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Copper-catalyzed methyl esterification of aromatic aldehydes and benzoic alcohols by TBHP as both oxidant and methyl source

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ABSTRACT

A copper-catalyzed synthesis of methyl esters from aromatic aldehydes in the presence of *tert*-butyl hydrogen peroxide (TBHP) was developed via a radical reaction mechanism. TBHP acts not only as an efficient oxidant, but also as a green methyl source in such transformation. Moreover, this method could also be efficiently extended to the methyl esterification of benzylic alcohols.

Classical methyl sources are mainly originated from methyl iodide (MeI), methyl sulfofluoridate ($MeSO_3F$), trifluoromethanesulfonate (MeOTf), dimethyl sulfate (Me_2SO_4), methyl carbonate (Me_2CO_3), diazomethane (CH_2N_2), and methyl organometallic reagents. Nevertheless, these reactive methylating agents more or less face some application limitations owing to their unfriendly properties (such as toxicity and causticity). Recently, the development of a green and efficient methyl source for specific molecular functionalization has received much attention. Augusto and coworkers reported Fe-catalyzed DNA methylation by TBHP as a methylation source.[1] Later on, Li et al. discovered a Pd-catalyzed direct methylation of aryl C–H bond using peroxides as both methyl reagent and oxidant.[2] More recently, Chen and co-workers described methylation of amides and carboxylic acids by using peroxides as the methylating reagents.[3] In addition, TBHP has been proved to be an efficient oxidant in the direct functionalization of aldehyde C–H bond to synthesize aryl ketones via an acyl radical intermediate,[4] but metal-catalyzed methyl esterification of aldehyde by dual TBHP has not been reported.

Methyl esterification is one of the most fundamental transformations in organic synthesis.[5] The common synthetic routes to methyl esters are the reactions of carboxylic acids (or their derivatives) with methanol in the presence of acid or base. Recently, Pd-catalyzed direct oxidative esterifications of aldehydes (or alcohols), with the necessary presence of silver salt or base additives, have been extensively studied and afforded facile alternatives for the direct synthesis of ester from more simple substrates.[6] Mechanistically, the oxidation of hemiacetal intermediate, in situ generated from the condensation of alcohol with aldehyde, is the key step for these conversions.[7] Herein, we wish to report a novel and non-precious metal-catalyzed methyl esterification procedure through direct oxidative functionalization of aldehydes and alcohols with peroxides as both the methyl source and the oxidant.

To achieve this goal, appropriate peroxides that could act as an efficient oxidant and provide methyl source were initially screened in the $CuBr_2$-catalyzed oxidative esterification of anisaldehyde (**1a**) in DMSO at 100 °C. As shown in Table 1, 16% HPLC yield of the methyl ester product, methyl 4-methoxybenzoate (**2a**), was obtained in the presence of TBHP (Table 1, entry 3), and no reaction or only trace amount of **2a** was observed when using *tert*-butyl peroxide (TBP) or *tert*-butyl peroxybenzoate[8] (TBPB) as the oxidant and the methyl feedstock (Table 1, entries 1 and 2), respectively. To our delight, by increasing the amount of TBHP, the yield of desired product could be raised to 53% (Table 1, entries 4 and 5). Subsequently, various copper catalysts were examined under the same reaction conditions (Table 1, entries 6–14). It should be mentioned that all the frequently-used copper sources were effective in generating the expected methyl 4-methoxybenzoate, but CuF_2 showed the best activity toward this direct esterification of **1a**, affording 69% isolated yield of **2a** (Table 1, entry 7). However, other representative metal oxidation catalysts, such as iron and silver as well as palladium, ruthenium, and rhodium catalysts, were found to be ineffective for this oxidative transformation (Table 1, entries

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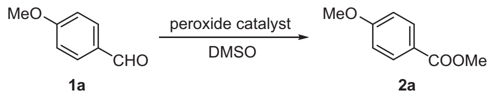
Table 1
Reaction optimization[a]



Entry	Peroxide (equiv)	Catalyst (5%)	*T* (°C)	Yield[b] (%)
1	TBP(2)	$CuBr_2$	100	0
2	TBPB(2)	$CuBr_2$	100	Trace
3	TBHP(2)	$CuBr_2$	100	16
4	TBHP(4)	$CuBr_2$	100	36
5	TBHP(6)	$CuBr_2$	100	62 (53)
6	TBHP(6)	$CuCl_2$	100	58
7	TBHP(6)	CuF_2	100	78 (69)
8	TBHP(6)	$Cu(OAc)_2$	100	54
9	TBHP(6)	$Cu(OTf)_2$	100	53
10	TBHP(6)	CuO	100	73 (63)
11	TBHP(6)	Cu_2O	100	76 (65)
12	TBHP(6)	CuBr	100	63
13	TBHP(6)	CuI	100	58
14	TBHP(6)	Cu	100	67
15	TBHP(6)	$FeCl_3$	100	0
16	TBHP(6)	$FeBr_2$	100	0
17	TBHP(6)	AgOAc	100	0
18	TBHP(6)	$PdCl_2$	100	0
19	TBHP(6)	$RuCl_3$	100	0
20	TBHP(6)	$RhCl_3$	100	0
21	TBHP(6)	CuF_2	80	37 (28)
22[c]	TBHP(6)	CuF_2	100	85 (75)
23[c,d]	TBHP(8)	CuF_2	120	94 (85)

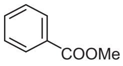
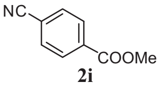
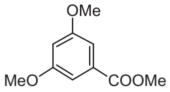
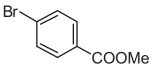
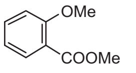
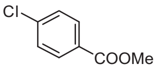
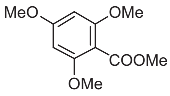
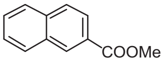
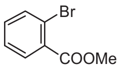
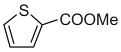
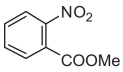
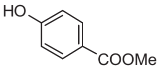
[a] Reaction conditions: 0.5 mmol scale in 3 mL of DMSO for 12 h.
[b] Yields determined by HPLC analysis, isolated yield in parentheses.
[c] Under argon in pressure tubes.
[d] $DMSO/H_2O = 1:1$; CuF_2 was increased to 10 mol %.

15–20). The present esterification was very sensitive to the reaction temperature, and a much lower yield (28%) was obtained when temperature was reduced from 100 °C to 80 °C (Table 1, entry 21). When the reaction was performed under argon in DMSO, the isolated yield could be further enhanced to 75% (Table 1, entry 22). Similar to peroxide, solvent also played an important role in controlling the catalytic reactivity. Only low yields (<5%) were obtained when DMSO was replaced by DMAc or DMF, and no target product was observed in other solvents such as CH_3CN, THF, DCE, and dioxane. In addition, we obtained trace amount of byproduct methylsulfinylmethyl 4-methoxybenzoate[9] which could be formed by the cross-coupling of PMPCOO$^{\cdot}$[10] and $CH_3SOCH_2^{\cdot}$.[11] Interestingly, the byproduct disappeared when using mixed solvent ($DMSO/H_2O = 1:1$). Yield of **2a** could be improved to 85% by increasing CuF_2 loading to 10 mol % and the reaction temperature to 120 °C.

With these satisfactory conditions in hand, we then turned to examine the scope of aldehydes (Table 2). As illustrated in Scheme 1, benzaldehyde itself (**2b**) and its derivatives (**2a**, **2c**–**2e**) with methoxyl groups at different positions on the phenyl ring all worked smoothly under CuF_2/TBHP catalytic system, giving 54–85% yields of the desired methyl benzoates. The aldehydes (**2f**–**2k**) substituted with electron-withdrawing groups (Cl, Br, CN, NO_2) at the *ortho*- or *para*-position could also be efficiently converted to the expected methyl esters in 65–75% yields. However, phthalaldehyde only afforded 44% yield of dimethyl phthalate (**2h**). Obviously, sterically hindered aldehydes (**2d**–**2h**) afforded relatively lower yields. Notably, the system also showed excellent activity toward the oxidative esterification of other representative aromatic aldehydes, such as 2-naphthaldehyde and thiophene-2-carbaldehyde, affording the desired ester products in 63% and 90% yields, respectively, (**2l**–**2m**). It was surprising that 4-hydroxybenzalde-

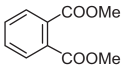
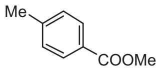
Table 2
Copper-catalyzed methyl ester of aldehyde[a]

$$\underset{\mathbf{1}}{\mathrm{RCHO}} \xrightarrow[\substack{\mathrm{DMSO:H_2O\ =\ 1:1} \\ 120\ ^{\circ}\mathrm{C}}]{\mathrm{TBHP,\ CuF_2}} \underset{\mathbf{2}}{\mathrm{RCOOMe}}$$

Entry	R	Product	Yield (%)	Entry	R	Product	Yield (%)
1	R = Ph (**1b**)	 **2b**	65	8	R = 4-NCC_6H_4 (**1i**)	 **2i**	70[c]
2	R = 3,5-$(MeO)_2C_6H_3$ (**1c**)	 **2c**	71	9	R = 4-BrC_6H_4 (**1j**)	 **2j**	75
3	R = 2-$MeOC_6H_4$ (**1d**)	 **2d**	67	10	R = 4-ClC_6H_4 (**1k**)	 **2k**	85
4	R = 2,4,6-$(MeO)_3C_6H_2$ (**1e**)	 **2e**	54	11	R = 2-naphthaleneyl (**1l**)	 **2l**	63
5	R = 2-BrC_6H_4 (**1f**)	 **2f**	65	12	R = 2-thiophenyl (**1m**)	 **2m**	90
6	R = 2-$NO_2C_6H_4$ (**1g**)	 **2g**	67	13	R = 4-HOC_6H_4 (**1n**)	 **2n**	44

(*continued on next page*)

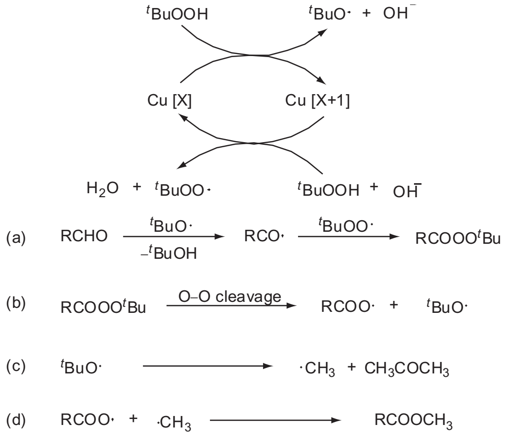
Table 2 (*continued*)

Entry	R	Product	Yield (%)	Entry	R	Product	Yield (%)
7	R = 2-(CHO)C_6H_4 (**1h**)	 **2h**	44[b]	14	R = 4-MeC_6H_4 (**1o**)	 **2o**	44

[a] A mixture of aldehyde (0.5 mmol), CuF_2 (0.05 mmol), and TBHP (4 mmol) in 3 mL solvent (DMSO/H_2O = 1:1) was stirred under argon in Schlenk tubes at 120 °C for 12 h. Isolated yields.

[b] TBHP (6 mmol) was added.

[c] Reaction was performed at 100 °C for 12 h.



Scheme 1. Plausible reaction mechanism.

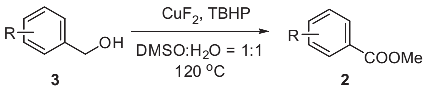
hyde could not only afford 44% yield of **2n**, but also gave a certain amount (5%) of **2a** produced by further methylation on the hydroxyl group of **2n**. Interestingly, 4-methylbenzaldehyde could not only generate the desired product **2o** in 44% yield, but also undergo further oxidation of the methyl group of **2o** to achieve 20% yield of dimethyl terephthalate (**2p**). Similarly, 1-bromo-2-methylbenzene could also afford 25% yield of the corresponding ester **2f**. These experimental results possibly suggested that such CuF_2/TBHP system could catalyze not only oxidative methyl esterification of the aldehyde C–H bond, but also the methyl C(sp^3)–H bond.[12]

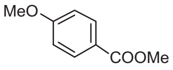
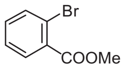
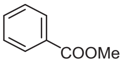
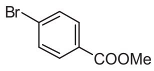
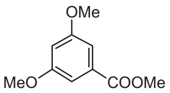
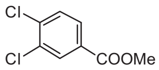
Comparing with aldehydes, oxidative methyl esterification of benzoic alcohols[13] represents a more sustainable alternative. To our delight, the direct methyl esterification of benzylic alcohols, substituted with electron-donating or -withdrawing groups at different positions, also proceeded efficiently under CuF_2/TBHP simple catalyst system, affording 60–85% yields of desirable esters (Table 3).

Deng and co-workers reported that DMSO could be a methyl source for the methylation reaction.[14a] Coincidently, our highest esterification yield was achieved in DMSO. In order to figure out whether the methyl came from TBHP or DMSO, we carried out the control reaction in DMSO-d_6 with TBHP (5.5 M in decane) instead of its aqueous solution (70 wt % TBHP). A 93% yield of **2a** was obtained with no deuterated ester detected, thus demonstrating the methyl group came from TBHP. Besides, 1-methoxy-2,2,6,6-tetramethylpiperidine was detected by NMR and GC–MS in the reaction of TEMPO with TBHP under the standard reaction conditions.[15] It was noteworthy that the expected methyl ester was not observed when anisaldehyde was replaced with the corresponding anisic acid, suggesting this transformation did not proceed via an acid intermediate.[3] This result ruled out forming methyl ester via copper carboxylate intermediate.[16] In addition, when 3 equiv of TEMPO was added into the reaction as radical scavenger, the yield sharply declined from 85% to 13%, possibly indicating that radical intermediates were involved in the catalytic cycle.

Based on above experimental results and the related reports,[17] a plausible catalytic cycle is proposed in Scheme 1. Initially, the low-valent copper species donated an electron to TBHP to generate a

Table 3
Copper-catalyzed methyl ester of benzoic alcohol[a]



Entry	R	Product	Yield (%)	Entry	R	Product	Yield (%)
1	R = 4-MeO (**3a**)	 **2a**	70	4	R = 2-Br (**3d**)	 **2f**	72
2	R = H (**3b**)	 **2b**	60	5	R = 4-Br (**3e**)	 **2j**	77
3	R = 3,5-(MeO)$_2$ (**3c**)	 **2c**	70	6	R = 3,4-Cl_2 (**3f**)	 **2q**	85

[a] A mixture of benzoic alcohol (0.5 mmol), CuF_2 (0.05 mmol), and TBHP (6 mmol) in 3 mL solvent (DMSO/H_2O = 1:1) was stirred under argon in Schlenk tubes at 120 °C for 12 h. All yields were isolated yields.

tert-butoxyl radical and a high-valent copper species. The latter absorbed an electron from another molecule of TBHP and switched back to the original low valent copper species along with the production of *tert*-butyl peroxy radical. *Tert*-butoxyl radical could abstract a hydrogen atom from aldehyde to generate the acyl radical,[18] which coupled with *tert*-butyl peroxy radical, affording a perester intermediate.[10] This intermediate underwent a homolytic cleavage to generate the acyloxyl radical and *tert*-butoxyl radical.[19] It is known that *tert*-butoxyl radical could produce the methyl radical and acetone,[1,3,20] these were successfully detected by NMR and GC–MS. Ultimately, the desired methyl ester could be formed by the cross-coupling of acyloxyl and methyl radicals.

In summary, we have developed a Cu-catalyzed methyl esterification of aldehydes and alcohols utilizing TBHP as the oxidant and methyl source. A radical reaction mechanism was proposed. Compared with previous esterifications of aldehydes and alcohols, this catalytic procedure represents a more sustainable alternative without the use of noble metal and base. Further explorations about the acyl radical and the methyl source are under investigation in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.11.040.

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