

# Efficient Aerobic Oxidation of Secondary Alcohols at Ambient Temperature with an ABNO/ $\text{NO}_x$ Catalyst System

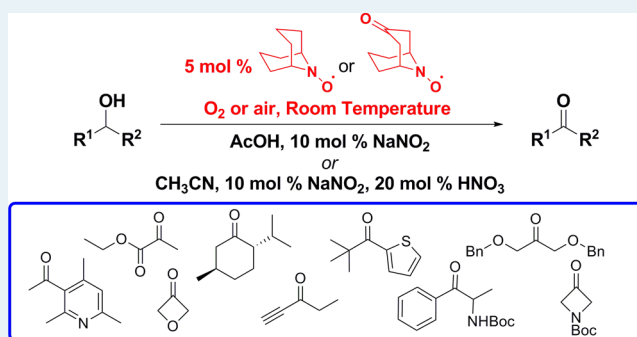
Markus B. Lauber and Shannon S. Stahl\*

Department of Chemistry, University of Wisconsin–Madison, 1101 University Avenue, Madison, Wisconsin 53706, United States

## Supporting Information

**ABSTRACT:** New highly practical methods are presented for aerobic oxidation of secondary alcohols with a nitroxyl radical in combination with  $\text{HNO}_3$ ,  $\text{NaNO}_2$ , or both as cocatalysts. Diverse nitroxyls are compared, including several novel bicyclic derivatives. Catalyst systems with the readily available nitroxyls, 9-azabicyclo[3.3.1]nonane-*N*-oxyl (ABNO) and 9-azabicyclo[3.3.1]nonan-3-one-*N*-oxyl (keto-ABNO), are optimized in acetic acid or acetonitrile as the solvent. The reactions are compatible with substrates bearing diverse functional groups and proceed efficiently under mild conditions at ambient pressure and temperature.

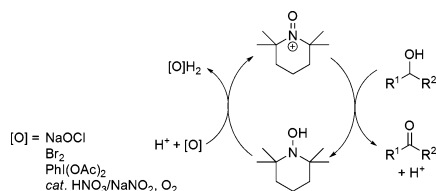
**KEYWORDS:** secondary alcohols, aerobic oxidation, nitroxyl radical, ABNO, keto-ABNO



## INTRODUCTION

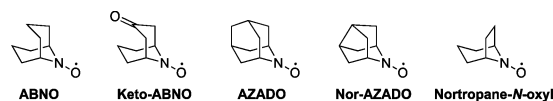
TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl) and related nitroxyl derivatives are widely used for the oxidation of alcohols to carbonyl compounds.<sup>1</sup> A wide range of catalytic methods have been developed wherein stoichiometric oxidants, such as bleach ( $\text{NaOCl}$ ),  $\text{Br}_2$ , and hypervalent iodine, are used to generate the reactive oxoammonium species (Scheme 1).<sup>2</sup> In recent years, a number of groups have developed TEMPO-catalyzed alcohol oxidations capable of using  $\text{O}_2$  as the terminal oxidant by employing nitric acid, nitrite sources, or both as cocatalysts.<sup>3–5</sup>

### Scheme 1. TEMPO-Catalyzed Alcohol Oxidation



TEMPO-catalyzed alcohol oxidation methods are appealing because the sterically encumbered oxoammonium group can promote chemoselective oxidation of primary alcohols, even in the presence of unprotected secondary alcohols.<sup>6</sup> This advantage, however, can be a drawback in the oxidation of secondary and sterically hindered primary alcohols. Use of less hindered bicyclic nitroxyls (Chart 1) provides a means to address this challenge. Such structures have been known for decades,<sup>7</sup> but their application to alcohol oxidation has been demonstrated only recently.<sup>8</sup>

### Chart 1. Stable Bicyclic Nitroxyl Derivatives



For example, Iwabuchi and co-workers have developed methods for the oxidation of alcohols using bicyclic nitroxyls in combination with various terminal oxidants, including bleach, azodicarboxylates, and hypervalent iodine reagents.<sup>8b,d–f</sup> Efficient aerobic catalytic turnover was achieved with 5-F-AZADO as the catalyst.<sup>9</sup> These methods are highly appealing and exhibit broad substrate scope; however, AZADO derivatives are difficult to access synthetically.<sup>10</sup>

In the present study, we investigate diverse nitroxyl derivatives to assess their ability to promote aerobic alcohol oxidation. We find that good catalytic reactivity may be achieved with the synthetically accessible nitroxyl derivatives, 9-azabicyclo[3.3.1]nonan-*N*-oxyl (ABNO) or 9-azabicyclo[3.3.1]nonan-3-one-*N*-oxyl (keto-ABNO). These compounds may be readily prepared in multigram quantities in 3–4 straightforward synthetic steps.<sup>11</sup> These efforts resulted in the identification of mild catalytic conditions for the aerobic oxidation of diverse secondary alcohols with ABNO and keto-ABNO.

## RESULTS AND DISCUSSION

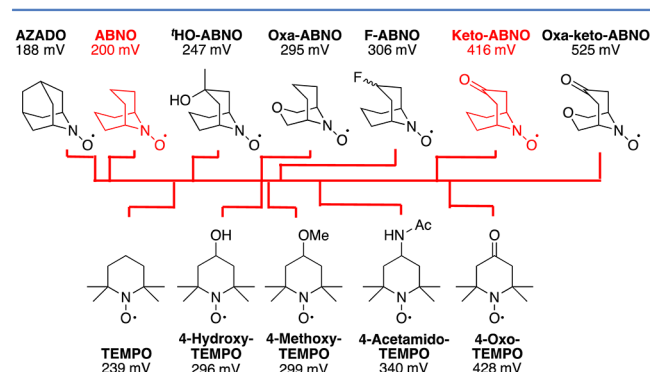
Relatively small modifications of the ABNO scaffold can have a significant impact on the oxoammonium/nitroxyl redox

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potential.<sup>12</sup> The synthetic accessibility of ABNO-based structures prompted us to prepare several new bicyclic nitroxyl derivatives to achieve a broad distribution of redox potentials. Three of these, <sup>1</sup>HO-ABNO, oxa-ABNO, and F-ABNO, exhibit potentials between those of ABNO and keto-ABNO, and oxa-keto-ABNO exhibits a potential >100 mV higher than keto-ABNO (Figure 1).



**Figure 1.** Redox potentials of nitroxyl radicals vs ferrocene in acetonitrile with 0.1 M LiClO<sub>4</sub>.

All of the bicyclic nitroxyl derivatives in Figure 1, together with a number TEMPO analogs, were evaluated as catalysts for the aerobic oxidation of cyclohexanol, as a representative secondary alcohol, under several different conditions. Recent precedents provided the basis for solvent selection. Iwabuchi's F-AZADO-catalyzed alcohol oxidation conditions employed acetic acid as the solvent.<sup>9</sup> Chlorinated solvents have been commonly used in TEMPO-based oxidations;<sup>3</sup> however, the negative environmental impact of these solvents prompted us to consider alternatives. Acetonitrile was selected on the basis of its use in a recent TEMPO-catalyzed aerobic alcohol oxidation method.<sup>31</sup>

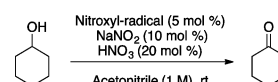
Tables 1 and 2 summarize the results obtained from reactions performed in acetic acid and acetonitrile, respectively, at room temperature. For the reactions in acetic acid, the nitroxyl radicals were employed at 5 mol % loading in

**Table 1. Comparison of Nitroxyl Catalysts for Aerobic Oxidation of Cyclohexanol in Acetic Acid<sup>a</sup>**

entry	nitroxyl	oxidant = O <sub>2</sub> yield/time	oxidant = air yield/time
1	ABNO	99%/1.5 h	35%/3 h
2	keto-ABNO	99%/1.5 h	34%/3 h
3	AZADO	98%/1.5 h	82%/3 h
4	F-ABNO	52%/1.5 h	34%/3 h
5	<sup>1</sup> HO-ABNO	80%/1.5 h	44%/3 h
6	oxa-ABNO	2%/1.5 h	2%/3 h
7	oxa-keto-ABNO	55%/1.5 h	32%/3 h
8	TEMPO	7%/1.5 h	8%/3 h
9	4-hydroxy-TEMPO	9%/1.5 h	8%/3 h
10	4-methoxy-TEMPO	10%/1.5 h	7%/3 h
11	4-oxo-TEMPO	0%/1.5 h	1%/3 h
12	acetamido-TEMPO	5%/1.5 h	9%/3 h

<sup>a</sup>Reactions have been carried out on a 1.31 mmol scale. Yields determined by GC with PhTMS as internal standard.

**Table 2. Comparison of Nitroxyl Catalysts for Aerobic Oxidation of Cyclohexanol in Acetonitrile<sup>a</sup>**



entry	nitroxyl	oxidant = O <sub>2</sub> yield/time	oxidant = air yield/time
1	ABNO	91%/2 h	71%/2 h
2	keto-ABNO	94%/2 h	42%/2 h
3	AZADO	86%/2 h	81%/2 h
4	F-ABNO	94%/2 h	36%/2 h
5	<sup>1</sup> HO-ABNO	87%/2 h	52%/2 h
6	oxa-ABNO	1%/2 h	1%/2 h
7	oxa-keto-ABNO	35%/2 h	20%/2 h
8	TEMPO	3%/2 h	4%/2 h
9	4-hydroxy-TEMPO	5%/2 h	4%/2 h
10	4-methoxy-TEMPO	6%/2 h	4%/2 h
11	4-oxo-TEMPO	24%/2 h	20%/2 h
12	acetamido-TEMPO	4%/2 h	4%/2 h

<sup>a</sup>Reactions have been carried out on a 1.31 mmol scale. Yields determined by GC with PhTMS as internal standard.







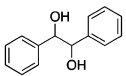
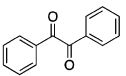




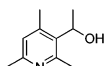
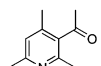


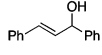
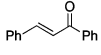


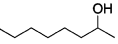
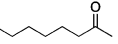
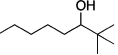
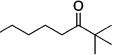
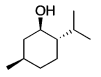
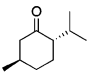










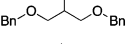
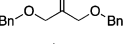
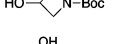
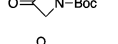
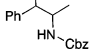
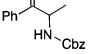
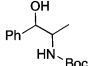
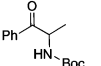
combination with 10 mol % NaNO<sub>2</sub> as a cocatalyst (Table 1). The reactions employed 1 atm O<sub>2</sub> or an air balloon as the source of oxidant. High yields were obtained with ABNO, keto-ABNO, and AZADO under O<sub>2</sub> with a 1.5 h reaction time. When air was used, AZADO proved to be the best catalyst. None of the TEMPO derivatives showed good reactivity (Table 1, entries 8–12).

For the reactions in acetonitrile, the nitroxyl radicals were again used at 5 mol % loading, but in combination with both 10 mol % NaNO<sub>2</sub> and 20 mol % nitric acid as cocatalysts (Table 2). Several bicyclic nitroxyls performed well. The amount of nitric acid influences the overall reactivity under these conditions, and good yields were obtained with 15–20 mol % HNO<sub>3</sub> (see Supporting Information). Furthermore, the reactivity under these conditions is dependent on the terminal oxidant that is used. When pure oxygen is used, an excellent yield of cyclohexanone was obtained with ABNO, keto-ABNO, and F-ABNO when the reaction was carried out with 1 atm O<sub>2</sub> (Table 2; entries 1, 2, and 4). With air as the source of the oxidant, ABNO and AZADO performed well (Table 2, entries 1, 3). Low yields were obtained throughout when TEMPO derivatives were used as catalyst (Table 2, entries 8–12).

The results in Tables 1 and 2 do not reveal a correlation between the nitroxyl redox potential and catalytic activity. In some cases, a poor yield may arise from decomposition of the nitroxyl under the reaction conditions. For example, cyclic voltammograms of nitroxyls containing an ether group (oxa-ABNO and oxa-keto-ABNO) exhibit a nitroxyl/oxoammonium redox feature that is not completely reversible, suggesting that these derivatives may be unstable (see Supporting Information for details). Studies to gain further insights into the catalytic mechanism and to elucidate factors that contribute to effective turnover have been initiated. Meanwhile, the results in Tables 1 and 2 suggest that the most synthetically accessible nitroxyl derivatives, ABNO and keto-ABNO, are effective catalysts for aerobic oxidation of secondary alcohols, and both show significantly better performance than TEMPO-based nitroxyls.

Our efforts to investigate the scope of the methods considered three different catalyst/reaction conditions: (A) 5% ABNO, 10% NaNO<sub>2</sub>, acetic acid, 1 atm O<sub>2</sub>; (B) 5% ABNO,

Table 3. Scope of the ABNO/keto-ABNO-Catalyzed Aerobic Oxidation of Alcohols

entry	alcohol	product	<div style="display: flex; justify-content: space-around; font-size: 0.8em;"> <div style="border: 1px solid black; padding: 2px;"> <b>Method A:</b> ABNO (5 mol %) NaNO<sub>2</sub> (10 mol %) AcOH (1 M), rt, O<sub>2</sub> (balloon)         </div> <div style="border: 1px solid black; padding: 2px;"> <b>Method B:</b> ABNO (5 mol %) NaNO<sub>2</sub> (10 mol %) HNO<sub>3</sub> (20 mol %) Acetonitrile (1 M), rt, air (balloon)         </div> <div style="border: 1px solid black; padding: 2px;"> <b>Method C:</b> keto-ABNO (5 mol %) NaNO<sub>2</sub> (10 mol %) HNO<sub>3</sub> (20 mol %) Acetonitrile (1 M), rt, O<sub>2</sub> (balloon)         </div> </div>		
			method A yield [%] / time [h]	method B yield [%] / time [h]	method C yield [%] / time [h]
1			99 <sup>b</sup> / 3	99 <sup>b</sup> / 3	98 <sup>b</sup> / 3
2			99 <sup>b</sup> / 3	99 <sup>b</sup> / 3	99 <sup>b</sup> / 3
3			87 <sup>a</sup> / 3	74 <sup>a</sup> / 3	94 <sup>a</sup> / 3
4			95 <sup>a</sup> / 5	25 <sup>c</sup> / 3	78 <sup>c</sup> / 3
5			96 <sup>a</sup> / 3	11 <sup>c</sup> / 3	2 <sup>c</sup> / 3
6			77 <sup>c</sup> / 3	35 <sup>c,d</sup> / 3	94 <sup>a,d</sup> / 3
7			73 <sup>c</sup> / 5	56 <sup>c,d</sup> / 5	92 <sup>a,d</sup> / 5
8			89 <sup>c</sup> / 2	50 <sup>c</sup> / 2	89 <sup>c</sup> / 2
9			95 <sup>a</sup> / 3	12 <sup>a</sup> / 3	6 <sup>a</sup> / 3
10			99 <sup>b</sup> / 4	85 <sup>b</sup> / 4	99 <sup>b</sup> / 4
11			98 <sup>b</sup> / 3	80 <sup>b</sup> / 3	35 <sup>b</sup> / 3
12			97 <sup>a</sup> / 5	40 <sup>c</sup> / 5	39 <sup>c</sup> / 5
13			97 <sup>a</sup> / 6	65 <sup>b</sup> / 6	49 <sup>b</sup> / 6
14			94 <sup>a</sup> / 6	95 <sup>a</sup> / 6	94 <sup>a</sup> / 6
15			98 <sup>a</sup> / 3	97 <sup>a</sup> / 3	95 <sup>a</sup> / 3
16			99 <sup>b</sup> / 3	85 <sup>b</sup> / 3	99 <sup>b</sup> / 3
17			99 <sup>b</sup> / 3	45 <sup>b</sup> / 3	99 <sup>b</sup> / 3
18			93 <sup>c</sup> / 2	20 <sup>c</sup> / 2	89 <sup>c</sup> / 2
19			94 <sup>a</sup> / 5	75 <sup>c</sup> / 5	98 <sup>c</sup> / 5
20			98 <sup>c</sup> / 3	7 <sup>c</sup> / 3	30 <sup>c</sup> / 3
21			94 <sup>c</sup> / 3	96 <sup>c</sup> / 3	98 <sup>c</sup> / 3
22			98 <sup>a</sup> / 2	98 <sup>c</sup> / 2	95 <sup>c</sup> / 2

All reactions performed on the 1 mmol scale. <sup>a</sup>Isolated yield. <sup>b</sup>GC yield; int. std = PhTMS. <sup>c</sup>NMR yield; int. std = PhTMS. <sup>d</sup>1.2 equiv of HNO<sub>3</sub> was used in the reaction to account for the basicity of the pyridine group.

10% NaNO<sub>2</sub>, 20% HNO<sub>3</sub>, acetonitrile, air balloon; and (C) 5% keto-ABNO, 10% NaNO<sub>2</sub>, 20% HNO<sub>3</sub>, acetonitrile, 1 atm O<sub>2</sub>. The results are summarized in Table 3. No dedicated effort was made to probe the origin of difference in yields among the three catalytic conditions, but the results in Table 3 show that at least one of the methods could be used to obtain excellent product yields for a wide range of substrates. Each of the three methods furnished excellent product yields with the prototypical benzylic alcohols in entries 1 and 2. A sterically demanding *tert*-butyl-substituted benzylic alcohol was oxidized in excellent yield with method C (entry 3), and method A showed the best reactivity in the oxidation of hydrobenzoin to benzil (entry 4).

Excellent results were also obtained with other activated alcohols, including those with thiophene and pyridine substituents (entries 5–7), a propargylic alcohol with a terminal alkyne (entry 8), an allylic alcohol (entry 9), and vicinal *N*-protected aminoalcohols (entries 21 and 22). Use of the ABNO/AcOH conditions (method A) led to good-to-excellent yields with each of these substrates. The thiophene-containing substrate formed an unidentified side product in acetonitrile (i.e., methods B and C). The keto-ABNO/CH<sub>3</sub>CN conditions (method C) were especially effective with the pyridine-containing alcohols. All three methods were effective with the vicinal aminoalcohols.

The ABNO/AcOH conditions proved to be the most broadly effective for oxidation of aliphatic alcohols (entries 10–20). Many of the reactions proceeded in near-quantitative yield within 2–6 h at room temperature. The keto-ABNO/CH<sub>3</sub>CN conditions also showed good generality (entries 10, 14–21). Method B has the advantage of employing ambient air as the oxidant, but lower yields were typically observed under these conditions.

Alcohols bearing oxygenated functional groups, including 1-methoxy-2-propanol, ethyl lactate, 3-hydroxyoxetane, and 1,3-dibenzyl-protected glycerol proceed in excellent yield (entries 16–19), despite electronic deactivation by the substituents.<sup>13</sup> The *N*-protecting groups Cbz and Boc present in the aminoalcohols in entries 20–22 are well tolerated under the ABNO/AcOH conditions. In the case of *N*-Boc-3-hydroxyazetidone, deprotection occurred in acetonitrile, but afforded quantitative yield of the ketone in acetic acid (entry 20).

Each of the substrates in Table 1 was performed on the 1 mmol scale. 2-Adamantanol and the dibenzyl glycerol derivative (entries 15 and 19) were performed on larger scale (1.5–2 g or ~10 mmol scale) using the ABNO/AcOH and keto-ABNO/CH<sub>3</sub>CN conditions, and these reactions afforded the ketone products in 99% and 96% yields, respectively.

A few limitations were identified in our studies. The aniline derivative in Scheme 2a led to no ketone product; a deep purple color was observed under all three reaction conditions, consistent with the formation of a diazo compound.<sup>14</sup> The ketone derived from 3-quinuclidinol oxidization was obtained

in 54% yield using keto-ABNO/CH<sub>3</sub>CN (Scheme 2b), provided 1.2 equiv of nitric acid was used. No oxidation was observed with the two ABNO-based methods. Alcohols containing tertiary amines could be problematic because they could interfere with the acid-promoted NO<sub>x</sub> redox cycle required to achieve aerobic catalytic turnover.

## CONCLUSION

The results described here provide highly practical and efficient reaction conditions for aerobic oxidation of a wide range of secondary alcohols, including those with significant steric hindrance and containing diverse functional groups. The reactions employ the nitroxyls ABNO and keto-ABNO, which are readily accessible synthetically. The mild reaction conditions and use of nonchlorinated solvents represent other advantageous features of these reactions. New bicyclic nitroxyl derivatives were prepared and tested, but none show activity superior to the parent ABNO/keto-ABNO nitroxyls. Nevertheless, the facile derivatization of these structures in a manner demonstrated here and elsewhere<sup>15</sup> could have other advantages. For example, the carbonyl group of keto-ABNO provides a reactive functional group that can be used to install tethers that will enable immobilization of bicyclic nitroxyls on solid supports or polymers.

## ASSOCIATED CONTENT

### Supporting Information

Detailed experimental procedures, cyclic voltammetry data, NMR spectra, and additional experimental data are included. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## AUTHOR INFORMATION

### Corresponding Author

\*E-mail: [stahl@chem.wisc.edu](mailto:stahl@chem.wisc.edu)

### Notes

The authors declare no competing financial interest.

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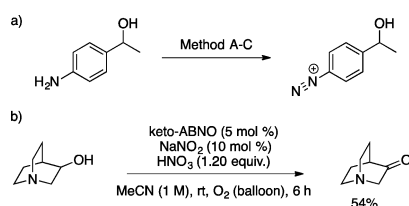
## ABBREVIATIONS

ABNO, 9-azabicyclo[3.3.1]nonane-*N*-oxyl; keto-ABNO, 9-azabicyclo[3.3.1]nonan-3-one-*N*-oxyl; <sup>t</sup>HO-ABNO, 9-azabicyclo[3.3.1]nonane-3-methyl-3-ol-*N*-oxyl; F-ABNO, 3-fluoro-9-azabicyclo[3.3.1]nonane-*N*-oxyl; oxa-ABNO, 7-oxa-9-azabicyclo[3.3.1]nonane-*N*-oxyl; oxa-keto-ABNO, 7-oxa-9-azabicyclo[3.3.1]nonan-3-one-*N*-oxyl; TEMPO, 2,2,6,6-tetramethylpiperidine-*N*-oxyl

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Scheme 2. Limitations of the Substrate Scope



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