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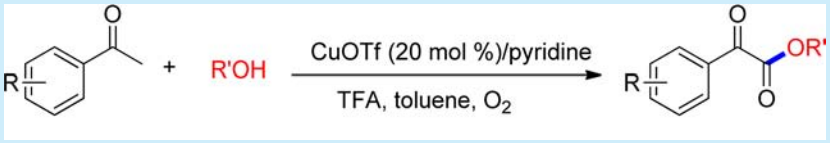
Cu-Catalyzed Aerobic Oxidative Esterification of Acetophenones with Alcohols to α-Ketoesters

Xuezhao Xu,[†] Wen Ding,[†] Yuanguang Lin,[‡] and Qiuling Song*[,†]

[†]Institute of Next Generation Matter Transformation, College of Chemical Engineering, and [‡]College of Materials Science & Engineering, at Huaqiao University, 668 Jimei Boulevard, Xiamen, Fujian 361021, P. R. China

Supporting Information



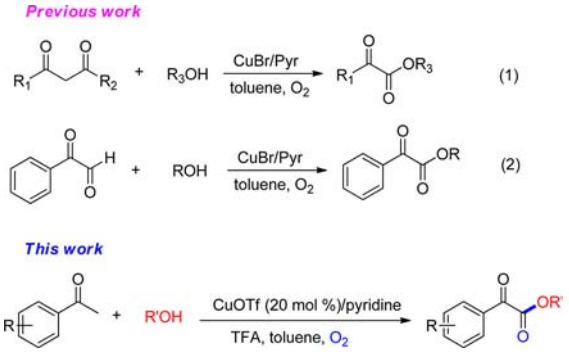
ABSTRACT: Copper-catalyzed aerobic oxidative esterification of acetophenones with alcohols using molecular oxygen has been developed to form a broad range of α-ketoesters in good yields. In addition to reporting scope and limitations of our new method, mechanism studies are reported that reveal that the carbonyl oxygen in the ester mainly originated from dioxygen.

The development of transition-metal-catalyzed aerobic oxidative C−C, C−O, C−N, and carbon−heteroatom bond formation continues to be widely pursued in modern synthetic chemistry in order to achieve environmentally benign transformations. Among them, the copper/O_2 system has attracted the most attention because copper is a cheap and low toxic transition metal and dioxygen is abundant, low cost, and sustainable. By eliminating the waste inherent in functional group manipulation, catalytic aerobic C−H bond functionalization reactions are emerging as green, efficient, and economical processes. Because of their low cost and ready availability, aryl methyl ketones or their derivatives are widely used in these transformations.

For example, Ji et al. reported one elegant method for the synthesis of α-ketoamides from aryl methyl ketones and secondary amines under copper-catalyzed aerobic oxidative condition.[1] Recently, we developed an efficient and chemoselective method for construction of 2-acylbenzothiazoles from aryl methyl ketones and benzothiazoles.[2] We also found that α-ketoamides were readily synthesized from aryl methyl ketones and DMF under copper-catalyzed oxidative reaction conditions.[3] Wu and co-workers developed various I_2-mediated methods which functionalized the sp^3 C−H bond in aryl methyl ketones.[4] Despite the advances in this field, there has been no report on C(sp^3)−H bond functionalization of aryl methyl ketones with alcohols with dioxygen as oxidant.

Based on our own research, we hypothesized that α-ketoesters should be formed when aryl methyl ketones were treated with alcohols under aerobic oxidative conditions. α-Ketoesters are important skeletons in bioactive compounds[5−7] and valuable precursors in synthetic organic chemistry.[8,9] Consequently, they have elicited many efforts[10−14] to streamline their synthesis. In addition to the traditional methods, very recently, two transition-metal-catalyzed aerobic oxidative methods have been reported by Jiao and co-workers to construct α-ketoesters from 1,3-dione compounds or α-carbonyl aldehydes with alcohols (Scheme 1).[15,16]

Scheme 1. Copper-Catalyzed Aerobic Oxidative α-Ketoester Formation



Although great progress has been achieved, there are still some drawbacks for the existing methods, such as low atom efficiency, expensive starting materials, or solvent. These weaknesses underscore the need to develop an efficient method for construction of α-ketoesters that uses cheap and readily available starting materials and reagents. To address these limitations, herein we report a copper-catalyzed aerobic oxidative esterification between aryl methyl ketones and alcohols to form a broad range of α-ketoesters and esters using molecular oxygen[17] as the terminal oxidant.

To probe the feasibility of the reaction between aryl methyl ketones and alcohol, acetophenone (**1a**) and *n*-butanol (**2a**) were selected as substrates in model reactions. When these were treated with 10 mol % of CuBr and 0.5 equiv of pyridine

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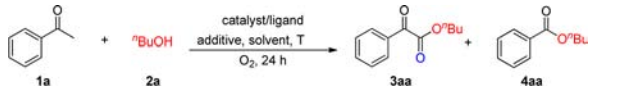
at 120 °C in 1 mL of toluene under O_2 in a sealed tube, we were pleased to find that α-ketoester **3aa** was formed in 20% isolated yield with ester **4aa** in 70% yield (Table 1, entry 1).

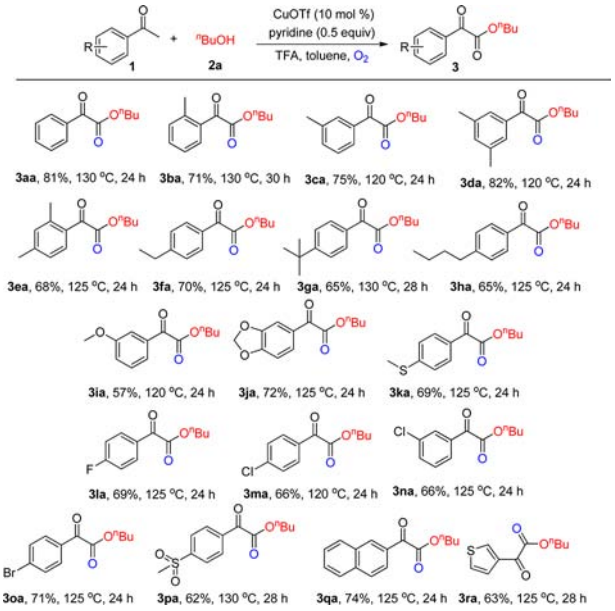
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst (mol %)	ligand (equiv)	additive (equiv)	solvent (mL)	temp (°C)	yield of **3aa** (%)[b]	yield of **4aa** (%)[b]
1	CuBr (10)	pyridine (0.5)		toluene (1)	120	20	70
2	$Cu(OAc)_2$ (10)	pyridine (0.5)		toluene (1)	120	trace	-
3	$Cu(TFA)_2$ (10)	pyridine (0.5)		toluene (1)	120	17	35
4	$CuCl_2$ (10)	pyridine (0.5)		toluene (1)	120	13	24
5	Cu_2O (10)	pyridine (0.5)		toluene (1)	120	15	12
6	CuOTf (10)	pyridine (0.5)		toluene (1)	120	39	9
7	CuOTf (10)	pyridine (0.5)		toluene (1)	130	29	9
8	CuOTf (10)	pyridine (0.5)		toluene (1)	100	53	3
9	CuOTf (10)	pyridine (0.5)		toluene (1)	80	23	trace
10	CuOTf (10)	3-Mepyridine (0.5)		toluene (1)	100	29	trace
11	CuOTf (10)	thiazole (0.5)		toluene (1)	100	52	4
12[c]	CuOTf (10)	pyridine (0.5)		toluene (1)	100	trace	
13	CuOTf (10)	pyridine (0.5)		THF (1)	100	trace	
14	CuOTf (10)	pyridine (0.5)		acetonitrile (1)	100	trace	
15	CuOTf (10)	pyridine (0.5)	TFA (0.5)	toluene (1)	100	83	4
16	CuOTf (10)	pyridine (0.5)	H_2SO_4 (0.5)	toluene (1)	100	40	3
17	CuOTf (20)	pyridine (0.5)	TFA (0.5)	toluene (1)	100	80	7
18	CuOTf (10)	pyridine (1.0)	TFA (0.5)	toluene (1)	100	66	4
19	CuOTf (20)	pyridine (0.5)	TFA (1.0)	toluene (1)	100	54	3
20	**CuOTf (10)**	**pyridine (0.5)**	**TFA (0.5)**	**toluene (1)**	**130**	**86 (81)**	**trace**
21	**CuBr (10)**	**pyridine (1.0)**		**toluene (1)**	**130**	**12**	**86 (80)**

[a]Conditions: **1a** (0.5 mmol), **2a** (1.5 mmol), catalyst, solvent (1 mL), additive, *T* (°C), under O_2 in a sealed tube. [b]GC yield, isolated yield listed in the paretheses. [c]Under N_2.

Scheme 2. Substrate Scope for the Formation of α-Ketoesters from Aryl Methyl Ketones 1 and *n*BuOH (2a)[a,b]



[a]Conditions: acetophenone **1** (0.5 mmol), alcohol **2** (1.5 mmol), CuOTf (10 mol %), pyridine (0.25 mmol), TFA (0.25 mmol) in O_2 in a sealed tube, corresponding temperature, 24 h. [b]Isolated yield based on **1**.

The formation of ester **4aa** could be maximized to 86% by increasing the pyridine amount (Table 1, entry 21). During preparation of this manuscript, Jiao and co-workers reported esterification of aryl ketones with alcohols leading to esters **4**.[18] Because of their report, we chose to focus on the formation of α-ketoester **3aa**. Further catalyst screening indicated that CuOTf is the best one among CuBr, $Cu(OAc)_2$, $Cu(TFA)_2$, $CuCl_2$, and Cu_2O (Table 1, entries 1−6). When temperature was increased to 130 °C, the yield was dropped to 29%, yet when the temperature was decreased to 100 °C the yield of desired product **3aa** increased to 53%. Further reduction of the reaction temperature, however, attenuated the formation of **3aa** (Table 1, entries 7−9). The identity of the ligand also affected the yield of our reaction: 3-methylpyridine and thiazole led to 9% and 52% yield at 100 °C correspondingly (Table 1, entries 10 and 11). Solvent screening indicated that toluene is the superior choice to dioxane, MeCN, THF, DMSO, and DMF (Table 1, entries 8, 13, and 14). If the reaction was conducted under N_2 atmosphere, only a trace amount product was detected (Table 1, entry 12). Additives were also screened, and the addition of TFA improved the yield to 83% (Table 1, entries 15−17). In contrast to our previous results, increasing the temperature to 130 °C slightly increased the yield of the desired product to 86% yield, a significantly higher yield than in the absence of TFA (Table 1, entry 20 vs entry 7).

The ketone scope for the formation of α-ketoester **3** was investigated using the optimized conditions (Scheme 2). A variety of acetophenones (**1**) worked well with *n*-BuOH (**2a**) to afford α-ketoesters **3** in good yields. Both electron-donating groups, like methyl, ethyl, *t*-Bu, *n*-Bu, methoxy, and methylthiol, and electron-withdrawing groups, such as halo and methylsulfonyl, were tolerated (Scheme 2, **3ba**−**pa**). In addition to monosubstituted aryl methyl ketones, bis-substituted aryl methyl ketones (**3da**, **3ea**, and **3ja**) were also well-behaved in this esterification reaction. Other aromatic rings, such as 2-naphthyl and 3-thiophene methyl ketone, were compatible in this reaction (**3qa** and **3ra**).

The scope of alcohol for this transformation was further explored by changing the identity of the alcohol reagent. As shown in Scheme 3, a variety of phenylmethanols and 2-phenylethanols could be used in our transformation regardless of their substitution pattern or electronic nature (Scheme 3, **3ab**−**ak**). Significantly, heteroaromatic ethanol, such as 2-thiophene ethanol, was also tolerated under the standard conditions to afford the desired product (Scheme 3, **3al**). Both primary and secondary aliphatic alcohols, which are susceptible to oxidative conditions, could be used to generate the α-ketoester in good yields (Scheme 3, **3aa**, **3am**, and **3an**). To demonstrate the potential use of our method in late-stage target-oriented applications, chloresterol was examined as a substrate. To our delight, α-ketoester **3an** was formed in good yield.

To gain insight into the mechanism of α-ketoester formation, several control experiments were performed (Scheme 4). We found that the reaction was inhibited if TEMPO and BHT were added to suggest that the oxidation proceeds through a radical pathway (Scheme 4, eq 1). The reactions of 2-oxo-2-phenylacetaldehyde monohydrate (**5**), 2-hydroxy-1-phenyl-ethanonebenzoic acid (**6**), and 2-oxo-2-phenylacetic acid (**7**) with *n*-BuOH under standard conditions were also investigated, and the desired products were afforded in 95%, 70%, and 61% yields respectively (Scheme 4, eqs 2−4). These results demonstrate that compounds **5**−**7** might be the intermediates in the reaction process.

In order to determine the origin of the oxygen in the new carbonyl group in the desired product, the reaction was performed using $^{18}O_2$. Analysis of the reaction mixture using GC−MS revealed that only $^{16}O^{18}O$-**3aa** was obtained

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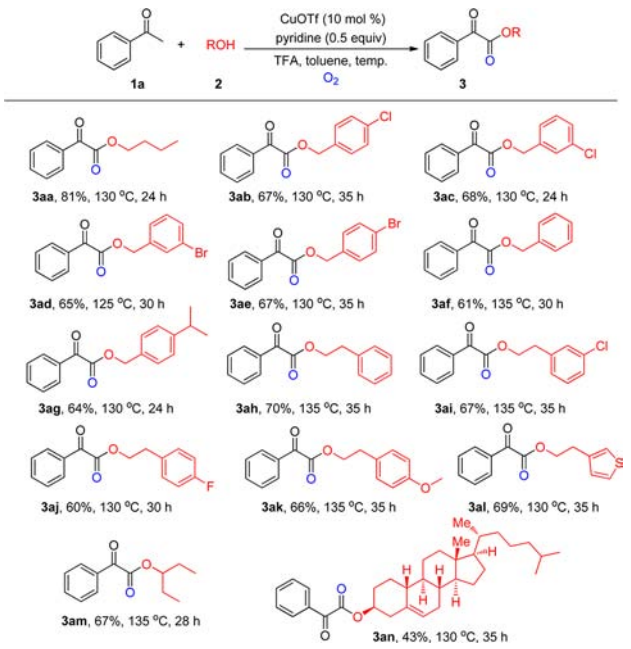
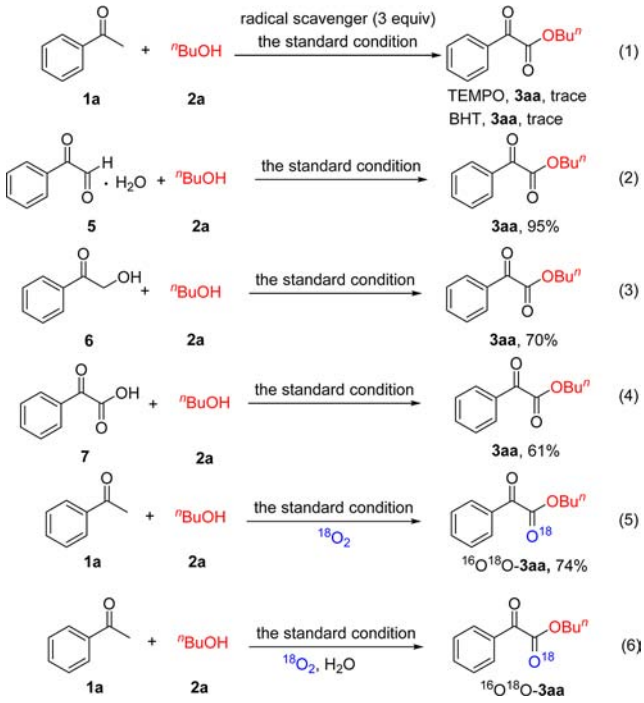
Scheme 3. Substrate Scope for the formation of α-Ketoesters from of Acetophenone (1a) and Alcohols 2[a,b]



[a]Conditions: acetophenone (**1a**) (0.5 mmol), alcohol **2** (1.5 mmol), CuOTf (10 mol %), pyridine (0.25 mmol), TFA (0.25 mmol) in O_2 in a sealed tube, corresponding temperature. [b]Isolated yield based on **1a**.

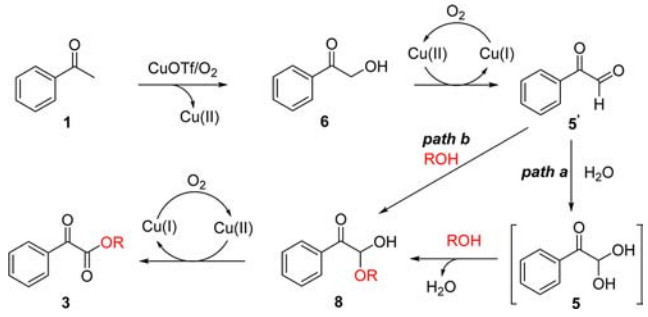
Scheme 4. Control Experiments under Standard Conditions



(Supporting Information, Scheme S1), yet the m/z 107 peak suggested that part of the carbonyl group which is adjacent to benzene ring has been labeled. Upon addition of 3 equiv of H_2O under $^{18}O_2$, no $^{16}O^{16}O$-**3aa** was detected, and all of the product contained ^{18}O (Scheme 4, eqs 5 and 6). Similarly, the m/z 107 peak existed. If the oxygen originated from water, the unlabeled product $^{16}O^{16}O$-**3aa** should be the major one under the $^{18}O_2/H_2O$ (3 equiv) system. From these two isotope-labeling experiments, it appears likely that the oxygen in the new carbonyl group of the desired product was mainly from dioxygen.

Based on the previous literature reports[15,16] and the above results, we propose that our Cu-catalyzed aerobic reaction proceeds through the mechanism in Scheme 5. First,

Scheme 5. Proposed Mechanism



acetophenone is oxidized into compound **6**, which was further oxidized into α-ketoaldehyde **5′**. Then two possible pathways, which could lead to the desired product, are possible: in path a, α-ketoaldehyde **5′** reacts with water to form monohydrate **5**, and then reaction with alcohol **2** produces hemiacetal **8**. Alternatively when the concentration of alcohol is significantly greater than water, α-ketoaldehyde **5′** directly produces hemiacetal **8**, which is oxidized to produce α-ketoester **3** (path b).

In conclusion, a Cu-catalyzed aerobic oxidative esterification of acetophenone with various alcohols has been developed using dioxygen as the sole terminal oxidant. α-Ketoesters could be obtained in good yields with a broad range of substrate scope. Further investigations on reaction scope, synthetic application, and the mechanism of this reaction are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details and copies of ^1H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: qsong@hqu.edu.cn.

Notes

The authors declare no competing financial interest.

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