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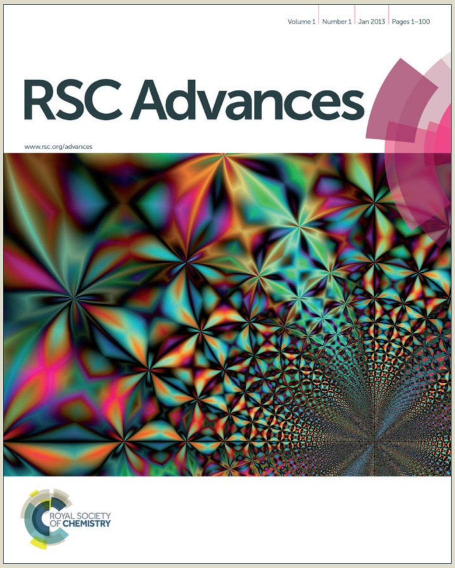

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Cu-Catalyzed Aerobic Oxygenation of 2-Phenoxyacetophenones to Alkyloxy Acetophenones

Cite this: DOI: 10.1039/x0xx00000x

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Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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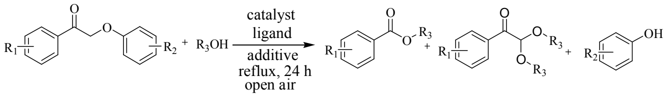
Cu-catalyzed aerobic oxygenation of 2-phenoxyacetophenones in the presence of alcohols was reported, and corresponding alkyl benzoates, alkyloxy acetophenones and phenols were produced in high yields.

Lignin that is the dominant aromatic biopolymer in nature can be considered as natural aromatic resource, and the production of aromatics from lignin-derived compounds has been paid much attention in recent years.[1,2] The cleavage of C-O/C-C bond is the key to produce aromatics from lignin platform compounds, which is usually achieved via hydrolysis, thermal cracking, reduction and oxidation.[3] Oxygen, hydrogen peroxide or ozone as oxidants is one of the most efficient way. Particularly, molecular oxygen is considered as an ideal oxidant in view of green and sustainable chemistry, owing to its abundant, natural and environmental friendly character. Transition-metal catalysts including ruthenium complex[4] and vanadium complex[5] have been applied in the production of aromatics from lignin-derived compounds. For example, Loh and coworkers[6] reported a method for the chemical conversion of β-O-4 linkage models through Cu-catalyzed aerobic amide bond formation with secondary amines, and a series of value-added aromatic nitrogen-containing compounds were produced.

Alkyl benzoates and alkyloxy acetophenones are important aromatics with many usages,[7] generally produced from petroleum-based feedstocks. Producing alkyloxy acetophenones suffer from complicated chemical processes and high costs.[8] The production from lignin platform compounds can provide alternative route for the synthesis of these chemicals. However, it has not been reported yet.

2-Phenoxyacetophenones is a kind of lignin platform compounds, which have been used as lignin model compounds to produce various aromatics.[9] In this work, we used 2-phenoxyacetophenones as feedstocks for the synthesis of alkyloxy acetophenones via a novel approach, as illustrated in Scheme 1. It was found that $CuCl_2$ combined with pyridine as a ligand and $BF_3{\cdot}Et_2O$ as an additive was effective for the aerobic oxidation of 2-phenoxyacetophenones in the presence of alcohols (e.g., methanol and ethanol) by refluxing the reaction solution under open air conditions, producing alkyl benzoate and alkyloxy acetophenones accompanied with phenols in high yields.



Scheme 1 Aerobic oxygenation of 2-phenoxyacetophenones.

2-Phenoxyacetophenone (**1a**) as a model substrate was first examined to react with methanol under different conditions, and the results are listed in Table 1. It was indicated that **1a** could not react with methanol in the absence/presence of O_2 without any catalyst and ligand/additive. To our delight, as **1a** (0.5 mmol) was treated in methanol (**2a**, 1mL) catalyzed by $CuCl_2$ (0.15 equiv.) with pyridine (0.5 equiv.) as a ligand and $BF_3{\cdot}Et_2O$ (1 equiv.) as an additive via refluxing the reaction solution under air atmosphere, the reaction proceeded well, affording methyl benzoate (**3a**), 2,2-dimethoxyacetophenone (**4a**) and phenol (**5a**) in 32.8%, 56.6% and 90.5% yields, respectively (Table 1, entry 2). No reaction took place using argon instead of air under the same other conditions (Table 1, entry 3), suggesting that the oxidative cleavage of C-C/C-O bond occurred in the reaction of **1a** with methanol under air atmosphere. Other copper salts including CuBr, CuCl, CuO, Cu_2O, CuI, CuOAc, $CuCl_2{\cdot}2H_2O$ instead of $CuCl_2$ were examined for this reaction (Table 1 and Table S1). It indicated that $CuCl_2$ displayed the

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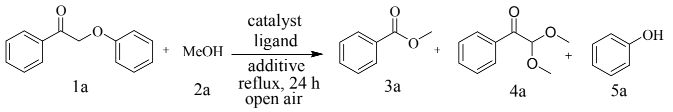
Electronic Supplementary Information (ESI) available: See DOI:10.1039/c000000x/

best performance with high conversion of **1a** and high yield of **4a**. In contrast, both CuCl and $CuBr_2$ were less effective for catalysing the transformation, especially for the production of **4a**. We inferred that Cu(I) species was less oxidative than Cu(II) species, and under the experimental conditions Cu(I) might be oxidized into Cu(II), which further catalysed the transformation. As for $CuBr_2$, it might influence the role of $BF_3.Et_2O$ in the reaction process, thus resulting in the declined activity of the catalytic system.[10] Notably, for the conversion of **1a** and for the production of **3a, 4a** and **5a**, the copper salts showed unique ability in this transformation, and the yield of product declined obviously without copper catalyst (Entry 6).

Table 1 Optimization of reaction conditions.[a]



Entry	Cat.	Additive	Ligand	Yield (%)[b]			Conv. (%)
				3a	4a	5a	
1	None	None	None	No reaction			
2	$CuCl_2$	$BF_3{\cdot}Et_2O$	Py	32.8	56.6	90.5	99.9
3[c]	$CuCl_2$	$BF_3{\cdot}Et_2O$	Py	No reaction			
4	CuCl	$BF_3{\cdot}Et_2O$	Py	21.4	13.2	52.9	99.9
5	$CuBr_2$	$BF_3{\cdot}Et_2O$	Py	27.1	13.0	59.5	85.9
6	None	$BF_3{\cdot}Et_2O$	Py	trace	trace	trace	12.6
7	$CuCl_2$	$BF_3{\cdot}Et_2O$	None	18.1	16.1	27.4	47.2
8	$CuCl_2$	$BF_3{\cdot}Et_2O$	Pip	No reaction			
9	$CuCl_2$	$BF_3{\cdot}Et_2O$	Pic	25.0	9.8	46.3	76.7
10	$CuCl_2$	None	Py	17.7	trace	46.8	54.0

[a] Conditions: 2-phenoxyacetophenone (1a) (0.5 mmol), methanol (2a) (1 mL), catalyst (0.15 equiv.), ligand (0.5 equiv.), $BF_3{\cdot}Et_2O$ (1.0 equiv.), 24h. [b] Isolated yields. [c] The reaction was performed under an argon atmosphere (1 atm). Py-pyridine; Pic-4-picoline; Pip-Piperidine.

Ligand played a very important role in this copper-catalyzed transformation. In the absence of ligand, the yields of products plummeted (Entry 7). Of the tested ligand, pyridine showed the best performance for this reaction. In this work, the use of additive could make the reaction proceed in open air system. $BF_3{\cdot}Et_2O$ as an additive had a great influence on the conversion of **1a** and the formation of **4a**, as shown in Figure 1. In the absence of $BF_3{\cdot}Et_2O$, **4a** was not detected in the reaction solution, meanwhile both the **1a** conversion and **3a** yield were low (Table 1, entry 10). Interestingly, the presence of $BF_3\text{-}Et_2O$ resulted in the formation of **4a** and further promoted the conversion of **1a** and formation of **3a** and **5a**. Meanwhile, the yields of **4a** and **5a** increased with the amount of $BF_3{\cdot}Et_2O$ in the range of 0-1.0 equiv., and almost kept unchanged as the amount of $BF_3{\cdot}Et_2O$ increased further. However, the **3a** yield plot had a maximum at the $BF_3{\cdot}Et_2O$ amount of 0.5equiv. From Figure 1, it can be observed that the sum of the yields of 3a and 4a was almost identical to that of 5a, implying that 3a and 4a might be produced from different reaction pathway, while 5a was produced at the both cases. With the less amount of $BF_3{\cdot}Et_2O$ in the reaction system, more 3a was produced than 4a, while the situation became contrary as the amount of $BF_3{\cdot}Et_2O$ gradually increased, suggesting that the presence of $BF_3{\cdot}Et_2O$ was more favourable to the formation of 4a. Thus, to get more **4a**, 1.0 equiv. $BF_3{\cdot}Et_2O$ was adopted in the following reactions.

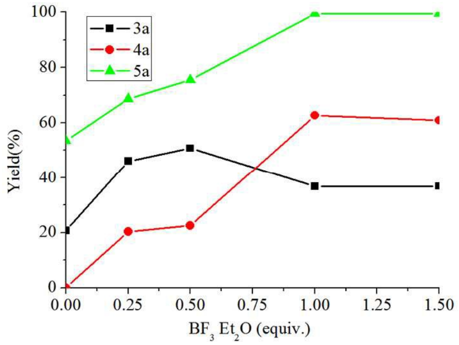


Fig. 1 Dependence of the product GC yields on the amount of $BF_3{\cdot}Et_2O$. Conditions: 1a (0.5 mmol), methanol (1 mL), catalyst (0.15 equiv.), ligand (0.5 equiv.), 24h.

Fig. 2 shows the dependence of the product yields on the reaction time, which indicates that all three products were detected in the reaction process, and their yields had the similar tendency with the reaction time. Especially, the sum of the yields of **3a** and **4a** was close to that of **5a**, and the yield ratio of **4a** to **3a** was almost kept unchanged with the time. It implies that **3a** and **4a** may be originated from different reaction pathways.

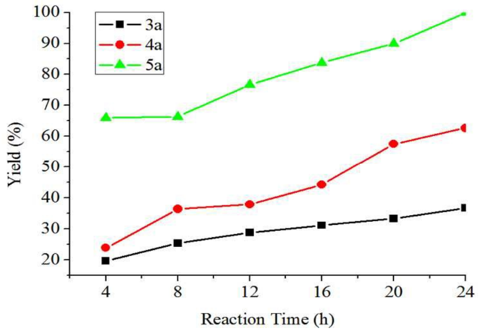
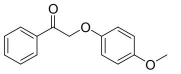
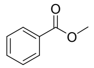
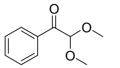
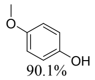
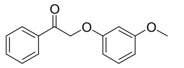
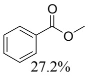
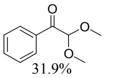
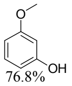
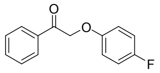
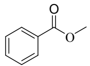
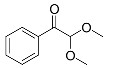
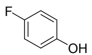
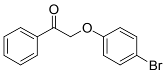
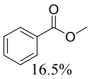
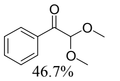
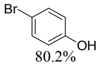
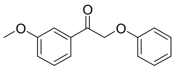
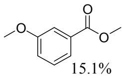
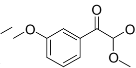
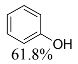
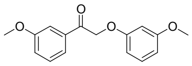
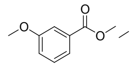
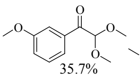
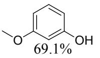


Fig. 2 Dependence of the product GC yields on reaction time. Conditions: 1a (0.5 mmol), methanol (1 mL), catalyst (0.15 equiv.), ligand (0.5 equiv.), $BF_3{\cdot}Et_2O$ (1.0 equiv.).

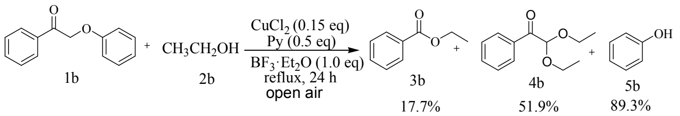
Based on the above results, we selected the optimal reaction conditions as listed in Table 1. Having optimized reaction conditions in hand, we explored the substrate scope, and the results are listed in Table 2. It was indicated that all the tested substrates could react with methanol under the experimental conditions, producing corresponding methyl benzoates, 2,2-dimethoxyacetophenones and phenols. The phenols were obtained in good to excellent yields, and the yields of 2,2-dimethoxyacetophenones were much higher than those of the corresponding methyl benzoates in each case, which was consistent with that observed for 2,2-dimethoxyacetophenone as the substrate. This suggests that the catalytic system could be extended to the tested substrates with high performances.

Table 2 Substrate scope of β-O-4^{a}

Entry	Substrate	Product &Yield (%)^{b}		
1		 22.5%	 53.4%	 90.1%
2		 27.2%	 31.9%	 76.8%
3		 14.7%	 56.4%	 78.6%
4		 16.5%	 46.7%	 80.2%
5		 15.1%	 38.9%	 61.8%
6		 13.4%	 35.7%	 69.1%

^{a}Reaction condition: substrate (0.5 mmol), methanol (1 mL), $CuCl_2$ (0.15 equiv.), pyridine (0.5 equiv.), $BF_3{\cdot}Et_2O$ (1.0 equiv.), reflux, 24h. ^{b}Isolated yield.

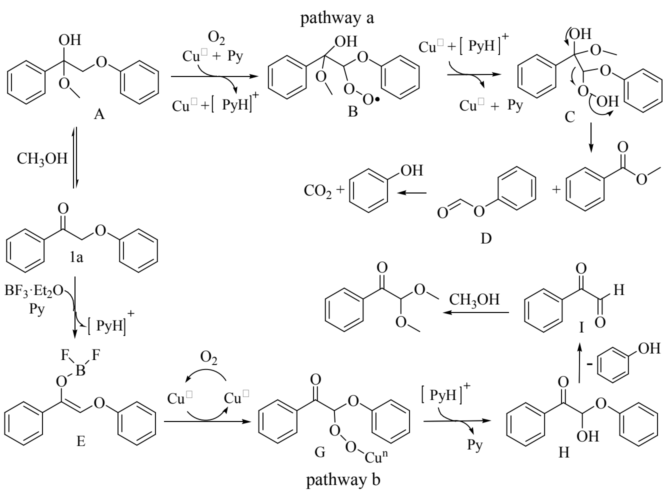
In addition, ethanol instead of methanol was used to react with 2-phenoxyacetophenoneas illustrated in Scheme 2. Excitingly, ethyl benzoate, 2,2-diethoxyacetophenone and phenol were obtained under the experimental conditions. High yield of 2,2-diethoxyacetophenone was achieved, suggesting that this reaction can provide a new route to produce this compound.



Scheme 2 Aerobic oxygenation of 2-phenoxyacetophenones in ethanol. Conditions: 1b (0.5 mmol), 2b (1 mL), $CuCl_2$ (0.15 equiv.), pyridine (0.5 equiv.), $BF_3{\cdot}Et_2O$ (1.0 equiv.), isolated yield.

To explore the reaction mechanism, several control experiments were performed. 2,2,6,6-Tetramethylpiperidinooxy (TEMPO) as a radical trapper was added in the reaction solution of 2-phenoxyacetophenone with methanol catalyzed by $CuCl_2$ with pyridine and $BF_3{\cdot}Et_2O$, and the yield was suppressed to some extent based on the amount of TEMPO added (see SI, Scheme S1). This suggests that the reaction was a radical mechanism. Moreover, this reaction was electron paramagmetic resonance (EPR) active (see Fig. S4). The reaction solution of **1a** with methanol under the experimental conditions performed for 12h was examined by GC-MS, and phenylglyoxal **I** was detected (see SI). Furthermore, phenylglyoxal was treated in methanol under the same experimental conditions, and **4a** was produced, suggesting that **I** was an intermediate. In addition, formyloxybenzene **D** was treated as well under the experimental conditions, and phenol was obtained accompanied with CO_2, suggesting that formyloxybenzene **D** was also an intermediate though it was not detected in the reaction process.

The oxidation states of the Cu species in the recovered catalyst of Table 1 Entry 2 were examined by XPS, and the Cu2p XPS spectrum is shown in Fig.S5. The band at the binding energy of 932.3 eV was assigned to Cu^{I}, and the bands at the binding energy of 935.0 eV, 937.2 eV, 941.9 eV, 944.6 eV, were assigned to Cu^{II}. These results indicated that Cu^{I} species were produced in the reaction process.



Scheme 3 Possible reaction pathways.

On the basis of the experimental results and the previous reports, two possible pathways were proposed to produce **3a** and **4**a, respectively, as illustrated in Scheme 3. These two pathways take place simultaneously. In pathway a, hemiketal A is first formed by nucleophilic addition of ketone with methanol in a reversible way before the aerobic oxidation process,[11] which is transformed to superoxide intermediate B under the experimental conditions.[12,13] Then, the single electron transfer (SET) reduction and subsequent protonation of B by Cu^{I} and [PyH]$^{+}$ occurs to generate hydroperoxide C,[14] which further rearranges, affording **3a** along with the intermediate formyloxybenzene D.[15] D further transforms to **5a** and CO_2 under the experimental conditions. The carbonyl group remains intact without the O atom incorporation in this pathway. In pathway b, **1a** first tautomerizes to its enolate, forming **E** by the addtion of $BF_3 \cdot Et_2O$.[16] Then **E** is oxidized to peroxy radical and trapped by Cu^n species to produce copper peroxide **G**.[17] Fenton-like fragmentation of **G** occurs to form hemiacetal **H**,[18] which eliminates phenol to provide phenylglyoxal **I**. Followed by further reaction with methanol, **4a** is produced.

In summary, we developed a new approach to produce alkyl benzoates and alkyloxy acetophenones via aerobic oxidative cleavage of C-C/C-O bond in 2-phenoxyacetophenones catalysed by $CuCl_2$ with the assistance of pyridine and $BF_3 \cdot Et_2O$ in the presence of alcohols under open air conditions. This work opens a novel and simple way to produce aromatics, which may have promising applications in the production of aromatics from lignin-derived compounds.

This work was financially supported by the National Natural Science Foundation of China (Grants Nos. 21125314, 21321063, 21402208) and the Chinese Academy of Sciences.

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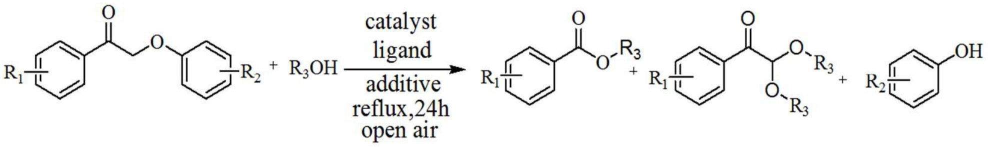
Graphic Abstract



Cu-catalyzed aerobic oxygenation of 2-phenoxyacetophenones in alcohols was achieved, producing alkyl benzoates, alkyloxy acetophenones and phenols in high yields.