a stoichiometric amount of bases. Alternatively, transition-metal-catalyzed coupling reactions using aryl halides, CO, and alcohols also offer an access to esters.[3] However，these reactions required base, air and moisture-sensitive reagants acyl halides, toxic CO gas, which limited functional group tolerance. Although great progress has been achieved in this field, there still remains significant challenges for synthesis of ester groups in both atom-economic and mild conditions.

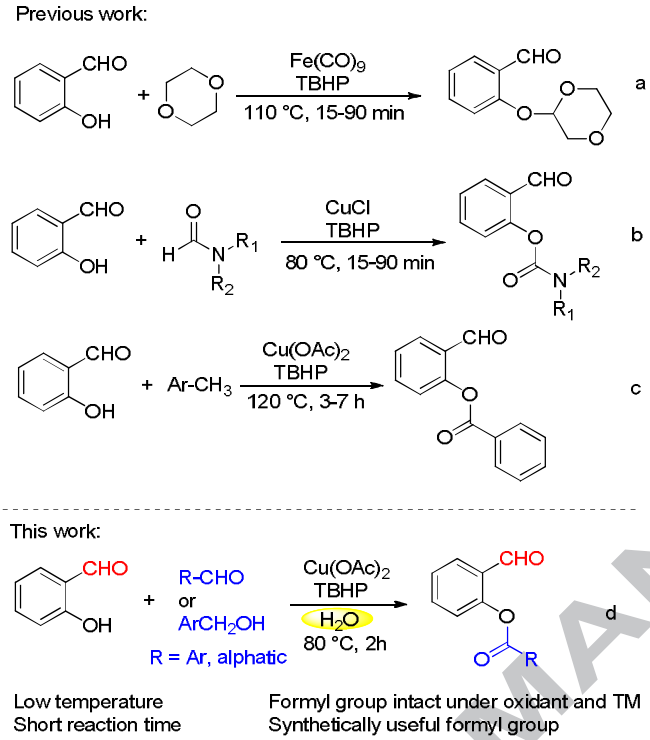
Direct C–H transformation has attracted continuous interest since early 1970s because it avoids prefunctionalization of starting materials and can maximize atom economy.[4] Among the many C–H bond activation protocols, cross-dehydrogenative coupling (CDC) has emerged as an attractive and useful method in formation of C–C, C–O, C–N, and C–S bond.[5, 6]

Recently, NHC ligands have been utilized for oxidative esterifications of phenol with aldehydes using Pd or Fe catalysts under base.[7] However, this approach was not suitable for *ortho*-substituted phenols.

Copper was found to be a cheap, and environmental friendly catalyst in many CDC reactions.[8] Recently, Cu-catalyzed directing-groups assisted CDC reaction under oxidative conditions have provided an atom-economic route for C-O bond formation of 2-carbonyl phenol and β-dicarbonyl compounds.[9]

Compared to *ortho*-keto phenol, the *ortho*-formyl phenol is considered to be sensitive to oxidants and transition metals, and is easily oxidized into salicylic acid under metal and oxidants.[10] Thus, the formation of C-O bond of *ortho*-formyl phenol under oxidative conditions while selectively keeping the formyl group intact is still a challenging task. Chang reported a Fe-catalyzed oxidative coupling reaction between salicylalhehydes and ether and a copper-catalyzed oxidative coupling of formamides with salicylaldehydes (Scheme1, a-b).[11a,11b] Recently, Patel reported an esterification reaction of *ortho*-formyl phenols with toluene derivatives without affecting the formyl group (Scheme 1, c).[11c] However, this reaction required high temperature and long reaction time, which may limit the functional tolerance. Furthermore, the use of TBHP decane solution increased cost (TBHP decane solution is relatively expensive than aq. TBHP). Thus, development of efficient approach for esterification of 2-formyl phenol, which preserves the formyl group under mild reaction conditions, is highly desirable. In view of green chemistry, water as an ideal reaction solvent with environmentally benign and nontoxic characters has been attracting considerable attention. Besides that, water has been proven to affect the selectivity of lots of organic reactions and to enhance the reaction rates. Herein, we reported Cu-catalyzed oxidative esterification of 2-formyl phenols with aldehydes using cheap aq. TBHP as oxidant in water (Scheme 1, d). Both aromatic and alphatic aldehydes undergo esterification smoothly. Benzylic alcohols,[12] which are environmentally friendly, low

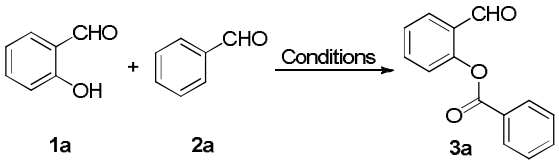
toxicities, stable, commercially available, and easy to handle compared to aldehydes, are also suitable for this reaction.



Scheme 1 Formyl-group assisted oxidative C-O bond formation reactions

We initially investigated the reaction between salicylaldehyde **1** with benzaldehyde **2** in the presence of 10 % mol $Cu(OAc)_2$ and 3 equiv of TBHP (*tert*-butyl hydroperoxide) in DMSO at 80 ℃ for 2h (Table1, entry 1). To our delight, the ester **3** was obtained in 59 % yield. Other copper catalysts, such as $CuCl_2{\cdot}2H_2O$, CuCl, CuBr, and CuI, failed to give any improvement (entries 2-5). TBHP as an oxidant was found to be superior over the other oxidants screened, such as DTBP, O_2, H_2O_2, and *m*CPBA (entries 6-9). When H_2O was selected as solvent, the yield increased to 65 % (entry 10). No significant increase in the yield of **3** was observed when extending or shorting reaction time (entries 11 and 12). Other solvents, such as PhCl, toluene, and DCE, were proved to be less efficient than H_2O (entries 13-15). Higher or lower temperatures seemed to be inappropriate for the reaction (entries 16 and 17). Furthermore, the reaction did not proceed without the use of Cu catalyst or TBHP (entries 18 and 19).

Table1. Optimization of reaction conditions.[a]



Entry	Catalyst	Oxidant (equiv.)	Solvent	Yield[b] (%)
1	$Cu(OAc)_2$	TBHP (3)	DMSO	59
2	$CuCl_2 \cdot 2H_2O$	TBHP (3)	DMSO	27
3	CuCl	TBHP (3)	DMSO	25
4	CuBr	TBHP (3)	DMSO	29
5	CuI	TBHP (3)	DMSO	24
6	$Cu(OAc)_2$	DTBP (3)	DMSO	trace
7	$Cu(OAc)_2$	O_2	DMSO	0
8	$Cu(OAc)_2$	H_2O_2 (3)	DMSO	trace
9	$Cu(OAc)_2$	*m*CPBA (3)	DMSO	0
10	**$Cu(OAc)_2$**	**TBHP** (3)	**H_2O**	**65**
11[c]	$Cu(OAc)_2$	TBHP (3)	H_2O	61
12[d]	$Cu(OAc)_2$	TBHP (3)	H_2O	58
13	$Cu(OAc)_2$	TBHP (3)	PhCl	62
14	$Cu(OAc)_2$	TBHP (3)	Toluene	16
15	$Cu(OAc)_2$	TBHP (3)	DCE	27
16[e]	$Cu(OAc)_2$	TBHP (3)	H_2O	36
17[f]	$Cu(OAc)_2$	TBHP (3)	H_2O	55
18		TBHP (3)	H_2O	0
19	$Cu(OAc)_2$		H_2O	0

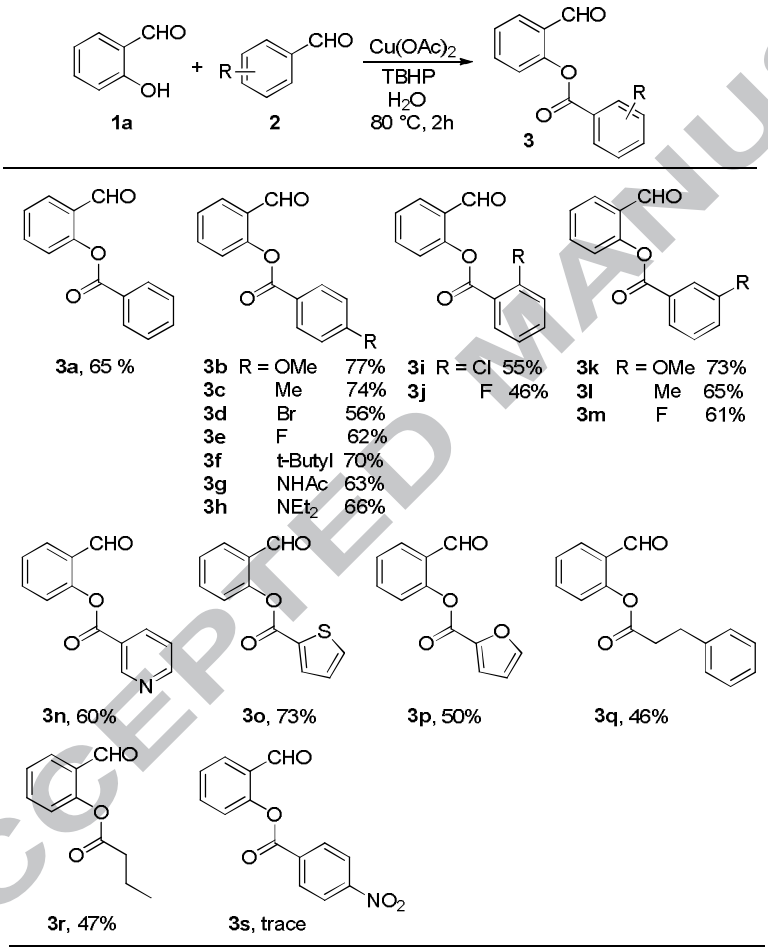
[a]Conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), catalyst (10 % mol), oxidant, solvent (2 ml), 80 ℃, 2h.
[b]Isolated yield.
[c]0.5 h.
[d]5 h.
[e]60 ℃.
[f]100 ℃.

With the optimized conditions in hand, we next explored the benzaldehyde scope of this oxidative esterification reaction. As showed in Table 2, benzaldehydes with electron-donating groups such as methoxy, methyl, *tert*-butyl, acetylamino, and diethylamino reacted with salicylaldehyde smoothly in good to moderate yield (**3b**, **3c**, **3f-3h**, **3k**, and **3l**). While weak electron-withdrawing groups (F, Cl, Br) substituted benzaldehydes gave the moderate yields (**3d**, **3e**, **3i**, **3j**, and **3m**). *Ortho*-, *meta*-, and *para*-substituted benzaldehydes could all proceed in this reaction. Slightly lower yields were obtained in the cases of *ortho*-substituted benzaldehyde in comparison to their *para* or *meta* analogues, possibly due to steric hindrance (**3i** and **3j**). Heteroaryl aldehydes, such as 3-pyridinecarboxaldehyde, 2-thiophenaldehyde, and 2-furanaldehyde, reacting with salicylaldehyde could also afforded the desired products in 60 %, 73 %, and 50% yields, respectively (**3n**-**3p**). Only trace of product was observed when salicylaldehyde reacted with benzaldehyde substituted with NO_2 group (**3s**). Besides aromatic aldehydes, aliphatic aldehydes could also react with salicylaldehyde under the optimized conditions, giving the desired products in

moderate yields (**3q** and **3r**).

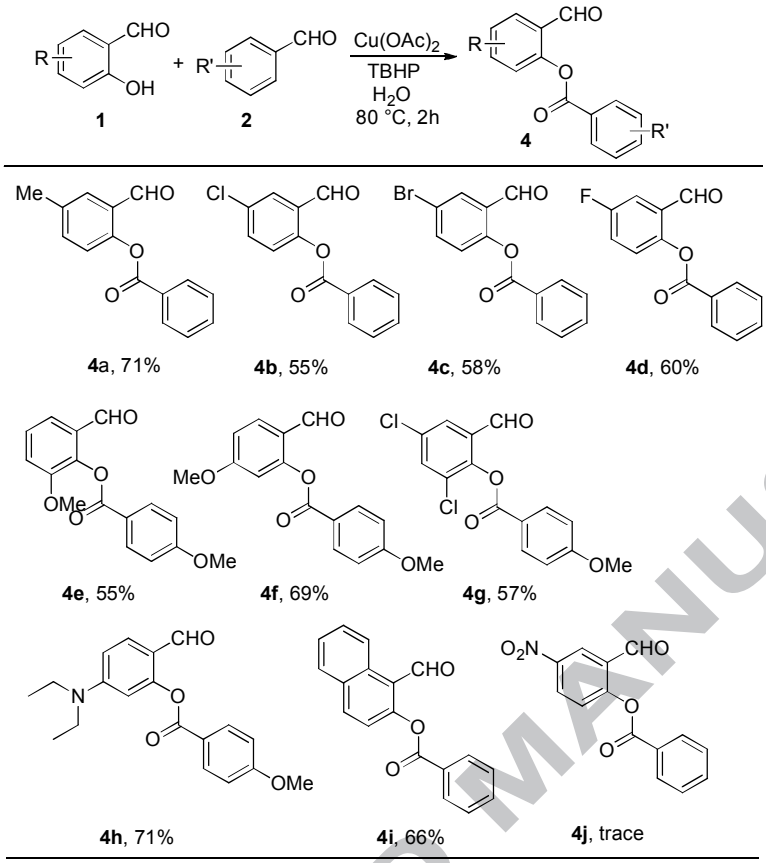
Next, a series of substituted salicylaldehydes were tried for this esterification reaction (Table 3). Both electron-rich (OCH_3, CH_3, and Et_2N) and electron-deficient (F, Cl, Br) salicylaldehydes could proceed smoothly and afford the corresponding acylated products in moderate to good yields (Table 3, **4a**-**4h**). The 3-substituted salicylaldehydes gave slightly poorer yields of the corresponding products possibly due to their steric hindrance (**4e** and **4g**). Furthermore, 2-hydroxy-1-naphthaldehyde provided the expected product in 66 % yield (**4i**). The strong electron-withdrawing group, such as NO_2, obviously restrained the reaction and afforded trace of the desired product under the standard reaction conditions (**4j**).

Table 2. Esterification of salicylaldehyde (**1**) with substituted aldehydes(**2**).[a,b]



[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol), $Cu(OAc)_2$ (10 % mol), TBHP (3 equiv), H_2O (2 ml), 80 °C, 2h.
[b]Isolated yield.

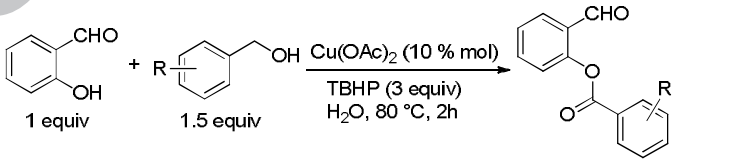
Table 3. Esterification of substituted sacylialdehydes (**1**) with aldehydes (**2**).[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), $Cu(OAc)_2$ (10 % mol), TBHP (3 equiv), H_2O (2 ml), 80 °C, 2h.
[b]Isolated yield.

Considering the stability and the availability of alcohols, we performed this esterification reaction between salicylaldehyde and benzilic alcohol under the standard conditions. To our delight, both electron-rich group (OMe) and electron-deficient groups (Cl, Br) proceeded well giving the esters in 54-72% yields (Scheme 2).

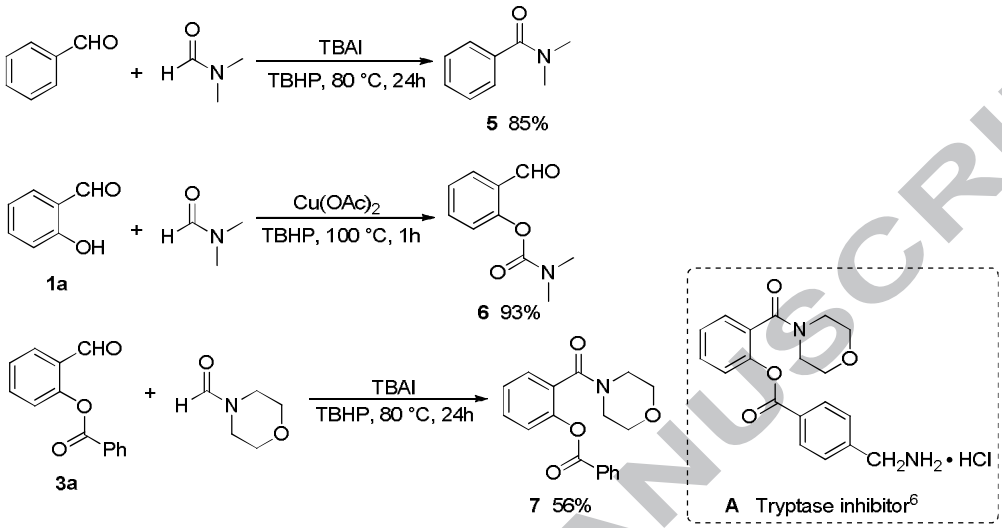
Scheme 2. Esterification of sacylialdehyde (**1**) with benzylic alcohols.



3a	R = H	63 %
3b	4-OMe	72 %
3d	4-Br	54 %
3i	2-Cl	58 %

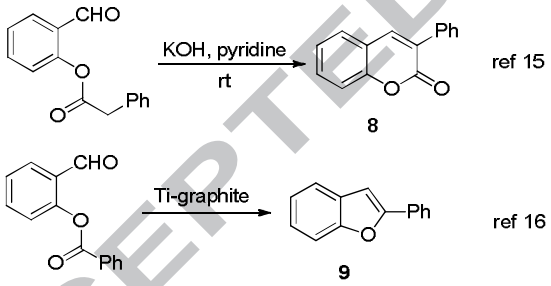
According to literature, formyl group transformed into amide under TBAI and aq.

TBHP using DMF as nitrogen source.[14] Benzaldehyde reacting with DMF under TBAI and TBHP, the amide **5** was obtained in good yield. When salicylaldehyde as substrate using $Cu(OAc)_2$ as catalyst and TBHP as oxidant, cabamate **6** was formed in 93% yield. **3a** reacting with *N*-formylmorpholine under TBAI and TBHP resulted in **7** in 56% yield, which has the similar structures with trypase inhibitor A (Scheme 3).[15]



Scheme 3. Benzaldehydes, salicylaldehyde and **3a** reacting with DMF or *N*-formylmorpholine.

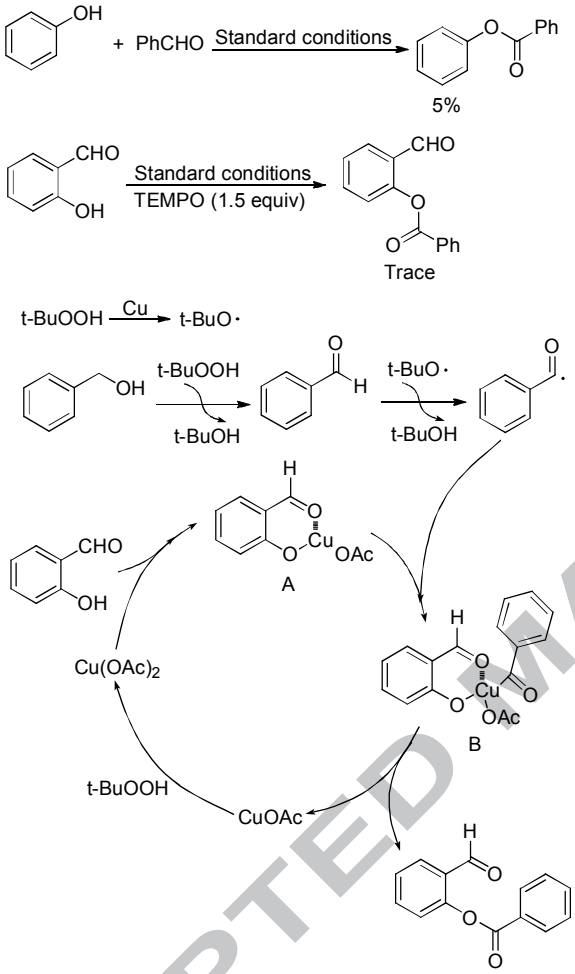
2-acyl benzaldehydes would be further transformed into different useful products, such as coumarin **8** and benzofuran **9** (Scheme 4).[15,16]



Scheme 4. Synthesis of coumarin and benzofuran from 2-acyl benzaldehydes.

On basis of previous literature results and our experiments, a plausible mechanism of this esterificaton reaction is proposed, as shown in Scheme 5. When the reaction underwent in the presence of radical scavenger TEMPO (1.5 equiv), only trace of product was formed, suggesting a possible radical pathway. TBHP generates *t*-BuO• in the presence of Copper, which abstracts an H atom from benzaldehyde (benzylic alcohol is oxidized to benzaldehyde by TBHP) to give the acyl radical.[17] Copper forms a coordinating complex **A** with formyl group. This hypothesis was supported by failure to obtain ester when simple phenol reacting with benzaldehyde under the standard condition, which indicated that directing group (formyl) is essential for the esterification reaction. The proposed complex, reacts with acyl radical to form the

complex **B**, which can undergo reductive elimination to afford the product and Cu(I) catalyst. Finally, Cu (I) is oxidized to Cu (II) by TBHP, which maintains the catalytic cycle.



Scheme 5. Proposed reaction mechanism

In summary, we have developed a copper-catalyzed oxidative esterification of *ortho*-formyl phenols with aldehydes using TBHP as oxidant. Both aromatic and aliphatic aldehydes proceed well giving the products in moderate to good yields. Benzylic alcohols are also suitable for this reaction. The labile formyl group remains intact under oxidative conditions, and can be further transformed into various useful products.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at

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Graphical abstract