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# Iron Catalysis for Room Temperature Aerobic Oxidation of Alcohols to Carboxylic Acids

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## Supporting Information Placeholder

**ABSTRACT:** Oxidation from alcohols to carboxylic acids, a class of essential chemicals in daily life, academic laboratories, and industry, is a fundamental reaction, usually using at least a stoichiometric amount of an expensive and toxic inorganic oxidant. Here, an efficient and practical sustainable oxidation technology of alcohols to carboxylic acids using pure O<sub>2</sub> or even O<sub>2</sub> in air as the oxidant has been developed: utilizing a catalytic amount each of Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O/TEMPO/**KCl**, a series of carboxylic acids were obtained from alcohols (also aldehydes) in high yields at room temperature. A 55 gram-scale reaction was demonstrated using air. As a synthetic application, the first total synthesis of a naturally occurring allene, i.e., phlomic acid, was accomplished.

As one of the most abundant metals in Earth's crust, iron is widely distributed in nature. Of particular interest, the heme iron compounds in hemoglobin play an important role in molecular oxygen transportation and activation in life at ambient temperature.<sup>1</sup> Iron is also a part of oxidative enzymes.<sup>2</sup> Thus, iron catalysts<sup>3</sup> may be a potentially viable catalyst for aerobic oxidation of alcohols to acids. On the other hand, the oxidation from alcohols to carboxylic acids is one of the most fundamental chemical transformations with great potential for daily life, academic research, and industry.<sup>4</sup> Traditionally, toxic and expensive oxidants such as KMnO<sub>4</sub>,<sup>5</sup> CrO<sub>3</sub>,<sup>6</sup> etc. have to be used, which would cause severe environmental burden due to the formation of waste from at least stoichiometric amounts of these oxidants, thus, it is highly desirable to develop environmentally friendly new oxidation protocols. Molecular oxygen is a clean, atom economic and sustainable oxidant. Although aerobic oxidation of alcohols to aldehydes is becoming a mature technology,<sup>7</sup> the process towards carboxylic acids remains to be a fundamental challenge since few studies on aerobic oxidization of alcohols to carboxylic acids have been reported with rather limited success or scope even with noble metal catalyst(s).<sup>8-16</sup> So far, a general catalytic method for the aerobic oxidation of alcohols to carboxylic acids has NOT been very well established. Here, we wish to report an efficient protocol to achieve this transformation with a broad scope and selectivity using a readily

available iron catalyst and TEMPO under pure oxygen or air conditions.

Based on the above literature data, the challenge to obtain carboxylic acids from alcohols via aerobic oxidation may be in the process of transforming aldehydes to carboxylic acids since most such aerobic oxidations of alcohols stop at the stage of aldehydes.<sup>7,17-19</sup> During further study of selective oxidation of alcohols to aldehydes catalyzed by Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O and TEMPO,<sup>19</sup> we observed that when lauraldehyde **1a** was treated with 10 mol% each of Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O, TEMPO, and **KCl** with an O<sub>2</sub> balloon in DCE at rt for 12 h, 94% isolated yield of lauric acid **2a** was formed. This recipe could be applied to the oxidation of normal alkyl aliphatic aldehydes (Table 1, Entries 1 and 3), cyclohexane-carboxaldehyde **1b** (Table 1, Entry 2), 3-phenylpropanal (Table 1, Entry 4) to the corresponding carboxylic acids in high yields. In addition, the yield remains high when a balloon of air was applied instead of pure O<sub>2</sub>.

Table 1. Aerobic oxidation of aldehydes using O<sub>2</sub> or air as oxidant.<sup>a</sup>

$$\text{RCHO } \mathbf{1} \xrightarrow[\text{O}_2 \text{ or air, DCE, r.t., 12 h or 16 h}]{\text{Fe(NO}_3)_3 \cdot 9\text{H}_2\text{O (10 mol\%)} \\ \text{TEMPO (10 mol\%)} \\ \text{KCl (10 mol\%)}} \text{RCOOH } \mathbf{2}$$

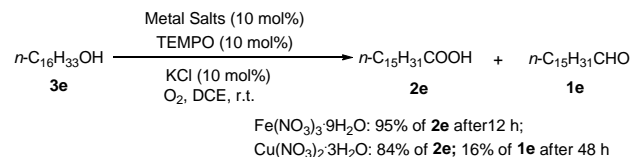
Entry	Substrate	Product	Yield of <b>2</b>	
			O <sub>2</sub> (12 h) Yield of <b>2</b> (%) <sup>b</sup>	Air (16 h) Yield of <b>2</b> (%) <sup>b</sup>
1	<i>n</i> -C <sub>11</sub> H <sub>23</sub> CHO ( <b>1a</b> )	<i>n</i> -C <sub>11</sub> H <sub>23</sub> COOH ( <b>2a</b> )	94	88
2	CyCHO ( <b>1b</b> )	CyCOOH ( <b>2b</b> )	90	83
3	<i>n</i> -C <sub>7</sub> H <sub>15</sub> CHO ( <b>1c</b> )	<i>n</i> -C <sub>7</sub> H <sub>15</sub> COOH ( <b>2c</b> )	96	97
4	Ph(CH <sub>2</sub> ) <sub>2</sub> CHO ( <b>1d</b> )	Ph(CH <sub>2</sub> ) <sub>2</sub> COOH ( <b>2d</b> )	96	98

<sup>a</sup> The reaction was carried out on a 1.0 mmol scale of **1** in 4.0 mL of DCE with a bag of O<sub>2</sub> or air. <sup>b</sup> Isolated yield.

With these observations, we attempted to apply this recipe to the direct oxidation of alcohols into carboxylic acids: cetyl alcohol **3e** was oxidized to palmitic acid **2e** within 12 h under

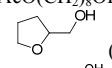
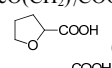
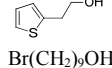
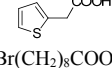
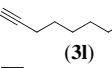
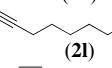
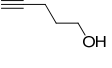
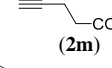
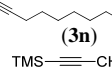
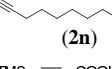
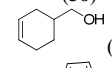
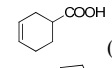
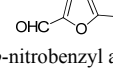
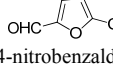
standard conditions (Scheme 1). We screened different nitrates and observed that  $\text{Co}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$  (**3e** recovery 84%),  $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$  (**3e** recovery 83%) and  $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$  (**3e** recovery 100%) were not effective at all.  $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$  worked much slower (Scheme 1).

Scheme 1. Aerobic oxidation of **3e** with different metal nitrates.



With standard conditions in hand, we explored the generality of the reaction with various alcohols. Apart from aliphatic alcohols (Table 2, Entries 1, 2, and 4) and 3-phenylpropanol (Table 2, Entry 3), the aerobic oxidation also tolerates synthetically useful functional groups: ester (Table 2, Entries 5-6), heterocycle (Table 2, Entries 7-8), halogen (Table 2, Entry 9), ether (Table 2, Entry 10) have all been well tolerated. Alcohols with a terminal or non-terminal C-C triple bond could all be oxidized to acids in moderate or high yields (Table 2, Entries 11-13). TMS-substituted propargyl alcohol could be converted into the corresponding acid under both  $\text{O}_2$  and air conditions when extending the time to 36 h and 48 h (Table 2, Entry 14). 3-Cyclohexene-1-methanol (**3p**) could be oxidized to **2p** smoothly with 20 mol% of TEMPO (Table 2, Entry 15). Two examples of arylmethyl alcohols were also presented (Table 2, Entries 16 and 17).

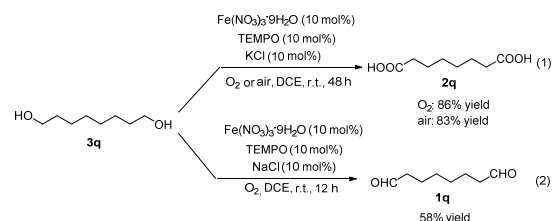
Table 2. Aerobic oxidation of alcohols using  $\text{O}_2$  or air as oxidant<sup>a</sup>

Entry	Alcohol	Product	$\text{O}_2$	Air
			(12 h)	(16 h)
			Yield of <b>2</b> (%) <sup>b</sup>	Yield of <b>2</b> (%) <sup>b</sup>
1	$n\text{-C}_{12}\text{H}_{25}\text{OH}$ ( <b>3a</b> )	$n\text{-C}_{11}\text{H}_{23}\text{COOH}$ ( <b>2a</b> )	100	95
2	$n\text{-C}_8\text{H}_{17}\text{OH}$ ( <b>3c</b> )	$n\text{-C}_7\text{H}_{15}\text{COOH}$ ( <b>2c</b> )	85	89
3	$\text{Ph}(\text{CH}_2)_2\text{OH}$ ( <b>3d</b> )	$\text{Ph}(\text{CH}_2)_2\text{COOH}$ ( <b>2d</b> )	98	99
4	$n\text{-C}_{16}\text{H}_{33}\text{OH}$ ( <b>3e</b> )	$n\text{-C}_{15}\text{H}_{31}\text{COOH}$ ( <b>2e</b> )	99	98
5	$\text{MeOOC}(\text{CH}_2)_5\text{OH}$ ( <b>3f</b> )	$\text{MeOOC}(\text{CH}_2)_4\text{COOH}$ ( <b>2f</b> )	94	86
6	$\text{AcO}(\text{CH}_2)_8\text{OH}$ ( <b>3g</b> )	$\text{AcO}(\text{CH}_2)_7\text{COOH}$ ( <b>2g</b> )	93	93
7	 ( <b>3h</b> )	 ( <b>2h</b> )	70	73
8	 ( <b>3i</b> )	 ( <b>2i</b> )	85	81
9	$\text{Br}(\text{CH}_2)_9\text{OH}$ ( <b>3j</b> )	$\text{Br}(\text{CH}_2)_8\text{COOH}$ ( <b>2j</b> )	98	98
10	$n\text{-C}_6\text{H}_{13}\text{O}(\text{CH}_2)_2\text{OH}$ ( <b>3k</b> )	$n\text{-C}_6\text{H}_{13}\text{OCH}_2\text{COOH}$ ( <b>2k</b> )	92	84
11	 ( <b>3l</b> )	 ( <b>2l</b> )	80	80
12	 ( <b>3m</b> )	 ( <b>2m</b> )	60	68
13	 ( <b>3n</b> )	 ( <b>2n</b> )	95	90
14	$\text{TMS}-\text{C}\equiv\text{C}-\text{CH}_2\text{OH}$ ( <b>3o</b> )	$\text{TMS}-\text{C}\equiv\text{C}-\text{COOH}$ ( <b>2o</b> )	66 <sup>c</sup>	65 <sup>d</sup>
15	 ( <b>3p</b> )	 ( <b>2p</b> )	81 <sup>d,e</sup>	70 <sup>d,e</sup>
16	 ( <b>3q</b> )	 ( <b>2q</b> )	55 <sup>d,e,f</sup>	-
17	$p\text{-nitrobenzyl alcohol}$	4-nitrobenzaldehyde	76	-

<sup>a</sup> The reaction was carried out on a 1.0 mmol scale of **3** in 4.0 mL of DCE with a bag of  $\text{O}_2$  or air. <sup>b</sup> Isolated yield. <sup>c</sup> The reaction time was 36 h. <sup>d</sup> The reaction time was 48 h. <sup>e</sup> 20 mol% TEMPO was used. <sup>f</sup> 20 mol% of  $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$  was used.

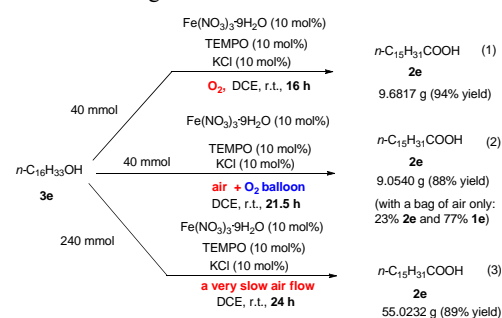
We could prepare octanedioic acid under the standard  $\text{O}_2$  or air conditions using 10 mol% each of  $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ /TEMPO/KCl system within 48 h (Scheme 2, Eq. 1) or 1,8-octane-dial using 10 mol% each of  $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ /TEMPO/NaCl within 12 h, from 1,8-octanediol, respectively (Scheme 2, Eq. 2).<sup>19</sup>

Scheme 2. Selective oxidation of 1,8-octanediol.



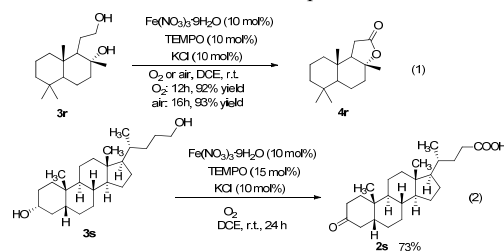
To further demonstrate the practicality of the catalytic system, a 40 mmol reaction of cetyl alcohol **3e** was conducted using pure  $\text{O}_2$  to give 9.6817 g of palmitic acid **2e** in 94% isolated yield (Scheme 3, Eq. 1 and apparatus (a) in SI). The purification of product only requires simple recrystallization of the crude product after removing the solvent instead of column chromatography. The reaction on the same scale may also be conducted by using a bag of air (size: 70 L, oxygen bag used in hospital) for 1.5 h first, which was followed by the supplement of a bag of pure  $\text{O}_2$  (commercial size: 2 L, may be expanded to 5 L, the white gas bag in apparatus (b) in SI) to provide the consumed oxygen in the air bag efficiently (Scheme 3, Eq. 2 and apparatus (b) in SI). Such a practice avoids the unsafe high concentration of pure  $\text{O}_2$  over DCE to make the procedure safer. The same reaction using a bag of air only was incomplete affording acid **2e** (23% yield by NMR) and aldehyde **1e** (77% yield by NMR). Furthermore, by applying a slow flow of air, the reaction was also easily conducted on the scale of 240 mmol scale in 89% isolated yield (Scheme 3, Eq. 3 and apparatus (c) in SI).<sup>20</sup>

Scheme 3. Large scale reactions with  $\text{O}_2$  or air



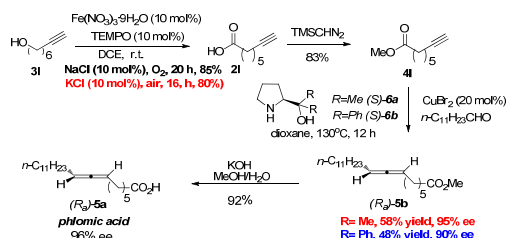
The sesquiterpenediol **3r** could also be oxidized to sclareolide **4r** in 92% yield with both pure  $\text{O}_2$  or air (Scheme 4, Eq. 1). Substrate **3s** bearing a steroid skeleton could also be oxidized to the corresponding acid **2s** smoothly in 73% yield with the secondary alcohol in the molecule **3s** being oxidized to the ketone group as well (Scheme 4, Eq. 2).

Scheme 4. Aerobic oxidation of complicated alcohols **3r** and **3s**.



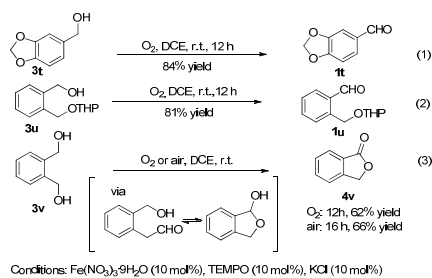
Furthermore, the reaction was applied to the first total synthesis of phlomic acid, a naturally occurring axial chiral allene, which was isolated from *Phlomis* in 1997.<sup>21</sup> By applying EATA (enantioselective allenation of alkynes reaction)<sup>22</sup> developed in our group as the key step for the formation of the chiral allene entity, we reasoned that phlomic acid ( $R_a$ )-**5a** could be synthesized from terminal alkyne **3i** and aldehyde **1a** (Scheme 5). Thus, 7-octynoic acid was prepared from 7-octyn-1-ol in 80% yield using 10 mol% each of  $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ /TEMPO/KCl catalyst in air. After esterification, ester **4i** was submitted to the EATA reaction. After screening of different prolinol derivatives, we found that when (*S*)-dimethylprolinol was used for the first time in the  $\text{CuBr}_2$ -catalyzed EATA reaction, product ( $R_a$ )-**5b** with 95% ee could be prepared in 58% yield while with (*S*)-diphenylprolinol, the ee dropped to 90%. ( $R_a$ )-**5b** was treated with KOH in  $\text{MeOH}/\text{H}_2\text{O}$  at 60 °C to yield *phlomic acid* (( $R_a$ )-**5a**) in 92% yield and 96% ee.

Scheme 5. Total synthesis of phlomic acid using aerobic oxidation and EATA.



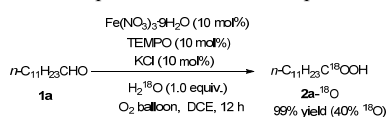
In addition, it was observed that the oxidation of benzylic alcohol such as piperitol (**3t**) or mono THP-protected 1,2-benzenedimethanol (**3u**) stopped at the stage of aldehyde (Scheme 6, Eq. 1-2). However, reaction of 1,2-benzenedimethanol (**3v**) gave 62% yield of isobenzofuran-1(3*H*)-one (**4v**) (Scheme 6, Eq. 3), indicating the possibility of the oxidation to aldehyde, then forming the corresponding hemiacetal, which was further oxidized to lactone.

Scheme 6. Aerobic oxidation of benzylic alcohol and 1,2-benzenedimethanol.



When the oxidation reaction of lauraldehyde **1a** was conducted in the presence of 1 equivalent of  $\text{H}_2^{18}\text{O}$ , lauric acid **2a**- $^{18}\text{O}$  was isolated in 99% yield with 40%  $^{18}\text{O}$  incorporation, indicating the involvement of  $\text{H}_2\text{O}$  in the reaction process. The lower level of  $^{18}\text{O}$  incorporation was caused by the 0.9 equivalent of  $\text{H}_2\text{O}$  in 10 mol% of  $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$  and the in-situ generated water (see Scheme 9).

Scheme 7. Isotopic  $^{18}\text{O}$  distribution experiment with **1a**



As a further evidence, reddish brown gas ( $\text{NO}_2$ ) was observed during the reaction and  $\text{NO}$  was detected by GS-MS (see supporting information for experimental details). We also

observed that alcohol **3a** was completely consumed within 6 hours, generating aldehyde **1a** as the initial product. Acid **2a** emerged after 2 h (pages S34-S35 in the SI). As a comparison, the same reaction with 10 mol% of  $\text{NaCl}$  failed to afford the formation of the carboxylic acid **2a** within 4 h (pages S36-S37 in the SI). Furthermore, the reaction with 5 mol% each of  $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ , TEMPO, and  $\text{NaCl}$ , the reaction conditions in the previous report,<sup>19</sup> led to the highly selective formation of aldehyde- $\text{No}$  acid was formed (pages S38-S39 in the SI). The counter ion effect of inorganic chloride on the oxidation is as follows:  $\text{K}^+ \sim \text{Rb}^+ > \text{Cs}^+ \sim \text{Na}^+ > \text{Mg}^{2+} \sim \text{Zn}^{2+} > \text{Bu}_4\text{N}^+$  (pages S34-S49 in the SI), which in accordance of the basicity order (although not a linear one);<sup>23</sup> when 18-crown-6 or kryptofix 222 (a typical cryptand) was used together with  $\text{KCl}$ , the reaction became much slower, indicating an obvious effect of the cation (pages S50-S53 in SI).

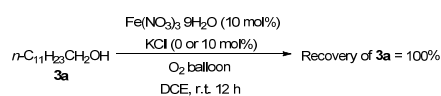
In addition, control experiments showed that the oxidation of aldehyde **1a** in oxygen alone failed to afford the acid **2a** (Table 3 Entry 2); the reaction in the absence of  $\text{KCl}$  is slower (Table 3 Entry 3); as reported,<sup>24</sup>  $\text{Fe}(\text{III})$  alone may afford peroxy acid **7a**, via the reaction of the acyl radical intermediate with oxygen. This peroxy acid may react with the starting aldehyde to afford the acid **2a** finally as a mixture (Table 3 Entry 4); in the absence of TEMPO, the reaction is slower and the formation of peroxy acid **7a** was also observed (Table 3 Entry 5); as a comparison under the standard reaction condition, the formation of peroxy acid **7a** was NOT detected (Table 3, Entry 1). The reaction could not occur without  $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$  (Table 3, Entry 6).

Table 3. Aerobic oxidation of aldehyde **1a**- the role of each catalytic component

Entry	$\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (x mol%)	TEMPO (y mol%)	$\text{KCl}$ (z mol%)	(NMR yield, %)		
				<b>1a</b>	<b>2a</b>	<b>7a</b>
1	10	10	10	0	95	0
2	-	-	-	98	2	0
3	10	10	-	14	81	0
4	10	-	-	0	78	11
5	10	-	10	15	64	12
6	-	10	10	100	0	0

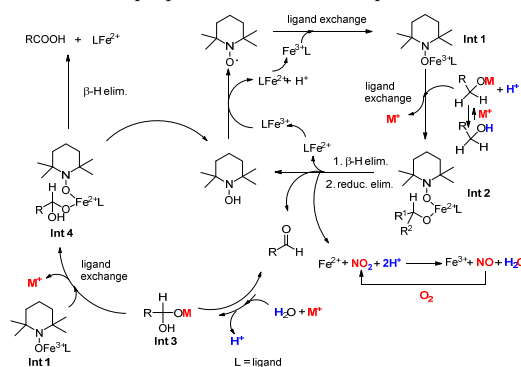
However, no reaction was observed for alcohol **3a** in the absence of TEMPO (Scheme 8)

Scheme 8. Aerobic oxidation of **3a**.



Based on these observations, we proposed a rationale for this aerobic oxidation (Scheme 9). **Int 1**, the coupling product of TEMPO and  $\text{Fe}^{3+}$ ,<sup>25</sup> reacted with the alcohol to form **Int 2**. **Int 2** produced the aldehyde, TEMPOH, and  $\text{Fe}^{2+}$  after  $\beta$ -H elimination and reductive elimination.  $\text{Fe}^{2+}$  would be reoxidized to  $\text{Fe}^{3+}$  by  $\text{NO}_2$  in the reaction system while  $\text{NO}_2$  was reduced to  $\text{NO}$  and regenerated by its reaction with  $\text{O}_2$ . TEMPOH was converted back into TEMPO by its reaction with  $\text{Fe}^{3+}$ . The aldehyde hydrate **Int 3** was formed by attack of  $\text{H}_2\text{O}$  at the aldehyde mediated by  $\text{Fe}^{3+}$ . The aldehyde hydrate **Int 3** would undergo a similar process to produce the carboxylic acid. As noted in our previous report, the reaction in the absence of  $\text{NaCl}$  is slow, the chloride may be working as the ligand (L) to iron.<sup>19</sup> According to data with different  $\text{MCl}$  in SI, different  $\text{M}^+$  may have a different effect on the ligand exchange rate for the formation of **Int 2**, **Int 3** and **Int 4**. However, further studies are required for the mechanism.

Scheme 9. A proposed mechanism—the possible role of the cation.



In summary, we have developed a practical and efficient environmentally benign catalytic protocol of  $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$  /TEMPO/MCl to accomplish the oxidation of alcohols to carboxylic acids using  $\text{O}_2$  or air as terminal oxidant at room temperature while the oxidation of benzylic alcohols stopped in the aldehyde stage. The reaction may be easily conducted on 9 to 55 gram-scale with pure  $\text{O}_2$ , air/pure  $\text{O}_2$ , or air flow conditions. First total synthesis of natural product phlomic acid was accomplished using this aerobic oxidation protocol and EATA. Further studies especially the mechanism are being actively pursued in this laboratory.

## ASSOCIATED CONTENT

### Supporting Information

Experimental procedure, spectroscopic data, and the  $^1\text{H}/^{13}\text{C}$  NMR spectra of all the 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 interests.

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