$NaNO_2$-activated, iron–TEMPO catalyst system for aerobic alcohol oxidation under mild conditions†

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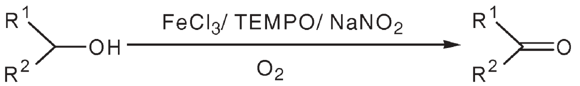
$FeCl_3$–TEMPO–$NaNO_2$ catalyses the selective and mild aerobic oxidation of a broad range of alcohols to the corresponding aldehydes and ketones.

The selective oxidation of alcohols into their corresponding aldehydes and ketones is of significant importance in laboratory and industrial synthetic chemistry.[1] Recently metal-catalyzed aerobic alcohol oxidation strategies have received intense research scrutiny for economical and environmental reasons.[2] However, many of these efficient catalyst systems require noble metals such as Ru and Pd, and only a few metal catalysts were reported to be capable of oxidizing heteroatoms-containing (N, S) substrates using molecular oxygen.[2e,2j] Therefore, the development of green and cheap metal catalysts for selective and mild aerobic oxidation of alcohols is of academic and industrial significance, especially when the catalysts are effective for a broad range of alcohols that contain other functional groups, *e.g.*, carbon–carbon double bond and heteroatoms, that are sensitive to oxidation and high temperature.[3] Herein, we describe a cheap and environmentally friendly iron–TEMPO–$NaNO_2$ catalyst system for aerobic oxidation of a broad range of alcohols that may contain carbon–carbon double bond and N, S heteroatoms under mild conditions (eqn 1).



(1)

The catalytic systems of alcohol oxidation involving transition metals and 2,2,6,6-tetramethylpiperidyl-1-oxy (TEMPO) have received great attention for the use of molecular oxygen as terminal oxidant.[4] Recently, we have developed a highly efficient transition-metal-free TEMPO–Br_2–$NaNO_2$ catalyst for the aerobic oxidation of a wide range of alcohols to the aldehydes and ketones.[5] However, the use of Br_2, albeit in catalytic amount, is undesirable due to its hazardous nature. Moreover, bromine tends to react with alkene and active aromatic compounds. Iron is an extremely abundant metal in the earth's crust and one of its important functions in living systems is responsibility for oxygen transport and electron transport linking the oxidation of substrates to the reduction of O_2.[6] We were intrigued as to whether the combination of Fe and TEMPO could lead to an efficient catalytic system for aerobic alcohol oxidation under mild conditions. But Fe(III and II) chlorides in combination with TEMPO showed no catalytic activity for aerobic alcohol oxidation.[4d] However, based on the understanding of nitrite reductase function process in living system[7] and previous research,[5,8] we reasoned that $NaNO_2$ might activate TEMPO–iron catalyst system for aerobic alcohol oxidation.

An initial experiment was carried out using octan-2-ol as a test substrate with 5 mol% TEMPO, 5 mol% $FeCl_3$ and 5 mol% $NaNO_2$ in acetonitrile under 0.1 MPa of oxygen at 80 °C for 1 h. The preliminary result (45.3% conversion) clearly suggested that our initial assumptions were feasible. In addition, control experiments showed that the catalytic system was ineffective in the absence of any component of the catalyst. Further experiments showed that the iron counterion is critical to the reaction with chloride proving to be superior to nitrate and sulfate and the reaction could be accomplished using $FeCl_2$ in place of $FeCl_3$. In addition, dichloromethane and trifluorotoluene are superior solvents to acetonitrile and lead to an important increase in reaction rates. It is interesting to find that $CuCl_2$ worked just as well as $FeCl_3$. The result demonstrated that $NaNO_2$ is also an activating agent for the copper–TEMPO catalytic system since the combination of $CuCl_2$ and TEMPO did not work well with less reactive alcohols such as 2-octanol.[4a] In fact, we have developed a highly efficient catalytic system for the aerobic oxidation of a wide range of alcohols except 1-octanol to their corresponding aldehydes and ketones in high isolated yields using iron–TEMPO–nitrite catalyst (see ESI for details†). The oxidation of 1-octanol can be completed within 6 h, accompanied by some acid and ester as by-product.

To further probe the potential of the new catalyst system, we carried out the reaction under ambient atmosphere (open system) using less noxious trifluorotoluene as solvent.‡ Interestingly, the reaction was completed at room temperature with a modest increase in catalyst amount. These conditions under ambient atmosphere were later applied to the aerobic oxidation of a variety of alcohols. As shown in Table 1, all benzylic alcohols were quantitatively converted into the corresponding aldehydes with >99% selectivity. Double bond was unaffected (entry 9). Secondary alcohols including 2-octanol, cyclohexanol, and 1-phenylethanol can be completely converted into corresponding ketones with >99% selectivity. It is noteworthy that sulfur-containing compounds (entries 7, 10, 11), which are problematic in other transition metal-catalyzed aerobic oxidation protocols, seldom interfered with the catalytic aerobic oxidation reaction. For example, when a mixture of alcohol and methyl phenyl sulfide was reacted with air (ambient atmosphere) in the presence

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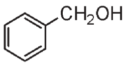
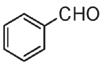
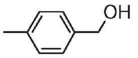
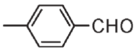
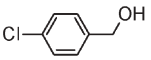
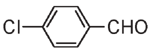
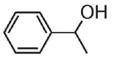
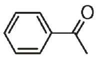
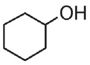
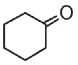
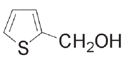
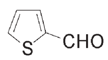
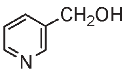
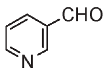
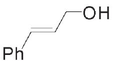
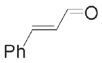
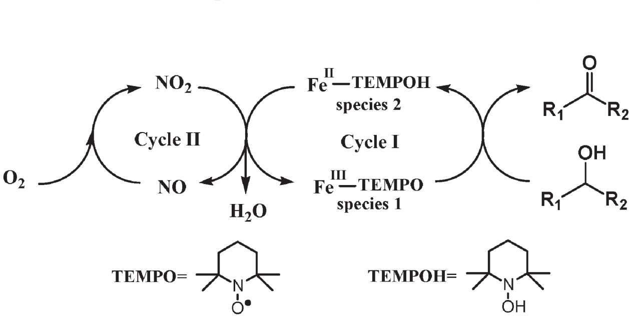
Table 1 Catalytic aerobic alcohol oxidation under air[a]

Entry	Substrate	Product	Time/h	Conv. (%)	Select. (%)
1			8	100	>99
2			8	100	>99
3			12	100	>99
4			10	100	>99
5	$2\text{-}C_8H_{17}OH$	2-Octanone	8[b]	100	>99
6			8[b]	100	>99
7			12[b]	100	>99
8			12[b,c]	100	>99
9			12[b]	100	>99
10	$PhCH_2OH + PhSCH_3$	$PhCHO + PhSCH_3$	16[b]	100	>99
11	$2\text{-}C_8H_{17}OH + PhSCH_3$	$2\text{-Octanone} + PhSCH_3$	16[b]	100	>99

[a] Aerobic oxidation conditions are as follows: alcohol (10 mmol), $NaNO_2$ (0.5 mmol), $FeCl_3{\cdot}6H_2O$ (0.5 mmol), TEMPO (0.2 mmol), $PhCF_3$ (10 mL), room temperature. Conversions and selectivities are based on gas chromatography (GC) with area normalization. [b] $NaNO_2$ (0.8 mmol), TEMPO (0.5 mmol) [c] 1 mL CH_3COOH was added.

of the iron–TEMPO–nitrite catalyst (entries 10 and 11), alcohols were selectively oxidized into aldehydes, whereas methyl phenyl sulfide remained unreacted. This selectivity may be of great interest in synthetic organic chemistry when two functions (alcohol and sulfide) are present in the same molecule.

A plausible overall mechanism of this catalytic oxidation can be described as a cascade of redox reactions involving two cycles in Scheme 1. Control experiment showed that 35% benzyl alcohol was oxidized to benzaldehyde in the presence of stoichiometric oxidant (1 eq. $FeCl_3$) and 5% TEMPO. Therefore, TEMPO is envisioned to carry out the main oxidation reaction of alcohols with the help of Fe^{3+} that initiates a series of electron and proton transfer steps in cycle I where species 1 is reduced to generate species 2. This process is analogous to the Cu(II)–TEMPO catalytic oxidation system.[9] The role of $NaNO_2$ could be a source of NO_2. The role of NO_2 is responsible to the oxidation of species 2 to species 1 and NO_2 is reduced to NO. This oxidation process (cycle II) involves the oxidation of Fe(II) to Fe(III) by NO_2[10] and the oxidation of TEMPOH to TEMPO by Fe(III).[11] The oxidation of NO to NO_2 can be easily performed with molecular oxygen.



Scheme 1 Proposed mechanism for the aerobic oxidation of alcohols.

In conclusion, $FeCl_3$–TEMPO–$NaNO_2$ can act as an efficient catalyst for aerobic alcohol oxidation. Under ambient atmosphere and at room temperature, a wide range of alcohols was transformed to the corresponding aldehydes and ketones. Moreover, the catalyst shows excellent substrate tolerance and is notably not deactivated by sulfur-containing compounds.

Notes and references

‡ *Experimental.* All alcohols and solvents were used as received without any further purification. The oxidation of alcohols was carried out under air in a 50 ml three-necked round-bottom flask equipped with a magnetic stirrer. Typically, the alcohol (10.0 mmol) and TEMPO (0.5 mmol) were dissolved in 10 ml trifluorotoluene. $FeCl_3\cdot 6H_2O$ (0.5 mmol) was added followed by $NaNO_2$ (0.5 mmol). The resulting mixture was stirred at room temperature and ambient pressure. The conversion and selectivity of the reaction was detected by GC without any purification.

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