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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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From Ketones to Esters by a Cu-Catalyzed Highly Selective C(CO)−C(alkyl) Bond Cleavage: Aerobic Oxidation and Oxygenation with Air

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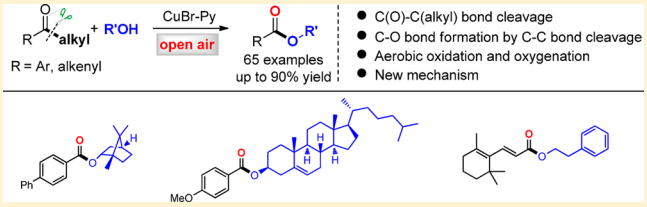
Supporting Information

ABSTRACT: The Cu-catalyzed aerobic oxidative esterification of simple ketones via C−C bond cleavage has been developed. Varieties of common ketones, even inactive aryl long-chain alkyl ketones, are selectively converted into esters. The reaction tolerates a wide range of alcohols, including primary and secondary alcohols, chiral alcohols with retention of the configuration, electron-deficient phenols, as well as various natural alcohols. The usage of inexpensive copper catalyst, broad substrate scope, and neutral and open air conditions make this protocol very practical. ^{18}O labeling experiments reveal that oxygenation occurs during this transformation. Preliminary mechanism studies indicate that two novel pathways are mainly involved in this process.



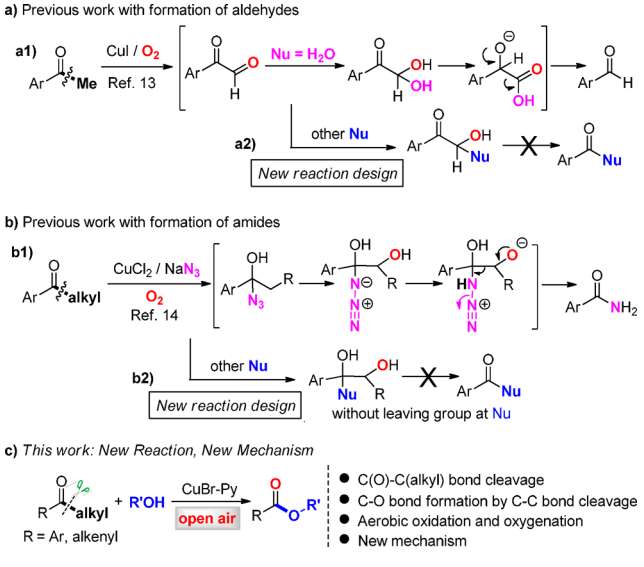
INTRODUCTION

Ketones are one of the most versatile and fundamental class of compounds.[1] The direct transformation of ketones has been widely used in organic synthesis, in which various kinds of chemical bonds could be constructed by the traditional reduction, addition, α-functionalization, and cyclization process through C−H and C−O bond cleavage.[1,2] Nevertheless, the direct transformation through the C(CO)−C bond cleavage of ketones is still limited and attracts the continuous attention of chemists. Encouraged by the traditional Baeyer−Villiger reaction,[3] Schmidt reaction,[4] Haller−Bauer reaction,[5] and haloform reaction,[6] some novel C(CO)−C bond functionalizations of ketones have been recently discovered through two strategies: (1) chelation assisted strategy;[7] (2) cleavage of prefunctionalized ketones with the release of functional fragments such as carbon dioxide, carboxylic acids, carbonyl species, nitriles, or others.[8] Despite the significance of these elegant methods, these developed protocols suffer from the limited substrate scopes, expensive noble transition-metal catalysts, and stoichiometric oxidants such as peroxides and toxic metal salts.

Molecular oxygen is considered as an ideal oxidant in view of green and sustainable chemistry, owing to its abundant, natural, and environmental friendly character.[9] Recently, the copper-catalyzed aerobic oxidation[10,11] and oxygenation[10,12] reaction with molecular oxygen has been a booming topic and has had rapid advancement. Accordingly, the exploration of new and environmental benign catalytic pathways for the direct transformation of ketones through C(CO)−C bond cleavage has been one of the most attractive but challenging tasks.

Recently, two elegant works on Cu-catalyzed aerobic oxidative C(CO)−C bond cleavage of common ketones have been developed.[13,14] Bi and Liu et al. disclosed a chemoselective cleavage of methyl ketones to aldehydes (a1, Scheme 1).[13] We reported the transformation of ketones to amides by

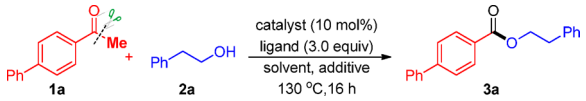
Scheme 1. Cu-Catalyzed Aerobic Oxidative C(CO)−C Bond Cleavage of Ketones



Received: July 18, 2014
Published: September 24, 2014

dx.doi.org/10.1021/ja5073004 | J. Am. Chem. Soc. 2014, 136, 14858−14865

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	ligand	solvent	additive	atmosphere[b]	yield of **3a**(%)[c]
1[d]	CuBr	Py	PhCl		O_2	62
2	CuBr	Py	PhCl		Ar	0
3	none	Py	PhCl		O_2	0
4[e]	other metals	Py	PhCl		O_2	0
5	CuBr	2,2′-Bpy	PhCl		O_2	11
6	CuBr	1,10-Phen	PhCl		O_2	0
7	CuBr	L-Proline	PhCl		O_2	0
8[f]	CuBr	none	PhCl		O_2	0
9	CuBr	Py	xylene		O_2	61
10	CuBr	Py	DMSO		O_2	7
11[g]	CuBr	Py	neat		O_2	77
12[h]	CuBr	Py	PhCl	NHPI	O_2	60
13	CuBr	Py	PhCl	HOAc	O_2	53
14	CuBr	Py	PhCl	$BF_3{\cdot}Et_2O$	O_2	81
15	CuBr	Py	PhCl	$BF_3{\cdot}Et_2O$	open air	83
16[i,j]	CuBr	Py	PhCl	$BF_3{\cdot}Et_2O$	open air	82 (82)

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.50 mmol), catalyst (0.025 mmol), ligand (0.75 mmol), and additive (0.50 mmol) in solvent (1.0 mL) was stirred at 130 °C for 16 h. [b]The pressure of O_2 is 1.0 atm. For the effects of reaction atmosphere, see Table S8 of SI. [c]Determined by ^{1}H NMR. The number in parentheses was isolated yield. [d]For the effects of CuBr loading, see Table S1 of SI; for the evaluation of Cu salts, see Table S6 of SI. [e]Other metals: Fe[Pc], $CoBr_2$, $Ni(OAc)_2$, $Mn(OAc)_3{\cdot}2H_2O$, $MnCl_2$, Ag_2CO_3, and $Pd(OAc)_2$, respectively. [f]For the effects of other amines, see Table S4 of SI; for the effects of electronic and steric effects of pyridine, see Table S3 of SI. [g]1.00 mmol of **2a** was employed. [h]0.0375 mmol of NHPI was employed. [i]For the effects of pyridine loading, see Table S2 of SI; for the effects of reaction temperature, see Table S5 of SI; for the effects of reaction concentration, see Table S7 of SI. [j]Py (0.50 mmol), $BF_3{\cdot}Et_2O$ (0.25 mmol), and PhCl (0.5 mL), 10 h. Py = pyridine; 2,2′-Bpy = 2,2′-bipyridine; 1,10-Phen = 1,10-phenanthrolin. NHPI = *N*-hydroxyphthalimide.

aerobic oxidative C(CO)−C bond cleavage (b1, Scheme 1).[14] Despite the significance of these novel reactions, the aerobic oxidative functionalization of simple ketones through C−C bond cleavage with other kinds of nucleophiles such as alcohol for the esterification is still a challenging task,[15] because of the following: (1) Both of the reported mechanisms (a1 and b1, Scheme 1) could not guide the C(CO)−C bond esterification. When a nucleophile was employed in the aldehyde formation pathway, the nucleophile could not be retained in the ketone partner (a2, Scheme 1). Alternatively, a nuleophile without a leaving group could not undergo the amide formation process (b2, Scheme 1). (2) The alcohol nucleophile could be oxidized to aldehyde byproduct in the presence of transition-metal catalyst under oxidative conditions such as pure dioxygen.[16] (3) The cleavage of inactive ketones with long-chain alkyl groups is still challenging. (4) A new mechanism should be disclosed to enable this kind of C−C bond esterification approach.

Herein, we report a Cu-catalyzed aerobic oxidative esterification of simple ketones via C(CO)−C bond cleavage with a broad range of ketones including inactive aryl long-chain alkyl ketones (c, Scheme 1). Varieties of primary and secondary alcohols and electron-deficient phenols, especially natural alcohols, are tolerant under the present Cu−air system. A novel mechanism and the detailed mechanistic studies are also presented.

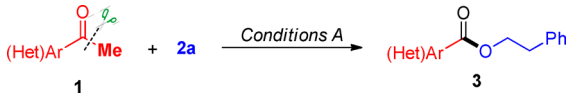
RESULTS AND DISCUSSION

We commenced our study by Cu-catalyzed aerobic oxidative C−C bond cleavage of **1a**. To our delight, when **1a** was treated with **2a**, 0.1 equiv of CuBr, and 3.0 equiv of pyridine in PhCl under O_2 (1.0 atm) at 130 °C, the desired product **3a** was obtained in 62% yield (entry 1, Table 1). As expected, no product was formed under argon atmosphere (entry 2). Copper salt showed unique ability in this transformation, as the reaction did not work without copper catalyst (entry 3, also see Tables S1 and S6, SI). On the other hand, other metal catalysts such as Fe[Pc], $CoBr_2$, $Ni(OAc)_2$, $Mn(OAc)_3{\cdot}2H_2O$, $MnCl_2$, Ag_2CO_3, and $Pd(OAc)_2$ could not accomplish the process (entry 4). When 2,2′-bipyridine was employed as the ligand, the yield of **3a** decreased to 11% with large amounts of **1a** recovered (entry 5). 1,10-Phenanthrolin and L-proline resulted in no efficiency (entries 6−7). Investigation on the effects of other amines (Table S4, SI) and the electronic and steric effects of pyridine (Table S3, SI) showed that pyridine was indispensable in this reaction (entry 8). Xylene gave a similar yield with PhCl, while the strong polar solvent DMSO led to only 7% yield (entries 9−10). It is noteworthy that the yield of **3a** increased to 77% under the neat condition with **2a** (4.0 equiv) (entry 11). Then we turned our attention to screen different additives (entries 12−14). It was found that the addition of $BF_3{\cdot}Et_2O$ delivered **3a** in 81% yield (entry 14). Notably, **3a** could be obtained in 83% yield by using air as the oxidant and oxygen source, which makes it easy to operate. After further screening of pyridine loading (Table S2, SI), temperature (Table S5, SI), and reaction concentration (Table S7, SI), the aerobic C(CO)−C bond cleavage of **1a** gave **3a** in 82% yield using the *Conditions A*: CuBr (0.025 mmol), pyridine (0.50 mmol), and $BF_3{\cdot}Et_2O$ (0.25 mmol) in PhCl (0.5 mL) with stirring at 130 °C open to air for 10 h (entry 16, Table 1).

Next, we explored the scope of the (het)aryl methyl ketones (Table 2). It was observed that the electronic variation at the *para*-substituents of the aryl ring of (het)aryl methyl ketones did not affect the C−C bond cleavage efficiency (entries 1−11, Table 2). Furthermore, the efficiency was affected by the

dx.doi.org/10.1021/ja5073004 | J. Am. Chem. Soc. 2014, 136, 14858−14865

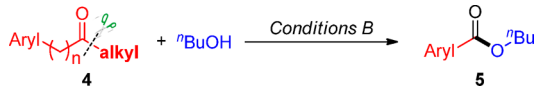
Table 2. Substrate Scope of (Het)Aryl Methyl Ketones[a]



entry	1		yield of 3 (%)[b]
1		R′ = 4-Ph (**1a**)	82% (**3a**)
2		4-OMe (**1b**)	81% (**3b**) 64%[c]
3		4-Me (**1c**)	66% (**3c**)
4		4-^{t}Bu (**1d**)	75% (**3d**)
5		4-F (**1e**)	72% (**3e**)
6		4-Cl (**1f**)	73% (**3f**)
7		4-Br (**1g**)	78% (**3g**)
8		4-NO_2 (**1h**)	81% (**3h**)
9		4-CN (**1i**)	71% (**3i**)
10		4-CF_3 (**1j**)	78% (**3j**)
11		4-SO_2Me (**1k**)	59% (**3k**)
12		3-OMe (**1l**)	78% (**3l**)
13		3-NO_2 (**1m**)	66% (**3m**)
14		3-Br (**1n**)	71% (**3n**)
15		2-Br (**1o**)	53% (**3o**)
16		3,4,5-tri-OMe (**1p**)	80% (**3p**)
17		(**1q**)	72% (**3q**)
18		(**1r**)	69% (**3r**)
19		(**1s**)	74% (**3s**)
20		(**1t**)	52% (**3t**)
21		(**1u**)	73% (**3u**)

[a]*Conditions A*: ketone (0.25 mmol), alcohol (0.50 mmol), CuBr (0.025 mmol), pyridine (0.50 mmol), and $BF_3{\cdot}Et_2O$ (0.25 mmol) in PhCl (0.5 mL) with stirring at 130 °C open to air for 10 h. [b]Isolated yields. [c]Yield of the reaction in 50 mmol scale.

Table 3. Substrate Scope of Alkyl Ketones[a]



entry	4		5	yield of 5 (%)[b]
	R		R	
1	R = H	**4a**	**5a**	74% (78%)
2	4-OMe	**4b**	**5b**	72%
3	4-Me	**4c**	**5c**	79%
4	4-Br	**4d**	**5d**	82%
5	3-Cl	**4e**	**5e**	84%
6	2-F	**4f**	**5f**	67%
	R		R	
7	R = H	**4g**	**5a**	(77%)
8	4-Cl	**4h**	**5h**	90%
9	Ph	**4i**	**5a**	(69%)
10	Ph	**4j**	**5a**	(50%)
11[c]	MeO	**4k**	**5b**	30%
12[d]	EtO	**4l**	EtO	**5l** 31%
13	Ph	**4m**	**5a**	(47%)
14	Ph	**4n**	**5a**	0%

[a]*Conditions B*: ketone (0.25 mmol), ^{n}BuOH (1.00 mmol), CuBr (0.025 mmol), and pyridine (0.50 mmol) in PhCl (0.5 mL) with stirring at 130 °C open to air for 24 h. [b]Isolated yields. The number in parentheses was GC yield. [c]28% of 4-methoxybenzaldehyde was obtained as a byproduct. [d]54% of 4-ethoxybenzaldehyde was obtained as a byproduct.

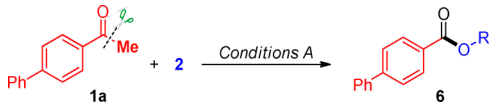
position of the substituents. For example, *o*-bromo-acetophenone **1o** gave lower yield than *p*-/*m*-bromo-acetophenone **1g**/**1n** (cf. entries 7, 14, and 15). A wide range of functional groups were tolerant in this C−C bond esterification. For instance, ketones bearing halo-, NO_2-, CN-, or CF_3- groups afforded the corresponding esters in moderate to good yields, respectively (entries 5−10). Interestingly, the C(CO)−C bond of 1-(4-(methylsulfonyl)phenyl)-ethanone **1k** was selectively cleaved with the retention of the methylsulfonyl group (entry 11). In addition, 2-acetonaphthone **1q** worked well, giving **3q** in 72% yield (entry 17). Obviously, the cleavage of various heteroaryl methyl ketones, including benzofuran, benzothiophene, thiophene, and pyridine fragments, proceeded smoothly to generate medicinally important heterocyclic esters in moderate to good yields (entries 18−21). The reaction of **1b** in 50 mmol scale afforded **3b** in 64% (8.21 g) yield. In some cases, the corresponding aryl aldehydes as byproduct could be obtained.[13]

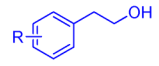
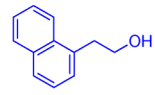
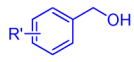
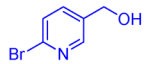
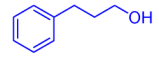
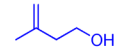
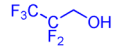
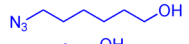
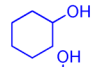
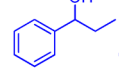
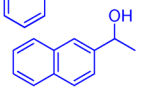
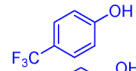
To highlight the broad substrate scope of this process, aryl ketones with long-chain alkyl groups and aliphatic ketones/aldehydes were investigated (Table 3). Remarkably, it is not necessary to add $BF_3{\cdot}Et_2O$ as a Lewis acid when the methyl group is replaced by a long-chain alkyl group. Employing 4.0 equiv of butan-1-ol as the nucleophile with longer reaction time (*Conditions B*), phenyl long-chain alkyl ketones containing various substituents provided the corresponding butyl benzoate in good yields (entries 1−10, Table 3). Intriguingly, aliphatic ketone/aldehyde **4k** and **4l** afforded **5b** and **5l** but in low yields (30% and 31%, respectively, entries 11 and 12). These two reactions might prefer the oxidative process to generate the phenylglyoxal intermediate, as reported by Bi and Liu,[13] followed by dehydrogenative coupling to generate the corresponding α-ketoesters,[11i] which underwent fragmentation under *Conditions B* (see eq S2, SI) to afford the corresponding esters **5b** and **5l**. However, the methylene at the α-position of the carbonyl group is necessary, as **4n** failed to undergo the transformation. These results proved the broad substrate scope of this C−C bond esterification process. In some cases, such as **4i** and **4j**, the aryl long-chain alkyl ketones were not consumed completely, leading to the low yields.

The scope of the reaction with respect to alcohols was investigated too (Table 4). We do not observe the oxidation of alcohols including benzylic alcohols in these reactions. The reactions of various substituted 2-phenylethanols and benzyl alcohols worked well, regardless of the electronic nature and position of the substituent groups (entries 1−14, Table 4). Significantly, an ester group and pyridine ring could be present

dx.doi.org/10.1021/ja5073004 | J. Am. Chem. Soc. 2014, 136, 14858−14865

Table 4. Substrate Scope of Alcohols[a]



entry	2		yield of 6 (%)[b]
1		R = H (**2a**)	82% (**3a**)
2		4-F (**2b**)	72% (**6b**)
3		4-^{t}Bu (**2c**)	75% (**6c**)
4		4-Br (**2d**)	71% (**6d**)
5		3-Br (**2e**)	80% (**6e**)
6		2-Br (**2f**)	77% (**6f**)
7		(**2g**)	69% (**6g**)
8		R' = 4-Me (**2h**)	78% (**6h**)
9		4-Cl (**2i**)	80% (**6i**)
10		4-Br (**2j**)	89% (**6j**)
11		4-COOMe (**2k**)	65% (**6k**)
12		2-Br (**2l**)	83% (**6l**)
13		3,4-di-OMe (**2m**)	59% (**6m**)
14		(**2n**)	78% (**6n**)
15		(**2o**)	64% (**6o**)
16		(**2p**)	55% (**6p**)
17		(**2q**)	59% (**6q**)
18		(**2r**)	58% (**6r**)
19		(**2s**)	62% (**6s**)
20		(**2t**)	59% (**6t**)
21		(**2u**)	62% (**6u**)
22[c]		(**2v**)	45% (**6v**)
23[c]		(**2w**)	50% (**6w**)

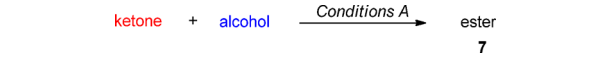
[a]All reactions were performed under *Conditions A*. [b]Isolated yields. [c]0.75 mmol of pyridine, and 0.50 mmol of $BF_3{\cdot}Et_2O$ were employed, and the reaction was run for 24 h.

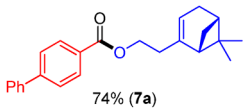
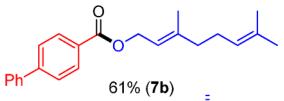
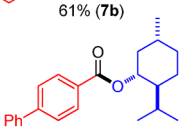
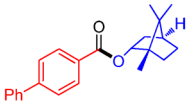
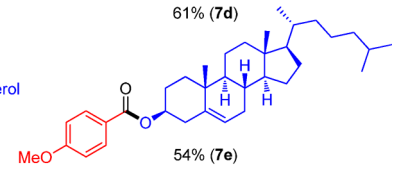
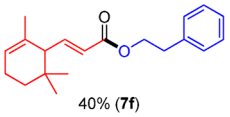
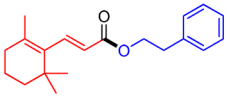
in the substrates (entries 11 and 14). Primary alkyl alcohols bearing vinyl and azido groups were well tolerated (entries 16 and 18). Interestingly, highly fluorinated alcohol was also proved to be reactive (entry 17). Delightfully, secondary alcohols, which are vulnerable to oxidative systems,[16,17] survived well under the oxidative conditions, giving the corresponding esters in moderate yields (entries 19–21). Phenols with strong electron-withdrawing groups performed well in the present C–C bond cleavage transformation (entries 22–23), while electron-rich phenols tended to decompose. Unfortunately, propargylic alcohols are not tolerated under the current oxidative conditions. Within the above scope of alcohols, the present method might provide an alternative pathway for esters synthesis from aryl ketones.

Ester moieties are widely found as key motifs in naturally existent and biologically active substances. In medicinal chemistry, the ester group is a good hydrogen bond acceptor and the esterification strategy is widely used in pro-drug design.[18] Therefore, it is of great interest to modify natural ketones and alcohols via the present protocol.

We were delighted to figure out that the current esterification reaction was capable of tolerating a wide range of natural alcohols in good yields (Table 5). For instance, nerol, bearing

Table 5. Modification of Natural Ketones and Alcohols[a]



entry	ketone	alcohol	yield of **7**[b]
1	**1a**	(-)-Nopol	 74% (**7a**)
2	**1a**	Nerol	 61% (**7b**)
3	**1a**	Menthol	 57% (**7c**)
4	**1a**	(-)-Borneol	 61% (**7d**)
5	**1b**	Cholesterol	 54% (**7e**)
6[c]	*α*-Ionone	**2a**	 40% (**7f**)
7[c]	*β*-Ionone	**2a**	 34% (**7g**)

[a]All reactions were performed under *Conditions A*. [b]Isolated yields. [c]Double bond isomerizations were not observed in these reactions.

an allyl alcohol, was proved to be competent (entry 2, Table 5). Notably, secondary natural alcohols, such as menthol, (−)-borneol, and cholesterol participated in the present transformation, highlighting the broad substrate scope and the potential utility of this protocol (entries 3–5). In addition, *α*-ionone and *β*-ionone, important spices, underwent C–C cleavage to provide **7f** and **7g** in acceptable yields, respectively, without the observation of double bond isomerization (entry 6–7).

Notably, the configuration of the product was totally retained, while the Mitsunobu reaction[19] featured complete inversion of configuration (eq 1).

Interestingly, when substrate **9** was employed using reaction *Conditions A*, the intramolecular esterification product **10** was obtained in 37% yield (eq 2).

To explore the mechanism of this transformation, some potential intermediates were subjected to the reaction system (Table 6). In contrast to the acetophenone (**11a**), the reactions

dx.doi.org/10.1021/ja5073004 | J. Am. Chem. Soc. 2014, 136, 14858–14865

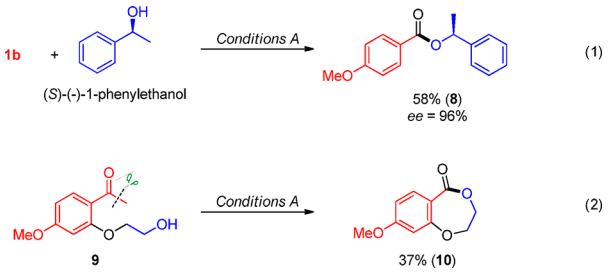
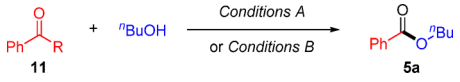
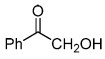
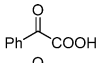
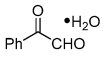
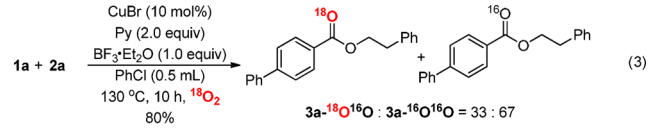


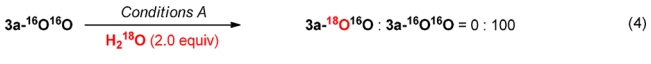
Table 6. Control Experiments

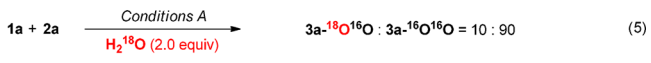


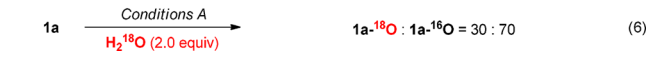
entry	11		GC yield of **5a** (%)	
			Conditions A	*Conditions B*
1		**11a**	63%	65%
2		**11b**	< 1%	< 1%
3		**11c**	1%	8%
4		**11d**	15%	14%
5		**11e**	6%	18%
6		**11f**	3%	54%
7		**11g**	10%	8%
8		**11h**	49%	44%

of the corresponding C−C bond cleavage intermediate benzaldehyde (**11b**) and benzoic acid (**11c**), as well as the oxidized intermediates **11d** and **11e** with ^{n}BuOH afforded ester **5a** in much lower yields under *Conditions A* or *Conditions B*. These results might rule out the possibility of **11b**−**11e** as intermediates of the reaction. One of the interesting results is that when phenylglyoxal monohydrate **11f** was employed as the substrate, the reaction afforded **5a** in 3% yield under *Conditions A*, but 54% yield under *Conditions B* (in the absence of BF_3·Et_2O). These results indicate that **11f** is not involved in the transformation under *Conditions A*. But, **11f** might be an alternative minor pathway under *Conditions B* (because the yield is still lower than 65%, cf. entries 1 and 6, Table 6). Furthermore, this result can reasonably account for the reaction of **4k** and **4l** (entries 11−12, Table 3) through the relay of









phenylglyoxal intermediates[13] and α-ketoester intermediates[11i] (see eq S2, SI). The reactions of 1-phenylvinylboronic acid pinacol ester **11g** under *Conditions A* and *Conditions B* were also investigated, respectively (entry 7, Table 6). These results indicate that **11g** is not involved in the transformation. Although silyl enol ether **11h** could be converted to **5a** in medium yield (entry 8 Table 6), the weakly basic conditions, as well as the absence of silicon and peroxyacid reagents in our system, exclude the possibility of a Rubottom-type oxidation.[20] On the basis of the above control experiments, it might be concluded that the initial interaction of alcohols and ketones might occur before the oxidative process and the C−C bond cleavage process.

As shown in entries 1−2 of Table 1, O_2 is crucial to this reaction. Therefore, isotope experiments were investigated under $^{18}O_2$ atmosphere. To our surprise, 33% of carbonyl oxygen atom was labeled (**3a**-^{18}**O**^{16}**O**: **3a**-^{16}**O** ^{16}**O** = 33:67, eq 3). Further control experiments proved that ester product **3a** could not undergo oxygen exchange with water (eq 4). Moreover, when the reaction was conducted in the presence of 2.0 equiv of $H_2{}^{18}O$ open to air, only 10% of **3a** was labeled (eq 5), which could be reasonably explained by the oxygen exchange between acetophenone **1a** and water (eq 6). These two reactions suggest that the oxygen atoms of the ester do not originated from water. Therefore, the above results demonstrate that the incorporation of O_2 to the ester products is one potential pathway involved in this novel transformation with a new mechanism.

Additionally, when employing TEMPO (2,2,6,6-tetramethylpiperidinooxy), BHT (2,6-di-*tert*-butyl-4-methylphenol), or 1,1-diphenylethene as radical trappers, the reactions were almost inhibited (see eq S8−S11, SI). To get more information about this transformation, EPR (electroparamagnetic resonance) experiments were conducted with the addition of free radical spin trapping agent DMPO (5,5-dimethyl-1-pyrroline *N*-oxide). To our delight, some signals of organic radicals were observed, and these signals would disappear with the addition of superoxide dismutase (SOD) (Figure S6−S8, SI). These results imply that some unknown radicals derived from superoxide compounds might exist during the reaction.[12c,g]

To explore the effects of the pyridine and BF_3·Et_2O in this transformation, some EPR experiments were carried out (Figure 1). The signals of Cu^{II} species did not appear when CuBr was stirred open to air at 130 °C (a, Figure 1). Similarly,

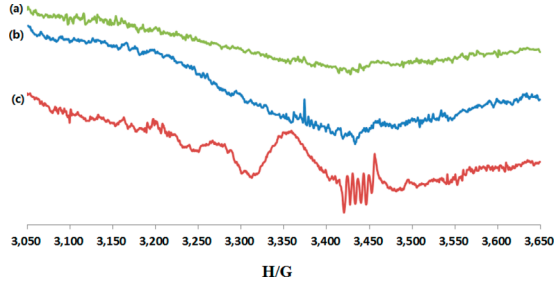
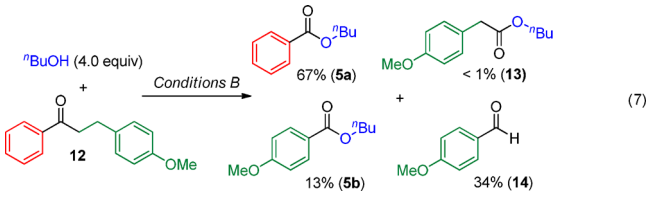


Figure 1. EPR spectra (X band, 9.7 GHz, RT) of conditions: (a) CuBr (0.025 mmol) in PhCl (0.5 mL) with stirring at 130 °C open to air for 1 h; (b) CuBr (0.025 mmol) and BF_3·Et_2O (0.25 mmol) in PhCl (0.5 mL) with stirring at 130 °C open to air for 1 h; (c) CuBr (0.025 mmol) and Py (0.50 mmol) in PhCl (0.5 mL) with stirring at 130 °C open to air for 1 h. The mixture was then analyzed by EPR, respectively.

dx.doi.org/10.1021/ja5073004 | J. Am. Chem. Soc. 2014, 136, 14858−14865

no Cu^{II} signals were detected in the sample of CuBr and $BF_3{\cdot}Et_2O$ in PhCl under air at 130 °C (b, Figure 1). Notably, when the pyridine was added to the above system, the signals corresponding to the Cu^{II} were observed clearly (c, Figure 1).[21] The above EPR results, in agreement with our previous reports,[15b] indicated that pyridine could enable the reaction of Cu^{I} with O_2 to generate Cu^{II} and superoxide radicals.[22] Based on the results in Tables 2 and 3, as well as the above experiments, we suggested that $BF_3{\cdot}Et_2O$ played as a Lewis acid that could coordinate to the carbonyl oxygen of the methyl ketones and activate the carbonyl group.[23]

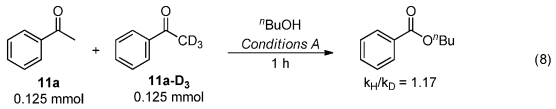
In order to identify the fragment of the ketones, substrate **12** was tested under *Conditions B* (eq 7). Apart from the



(7)

generation of **5a**, 13% yield of **5b** and 34% yield of **14** were isolated. Moreover, only trace amount (<1%) of **13** was detected by GC-MS. There were still some other unknown products observed by GC-MS, which could not be isolated and identified yet. On the basis of these results, we could conclude that the corresponding 2-(4-methoxyphenyl)acetaldehyde was produced as the early stage byproduct, which then underwent the C−C bond cleavage process to get aldehyde **14**[13] or the esterification process to form ester **5b**, which is in accord with the reaction of **4l** (entry 12, Table 3).

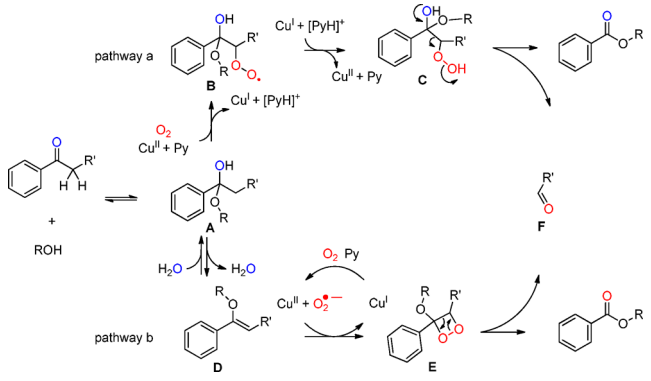
Furthermore, we invested the proton/deuterium kinetic isotope effect of the reaction. The value of k_H/k_D is 1.17, which indicates that the C−H bond cleavage might not be involved in the rate-determining step (eq 8).[24]



(8)

On the basis of the above results and previous reports, two possible pathways were proposed in Scheme 2. Initially, hemiketal **A** is formed by the nucleophilic addition of ketone with alcohol in a reversible way before the aerobic oxidation process.[25] In pathway a, the single electron transfer (SET) of **A** and Cu^{II} forms a carbon-centered radical intermediate, Cu^{I}, and

Scheme 2. Proposed Mechanistic Pathways



[PyH].[10h] Then, the carbon-centered radical intermediate is intercepted by molecular oxygen, generating superoxide intermediate **B**.[26] Then, the SET reduction and subsequent protonation of intermediate **B** by Cu^{I} and [PyH] generates hydroperoxide intermediate **C**.[27] Further rearrangement of hydroperoxide intermediate **C** leads to C−C bond cleavage, affording ester along with the formation of aldehyde **F**.[28] In this way, the carbonyl group remains intact without the O atom incorporation.

Alternatively, in pathway b, dehydration of hemiketal **A** generates vinyl ether **D** reversibly. Subsequently, Cu^{II} and superoxide radical, which are formed through the reaction of Cu^{I} and O_2 in the presence of pyridine,[22] react with vinyl ether **D** to produce dioxetane intermediate **E**.[29] Finally, the C−C bond and O−O bond cleavage of dioxetane intermediate **E** affords ester and aldehyde byproduct **F**.[29] In pathway b, the oxygen atom of the carbonyl group is derived from molecular oxygen, which is consistent with the labeling experiment (eq 3).

In addition, when aryl methyl ketones (R′ = H, Scheme 2) were subjected to *Conditions B* (in the absence of $BF_3{\cdot}Et_2O$ as Lewis acid), the oxidation of this kind of substrates to phenylglyoxals might be accompanied by the above pathways a and b. Then the subsequent α-ketoesters formation[11i] and fragmentation (see eq S2, SI), to afford the corresponding esters, could not be excluded as a minor pathway (entry 6, Table 6).

CONCLUSION

In summary, we have developed a new type of copper-catalyzed C(CO)−C(alkyl) bond cleavage of common ketones for the synthesis of esters via an aerobic oxidation and oxygenation process with air. The usage of inexpensive copper catalyst under open air conditions makes this protocol very green and practical. A wide range of inactive ketones including more challenging aryl long-chain alkyl ketones selectively undergo the C(O)−C bond esterification. The reaction tolerates a variety of primary and secondary alcohols and electron-deficient phenols, especially natural alcohols. ^{18}O labeling experiments demonstrate that part of the carbonyl oxygen atom of ester is originated from molecular oxygen. Preliminary mechanism studies indicate that two pathways are mainly involved in this transformation. Further investigations of the synthetic applications are ongoing in our group.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical data for products, NMR spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support from the National Natural Science Foundation of China (Nos. 21325206, 21172006), the National Young Top-notch Talent Support Program, and the Ph.D. Programs Foundation of the Ministry of Education of China

(No. 20120001110013) is greatly appreciated. We thank Wujie Zou in this group for reproducing the reactions of **1h** and **4i**.

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