

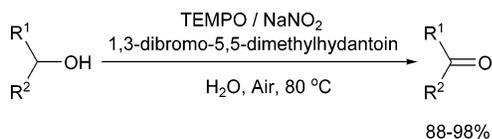
Highly Efficient Catalytic Aerobic Oxidations of Benzylic Alcohols in Water

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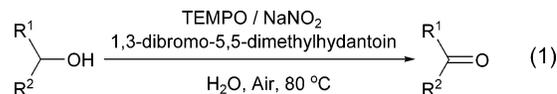
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A highly efficient catalytic system without transition metals in water has been developed for aerobic oxidations of benzylic alcohols. The newly developed catalyst system could oxidize benzylic alcohols and heteroaromatic analogues with 1 mol % TEMPO as a catalyst and with a catalytic amount of 1,3-dibromo-5,5-dimethylhydantoin and NaNO₂ as cocatalysts. Under the optimal conditions, various alcohols could be converted into their corresponding aldehydes or ketones in high yields.

The use of water as a reaction solvent has attracted great attention and become an active area of research in green chemistry because water is a cheap, safe, convenient solvent and benign to the environment.¹ Although much progress has been made with water-based catalytic systems in the past few years, there still remains a great challenge for some reactions.² Transition-metal-catalyzed aerobic oxidation of alcohols³ is one of the typical examples. Although many highly efficient aerobic alcohol oxidation systems either catalyzed by transition-metal catalysts (mainly copper,⁴ palladium,^{5,6} or ruthenium⁷) alone or in combination with nitroxyl radical 2,2,6,6-tetramethyl-piperidyl-1-oxy (TEMPO)^{8,9} have been developed, only a few examples of catalytic aerobic oxida-

tions of alcohols in water have been reported to date.^{6c,e,i} A crucial reason is that water can easily deactivate the catalyst by competing with the substrates and/or intermediates for vacant coordination sites on active metal catalysts.¹⁰ Recently, we reported a transition-metal-free aerobic oxidation system,¹¹ where a wide range of alcohols can be converted into their corresponding aldehydes or ketones in high yields with a catalytic amount of TEMPO, Br₂, and NaNO₂. As it did not involve transition metals in the catalytic system, we envision that the newly designed process could overcome the intrinsic disadvantage that transition metal catalysts were often involved in the aerobic alcohol oxidation with water as a solvent. If we could replace bromine, which is undesirable due to its hazardous nature albeit in catalytic amount, we could then establish a green aerobic alcohol oxidation system. In this communication, we report a TEMPO-catalyzed aerobic alcohol oxidation in water, using 1,3-dibromo-5,5-dimethylhydantoin and NaNO₂ as cocatalysts (eq 1).



Our previous study demonstrated that the transition-metal-free oxidation system was sequentially a cascade

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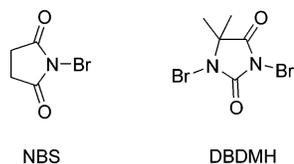


FIGURE 1. Structures of NBS and DBDMH.

TABLE 1. Aerobic Oxidation of Benzyl Alcohol^a

entry	solvent (10 mL)	H ₂ O (mL)	conversion (%) ^b	selectivity (%) ^b
1 ^c	CH ₂ Cl ₂	0	12.3	90.2
2	CH ₂ Cl ₂	0	13.9	71.9
3	CH ₂ Cl ₂	1.0	100	100
4	CH ₂ Cl ₂	2.0	72.5	100
5	CH ₂ Cl ₂	0.5	100	100
6 ^d	DCE	0.5	100	100
7	PhCl	0.5	100	98.6
8	PhF	0.5	100	100
9	toluene	0.5	100	98.8
10 ^d	TFT	0.5	100	100
11	MeCN	0.5	100	100
12	^t BuOH	0.5	86	100
13	AcOH	0.5	100	100

^a Reaction conditions: benzyl alcohol (10 mmol), TEMPO (0.1 mmol), DBDMH (0.4 mmol), NaNO₂ (0.4 mmol), air (0.4 MPa), 80 °C (oil bath temperature), 1 h. ^b Conversion and selectivity were determined by GC with area normalization. ^c NBS used as a bromine surrogate. ^d DCE = 1,2-dichloroethane; TFT = α,α,α -trifluorotoluene.

of triple redox reactions¹¹ and suggested that each of the cycles can be adjusted to match the activity of substrates. On the basis of these findings, a safer and more convenient source of positive bromine was considered, including common bromination reagents such as *N*-bromosuccinimide (NBS, Figure 1) and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH, Figure 1) in the process. We then selected benzyl alcohol as a typical substrate to test the active surrogates of bromine with the previously reported reaction conditions (10 mmol of substrate, 1 mol % TEMPO, 4 mol % NaNO₂, and 10 mL of solvent, 0.4 MPa air, 80 °C) (Table 1). NBS (entry 1) and DBDMH (entry 2) exhibited low conversions with good selectivity in TEMPO-catalyzed aerobic oxidation under the same conditions as described in the previous report, while NaBr showed no activity. We chose DBDMH for optimization since it is less expensive and commercially available in bulk as a common disinfectant.

Considering that homogeneous bromine was essential for the redox couples, we opted to add a small amount of water to the reaction media to modulate the solubility behavior of NaNO₂ and the bromine surrogates. It was found that a proper amount of water could greatly accelerate the aerobic oxidations (entries 3–5). Because of the lower boiling point of dichloromethane, we then screened other solvents for the aerobic oxidation under the assistance of water (entries 6–13). Experimental results showed that most solvents screened are suitable for the aerobic oxidation; only slightly slower conversion in *tert*-butyl alcohol was observed (entry 12).

In fact, our research interests focus on the reaction in water (Table 2). It was found that only 25% of benzyl alcohol was oxidized into benzaldehyde (entry 1). However, when the air pressure was raised to 0.9 MPa, the conversion was significantly increased to 58% (entry 2).

TABLE 2. Catalytic Aerobic Oxidation of Benzyl Alcohol in Water^a

entry	substrate (mmol)	air (MPa)	time (h)	conversion (%) ^b	selectivity (%) ^b
1	10	4	1	25.1	90
2	10	9	1	58.5	100
3	5	9	1	14.7	100
4	20	9	1	80	100
5	30	9	1	96.3	100
6	40	9	1	95.6	100
7	30	9	1.5	99.8	100

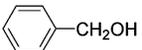
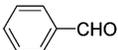
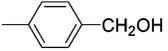
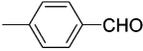
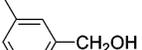
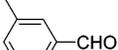
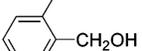
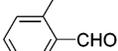
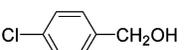
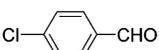
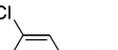
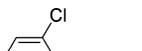
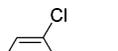
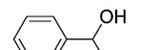
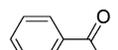
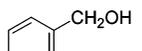
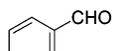
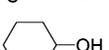
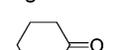
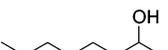
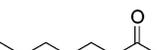
^a Reaction conditions: benzyl alcohol/TEMPO/DBDMH/NaNO₂ = 1:0.01:0.04:0.04, 10 mL of water, 80 °C (oil bath temperature). ^b Conversion and selectivity were determined by GC with area normalization.

To further optimize the aerobic oxidation in water, we decreased the concentration of substrate and catalyst, which resulted in an unexpectedly low conversion (entry 3), while increasing the concentration of substrate and the catalyst obviously accelerated the reaction (entries 4–6). When 30 mmol of benzyl alcohol and the same ratio of catalyst were used, more than 96% of benzyl alcohol was transformed into benzaldehyde. Further increasing benzyl alcohol to 40 mmol resulted in slow reaction (entry 6). This may be ascribed to the shortage of oxygen or the very low partial pressure of oxygen in the reaction system. Thus, with 30 mmol of substrate with 10 mL of water and prolonging the reaction time to 1.5 h, almost all benzyl alcohol was oxidized into benzaldehyde (entry 7).

Thus, we chose the following reaction conditions as the optimal conditions and then applied them to the aerobic oxidation of a wide range of various alcohol substrates: 30 mmol substrate, 0.3 mol % TEMPO, 1.2 mol % DBDMH, 1.2 mol % NaNO₂, 10 mL of H₂O, 0.9 MPa of air, and 80 °C (Table 3). As we can see from Table 3, all benzylic alcohols were converted into their corresponding benzaldehydes in high isolated yields (entries 1–7), although the reaction times were significantly affected by the electronic property of the substituents on the benzene ring. α -Methyl benzyl alcohol can also be oxidized into acetophenone smoothly (entry 8). Surprisingly, 3-pyridine methanol and 2-thiophene methanol, which are usually regarded as difficult substrates in most aerobic oxidations involving transition metals due to their strong coordination ability, were also very smoothly converted into their corresponding aldehydes (entries 9 and 10). When 3-pyridine methanol was used as a substrate (entry 9), high conversion could be achieved with the help of the same equivalent of acetic acid. When 2-thiophene methanol was used as the substrate (entry 10), the strong ring bromination ability of DBDMH to the electron-rich thiophene ring resulted in incomplete oxidation. In this case, 2 mol % pyridine hydrobromide perbromide (PyHBr₃) was used as the bromine surrogate to perform the total conversion. A satisfactory selectivity, with a small amount of 5-bromo-2-thiophene-carboxaldehyde, was obtained.¹² Compared to benzylic alcohols, aliphatic alcohols are rather difficult to oxidize under the same conditions (entries 11 and 12). Using more catalyst and prolonging the reaction time, a complete conversion of 2-octanol to 2-octanone could be achieved (entry 13).

(12) See Supporting Information.

TABLE 3. Aerobic Alcohol Oxidation in Water^a

Entry	Substrate	Product	Time (h)	Conv. (%) ^b	Select. (%) ^b	Yield (%) ^c
1			1.5	99.8	100	88
2			2	100	100	98
3			2	99.7	100	98
4			2.5	100	100	95
5			6	100	100	95
6			6	100	100	96
7			7	99.2	99.8	96
8			4	99.6	100	97
9 ^d			6	98.2	100	92
10 ^e			6	100	98.4	93
11			6	10.7	100	-
12			6	15.3	100	-
13 ^f			6	100	100	94

^a Alcohol (30 mmol), TEMPO (0.3 mmol), DBDMH (1.2 mmol), NaNO₂ (1.2 mmol), H₂O (10 mL), 80 °C (oil temperature). ^b Conversion and selectivity were determined by GC. ^c Isolated yields. ^d With 2.0 mL of AcOH. ^e With PyHBr₃ (0.6 mmol) as instead of DBDMH. ^f 2-Octanol/TEMPO/DBDMH/NaNO₂ = 1:0.1:0.1:0.1 (mole ratio).

In conclusion, we have successfully developed an efficient transition-metal-free aerobic alcohol oxidation with water as a solvent. The new oxidation system is suitable for the oxidation of benzylic alcohols, including heteroaromatic analogues. In the current system, the catalytic behavior of DBDMH was rather different from bromine in our previous report.¹¹ As a common disinfectant, DBDMH can easily release HBrO under aqueous conditions. In fact, HBrO is favorable for the oxidation of TEMPOH to TEMPO cation in the catalytic cycle, although we do not have enough proof to exclude the possibility that Br₂ performs this transformation. Probably the low concentration of HBrO in water system benefits the oxidations of active alcohol substrates.

Experimental Section

General Procedure for Catalytic Aerobic Alcohol Oxidation in Water. To a 300 mL Teflon-lined autoclave were added 30 mmol of alcohol substrate, 10 mL of deionized water, 0.3 mmol of TEMPO, 1.2 mmol of DBDMH, and 1.2 mmol of NaNO₂. The autoclave was then carefully closed and charged with air to 0.9 MPa. The autoclave was put into a preheated 80

°C oil bath for the desired reaction time, cooled to room temperature, and carefully depressurized. The sample was diluted with CH₂Cl₂, and the conversion and selectivity were determined by GC without any purification. When GC showed the reaction to be complete, the liquid in the autoclave was transferred into a separation funnel, and the autoclave was carefully washed with CH₂Cl₂. The combined organic layers were washed with aqueous Na₂S₂O₃ and saturated NaHCO₃. The organic layer was dried over anhydrous Na₂SO₄ and concentrated to dryness. The yield was calculated on the basis of 30.0 mmol of substrate. The ¹H NMR spectrum was recorded using isolated product directly.

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Supporting Information Available: GC diagrams for all substrates and products and ¹H NMR spectra for all isolated products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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