Aerobic Oxidations

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Green, Transition-Metal-Free Aerobic Oxidation of Alcohols Using a Highly Durable Supported Organocatalyst**

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Dedicated to Süd-Chemie on the occasion of its 150th anniversary

Selective oxidation of alcohols to carbonyl compounds is one of the most important and challenging transformations in the synthesis of fine chemicals and intermediates.[1] Traditionally, the oxidation of alcohols has been achieved with stoichiometric inorganic oxidants, notably Cr^{VI}-based reagents.[2] Unfortunately, these oxidants are not only relatively expensive but they also produce large quantities of noxious heavy-metal waste. Consequently, the use of molecular oxygen as the terminal oxidant in the transition-metal-catalyzed oxidation of alcohols has received great attention in recent years to achieve both economic and environmental benefits.[3,4] Of particular interest in this field is the use of the stable nitroxyl radical 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) in combination with a co-oxidant as an alternative to metal-based oxidants.[5] Additionally, it was shown that TEMPO-catalyzed oxidations can be performed on a large industrial scale using household bleach under non-aerobic conditions.[6]

Only a few groups have reported catalytic systems involving TEMPO in combination with transition metals such as Ru[7] and Cu[8,9] as alternative catalysts for the oxidation of alcohols using molecular oxygen or air under mild reaction conditions. However, many of these methods are inefficient with aliphatic[8] and secondary alcohols,[9] and their applicability are therefore limited. Furthermore, some of them require an expensive transition-metal complex and/or operate at relatively high temperatures (100°C).[7] Although, some of these drawbacks can be partly avoided by using a combination of TEMPO with a catalytic amount of Mn^{II}-Co^{II},[10] the recyclability of the catalysts and product isolation are still key important issues. TEMPO is a rather expensive chemical reagent, and therefore its efficient recycling is highly desirable, especially when the reactions are run on a large scale. Therefore, several research groups have addressed the problem of recyclability of TEMPO by designing various types of supported TEMPO.[11,12] These catalysts were then employed in combination with O_2 and transition-metal salts,[8–10] or other types of stoichiometric oxidizing agents in the oxidation of alcohols.[5] However, while these catalytic systems afford high product yields and selectivities, in most cases partial degradation of the supported TEMPO catalysts was observed. It is also worth mentioning that these protocols still use non-recoverable, hazardous or expensive transition metals. Recently, Toy and co-workers have developed an attractive multipolymer reaction system for the aerobic oxidation of alcohols and to recover both TEMPO and the catalytic Cu^{II} complex at the same time.[13] However, this method is only effective for the aerobic oxidation of highly active primary benzylic alcohols after prolonged heating (18 h) in CH_3CN-H_2O solvent mixtures.

It seems that while chemists have paid much attention to designing new improved protocols based on TEMPO/transition-metal/O_2 systems, they have largely ignored the advantages inherent in a metal-free catalytic system. If such oxidations could be performed in a transition-metal-free catalytic system using air as terminal oxidant, the processes would be significantly safer, cheaper, and greener than many of the processes in use today. Recently, Hu and co-workers presented a novel metal-free TEMPO-catalyzed aerobic oxidation of alcohols.[14] While this method provided an interesting achievement in the field of aerobic oxidation of alcohols, it required expensive teflon-lined apparatus, high loadings of TEMPO which is not recoverable (homogeneous, up to 10 mol%), high operating pressures (up to 9 bar), relatively high temperatures (up to 80°C), and an environmentally undesirable chlorinated solvent (CH_2Cl_2). Thus, from the standpoint of practical, environmental, and economic concerns, it is still highly desirable to develop cleaner, milder, cheaper, and recyclable TEMPO catalytic systems for the aerobic oxidation of alcohols, especially for large-scale operations.

While several types of supported aminoxyl radicals have already been reported,[11,12] to the best of our knowledge, none of them have been studied in the transition-metal-free aerobic oxidation of alcohols. We report herein for the first time the use of a novel and extremely stable version of supported TEMPO for the effective aerobic oxidation of alcohols, with both activated and non-activated hydroxy groups, in the absence of any transition-metal-containing co-catalyst. It has been well documented that ordered mesoporous materials (such as MCM-41[15] and SBA-15[16]) with relatively uniform pore diameters (2–30 nm), large void volumes, and high surface areas can serve as more well-

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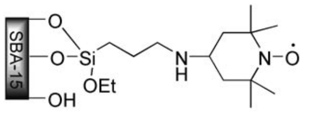
defined support materials, in comparison to amorphous solids, onto which organic groups can be anchored.[17] These nanostructured materials are also superior to organic polymers, because the application of the latter is significantly restricted as a result of their high price and easy thermal and chemical damage of the organic backbone.[18] Here, we chose to employ the mesoporous silica SBA-15 as a support for nitroxyl radicals not only because it has larger and more accessible channels but also as it displays higher thermal and hydrothermal stability than MCM-41.[16]

SBA-15 was obtained by treating pluronic P123 $[EO_{20}PO_{70}EO_{20}$ (EO = ethylene oxide, PO = propylene oxide), $M_{av} = 5800\,g\,mol^{-1}$; Aldrich] and $(EtO)_4Si$ under acidic conditions following the reported procedure.[20] The resulting SBA-15 was then functionalized with aminopropyl spacers followed by reductive amination with 1-hydroxy-4-oxo-2,2,6,6-tetramethylpiperidine to afford the corresponding immobilized TEMPO **1** according to known procedures with slight modifications.[11b,19] Catalyst **1** was characterized by simultaneous thermal analysis (STA), diffuse reflectance Fourier transform (DRIFT) IR spectroscopy, surface analysis, and transmission electron microscopy (TEM).[19]



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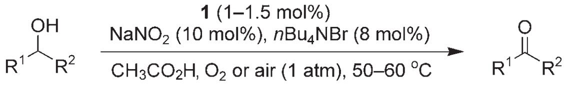
The SBA-15-supported TEMPO catalyst **1** was initially investigated for the oxidation of benzyl alcohol as shown in Scheme 1, in the absence of any transition-metal co-catalyst (1 mol% **1**, 10 mol% $NaNO_2$, 8 mol% nBu_4NBr, CH_3CO_2H as solvent, O_2 (1 atm), 50°C). Under these conditions, catalyst **1** was highly active for the transformation, and the selectivity to benzaldehyde was 99.8% or greater at 100% conversion, with the only by-product being benzyl acetate (less than 0.2%). Interestingly, note that while the initial selectivity of **1** for benzaldehyde was approximately 93% owing to the fast formation of benzyl acetate (after 10 min), smooth hydrolysis of benzyl acetate by the by-product water followed by oxidation of the resulting benzyl alcohol led to an increase of the final selectivity to benzaldehyde (Figure 1).



Scheme 1. General protocol for the aerobic oxidation of alcohols using catalyst **1**.

Supported reagent **1** (1–1.5 mol%) is also a highly efficient and selective heterogeneous catalyst for the aerobic oxidation of a wide range of primary, secondary, and even sterically hindered alcohols under similar reaction conditions (Table 1). Air can also be conveniently used instead of pure oxygen without affecting the efficiency of the reaction. Although, the use of air requires slightly longer reaction times, it does not affect the final product selectivities (Table 1).

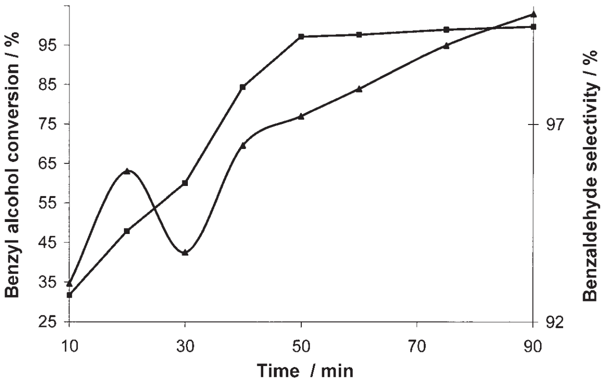


Figure 1. Benzyl alcohol conversion (■) and selectivity (▲) for benzaldehyde formation as a function of reaction time (50°C, atmospheric pressure of O_2 (1 atm)).

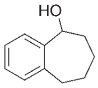
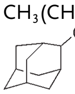
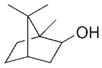
In contrast to homogeneous TEMPO procedures that are equally applicable to the conversion of a variety of alcohols in different reaction media,[5] heterogeneous TEMPO catalysis often fails to show similar versatility. This is unfortunate as the low product volumes of the fine chemical industries and the new combinatorial applications of solid-phase synthesis do indeed require such a high degree of versatility. Here catalyst **1** shows excellent reactivity for the selective oxidation of various types of secondary and highly hindered alcohols, a feature not observed with the previous heterogeneous TEMPO/transition-metal/O_2 protocols (Table 1, entries 11–15, 19, 20).[13]

Generally, many of the reported transition-metal-based systems are unable to catalyze the aerobic oxidation of alcohols that contain heteroatoms, because of the strong coordination of these alcohols to a metal center which results in deactivation of the catalyst. However, catalyst **1** also shows excellent tolerance for a broad range of bifunctional alcohols and is notably not deactivated by nitrogen- and sulfur-containing substrates (Table 1, entries 8, 9).

The most important issues that must be resolved for heterogeneous catalysts are the lifetimes of the catalyst and the possibility that the active component (i.e. TEMPO) can leach from the solid into solution, thereby leading to gradual deactivation of the catalyst. The heterogeneous nature of the catalyst was confirmed in a filtration experiment, in which the reaction mixture was filtered after 30 min (60% conversion). No catalytic activity was observed in the filtrate during 5 h after filtration. To show that no deactivation occurred in the aerobic oxidation of benzyl alcohol to give benzaldehyde (Table 1, entry 1), the recovered catalyst was successively used in a second run. When the reaction time was set to 1.5 h, which proved to be sufficient for conversion of benzyl alcohol, comparably excellent yields of benzaldehyde were obtained in 14 subsequent runs using the same catalyst to give a total turnover number (TON) of over 1000.[19]

To the best of our knowledge, these recovery results are far superior compared to those reported in the case of recyclable nitroxyl radicals under aerobic oxidation conditions. This reusability also demonstrates the high stability of our new heterogeneous system. Although no significant

Table 1: Aerobic oxidation of alcohols using **1**.

Entry	R^1	R^2	t [h]		Product yield [%][a,b,c]	
			O_2	air	O_2	air
1	Ph	H	1.5	2.5	100 (99.8)	100 (99.1)
2	2,6-$Cl_2C_6H_4$	H	1.5	3	100 (99.8)	100 (99.1)
3	2-MeC_6H_4	H	1.5	3	99 (99.1)	94.5 (97.4)
4	3-BrC_6H_4	H	1.5	3	99.7 (99.4)	100 (99.4)
5	4-$MeOC_6H_4$	H	1.5	2.5	100 (99.5)	100 (99.2)
6	3-ClC_6H_4	H	1.5	2.5	99.8 (99.6)	99.4 (98.9)
7	4-$NO_2C_6H_4$	H	1.5	3	100 (98.8)	100 (99)
8	4-$MeSC_6H_4$	H	1.5	–	98.1 (97.1)	–
9	3-pyridyl	H	3	–	92 (99.2)	–
10	2-furyl	H	1.5	3	98 (99.0)	94.2 (98)
11	Ph	Me	2.5	4.5	97.6 (99)	100 (99)
12	Ph	Et	3	4.5	100 (99.8)	100 (99.2)
13			3	4.5	100 (99.8)	100 (99.8)
14	Ph	Ph	4.5	6	100 (99.3)	100 (99.8)
15	4-BrC_6H_4	Ph	4.5	8	100 (99.1)	100 (99.8)
16	$PhCH_2CH_2CH_2$	H	2	3	99 (95.0)	99 (94.6)
17	$CH_3(CH_2)_4CH_2$	H	2.5	3	100 (76.2)[d]	98 (79)[e]
18	$CH_3(CH_2)_4CH_2$	Me	3	4	93 (98.0)	88 (98.0)
19			9.5	–	96 (97.0)	–
20			10	11	100 (99.6)	99 (99.8)

[a] GC yield based on internal standard method unless otherwise stated. [b] Numbers in parentheses refer to selectivity for formation of carbonyl compound. [c] Conditions: Method A: primary and secondary benzylic alcohols (10 mmol), nBu_4NBr (8 mol%), $NaNO_2$ (10 mol%), and catalyst **1** (≈1 mol%) in CH_3CO_2H (3 mL) at 50°C; Method B: aliphatic and hindered alcohols (10 mmol), nBu_4NBr (14 mol%), $NaNO_2$ (20 mol%), and catalyst **1** (≈1.5 mol%) in CH_3CO_2H (10 mL) at 60°C. [d] Approximately 10% of the corresponding acid was formed. [e] Approximately 11.5% of the corresponding acid was formed.

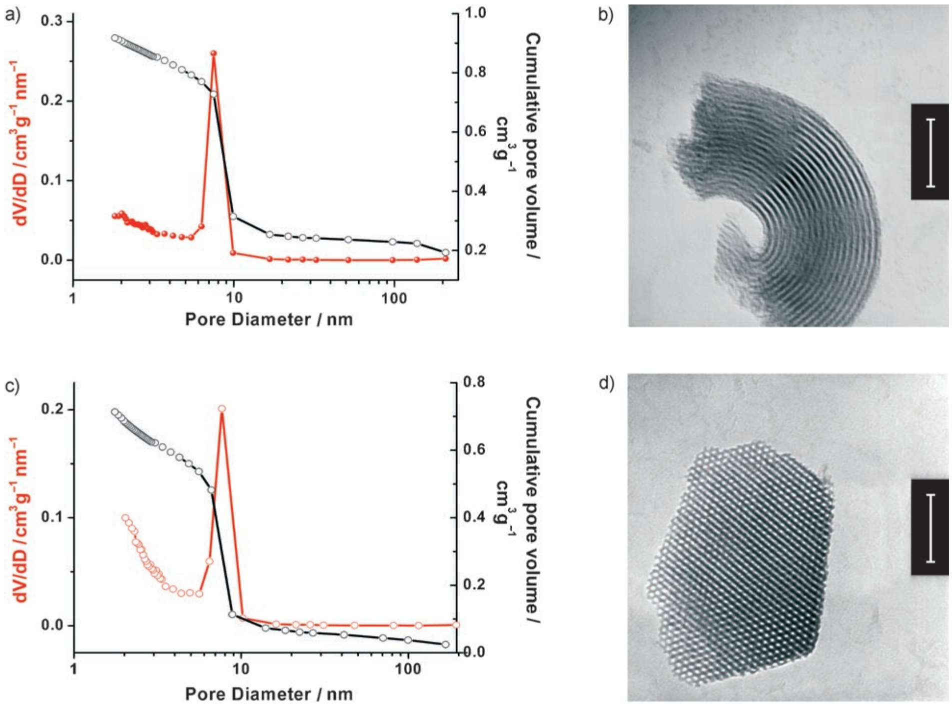


Figure 2. a) BJH average pore diameter of catalyst **1** prior to the oxidation. b) TEM image of catalyst **1** prior to the oxidation. c) BJH average pore diameter of catalyst **1** after the 14th reaction cycle. d) TEM image of catalyst **1** after the 14th reaction cycle. Scale bars: 100 nm.

change in the activity of the catalyst was observed, we performed several studies (surface analysis, DRIFT-IR spectroscopy measurements, kinetic measurement of NH_3, simultaneous thermal and TEM analysis) on catalyst **1** after the 14th reaction cycle to determine any change in the catalyst structure at a molecular level. Surface analysis showed that there is no significant change in the surface area (from 517 to 516 $m^2 g^{-1}$) and a slight decrease in the total pore volume from 0.68 to 0.65 $cm^3 g^{-1}$. Note also that the N_2 adsorption/desorption analysis of the recovered catalyst showed very similar isotherms to those of the fresh catalyst **1**, with relatively sharp adsorption and desorption of type IV in the P/P_0 range 0.5–0.8, which is characteristic of highly ordered mesoporous materials (Figures 1S vs 4S in the Supporting Information).

Interestingly, BJH calculations also show a narrow mesoporous diameter of 7.9 nm for **1** prior to and after the 14th reaction cycle, a value which is in good agreement with the mesoporous diameter estimated from the TEM images (Figure 2 a,b vs 2c,d). These observations are remarkable and suggest that most of the nanometer-scale void space and the channels of the parent SBA-15 remain intact during the catalysis and recycling processes.

Further evidence for lack of degradation of the anchored organic nitroxyl group in our protocol was obtained by FTIR analysis of the catalyst prior to and after the 14th oxidation run (Figure 6S in the Supporting Information). The absorption bands in the 2850–2980 cm^{-1} region (asymmetric and symmetric vibrations of alkyl groups in the catalyst) and the broad signals overlapping in the 1070–1220 cm^{-1} region (Si-O-Si symmetric stretching)[20] clearly show that neither the anchored organic groups nor the silica polymeric backbone of SBA-15 are significantly affected by prolonged use in the reaction system. Kinetic comparison of simultaneous thermal decomposition also shows nearly the same profile for weight loss after the 14th use as for the fresh catalyst (Figure 7S in the Supporting Information). There is only a slight change in the amount of NH_3 created during thermal analysis from 0.66 to 0.60 ($\approx 9\,\%$ decrease) from the surface of SBA-15 after the 14th use (Figure 7S D vs 7S B in the Supporting Information). These results clearly show that the catalyst is very durable and no significant restructuring of the catalyst takes place on multiple uses.

In conclusion, we have shown that SBA-15 can be used to support the nitroxyl radical TEMPO to give an extremely stable and reusable catalyst for the aerobic oxidation of alcohols (including primary, secondary, and highly hindered ones) in the absence of any transition-metal-containing cocatalyst. TEM, DRIFT IR, kinetic measurement of NH_3, and simultaneous thermal analyses of the catalyst prior to and after the 14th reaction cycle clearly show that neither the anchored organic group nor the nanometer-scale voids and channels of the parent SBA-15 are significantly affected by prolonged use in the reaction system. To the best of our knowledge, this method is the first example of transition-metal-free aerobic oxidation of a wide range of alcohols using a nanostructured supported organocatalyst under normal pressure of air. The general achievements in this study have established a pathway for the development of new transition-metal-free catalytic protocols in the aerobic oxidation of alcohols.

Experimental Section

Oxidation of primary and secondary benzylic alcohols (Method A): A mixture of alcohol (10 mmol), $n\mathrm{Bu_4NBr}$ (0.26 g, ≈ 8 mol %), $NaNO_2$ (0.070 g, 10 mol %), and catalyst **1** (0.303 g, ≈ 1 mol %) in CH_3CO_2H (3 mL) was prepared in a two-necked flask at 50 °C. The flask was then filled with pure oxygen or air (balloon-filled), and the resulting mixture was stirred at 50 °C under an oxygen/air atmosphere (for the time indicated in Table 1. The progress of the reaction was monitored by GLC using the internal standard addition method. After completion of the reaction, the reaction mixture was filtered off and the catalyst was rinsed with Et_2O (3×25 mL). The excess of solvent was removed from the filtrate under reduced pressure to give the corresponding carbonyl compounds (Table 1). In most cases, the purity of the products was analyzed by GC to be greater than 99 % without any chromatographic purification.

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