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New protocol of copper-catalyzed oxidative C(CO)—C bond cleavage of aryl and aliphatic ketones to organic acids using O_2 as the terminal oxidant

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ABSTRACT

Catalytic oxidation of C—C bond is a key technology to transform petroleum-based as well as sustainable biomass feedstock into more valuable oxygenates. We herein describe a convenient and useful oxidation strategy of converting ketones into carboxylic acids using homogeneous copper catalyst without additives and with O_2 as the terminal oxidant. A wide range of aryl and aliphatic ketones as well as β–O–4 lignin models were selectively oxidized to acids via C—C bond cleavage. Mechanism studies by EPR and in situ NMR elucidate the principles of Cu/O_2 reactivity that involves C—H bond and O_2 activation via a peroxide species. This provides an important foundation for expanding the scope of useful aerobic oxidation reactions using copper catalysts.

1. Introduction

The selective oxidation of C—C bonds and the use of O_2 as a stoichiometric oxidant represent two prominent challenges in catalysis [1]. Copper has demonstrated excellent activity in aerobically oxidative functionalization of C—C bonds, especially for direct transformation of ketones recently. For example, ketone α-C—C bond conversion renders the synthesis of versatile functionalized compounds, such as aldehydes [2,3], amides [4–6], nitriles [7–9], and esters [10–12]. On the other hand, direct C—C bond oxidative cleavage of ketones to carboxylic acids has not been reported using copper catalyst under additive-free conditions.

Direct conversion of ketone to acid using O_2 as the terminal oxidant is an attractive and challenging pathway. Precedents of ketones to acids conversion either use electron-rich ketone substrates featuring electron-transfer to catalytic sites or require additives to activate inert ketone C—C bond or use non-green oxidants [13–15]. For instance, hypervalent iodine compound, or sequential reaction with urea and H_2O_2 in ionic liquids was used for the conversion of aryl ketones to acids [16–18]. Only two metal catalysts (Rh and Mn) have been reported for ketone oxidation in acetic acid [19–22]. A recent example reports a metal-free approach but requires the mixture of ozone and trifluoroacetic acid [23]. An excellent work by Pochampalli and co-workers reports the conversion of aryl/alkyl/vinyl ketones to aromatic acids, but NH_2OH is indispensable to activate ketones via oxime intermediates [24]. Therefore, a direct, efficient catalytic system that can convert ketones to acids in high selectivity using O_2 as the oxidant needs to be developed, which involves the cleavage of robust C—C bond.

The activation of O_2 and oxidation of C—H bond are usually the most important procedures during the Cu-catalyzed oxidation and oxygenation reactions [25–33]. In general, base additives are essential to promote hydrogen abstraction. Besides, organic ligands are usually indispensable for generating active copper complex cores with O_2. Therefore, it is difficult to achieve the direct C—C cleavage with single copper catalyst. Meanwhile, excellent works and mechanistic insights have proposed metal-free transformation of diarylethanones to arylmethanoic acids promoted by base [34], or copper catalyzed ketone transformations to esters and amides [4,6,10–12,35]. And for simple aryl methyl ketones to carboxylic acids through C—C cleavage, there is no systematic report about the applications and mechanism of this transformation catalyzed by copper with O_2.

We here demonstrate the Cu-catalyzed C(CO)—C bond cleavage without any base additive or additional complex ligand (Scheme 1). As a continuation of our previous work on cleavage of C—C bond at interfacial $CuO-Cu_2O$ sites [36,37], we here report an unexpected and remarkably active and selective C—C cleavage by $Cu(NO_3)_2$

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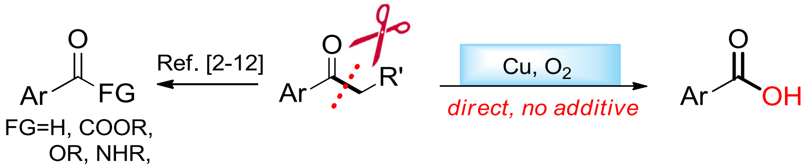


Scheme 1. The Cu-catalyzed C(CO)–C(α) bond cleavage of ketones.

catalyst, which is easily reached in laboratory, cheap to use in industry and safe to handle. The copper catalyst is highly effective for the oxidative cleavage of aryl ketones, aliphatic ketones as well as sustainable lignin β–O–4 ketones to acids in acetonitrile. Mechanistic studies show that ketone is activated by $Cu(NO_3)_2$ catalyst via a single electron transfer process, with the following multiple-step oxidation and C—C cleavage on copper site giving the final acid.

2. Experimental

2.1. Materials

All reagents were of analytical-reagent grade purchased from Aladdin, Alfa, and J&K Chemicals, and were used without further purification.

2.2. Experimental procedures

2.2.1. The oxidation of acetophenone and substituted aryl ketones

The catalytic reactions were performed in a 15-mL autoclave reactor with an internal Teflon insert. Typically, 0.5 mmol of ketone, 0.1 mmol of copper salt and 2 mL of solvent were added into the reactor. Then, the reactor was charged with 0.6 MPa O_2 and heated to 120 °C under magnetic stirring. After cooling to the room temperature, the reaction mixture was diluted with 4 mL methanol before analysis. The products were identified and quantified using gas chromatography-mass spectrometry (GC–MS) and an Agilent 7890A/5975C instrument equipped with an HP-5 MS column (30 m in length, 0.25 mm in diameter). p-Xylene was used as the internal standard.

2.2.2. The oxidation of β–O–4 and β–1 lignin model ketones procedure for preparation of 2-phenoxy-1-phenylethanone (**4a**)

2-Phenoxy-1-phenylethanone was prepared by the literature procedures [38,39]. A 350 mL pressure bottle was charged with phenol (6.9 g, 73 mmol) and K_2CO_3 (10.4 g, 75 mmol) in acetone (150 mL) in Ar atmosphere and stirred at room temperature (RT) for 30 min. To this solution, 2-bromoacetophenone (14.0 g, 70 mmol) was added, and the resulting suspension was stirred at RT for 16 h, after which the suspension was filtered and concentrated *in cacuo*. The solid was dissolved in ethyl acetate and washed with NaOH aqueous (5%, 30 mL) and water (30 mL). The organic phase was dried over anhydrous Na_2SO_4. The crude product was recrystallized from ethanol to give 2-phenoxy-1-phenylethanone as a white solid in 87% yield. Spectral data were in accordance with those previously reported. For the other methoxyl substituted 2-phenoxy-1-phenylethanone, the preparation procedure is the same as described above, except for using different stating materials.

The procedure and product detection methods for the oxidation reactions were unchanged, while the amount of substrate was reduced to 0.1 mmol, with the molar ratio of catalysts and substrates consistent with the optimized conditions.

2.2.3. The oxidation of aliphatic methyl ketones

The procedures and amounts of materials were the same as depicted above. After reactions, the mixture was diluted with 0.005 M H_2SO_4 aqueous solution to certain volume. The products were identified and quantified using High Performance Liquid Chromatography (HPLC) of an Agilent 1260 Infinity System equipped with an Hi-plex H column (8 um, 300 $*$ 7.7 mm), using external standard method with RID and UV (210 nm) detectors.

For the oxidation of acetone, 2-pentanone and 2-heptanone, the product yield was quantified using HPLC (data shown in Scheme S1).

$$\text{Yield of acid} = \frac{\text{moles of certain carboxylic acid product}}{\text{moles of substrate}}$$

$$\text{YC} = \text{Yield of carbon} = \frac{\text{moles of carbon atoms in acid product}}{\text{total moles of carbon atoms in substrate}}$$

TYC means the total yield of carbon for all the carboxylic acid products.

2.3. The analytical procedure

2.3.1. The detection of reaction compounds

For aryl ketones, the carboxylic acid products were esterified to the methyl esters before analysis using GC–MS. After cooling to room temperature, excess amount of absolute methanol and catalytic amount of H_2SO_4 were added and refluxed for 6 h, and then the esterified sample was analyzed and quantified using GC–MS and GC. The typical GC traces of the product analysis (oxidation of acetophenone for 3 h) are shown in Figs. S1 and S2. As for the isolated yield, after the autoclave was cooled, aqueous HCl solution (0.1 M) was added into the system. The precipitated solids were washed with cold water for three times and then vacuum dried for 10 h at 50 °C. If no obvious solid appeared after acidification, the mixture was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were rotary evaporated to remove ethyl acetate. Solid products obtained were vacuum dried for 10 h at 60 °C.

2.3.2. Spectroscopic measurements

Electron paramagnetic resonance (EPR) spectra were taken on a Bruker spectrometer in the X-band at 77 K with a field modulation of 100 kHz. The microwave frequency was maintained at 9.4 GHz. The prepared solutions of indicated components were taken out into a small capillary tube and preserved in liquid nitrogen for low temperature EPR examination.

Gas products analysis was conducted in a U-type quartz tube connected to a Mass spectrometer (GSD320 Thermostar). ^1H NMR and ^{13}C NMR spectra of isolated products were recorded with a Bruker 400 M spectrometer while the NMR spectra of mixtures for intermediates during reaction were recorded on Bruker 700 M spectrometer.

2.3.3. Cyclic voltammetry

ACHI 650D Bipotentiostat (Shanghai Chenhua) was used for the electrochemical measurements in a conventional three-electrode electrochemical cell installed with platinum mesh as the counter electrode and a saturated calomel electrode (SCE) as the reference electrode with $E^0 = 0.242$ V vs. NHE. The cyclic voltammograms were recorded an X-Y recorder and all the electrochemical experiments were done at 25 °C in an inert atmosphere by purging the cell solution with nitrogen gas for about 20 min before recording. The redox behaviors of 3×10^{-3} M $Cu(NO_3)_2{\cdot}3H_2O$ have been examined at Platinum electrode in methanol (CH_3OH), acetonitrile (CH_3CN) and dimethylsulfoxide (DMSO)/0.05 M tetrabutyl ammonium hexafluorophosphate using cyclic voltammetry (Fig. 6a). Meanwhile, redox behaviors of different cupric salts in acetonitrile were studied using the same method (Fig. 6b).

3. Results and discussion

3.1. Oxidation of acetophenone to benzoic acid

Initially, acetophenone (**1a**) was chosen as the model substrate for the catalyst screening under 0.6 MPa O_2 atmosphere (Table 1). No reaction occurred without adding a catalyst (Table 1, entry 1). Initial copper catalysts screening showed that $CuCl_2{\cdot}2H_2O$, $CuBr_2$, CuBr and CuO were ineffective for the acetophenone oxidation (Table 1, entries 2–4, 7), while $Cu(OAc)_2{\cdot}H_2O$ and CuCl showed moderate activity with 35% and 32% yields of benzoic acid, respectively. Unexpectedly, $Cu(NO_3)_2{\cdot}3H_2O$ was the best catalyst with 99% yield of benzoic acid in acetonitrile (Table 1, entry 8).

Different solvents were then tested for this transformation. Weak polar solvents such as CH_2Cl_2 and $PhCH_3$ were detrimental to the reaction, which could be due to the relatively low solubility of Cu salt and the mediation of electrostatic effects [40,41]. Only 26% yield of benzoic acid and 20% yield of methyl benzoate were obtained simultaneously in CH_3OH. Reaction in DMF generated a great amount of by-products and DMF participated in the reaction with the ketone, without generation of target acid product (Table 1, entry 11). Surprisingly, in acetonitrile solution, **1a** was completely converted to benzoic acid with 98% yield (Table 1, entry 8) and a quite high selectivity. The role of CH_3CN may be ascribed to its weak metal-coordinating properties [42–44] and the high redox potential of cupric ion in CH_3CN (Fig. 6a) [45,46], which is investigated in this work below.

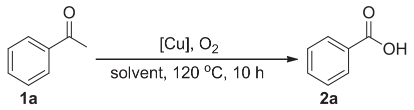
The reaction conditions for $Cu(NO_3)_2$ catalyzed oxidation of acetophenone to benzoic acid have been optimized (Table 2). We can see that O_2 is indispensible for this reaction. Increasing the O_2 pressure or reaction temperatures facilitates the transformation (Table 2, entries 1–6). Reducing the catalyst amount to 5 mol% still allows complete conversion of acetophenone, but the yield of the target product slightly decreased (Table 2, entries 7–8).

To identify other products, we used the mass spectrometer to detect the gas species after reaction. In a typical experiment, pulses of gas above the reacted system were injected into the quartz tube using a 5 mL of gas syringe. The carrier gas was flowing Ar (15 mL min^{-1}). The gas effluents during this process were analyzed by an on-line mass spectrometer and the m/z data of different molecules could be collected (shown in Fig. 1). When reaction gas was injected, the peak of CO_2 ($m/z = 44$) and H_2O ($m/z = 18$) appeared; meanwhile, H_2 ($m/z = 2$), NO ($m/z = 30$) or NO_2 ($m/z = 46$) were not detected. Besides, CO_2 was also detected with lime-water test (Fig. S3). So the generation of H_2O and CO_2 was confirmed by these results and the decomposition of copper nitrate was excluded. We concluded that during the oxidative cleavage of acetophenone, HCOOH was generated as the other product (detected with HPLC) except for benzoic acid, and was further dissociated into CO_2 and H_2O in this system.

3.2. Reactions of aryl ketones and aliphatic ketones

The substrate scope of ketones was tested under the optimized reaction conditions. In general, the substituted phenyl methyl ketones were converted to acids (**2b**-**2f**) with 70–99% yields (Table 3). Aryl methyl ketones with electron-withdrawing groups were slightly harder to be completely converted, affording acids in yields of 93% (—Cl, **2d**) and 83% (—NO_2, **2e**), respectively. For the 2-methyl acetophenone (**1f**), o-phthalic anhydride formed as minor product, which might come from the oxidation of —CH_3 and the following intramolecular dehydration of phthalic acid. Interestingly, for several cyclic aryl ketones (**1g-1i**), including 1-tetralone, 1-indanone and 2-indanone, the phthalic anhydride

Table 1
Reaction condition screening.[a]



Entry	Catalyst	Solvent	Conv. (%)	TOF (h^{-1})	Yield of **2a**[b] (%)
1	–	CH_3CN	<1	~0	n.d.
2	$CuCl_2{\cdot}2H_2O$	CH_3CN	<1	~0	n.d.
3	$CuBr_2$	CH_3CN	<1	~0	n.d.
4	CuO	CH_3CN	<1	~0	n.d.
5	$Cu(OAc)_2{\cdot}H_2O$	CH_3CN	66	0.33	35
6	CuCl	CH_3CN	45	0.23	32
7	CuBr	CH_3CN	<1	~0	n.d.
8	$Cu(NO_3)_2{\cdot}3H_2O$	CH_3CN	>99	0.90[c]	98[d]
9	$Cu(NO_3)_2{\cdot}3H_2O$	CH_3OH	85	0.43	26
10	$Cu(NO_3)_2{\cdot}3H_2O$	DMSO	51	0.26	32
11	$Cu(NO_3)_2{\cdot}3H_2O$	DMF	86	0.43	n.d.
12	$Cu(NO_3)_2{\cdot}3H_2O$	CH_2Cl_2	<1	~0	n.d.
13	$Cu(NO_3)_2{\cdot}3H_2O$	$PhCH_3$	<1	~0	n.d.

n.d. = not detected.

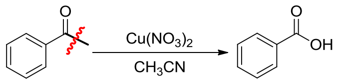
[a] Reaction conditions: 0.5 mmol of acetophenone, 0.1 mmol of catalyst, 2 mL of solvent, 120 °C, 10 h, O_2 0.6 MPa.

[b] GC yield of corresponding methyl benzoate.

[c] TOF of entry 8 was calculated with 18% conversion at 0.5 h.

[d] Isolated yield of benzoic acid. DMSO = dimethyl sulfoxide, DMF = *N*,*N*′-dimethylformamide.

Table 2
Optimization of reaction conditions.[a]



1a **2a**

Entry	$Cu(NO_3)_2$ (mol%) (%)	Atmosphere (MPa)	Temp. (°C)	Conv. (%)	Yield (%)
1	20	Ar 0.6	120	23	19
2	20	Air 0.1	120	76	36
3	20	O_2 0.3	120	>99	87
4	20	O_2 0.6	120	>99	>98
5	20	O_2 0.6	60	20	13
6	20	O_2 0.6	90	68	41
7	10	O_2 0.6	120	>99	78
8	5	O_2 0.6	120	>99	74

[a] Reaction Conditions: **1a** (0.5 mmol), CH_3CN (2 mL), reaction time 10 h.

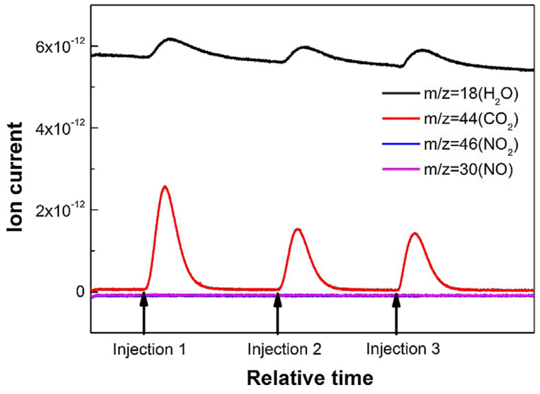


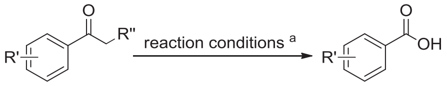
Fig. 1. Detection of the gas species after oxidation of acetophenone.

(**3a**) was obtained as the main product in good to high yields, following a pathway of multi-step oxidation proposed in our previous work [36].

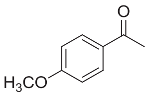
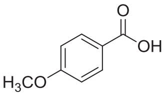
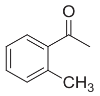
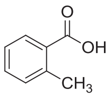
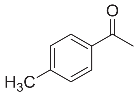
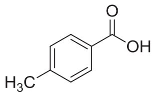
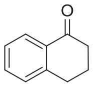
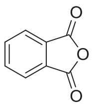
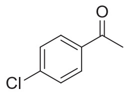
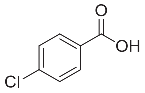
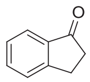
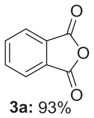
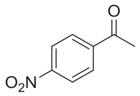
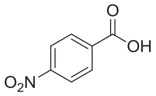
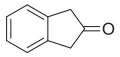
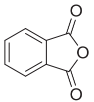
Lignin is a sustainable and biggest reservoir for benzene rings, which are interlinked by C—C and C—O bond. Numerous studies including theoretical calculation have focused on getting phenol or alkane products via C—O bond cleavage [47–57]. Oxidative strategies are also useful for the fragmentation of lignin by cleaving both C—C and C—O bonds [38,58–66], while few studies obtain acids selectively [67,68]. Oxidative system without complex ligands or base was used to cleave C—C bonds to acid groups in this study. We tested the β–O–4 and β–1 lignin models using $Cu(NO_3)_2·3H_2O$ catalyst in acetonitrile.

The β–O–4 ketones were totally converted to acids and phenols except for **4g** with γ-C—OH (Table 4, 20% yield of **2g**), indicating the

Table 3
Reactions of aryl ketones and aromatic cyclic ketones.

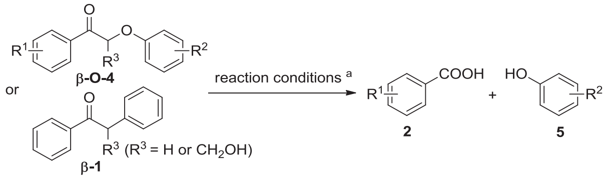


1 **2**

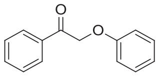
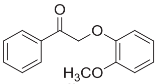
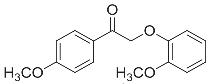
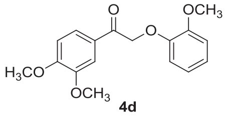
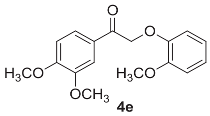
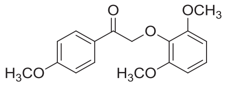
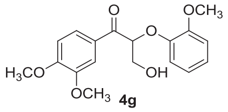
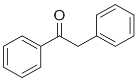
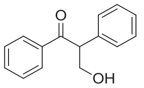
substrate	product (isolated yields)	substrate	product (GC yields)
 **1b**	 **2b:** 99%	 **1f**	 **2f:** 70%
 **1c**	 **2c:** 97%	 **1g**	 **3a:** 98%
 **1d**	 **2d:** 93%	 **1h**	 **3a:** 93%
 **1e**	 **2e:** 83%	 **1i**	 **3a:** 77%

[a] Reaction conditions: 0.5 mmol of substrate, 0.1 mmol of $Cu(NO_3)_2·3H_2O$, 2 mL of CH_3CN, 120 °C, 10 h, O_2 0.6 MPa.

Table 4
The C—C bond cleavage of β–O–4 and β–1 ketones.



4

 **4a** (**2a**: >99% **5a**: 43%)	 **4b** (**2a**: >99% **5b**: 18%)	 **4c** (**2b**: >99% **5b**: 69%)
 **4d** (**2g**: >99% **5b**: 80%)	 **4e** (**2g**: >99% **5b**: 67%)	 **4f** (**2b**: >99% **5c**: <5%)
 **4g** (**2g**: 20% **5b**: <5%)	 **4h** (**2a**: 89%)	 **4i** (**2a**: 44%)

[a] Reaction conditions: 0.1 mmol of **4a-4g** or 0.5 mmol of **4h-4i**, $Cu(NO_3)_2\cdot 3H_2O$ 20 mol%, 2 mL of CH_3CN, 120 °C, 10 h, O_2 0.6 MPa.

substrates underwent both the C—C bond and C—O bond cleavage reaction. Nearly quantitative yields of the acid products were obtained, but yields were low for the methoxy-substituted phenols that are easy to be over-oxidized under oxidative circumstances (**5b** and **5c**). For β–1 ketones such as 1,2-diphenylethanone (**4h**) and 3-hydroxy-1,2-diphenylpropan-1-one (**4i**), products were different without the generation of phenols. Benzil was formed as by-product for these two substrates and couldn't be further cleaved in our reaction system. For substrate **4h**, major products were benzoic acid and benzaldehyde, with a small amount of benzil, which indicated that the benzyl group was possibly oxidized to benzaldehyde and transformed to benzaldehyde dimethylacetal during the derivative procedure. For substrate **4i**, benzoic acid and benzil were detected, with only trace of benzaldehyde, implying one substrate molecule might produce two molecular cleavage products theoretically, so the acid product yield was halved when calculating. The study, although limited to lignin models, is interesting to breaking lignin C—C bonds to aromatic acids.

With the excellent catalytic system in hands, we then applied this method to aliphatic ketones that, in comparison with aryl ketones, are more difficult to be oxidized to acids. A few of Mn/V-based catalysts have been reported for the oxidation of aliphatic ketones to acids [19,69,70], but this transformation has never been achieved using single copper catalyst. Here, short-chain aliphatic methyl ketones (**6a-6c**) were tested using catalytic amount of $Cu(NO_3)_2\cdot 3H_2O$ under the standard conditions for 7 h. The C—C cleavage occurred at both sides adjacent to the carbonyl group. Further decarboxylation reactions led to carbon-chain-decreased acids. The oxidation preferably occurred between the carbonyl and terminal methyl group rather than with the α-methylene group. Yields of 51%, 70% and 62% of total carbon recovery were obtained for acetone, 2-pentanone and 2-heptanone, respectively (Fig. 2). The total carbon yield was smaller than 100% because of the gas loss like CO_2 and the unquantified products. Reaction conditions were not optimized here in our tentative research for oxidative cleavage of aliphatic ketones, and it still verifies that our method is feasible for some saturated methyl ketones.

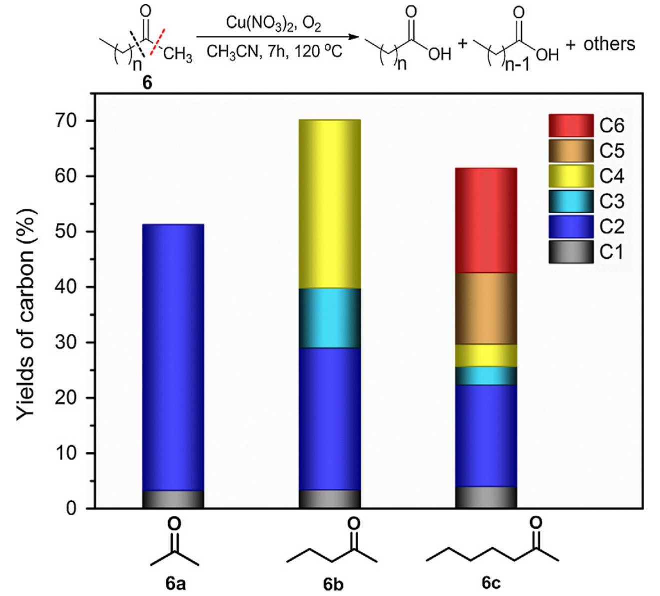
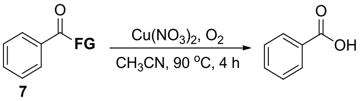


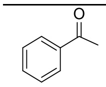
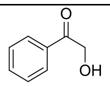
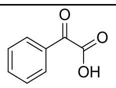
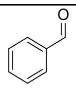
Fig. 2. The carbon yield distribution of carboxylic acid products for the conversion of representative alkyl methyl ketones. (*Note:* Cn means the saturated carboxylic acid with n carbon atoms.)

3.3. Mechanistic studies

To gain insight into the reaction mechanism, we conducted control experiments using several representative derivatives (Table 5). In contrast to **1a**, the oxidation of 2-hydroxy-1-phenylethanone (**7a**) and phenylglyoxylic acid (**7b**) to benzoic acid was much faster, and **7a-b** could achieve quantitative conversion even under milder conditions (60 °C, 2 h). These results imply the possible multiple step oxygenation of α-methyl group from **1a** to **7a** and further to **7b**.

Table 5
Oxidation of acetophenone derivatives and putative intermediates.



			
1a	**7a**	**7b**	**7c**
Conv. 18%	Conv. >98% >98% (60 °C, 2 h)	Conv. >98% >98% (60 °C, 2 h)	Conv. 95%

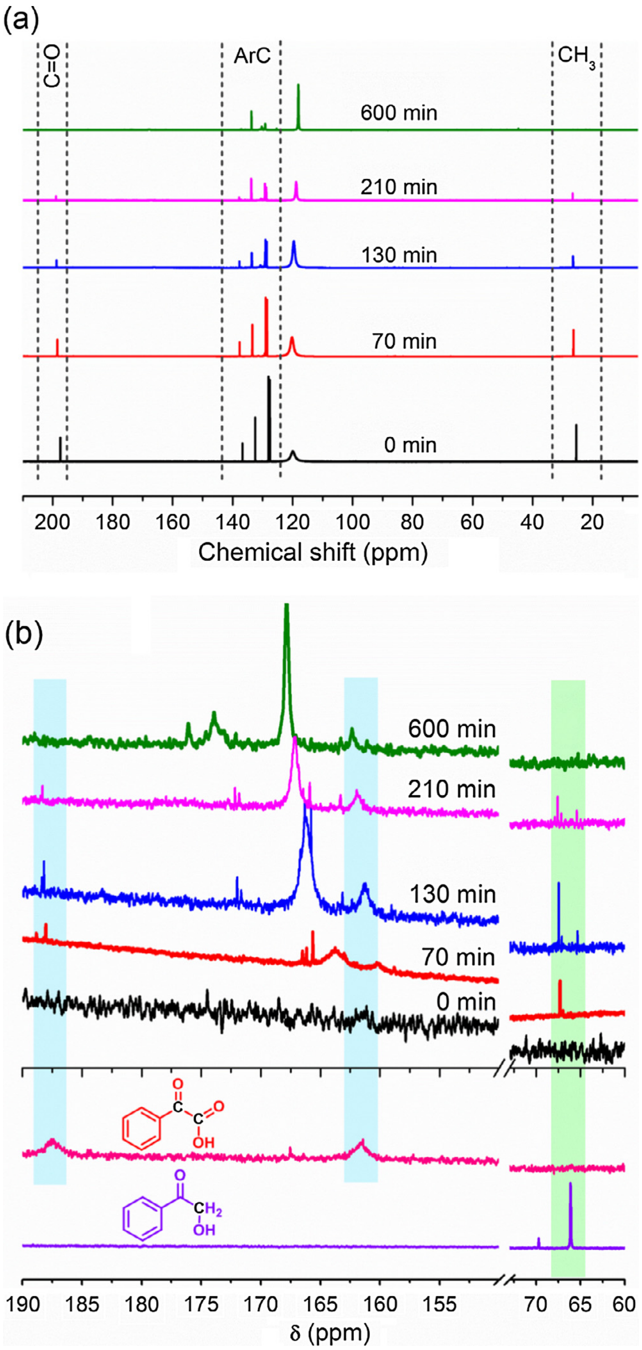


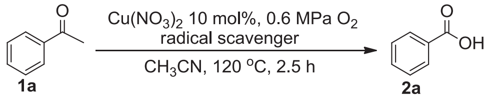
Fig. 3. (a) 13C NMR spectra of reaction mixtures at different times during the oxidation of acetophenone in CD_3CN at 120 °C. (b) The sectional 13C NMR spectra of reaction systems compared with possible intermediate samples.

The presence of **7a** and **7b** was confirmed by ^{13}C NMR through comparing the reaction mixtures at different times with pure substances and juxtaposing the characteristic peaks. The reaction of acetophenone was first monitored using the ^{1}H- and ^{13}C NMR. For the reaction of acetophenone in deuterated acetonitrile, the system was rapidly quenched at certain time and mixtures were detected at room temperature. Fig. 3a shows the ^{13}C NMR spectra of the overall reaction system, with obvious attenuations of the substrate signals. As the characteristic ^{1}H NMR peaks of various species in this reaction system are difficult to distinguish, we conducted intense ^{13}C NMR to capture possible intermediates.

By comparing the characteristic ^{13}C NMR peaks of reaction mixtures and possible intermediates, we found the putative intermediates in line with our speculation. The slight deviation of chemical shifts might arise from the coordination of Cu(II) ion with certain substances in this system. Peak of chemical shift at 66 ppm was designated as the methylene carbon in **7a**, and the enhancement and following decline trend identified **7a** as the possible intermediate. **7b** was also determined by peaks of chemical shift at 187 and 162 ppm, designated as carbonyl and carboxyl carbon respectively. Therefore, control experiments and NMR characterizations conducted in this work have confirmed the transformation process to some extent.

Meanwhile, benzaldehyde (**7c**) could be quickly converted to benzoic acid under the reaction conditions when used as a substrate, with only a small amount of residual aldehyde detected (Table 5). Li's group has done excellent work in silver(I) or copper catalyzed aerobic oxidation of aldehydes toward carboxylic acids in water [71,72], which is instructive but not the focus of our study. Radicals play an important role in many oxidation reactions like this and the radical trapping experiments were carried out using

Table 6
Radical trapping experiments for the oxidation of acetophenone.[a]



Entry	Radical scavenger	Equivalent	Conversion (%)
1	–	–	60
2	TEMPO	0.1	39
3	TEMPO	0.2	33
4	TEMPO	0.5	20
5	BHT	0.1	47
6	BHT	0.2	44
7	BHT	0.5	21

[a] Reaction conditions: 0.5 mmol of acetophenone, 2 mL of CH_3CN, $Cu(NO_3)_2$ 10 mol%, 0.6 MPa of O_2, 120 °C, 2.5 h. The equivalent means the molar ratio of added radical scavenger to acetophenone.

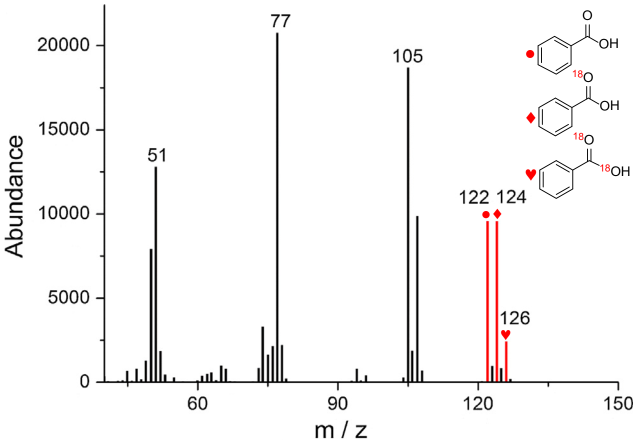


Fig. 4. Mass spectra of benzoic acid when using $18O_2$ as oxidant.

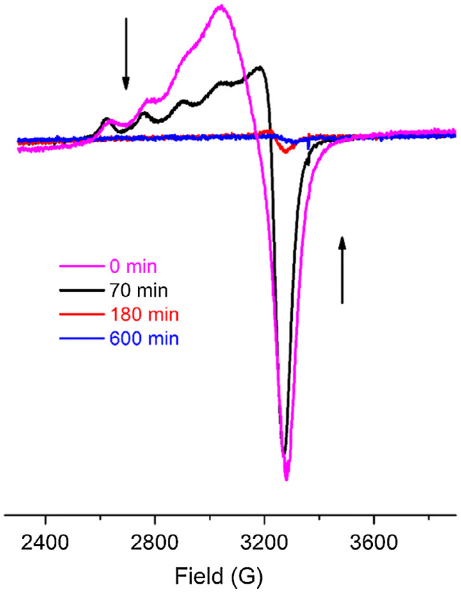
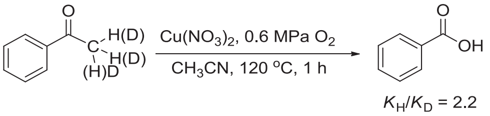


Fig. 5. The electron paramagnetic resonance (EPR) spectra (X band, 9.4 GHz, 77 K) of $Cu(NO_3)_2{\cdot}3H_2O$ (0.1 mmol) and acetophenone (0.5 mmol) in CH_3CN (4 mL) at 120 °C for 0 min, 75 min, 180 min and 600 min, respectively.

different amounts of trapping agents. When 2,2,6,6-tetramethylpiperidi-nyloxy (TEMPO) or 2,6-di-*tert*-butyl-p-cresol (BHT) was added during the oxidation of acetophenone, the reaction was suppressed but not completely impeded with the amount of trapping agents increased (Table 6), indicating a free radical redox mechanism here. We postulated that some peroxides were formed as intermediates [33,73]. Triphenylphosphine (Ph_3P) was used as peroxide scavenger and $Ph_3P = O$ was detected (Fig. S4), which indicates the in situ generation of organic peroxide during reaction.

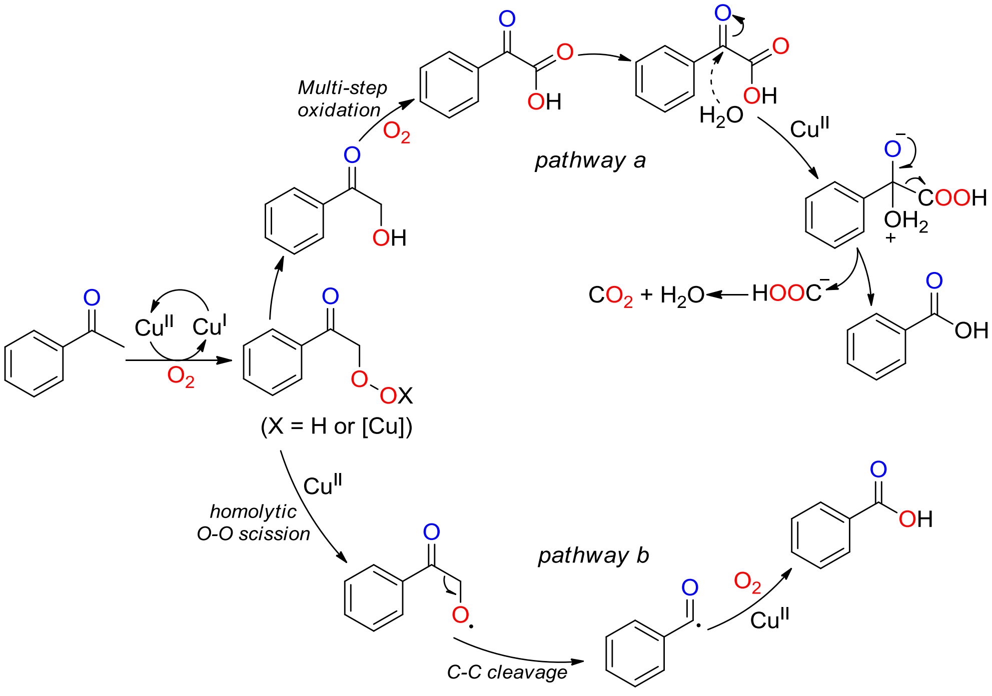


(1)

Deuterium-labeling studies revealed a primary kinetic isotope effect (KIE) ($K_H/K_D = 2.2$) (Eq. (1)) in the oxidation of acetophenone, which shows that the α-C—H bond oxidation is the rate-determining step [74]. Meanwhile, isotope-labeling experiments were conducted with $^{18}O_2$ as oxidant. The benzoic acid was significantly enriched in ^{18}O (Fig. 4, **2a**-$^{18}O^{16}O$: **2a**-$^{16}O^{16}O$: **2a**-$^{18}O^{18}O$ = 44: 44: 11), which proved the oxygen incorporation into the product, further affirming the oxygen transfer from O_2 to acids. Furthermore, the abundance of ^{18}O in the products suggests that more than one pathways may exist during the transformation and reaction substances undergo oxygen exchange with water molecule [10]. An increase in the abundance of ^{18}O in carbon dioxide was also observed. These results further affirm that oxygen atom transfers from the oxygen molecule to the products during the C—C bond cleavage.

The role of copper in activating the substrate and O_2 molecule is the key point in this catalytic transformation. We then investigated the interaction of copper with acetophenone under Ar atmosphere by EPR. To detect the valence of Cu during the reaction under Ar, the reaction mixture was freeze-dried and outgassed to remove O_2, and reacted for different times under Ar at 120 °C (Fig. 5). Along with the reaction, the intensity of Cu^{II} signal decreased gradually and nearly disappeared after 10 h, indicating Cu^{II} was reduced to Cu^{I} via single electron transfer from the ketone at the initial stage. In the presence of O_2, Cu^{II} was the main species with steady intensity in the system (Fig. S6) and could be regenerated quickly from Cu^{I}.

Based on the above examinations, we proposed a reaction mechanism for the oxidative cleavage of acetophenone to carboxylic acid in two possible pathways (Scheme 2). Firstly, α-C—H adjacent to the carbonyl group was activated through the Cu^{II}-induced electron transfer process in acetonitrile [32,75–79], with the radical species ready to be oxygenated by O_2 and forming organic peroxide [32,33,71,73,76,80,81]. In pathway a, 2-hydroxy-1-phenylethanone (**7a**) was formed as the intermediate and the following multi-step oxidation led to phenylglyoxylic acid (**7b**), which would facilitate the C—C bond scission. Then C—C cleavage of **7b** proceeded through the Cu^{II}-promoted nucleophilic



Scheme 2. Possible reaction mechanism for oxidation of acetophenone.

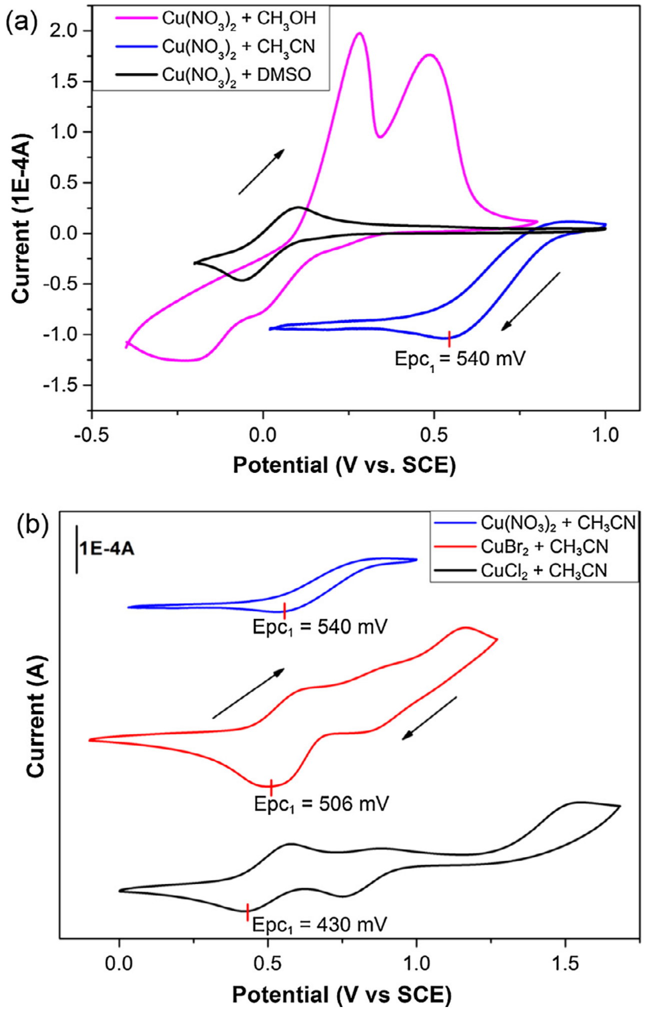


Fig. 6. (a) Cyclic voltammogram (CV) of 3×10^{-3} M $Cu(NO_3)_2 \cdot 3H_2O$ in CH_3OH, CH_3CN and DMSO at $v = 50\ mV\ s^{-1}$. (b) CV of several cupric salts (3×10^{-3} M) in CH_3CN at $v = 50\ mV\ s^{-1}$.

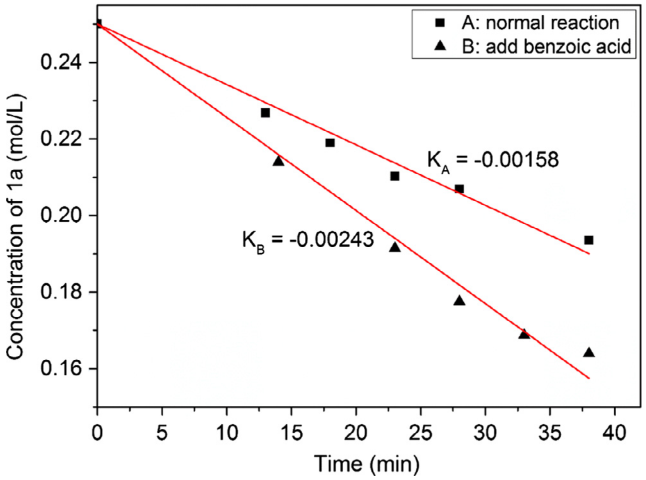


Fig. 7. Kinetic data for reactions of acetophenone at 120 °C with 0.1 MPa O_2 catalyzed by 20 mol% copper. (a) Normal reaction conditions with initial concentration of acetophenone at 0.25 mol/L; (b) Adding 10 mol% benzoic acid before reaction with other conditions remaining the same.

attack by H_2O molecule [82], giving the final benzoic acid product, along with the release of formic acid. The decomposition of HCOOH led to CO_2. In this case, the oxygen incorporated into benzoic acid is not from O_2.

In pathway b, the peroxide might be homolytically cleaved to the α-oxy radical catalyzed by copper, which could trigger the C—C bond cleavage, according to previous examination by Franziska Schoenebeck in their work [33]. The benzaldehyde radical species was then oxidized to benzoic acid, with oxygen incorporation from O_2. The whole mechanism shows that both electron transfer and oxygen transfer greatly rely on single Cu^{II} site. Still, the role of NO_3^- is not clear now and no NO_x species was detected in our experiments.

3.4. Electrochemical and kinetic studies

After the above explorations, we wonder why $Cu(NO_3)_2 \cdot 3H_2O$ catalyst in CH_3CN shows superiority in this process. Previous electrical studies have confirmed that cupric salts in various solvents have different redox ability [83,84]. We have made some attempts to explain their differences in catalytic activity in certain aspects, but cannot not account for all the influencing factors in a catalytic reaction. Some electrochemical tests were conducted in this work to further illustrate the difference in activity.

Fig. 6 shows cyclic voltammograms for different copper(II) complex species in various environments. For $Cu(NO_3)_2 \cdot 3H_2O$ in CH_3OH, CH_3CN and DMSO (Fig. 6a), cathodic peak potential was the most positive in CH_3CN, nearly 0.54 V vs SCE. Besides, for different cupric salts in acetonitrile (Fig. 6b), the reduction potential Epc_1 assigned to Cu^{2+}/Cu^{+} couple increases in following sequence: $CuCl_2 < CuBr_2 < Cu(NO_3)_2$. It indicates that the reduction of copper(II) is easier in system of $Cu(NO_3)_2$ in CH_3CN compared with the others, meaning that counter anions and solvents affect the stabilization of copper(II) complex species. Therefore, the combination of cupric catalyst $Cu(NO_3)_2$ and CH_3CN solvent provides a thermodynamic driving force for copper(II) reduction, which might be one reason for the good performance in activating the substrate.

Moreover, for the process of ketone to carboxylic acid catalyzed by copper here, the acid product is supposed to accelerate further conversion of the substrate in turn because of the coordination capability of carboxyl group to copper, and this was demonstrated in our work. We have collected the kinetic data of the normal reaction process and the process adding a small amount of benzoic acid and found that, the initial reaction stage with adding benzoic acid in advance was accelerated. Based on the experimental data at low conversions, we considered that the substrate concentration was in a linear relationship with reaction time at the initial stage. When small amount of benzoic acid was added before reaction, it gave a larger initial reaction rate ($K_B = 2.43 \times 10^{-3}\ mol\ L^{-1}\ min^{-1}$ after calculation) compared with normal reaction ($K_A = 1.58 \times 10^{-3}\ mol\ L^{-1}\ min^{-1}$) under the same conditions (Fig. 7). Although the reaction rate would decrease with prolonging the reaction time, whether adding the acid or not, we believed that benzoic acid produced during this reaction could promote further conversion of the substrate in this catalytic process. The role of other factors is not particularly clear and needs further exploration.

4. Conclusions

In summary, we have described the Cu-catalyzed oxidative cleavage of the C(CO)—C bond of ketones with O_2 to generate carboxylic acids without any base additive or ligand, making this protocol really simple and effective. A wide range of ketones, including the aryl ketones, lignin model compounds β–O-4 and β–1 ketones, and saturated aliphatic ketones, can be subjected to this Cu-catalyzed method. Preliminary studies about the mechanism show certain oxidative substances or the active radicals play intermediate roles. These findings could supply novel insight into

Cu-catalyzed C—C bond cleavage, and show wide applications even in the area of biomass conversion.

Acknowledgments

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jcat.2016.12.016.

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