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Catalytic oxidations mediated by metal ions and nitroxyl radicals

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Abstract

The use of nitroxyl radicals, alone or in combination with transition metals, as catalysts in oxidation processes is reviewed, from both a synthetic and a mechanistic viewpoint. Two extremes of reactivity can be distinguished: stable (persistent) dialkylnitroxyls, such as TEMPO, and reactive diacylnitroxyls, derived from *N*-hydroxy imides, such as *N*-hydroxyphthalimide (NHPI).

NHPI catalyzes a wide variety of free radical autoxidations, improving both activities and selectivities by increasing the rate of chain propagation and/or decreasing the rate of chain termination. In the absence of metal cocatalysts improved conversions and selectivities are obtained in the autoxidation of hydrocarbons to the corresponding alkyl hydroperoxides. In combination with transition metal cocatalysts, notably cobalt, NHPI and related compounds, such as *N*-hydroxysaccharin (NHS), afford effective catalytic systems for the autoxidation of hydrocarbons, e.g. toluenes to carboxylic acids and cycloalkanes to the corresponding ketones.

Stable dialkylnitroxyl radicals, exemplified by TEMPO, catalyze oxidations of, e.g. alcohols, with single oxygen donors such as hypochlorite via the intermediate formation of the corresponding oxoammonium cation. Alternatively, in conjunction with transition metals, notably ruthenium and copper, they catalyze aerobic oxidations of alcohols via metal-centred dehydrogenation. The role of the TEMPO is to facilitate regeneration of the catalyst (Ru and Cu). In contrast, oxoammonium cations are involved in the aerobic oxidation of alcohols catalyzed by the copper-dependent oxidase, laccase, in combination with TEMPO. This different mechanistic pathway is attributed to the much higher redox potential of the copper(II) in the enzyme.

Keywords: Nitroxyl radicals; Oxidation; Homogeneous catalysis; Laccase; Tempo

1. Introduction to nitroxyl radicals

Conjugated organic nitroxyl radicals, such as the diphenylnitroxyl radical (**1**) have been known for almost a century [1]. The stable, nonconjugated nitroxyl radicals di-*tert*-butylnitroxyl (**2**) and 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO; **3**) were first reported in the 1960s [2,3]. The unpaired electron is delocalized over the nitrogen–oxygen bond (see Fig. 1) which accounts for their high stability [4] (they can be stored for long periods of time without decomposition). A wide variety of this type of stable free radical has since been reported and forms the subject of several reviews [4–9].

Based on their propensity to scavenge free radicals, stable nitroxyl radicals have found important applications as powerful inhibitors of free radical chain processes such as autoxidation and polymerization [10]. They are often added as the amine precursor, which is converted in situ to the corresponding nitroxyl radical. More recently, TEMPO and its derivatives have found wide application as catalysts for the oxidation of alcohols, with single oxygen donors, notably hypochlorite (see later) [11,12].

In contrast with the stable dialkylnitroxyl radicals, which inhibit free radical autoxidations, *N*-hydroxyphthalimide (NHPI) catalyzes autoxidations via the formation of the diacylnitroxyl radical, PINO (see Fig. 1). A plausible explanation for this contrasting behavior can be found by considering the relative stabilities of TEMPO and PINO, which in turn are related to the bond dissociation energy (BDE) of the O–H bond in the parent hydroxylamine. Two groups [13,14] have recently determined the BDE of the O–H bond in NHPI and mixed acylalkylhydroxylamines (substituted hydroxamic acids), and compared them (see Fig. 2) with that of the O–H bond in TEMPOH which was already known [15].

The chemistry of nitroxyl radicals is well documented [4–9,16,17] and the higher reactivity of acylalkylnitroxyls compared to dialkylnitroxyls is well known. This effect is further amplified in a diacylnitroxyl, such as PINO. Replacing

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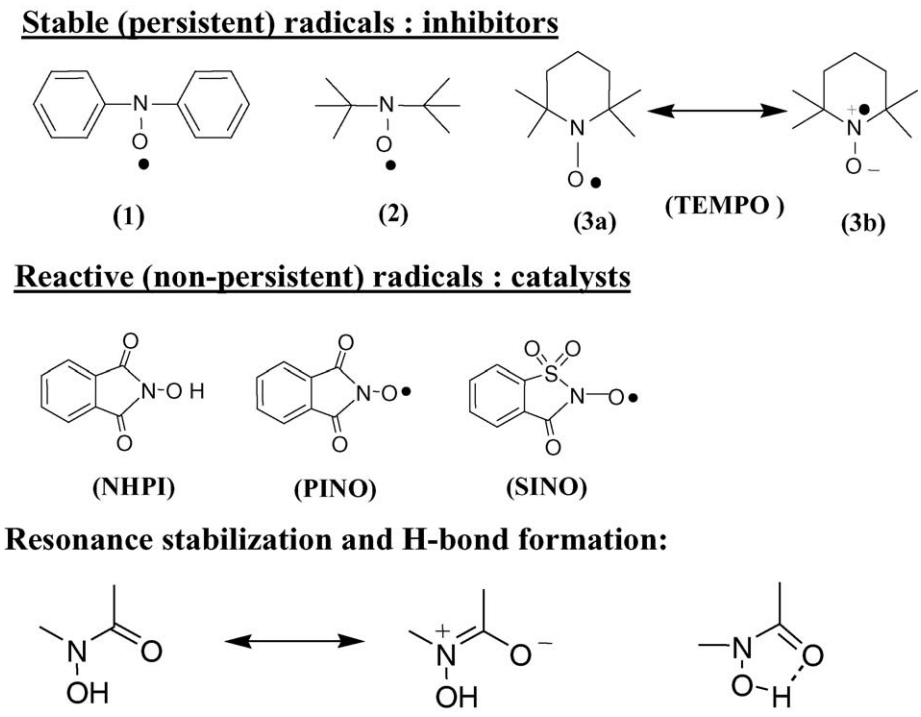


Fig. 1. Structures of organic nitroxyl radicals.

an alkyl group in a dialkylhydroxylamine with an acyl group results in an increase in the BDE of the O–H bond of ca. 40 kJ/mol (see Fig. 2). This translates to a higher reactivity of the corresponding nitroxyl radical, which can be ascribed to the effect of the carbonyl group(s) on the stability of the nitroxyl radical and the parent hydroxylamine [13]. The presence of electron-withdrawing carbonyl groups has a destabilizing effect by reducing the importance of the mesomeric structure **3b** in Fig. 1. By the same token, the carbonyl group increases the stability of the acylhydroxylamine via resonance stabilization and the formation of an intramolecular hydrogen bond (Fig. 1).

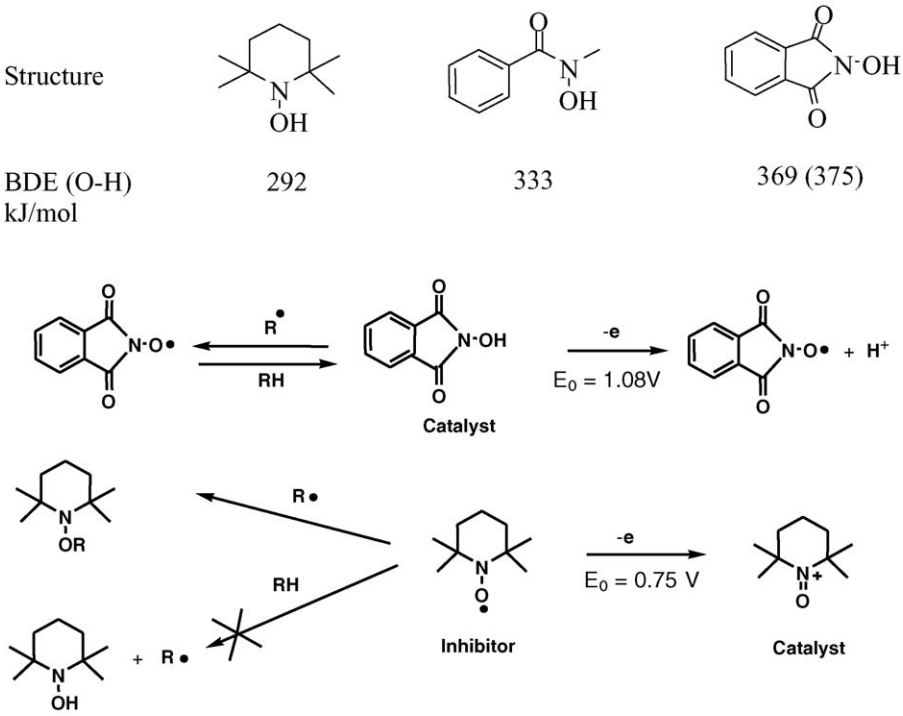


Fig. 2. Stabilization of *N*-acylhydroxylamines.

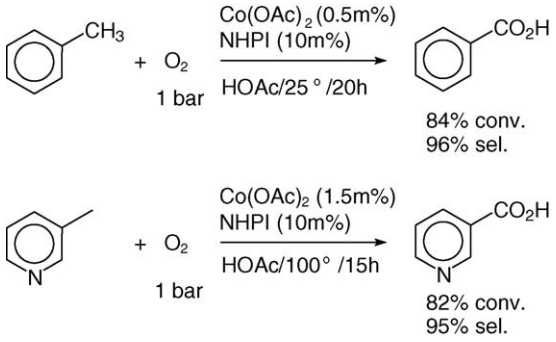


Fig. 3. Autoxidation of alkylaromatics.

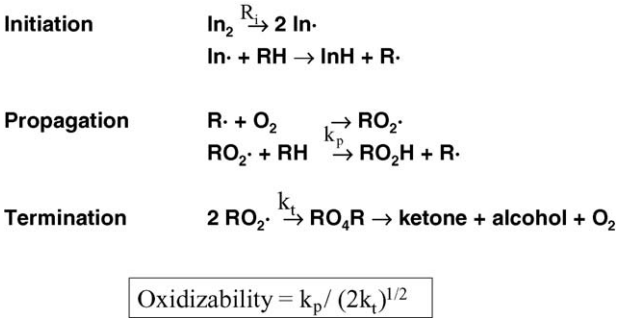


Fig. 4. Mechanism of free radical chain autoxidation.

Based on the above mentioned BDEs, one can conclude that hydrogen abstraction by TEMPO will be highly endothermic with most organic substrates and, by efficiently scavenging free radicals, it acts as an autoxidation inhibitor. In contrast, the O–H bond energy in NHPI is very close to that of the O–H bond in alkylhydroperoxides (378 kJ/mol) and hydrogen abstraction from many organic compounds will be thermoneutral or mildly exothermic.

2. *N*-Hydroxyphthalimide (NHPI) as an autoxidation catalyst

The use of NHPI in an autoxidation reaction was first reported by Foricher et al. of Hoffmann La Roche in 1986 [18]. Various terpenes and steroids were oxidized to the corresponding allylic hydroperoxides in the presence of a stoichiometric amount of NHPI. Ishii and coworkers subsequently showed [19,20] that the combination of NHPI with a variable valence metal, notably cobalt (what has become known as the 'Ishii system'), affords an effective catalytic system for the autoxidation of a broad range organic substrates, e.g. alkanes [21] and alkylaromatics [22].

Aerobic oxidation of toluenes to the corresponding carboxylic acids is a widely used industrial technology [23], involving rather harsh conditions, e.g. the oxidation of toluene to benzoic acid involves cobalt-catalyzed oxidation at 150 °C and 10 bar air. In sharp contrast, the oxidation of toluene in the presence of NHPI (10 mol%) and $Co(OAc)_2$ (0.5 mol%) in acetic acid can be performed at ambient temperature and pressure (Fig. 3) [22]. Even the notoriously recalcitrant methylpyridines are oxidized, under relatively mild conditions, using the Ishii system (see Fig. 3) [24]. The products are commercially important fine chemicals that are generally prepared by stoichimetric oxidations with nitric acid or permanganate.

3. Mechanism of NHPI catalysis

In order to understand the fundamental steps underlying the catalysis of autoxidation by NHPI and related *N*-hydroxyimides it is necessary to first consider the mechanism of free radical autoxidation. It is a classical free radical chain process involving initiation, propagation and termination steps (see Fig. 4). Initiation can occur by thermal decomposition of adventitious alkyl hydroperoxides in the substrate or by the deliberate addition of free radical initiators. The relative rates of autoxidation of organic substrates are determined by the ratio of the propagation and termination rate constants, as expressed in the so-called oxidizability, $k_p/[2k_t]^{1/2}$ [23]. The rates of autoxidations can be increased in two ways: by increasing the rate of propagation or by decreasing the rate of termination.

Ishii suggested [19,20] the mechanism shown in Fig. 5 to account for the autoxidation of hydrocarbons in the presence of NHPI/$Co(acac)_2$. Initiation involves a two-step process in which cobalt(II) first reacts with oxygen followed by abstraction of a hydrogen from NHPI by the resulting superoxocobalt(III) species, affording the chain propagating PINO radical.

The reaction can also be initiated by cobalt(III) complexes, e.g. $Co(acac)_3$, and whether cobalt(II) or cobalt(III) gives the better results is dependent on inter alia the solvent used. Although the exact mechanism of initiation remains a matter of debate, once PINO is generated the autoxidation can proceed further by the chain propagation steps shown in Fig. 5. Hence, NHPI has been called a carbon radical producing catalyst (CRPC), although we prefer the term carbon radical chain promoter (CRCP).

In this scheme the cobalt has two functions: it acts as an initiator in generating PINO radicals and it catalyzes the decomposition of intermediate hydroperoxides into products. Hence, the main role of the cobalt is one of initiator while the NHPI acts as a catalyst.

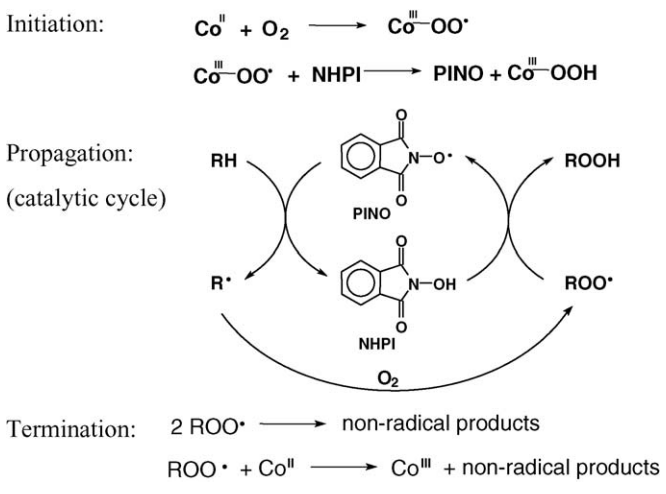


Fig. 5. Mechanism of autoxidations catalyzed by NHPI/$Co(acac)_2$.

Table 1
Rate constants per active hydrogen for hydrogen abstraction from RH

RH	Rate constant (M^{-1} s^{-1}) at 25 °C			
	t-BuOO•	ROO•	PINO	
$PhCH_3$	0.012	0.08	0.21[a]	0.13[b]
$PhCH_2CH_3$	0.10	0.65	2.7[a]	1.1[b]
$PhCH(CH_3)_2$	0.22	0.18	26.6[a]	3.25[b]
$PhCH_2OH$	0.065	2.4	5.7[a]	14.2[b]
c-C_6H_{12}	0.003	0.53[c]	0.05[a]	0.002[b]

[a] In PhH/10% CH_3CN [13].
[b] In HOAc [14].
[c] At 60 °C.

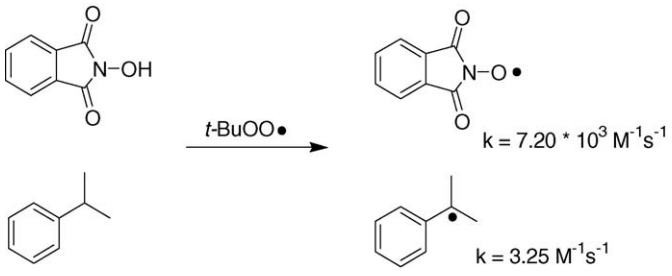


Fig. 6. Rate constants for reaction of *t*-BuOO• with NHPI vs. cumene.

The catalytic effect of NHPI can be readily understood by comparing the rate constants for the reaction of PINO with hydrocarbons and alkylperoxy radicals with NHPI with the corresponding propagation steps in the classical autoxidation mechanism. The rate constants for the reaction of PINO with different substrates have recently been determined by two groups [13,14] using the 'EPR titration' method. The relevant data are compared with those of the corresponding reactions with ROO• in Table 1. Although there are serious discrepancies between the two sets of data it is clear that PINO reacts faster than ROO• with the various substrates.

The rate constant for the reaction of *t*-BuOO• with NHPI (Fig. 6) has also been determined [25]. It was found to be more than 1000 times larger than the corresponding rate constant for reaction with cumene. The catalytic effect of NHPI on free radical autoxidations is clearly a result of both a higher rate of propagation and, more importantly, of a decreased rate of termination owing to the extremely efficient scavenging of alkylperoxy radicals by NHPI. Since there is an increase in rate constant by more than a thousand, a significant effect should be seen at NHPI concentrations of 1 mol% or lower.

Because the cobalt is acting as an initiator, while the NHPI is the true catalyst, we reasoned that the use of catalytic amounts of NHPI, in the presence of a free radical initiator rather than a metal compound, (Fig. 7) should afford the corresponding alkylhydroperoxides in high rates and selectivities. The former are a result of a higher rate of propagation and/or lower rate of termination and the latter are a result of less by-product formation via termination and cobalt-catalyzed decomposition of the hydroperoxide.

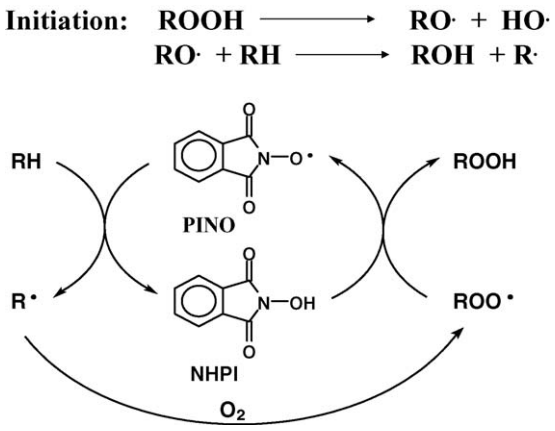


Fig. 7. Mechanism of NHPI catalyzed autoxidation.

4. Selective autoxidation of cyclohexylbenzene: a coproduct free route to phenol

Selective autoxidation of cyclohexylbenzene (CHB) to the 1-hydroperoxide forms the basis for a co-product free route to phenol from benzene (Fig. 8) [26], analogous to the Hock process based on cumene. Every step in the process has, in principle, been demonstrated but for commercial viability it is necessary to achieve a very high selectivity, at reasonable conversions (25–30%), in the autoxidation step. A priori, one can expect problems as the cyclohexylbenzene (CHB) substrate contains one tertiary C–H bond and 10 secondary C–H bonds, significantly less favorable than the situation with cumene where one tertiary C–H competes with six primary C–H bonds.

This proved to be the case: the best results were obtained using the product hydroperoxide, CHBHP, as the initiator (2 mol%)—in combination with 0.05–0.5 mol% NHPI, in the absence of solvent, at 100 °C [27]. The results are shown in Table 2.

In the absence of NHPI the conversion after 8 h was 3% and selectivity to CHBHP was 86%. The addition of increasing amounts of NHPI resulted in an increase in both the rate (conversion) and the selectivity to CHBHP. The optimum result (97.6% selectivity at 32% CHB conversion) was obtained with 0.5 mol% NHPI. Increasing the amount of NHPI further did not lead to further improvements, probably due to the lim-

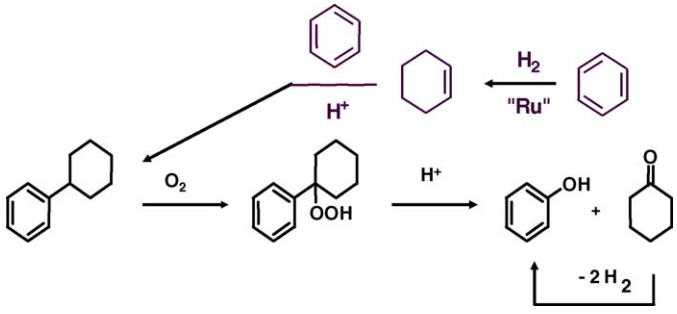


Fig. 8. A coproduct free route from benzene to phenol.

Table 2
Oxidation of CHB at 100 °C[a]

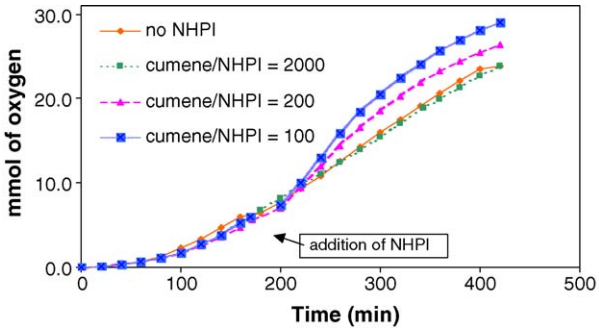
NHPI (mol%)	Conv. CHB (%)	Selectivity (%)			
		1-ROOH	2-ROOH	4-ROOH	A[b]
None	3.2	86.0	0.9	6.0	2.9
0.05	14	94.1	0.3	4.0	1.7
0.1	19	96.7	0.1	3.2	–
0.5	32	97.6	–	1.2	0.4

[a] Conditions: no solvent, 2 mol% CHBHP, 1 bar O_2, 100 °C, 8 h.
[b] See Fig. 9 for structure of A.

ited solubility of NHPI in CHB, which is close to 0.5 mol% at 100 °C.

The main by-products were the cyclohexylbenzene-4-hydroperoxide and the 1,3-dihydroperoxide (A) which is formed via transannular hydrogen abstraction by the intermediate cyclohexylbenzene-1-peroxy radical as shown in Fig. 9.

These results can be rationalized on the basis of the rate constants discussed in the preceding section. The rate constant for the reaction of the intermediate alkylperoxy radical with NHPI is 3–4 orders of magnitude larger than its reaction with the CHB substrate. This means that, even at concentrations as low as 0.1 mol%, alkylperoxy radicals will be effectively scavenged by NHPI. This results not only in an increase in rate but also in an increase in selectivity, by virtue of a decrease in the amounts of alcohol and ketone formed in the termination of two alkylperoxy radicals and suppression of the transannular hydrogen abstraction. An increase in rate and an increase in selectivity to the 1-hydroperoxide with respect to the 2- and 4-isomers can be explained by assuming that the chain propagating hydrogen abstraction from the substrate mainly proceeds via the PINO radical, and that this is more selective than ROO• and RO•, which are the chain propagating radicals in the absence of NHPI.



Cumene/NHPI	No NHPI	2000	200
Conversion (%)	40	42	46
Sel. CHP (%)	**88.9**	**90.2**	**92.3**
Cumyl alcohol (%)	9.1	8.2	6.6
Acetophenone (%)	2.0	1.6	1.1

115°C, 1 bar O_2, 2 mol% CHP, 60 mmol cumene

Fig. 10. NHPI catalyzed autoxidation of cumene.

Encouraged by the excellent results obtained in the autoxidation of CHB, we examined the autoxidation of cumene in the presence of 0.05–0.5 mol% NHPI and the corresponding hydroperoxide (CHP) as the initiator. Cumene hydroperoxide (CHP) is the intermediate in the existing process for phenol manufacture. Increased rates and selectivities towards CHP were obtained in the presence of 0.5–1% NHPI even when the latter was added during the course of the reaction (Fig. 10).

Similarly, increased selectivities and rates were observed in the autoxidation of ethylbenzene to the corresponding hydroperoxide (Fig. 11) [28]. The latter (EBHP) is an intermediate in the SMPO process for the co-manufacture of styrene and propylene oxide [29].

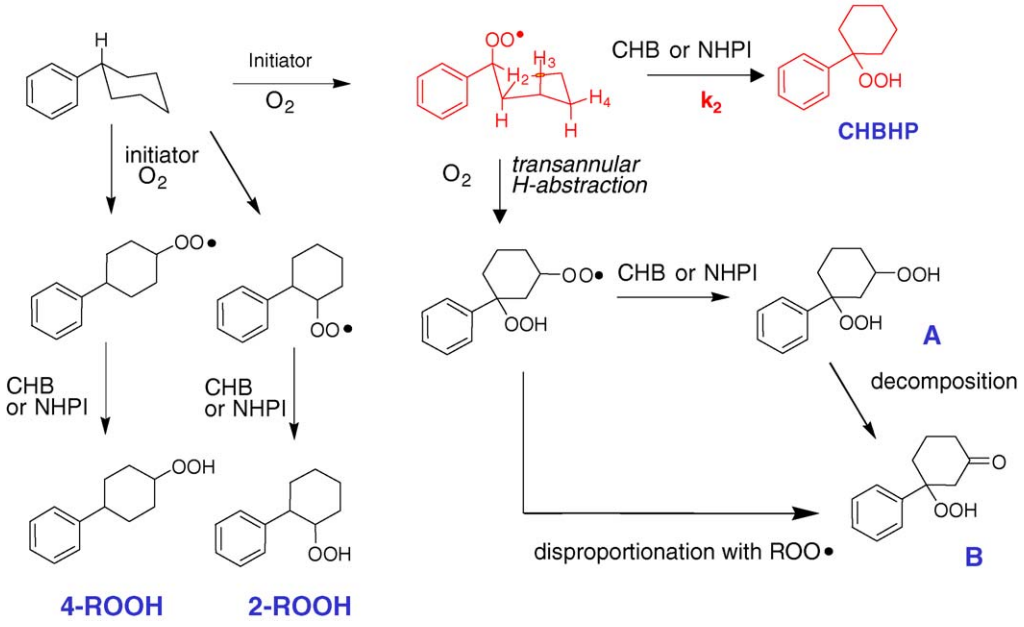
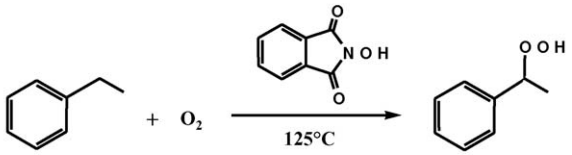


Fig. 9. Product formation in the autoxidation of cyclohexylbenzene (CHB).



% mol NHPI	% mol EBHP	time	Conv. (%)	Selectivity EBHP	Selectivity acetophenone
0	0	8 h	5	88	12
0	2	8 h	14	27	48
0.1	0.1	8 h	10	91	8
0.25	0.1	8 h	10	92	7
0.5	0.1	8 h	12	89	9
1	0.1	6 h	9	94	6
		8 h	12	88	9

Fig. 11. NHPI catalyzed autoxidation of ethylbenzene.

5. *N*-Hydroxysaccharin (NHS) as a carbon radical chain promoter in cycloalkane autoxidations

The selective oxidation of saturated hydrocarbons (alkanes) is a reaction of considerable industrial importance [23]. The selective oxidation of large-ring cycloalkanes, e.g. cyclododecane and cyclopentadecane, to the corresponding ketones is particularly important as the products are intermediates for the production of polyamides and polyesters or fragrances, respectively. However, aerobic oxidations of cycloalkanes generally proceed in low selectivities, even at low conversions. In order to obtain reasonable selectivities the reaction is usually performed according to the Bashkirov method [30]. This involves aerobic oxidation in the presence of stoichiometric amounts of B_2O_3 to give the borate ester of the cyclic alcohol product. The borate ester is subsequently hydrolyzed to the alcohol and boric acid, followed by dehydrogenation of the alcohol to the ketone. A serious shortcoming of this method is that it is circuitous, involving three steps – oxidation, hydrolysis and dehydrogenation – and recycling of large quantities of boric acid.

It is known that the introduction of electron-withdrawing substituents in the benzene ring of NHPI has a beneficial effect on the catalyst performance in the aerobic oxidation of alkylbenzenes [31]. This is presumably a result of the increase in reactivity of the corresponding nitroxyl radical (see earlier). Hence, we reasoned that the use of *N*-hydroxysaccharin (NHS), in which one carbonyl group in NHPI is replaced by the more strongly electron-withdrawing sulfonyl (SO_2) group, should provide an even more effective carbon radical chain promoter for the autoxidation of a cycloalkane.

Hence, we studied the autoxidation of large-ring cycloalkanes in the presence of NHS or NHPI in combination with cobalt compounds [32,33]. Interestingly, the optimum cobalt cocatalyst was dependent on the solvent used.

Superior results were observed when the reaction was conducted in $PhCF_3$ as solvent using $Co(acac)_3$ as the cocatalyst. The optimum result was obtained at 80 °C: 90% selectivity to a 4:1 mixture of ketone and alcohol at 24% conversion (Fig. 12). NHS was shown to be a more effective catalyst than NHPI allowing the reactions to be performed at a lower temperature with a consequent increase in selectivity. No oxidative cleavage to 1,12-dodecanedioc acid was observed under these conditions. Competition experiments were performed with a mixture of cyclododecane and cyclopentadecanone, in a molar ratio of 5:1 (corresponding to ca. 17% conversion in a cycloalkane oxidation). These substrates were chosen because both cyclododecanone and cyclopentadecanone are industrially interesting targets (see above). The results strongly suggested that the formation of cleavage products does not arise from further oxidation of the ketone, as commonly assumed, but via β-cleavage of the intermediate cycloalkoxy radicals. The latter reaction is strongly solvent and temperature dependent. Consequently, the suppression of the formation of cleavage products under the above conditions can be ascribed to the lower temperature and the solvent effect. In acetic acid as solvent, in contrast, substantial cleavage was observed.

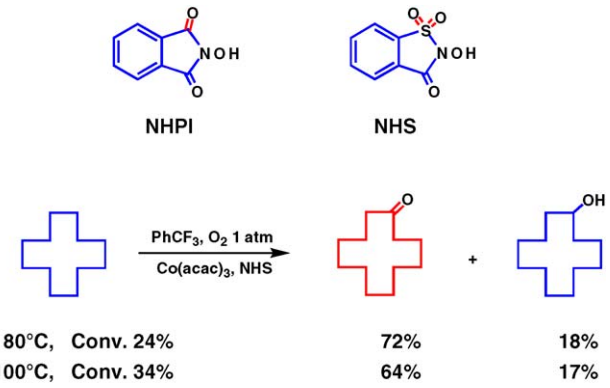


Fig. 12. NHS/Co catalyzed oxidation of cyclododecane.

The formation of carbonyl compounds via β-cleavage of alkoxy radicals is a well-documented reaction [34–36] which in the case of cyclic alkoxy radicals leads to ring opening. In the presence of NHS (or NHPI), efficient scavenging of alkoxy radicals suppresses β-cleavage in favor of alcohol formation. The observation that reaction in acetic acid led to more cleavage products than in $PhCF_3$ is also consistent with a β-cleavage pathway. Thus, Ingold and coworkers showed that the rate of β-scission of alkoxy radicals increases with increasing polarity of the solvent, owing to polar contributions to the transition state [37]. In contrast, rates of hydrogen abstraction, by alkoxy radicals from polar molecules such as ROOH and PhOH, decrease with increasing solvent polarity [38]. Hence, one would expect a similar effect with the polar NHPI or NHS. Consequently, the proportion of ring opened products would increase in acetic acid compared to $PhCF_3$, as a result of a faster β-cleavage of the alkoxy radical and a slower hydrogen abstraction from NHS or NHPI.

6. TEMPO: from inhibitor to catalyst

Although TEMPO is an extremely efficient inhibitor of aerobic oxidations, its one-electron oxidation with, for example, chlorine or bromine, produces the corresponding oxoammonium cation, which is a relatively strong oxidant ($E^0 = 0.75$ V).

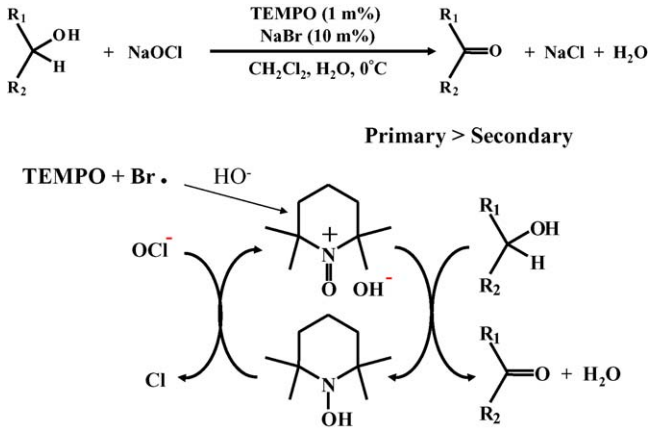


Fig. 13. Mechanism of alcohol/oxidation with TEMPO/NaOCl.

The stoichiometric oxidation of primary alcohols, to the corresponding aldehydes, by the oxoammonium cation was first reported by Golubev et al. in 1965 [39]. The oxoammonium cation derived from 4-methoxy TEMPO was shown [40] to selectively oxidize a variety of both primary and secondary alcohols and diols. The reaction was rendered catalytic in TEMPO by using single oxygen donors such as *m*-chloroperbenzoic acid [41], persulfate(oxone) [42], periodic acid (H_5IO_6) [43] and sodium hypochlorite [44] to generate the oxoammonium cation in situ. In particular the TEMPO/hypochlorite (household bleach) protocol, using 1 mol% TEMPO in combination with 10 mol% sodium bromide as cocatalyst in dichloromethane/water at pH 9 and 0 °C, has been widely applied in organic synthesis [11,12]. The method was first described in 1987 by Montanari and coworkers who used 4-methoxy TEMPO as the catalyst [44]. The commonly accepted mechanism for alcohol oxidations with hypochlorite/TEMPO is shown in Fig. 13 [12,45].

The catalytic cycle involves alternating oxidation of the alcohol by the oxoammonium cation and regeneration of the latter by reaction of the TEMPOH with the primary oxidant (hypochlorite). Hence, TEMPO is the catalyst precursor which is presumably oxidized by bromine or chlorine (see Fig. 13) to the oxoammonium cation which enters the catalytic cycle.

The Montanari protocol, although widely applicable, suffers from several environmental and/or economic drawbacks. It is not waste-free: at least one equivalent of sodium chloride is produced per molecule of alcohol oxidized and the use of hypochlorite as oxidant can also lead to the formation of chlorinated by-products. Other shortcomings are the use of 10 mol% bromide as a cocatalyst and dichloromethane as a solvent. Furthermore, although only 1 mol% is used, TEMPO is rather expensive, which means that efficient recycling is an important issue. Hence, several groups have addressed this problem by designing heterogeneous variants of TEMPO, e.g. by anchoring TEMPO to solid supports such as silica [46–51], the mesoporous silica, MCM-41 [49] and coupling of 4-hydroxy-TEMPO to a carboxylic acid functionalized polymer [50] or by entrapping TEMPO in a silica sol–gel [51].

In this context, our attention was attracted to the structure of the commercially available antioxidant and light stabilizer, chimassorb 944, an oligomeric sterically hindered amine (MW ~3000) [52]. We surmised that oxidation of chimassorb 944 with hydrogen peroxide and a catalytic amount of $Na_2WO_4{\cdot}2H_2O$ [5,7] would generate a recyclable oligomeric TEMPO (Fig. 14). This new polymer-immobilized TEMPO, which we refer to as polymer-immobilized piperidinyloxyl (PIPO), proved to be a very effective catalyst for the oxidation of alcohols with hypochlorite [53–55].

Under the standard conditions (see earlier), PIPO dissolved in the dichloromethane layer. In contrast, in the absence of a solvent, or in the presence of apolar solvents, PIPO was a very effective recyclable heterogeneous catalyst (see Table 3). Furthermore, PIPO exhibited a higher activity (per nitroxyl group) than TEMPO, which made the need for a bromide cocatalyst redundant. Hence, the use of PIPO in an amount equivalent to 1 mol% of nitroxyl radical provided an effective (heterogeneous) catalytic method for the oxidation of a variety of alcohols with 1.25 equiv. of 0.35 M NaOCl (pH 9.1) in a bromide- and chlorinated hydrocarbon solvent-free medium (Table 3).

In the solvent-free system, aliphatic primary alcohols underwent overoxidation to the corresponding carboxylic acids. This problem was circumvented, resulting in high selectivities to aldehydes, by using *n*-hexane as the solvent (entry 2 in Table 3). In competition experiments, a marked preference for primary

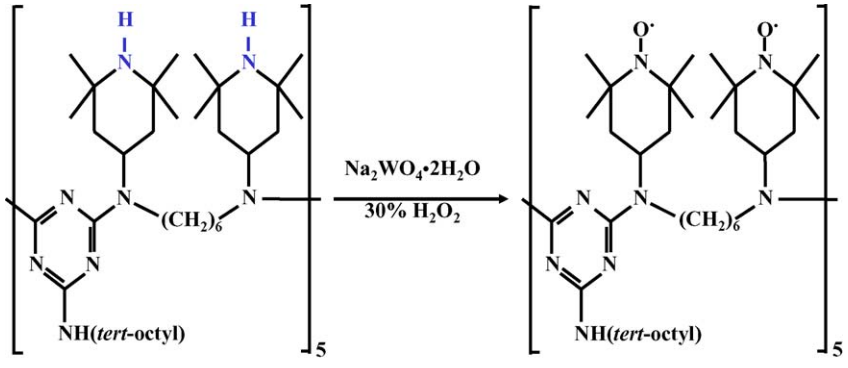


Fig. 14. Synthesis of PIPO.

Table 3
Chlorinated solvent- and bromide-free PIPO-catalyzed oxidation of alcohols with hypochlorite[a]

Entry	Substrate	Time (min)	Conv. (%)	Sel. (%)
1	Octan-1-ol	45	90	50[c]
2[b]		60	95	94
3	Octan-2-ol	45	99	>99
4[b]	Octan-1-ol/octan-2-ol	45	86/<1	96
5	Cyclooctanol	45	100	>99
6	Benzyl alcohol	30	100	>99
7	1-Phenylethanol	30	100	>99
8	Benzyl alcohol/1-phenylethanol	30	95/4	>99
9	(S)-2-methyl-1-butanol	45	90	>99

[a] Reaction conditions: 0.8 mmol substrate, 2.5 mg PIPO (1 mol% nitroxyl), 2.86 ml 0.35 M hypochlorite-sol. (1.25 equiv.), 0.14 g $KHCO_3$ (for pH 9.1), 0 °C.
[b] 2 ml *n*-hexane as solvent.
[c] Octanoic acid and octyl octanoate formed as side products.

compared to secondary alcohols was observed (see Table 3) analogous to results obtained with TEMPO [44] and other heterogenized TEMPO systems [46]. A stereogenic centre at the α-position was not affected during oxidation as illustrated by the selective oxidation of (S)-2-methylbutan-1-ol to (S)-2-methylbutanal using the PIPO/NaOCl system [55].

7. Oxygen as the terminal oxidant

Notwithstanding the substantial improvement of the PIPO/NaOCl system, from both an economic and an environmental viewpoint, compared to the currently employed TEMPO/NaOCl system, the use of the 'green oxidants', oxygen or hydrogen peroxide, would be preferred over that of hypochlorite The use of a combination of a stable nitroxyl radical (di-*tert*-butylnitroxyl) and a copper(II) phenanthroline complex for the catalytic aerobic oxidation of methanol to formaldehyde (Fig. 15) was described by Brackman and Gaasbeek in 1966 [56]. To explain their results they proposed a catalytic cycle in which a key step was the reaction of the nitroxyl radical with a copper(II)/phenanthroline/methanol ternary complex, to afford the corresponding hydroxylamine, copper(I) and formaldehyde. Regeneration of the nitroxyl radical proceeds by reaction of the hydroxylamine with a second equivalent of the copper(II)

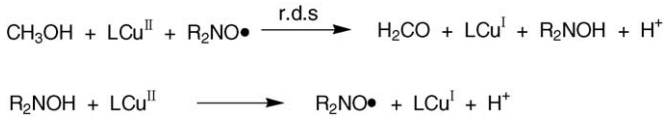


Fig. 15. Oxidation of methanol by Cu(II) phenanthroline/di-*tert*-butylnitroxyl.

phenanthroline complex. They further proposed that copper(II) was regenerated by reaction of copper(I) with oxygen, to complete the catalytic cycle. Two decades later Semmelhack et al. [57] reported the use of TEMPO in combination with cuprous chloride as a catalyst for the aerobic oxidation of benzylic and allylic alcohols. They proposed a different role for the TEMPO in the catalytic cycle, namely that copper(II) oxidizes TEMPO to the oxoammonium cation (see Fig. 16) which is the actual oxidant. Subsequent oxidation of the alcohol affords TEMPOH which undergoes syn proportionation with a molecule of oxoammonium cation to regenerate two equivalents of TEMPO. The copper(II) is regenerated by reaction of copper(I) with oxygen. A serious shortcoming of this method is that it is ineffective with less reactive aliphatic and alicyclic alcohols, i.e. it does not have the broad scope that the TEMPO/NaOCl system has.

Hence, we tested a range of metal catalysts for the aerobic oxidation of octan-2-ol in the presence of TEMPO as a cocatalyst [58]. We found that a combination of $RuCl_2(PPh_3)_3$ (1 mol%) and TEMPO (3 mol%) was particularly effective [59,60]. Other ruthenium compounds, e.g. $RuCl_3$, gave lower rates and coordinatively saturated 18-electron complexes, e.g. $RuCl_2(bipy)_2$ and $RuCl_2(DMSO)_4$, were completely unreactive. The $RuCl_2(PPh_3)_3$/TEMPO system was effective for the aerobic oxidation of a broad range of alcohols (Table 4).

The general procedure involved the use of 0.5–2 mol% $RuCl_2(PPh_3)_3$ and 1.5–6 mol% TEMPO in chlorobenzene at 100 °C, either under an atmosphere of pure oxygen or using a flow of an O_2/N_2 (8:92 v/v) mixture at 10 ml/min at 10 bar in an autoclave [59,60]. The latter procedure is preferred for safety reasons: gas phase mixtures of oxygen and organic compounds remain outside the explosion limits during the reaction. Chlorobenzene was used as the solvent to facilitate GC analysis of the reaction mixtures (it did not interfere with product peaks). However, it was also shown that the reactions perform equally well in toluene or, better still, with no solvent at all [60,61].

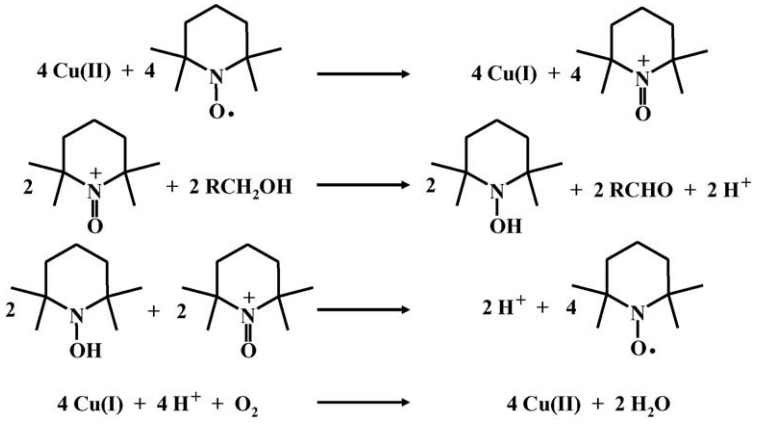
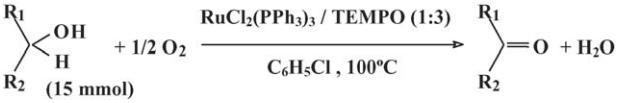


Fig. 16. Semmelhack mechanism for CuCl/TEMPO catalyzed oxidation of alcohols.

Table 4
Ruthenium-TEMPO-catalyzed aerobic oxidation of alcohols



Alcohol	*S*/*C* ratio	Time (h)	Conv. (%)	Sel. (%)
Primary aliphatic	50	3–7	78–88	95–98
Secondary aliphatic	100	7	75–100	>99
Primary allylic	67	7	87–96	>99
Secondary allylic	100	24	67–81	>99
Primary benzylic	200	3–6	95–100	>99
Secondary benzylic	100	4–6	95–100	>99
Cyclic ($n = 4, 5, 6$)	100	22	45–65	>99
Cyclic ($n \geq 8$)	100	6–7	94–9	>99

Secondary alcohols afforded the corresponding ketones in >99% selectivity at complete conversion. Primary alcohols afforded the corresponding aldehydes in high selectivity which was surprising since aldehydes are known to undergo facile autoxidation to the corresponding carboxylic acid [26]. However, control experiments revealed that the autoxidation of aldehydes is completely suppressed by catalytic amounts of TEMPO, consistent with its well-known (see earlier) propensity for scavenging free radicals, thereby acting as an effective autoxidation inhibitor. Primary allylic alcohols were selectively converted to the corresponding α,β-unsaturated aldehydes, e.g. geraniol afforded geranial in 99% selectivity at 91% conversion. No competing rearrangement of the allylic alcohol to the saturated ketone via ruthenium-catalyzed intermolecular hydrogen transfer [62] was observed. As with the TEMPO/NaOCl system, the Ru/TEMPO catalyst displayed a marked preference for primary versus secondary alcohols [60,61]. Unfortunately, a number of alcohols containing additional heteroatoms, were unreactive which was attributed to deactivation of the catalyst by coordination of the heteroatom to ruthenium [60,61].

8. Mechanism of the Ru/TEMPO system

The results of detailed mechanistic studies, including stoichiometric oxidations with TEMPO under anaerobic conditions, kinetic isotope effects and Hammett correlation plots, of the Ru/TEMPO system [60,61], were consistent with the mechanism shown in Fig. 17.

The alcohol substrate undergoes dehydrogenation by the $RuCl_2(PPh_3)_3$, affording the corresponding carbonyl compound and a ruthenium hydride. The function of the TEMPO is to regenerate the ruthenium catalyst by abstracting a hydrogen atom, affording TEMPOH. A likely candidate for the RuH species is $RuH_2(PPh_3)_3$, as observed in $RuCl_2(PPh_3)_3$-catalyzed hydrogen transfer reactions [63]. Consistent with this notion, $RuH_2(PPh_3)_4$ exhibited the same activity as $RuCl_2(PPh_3)_3$ in the Ru/TEMPO catalyzed aerobic oxidation of octan-2-ol [60]. When $RuH_2(PPh_3)_3$ was allowed to react with an excess of TEMPO, in chlorobenzene under an inert atmosphere at 25 °C, its disappearance (monitored with in situ IR) was accompanied

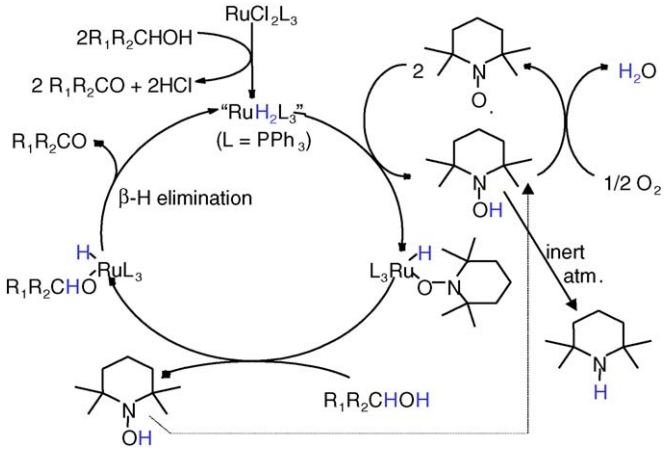
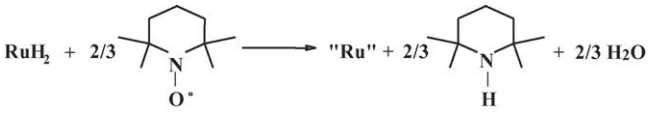


Fig. 17. Catalytic cycle for the Ru/TEMPO catalyzed aerobic oxidation of alcohols.

by the formation of the corresponding amine, TEMPH, according to the stoichiometry shown in Reaction 1. The TEMPH is formed via disproportionation of the initially formed TEMPOH [60].



9. Copper/TEMPO revisited

Based on our results (see earlier) with the Ru/TEMPO system we suspected that the Cu/TEMPO system may involve a copper-centred oxidative dehydrogenation of the alcohol rather than an oxoammonium cation as the oxidant. This prompted us to reinvestigate the Semmelhack system [64] by subjecting it to the same mechanistic studies as with the Ru/TEMPO system [65].

We first confirmed that benzylic and allylic alcohols underwent smooth oxidation using the Semmelhack procedure (CuCl/TEMPO in dimethylformamide at 25 °C). In contrast, simple aliphatic alcohols were unreactive which did not seem to be consistent with an 'oxoammonium' mechanism since oxoammonium cations are known to have broad scope, including the facile oxidation of simple aliphatic alcohols [11,12].

Stoichiometric experiments in an inert atmosphere demonstrated that copper(I) is oxidized by TEMPO (see Fig. 18) to produce piperidinyloxycopper(II), analogous to one-electron oxidations of other metal ions by TEMPO [66–68]. Addition of one equivalent of benzyl alcohol to this solution resulted in the formation of copper(I), benzaldehyde and the amine, TEMPH, in a 1:1:1 ratio. When a catalytic amount of CuCl, in dimethylformamide, was used for the oxidation of benzyl alcohol with a stoichiometric amount of TEMPO, in an inert atmosphere, benzaldehyde and TEMPH were formed in a 3:2 molar ratio. These results can be rationalized on the basis of the reaction scheme shown in Fig. 18 [65].

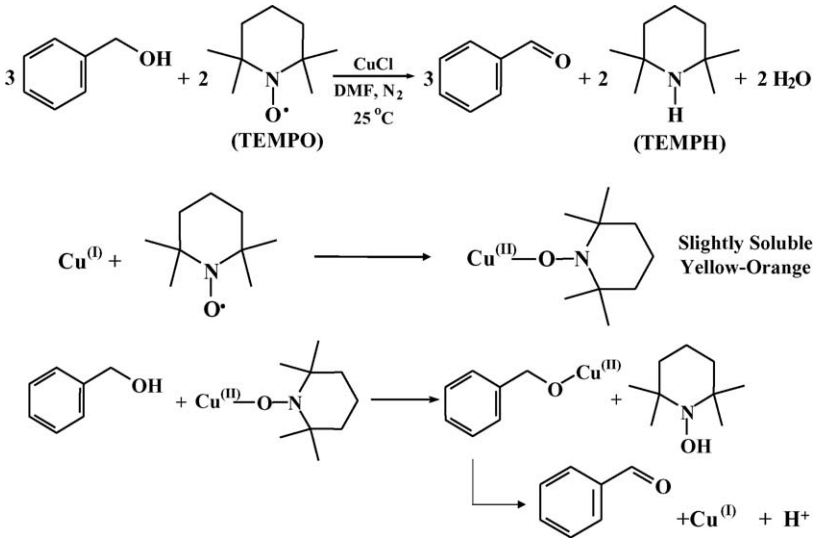


Fig. 18. CuCl-catalyzed stoichiometric oxidation of an alcohol by TEMPO.

Oxidation of the alcohol by TEMPO, catalyzed by copper, affords the corresponding carbonyl compound and TEMPOH in a 1:2 molar ratio. The latter spontaneously disproportionates to a 2:1 mixture of TEMPO and TEMPH resulting in the overall stoichiometry shown in Fig. 18 [65]. In the presence of oxygen TEMPOH is rapidly oxidized to TEMPO [59,60], rendering the reaction catalytic in TEMPO.

Additional evidence for the copper-centred dehydrogenation mechanism for the Semmelhack system was obtained from kinetic isotope effects and Hammett correlation studies [65]. The primary kinetic isotope effect (k_H/k_D) for the Cu/TEMPO catalyzed aerobic oxidation of α-deutero-*p*-methylbenzyl alcohol at 25 °C was determined to be 5.42. This value compares well with isotope effects (see Table 5) observed with other metal-centred dehydrogenations of alcohols, such as the Ru/TEMPO system and a galactose oxidase mimic [69] (see below). In contrast, a much smaller kinetic isotope effect was observed in the stoichiometric oxidation of the same alcohol with the oxoammonium cation derived from TEMPO [64]. Similarly, the Hammett ρ value obtained from the oxidation of a series of substituted benzylic alcohols with the CuCl/TEMPO system compared well with that observed with the galactose oxidase mimic [69] (see Table 5).

Table 5
Kinetic isotope effects and Hammett ρ-values for the oxidation of benzyl alcohols

System	Kinetic isotope effect (k_H/k_D)[a]	Hammett ρ-value	References
CuCl/TEMPO/O_2	5.42	−0.16	[65]
Oxoammonium chloride	1.7–2.3	−0.3	[64]
$RuCl_2(PPh_3)_3$/TEMPO/O_2	5.12	−0.58	[60]
CuCl/TEMPO/N_2[b]	5.77	–	[65]
[Cu(II)BSP]/O_2[c]	5.3	−0.14	[69]
Galactose oxidase	5.02	−0.09	[72]

[a] α-deutero, *p*-methyl benzyl alcohol was used for the determination of KIE.
[b] TEMPO is used as stoichiometric oxidant under an inert nitrogen atmosphere.
[c] Galactose oxidase mimic.

The catalytic cycle shown in Fig. 19 was proposed to account for the above described results in the Cu/TEMPO catalyzed aerobic oxidation of alcohols [65]. The key oxidation step involves intramolecular hydrogen abstraction within an alkoxycopper(II)/TEMPO complex, in which the TEMPO is coordinated in a η^2 fashion, analogous to that in previously reported copper(II)-TEMPO complexes [70]. This generates a coordinated ketyl radical anion and TEMPOH. Subsequently, inner-sphere electron transfer affords Cu(I) and the carbonyl product (alternatively, these two steps could be a concerted process).

This closely resembles the rate-determining step in the oxidation of primary alcohols catalyzed by the copper-dependent oxidase, galactose oxidase [71,72], in which a ring-substituted cysteinyl tyrosinyl radical is coordinated to an alkoxycopper(II) complex in the active site (Fig. 20).

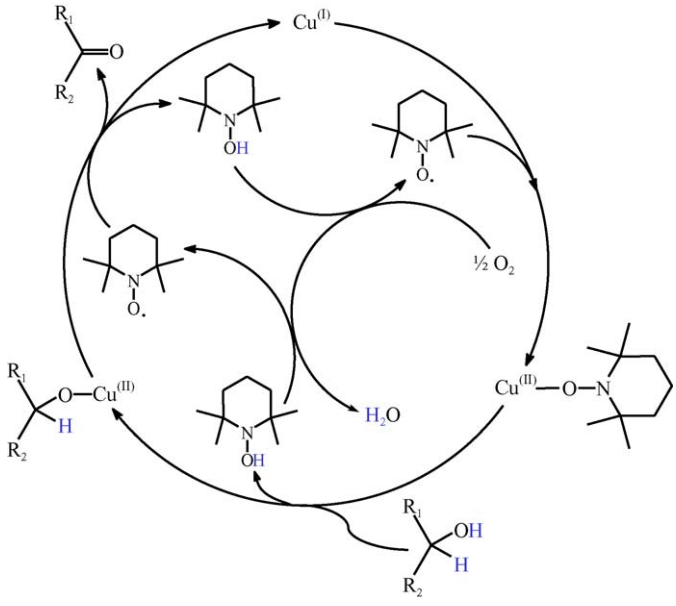


Fig. 19. Mechanism of CuCl/TEMPO catalyzed aerobic oxidation of alcohols.

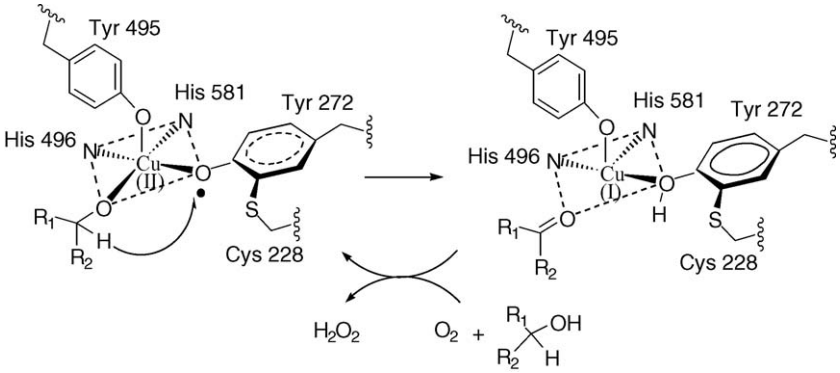
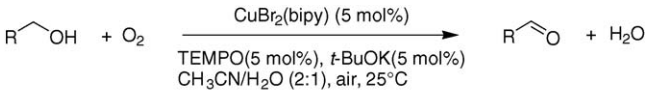


Fig. 20. Mechanism of galactose oxidase.



Alcohol	Time/h	Conversion [%]
Benzyl alcohol	2.5	100
1-Phenylethanol	5	No reaction
Crotyl alcohol	5	91
Geraniol	5	100
Octan-1-ol	24	61
Octan-1-ol	24	95
Octan-2-ol	5	No reaction
Benzyl alcohol + Phenylethanol	1.5	63/0

Fig. 21. Cu/TEMPO catalyzed oxidations of alcohols.

More recently, we showed that a mixture of $CuBr_2$(2,2′-bipyridine) and TEMPO, in the presence of a base, catalyzed the aerobic oxidation of primary alcohols to aldehydes at room temperature (Fig. 21) [73].

This system showed a remarkable chemoselectivity for a primary versus secondary alcohol moiety. For example, complete conversion of benzyl alcohol was observed in 2.5 h while no reaction was observed in 5 h with α-methylbenzyl alcohol [73]. This was explained on the basis of steric hindrance by the methyl group in the intramolecular hydrogen abstraction by the coordinated TEMPO ligand as depicted in Fig. 22. In addition, in the case of primary alcohols the second β-hydrogen atom can form a hydrogen bond with the oxygen atom of coordinated TEMPOH, thereby stabilizing the coordinated ketyl radical intermediate (see Fig. 22).

Similarly, PIPO (see earlier) in combination with CuCl in dimethylformamide catalyzed the aerobic oxidation of benzylic alcohols with an activity comparable to that of TEMPO [54,55]. Other noteworthy developments are the CuCl/TEMPO catalyzed aerobic oxidation of alcohols [74] in the ionic liquid, [bmim][PF_6] and the use of TEMPO in combination with a copper complex of a bipyridine ligand containing perfluorinated ponytails for alcohol oxidation in a fluorous biphasic system [75]. Interestingly, the latter system was also capable of oxidizing simple aliphatic alcohols. More recently, metal-free systems have been described based on combinations of

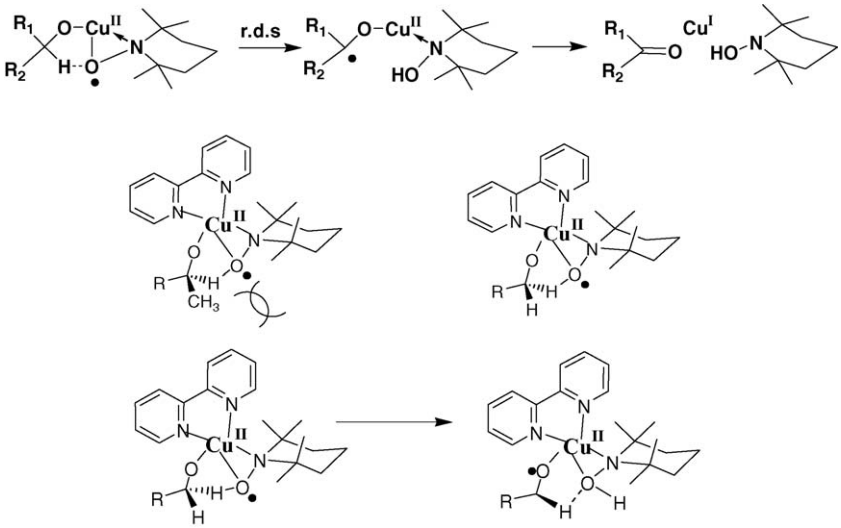


Fig. 22. Possible explanations for the lack of reactivity of secondary alcohols.

TEMPO with $NaNO_2$ and bromide with air as the oxidant [76].

10. Aerobic oxidations catalyzed by laccase/TEMPO

Another copper-dependent oxidase that has attracted much attention recently is laccase (EC 1.10.3.2) [77]. Laccases are a group of isoenzymes, so-called multicopper oxidases [78], that contain four copper centres per protein molecule and catalyze the oxidation of electron rich aromatic substrates, usually phenols or amines, via four single electron oxidation steps concomitant with the four electron reduction of oxygen to water. They are extracellular enzymes that are secreted by white rot fungi and play an important role in the delignification of lignocellulose, the major constituent of wood, by these microorganisms [79]. In this process laccase alone is ineffective since it is too large a molecule to penetrate the cell wall of wood and react with the lignin. Consequently, so-called mediators, low molecular weight electron transfer agents, are employed to shuttle electrons from the lignin to the copper centre of the enzyme. For example, 3-hydroxyanthranilic acid is produced by the white rot fungus, *Pycnoporous cinnabarinus* and is believed to play the role of an electron mediator [80].

Current interest in laccases stems from the various commercial applications that are envisaged for these enzymes, which include pulp bleaching (as a replacement for chlorine) in paper manufacture, remediation of phenol-containing waste streams, amperometric biosensors for phenol detection and in the processing of foods and beverages. The laccase/mediator systems are also potentially interesting catalysts for organic synthesis, including the aerobic oxidation of alcohols and carbohydrates such as starch. A variety of mediators that have been used in conjunction with laccase are shown in Fig. 23.

Table 6
Laccase/mediator catalyzed oxidation of benzylalcohol [82]

Mediator	Aldehyde yield (%)
ABTS	2
HBT	30
VLA	42
NHPI	54
TEMPO	92

2,2-Azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) was the first compound shown to mediate laccase-catalyzed oxidation of a nonphenolic compound: the oxidation of veratryl alcohol to the corresponding aldehyde [79]. Subsequently, 1-hydroxybenzotriazole (HBT) [81] and other *N*-hydroxy compounds such as *N*-hydroxyacetanilide (NHA), violuric acid (VLA) and NHPI were shown to act as mediators [82]. A common feature of most of these mediators appears to be their propensity to form nitroxyl radicals, which presumably is the key to their activities.

In 1996 Potthast et al. reported that the laccase/ABTS combination catalyzed the aerobic oxidation of a series of benzylic alcohols to the corresponding benzaldehydes [83]. Subsequently, Galli and coworkers reported that the combination laccase/TEMPO catalyzes the aerobic oxidation of primary benzylic alcohols [84]. The selective oxidation of the primary alcohol moiety in carbohydrates had been previously reported in two patents [85,86]. In a subsequent comparison of the various mediators, in the laccase/mediator catalyzed aerobic oxidation of benzylic alcohols, TEMPO proved to be the most effective (Table 6) [87]. It should be noted, however, that large amounts of TEMPO (20–30 mol%) are required and, in common with the CuCl/TEMPO system, smooth reactions are observed only with reactive, e.g. benzylic, alcohols.

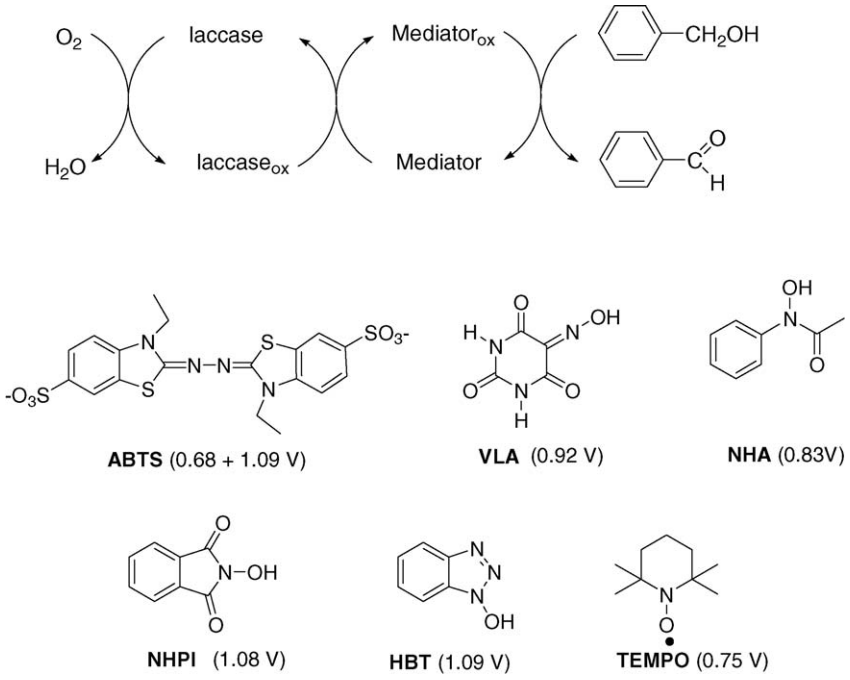


Fig. 23. Mechanism of alcohol oxidation in laccase/mediator systems.

11. Mechanism of the laccase/mediator systems

The mechanistic details of these processes are still a matter of conjecture but they are generally believed to involve one-electron oxidation of the mediator by the oxidized (cupric) form of the laccase, followed by reaction of the oxidized mediator with the substrate, either via electron transfer (ET), e.g. with ABTS, or via hydrogen atom transfer (HAT), e.g. with *N*-hydroxy compounds which form nitroxyl radicals [88]. TEMPO and its derivatives form a unique case and are assumed to involve the formation of the corresponding oxoammonium cation via electron transfer to the copper(II) of laccase, i.e. via the Semmelhack mechanism proposed for CuCl/TEMPO (see earlier).

As noted above, laccases generally contain four copper ions per protein molecule. They are classified into three types according to their spectroscopic properties: one type 1 (T1), in which the copper is coordinated to two histidines and a cysteine, one type 2 (T2) which coordinates to two histidines and a water molecule, and two type 3 (T3) coppers, coordinated to three histidines and a bridging hydroxyl group [89]. It is generally believed that the substrate, in this case the mediator, undergoes one-electron oxidation at the T1 copper site while reduction of oxygen to water occurs at the trinuclear T2/T3 site, with electrons being shuttled between the two sites [90].

The T1 copper(II) centre in fungal laccases has a redox potential (E^0) of ca. 0.8 V versus the normal hydrogen electrode (NHE). This is very high for the Cu^{II}/Cu^{I} couple, which normally has a redox potential, in aqueous solution, of ca. 0.15 V [23]. This is an example of the so-called 'entatic state', common in blue copper proteins, whereby coordination to the protein forces the metal ion, copper(II) in this case, into a strained geometry which manifests itself in a high redox potential [91]. Consequently, the T1 copper(II) in fungal laccases can oxidize TEMPO to the corresponding oxoammonium cation which has a redox potential of 0.75 V.

Evidence in support of an oxoammonium cation intermediate in the laccase/TEMPO was obtained from a study of the kinetic isotope effect in the oxidation of a benzylic alcohol [92]. We found a k_H/k_D of 2.05 which is consistent with an oxoammonium intermediate rather than a copper-centred dehydrogenation mechanism (see Table 5). The different mechanisms of the laccase/TEMPO and CuCl/TEMPO (see earlier) systems can be rationalized on the basis of the much higher redox potential of the copper(II) in the former.

With *N*-hydroxy mediators, such as HBT, NHA, VLA and NHPI, it is generally believed [87] that laccase-catalyzed oxidations involve one-electron oxidation of the mediator, followed by loss of a proton from the intermediate radical cation, to afford the corresponding nitroxyl radical. This is followed by hydrogen abstraction from the alcohol substrate by the nitroxyl radical [87].

Xu et al. [93] measured the redox potentials of a series of *N*-hydroxy compounds and found a direct correlation of E^0 with the rate of oxidation of the mediator by laccase from *Trametes villosa*. *N*-hydroxy imides, such as NHPI, have a much higher redox potential than, for example, *N*-hydroxyacetanilide (NHA). This is a reflection of the higher BDE of the O–H bond in NHPI (see earlier) and, hence, higher reactivity of the PINO radical. Hence, NHPI has a high redox potential (1.01 V) and, consequently, a low rate of oxidation by laccase compared to, for example, TEMPO [93]. If this is the rate-limiting step it will result in a lower overall rate of alcohol oxidation. It should be noted, however, that a histidine residue in the T1 active site may be able to deprotonate the *N*-hydroxyimide. The resulting anion will more easily undergo one-electron oxidation to the corresponding nitroxyl radical. Clearly more investigations are necessary to elucidate the mechanistic details of the laccase/mediator systems and provide a sound basis for their further optimization.

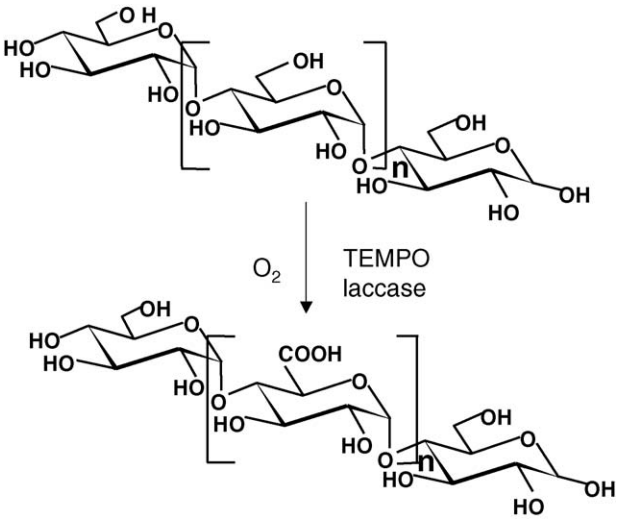


Fig. 24. Oxidation of starch.

The selective oxidation of the primary alcohol groups in starch, to carboxyl functionalities, is a reaction of commercial importance. The carboxystarch product is a biodegradable polymer with potential applications as a water super absorbent, e.g. in baby diapers. Carboxystarch is an environmentally attractive alternative for the currently used polyacrylates. It has been shown [85,86,94] that laccase, in combination with TEMPO, or derivatives thereof, is able to catalyze the aerobic oxidation of the primary alcohol moieties in carbohydrates (see Fig. 24) but the relatively high enzyme costs form an obstacle to commercialization. Inefficient laccase use is a result of its instability under the reaction conditions. Laccase is a glycosylated enzyme and, hence, its instability is presumably a consequence of competing oxidation of glycosyl moieties and/or essential amino acid residues by the oxoammonium cation intermediate. We have recently shown that the stability of the laccase under reaction conditions can be improved by immobilization as a cross-linked enzyme aggregate (CLEA) [95]. Indeed, laccase CLEA has broad potential as a catalyst for a variety of applications (see earlier).

12. Concluding remarks

Oxidations catalyzed by nitroxyl radicals have a history dating back four decades and are characterized by a broad synthetic potential and a rich mechanistic diversity. Moreover, they have been shown to have beneficial antioxidant behavior in a variety

of biological processes, which can be ascribed to redox reactions of the nitroxyl/oxoammonium couple [96].

A broad range of oxidative transformations of synthetic interest can be accomplished using one of the two types of nitroxyl radicals – stable (persistent) dialkylnitroxyls or reactive diacylnitroxyls (introduced as the *N*-hydroxy precursor) – alone or in combination with a transition metal as a cocatalyst. Oxidations have been achieved using oxygen or single oxygen donors. Both chemo- and biocatalytic systems are known. In the latter case – laccase in combination with nitroxyl radicals or *N*-hydroxy compounds as mediators – activities and substrate scope are less than one would wish. However, based on the mechanistic insights emerging from recent mechanistic studies, we expect that improvements will be forthcoming.

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