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Cu-Catalyzed Esterification Reaction via Aerobic Oxygenation and C−C Bond Cleavage: An Approach to α-Ketoesters

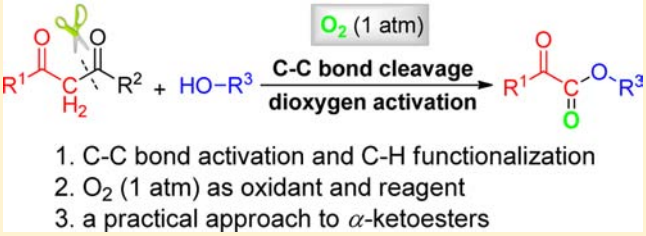
Chun Zhang,[†] Peng Feng,[†] and Ning Jiao*[,†,‡]

[†]State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Xue Yuan Road 38, Beijing 100191, P.R. China

[‡]State Key Laboratory of Organometallic Chemistry, Chinese Academy of Sciences, Shanghai 200032, P.R. China

Supporting Information

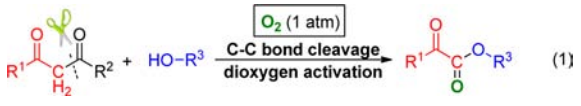
ABSTRACT: The Cu-catalyzed novel aerobic oxidative esterification reaction of 1,3-diones for the synthesis of α-ketoesters has been developed. This method combines C−C σ-bond cleavage, dioxygen activation and oxidative C−H bond functionalization, as well as provides a practical, neutral, and mild synthetic approach to α-ketoesters which are important units in many biologically active compounds and useful precursors in a variety of functional group transformations. A plausible radical process is proposed on the basis of mechanistic studies.



INTRODUCTION

The transition-metal-catalyzed unstrained C−C bond activation has attracted much attention and emerged as a tremendous challenge in the past years.[1,2] This strategy enables the possibility of the direct transformation of inert starting materials. However, to make C−C bond cleavage strategy more useful and practical in organic synthesis, at least three big challenges should be addressed. (1) The selectivity between C−C bond and C−H bond cleavage of unstrained substrates should be controlled. (2) There should be enough energy to activate C−C σ-bond under mild conditions. (3) The reaction system should ensure that other starting materials do not undergo degradation under the necessary oxidative reaction conditions.

Because of the above challenging issues, the oxidative esterification reaction via C−C σ-bond cleavage with alcohol as a partner has not been realized, although it would substantially broaden the field of cross-coupling and offer more functionalized products. Herein, we demonstrate the first example of aerobic oxidative esterification reaction of 1,3-dione compounds with alcohols through C−C σ-bond cleavage and oxygenation with molecular oxygen (eq 1). This method



(1)

successfully combines C−C bond cleavage, dioxygen activation[3,4] and oxidative C−H bond functionalization.[5] This protocol also provides a practical, neutral, and mild synthetic approach to α-ketoesters[6−9] which are important units in many biologically active compounds[10] and useful precursors in a variety of functional group transformations.[11]

RESULTS AND DISCUSSION

Our study commenced with the reaction of 1,3-diphenylpropane-1,3-dione (**1a**) and 2-phenylethanol (**2a**) catalyzed by copper salts. The screening of different parameters was summarized in Table 1 and Supporting Information (SI). Interestingly, phenethyl 2-oxo-2-phenylacetate (**3aa**) was produced in 78% yield when CuBr was used as the catalyst (entry 1, Table 1). It is noteworthy that phenethyl benzoate (**4aa**) as a byproduct was also obtained in 56% yield in this case (entry 1, Table 1), which demonstrates that the other part of 1,3-diones execute the coupling process also with alcohol substrates (**1**) to produce the corresponding esters.[12] The reaction in the absence of Cu-catalyst did not work (entry 2). Other copper catalysts including Cu(II) salts showed low efficiencies (entries 1, and 3, Table 1, and SI). Toluene is the best choice as solvent for this transformation (see SI). Further studies indicated that pyridine is crucial to this transformation. The reaction did not work in the absence of pyridine (entry 5). The optimal dosage is 50 mol % equivalent of pyridine which may play the key role as ligand, (entries 1, 6, and 7). In contrast, the reactions with some bidentate ligands did not work (entries 8, 9, Table 1). When this reaction was performed under air, **3aa** was obtained in 25% yield (entry 10, Table 1). The addition of external oxidants such as H_2O_2 and TBHP under air or argon conditions could not improve the efficiency of this transformation (entries 11−14, Table 1).

With a set of optimized conditions in hand, the scope of ketones (**1**) was investigated (Table 2). Both electron-rich and electron-deficient aryl-substituted 1,3-diketones could be smoothly transformed into the desired products. Furthermore,

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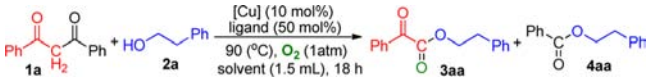
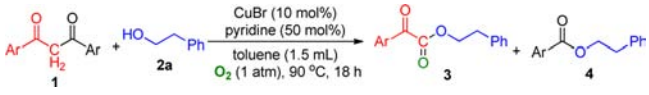
Table 1. Effect of Different Parameters on the Reaction of 1a and 2a[a]

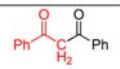
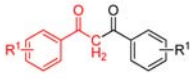
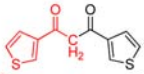
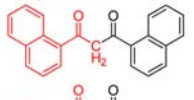
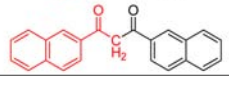


entry	[Cu]	ligand (50 mol %)	solvent	yield of **3aa** (%)[b]	yield of **4aa** (%)[c]
1	CuBr	pyridine	toluene	78	56
2	none	pyridine	toluene	0	0
3	$CuBr_2$	pyridine	toluene	70	50
4	CuBr	pyridine	CH_3CN	20	14
5	CuBr	none	toluene	0	0
6[d]	CuBr	pyridine	toluene	76	56
7[e]	CuBr	pyridine	toluene	74	51
8[f]	CuBr	2,2′-bipyridine	toluene	0	0
9[f]	CuBr	1,10-phenanthroline	toluene	0	0
10[g]	CuBr	pyridine	toluene	25	13
11[h]	CuBr	pyridine	toluene	trace	trace
12[i]	CuBr	pyridine	toluene	30	16
13[j]	CuBr	pyridine	toluene	0	0
14[k]	CuBr	pyridine	toluene	0	0

[a] **1a** (0.25 mmol), **2a** (0.75 mmol), catalyst (0.025 mmol), toluene (1.5 mL), ligand (0.125 mmol), O_2 (1 atm), at 90 °C, 18 h. [b] Isolated yields. [c] HPLC yields. [d] 20 mol % of pyridine was used. [e] 2.0 equiv of pyridine was used. [f] 10 mol % ligand was used. [g] Under air (1 atm) condition. [h] 0.5 mmol H_2O_2 was employed as oxidant under air (1 atm) condition. [i] 0.5 mmol TBHP was employed as oxidant under air (1 atm) condition. [j] 0.5 mmol H_2O_2 was employed as oxidant under Ar (1 atm) condition. [k] 0.5 mmol TBHP (*tert*-butylhydroperoxide) was employed as oxidant under Ar (1 atm) condition.

Table 2. Cu-catalyzed Aerobic Oxidative Coupling of Different 1,3-Diketone (1) with 2a[a]



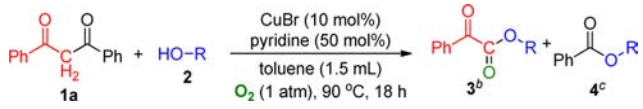
entry	1		yield of **3** (%)[b]	yield of **4** (%)[c]
1		(**1a**)	78% (**3aa**)	56% (**4aa**)
2		R^1 = 4-Me (**1b**)	58% (**3ba**)	55% (**4ba**)
3		3,4-Me_2 (**1c**)	50% (**3ca**)	35% (**4ca**)
4		2-Me (**1d**)	41% (**3da**)	37% (**4da**)
5		4-OMe (**1e**)	65% (**3ea**)	60% (61%)[b] (**4ea**)
6		4-^{t}Bu (**1f**)	64% (**3fa**)	61% (**4fa**)
7		4-F (**1g**)	66% (**3ga**)	63% (**4ga**)
8		4-Cl (**1h**)	59% (**3ha**)	56% (**4ha**)
9		4-Br (**1i**)	66% (**3ia**)	46% (**4ia**)
10		4-CF_3 (**1j**)	51% (**3ja**)	45% (**4ja**)
11		(**1k**)	75% (**3ka**)	66% (**4ka**)
12		(**1l**)	62% (**3la**)	51% (**4la**)
13		(**1m**)	66% (**3ma**)	56% (**4ma**)

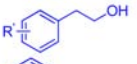
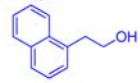
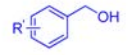
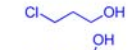
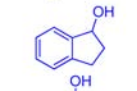
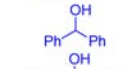
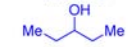
[a] Standard reaction conditions: **1** (0.25 mmol), **2a** (0.75 mmol), CuBr (0.025 mmol), toluene (1.5 mL), pyridine (0.125 mmol), O_2 (1 atm), at 90 °C, 18 h. [b] Isolated yields. [c] HPLC yields.

substituents at different positions of the aryl ring (para-, meta-, and ortho-position) do not affect the efficiency. It is noteworthy that halo-substituted aryl ketones survived well, leading to halo-substituted products, which could be used for further transformations (**3ga**, **3ha**, and **3ia**, Table 2). In addition, naphthyl substituted ketones, 1,3-di(naphthalen-1-yl)propane-1,3-dione and 1,3-di(naphthalen-2-yl)propane-1,3-dione were also tolerant in this transformation, generating **3la** and **3ma** in 62% and 66% yield, respectively (Table 2). Moreover, a heteroaryl substituted acetaldehyde, 1,3-di-(thiophen-3-yl)propane-1,3-dione, performed well, generating **3ka** in 75% yield (Table 2). In the above reactions, the conversions of 1,3-diketone derivates (**1**) are nearly 100%.

The scope of the copper-catalyzed aerobic oxidative coupling leading to α-ketoesters was further expanded to a variety of substituted alcohols (**2**) (Table 3). The aromatic rings of 2-phenylethanol and phenylmethanol are of great variety containing electron-rich groups (**3af**, **3ag**, **3ah**, **3ac**, and **3al**), electron-deficient groups (**3am**, and **3an**), and halo-groups (**3ab**, **3ai**, **3aj**, and **3ak**). It is noteworthy that alkyl alcohols with low boiling-points also worked well (**3ao** and **3ap**). Furthermore, alkyl alcohols containing alkynyl or halogen also give desired products smoothly (**3aq**, **3ar**, and **3as**). In addition, a secondary alcohol, such as 1-hydroxyhydrindene or diphenylmethanol, also works well in this transformation (**3at** and **3au**). However, noncyclic secondary alkyl alcohols (**2v**) only gave a trace amount of desired products. In the above reactions, the conversions of 1,3-diphenylpropane-1,3-dione (**1a**) are nearly 100%.

Table 3. Cu-Catalyzed Aerobic Oxidative Coupling of 1a with different alcohol (2)[a]



entry	2		yield of **3** (%)[b]	yield of **4** (%)[c]
1		R = H (**2a**)	78% (**3aa**)	56% (**4aa**)
2		4-Br (**2b**)	76% (**3ab**)	71% (**4ab**)
3		4-OMe (**2c**)	87% (**3ac**)	82% (**4ac**)
4		(**2d**)	75% (**3ad**)	70% (73%)[b] (**4ad**)
5		R = H (**2e**)	78% (**3ae**)	36% (**4ae**)
6		4-Me (**2f**)	76% (**3af**)	23% (**4af**)
7		2-Me (**2g**)	72% (**3ag**)	44% (**4ag**)
8		3-Me (**2h**)	77% (**3ah**)	46% (**4ah**)
9		4-F (**2i**)	83% (**3ai**)	35% (**4ai**)
10		4-Cl (**2j**)	73% (**3aj**)	20% (**4aj**)
11		4-Br (**2k**)	77% (**3ak**)	28% (**4ak**)
12		3-OMe (**2l**)	87% (**3al**)	43% (47%)[b] (**4al**)
13		4-CN (**2m**)	92% (**3am**)	25% (22%)[b] (**4am**)
14		4-CF_3 (**2n**)	58% (**3an**)	53% (**4an**)
15	MeOH	(**2o**)	73% (**3ao**)	40% (**4ao**)
16	EtOH	(**2p**)	74% (**3ap**)	43% (**4ap**)
17		(**2q**)	30% (**3aq**)	23% (**4aq**)
18		(**2r**)	60% (**3ar**)	48% (**4ar**)
19		(**2s**)	62% (**3as**)	49% (**4as**)
20		(**2t**)	45% (**3at**)	17% (**4at**)
21		(**2u**)	46% (**3au**)	38% (**4au**)
22		(**2v**)	trace (**3av**)[d]	trace (**4av**)[d]

[a] Standard reaction conditions: **1a** (0.25 mmol), **2** (0.75 mmol), CuBr (0.025 mmol), toluene (1.5 mL), pyridine (0.125 mmol), O_2 (1 atm), at 90 °C, 18 h. [b] Isolated yields. [c] HPLC yields. [d] Detected by GC–MS.

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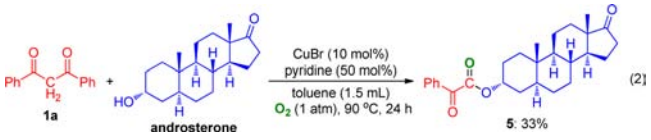
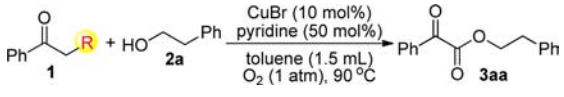
Theoretically, the corresponding esters **4** as byproducts of this transformation should be produced in yields similar to those of the desired α-ketoester products **3**. However, the yields of **3** and **4** are different in most cases (Table 2 and 3). For some, results such as **4ba**, **4fa**, **4ga**, **4ha**, **4ab**, **4ac**, **4ad**, and **4an** were produced nearly equal to the yield of the corresponding α-ketoester product (**3**). However, most of the other substrates in Tables 2 and 3 afforded the esters (**4**) with lower yields than those of the corresponding α-ketoester products (**3**). These results indicate that another pathway for the generation of α-ketoester products **3** without the formation of **4** may be involved in the reaction processes.

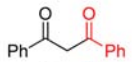
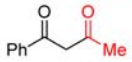
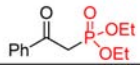
Late-stage modification of drug candidates is valuable for structure−activity relationship (SAR) studies since the complex target molecules are otherwise more challenging to obtain. By the present protocol, androsterone which is a biological active molecule, performed well to access complex α-ketoester molecules (eq 2).



To our delight, besides 1,3-diphenylpropane-1,3-dione (**1a**, entry 1, Table 4), other kinds of ketone substrates such as 1-phenylbutane-1,3-dione (**1n**, entry 2, Table 4) and diethyl 2-oxo-2-phenylethylphosphonate (**1o**, entry 3, Table 4) were also tolerant under the optimal reaction conditions generating **3aa** in 45% and 31% yields, respectively.

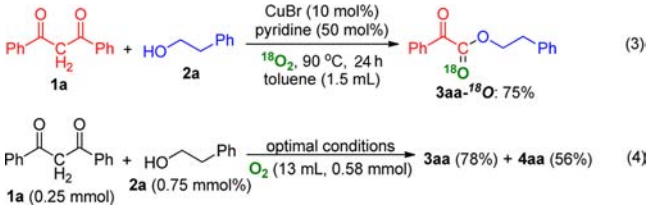
Table 4. Cu-catalyzed aerobic oxidative coupling of different ketone (1) with 2aa.[a]



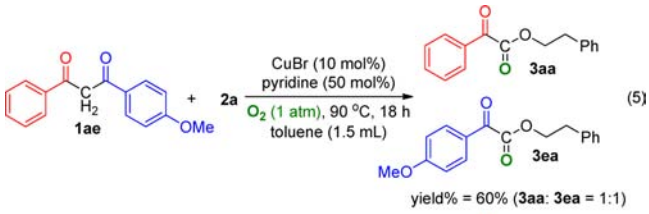
entry	1		yield of **3aa**[b]
1		**1a**	78%
2		**1n**	45%
3		**1o**	31%

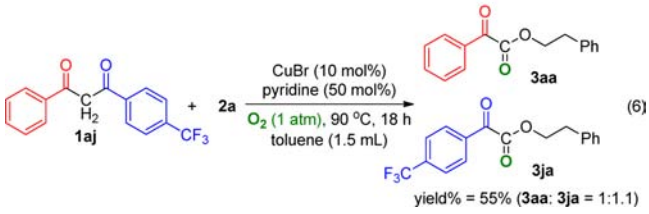
[a]Standard reaction conditions: **1** (0.25 mmol), **2a** (0.75 mmol), CuBr (0.025 mmol), toluene (1.5 mL), pyridine (0.125 mmol), O_2 (1 atm), at 90 °C, 18 h. [b]Isolated yields.

The transformation of **1a** and **2a** in the presence of $^{18}O_2$ (1 atm) generated ^{18}O-labeling product **^{18}O-3aa** in 75% yield (eq 3, determined by HRMS, see SI). This result indicates that the oxygen atom of the α-ketoester originated from molecular oxygen. Furthermore, we estimated the consumed amount of O_2. The reaction of **1a** (0.25 mmol) and **2a** consumed 0.58 mmol O_2 under optimal condition (eq 4 and SI). From the balance of this chemical equation, it is noted that maximal 0.5 mmol O_2 is required for this transformation. On the basis of the experimental research, we find that the excess amount of dioxygen may be used to oxidize the toluene to benzaldehyde which could be detected by GC−MS.

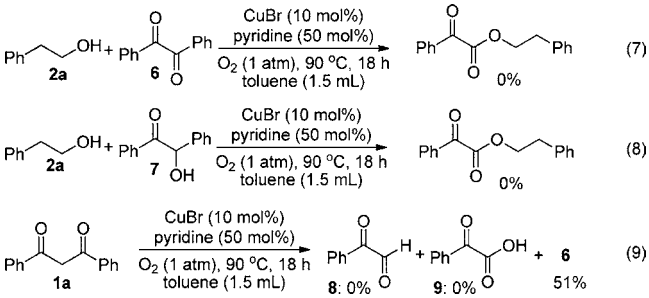


To get more information of reaction mechanism, the reactions of 2-phenylethanol (**2a**) coupling with asymmetric aryl ketones **1ae** and **1aj** were investigated (eq 5 and eq 6). The results indicate that the electron density of aryl-group does not affect the chemoselectivity obviously (eq 5 and eq 6).





There are some competitive reactions which could affect the efficiency of the desired transformation. For example, 1,3-diphenylpropane-1,3-dione (**1a**) could converted into benzil (**6**) under standard conditions (see SI). However, it is noteworthy that the reactions of **2a** with benzil (**6**) or 2-hydroxy-1,2-diphenylethanone (**7**) under the standard conditions did not afford the desired product **3aa** (eq 7 and 8).



Although 2-oxo-2-phenylacetaldehyde (**8**) and 2-oxo-2-phenylacetic acid (**9**) could couple with alcohol to afford the desired product under the standard conditions, **8** and **9** were not detected in the reaction of **1a** in the absence of alcohol substrate under the standard conditions, but with the benzil (**6**) as the main product in 51% yield (eq 9). The control reactions indicate that the 2-oxo-2-phenylacetaldehyde (**8**) is relatively more stable than 2-oxo-2-phenylacetic acid (**9**) under standard conditions and can be recovered after 1 h under standard conditions (eqs S1−S2, SI). However, both of **8** and **9** were not detected by GC−MS in situ (see eq 9). These results might exclude **6**, **7**, **8**, or **9** as the possible intermediates of this copper-catalyzed aerobic oxidative transformation.

The results in Tables 2 and 3 show that the ester products (**4**) were produced with the similar or lower yield than that of the corresponding α-ketoester products (**3**). The data of Table

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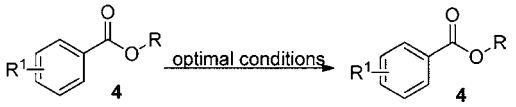
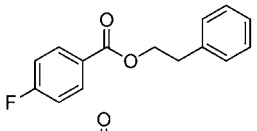
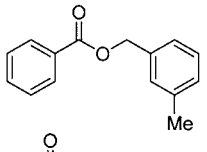
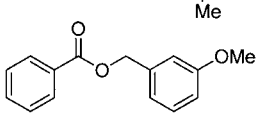
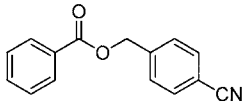
5 indicate that the ester products (**4**) are stable under the standard conditions, because all the recovered yields of **4** are nearly 100% (Table 5). The above results support that hypothesis that another pathway for the generation of α-ketoester products **3** without the formation of **4** may be involved in the reaction processes.

Table 5. The Control Recovery Experiments of 4 under the Standard Conditions[a]

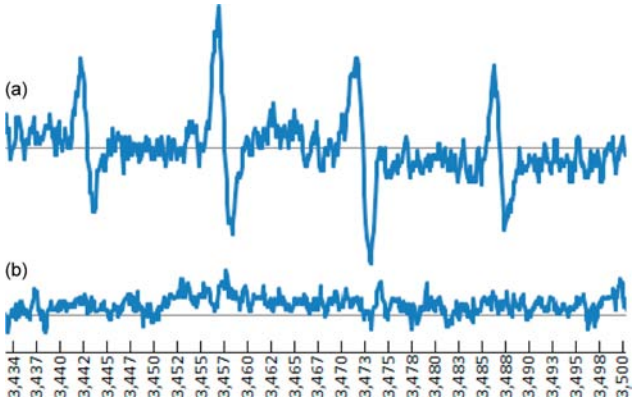


entry	4		recovery of **4** (%)[b]
1		**4ga**	99%
2		**4ah**	99%
3		**4al**	98%
4		**4am**	99%

[a]Standard reaction conditions: **4** (0.25 mmol), CuBr (0.025 mmol), toluene (1.5 mL), pyridine (0.125 mmol), O_2 (1 atm), at 90 °C, 18 h. [b]Isolated yields.

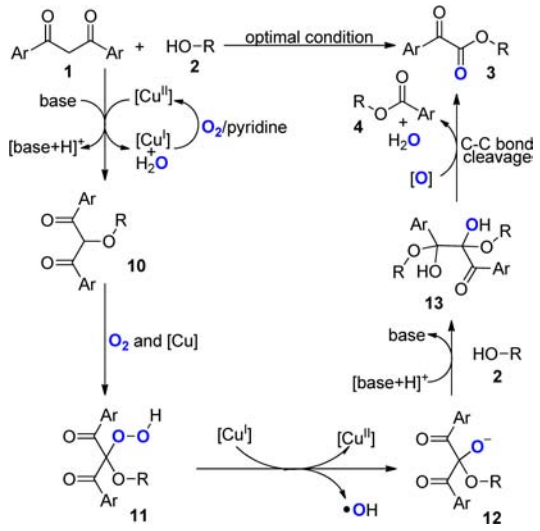
To get more information about the mechanism of this transformation, we also tried to catch some intermediates by EPR. In the EPR spectra monitored with the addition of the radical trap 5-,5-dimethyl-1-pyrroline *N*-oxide (DMPO), the signal corresponding to DMPO−O(H) has been identified[13] ((a), Scheme 1), which are classical four peaks. The calculated hyperfine splittings are g_0 (2.019), α^H (14.9 G). Furthermore, the (a) signal disappeared with the addition of the superoxide dismutase (SOD) (b, Scheme 1). These EPR results demonstrate that the hydroxyl radical (Scheme 2) may be derived from a superoxide compound such as **11** (Scheme 2), which also produces the anion intermediate **12** by this process.

Scheme 1. Electroparamagnetic Resonance (EPR) Studies of This Transformation[a]



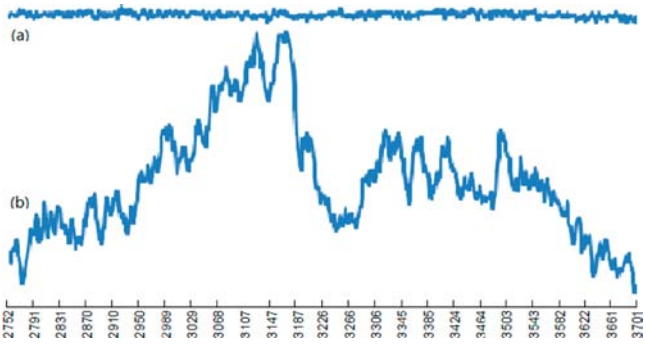
[a]The electroparamagnetic resonance (EPR) spectra (X band, 9.7 GHz, RT) of (a) reaction mixture in the presence of the radical trap DMPO (2.5×10^{-2} M); (b) with the addition of superoxide dismutase (SOD).

Scheme 2. Proposed Main Mechanism of the Alcohol Substrate without Serious Steric Hindrance



To probe the role of pyridine in this transformation, we also designed some EPR experiments. The signal of (a) support that CuBr (0.25 mmol) being under O_2 (1 atm) in toluene (1.5 mL) at 90 °C hardly generated Cu^{II} species (Scheme 3). In contrast, the EPR signal of Cu^{II} catalyst was observed clearly if 1.0 mmol pyridine was added into the above reaction system ((b), Scheme 3).[14] The above EPR studies indicate that the presence of pyridine could enable the [Cu^{II}] formation from [Cu^{I}] under molecular oxygen atmosphere.

Scheme 3. Electroparamagnetic Resonance (EPR) Studies of Pyridine and Cu Catalyst[a]



[a]The electroparamagnetic resonance (EPR) spectra (X band, 9.7 GHz, RT) of (a) reaction of CuBr with dioxygen; (b) pyridine was added into the reaction of CuBr with dioxygen.

On the basis of above results, a possible mechanism is proposed in Scheme 2. Under copper-catalyzed aerobic oxidative conditions, intermediate **10** is initially generated by the dehydrogenative coupling of substrates **1** and **2**.[15] The active intermediate **10** which could not be isolated, is subsequently oxidized to superoxide intermediate (**11**) via a copper-mediated pathway under O_2.[16] Then, copper-mediated

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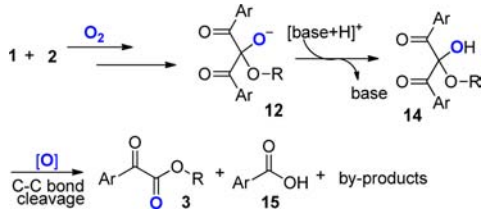
SET reduction of superoxide intermediate **11** form anion intermediate **12** and hydroxyl radical.[17] The subsequent reaction of **12** and **2** afford the hemiacetal intermediate **13**.[18] Further oxidative fragmentation of **13** would produce the desired **3** with the formation of **4** as the byproduct.[19] In this step, hydroxyl radical or molecular oxygen could play the role of the oxidant.

The results of Tables 2, 3 and 5 have supported the hypothesis that another pathway for the generation of α-ketoester products **3** without the formation of **4** may be involved in the reaction processes. Furthermore, from the results in Table 3, it is noted that the alcohols with steric hindrance, such as benzyl alcohol derivatives, tend to give low yields of **4**. In contrast, the alcohol substrates with less steric hindrance prefer to afford **3** and **4** in similar efficiency. In order to explain these results, another pathway especially for the alcohol substrate with steric hindrance is proposed in Scheme 4. After the generation of intermediate **12** by the same reaction

Scheme 4. Concomitant Mechanism for This Transformation



path with Scheme 2, the interemediate **13** is partly produced from intermediate **12** especially in the cases of the steric hindrance alcohols. Alternatively, neutral intermediate **14** is afforded from intermediate **12**. Further oxidative fragmentation of **14** would produce the desired **3** with the formation of carboxylic acid and some unknown fragment as the by-product.[20] From these reactions we detected the corresponding acid (**15**), which could support the rationality of this concomitant pathway (Scheme 4).

CONCLUSION

In conclusion, a novel and efficient copper-catalyzed aerobic oxidative C−C bond cleavage of ketone with dioxygen activation has been developed. This method provides a practical, neutral, and mild synthetic approach to α-ketoesters, which are important units in biologically active molecules. The usage of molecular oxygen (1 atm) as oxidant and reactant makes this transformation very green and practical. Further studies to clearly understand the reaction mechanism and the synthetic applications are ongoing in our laboratory.

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.

AUTHOR INFORMATION

Corresponding Author

jiaoning@bjmu.edu.cn

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For some reviews on C−C bond activation, see: (a) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245. (b) Bishop, K. C., III. *Chem. Rev.* **1976**, *76*, 461. (c) Gooßen, L. J.; Rodríguez, N.; Gooßen, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3100. (d) Rybtchinski, B.; Milstein, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 870. (e) Park, Y. J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008**, *41*, 222. (f) Jun, C.-H. *Chem. Soc. Rev.* **2004**, *33*, 610. (g) Nájera, C.; Sansano, J. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2452. (h) Tobisu, M.; Chatani, N. *Chem. Soc. Rev.* **2008**, *37*, 300. (i) Horino, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 2144. (j) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (k) de Meijere, A., Ed. *Carbocyclic Three- and Four-Membered Ring Compounds*; Houben-Weyl Methods in Organic Chemistry, Thieme: Stuttgart, 1996; Vol. *E17a−c*. (l) de Meijere, A. *Chem. Rev.* **2003**, *103*, 931.

(2) For some selected examples in the recent 3 years, see: (a) He, C.; Gou, S.; Huang, L.; Lei, A. *J. Am. Chem. Soc.* **2010**, *132*, 8273. (b) Seiser, T.; Cramer, N. *J. Am. Chem. Soc.* **2010**, *132*, 5340. (c) Sattler, A.; Parkin, G. *Nature* **2010**, *463*, 523. (d) Song, R.-J.; Liu, Y.; Hu, R.-X.; Liu, Y.-Y.; Wu, J.-C.; Yang, X.-H.; Li, J.-H. *Adv. Synth. Catal.* **2011**, *353*, 1467. (e) Tobisu, M.; Kinuta, H.; Kita, Y.; Rémond, E.; Chatani, N. *J. Am. Chem. Soc.* **2012**, *134*, 115. (f) Hirata, Y.; Yada, A.; Morita, E.; Nakao, Y.; Hiyama, T.; Ohashi, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2010**, *132*, 10070. (g) Hu, P.; Zhang, M.; Jie, X.; Su, W. *Angew. Chem., Int. Ed.* **2012**, *51*, 227. (h) Li, H.; Li, W.; Liu, W.; He, Z.; Li, Z. *Angew. Chem., Int. Ed.* **2011**, *50*, 2975. (i) Waibel, M.; Cramer, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 4455. (j) Jun, C.-H.; Lee, H.; Lim, S.-G. *J. Am. Chem. Soc.* **2001**, *123*, 751. (k) Li, H.; Li, Y.; Zhang, X.-S.; Chen, K.; Wang, X.; Shi, Z.-J. *J. Am. Chem. Soc.* **2011**, *133*, 15244. (l) Baidya, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2011**, *133*, 13880. (m) Zhang, C.; Xu, Z.; Shen, T.; Wu, G.; Zhang, L.; Jiao, N. *Org. Lett.* **2012**, *14*, 2362. (n) Wang, C.; Deng, L.; Yan, J.; Wang, H.; Luo, Q.; Xi, Z. *Chem. Commun.* **2009**, 4414. (o) Takahashi, T.; Kuzuba, Y.; Kong, F.; Nakajima, K.; Xi, Z. *J. Am. Chem. Soc.* **2005**, *127*, 17188.

(3) For some reviews about aerobic oxidative reactions, see: (a) Punniyamurthy, T.; Velusamy, S.; Iqbal, J. *Chem. Rev.* **2005**, *105*, 2329. (b) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400. (c) Sigman, M. S.; Jensen, D. R. *Acc. Chem. Res.* **2006**, *39*, 221. (d) Gligorich, K. M.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 6612. (e) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3381. (f) Wu, W.; Jiang, H. *Acc. Chem. Res.* **2012**, *45*, 1736. (g) Campbell, A. N.; Stahl, S. S. *Acc. Chem. Res.* **2012**, *45*, 851.

(4) For some selected examples about copper-cataltzed reactions on dioxygen activation in the recent 3 years, see: (a) Garcia-Bosch, I.; Company, A.; Frisch, J. R.; Torrent-Sucarrat, M.; Cardellach, M.; Gamba, I.; Güell, M.; Casella, L.; Que, L.; Ribas, X., Jr.; Luis, J. M.; Costas, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2406. (b) Chiba, S.; Zhang, L.; Lee, J.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 7266. (c) Zhang, C.; Jiao, N. *J. Am. Chem. Soc.* **2010**, *132*, 28. (d) Wang, H.; Wang, Y.; Liang, D.; Liu, L.; Zhang, J.; Zhu, Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 5678. (e) Schröder, K.; Join, B.; Amali, A. J.; Junge, K.; Ribas, X.; Costas, M.; Beller, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 1425. (f) Zhang, C.; Zhang, L.; Jiao, N. *Adv. Synth. Catal.* **2012**, *354*, 1293. (g) Liu, Q.; Wu, P.; Yang, Y.; Zeng, Z.; Liu, J.; Yi, H.; Lei, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 4666. (h) Xu, Z.; Zhang, C.; Jiao, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 11367. (i) Li, X.; Huang, L.; Chen, H.; Wu, W.; Huang, H.; Jiang, H. *Chem. Sci.* **2012**, *3*, 3463. (j) Du, F.-T.; Ji, J.-X. *Chem. Sci.* **2012**, *3*, 460.

(5) For some reviews on dehydrogenative functionalization in the recent 5 years, see: (a) Whited, M. T.; Grubbs, R. H. *Acc. Chem. Res.* **2009**, *42*, 1607. (b) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013. (c) Herrerias, C. I.; Yao, X.; Li, Z.; Li, C.-J. *Chem. Rev.* **2007**, *107*, 2546. (d) Díaz-Requejo, M. M.; Pérez, P. J. *Chem. Rev.* **2008**, *108*, 3379. (e) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (f) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (g) Copéret, C. *Chem. Rev.* **2010**, *110*, 656. (h) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (i) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890. (j) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704. (k) Gunay, A.; Theopold, K. H. *Chem. Rev.* **2010**, *110*, 1060. (l) Balcells, D.; Colt, E.; Eisenstein, O. *Chem. Rev.* **2010**, *110*, 749. (m) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082. (n) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (o) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215.

(6) For some methods through esteration of α-keto acids and α-keto acyl halides, see: (a) Kashima, C.; Shirahata, Y.; Tsukamoto, Y. *Heterocycles* **1998**, *49*, 459. (b) Kayser, M. M.; Mihovilovic, M. D.; Kearns, J.; Feicht, A.; Stewart, J. D. *J. Org. Chem.* **1999**, *64*, 6603. (c) Wipf, P.; Stephenson, C. R. J. *Org. Lett.* **2003**, *5*, 2449.

(7) For some methods through double carbopalladative esterification, see: (a) Ozawa, V.; Kawasaki, N.; Yamamoto, T.; Yamamoto, A. *Chem. Lett.* **1985**, 567. (b) Sakakura, T.; Yamashita, H.; Kobayashi, T.; Hayashi, T.; Tanaka, M. *J. Org. Chem.* **1987**, *52*, 5733.

(8) For some methods through oxidation of α-hydroxy esters, see: (a) Reddy, S. R.; Stella, S.; Chadha, A. *Synth. Commun.* **2012**, *42*, 3493. (b) Hosseinzadeh, R.; Mohadjerani, M.; Tajbakhsh, M.; Nouzarian, M. *Synth. Commun.* **2011**, *41*, 1725. (c) Johnston, E. V.; Karlsson, E. A.; Tran, L.-H.; Aakermark, B.; Baeckvall, J.-E. *Eur. J. Org. Chem.* **2010**, *10*, 1971. (d) Pandey, S. K.; Bisai, A.; Singh, V. K. *Synth. Commun.* **2007**, *37*, 4099.

(9) For some other methods, see: (a) Screttas, C. G.; Steele, B. R.; Micha-Screttas, M.; Heropoulos, G. A. *Org. Lett.* **2012**, *14*, 5680. (b) Hu, F.; Guan, X.; Shi, M. *Tetrahedron* **2012**, *68*, 4782. (c) Wusiman, A.; Tusun, X.; Lu, C.-D. *Eur. J. Org. Chem.* **2012**, *16*, 3088. (d) Moriyama, K.; Takemura, M.; Togo, H. *Org. Lett.* **2012**, *14*, 2414. (e) Raghunadh, A.; Meruva, S. B.; Kumar, N. A.; Kumar, G. S.; Rao, L. V.; Kumar, U. K. S. *Synthesis* **2012**, *44*, 283. (f) Kim, S. H.; Kim, K. H.; Kim, J. N. *Adv. Synth. Catal.* **2011**, *353*, 3335. (g) Su, Y.; Zhang, L.; Jiao, N. *Org. Lett.* **2011**, *13*, 2168. (h) Freire, F.; Seco, J. M.; Quinoa, E.; Riguera, R. *Org. Lett.* **2010**, *12*, 208.

(10) (a) Griess, P. *Philos. Trans. R. Soc. (London)* **1864**, *13*, 377. (b) Nie, Y.; Xiao, R.; Xu, Y.; Montelione, G. T. *Org. Biomol. Chem.* **2011**, *9*, 4070. (c) Elsebai, M. F.; Kehraus, S.; Lindequist, U.; Sasse, F.; Shaaban, S.; Gutschow, M.; Josten, M.; Sahl, H.-G.; Konig, G. M. *Org. Biomol. Chem.* **2011**, *9*, 802. (d) Hemeon, I.; Bennet, A. J. *Synthesis* **2007**, *13*, 1899. (e) Morgan, E. H.; Laurell, C. B. *Nature* **1963**, *197*, 921. (f) Unger, F. M. *Adv. Carbohydr. Chem. Biochem.* **1981**, *38*, 323. (g) Wardrop, D. J.; Zhang, W. *Tetrahedron Lett.* **2002**, *43*, 5389. (h) Burke, S. D.; Sametz, G. M. *Org. Lett.* **1999**, *1*, 71;Schulte, K.Meinzinger, E. DE 949,521 1956; *Chem. Abstr.* **1958**, *52*, 19024.

(11) (a) Gravenfors, Y.; Viklund, J.; Blid, J.; Ginman, T.; Karlström, S.; Kihlström, J.; Kolmodin, K.; Lindström, J.; Berg, S.; Kieseritzky, F.; Slivo, C.; Swahn, B.-M.; Olsson, L.-L.; Johansson, P.; Eketjäll, S.; Fälting, J.; Jeppsson, F.; Strömberg, K.; Janson, J.; Rahm, F. *J. Med. Chem.* **2012**, *55*, 9297. (b) Boughton, B. A.; Hor, L.; Gerrard, J. A.; Hutton, C. A. *Bioorg. Med. Chem.* **2012**, *20*, 2419. (c) Sarabu, R.; Bizzarro, F. T.; Corbett, W. L.; Dvorozniak, M. T.; Geng, W.; Grippo, J. F.; Haynes, N.-E.; Hutchings, S.; Garofalo, L.; Guertin, K. R.; Hilliard, D. W.; Kabat, M.; Kester, R. F.; Ka, W.; Liang, Z.; Mahaney, P. E.; Marcus, L.; Matschinsky, F. M.; Moore, D.; Racha, J.; Radinov, R.; Ren, Y.; Qi, L.; Pignatello, M.; Spence, C. L.; Steele, T.; Tengi, J.; Grimsby, J. *J. Med. Chem.* **2012**, *55*, 7021.

(12) For the aerobic oxidative coupling of alcohols for esters, see: (a) Gowrisankar, S.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 5139. (b) Liu, C.; Wang, J.; Meng, L.; Deng, Y.; Li, Y.; Lei, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 5144. (c) Zhang, M.; Zhang, S.; Zhang, G.; Chen, F.; Cheng, J. *Tetrahedron Lett.* **2011**, *52*, 2480.

(13) (a) Samuni, A.; Krishna, C. M.; Riesz, P.; Finkelstein, E.; Russo, A. *Free Radical Biol. Med.* **1989**, *6*, 141. (b) Zhao, H.; Joseph, J.; Zhang, H.; Karoui, H.; Kalyanaraman, B. *Free Radical Biol. Med.* **2001**, *31*, 599. (c) Zhang, C.; Xu, Z.; Zhang, L.; Jiao, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 11088.

(14) (a) Håkansson, P.; Nguyen, T.; Nair, P. B.; Edge, R.; Stulz, E. *Phys. Chem. Chem. Phys.* **2013**, *15*, 10930. (b) Caretti, I.; Carter, E.; Fallis, I. A.; Murphy, D. M.; Doorslae, S. V. *Phys. Chem. Chem. Phys.* **2011**, *13*, 20427.

(15) (a) Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346. (b) Covell, D. J.; White, M. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 6448.

(16) (a) Milas, N. A. *Chem. Rev.* **1932**, *10*, 295. (b) Rieche, A.; Hoeft, E.; Schultze, H. *Chem. Ber.* **1964**, *97*, 195. (c) Berkessel, A., Ed.; *Compounds with One Saturated Carbon-Heteroatom Bond. Peroxides*; Thieme: Stuttgart, Science of Synthesis: Houben-Weyl Methods of Molecular Transformations, 2009; Vol. *38*, pp 9−141. (d) Davies, A. G.; Foster, R. V.; Nery, R. *J. Chem. Soc.* **1954**, 2204. (e) Pintér, Á.; Sud, A.; Sureshkumar, D.; Klussmann, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 5004.

(17) (a) Rao, H.; Wang, P.; Li, C.-J. *Eur. J. Org. Chem.* **2002**, 6503. (b) Tokumaru, K. *Res. Chem. Intermed.* **1996**, *22*, 255.

(18) Schmidt, A.-K. C.; Stark, C. B. W. *Org. Lett.* **2011**, *13*, 4164.

(19) (a) Simándi, L.; Simándi, T. M.; May, Z.; Besenyei, G. *Coord. Chem. Rev.* **2003**, *245*, 85. (b) Schank, K.; Beck, H.; Werner, F. *Helv. Chim. Acta* **2000**, *83*, 1611. (c) Pusterla, I.; Bode, J. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 513. (d) Liu, H.; Dong, C.; Zhang, Z.; Wu, P.; Jiang, X. *Angew. Chem., Int. Ed.* **2012**, *51*, 12570.

(20) (a) Chiba, S.; Zhang, L.; Ang, G. Y.; Hui, B. W.-Q. *Org. Lett.* **2010**, *12*, 2052. (b) Mecinovic, J.; Hamed, R. B.; Schofield, C. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2796. (c) Wang, A.; Jiang, H. *J. Am. Chem. Soc.* **2008**, *130*, 5030.