

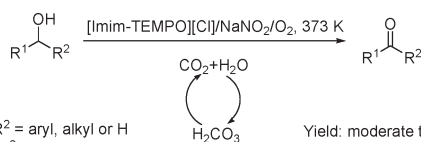
**Self-Neutralizing in Situ Acidic CO<sub>2</sub>/H<sub>2</sub>O System for Aerobic Oxidation of Alcohols Catalyzed by TEMPO Functionalized Imidazolium Salt/NaNO<sub>2</sub>**

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R<sup>1</sup> = aryl, R<sup>2</sup> = aryl, alkyl or H  
R<sup>1</sup> = alkyl, R<sup>2</sup> = alkyl or H

Yield: moderate to almost quantitative

A reversible in situ acidic catalytic system comprising recyclable TEMPO functionalized imidazolium salt ([Imim-TEMPO][Cl])/NaNO<sub>2</sub>/CO<sub>2</sub>/H<sub>2</sub>O was developed for selective transformation of a series of aliphatic, allylic, heterocyclic, and benzylic alcohols to the respective carbonyl compounds. Notably, the system avoids any conventional acid and can eliminate unwanted byproducts, facilitate reaction, ease separation of the catalyst and product, and also provide a safe environment for oxidation involving oxygen gas.

Recently, carbon dioxide as either an abundant and cheap carbon resource or a nontoxic reaction medium has attracted great attention and gradually has become an active area of research.<sup>1</sup> Particularly, CO<sub>2</sub> appears to be an ideal solvent for use in oxidation, because CO<sub>2</sub> as a reaction medium could not only eliminate byproducts originating from solvents but also provide a safe reaction environment with excellent mass and heat transfer for aerobic oxidations.<sup>2</sup>

On the other hand, acids are the most common industrial catalysts but have the disadvantage of requiring postreaction neutralization and salt disposal. In this context, the reversible

reaction of CO<sub>2</sub> with water to form carbonic acid is well-known, resulting in low pH values of about 3. This provides in situ formation of the acid catalyst. Indeed, self-neutralizing in situ acid catalysis from CO<sub>2</sub> has shown great applications,<sup>3–5</sup> e.g., decarboxylation, diazotization, and cyclization, with profound advantages for both green chemistry and improved economics. Particularly, the CO<sub>2</sub>/H<sub>2</sub>O system provides in situ acid formation for catalysis which can be readily neutralized by the removal of CO<sub>2</sub>. In other words, the acid formation is reversible upon the removal of CO<sub>2</sub>. Thus carbonic acid offers simple neutralization and does not require any waste disposal.

The selective oxidation of primary and secondary alcohols into the corresponding aldehydes and ketones is undoubtedly one of the most important and challenging transformations in organic chemistry.<sup>6</sup> Recently, utilization of the stable nitroxyl radical 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) in combination with oxygen as terminal oxidant for oxidation of alcohols<sup>3</sup> appears very appealing in view of catalytic efficacy and green chemistry. Liang and Hu have made a great breakthrough in this respect. First, they developed a three-component transition metal-free catalyst system, including TEMPO/Br<sub>2</sub>/NaNO<sub>2</sub>,<sup>7</sup> which would be considered to go through a three-sequence-cycle with a two-electron-transfer mechanism. In the system, bromine would offer bromide ion as well as create acid, which causes NaNO<sub>2</sub> to release NO and NO<sub>2</sub>. Continuing their own work, a NaNO<sub>2</sub>-based catalyst system comprising TEMPO/1, 3-dibromo-5,5-dimethylhydantoin/NaNO<sub>2</sub>,<sup>8</sup> or TEMPO/HCl/NaNO<sub>2</sub><sup>9</sup> was reported, in which acid conditions are essential either by initial input or being created in situ. On the other hand, Karimi<sup>10</sup> also developed a heterogeneous catalyst system consisting of the SBA-15 supported TEMPO/Bu<sub>4</sub>NBr/NaNO<sub>2</sub> to recover the supported TEMPO in CH<sub>3</sub>CO<sub>2</sub>H. Accordingly, the acidic condition is essential to the TEMPO-catalyzed oxidation of alcohols when simple, inexpensive, and biodegradable NaNO<sub>2</sub> is used as the activator of oxygen. Although much progress has been made, toxic, highly volatile, corrosive conventional acids, such as HCl, HBr, or CH<sub>3</sub>CO<sub>2</sub>H, are commonly used in the literature and the

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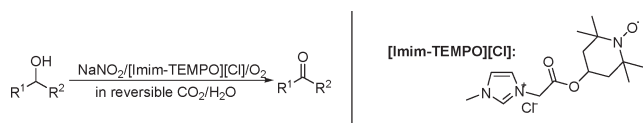
(3) Typical examples for utilizing the acidity of the CO<sub>2</sub>/H<sub>2</sub>O system: (a) Hunter, S. E.; Ehrenberger, C. E.; Savage, P. E. *J. Org. Chem.* **2006**, *71*, 6229. (b) Rayner, C. M. *Org. Process Res. Dev.* **2007**, *11*, 121. (c) Tundo, P.; Loris, A.; Selva, M. *Green Chem.* **2007**, *9*, 777. (d) Yamaguchi, A.; Hiyoshi, N.; Sato, O.; Bando, K. K.; Shirai, M. *Green Chem.* **2009**, *11*, 48. (e) Cheng, H. Y.; Meng, X. C.; Liu, R. X.; Hao, Y. F.; Yu, Y. C.; Cai, S. X.; Zhao, F. Y. *Green Chem.* **2009**, *11*, 1227.

TABLE 1. Aerobic Oxidation of Benzyl Alcohol<sup>a</sup>

entry	P <sub>O2</sub> /MPa	P <sub>CO2</sub> + P <sub>O2</sub> /MPa	T/K	V <sub>H2O</sub> /mL	t/h	conv/ % <sup>b</sup>	yield <sup>b</sup> of aldehyde/%
1	1	4	373	0	2	5	3
2	1	1	373	0.1	2	3	2
3 <sup>c</sup>	1	4	373	0.1	2	1	1
4 <sup>d</sup>	1	4	373	0.1	2	0.5	0.4
5	0	3	373	0.1	2	4	3
6	1	4	373	0.1	2	73	73
7	1	4	353	0.1	2	41	41
8	1	4	333	0.1	2	11	10
9	1	4	303	0.1	24	45	44
10	1	2	373	0.1	2	66	66
11	1	7	373	0.1	2	52	52
12	1	11	373	0.1	2	93	93
13	1	15	373	0.1	2	37	37
14	1	11	373	0.2	2	97	97
15 <sup>e</sup>	1	11	373	0.2	2	0	0
16 <sup>f</sup>	1	11	373	0.2	2	93	93
17 <sup>g</sup>	1	11	373	0.2	2	92	92
18	1	11	373	0.5	2	40	40
19	1	11	373	0.05	2	56	56
20 <sup>h</sup>	1	11	373	0.2	2	52	51
21 <sup>i</sup>	1	11	373	0.2	12	34	34
22 <sup>j</sup>	1	11	373	0.2	2	20	19

<sup>a</sup>Unless otherwise noted, all the experiments were run with benzyl alcohol (0.2 mL, 1.93 mmol), NaNO<sub>2</sub> (6.7 mg, 5 mol %), and [Imim-TEMPO][Cl] (31.9 mg, 5 mol %). <sup>b</sup>Determined by GC. <sup>c</sup>Without [Imim-TEMPO][Cl]. <sup>d</sup>Without NaNO<sub>2</sub>. <sup>e</sup>The second run after entry 14, only benzyl alcohol were replenished. <sup>f</sup>The third run after entry 14, NaNO<sub>2</sub> and benzyl alcohol were replenished. <sup>g</sup>The fourth run after entry 14, NaNO<sub>2</sub> and benzyl alcohol were replenished. <sup>h</sup>[Imim-TEMPO][Cl] (1 mol %). <sup>i</sup>[Imim-TEMPO][Cl] (0.5 mol %). <sup>j</sup>TEMPO instead of [Imim-TEMPO][Cl].

### SCHEME 1. Aerobic Oxidation of Alcohols Catalyzed by NaNO<sub>2</sub>/[Imim-TEMPO][Cl]/CO<sub>2</sub>/H<sub>2</sub>O



inherent disadvantages related to the workup procedure are unavoidable.

In our previous work,<sup>11</sup> recyclable acidic imidazolium salts were developed to replace those conventional acids used in the TEMPO-catalyzed oxidation of alcohols. We herein would like to apply the self-neutralizing acids that form in situ in the CO<sub>2</sub>/H<sub>2</sub>O system to an aerobic oxidation of alcohols catalyzed by [Imim-TEMPO][Cl]/NaNO<sub>2</sub> (Scheme 1) in order to avoid the tedious synthesis of the above recyclable acid. Improved reaction with facilitated separation of the catalyst and products were achieved.

The exploratory experiments were started by testing this protocol and screening the reaction conditions with benzyl alcohol as the model substrate (Table 1). Oxygen, CO<sub>2</sub>, water, NaNO<sub>2</sub>, and [Imim-TEMPO][Cl] were essential to the aerobic oxidation of benzyl alcohol (Table 1, entries 1–5). Preliminary results indicate that the reaction temperature has a significant effect on the oxidation. Good catalytic performance was shown at 373 K (entry 6). Subsequently, the partial pressure of CO<sub>2</sub> was examined. Delightedly, the presence of CO<sub>2</sub> was found to enhance the oxidation (entry 2 vs. 10). In the range of 1–14 MPa, the appropriate CO<sub>2</sub> pressure could be 10 MPa, at which excellent yield and selectivity were attained (entry 12).

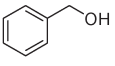
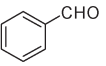
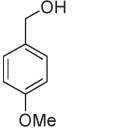
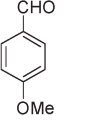
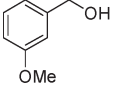
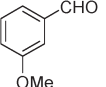
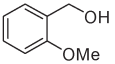
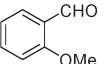
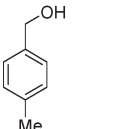
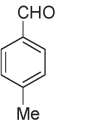
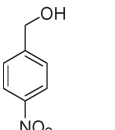
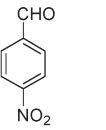
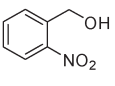
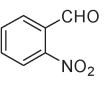
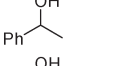
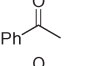
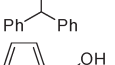
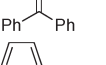
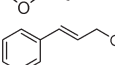
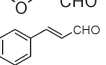
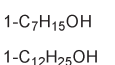
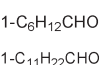
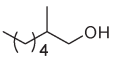
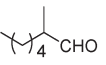
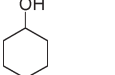
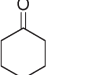
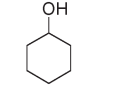
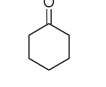
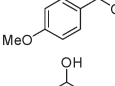
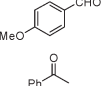
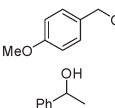
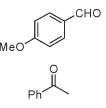
As the TEMPO-catalyzed oxidation of alcohols with NaNO<sub>2</sub> to activate dioxygen would be a pH-dependent reaction and the pH of the CO<sub>2</sub>/H<sub>2</sub>O system at a given temperature and pressure is constant,<sup>5</sup> the effect of the

quantity of water was further evaluated under 11 MPa of total pressure and 373 K (entries 12, 14, 18, and 19). An almost quantitative result was obtained in the presence of 0.2 mL of water (entry 14). It is also worth mentioning that the reaction could go smoothly even with 0.5 mol % of [Imim-TEMPO][Cl] (entry 21).

Another practical feature of the designed catalyst system is the facile separation from the reaction mixture. Moreover, the remaining [Imim-TEMPO][Cl] in the aqueous phase could be recovered. In each cycle, the catalysts were dissolved in water, and the product could be extracted by diethyl ether (see the Supporting Information). Fortunately, [Imim-TEMPO][Cl] could be reused at least three times with slight loss of activity as anticipated (entries 14, 16, and 17). In addition, NaNO<sub>2</sub> should be replenished for the subsequent run (entry 15).

To examine the utility and generality of this methodology for the oxidation of alcohols, we applied the present catalyst system to a variety of alcohols as shown in Table 2. Obviously, all primary benzylic alcohols were converted into their corresponding aldehydes in high yields with excellent selectivity (entries 1–7). It was found that electronic properties and steric hindrance of the substituents on the benzene rings have a negligible influence on the reactivity in the cases of primary benzylic alcohols. Whereas the reactivity of the secondary benzylic alcohols was affected by  $\alpha$  substituent groups probably due to the steric hindrance, moderate yields were attained by prolonging the reaction time (entries 8 and 9). Notably, a type of heterocyclic alcohol (such as 2-furfuryl-methanol), being less active in many reported systems, worked well in the NaNO<sub>2</sub>/[Imim-TEMPO][Cl]/CO<sub>2</sub>/H<sub>2</sub>O system. Furthermore, the present protocol was also applicable to the oxidation of allylic alcohol such as cinnamyl alcohol, which is sensitive to acid during the aerobic oxidation. Moderate yield of cinnamaldehyde was obtained with ca. 5% of benzyl aldehyde under 3 MPa of CO<sub>2</sub> (entry 11).

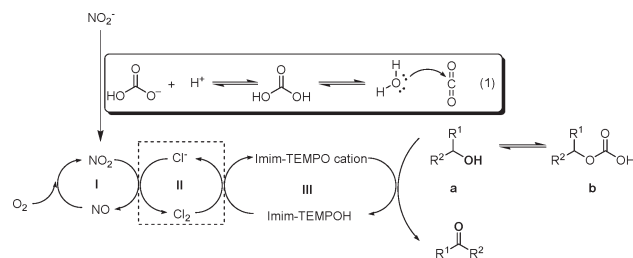
TABLE 2. Catalytic Aerobic Oxidation of Various Alcohols<sup>a</sup>

Entry	Substrate	product	t/h	Conv /% <sup>b</sup>	Yield/% <sup>b</sup>
1			8	97	97
2			3	100	100(98)
3			3	91	89(85)
4			5	83	83(80)
5			3	100	99.7(98)
6			3	100	99(97)
7			3	100	100(99)
8			12	56	55(53)
9			12	50	49(48)
10			5	87	78
11 <sup>c</sup>			12	50	40(36)
12	1-C <sub>7</sub> H <sub>15</sub> OH	1-C <sub>6</sub> H <sub>12</sub> CHO	12	27	19
13	1-C <sub>12</sub> H <sub>25</sub> OH	1-C <sub>11</sub> H <sub>22</sub> CHO	12	48	45(41)
14	1-C <sub>16</sub> H <sub>33</sub> OH	1-C <sub>15</sub> H <sub>30</sub> CHO	12	75	67(64)
15			12	26	23
16			24	(59)	(48)
17	1-C <sub>16</sub> H <sub>33</sub> OH	1-C <sub>15</sub> H <sub>30</sub> CHO	12	44	38
				+	+
				0	0
18			4	81	77
				+	+
				0	0

<sup>a</sup>Reaction conditions: alcohol (1.93 mmol), [Imim-TEMPO][Cl] (31.9 mg, 5 mol %), NaNO<sub>2</sub> (6.7 mg, 5 mol %), V<sub>H<sub>2</sub>O</sub> = 0.2 mL, P<sub>O<sub>2</sub></sub> = 1 MPa, P<sub>O<sub>2</sub></sub> + P<sub>CO<sub>2</sub></sub> = 11 MPa, T = 373 K. <sup>b</sup>Determined by GC, and data in parentheses refer to isolated yields. <sup>c</sup>V<sub>H<sub>2</sub>O</sub> = 0.05 mL, P<sub>O<sub>2</sub></sub> = 1 MPa, P<sub>O<sub>2</sub></sub> + P<sub>CO<sub>2</sub></sub> = 4 MPa, and 5% of benzyl aldehyde was obtained.

Several aliphatic alcohols were further examined to extend the substrate scope for this methodology. In the cases of

SCHEME 2. The Proposed Mechanism for the in Situ Acid Catalysis



primary aliphatic alcohols, the longer the chain, the better the activity (entries 12–15). As expected, the formation of alkylcarboxylic acid in the system (Scheme 2, **b**) could compete with the oxidation of the alcohol. The reaction rate of forming alkylcarboxylic acid could presumably be affected by the chain length and the steric hindrance,<sup>4</sup> being in good accordance with the experimental findings. In addition, the primary aliphatic alcohols with branched chain or secondary aliphatic alcohol gave poor results possibly owing to the steric effect (entries 15 and 16).

Interestingly, the designed oxidation system proved to be chemoselective. An equimolar mixture of primary and secondary alcohols was used in the system. 1-Hexadecanol or 4-methoxybenzyl alcohol was converted to the corresponding aldehydes while secondary alcohols recovered completely (entries 17 and 18).

On the basis of the experimental results, a possible mechanism for the transition metal-free aerobic oxidation of alcohols in the CO<sub>2</sub>/H<sub>2</sub>O system was proposed as shown in Scheme 2. The designed system was completed by a two- or three-sequence cycle with a two-electron-transfer process. Intrinsically, the combination of CO<sub>2</sub> with water leads to the formation and dissociation of carbonic acid, resulting in low pH values of about 3 (Scheme 2, cycle I).<sup>3,5</sup> This provides in situ acid formation of catalysts to release nitric oxide from the NO<sub>2</sub><sup>-</sup>. TEMPO instead of [Imim-TEMPO][Cl] could also promote the reaction; however, the low solubility of TEMPO likely leads to poor catalytic activity (entry 22, Table 1). In other words, cycle II, as depicted in Scheme 2, is not required for the catalytic cycle to proceed. In this regard, TEMPO derivatives and NO<sub>2</sub> could indirectly or directly react to generate the Imim-TEMPO cation (I, III). Subsequently, Imim-TEMPO cation oxidizes the alcohol to the corresponding carbonyl compound (III). Moreover, possible formation of alkylcarboxylic acid especially for the aliphatic alcohols could have an adverse effect on the reaction (Table 2, entries 12–15).

In summary, we developed a self-neutralizing in situ acidic catalyst system from CO<sub>2</sub> comprised of a recyclable TEMPO functionalized imidazolium salt/NaNO<sub>2</sub>/CO<sub>2</sub>/H<sub>2</sub>O for the selective oxidation of a series of aliphatic, allylic, heterocyclic, and benzylic alcohols to the respective carbonyl compounds. The present protocol offers simple neutralization, which does not require any waste disposal with advantages of improved reaction, facilitated separation of the catalyst and products, and safe operation for aerobic oxidation.

## Experimental Section

**Representative Procedure for the Aerobic Oxidation of Alcohol.** A mixture of substrate (1.93 mmol), [Imim-TEMPO][Cl]

(31.9 mg, 5 mol %), NaNO<sub>2</sub> (6.7 mg, 5 mol %), and 0.20 mL of water was placed in a 25 mL autoclave equipped with an inner glass tube. CO<sub>2</sub> (2 MPa) and O<sub>2</sub> (1 MPa) were introduced into the autoclave and the system was heated to the reaction temperature. Then the final pressure was adjusted to the desired pressure at the reaction temperature by introducing the correct amount of CO<sub>2</sub>. The mixture was stirred continuously for the desired reaction time. After cooling, products were then extracted by diethyl ether and analyzed by gas chromatograph (Shimadzu GC-2014) equipped with a capillary column (RTX-5 30 m × 0.25 μm) using a flame ionization detector by comparing retention times of authentic samples. The residue was purified by column chromatography on silica gel (200–300 mesh, eluting with 20:1 petroleum ether/ethyl acetate) to afford the desired product. The isolated products were further identified with NMR spectra (Bruker-300 MHz, 400 MHz), which are consistent with those reported in the literature.<sup>7–9</sup>

**Safety Warning.** Experiments with large amounts of compressed gases, especially molecular oxygen and supercritical

fluids, are potentially hazardous and must only be carried out by using the appropriate equipment and under rigorous safety precautions. In particular, oxygen is introduced into the substrate-loaded reactor after CO<sub>2</sub>. Moreover, the oxygen content should not exceed 14 vol % when CO<sub>2</sub> is used as a reaction medium.

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**Supporting Information Available:** General experimental methods, synthetic procedure of [Imim-TEMPO][Cl], characterization of [Imim-TEMPO][Cl], and the isolated product and GC diagrams for substrates and products. This material is available free of charge via the Internet at <http://pubs.acs.org>.