Novel [4-Hydroxy-TEMPO + NaCl]/SiO_2 as a Reusable Catalyst for Aerobic Oxidation of Alcohols to Carbonyls

Naoya Tamura,[a] Tadashi Aoyama,*[a,b] Toshio Takido,[a] Mitsuo Kodomari[c]

[a] Department of Materials and Applied Chemistry, College of Science and Technology, Nihon University, Kanda Surugadai, Chiyoda-ku, Tokyo 101-8308, Japan
Fax +81(3)32590818; E-mail: aoyama.tadashi@nihon-u.ac.jp

[b] The Center for Creative Materials Research, Research Institute of Science and Technology, College of Science and Technology, Nihon University, Kanda Surugadai, Chiyoda-ku, Tokyo 101-8308, Japan

[c] Department of Bioscience and Engineering, Shibaura Institute of Technology, Fukasaku, Minuma-ku, Saitama 337-8570, Japan

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Abstract: A convenient method for the preparation of [4-hydroxy-TEMPO + NaCl]/SiO_2 was developed. And [4-hydroxy-TEMPO + NaCl]/SiO_2 with $Fe(NO_3)_3 \cdot 9H_2O$ was used for an aerobic oxidation of alcohols to carbonyls under mild reaction conditions. Alcohols were converted to the corresponding carbonyls in good to excellent yields. [4-Hydroxy-TEMPO + NaCl]/SiO_2 can be easily separated from the reaction mixture by filtration and reused at least six times.

Key words: alcohols, TEMPO, oxidation, supported catalyst, ketones

The oxidation of alcohols to aldehydes or ketones is one of the important reactions in organic synthesis. Chromic acid oxidant has long been employed for the oxidation of alcohols.[1] However, chromic acid has a strong toxicity. In the oxidation of alcohols using chromic acid as an oxidant, excess amount of chromic acid is required against an alcohol, and a large amount of toxic waste is generated. Swern and Dess–Martin oxidation are also known as metal-free oxidation. Swern oxidation,[2] however, emits a bad smell because dimethyl sulfide is generated during the reaction, and Dess–Martin oxidation[3] uses an explosive reagent as an oxidant. In 1975, Cella et al.[4] and Ganem[5] independently reported a novel method for the oxidation of alcohols using 2,2,6,6-tetramethyl-piperidine-1-oxyl (TEMPO). Since then, many studies on the oxidation of alcohols using TEMPO have been reported. In the oxidation using TEMPO, reoxidants such as NaClO, $PhI(OAc)_2$,[6,7] and oxygen are employed along with TEMPO, because TEMPO should be reoxidized again and again in order to oxidize alcohols into carbonyls. The oxidation using oxygen as a reoxidant is an ideal method for the oxidation of alcohols, because; (1) oxygen exists a lot in air; (2) only H_2O is yielded as a side product. Semmelhack et al. has reported an aerobic oxidation of alcohols using TEMPO and CuCl.[8] This method, however, is not suitable for secondary alcohols. Wang et al. reported an aerobic oxidation of alcohols using 4-hydroxy-TEMPO and $Fe(NO_3)_3 \cdot 9H_2O$. This method needs long reaction time (10–36 h).[9] Yin et al. reported the oxidation of alcohols using 4-acetoamide TEMPO, $FeCl_3$, and $NaNO_2$. The reaction was carried out under severe conditions (50 °C, 0.4 MPa O_2).[10] Metal nitrates played a role as promoter of reoxidation of TEMPO. Recently, procedures of transition-metal-free aerobic oxidation have been reported.[11]

As mentioned above, many methods for the oxidations of alcohols using TEMPO derivatives have been reported. However, in these methods, TEMPO derivatives have not been reused. Recently, the oxidation using supported TEMPO derivatives has been reported. For instance; (1) Fey et al. have reported Anelli oxidation of alcohols using silica gel supported TEMPO as a catalyst;[12] (2) PEG-supported TEMPO radicals were developed for an aerobic oxidation under Minisci's conditions by Benaglia;[13] (3) Fall et al. have described ionic liquid supported TEMPO for the oxidation of alcohols to aldehydes and ketones;[14] (4) Karimi et al. have prepared magnetically separable TEMPO, magnetic core-shell nanoparticle-supported TEMPO, and have described the metal- and halogen-free aerobic oxidation of alcohols in water,[15] etc.[16] The point, supported TEMPO can be reused for subsequent reaction, is significant progress. But many steps and long times were taken for the preparation of this supported TEMPO.

In the course of our study using inorganic solid-supported reagents, we found out that 4-hydroxy-TEMPO was easily supported onto silica gel in nonpolar solvents such as toluene, 1,2-dichloroethane (DCE), and chloroform. When SiO_2 was added to the solution of 4-hydroxy-TEMPO in toluene, which is orange, 4-hydroxy-TEMPO was adsorbed on the surface of SiO_2, and the color of SiO_2 changed from white to orange (Figure 1).

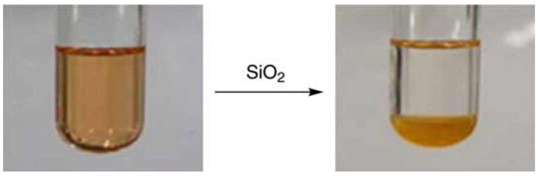

Figure 1 Adsorption of 4-hydroxy-TEMPO to SiO_2

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This result interested us very much because this silica gel supported TEMPO (TEMPO–SiO_2), which was easily prepared, was expected as a catalyst for the oxidation of alcohols in nonpolar solvent. In this paper, we describe the aerobic oxidation of alcohols using TEMPO–SiO_2.

Various inorganic solids were tested in order to find out the most effective adsorbent for 4-hydroxy-TEMPO (Table 1). When various inorganic supports were added to the solution of 4-hydroxy-TEMPO in toluene, 4-hydroxy-TEMPO was adsorbed on the support, and the solution changed from orange to colorless. Silica gel is the most effective adsorbent among the supports tested (Table 1, entry 1). Alumina and bentonite also adsorbed 4-hydroxy-TEMPO, whereas celite and molecular sieves 4A did not adsorb (Table 1, entries 2–5). When TEMPO was used instead of 4-hydroxy-TEMPO, a large amount of silica gel was needed to adsorb TEMPO completely (Table 1, entry 6). This result suggests that the silanol on the surface of SiO_2 and the hydroxy group in TEMPO interacted strongly with each other.

Table 1 Amount of 4-Hydroxy-TEMPO Adsorbed on Various Supports

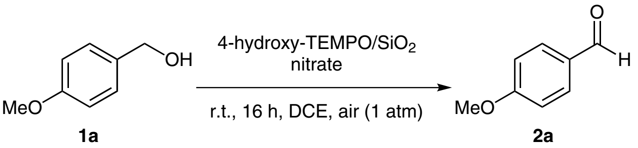
Entry[a]	Support	TEMPO/support (mmol/g)
1	SiO_2	8.3
2	Al_2O_3	2.0
3	bentonite	3.3
4	celite	–
5	MS-4A	–
6[b]	SiO_2	1.1

[a] 4-Hydroxy-TEMPO (mmol) adsorbed on an inorganic support (1 g) in toluene.
[b] TEMPO.

Oxidation of 4-methoxybenzyl alcohol (**1a**) was employed as a model reaction in order to determine the optimum reaction conditions (Table 2). A mixture of **1a** (2 mmol) and 4-hydroxy-TEMPO/SiO_2 (0.1 mmol, 1.0 g) was stirred in DCE (5 mL) at room temperature for 16 hours, but the reaction did not proceed (Table 2, entry 1). When this reaction was carried out in the presence of various nitrates under the same conditions, the reaction was slightly promoted. In the cases using $Fe(NO_3)_3{\cdot}9H_2O$ and $Cu(NO_3)_2{\cdot}9H_2O$, the oxidized product **2a** was yielded in 17% and 15% yields (Table 2, entries 2 and 3).

Recently, Ma et al. reported that a catalytic amount of chlorides such as RbCl, CsCl, and NaCl act as an accelerator in the $Fe(NO_3)_3{\cdot}9H_2O$/TEMPO-catalyzed aerobic oxidation of alcohols.[17] Various chlorides were supported onto silica gel along with 4-hydroxy-TEMPO, and the supported reagents were used as an oxidant (Table 3). The supported reagents containing $FeCl_3$, $FeCl_2{\cdot}4H_2O$, $CuCl_2{\cdot}2H_2O$, and NaCl converted **1a** into **2a** in a short time, and **2a** was obtained in excellent yields (Table 3, entries 2, 3, 5, and 7). The reaction using a reagent containing $FeCl_3$ was the fastest among them, **1a** was converted completely in one hour, and **2a** was yielded in 86% yield along with small amount of side products. Oxidation of benzhydrol (**1i**) using $FeCl_3$, however, did not primarily yield benzophenone (**2i**), and bis(diphenylmethyl)ether (**3i**) was formed as a main product, because $FeCl_3$ acts as Lewis acid (Table 3, entry 8). When this reaction was carried out in the presence of [4-hydroxy-TEMPO + NaCl]/SiO_2 for seven hours, **2i** was obtained quantitatively and **3i** was not formed (Table 3, entry 9).

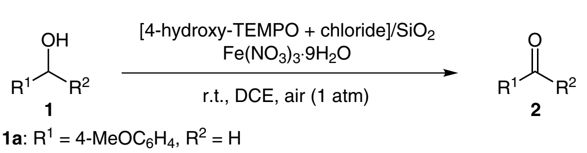
Table 2 Oxidation of Alcohols in the Presence of Various Nitrates



Entry[a]	Nitrate	Yield (%)[b]
1	none	trace
2	$Fe(NO_3)_3{\cdot}9H_2O$	17
3	$Cu(NO_3)_2{\cdot}3H_2O$	15
4	$Ce(NH_4)_2(NO_3)_6$	3
5	$Co(NO_3)_2{\cdot}6H_2O$	trace

[a] A mixture of **1a** (2.0 mmol), 4-hydroxy-TEMPO/SiO_2 (0.1 mmol/g, 1.0 g), and nitrate (5 mol%) was stirred in DCE (5 mL) at r.t. for 16 h.
[b] Determined by GLC analysis using *n*-dodecane as internal standard.

Table 3 An Effectiveness of Chloride in Supported Reagent on the Oxidation of Alcohols



1a: R^1 = 4-$MeOC_6H_4$, R^2 = H
1i : R^1 = Ph, R^2 = Ph

Entry[a]	Alcohol	Chloride	Time (h)	Yield (%)[b]
1	**1a**	none	16	17
2	**1a**	$FeCl_3$	1	86
3	**1a**	$FeCl_2{\cdot}4H_2O$	2	93
4	**1a**	$CoCl_2$	7	94
5	**1a**	$CuCl_2{\cdot}2H_2O$	3	93
6	**1a**	$MnCl_2{\cdot}4H_2O$	7	27
7	**1a**	NaCl	3	96
8	**1i**	$FeCl_3$	3	24
9	**1i**	NaCl	7	99

[a] A mixture of alcohol (2.0 mmol), [4-hydroxy-TEMPO + chloride]/SiO_2 [(0.1 + 0.1) mmol/g, 1.0 g] and $Fe(NO_3)_3{\cdot}9H_2O$ (5 mol%) was stirred in DCE (5 mL) at r.t.
[b] Determined by GLC analysis using *n*-dodecane as internal standard.

The activity of 4-hydroxy-TEMPO/SiO_2 was influenced by the conditions for preparing it (Table 4). [4-Hydroxy-TEMPO + NaCl]/SiO_2 was prepared as follows: Silica gel (9.77 g) was added to the solution of 4-hydroxy-TEMPO (0.17 g) and NaCl (0.06 g) in water (50 mL), and the mixture was stirred at room temperature for half an hour. The water was removed by rotary evaporator under reduced pressure. When the supported reagent prepared by removing water at 75 °C, and 20 mbar was used for the oxidation of **1a**, it took five hours to oxidize **1a** completely (Table 4, entry 1).

Table 4 Effectiveness of Preparative Method of [4-Hydroxy-TEMPO + NaCl]/SiO_2

$$\mathbf{1a} \xrightarrow[\text{r.t., DCE, air (1 atm)}]{\substack{\text{[4-hydroxy-TEMPO + NaCl]/SiO}_2 \\ \text{Fe(NO}_3\text{)}_3\cdot 9\text{H}_2\text{O}}} \mathbf{2a}$$

Entry[a]	Conditions[b]	Water (%)[c]	Time (h)	Yield (%)[d]
1	75 °C, 20 mbar	2.2	5	96
2	65 °C, 20 mbar	3.7	2	97
3	65 °C, 40 mbar	5.1	2	97
4	65 °C, 70 mbar	8.3	3	6

[a] A mixture of 1a (2.0 mmol), [4-hydroxy-TEMPO + NaCl]/SiO_2 [(0.1 + 0.1) mmol/g, 1.0 g] and $Fe(NO_3)_3\cdot 9H_2O$ (5 mol%) was stirred in DCE (5 mL) at r.t.

[b] Evaporating conditions for the preparation of [4-hydroxy-TEMPO + NaCl]/SiO_2.

[c] Content of water in [4-hydroxy-TEMPO + NaCl]/SiO_2.[18]

[d] Determined by GLC analysis using *n*-dodecane as internal standard.

Reactions using the supported reagent prepared by removing water at 65 °C under 20 mbar and 40 mbar gave **2a** quantitatively in two hours (Table 4, entries 2 and 3). The reaction rate rose according to the increase of water content in the supported reagent. However, when the reaction was carried out using a supported reagent prepared by removing water at 65 °C under 70 mbar, the reaction hardly progressed (Table 4, entry 4).

The reaction also proceeded in various solvents. When toluene was used as a solvent, **2a** was obtained in 92% yield in four hours. The yield of that using chloroform as a solvent was 98% in three hours (Table 5, entry 3). THF, EtOAc, and MeCN also gave **2a** in moderate to excellent yield but 4-hydroxy-TEMPO was dissolved in the solvent. Therefore supported reagent, [4-hydroxy-TEMPO + NaCl]/SiO_2, could not be reused.

The possibility of recycling of [4-hydroxy-TEMPO + NaCl]/SiO_2 was examined (Table 6). [4-Hydroxy-TEMPO + NaCl]/SiO_2 was recovered from the reaction mixture by filtration and used for the next reaction without after-treatment. [4-Hydroxy-TEMPO + NaCl]/SiO_2 was reused for the oxidation of **1a** at least six times without loss of catalytic activity.

Table 5 An Effectiveness of Solvent on the Oxidation of **1a**

$$\mathbf{1a} \xrightarrow[\text{r.t., air (1 atm)}]{\substack{\text{[4-hydroxy-TEMPO + NaCl]/SiO}_2 \\ \text{Fe(NO}_3\text{)}_3\cdot 9\text{H}_2\text{O}}} \mathbf{2a}$$

Entry[a]	Solvent	Time (h)	Yield (%)[b]
1	toluene	4	92
2	DCE	2	97
3	$CHCl_3$	3	98
4	THF	5	41
5	EtOAc	5	96
6	acetone	5	trace
7	MeCN	6	94

[a] A mixture of **1a** (2.0 mmol), [4-hydroxy-TEMPO + NaCl]/SiO_2 [(0.1+0.1) mmol/g, 1.0 g] and $Fe(NO_3)_3\cdot 9H_2O$ (5 mol%) was stirred in solvent (5 mL) at r.t.

[b] Determined by GLC analysis using *n*-dodecane as internal standard.

Table 6 Recyclability of [4-Hydroxy-TEMPO + NaCl]/SiO_2 on the Aerobic Oxidation of **1a**

$$\mathbf{1a} \xrightarrow[\text{r.t., 2 h, DCE, air (1 atm)}]{\substack{\text{[4-hydroxy-TEMPO + NaCl]/SiO}_2 \\ \text{Fe(NO}_3\text{)}_3\cdot 9\text{H}_2\text{O}}} \mathbf{2a}$$

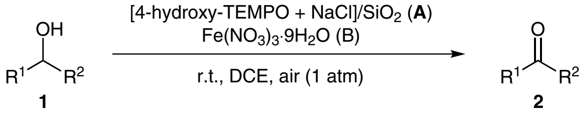
Cycle[a]	Yield (%)[b]
1	98
2	99
3	96
4	96
5	99
6	97

[a] A mixture of 1a (2.0 mmol), [4-hydroxy-TEMPO + NaCl]/SiO_2 [(0.1 + 0.1) mmol/g, 1.0 g] and $Fe(NO_3)_3\cdot 9H_2O$ (5 mol%) was stirred in DCE (5 mL) at r.t. for 2 h.

[b] Determined by GLC analysis using *n*-dodecane as internal standard.

Table 7 shows the results of the oxidation of various alcohols under optimized reaction conditions by this method.[19] All alcohols employed were oxidized at room temperature to give the corresponding carbonyl compounds in good to excellent yields. Benzylic alcohols afforded the corresponding aldehydes quantitatively in a short reaction time except for 4-nitrobenzyl alcohol (Table 7, entries 1–8). 4-Nitrobenzyl alcohol required 6 hours to obtain the oxidized product in good yields. In the case of benzhydrols, it took 5–8 hours to obtain diaryl ketones in high yields (Table 7, entries 9–11). In the reactions of acyclic aliphatic alcohols and allylic alcohols, 8 mol% of $Fe(NO_3)_3\cdot 9H_2O$ and long reaction times were needed to obtain the corresponding carbonyls in good yields (Table 7, entries 12, 13, and 15–17).

Table 7 Aerobic Oxidation of Alcohols Using [4-Hydroxy-TEMPO + NaCl]/SiO_2 and $Fe(NO_3)_3·9H_2O$



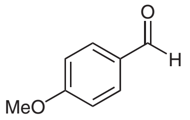
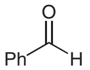
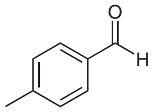
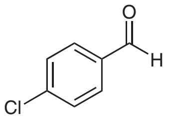
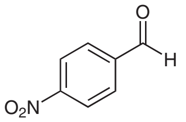
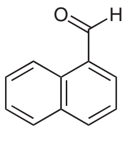
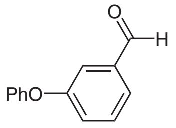
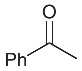
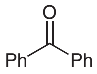
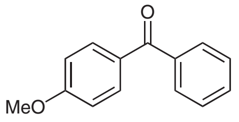
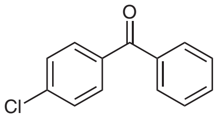
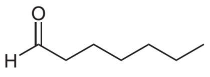
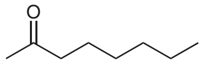
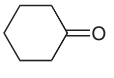
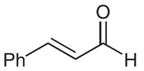
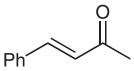
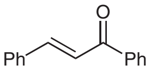
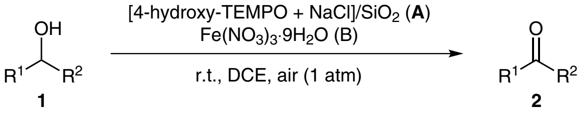
Entry[a]	Product		Catalyst **A**:**B** (mol%)	Time (h)	Yield (%)[b]
1		**2a**	5:5	2	97
2		**2b**	5:5	2	96
3		**2c**	5:5	2	95
4		**2d**	5:5	3	99
5		**2e**	5:5	6	91
6		**2f**	5:5	2	95
7		**2g**	5:5	3	98
8		**2h**	5:5	2	97
9		**2i**	5:5	5	96
10		**2j**	5:8	8	94
11		**2k**	5:5	8	90
12		**2l**	5:8	7	78
13		**2m**	5:8	4	93
14		**2n**	5:5	4	96
15		**2o**	5:8	4	91
16		**2p**	5:8	7	61
17		**2q**	5:8	2	90

Table 7 Aerobic Oxidation of Alcohols Using [4-Hydroxy-TEMPO + NaCl]/SiO_2 and $Fe(NO_3)_3·9H_2O$ (continued)



[a] A mixture of alcohol (2.0 mmol), [4-hydroxy-TEMPO + NaCl]/SiO_2 [(0.1 + 0.1) mmol/g] and $Fe(NO_3)_3·9H_2O$ was stirred in DCE (5 mL) at r.t.

[b] Determined by GLC analysis using *n*-dodecane as internal standard.

In conclusion, we found out that 4-hydroxy-TEMPO was easily adsorbed on the surface of SiO_2 in nonpolar solvent such as DCE, toluene, and chloroform. The silica gel adsorbed 4-hydroxy-TEMPO catalyzed the aerobic oxidation of alcohols in the presence of $Fe(NO_3)_3·9H_2O$ and NaCl in a nonpolar solvent. The oxidation of various alcohols using [4-hydroxy-TEMPO + NaCl]/SiO_2 and $Fe(NO_3)_3·9H_2O$ proceeded smoothly at room temperature, and afforded the products in excellent yields. [4-Hydroxy-TEMPO + NaCl]/SiO_2 was able to be recovered by filtration and reused at least six times without loss of catalytic activity. Further application of this supported reagent to the other oxidation is now in progress.

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(18) The content of water was estimated by weight difference between [4-hydroxy-TEMPO + NaCl]/SiO_2 and [4-hydroxy-TEMPO + NaCl]/SiO_2 which was dried at 160 °C under reduced pressure (8 mmHg) for 3 h.

(19) **Aerobic Oxidation of Alcohols**
A mixture of alcohols (2.0 mmol), $Fe(NO_3)_3·9H_2O$ (5–8 mol%) and [4-hydroxy-TEMPO + NaCl]/SiO_2 [(0.1 + 0.1) mmol/g, 1.0 g] was stirred in DCE (5 mL) under air (1 atm) at r.t., and then the used supported reagent were removed by filtration. Product yield was determined by GLC analysis using *n*-dodecane as internal standard.