

Intensification of TEMPO-mediated aerobic alcohol oxidations under three-phase flow conditions†

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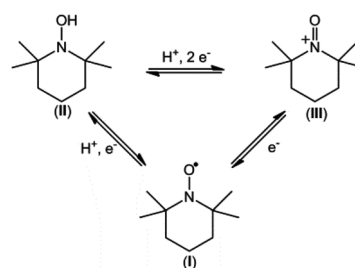
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Various homogeneous and heterogeneous catalytic systems based on 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and different (co-)oxidants have been reported for the selective oxidation of alcohols. Herein we report the use of a commercially available silica-immobilized TEMPO catalyst, in combination with catalytic amounts of HNO₃ as a NO_x source under continuous three-phase flow conditions. First the stability of the catalyst was evaluated with benzyl alcohol and the reaction parameters were optimized. Subsequently different substrates were tested, focusing on the oxidation of renewable substrates like lactic acid and 5-hydroxymethylfurfural (HMF).

Introduction

The selective oxidation of alcohols remains a difficult task.^{1,2} Recently, some of us reported on the metal-free oxidation of alcohols using sub-stoichiometric amounts of HNO₃ in combination with the ion-exchange resin Amberlyst-15 in a protonic form, leading to an (H)NO_x-propagated chain oxidation with O₂ as a terminal oxidant.^{3,4} The system was applied for different primary and secondary alcohols under continuous flow conditions. This application showed a significant increase in the space-time-yield (*i.e.* the product yield per unit of time and per reactor volume) and a decrease in N₂O formation, compared to a conventional batch reactor.⁵ However the use of strong acids such as Amberlyst-15 as a co-catalyst limits the substrate scope, due to acid-catalyzed dehydration under reaction conditions. Therefore the search for a milder catalytic system is necessary to increase the range of substrates for nitric acid-based alcohol oxidations.

The use of the nitroxyl radical 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) as a catalyst in the oxidation of alcohols has gained much attention in recent years. The redox cycle involves besides TEMPO (I) also hydroxylamine (II) and the oxoammonium cation (III) (Scheme 1).⁶ The oxoammonium cation is supposed to oxidize the alcohol substrate and is thereby converted to TEMPOH. TEMPOH can be re-oxidized to the oxoammonium ion, closing a catalytic cycle. In the literature, different co-oxidants are used for the re-oxidation of TEMPOH. Various inorganic and organic compounds in organic solvents, water or ionic liquids have been reported.⁷



Scheme 1 Redox-cycle of TEMPO (I), including TEMPOH (II) and the oxoammonium cation (III).

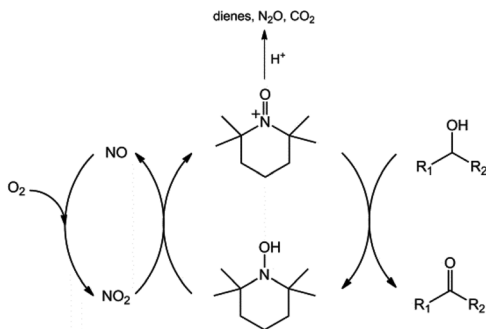
From an ecological and an economical point of view, the use of stoichiometric oxidation agents such as chromates or permanganates should be abandoned and replaced by peroxides or, preferably, molecular oxygen.⁸ Therefore the use of catalytic mediators, such as transition metals⁹ or other inorganic compounds,¹⁰ with O₂ as a terminal oxidant is preferred. Nevertheless, even the use of catalytic amounts of transition metals can cause problems like catalyst deactivation and the possibility of metal contamination in the product mixture.

Several papers report on the use of catalytic amounts of NO_x sources such as *tert*-butyl-nitrite as a co-catalyst, and O₂ as a terminal oxidant in TEMPO-mediated alcohols oxidations (Scheme 2).^{11–13} All of these reactions have been performed in batch mode under relatively mild conditions (room temperature to 80 °C, ambient pressure). That is the reason why these systems very often suffer from limited space-time-yields and therefore also require high amounts of TEMPO (typically 10–20 mol%) and a co-catalyst, in order to obtain acceptable reaction rates. The use of a continuous plug-flow reactor not only increases the space-time-yield due to a higher catalyst-to-substrate-ratio and enhanced mass-transfer, but also leads to a

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Scheme 2 Catalytic cycle of TEMPO using NO_x as a co-oxidant and the competing, acid-catalyzed decomposition of the oxoammonium cation.

decrease in the amount of co-oxidant needed in order to reach full conversion. This is an advantage from both an economic and an ecological point of view.

In the present work the use of a continuous three-phase flow reactor with commercially available silica-immobilized TEMPO and catalytic amounts of HNO_3 as an inexpensive NO_x source for the oxidation of different primary and secondary alcohols is examined.

Results and discussion

Reactor set-up

A continuous flow reactor on a small scale can offer several advantages compared to a standard batch reactor such as enhanced heat- and mass-transfer, improved control of the reaction parameters, faster mixing of the reactants and shorter reaction times. Enhanced mass-transfer between the different phases, due to the generation of large interfacial areas, is indeed important for the present reaction.¹⁰

The liquid feed (solvent, alcohol, HNO_3 and biphenyl standard) was pumped with an HPLC pump and combined with the O_2 gas flow in a T-mixer, generating a gas-liquid slug flow as visually verified (ESI†). Such segmented flows efficiently promote gas-liquid mass transfer.¹⁴ The gas-liquid feed enters a packed-bed reactor filled with silica immobilized-TEMPO particles. The system pressure is set by a back-pressure regulator. The product mixture coming out of the reactor is sent to a phase separator. The gas phase is analysed by infrared spectroscopy in a transmission cell and the liquid phase is analysed by gas chromatography (GC). The reactor was operated at 5 bar to keep a stable segmented flow.

Benchmarking experiments with benzyl alcohol

Benzyl alcohol was taken as a model substrate in order to examine the performance of the system and the stability of the catalyst. Screening of different solvents (Table 1) reveals that 1,2-dichloroethane (DCE) gives the best results. The molar vaporization enthalpy of DCE (*i.e.*, 34 kJ mol^{-1}) is moreover 20% lower than that of water (*i.e.*, 43 kJ mol^{-1}), leading to a lower energy consumption in the downstream solvent recovery.

Table 1 Aerobic oxidation of benzyl alcohol in different solvents mediated by 5 mol% HNO_3 and TEMPO on silica at 55°C , 5 bar O_2 and a contact time of 0.5 min

Solvent	Vaporization enthalpy/ kJ mol^{-1}	Conv./%
1,2-Dichloroethane	34	98
Dichloromethane	29	85
Ethyl acetate	32	73
Acetonitrile	33	41
1,4-Dioxane	38	0

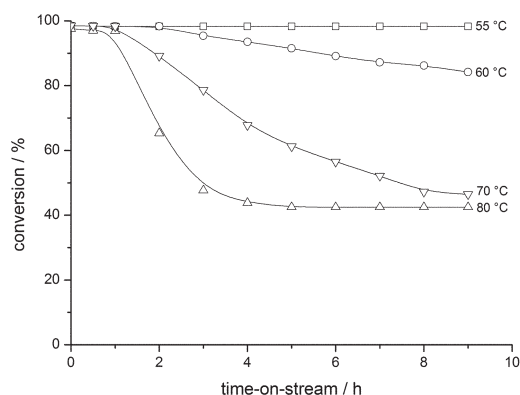


Fig. 1 Conversion vs. time-on-stream for different temperatures, a contact time of 0.5 min (solvent: DCE, $[\text{BzOH}]_0 = 500 \text{ mM}$, $[\text{HNO}_3] = 5 \text{ mol}\%$, 5 bar O_2).

Fig. 1 shows the conversion of benzyl alcohol for a contact time of 0.5 min (see the ESI†) against the time-on-stream. A clear deactivation of the catalyst can be observed for temperatures above 55°C . It is known that the oxoammonium ion of TEMPO can decompose under acidic conditions, forming N_2O , CO_2 and dienes as products (Scheme 2).⁶ This hypothesis is confirmed by the transmission IR spectra of the gas phase (Fig. 2) revealing the presence of N_2O during the decomposition phase of the reaction, pointing to the degradation of TEMPO species. Additional support for this hypothesis is obtained from the EPR spectra of the TEMPO catalyst, taken

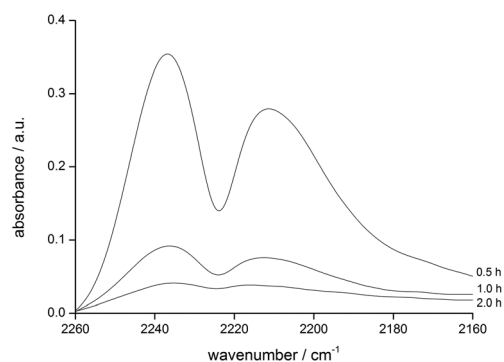


Fig. 2 Gas-phase transmission IR spectra from an oxidation reaction of benzyl alcohol performed at 80°C , contact time of 0.5 min: ν_3 vibrational mode of N_2O around 2220 cm^{-1} (solvent: DCE, $[\text{BzOH}]_0 = 500 \text{ mM}$, $[\text{HNO}_3] = 5 \text{ mol}\%$, 5 bar O_2).

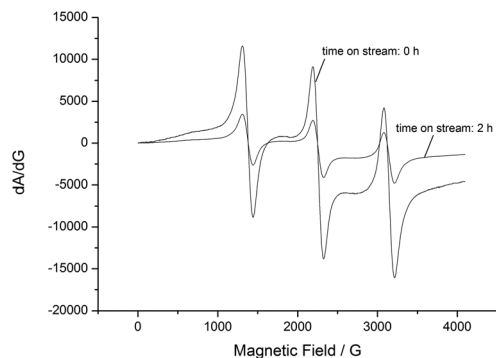
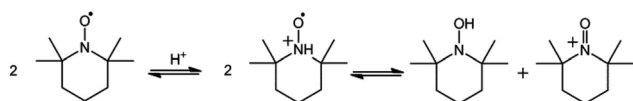


Fig. 3 EPR spectra of the initial catalyst and of the used catalyst after 2 hours time-on-stream at 80 °C and a contact time of 0.5 min (solvent: DCE, $[\text{BzOH}]_0 = 500 \text{ mM}$, $[\text{HNO}_3] = 5 \text{ mol\%}$, 5 bar O_2).

before and after 2 hours of reaction (Fig. 3). Clearly, a significant amount of TEMPO is lost during the reaction, explaining the levelling off of the conversion. The catalyst bed is characterized by a pale green colour after exposure to temperatures above 70 °C, in line with the literature indicating different decomposition products of TEMPO.⁶ Blank activity of silica gel (*i.e.*, the support) can be excluded since pure silica did not show any activity at temperatures between 55 °C and 80 °C.

No decomposition of the catalyst could be observed at 55 °C for over 8 hours (Fig. 1). Additionally, only traces of N_2O could be observed in the gas phase and the EPR signals have the same magnitude before and after the reaction (see the ESI^\dagger), pointing to the fact that at this temperature the catalyst does not decompose. This is the reason why all subsequent reactions were performed at 55 °C. Additionally, the reaction was also performed with catalyst particles of half the size (0.08–0.12 mm), keeping the amount of active sites the same. This clearly showed that the conversion *versus* time and the selectivity were the same as those for the standard reaction for benzyl alcohol oxidation. We conclude from this that intragranular mass-transfer is not the rate limiting step in this system.

Although the oxoammonium cation is formed during the catalytic cycle (Scheme 2), we believe that there is most likely an additional source *via* the interaction of TEMPO species on the surface at temperatures above 60 °C. This could be possible because the statistical density of active sites is estimated to be 1 TEMPO molecule per nm^2 . Moreover, it is well known that two TEMPO molecules can disproportionate, acid-catalyzed, into one TEMPOH and one oxoammonium ion (Scheme 3). This assumption was confirmed by experiments where anaerobic 0.1 mol L^{-1} of HCl in dichloroethane was run over the catalyst at 80 °C clearly leading to a red colour of the catalyst bed, indicating the formation of the oxoammonium ion. Due to the



Scheme 3 Acid-catalyzed disproportionation of TEMPO species leading to TEMPOH and the oxoammonium ion.

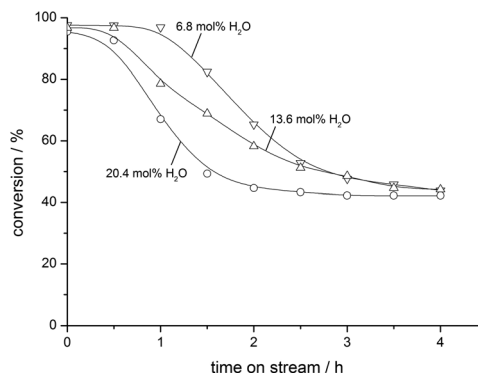


Fig. 4 Conversion vs. time-on-stream for benzyl alcohol at 80 °C and a contact time of 0.5 min for different initial amounts of water present in the system (solvent: DCE, $[\text{BzOH}]_0 = 500 \text{ mM}$, $[\text{HNO}_3] = 5 \text{ mol\%}$, 5 bar O_2).

increased concentration of these species, their irreversible acid-catalyzed decomposition is enhanced, especially during the oxidation of less reactive alcohols. This degradation can take place until the distance between the active sites is too large for the disproportionation reaction to take place. This could indeed explain why the conversion always seems to level off, irrespective of the precise reaction conditions (see Fig. 1).

The decomposition rate depends on the amount of water initially present in the reaction mixture (Fig. 4). This effect is most likely due to the fact that at higher H_2O concentrations more NO_x species are present as HNO_3 and HNO_2 , increasing the rate of irreversible catalyst decomposition.

Table 2 shows the space-time-yields for the oxidation of benzyl alcohol for different heterogeneous TEMPO catalyst systems with different NO_x sources as co-oxidants. An excellent performance can be seen with the continuous flow system, featuring three-orders-of-magnitude higher space-time-yields than comparable batch systems.

Screening of different alcohols

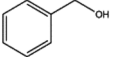
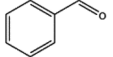
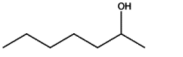
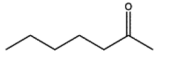
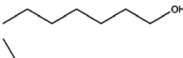
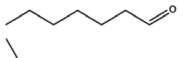




In order to extend the substrate scope, several primary and secondary alcohols were tested (Table 3). High reaction rates and selectivities towards the corresponding aldehyde or ketone products were obtained. Over-oxidation to the corresponding acids is limited and selectivities close to 90% can be obtained. Due to the moderate reaction conditions (*viz.*, 55 °C), alcohols that usually dehydrate under acidic conditions like prenol or isoprenol were smoothly oxidized to the corresponding

Table 2 Space-time-yields for the aerobic oxidation of benzyl alcohol in different systems with NO_x species as a co-catalyst

Ref.	Catalyst	$T/^\circ\text{C}$	Space-time-yield ^a
This work	TEMPO on silica ^b	55	4.1×10^5
12	TEMPO on silica ^c	R.T.	4.4×10^2
13	TEMPO on magnetic nanoparticles ^d	50	8.3×10^4

^a mol BzOH (mol TEMPO)⁻¹ h⁻¹ (L reactor volume)⁻¹. ^b Solvent: DCE, co-oxidant: HNO_3 . ^c Solvent: DCE, co-oxidant: NO_x absorbed on silica. ^d Solvent: H_2O , co-oxidant: *tert*-butyl-nitrite.

Table 3 Aerobic oxidation of different alcohols in DCE mediated by 10 mol% HNO₃ and TEMPO on silica at 55 °C and 5 bar O₂

Substrate	Product	τ^a /min	Conv./%	Sel./%
		0.5 ^b	98 ^b	99 ^b
		2	95	99
		2	67	88
		2	93	87
		2	65	70 (80 ^c)

^a Contact time was not optimized for full conversion. ^b 5 mol% HNO₃.

^c Combined selectivity towards isoprenal and prenal.

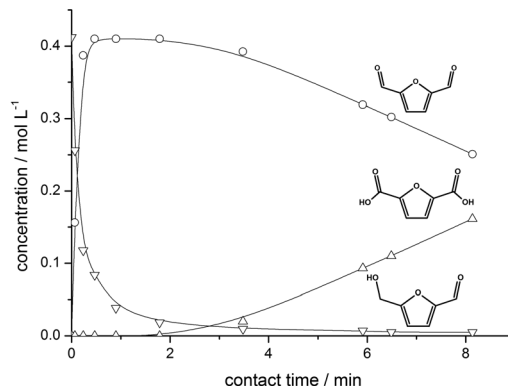
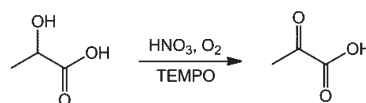
carbonyls. The liquid phase oxidation of isoprenol offers an interesting alternative to the currently used gas-phase oxidation over a Ag-catalyst, affording 75% selectivity towards the sum of isoprenal and the thermodynamically more stable prenal (ratio of 4 : 1).¹⁷ Indeed, for the synthesis of citral, the isomerization is irrelevant as the crude product is treated with a weak base, isomerizing isoprenal to prenal, during the work-up of the reaction mixture.

Renewable substrates

Sugars are a readily available feedstock from biomass in future biorefineries. Especially 5-hydroxymethylfurfural, which can be obtained upon dehydration of glucose and fructose, has gained considerable attention as a possible key-intermediate in the manufacturing of chemicals and fuels.¹⁸ One possible application is the selective oxidation of HMF to the corresponding 2,5-diformylfuran (DFF). DFF has been described to be a possible starting material for pharmaceuticals, macrocyclic ligands, monomers for many functional materials and others.¹⁶

The selective oxidation of HMF to DFF was performed with our silica-immobilized TEMPO system at 55 °C, 5 bar O₂ and 5 mol% of HNO₃. With a contact time of 2 min, 97% conversion in HMF could be achieved with 98% selectivity towards DFF (Fig. 5). When the contact time is increased, over-oxidation of DFF to 2,5-furandicarboxylic acid (FDCA) can be observed (Fig. 5). FDCA is another interesting building block being a possible replacement for terephthalic acid in the production of polymers.¹⁵ The present system presents promising results for the manufacturing of both DFF and FDCA, depending on the reaction conditions. However for contact times higher than 6 min FDCA starts to crystallize out, due to the low solubility in DCE. This problem could be solved by adding a co-solvent or working in a different solvent. This approach should be further investigated in the future.

Another interesting renewable substrate is lactic acid which on an industrial scale is mainly produced by fermentation of carbohydrates. Especially lignocellulosics have the potential to

**Fig. 5** Concentration vs. time-on-stream for HMF at 55 °C and different contact times (solvent: DCE, [HMF]₀ = 410 mM, [HNO₃] = 5 mol%, 5 bar O₂).**Scheme 4** Oxidation of lactic acid to pyruvic acid.

become a clean, renewable and low-cost source of lactic acid.¹⁹ The oxidation of lactic acid to pyruvic acid (Scheme 4) has some difficulties because of the fast decarboxylation of the substrate. Therefore mild conditions and small amounts of oxidants are a prerequisite. Pyruvic acid is mainly used as an intermediate for pharmaceutical applications but it is also used in the production of crop protection agents, polymers, cosmetics and foods.²⁰ With the present system, the selective oxidation of lactic acid (500 mM) to pyruvic acid was performed at 55 °C, 5 bar O₂ and 5 mol% of HNO₃. With a contact time of only 15 seconds, 98% conversion in lactic acid and over 98% selectivity towards pyruvic acid could be obtained.

Conclusions

The continuous aerobic oxidation of different alcohols using a heterogeneous immobilized TEMPO catalyst was examined. High reaction rates, conversions and selectivities could be obtained. The catalyst remained stable over several hours under mild conditions making the process attractive, compared to transition metal-catalyzed systems that very often suffer from deactivation and/or low activities. Due to the high reaction rates, only small amounts of HNO₃ as a co-oxidant have to be used. Since O₂ is the terminal oxidant the process is attractive both from an economic and an ecological point of view.

The system is broadly applicable to a wide range of primary and secondary alcohols, always showing high reaction rates and selectivities. Another advantage of this continuous system is the flexibility in tuning the selectivity in consecutive reactions, depending on the application. This can be seen in the

case of HMF oxidation where high yields of either DFF or FDCA can be obtained, depending on the contact time. Additionally, less stable alcohols like lactic acid or prenols could be smoothly oxidized, due to the moderate conditions of only 55 °C and 5 bar O₂.

Overall, the reported system offers a promising alternative to state-of-the-art stoichiometric oxidants or transition metal catalysts for the environmentally benign and economical oxidation of alcohols.

Experimental section

The continuous flow reactor (Teflon®, internal diameter 1.65 mm) was packed with a commercially available TEMPO catalyst attached to a silica support (Sigma-Aldrich, 0.7 mmol g⁻¹ active sites; particle size 0.16–0.24 mm, void fraction of 65%) and connected to an HPLC pump and an O₂ mass flow controller. When the oil bath reached the desired temperature the packed bed was put inside the oil bath and the reaction was started. For all benzyl alcohol oxidation experiments a liquid flow rate of 0.4 mL min⁻¹ and a gas flow rate of 5 mL min⁻¹ was chosen. For other contact times the ratio of liquid to gas flow-rate was kept constant. For the rest of the substrates a liquid flow rate of 0.1 mL min⁻¹ and a gas flow rate of 1.3 mL min⁻¹ was chosen. Segmented flow could be visually verified in the transparent Teflon® tubes (see the ESI†). Liquid hold ups in order to determine contact times were calculated with the correlation of Larachi *et al.* (see the ESI†).²¹ The pressure was set to 5 bar with a back pressure regulator and the reaction was run for 30 min before taking the first sample. The gas phase effluent of the reactor could be monitored with IR spectroscopy. The liquid products were quantified against a biphenyl internal standard using gas chromatography (HP-FFAP column, a flame ionization detector).

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