

## Aerobic Oxidation of Alcohols by Using a Completely Metal-Free Catalytic System

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A metal-free reaction system of air,  $\rm NH_4NO_{3(cat)}$ , 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)<sub>(cat)</sub>, and  $\rm H^+_{(cat)}$  is introduced as a simple, safe, inexpensive, efficient and chemoselective mediator for aerobic oxidation of various primary and secondary benzyl and alkyl alcohols, including those bearing oxidizable heteroatoms (N, S, O) to the corresponding aldehydes or ketones. Air oxygen under slight overpressure plays the role of the terminal oxidant, which is catalytically activated by redox cycles of nitrogen oxides released from a catalytic amount of  $\rm NH_4NO_3$  and cocatalyzed by TEMPO (nitroxyl radical compound), under acidic conditions, which are essential for an overall activation of the reaction system. The synthetic value of this reaction system and its green chemical profile was illustrated by a 10 g scale-up experiment, performed in an open-air system by using a renewable and reusable polymer-supported form of TEMPO (OXYNITROX<sup>®</sup>S100). The reaction solvent was recovered by distillation under atmospheric pressure, and the pure final product was isolated under reduced pressure; the acid activators (HCl or  $H_2SO_4$ ) were recovered as ammonium salts.

### Introduction

The selective oxidation of alcohols to the corresponding carbonyl compounds is among the most important functional group transformations in organic synthesis on laboratory as well as on industrial scale.<sup>[1]</sup> Traditionally, these transformations have been performed by using stoichiometric amounts of toxic organic or inorganic oxidizing agents such as dimethyl sulfoxide (DMSO), lead acetates, chromates and manganese oxides.<sup>[1]</sup> Following modern trends in chemistry, regulated with principles of green and sustainable chemical demands,<sup>[2]</sup> the use of such reagents have become unacceptable. During the last two decades there has been a very intense development in the field, mainly following the application of environmentally friendly oxidants that lead to a minimum amount of waste formation after catalytic, rather than noncatalytic processes. From the viewpoint of cost efficiency, atom economy and overall green and sustainable development, aqueous hydrogen peroxide and especially atmospheric molecular oxygen, represent the

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most acceptable and desirable choice of reagent for these tasks.<sup>[3]</sup> Hydrogen peroxide has some drawbacks, however, such as the requirement for certain safety precautions when used in larger amounts or in concentrations higher than 30% aqueous solution, because higher temperatures and/or impurities and trace amounts of metallic catalysts can induce undesirable decomposition to H<sub>2</sub>O and O<sub>2</sub> during reactions.<sup>[4]</sup> The molecular oxygen, especially when used in its natural diluted source as air, is the most abundant terminal oxidant, with clear benefits from the viewpoints of atom economy, cost efficiency and green chemistry.<sup>[4,5]</sup>

To establish the desired reactivity, much effort has been directed towards the development of oxidation methodologies under molecular oxygen with either heterogeneous or homogeneous activation with transition-metal-based catalysis such as Pd, V, W, Mo, Ru, Ag, Co and Au.<sup>[6]</sup> Nevertheless, their scarcity, highly undesirable environmental impact, high price, and toxicity present a significant limitation in the industrial use of such catalysts, especially in the last synthetic stages of the production of flavors, fragrances and active pharmaceutical ingredients.<sup>[6]</sup> As a result of these drawbacks, further efforts have been made, and nonprecious metal catalysts or transition-metal-free reaction systems for aerobic oxidation have been developed by taking advantage of the oxidative power of molecules bearing a nitroxyl radical functional moiety (TEMPO, TEMINO, NHPI, PINO etc.,<sup>[7]</sup> and very recently 2-azaadamantane-N-oxyl-based compounds<sup>[8]</sup>), often in combination with metal<sup>[9a]</sup> and very seldom with metal-free<sup>[10]</sup> cocatalysts. Likewise, in the last few years an aerobic biocatalytic approach based on

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glycolated copper-containing oxygenase enzyme laccases in combination with nitroxyl radicals has been established.<sup>[9b-9e]</sup> Among these, nitric oxide donors play an important role as reactive compounds that are useful in several chemical and biological applications.<sup>[11]</sup> Inorganic and organic nitrites or even aqueous hydroxylamines were introduced as sources of NO/NO2, which were generated in situ and involved in a redox cycle supporting the electron flow between oxidizable functional groups and molecular oxygen, often through metal, nonmetal or nitroxyl radicalbased additional redox moieties. The development of such catalytic methods has led to important improvements in the area of aerobic oxidation of alcohols but, in most cases, the reactions require high operating oxygen pressures up to 10 bar, temperatures between 80 and 100 °C, special Teflonlined autoclave reactors, and the use of undesirable chlorinated solvents such as ClCH2CH2Cl, CH2Cl2 and 1,2-dichlorobenzene.<sup>[12,13]</sup> It should be mentioned that investigations into the use of inorganic nitrates as potential sources of nitric oxides in aerobic oxidation are rare,<sup>[14,28b]</sup> and there is clearly still room for further investigation. Studies dealing with transition-metal nitrates as catalysts such as Fe-(NO<sub>3</sub>)<sub>3</sub>, Co(NO<sub>3</sub>)<sub>2</sub> or different copper(II) salts<sup>[15]</sup> for aerobic oxidation of alcohols have revealed that transition-metal cations (Fe<sup>2+</sup>/Fe<sup>3+</sup>, Co<sup>2+</sup>/Co<sup>3+</sup>, Cu<sup>+</sup>/Cu<sup>2</sup> redox pairs) are basic carriers of oxidation potential and are crucial for successful overall transformation of the substrate alcohols into the desired carbonyl products.<sup>[16]</sup> In the absence of transition-metal cations, the use of NaNO<sub>3</sub><sup>[16c]</sup> or HNO<sub>3</sub>, even in equimolar or excess amounts,<sup>[17]</sup> led to either no or minimal conversion of the starting material. In reactions where catalytic amounts of HNO<sub>3</sub> were used, even when combined with persistent free radicals such as 2,2,6,6-tetramethylpiperidine-N-oxyl (TEMPO) derivatives, the aerobic oxidation of benzyl alcohol to benzaldehyde was found to be inefficient in the absence of carbon materials (nanoshell carbon or activated carbon) as crucial additional accelerators of the overall process of nitric-acid-assisted carbon-catalyzed oxidation systems (NACOS).<sup>[18]</sup> Recently, HNO<sub>3</sub> has been utilized exclusively as a cocatalyst component in an efficient 4-acetamido-TEMPO-HNO3 catalytic system for oxidation of methyl α-D-glucopyranoside<sup>[19]</sup> or used in combination with a 4-acetamido-TEMPO-HCl catalytic system for the chemoselective metal-free aerobic oxidation of lignins.<sup>[20]</sup> A notable report by Hermans and co-workers<sup>[21]</sup> described the aerobic oxidation of different alcohols and 5-(hydroxymethyl)furfural with an HNO<sub>3</sub>-imobilized TEMPO system under slight overpressure.

Impressed by the aforementioned chemistry and motivated by a desire to develop this field further, in view of our continuing interest in green chemical transformations of organic compounds, especially stressing the role of air oxygen in these transformations,<sup>[22]</sup> we now report an efficient and selective oxidation of various alcohols to aldehydes or ketones by using a novel three-component, completely metal-free and cost-beneficial catalytic system based on NH<sub>4</sub>NO<sub>3</sub>/TEMPO/H<sup>+</sup> under mild, aerobic conditions.

## **Results and Discussion**

### **Optimization of Reaction Conditions**

To establish a practical, green and economical procedure for the selective aerobic oxidation of a comprehensive range of alcohols to their carbonyl derivatives, we aimed to develop a catalytic system with the following criteria: (i) use of air as the terminal oxidant under slight overpressure or even under open air; (ii) use of a metal-free catalytic system for its activation; (iii) use of inexpensive standard chemicals in the overall process producing minimum waste; (iv) regeneration of nitroxyl cocatalyst for potential reuse; (v) largescale efficiency and selectivity of the overall process, with, if possible, organic-solvent-free isolation and purification of final products. If achieved, these attributes would make the aerobic catalytic methodology fully suitable and very useful for industrial oxidation processes.

Based on previous reports dealing with aerobic oxidation of alcohols, supported by either catalytic or equimolar amounts of a nitric oxide source, we decided to further investigate various inorganic nitrates as potential catalytic promoters of these processes. In our initial experiments, we used benzyl alcohol (1a) as a model substrate. Promising preliminary results were achieved and are presented in Table 1. We assumed that nitrates as a potential source of nitric oxides would not be suitable for the catalytically mediated direct oxidation, because NO/NO2 has an insufficient redox potential  $[E^{\circ}(NO_2/NO) = 1.03 \text{ V}]$ . The presence of stable nitroxyl radicals as additional electron-flow carriers could be beneficial for the efficiency of the overall process. The increased reactivity of the nitroxyl radicals under ordinary acidic conditions causes disproportionation and formation of active oxoammonium cation intermediates [ $E^{\circ}$ (TEMPO cation/TEMPO) = 0.76 V],<sup>[7]</sup> as well as nitric oxide sourcing compounds. Accordingly, we chose TEMPO and HClO<sub>4</sub> as cocatalysts to establish an efficient and selective aerobic process. We started our investigation with the most widespread and environmentally friendly transition-metal catalyst, iron(III) nitrate, which appeared to be a good candidate for the task. However, as much as 20 mol-% acid was necessary to achieve good conversion of alcohol into benzaldehyde at room temperature (Table 1, Entry 1). On the other hand, the use of copper(II) nitrate as an alternative was efficient even without the presence of acid (Entries 2 and 3). Sodium nitrate as an alkali metal candidate was found to be inefficient at room temperature (Entry 5), but catalyzed the reaction to completion at 60 °C in the presence of 10 mol-% acid (Entry 6). In an attempt to establish a fully metal-free catalytic system, ammonium nitrate appeared to be the logical choice and, as it turned out, the right one. Under neutral conditions, the catalyst was found to be unreactive (Entry 7), but when an appropriate acidic activator was added at room temperature, moderate efficiency was obtained (Entry 8). Encouraged with this result, we increased the temperature to 60 °C and achieved quantitative conversion into benzaldehyde (Entry 9). Therefore, the three-component catalytic system NH<sub>4</sub>NO<sub>3</sub>/TEMPO/H<sup>+</sup> was used in subsequent studies.

Table 1. Aerobic oxidation of benzyl alcohol by using nitrate salt/ TEMPO/HClO<sub>4</sub> in acetonitrile.<sup>[a]</sup>

	CH <sub>2</sub> OHair, M	NO <sub>3(cat.)</sub> , TEM	PO <sub>(cat.)</sub>	H <sup>+</sup> (cat.)	СНО
1a					2a
Entry	Nitrate catalyst	Acid (mol-%)	Т [°С]	Time [h]	Conv. $1a \rightarrow 2a$ $ [^{0}/_{0}]^{[b]} $
1	Fe(NO <sub>3</sub> ) <sub>2</sub>	HClO <sub>4</sub> (20)	20	5	81
2	$Cu(NO_3)_2$	_	20	6	86
3	$Cu(NO_3)_2$	_	60	7	100
4	NaNO <sub>3</sub>	_	60	6	0
5	NaNO <sub>3</sub>	$HClO_4(10)$	20	8	4
6	NaNO <sub>3</sub>	$HClO_4(10)$	60	5	100
7	NH <sub>4</sub> NO <sub>3</sub>	_	60	7	0
8	NH <sub>4</sub> NO <sub>3</sub>	$HClO_4(10)$	20	7	29
9	NH <sub>4</sub> NO <sub>3</sub>	$HClO_4$ (10)	60	4	100

[a] Reaction conditions: benzyl alcohol (1a; 1 mmol), nitrate salt (0.1 mmol), HClO<sub>4</sub> (0–0.2 mmol), TEMPO (0.05 mmol), MeCN (2 mL), 20–60 °C, 5–6 h under air balloon (1 L). [b] Conversion of 1a into 2a determined from <sup>1</sup>H NMR spectra of crude reaction mixtures.

We further evaluated the role of the acids in the oxidation process and found that acids with  $pK_a$  values of at least -5 support the process quantitatively (Table 2), whereas weaker acids gave worse or even negative results. For this reason, HCl (aq. 37%) or H<sub>2</sub>SO<sub>4</sub> (aq. 98%) were used for further experiments as the most abundant acids.

Table 2. The effect of acid on the aerobic oxidation of benzyl alcohol with  $\rm NH_4NO_3$  and TEMPO.^{[a]}

CH	<sub>2</sub> OH air, NH <sub>4</sub> NO <sub>3(cat</sub>	.), TEMPO <sub>(cat.)</sub> ,	acid <sub>(cat.)</sub> CHO
	Me	CN, T, time	
1a			2a
Entry	Acid	pK <sub>a</sub>	Conv. $1a \rightarrow 2a$ $\begin{bmatrix} 0 & 0 \\ 0 \end{bmatrix}^{[b]}$
1	HCOOH	3.75	0
2	CF <sub>3</sub> COOH	-0.6	0
3	PTSA	-2.8	1
4	MeSO <sub>3</sub> H	-1.9	83
5	$HClO_4$	-5	100
6	HCl	-6	100
7	$H_2SO_4$	-9	100

[a] Reaction conditions: **1a** (1 mmol), TEMPO (5 mol-%), NH<sub>4</sub>NO<sub>3</sub> (10 mol-%), acid (aq., 10 mol-%), MeCN (2 mL), 60 °C, 4 h, air balloon. [b] Conversion of **1a** into **2a** determined from <sup>1</sup>H NMR spectra of crude reaction mixtures.

The use of organic solvents in chemical processes is one of the most conflicting issues from the green-chemistry point of view.<sup>[23]</sup> The most desirable are solvent-free transformations or those performed in recyclable and reusable reaction media such as alcohols, ethyl acetate, green ethers etc. Unfortunately, aerobic oxidation of benzyl alcohol by using our catalytic system under solvent-free reaction conditions was unsuccessful. Equally unsuccessful were reactions in H<sub>2</sub>O, MeOH, 2-methyltetrahydrofuran and Solkane (1,1,1,3,3-pentafluorobutane, HFC 365) as preferred envi-



ronmentally benign reaction media. Good conversion was observed by using cyclopentyl methyl ether (66%), and quantitative conversion was achieved in acetonitrile (see the Supporting Information Table S1 for a summary of the study).

We also checked the efficiency of four chosen nitroxide radicals, including TEMPO and three TEMPO derivatives (4-HO-TEMPO, 4-HO-TEMPO benzoate, and 4-MeO-TEMPO) (Figure 1). Trial oxidations were carried out with benzyl alcohol (**1a**) in acetonitrile with variations of nitroxide catalyst loading and 5 mol-% HCl (aq. 37%) and 5 mol-% NH<sub>4</sub>NO<sub>3</sub> at mild temperature for 24 h. Under identical conditions, 4-substituted derivatives were somewhat more efficient than TEMPO; however, because the latter is considerably less expensive, its use seems to be more reasonable. Of the tested nitroxide radicals, 4-HO-TEMPO benzoate seemed to be the most efficient under the same conditions. Full conversion of benzyl alcohol into benzaldehyde was achieved by using only 0.075 mol-% catalyst.



Figure 1. Efficiency of TEMPO, 4-HO-TEMPO, 4-HO-TEMPO benzoate and 4-MeO-TEMPO cocatalysts in the aerobic oxidation of benzyl alcohol by using the  $NH_4NO_3/TEMPO/HCl$  catalytic system. For reaction conditions see the Supporting Information.

It is worth mentioning that all control experiments highlighting the essential role of each member of the described reaction system, i.e., air oxygen as reagent and  $NH_4NO_3$ , TEMPO and HCl as catalysts, were performed; all the control systems gave negative results under argon or under air. In the absence of any one of the three components of the catalytic system, benzyl alcohol was not converted into benzaldehyde (see the Supporting Information for details).

#### Scope of the Reaction

Having identified the optimal reaction conditions for the aerobic oxidation of benzyl alcohols by using the  $NH_4NO_3/TEMPO/H^+$  catalytic system, we turned our attention to examining the scope and limitations of the present method. The results of the reaction of substituted primary and secondary benzyl alcohols are summarized in Table 3. All tested primary and secondary benzyl alcohols were quantitatively and selectively converted into their corresponding aldehydes or ketones in high isolated yields.

Table 3. Aerobic oxidation of substituted primary and secondary benzyl alcohols by using the air/NH<sub>4</sub>NO<sub>3</sub>/TEMPO/HCl catalytic system in acetonitrile.<sup>[a]</sup>

O Ph R	H `R <sup>1 -</sup>	air, NH <sub>4</sub> NO	3(cat.), TEMPO(cat.), HCI(cat.) MeCN, 60 °C			Ph R R	
1(a–	m)					2(a–m)	
Entry	R	Alcohol 1 R <sup>1</sup>		Time [h]	Conv. $1 \rightarrow 2$ $\begin{bmatrix} 0 \\ 0 \end{bmatrix}^{[b]}$	Yield <b>2</b> [%] <sup>[c]</sup>	
$     \begin{array}{c}       1 \\       2 \\       3 \\       4 \\       5 \\       6^{[d]} \\       7 \\       8 \\       9 \\       10 \\       11 \\       11     \end{array} $	H 4-MeC 4-Cl 4-F <sub>3</sub> C 4-O <sub>2</sub> N 3-F H 4-MeC 4-MeC 4-F	H H H H H H H Me Me Me Me	a b c d e f g h i j k	6 5 3 6 8 21 6 6 5 6 6	$     \begin{array}{r}       100 \\      1$	90 95 80 82 73 87 95 95 89 80 95	
12 13 <sup>[d]</sup>	4-F <sub>3</sub> C 3-O <sub>2</sub> N	Me Me	l m	7 25	100 100	91 82	

[a] Reaction conditions: Alcohol 1 (1 mmol), TEMPO (2.5–12.5 mol-%), NH<sub>4</sub>NO<sub>3</sub> (5–25 mol-%), HCl (aq. 37%, 5–12.5 mol-%), MeCN (2 mL), 60 °C, 5–7 h, air balloon (1 L); exact conditions for each reaction are given in the Supporting Information. [b] Determined from <sup>1</sup>H NMR spectroscopic analysis of the crude reaction mixture. [c] Yield determined after purification by flash chromatography (SiO<sub>2</sub>; ethyl acetate). [d] Reaction time 24 h.

The required reaction times could be correlated with the substituents on the substrate. However, even highly electron-deficient (4-nitrophenyl)methanol (1f; Table 3, Entry 6), 1-(3-nitrophenyl)ethanol (1m; Entry 13), [4-(trifluoromethyl)phenyl]methanol (1e; Entry 5), and 1-[4-(trifluoromethyl)phenyl]ethanol (1l; Entry 12) could be smoothly oxidized to the desired pure product in 73-91% yield after an extended reaction time. Moreover, the catalytic methodology enabled high chemoselectivity. No benzoic acid derivatives or any other impurities were detected in the crude reaction mixture.

We extended the range of benzyl alcohols to include polysubstituted derivatives bearing two or more electron-donating substituents (**3a–h**). As evident from the results collected in Table 4, high to quantitative amounts of the corresponding benzaldehyde derivatives **4a–h** were obtained from the reactions in MeCN, under air by using the NH<sub>4</sub>NO<sub>3</sub>/TEMPO/HCl catalytic system, without the formation of any benzoic acid or quinone derivatives. Significantly, phenol **3h** (Entry 8) with a structure moiety that is present in bioactive molecules, could be smoothly converted into the corresponding aldehyde **4h**.

Furthermore, benzyl alcohols bearing a cycloalkyl ring (**5a**–**d**; Table 5, Entries 1–4) or phenyl aromatic backbone (**5e**; Entry 5) were also quantitatively converted into their respective carbonyl derivatives 2,3-dihydro-1*H*-inden-1-one (**6a**), 3,4-dihydronaphthalen-1(2*H*)-one (**6b**), 9*H*-fluoren-9-one (**6c**), anthracen-9(10*H*)-one (**6d**), or 2-naphthaldehyde (**6e**).

Table 4. Aerobic oxidation of methoxy- and methyl-polysubstituted benzyl alcohols by using the  $NH_4NO_3/TEMPO/HCl$  catalytic system in acetonitrile.<sup>[a]</sup>

$R^{6}$ $R^{5}$ $R^{4}$	OH $\sim R^2 \frac{\text{air, NH}_4 NO_{3(c}}{R^3} N$	<sub>at.)</sub> , TEMP( leCN, 60 °(	$\frac{D_{(cat.)}, HCI_{(cat.)}}{C} \sim R^{\xi}$	
3(a–h	)			4(a–h)
Entry	Alcohol <b>3</b> R <sup>2</sup> , R <sup>3</sup> , R <sup>4</sup> , R <sup>5</sup>	, R <sup>6</sup>	Conv. $3 \rightarrow 4$ $ [\%]^{[b]} $	Yield <b>4</b> [%] <sup>[c]</sup>
1	2,3-(MeO) <sub>2</sub>	a	100	95
2	2,3,4-(MeO) <sub>3</sub>	b	100	90
3	3,4,5-(MeO) <sub>3</sub>	c	100	95
4	3,5-(MeO) <sub>2</sub>	d	100	93
5	2,5-(MeO) <sub>2</sub>	e	90	85
6	2,3,4,5,6-Me <sub>5</sub>	f	100	80
7	3,5-Me <sub>2</sub>	g	100	85
8 <sup>[d]</sup>	3-HO-4-MeO	ĥ	75	60

[a] Reaction conditions: Alcohol **3** (1 mmol), TEMPO (2.5–5 mol-%), NH<sub>4</sub>NO<sub>3</sub> (5–10 mol-%), HCl (aq. 37%, 5–10 mol-%), MeCN (2 mL), 60 °C, 5–6 h, air balloon (exact conditions for each reaction are given in the Supporting Information). [b] Determined from <sup>1</sup>H NMR spectroscopic analysis of the crude reaction mixture. [c] Yield determined after purification by flash chromatography (SiO<sub>2</sub>; ethyl acetate). [d] Reaction time 21 h.

Table 5. Aerobic oxidation of aromatic alcohols by using the  $\rm NH_4NO_3/TEMPO/HCl$  catalytic system in acetonitrile.^[a]

Entry	Alcohol 5		Product 6	Time [h]	Conv. $5 \rightarrow 6$ $[\%]^{[b]}$	Yield 6 [%] <sup>[c]</sup>
1	OH	a		7	100	90
2	OH	b		9	100	92
3	OH	c		6	100	90
4	OH	d		9	100	82
5	CH <sub>2</sub> OH	e	СНО	6	100	92

[a] Reaction conditions: Alcohol **5** (1 mmol), TEMPO (2.5–5 mol-%), NH<sub>4</sub>NO<sub>3</sub> (5–10 mol-%), HCl (aq. 37%, 5–10 mol-%), MeCN (2 mL), 60 °C, 5–6 h, air balloon (exact conditions for each reaction are given in the Supporting Information). [b] Determined from <sup>1</sup>H NMR spectroscopic analysis of the crude reaction mixture. [c] Yield determined after purification by flash chromatography (SiO<sub>2</sub>; ethyl acetate).

An additional presence of functional groups bearing heteroatoms such as sulfur, nitrogen or oxygen could represent competitive reaction centers to the oxidation of the hydroxy functional group in the target molecule. As can be seen from Table 6, we examined the selectivity of oxidation of some heterocyclic alcohols and made the methodology more general. Sulfur-containing heterocyclic alcohol derivatives such as 2-thienylmethanol (7a; Entry 1), thiochroman-4-ol (7b; Entry 2) and 9*H*-thioxanthen-9-ol (7c; Entry 3) were efficiently converted into their respective carbonyl derivatives 8a–c, without any detection of possible sulfoxide or sulfone side products. Cyclic ethers 4*H*-chromen-4-ol (7d; Entry 4) and 9*H*-xanthen-9-ol (7e; Entry 5) were also quantitatively converted into their respective carbonyl derivatives 8d and 8e. In the case of pyridinyl-substituted alcohols (7f–h; Entries 6–8), longer reaction times and reaction media based on AcOH were necessary to achieve quantitative conversion into the corresponding carbonyl derivatives 8f–h.

Table 6. Aerobic oxidation of benzylic alcohols bearing oxidizable heteroatoms by using the  $NH_4NO_3/TEMPO/HCl$  catalytic system in acetonitrile.<sup>[a]</sup>



[a] Reaction conditions: Alcohol 7 (1 mmol), TEMPO (2.5–5 mol-%), NH<sub>4</sub>NO<sub>3</sub> (5–10 mol-%), HCl (5–10 mol-%), MeCN (2 mL), 60 °C, 5–6 h, air balloon (exact conditions for each reaction are given in the Supporting Information). [b] Determined from <sup>1</sup>H NMR spectroscopic analysis of the crude reaction mixture. [c] Yield determined after purification by flash chromatography (SiO<sub>2</sub>; ethyl acetate). [d] AcOH was used as the solvent.

Aliphatic alcohols are usually more resistant to oxidation, and this was also noticed in the case of the aerobic process using the  $NH_4NO_3/TEMPO/HCl$  catalytic system. Encouragingly, we tested some aliphatic, cycloaliphatic and allylic alcohols, and the results are collected in Table 7. We found that increased reaction times and loading of TEMPO as well as addition of ammonium nitrate and acid were necessary to obtain good conversions to the carbonyl compounds. Aliphatic alcohols 1- and 2-octanol **9a** and **9b** (Entries 1 and 2) showed good conversions under aerobic conditions, whereas the cyclic analogue 4-*tert*-butylcyclohexanol (**9c**; Entry 3) was oxidized with very satisfying efficiency. The oxidation of allylic alcohols (Entries 4 and 5)



was not very promising using TEMPO, but with the use of more active 4-HO-TEMPO benzoate catalyst, cinnamyl alcohol (9d; Entry 4) and 1-phenylprop-2-en-1-ol (9e; Entry 5) as standard representatives of allylic alcohols were fully converted into the corresponding carbonyl compounds.

Table 7. Aerobic oxidation of aliphatic and allylic alcohols catalyzed by the  $\rm NH_4NO_3/TEMPO/HCl$  system in acetonitrile.<sup>[a]</sup>

Entry	Alcohol 9		Product 10	Time [h]	Conv. $9 \rightarrow 10$ [%] <sup>[b]</sup>	Yield 10 [%] <sup>[c]</sup>
1 <sup>[d]</sup>	1-octanol	a	1-octanal	24	85	77
2 <sup>[d]</sup>	2-octanol	b	2-octanone	24	72	65
3	tBu-OH	c	tBu	25	87	80
4	Ph	d	Ph	24	23 <sup>[e]</sup> 100 <sup>[f]</sup>	90
5	Ph	e	Ph	24	19 <sup>[e]</sup> 100 <sup>[f]</sup>	92

[a] Reaction conditions: Alcohol **9** (1 mmol), TEMPO (5–10 mol-%), NH<sub>4</sub>NO<sub>3</sub> (10–20 mol-%), HCl (aq. 37%, 10–20 mol-%), MeCN (2 mL), 60 °C, 23–25 h, air balloon (exact conditions for each reaction are given in the Supporting Information). [b] Determined from <sup>1</sup>H NMR spectroscopic analysis of the crude reaction mixture. [c] Yield determined after purification by flash or column chromatography (SiO<sub>2</sub>; ethyl acetate/petroleum ether). [d] O<sub>2</sub> balloon. [e] 10 mol-% TEMPO was used. [f] 5 mol-% 4-HO-TEMPO benzoate was used.

### Optimization of Reaction Conditions to Fulfill Green-Chemistry Demands

When exploring and developing new reagents, catalysts or protocols for any chemical transformation, small-scale reactions (mmol scale) are typically used to gain basic knowledge on the system. However, it is very desirable to demonstrate the practical applicability of a new procedure at least on the laboratory level, and ideally to indicate its potential use in industrial applications. We thus believe that a scale-up investigation should also be performed as part of the basic level of research, to further evaluate the preparative potential of a new method, especially in the view of green chemistry. To demonstrate the practicality of scaling up the current procedure, we treated 10.8 g (0.1 mol) of benzyl alcohol in MeCN (40 mL) solution with 5 mol-% NH<sub>4</sub>NO<sub>3</sub>, 5 mol-% 4-MeO-TEMPO, and 5 mol-% of 98%  $H_2SO_4$  in a flask (250 mL) equipped with condenser and opened to air. We chose 98% sulfuric acid, rather than 37%hydrochloric acid used in the mmol-scale experiments, to introduce as little water as possible into the reaction system and exclude chlorides, which very often cause the formation of chlorinated genotoxic impurities especially in scale-up pharmaceutical industrial processes. After completion of the reaction, white solid was filtered off and identified as almost pure (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>, solvent was recovered (38 mL) by distillation at atmospheric pressure, and further distillation under reduced pressure gave a colorless liquid (9.8 g, 92.4%) that was identified as benzaldehyde. An attempt to regenerate the 4-MeO-TEMPO cocatalyst for potential reuse from the distillation residue failed, which is a limitation

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of the green profile of the overall reaction protocol. To avoid this inconvenience, we examined the use of backbonesupported and thus potentially regenerative forms of TEMPO catalyst for the aerobic oxidation. It is known that many immobilized forms of TEMPO, typically bridged to a backbone through C(4)-O or C(4)-N bonds, have been used as cocatalyst in various oxidation processes involving alcohol to carbonyl transformations. These potentially recoverable and reusable materials, bearing TEMPO on magnetic supporters,<sup>[24]</sup> various polymers,<sup>[25a]</sup> mesoporous materials<sup>[25b]</sup> or silica backbone.<sup>[25a]</sup> ionic liquids matrix.<sup>[26]</sup> and immobilization on hydrophobic resins<sup>[27]</sup> were mainly studied on the mmol scale. One system that has been promoted<sup>[25c]</sup> and elaborated<sup>[7c]</sup> on the basic level as PIPO (Polyamine Immobilised Piperidyl Oxyl) and used on an industrial level as OXYNITROX®S100,<sup>[28]</sup> seemed to be the most promising choice for our task. Since this material, to the best of our knowledge, has not been tested as a catalyst for aerobic oxidation of alcohols under open-air conditions, we first checked its efficiency under NH4NO3/TEMPObased cocatalyst/H<sup>+</sup> reaction-system conditions. The results of this investigation performed on benzyl alcohol are shown in Figure 2. Recycling and reuse of OXYNITROX®S100 was performed for five consecutive runs. Quantitative conversions were achieved in all cycles, although the loss of catalyst per cycle was 9% on average.



Figure 2. Successful recycling and reuse of cocatalyst OXYNI-TROX $^{\otimes}$ S100 for efficient aerobic oxidation of benzyl alcohol by using the NH<sub>4</sub>NO<sub>3</sub>/OXYNITROX $^{\otimes}$ S100/HCl catalytic system. Reaction conditions are given in the Supporting Information.

Encouraged by these results, OXYNITROX<sup>®</sup>S100 was used as a TEMPO-based cocatalyst for the scale-up experiment. These experiments also established that, under similar reaction conditions, this material could also be regenerated for further use. The only concern in our attempt to optimize the green profile of the method was the potential emission of NO<sub>x</sub>; however, such concerns have been technologically resolved.<sup>[29]</sup>

#### **Mechanistic Discussion**

Mechanistic elucidation of aerobic oxidation of alcohols, catalyzed by nitric oxides redox cycle assisted by nitroxyl radicals have been elaborated several times.<sup>[8,12,25]</sup> Observations related to the behavior of the NH<sub>4</sub>NO<sub>3</sub>/TEMPO/H<sup>+</sup> catalytic system, the essential role of each component, isolation and identification of reaction products, and the study of substituent effects on the reaction kinetics based on Hammett correlation analysis (see the Supporting Information for details) of the reaction are consistent with the known sequence of catalytic cycles that take place during air oxygen oxidation of alcohols to aldehydes or ketones. The acid is assumed to have two main roles: its first role is to hydrolyze ammonium nitrate to  $HNO_3$  [Equation (1)], which is in thermally accelerated decomposing equilibrium with  $NO_2$  [Equation (2)], and the second is to accelerate the interconversion in the disproportion equilibrium of TEMPO to TEMPO<sup>+</sup> and TEMPOH, which function as active intermediates through their redox cycle in the last phase of oxidation, i.e., proton pumping from an alcohol molecule. On the other hand, higher oxidation potential of air oxygen and activation of poorly reactive alcohols in the acidic environment could not be overlooked. Isolation of ammonium salts (chloride when HCl was used, or sulfate when  $H_2SO_4$  was used) supports the first role, whereas the second has already been discussed.<sup>[7e]</sup> Hammett plots  $(\log k_{\rm rel}/\sigma^+)$  conducted with our catalytic system revealed good correlation for aerobic oxidation of a series of substituted benzyl alcohols and the value of the resulting reaction constant  $\rho^+ = -0.96$  supports the development of a partial positive charge in the transition state of the rate-determining step of the reaction. This result is consistent with the accepted model of the interaction of the TEMPO+-active intermediate and an alcohol molecule. The assumption that

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 $NH_4NO_3 + HCI \implies HNO_3 + NH_4CI \quad (1)$   $4 HNO_3 \implies 4 NO_2 + 2 H_2O + O_2 \quad (2)$ 

### **Conclusions and Perspectives**

We have successfully developed a three-component, completely metal-free catalytic system of  $NH_4NO_3/TEMPO/H^+$ that can be used for efficient and selective oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones under mild aerobic conditions. The presented catalytic system enables moderate to quantitative, chemoselective oxidation of a comprehensive range of

the NO/NO<sub>2</sub> redox pair actually collaborates in the catalytic

cycles is supported by the observation that several cycles of

color changes of the reacting solution from brown (NO<sub>2</sub>)

to colorless (NO) occurred during the reactions. We also established that HCl-mediated processes are faster than

those catalyzed by  $H_2SO_4$ . This could be explained by possible formation of NOCl, which has a beneficial effect on

the overall oxidizing power of the reaction system, which

has already been observed when halides are involved in aer-

obic oxidative processes mediated by  $NO_x$  sources.<sup>[12c,22c]</sup>



alcohols including those bearing oxidizable heteroatoms (S, N, O), alkyl-, cycloalkyl-, and allyl-type substituted substrates. To the best of our knowledge, the developed catalytic system constitutes for the first time that an aerobic oxidative transformation of organic compounds has been used in which each member has an essential role in the reaction system. A plausible mechanistic interpretation of the present catalytic system including relative kinetic measurements based on Hammett correlations is also suggested. We believe that our invention could open new opportunities and help in the development of more economical, mild, simple, and environmentally friendly catalytic oxidation methodologies that use atmospheric air as terminal oxidant. In addition, the NH<sub>4</sub>NO<sub>3</sub>/OXYNITROX<sup>®</sup>S100/H<sup>+</sup> catalytic system, successfully tested for aerobic oxidation of benzyl alcohols, offers the advantages of easy recycling of TEMPO-based cocatalyst over several consecutive cycles. Finally, the promising scale-up procedures with a preparative example of the catalytic method was achieved; further modifications of the reaction protocol and isolation and purification of products were directed towards making the overall process industrially more acceptable and as green as possible. The use of NH<sub>4</sub>NO<sub>3</sub> as a simple, inexpensive and metal-free catalyst, the application of an open-air system instead of high-oxygen-pressure systems (autoclave), the generation of minimal amounts of waste and the possibility of process scale-up including recovery of all possible hazardous solvents and reactants make the methodology useful and interesting from both environmental and economic points of view.

## **Experimental Section**

**General:** All chemicals used in this study were analytical grade, commercially available and used without further purification unless otherwise noted. Reactions were carried out in 5 or 10 mL glass flasks. Balloons (1 L) with 10 mil wall thickness were purchased from Sigma Aldrich and used as air reservoir. Reactions were monitored by thin-layer chromatography on TLC Silica gel 60 F<sub>254</sub> aluminum sheets ( $20 \times 20$  cm). Column chromatography (CC) and flash chromatography (FC) were performed by using silica gel 60 (particle size: 0.063–0.200 mm) and preparative thin-layer chromatography (preparative TLC) with PLC Silica gel 60 F<sub>254</sub>, 2 mm plates.

**General Measurement:** Conversions and yields were determined on the basis of NMR spectroscopic analysis. NMR spectra were recorded with a Varian INOVA 300 NMR instrument (<sup>1</sup>H: 303.0 MHz; <sup>13</sup>C: 76.2 MHz) using CDCl<sub>3</sub> as solvent with SiMe<sub>4</sub> (TMS) as an internal reference. Melting points were determined with a Büchi 535 instrument.

### **General Experimental Procedures**

Aerobic Oxidation of Alcohols with the NH<sub>4</sub>NO<sub>3</sub>/TEMPO/HCl Catalytic System (mmol Scale). General Procedure: A 10 mL glass flask equipped with magnetic stirring bar was charged with alcohol (1 mmol) and acetonitrile (2 mL). To the solution, NH<sub>4</sub>NO<sub>3</sub> (5–25 mol-%), TEMPO (1.2–12.5 mol-%) and hydrochloric acid (aq. 37%, 5–25 mol-%) were consecutively added in 2 min intervals, and the flask was further fitted with a balloon filled with air (1 L) and magnetically stirred at 60 °C. In the reaction system, which periodi-

cally changed the color from brown to colorless, the consumption of starting material was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL), insoluble material (identified as ammonium chloride) was filtered off, the filtrate was washed with aq. NaHCO<sub>3</sub> (10%, 10 mL) and Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10%, 10 mL), and the organic phase was dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>. Organic solvent was distilled off under reduced pressure, and the crude product was analyzed by <sup>1</sup>H NMR spectroscopy. Finally, the crude product was purified by flash chromatography (SiO<sub>2</sub>; ethyl acetate) to afford pure material, which was compared to authentic samples. Detailed data, including catalyst loading, reaction times, yields of pure products and their spectroscopic and other identification data are given in the Supporting Information.

Aerobic Oxidation of Benzyl Alcohol with the NH4NO3/4-OMe-TEMPO/H<sub>2</sub>SO<sub>4</sub> Catalytic System. Scale-Up Procedure: A 250 mL glass reactor equipped with a magnetic stirring bar and open condenser was charged with substrate benzyl alcohol (0.1 mol, 10.8 g) dissolved in acetonitrile (40 mL). The solution was heated at 60 °C, then catalyst NH<sub>4</sub>NO<sub>3</sub> (5 mol-%, 0.4 g), cocatalyst 4-MeO-TEMPO (5 mol-%, 0.93 g) and acid activator aq. 98% H<sub>2</sub>SO<sub>4</sub> (5 mol-%, 278 µL) were added in consecutive 2 min intervals. The reaction mixture was stirred (600 rpm) under open-air conditions at 60 °C for 48 h. Upon completion of the reaction, the reaction mixture was cooled to room temperature, and salt (identified as ammonium sulfate; 360.4 mg recovered) was filtered off and washed with acetonitrile (5 mL). To obtain carry-over of the solvent, the filtrate was distilled at atmospheric pressure at 85 °C; full recovery of acetonitrile was achieved and successfully reused again. The distillation program was then changed: the pressure was decreased to 5 mbar and the temperature raised to 100 °C, whereupon the desired product benzaldehyde (9.8 g; 92% yield) was obtained as a colorless liquid.

Aerobic Oxidation of Benzyl Alcohol with the NH4NO3/ OXYNITROX®S100/H<sub>2</sub>SO<sub>4</sub> Catalytic System. Scale-Up Procedure: A 250 mL glass reactor equipped with magnetic stirring bar and open condenser was charged with acetonitrile (40 mL). The solvent was heated at 60 °C, then catalyst NH<sub>4</sub>NO<sub>3</sub> (20 mol-%, 0.8 g), acid activator  $H_2SO_4$  (aq. 98%, 20 mol-%, 1112 µL) and cocatalyst OXYNITROX®S100 (10 mol-%, 4.34 g) were added in consecutive 2 min intervals. After 10 min, model substrate benzyl alcohol (0.1 mol, 10.8 g) was added, and the reaction mixture was stirred (600 rpm) under open-air conditions at 60 °C for 48 h. After completion of the reaction, the reaction mixture was cooled to room temperature, and salt (identified as ammonium sulfate) was filtered off (762.4 mg recovered) and washed with acetonitrile (5 mL). To obtain carry-over of the solvent, the filtrate was distilled at atmospheric pressure at 85 °C; full recovery of acetonitrile was achieved and successfully reused. After evaporation of solvent, cold diethyl ether (20 mL) was added; the precipitated OXYNITROX®S100 (3.7 g recovered) was filtered off with a sintered glass funnel, washed with cold diethyl ether  $(3 \times 5 \text{ mL})$ , and dried in air for further use. Further diethyl ether was distilled from benzaldehyde under normal pressure at 35 °C. The distillation program was then changed: the pressure was decreased to 5 mbar and the temperature raised to 100 °C, whereupon the desired product benzaldehyde (9.7 g, 90% yield) was obtained as a colorless liquid.

**Supporting Information** (see footnote on the first page of this article): Full experimental details for each substrate, Hammett correlation, study of solvent effect and characterizations for isolated products (<sup>1</sup>H and <sup>13</sup>C NMR spectra).

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