Part I
Innovative Processes in Organic Chemistry

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1
N-Hydroxy Derivatives: Key Organocatalysts for the Selective Free Radical Aerobic Oxidation of Organic Compounds

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1.1
Introduction

Oxidative processes of organic compounds represent some of the most important chemical transformations involved in many fundamental areas, including general synthesis, industrial processes, materials, energy, biology, and so on. In particular, eco-friendly standards require oxidants to be able to combine a low environmental impact with an economical convenience. Molecular oxygen and hydrogen peroxide are the ideal oxidants from this point of view [1]. Nevertheless, their use strictly depends upon the employment of catalytic systems, which allow operating with high selectivity under mild and environmentally benign conditions [2–4]. Thus we can say that, in this case also, catalysis represents the key to waste minimization.

N-hydroxy derivatives (NHDs) proved to be of particular importance for this purpose, allowing development of innovative synthetic processes of great relevance, as it has been demonstrated by the several patents involving the use of the two most commonly employed NHD catalysts: 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and *N*-hydroxyphthalimide (NHPI) [5].

This chapter will focus on the key role played by NHDs as catalysts in the aerobic oxidation of organic compounds. After a brief overview of the thermochemical and kinetic aspects, that we have contributed to determine and are responsible for the differences in reactivity among the various families of *N*-hydroxy derivatives, we will discuss our recent results in the field by employing, in turn, *N*-hydroxy amines, amides, and imides with the aim to develop selective oxidative processes characterized by high conversions and selectivity.

1.2
General Reactivity of *N*-Hydroxy Derivatives

In spite of their similar structure, TEMPO (**1**) and phthalimide-*N*-oxyl (PINO) radicals (**2**), generated *in situ* from NHPI, show a completely different behavior. In fact, being a persistent radical, TEMPO inhibits radical processes, whereas PINO,

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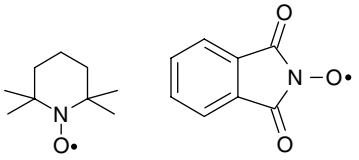
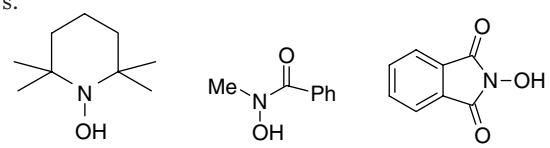
with its nonpersistent character (it decays by first order kinetics with a $k = 0.12\ s^{-1}$) [6], is able to promote free radical chains.



1 (TEMPO) **2** (PINO)

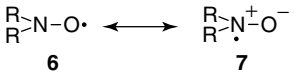
The consequence of thermochemical studies conducted on a wide range of NHDs (including TEMPO-H (**3**), *N*-methylbenzo-hydroxamic acid (NMBHA, **4**), and NHPI (**5**)), shows that this opposite behavior has to be ascribed to enthalpic factors.



3 **4** **5**

By means of EPR radical equilibration technique [7], in collaboration with Lucarini and coworkers, it was possible to measure the bond dissociation enthalpy (BDE) of the O–H bonds in hydroxylamine derivatives [8]. The most significant results, reported in Table 1.1, clearly indicated that the carbonyl groups directly bonded to the nitrogen atom strongly increase BDE values.

This effect can be ascribed to the energy difference between the oxygen-centered radicals and the corresponding hydroxyl derivatives. More specifically, the carbonyl group, owing to its electron-withdrawing character, reduces the importance of the mesomeric structure **7** in the resonance equilibrium of the nitroxyl radical Eq. (1.1). As a consequence, the radical is less stabilized and the corresponding O–H BDE increases.



6 **7** (1.1)

On the basis of these results, it is apparent that the general reaction of hydrogen abstraction from a C–H bond by an oxygen-centered nitroxyl radical cannot occur with TEMPO, the process being largely endothermic with any kind of organic substrate.

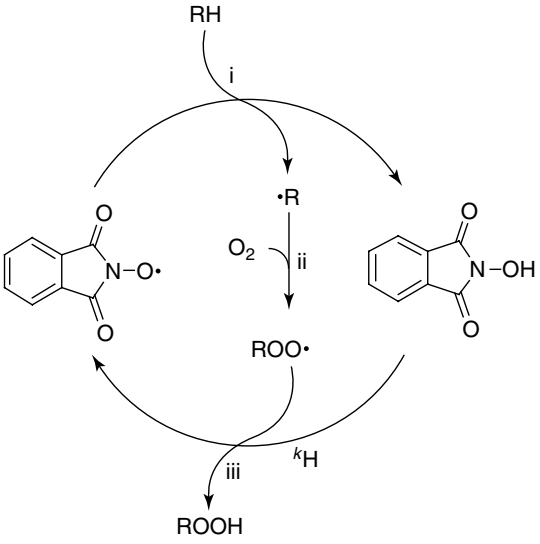
Table 1.1 BDE Values of the O–H bonds in the hydroxylamines **3**, **4**, and **5**.

Hydroxylamine	BDE (kcal mol^{-1})
3	69.6
4	79.2
5	88.1

Nevertheless, TEMPO has been widely employed as a catalyst for the oxidation of alcohols with a variety of oxidants [9], including aerobic oxidation when used in combination with transition metal salt complexes [10–12]. In these cases, TEMPO plays two key functions: it promotes the oxidation of the alcohols, following an ionic mechanism, but, being a persistent radical, it also inhibits the subsequent free radical oxidation of aldehydes and ketones.

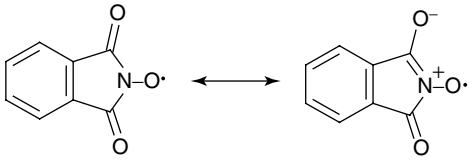
On the contrary, due to the relatively high BDE value of the O–H bond in NHPI, the PINO radical is able to catalyze the aerobic oxidation of a wide range of organic substrates through the formation of a carbon-centered radical by hydrogen abstraction from a C–H bond, according to the general radical chain reported in Scheme 1.1.[13].

Many concomitant aspects make NHPI an intriguing catalyst for selective oxidations. As we have seen, from a thermochemical point of view, the hydrogen transfer reaction from a C–H bond to PINO may be in many cases exothermic or only slightly endothermic. Nevertheless, other factors need to be taken into consideration in order to justify the catalytic role of NHPI. Kinetic experiments, carried out by Lucarini and coworkers using EPR technique [8], have clearly demonstrated that the hydrogen abstraction from a C–H bond (path i) by PINO radical is always faster than by a generic peroxyl radical (*t*-BuOO$^{\bullet}$). These results explain why PINO is able to selectively catalyze a classical autoxidation, leading to the formation of a carbon-centered radical which, in turn, reacts fast with oxygen, forming the corresponding peroxyl radical (path ii). The observed behavior cannot be ascribed to enthalpic reasons (the O–H BDEs in NHPI and in *tert*-butyl hydroperoxide are almost identical, $\sim$ 88 kcal mol^{-1}) but, instead, to a polar effect



Scheme 1.1

due to a more pronounced electrophilic character of PINO with respect to the peroxyl radical. Such a behavior is common to nitroxyl radicals, but in this case it is considerably enhanced by the presence of the two carbonyl groups in α to the nitrogen atom Eq. (1.2).



(1.2)

Moreover, the same research group determined the rate constant for the hydrogen atom abstraction from NHPI by peroxyl radicals (path iii). The unexpected moderately high value obtained ($k_H = 7.2 \times 10^3$ M^{-1} s^{-1}) [8] allows the complete insight of the catalytic effect of the PINO radical in the aerobic oxidation of organic substrates.

Ishii *et al.* [14] have reported many examples of oxidations catalyzed by NHPI, based on the *in situ* generation of PINO radical through different methodologies, including the employment of radical initiators [15], transition metal salts (mainly Co(II) and Mn(II)) [13], cerium ammonium nitrate (CAN) [16], acetaldehyde [17], bromine [18], enzymes [19], NO_2 [20], and so on.

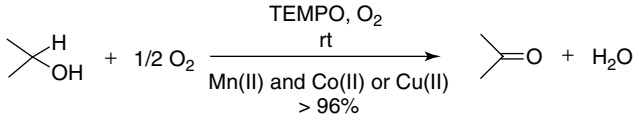
However, the high potentiality of NHPI, in terms of conversions and selectivity, was evidenced solely upon the mechanistic investigation of the catalytic cycle. In this deep rationalization relies the secret of our success in developing several selective oxidative processes under aerobic conditions, at room temperature and atmospheric pressure.

Finally, *N*-hydroxy amides, having a halfway O–H BDE value between TEMPO and NHPI, result to be ideal catalysts for free radical aerobic oxidations of organic derivatives bearing weak C–H bonds, whereas NHPI would undergo high exothermic hydrogen atom transfer reactions, negatively affecting the selectivity of the process [21].

1.3 Aerobic Oxidation Catalyzed by *N*-Hydroxy Amines

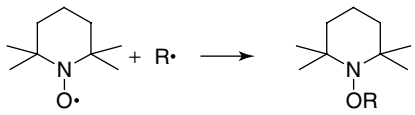
1.3.1 Aerobic Oxidation of Alcohols to Aldehydes and Ketones

TEMPO, when used in combination with Mn(II)–Co(II) or Mn(II)–Cu(II) nitrates, is an ideal catalyst for the selective aerobic oxidation of aliphatic and aromatic alcohols to the corresponding aldehydes or ketones Eq. (1.3), under very mild conditions [22, 23].



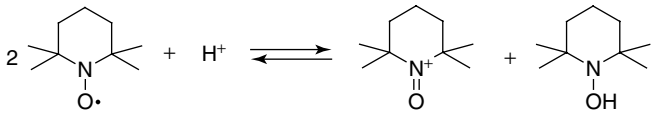
(1.3)

Under the same conditions, in the absence of TEMPO, aldehydes and ketones are readily oxidized to carboxylic acids via free radical chains [24], while the corresponding alcohols are quite inert [25]. This clearly demonstrates that the reaction catalyzed by TEMPO follows a nonradical mechanism, while TEMPO itself, thanks to its persistent character, rapidly traps the forming radicals Eq. (1.4), inhibiting further oxidation of aldehydes and ketones.



(1.4)

Thus, oxidation of alcohols occurs by means of an oxammonium cation Eq. (1.6), formed *in situ* by disproportionation of TEMPO in acidic medium Eq. (1.5), while the metal salts catalyze the reoxidation of the *N*-hydroxypiperidine (**3**) to TEMPO Eq. (1.7), so that molecular oxygen results to be the unique consumed oxidant.



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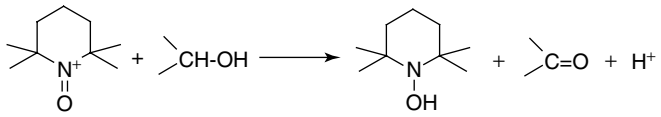
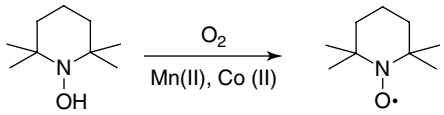


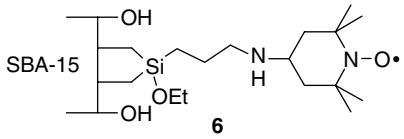
(1.6)



(1.7)

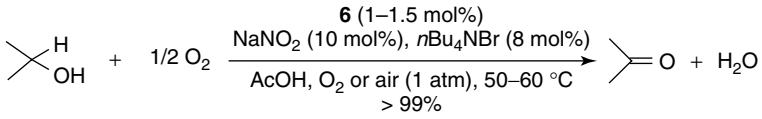
In spite of the efficiency of this catalytic system in terms of conversion and selectivity, the use of TEMPO has a significant limitation: it is rather expensive, so that recycling of the catalyst is necessary but, at the same time, its recovery from the reaction medium is difficult. Many efforts were devoted to the design of easy-recycling catalysts by anchoring TEMPO to solid supports [26]. However, till now, many drawbacks have been encountered by using TEMPO in heterogeneous systems. In most of these cases [27], NaOCl had to be used as oxidizing agent instead of oxygen, the latter leading to poor conversion in the desired products. Furthermore, in several circumstances, partial degradation of the supported TEMPO catalysts was observed.

Recently, a TEMPO-type catalyst supported on SBA-15 (**6**) (an ordered mesoporous material) was reported by Karimi *et al.* [28].



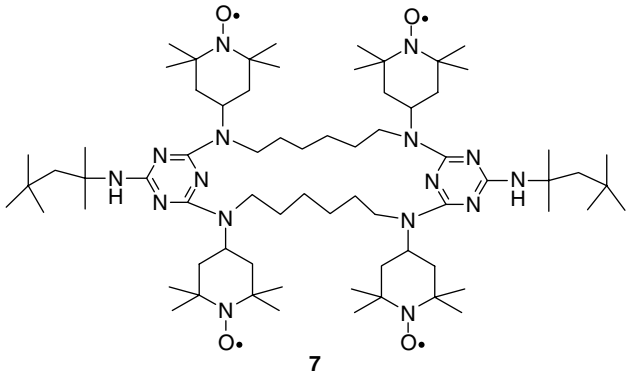
6

When **6** is employed in combination with catalytic amounts of $NaNO_2$ and *n*-Bu_4NBr under an atmosphere of oxygen or air, alcohols are completely and selectively converted to the corresponding aldehydes and ketones Eq. (1.8).



(1.8)

However, in many cases, homogenous catalysis remains the best solution for the development of selective oxidative processes, due to the usually higher versatility of the catalytic systems in terms of applicability (wider range of substrates) and operative conditions (room temperature). Thus, in order to eliminate the disadvantages in using TEMPO catalysis, we developed, in collaboration with CIBA Speciality Chemicals, a new TEMPO-analogous catalyst [23, 29], characterized by a macrocyclic polypiperidine-*N*-oxyl radical structure (**7**).



7

This derivative, which is even more active than TEMPO for the aerobic oxidation of alcohols to the corresponding aldehydes and ketones, has amino groups that confer to **7**, the great advantage of being easily recovered and recycled in the form of its ammonium salt, considering that the catalysis is effective only in acidic medium.

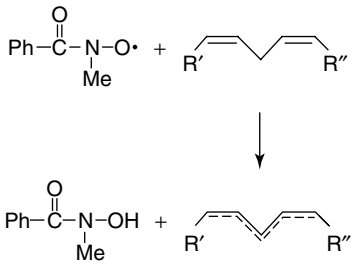
1.4
Aerobic Oxidation Catalyzed by *N*-Hydroxy Amides

1.4.1
Peroxidation of Polyunsaturated Fatty Acids

Peroxidation of polyunsaturated fatty acids (PUFAs) and esters has attracted increased research attention, due to the mounting evidence that uncontrolled peroxidation is involved in the origin and development of many pathologies such as tumor promotion and the deposition of arterial plaques.

Lipid hydroperoxides are the primary products of free radical chain oxidations and their synthesis is of interest in order to simplify the study and characterization of secondary oxidation products, which seem to be the real promoters of diseases.

In order to provide a diasteroselective synthesis of *trans–cis* hydroperoxides (in place of the undesired *trans–trans* products, deriving from the β-fragmentation of peroxyl radicals), in collaboration with Porter's research group we have introduced a new N–OH derivative, *N*-methylbenzohydroxamic acid (NMBHA, **4**) [21], for the selective oxidation of PUFA in the presence of a radical initiator (2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile)) at 37 °C. The O–H BDE value of **4** (79.2 kcal mol^{-1}), is lower when compared with that of NHPI (88.1 kcal mol^{-1}), but higher than that of the C–H bond in the bisallylic position of a fatty acid ($\sim$ 76 kcal mol^{-1}), determining an increase in the value of the rate constant for hydrogen abstraction by peroxyl radical Eq. (1.11), $k_{\mathrm{NMBHA}} = 1.2 \times 10^5$ M^{-1} s^{-1}. This suggested that NMBHA might behave as an ideal catalyst for selective lipid peroxidation Eqs. (1.9–1.11) by favoring the hydrogen abstraction from the weaker C–H bond Eq. (1.9) and, being a suitable H donor, by trapping the peroxyl radicals Eq. (1.11) derived from Eq. (1.10).



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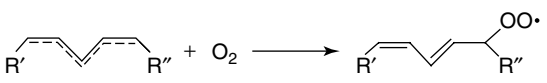
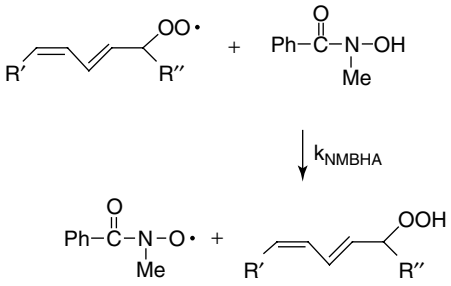
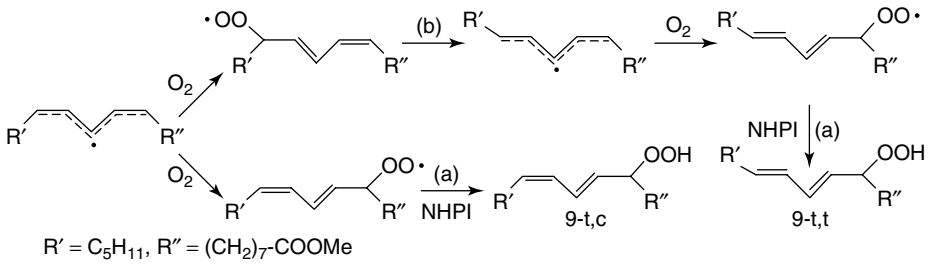


(1.10)



(1.11)

The same process, conducted in the presence of NHPI instead of NMBHA, did not afford the same interesting products. In fact, in spite of the good conversions observed, the diasteroselectivity of the process, that is, the ratio of *trans–cis* to *trans–trans* oxidation products, was poor. This was because the undesired *trans–trans* hydroperoxides arise from the β-fragmentation of primary peroxyl radicals (Scheme 1.2b), a process for which the rate is competitive with that of the hydrogen transfer from NHPI (Scheme 1.2a).



Scheme 1.2

1.5
Aerobic Oxidation Catalyzed by *N*-Hydroxy Imides

1.5.1
Oxidation of Benzylalcohols to Aldehydes

The aerobic oxidation of primary benzylic alcohols, catalyzed by NHPI and Co(II) salts, leads to aromatic aldehydes without appreciable formation of carboxylic acids [30] Eq. (1.12). In contrast, the oxidation of primary aliphatic alcohols leads to carboxylic acids without significant formation of aldehydes, even at low conversions. This selectivity observed in the catalysis with NHPI clearly indicates that benzyl alcohols are much more reactive than the corresponding aldehydes while, in the case of nonbenzylic alcohols, the corresponding aldehydes are much more reactive than the starting alcohols.

$$\mathrm{PhCH_2OH} \xrightarrow[\text{rt 2 h}\\ \text{92\%}]{\mathrm{NHPI\ O_2}\\ \text{Co(II) } m\text{CPBA}} \mathrm{PhCHO} \qquad (1.12)$$

Both polar and enthalpic effects present in the NHPI catalysis explain this behavior well. To better understand the reasons of these results, we investigated the effect of aromatic ring substituents on benzyl alcohols in their aerobic oxidation by NHPI catalysis [23]. A good Hammett correlation was obtained (Figure 1.1) with the exception of *p*-nitro and *p*-cyano substituents, which have a negligible effect on the reactivity, while *m*-nitro and *m*-cyano benzyl alcohols were significantly deactivated.

This behavior is due to the captodative effect, which qualitatively suggests that pairs of substituents having opposite polarities both concur to the stabilization of a radical according to the resonance structures showed in Eq. (1.13). While the captodative effect causes a significant decrease in the BDE values for benzylic C–H bonds in *p*-cyano- and *p*-nitrobenzyl alcohols, the favorable enthalpic effect balances the unfavorable polar effect due to the presence of *p*-cyano and *p*-nitro groups.

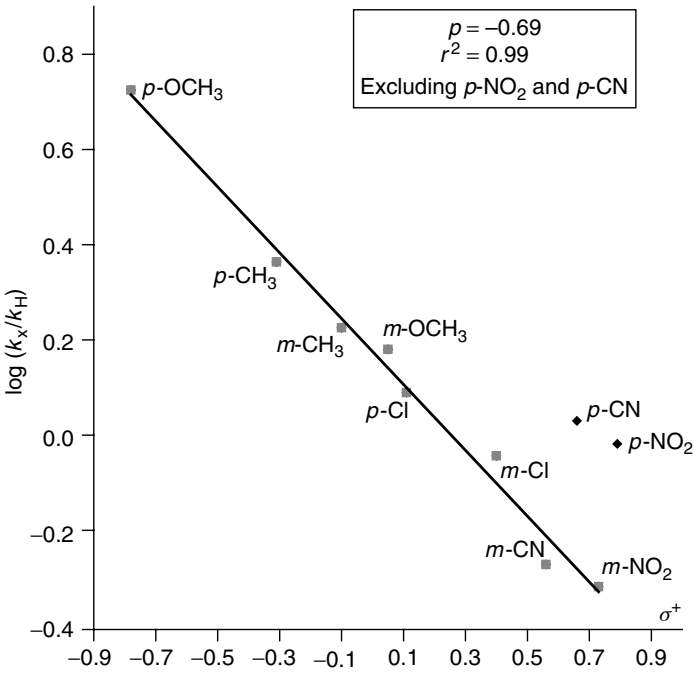
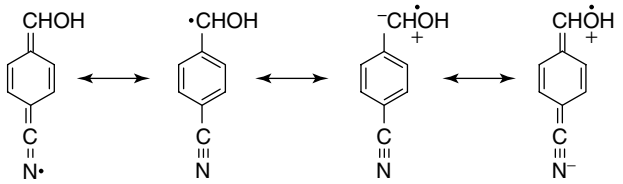


Figure 1.1 Substituent effect in the aerobic oxidation of substituted benzyl alcohols with NHPI catalysis.



(1.13)

Lanzalunga *et al.* also reported the effect of aryl-substituted *N*-hydroxyphthalimides (X-NHPI) used as catalysts in the aerobic oxidation of primary and secondary benzylic alcohols to the corresponding aldehydes and ketones respectively [31]. It was found that, when X was an electron-withdrawing group, the O–H BDE of X-NHPI, determined by using the EPR radical equilibration technique, increased. Kinetic studies proved that this behavior was reflected in an increasing of the substrate oxidation rate, thus indicating that the hydrogen atom transfer from the alcohol to X-PINO represented the rate-determining step. Besides enthalpic effects, polar effects were also emphasized in the same report for the hydrogen atom transfer process. In particular, a negative ρ value of the Hammett correlation for the oxidation of substituted primary benzylic alcohols and the decrease of the ρ values by increasing the electron-withdrawing properties of the substituents, have been observed.

1.5.2
Oxidation of Silanes

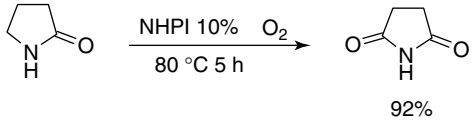
The classic routes for the synthesis of silanols involve the oxidation of silanes by a variety of metal-based oxidants, ozone, and dioxiranes. Most of these methods, however, afford the corresponding siloxanes as undesired side products and use expensive oxidants, which often involve environmental drawbacks. The aerobic oxidation of silanes, catalyzed by NHPI and Co(II) salts, revealed to be particularly effective for the selective synthesis of silanols, without appreciable formation of side products [32] Eq. (1.14).

$$Ph_3SiH + 1/2\ O_2 \xrightarrow[\text{rt 24 h 97\%}]{\text{NHPI } O_2 \text{ Co(II)}} Ph_3SiOH \qquad (1.14)$$

1.5.3
Oxidation of *N*-Alkylamides

The oxidation of *N*-alkylamides by O_2, catalyzed by NHPI and Co(II) salt Eqs. (1.15–1.17), leads to the corresponding carbonyl derivatives (aldehydes, ketones, carboxylic acids, imides) whose distribution depends upon the nature of the alkyl group and the reaction conditions [33]. Lactams are oxidized to the corresponding imidoderivatives Eq. (1.15). Primary *N*-benzylamides lead to imides and aromatic aldehydes at room temperature without any appreciable amount of carboxylic

acids Eq. (1.16) while, under the same conditions, nonbenzylic derivatives give carboxylic acids and imides with no trace of aldehydes, even at very low conversions Eq. (1.17).



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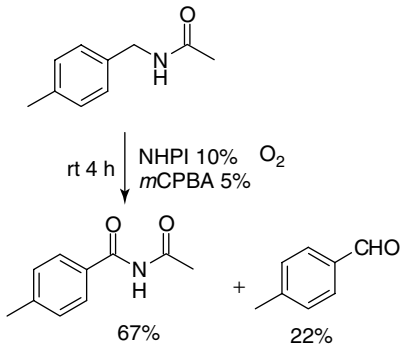

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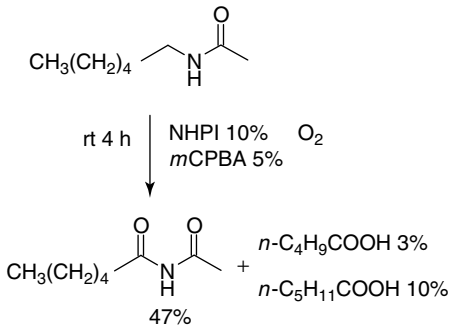
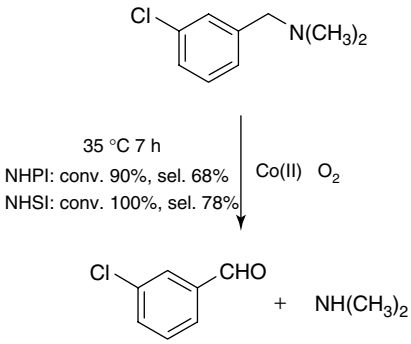


(1.17)

1.5.4
Oxidation of Tertiary Benzylamines to Aldehydes

Tertiary benzylamines are easily oxidized to the corresponding arylaldehydes under aerobic conditions in the presence of NHPI or *N*-hydroxysuccinimide (NHSI) and Co(II) salts [34] Eq. (1.18).

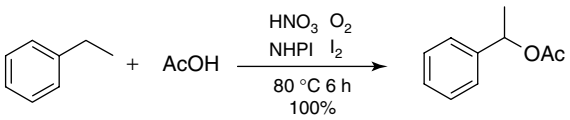


(1.18)

With NHSI, the reaction is slower, but it goes to completion without deactivation of the catalyst. Competitive experiments with NHPI and NHSI in the presence of *N,N*-dimethyl-*m*-Cl-benzylamine showed that the former reacts faster than the latter. Moreover, the faster oxidation by NHPI catalysis makes the reaction somewhat less selective compared with the slower NHSI catalysis.

1.5.5
Oxidative Functionalization of Alkylaromatics

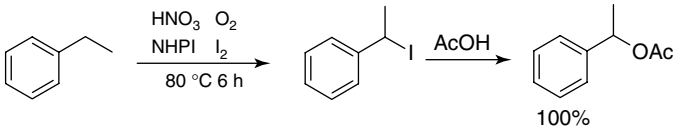
Alkylbenzenes are selectively oxidized to the corresponding acetates by nitric aerobic oxidation catalyzed by NHPI and I_2 [35] Eq. (1.19).



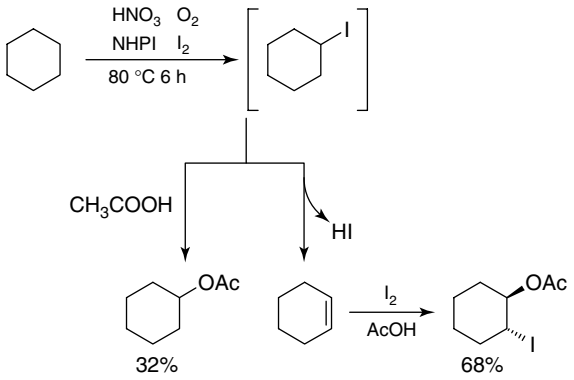
(1.19)

The winning point of these reactions is the fact that the product is less prone toward further oxidation than the starting hydrocarbon, making it possible to obtain products with high selectivity.

The role of I_2 is to trap the intermediate benzyl radical giving the corresponding aryl iodide Eq. (1.20). Under these reaction conditions the iodide undergoes fast SN2 substitution by the acetic acid, which is used as a solvent, achieving the final acetoxy derivative. The same reaction carried out in cyclohexane gives cyclohexyl acetate and *trans*-iodocyclohexyl acetate: the elimination of HI from the intermediate cyclohexyl iodide leads to cyclohexene which, in the presence of I_2 and AcOH, gives rise to the *trans* adduct Eq. (1.21).



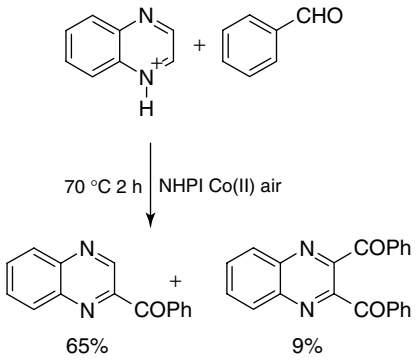
(1.20)



(1.21)

1.5.6
Oxidative Acylation of *N*-Heteroaromatic Bases

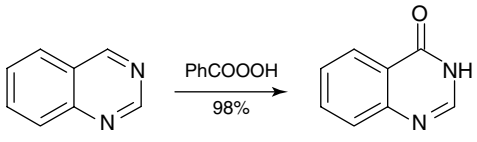
Protonated *N*-heteroaromatic bases are efficiently functionalized to the corresponding acyl derivatives by using aldehydes, as acyl radical sources, in the presence of NHPI and Co(II) salts under aerobic conditions [36] Eq. (1.22).



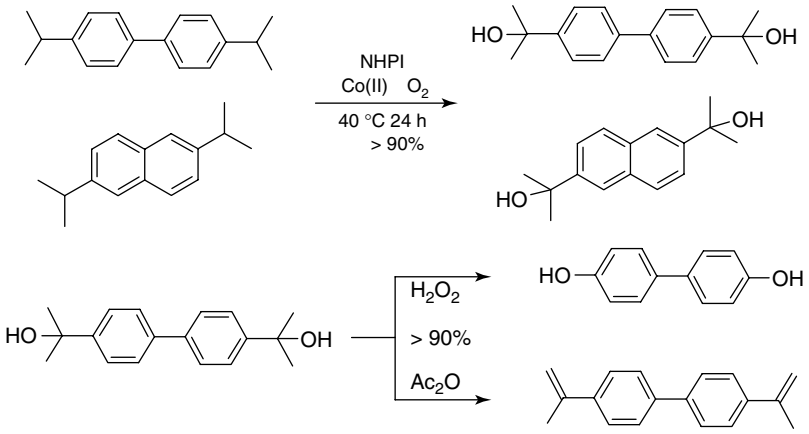
(1.22)

Depending on the operative temperature, the direct aerobic oxidation of the aldehydes may afford carboxylic acids as by-products.

Quinazoline has an anomalous behavior compared with other aromatic bases: no acylation occurs, but 3*H*-quinazolin-1-one is the sole product Eq. (1.23). This behavior might be ascribed to the oxidation by the peracid, a possible intermediate formed from the aldehyde in the reaction media.



(1.23)



Scheme 1.3

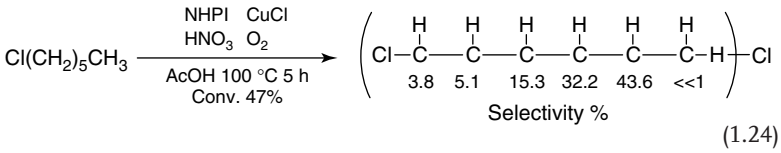
1.5.7
Aerobic Synthesis of *p*-Hydroxybenzoic Acids and Diphenols

The aerobic oxidation of 4,4-diisopropyldiphenyl and 2,6-diisopropylnaphthalene, catalyzed by NHPI and Co(II) salts, leads to the corresponding tertiary benzyl alcohols with high conversion and selectivity. The latter are efficiently converted either to diphenols (useful in the production of liquid crystals) by reaction with H_2O_2 or to dienes (useful as cross-linking agents) by dehydration [37] (Scheme 1.3).

A screening in different solvents showed that low polar solvents such as chlorobenzene, are particularly convenient for the synthesis of cumyl alcohol. However, the low solubility of NHPI in these solvents does not allow high conversions. On the other hand, high polar solvents increase the solubility of NHPI but, at the same time, reduce the selectivity to benzyl alcohol. Therefore, a compromise has been achieved with acetonitrile, which grants a good solubility of NHPI and allows high yield of dibenzyl alcohol at low temperature.

1.5.8
Selective Halogenation of Alkanes

The strong polar effect due to the two carbonyl groups of NHPI plays a key role in the selective halogenation of alkanes. PINO is generated in the presence of a catalytic amount of HNO_3 when the reaction is carried out under aerobic conditions [38] Eq. (1.24).



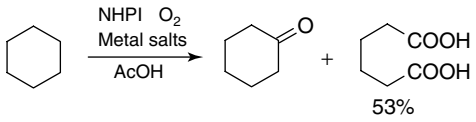
(1.24)

In the reactions catalyzed by NHPI, the chemoselectivity is much higher than in free radical halogenations by Cl_2: the introduction of an electron-withdrawing group determines a significant deactivation of the substrate, allowing selective monosubstitution even at considerable conversions. The quite different regioselectivity observed for chlorination in the presence of NHPI with respect to the one with Cl_2 in the absence of NHPI, suggests a high polar effect in H abstraction by PINO. Enthalpic effects also considerably affect the selectivity: the methyl group, despite being the less deactivated by a polar substituent, reacts only in traces, because of the higher BDE values of C–H bonds compared with those of $-CH_2-$ groups.

1.5.9
Aerobic Oxidation of Cycloalkanes to Diacids

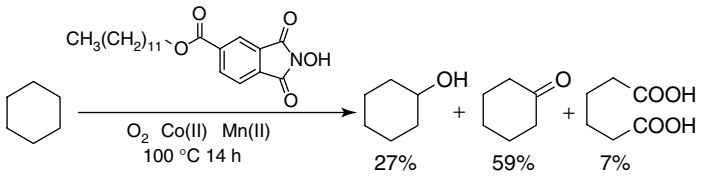
The aerobic oxidation catalyzed by nitroxyl imides has been applied to the synthesis of aliphatic dicarboxylic acids. Great attention has been devoted to the production of adipic acid, an important intermediate in the synthesis of 6,6-nylon.

Ishii and Daicel Chemical Company patented a method for the direct aerobic oxidation of cyclohexane to adipic acid by using NHPI together with suitable metal salts as cocatalysts Eq. (1.25). The process is currently under evaluation at a pilot scale for further commercial applications [39a]. The best result claimed so far is a 73% conversion of cyclohexane with 73% selectivity for adipic acid.



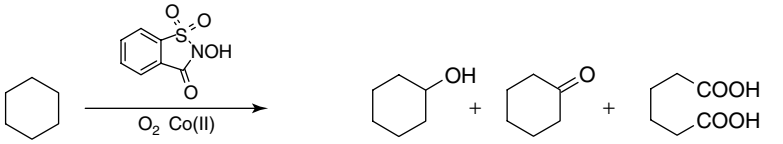
(1.25)

These processes are usually carried out in polar solvents such as acetic acid, acetonitrile, or ethyl acetate due to the low solubility of NHPI in nonpolar solvents. Thus, the use of 4-lauryloxycarbonyl-*N*-hydroxyphthalimide has given the possibility to perform the reaction directly in neat substrate [39b] Eq. (1.26).



(1.26)

Sheldon *et al.* have reported the use of *N*-hydroxysaccharin (NHS), as an alternative to NHPI, in the oxidative catalysis of cycloalkanes to dicarboxylic acids. The mechanism is expected to be similar to that of NHPI catalysis [39c] Eq. (1.27).

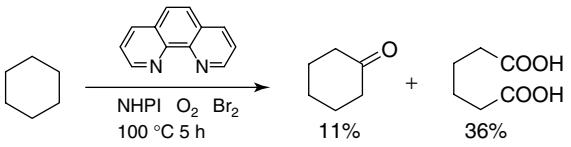


100 °C, 6 h				
NHPI: conv. 58%	Sel. %	5	29	30
NHS: conv. 64%		8	31	16
50 °C, 24 h				
NHPI: conv. 0%	Sel. %	0	0	0
NHS: conv. 42%		14	47	20

(1.27)

NHS shows greater catalytic activity than NHPI, especially at lower temperatures, because both an enhanced polar effect and an expected higher BDE of the O–H group in NHS hastens the H abstraction from hydrocarbons.

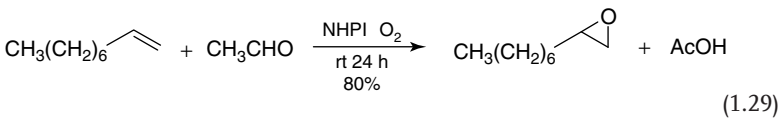
Recently, Xu *et al*. have reported an efficient metal-free aerobic oxidation of cyclohexane to adipic acid and cyclohexanone using catalytic amounts of NHPI in the presence of *o*-phenanthroline and Br_2 [39d] Eq. (1.28).



(1.28)

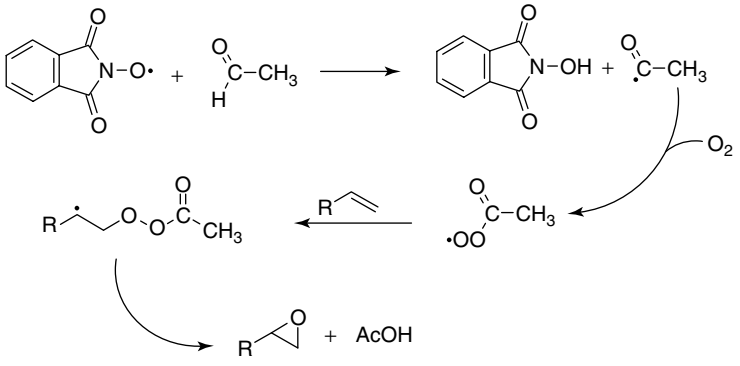
1.5.10
Epoxidation of Olefins

The induced homolysis of NHPI in the presence of peracids or dioxiranes has been employed to promote the aerobic oxidation of olefins to the corresponding epoxides Eq. (1.29) [40].

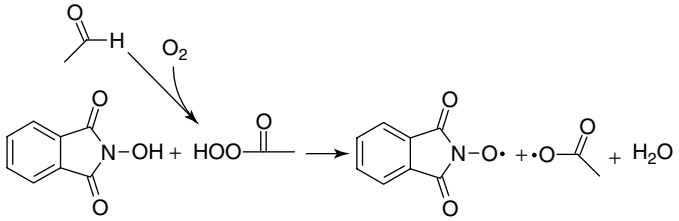


(1.29)

Aldehydes in the presence of oxygen slowly give *in situ* formation of peracids, which promote the homolysis of NHPI leading to the formation of PINO and H_2O Eq. (1.30).



Scheme 1.4



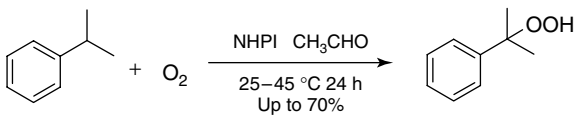
(1.30)

PINO abstracts the formyl-hydrogen from the aldehyde affording the corresponding acyl radical, which is fast trapped by oxygen. The resulting acylperoxyl radical adds to the double bond of the olefin leading to the formation of the epoxide (Scheme 1.4).

1.5.11
Oxidation of Alkylaromatics

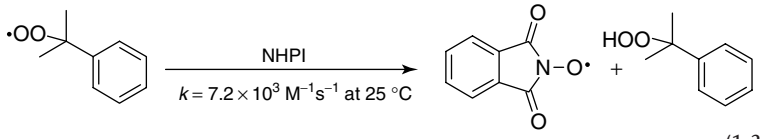
The same catalytic system used in the epoxidation of olefins has been successfully applied to the oxidation of alkylaromatic compounds to the corresponding hydroperoxides. It is well known that, in the presence of metal salts, hydroperoxides undergo fast decomposition to the corresponding alcohols. In this case, the catalytic system acts under aerobic conditions in the absence of metal species, allowing hydroperoxides with high selectivity to be obtained.

This system has been applied in the oxidation of cumene to cumyl hydroperoxide (CHP), an important intermediate in the industrial production of phenol [41]. The reaction is carried out at a lower temperature compared with classic autoxidation processes (110–140 °C), affording a similar conversion of the reactant (up to 70% after 24 hours) and a selectivity up to 90% in CHP Eq. (1.31).



(1.31)

The high efficiency of the process is due to the fast reaction of the intermediate cumyloxyl radical with NHPI to give CHP and PINO. In this way, during the process, the concentration of peroxyl radical is kept very low and the chain termination is strongly disfavored Eq. (1.32).



(1.32)

The same reaction, carried out with NHSI, instead of NHPI, led to no conversion.

1.6 Conclusions

In the last decade, NHDs were widely studied as organocatalysts for the development of oxidative processes worldwide and we intensely contributed to the design and investigation of the mechanistic aspects of oxidation processes involving NHDs.

However, in spite of the many results previously disclosed within this field, a thorough investigation related to such catalysts and catalytic processes is still mandatory. The potential of NHD catalysts is well documented, but the industrial exploitation of such catalysts is rather absent. This represents the real gap to be filled. Thus, the progress beyond the state of the art, which is expected in the future years, is to transform ''interesting synthetic routes'' into ''winning industrial processes'' by acting, in particular, on two fronts: (i) the main limitations to the employment of NHDs as catalysts for industrial processes are due to the fact that they are commonly considered expensive and instable. The reasons for this instability need to be exhaustively investigated and explained once and for all. This should induce to find out new NHDs, which might be employed under milder conditions, in order to be easily recovered and recycled; (ii) the cost and environmental demands, as well as the effect that the metals have on the instability of these catalysts, urge the development of cleaner metal-free routes for the activation of NHDs.

Nevertheless, it is apparent that NHDs will play a key role in the future regarding the development of oxidative industrial processes of strategic relevance.

Acknowledgments

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References

1. Suresh, A.K., Sharma, M.M., and Sridhar, T.T. (2000) Engineering aspects of industrial liquid-phase air oxidation of hydrocarbons. *Ind. Eng. Chem. Res.*, **39**, 3958–3997.
2. (a) Simandi, L.L. (1991) *Dioxygen Activation and Homogeneous Catalytic Oxidation*, Elsevier, Amsterdam; (b) Parshall, G.W. and Ittel, S.D. (1992) *Homogeneous Catalysis*, 2nd edn, John Wiley & Sons, Inc., New York; (c) Barton, D.H.R., Martell, A.E., and Sawyer, D.T. (1993) *The Activation of Dioxygen and Homogeneous Catalytic Oxidation*, Plenum, New York; (d) Sheldon, R.A. and Kochi, J.K. (1981) *Metal-catalysed Oxidations of Organic Compounds*, Academic, New York.
3. Bäckvall, J.-E. (ed.) (2004) *Modern Oxidation Methods*, Wiley-VCH Verlag GmbH, Weinheim.
4. (a) Centi, G., Trifirò, F., and Cavani, F. (2001) *Selective Oxidation by Heterogeneous Catalysis*, Kluwer Academic/Plenum, New York; (b) Sheldon, R.A. and van Bekkum, H. (2001) *Fine Chemicals through Heterogeneous Catalysis*, Wiley-VCH Verlag GmbH, Weinheim.
5. (a) Zedda, A., Sala, M., and Schneider, A. (2002) Stable free nitroxyl radicals as oxidation catalysts and process for oxidation. WO02/058844; (b) Baucherel, X. and Sheldon, R.A. (2002) Catalytic oxidation process. WO02/100810; (c) Kühnle, A., Jost, C., Sheldon, R.A., Chatel, S., and Arends, I. (2003) Method for producing saturated alcohols, ketones, aldehydes and carboxylic acids. WO03/004447; (d) Kühnle, A., Duda, M., Sheldon, R.A., Sasidharan, M., Arends, I., Schiffer, T., Fries, G., and Kirchhoff, J. (2001) Method for oxidizing hydrocarbons. WO01/74742.
6. Lucarini, M., Ferroni, F., Pedulli, G.F., Gardi, S., Lazzari, D., Schlingloff, G., and Sala, M. (2007) Metal free in situ formation of phthalimide N-oxyl radicals by light-induced homolysis of N-alkoxyphthalimides. *Tetrahedron Lett.*, **48**, 5331–5334.
7. (a) Lucarini, M., Pedulli, G.F., and Cipollone, M. (1994) Bond dissociation enthalpy of α-tocopherol and other phenolic antioxidants. *J. Org. Chem.*, **59**, 5063–5070; (b) Lucarini, M., Pedulli, G.F., Pedrielli, P., Cabiddu, S., and Fattuoni, C. (1996) Bond dissociation energies of O-H bonds in substituted phenols from equilibration studies. *J. Org. Chem.*, **61**, 9259–9263; (c) Lucarini, M., Pedulli, G.F., Valgimigli, L., Amorati, R., and Minisci, F. (2001) Thermochemical and kinetic studies of a bisphenol antioxidant. *J. Org. Chem.*, **66**, 5456–5462; (d) Brigati, G., Lucarini, M., Mugnaini, V., and Pedulli, G.F. (2002) Determination of the substituent effect on the O-H bond dissociation enthalpies of phenolic antioxidants by the EPR radical equilibration technique. *J. Org. Chem.*, **67**, 4828–4832.
8. Amorati, R.R., Lucarini, M.M., Mugnaini, V.V., Pedulli, G.F.G. F., Minisci, F.F., Fontana, F.F., Recupero, F.F., Astolfi, P.P., and Greci, L.L. (2003) Hydroxylamines as oxidation catalysts: thermochemical and kinetic studies. *J. Org. Chem.*, **68**, 1747–1754.
9. de Nooy, A.E.J., Besemer, A.C., and van Bekkum, H. (1996) On the use of stable organic nitroxyl radicals for the oxidation of primary and secondary alcohols. *Synthesis*, **10**, 1153–1174.
10. (a) Sheldon, R.A., Arends, I.W.C.E., Brink, G.J., and Dijksman, A. (2002) Green, catalytic oxidations of alcohols. *Acc. Chem. Res.*, **35**, 774–781; (b) Dijksman, A., Arends, I.W.C.E., and Sheldon, R.A. (1999) Efficient ruthenium–TEMPO-catalysed aerobic oxidation of aliphatic alcohols into aldehydes and ketones. *Chem. Commun.*, 1591, 1592; (c) Dijksman, A., Arends, I.W.C.E., and Sheldon, R.A. (2001) The Ruthenium/TEMPO-catalysed aerobic oxidation of alcohols. *Platinum Metals Rev.*, **45**, 15; (d) Dijksman, A., Marino-Gonzalez, A., Mairata I Payeras, A., Arends, I.W.C.E., and Sheldon, R.A. (2001) Efficient and selective aerobic oxidation of alcohols into aldehydes and

ketones using Ruthenium/TEMPO as the catalytic system. *J. Am. Chem. Soc.*, **123**, 6826–6833.

11. Betzemeier, B.B., Cavazzini, M.M., Quici, S.S., and Knochel, P.P. (2000) Copper-catalysed aerobic oxidation of alcohols under fluorous biphasic conditions. *Tetrahedron Lett.*, **41**, 4343–4346.
12. Brink, G.J., Arends, I.W.C.E., and Sheldon, R.A. (2000) Green, catalytic oxidation of alcohols in water. *Science*, **287**, 1636–1639.
13. (a) Recupero, F. and Punta, C. (2007) Free radical functionalization of organic compounds catalysed by N-hydroxyphthalimide. *Chem. Rev.*, **107**, 3800–3842; (b) Minisci, F., Punta, C., and Recupero, F. (2006) Mechanisms of the aerobic oxidations catalysed by N-hydroxyderivatives. Enthalpic, polar and solvent effects, ''molecule-induced homolysis'' and synthetic involvements. *J. Mol. Catal. A Chem.*, **251**, 129–149.
14. Ishii, Y., Sakaguchi, S., and Iwahama, T. (2001) Innovation of hydrocarbon oxidation with molecular oxygen and related reactions. *Adv. Synth. Catal.*, **343**, 393–427.
15. (a) Fukuda, O., Sakaguchi, S., and Ishii, Y. (2001) A new strategy for catalytic Baeyer–Villiger oxidation of KA-oil with molecular oxygen using N-hydroxyphthalimide. *Tetrahedron Lett.*, **42**, 3479–3481; (b) Aoki, Y., Hirai, N., Sakaguchi, S., and Ishii, Y. (2005) Aerobic oxidation of 1,3,5-triisopropylbenzene using N-hydroxyphthalimide (NHPI) as key catalyst. *Tetrahedron*, **61**, 10995–10999; (c) Foricher, J., Furbringer, C., and Pfoertner, K. (1986) Catalytic oxidation with *N*-hydroxydicarboxylic acid imides. EP Patent 0198351; (d) Foricher, J., Furbringer, C., and Pfoertner, K. (1991) Process for the catalytic oxidation of isoprenoids having allylic groups. US Patent 5,030,739.
16. Minisci, F., Recupero, F., Punta, C., Gambarotti, C., Antonietti, F., Fontana, F.F., and Pedulli, G.F. (2002) A novel, selective free-radical carbamoylation of heteroaromatic bases by Ce(IV) oxidation of formamide, catalysed by N-hydroxyphthalimide. *Chem. Commun.*, 2496–2497.
17. Einhorn, C., Einhorn, J., Marcadal, C., and Pierre, J.-L. (1997) Oxidation of organic substrates by molecular oxygen mediated by N-hydroxyphthalimide (NHPI) and acetaldehyde. *Chem. Commun.*, 447–448.
18. Tong, X., Xu, J., and Miao, H. (2005) Highly efficient and metal-free aerobic hydrocarbons oxidation process by an o-phenanthroline-mediated organocatalytic system. *Adv. Synth. Catal.*, **347**, 1953–1957.
19. (a) Baiocco, P., Barreca, A.M., Fabbrini, M., Galli, C., and Gentili, P. (2003) Promoting laccase activity towards non-phenolic substrates: a mechanistic investigation with some laccase–mediator systems. *Org. Biomol. Chem.*, **1**, 191–197; (b) Astolfi, P., Brandi, P., Galli, C., Gentili, P., Gerini, M.F., Greci, L., and Lanzalunga, O. (2005) New mediators for the enzyme laccase: mechanistic features and selectivity in the oxidation of non-phenolic substrates. *New J. Chem.*, **29**, 1308–1317.
20. Sheldon, R.A. and Arends, I.W.C.E. (2004) Organocatalytic oxidations mediated by nitroxyl radicals. *Adv. Synth. Catal.*, **346**, 1051–1071.
21. Punta, C., Rector, C.L., and Porter, N.A. (2005) Peroxidation of polyunsaturated fatty acid methyl esters catalysed by N-methyl benzohydroxamic acid: a new and convenient method for selective synthesis of hydroperoxides and alcohols. *Chem. Res. Toxicol.*, **18**, 349–356.
22. Cecchetto, A., Fontana, F., Minisci, F., and Recupero, F. (2001) Efficient Mn–Cu and Mn– Co– TEMPO-catalysed oxidation of alcohols into aldehydes and ketones by oxygen under mild conditions. *Tetrahedron Lett.*, **42**, 6651–6653.
23. Minisci, F., Recupero, F., Cecchetto, A., Gambarotti, C., Punta, C., Faletti, R., Paganelli, R., and Pedulli, G.F. (2004) Mechanisms of the aerobic oxidation of alcohols to aldehydes and ketones, catalysed under mild conditions by persistent and non-persistent nitroxyl radicals and transition metal salts. polar, enthalpic, and captodative effects. *Eur. J. Org. Chem.*, **1**, 109–119.

24. Minisci, F., Fumagalli, C., and Pirola, R. (2001) Process for the preparation of carboxylic acids. WO01/58845A1.
25. (a) Minisci, F., Recupero, F., Pedulli, G.F., and Lucarini, M. (2003) Transition metal salts catalysis in the aerobic oxidation of organic compounds: Thermochemical and kinetic aspects and new synthetic developments in the presence of N-hydroxy-derivative catalysts. *J. Mol. Catal. A Chem.*, **204-205**, 63–90; (b) Minisci, F., Recupero, F., Fontana, F., Bjørsvik, H.R., and Liguori, L. (2002) Highly selective and efficient conversion of alkyl aryl and alkyl cyclopropyl ketones to aromatic and cyclopropane carboxylic acids by aerobic catalytic oxidation: a free-radical redox chain mechanism. *Synlett*, 610–612.
26. (a) Benaglia, M., Puglisi, A., and Cozzi, F. (2003) Polymer-supported organic catalysts. *Chem. Rev.*, **103**, 3401; (b) Cozzi, F. (2006) Immobilization of organic catalysts: when, why, and how. *Adv. Synth. Catal.*, **348**, 1367.
27. (a) Fey, T., Fischer, H., Bachmann, S., Albert, K., and Bolm, C. (2001) Silica-supported TEMPO catalysts: synthesis and application in the Anelli oxidation of alcohols. *J. Org. Chem.*, **66**, 8154; (b) Bolm, C. and Fey, T. (1999) TEMPO oxidations with a silica-supported catalyst. *Chem. Commun.*, 1795; (c) Verhoef, M.J., Peters, J.A., and van Bekkum, H. (1999) MCM-41 supported TEMPO as an environmentally friendly catalyst in alcohol oxidation. *Stud. Surf. Sci. Catal.*, **125**, 465–472; (d) Ciriminna, R., Blum, J., Avnir, D., and Pagliaro, M. (2000) Sol– gel entrapped TEMPO for the selective oxidation of methyl α-D-glucopyranoside. *Chem. Commun.*, 1441; (e) Dijksman, A., Arends, I.W.C.E., and Sheldon, R.A. (2000) Polymer immobilised TEMPO (PIPO): an efficient catalyst for the chlorinated hydrocarbon solvent-free and bromide-free oxidation of alcohols with hypochlorite. *Chem. Commun.*, 271.
28. Karimi, B., Biglari, A., Clark, J.H., and Budarin, V. (2007) Green, transition-metal-free aerobic oxidation of alcohols using a highly durable supported organocatalyst. *Angew. Chem. Int. Ed.*, **46**, 7210–7213.
29. Minisci, F., Recupero, F., Rodinò, M., Sala, M., and Schneider, A. (2003) A convenient nitroxyl radical catalyst for the selective oxidation of primary and secondary alcohols to aldehydes and ketones by O_2 and H_2O_2 under mild conditions. *Org. Process Res. Dev.*, **7**, 794–798.
30. Minisci, F., Punta, C., Recupero, F., Fontana, F., and Pedulli, G.F. (2002) A new, highly selective synthesis of aromatic aldehydes by aerobic free-radical oxidation of benzylic alcohols, catalysed by N-hydroxyphthalimide under mild conditions. Polar and enthalpic effects. *Chem. Commun.*, 688–689.
31. Annunziatini, C., Gerini, M.F., Lanzalunga, O., and Lucarini, M. (2004) Aerobic oxidation of benzyl alcohols catalysed by aryl substituted N-hydroxyphthalimides. Possible involvement of a charge-transfer complex. *J. Org. Chem.*, **69**, 3431–3438.
32. Minisci, F., Recupero, F., Punta, C., Guidarini, C., Fontana, F., and Pedulli, G.F. (2002) A new, highly selective, free-radical aerobic oxidation of silanes to silanols catalysed by N-hydroxyphthalimide under mild conditions. *Synlett*, **7**, 1173–1175.
33. Minisci, F., Punta, C., Recupero, F., Fontana, F., and Pedulli, G.F. (2002) Aerobic oxidation of N-alkylamides catalysed by N-hydroxyphthalimide under mild conditions. Polar and enthalpic effects. *J. Org. Chem.*, **67**, 2671–2676.
34. Cecchetto, A., Minisci, F., Recupero, F., Fontana, F., and Pedulli, G.F. (2002) A new selective free radical synthesis of aromatic aldehydes by aerobic oxidation of tertiary benzylamines catalysed by N-hydroxyimides and Co(II) under mild conditions. Polar and enthalpic effects. *Tetrahedron Lett.*, **43**, 3605–3607.
35. Minisci, F., Recupero, F., Gambarotti, C., Punta, C., and Paganelli, R. (2003) Selective functionalisation of hydrocarbons by nitric acid and aerobic oxidation catalysed by N-hydroxyphthalimide and iodine under

mild conditions. *Tetrahedron Lett.*, **44**, 6919–6922.

36. Minisci, F., Recupero, F., Cecchetto, A., Punta, C., Gambarotti, C., Fontana, F.F., and Pedulli, G.F. (2003) Polar effects in free-radical reactions. a nove1 homolytic acylation of heteroaromatic bases by aerobic oxidation of aldehydes, catalysed by N-hydroxyphthalimide and Co salts. *J. Heterocycl. Chem.*, **40**, 235–328.

37. Minisci, F., Recupero, F., Cecchetto, A., Gambarotti, C., Punta, C., Paganelli, R., Pedulli, G.F., and Fontana, F. (2004) Solvent and temperature effects in the free radical aerobic oxidation of alkyl and acyl aromatics catalysed by transition metal salts and N-hydroxyphthalimide: new processes for the synthesis of p-hydroxybenzoic acid, diphenols, and dienes for liquid crystals and cross-linked polymers. *Org. Process Res. Dev.*, **8**, 163–168.

38. Minisci, F., Porta, O., Recupero, F., Gambarotti, C., Paganelli, R., Pedulli, G.F., and Fontana, F. (2004) New free-radical halogenations of alkanes, catalysed by N-hydroxyphthalimide. Polar and enthalpic effects on the chemo- and regio-selectivity. *Tetrahedron Lett.*, **45**, 1607–1609.

39. (a) (2004) Daicel Chemical employs NHPI catalyst method for adipic acid. *Focus Catal.*, **1**, 7; (b) Sawatari, N., Yokota, T., Sakaguchi, S., and Ishii, Y. (2001) Alkane oxidation with air catalysed by lipophilic N-hydroxyphthalimides without any solvent. *J. Org. Chem.*, **66**, 7889–7891; (c) Baucherel, X., Gonsalvi, L., Arends, I.W.C.E., Ellwood, S., and Sheldon, R.A. (2004) Aerobic oxidation of cycloalkanes, alcohols and ethylbenzene catalysed by the novel carbon radical chain promoter NHS (N-hydroxysaccharin). *Adv. Synth. Catal.*, **346**, 286–296; (d) Tong, X., Xu, J., and Miao, H. (2005) Highly efficient and metal-free aerobic hydrocarbons oxidation process by an o-phenanthroline-mediated organocatalytic system. *Adv. Synth. Catal.*, **347**, 1953–1957.

40. (a) Minisci, F., Gambarotti, C., Pierini, M., Porta, O., Punta, C., Recupero, F., Lucarini, M., and Mugnaini, V. (2006) Molecule-induced homolysis of N-hydroxyphthalimide (NHPI) by peracids and dioxirane. A new, simple, selective aerobic radical epoxidation of alkenes. *Tetrahedron Lett.*, **47**, 1421–1424; (b) Punta, C., Moscatelli, D., Porta, O., Minisci, F., Gambarotti, C., and Lucarini, M. (2008) Selective aerobic radical epoxidation of α-olefins catalysed by N-hydroxyphthalimide, in *Mechanisms in Homogeneous and Heterogeneous Epoxidation Catalysis* (ed. S.T.Oyama), Elsevier, pp. 217–229.

41. Minisci, F., Porta, O., Punta, C., Recupero, F., Gambarotti, C., and Pierini, M. (2008) Process for the preparation of phenol by means of new catalytic systems. WO2008037435A1.