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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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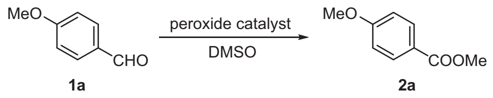
**Table 1**
Reaction optimization[a]



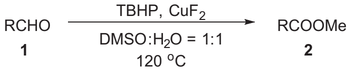
| Entry | Peroxide (equiv) | Catalyst (5%) | T (°C) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | TBP(2) | $CuBr_2$ | 100 | 0 |
| 2 | TBPB(2) | $CuBr_2$ | 100 | Trace |
| 3 | TBHP(2) | $CuBr_2$ | 100 | 16 |
| 4 | TBHP(4) | $CuBr_2$ | 100 | 36 |
| 5 | TBHP(6) | $CuBr_2$ | 100 | 62 (53) |
| 6 | TBHP(6) | $CuCl_2$ | 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) |

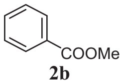
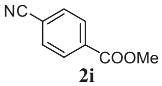
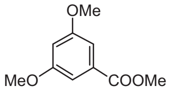
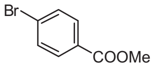
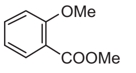
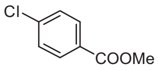
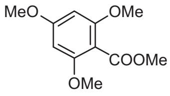
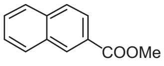
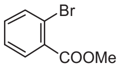
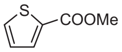
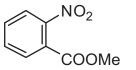
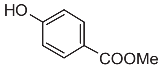
[a] Reaction conditions: 0.5 mmol scale in 3 mL of DMSO for 12 h.
[b] Yields determined by HPLC analysis, isolated yield in parentheses.
[c] Under argon in pressure tubes.
[d] $DMSO/H_2O = 1:1$; $CuF_2$ was increased to 10 mol %.

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·[10] and $CH_3SOCH_2$·.[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]



| 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*)