Organocatalytic Oxidations Mediated by 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 the archetypal TEMPO, and reactive diacylnitroxyls, derived from *N*-hydroxy imides, such as *N*-hydroxyphthalimide (NHPI). The different types of reactivity observed are rationalized by considering the bond dissociation energies (BDEs) of the respective *N*-hydroxy precursors, substrates and reaction intermediates. Reactive diacylnitroxyl radicals are generated *in situ* from the corresponding *N*-hydroxy compound. The protagonist, 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 co-catalysts improved conversions and selectivities are obtained in the autoxidation of hydrocarbons to the corresponding alkyl hydroperoxides. For example, cyclohexylbenzene afforded the 1-hydroperoxide in 97.6% selectivity at 32% conversion when the autoxidation was performed in the presence of 0.5 mol % NHPI, and the product hydroperoxide as initiator, at 100 °C. This forms the basis for a potential coproduct-free route from benzene to phenol. In combination with transition metal co-catalysts, notably cobalt, NHPI and related compounds, such as *N*-hydroxysaccharin NHS, afford effective catalytic systems for the effective autoxidation of hydrocarbons, e.g., toluenes to carboxylic acids, under mild conditions. In the case of the less reactive cycloalkanes, NHS proved to be a more active catalyst than NHPI which is attributed to the higher reactivity of the intermediate nitroxyl radical, resulting from the replacement of a carbonyl group in NHPI by the more strongly electron-attracting sulfonyl group. Stable dialkylnitroxyl radicals, exemplified by TEMPO, catalyze oxidations of, e.g., alcohols, with single oxygen donors such as hypochlorite and organic peracids. The reactions involve the intermediate formation of the corresponding oxoammonium cation as the active oxidant. Alternatively, in conjunction with transition metals, notably ruthenium and copper, they catalyze aerobic oxidations of alcohols. These reactions involve metal-centered dehydrogenations and the role of the TEMPO is to facilitate regeneration of the catalyst (Ru and Cu) and oxidation of the alcohol (Cu) *via* hydrogen abstraction or one-electron oxidation processes. Detailed mechanistic investigations, including kinetic isotope effects, revealed that oxoammonium cations are not involved as intermediates in these reactions. 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. Similarly, *N*-hydroxy compounds such as NHPI also act as mediators in laccase-catalyzed oxidations of alcohols. These reactions are assumed to involve one electron oxidation of the *N*-hydroxy compound, leading to the formation of a proton and the nitroxyl radical, which abstracts a hydrogen atom from the substrate. However, neither of these laccase-based systems has, as yet, attained the activity and scope of the TEMPO/hypochlorite system.

Keywords: enzyme catalysis; heterogeneous catalysis; homogeneous catalysis; nitroxyl radicals; oxidation; radical reactions

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Roger Sheldon (1942) received a PhD in organic chemistry from the University of Leicester (UK) in 1967. This was followed by post-doctoral studies with Prof. Jay Kochi in the U.S.A. From 1969 to 1980 he was with Shell Research in Amsterdam and from 1980 to 1990 he was R&D Director of DSM Andeno. In 1991 he moved to his present position as Professor of Organic Chemistry and Catalysis at the Delft University of Technology (The Netherlands). His primary research interests are in the application of catalytic methodologies – homogeneous, heterogeneous and enzymatic – in organic synthesis, particularly in relation to fine chemicals production. He developed the concept of E factors for assessing the environmental impact of chemical processes.

Isabel W. C. E. Arends (born 1966) studied chemistry at the University of Leiden (The Netherlands), where she received her PhD in physical organic chemistry in 1993, under the supervision of Prof. R. Louw and Dr. P. Mulder. Postdoctoral work followed with Prof. K. U. Ingold at the National Research Council in Canada on liquid-phase oxidations catalyzed by biomimetic iron complexes. She joined the group of R. A. Sheldon in 1995, where she was appointed Assistant Professor in 2001. Her research interests focus on enzyme- and metal-catalyzed redox reactions, and green selective oxidations employing O_2 and H_2O_2 in particular.

1 Introduction to Nitroxyl Radicals

Conjugated organic nitroxyl radicals, such as the diphenylnitroxyl radical (**1**) have been known since the early 20th century.[1] The stable, non-conjugated nitroxyl radicals 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO; **2**) and di-*tert*-butylnitroxyl (**3**) were first reported by Lebedev and Kazarnovskii[2] and Hoffmann and Henderson,[3] in 1960 and 1961, respectively. The unpaired electron in these radicals is delocalized over the nitrogen-oxygen bond, as shown in Figure 1, and this accounts for their high stability. The delocalization energy of

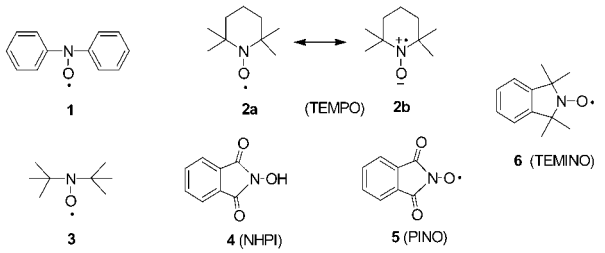
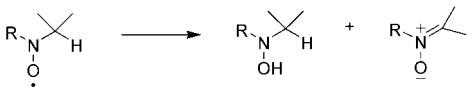


Figure 1. Structures of organic nitroxyl radicals.

the free electron in dialkylnitroxyls has been estimated at 125 kJ/mol.[4] Thus, radicals of this type can be stored for long periods of time without decomposition. They dissolve in both polar and apolar solvents to form brightly colored solutions, e.g., TEMPO is bright orange.

Numerous variants of this type of stable free radical have since been reported and form the subject of several reviews.[4–8] The absence of α-hydrogen atoms is essential for stability: if one or more are present the radical undergoes disproportionation to a hydroxylamine and a nitrone, Equation (1).[9]



(1)

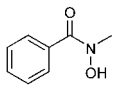
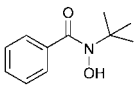
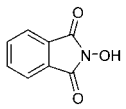
These stable nitroxyl radicals have found important applications as spin labels in biology and, based on their propensity to scavenge free radicals, as powerful inhibitors of free radical chain processes such as autoxidation and polymerization.[10] They are often added as the amine precursor, which is converted *in situ* to the corresponding nitroxyl radical. Hindered amines of this type are widely used as polymer stabilizers under the general name HALS (hindered amine light stabilizer). More recently, TEMPO and its derivatives have found wide application as catalysts for the oxidation of alcohols, with single oxygen donors, notably hypochlorite (see below).[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 Figure 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 Table 1) with that of the O–H bond in TEMPOH which was already known.[15]

The chemistry of nitroxyl radicals was extensively investigated in the 1960s and 1970s by Perkin[16–19] and others[20] and the higher reactivity of acylalkylnitroxyls

Table 1. O–H bond dissociation energies (BDE) in *N*-substituted hydroxylamines.

Structure				
BDE (O–H) kJ/mol	292[a]	333[b]	323[c]	369[b] (375[c])

[a] Ref.[15]
[b] Ref.[13]
[c] Ref.[16]

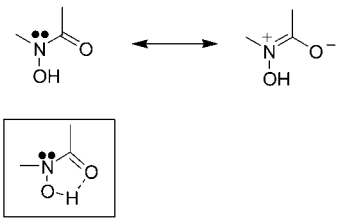


Figure 2. Stabilization of *N*-acylhydroxylamines.

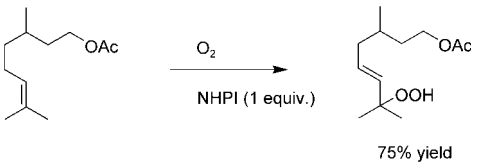
compared to dialkylnitroxyls was recognized. This effect is further amplified in a diacylnitroxyl, such as PINO. It is clear from the data presented in Table 1 that replacing an alkyl group in a dialkylhydroxylamine with an acyl group results in an increase in the BDE of the O–H bond of *ca.* 40 kJ/mol. This substantial increase in bond energy, which translates to a higher reactivity of the corresponding nitroxyl radical, can be understood by considering 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 **2b**. By the same token, the carbonyl group increases the stability of the acylhydroxylamine *via* resonance stabilization and the formation of an intramolecular hydrogen bond (Figure 2).

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 alkyl hydroperoxides (378 kJ/mol) and hydrogen abstraction from many organic compounds will be thermoneutral or mildly exothermic.

2 *N*-Hydroxyphthalimide (NHPI) as an Autoxidation Catalyst

NHPI was first used in 1977 by Grochowski and coworkers[21] to catalyze the reaction of ethers with azodicarboxylate and the oxidation of isopropanol with *m*-chloroperbenzoic acid. The reactions were assumed to involve the intermediacy of the PINO radical, which had already been described in 1968.[22] Subsequently, Masui and coworkers reported that NHPI acts as an efficient electron carrier in the electrochemical oxidation of secondary alcohols.[23]

The use of NHPI in an autoxidation reaction was first reported by Foricher and coworkers of Hoffmann La Roche in 1986.[24] Various terpenes and steroids were oxidized to the corresponding allylic hydroperoxides in the presence of a stoichiometric amount of NHPI. For example, citronellol acetate afforded the corresponding hydroperoxide in 75% yield, Equation (2).



(2)

Extrapolating from the results of Masui and coworkers,[23] Ishii and coworkers[25] reasoned that combination of NHPI with the heteropolyanion, $(NH_4)_5H_6PV_8Mo_4O_{40}$, could produce an effective catalyst for the aerobic oxidation of alcohols, *via* the intermediacy of PINO (Figure 3). This proved to be the case. Further experiments revealed that NHPI alone also acts as a catalyst for the aerobic oxidation of alcohols.

Ishii and coworkers subsequently showed[26,27] that the combination of NHPI with a variable valence metal (what has become known as the 'Ishii system'), notably cobalt, affords an effective catalytic system for the autoxidation of a broad range organic substrates, e.g., alkanes[28] and alkylaromatics.[29] For example, the selective autoxidation of adamantane to adamantanediol[28] and/or -triol [Equation (3)] in the presence of a catalyst

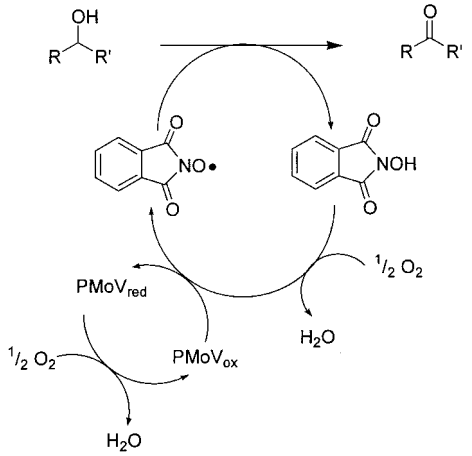


Figure 3. Alcohol oxidation catalyzed by NHPI/heteropoly acid.

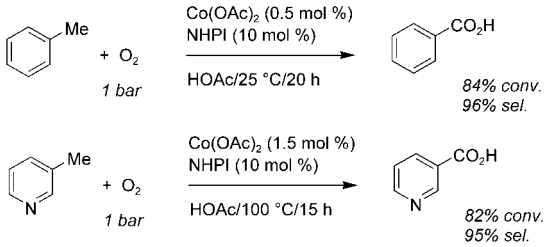
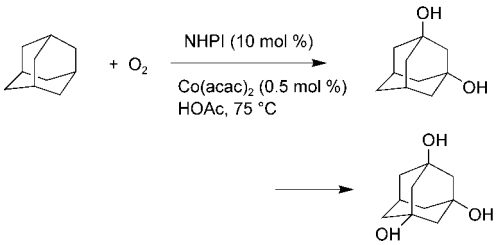


Figure 4. Autoxidation of alkylaromatics.

consisting of NHPI (10 mol %) and $Co(acac)_2$, has been commercialized by the Daicel Chemical Company. The products are used in the manufacture of photoresistant polymers.[26]



(3)

Aerobic oxidation of toluenes to the corresponding carboxylic acids is a widely used industrial technology.[30] Rather harsh conditions are generally required for a smooth reaction, 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 (Figure 4).[29] Even the notoriously recalcitrant methylpyridines are oxidized, under relatively mild conditions, using the Ishii system (see Figure 4 for an example).[31] The product pyridinecarboxylic acids are commercially important fine chemicals and are generally prepared by stoichiometric oxidations with nitric acid or permanganate.

Similarly, one of the largest volume bulk chemicals, terephthalic acid (*ca.* 17 mio tons worldwide annual production), is produced by aerobic oxidation of *p*-xylene under forcing conditions: 175–225 °C and 15–30 bar using a Co/Mn/Br catalyst. Although the combination NHPI/Co/Mn was shown to catalyze this oxidation under milder conditions (100 °C and 1 bar), it required large amounts of NHPI (20 mol %) owing to decomposition of the latter to a mixture of phthalimide and phthalic anhydride.[27] By using *N*-acetoxyphthalimide (NAPI) instead of NHPI this amount could be reduced to 5 mol %.[33] NAPI is presumably resistant to decomposition and serves as a 'slow release' source of NHPI by reacting with the water formed in the reaction.

More recently, Ishii and coworkers[34] have reported the use of *N,N′,N″*-trihydroxyisocyanuric acid (THICA) in combination with $Co(OAc)_2$ as a catalyst for the aerobic oxidation of toluenes (Figure 5). THICA was more effective than NHPI which allowed for a reduction in the amount used to 1 mol %. This was attributed to the greater stability of the corresponding nitroxyl radical towards decomposition (see above). *Ab initio* calculations showed that the BDE of the O–H bond in THICA is even higher than that in NHPI (385 *vs.* 370 kJ/mol), consistent with the higher reactivity towards hydrogen abstraction of the radical derived from THICA.

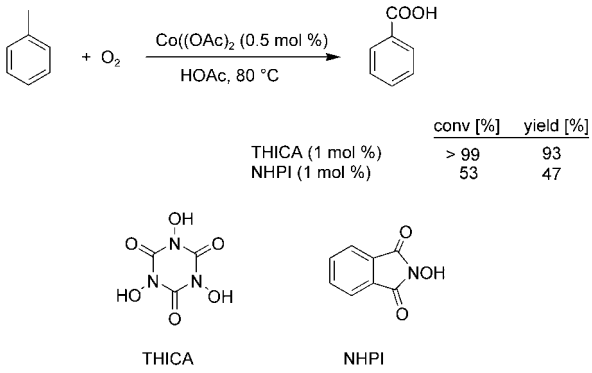


Figure 5. Oxidation of toluenes with THICA/Co^{II}.

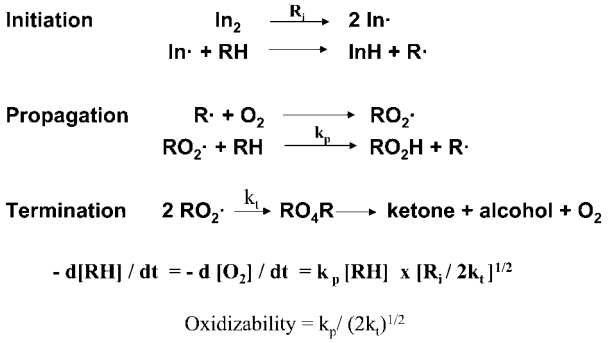


Figure 6. Mechanism of free radical chain autoxidation.

3 Mechanistic Considerations of NHPI Catalysis

In order to understand the fundamental steps underlying the catalysis of autoxidation by NHPI and related *N*-hydroxy imides it is necessary to first consider the mechanism of free radical autoxidation. The classical mechanism for the free radical autoxidation of hydrocarbons is delineated in Figure 6.[30] It is a classical free radical chain process involving initiation, propagation and termination steps. Initiations 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, $k_p/[2k_t]^{1/2}$.[30]

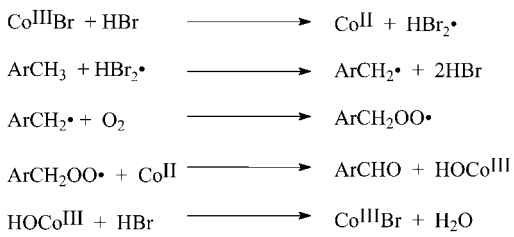


Figure 7. Synergistic effect of bromide.

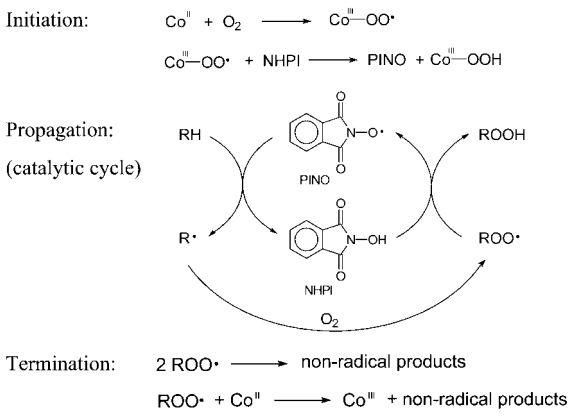
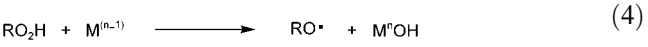


Figure 8. Mechanism of autoxidations catalyzed by NHPI/$Co(acac)_2$.

It is readily apparent from this mechanism that the rates of autoxidations can be increased in two ways: by increasing the rate of propagation or by decreasing the rate of termination. The synergistic effect of bromide on autoxidations (see above) is a result of the much higher rate of hydrogen abstraction by the $HBr_2^{\cdot}$ radical (the predominant species formed by oxidation of bromide in acetic acid solution) compared to the alkylperoxy radical (Figure 7). Thus, the rate constant for reaction of $HBr_2^{\cdot}$ with toluene (in HOAc) is $>10^4$ times that for the benzylperoxy radical.[14,35]

Variable valence metal ions, such as cobalt and manganese, serve as catalysts of autoxidations by undergoing one electron redox reactions with alkyl hydroperoxides to produce alkoxy and alkylperoxy radicals.[30] The former abstract hydrogen atoms from C–H bonds with a rate constants $10^5 - 10^7$ larger than for alkylperoxy radicals,[13] a reflection of the much larger BDE of RO–H (437 kJ/mol) compared to ROO–H (370 kJ/mol).



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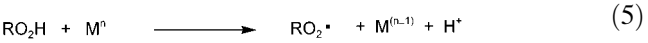


(5)

Ishii suggested[26] the mechanism shown in Figure 8 to account for the autoxidation of hydrocarbons in the presence of NHPI/$Co(acac)_2$.

Table 2. Rate constants per active hydrogen for hydrogen abstraction from RH.

RH	Rate constant ($M^{-1} s^{-1}$) at 25 °C			
	t-BuOO$^{\cdot}$	ROO$^{\cdot}$	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.

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.

It is worth noting, however, that reaction of cobalt(II) with oxygen is thermodynamically unfavorable and formation of cobalt(III) from cobalt(II) acetate in a refluxing oxygenated solution in acetic acid was shown to be due to reaction with trace amounts of peroxides.[36] 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 (see below). 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 Figure 8. Hence, NHPI has been called a ***c***arbon ***r***adical ***p***roducing ***c***atalyst (CRPC), although we prefer the term ***c***arbon ***r***adical ***c***hain ***p***romoter (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.

Why is NHPI such an effective autoxidation catalyst? This readily becomes apparent on 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$^{\cdot}$ in Table 2.

Although there are serious discrepancies between the two sets of data it is clear that PINO reacts faster than ROO$^{\cdot}$ with the various substrates.

The rate constant for the reaction of *t*-BuOO$^{\cdot}$ with NHPI (Figure 9) has been determined.[37] It was found to be more than 1000 times larger than the corresponding rate constant for reaction with cumene.

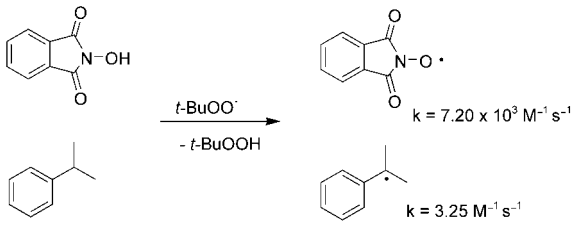


Figure 9. Rate constants for reaction of *t*-BuOO· with NHPI *vs.* cumene.

Based on the above-mentioned results we can conclude that the catalytic effect of NHPI on free radical autoxidations has two origins. It is a result of 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.

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 coproduct-free route to phenol from benzene (Figure 10),[38] 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 ten secondary C–H bonds, significantly less favorable than the situation with cumene where one tertiary C–H competes with six primary C–H bonds.

Based on the mechanistic arguments outlined in the preceding section, we reasoned that the use of catalytic amounts of NHPI, *in the presence of a free radical initiator rather than a metal compound,* (Figure 11) should afford alkyl hydroperoxides 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 byproduct formation *via* termination and/or more selective hydrogen abstraction by the PINO radical.

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.[39] The results are shown in Table 3.

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

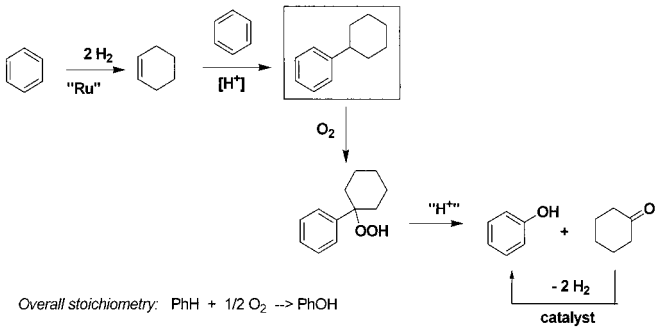


Figure 10. A coproduct-free route from benzene to phenol.

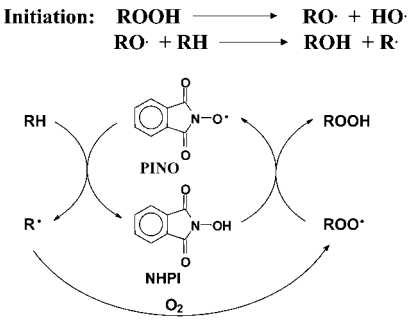


Figure 11. NHPI-catalyzed autoxidation.

Table 3. Oxidation of CHB at 100 °C.

NHPI [mol %]	Conv. CHB [%]	Selectivity [%]			
		1-ROOH	2-ROOH	4-ROOH	A
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

Conditions: no solvent, 2 mol % CHBHP, 1 bar O_2, 100 °C, 8 h.

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

The main byproducts 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 Figure 12.

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

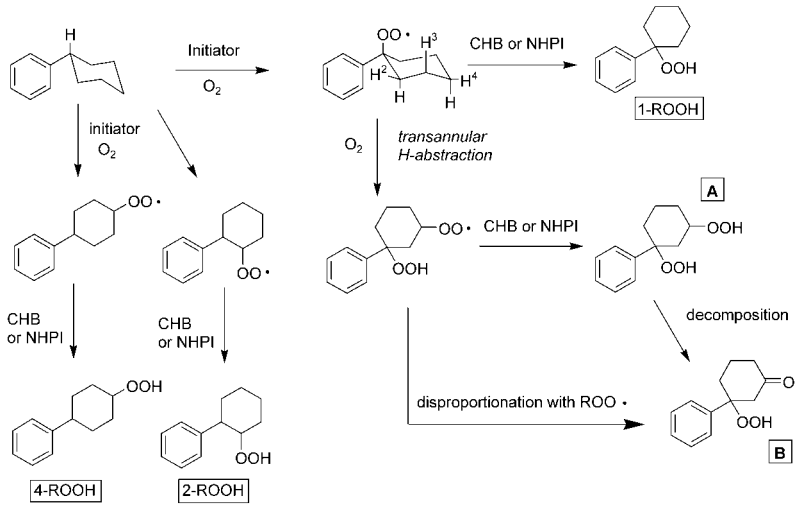


Figure 12. Product formation in the autoxidation of cyclohexylbenzene (CHB).

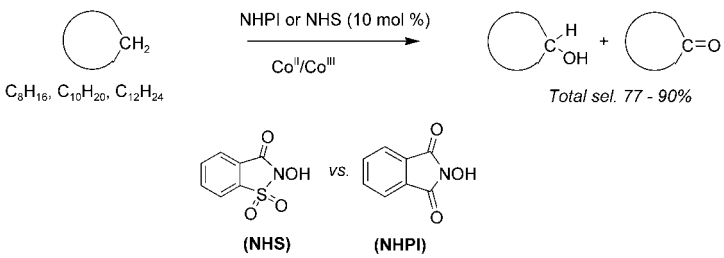
means that, even at concentrations as low as 0.1 mol %, alkylperoxy radicals will be effectively scavenged by NHPI. This results not only in an increase in rate but also in an increase in selectivity, by virtue of a decrease in the amounts of alcohol and ketone formed in the termination of two alkylperoxy 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.

Encouraged by the excellent results obtained in the autoxidation of CHB, we examined the autoxidation of cumene and ethylbenzene in the presence of 0.05–0.5 mol % NHPI and the corresponding hydroperoxide (CHP or EBHP) as the initiator. Cumene hydroperoxide (CHP) is the intermediate in the existing process for phenol manufacture and ethylbenzene hydroperoxide (EBHP) is an intermediate in the SMPO process for the co-manufacture of styrene and propylene oxide.[40] In both cases we observed increased selectivities to the corresponding hydroperoxide in the presence of NHPI.[41]

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.[30] The selective oxidation of large-ring cycloalkanes, e.g., cyclododedane 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.[42] 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[43] and the electrocatalytic oxidation of alcohols.[44] 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, Equation (6).



(6)

Table 4. Oxidation of cyclododecane in AcOH in the presence of $Co(acac)_2$.[a]

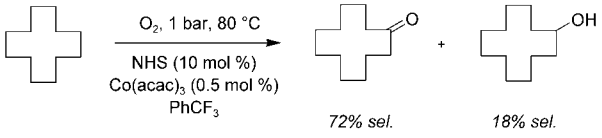
Run	Co-catalyst	T [°C]	Time [h]	Conv.[b] [%]	Ketone[b,c] [%]	Alcohol[b,c,d] [%]	Diacid[c,e] [%]
1	none	100	24	<4	0	0	0
2	NHS	100	6	64	31	8	16
3	NHPI	100	6	58	29	5	30
4	NHS	75	8	47	41	10	12
5	NHPI	75	8	36	42	8	23
6	NHS	50	24	42	47	14	20
7	NHPI	50	24	0	0	0	0

[a] Experimental conditions: 0.5 mol % $Co(acac)_2$, 10 mol % co-catalyst (0.3 mmol), 3 mmol cyclododecane, 1 atm O_2, 7.5 mL acetic acid.
[b] Conversions and selectivities are determined by GC using 1,2,4-trichlorobenzene as internal standard.
[c] Based on cyclododecane reacted.
[d] Alcohol + acetate ester.
[e] Determined by HPLC using octanoic acid as internal standard.

Hence, we studied the autoxidation of large-ring cycloalkanes in the presence of NHS or NHPI in combination with cobalt compounds.[45,46] Interestingly, the optimum cobalt co-catalyst was dependent on the solvent used. In acetic acid $Co(acac)_2$ was superior to $Co(acac)_3$ while in $PhCF_3$ the opposite reactivity was observed. Results obtained in the autoxidation of cyclododecane in acetic acid at different temperatures are shown in Table 4. As expected, NHS proved to be more reactive than NHPI which allowed for a lower reaction temperature with the former. At 50 °C NHPI completely failed to promote the oxidation while NHS gave 42% conversion in 24 h and a selectivity to ketone and alcohol of 47% and 14%, respectively.

The byproducts were 1,12-dodecanedioc acid and products derived from transannular hydrogen abstraction by the intermediate cyclododecylperoxy radical, analogous to that observed in the autoxidation of cyclohexylbenzene (see above).

Higher selectivities were observed when the reaction was conducted in $PhCF_3$ as solvent using $Co(acac)_3$ as the co-catalyst. The optimum result was obtained at 80 °C: 90% selectivity to a 4:1 mixture of ketone and alcohol at 24% conversion, Equation (7).



(7)

It is interesting to note that no oxidative cleavage to 1,12-dodecanedioc acid was observed in $PhCF_3$ as solvent. Since it is generally assumed that oxidative cleavage is a result of the further oxidation of the cycloalkanone product we decided to test this hypothesis. To this end we performed competition experiments in which a mixture of cyclododecane and cyclopentadecanone, in a molar ratio of 5:1 (corresponding to *ca.* 17% conversion in a cycloalkane oxidation) was subjected to aerobic oxidation. When the reaction was conducted with NHS/$Co(acac)_3$ in $PhCF_3$ at 100 °C (Figure 13) the conversion of cyclopentadecanone was 25% and 12%, respectively, when it was added at $t=0$ or $t=1$ h. In neither case was any formation of 1,15-pentadecanedioic acid observed. When the reaction was performed with NHS/$Co(acac)_2$ in acetic acid the cyclopentadecanone conversions were 43% and 24%, respectively. No dicarboxylic acid formation was observed in the latter case while in the former a small amount (<5%) was observed. These results are clearly not consistent with the consecutive oxidation of the ketone product being the primary source of ring-opened products in cycloalkane oxidations. The observed disappearance of the ketone in the competition experiments is probably a result of oxidation at other C–H bonds in the ring than those adjacent to the carbonyl group.

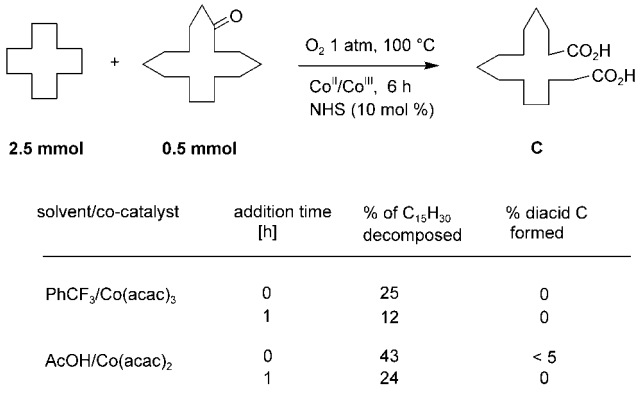


Figure 13. Competitive oxidation of cycloalkane/cycloalkanone.

We propose that ring-opened products are formed *via* β-cleavage of cycloalkoxy radicals, formed *via* metal-catalyzed decomposition of the intermediate cycloalkyl hydroperoxide (Figure 14).

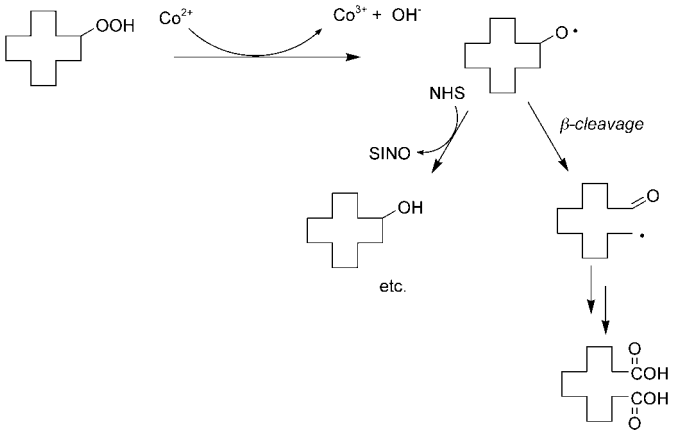


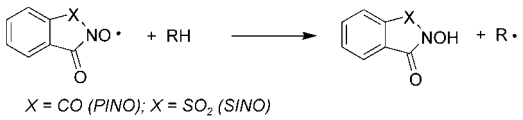
Figure 14. Mechanism of oxidative cleavage.

The formation of carbonyl compounds *via* β-cleavage of alkoxy radicals is a well-documented reaction,[47–49] which in the case of cyclic alkoxy radicals leads to ring opening. In the presence of NHS (or NHPI), efficient scavenging of alkoxy radicals, which is orders of magnitude faster than the corresponding reaction of alkylperoxy radicals (see above), suppresses β-cleavage in favor of alcohol formation. In contrast, the autoxidation of alcohols does not involve the intermediacy of alkoxy radicals as α-hydroxyalkyl radicals are preferentially formed *via* hydrogen abstraction from the more reactive α-C–H bond. This was confirmed in competition experiments with mixtures of cyclododecane and cyclopentadecanol, which afforded cyclopentadecanone in high selectivity.

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.[50] In contrast, rates of hydrogen abstraction, by alkoxy radicals from polar molecules such as ROOH and PhOH, decrease with increasing solvent polarity.[51] 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 and NHPI.

It was subsequently shown[46] that NHS/$Co(acac)_3$ catalyzes the selective autoxidation of primary and secondary alcohols to carboxylic acids and ketones, respectively, albeit with lower rates than those observed with NHPI/$Co(acac)_3$.[49] Similarly, NHPI showed a higher catalytic activity than NHS in the autoxidation of ethylbenzene.[46]

A possible explanation for the contrasting behavior of cycloalkanes on the one hand (higher rate with NHS) and alcohols and ethylbenzene on the other hand (higher rate with NHPI) is that the rate limiting step is different. The BDE of the C–H bonds in cycloalkanes (450 kJ/mol) is significantly higher than the α-C–H bond in alcohols and alkylbenzenes (360 kJ/mol). Hence, in the oxidation of cycloalkanes hydrogen abstraction by the nitroxyl radical [Equation (8)] will be rate limiting and will be faster with SINO than with PINO. In contrast, with the more reactive alcohol and alkylbenzene substrates, the reaction of Equation (8) is much faster and that of Equation (9) could become rate limiting. Based on the same BDE arguments this reaction is expected to be more favorable with NHPI than with NHS. More detailed kinetic studies are necessary to test this hypothesis.



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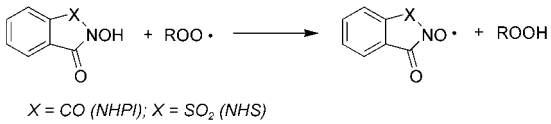


(9)

Another matter which is not completely clear is the mechanism of initiation by cobalt compounds. Depending on the solvent and temperature (see above) either cobalt(II) or cobalt(III) is the better initiator. When $Co(acac)_3$ is used the nitroxyl radical could be formed *via* one-electron oxidation of the acac ligand, leading eventually to the formation of alkylperoxy radical (see Figure 15) which abstracts hydrogen from NHS (or NHPI). Alternatively, substitution of an acac ligand by

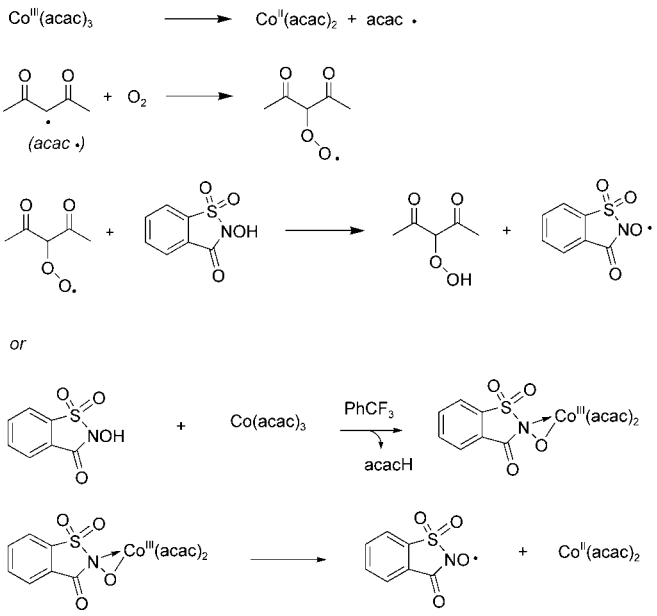


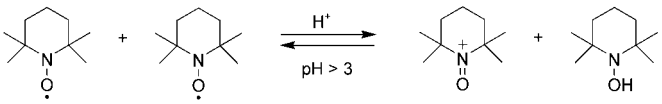
Figure 15. Mechanism of initiation.

NHS, followed by one-electron oxidation of the nitroxide anion ligand by cobalt(III), could also form the nitroxyl radical.

When $Co(acac)_2$ is the catalyst, Ishii proposed a mechanism involving the formation of a superoxocobalt(III) complex, by reaction with oxygen, followed by hydrogen abstraction from NHPI. As mentioned above this reaction is thermodynamically unfavorable with, e.g., cobalt(II) acetate. On the other hand, cobalt(II) complexes of electron-rich N,O ligands such as salen readily react with oxygen to form superoxocobalt(III) complexes.[52] Hence, we may speculate that one or both of the acac ligands in $Co(acac)_2$ are replaced by NHPI or NHS [nucleophilic substitution at cobalt(II) is much faster than at cobalt(III)], which binds in a bidentate fashion (see Figure 15). The resulting complex may well react with oxygen to afford a superoxocobalt(III) complex. Further work is necessary to confirm this hypothesis.

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 ($E^0 = 0.53$ V). Alternatively, at strongly acidic pH TEMPO disproportionates to the oxoammonium cation and TEMPOH, Equation (10).



(10)

Above pH 3 the reverse reaction occurs and TEMPOH undergoes one electron oxidation by the oxoammonium cation, to afford two molecules of TEMPO.

The stoichiometric oxidation of primary alcohols, to the corresponding aldehydes, by the oxoammonium cation was first reported by Golubev and coworkers in 1965.[6,53] The oxoammonium chloride was subsequently shown[54] to effect the stoichiometric oxidation of enolizable ketones to 1,2-dicarbonyl compounds and phenols to 1,2- or 1,4-quinones. The oxoammonium cation derived from 4-methoxy TEMPO was shown[55] to selectively oxidize a variety of both primary and secondary alcohols and diols. The oxoammonium cation could also be generated *in situ* by the acid-catalyzed disproportionation of TEMPO (see above)[56] or by electrochemical oxidation.[57]

The oxoammonium cation can also be generated *in situ* using single oxygen donors such as *m*-chloroperbenzoic acid,[58] sodium bromite,[54] sodium chlorite,[60] persulfate (oxone),[61] periodic acid (H_5IO_6),[62] and sodium

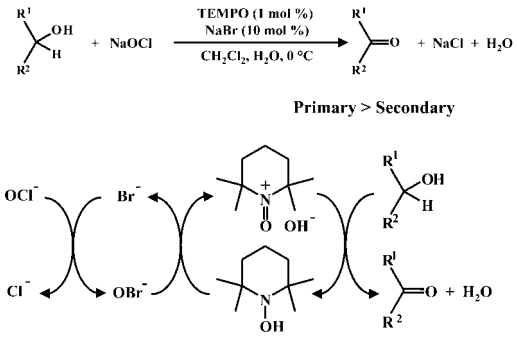


Figure 16. Mechanism of alcohol/oxidation with TEMPO/NaOCl.

hypochlorite.[63] In particular the TEMPO/hypochlorite (household bleach) protocol, using 1 mol % TEMPO in combination with 10 mol % sodium bromide as co-catalyst 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 Anelli and coworkers who used 4-methoxy-TEMPO as the catalyst.[63] Trichloroisocyanuric acid can also be used as a hypochlorite equivalent.[64] The commonly accepted mechanism for alcohol oxidations with hypochlorite/TEMPO is shown in Figure 16.[12,65]

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 above) to the oxoammonium cation which enters the catalytic cycle. The promoting effect of bromide is generally assumed to involve the formation of hypobromite (see Figure 16) which is more reactive towards TEMPO than hypochlorite.

The Anelli 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 co-catalyst 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,[66–68] and the mesoporous silica, MCM-41,[69] or by entrapping TEMPO in a silica sol-gel.[70]

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).[71] We surmised that oxidation of chimassorb 944 with hydrogen peroxide and a catalytic amount of $Na_2WO_4 \cdot 2\ H_2O$[4,6] would gen-

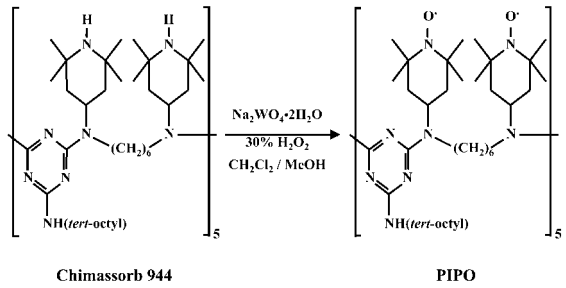


Figure 17. Synthesis of PIPO.

Table 5. 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	butylproxitol	90	89	>99

[a] Experimental conditions: 0.8 mmol substrate, 2.5 mg PIPO (1 mol % nitroxyl), 2.86 mL 0.35 M hypochlorite solution (1.25 equivs.), 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.

erate a recyclable oligomeric TEMPO (Figure 17). 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.[72–74]

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 5). Furthermore, PIPO exhibited a higher activity (per nitroxyl group) than TEMPO, which made the need for a bromide co-catalyst 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 equivs. of 0.35 M NaOCl (pH 9.1) in a bromide- and chlorinated hydrocarbon solvent-free medium (Table 5).

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 5). In competition experiments, a marked preference for primary compared to

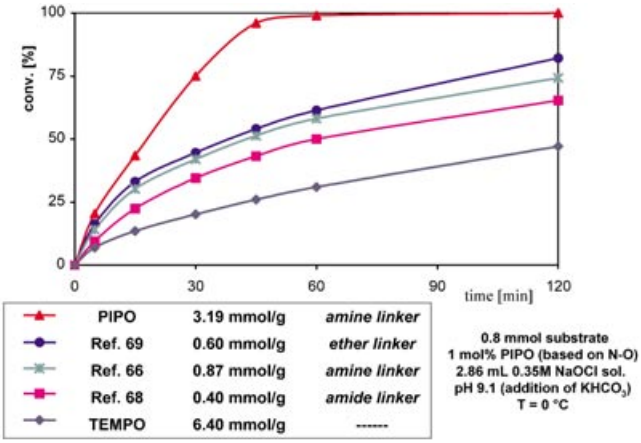
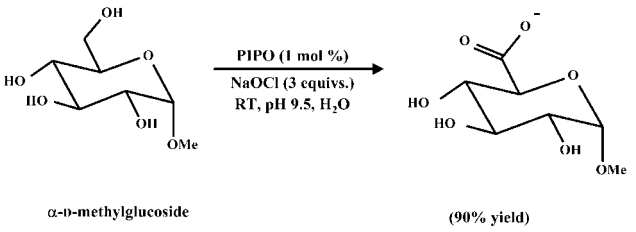


Figure 18. Bleach oxidation of octan-2-ol using 1 mol % of nitroxyl catalyst.

secondary alcohols was observed (see Table 5) analogous to results obtained with TEMPO[63] and other heterogenized TEMPO systems.[66] A stereogenic center 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.[74]

PIPO was compared with the silica- and MCM-41-supported TEMPO catalysts in the bleach oxidation of octan-2-ol, under the chlorinated solvent- and bromide-free conditions.[73] As shown in Figure 18, PIPO is the most active catalyst. Surprisingly, all of the immobilized catalysts exhibited a higher activity than homogeneous TEMPO. This suggests that there is a non-productive process that is second-order in TEMPO in competition with the oxidation of the alcohol. This would be suppressed in the immobilized catalysts.

Carbohydrates are also efficiently oxidized by the PIPO/NaOCl system, analogous to reaction with TEMPO/NaOCl.[12,65,75,76] For example, methyl α-D-glucopyranoside afforded methyl α-D-glucopyranosiduronate [Equation (11)] in 90% yield.[77]



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7 Ruthenium/TEMPO-Catalyzed Aerobic Oxidation of Alcohols

Notwithstanding the substantial improvement of the PIPO/NaOCl system, from both an economic and an

Table 6. Ruthenium-TEMPO-catalyzed aerobic oxidation of alcohols.[a]

Entry	Substrate	S/C ratio[b]	Solvent	Time [h]	Conv. [%][c]	TON[d]
1	octan-2-ol	100	chlorobenzene	7	98	98
2		100	toluene	7	95	95
3		1225	–[e]	1	8.5	104
				5	17	208
4[f]	octan-1-ol	50	chlorobenzene	7	85	43
5[f]	oleyl alcohol[g]	50	chlorobenzene	7	80	40
6[f]		50	toluene	7	75	38
7[f]		380	-[e]	1	8.1	31
				5	14	53
8	benzyl alcohol	200	chlorobenzene	2.5	>99	200
9	1-phenylethanol	100	chlorobenzene	4	>99	100
10	cyclooctanol	100	chlorobenzene	7	92	92
11[f]	geraniol	67	chlorobenzene	7	91	61
12[f]	octan-1-ol/octan-2-ol	50	chlorobenzene	7	80/10	40/5
13	benzyl alcohol/1-phenylethanol	200	chlorobenzene	3	90/5	180/10

[a] Experimental conditions: 15 mmol substrate, $RuCl_2(PPh_3)_3$/TEMPO ratio of 1/3, 30 mL solvent, 10 mL min^{-1} O_2/N_2 (8/92; v/v), 10 bar, 100 °C.
[b] S/C ratio = substrate to catalyst ratio in mmol per mmol.
[c] Selectivities > 99% in all cases.
[d] TON = turn-over number in mmol product per mmol Ru-catalyst.
[e] "Solvent-free": 30 mL substrate.
[f] O_2 atmosphere.
[g] Octadec-9-en-1-ol.

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 the combination CuCl/TEMPO as a catalyst for the aerobic oxidation of benzylic alcohols was already reported by Semmelhack in 1984.[78] A serious shortcoming of this method, however, 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 co-catalyst.[77] We found that a combination of $RuCl_2(PPh_3)_3$ (1 mol %) and TEMPO (3 mol %) was particularly effective.[79,80] 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. We also tested other nitroxyl radicals and N-OH compounds in combination with $RuCl_2(PPh_3)_2$. Little activity was observed with NHPI but TEMINO (see Figure 1 for structure) exhibited a comparable activity to TEMPO,[77] confirming the requirement for a stable dialkylnitroxyl radical. The $RuCl_2(PPh_3)_3$/TEMPO system was effective for the aerobic oxidation of a broad range of alcohols (Table 6).

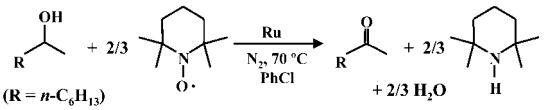
The general procedure involved the use of 0.5–2 mol% $RuCl_2(PPh_3)_3$ and 1.5–6 mol % TEMPO in chlorobenzene at 100 °C, either under an atmosphere of pure oxygen or using a flow of an O_2/N_2 (8:92 v/v) mixture at 10 mL/min at 10 bar in an autoclave.[79,80] The latter procedure is preferred for safety 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.[80,81]

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.[30] However, control experiments revealed that the autoxidation of aldehydes is completely suppressed by catalytic amounts of TEMPO, consistent with its well-known (see above) 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[82] was observed. As with the TEMPO/NaOCl system, the Ru/TEMPO catalyst displayed a marked preference for primary *versus* secondary alcohols.[80,81] Unfortunately, a number of alcohols containing additional heteroatoms, were unreactive which was attribut-

ed to deactivation of the catalyst by coordination of the heteroatom to ruthenium.[80,81]

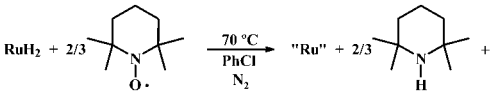
8 Mechanistic Aspects of the Ru/TEMPO System

In mechanistic studies of the Ru/TEMPO system,[80,81] $RuCl_2(PPh_3)_3$ was shown to catalyze the stoichiometric oxidation of octan-2-ol and benzyl alcohol in an inert atmosphere (N_2) according to the stoichiometry shown in Equation (12).



(12)

These results were rationalized by assuming that 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.[83] 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.[80] Further support was obtained by monitoring the stoichiometric reaction of $RuH_2(PPh_3)_3$ with an excess of TEMPO, in chlorobenzene under an inert atmosphere at 25 °C, by measuring the intensity of the Ru–H vibration using *in situ* IR.[80] The ruthenium dihydride disappeared with concomitant formation of the corresponding amine, TEMPH, according to the stoichiometry shown in Equation (13). The TEMPH is formed *via* disproportionation of the initially formed TEMPOH.[80] Thus, all attempts to prepare TEMPOH under an inert atmosphere resulted in the formation of TEMPH.[83]



(13)

Based on the results of the stoichiometric reactions and Hammett correlations and kinetic isotope studies[80] the catalytic cycle shown in Figure 19 was proposed[80] to explain the $RuCl_2(PPh_3)_3$/TEMPO-catalyzed aerobic oxidation of alcohols.

9 Copper/TEMPO-Catalyzed Aerobic Oxidation of Alcohols

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 was described by Brackman and Gaasbeek in 1966.[84] 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 according to Equation (14). Regeneration of the nitroxyl radical occurs by reaction of the hydroxylamine with a second equivalent of the copper(II) phenanthroline complex as shown in Equation (15). They further proposed that copper(II) was regenerated by reaction of copper(I) with oxygen, to complete the catalytic cycle.

$$CH_3OH + LCu^{II} + R_2NO\cdot \xrightarrow{\text{slow}} H_2CO + LCu^{I} + R_2NOH + H^+ \quad (14)$$

$$R_2NOH + LCu^{II} \longrightarrow R_2NO\cdot + LCu^{I} + H^+ \quad (15)$$

Two decades later Semmelhack and coworkers reported the use of TEMPO in combination with cuprous chloride as a catalyst for the aerobic oxidation of benzylic and allylic alcohols.[75,85] They proposed a different role for the TEMPO in the catalytic cycle, namely that copper(II) oxidizes TEMPO to the oxoammonium cation (see Figure 20) 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.

Based on our results (see above) with the Ru/TEMPO system we suspected that the Cu/TEMPO system may involve a copper-centered oxidative dehydrogenation of the alcohol rather than an oxoammonium cation as the oxidant. This prompted us to reinvestigate the Sem-

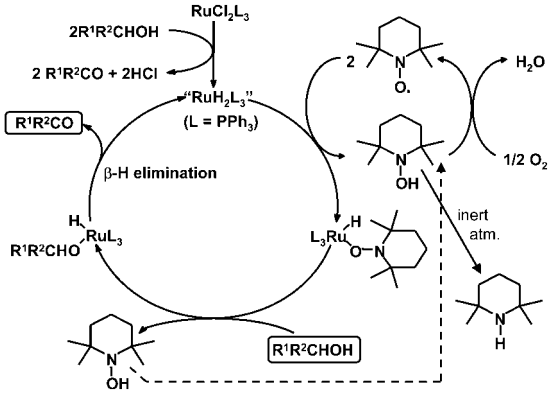


Figure 19. Catalytic cycle for the Ru/TEMPO-catalyzed aerobic oxidation of alcohols.

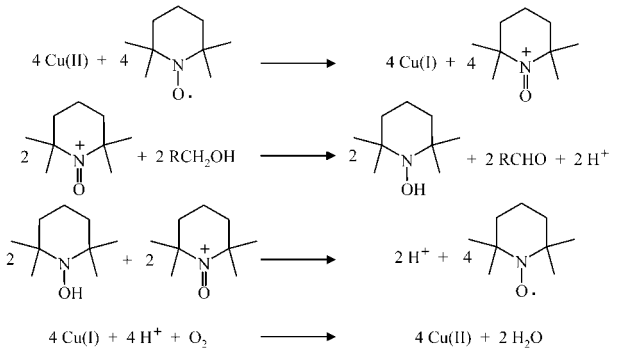


Figure 20. Semmelhack mechanism for CuCl/TEMPO-catalyzed oxidation of alcohols.

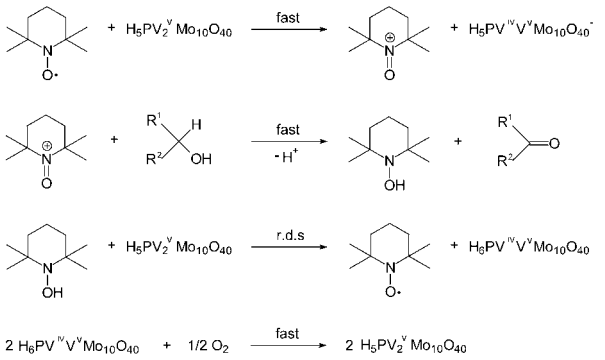


Figure 22. $H_5PV_2Mo_{10}O_{40}$/TEMPO-catalyzed aerobic oxidation of alcohols.

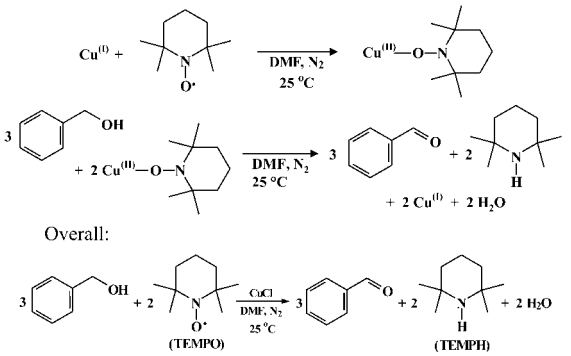


Figure 21. CuCl-catalyzed oxidation of an alcohol by TEMPO.

melhack system by subjecting it to the same mechanistic studies as with the Ru/TEMPO system.[86]

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.[11,54]

Subsequent stoichiometric experiments in an inert atmosphere demonstrated that copper(I) is oxidized by TEMPO (see Figure 21) to produce piperidinyloxycopper(II), analogous to one-electron oxidations of other metal ions by TEMPO.[87–89] 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 Figure 21.[86]

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 Figure 21.[86] In the presence of oxygen TEMPOH is rapidly oxidized to TEMPO,[79,80] rendering the reaction catalytic in TEMPO.

The observed facile conversion of TEMPOH to TEMPO in air contrasts with the results of Neumann and coworkers[90] who studied the oxidation of alcohols catalyzed by TEMPO in combination with a heteropoly acid, $H_5PV_2Mo_{10}O_{40}$. They postulated that the oxidation of TEMPOH to TEMPO is the slower, rate-determining step. A similar proposal was made to explain the aerobic oxidation of alcohols catalyzed by TEMPO in combination with a mixture of Mn(II) and Co(II) or Mn(II) and Cu(II) nitrates in acetic acid.[91] These apparently contradictory results can be rationalized on the basis of the pH dependence of the rate of aerobic oxidation of TEMPOH. When the latter was generated in water, by ascorbic acid reduction of TEMPO, the orange color of TEMPO reappeared instantaneously on exposing the solution to oxygen, under neutral or basic conditions. In contrast, at acidic pH the solution remained colorless for more than an hour in the presence of oxygen. Presumably, at acidic pH the nitrogen atom of TEMPOH is protonated, rendering it less susceptible to oxidation. In this case regeneration of TEMPO, by metal mediated oxidation of TEMPOH, may be rate-limiting as proposed by Neumann and coworkers.[90] The total reaction scheme is shown in Figure 22.

The oxoammonium cation is generated by one-electron oxidation of TEMPO by $H_5PV_2^{V}Mo_{10}O_{40}$. Oxidation of the alcohol by the oxoammonium cation affords TEMPOH followed by rate-limiting oxidation of the latter by a second equivalent of the heteropoly acid. The reduced form, $H_5PV^{iv}V^{v}Mo_{10}O_{40}$ is rapidly reoxidized by oxygen. Minisci and coworkers[91] proposed an alternative mechanism for alcohol oxidation with TEMPO in combination with Mn(II)-Co(II) or Mn(II)-Cu(II) in acetic acid. Formation of the oxoammonium cation was proposed to occur *via* the known disproportionation

Table 7. Kinetic isotope effects and Hammett ρ values for the oxidation of benzyl alcohols.

System	Kinetic isotope effect (k_H/k_D)[b]	Hammett ρ value	Reference
$CuCl/TEMPO/O_2$	5.42	−0.16	[86]
oxoammonium chloride	1.7–2.3	−0.3	[57c]
$RuCl_2(PPh_3)_3/TEMPO/O_2$	5.12	−0.58	[80]
$CuCl/TEMPO/N_2$[a]	5.77	–	[86]
[Cu(II)BSP]/O_2	5.3	−0.14	[98d]
Galactose oxidase	5.02	−0.09	[92d]

[a] TEMPO is used as stoichiometric oxidant under an inert nitrogen atmosphere.
[b] In all cases α-deutero-*p*-methylbenzyl alcohol was used for the determination of KIE.

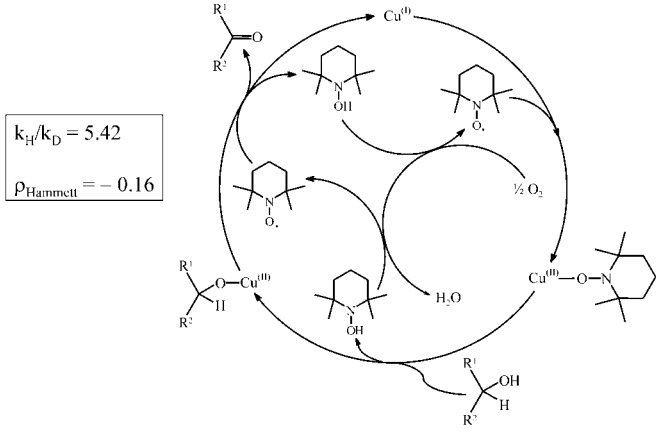


Figure 23. Postulated mechanism for the CuCl/TEMPO-catalyzed aerobic oxidation of alcohols.

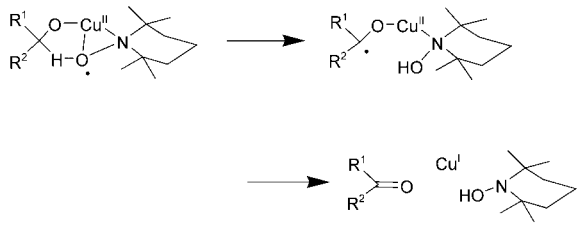


Figure 24. Intramolecular hydrogen transfer followed by oxidative elimination.

of TEMPO to oxoammonium + TEMPOH (see above). Reaction of the latter with the metal ion in the presence of oxygen was assumed to lead to regeneration of TEMPO.

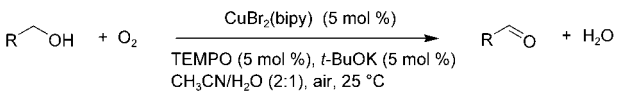
Additional evidence for the copper-centered dehydrogen mechanism for the Semmelhack system was obtained from kinetic isotope effects and Hammett correlation studies.[86] The primary kinetic isotope effect (k_H/k_D) for the Cu/TEMPO catalyzed aerobic oxidation of α-deutero-*p*-methylbenzyl alcohol at 25 °C was determined to be 5.42. This value compares well with isotope effects (see Table 7) observed with other metal-centered dehydrogenations of alcohols, including galactose oxidase[92,93] and a galactose oxidase mimic reported by Stack and coworkers.[94] 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.[85] 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 (see Table 7).

The catalytic cycle shown in Figure 23 was proposed to account for the above described results in the Cu/TEMPO-catalyzed aerobic oxidation of alcohols.[86]

The key oxidation step involves intramolecular hydrogen abstraction within an alkoxycopper(II)/TEMPO complex (Figure 24), in which the TEMPO is coordinated in a η^2 fashion, analogous to that in previously reported copper(II)-TEMPO complexes.[95] 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 bears a close resemblance to the rate-determining step in the oxidations of primary alcohols catalyzed by galactose oxidase,[96] and mimics thereof,[94,97–99] in which a ring-substituted cysteinyl tyrosinyl radical is coordinated to an alkoxycopper(II) complex in the active site (Figures 25 and 26).

More recently, a mixture of $CuBr_2$(2,2′-bipyridine) and TEMPO, in the presence of a base, was shown to catalyze the aerobic oxidation of primary alcohols to aldehydes at room temperature [Equation (16)].[100] All three components were necessary for efficient oxidation.



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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-meth-

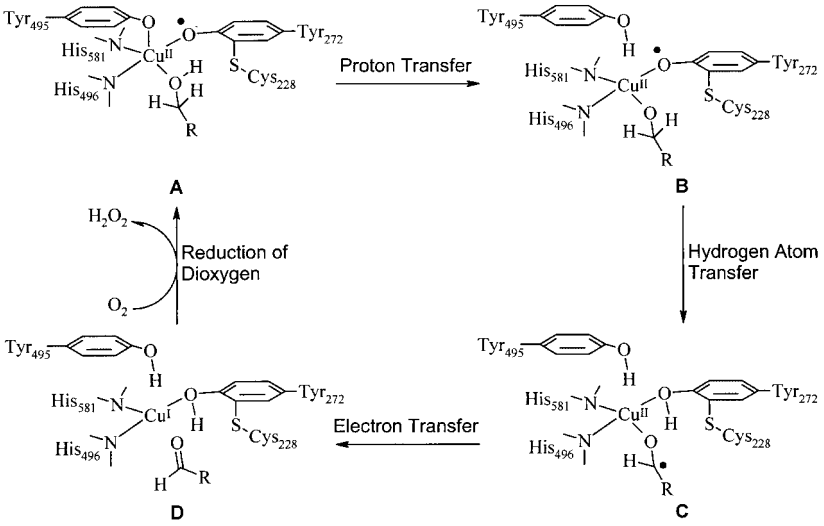


Figure 25. Mechanism of galactose oxidase.

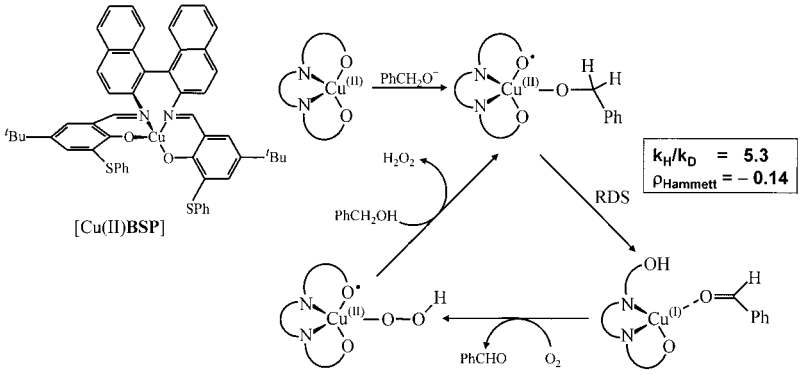


Figure 26. Stack model, mimicking galactose oxidase.[98d]

ylbenzyl alcohol.[100] 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 Figure 27. 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 Figure 27).

We have also shown that PIPO (see above) in combination with CuCl in dimethylformamide catalyzes the aerobic oxidation of benzylic alcohols with an activity comparable to that of TEMPO.[73,74] Similarly, Minisci and coworkers[101] have recently described the use of the oxidized form of another hindered amine precursor, chimassorb 966, analogous to PIPO, as a co-catalyst (see Figure 28) for the aerobic oxidation of a range of alcohols. Good results were obtained in combination with Mn(II) and Co(II) or Cu(II) nitrates (see above) in acetic acid solution, in the presence of a strong acid such as *p*-toluenesulfonic acid, at room temperature and atmospheric pressure.

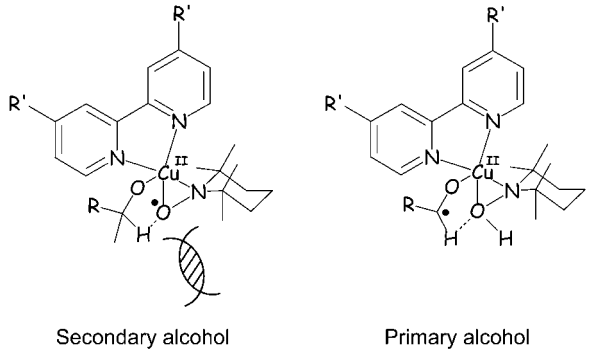


Figure 27. Possible explanations for the lack of reactivity of secondary alcohols.

The presence of the strong acid was necessary to prevent oxidative degradation of the tetranitroxyl radical by protonating the reactive amino groups. In addition, it was suggested that the higher acidity favors disproportionation of the nitroxyl radical to the oxoammonium

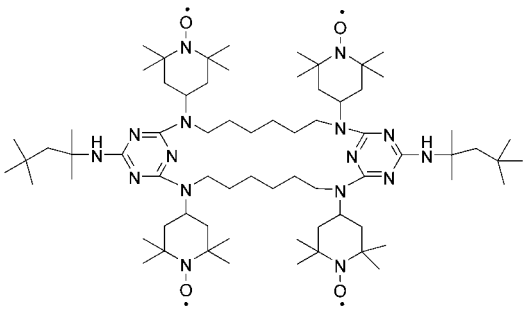
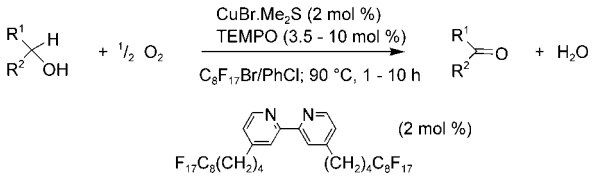


Figure 28. Structure of the tetranitroxyl radical from chimassorb 966.

cation and the corresponding hydroxylamine (see above) and increases the electrophilic character (oxidizing power) of the oxoammonium cation.

Interestingly, the tetranitroxyl radical in combination with a mixture of Mn(II) and Co(II) nitrate was also able to catalyze the oxidation of alcohols with 30% aqueous H_2O_2 in acetic acid.[101]

Other noteworthy developments are the CuCl/TEMPO-catalyzed aerobic oxidation of alcohols[102] 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 [Equation (17)].[103] Interestingly, the latter system was also capable of oxidizing simple aliphatic alcohols.



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10 Aerobic Oxidations Catalyzed by Laccase in Combination with Nitroxyl Radicals

Another copper-dependent oxidase that has attracted much attention recently is laccase (EC 1.10.3.2).[104–106] Laccases are a group of isoenzymes, so-called multicopper oxidases,[107] that contain four copper centers 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.[104] They are extracellular enzymes that are secreted by white rot fungi[105] and play an important role in the delignification of lignocellulose, the major constituent of wood, by these microorganisms.[108] 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 center 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.[109]

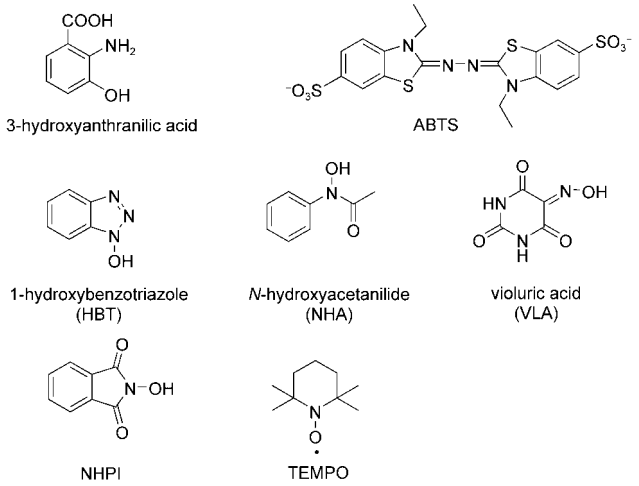

Figure 29. Structures of laccase mediators.

The 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. A variety of mediators that have been used in conjunction with laccase are shown in Figure 29.

2,2-Azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) was the first compound shown to mediate laccase-catalyzed oxidation of a non-phenolic compound: the oxidation of veratryl alcohol to the corresponding aldehyde.[108] Subsequently, 1-hydroxybenzotriazole (HBT)[110] and other *N*-hydroxy compounds such as *N*-hydroxyacetanilide (NHA), violuric acid (VLA) and NHPI were shown to act as mediators.[111] 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 and coworkers reported that the laccase/ABTS combination catalyzed the aerobic oxidation of a series of benzylic alcohols to the corresponding benzaldehydes.[112] Subsequently, Galli and coworkers reported that the combination laccase/TEMPO catalyzes the aerobic oxidation of primary benzylic alcohols.[113] The selective oxidation of the primary alcohol moiety in carbohydrates had been previously reported in two patents.[114,115] In a subsequent comparison of the various mediators, in the laccase/mediator-catalyzed aerobic ox-

Table 8. Laccase/mediator catalyzed oxidation of benzyl alcohol[116]

Mediator	Aldehyde yield [%]
ABTS	2
HBT	30
VLA	42
NHPI	54
TEMPO	92

idation of benzylic alcohols, TEMPO proved to be the most effective (Table 8).[116]

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.

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 (Figure 30), 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.[117]

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 hydroxy group (see Figure 31).[118]

It is generally accepted 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.[119]

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.[30] 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.[120] Consequently, the T1 copper(II) in fungal laccases can easily oxidize TEMPO to the corresponding oxoammonium cation which has a redox potential of 0.56 V.

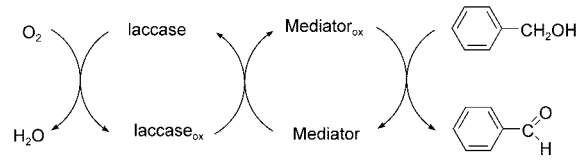

Figure 30. Mechanism of alcohol oxidation in laccase/mediator systems.

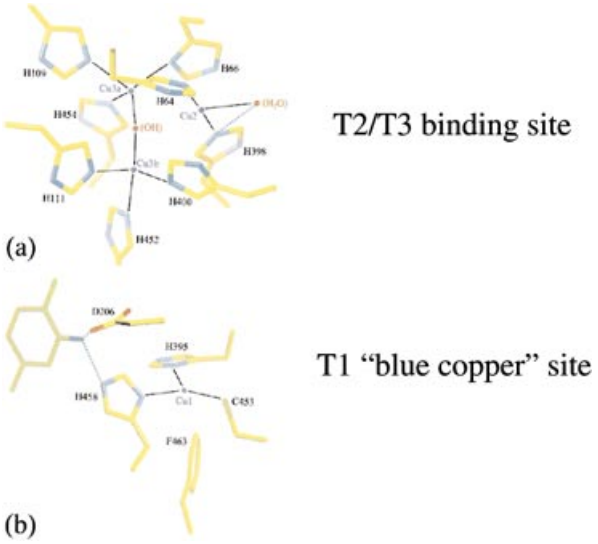

Figure 31. Structure of laccase from *Trametes versicolor*.[118]

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.[121] We found a k_H/k_D of 2.05 which is consistent with an oxoammonium intermediate rather than a copper-centered dehydrogenation mechanism (see Table 7).

The different mechanisms of the laccase/TEMPO and CuCl/TEMPO (see above) 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[116] 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 as illustrated in Figure 32 for HBT. This is followed by hydrogen abstraction from the alcohol substrate by the nitroxyl radical.[116]

Xu and coworkers[122] 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

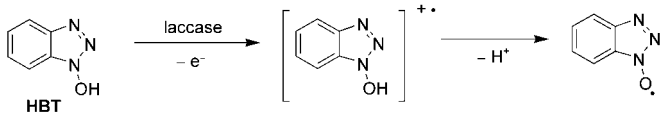

Figure 32. H atom transfer (HAT) mechanism for laccase/HBT oxidation of an alcohol.

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 above) 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.[122] 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*-hydroxy imide. 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.

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, their precursors, *N*-hydroxy compounds, play important roles in a variety of biological processes, which may involve redox reactions of transient nitroxyl radicals.[122]

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 co-catalyst. Oxidations have been achieved using oxygen or single oxygen donors including hydrogen peroxide as the primary oxidant. 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.

In short, research on nitroxyl radicals as oxidation catalysts, as it enters its fifth decade, is flourishing. The best is yet to come.

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