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Copper-catalyzed oxidative esterification of alcohols with aldehydes activated by Lewis acids

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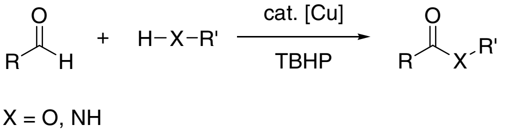
Abstract—An efficient oxidative esterification of aromatic and aliphatic aldehydes with simple alcohols was accomplished using catalytic amounts of $Cu(ClO_4)_2{\cdot}6H_2O$ and $InBr_3$ with *tert*-hydroperoxide as an oxidant.

C–H bonds are ubiquitous in nature and thus the ability to perform selective C–H bond functionalization has long attracted the attention of chemists.[1] Recently, we have described a variety of copper-catalyzed cross-dehydrogenative coupling (CDC) protocols in which the sp^3-hybridized C–H bond adjacent to a heteroatom can be functionalized with a variety of pronucleophiles in the presence of an oxidant.[2] Furthermore, a copper-catalyzed oxidative allylic alkylation of cyclic alkenes and activated methylene units was also demonstrated in the presence of *tert*-butyl hydroperoxide (TBHP) as the oxidant.[3]

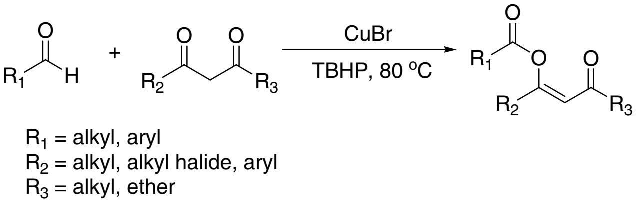
During our investigation into the CDC reaction, we discovered that the acyl C–H bond can be selectively functionalized with alcohols[4] and amines[5] to generate the corresponding esters and amides using copper salts and TBHP as an oxidant (Scheme 1).



Scheme 1. Copper-catalyzed oxidative esterification and amidation of aldehydes.

While the oxidative amidation of aldehydes can be accomplished rapidly under mild conditions, the analogous oxidative esterification of aldehydes required longer reaction time and higher temperature. Furthermore, the reaction performed poorly without the presence of a carbonyl directing group. Thus, unlike simple alcohols, the enol forms of 1,3-diketones and β-ketoesters proved to be excellent substrates for the stereoselective oxidative esterification of aldehydes (Scheme 2).

While a variety of procedures[6] exist for the direct oxidative esterification of aldehydes, these protocols are often hindered by the need for excess reagents and/or expensive catalyst. Furthermore, competing side reactions, such as the oxidation of the alcohol and aldehyde substrates, often complicate matters and limit the application of this functional group transformation. However, unlike most oxidative esterification protocols, the copper-catalyzed oxidative esterification with β-dicarbonyl compounds using TBHP as an oxidant do not suffer from these disadvantages. Thus, we became interested in utilizing the copper-catalyzed system to induce the oxidative esterification to occur with aldehydes and simple alcohols while avoiding the limitations faced by most oxidative esterification protocols.



Scheme 2. Copper-catalyzed stereoselective oxidative esterification of aldehydes with β-dicarbonyl compounds.

Keywords: Copper; Indium; C–H Transformation; Oxidative esterification.

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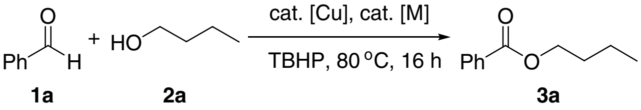
Table 1. Optimization of the oxidative esterification of benzaldehyde with 1-butanol[a]



Entry	[Cu]	[M]	Yield[b] (%)
1	CuBr	—	33
2	CuBr	$RhCl_3 \cdot H_2O$	49
3	CuBr	$Ga(OTf)_3$	64
4	CuBr	$InCl_3$	45
5	CuBr	$InBr_3$	62
6	CuCl	$InBr_3$	64
7	CuOTf[c]	$InBr_3$	56
8	$CuBr_2$	$InBr_3$	62
9	$Cu(OTf)_2$	$InBr_3$	67
10	$Cu(ClO_4)_2 \cdot 6H_2O$	$InBr_3$	78
11[d]	$Cu(ClO_4)_2 \cdot 6H_2O$	$InBr_3$	91

[a] Benzaldehyde (1.0 equiv), 1-butanol (1.5 equiv), TBHP (1.1 equiv, C = 5.5 M in decane), copper salt (5.0 mol %), and Lewis acid (5.0 mol %).

[b] Reported yields were based on benzaldehyde and determined by NMR using an internal standard.

[c] As a toluene complex.

[d] At 100 °C.

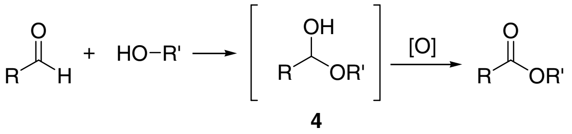
Under the hypothesis that the copper-catalyzed oxidative esterification occurs through a hemiacetal intermediate, we rationalized that a Lewis acid may aid its development and ultimately lead to the formation of the desired ester. Thus, we began our study with the examination of a variety of high-valent metal salts as co-catalyst for the oxidative esterification of benzaldehyde **1a** with 1-butanol **2a** (Table 1).

In the presence of Lewis acids, the formation of the desired ester **3a** increased (entries 2–5). Re-investigation of the copper source demonstrated that both copper(I) and copper(II) salts were viable catalysts, although $Cu(ClO_4)_2 \cdot 6H_2O$ proved to be the best choice (entries 6–10).[7] Finally, increasing the reaction temperature (entry 11) furnished the desired ester **3a** in high yield. Attempts at improving the yield with the introduction of a solvent (toluene, acetonitrile, water, etc.) or a different oxidant (O_2, H_2O_2, cumene hydroperoxide, *tert*-butyl peroxybenzoate, etc.) failed.

With the optimized reaction conditions in hand, we examined the scope of the copper/indium catalyst system for the oxidative esterification of aldehydes with simple alcohols (Table 2).[8] In general, the copper/indium catalyzed oxidative esterification occurs smoothly to provide the desired ester in good yields. Sterically hindered alcohols diminish the effectiveness of the reaction (entries 2–4). The oxidative esterification reaction was amenable to both electron-rich and electron-poor aromatic aldehydes (entries 6–9). More gratifying was the compatibility of the reaction to proceed successfully with primary and secondary aliphatic aldehydes as substrates (entries 10–11). Unfortunately, due to the oxidative nature of the reaction conditions, substrates containing functional groups that readily oxidizes, such as allyl alcohols and sulfides were shown to be poor substrates for the oxidative esterification reaction.

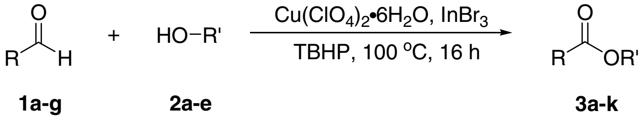
A tentative mechanism for the oxidative esterification of aldehydes with simple alcohols is proposed in Scheme 3. The oxidative esterification reaction may precede through the initial formation of a hemiacetal intermediate **4**, followed by oxidation of **4** by TBHP to generate the corresponding ester.[9]

In conclusion, we have developed an oxidative esterification reaction between aldehydes and alcohols catalyzed



Scheme 3. Tentative mechanism for the oxidative esterification of aldehydes with alcohols.

Table 2. Oxidative esterification of aldehydes with simple alcohols[a]



Entry	Aldehyde	R	Alcohol	R′	Product	Yield[b] (%)
1	**1a**	Ph	**2a**	*n*-Bu	**3a**	91
2	**1a**	Ph	**2b**	Me	**3b**	83
3	**1a**	Ph	**2c**	Et	**3c**	89
4	**1a**	Ph	**2d**	2-Propyl	**3d**	57
5	**1a**	Ph	**2e**	^{t}Bu	**3e**	Trace
6	**1b**	4-Me–C_6H_4	**2a**	*n*-Bu	**3f**	87
7	**1c**	4-MeO–C_6H_4	**2a**	*n*-Bu	**3g**	65
8	**1d**	4-Cl–C_6H_4	**2a**	*n*-Bu	**3h**	81
9	**1e**	4-CN–C_6H_4	**2a**	*n*-Bu	**3i**	42
10	**1f**	*n*-Pentyl	**2a**	*n*-Bu	**3j**	91
11	**1g**	Cyclohexyl	**2a**	*n*-Bu	**3k**	85

[a] Aldehyde (1.0 equiv), alcohol (1.5 equiv), TBHP (1.1 equiv, C = 5.5 M in decane), $Cu(ClO_4)_2 \cdot 6H_2O$ (5.0 mol %), and $InBr_3$ (5.0 mol %).

[b] Isolated yields were based on the aldehyde.

by a combination of $Cu(ClO_4)_2{\cdot}6H_2O$ and $InBr_3$ using TBHP as an oxidant. Both aliphatic and aromatic aldehydes were compatible to the reaction conditions and large excess of the alcohol was not required to obtain the desired ester. Further investigation into the scope and synthetic application are in progress and will be reported in due course.

Acknowledgments

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8. *General procedure for oxidative esterification of aldehydes with alcohols*: Under an atmosphere of nitrogen, TBHP (0.99 mmol, 1.1 equiv) was added to a mixture of $Cu(ClO_4)_2{\cdot}6H_2O$ (0.046 mmol, 5.0 mol %), $InBr_3$ (0.046 mmol, 5.0 mol %), aldehyde **1a**–**g** (0.93 mmol, 1.0 equiv), and alcohol **2a**–**e** (1.42 mmol, 1.5 equiv) at room temperature. The reaction vessel was capped and allowed to stir magnetically for 16 h at 100 °C.[10] The crude reaction mixture was purified by column chromatography (EtOAc–hexanes mixtures) to provide the esters **3a**–**k**.
9. The oxidation of the hemiacetal intermediate **4** likely occurs through a radical mechanism since radical scavenger, 2,6-di-*tert*-butyl-4-methyl phenol (BHT) inhibits the reaction. Radical based mechanisms have been proposed for the oxidation of alcohols to aldehydes by galactose oxidases. For recent mechanstic studies, see: (a) Himo, F.; Eriksson, L. A.; Maseas, F.; Siegbahn, P. E. M. *J. Am. Chem. Soc.* **2000**, *122*, 8031; (b) Whittaker, M. M.; Ballou, D. P.; Whittaker, J. W. *Biochemistry* **1998**, *37*, 8426; (c) Wachter, R. M.; Montague-Smith, M. P.; Branchaud, B. P. *J. Am. Chem. Soc.* **1997**, *119*, 7743.
10. While no explosions were experienced during the synthesis of the esters reported in this letter, great care should always be exercised when handling peroxides in the presence of metal salts and high temperatures.