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## Bis(methoxypropyl) ether-promoted oxidation of aromatic alcohols into aromatic carboxylic acids and aromatic ketones with O<sub>2</sub> under metal- and base-free conditions†

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We describe an eco-friendly, practical and operationally simple procedure for the bis(methoxypropyl) ether-promoted oxidation of aromatic alcohols into aromatic carboxylic acids and aromatic ketones with atmospheric dioxygen as the sole oxidant. This chemical process is clean with high conversion and good selectivity, and an external initiator, catalyst, additive and base are not required. The virtue of this reaction is highlighted by its easily available and economical raw materials and excellent functional group tolerance (acid-, base- and oxidant-labile groups).

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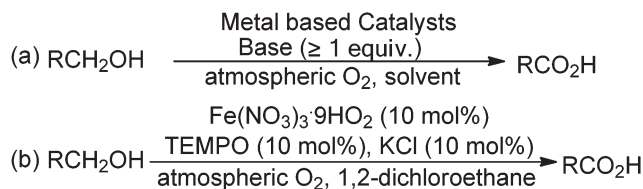
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### Introduction

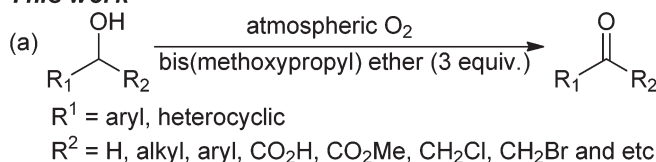
The selective oxidation of alcohols into carboxylic acids and ketones is one of the most fundamental chemical processes in the chemical industry and a challenging task in the realm of green organic synthesis.<sup>1</sup> Generally, toxic and expensive (super)stoichiometric quantities of inorganic or organic oxidants<sup>2</sup> are employed to achieve this chemical transformation, which would lead to an environmental burden due to the generation of a large amount of chemical waste. Compared with traditional oxidants, molecular oxygen<sup>3</sup> is perfect for incorporation into organic molecules because of its low cost, natural abundance and eco-friendly advantages.<sup>1a,4</sup>

Many impressive achievements have been accomplished in base-promoted<sup>5</sup> noble metal–ligand complex (Ni,<sup>6</sup> Ag,<sup>7</sup> Pt,<sup>8</sup> Rh,<sup>9</sup> Ru,<sup>10</sup> and Pd<sup>11</sup>) and commercially unavailable supported-metal catalyst<sup>12</sup> catalyzed oxidation of alcohols with molecular oxygen (Scheme 1a). Although these improved protocols revealed remarkable characteristics, all the processes show the need for two-step operation procedures (oxidation and acidification), noble metal catalysts and (super)stoichiometric

### Previous works



### This work



**Scheme 1** Oxidation of aromatic alcohols with atmospheric oxygen.

amounts of strong bases to facilitate the oxidation reaction, which not only leads to environmental pollution problems and high manufacturing cost but also hampers subsequent direct transformations. In 2016, Ma's group developed the oxidation of alcohols catalyzed by Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O/TEMPO/KCl concertedly in 1,2-dichloroethane (Scheme 1b).<sup>13</sup> However, to our knowledge, there exists no example of metal- and base-free oxidation of alcohols into carbonyl compounds with atmospheric oxygen. With our continuing interest in green organic synthesis,<sup>14</sup> we herein present a practical and eco-friendly bis(methoxypropyl) ether-promoted oxidation of aromatic alcohols into aromatic carboxylic acids and aromatic ketones with atmospheric dioxygen as the sole oxidant under catalyst- and base-free conditions.

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## Results and discussion

We commenced our studies using benzyl alcohol (**1a**) as the model substrate. Gratifyingly, when oxidation of **1a** was carried out in ethylglyme (3 equiv.) with O<sub>2</sub> as the sole oxidant at 100 °C, a 56% yield (determined by GC-MS) of benzoic acid (**2a**) based on 63% conversion of **1a** was obtained after 18 hours (Table 1, entry 1). Further investigation experiments indicated that the use of high-boiling-point ethers led to moderate to high yields (entries 2 and 3), whereas the relatively low-boiling-point ethers (boiling point ≤101 °C) or other non-ether promoters resulted in a trace amount of **2a** or no conversion of **1a** (entries 4–11). The efficiency of the oxidation of alcohols was strongly affected by the peroxy radical producing ability of ether solvents.<sup>15</sup> Subsequent investigation on the effect of the reaction temperature suggested that such a reaction is quite sensitive to reaction temperature variations (entries 12–16) and 120 °C was appropriate for the oxidation (entry 13). It is noteworthy that no oxidation product was detected when the oxidation was performed at 70 °C (entry 16). A 91% conversion of **1a** could be detected in the presence of 2 equiv. of bis(methoxypropyl) ether<sup>16</sup> (entry 17). However, further decreasing the amount of bis(methoxypropyl)

ether led to lower yields of **2a** (entry 18). Running the reaction in the dark did not affect the reaction outcome, clearly ruling out the possibility that this oxidation involves a photochemical process (entry 19). A significantly lower yield of **2a** was observed when ambient air was used instead of molecular oxygen (entry 20). With 2 equiv. of H<sub>2</sub>O<sub>2</sub> or TBHP as the oxidant under a nitrogen atmosphere, a trace amount of **2a** was detected (entries 21 and 22). When the oxidation was conducted in the absence of bis(methoxypropyl) ether, a trace amount of **2a** was detected by GC-MS after running the reaction for 24 h (entry 23). Conducting the oxidation in freshly distilled bis(methoxypropyl) ether did not affect the reaction yield but prolonged the reaction time to 15 h.

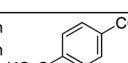
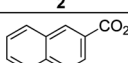
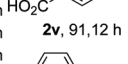
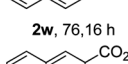
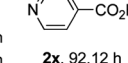
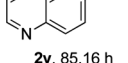
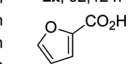
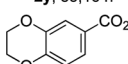
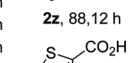
Under the optimal reaction conditions (Table 1, entry 13), the scope of this oxidation was examined with respect to both aromatic primary alcohols and aromatic secondary alcohols. As illustrated in Table 2, substituted benzyl alcohols with various synthetically valuable functional groups underwent oxidation to selectively deliver the desired benzoic acids in good to excellent yields (**2a–2v**). Neither the electronic nor steric factors of benzyl alcohols had a significant influence on this transformation except for the strong electron-withdrawing nitro-group (**2o**). To our satisfaction, sensitive functional groups, including acid-labile (**2g**), oxidizable (**2h** and **2i**), and base-labile (**2p** and **2q**) groups, did not reduce the reaction effectiveness. Notably, 4-vinylbenzyl alcohol (**1r**) is readily oxidized into 4-vinylbenzoic acid (**2r**) in 82% yield and the conjugated C=C bond did not have a significant influence under the standard reaction conditions. Terephthalic acid (**2v**), which is a monomer for polyester (PET) and has an annual consump-

Table 1 Optimization of the reaction conditions<sup>a</sup>

PhCH <sub>2</sub> OH		O <sub>2</sub> balloon		PhCOOH	
<b>1a</b>		promoter, conditions		<b>2a</b>	
Entry	Promoter (equiv.)	[O]	Conditions	Con. (%)	Yield <sup>b</sup> (%)
1	Ethylglyme (3)	O <sub>2</sub>	100 °C, 18 h	63	56
2	BME (3) <sup>c</sup>	O <sub>2</sub>	100 °C, 18 h	83	79
3	NMP (3)	O <sub>2</sub>	100 °C, 18 h	34	22
4	1,4-Dioxane (3)	O <sub>2</sub>	100 °C, 18 h	19	5
5	Glyme (3)	O <sub>2</sub>	100 °C, 12 h	Trace	Trace
6	THF (3)	O <sub>2</sub>	100 °C, 12 h	Trace	Trace
7	2-MeTHF (3)	O <sub>2</sub>	100 °C, 12 h	Trace	Trace
8	1-Pentanol (3)	O <sub>2</sub>	100 °C, 12 h	Trace	Trace
9	PEG 400 (3)	O <sub>2</sub>	100 °C, 12 h	Trace	Trace
10	MeCN (3)	O <sub>2</sub>	100 °C, 12 h	N.D.	N.D.
11	DCE (3)	O <sub>2</sub>	100 °C, 12 h	N.D.	N.D.
12	BME (3)	O <sub>2</sub>	110 °C, 15 h	93	86
13	BME (3)	O <sub>2</sub>	120 °C, 12 h	98	97
14	BME (3)	O <sub>2</sub>	90 °C, 18 h	42	31
15	BME (3)	O <sub>2</sub>	80 °C, 18 h	35	17
16	BME (3)	O <sub>2</sub>	70 °C, 18 h	N.D.	N.D.
17	BME (2)	O <sub>2</sub>	120 °C, 16 h	91	88
18	BME (1)	O <sub>2</sub>	120 °C, 16 h	62	58
19 <sup>c</sup>	BME (3)	O <sub>2</sub>	120 °C, 12 h	99	97
20	BME (3)	Air	120 °C, 12 h	60	52
21 <sup>d</sup>	BME (3)	TBHP	120 °C, 24 h	15	7
22 <sup>d</sup>	BME (3)	H <sub>2</sub> O <sub>2</sub>	120 °C, 24 h	13	5
23	—	O <sub>2</sub>	120 °C, 24 h	Trace	Trace
24 <sup>e</sup>	BME (3)	O <sub>2</sub>	120 °C, 15 h	98	97

<sup>a</sup> Reaction conditions: **1a** (0.3 mmol), promoter (3 equiv.), heat, O<sub>2</sub> balloon. <sup>b</sup> Estimated by GC-MS. <sup>c</sup> This oxidation was carried out in the dark. <sup>d</sup> This oxidation was conducted under nitrogen. <sup>e</sup> Using freshly distilled bis(methoxypropyl) ether (by passing through the activated alumina column). BME: bis(methoxypropyl) ether.

Table 2 Reaction scope of primary alcohols<sup>a</sup>

R-CH <sub>2</sub> OH		O <sub>2</sub> balloon		R-CO <sub>2</sub> H	
<b>1</b>		bis(methoxypropyl) ether (3 equiv.), 120 °C		<b>2</b>	
R = 4-H,	<b>2a</b> , 93, 12 h		<b>2v</b> , 91, 12 h		<b>2w</b> , 76, 16 h
4-Me,	<b>2b</b> , 95, 12 h		<b>2x</b> , 92, 12 h		<b>2y</b> , 85, 16 h
4-Pr,	<b>2c</b> , 89, 10 h		<b>2z</b> , 88, 12 h		<b>2aa</b> , 82, 16 h
4-OH,	<b>2d</b> , 81, 16 h		<b>2ab</b> , 85, 16 h		<b>2ac</b> , 78 <sup>b</sup> , 16 h
4-OMe,	<b>2e</b> , 82, 12 h		<b>2ad</b> , 82, 12 h		
4-OCF <sub>3</sub> ,	<b>2f</b> , 96, 9 h				
4-OTBDS,	<b>2g</b> , 91, 10 h				
4-SH,	<b>2h</b> , 84, 16 h				
4-SMe,	<b>2i</b> , 87, 11 h				
4-CF <sub>3</sub> ,	<b>2j</b> , 91, 13 h				
4-F,	<b>2k</b> , 95, 10 h				
4-Cl,	<b>2l</b> , 95, 10 h				
4-Br,	<b>2m</b> , 93, 10 h				
4-I,	<b>2n</b> , 92, 10 h				
4-NO <sub>2</sub> ,	<b>2o</b> , 68 <sup>c</sup> , 16 h				
4-CN,	<b>2p</b> , 81, 16 h				
4-CO <sub>2</sub> Me,	<b>2q</b> , 85, 16 h				
4-C=C	<b>2r</b> , 82, 14 h				
3-Me,	<b>2s</b> , 81, 16 h				
2-Me,	<b>2t</b> , 78, 16 h				
3,4-di-Cl,	<b>2u</b> , 83, 16 h				





<sup>a</sup> All reactions were carried out in a 5 mL round flask in the presence of **1** (0.6 mmol) and bis(methoxypropyl) ether (1.8 mmol) at 120 °C; isolated yields (%) are reported. <sup>b</sup> 2.4 mmol of bis(methoxypropyl) ether was used. <sup>c</sup> 80% conversion of the starting material **1o**.

tion of 12.6 million tons, was obtained in 91% yield from 1,4-benzenedimethanol (**1v**) through double oxidation. The oxidation of the polycyclic and heteroaromatic motifs was possible and proceeded in good to excellent yields (**2w–2ab**), thus further enhancing the substrate scope of our present oxidation. It is worth noting that ferrocenemethanol was also a suitable substrate for this oxidation, affording the desired ferrocenecarboxylic acid (**2ac**) in 78% yield, which highlighted that this oxidation is a useful approach for producing metal-containing carboxylic acids. In addition, when phthalyl alcohol was used as the substrate, isobenzofuran-1(3*H*)-one (**2ad**) was obtained.

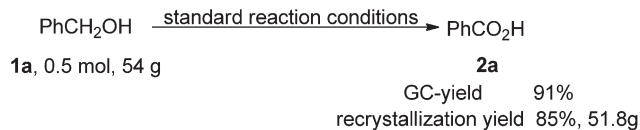
Subsequently, a series of distinct aromatic secondary alcohols **3** were investigated under the optimal conditions (Table 3). 1-Phenethylalcohols possessing either electron-rich or electron-poor groups at the 4-positions of the benzene ring were well tolerated in this transformation, delivering the expected ketones in excellent yields (**4a–4f**).  $\beta$ -Substituted 1-phenethylalcohols (**3g–3l**) with various functional groups smoothly underwent the oxidation process to provide the corresponding products (**4g–4l**). Furthermore, a series of cyclic secondary alcohols (**3m–3p**) could be successfully converted to the expected cyclic ketones in 90–92% yields (**4m–4p**).

In order to demonstrate the practicability of this strategy, oxidation of benzyl alcohol **1a** was conducted on a 54 g scale under standard conditions (Scheme 2). To our delight, a GC yield (91%) and a selectivity comparable to those of the small-scale oxidation experiment were furnished. Importantly, the

**Table 3** Reaction scope of secondary alcohols<sup>a</sup>

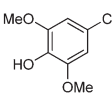

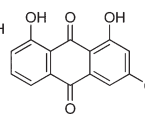

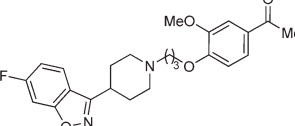

$\text{R}^1-\text{CH}(\text{OH})-\text{R}^2 \xrightarrow[\text{bis(methoxypropyl) ether (3equiv.), 120 }^\circ\text{C}]{\text{O}_2 \text{ balloon}}$ $\text{R}^1-\text{C}(=\text{O})-\text{R}^2$	
FG = H, <b>4a</b> , 94, 8 h 4-Me, <b>4b</b> , 93, 8 h 4-OMe, <b>4c</b> , 92, 8 h 4-F, <b>4d</b> , 96, 8 h 4-Cl, <b>4e</b> , 92, 8 h 4-Br, <b>4f</b> , 94, 8 h	R = Et, <b>4g</b> , 91, 8 h Ph, <b>4h</b> , 90, 8 h CO <sub>2</sub> H, <b>4i</b> , 86, 9 h CO <sub>2</sub> Me, <b>4j</b> , 92, 9 h CH <sub>2</sub> Cl, <b>4k</b> , 85, 8 h CH <sub>2</sub> Br, <b>4l</b> , 82, 8 h
 <b>4m</b> , 91, 8 h	 <b>4n</b> , 92, 8 h
 <b>4o</b> , 92, 8 h	 <b>4p</b> , 90, 8 h

<sup>a</sup> All reactions were carried out in a 5 mL round flask in the presence of **3** (0.6 mmol) and bis(methoxypropyl) ether (1.8 mmol) at 120 °C; isolated yields (%) are reported.



**Scheme 2** Large scale experiment.

**Table 4** Oxidation of complex molecules and one-pot transformations<sup>a</sup>

Substrate	Yield (%)	Time (h)	Product	Yield (%)	Time (h)
	93%	12 h		86%	
	93%	14 h		84%	
	90%	10 h		76%	

<sup>a</sup> The oxidations of complex molecules were carried out in a 5 mL round flask in the presence of alcohol **1** or **3** (0.6 mmol) and bis(methoxypropyl) ether (2.4 mmol) at 120 °C; isolated yields (%) are reported.

reaction mixture was easily recrystallized to afford pure benzoic acid in 85% yield (51.8 g).

Furthermore, several complex bioactive molecules were subjected to the optimal reaction conditions. As shown in Table 4, the oxidation of all the complex aromatic alcohol substrates proceeded well with the current oxidation, delivering the expected products in excellent yields (**2ae**, **2af** and **4q**). Since silica-gel column chromatographic purification is universally required for the metal- and organo-catalyzed oxidation reaction to remove the catalyst residue and by-product that might restrain subsequent transformations, the present oxidation was environmentally benign and did not employ any external catalyst, initiator or additive. To further prove the superiority of this approach, three one-pot reactions starting from **1a** were conducted. The un-purified benzoic acid smoothly underwent the subsequent esterification (**1a** → **5a**),<sup>17</sup> hydrazidation (**1a** → **5b**)<sup>18</sup> and cyclization (**1a** → **5c**)<sup>19</sup> in good yields.

It has been widely acknowledged that etheric compounds could be converted to peroxide in the presence of dioxygen at room temperature but the rate is slow. We conjectured that the oxidation rate is related to the concentration of dioxygen, and explored the dioxygen concentration factor by studying the kinetic behavior of the oxidation of **1a** with O<sub>2</sub> in bis(methoxypropyl) ether. Various O<sub>2</sub> concentrations (indicated by different colors in Fig. 1) were achieved by manipulating O<sub>2</sub> partial pressure under 1 atmosphere pressure. Decreasing the partial pressure of O<sub>2</sub> had a negative effect on the reaction rate, confirming our hypothesis that O<sub>2</sub> concentration is a crucial parameter for the reaction rate enhancement.

To gain insight into the oxidation process, a series of control experiments were carried out. The presence of trapping agents (such as BHT or TEMPO) strongly suppressed the carbonyl compound formation, which indicated that a free radical pathway may be involved in the present oxidation reaction (Scheme 3a and b). When bis(methoxypropyl) ether was exposed to an oxygen atmosphere at 70 °C for 2 min, we successfully obtained a strong peroxy radical signal ( $g = 2.002$ , AN

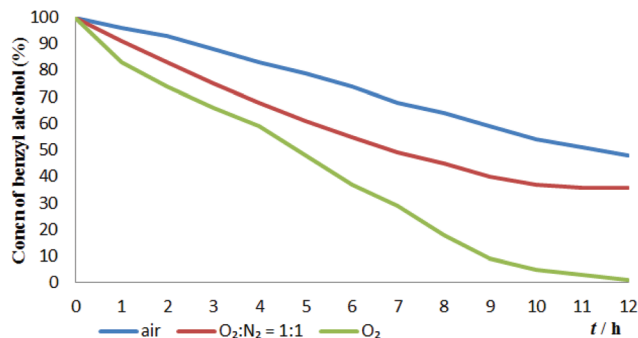
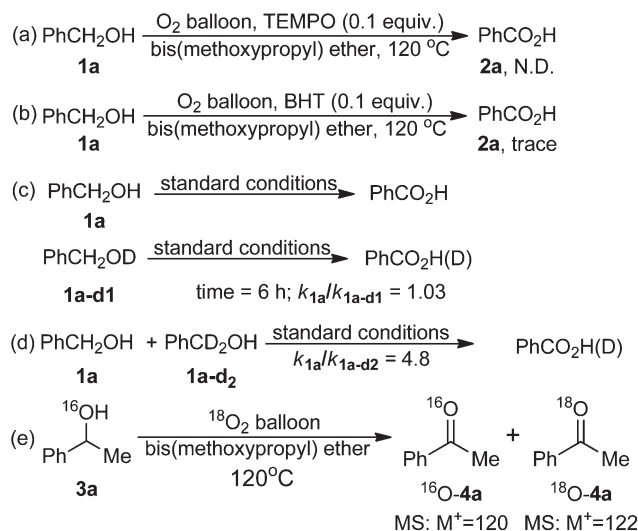


Fig. 1 Kinetic profile of the oxidation of **1a** (0.6 mmol) in bis(methoxypropyl) ether (1.8 mmol) at 120 °C for 12 h under different oxygen concentrations.



Scheme 3 Control experiments.

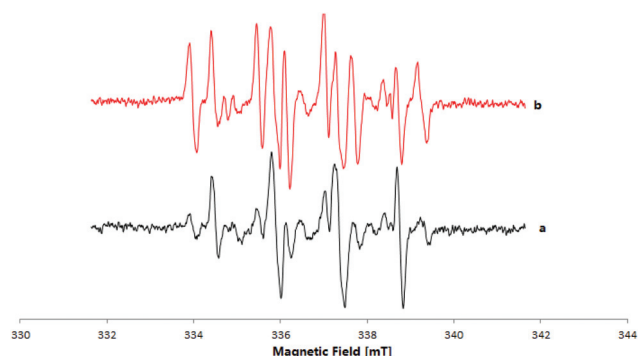
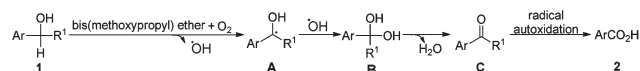


Fig. 2 Electron paramagnetic resonance (EPR) experiments.

= 1.46 mT,  $\Delta H = 1.37$  mT) through EPR experiment (Fig. 2a).<sup>20</sup> After the treatment of benzyl alcohol **1a** with bis(methoxypropyl) ether under the aforementioned conditions, the signal of a carbon-centered radical ( $g = 2.002$ ,  $\Delta N = 1.54$  mT,  $\Delta H =$



Scheme 4 The proposed mechanism.

2.206 mT) was clearly observed (Fig. 2b). These observations demonstrated that a peroxy radical was first produced and then the peroxy radical reacted with alcohol to generate a carbon-centered radical.

The kinetic isotope effect (KIE) was investigated with respect to both alcoholic O–H/D bonds and benzylic C(sp<sub>3</sub>)–H/D bonds. A clear  $k_{1a}/k_{1a-d1}$  value of 1.03 was determined by two independent reactions using benzyl alcohol (**1a**) and benzyl alcohol-d1 (**1a-d1**) as the substrates (Scheme 3c). The intermolecular  $k_H/k_D$  value for **1a** and benzyl alcohol-d2 (**1a-d2**) was determined to be 4.8 (Scheme 3d). Taken together, these experimental results suggested that the cleavage of the benzylic C(sp<sub>3</sub>)–H bond would be the rate-determining step in the oxidation process. When <sup>18</sup>O<sub>2</sub> was employed as the sole oxidant, the oxidation of **3a** afforded a mixture of <sup>16</sup>O-labeled and <sup>18</sup>O-labeled product **4a**, which confirmed that the oxygen atom of the carbonyl originated from atmospheric dioxygen and the cleavage of the C(sp<sub>3</sub>)–O bond of the alcohol was involved (Scheme 3e).

Based on the above experimental results and previous related reports,<sup>15b,d,21</sup> a possible mechanism of this oxidation is outlined in Scheme 4. Bis(methoxypropyl) ether first reacted with hot dioxygen to produce a hydroperoxide, which oxidized aromatic alcohol **1** to generate a carbon-centered radical **A** with the release of a hydroxyl radical. The intermediate **A** was readily coupled with the hydroxyl radical to generate a diol intermediate **B**, which is rapidly converted into carbonyl compound **C** (aromatic aldehyde or aromatic ketone), along with water as a byproduct. Then the aromatic aldehyde **C** (R<sup>1</sup> = H) was oxidized by hot dioxygen to generate the corresponding aromatic carboxylic acid **2** through radical autoxidation.<sup>22</sup>

## Conclusions

In summary, we have for the first time established an eco-friendly and practical protocol for the synthesis of aromatic carboxylic acids and aromatic ketones through bis(methoxypropyl) ether-promoted oxidation of aromatic alcohols with atmospheric dioxygen as the sole oxidant under external initiator-, catalyst- and base-free conditions. Noteworthy characteristics of this oxidation are as follows: (1) the reaction proceeds under mild reaction conditions with remarkable functional-group tolerance, as demonstrated by the acid-, base-labile and oxidant-sensitive groups that remain intact under the standard conditions; (2) the dual roles of bis(methoxypropyl) ether simplified this oxidation, thus several one-pot sequential transformations starting from alcohols were successfully accomplished; (3) the oxidation could be readily scaled up to a 50 g scale.



## Experimental

### General procedure for the synthesis of carbonyl compound 2 and ketones 4

A mixture of alcohols 1 or 3 (0.6 mmol) and bis(methoxypropyl) ether (1.8 mmol) was added to a 5 mL round-bottom flask with an oxygen balloon at room temperature, then the contents were stirred at 120 °C. The reaction typically took 12 hours. The progress of this oxidation was monitored by TLC or GC-MS. Upon the completion of the reaction, the reaction mixture was cooled down to room temperature. The reaction mixture was purified by silica gel column chromatography to afford the desired 2 and 4.

## Conflicts of interest

There are no conflicts to declare.

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