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Efficient Aerobic Oxidation of Secondary Alcohols at Ambient Temperature with an ABNO/NOx Catalyst System

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Figure 1. Redox potentials of nitroxyl-radicals vs. ferrocene in acetonitrile with 0.1 M LiClO₄.

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 2° 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.⁹ Chlorinated solvents have been commonly used in TEMPO-based oxidations;³ 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.³¹

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 nitroxylradicals were employed at 5 mol % loading in combination with 10 mol % NaNO₂ as a cocatalyst (Table 1). The reactions employed 1 atm O₂ or an air balloon as the source of oxidant. High yields were obtained with ABNO, keto-ABNO and AZADO under O₂ 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 % NaNO₂ and 20 mol % nitric acid as co-catalysts (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 % HNO₃ (see supporting information). The reactivity under these conditions is furthermore depending on the used terminal oxidant. 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 O₂ (Table 2; entries 1, 2, and 4). With air as the source of oxidant, ABNO and AZADO performed well (Table 2, entry 1, 3). Low yields were obtained throughout when TEMPOderivatives 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.

Table 1. Comparison of Nitroxyl Catalysts for AerobicOxidation of Cyclohexanol in Acetic Acid.

	OH Nitroxyl-radii NaNO ₂ (AcOH	cal (5 mol %) 10 mol %) (1 M), rt	
Entry	Niture	Oxidant O ₂	Oxidant Air
Епиу	INITIOXYI	Yield / Time	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	^t 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

Reactions have been carried out 0n a 1.31 mmol scale. Yields determined by GC with PhTMS as internal standard.

Table 2.	Comparison	of Nitroxyl	Catalysts	for	Aerobic
Oxidatio	n of Cyclohexa	anol in Aceto	nitrile.		

OH Nitroxyl-radii NaNO ₂ (HNO ₃ (2 Acetonitri	cal (5 mol %) 10 mol %) 0 mol %) le (1 M), rt	
Nitroxyl	Oxidant O ₂	Oxidant Air
INHOXYI	Yield / Time	Yield / Time
ABNO	91% / 2 h	71% / 2 h
keto-ABNO	94% / 2 h	42% / 2 h
AZADO	86% / 2 h	81% / 2 h
F-ABNO	94% / 2 h	36% / 2 h
^t HO-ABNO	87% / 2 h	52% / 2 h
oxa-ABNO	1% / 2 h	1% / 2 h
oxa-keto-ABNO	35 % / 2 h	20% / 2 h
TEMPO	3% / 2 h	4% / 2 h
4-hydroxy-TEMPO	5% / 2 h	4% / 2 h
4-methoxy-TEMPO	6% / 2 h	4% / 2 h
4-oxo-TEMPO	24% / 2 h	20% / 2 h
acetamido-TEMPO	4% / 2 h	4% / 2 h
	HITCRYI-FAGI NABNO ACCOUNT Nitroxyl ABNO Keto-ABNO AZADO F-ABNO 'HO-ABNO 'HO-ABNO oxa-ABNO oxa-ABNO oxa-ABNO oxa-ABNO oxa-ABNO 4-hydroxy-TEMPO 4-nethoxy-TEMPO acetamido-TEMPO	$\begin{array}{c} \stackrel{\text{Nitroxyl-radical (5 m01 %)}{\text{NANO}_{2} (20 m01 \%)}}{\text{Acetonitrile (1 M), rt}} & \begin{array}{c} \circ \\ & & \\ & \\ \hline \end{array} \\ \hline \end{array} \\ \hline \end{array} \\ \begin{array}{c} \stackrel{\text{Nitroxyl}}{\text{Nitroxyl}} & \begin{array}{c} Oxidant O_2 \\ & & \\ \hline \end{array} \\ \hline \end{array} \\ \hline \end{array} \\ \begin{array}{c} \text{ABNO} & 91\% / 2 h \\ \hline \end{array} \\ \hline \end{array} \\ \hline \end{array} \\ \hline \end{array} \\ \begin{array}{c} \text{ABNO} & 94\% / 2 h \\ \hline \end{array} \\ \hline \end{array} \\ \hline \end{array} \\ \hline \end{array} \\ \begin{array}{c} \text{ABNO} & 94\% / 2 h \\ \hline \end{array} \\ \hline \end{array} \\ \hline \end{array} \\ \hline \end{array} \\ \begin{array}{c} \text{ABNO} & 94\% / 2 h \\ \hline \end{array} \\ \hline \end{array} \\ \hline \end{array} \\ \hline \end{array} \\ \begin{array}{c} \text{ABNO} & 94\% / 2 h \\ \hline \end{array} \\ \begin{array}{c} \text{ABNO} & 94\% / 2 h \\ \hline \end{array} \\ \hline \end{array} \\ \hline \end{array} \\ \hline \end{array} \\ \begin{array}{c} \text{ABNO} & 94\% / 2 h \\ \hline \end{array} \\ \begin{array}{c} \text{ABNO} & 94\% / 2 h \\ \hline \end{array} \\ \begin{array}{c} \text{ABNO} & 94\% / 2 h \\ \hline \end{array} \\ \begin{array}{c} \text{ABNO} & 94\% / 2 h \\ \hline \end{array} \\ \begin{array}{c} \text{ABNO} & 94\% / 2 h \\ \hline \end{array} \\ \begin{array}{c} \text{ABNO} & 94\% / 2 h \\ \hline \end{array} \\ \begin{array}{c} \text{ABNO} & 94\% / 2 h \\ \hline \end{array} \\ \begin{array}{c} \text{ABNO} & 94\% / 2 h \\ \hline \end{array} \\ \begin{array}{c} \text{ABNO} & 94\% / 2 h \\ \hline \end{array} \\ \hline \end{array} \\ \hline \end{array} \\ \\ \hline \end{array} \\ \begin{array}{c} \text{ABNO} & 94\% / 2 h \\ \hline \end{array} \\ $ \\ \hline \end{array} \\ \\ \hline \end{array} \\ \hline \end{array} \\ \\ \end{array} \\ \hline \end{array} \\ \\ \end{array} \\ \hline \end{array} \\ \hline \end{array} \\ \hline \end{array} \\ \\ \end{array} \\ \\ \end{array} \\ \hline \end{array} \\ \hline \end{array} \\ \hline \end{array} \\ \end{array} \\ \\ \end{array} \\ \\ \end{array} \\ \\ \end{array} \\ \\ \hline \end{array} \\ \\ \end{array} \\ \hline \end{array} \\ \\ \\ \end{array} \\ \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \end{array} \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \\ \end{array} \\ \\ \\ \\ \end{array} \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \\ \\

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

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

	он 	Method A: ABNO (5 mo 1%) NaNO ₂ (10 mol %) AcOH (1 M), rt, O ₂ (balloon)	Acetonitrile (1 M), rt, air (balloon)	NaNO ₂ (10 mo 1%) HNO ₃ (20 mo 1%) Acetonitrile (1 M), rt, O ₂ (balloon)	`B ²
Entry	Alcohol	Product	Method A Yield [%] / Time [h]	Method B Yield [%] / Time [h]	Method C Yield [%] / Time [l
1	ОН	0	99 ^b / 3	99 ^b / 3	98 ^b / 3
2	ОН	C - o	99 ^b / 3	99 ^b / 3	99 ^b / 3
3	OH		87 ^a / 3	74 ^{<i>a</i>} /3	94 ^{<i>a</i>} / 3
4	OH OH		95 ^{<i>a</i>} / 5	25 ^c / 3	78 ^c / 3
5	Cs→OH		96 ^{<i>a</i>} / 3	11 ^c / 3	2 ^c / 3
6	C N OH		77 ^c / 3	35 ^{<i>c</i>,<i>d</i>} / 3	94 ^{<i>a,d</i>} / 3
7	ОН	N N	73 ^c / 5	56 ^{<i>c,d</i>} / 5	92 ^{<i>a,d</i>} / 5
8	ОН		89 ^c / 2	50 ^c / 2	89 ^c / 2
9	OH Ph	Ph	95 ^{<i>a</i>} / 3	12 ^{<i>a</i>} / 3	6 ^{<i>a</i>} / 3
10	ОН	⊂,°	99 ^b / 4	85 ^b / 4	99 ^b / 4
11	ОН		98 ^b / 3	80 ^b / 3	35 ^b / 3
12	OH		97 ^a /5	40 ^c / 5	39 ^c / 5
13	OH		97 ^{<i>a</i>} / 6	65 ^b / 6	49 ^b / 6
14	И	× o	94 ^{<i>a</i>} / 6	95 ^{<i>a</i>} / 6	94 ^{<i>a</i>} / 6
15	ОН	GT.o	98 ^{<i>a</i>} / 3	97 ^{<i>a</i>} / 3	95 ^{<i>a</i>} / 3
16	OH		99 ^b / 3	85 ^b / 3	99 ^b / 3
17	→0 ↓ O H		99 ^b / 3	45 ^b / 3	99 ^b / 3
18	но{О	o=∕o	93 ^c / 2	$20^{c} / 2$	89 ^c / 2
19	OH Bn_OO_Bn	Bn ^O , O, Bn	94 ^{<i>a</i>} / 5	75 ^c / 5	98 ^c / 5
20	HO	O=N-Boc	98 ^c / 3	7 ^c / 3	30 ^c /3
21	Ph HN Cbz	Ph HN _{Cbz}	94 ^c / 3	96 ^c / 3	98 ^c / 3
22			98 ^a / 2	98 ^c / 2	95 ^c / 2

HNO₃ used in reaction to account for the basicity of the pyridine group.

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Our efforts to investigate the scope of the methods considered three different catalyst/reaction conditions: (A) 5% ABNO, 10% NaNO₂, acetic acid, 1 atm O₂, (B) 5% ABNO, 10% NaNO₂, 20% HNO₃, acetonitrile, air balloon, and (C) 5% keto-ABNO, 10% NaNO₂, 20% HNO₃, acetonitrile, 1 atm O₂. 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 shown 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 alcohols was oxidized in excellent yield with method C (entry 3), while method A showed the best reactivity in the oxidation of hydrobenzoin to benzil (entry 4).

15 Excellent results were also obtained with other activated 16 alcohols, including those with thiophene and pyridine 17 substituents (entries 5-7), a propargylic alcohol with a terminal 18 alkyne (entry 8), an allylic alcohol (entry 9), and vicinal N-19 protected aminoalcohols (entries 21 and 22). Use of the 20 ABNO/AcOH conditions (method A) led to good-to-excellent 21 vields with each of these substrates. The thiophene-containing 22 substrate formed an unidentified side product in acetonitrile 23 (i.e., methods B and C). The keto-ABNO/CH₃CN conditions (method C) were especially effective with the pyridine-24 containing alcohols. All three methods were effective with the 25 vicinal aminoalcohols. 26

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/CH₃CN 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 1methoxy-2-propanol, ethyl lactate, 3-hydroxyoxetane and 1,3dibenzyl-protected glycerol proceed in excellent yield (entries 16–19), in spite of electronic deactivation by the substituents.¹³ 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-3hydroxyazetidine, 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 1 mmol scale. 2-Adamantanol and the dibenzyl glycerol derivative (entries 15 and 19) were performed on larger scale (1.5–2g or approx. 10 mmol scale) using the ABNO/AcOH and keto-ABNO/CH₃CN 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 reactions conditions, consistent with the formation of a diazo compound.¹⁴ The ketone derived from 3-quinuclidinol oxidization was obtained in 54% yield using keto-ABNO/CH₃CN (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_x redox cycle required to achieve aerobic catalytic turnover.

Scheme 2. Limitations of the Substrate Scope.



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 non-chlorinated 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 elsewhere¹⁵ 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.

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Notes

The authors declare no competing financial interest.

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Abbreviations

ABNO, 9-azabicyclo [3.3.1] nonane *N*-oxyl; keto-ABNO, 9azabicyclo[3.3.1]nonan-3-one *N*-oxyl; 'HO-ABNO, 9azabicyclo[3.3.1]nonan-3-methyl-3-ol *N*-oxyl, F-ABNO, 3-Fluor-9-azabicyclo[3.3.1]nonan *N*-oxyl; oxa-ABNO, 7-oxa-9azabicyclo[3.3.1]nonan *N*-oxyl; oxa-keto-ABNO, 7-oxa-9azabicyclo[3.3.1]nonan-3-one *N*-oxyl; TEMPO, 2,2,6,6tetramethyl-1-piperidinyl *N*-oxyl

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TOC Graphic

