

TEMPO-*tert*-Butyl Nitrite: An Efficient Catalytic System for Aerobic Oxidation of Alcohols

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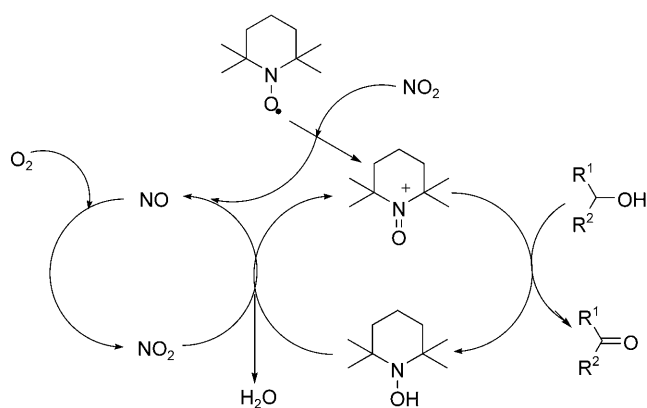
Abstract: A metal-free catalytic system consisting of 2,2,6,6-tetramethylpiperidine *N*-oxyl (TEMPO) and *tert*-butyl nitrite has been developed to activate molecular oxygen for the aerobic oxidation of alcohols. A variety of active and non-active alcohols were oxidized to their corresponding carbonyl compounds in high selectivity and yields.

Keywords: alcohols; *tert*-butyl nitrite; molecular oxygen; oxidation; TEMPO; 2,2,6,6-tetramethylpiperidine *N*-oxyl (TEMPO)

Selective oxidation of alcohols is an important reaction in organic chemistry.^[1,2] Among the stoichiometric oxidants, molecular oxygen is a preferred terminal oxidant from both economical and environmental perspectives. We have previously developed a three-component catalyst system, consisting of 2,2,6,6-tetramethylpiperidine *N*-oxyl (TEMPO), Br₂ and NaNO₂, to activate molecular oxygen for the selective aerobic oxidation of alcohols to their corresponding carbonyl compounds.^[3] The method hinges upon a key finding that the inorganic salt, NaNO₂, could serve as an NO equivalent to activate molecular oxygen under acidic conditions. This concept has been extended and applied for a broad array of substrates with good selectivities.^[4] However, most of these methods require a Br source as the co-catalyst to bridge the two catalytic cycles between TEMPO cation/TEMPOH and NO/NO₂. As a result, those substrates bearing an olefin moiety are not favored due to side reactions of HBr or Br₂ with the carbon-carbon double bonds.^[5] Moreover, the aerobic oxidation of aliphatic primary alcohols remains a challenge because their propensity toward being overoxidized into acids and/or ortho esters under these conditions.^[6]

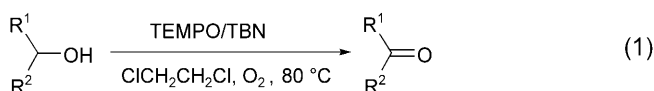
Therefore, it is desirable to develop of an efficient and selective catalyst system for the aerobic oxidation of a broad range of alcohols. Although the catalytic system TEMPO/NaNO₂/HCl was recently developed for selective aerobic oxidation of a variety of primary and secondary alcohols under mild conditions,^[7] its application to substrates containing acid-sensitive functional groups might be limited because a high loading of HCl (10–16 mol%) was used. Very recently, we have reported an efficient aerobic oxidation of various active alcohols with high turnover number (TON) under almost neat condition with TEMPO/*tert*-butyl nitrite (TBN)/aqueous HBr as the catalytic system.^[8] In this system, the organic nitrite, TBN, served as an efficient NO equivalent to activate molecular oxygen and enabled the aerobic oxidation at very high-volume efficiency.

Generally, the TEMPO cation, which was initially formed *via* oxidation of TEMPO, acts as the active oxidant in the TEMPO-catalyzed oxidation of alcohols. According to the literature, the electrode potential (E^0) of TEMPO cation/TEMPO is 0.75 V,^[2h] while E^0 of N₂O₄/NO is 1.03 V.^[9] Based on this information, we reckoned that NO₂ can oxidize TEMPO into the TEMPO cation to initialize the oxidation (Scheme 1). Under high temperatures TBN can release NO or NO₂ because of its thermal instability. NO can be quickly oxidized into NO₂ by molecular oxygen. Consequently, NO₂ oxidizes TEMPO into the TEMPO cation, which can fulfil the oxidation of an alcohol substrate to its corresponding carbonyl compound. Upon completion of the alcohol oxidation, the TEMPO cation turns into its reduced state, TEMPOH, which on further reaction with NO₂ forms the TEMPO cation, and thus completes a catalytic cycle. Therefore, a potential double-component catalytic system, TEMPO/NO₂, could be established to furnish the aerobic oxidation using TBN as the NO equivalent.



Scheme 1. A proposed overall mechanism of the TEMPO-TBN catalytic system for the aerobic oxidation of alcohols.

Herein, we report a TEMPO/TBN double-component catalyst system for the highly selective aerobic oxidation of various alcohols, including benzyl alcohols, as well as primary and secondary aliphatic alcohols [Eq. (1)].



Our initial experiment of aerobic oxidation of benzyl alcohol to benzaldehyde was carried out with 2 mol% of TEMPO, 8 mol% of TBN in 1,2-dichloroethane at 80°C under 0.2 MPa of oxygen. It was found that benzyl alcohol was smoothly converted into benzaldehyde in full conversion with a little benzoic acid.^[10] This preliminary result showed that the Br-free catalytic system for aerobic oxidation of alcohols designed in Scheme 1 was feasible. After optimization of reaction temperature, oxygen pressure and molar ratio of both catalytic components, this reaction could be completed with 0.5 mol% of TEMPO and 4 mol% of TBN under 0.2 MPa of oxygen at 80°C in 2 h. The end point of reaction time could be determined simply by observation of the vessel pressure through a barometer. Several solvents, such as *t*-BuOH, toluene, PhCl, PhCF₃, AcOH, CH₃CN and H₂O were also tested under the same reaction conditions, the conversions of benzyl alcohol were only 1.0, 2.0, 2.2, 2.2, 42.3, 60.6 and 4.5%, respectively.^[11] The dramatic difference of conversions of benzyl alcohol might be relevant to real electrode potentials of redox pairs in these solvents.

To explore the substrate scopes, we applied this newly developed method to a variety of alcohols. The results of benzylic alcohols and their heteroaromatic analogs are summarized in Table 1. As can be seen from Table 1, all tested benzylic alcohols were fully converted into their corresponding aldehydes in high

Table 1. Aerobic oxidation of benzyl alcohols.^[a]

Entry	Substrate	Product	Catalyst [mol%]	Time [h]	Yield [%] ^[b]
1			0.5:4	2	96
2			0.5:4	4	95
3			0.5:4	3	96
4			0.5:4	5	94
5			0.5:4	4	95
6			0.5:4	2	96
7			0.5:4	2	95
8			0.5:4	3	96
9			0.5:4	20	97
10			1:4	3	94
11			1:4	2	93
12 ^[c]			0.5:4	3	95
13 ^[c]			0.5:4	3	93
14			0.5:4	4	96

^[a] All reactions were carried out with 10 mmol of substrate in 10 mL of ClCH₂CH₂Cl. Catalyst = TEMPO/TBN in the specified molar ratio, O₂ (0.2 MPa), 80°C, 100% conversions for all substrates according to GC analysis.

^[b] Isolated yield.

^[c] AcOH (1 mL) was added.

isolated yields (entries 1–9). The reaction time displayed a correlation with the substituent effects. Even the highly electron-deficient *p*-nitrobenzyl alcohol can be smoothly oxidized after an extended reaction time (entry 9, Table 1).

For electron-rich alcohol substrates, such as 2-furylmethanol and 2-thiophenemethanol, this catalyst system can provide clean aldehyde products (entries 10 and 11, Table 1) without affecting the aromatic ring, while some brominated aldehyde by-product was observed^[3,4a,8] in the previous Br-containing catalytic system for this type of alcohol. As usual, for the oxidation of pyridine-methanols, one equivalent of AcOH was needed to control the pH during the oxidation (entries 12 and 13, Table 1). Notably, 4-methylthiobenzyl alcohol, which bears two labile function

groups, could be selectively converted into 4-methylthiobenzaldehyde without any detectable sulfur oxidation. This result demonstrates that thioethers can tolerate the aerobic oxidation under the TEMPO/TBN catalytic system (entry 14, Table 1).

With these results in hand, we examined the aerobic oxidation of various alcohols including secondary benzylic, primary, secondary aliphatic alcohols, and also cinnamyl alcohol. The results summarized in Table 2 demonstrate the effectiveness of this bromine-free catalytic system for the preparation of various aldehydes and ketones. All substituted α -phenylethanol could be smoothly converted into their corresponding acetophenones in high yields (entries 1–5, Table 2). For 1,2-diphenylethane-1,2-diol, which is prone to forming benzaldehyde because of the easy carbon-carbon bond cleavage in some other oxidation systems,^[4b] it could be also smoothly oxidized to ben-

zoin in 12 h (entry 6, Table 2). Compared with benzylic alcohols, aliphatic alcohols are less active substrates for oxidation. Indeed, secondary aliphatic alcohols could be oxidized into ketones by increasing the loading of TEMPO (entries 7–9, Table 2). To our delight, high selectivities were achieved in the oxidation of primary alcohols. For example, with 1-octanol as the substrate, only a trace amount of 1-octyl octanoate was observed (entry 10, Table 2). A high isolated yield of phenylacetaldehyde was also obtained under similar conditions (entry 11, Table 2). Unfortunately, the oxidation of cinnamyl alcohol, a typical allylic-type alcohol substrate, did not provide the expected result. Only a 13.6% conversion was observed, although the selectivity was as good as usual (entry 12, Table 2). A slight improvement was observed with the addition more TEMPO in the catalytic system. According to our proposed mechanism in Scheme 1, we postulate that the alcohol oxidation step was a slow transformation. TEMPO cation was decomposed to form of 2,2,6,6-tetramethylpiperidine (TEMPOH), which discontinued the catalytic cycle, rather than the normal TEMPOH.

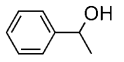
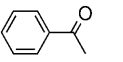
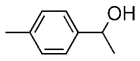
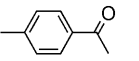
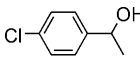
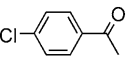
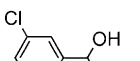
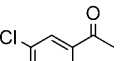
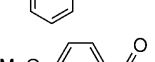
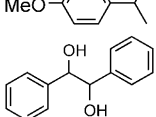
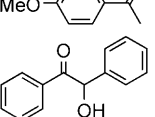
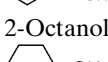
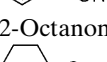
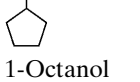
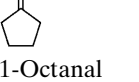
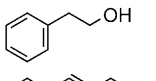
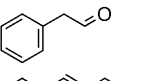
In conclusion, we have successfully developed a new metal-free catalytic system, with TBN as the NO equivalent to activate molecular oxygen, and which was applied in the aerobic oxidation of a broad range of alcohol substrates, including benzylic alcohols, heteroaromatic analogues, substituted α -phenylethanol, primary and secondary aliphatic alcohols, to their corresponding aldehydes and ketones. This novel catalytic system not only provides an efficient method to prepare various aldehydes and ketones from alcohols but may also inspire other uses of organic NO equivalents in the oxidation chemistry.

Experimental Section

Typical Procedure for Aerobic Oxidation of Benzyl Alcohol to Benzaldehyde

To a Teflon-lined 316 L stainless steel autoclave (300 mL) with magnetic stirring bar, were added 10 mL of 1,2-dichloroethane, which contained 7.8 mg of TEMPO (0.05 mmol, 0.5 mol%), 46 μ L of TBN (41 mg, 0.4 mmol, 4 mol%) and 1.08 g of benzyl alcohol (10 mmol). Then the autoclave was closed and charged with oxygen to 0.2 MPa. The autoclave was placed in an oil bath, which was preheated to 80°C. Two hours later, the barometer dropped to 0.18 MPa and indicated that the reaction was finished. The autoclave was taken out from the oil bath, cooled to room temperature and carefully depressurized. The sample was diluted with 1,2-dichloroethane and the conversion and selectivity were detected by GC without any purification. GC results showed the reaction to be complete, the liquid in the autoclave was transferred into a separation funnel, washed with aqueous Na₂S₂O₃ solution (10 mL $\times$ 3), the organic layer was dried over anhydrous Na₂SO₄, concentrated to dryness

Table 2. Aerobic oxidation of benzylic secondary, primary and secondary aliphatic alcohols.^[a]

Entry	Substrate	Product	Catalyst [mol%]	Time [h]	Yield [%] ^[b]
1			0.5:4	3	96
2			0.5:4	3	97
3			0.5:4	2	97 ^[c]
4			0.5:4	2	98
5			0.5:4	4	96
6			0.5:4	12	95
7	2-Octanol	2-Octanone	2:4	7	95
8			4:4	10	93
9			4:4	12	95
10	1-Octanol	1-Octanal	2:4	6	94 ^[d]
11			2:4	3	90
12			2:4	12	13.6 ^[e]

^[a] All reactions were carried out with 10 mmol of substrate in 10 mL of ClCH₂CH₂Cl. Catalyst = TEMPO/TBN in the specified molar ratio, O₂ (0.2 MPa), 80°C. 100% conversions by GC analysis unless otherwise specified.

^[b] Isolated yield.

^[c] 99% conversion.

^[d] 1% of 1-octyl 1-octanoate was observed.

^[e] GC conversion with a > 99% selectivity.

to yield the product as a liquid; yield: 1.02 g (96%).
¹H NMR confirmed that it was the desired benzaldehyde.

Acknowledgements

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- [10] The formation of some acids was observed for most primary alcohols listed in Table 1 and Table 2 if a prolonged reaction time was employed.
- [11] Although 1,2-dichloroethane is not a green solvent, it is more convenient in laboratory work and was employed in the current research. As for the concept of green chemistry, AcOH can be used as the solvent in this aerobic oxidation to achieve a complete conversion with slightly adjustment of the reaction conditions.