Free Radical Functionalization of Organic Compounds Catalyzed by *N*-Hydroxyphthalimide†

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† Dedicated to Prof. Francesco Minisci on the occasion of his 75th birthday.

1. Introduction and Historical Background

In the future, standard procedures for chemical processes should require only inexpensive reagents used in standard equipment under the mildest possible conditions, and they should give the desired products in quantitative yields with, when possible, 100% atom economy.[1]

Only a very few chemical transformations which fulfill these criteria are currently known, and this need for an environmentally acceptable chemistry has induced great efforts by the chemical community to develop industrially interesting processes of this kind quickly.

Academic research especially has recently achieved important successes in this direction, but because of the resistance to change with which important innovations, particularly those requiring large investments, are met, only a few such processes have been brought to market. However, because of increasing energy costs and growing environmental concerns, the current trend toward the greenest possible chemistry cannot be reversed.

The outstanding challenge in this direction is still the development of processes for the selective functionalization of C−H bonds,[2] since saturated hydrocarbons in the form of natural gas and oil are the largest natural sources of chemicals.

Dyoxygen is the most ubiquitous and available oxidizing agent, and as Cheves Walling in underlining its importance stated simply, "through respiration its reaction with organic molecules sustains life and, through combustion, provides most of our heat and energy".[3] We may add that oxygen, through controlled oxidation reactions of organic molecules, sustains the chemical industry and, consequently, considering the penetration of chemistry into all sectors of life, the modern economy.

Since the beginnings of organic chemistry, chemists have understood that the cheapest way to synthesize more complex molecules starting from natural materials was to introduce oxygen atoms into C−H bonds by the reaction of hydrocarbons with oxygen.

Most organic compounds react spontaneously with oxygen at or near room temperature at a rate strictly dependent on their chemical structure, and this is sometimes a problem in preserving bulk materials such as plastic, rubber, lubricating oil, and many foodstuffs. These spontaneous transformations, which are called autoxidations, can be avoided by addition of natural or synthetic antioxidants.

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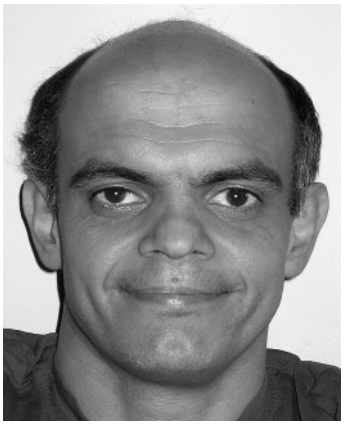


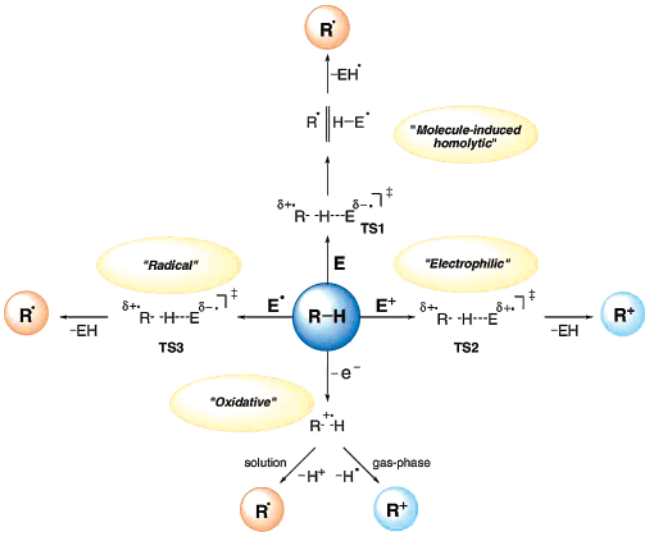
Francesco Recupero was born in 1969 in Furnari, a small village on the north coast of Sicily (Italy). After his "Laurea" in Chemistry, received from the University of Messina (1993), he moved to Politecnico di Milano. He obtained his Ph.D. in Industrial Chemistry from Politecnico di Milano in 1998, under the direction of F. Minisci. In 1997 he was a Visiting Scholar at the University of Illinois at Chicago in the lab of D. Crich. After his Ph.D. he spent a period at the University of Basel as a post-doc in the lab of B. Giese. He worked in the industry, for Mapei S.p.A, before getting, in 2000, his present position as a Research Associate at the Politecnico di Milano. His research interests have always been related to the chemistry of free radicals. In particular, he has been involved in the elucidation of the reaction mechanisms of Gif–Barton reactions and in the development of new free radical processes for selective oxidation of organic compounds, with special focus on the catalysis of such processes by using *N*-hydroxyphthalimide. His interests have also included studies on polarity reversal catalysis by using selenium compounds, the developments of synthetic methodologies for introducing perfluoroalkyl tails in organic molecules, and the use of TiO_2 as photoactivator of selective functionalization of protonated heterocyclic bases.

Carlo Punta was born in 1976 in Genoa (Italy), received his "Laurea in Chemistry" at the University of Genoa (2001), and gained the title of Doctor in "Industrial Chemistry and Chemical Engineering" in 2005 under the supervision of Professor Minisci. Since March 2005 he has been working as a Research Associate at Politecnico di Milano. His main research interests concern the development of new catalytic systems for the selective oxidation of organic substrates in mild and ecofriendly conditions and for the free radical selective synthesis of known and new molecules of industrial and biological interest.

On the other hand, autoxidations carried out under conditions suitable for obtaining commercially interesting conversions are the source of fundamental chemicals such as acetic acid, KA oil (a mixture of cyclohexanone and cyclohexanol), benzoic acid, terephthalic acid, phenol accompanied by acetone, etc. The production of these chemicals is impressive (Table 1)[4] and underlines the industrial importance of liquid phase oxidations.

Among all organic transformations, hydrocarbon oxidations suffer a major limitation imposed by their intrinsic nature: the reaction products are very often more reactive than the starting material. Thus, an oxidation reaction with quantitative conversion of the starting material and 100% selectivity to give the desired product remains the "holy grail" for all chemists involved in this fascinating area.

Scheme 1. Various Methods of C−H Bond Alkane Functionalization (From Ref 9, Copyright 2004, Reprinted with permission of John Wiley & Sons, Inc.)



Inexpensive oxidation processes having complete atom economy are feasible research targets when using oxygen as the oxidant, since both oxygen atoms can be incorporated into the reaction product, but usually only one of the two atoms can be incorporated productively, which reduces the oxidative efficiency to 50%.

However, despite its diradical character, oxygen is a relatively unreactive molecule, especially toward strong bonds such as the C−H bonds of hydrocarbons. Its direct utilization is restricted by the Wigner spin conservation rule[5] due to its triplet ground state structure. Thus, catalysis is necessary for aerobic oxidations under mild conditions, and both homogeneous[6,7] and heterogeneous catalysis have been widely utilized.[8]

Different approaches have been proposed in the pursuit of good conversions and selectivity in the aerobic activation of hydrocarbons. A comprehensive view (Scheme 1) of the different ways to functionalize C−H bonds has been proposed recently by Schreiner and Fokin.[9−11]

In addition to high selectivity, another target for any chemical process is low environmental impact, in which waste minimization is a major factor. As pointed out by Sheldon,[12] catalysis represents the "key to waste minimization".

Most of the transition metals play a unique role in the catalytic activation of molecular oxygen and thereby allow the functionalization of a wide range of organic compounds.[13] Nature itself suggests efficient catalysts for this purpose: the cytochromes P450 constitute a large family of cysteinato-heme enzymes which are present in all forms of life and which play a key role in the oxidative transformation of endogenous and exogenous molecules.[14]

Alternatively, oxidatively resistant organic substances,[15] which mediate catalytic homogeneous oxidations without the need of metal complexes, have gained much attention because they offer the major advantage of better environ-

Table 1. Major Chemical Processes Utilizing Hydrocarbon Oxidation[a]

product	capacity[a] (10^6 tpy)	oxidation step	main application
purified terephthalic acid (PTA)	11.38 (1995)	*p*-xylene to terephthalic acid	PET (fiber, film, resin)
dimethylterephthalate (DMT)	4.06 (1995)	*p*-xylene to *p*-toluic acid and monomethyl ester of *p*TA to DMT	PET (fiber, film, resin)
cumylhydroperoxide (CHPO)	6.5 (1998)	cumene to cumyl hydroperoxide	phenol
benzoic acid	0.28 (1995)	toluene to benzoic acid	phenol and salts esters of benzoic acid
ϵ-caprolactam	3.7 (1995)	cyclohexane to KA	Nylon-6 (Perlon)
adipic acid	2.2 (1993)	cyclohexane to KA and KA to adipic acid	Nylon-6,6
propylene oxide	4.0 (1993)	*iso*-butane to *tert*-butylhydroperoxide or ethylbenzene to hydroperoxide	propylene glycol polyols
			styrene
acetic acid	6.0 (1994)	butane/naphtha	vinylacetate
			cellulose acetate
			PTA, solvent

[a] Capacities shown are worldwide figures and refer to the year indicated in parentheses.

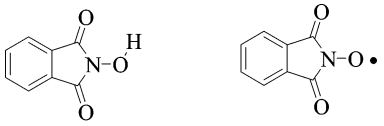


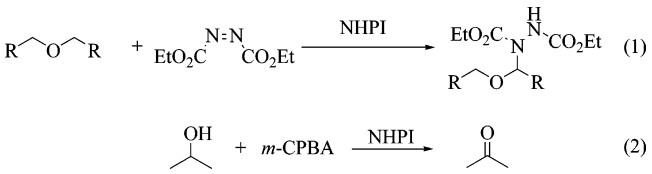
Figure 1. Structures of NHPI and PINO.

mental acceptance as compared to the usually toxic transition metal catalysts.

A new organocatalyst, *N*-hydroxyphthalimide (NHPI), has recently been introduced as an effective system for C−H activation by hydrogen abstraction (Figure 1).[16−20] Due to its particular behavior, which is very different from that of any system proposed up until now, and to its general efficiency, NHPI has attracted increasing interest in the past decade, both in academia and in industry.

NHPI is a cheap, nontoxic catalyst easily prepared by the reaction of phthalic anhydride and hydroxylamine.[21] It acts as a precursor of phthalimido-*N*-oxyl (PINO) radical, which is the effective abstracting species in all of the free radical processes mediated by this *N*-hydroxy derivative.

Grochowski and co-workers reported the first free radical reaction in the presence of NHPI in 1977: they found NHPI to be a good catalyst for the addition of ethers to diethyl azodicarboxylate (eq 1) and for the oxidation of 2-propanol to acetone in the presence of *m*-chloroperbenzoic acid (eq 2).[22]



In the 1980s, Masui's group published a series of papers describing reactions in which NHPI mediated the electrochemical oxidation of alcohols, benzylic compounds, olefins, amides, lactams, and acetals to obtain the corresponding oxygen-containing derivatives.[23−28]

In 1986, Foricher proposed the first autoxidation reaction in the presence of stoichiometric amounts of NHPI; he succeeded in oxidizing various isoprenoids containing at least one allylic hydrogen atom to give the corresponding hydroperoxides.[29]

However, the history of oxidations catalyzed by NHPI started in 1995 when Ishii and co-workers, extrapolating from Masui's and Foricher's results, reported that, in the presence of oxygen and catalytic amounts of NHPI, alkanes and alcohols could be effectively oxidized to their corresponding carbonyl compounds and/or carboxylic acids at 100 °C.[30]

Since then, NHPI has been used by Ishii's group and, more recently, by a number of research teams involved in homogeneous oxidation chemistry, to catalyze the oxidation of many different classes of organic compounds. Many patents based on this kind of catalysis have been proposed, particularly by Ishii. In 2001 the Daciel Chemical Company commercialized the process to synthesize dihydroxyadamantane.

The pilot scale trials for the production of adipic acid and terephthalic acid were due to be completed in 2005 by Daicel.[31] The new process produces no nitrogen oxides, is more environmentally friendly,[32] and does not require the use of denitration equipment. Special anticorrosive metals are currently required in the production of terephthalic acid because of the use of bromine. Using NHPI does not require such precautions, so stainless steel is suitable for the equipment.

This new catalytic system has also been used as a catalyst for the in situ production of epoxidizing agents and for the oxidation of KA oil to obtain a useful intermediate for the preparation of caprolactone or caprolactam, as we will discuss later in this review.

The use of NHPI in free radical reactions is suitable not only for classical oxidations but also for some important synthetic transformations such as carbon−carbon, carbon−nitrogen, and carbon−silicon bond formation reactions. Thus, this review of the literature appearing up to the beginning of 2006 will focus not only on the wide range of oxidations carried out with NHPI catalysis but also on the several processes developed for the selective functionalization of organic compounds by forming C−C, C−N, and C−Si bonds.

However, we will first center our attention on the kinetic, thermodynamic, and mechanistic aspects, which have been the object of several studies that provided a better understanding of the key role of *N*-hydroxyphthalimide as a catalyst and, therefore, that also provided a better basis for planning innovative, favorable strategies for the synthesis of products of industrial interest. In the past few years, several research groups, and particularly Ishii's group, have proposed other organocatalysts, which act similarly to NHPI. These catalysts will be discussed later and compared to NHPI.

Figure 2. EPR spectrum of PINO.

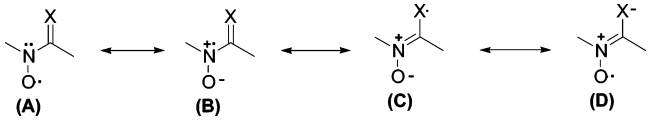


Figure 3. Resonance structures of nitroxides bearing C═X groups.

2. Thermodynamics, Kinetics, and Mechanisms of Processes Catalyzed by NHPI

2.1. Characterization of PINO radical

For reactions of PINO with organic compounds, most of the kinetic data obtained so far have used EPR or UV spectroscopy to follow the variation of PINO concentration (*vide infra*).

The UV spectrum of PINO recorded by Espenson et al.[33] in AcOH had a maximum at 382 nm with a molar absorptivity of 1.36×10^3 L mol^{-1} cm^{-1} while that recorded by Masui et al.[34] in CH_3CN had its maximum at 380 nm and a molar absorptivity of 1.46×10^3 L mol^{-1} cm^{-1}. The wavelengths of maximum absorption and the molar absorptivity of substituted PINO radicals (4-Cl, 4-F, 4-Me, and 3-F PINO) change little from one to the other.[35]

PINO and similar imido-*N*-oxyl radicals have been detected and characterized by ESR spectroscopy since the 1960s.[36] In particular, PINO presents a triplet signal (Figure 2) with a hyperfine coupling constant in *t*-BuOH of a_N = 4.36 G,[37] which is quite small in comparison with that of other nitroxyl radicals.[38] On the other hand, the *g*-factor of PINO, g = 2.0073, is larger than that of other nitroxyl radicals, and this is a well-known effect due to the presence of acyl groups linked to the nitrogen atom.

In nitroxides with coniugated C═X groups, the decrease of a_N is a well-known effect and is easy to understand on the basis of the resonance structures **A**−**D** (Figure 3): the effect is due to the delocalization of spin density on X (structure **C**) when X is a carbon atom, while it is due to a redistribution of spin density from the nitrogen to the oxygen of the NO group (structure **D**) when X is the strongly electronegative oxygen atom.[37] Thus, while substitution of an alkyl with an aryl group induces a decrease of spin density on both the nitrogen and the oxygen atom, substitution with an acyl group produces a strong decrease of spin density on nitrogen and a small increase on oxygen. The latter effect is consistent with the larger *g*-value measured in acyl nitroxides.[37]

The π-spin density, ρ_N, at the nitrogen can be calculated by eq 3.[40]

$$\rho_N = a_N\,(\mathrm{G})/33.1\ \mathrm{G} \qquad (3)$$

PINO, with ρ_N = 0.13, is essentially an oxygen centered radical due to the destabilization of resonance structure, with the unpaired electron delocalized on the nitrogen atom induced by the presence of two carbonyl groups.

2.2. Electrochemical Behavior

Knowledge of the electrochemical behavior of NHPI is of crucial importance, since it is often involved as a catalyst in redox reactions. Most of the relevant data is derived from cyclic voltammetry (CV) done under a variety of different conditions.

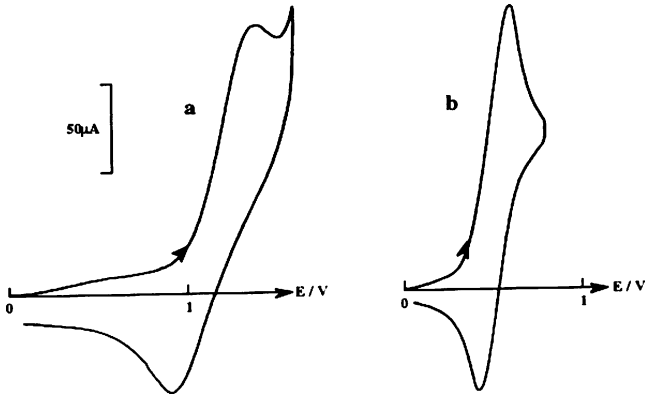


Figure 4. CV in a solution of 4-chloro-*N*-hydroxyphthalimide in acetonitrile: curve a, in the absence of collidine; curve b, in the presence of 1 molar equiv of collidine. **(**Reprinted from ref 41, Copyright 1998, with permission from Elsevier.)

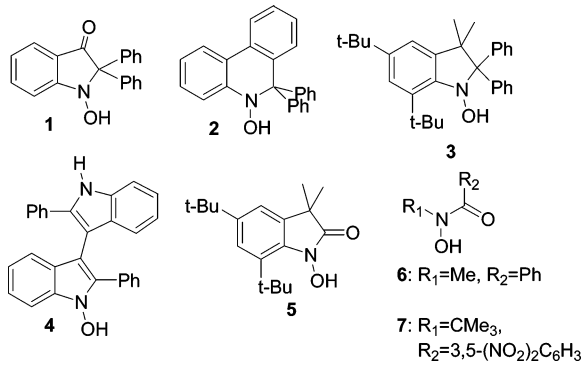


Figure 5. A series of *N*-hydroxy derivatives.

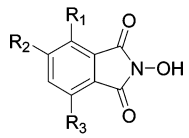
The CV of NHPI was first reported by Masui et al.[34] in CH_3CN containing 0.1 M $NaClO_4$ and 10 mM pyridine with an NHPI concentration of ca. 5 mM. Under these conditions, it showed a nearly reversible redox couple at 0.78 V vs SCE.

A more systematic study of the electrochemical behavior of NHPI and its derivatives was reported by Lepretre, Saint-Aman, et al.,[41] who describe the CV of NHPI and some derivatives. For example, the CV of 4-chloro-*N*-hydroxyphthalimide, shown in Figure 4, exhibits an anodic peak at E_{pa} corresponding to the one-electron oxidation of NO−H, leading to N−O$^{\bullet}$. The reduction of this radical occurs on the reverse scan at E_{pc}. Upon addition of 1 equiv of a basic agent such as collidine, the hydroxylamine moiety is deprotonated, leading to a one-electron reversible wave at an $E_{1/2}$ value less positive than that in the absence of collidine. These authors also found that the $E_{1/2}$ values for substituted NHPIs in the presence of collidine were linearly dependent on the σ Hammett parameter of the substituent, which shows that the oxidizing character of the nitroxyl radical is correlated to the electronic effect of the substituent.

Lanzalunga et al.[42] determined the CV in buffered aqueous solutions (pH = 5) for various NHPI derivatives. The $E_{1/2}$ value for NHPI, determined as $(E_{pa} + E_{pc})/2$ for the one-electron reversible wave, was 1.08 V versus NHE.

2.3. Thermochemistry

The reactivity of PINO and related radicals in hydrogen abstraction reactions is strongly dependent upon the BDE of the NO−H bond formed as the H is abstracted from the substrate.



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9a 4-CH_3OCO-NHPI
9b 3-F-NHPI
9c 4-CH_3-NHPI
9d 4-CH_3O-NHPI
9e 3-CH_3O-NHPI
9f 3,6-$(CH_3O)_2$-NHPI

R_1 = H	R_2 = CH_3OCO	R_3 = H
R_1 = F	R_2 = H	R_3 = H
R_1 = H	R_2 = CH_3	R_3 = H
R_1 = H	R_2 = CH_3O	R_3 = H
R_1 = CH_3O	R_2 = H	R_3 = H
R_1 = CH_3O	R_2 = H	R_3 = CH_3O

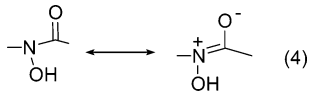
Figure 6. A series of ayl-substituted *N*-hydroxyphthalimides.

Table 2. BDE Values of O−H Bonds for *N*-Hydroxy Derivatives

N-hydroxy derivative	BDE (kcal/mol)
1	69.6
2	70.6
3	71.4
4	69.7
5	78.5
6	79.2
7	80.2
NHPI	88.1

A thermochemical study was undertaken by Pedulli et al.[37] to investigate the effect of alkyl, aryl, and carbonyl substituents on the BDE values of the O−H bond in a series of *N*-hydroxy derivatives (**1**−**7**, Figure 5) including NHPI. The BDE values obtained by using the EPR radical equilibration technique are shown in Table 2.

The carbonyl groups adjacent to the nitrogen atom considerably increase the BDE values of the O−H bonds in the *N*-hydroxy derivatives. Three factors, which are depicted in eqs 4 and 5 and in structure **8,** appear to be important in increasing the strength of the O−H bonds. The resonance in eq 4 and the hydrogen bonding in structure **8** stabilize the acyl hydroxylamines, while the resonance in eq 5 destabilizes the nitroxyl radical.



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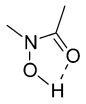

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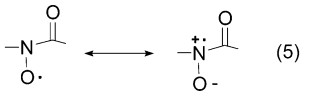


(5)

The same effect was observed for an adjacent acyl group in comparing the BDE values of O−H bonds in alcohols (∼104 kcal/mol) to those in carboxylic acids (∼110 kcal/mol) and in similar comparisons of hydroperoxides (∼88 kcal/mol) to peracids (∼93 kcal/mol).

The BDE value of NHPI obtained by Pedulli[37] has been essentially confirmed by Espenson et al.[43] with an estimate using a semiempirical equation based on a thermodynamic cycle.[44]

Lanzalunga et al.[45] have measured the BDEs of a series of aryl-substituted *N*-hydroxyphthalimides (compounds **9a**−**f**, Figure 6) by using the EPR radical equilibration technique. They have observed that the BDE values of the O−H bonds increase with increasing electron-withdrawing strength of the aryl substituent (Table 3).

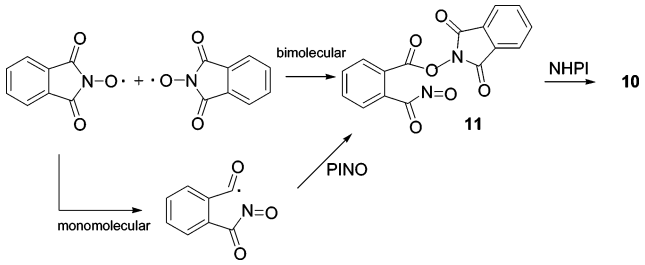
2.4. Self-Decomposition of PINO Radical

The main limitation of free radical processes involving NHPI as a catalyst is the self-decomposition of PINO under the required reaction conditions, especially at the high temperatures (>80 °C) required for the reactions of less reactive substrates such as, particularly, alkanes.

Table 3. O−H BDEs of Aryl-Substituted NHPI Derivatives (9a−f) Measured at −10 °C in CH_3CN

catalyst	BDE (kcal/mol)
9a	88.9
9b	88.6
9c	88.2
9d	87.3
9e	87.9
9f	87.1

Scheme 2. Proposed Mechanism for the Formation of 10

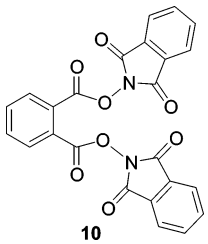


Several kinetic studies following the decay of PINO under different conditions have been done.

Pedulli et al. reported a first-order self-decay of PINO with a $k_d = 0.1\ s^{-1}$,[37] which probably occurs with a fragmentation at one of the carbonyl−nitrogen bonds, similarly to that previously reported by Perkins et al. for another acyl nitroxide.[46]

All of the observed rate constants were scattered in the range of ±10%.

The self-decomposition products of PINO were investigated by the exhaustive electrolysis of NHPI in acetonitrile solution in the presence of pyridine and $NaClO_4$. The trimer **10** was isolated in 71% yield from the resulting solution, and phthalic acid (2.5%) and phthalic anhydride (8%) were also found as byproducts.[34]



10

A possible explanation of the formation of the product **10** involves the steps outlined in the Scheme 2. In this scheme both monomolecular and bimolecular decomposition pathways of PINO are considered even though, under the conditions in which **10** was isolated, the bimolecular pathway seems to be more probable. The reaction between the nitrosyl derivative **11** and NHPI, which acts as a nucleophile toward the nitrosyl group, is an assumption based on a reported

reaction between a nitrosyl derivative and an amine.[47] In addition, the presence of pyridine in the reaction medium may activate a nucleophilic substitution like that which may occur on the nitroxyl derivative **11**.

Espenson et al.[33] have confirmed the second-order self-decay of PINO in both acetic acid and acetonitrile ($k_d = 0.6$ M^{-1} s^{-1} in both AcOH and CH_3CN), but the process seems to be rather slower than that reported by Masui et al. ($k_d =$ 24.1 M^{-1} s^{-1} in CH_3CN).[34] The difference between the Espenson and Masui values for k_d was probably caused by Masui's use of pyridine,[33] which accelerates the self-decomposition of PINO, rather than by the method of generation of PINO (electrolytically in the case of Masui, and with a strong oxidant such as $Pb(OAc)_4$ for Espenson).

Espenson's data have been essentially confirmed by Baciocchi et al.,[48] who have reported k_d's of 0.4, 4.0, and 0.4 in the solvents CH_3CN, CCl_4, and 1,1,1,3,3,3-hexafluoro-2-propanol (HFP), respectively. Despite their strongly different abilities as hydrogen bond donors, the decay rates are very close in HFP and CH_3CN. From these data it can be deduced that the self-decomposition of PINO is little influenced by hydrogen bond formation at the radical center.

Espenson et al. reported the self-decomposition rate constants of substituted PINO radicals and found no great differences in the second-order k_d values between the differently substituted radicals.[33]

The monomolecular decay of PINO may operate in very dilute conditions such as those employed by Pedulli et al.,[37] while the second-order decay can be observed at a higher concentration of PINO such as that generated in the experimental works of Masui,[34] Espenson,[33] and Baciocchi.[48] A reason for this different observed behavior may be the reversible formation of a dimer of PINO. Further work is necessary to confirm this hypothesis.

2.5. Kinetics of Reactions of PINO Radical

The generation of PINO in the presence of an organic compound (R-H) made possible the measurement of a variety of kinetic constants for H-abstraction reactions from R-H (k_{PINO}) (eq 6)

$$\text{R-H} + \text{PINO} \xrightarrow{k_{PINO}} \text{R}^\bullet + \text{NHPI} \qquad (6)$$

Since the radical generated by eq 6 combines with another PINO to form a radical adduct PINO-R, eq 7 below was used for the calculation of k_{PINO}.

$$k_{PINO} = k_{obs}/2[\text{R-H}] \qquad (7)$$

In Table 4 the results are compared when possible with the relative values for hydrogen abstraction by peroxyl radicals ($k_{ROO^\bullet}$) formed during simple autoxidation and by *tert*-butyl peroxyl radical ($k_{t-BuOO^\bullet}$). From this set of data it appears that PINO is more reactive than ROO$^\bullet$ with respect to the same C−H bond, but in general, PINO is even more reactive when compared to the peroxyl radical *t*-BuOO$^\bullet$. These great differences in reactivity cannot be due to an enthalpic effect, in view of the very similar BDEs for the O−H bonds in NHPI and hydroperoxides, which are the products of H-abstractions by PINO and peroxyl radicals, respectively.

In fact, in 1970 Mahoney and DaRooge reported that the BDEs of all hydroperoxides are about 88 kcal/mol[52] while, as discussed above, the BDE of the O−H bond in NHPI is 88 kcal/mol.

In hydrogen-transfer reactions, the other main factor affecting the absolute rate constant is the polar effect.

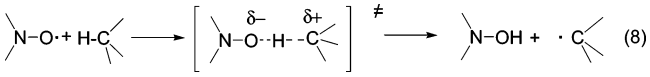
It is well-known that ROO$^\bullet$ radicals, although stabilized by the α-oxygen, are electron-poor species and attack points of high electron density. Evidence of this is given by the application of the Hammett equation to the oxidizability of differently substituted cumenes, which gives a ρ value of −0.43.[53]

The effect of a group at the α position relative to the reactive C−H bond is demonstrated by the difference of reactivity between the ROO$^\bullet$ and the reference radical *t*-BuOO$^\bullet$, as shown by the ratio $k_{ROO^\bullet}/k_{t-BuOO^\bullet}$ (Table 4): the more electron poor the group R, the larger is the ratio $k_{ROO^\bullet}/k_{t-BuOO^\bullet}$.

This effect is highly pronounced in the case of benzyl alcohol, where $k_{ROO^\bullet}/k_{t-BuOO^\bullet} = 37$. This is because the polar effect in the α-hydroxy-α-phenyl peroxyl radical derived from benzyl alcohol is enhanced relative to that in *t*-BuOO$^\bullet$. The presence of a phenyl group has a similar effect, although less pronounced, as in the case of ethylbenzene and toluene, whereas with cumene this effect is not observed, probably because of the steric effects of two methyl groups α to the −OO$^\bullet$ group.

The presence of O, N, and S atoms greatly enhances the reactivity of adjacent C−H bonds. The facile autoxidation of ethers is notorious because of the hazardous peroxides produced.

When the same reactions are carried out in the presence of NHPI rather than peroxides, PINO radical is always found to be more reactive than peroxyl radicals in the hydrogen abstraction step, as is apparent from the relevant ratio ($k_{PINO}/k_{ROO^\bullet}$ or $k_{PINO}/k_{t-BuOO^\bullet}$) in Table 4. This can only be explained by the fact that the H-abstraction polar effect for PINO radical is stronger than that for peroxyl radical, which leads to a greater stabilization of the partial charge in the transition state during the hydrogen-transfer reaction using PINO than in the hydrogen-transfer reaction using peroxyl (eq 8).



(8)

From the data in Table 5, where the rate constants and their ratios for the reaction of PINO and *t*-BuOO$^\bullet$ are reported, it is clearly evident that although both of these reagents are electrophilic radicals, the polar effect is much more pronounced with PINO than with *t*-BuOO$^\bullet$: in that table, the more electron rich the substituted toluene, the larger is the ratio $k_{PINO}/k_{t-BuOO^\bullet}$.

The polar effect may be emphasized by changing the nature of the abstracting species, which in this case means introducing suitable substituents into the aromatic ring of NHPI. Lanzalunga and co-workers[45] have used a series of aryl-substituted *N*-hydroxyphthalimides (compounds **9a**−**f**) as catalysts for the aerobic oxidation of primary and secondary alcohols. With increasing electron-withdrawing strength of the aryl substituent, they have observed both higher BDE values for the O−H bonds, as determined by

Table 4. Second-Order Rate Constants (M^{-1} s^{-1}) for Hydrogen Abstraction by PINO, ROO•, and *t*-BuOO• Radicals (per Reactive H)

R-H	$k_{ROO•}$[a]	$k_{t-BuOO•}$[a]	k_{PINO}[b]	$k_{ROO•}/k_{t-BuOO•}$	$k_{PINO}/k_{ROO•}$	$k_{PINO}/k_{t-BuOO•}$
9,10-dihydroanthracene	82.5	17.5	2510 (E)	4.7	30.4	143
benzhydrol			57.5 (E)			
Ph_3CH			58.5 (E)			
fluorene			20.3(E)			
isopropanol			1.89 (M)			
cyclohexanol			4.52 (M)			
benzyl alcohol	2.4	0.065	5.65(E)	37	2.4	87
Ph_2CH_2	1.05	0.25	6.63 (E)	4.2	6.3	25.5
tetralin	1.6	0.5	10.8 (M)	3.2	6.7	21.6
cumene	0.18	0.22	3.25 (P)	0.81	18	14.8
ethylbenzene	0.65	0.10	1.12 (P)	6.5	1.72	11.2
1-methylnaphthalene			1.43 (E)			
toluene	0.08	0.012	0.127 (P)	6.7	1.6	10.5
cyclohexane		0.00026	0.0039 (P)			15
adamantane (4 reactive tertiary-H considered)			0.0118 (P)			
cyclopentene			7.1 (M)			
cyclohexene	1.5	0.75	5.05 (M)	2	3.4	6.7
trans-4-octene			3.2 (M)			
2,3-dimethyl-2-butene			6.47 (M)			
tetrahydrofuran	1.1	0.085	0.72 (M)	12.9	0.65	8.5
dibutyl ether			0.375 (M)			
dibutyl sulfide			9.075 (M)			
N-acetylpyrrolidine			11.9 (M)			
N-benzolypyrrolidine			6.55 (M)			
N-benzoylpiperidine			0.144 (M)			

[a] Reference 58. [b] (E) = Espenson (ref 43); (M) = Masui (ref 34); (P) = Peduli (ref 37).

Table 5. Second-Order Rate Constants (M^{-1} s^{-1}) for Reaction of PINO and *t*-BuOO•, Per Reactive H, at 25 °C

Ar−CH_3	$k_{t-BuOO•}$	k_{PINO}	$k_{PINO}/k_{t-BuOO•}$
4-MeO	0.0277	3.43	124
4-Me	0.0186	0.992	53.3
3-Me	0.0117	0.509	43.5
none	0.0103	0.207	20
4-NO_2	0.0048	0.0395	8.2

using the EPR radical equilibration technique (Table 5), and more negative ρ values in the Hammett correlation with σ^+ (Figure 7).

Baciocchi et al.[48] have reported that the reaction of PINO with phenols is much faster than the reaction with C−H bonds which have a similar BDE, as shown in Table 6. In that data, one also sees the expected trend linking increasing k_H with increasing electron richness in phenols. These data give a good Hammett correlation (using σ^+) with a relatively large $\rho = 3.1$, which would suggest a strong polar effect.[48]

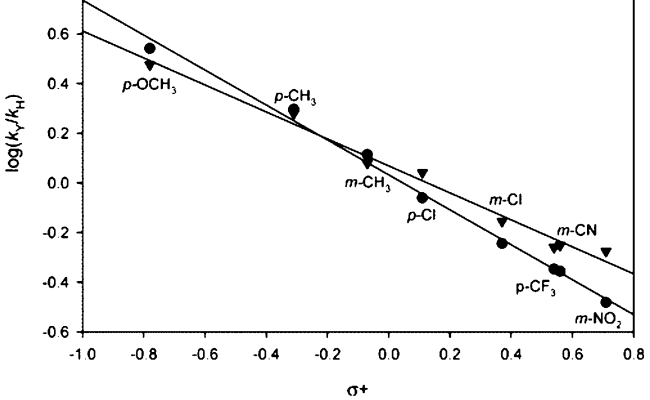


Figure 7. Hammett plot for the oxidation of different benzylic alcohols with the **9a**/Co(II)/*m*-CBA/O_2 (●, $\rho = -0.70$) and **9f**/Co(II)/MCBA/O_2 (▼, $\rho = -0.54$) systems.

Table 6. Second-Order Rate Constants (M^{-1} s^{-1}) for the Reaction of PINO Radical with 4-X-Substituted Phenols in CH_3CN at 25 °C

X	k_H[a]	k_D[b]	k_H/k_D
CN	6.0	1.6	3.7
CF_3	6.4		
$COOCH_2CH_3$	23.0		
Br	248		
Cl	298		
H	328	102	3.2
C_6H_5	2680		
CH_3	2850	910	3.1

[a] Reaction run in CH_3CN containing 1% CH_3COOH. [b] Reaction run in CH_3CN containing 1% CH_3COOD.

Actually, a factor of crucial importance should be considered in drawing this conclusion: it is well-known that the BDE of a phenol is strongly influenced by the nature of the substituents on the aromatic ring.[54] In particular, considering substituents in the para position, electron-donating groups lower the O−H BDE relative to phenol while electron-withdrawing groups raise it. Furthermore, these O−H BDEs correlate linearly with σ^+.[54]

Thus, the negative ρ may be ascribed both to polar and to enthalpic effects, with the latter prevailing. This is a very clear example of a case in which a Hammett correlation does not simply express the presence of a polar effect in free radical reactions. The BDE of all of the reactive bonds considered in the correlation should be carefully taken into account.

In a study of several examples of H-abstraction from O−H bonds by oxygen centered radicals, Ingold et al.[55,56] also found a significant solvent effect in the reaction between PINO and phenol (Table 7).

PINO reacts much faster with O−H bonds than with C−H bonds having the same BDE. This conforms to the general observation that H transfer between −OH and −O• is favored kinetically over transfers between −CH and −O• even where

Table 7. Rate Constants for Reaction of PINO with Phenol in Various Solvents at 25 °C

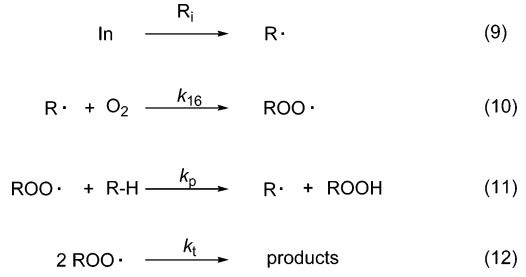
solvent	k_{PhOH} (M^{-1} s^{-1})
HFP	$>3 \times 10^3$
CCl_4	$>3 \times 10^3$
AcOH	550
CH_3CN	328

Table 8. Overall Chain-Termination Rate Constants for Autoxidation of Organic Compounds in Solution at 30 °C

peroxyl[a]	$2k_t$ ($\times 10^{-6}$ M^{-1} s^{-1})
hydro[b]	1260
methyl	370
n-butyl	43
sec-butyl	1.5
tert-butyl	0.0013
cyclohexyl	2
1,1-dimethylbenzyl	0.015
1-tetralyl	7.6
tetrahydrofuranyl	3
cyclohexenyl	5.6
p-methylbenzyl	300
oct-2-en-1-yl	260
2,5-dimethylhex-3-en-2-yl	0.18
1-phenylethyl	32
diphenylmethyl	28

[a] In most cases the parent substrate is the solvent. [b] In chlorobenzene.

Scheme 3. Mechanism for the Free Radical Chain Process of Autoxidation



the BDEs for the −OH and −CH are similar. Shaik et al.[57] explain this phenomenon by a VB model in which the H transfer between oxygen atoms involves the formation of a hydrogen bond in the transition state, where each terminal H is oriented toward the lone pair of the oxygen in the other terminus. The hydrogen bond present in the O···H···O system lowers the activation energy relative to that for the O···H···C, where such an interaction is not present.

2.6. Reaction Mechanism of Autoxidation in the Absence and in the Presence of NHPI

The generally accepted mechanism for the autoxidation reaction is a free radical chain, characterized by initiation, propagation, and termination steps, as outlined in Scheme 3.[58] Usually, oxygen addition to R• (eq 10) is diffusion controlled ($k_{16} \sim 10^9$ M^{-1} s^{-1} at 30 °C),[59] while k_p ranges from 10^{-4} to 10^4 M^{-1} s^{-1}, depending on the nature of R-H and ROO•.[60] Thus, [ROO•] ≫ [R•] and ROO• can be considered the only species involved in the termination step, while eq 11 represents the rate-determining step in the propagation phase.

With a chain length above ca. 10, the overall rate of autoxidation is expressed by eq 13.

$$R = -\mathrm{d}[O_2]/\mathrm{d}t = k_p[RH](R_i/2k_t)^{1/2} \quad (13)$$

The value of $2k_t$ varies by a factor of about 10^5, as shown in Table 8.[58]

Equation 13 predicts that the rate does not depend on oxygen pressure. This is not true at very low oxygen pressures, since in this case the termination phase may involve alkyl radicals R•, which were not trapped because of the insufficient concentration of O_2.

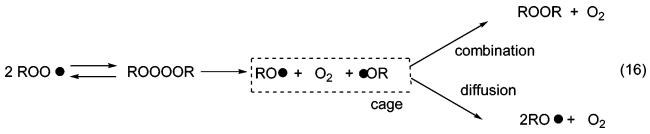
For a given R_i, R depends on the rate constant ratio, $k_p/(2k_t)^{1/2}$, known as the *oxidizability* of an organic substrate. Another important parameter concerning the autoxidation is the kinetic chain length, which is the ratio between the overall rate, R, and the rate of chain initiation, R_i (eq 14).

$$R/R_i = k_p[RH](2R_ik_t)^{-1/2} \quad (14)$$

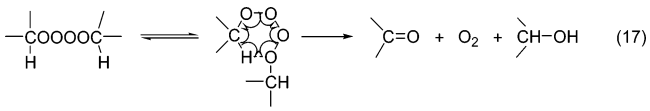
The lifetime of a kinetic chain is obtained by the ratio between the peroxyl radical concentration and its destruction rate (eq 15).

$$[ROO^\bullet]/2k_t[ROO^\bullet]^2 = k_p[RH]/2k_tR \quad (15)$$

The BDEs of the C−H bonds strongly influence k_p, while the major factor affecting k_t is whether the peroxyl radical is primary, secondary, or tertiary. In fact, the k_t is much higher for primary and secondary hydrocarbons than for tertiary ones. The termination step in all cases involves the formation of the tetraoxide ROOOOR, which, in the case of tertiary peroxyl radicals, dissociates in the cage to molecular oxygen and two alkoxyl radicals (eq 16) with a relatively slow rate, e.g., $k_t = 6.5 \times 10^2$ M^{-1} s^{-1} for R = *tert*-butyl. The two alkoxyl radicals in the cage can combine to form the di-*tert*-butyl peroxide or escape the cage by diffusion.[61]



On the other hand, according to the Russell mechanism, primary and secondary peroxyl radicals react by a nonradical, six-center 1,5-H-atom shift, leading to the formation of equal yields of alcohol and ketone (eq 17).



These two mechanisms explain the large difference between the termination rates for primary or secondary peroxyl radicals, both of which do have α H atoms, and the termination rates for tertiary peroxyl radicals, which do not have α H atoms.

From eqs 16 and 17 it might be deduced that, unlike the case for tertiary peroxyl radicals, all intermolecular interactions of primary and secondary radicals in solution at low temperature are chain terminations. However, this is not always true, and nonterminating interactions have been observed for primary and secondary peroxyl radicals at room temperature.[61]

In the presence of NHPI as catalyst, two more steps should be added to the noncatalyzed reaction (eqs 18 and 19).[37]

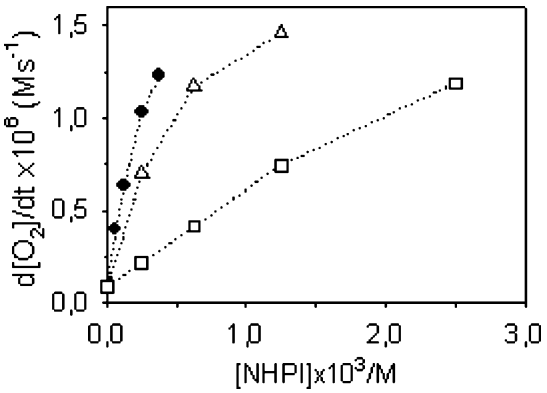


Figure 8. Dependence of the oxygen consumption rate, observed during autoxidation of cumene (0.89 M) at 30 °C in chlorobenzene, on the NHPI concentration. The three plots were obtained at different concentrations of CH_3CN: ●, 0.5%; △, 3%; □, 37.5%.

Thus, the new expression for the rate of the autoxidation, under the assumption that the steady state approximation holds for all free radical species, contains a second term, as shown in eq 20.

$$R'_2NO\text{-}H + ROO^\bullet \xrightarrow{k_f} R'_2NO^\bullet + ROOH \qquad (18)$$

$$R'_2NO^\bullet + RH \xrightarrow{k_H} R^\bullet + R'_2NO\text{-}H \qquad (19)$$

$$R = -\frac{d[O_2]}{dt} = k_p[RH]\left(\frac{R_i}{2k_t}\right)^{1/2} + k_f[R'_2NO\text{-}H]\left(\frac{R_i}{2k_t}\right)^{1/2} \qquad (20)$$

Working at low concentrations of R-H, the only important term in eq 20 is the last one, and therefore, the rate of oxidation is expected to depend on three parameters: (a) the NHPI concentration; (b) the square root of the rate of initiation, R_i; and (c) the inverse of the square root of the rate of termination of the peroxyl radicals.

The first two predictions have been verified experimentally. In particular, from the autoxidation of cumene in chlorobenzene at 30 °C, Pedulli and co-workers[37] obtained a linear correlation between the rate of oxygen consumption and the NHPI concentration, at least for very low levels of NHPI. At higher concentrations of NHPI, the rate of oxidation was lower than expected (Figure 8).

The independence of the reaction rate from the cumene concentration as predicted by eq 20 has been demonstrated by the same research group by carrying out reactions at different concentrations of cumene, in both the presence and the absence of NHPI, and then subtracting the rate of noncatalyzed oxidations from the rate of catalyzed oxidations (Figure 9).[37]

Finally, they studied the solvent effect for this kind of reaction by carrying out experiments in the presence of different amounts of acetonitrile. On increasing the acetonitrile concentration, a large reduction in the rate of reaction as well as a decrease in the nonlinearity of the plots was observed (Figure 10). This trend was explained by the formation of hydrogen bonds between CH_3CN (a good hydrogen-bond-accepting solvent) and the hydroxyl proton of NHPI.

These results were analyzed on the basis of a simple model proposed by Ingold and co-workers,[55] which states that the hydrogen bonding acceptor (HBA) solvent S and R'_2NO-H give rise to a 1:1 hydrogen-bonded complex $R'_2NO-H\cdots S$

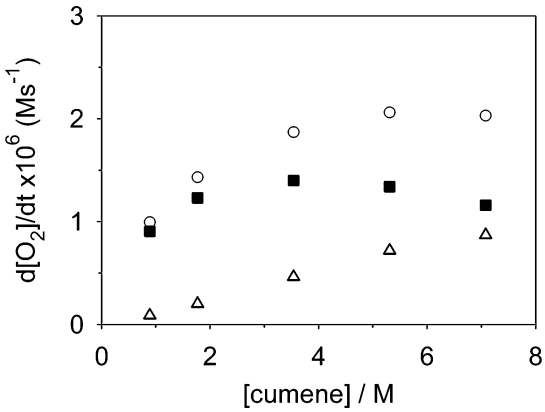


Figure 9. Oxygen consumption rates at 30 °C observed during the autoxidation of cumene, at increasing concentration, in chlorobenzene and 0.5 % CH_3CN: △, without NHPI; ○, in the presence of 2.5×10^{-4} M NHPI; ■, difference between the catalyzed and the noncatalyzed oxygen consumption rates.

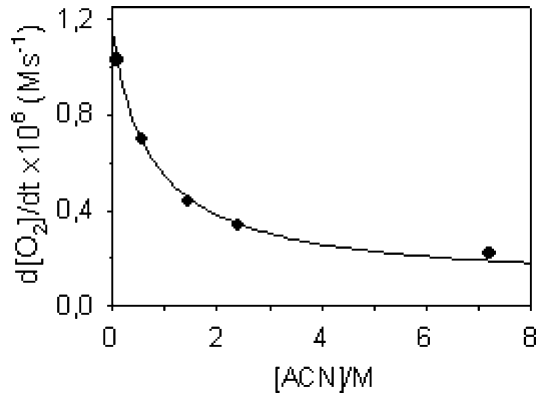
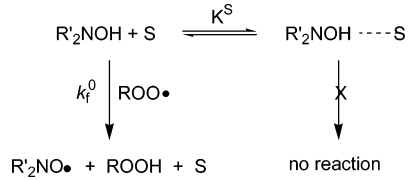


Figure 10. Dependence of the oxygen consumption rate, observed during autoxidation of cumene (0.89 M) at 30 °C in chlorobenzene, on the content of the CH_3CN in solution, at a NHPI concentration of 2.5×10^{-4} M.

Scheme 4. Complex Formation between a HBA Solvent (S) and the Substrate (R_2NO-H)



which is much less reactive toward peroxyl radicals but which is in equilibrium with the hydroxylamine (Scheme 4).

Thus, by using the measured values of $R_i = 5.5 \times 10^{-9}$ M s^{-1} and $2k_t = 1.6 \times 10^4$ M^{-1} s^{-1} in chlorobenzene at 30 °C,[62] it has been possible to determine the kinetic constant for the peroxyl hydrogen abstraction from NHPI ($k_f° = 7.2 \times 10^3$ M^{-1} s^{-1}) and the equilibrium constant for the complexation of NHPI by CH_3CN ($K^S = 1.3$ M^{-1}).[37]

Although eq 20 allowed the determination of the key absolute rate constant for eq 18, it should be noted that it is valid only under NHPI concentrations that are very low relative to the normal operational conditions (0.02−0.2 M). Under these conditions, the steady state approximation is not valid, and in a more complex kinetic expression, eq 19 is presumably the rate determining step. This is due to the increased reactivity of PINO radical with respect to peroxyl radicals, which, on the other hand, are quenched by NHPI with a relatively fast reaction (eq 18).

Realistically, as suggested by Hermans et al.,[63] the reaction between ROO• and NHPI is reversible (eq 21) even if, as is estimated by a DFT calculation, the reaction is shifted to the right for NHPI (K_{21}(NHPI) = 32.4).

$$R'_2NO\text{-}H + ROO^\bullet \overset{k_t}{\rightleftharpoons} R'_2NO^\bullet + ROOH \qquad (21)$$

With *N*-hydroxysuccinimide (NHSI), the same kind of calculation gives K_{21}(NHSI) = 0.06, which means that NHPI is in general a much more active catalyst for aerobic oxidations, as is confirmed experimentally.[30,33]

As stated by Hermans, "the driving force of the catalytic activity of NHPI is that equilibrium of eq 21 is shifted towards the non-terminating PINO chain propagation radicals". Obviously, the catalyst efficiency is also determined by the ratio $k_{PINO}/k_{ROO•}$ in the hydrogen abstraction from R-H (see Table 4), and, therefore, also from the couple R′$_2$NO-H/R-H.

A reduction in the overall termination rate like that observed in the presence of NHPI has been reported when the classical autoxidation is carried out in the presence of a hydroperoxide. For example, Thomas discovered that the rate of autoxidation of cumene is increased by ca. 60% by the addition of cumene hydroperoxide.[64]

In these cases, the rapid exchange reaction reported in eq 22 increases the stationary concentration of the ROO• as a consequence of the decrease of $2k_t$ because the main reaction in which the peroxyl radicals are involved is the self-exchange process of eq 22.

$$ROO^\bullet + R'OOH \rightarrow ROOH + R'OO^\bullet \qquad k_{22} = \text{ca. } 10^3\ M^{-1}\ s^{-1} \qquad (22)$$

The rate constant of the self-exchange reaction of peroxyl radicals and ROOH lies in the same range as the self-exchange between NHPI and its derivatives and their respective nitroxyl radicals.[35] For PINO radical and NHPI, it has been evaluated to be ca. 500 $M^{-1}\ s^{-1}$.[35]

2.7. Autoxidation in the Presence of NHPI and Metal Salt Cocatalysts

It is well-known that the addition of transition metal salts, e.g., Cu, Mn, Co, and Fe salts, catalyzes autoxidation, and for this reason, they are widely used in industrial processes for which the hydroperoxides are not the desired products.

The main role of metal salts, e.g., Co salts, is usually to accelerate the autoxidation reaction by decomposition of the intermediate hydroperoxides, ROOH, leading to the formation of alkoxyl or peroxyl radicals, according to eqs 23 and 24.

$$ROOH + Co(II) \rightarrow RO^\bullet + Co(III) + OH^- \qquad (23)$$

$$ROOH + Co(III) \rightarrow ROO^\bullet + Co(II) + H^+ \qquad (24)$$

The formation of alkoxyl radicals may decrease the selectivity of the autoxidation for two different reasons: they participate in a fast H-abstraction from an available substrate (eq 25), or they undergo a unimolecular β-scission reaction, as for tertiary alkoxyl radicals, which leads to the formation of an alkyl radical and a carbonyl derivative (eq 26).

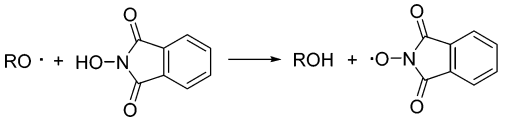
$$RO^\bullet + H\text{-}R \rightarrow ROH + R^\bullet \qquad k_{25} = 10^4\text{–}10^7\ M^{-1}\ s^{-1} \qquad (25)$$

$$R_1R_2R_3CO^\bullet \rightarrow R_1R_2C{=}O + R_3^\bullet \qquad (26)$$

A high concentration of metal salts, usually used in their lower oxidation states, may inhibit the oxidation process because of their ability to reduce the peroxyl radicals to the corresponding alkylperoxyl anions (eq 27).

$$ROO^\bullet + Co(II) \rightarrow ROO^- + Co(III) \qquad (27)$$

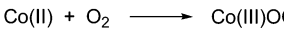
In the presence of both NHPI and metal salts (use of simple $Co(OAc)_2$ is very common), the alkoxyl radicals formed by hydroperoxide decomposition are trapped by NHPI in a diffusion controlled process (eq 28).[50]



(28)

This drastically reduces β-scission, thus favoring, at least in principle, the formation of alcohols. These aspects were experimentally observed in the oxidation of lower weight alkanes: the distribution of the oxygen-containing products depends on the conversion, the reaction conditions, and the alkane structure.

In the presence of metal salts such as Co(II), the autoxidation reaction does not require a thermal initiator, and the initiation probably involves the formation of Co(III)OO• (eq 29), which reacts with NHPI to generate the PINO radical (eq 30).



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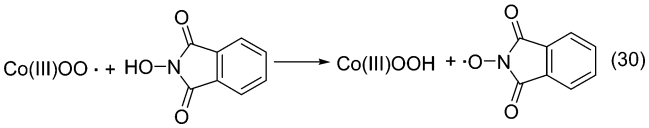


(30)

In most instances, cobalt salts are used in the initiation step because Co(II) binds oxygen molecules with particular effectiveness. The presence of ligands may greatly influence the redox potential of Co(II) and Co(III), which explains the different behavior of different salts and/or complexes.

The nature of the solvent also has a great influence both on NHPI catalysis, as shown before, and on metal cocatalysis.

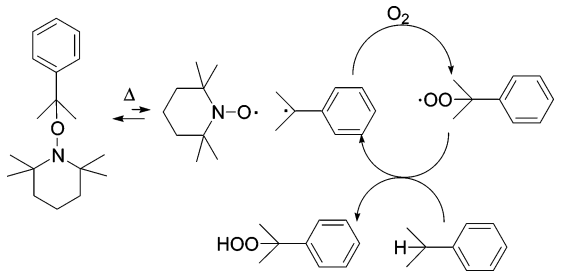
2.8. Persistency of Nitroxyl Radicals and Catalysis of Oxidation Reactions by Nitroxyl Radicals

Hydrogen abstraction by nitroxyl radicals is a topic of interest from both a kinetic and a thermodynamic point of view, as evidenced above. The persistence of these radicals is an important property to consider.

Persistent nitroxyl radicals such as TEMPO are able to abstract hydrogen only from weak hydrogen bonds.[50] Nevertheless, in the photoexcited state, these radical species have been shown to be able to abstract hydrogen atoms from unactivated C−H bonds.[65]

To participate in free chain radical processes in which hydrogen abstraction by nitroxyl radicals is a key step, these radicals in general should not be persistent, because if they are, any possible propagation phase would be interrupted as a consequence of their fast reaction with the carbon centered radicals formed during the process.

Scheme 5. TEMPO Catalyzed Aerobic Oxidation of Cumene to CHP



Even in the presence of oxygen, such as in an autoxidation process, the formation of peroxyl radicals is inhibited when a persistent nitroxyl radical is present. In fact, the trapping rates of carbon centered radicals by oxygen and by persistent nitroxyl radicals are similar, but the concentration of the latter is expected to be sufficiently greater so as to prevent the autoxidation.

An exception is presented by the interesting example of the TEMPO catalyzed aerobic oxidation of cumene.[66] In this case, the key factor is the reversibility of the trapping reaction of cumyl radical by TEMPO, which behaves as it does in the TEMPO mediated free radical living polymerization,[67] lowering the free radical concentration (Scheme 5) and enhancing the selectivity in the formation of cumene hydroperoxide (CHP) as shown in Figure 11. In this case, the TEMPO radical essentially acts only as a reversible trap for cumyl radical and releases it in small amounts to be trapped by O_2. It does not interfere with the peroxyl radicals because the O−O BDE in TEMPO-OOR would be so close to zero as to make no difference.

The oxidation of benzylamines to their corresponding imines in the absence of oxygen by a stoichiometric amount of a persistent radical such as di-*tert*-butyliminoxyl radical is well-known.[68]

On the other hand, stable nitroxyl radicals can catalyze oxidation processes by reaction mechanisms in which they do not act as hydrogen atom abstractors. However, the discussion of such reactions is beyond the scope of this review, so all of the nitroxyl radicals cited henceforth are implicitly assumed not to be persistent.

3. Oxidations Catalyzed by NHPI and Related Radicals

3.1. Oxidation of Alkanes

Nowadays, the selective oxidation of alkanes with high conversion is one of the most challenging problems remaining to be solved. Nevertheless, these kinds of reaction are used in large-scale production of several crucial substrates of industrial and biological interest. For example, cyclohexane is the starting material for the preparation of adipic acid, which, with an annual production exceeding 2×10^6 tons, is one of the most important monomers, since it is widely used for the preparation of a variety of polymers.

The present protocol for the production of adipic acid involves a two-step process: in the first step, cyclohexane is oxidized by air[69] to a cyclohexanone/cyclohexanol mixture known as KA oil. In the second step, the KA oil is oxidized to adipic acid by HNO_3. The main problem related to this method concerns environmental issues, which should require an immediate solution. An excellent solution to this problem has been proposed by Ishii, who, with 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 31). The process is currently under evaluation at pilot scale for further commercial applications.[31] The best result claimed so far is a 73% conversion of cyclohexane with 73% selectivity for adipic acid.

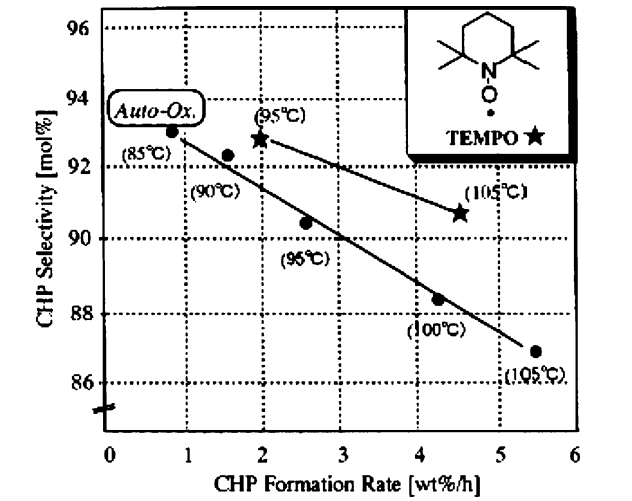
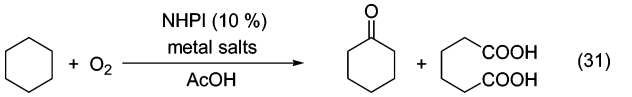


Figure 11. Effect of TEMPO on the conversion and selectivity in the autoxidation of cumene. (Reprinted from ref 66, Copyright 2001, with permisison from Elsevier.)

Table 9. Oxidation of Cyclohexane with Dioxygen Catalyzed by NHPI[a]

				selectivity (%)	
metal salts (%)	*t* (h)	*T* (°C)	conversion (%)	cyclohexanone	adipic acid
	6	100	<1	trace	
$Mn(acac)_2$ (0.5)	6	100	36	20	46
$Mn(acac)_3$ (0.5)	6	100	44	3	77
$Mn(acac)_2$ (1.0)	20	100	73	trace	73
$Mn(acac)_2$ (0.5) $Co(OAc)_2$ (0.05)	24	80	63	trace	69
$Mn(acac)_2$ (1.0) $Co(OAc)_2$ (0.05)	24	80	60	8	64
$Co(OAc)_2$ (0.05)	6	100	40	36	34
$Co(OAc)_2$ (0.05)	6	75	13	78	13

[a] 3 mmol of cyclohexane, 0.3 mmol of NHPI, and metal salts were stirred in 7 mL of AcOH under O_2 at atmospheric pressure.



As shown in Table 9, the simultaneous use of $Co(OAc)_2$ and $Mn(acac)_2$ gave good results at lower temperature. The synergistic effect of Co(II) and Mn(II) catalysis has previously been observed and reported,[70] and more recently it has been discussed by us (Scheme 6)[18] and also by Shimizu and co-workers.[71]

The cobalt salt is particularly effective in the initiation phase, where it activates the molecular oxygen (eq 32). Mn(II), which forms Mn(III) either by oxidation with peroxyl radicals (eq 37) or by a redox reaction with Co(III) (eq 33), is essential for the cleavage of the cyclohexanone, formed at first instance in the autoxidation. This cleavage proceeds through the formation of the α-keto radicals via oxidation of the enol form of the ketone (eq 34). Once formed, the

Scheme 6. Mechanism for the Oxidation of Cyclohexanone to Adipic Acid Catalyzed by $Co(NO_3)_2$ and $Mn(NO_3)_2$

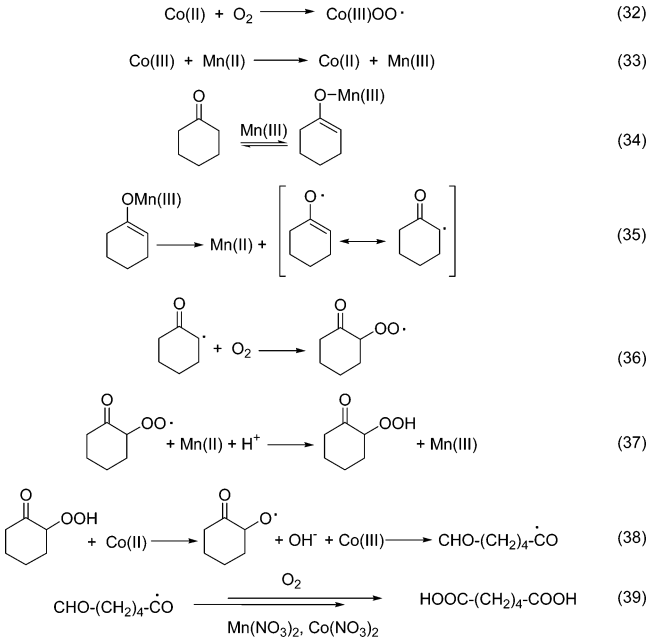


Table 10. Oxidation of Cycloalkanes with Dioxygen Catalyzed by NHPI in the Presence of $Mn(acac)_2$[a]

metal salts (%)	*t* (h)	conversion (%)	selectivity (%) cycloalkanone	selectivity (%) dicarboxylic acid
cyclooctane	100	83	2	53
cyclodecane	100	90	2	55
cyclododecane	70	81	3	68

[a] 3 mmol of cyclohexane, 0.3 mmol of NHPI, and $Mn(acac)_2$ (1%) were stirred in 7.5 mL of AcOH under O_2 at atmospheric pressure for 14 h.

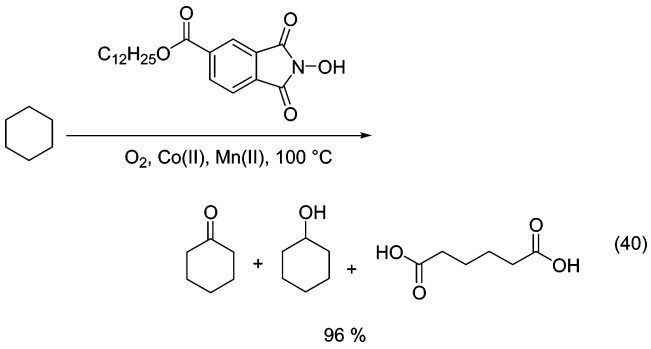
α-keto radicals are quickly trapped by oxygen, leading to the formation of adipic acid (eqs 35−39). This method has been applied to other cyclic hydrocarbons, and the results are reported in Table 10.

These processes are normally carried out in AcOH, acetonitrile, or ethyl acetate due to the low solubility of NHPI in apolar solvents such as hydrocarbons. An example of oxidation in ionic liquids has been reported.[72] Nevertheless, as pointed out by Pedulli et at.,[37] a catalytic process based on NHPI in apolar solvents is expected to be more effective.

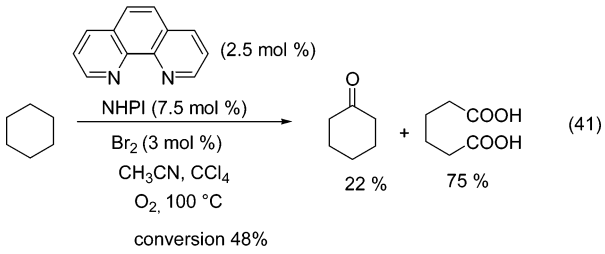
Thus, the use of 4-lauryloxycarbonyl-*N*-hydroxyphthalimide was found to be particularly effective and permits working directly in neat substrate.[73] The oxidation of cyclohexane (∼37 mmol) under air (10 atm) in the presence of the lipophilic NHPI (30 μmol), $Co(OAc)_2$ (3 μmol), and $Mn(OAc)_2$ (0.3 μmol) in the absence of solvent at 100 °C for 14 h leads to the formation of a mixture of cyclohexanone, cyclohexanol, and adipic acid in the ratio 61:28:7 with a conversion of 96% (eq 40).

Sheldon et al. reported the use of *N*-hydroxysaccharin (NHS)[74] as an alternative to NHPI in the catalysis of oxidations of cycloalkanes to open chain dicarboxylic acids. The mechanism of NHS catalysis is expected to be similar to that of NHPI catalysis.

NHS shows greater catalytic activity than NHPI, especially at lower temperatures. This may be caused by its faster H-abstraction from hydrocarbons, which in turn is caused by either or both of an enhanced polar effect and an expected higher BDE of the O−H group in NHS.

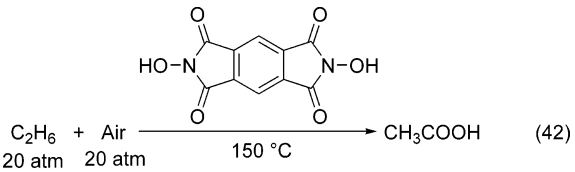


Recently, Xu et al.[75] reported an interesting metal-free aerobic oxidation of cyclohexane to adipic acid and cyclohexanone using catalytic amounts of NHPI, *o*-phenanthroline, and bromine (eq 41).

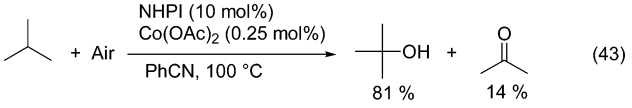


Another important issue in hydrocarbon oxidation is the selective oxidation of lower alkanes, such as methane, ethane, and isobutane. A catalyst for the oxidation of ethane needs to form during H-abstraction an O−H bond with greater BDE than that in NHPI in order to match the larger BDE of the C−H bonds in the methyl groups of ethane (BDE = 100.5).[76]

In fact, as shown in Table 11, *N*,*N*-dihydroxypyromellitimide (NDHPI), an NHPI derivative expected to have a stronger O−H bond, is more effective in the catalysis of the oxidation of ethane to AcOH (eq 42).[77]



The oxidation of isobutane by air (10 atm) in the presence of NHPI (10 mol %) and $Co(OAc)_2$ (0.25 mol %) in benzonitrile at 100 °C for 8 h produced *tert*-butyl alcohol in high yield (81%) along with acetone (14%) (eq 43)



Under the same conditions, 2-methylbutane was converted into acetone and AcOH via C−C bond cleavage rather than into alcohols (eq 44).[78]

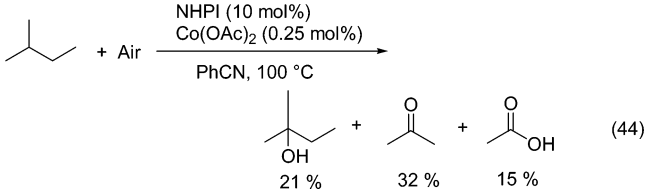
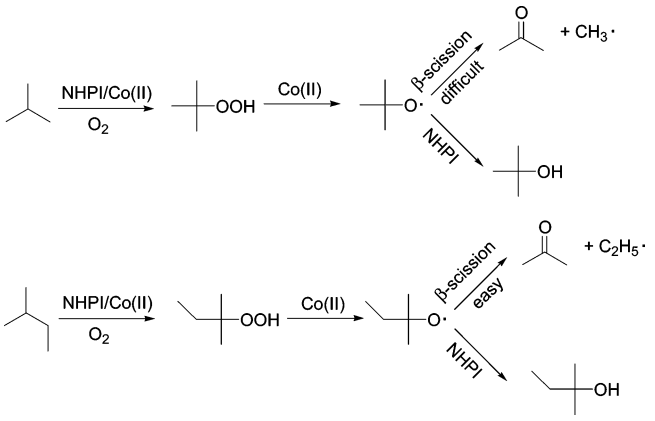


Table 11. Oxidation of Ethane with Dioxygen Catalyzed by Different *N*-Hydroxy Derivatives

catalyst (μmol)	solvent	yield (μmol)	turnover number
NHPI/$Co(OAc)_2$ (200/30)	CH_3CN	530	2.7
NDHPI/$Co(OAc)_2$ (100/30)	CH_3CN	830	8.3
NDHPI/$CoCl_2$ (100/30)	CH_3CH_2COOH	1532	15.3

Scheme 7. Different Reactivity of Isobutene and 2-Methylbutane in the Presence of NHPI under Dioxygen Atmosphere



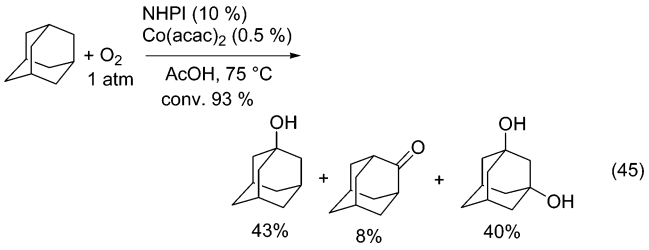
The observed difference is due to the β-scission of alkoxyl radicals, which is much slower for *tert*-butoxyl radical than for 2-methylbutoxyl radical.[79] Thus, for *tert*-butoxyl radical, the diffusion-controlled H-abstraction from NHPI is fast enough to prevent most of the β-scission, while, for 2-methylbutoxyl radical, the formation of the more stable ethyl radicals makes the monomolecular β-scission reaction more favorable than the hydrogen-transfer reaction from NHPI (Scheme 7).

The most important oxidation of isobutane is that which yields *tert*-butyl hydroperoxide. The relatively high BDE value of the tertiary C−H bond of isobutane (BDE = 99.3)[80] and the consequently low expected absolute rate constant for the H-abstraction by PINO radical currently make catalysis by NHPI for the production of *t*-BuOOH impossible because higher temperatures are required and metal cocatalysis must be avoided. However, peroxidation of weaker tertiary C−H bonds (e.g., cumene) to the corresponding hydroperoxides in the presence of NHPI is a facile process, as is shown later.

Adamantane is a noteworthy case in hydrocarbon chemistry. The tertiary C−H bonds have a BDE similar to that of the secondary ones, which is uncommon in hydrocarbon chemistry: secondary C−H bonds are usually stronger than tertiary ones. On these bases, similar reactivity of all of the C−H bonds in adamantane would be expected, but this is not the case.[11] We have clarified this anomalous behavior by means of kinetic studies which demonstrate the exceptional enhanced nucleophilic character of the tertiary C−H bonds and their respective radicals.[81]

As discussed before, the PINO radical is more electrophilic than the peroxyl one. For H-transfer reactions by peroxyl radicals, the relative reactivity of the tertiary C−H bond compared to the secondary C−H bond is 3.8−5.4.[19] However, when the oxidation of adamantane was carried out in the presence of NHPI and $Co(acac)_2$ under O_2 (eq 45), this ratio was found to be 31.1.[82]

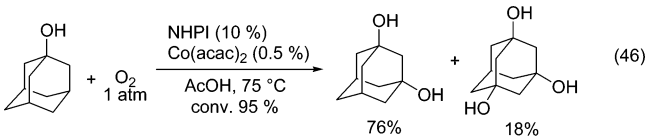
This high selectivity can be ascribed mainly to the reactivity of PINO. In fact, the other radicals possibly



(45)

involved, e.g., alkoxyl radicals, are much less selective (2.7),[83] and it is supposed that they are rapidly trapped by hydrogen abstraction from NHPI in a rapid diffusion controlled process.[50] The high selectivity at the tertiary position permits a good yield of 1,3-adamantanediol, which is rarely produced selectively by conventional oxidations (eq 46).

In a stepwise process, the hydroxylation of adamantane catalyzed by the NHPI/$Co(acac)_2$ system permitted synthesis of 1,3,5-adamantanetriol with high selectivity (eq 47).



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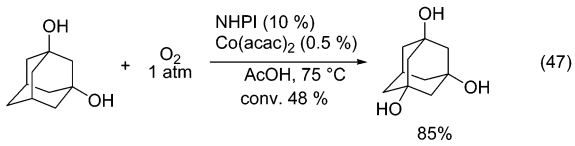
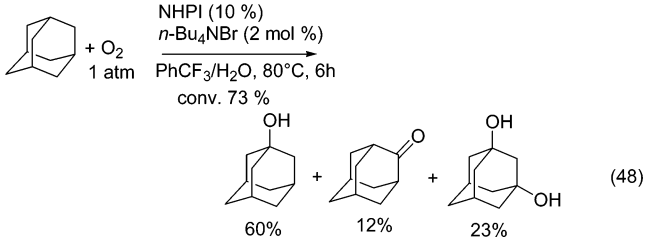


(47)

Both diol and triol, which are used as components of photoresistant polymer materials, are produced industrially by Daicel Chemical Company using this catalytic process.

Adamantane can also be oxidized under metal-free conditions by using a catalytic amount of NHPI in the presence of tetrabutyl ammonium bromide (eq 48).[84]



(48)

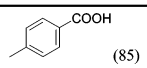
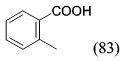
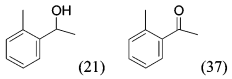
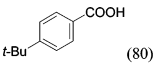
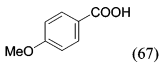
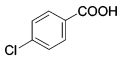
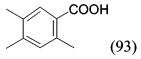
3.2. Oxidation of Alkylaromatics

Several bulk chemicals such as phenol, terephthalic acid, benzoic acid, etc. are produced on a large scale by homogeneous aerobic liquid-phase oxidations. NHPI catalysis of such oxidations gives important improvements in energy consumption and in environmental impact relative to the classical processes.

3.2.1. Oxidation of Methylaromatics

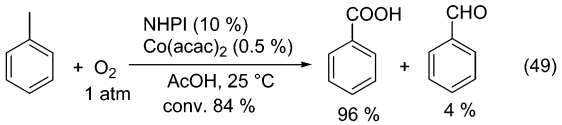
Terephthalic acid, mainly used in the preparation of polyethylene terephthalate, is the most important monomer with ca. 20 million tons produced every year, and benzoic acid is an important intermediate for several applications. These acids are commonly produced by transition metal catalysis of high temperature aerobic oxidations starting from the raw materials *p*-xylene and toluene, respectively.

Table 12. Aerobic Oxidation of Various Alkylbenzenes at Room Temperature[a]

Substrate	t (h)	Conversion (%)	Products (yield (%))
p-xylene	20	95	 (85)
o-xylene	20	93	 (83)
2-ethyltoluene	20	82	 (21) (37)
4-*t*-buthyltoluene	20	95	 (80)
4-methoxytoluene[b]	6	89	 (67)
4-chlorotoluene	20	71	
4-nitrotoluene	20	--	--
1,2,4,5-tetramethylbenzene	12	>99	 (93)

[a] 3 mmol of substrate, 0.3 mmol of NHPI, and $Co(OAc)_2$ (0.5%) were stirred in 5 mL of AcOH under O_2 at atmospheric pressure and room temperature. [b] CH_3CN was used as solvent.

In catalytic amounts, a combination of NHPI and $Co(OAc)_2$ achieved toluene oxidation at room temperature under O_2 at atmospheric pressure (eq 49),[85] but under the same reaction conditions, *p*-xylene was oxidized at just one methyl group, as shown in Table 12. For the oxidation of xylenes to the corresponding dicarboxylic acids, higher temperatures and a combination of Co and Mn salts as cocatalysts are required (eq 50).[86]



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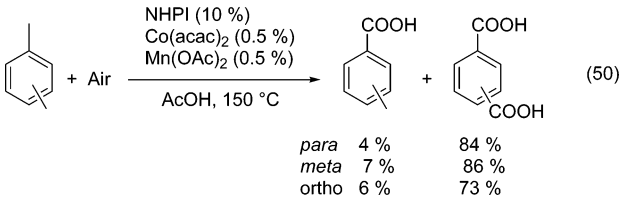
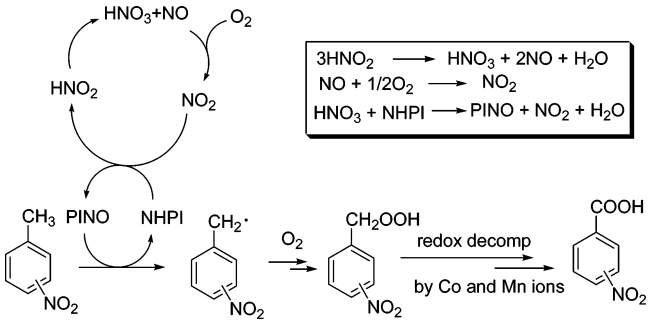


(50)

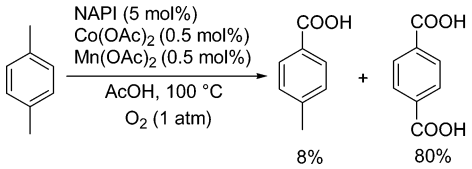
The main drawback associated with NHPI catalysis is its decomposition to inert phthalimide and phthalic anhydride during oxidations in protic solvents such as AcOH. Its degradation, which is faster at higher temperatures, may also involve the PINO radical itself.

A kinetic study of the *p*-xylene oxidation reaction catalyzed by NHPI and substituted *N*-hydroxy-phthalimides was reported by Espenson et al.[87] Important effects covered in that study are the acceleration of the reaction by Mn(II) or Ce(III) metal salts added to $Co(OAc)_2$ and the inhibition of the reaction caused by the decomposition of PINO with the relative breaking of the catalytic cycle.

Scheme 8. Oxidation of Nitrotoluenes Catalyzed by NHPI, NO_2, and a Mixture of Co(II) and Mn(II)



In situ generation of NHPI from *N*-acetoxyphthalimide (NAPI) is an efficient alternative for reducing the degradation of NHPI in high temperature (>100 °C) oxidation processes in protic solvents, as is shown by the oxidation of *p*-xylene to terephthalic acid (eq 51).[87]

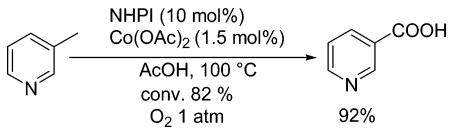


(51)

The oxidation of nitrotoluenes is a more difficult process, but in the presence of catalytic amounts of NO_2, it can give the corresponding acids with relatively good conversions and high selectivity. The role of NO_2 is related to a more effective generation of PINO radicals by hydrogen abstraction from NHPI, as illustrated in Scheme 8.

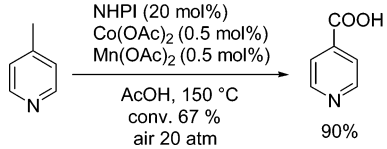
The oxidation of methylpyridines to their respective carboxylic acids, which are important pharmaceutical intermediates, should be straightforward, but it is usually hard to carry out with high selectivity because of their low reactivity.[88]

The oxidation of β-picoline to nicotinic acid, an important precursor of vitamin B_3, is relatively easy to carry out under oxygen in the presence of NHPI/$Co(OAc)_2$ (eq 52).[89]



(52)

On the other hand, the oxidation of γ-picoline under the same conditions affords only 22% of the corresponding acid, and harsher conditions are required in this case to get conversion to a single product with good selectivity (eq 53).[89]



(53)

Quinolines and their derivatives are frequently found in natural products and are used as pharmaceuticals and agrochemicals.[90]

The quinolinecarboxylic acids are commonly obtained by using stoichiometric amounts of transition-state metal salts as oxidants,[91] which has a high environmental impact.

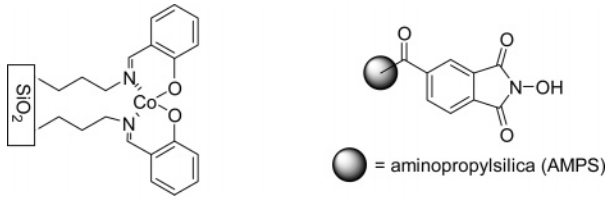


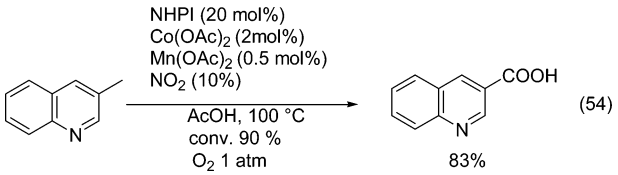
Figure 12. Supported cobalt complexes and NHPI.

Table 13. Oxidation of Alkylbenzenes Catalyzed by NHPI[a]

Substrate	Products (%Yield)	
	(37)	(13)
	(42)	(7)
	(99)	
	(34)	
	(64)	(8)

[a] Substrate (2 mmol) and NHPI (10%) were stirred under a dioxygen atmosphere at 100 °C for 20 h in PhCN (5 mL).

Using the conditions indicated in (eq 54), the oxidation of 3-methylquinoline did not give any product at all. In order to obtain a high conversion (i.e., a 75% yield), a catalytic amount of NO_2 was added to the NHPI/Co(II)/Mn(II) system.[92]



Similar conditions are usually required for the oxidation of other methylquinolines.[92]

Aromatic aldehydes can be prepared in an aqueous medium by oxidation of the corresponding methylbenzenes in the presence of oxygen, the enzyme laccase, and different *N*-hydroxy mediators.[93] Conversions and selectivity depend on the mediator used in the process.

Methylaromatics can be selectively oxidized to benzaldehydes in AcOH with O_2 at 1 atm in the presence of a stable heterogeneous catalytic system consisting of a combination of a cobalt complex supported on SiO_2 and a supported NHPI (Figure 12).[94] However, the reported conversions are low.

3.2.2. Oxidation of Secondary Alkylaromatics

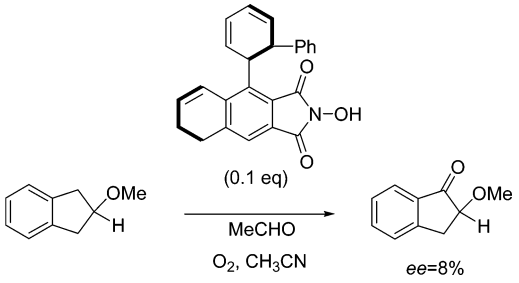
A variety of benzylic compounds can be oxidized to their corresponding oxygenated derivatives by using O_2 in the presence of NHPI, even in the absence of metal salts as cocatalysts (Table 13).[30]

Table 14. Oxidation of Fluorene to the Corresponding Ketone with Dioxygen, Catalyzed by Different *N*-Hydroxy Derivatives[a]

catalyst (%)	yield (%)
NHPI	80
	trace
NHSI	62
NHMI	41

[a] Substrate (2 mmol) and catalyst (10%) were stirred under a dioxygen atmosphere at 100 °C for 20 h.

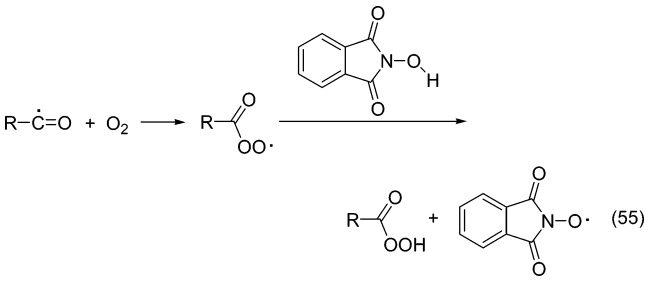
Scheme 9. Enantioselective Oxidation at Benzylic Positions



Other cheap *N*-hydroxyimides, such as *N*-hydroxysuccinimide (NHSI) and *N*-hydroxymaleiimide (NHMI), are commercially available, but as shown in Table 14 in the case of fluorene, their efficiency is much lower than that of NHPI.

Einhorn et al.[95] reported the oxidation of various benzylic derivatives at room temperature catalyzed by NHPI and acetaldehyde, obtaining high conversions.

The acylperoxyl radical generated under these conditions has a crucial role in the formation of PINO (eq 55).



By using a chiral NHPI derivative, this method was employed for the asymmetric oxidation of indane derivatives (Scheme 9).[96]

Although the reported enantiomeric excess is very poor, these preliminary experiments represent, to the best of our knowledge, the first example of the application of organocatalysts in enantioselective aerobic oxidation involving free radicals.[97]

Secondary benzylic C−H bonds can be oxidized at room termperature to their respective ketones by catalyzing the reaction with NHPI and heterogeneous Fe/MgO.[98]

Ethylbenzene is selectively oxidized to acetophenone by a biomimetic system composed of anthraquinone, NHPI, zeolite, and oxygen.[99] It is thought that PINO is formed by an electron-transfer process involving anthraquinone and NHPI (eq 56).

The same group also reported a systematic study of the effect of anthraquinone substituents[100] in the absence of the zeolite. Once the substituents giving the best performance (Figure 13) had been identified, a screening of the reaction on different hydrocarbons was done. (Table 15).

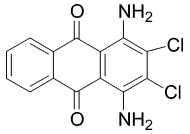
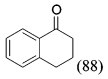
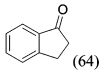
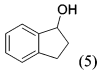
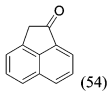
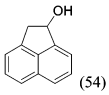
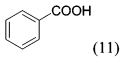
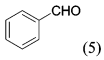
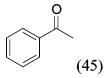
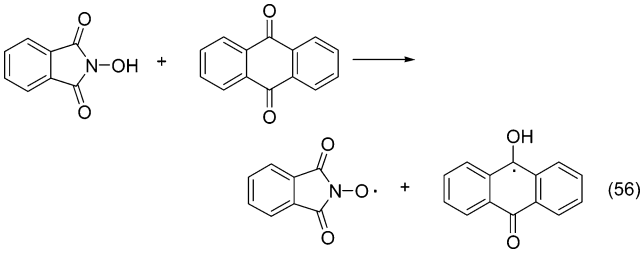


Figure 13. 1,4-Diamino-2,3-dichloroanthraquinone.

Table 15. Oxidation of Alkylbenzenes Catalyzed by 1,4-Diamino-2,3-dichloroanthraquinone and NHPI[a]

Substrate	Conversion (%)	Products (Yield (%))	
	91	 (88)	 (2)
	94	 (64)	 (5)
	92	 (54)	 (54)
	17	 (11)	 (5)
	59	 (45)	 (7)

[a] 5 mmol of substrate, NHPI (5%), and 1,4-diamino-2,3-dichloroanthraquinone (1.25%) were stirred at 80 °C in 10 mL of CH_3CN under 0.3 MPa of O_2.



(56)

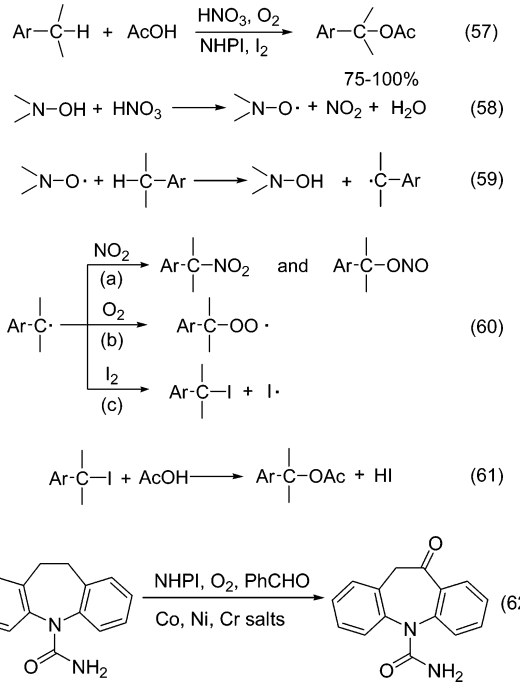
Primary and secondary alkylbenzenes cannot be selectively converted to their corresponding alcohols because the products are of higher reactivity than the starting hydrocarbons.

We have developed a protocol in which the alkylbenzenes are selectively converted into the corresponding acetoxyl derivatives by a metal-free oxidation carried out in the presence of catalytic amounts of NHPI, I_2, and HNO_3 (eq 57).[101] The results are reported in Table 16.

The key steps of this process (Scheme 10) are the trapping of the benzyl radicals by I_2 (eq 60c) and the solvolysis of the alkyl iodides to the corresponding acetates (eq 61). The first key step is favored by keeping the stationary concentration of I_2 much higher than that of both NO_2 and O_2. The introduction of the acetate group decreases the reactivity of the α C−H bonds relative to the starting hydrocarbons.

Oxcarbazepine is used in the treatment of epilepsy to control some types of seizures. The selective oxidation of 10,11-dihydrocarbamazepine to yield oxcarbazepine is difficult because of the instability of the reaction product under classical aerobic oxidation conditions. A systematic study on performing this oxidation using a catalytic amount of NHPI together with benzaldehyde and various metal salt cocatalysts (eq 62) has been reported.[102]

Scheme 10. Mechanism for the Selective Aerobic Oxidation of Alkylbenzenes to the Corresponding Acetoxyl Derivatives



(57)

75-100%

(58)

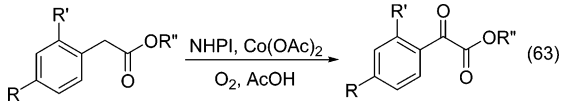
(59)

(60)

(61)

(62)

Arylacetic esters represent another interesting family of benzylic substrates which can be oxidized in the presence of NHPI and $Co(OAc)_2$ to form, in good yields in a few cases, the corresponding aryl glyoxylates (eq 63).[103]



(63)

Table 17 shows that the reactivity of the substituents on the aromatic ring appears much lower than that of the benzylic-CH_2 α to the carboxylic group. Doubly oxidized products were not observed. Electron-donating groups in the 4-position increase the reactivity enough to achieve complete conversion. On the other hand, in the ortho or para position, electron-withdrawing substituents such as Br deactivate the benzylic CH_2 and inhibit the oxidation.

Heteroaromatic substrates are less reactive than the corresponding arylacetic derivatives (Table 18). It is well-known that a pyridine ring deactivates hydrogen abstraction from the benzylic position, since the nitrogen atom has an electron-withdrawing effect. The low reactivity of thiophene and thiazole heterocycles may be caused by the formation of sulfoxides or nitroxides, which would deactivate the substrate for oxidation.

3.2.3. Oxidation of Isopropylaromatics

Selective oxidation of isopropyl aromatics to hydroperoxides is an important process because the hydroperoxides are widely used as epoxidizing agents[7] and as free radical process initiators.[104] But, from the industrial point of view, the largest application of a particular hydroperoxide, the one

Table 16. Oxidation of Hydrocarbons by O_2 and or HNO_3, Catalyzed by NHPI and I_2[a]

substrate	I_2 (mmol)	HNO_3 (mmol)	T (°C)	conversion (%)	selectivity (%)
$PhCH_2Me$	2	0.4	80	100	PhCH(OAc)Me (100)
$PhCH_2Me$	0.8	0.4	80	88	PhCH(OAc)Me (91) PhCOMe (8)
$PhCH_2Me$	0.4	0.4	80	78	PhCH(OAc)Me (78) PhCOMe (23)
$PhCH_2CHMe_2$	2	0.4	80	100	$PhCH(OAc)CHMe_2$ (97)
toluene	0.8	0.4	80	64	$PhCH_2OAc$ (89) PhCHO (11)
p-Cl-toluene[b]	2	4	100	78	*p*-Cl-C_6H_4-CH_2OAc (72) *p*-Cl-C_6H_4-$CH(OAc)_2$ (10) *p*-Cl-C_6H_4-CHO (18)
p-NO_2-toluene	0.8	0.4	100	20	*p*-NO_2-C_6H_4-CH_2I (94)
p-CN-toluene[b]	4	4	100	58	*p*-CN-C_6H_4-CH_2I (86) *p*-CN-C_6H_4-CH_2OAc (14)

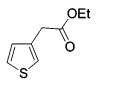
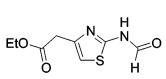
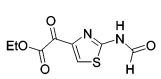
[a] 4 mmol of substrate, 0.2 mmol of NHPI, 0.01 mmol of $Co(OAc)_2$, I_2, and HNO_3 in the amounts reported in the table, in 10 mL of AcOH with O_2 at atmospheric pressure for 6 h. [b] Under nitrogen atmosphere.

Table 17. Benzylic Aerobic Oxidation of Arylacetic Esters Catalyzed by NHPI and $Co(OAc)_2$[a]

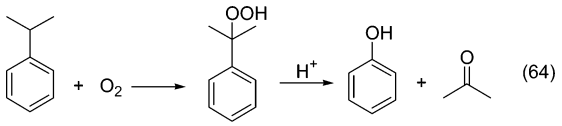
R	R′	R″	conversion (%)	yield (%)
H	OMe	Me	15	0
OMe	H	Me	100	99
H	Br	Me	9	0
Br	H	Me	12	0
H	H	Et	100	73
H	OMe	Et	11	0
OMe	H	Et	100	99
Me	H	Et	100	64

[a] Reaction conditions: 10 mmol of substrate, NHPI (10%), and $Co(OAc)_2$ (0.5%) in 10 mL of AcOH under O_2, at atmospheric pressure and 40 °C.

Table 18. Hydroxysilylation of Alkenes with Et_3SiH, Catalyzed by NHPI

Substrate	Reaction conditions	Product	Yield (%)
	0.5 % Co(II) 20% NHPI 80 °C for 24 hrs		22
	3 % Co(II) 10 % NHPI 40 °C for 16 hrs		21

derived from cumene, is its rearrangement in acidic medium to obtain phenol and acetone (Hock process, eq 64).[105]

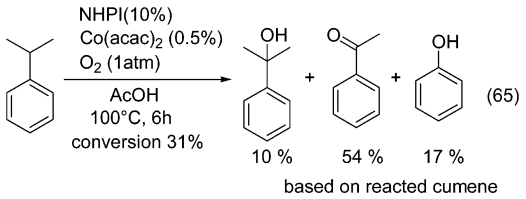


(64)

About 95% of the phenol produced worldwide is manufactured by this method.

Dihydroxyaromatics such as 4,4′-dihydroxydiphenyl and 2,6-dihydroxynaphthalene are useful compounds for the production of liquid crystals and high performance polyesters. In principle, these compounds could be obtained from the corresponding diisopropyl aromatics, 4,4′-diisopropyldiphenyl and 2,6-diisopropylnaphthalene, by processes similar to that for the production of phenol from cumene. Nevertheless, high conversions of both isopropyl groups of the diisopropylaromatics are required for potential industrial applications.

Cumene hydroperoxide is usually obtained by the autoxidation of cumene by using air at high temperatures. Limiting the conversion to ca. 30% gives good selectivity in the hydroperoxide, NHPI catalysis offers different entries to hydroxyaromatic compounds. However, carrying out the reactions using the classical NHPI/Co(II) catalytic system does not lead to the hydroperoxides, since, as already discussed, the metal salt induces hydroperoxide decomposition. Actually, the first data reported by Ishii[106] for using NHPI/$Co(acac)_2$ were unsatisfactory from both the conversion and the selectivity points of view (eq 65).



(65)

The low conversion is due to the inhibiting effect of the phenol, which is formed by the acid-catalyzed decomposition of the cumyl hydroperoxide, and the formation of acetophenone results from cumyloxyl radical β-scission, which is favored both by the protic nature of the solvent[55,107] and by the high reaction temperature.

By understanding the reasons for this failure, we planned to modify the reaction conditions to reduce the formation of phenol and of acetophenone. We succeeded in this purpose by changing the solvent and decreasing the reaction temperature as shown in Table 19.[108]

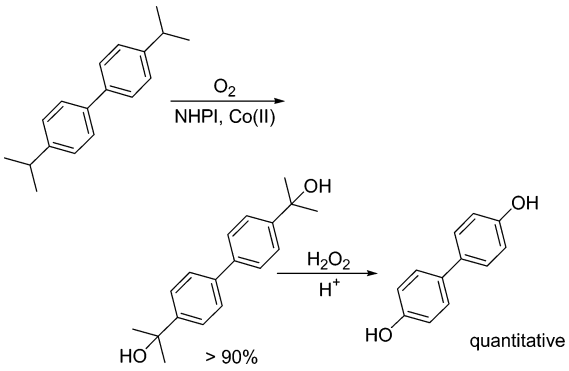
These results suggest that solvents such as chlorobenzene would be particularly convenient for the synthesis of cumyl alcohol. However, the low solubility of NHPI in this solvent does not allow high conversions. This is the major drawback for the oxidation of diisopropylaromatics, since a complete oxidation of both isopropyl groups is required for industrial application of the process.

On the other hand, a highly polar solvent increases the solubility of NHPI but reduces the selectivity for benzyl alcohol. A compromise between these effects is reached by

Table 19. Aerobic Oxidation of Cumene, Catalyzed by NHPI

solvent	*T* (°C)	time (h)	conversion (%)	cumyl alcohol (%)	acetophenone (%)
t-BuOH	50	24	77	62	38
MeCN	80	8	72	69	31
MeCN	70	24	98	76	23
MeCN	50	24	100	91	9
MeCN	40	9	100	99	
Ph-Cl	50	24	40	100	
1,2-$C_6H_4Cl_2$	50	24	64	100	

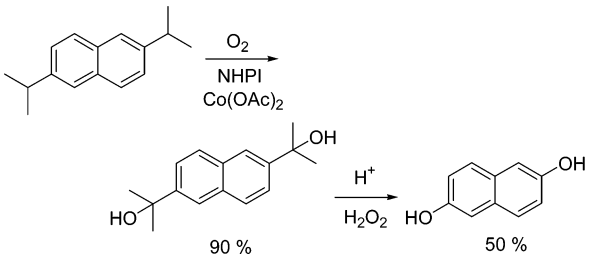
using acetonitrile as solvent, which gives good solubility for the NHPI catalyst and also allows complete conversion of the diisopropylaromatics at a temperature low enough to favor the selectivity for benzyl alcohol. Thus, by working at 40 °C under atmospheric oxygen pressure, yields greater than 90% were obtained for the dibenzyl alcohol of eq 66. That alcohol can be easily transformed in situ to phenols through the dihydroperoxides obtained from acid-catalyzed reaction with H_2O_2 (eq 66).[109]



(66)

The compound 4,4′-di(hydroxyisopropyl)biphenyl was previously prepared by a much more expensive procedure involving reaction of 4,4′-diacetylbiphenyl with MeMgI. It was then reacted with acetic anhydride to yield the 4,4′-diisopropenylbiphenyl, which was used for the synthesis of cross-linked polymers by copolymerization with styrene.[110]

Similar results have been obtained from the catalytic oxidation of 2,6-di-isopropylnaphthalene (eq 67).



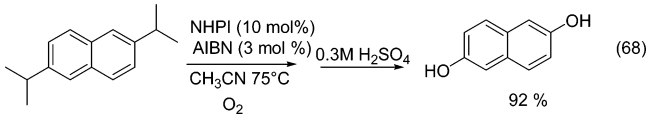
(67)

The mechanism of the formation of the alcohols is the same as that discussed for the oxidation of isobutane to *tert*-butanol.

Also, for diisopropylaromatics, the highly selective conversion of the hydrocarbon to the corresponding alcohol is made possible by diffusion-controlled H-abstraction from NHPI by alkoxyl radical intermediates.

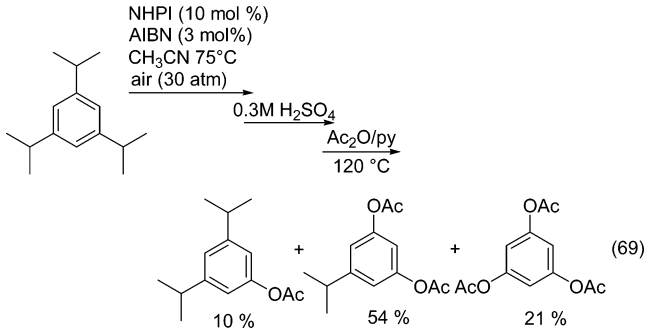
Ishii et al. obtained the 2,6-dihydroxynaphthalene directly from the corresponding diisopropyl derivative by a two-step one-pot reaction (eq 68).[111]

In this case, the reaction proceeds through the formation of the dihydroperoxide, which is converted in situ to the diphenol.



(68)

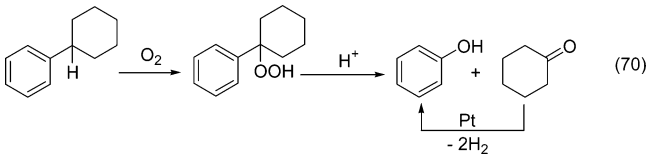
Another intriguing multistep, one-pot process is the synthesis of the 1,3,5-triacetoxybenzene directly from the triisopropyl derivative (eq 69).[112]



(69)

The other products of this reaction are the mono- and the diacetoxy derivatives.

Cyclohexylbenzene is an interesting cheap hydrocarbon which is easily obtained by the acid catalyzed reaction between benzene and cyclohexene. The oxidation of cyclohexylbenzene to the corresponding hydroperoxide has been proposed[113] as a free radical method for the production of phenol and cyclohexanone without coproducts (eq 70).



(70)

In fact, one of the main problems associated with the industrial cumene process is that production of the coproduct acetone exceeds the market demand.

However, by using cyckohexylbenzene instead of cumene, the conversion of the ketonic byproduct (cyclohexanone) into the desired product (phenol) by dehydrogenation is made possible.[114]

Catalysis by NHPI improves the selectivity of the hydroperoxidation of cyclohexylbenzene both when using AIBN as initiator in CH_3CN at 75 °C and when using the 1-cyclohexylhydroperoxide itself as a thermal initiator in neat cyclohexylbenzene at 100 °C.

The higher selectivity of these NHPI catalyzed processes can be explained by a faster scavenging of the intermediate peroxyl radical, which avoids competition from other intramolecular side reactions, as shown in Scheme 11.

3.3. Oxidation of Alcohols

The aerobic oxidations of primary alcohols to the corresponding aldehydes and carboxylic acids, and of secondary alcohols to ketones are fundamental transformations in organic chemistry. Traditionally, such processes have been carried out with the use of a stoichiometric amount of inorganic oxidants.[115] In the last few decades, growing environmental consciousness has suggested that research should be focused on green methods which use clean oxidants such as O_2 and H_2O_2, preferably activated by suitable recyclable catalysts.[7] Very good results have been

Scheme 11. Mechanism for the Aerobic Oxidation of Cyclohexylbenzene to the Corresponding Hydroperoxide

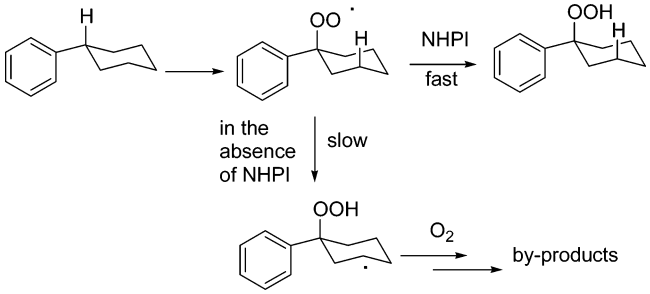


Table 20. Oxidation of Various Alcohols with O_2 Catalyzed by NHPI Combined with $Co(OAc)_2$ at Room Temperature[a]

Alcohol	Conversion (%)	Product	Yields (%)
	75		75
	>99		98
	86		83
	97		94
	59		47
	91		91
	79[b]		78
	70[b]		66
	79		67

[a] Alcohol (3 mmol) was allowed to react with O_2 (1 atm) for 15−20 h in the presence of NHPI (10 mol %), $Co(OAc)_2$ (0.5 mol %), and MCBA (5 mol %) in AcOEt (5 mL) at room temperature. [b] MCPBA (1 mol %) was used instead of MCBA.

obtained by using many different methods based on transition metal catalysts or on an emerging new class of catalysts called organocatalysts,[15] which are composed exclusively of organic molecules.

The oxidation of alcohols catalyzed by NHPI was first reported in a single experiment in 1977[22] and then subsequently studied by Masui et al.[23] in an electrocatalytic version. The yields obtained for the oxidation of secondary alcohols to the corresponding ketones were reasonably good, whereas the yields of aldehydes obtained from the oxidation of the corresponding primary alcohols were rather poor, except in the case of ethanol. The main drawbacks of electrocatalytic oxidation arise from fast degradation of electrogenerated PINO occurring during electrolysis.

Electron-withdrawing substituents on the NHPI molecule are beneficial, but catalyst degradation during electrolysis cannot be avoided.[41] The reaction mechanism involves H-abstraction from the substrate by electrogenerated nitroxyl radical and the subsequent oxidation of the alkyl radical α to oxygen. The resulting carbocation rapidly loses a proton, forming carbonyl derivatives. In the presence of O_2, an autoxidation-like mechanism may occur instead.

The main improvements made by Lepretre, Saint-Aman, et al.[41] by using substituted NHPI concern the selective oxidation of primary alcohols to the corresponding aldehydes under anaerobic conditions. In the presence of oxygen, both aldehydes and acids are obtained. The aliphatic primary alcohols are still relatively inert toward the oxidation, both in the presence and in the absence of oxygen. With weakly activated alcohols, the competitive degradation of the nitroxyl radicals prevents the reaction.

Ishii et al.[30] first reported a nonelectrolytic method for the aerobic oxidation of alcohols catalyzed by NHPI in the presence of a mixed-addenda vanadomolybdophosphate (NPMoV) whose composition is approximately indicated as $(NH_4)_5H_6PV_8Mo_4O_{40}$. NPMoV in its oxidized state ($NPMoV_{ox}$) generates PINO radical from NHPI, and it is reduced to $NPMoV_{red}$, which in turn is reoxidized to $NPMoV_{ox}$ by O_2. PINO radical is the actual species abstracting H from the alcohol to produce a radical, which, once trapped by O_2, leads to the formation of the carbonyl compounds.

The results obtained by this system are not satisfactory. By using the simple $Co(OAc)_2$ together with NHPI, Ishii et al.[116] in general obtained better results for both the conversions and the selectivities, as shown in Table 20.

Under the reaction conditions used, primary alcohols were directly oxidized to their corresponding carboxylic acids. For the success of the reaction of primary alcohols, a small amount of *m*-chlorobenzoic acid (MCBA) or *m*-chloroperbenzoic acid was added to the catalytic system. It was found that the MCBA turns $Co(OAc)_2$ into a Co−MCBA complex, which promotes the decomposition of the hydroperoxides.

Internal *vic*-diols were oxidized to diketones, but cyclic diols also gave cleavage products such as the corresponding dicarboxylic acids (Table 21).[117]

Thus, 1,2-diols are cleaved to carboxylic acids, and this may be the result of intermediate ketoacids undergoing oxidative decarboxylation caused by Co(III). The 1,3 and 1,4 diols are oxidized into the corresponding hydroxyketones rather than the diketones, since the polar effect of the first C═O formed deactivates the remaining CH−OH bond. The corresponding dicarboxylic acids were formed from the reaction of 1,5-pentanediol.

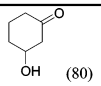
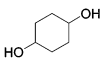
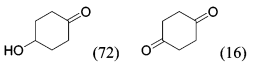
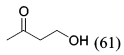
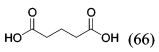
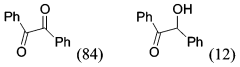
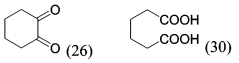
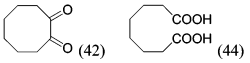
Woodward et al.,[118] working at a higher temperature than the ones used by Ishii et al. and using AcOH or *t*-BuOH as solvent, reported a practical oxidative cleavage of 1,2 diols obtained from unsaturated fatty acids.

The selective oxidation of primary alcohols to the corresponding aldehydes is always a challenge in these kinds of processes, particularly in free radical reactions. In uncatalyzed autoxidation processes, this is due to the oxidation rate of aldehydes being higher than that of the corresponding primary alcohols.

Enthalpic and also polar effects are consistent with this behavior, since hydrogen abstraction by the peroxyl radical is the rate-determining step both for aldehydes (eq 71) and for primary alcohols (eq 72).

From the enthalpic point of view, eq 71 is always exothermic, while eq 72 is either exothermic (with benzyl alcohols)[119] or endothermic (with aliphatic alcohols). The rates of both eqs 71 and 72 are also affected by a polar effect (Figure 14). However, the acylperoxyl radical is significantly more electrophilic compared to the α-hydroxyperoxyl radical.

Table 21. Oxidation of Various Diols with Molecular Oxygen[a]

Alcohol	Conversion (%)	Products (yield %)
	80	 (80)
	88	 (72) (16)
	75	 (61)
	80	 (66)
	80	 (70)
	89	 (71)
	96	 (86)
	97	 (84) (12)
	62	 (26) (30)
	94	 (42) (44)

[a] Alcohol (3 mmol) was allowed to react with O_2 (1 atm) in the presence of NHPI (10 mol %) and $Co(acac)_3$ (1 mol %) in CH_3CN (5 mL).

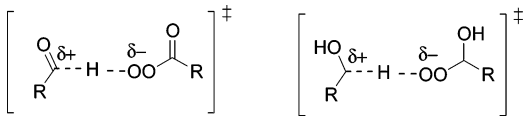
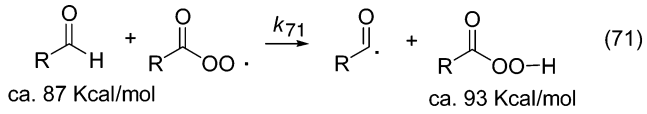
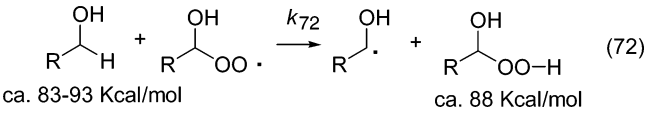


Figure 14. Transition states for the reactions of an aldehyde with an acyloxy radical and of an alcohol with an α-hydroxyperoxyl radical.



(71)

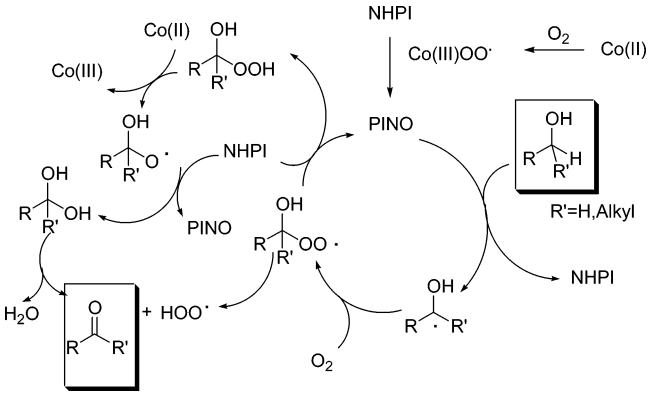


(72)

Thus, both the enthalpic and polar effects contribute toward making $k_{71} \gg k_{72}$.

This behavior has often led to the commonplace assumption that, in aerobic oxidations, aldehydes are always more reactive than the corresponding primary alcohols when oxygen centered radicals are involved, even if the autoxidation is catalyzed. Actually, that is not the case, as will be discussed later. However, for secondary alcohols, both enthalpic and polar effects contribute to making the alcohols much more reactive in uncatalyzed autoxidations than the corresponding ketones. For example, the BDE values of all the C−H bonds in cyclohexanone[120] are higher (C−H in the α position, 94.1 kcal/mol; C−H in the β and γ positions, 98 kcal/mol) than the BDE value of the C−H bond $R_2C(OH)$-H in cyclohexanol[121] (92.4 kcal/mol).

Scheme 12. Mechanism for the Aerobic Oxidation of Alcohols Catalyzed by NHPI and Co(II) Salts

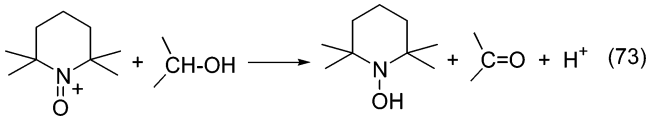


On the other hand, the carbonyl group deactivates by means of a polar effect hydrogen abstraction by peroxyl radicals while the hydroxyl group activates the $R_2C(OH)$-H further and contributes to the higher reactivity of cyclohexanol.

As previously discussed, the BDE of the *N*-hydroxyimide derivatives is a key factor in determining their catalytic efficiency in autoxidation processes.

We have shown for alcohols that both persistent and transient nitroxyl radicals, i.e., TEMPO and PINO, respectively, can act as oxidation mediators in the presence of oxygen and transition metal cocatalysts.

In the case of TEMPO, the reaction of the alcohol with the oxonium salt formed in situ is a key reaction step leading to the carbonyl compound and the reduced form of TEMPO, i.e., TEMPO-H (eq 73). The latter is transformed back to TEMPO by O_2 and the transition metal cocatalyst. In the oxidation of primary alcohols, TEMPO, being a persistent nitroxyl radical, allows high selectivity in the formation of aldehydes because of the inhibition of free radical chain processes such as aldehyde autoxidation.



(73)

Oxidation of alcohols by NHPI proceeds via a free radical chain mechanism. (Scheme 12)

The radical HOO•, formed as shown in Scheme 12, obviously may react with NHPI and/or C−H bonds to form HOOH, which decomposes in the presence of Co(II), forming hydroxyl radicals. These last are even more reactive and promote other radical chains.

Hydrogen abstraction from the C−H bonds of alcohols by aminoxyl radicals such as TEMPO is always much too endothermic to occur under mild conditions. In the aerobic oxidation of alcohols catalyzed by NHPI, hydrogen abstraction from the O−H group by PINO is allowed, since the BDE value indicates that abstraction is slightly exothermic for benzyl alcohols and moderately endothermic for aliphatic alcohols. However, on the basis of the pure enthalpic effect, no advantage can be discerned for the NHPI catalyzed aerobic alcohol oxidation when compared to the uncatalyzed oxidation. In fact, in the first case the hydrogen is abstracted by the PINO radical, while in the second case the hydrogen is abstracted by the peroxyl radical, and the BDE values of

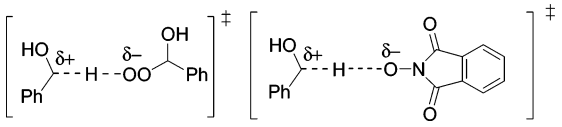


Figure 15. Transition states involved in the reactions of benzyl alcohol with α-hydroxyperoxyl radical and PINO radical.

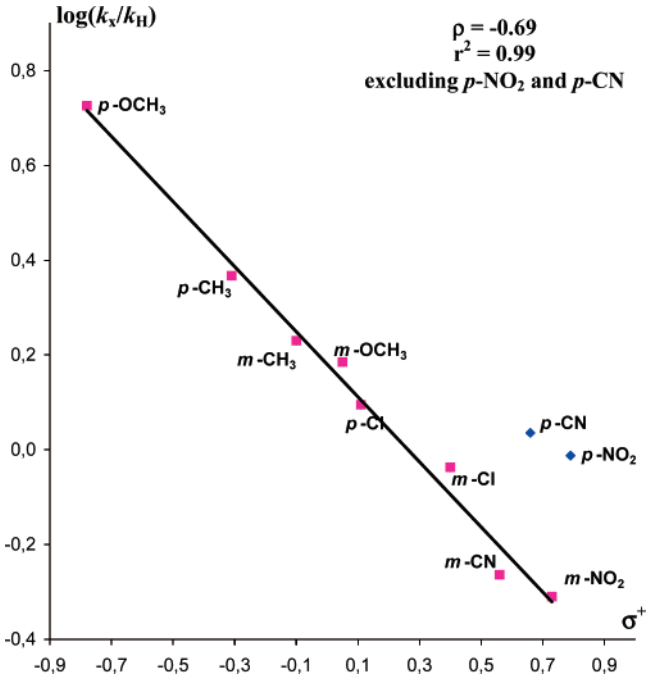


Figure 16. Substituent effect in the aerobic oxidation of substituted benzyl alcohols with NHPI catalysis.

Table 22. Oxidation of Benzylic Alcohols, X-C_6H_4-CH_2OH, to Aromatic Aldehydes by Oxygen[a]

X	time (h)	conversion (%)	selectivity (%)
H	4	85	94
p-OMe	1	75	94
p-OMe[b]	2	100	
m-OMe	3	85	99
p-NO_2	3	100	98
m-NO_2	4	88	91
p-Cl	3	100	95

[a] According to the standard procedure: 3 mmol of benzylic alcohol, 0.3 mmol of NHPI, 0.015 mmol of $Co(OAc)_2$, and 0.15 mmol of *m*-chlorobenzoic acid, under O_2 at atmospheric pressure and room temperature. [b] 98% of *p*-methoxybenzoic acid was obtained.

the O−H bonds in NHPI and ROO-H are substantially identical (~88 kcal/mol).

Table 4 shows that, in spite of similar expected enthalpy variations, PINO radical reacts faster than the α-hydroxyl peroxyl radicals involved in the autoxidation of benzyl radicals.

This difference in reactivity may be ascribed mainly to the more pronounced electrophilic character of the PINO radical (Figure 15) relative to the α-hydroxyperoxyl radical. Because of the O atom α to the peroxyl group, this holds even in the case of an alcohol-derived peroxyl radical, which is more electrophilic than the well-known *t*-BuOO·

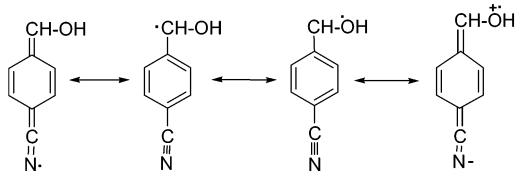
Regarding the oxidation of alcohols, Ishii et al. did not realize, however, the difference between the behavior of the benzylic and aliphatic alcohols.

We have shown[49] that the NHPI catalyzed oxidation of primary benzyl alcohols leads to aromatic aldehydes with high selectivity and that only after the complete conversion of benzyl alcohols to aldehydes does further oxidation of aromatic aldehydes take place. These results are reported in Table 22.

In contrast, the oxidation of primary aliphatic alcohols leads to carboxylic acids without significant formation of aldehydes, even at low conversions.

This selectivity clearly indicates that, in the catalysis of primary benzyl alcohols with NHPI, the alcohols are much more reactive than the corresponding aldehydes, while, in the case of non-benzylic alcohols, the corresponding aldehydes are much more reactive than the starting alcohols. Polar and enthalpic effects explain this behavior well, as will be discussed later.

To evaluate the polar effect, we have investigated[122] aromatic ring substituent effects on the NHPI catalyzed aerobic oxidation of benzyl alcohols (Figure 16). A good correlation was obtained, 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 are significantly deactivated. We explain this behavior by a captodative effect, which qualitatively[123] suggests that pairs of substituents having opposite polarities act in synergy for the stabilization of a radical according to the resonance structures of eq 74.



(74)

The captodative effect causes a significant decrease in the BDE values for benzylic C−H bonds in *p*-cyano- and *p*-nitrobenzyl alcohol, and the favorable enthalpic effect balances the unfavorable polar effect due to the presence of *p*-cyano and *p*-nitro groups.

Galli et al.[124] recently reported the aerobic oxidation of alcohol catalyzed with laccase and NHPI. At room temperature, the ρ value of the Hammett correlation obtained by Galli (−0.89 in the presence of laccase in H_2O) is comparable to the one reported by us (−0.69 in our system in CH_3CN), where the same parameter σ^+ was used.

The formation of PINO radical as the reactive intermediate is also invoked in the laccase/NHPI procedure; strangely enough, no deviation from the straight line was observed by Galli et al. for the case of the *p*-NO_2-benzyl alcohol (the *p*-CN-benzyl alcohol was not included in the list of oxidized alcohols).

In spite of the commonplace assumption that aldehydes are more reactive than alcohols in aerobic oxidations, in NHPI catalyzed aerobic oxidations, the selective formation of aromatic aldehydes is observed because of the higher rate of hydrogen abstraction from benzyl alcohols by the PINO radical, as compared to the rate of hydrogen abstraction from the aldehydes. This different reactivity can be explained by two effects, with the first being a presumably more marked polar effect for hydrogen abstraction from alcohols and the second being an enthalpic effect arising from the lower BDE values of the C−H bonds involved in benzyl alcohols (82−85 kcal/mol)[125] compared to the higher BDE values of the C−H bonds involved in aromatic aldehydes (~88 kcal/mol).[126]

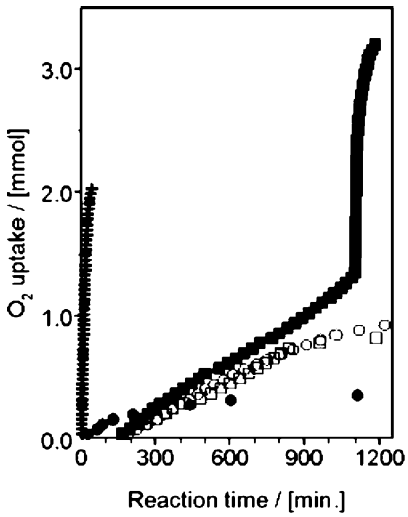


Figure 17. Aerobic oxidation of benzyl alcohol in MeCN (□, ■), of cyclohexanol in EtOAc (○, ●) catalyzed by the NHPI/$Co(OAc)_2$/MCBA (solid symbol) and NHPI/Bu_4NVO_3 (open symbol) systems, respectively, and of benzaldehyde in MeCN (+) catalyzed by NHPI/$Co(OAc)_2$/MCBA at 30 °C. (From ref 127, Copyright 2004. Reproduced by permission of The Royal Society of Chemistry.)

Sobczak et al., who have reported the aerobic oxidation of alcohols catalyzed by NHPI and vanadium salts, have confirmed our results.[127]

As shown in Figure 17, it is clear that as long as the benzyl alcohol is not completely consumed, the oxygen uptake rate in the oxidation of the alcohol is much slower than in the case of the aldehydes alone. Once the alcohol is oxidized, the oxidation of the benzaldehyde formed begins, and the oxygen uptake rate is identical to that reported for starting directly from the aldehyde.

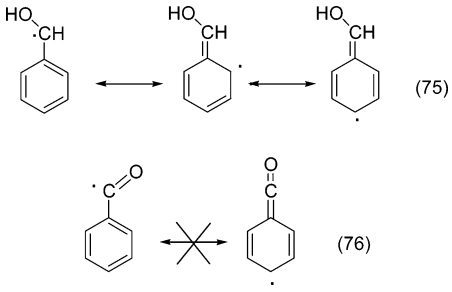
Sobczak et al.[128] also reported that the combination of NHPI and various cocatalyst acids, tertiary and quaternary ammonium salts, and typical Lewis acids (e.g. BF_3) affords an efficient catalytic system for the aerobic oxidation of organic substrates.

Obviously, the kinetic data obtained in AcOH concerning the comparable reactivity of benzyl alcohols and their corresponding aldehydes[33] cannot be compatible with this observed behavior. As reported by Espenson, the reactivity of benzylic alcohols in CH_3CN should be somewhat higher than the reactivity of their corresponding aldehydes,[33] although no quantitative arguments were given to substantiate this conclusion.

Concerning the use of the $Pb(OAc)_4$/NHPI system, employed by Espenson to measure the kinetic constants, Coseri et al.[50] observed that this method for generating PINO radicals "should be treated with caution".

The situation is quite different with primary aliphatic alcohols; in these cases, the enthalpic effect is dominant (the BDE values for RCHOH−H bonds are 5−6 kcal/mol larger than those of RCO−H bonds), and that makes the aldehydes much more reactive than the corresponding alcohols, which are selectively oxidized to carboxylic acids, even at low conversions.

The overall behavior is due to the different electronic configurations of benzyl (π-type) and benzoyl (σ-type) radicals. The benzyl radicals are stabilized by the resonance with the aromatic ring (eq 75), which is not possible for the benzoyl radical (eq 76). Thus, the BDE values of ArCHOH−H bonds are lower than those of aliphatic RCHOH−H bonds, while the BDE values of ArCO−H are identical to those of RCO−H.



Aerobic oxidation of various secondary alcohols to their corresponding carbonyl compounds has been accomplished also by using NHPI/ceric ammonium nitrate (CAN). Primary and allylic alcohols were transformed in relatively moderate yield.[129]

Electron-rich benzylic alcohols have been used by Galli et al. as a non-phenolic lignin model for testing directed at finding a suitable wood pulp delignification system based on the enzyme laccase, which should have an acceptable environmental impact.[130]

Laccase is a phenoloxidase, widely produced by lignin-olytic fungi,[131] which in the presence of a variety of mediators[132] (Scheme 13) can catalyze the oxidation of non-phenolic substrates.

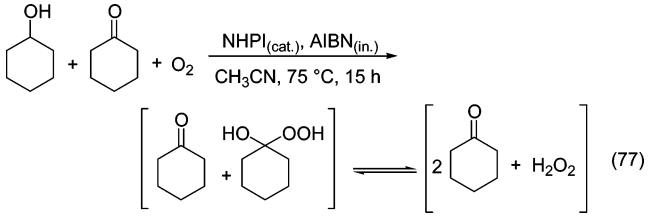
Several *N*-hydroxyimide derivatives, which act similarly to NHPI in promoting oxidation of model compounds such as *p*-anisyl alcohol, are shown in Table 23. Among the catalysts reported, NHPI certainly has the best cost/effectiveness ratio, which is significant, since, for delignification of pulp, only cheap catalytic systems would have potential industrial applications.

Aryl substituted *N*-hydroxyphthalimides bearing electron-donating groups in the aromatic ring, in particular 4-Me-NHPI and 4-MeO-NHPI, increase the yields in the oxidation of the monomeric and dimeric lignin models (primary and secondary benzylic alcohols) as well as the efficiency of the delignification of kraft pulps.[42]

3.4. Oxidation of KA Oil for the Synthesis of ϵ-Caprolactone and ϵ-Caprolactam

KA oil is a mixture of cyclohexanone and cyclohexanol derived from the aerobic oxidation of cyclohexane. It is a crucial intermediate in the synthesis of adipic acid and ϵ-caprolactam, two key monomers in the production of nylon-6,6 and nylon-6, respectively.

Ishii et al. have developed a new KA oil aerobic oxidation catalyst system based on NHPI in the presence of small amounts of initiator (AIBN) which converts the alcohol component into a mixture of ketone and hydrogen peroxide through the formation of 1-hydroxy-1-hydroperoxycyclohexane (eq 77).[133]



Scheme 13. The Role of a Mediator of Laccase Activity

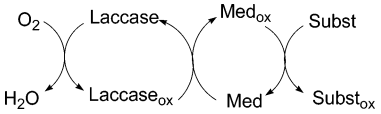
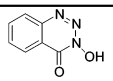
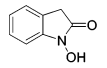
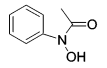
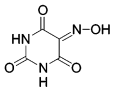
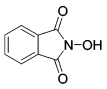
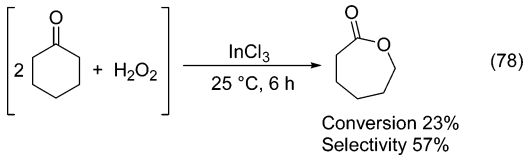


Table 23. Benchmark Aerobic Oxidation of *p*-Anisyl Alcohol with Laccase/Mediator Systems[a]

Mediators	Yields o p-anisyl aldehydes (%)
	19
	7
	54
	85
	70
	76

[a] Conditions: [*p*-anisyl alchol] = 20 mM, [mediator] = 6 mM, laccase = 3 U/mL.

The addition of catalytic amounts of $InCl_3$ in the second step converts the mixture to ϵ-caprolactone (eq 78), which furnishes an alternative method to the classical Bayer−Villiger oxidation, even if conversion and selectivity for the desired product are low.[133]



(78)

The possibility of converting cyclohexanone/H_2O_2 to ϵ-caprolactam is even more important because of the increasing demand for nylon-6 (Scheme 14).[134] This led the same research group to develop a new process by adding aqueoues NH_3 to open a second reaction pathway yielding **12** and **13** as major products with a smaller amount of **14** (PDHA) (eq 79). **14** is directly converted to the ϵ-caprolactam by treatment with catalytic amounts of LiCl (eq 80), whereas **12** can be converted to **13** by reaction with NH_3 in the presence of NHPI (eq 81).

3.5. Oxidation of Alkenes and Alkynes

3.5.1. Oxidation of Alkenes

The first reported oxidation of olefins under NHPI catalysis was an electrocatalytic system developed by Masui et al.[25] The compounds obtained are the corresponding enones with a product distribution similar to that observed in free radical autoxidation of olefins. Allylic hydrogen abstraction by PINO generated from NHPI by anodic oxidation is the key step of the reaction mechanism (Scheme 15). However, the yields of enones are low from a preparative point of view, since most of the NHPI is destroyed under the reaction conditions used.

In 1986, Foricher and co-workers patented the oxidation of isoprenoid derivatives having a free allylic group.[29] The reactions take place by using O_2 or air and stoichiometric amounts of NHPI, which acts as a catalyst and is claimed to be easily recovered at the end of the process. Benzoyl peroxide is used as an initiator, and the solvents of choice are acetone or ethyl acetate, generally under reflux. The primary products of oxidation are hydroperoxides, which subsequently can be transformed, without purification, to alcohols or carbonyl compounds (e.g., by dehydration with pyridine in acetic anhydride).

Some of the examples claimed are shown in eqs 82−84. In eq 85, a rearrangement of the double bond occurs because of the more stable tertiary allylic radical.

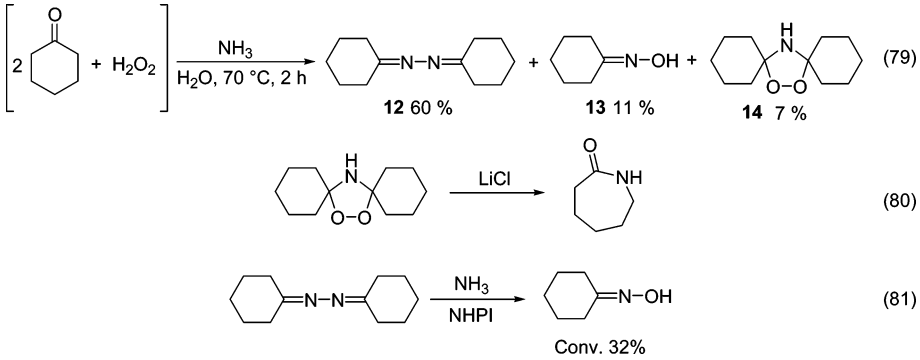
Ishii has reported the oxidation of cyclohexene to cyclohexenone and cyclohexenol with O_2 and a catalytic amount of NHPI in the absence of metal cocatalyst (eq 86).[30] However, the mass balance of the reported products is not satisfactory with respect to the converted olefin. In fact, it accounts for only 61% of the converted starting material.

This low yield might be explained at least in part by referring to a recently reported study on the reactivity of the PINO radical with cylclohexene.[50] PINO, as well as other nitroxyl radicals such as TEMPO and di-*tert*-butyliminoxyl, can also add to the double bond as well as abstract H.

This behavior is not new in oxygen centered free radicals. In fact, while *tert*-RO$^\bullet$ and ROO$^\bullet$ add to cyclohexene for 3.8%[135] and 4.4%,[136] respectively, the addition of ROO$^\bullet$ to cyclooctene provides a 77% yield of monoadduct.[137]

In this kind of reaction, norbornene shows a particular reactivity, since its bridged structure makes the allylic

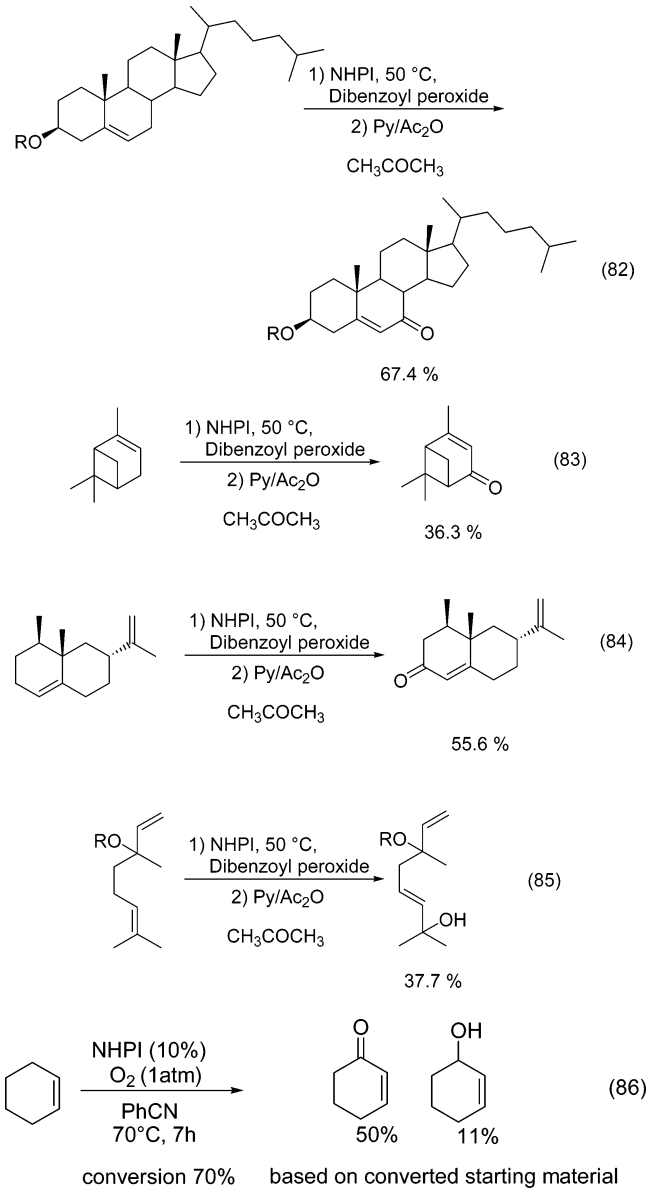
Scheme 14. Mechanism for the Synthesis of ϵ-Caprolactam Catalyzed by NHPI



(79)

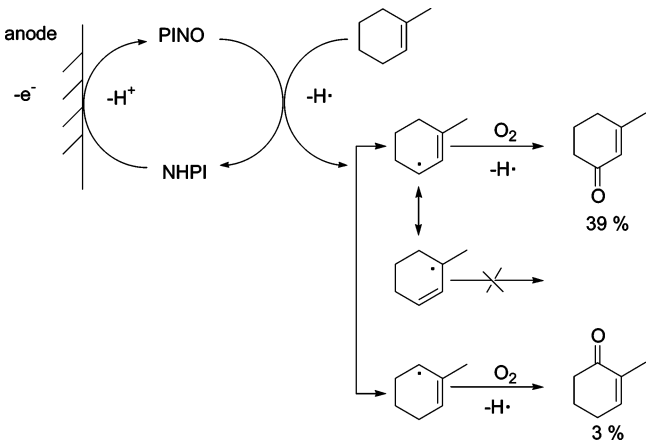
(80)

(81)

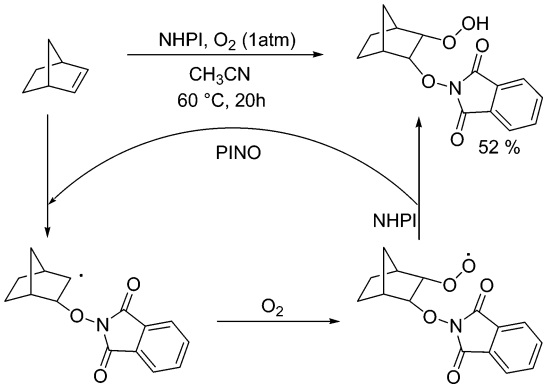


hydrogen particularly unreactive because of the impossibility for the radical formed there to delocalize its unpaired electron via the double bond as usually happens in an allylic system. Thus, in this case, Ishii has shown that in aerobic conditions PINO adds to the double bond, and the radical adduct formed

Scheme 15. Mechanism for the Electrocatalytic Oxidation of Olefins in the Presence of NHPI

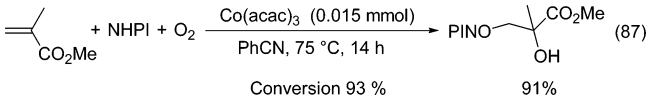


Scheme 16. PINO Addition to Norbornene



is trapped by oxygen, giving rise to the hydroperoxide in good yield relative to the NHPI consumed (Scheme 16).[138]

NHPI gives a similar reaction with norbornene in the presence of a metalloporphyrine (Mn(III)TTPCl), O_2, and pyridine.[139] Under the same conditions, PINO also adds to electron-rich olefins, such as indene and styrene, whereas addition to an electron poor alkene such as methyl methacrylate is obtained by carrying out the reaction under oxygen atmosphere in the presence of catalytic amounts of NHPI and cobalt salts (eq 87).[140]

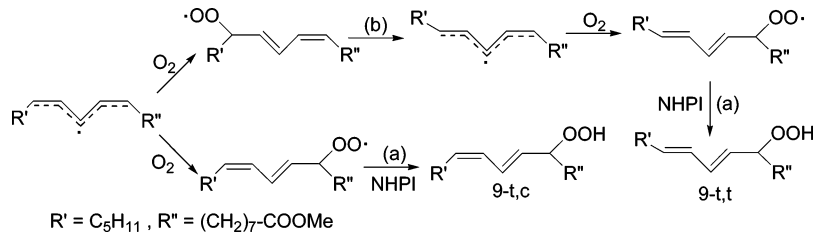


The autoxidation of polyunsaturated fatty acids is an important topic in free radical autoxidation. Peroxidized lipids, in fact, seem to be involved in the promotion of several pathologies, including atherosclerosis and Parkinson's disease. For this reason, the selective synthesis of the corresponding hydroperoxides appears to be of interest, since it will simplify the study of the mechanisms that lead to the formation of the secondary oxidation products. However, procedures currently found in the literature give low conversions and have limited applications.

Recently, Porter and co-workers have reported the peroxidation of methyl linoleate in the presence of NHPI and small amounts of 2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile) (MeOAMVN).[141] In this case, the *N*-hydroxy derivative plays a double role: it catalyzes hydrogen abstraction from the bisallylic position, and being a good hydrogen donor, it traps the peroxyl radicals derived from the reaction of the allylic radical with oxygen (Scheme 17a). Nevertheless, in spite of the good conversions observed, the diasteroselectivity of the process, i.e., the ratio of the *trans-cis* to the *trans-trans* oxidation products, is poor. In fact, the undesired *trans-trans* hydroperoxides derive from the β-fragmentation of primary peroxyl radicals, a process for which the rate is competitive with that for the hydrogen transfer from NHPI (Scheme 17b).

In order to provide a selective synthesis of *trans*/*cis* hydroperoxides, the same research group has introduced a new N−OH derivative, *N*-methylbenzohydroxamic acid (NMBHA, **15**). The lower O−H BDE value of this compound (79.2 kcal/mol), and the consequent higher kinetic constant for hydrogen abstraction from the O−H bond by peroxyl radical (eq 90, $k_{NMBHA} = 1.2 \times 10^5$ M^{-1} s^{-1}), suggested that NMBHA could be a suitable H-donor and an ideal catalyst for selective lipid peroxidation (Scheme 18).

Scheme 17. Peroxidation of Methyl Linoleate in the Presence NHPI: (a) Hydrogen-Transfer Reaction from NHPI; (b) *β*-Fragmentation of Peroxyl Radicals



Scheme 18. Peroxidation of Methyl Linoleate in the Presence NMBHA

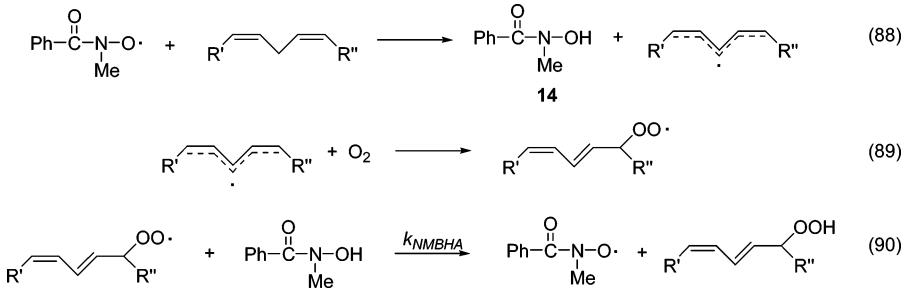


Table 24. Oxidation of Diene Fatty Acid Methyl Esters at 37 °C under Air Atmosphere in CH_3CN

substrate	[lipid] (M)	[NMBHA] (M)	time (h)	conversion[a] (% by HPLC)	selectivity[a] (% by HPLC)	yield (% isolated products)
methyl linoleate	0.20	0.20	48	63	>99[b]	59 (OOH)
methyl linoleate	0.55	0.20	48	69	>99[b]	55 (OH)
methyl linoleaidate	0.20	0.07	48	55	>99[c]	43 (OH)
methyl linoleaidate	0.20	0.20	48	53	>99[c]	48 (OOH)

[a] Conversions and selectivities have been determined using allylbenzene as an internal standard. Product selectivity indicates *trans,cis* hydroperoxides for methyl linoleate and *trans,trans* for methyl linoleaidate. [b] Determined by the ratio of *trans,cis*/*trans,trans* products. [c] Determined by the ratio of *trans,trans*/*trans,cis* products.

Table 25. Oxidation of Polyunsaturated Fatty Acid Methyl Esters at 37 °C under Air Atmosphere in CH_3CN

substrate	[lipid] (M)	[NMBHA] (M)	time (h)	conversion[a] (% by HPLC)	yield (% isolated products)
γ-methyl linolenate	0.40	0.30	48	36	30 (OOH)
α-methyl linolenate	0.20	0.40	33	40	30 (OOH)
α-methyl linolenate	0.20	0.40	33	40	37 (OH)
methyl arachidonate	0.20	0.40	33	43	39 (OH)
methyl arachidonate	0.40	0.30	48	44	36 (OH)

[a] Percent conversions were determined using allylbenzene as an internal standard. All products measured were *trans,cis*.

As a result, this catalytic system is particularly effective both for diene fatty acid methyl esters (Table 24) and for polyunsaturated fatty acid methyl esters (Table 25).

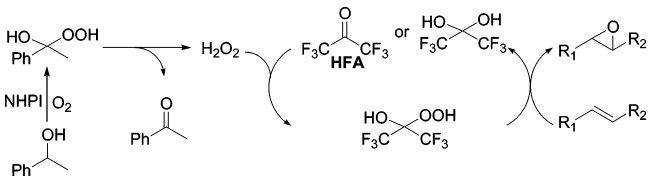
The lower conversions for the polyunsaturated compounds are necessary to avoid the formation of dihydroperoxides due to the presence of a second allylic position in the molecule. Nevertheless, the final yields can be increased by additional catalytic cycles, since the unreacted starting material is easily recovered, as is also the catalyst by a flash column.

3.5.2. Epoxidation of Olefins

The epoxidation of olefins is an important tool for the introduction of an oxygen atom into an organic molecule bearing a double bond. Many methods can be employed for this purpose by using a wide range of reagents, both without and more commonly with the presence of catalysts, especially when dioxygen is the oxidizing agent.[19]

Masui et al. first attempted the direct epoxidation of olefins by using oxygen and NHPI with metalloporphyrins, but they obtained poor results.[139] Ishii and co-workers have proposed different methods. In their first protocol, the epoxidizing agent is obtained in situ by the aerobic oxidation of a suitable organic compound in the presence of catalytic amounts of NHPI. The resulting oxidant, which is not able to promote the epoxidation by itself, is then activated in the presence of an olefin by catalytic amounts of hexafluoroacetone (HFA).[142] For example, the oxidation of secondary alcohols catalyzed by NHPI leads to the formation of the corresponding hydroperoxides, which, in the absence of a metal cocatalyst, react further to form ketones and hydrogen peroxide. Hydrogen peroxide then forms a very electrophilic

Scheme 19. Mechanism for the Epoxidation of Alkenes Catalyzed by NHPI in the Presence of Alcohols and HFA



Scheme 20. Mechanism for the Epoxidation of Alkenes Catalyzed by NHPI in the Presence of Ethyl Benzene and $Mo(CO)_6$

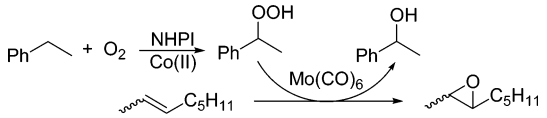
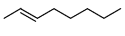
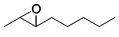
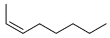
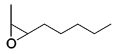
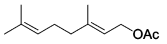
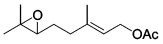
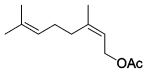
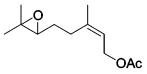
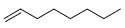
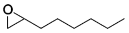
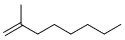
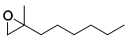
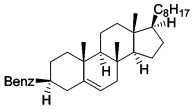
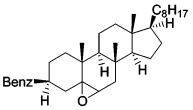
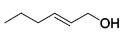
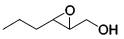
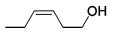
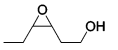


Table 26. Epoxidation of Olefins with O_2 and Benzhydrol, Catalyzed by NHPI and HFA[a]

Substrate	Product	Conversion (%)	Selectivity[b] (%)
		93	93 (99/1)
		94	86 (2/98)
		96	83 (1/99)
		88	81
		89	83
		80	90
		83	84
		78	80
		72	83 (75/25)
		82	87
		90	82

[a] General procedure: olefin (3 mmol), NHPI (10%), HFA (0.3 mmol), and alcohol (15 mmol) were stirred under O_2 in PhCN (6 mL) at atmospheric pressure and 80 °C for 24 h. [b] Parentheses show the ratio of *trans*/*cis*.

Table 27. Epoxidation of Olefins with O_2 and Tetralin or Ethylbenzene, Catalyzed by NHPI, $Co(OAc)_2$, and $Mo(CO)_6$[a]

alkene	*T* (°C)	conversion[b] (%)	selectivity[b] (%)
trans-oct-2-ene	60 (60)	78 (71)	88 (79)
cis-oct-2-ene	50 (60)	83 (75)	87 (71)
2,4,4-trimethylpent-2-ene	70 (70)	90 (76)	84 (80)
oct-1-ene	60 (70)	38 (37)	80 (81)
cyclohexene	60	80	74
cyclooctene	60	89	83
trans-hex-2-ene-1-ol	60	79	65

[a] General procedure: olefin (4 mmol), NHPI (10%), $Co(OAc)_2$ (0.1%), $Mo(CO)_6$ (5%), tetralin (40 mmol) or ethylbenzene (20 mmol), and MS-4A (200 mg) were stirred under O_2 in PhCN (2 mL) at atmospheric pressure for 14 h. [b] Parentheses show the results using tetralin.

α-hydroxyhydroperoxide by addition to HFA, and that addition product is then able to epoxidize olefins (Scheme 19).

Table 28. Epoxidation of Olefins by Aerobic Oxidation of Acetaldehyde, Catalyzed by NHPI[a]

Olefin	Catalyst (%)	t (h)	Yield(%)
1-hexene	NHPI (10)	24	61
1-hexene	NHPI (10)	48	70
1-octene	NHPI (10)	24	80
1-decene	NHPI (10)	24	81
1-decene	NHPI (10)	48	94
1-decene	--	24	--
1-dodecene	NHPI (10)	23	81
Methyl oleate	NHPI (10)	24	--
cis-2-hexene	NHPI (10)	24	--
cyclooctene	NHPI (10)	27	96
cyclooctene	--	24	--
 R(+)-limonene	NHPI (10)	14	 *cis* (67), *trans* (33)
2-methyl-2-butene	NHPI (10)	24	--

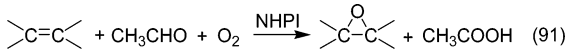
[a] General procedure: a solution of 5 mmol of olefins, 15 mmol of acetaldehyde, and 0.5 mmol of NHPI in 10 mL of acetonitrile was stirred at room temperature in atmospheric pressure of O_2 for the time reported in the table.

The use of benzhydrol as the alcohol in this reaction has been particularly effective and has given good conversions with high selectivity in the epoxides (Table 26).

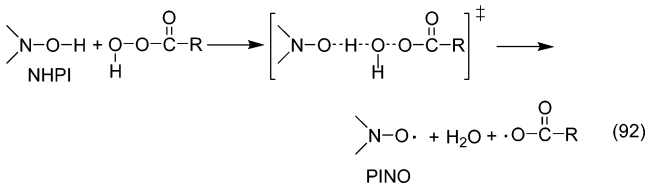
A second method proposed by Ishii uses hydroperoxides from the in situ NHPI catalyzed oxidation of tetralin or ethylbenzene to epoxidize olefins directly by means of $Mo(CO)_6$.[143] In fact, it is well-known that Mo(VI) complexes in the presence of alkyl hydroperoxides exhibit efficient catalytic activity in the epoxidation of alkenes.[144]

The reaction mechanism is shown in Scheme 20, and the results are outlined in Table 27.

Very recently, we suggested a new and effective metal-free NHPI catalyzed aerobic epoxidation of primary olefins based on the in situ generation of peracetic acid from acetaldehyde (eq 91).[145]

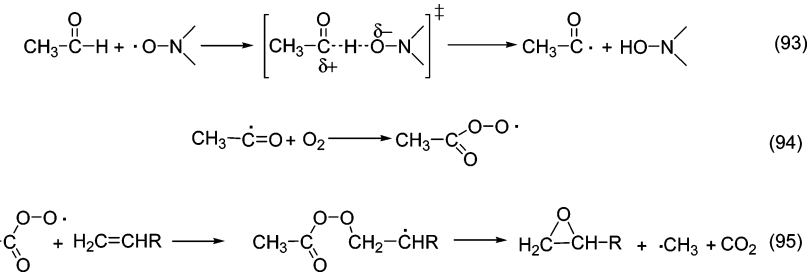


Our interpretation of the mechanism involves the "molecule induced homolysis" of *N*-hydroxyphthalimide by peracids (eq 92), leading to the formation of PINO radical. The driving force for this path is the dissociation enthalpy of the O−H bond in water (119 kcal/mol), which is much higher than that of the O−H bond in NHPI (88.1 kcal/mol).



With this mode of activation of the catalyst, it has been possible to epoxidize a wide range of primary alkenes (Table 28). The unreactivity of internal olefins clearly indicates that the oxidizing agent in the epoxidation is not the peracetic acid, which would not show this selectivity, but the peroxyl

Scheme 21. Mechanism for the Epoxidation of Alkenes Catalyzed by NHPI in the Presence of Acetaldehyde



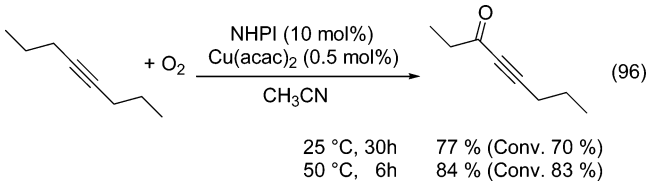
radical (eq 95) formed according to the mechanism shown in Scheme 21.

3.5.3. Oxidation of Alkynes

Ynones (α,β-acetylenic ketones) are useful intermediates for the synthesis of highly valuable heterocyclic derivatives, α,β-unsaturated ketones, nucleosides, and pheromones.[146]

Most of the selective methods available up until now use reagents with high environmental impact. On the other hand, conventional autoxidations at high temperature are unselective.

Since the BDE of the propargyl C−H bond (87 kcal/mol) is similar to that of toluene (88 kcal/mol), it is reasonable to expect that alkynes will exhibit the same reactivity as toluene in the presence of NHPI. In fact, alkynes can be selectively oxidized with good yields to their corresponding ketones using O_2 and catalytic amounts of both NHPI and $Cu(acac)_2$ under mild conditions (eq 96).[146]

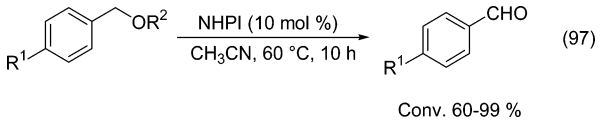


Like other oxygen centered radicals, PINO in the absence of O_2 will add to the triple bond of cycloalkynes to give an oxidative radical cyclization cascade which is terminated by release of the N-centered phthalimido radical (Scheme 22).[147] Wille et al., who introduced this interesting concept in free radical chemistry, have called this process Self-Terminating Radical Oxygenation.[147] Similar results are obtained with other nitroxyl radicals which were generated with strong oxidants such as CAN and which were reacted under ultrasound stimulation to improve the yields of the bicyclic ketones. Competitive abstraction of the propargyl C−H bond may account for the relatively low yields obtained in all of the cases explored which involved nitroxyl radicals.

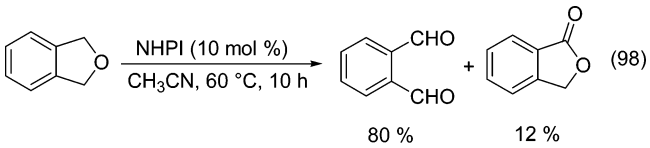
3.6. Oxidations of Ethers, Silyl Ethers, and Acetals

3.6.1. Oxidation of Ethers

Classical methods for the oxidation of ethers to the related oxygen-containing compounds often have low selectivity for the desired products. Ishii and co-workers have developed a new catalytic system based on NHPI under an NO atmosphere which gives good as well as selective conversion of benzylic ethers to the corresponding aldehydes (eq 97).[148]



For example, under these reaction conditions, phthalane has been converted to the corresponding phthalaldehyde and a smaller amount of phthalide. Phthalaldehyde is a key material in the synthesis of several pharmaceuticals (eq 98).



The proposed mechanism shows the formation of a carbocation as a transient intermediate, whereas the role of NO is to generate radical PINO (Scheme 23).

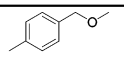
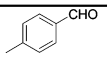
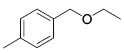
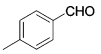
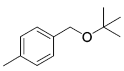
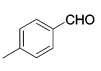
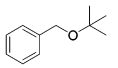
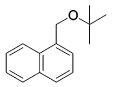
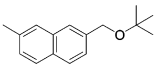
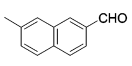
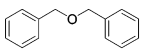
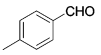
In Table 29 a few examples of the benzyl ethers tested are shown.

Laccase enzyme catalyzes the aerobic oxidation of benzylic ethers in the presence of NHPI in reasonable to good yields.[149]

3.6.2. Oxidation of Silyl Ethers

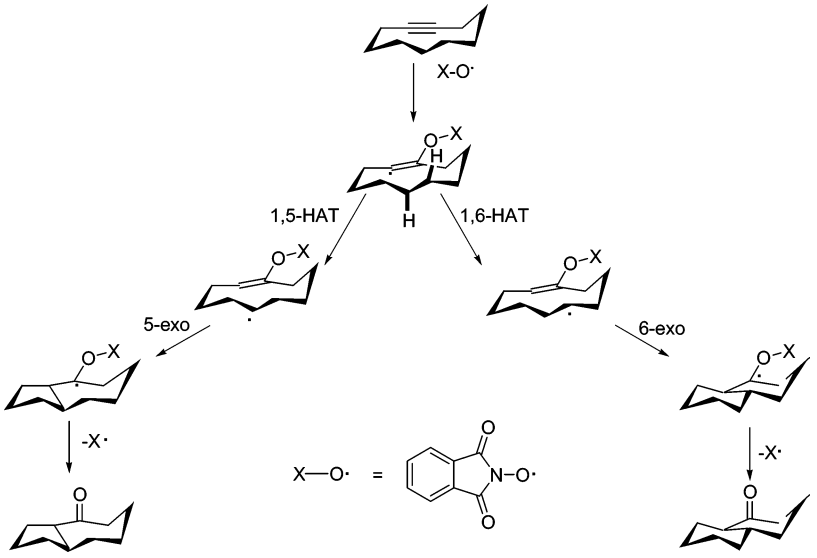
Silyl ethers, which are useful protecting groups often employed in synthetic reactions, have a structure very similar to that of classical ethers. Thus, it is reasonable to expect

Table 29. Reaction of Benzyl Ethers by the NO/NHPI System[a]

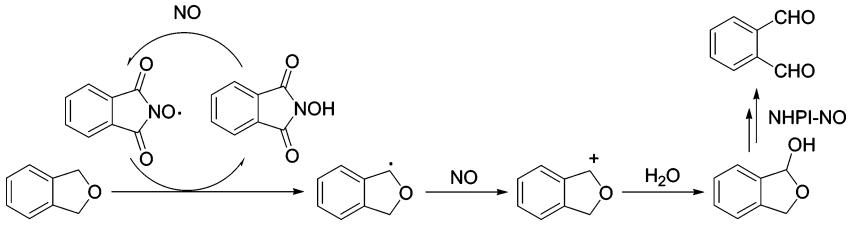
Substrate	Conversion (%)	Product	Yield (%)
	56		50
	70		60
	90		72
	80		70
	87		80
	93		85
	82		64

[a] Substrate (1 mmol) was allowed to react in the presence of NHPI (10 mol %) under NO atmosphere (1 atm) in acetonitrile (5 mL) at 60 °C for 10 h.

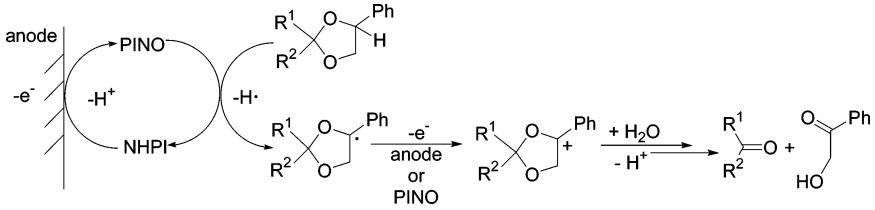
Scheme 22. PINO Addition to the Triple Bond of Cycloalkynes



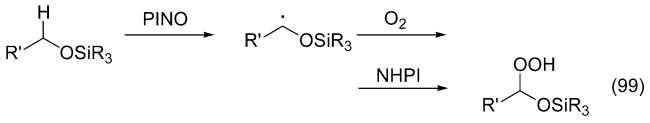
Scheme 23. Mechanism for the Aerobic Oxidation of Benzyl Ethers by the NO/NHPI System



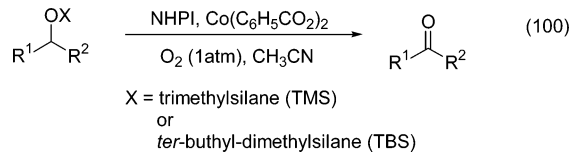
Scheme 24. Mechanism for the Electrochemical Deprotection of the 4-Phenyl-1,3-dioxolane Protecting Group



that the PINO radical would be able to abstract the hydrogen α to the oxygen to generate a carbon centered radical which would lead in the presence of oxygen to the formation of hydroperoxides (eq 99).



Very recently, a new catalytic system based on NHPI and lipophilic Co(II) complexes has been reported for the selective oxidation of silyl ethers to the corresponding carbonyl derivatives (eq 100).[150]



The oxidation of substituted primary benzylic TMS and TBS ethers with O_2 at room temperature leads to the formation of the corresponding benzaldehydes, thus confirming the selectivity already discussed for the oxidation of benzyl alcohols. As expected, primary aliphatic silyl ethers give instead the related carboxylic acids in high yields (Table 30).

The higher efficiency of lipophilic cobalt complexes as compared to the classical cobalt salts used for this kind of catalysis is probably caused not only by a higher solubility in the reaction medium but also by avoiding the Co−NHPI adduct formation, which might otherwise occur during the reaction and decrease the efficiency of the process.[151]

3.6.3. Oxidation of Acetals

Acetals represent another important class of protecting groups whose removal under mild conditions is a crucial point in organic synthesis. The first employment of NHPI as a mediator for this purpose was reported by Masui and co-workers,[27] who achieved the electrochemical deprotection of the 4-phenyl-1,3-dioxolane group from a series of organic derivatives, recovering the corresponding ketones in good yields (Scheme 24).

However, as already discussed, the electrochemical technique leads to the decomposition of NHPI, as is highlighted by the small amount of recovered catalyst.

The oxidative cleavage of benzylidine acetals derived from 1,2- and 1,3-diols gave the corresponding hydroxybenzoate

Scheme 25. Mechanism for the Aerobic Oxidative Cleavage of Benzylidene Acetals

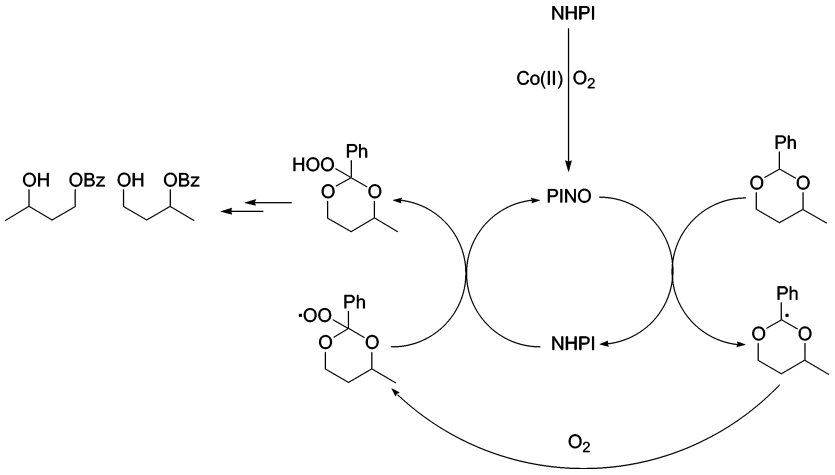
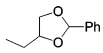
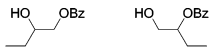
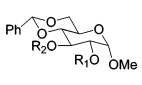
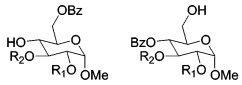


Table 30. Aerobic Oxidative Deprotection of Silyl Ethers Catalyzed by NHPI and Cobalt Benzoate[a]

R^1	R^2	X	yield (%)
Ph	H	TMS	92[b]
Ph	H	TBS	90[b]
4-$(NO_2)C_6H_4$	H	TMS	86[b]
4-$(NO_2)C_6H_4$	H	TBS	91[b]
4-(MeO)C_6H_4	H	TMS	95[b]
4-(MeO)C_6H_4	H	TBS	95[b]
4-(*i*-Pr)C_6H_4	H	TMS	89[b]
4-(*i*-Pr)C_6H_4	H	TBS	90[b]
$PhCH_2CH_2$	H	TMS	86[c]
$PhCH_2CH_2$	H	TBS	91[c]
Ph	CH_3	TMS	92[d]
Ph	CH_3	TBS	87[d]
Ph	Et	TMS	91[d]
Ph	Et	TBS	93[d]
4-(Ph)C_6H_4	CH_3	TMS	85[d]
4-(Ph)C_6H_4	CH_3	TBS	90[d]
cycloheptyl		TMS	89[d]
cycloheptyl		TBS	92[d]
Ph	PhCO	TMS	93[d]

[a] General procedure: silyl ether (1 mmol), NHPI (10%), and $Co(C_6H_5CO)_2$ (0.5%) were stirred in 5 mL of CH_3CN in the presence of O_2 at room temperature and atmospheric pressure. [b] Aldehyde. [c] Carboxylic acid. [d] Ketone.

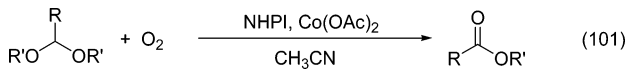
Table 31. Oxidative Cleavage of Benzylidene Acetals[a]

Substrate	Products		Yield (%)
			85
			87
			90
			87
			
1 R_1 = H, R_2 = Bz	**1a**	**1b**	82
2 $R_1 = R_2$ = Bz	**2a**	**2b**	91
3 $R_1 = R_2$ = Ac	**3a**	**3b**	66
4 $R_1 = R_2$ = Bn	**4a**	**4b**	34

[a] General procedure: benzylidene acetal (0.64 mmol), NHPI (10%), $Co(OAc)_2$ (0.5%), and MCPBA in EtOAc (5 mL) were stirred at room temperature and atmospheric pressure under O_2 for 15 h.

esters when treated with a simpler system based on the NHPI/$Co(OAc)_2$ catalyst pair.[152] Many derivatives were shown to be suitable for this reaction, including several sugars (Table 31). A possible reaction path is shown in Scheme 25. PINO radical, generated by the complex Co(III)−O_2, again plays a key role in hydrogen abstraction from the substrate.

More recently, the same catalytic system has been used in the selective aerobic oxidation of a wider range of acetals to obtain the corresponding esters in excellent yields without the addition of *m*-CPBA (eq 101).[153] The mechanism is quite similar to that reported in Scheme 24.



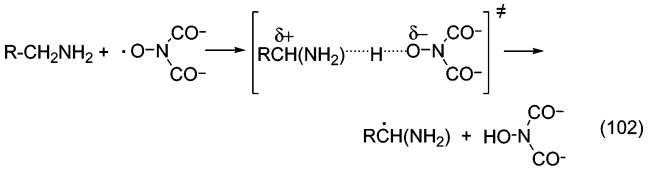
(101)

The aerobic oxidation of substituted benzaldehyde dialkylacetals under NHPI/Co(II) catalysis led to the corresponding alkyl benzoates. Cyclic acetals, however, were found to be suitable substrates for the selective synthesis of diol monoesters with no further oxidation of the hydroxy group being observed. A few indicative examples are shown in Table 32. Aromatic substrates bearing strongly electron-withdrawing groups yielded no products in this reaction.

3.7. Oxidation of Amines and Amides

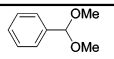
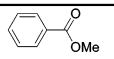
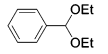
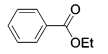
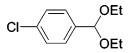
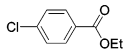
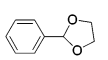
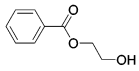
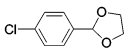
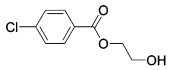
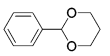
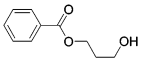
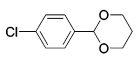
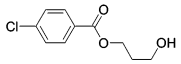
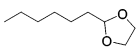
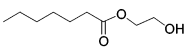
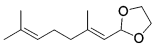
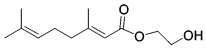
3.7.1. Oxidation of Amines

On the basis of the previous discussion of the oxidation of alcohols, it is reasonable to expect, both on polar and on enthalpic grounds, that amines could be even more reactive in the presence of oxygen with catalytic amounts of imidoxyl radicals. Having a better electron-releasing group, the amino derivatives would be expected to show a stronger polar effect in hydrogen abstraction by PINO (eq 102).



(102)

Table 32. Aerobic Oxidation of Acetals to Esters Catalyzed by NHPI and $Co(OAc)_2$[a]

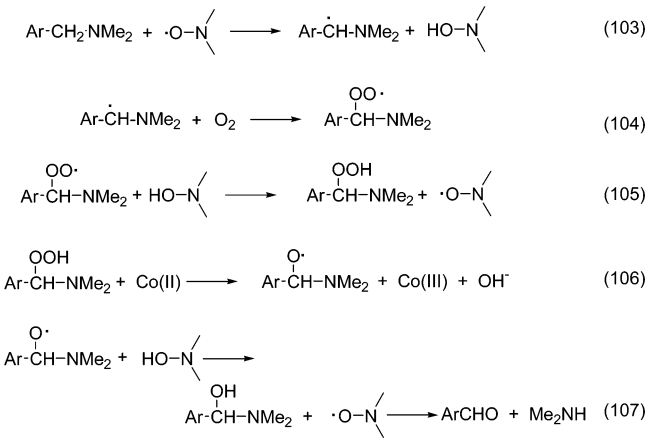
Substrate	Products	Time (h)	Yield (%)
		20	91
		20	88
		8	83
		10	82
		8	85
		12	84
		5	89
		15	89
		20	34

[a] General procedure: acetal (10 mmol), NHPI (20%), and $Co(OAc)_2$ (1%) were stirred at room temperature under oxygen atmosphere (1 atm) in CH_3CN for the indicated optimized time.

The BDE values of the C−H bonds α to the amino groups are lower than those of the corresponding BDE values for alcohols, so that eq 107 is also more favored for amines.[121,154] Thus, amines should be suitable substrates for selective oxidations in the presence of NHPI. In fact, our research group has proposed a new catalytic system based on the use of $Co(OAc)_2$ either with *N*-hydroxysuccinimide (NHSI) or with NHPI for the selective synthesis of aromatic aldehydes by aerobic oxidation of tertiary benzylamines (Scheme 26).[155]

The use of NHSI instead of NHPI gives greater selectivity (Table 33) because the hydrogen abstraction by succinimido-*N*-oxyl (SINO) radical is slower than that by PINO radical. As a consequence, in the presence of PINO radical, primary benzyl groups give an increased amount of amide byproduct derived from further oxidation of the α-hydroxy amine (eq 108) before its transformation into the aromatic aldehyde (eq 107).

Scheme 26. Mechanism for the Aerobic Oxidation of Tertiary Benzylamines to Aldehydes, Catalyzed by NHSI or NHPI and $Co(OAc)_2$



(103)

(104)

(105)

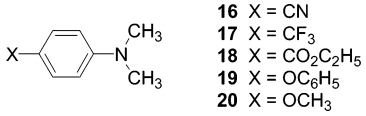
(106)

(107)

Table 33. Aerobic Oxidation of Benzyldimethylamines $X-C_6H_4-CH_2-N(CH_3)_2$ to the Aldehydes $X-C_6H_4-CHO$ Catalyzed by NHSI and NHPI[a]

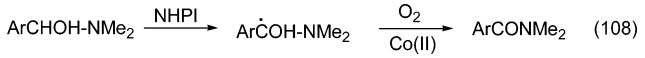
X	catalyst	*T* (°C)	reaction time (h)	conversion (%)	selectivity (%)
H	NHSI	35	2	42	91
H	NHSI	50	2.5	100	88
H	NHPI	35	2	75	81
H	NHPI	50	9	90	70
p-OMe	NHPI	40	3	96	84
p-Cl	NHSI	50	7	100	86
p-Cl	NHPI	50	7	90	86
m-Cl	NHSI	35	7	100	78
m-Cl	NHPI	35	7	90	68
p-NO_2	NHSI	50	9	90	80
p-NO_2	NHPI	50	9	86	60
p-CN	NHSI	50	4	100	86
p-CN	NHPI	50	4	86	68

[a] 7 mmol of benzylamine, 0.7 mmol of NHSI or NHPI, and 0.07 mmol of $Co(OAc)_2 \cdot 4H_2O$ in 15 mL of MeCN with O_2 at atmospheric pressure.



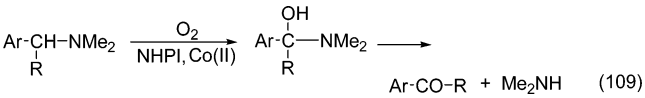
16 X = CN
17 X = CF_3
18 X = $CO_2C_2H_5$
19 X = OC_6H_5
20 X = OCH_3

Figure 18. 4-X-Substituted *N*,*N*-dimethylanilines.



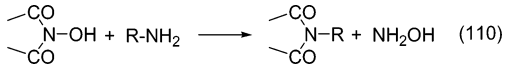
(108)

Amines with secondary benzyl groups lead to the formation of the corresponding ketones with higher selectivity, since the α-hydroxyamine cannot be oxidized further (eq 109).



(109)

A similar aerobic oxidation in the presence of NHPI cannot be carried out on primary and secondary amines, since, as it has been observed,[155] in this case the amino groups can deactivate the *N*-hydroxyimides according to eq 110 and thus inhibit the reaction.



(110)

More recently, Baciocchi and co-workers[156] have found that PINO radical generated in situ by $Pb(OAc)_4$ is able to promote the oxidative *N*-demethylation of *N*,*N*-dimethylanilines (DMAs) (Figure 18).

Kinetic investigations, including reactivity studies for a number of 4-X substituted *N*,*N*-dimethylamines as well as inter- and intramolecular deuterium isotopic effects, have led to the conclusion that the reaction between PINO and DMAs, contrary to the usual case, follows an electron-transfer mechanism (Scheme 27).[26]

3.7.2. Oxidation of Amides

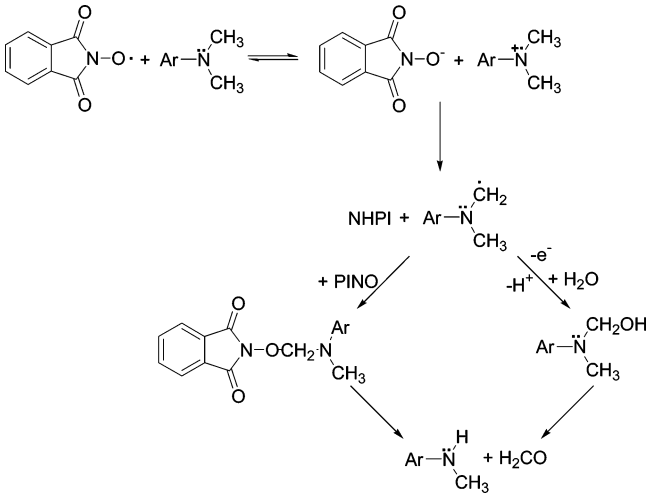
In order to prevent the deactivation of the *N*-hydroxyimide catalyst, the amino group of primary and secondary amines

Table 34. Products of Electrochemical Oxidation of Amides (20 mM) Using NHPI (5 mM) as Electron Carrier

Compound	F/mol[a]	Product	Yield (%)[b]	NHPI recovered (%)
MeCONHEt	2.0	$(MeCO)_2NH$	69	34
$MeCONEt_2$	1.9[c]	$(MeCO)_2NEt$	54	20
	2.0		80	66
	2.0		79	53
	1.3[c]		9[d]	--[e]

[a] Electricity passed per mole of the amides. [b] Based on the amides. [c] Electrolysis did not proceed further. [d] 44% of starting material was recovered. [e] Not determined.

Scheme 27. Proposed Mechanism for the Oxidative *N*-Demethylation of *N,N*-Dimethylanilines in CH_3CN at 25 °C



can be protected by acetylation to form the corresponding amides.

These derivatives have lower polar and enthalpic effects than the corresponding amines, but those effects are still sufficient to make these acetylated amines suitable substrates for hydrogen abstraction in the presence of NHPI from the C−H bonds α to the acetamido group.

Masui et al. first reported the oxidation of amides and lactams using NHPI as a mediator by using an electrochemical system to generate PINO radical (Scheme 28).

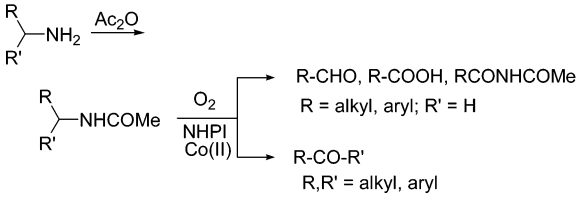
Table 35. Products of Electrochemical Oxidation of *N*-Alkylpyrrolidinone (20 mM) Using NHPI (5 mM) as Electron Carrier

Compounds	F/mol[a]	Product	Yield (%)[b]	NHPI recovered (%)
	2.0		81	45
			--[c]	
	2.0		73	46
			11	
	2.0		47	36
			34	

[a] Electricity passed per mole of *N*-alkyllactams. [b] Based on *N*-alkyllactams. [c] Not detected.

The oxidation of linear and cyclic amides (Table 34) provided the corresponding imides and *N*-acyllactams in good yields and high selectivity, whereas the oxidation of *N*-alkylpyrrolidinones (Table 35) led to the respective cyclic imides and lower amounts of *N*-acyllactams. However, the amount of the recovered catalyst reported in the tables clearly shows that, under electrochemical conditions, NHPI undergoes partial decomposition.

On the basis of previous reports, our group has suggested a simpler catalytic system which uses small amounts of Co(II) salts in the presence of NHPI to generate the PINO radical for the aerobic oxidation of acetamides and lactams (eq 111).[157]



(111)

The reaction mechanism is similar to that already shown for the oxidation of tertiary amines (Scheme 26).

Scheme 28. Mechanism for the Anodic Oxidation of Amides and Lactams Using *N*-Hydroxyphthalimide as a Mediator

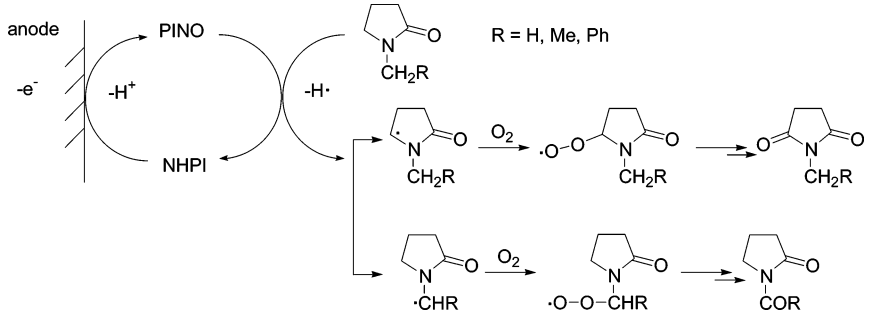
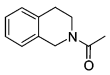
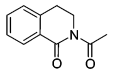
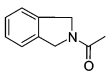
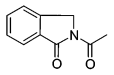
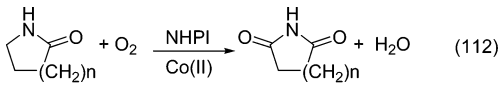


Table 36. Aerobic Oxidation of Lactams or Acetamides of Cyclic Amines Catalyzed by NHPI[a]

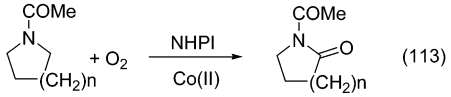
Amide	T(°C)	Reaction Time (h)	Conversion (%)	Products Selectivity (%)
	80	3	96	 (98)
	80	5	87	 (95)
	80	5	97	 (93)
	80	4	45	 (94)
	80	5	63	 (96)
	20	1	100	 (91)
	20	3	96	 (94)

[a] 5 mmol of amide, 0.5 mmol of NHPI, 0.025 mmol of $Co(OAc)_2 \cdot 4H_2O$, and 0.25 mmol of *m*-chlorobenzoic acid in 10 mL of MeCN with O_2 at atmospheric pressure.

The oxidation of lactams or acetamides of cyclic amines leads to the formation of cyclic imides (eq 112) or acetyllactams, respectively (eq 113) (Table 36)).

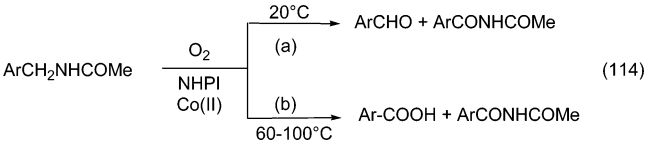


(112)



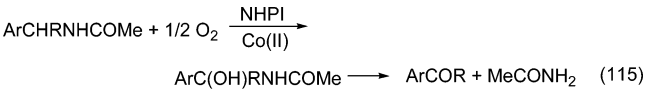
(113)

The oxidation of *N*-benzylacetamides (Table 37) at room temperature leads to imides and minor amounts of aromatic aldehydes, while at higher temperatures (60−100 °C) it yields carboxylic acids and variable amounts of imides, depending on the reaction solvent (eq 114).



(114)

With secondary benzyl groups, the oxidation selectively gives the corresponding ketones (eq 115).



(115)

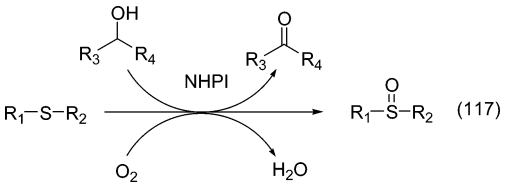
In contrast, for *N*-alkylacetamides, no trace of aldehyde is formed at room temperature, even at low conversions, but when a primary alkyl group is involved, the reaction products are the carboxylic acid and the imide (eq 116, Table 38).

(116)

Good results have been obtained from catalyzing the oxidation of the amide in ionic liquid,[158] with NHPI or with 3-pyridinemethyl-*N*-hydroxyphthalimide.

3.8. Oxidation of Sulfides

Sulfides may be oxidized to the corresponding sulfoxides in good to excellent yields by aerobic oxidation at atmospheric pressure in the presence of NHPI and an excess of alcohol (eq 117).[159]



(117)

The ease of hydrogen abstraction from the C−H bond α to the hydroxy group, a key step in the mechanism, depends on the correct choice of the alcohol (Scheme 29). Thus, cyclohexanol gives higher conversions, but 1-phenylethanol gives higher selectivity for sulfoxide, which is to say, a smaller amount of sulfone.

The role of the NHPI is to catalyze the aerobic conversion of the alcohol to the corresponding hydroperoxide, which is actually responsible for the oxidation of the sulfide (Scheme 29).

From the experimental results (Table 39), it appears evident that aliphatic sulfides are much less reactive than aromatic sulfides. Attempts in the presence of H_2O_2 and in the absence of ketone have given a lower conversion, demonstrating that the oxidizing agent in the second step of the process is not the hydrogen peroxide, but the hydroperoxide itself.

4. Reactions of Silanes

4.1. Oxidation of Silanes

Since the BDE values for the Si−H bonds are usually lower than those for the C−H bonds in corresponding

Scheme 29. Mechanism for the Aerobic Oxidation of Sulfides to Sulfoxides

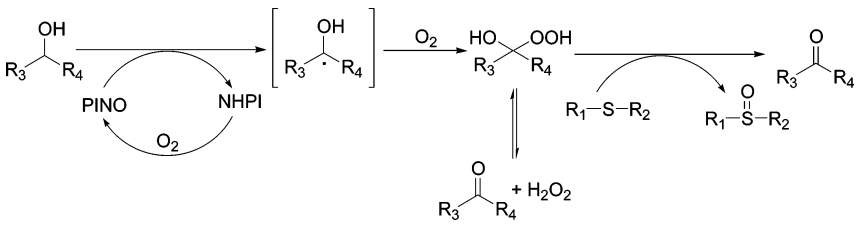


Table 37. Aerobic Oxidation of *N*-Benzylacetamides, $ArCH_2NHCOCH_3$, Catalyzed by NHPI[a]

Ar	solvent	*T* (°C)	reaction time (h)	conversion (%)	products selectivity (%)
Ph	CH_3CN	20	4	89	ArCHO (21) ArCO−NHCOCH$_3$ (77)
Ph	AcOH	100	2.5	75	ArCOOH (96) ArCO−NHCOCH$_3$ (3)
p-CH_3-C_6H_4−	CH_3CN	20	4	92	ArCHO (24) ArCO−NHCOCH$_3$ (73)
p-CH_3-C_6H_4−	AcOH	100	3	91	ArCOOH (93) ArCO−NHCOCH$_3$ (4)
m-CH_3-C_6H_4−	CH_3CN	20	4	88	ArCHO (22) ArCO−NHCOCH$_3$ (76)
m-CH_3-C_6H_4−	ACOH	100	3	93	ArCOOH (89) ArCO−NHCOCH$_3$ (8)
p-CH_3O-C_6H_4−	CH_3CN	20	2	97	ArCHO (16) ArCO−NHCOCH$_3$ (82)
p-CH_3O-C_6H_4−	AcOH	100	1	97	ArCHO (13) ArCOOH (82) ArCO−NHCOCH$_3$ (3)
p-Cl-C_6H_4−	CH_3CN	20	4	87	ArCHO (19) ArCO−NHCOCH$_3$ (78)
p-Cl-C_6H_4−	AcOH	100	2	92	ArCOOH (66) ArCO−NHCOCH$_3$ (32)

[a] The same procedure reported in Table 36 was utilized.

Table 38. Aerobic Oxidation of *N*-Alkylacetamides, $RNHCOCH_3$, Catalyzed by NHPI[a]

R	*T* (°C)	conversion (%)	products selectivity (%)
n-hexyl	20	70	*n*-C_4H_9-COOH (4) *n*-C_5H_{11}-COOH (15) *n*-C_5H_{11}-CONHCOCH$_3$ (67)
n-hexyl	80	98	*n*-C_4H_9-COOH (14) *n*-C_5H_{11}-COOH (13) *n*-C_5H_{11}-CONHCOCH$_3$ (68)
n-dodecyl	20	74	*n*-$C_{10}H_{21}$-COOH (2) *n*-$C_{11}H_{23}$-COOH (13) *n*-$C_{11}H_{23}$-CONHCOCH$_3$ (81)
n-dodecyl	80	97	*n*-$C_{10}H_{21}$-COOH (6) *n*-$C_{11}H_{23}$-COOH (11) *n*-$C_{11}H_{23}$-CONHCOCH$_3$ (81)
cyclohexyl	80	60	cyclohexanone (98)

[a] The same procedure reported in Table 36 was utilized.

Table 39. Aerobic Oxidation of Sulfides to Sulfoxides Catalyzed by NHPI in the Presence of Cyclohexanol[a]

R_1-S-R_2		conversion (%)	selectivity (%)
R_1 = Ph	R_2 = Me	99	86
R_1 = 4-ClPh	R_2 = Me	88	92
R_1 = 4-MePh	R_2 = Me	24	94
R_1 = 4-MePh	R_2 = Me	87	96
R_1 = 4-NO_2Ph	R_2 = Me	<5	trace
R_1 = Ph	R_2 = Et	51	83
thianthrene		86	87
R_1 = *tert*-butyl	R_2 = *tert*-butyl	15	60

[a] General procedure: 2 mmol of sulfide, NHPI (10%), and cyclohexanol (5 equiv) were stirred in 1 mL of benzonitrile at 90 °C for 12 h, under O_2 at atmospheric pressure.

Table 40. BDE Values of Si−H and C−H Bonds

	BDE (kcal/mol)		BDE (kcal/mol)
H_3Si-H	90.3	H_3C-H	105.0
Me_3Si-H	90.3	Me_3C-H	95.7
$PhSiH_2-H$	88.2	$PhCH_2-H$	88.5

hydrocarbons (Table 40),[160] silanes are particularly suitable substrates for aerobic oxidation catalyzed by NHPI and cobalt salts.

Table 41. Aerobic Oxidation of Silanes to Silanols Catalyzed by NHPI[a]

substrate	*t* (h)	*T* (°C)	conversion (%)	selectivity (%)
triethylsilane[b]	3	20	100	87
triphenylsilane[b]	4	20	68	98
triphenylsilane[a]	7	20	100	97
tri-*n*-butylsilane[b]	6	70	0	
cyclohexyldimethylsilane[b]	4	20	86	87
cyclohexyldimethylsilane[a]	6	20	100	100
methyldiphenylsilane[b]	6	20	60	100
methyldiphenylsilane[a]	6	20	100	100
methyldiphenylsilane[b]	6	50	82	100
n-$C_{18}H_{37}SiMe_2H$[b]	7	50	48	82
dimethylphenylsilane[b]	2	50	63	100
dimethylphenylsilane[a]	7	50	100	100
diphenyl-*t*-butylsilane[b]	8	50	0	

[a] 3 mmol of silane, 0.3[a] or 0.6[b] mmol of NHPI, 0.015 mmol of $Co(OAc)_2 \cdot 4H_2O$, and 0.25 mmol of *m*-chlorobenzoic acid in 5 mL of MeCN with O_2 at atmospheric pressure.

This reaction leads to a selective synthesis of silanols without any trace of siloxanes (eq 118),[161] as opposed to classical oxidations of silanes, for which the main byproducts are siloxanes.

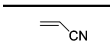
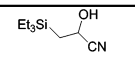
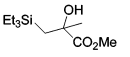
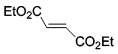
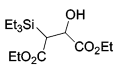
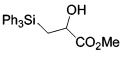
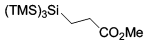
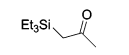
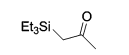
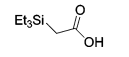
$$2\ R_3SiH + O_2 \xrightarrow[Co(II)]{NHPI} 2\ R_3Si\text{-}OH \quad (118)$$
$$> 90\ \%$$

Tertiary silanes have been oxidized to the corresponding silanols with high conversions and complete selectivity[161] (Table 41). However, the process is affected by steric effects, as is evidenced by the fact that diphenyl-*tert*-butylsilane and tri-*n*-butylsilane are not converted to the expected products. The reaction proceeds via a classical free radical chain mechanism (Scheme 30).

4.2. Hydroxysilylation of Alkenes

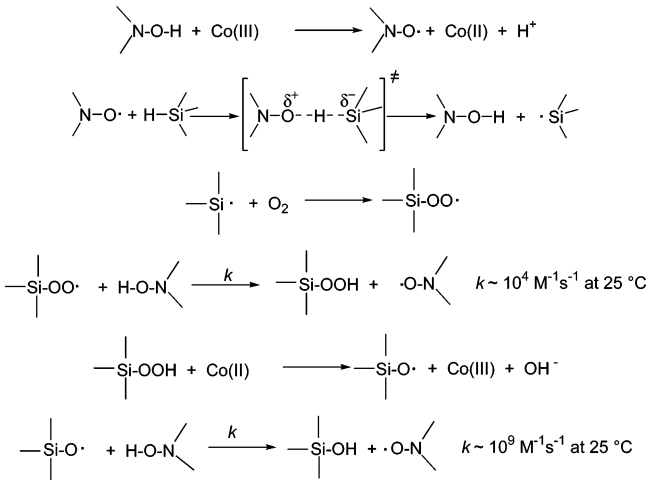
Ishii and co-workers[162] have used the reactivity of silanes in the presence of NHPI to develop a new reaction, which

Table 42. Hydroxysilylation of Alkenes with Et_3SiH, Catalyzed by NHPI[a]

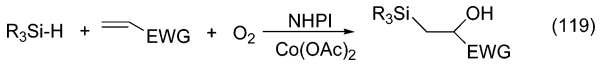
Substrate	t (h)	T (°C)	Conversion (%)	Product	Selectivity[b] (%)
	10	60	67		90
	10	50	57		97
	12	r.t.	99		66
	6	r.t.	61		82
	14	75	99		85
	4	70	-		52
	4	70	78		52
	2	70	68		77

[a] General procedure: alkene (2 mmol) was reacted with trialkylsilane in excess (5−15 mmol) in the presence of NHPI (10%) and $Co(OAc)_2$ (0.5%) in EtOAc (2 mL) under O_2 (1 atm). In a few cases $Co(acac)_3$ (0.1%) has been added. [b] Based on amount of alkene consumed.

Scheme 30. Mechanism for the Aerobic Oxidation of Silanes Catalyzed by NHPI and Cobalt Salts



accomplishes the simultaneous introduction of silyl and hydroxyl functions on olefins (eq 119).



(119)

Substituted alkenes bearing an electron-withdrawing group such as methyl acrylate undergo hydroxysilylation in good yields under an oxygen atmosphere in the presence of trialkylsilanes and catalytic amounts of cobalt salts (Table 42).

Even in this case, PINO generates, for example, the triethylsilyl radical by hydrogen abstraction (Scheme 31). The $Et_3Si^{\bullet}$ produced is then able to add to the double bond of the olefin to form a radical adduct which is quickly trapped by molecular oxygen. The resulting hydroperoxide is converted to the corresponding alcohol by reaction with cobalt salts.

Scheme 31. Mechanism for the Aerobic Hydroxysilylation of Alkenes Catalyzed by NHPI

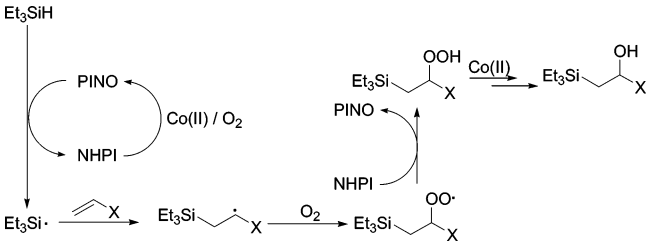
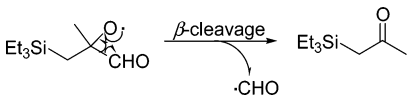


Table 43. Isomer Distribution in Halogenation of Substituted Alkanes, Catalyzed by NHPI

	MeOCO—CH_2—CH_2—CH_2—CH_3				
$HCl + O_2$ (NHPI)[a]		8.2	27.1	64.7	-
$HBr + O_2$ (NHPI)[b]		9.4	26.6	64.0	-
	MeOCO—CH_2—CH_2—CH_2—CH_2—CH_3				
$HCl + O_2$ (NHPI)[a]	6.1	12.1	28.3	53.5	-
$HBr + O_2$ (NHPI)[b]	6.3	16.0	27.0	50.7	-
	Cl—CH_2—CH_2—CH_2—CH_2—CH_2—CH_3				
$HCl + O_2$ (NHPI)[a]	3.8	5.1	15.3	32.2	43.6	-
$HBr + O_2$ (NHPI)[b]	6.1	5.5	13.6	30.9	43.9	-
	O_2N—CH_2—CH_2—CH_2—CH_2—CH_2—CH_3				
$HCl + O_2$ (NHPI)[a]	-	-	9.2	32.2	58.6	-

[a] Typical procedure of halogenation: 2 mmol of substrate, 0.4 mmol of HNO_3, 2 mmol of $CuCl_2$, and 0.4 mmol of NHPI were stirred in 10 mL of AcOH at 100 °C for 5 h under O_2. Conversion: 47%. [b] 2 mmol of Br_2 instead of $CuCl_2$ and 0.02 mmol of $Cu(OAc)_2$ at 80 °C. Conversion: 35%.

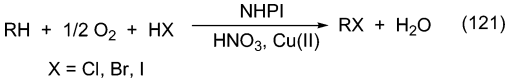
The formation of triethylsilylacetone (Table 42) can be due to the β-cleavage of the alkoxyl radical formed during the hydroperoxide decomposition (eq 120).



(120)

5. Halogenations of Alkanes

We recently have reported a new method for the selective halogenation of a wide range of aliphatic derivatives in the presence of NHPI as cocatalyst (eq 121).[163] The results are shown in Table 43.

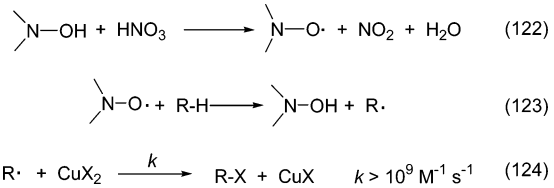


(121)

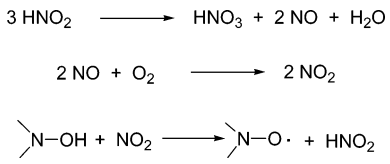
The proposed mechanism (Scheme 32) involves the generation of PINO radical by HNO_3 as an induced homolysis driven by enthalpic effects (eq 122). PINO is then able to abstract a hydrogen from hydrocarbons (eq 123), forming a carbon centered radical which undergoes a fast halogen-transfer reaction in the presence of $CuCl_2$ or $Cu(OAc)_2$ and Br_2 (eq 124).

The process is made catalytic by the presence of O_2, which oxidizes the NO derived from disproportionation of nitrous

Scheme 32. Mechanism for the Selective Halogenation of Alkanes Catalyzed by NHPI



Scheme 33. The Role of Oxygen in the Halogenation of Alkanes



acid to NO_2, which can then produce PINO from NHPI (Scheme 33).

The distribution of products is quite different from that observed for classical free radical halogenation by Cl_2 or Br_2 (Table 44), in which $Cl^•$ or $Br^•$, respectively, is the hydrogen abstracting species.[164] In fact, in the presence of NHPI, the regioselectivity for chlorination is similar to that for bromination, indicating that the actual abstracting species is indeed PINO radical in both cases.

The reported results clearly show the presence of both an enthalpic and a polar effect: the enthalpic effect is emphasized by the fact that the methyl group, with its high BDE C−H bonds, reacts only in traces; the marked polar effect explains both the deactivation of the substrate after the first halogen insertion (which allows selective monosubstitution) and also the lower reactivity of CH_2 groups which are nearer to electron-withdrawing substituents.

Working in AcOH in the presence of iodine, the alkyl iodides, although initially formed, undergo solvolysis, leading to acetoxy derivatives.

6. Formation of C–N Bonds Catalyzed by NHPI.

The transformation of a C−H bond into a C−N bond is a process which adds much value in organic chemistry. The most important industrial method for doing this is probably the ammonoxidation of propene for the production of acrylonitrile, which is one of the most important monomers in polymerization chemistry.

The direct introduction of nitrogen into an aromatic C−H bond is preferably done by direct electrophilic substitution using HNO_3. The nitro derivatives obtained in this way are valuable compounds in all fields of organic chemistry because they can be converted into many different nitrogen-containing compounds.[165]

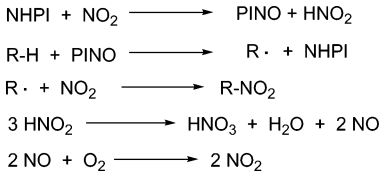
The nitration of aliphatic C−H bonds is a difficult reaction, although the direct nitration of methane and ethane by HNO_3 or NO_2 is applied industrially for the production of the corresponding nitroalkanes.[166] The reaction conditions are very harsh (250−400 °C), because of the low reactivity of NO_2 in hydrogen abstraction from strong C−H bonds. With higher alkanes, this method gives very unselective results, which also include formation of carbon−carbon bond cleavage products.

With this background, Ishii et al. studied the possibility of using NHPI catalysis to get selective alkane nitration reactions.

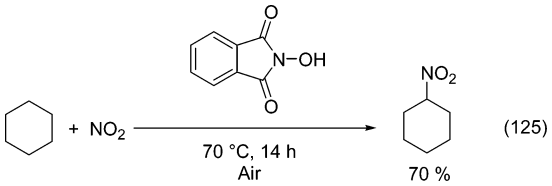
Table 44. Isomer Distribution in Halogenation of Substituted Alkanes with Chlorine and Bromine

	MeOCO—CH_2—	—CH_2—	—CH_2—	—CH_3
Cl_2	5.4	30.1	44.5	18.7
Br_2	35.4	19.6	45.4	-

Scheme 34. Mechanism for the NHPI-Catalyzed Alkane Nitration with NO_2 under Air



NO_2 added to NHPI in an EPR cavity instantly forms PINO at room temperature. Treating alkanes, e.g., cyclohexane, with this catalytic system formed nitro derivatives in good yields (eq 125).[167]



The reaction gives higher yields in the presence of air than in anaerobic conditions, because O_2 regenerates NO_2 from the NO formed in the course of the proposed reaction mechanism outlined in Scheme 34.

Because of the higher concentration of NO_2 in the reaction medium compared to that of O_2 in the air, the alkyl radicals formed react predominately with NO_2 rather than O_2, giving selectivity for nitroalkanes over oxygenated products.

A variety of alkanes were successfully nitrated by the NHPI/NO_2 system, as illustrated in Figure 19.

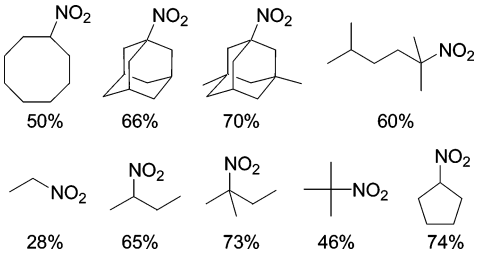
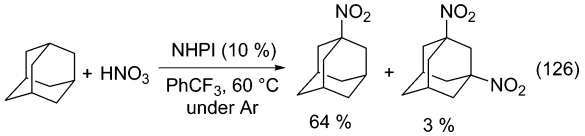
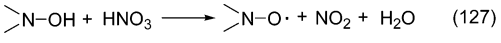


Figure 19. Nitration of various alkanes by the NHPI/NO_2 system.

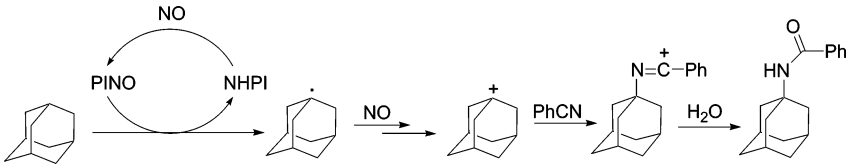
HNO_3 itself is able to nitrate alkanes in the presence of NHPI, as shown in the case of adamantane (eq 126). HNO_3 generates PINO radical by simple oxidation of NHPI with NO_2 as a byproduct (eq 127).





Both HNO_3 and NO_2 were successfully used for alkylbenzene nitration catalyzed either by NHPI itself or by NAPI

Scheme 35. Mechanism for the NHPI-Catalyzed Ritter-Type Reaction in the Presence of NO



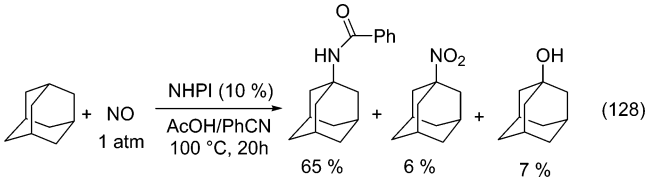
as an in situ source of NHPI. Side chain nitration of alkylbenzenes exemplified by toluene led selectively to α-nitrotoluenes without ring nitration. The results obtained are reported in Table 45.[168]

Table 45. Nitration of Aromatic Compounds with HNO_3 or NO_2 Catalyzed by NHPI

Substrate	t (h)	T (°C)	Products (yield (%))	
Ethylbenzene	14	90	Ph, NO_2 (63)	Ph, O (26)
Cumene	5	70	Ph, NO_2 (55)	Ph, OH (28)
1,2-dimethylbenzene	5	90	NO_2 (69)	OH (24)
1,3-dimethylbenzene	5	90	NO_2 (61)	OH (28)
1,4-dimethylbenzene	5	90	NO_2 (59)	OH (28)
1,3,5-trimethylbenzene	5	70	NO_2 (32)	NO_2 (2)
p-Cl-toluene	15	90	Cl, NO_2 (69)	Cl, OH (13)

Another approach proposed by Ishii et al. for the functionalization of alkanes by the introduction of a nitrogen-containing group involved using NO in the presence of NHPI.[169]

Applied to adamantane in AcOH with PhCN as cosolvent, it gave Ritter-type products such as *N*-adamantylbenzamide with small amounts of nitroadamantane and 1-adamantanol as byproducts (eq 128).



(128)

A plausible reaction mechanism is depicted in Scheme 35.

A more general Ritter-type reaction was devised by Ishii et al.[170] by using the CAN/NHPI system, in which the Ce(IV) salt plays a double role: it generates PINO by oxidation of NHPI, and it also forms the carbocation from oxidation of the alkyl radical formed by H abstraction by PINO. The carbocation then goes on to trap the nitrile to form the amide, as illustrated in Scheme 36.

The interesting results obtained are shown in Table 46.

Ishii et al. also proposed a new route for the synthesis of lactam precursors from cycloalkanes. This new route involved reacting *tert*-butyl nitrite with cycloalkanes in the presence of NHPI to form a mixture of nitrosocycloalkanes and cycloalkanone oximes (Scheme 37).[171]

Scheme 36. Mechanism for the NHPI-Catalyzed Ritter-Type Reaction in the Presence of CAN

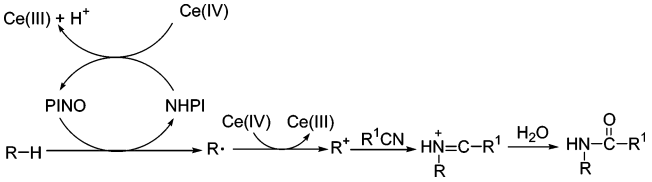
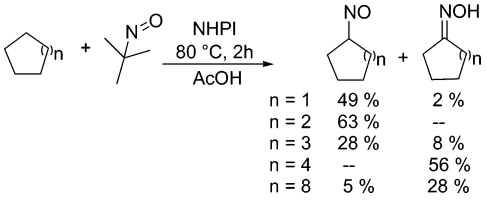


Table 46. Nitration of Aromatic Compounds with HNO_3 or NO_2 Catalyzed by NHPI[a]

Substrate	Conversion (%)	Products (selectivity (%))
Ph	69	HN–C(=O)–Et, Ph (69)
Ph	63	HN–C(=O)–Et, Ph (93)
	93	HN–C(=O)–Et (74)
	93	H, N, C(=O), Et (74)
	51	N, H, C(=O), Et (80)
	57	N, H, C(=O), Et (93)

[a] Substrate (1 mmol) was allowed to react with CAN (1.5 mmol) in the presence of NHPI (0.1 mmol) in EtCN (5 mL) at 100 °C for 6 h under Ar.

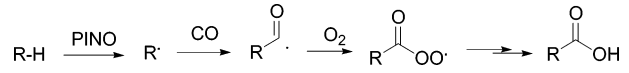
Scheme 37. Synthesis of Lactam Precursors from Cycloalkanes



7. C–C Forming Reactions Catalyzed by NHPI

The formation of C−C bonds has always been a key reaction for all organic chemists. In fact, the most available

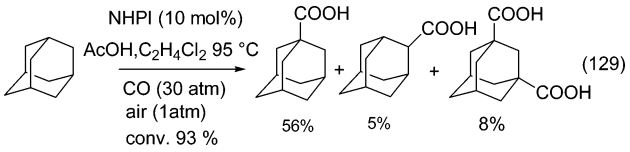
Scheme 38. Mechanism for the NHPI-Catalyzed Formation of C−C Bonds in the Presence of CO



starting materials are very often small molecules derived from functionalization of raw materials obtained mostly from the petrochemical industry (low molecular weight olefins, alcohols, carbonylic compounds, carboxylic acids, epoxides, etc.).[172]

Several approaches, most of which are based on ionic chemistry, have been proposed for the formation of carbon−carbon bonds. In the last few decades, free radical reactions have gained plausibility for these kinds of reactions because of the singular peculiarity of free radicals[173] and also because of the availability of several different methods, some of which allow stereocontrol of the reaction.[174]

Among these methods are the different approaches proposed by Ryu et al.[175] for using carbon monoxide to make C−C bonds. Based on that work, Ishii et al.[176] have used CO in an NHPI catalyzed aerobic oxidation of alkanes to obtain carboxylic acids. Adamantane under a CO/air (15/1 atm) mixture in the presence of NHPI gives adamantane carboxylic acids (eq 129) along with 1-adamanantol and 2-adamantanone as oxygenated byproducts.

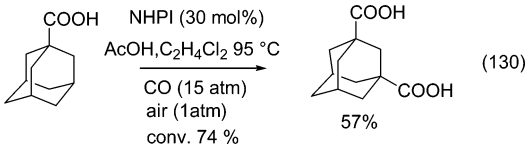


(129)

The reaction mechanism is illustrated in Scheme 38.

In the presence of O_2 instead of air, the relative amount of the oxygenated products increases.

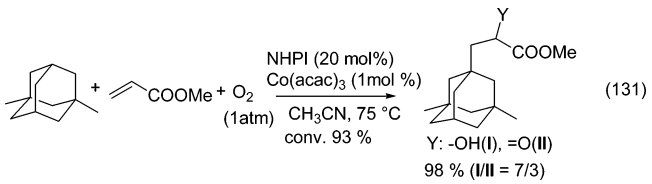
The dicarboxylic acid of adamantane, a monomer of some interest in polymer chemistry, is very difficult to obtain by conventional methods, but it was successfully obtained in a stepwise procedure (eq 130).



(130)

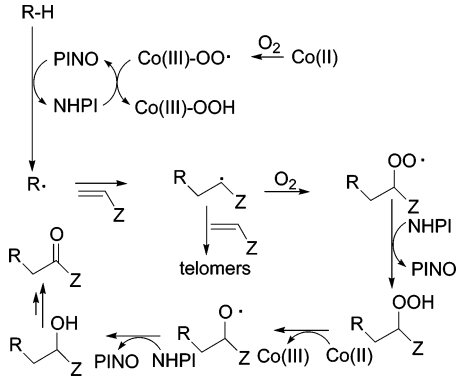
Other cyclic alkanes, such as 1,3-dimethyladamantane and *endo*-tricyclo[5.2.1.0^{2,6}]decane, were successfully carboxylated with good selectivity.[176]

In organic synthesis, free radical reactions offer very interesting opportunities for making carbon−carbon bonds by inter- or intramolecular addition of carbon radicals to alkenes.[173] Ishii et al.[177] have proposed simple systems for making C−C bonds by radical addition with NHPI catalysis in a wide range of compounds. The addition of alkanes to electron poor olefins is possible simply by introducing the olefin under the classical reaction conditions necessary for the oxidation of alkanes (eq 131).

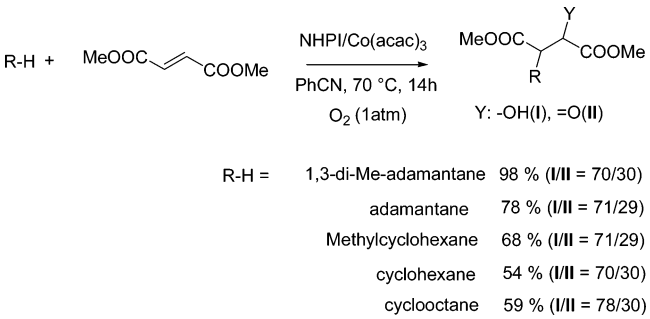


(131)

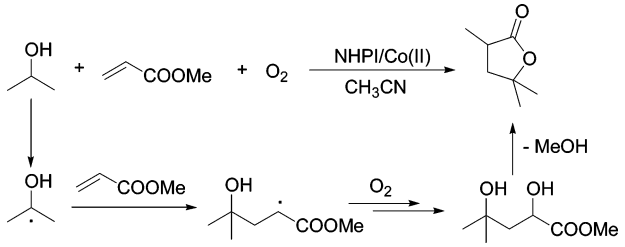
Scheme 39. Mechanism for the NHPI-Catalyzed Addition of Alkanes to Olefins



Scheme 40. NHPI-Catalyzed Addition of Alkanes to Fumarate



Scheme 41. NHPI-Catalyzed Synthesis of α-Hydroxy-γ-lactones



The reaction mechanism is illustrated in Scheme 39. By this procedure a double functionalization of the olefin, namely oxoalkylation, takes place.

The corresponding alcohols and ketones, with the alcohols usually prevailing, are obtained from decomposition of the intermediate hydroperoxides.

Generally, the best yields were obtained with adamantanes, as shown in the reactions of different alkanes with methylfumarate (Scheme 40). This may be ascribed to the enhanced nucleophilic character of 1-adamantyl radicals,[81] which makes these bicyclic radicals more reactive toward the olefins.

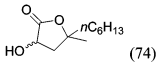
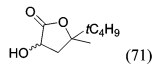
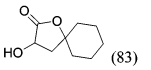
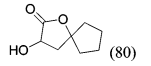
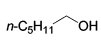
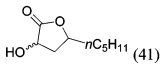
A similar reaction mechanism was successfully used in the synthesis of α-hydroxy-γ-lactones by addition of α-hydroxy carbon radicals to unsaturated esters (Scheme 41).[178]

α-Hydroxy-γ-lactones are important precursors of α-β-butenolides, for which few practical synthetic methods are available.[179]

α-β-Butenolides are valuable monomers for the synthesis of biodegradable polymers,[180] are efficient food intake controllers,[181] and have potent biological activity.[182]

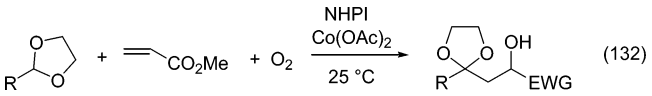
α-Hydroxy-γ-spirolactones are obtained in good yields from cyclic alcohols (Table 47).

Table 47. Reactions of Methyl Acrylate with Various Alcohols Catalyzed by NHPI[a]

Substrate	t (h)	Products (selectivity (%))
	5	 (74)
	8	 (71)
	3	 (83)
	8	 (80)
	5	 (41)

[a] Methyl acrylate (3 mmol) was allowed to react with alcohols (5 mmol) in the presence of NHPI (10%), $Co(OAc)_2$ (0.1%), and $Co(acac)_3$ (1%) under O_2 (1 atm) in MeCN (0.5 mL).

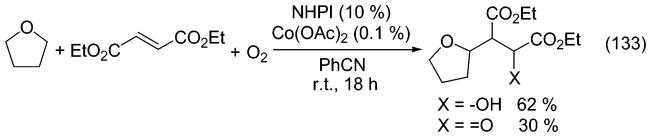
Similarly, aldehydes masked as 1,3-dioxolanes were added to alkenes to form the corresponding β-hydroxy derivatives (eq 132).[183] Direct hydroxyacylation is limited by decarbonylation of the acyl radicals[184] and by competition with the reaction with O_2, which leads to carboxylic acids and other undesired byproducts.[185]



(132)

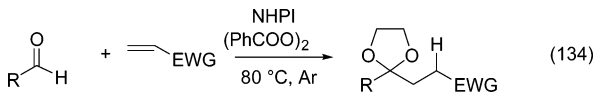
Dioxolane can be deprotected under acidic conditions to give the β-hydroxy carbonyl compounds, which are important intermediates in the synthesis of pharmaceuticals.[186]

Ethers behave like the dioxolanes and give good yields of the corresponding adducts with the olefins (eq 133).[187]



(133)

Very interesting hydroacylations of olefins occur under anaerobic conditions in the presence of NHPI, an initiator, and aldehydes (eq 134).[188]



(134)

In the absence of NHPI, this reaction occurs via a simple radical chain addition mechanism.[189]

It is interesting to note that this reaction also takes place with electron-rich olefins. When carried out without a suitable organocatalyst, the major problem with this process is hydrogen abstraction from the aldehyde by the olefin−radical adduct, which is competitive because of the similar polar nucleophilic character of the radical adduct and the acyl adduct.

This inconvenience has been successfully removed by operating in the presence of methyl thioglycolate ($HSCH_2CO_2Me$), which acts as a polarity-reversal catalyst. Polarity-reversal catalysis, an idea introduced by Roberts,[190] makes it possible to follow reaction pathways which are inhibited by unfavorable polar effects just by the inversion of the polar character using a suitable mediator. Ishii et al. have shown that NHPI is able to act as a polarity-reversal catalyst, as shown in Scheme 42.[191]

Scheme 42. Mechanism for Hydroacylation Using NHPI as a Polarity-Reversal Catalyst

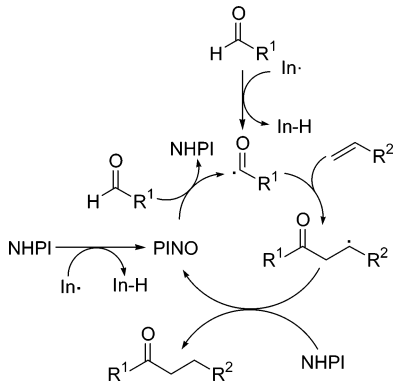
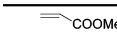
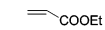
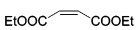
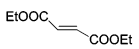


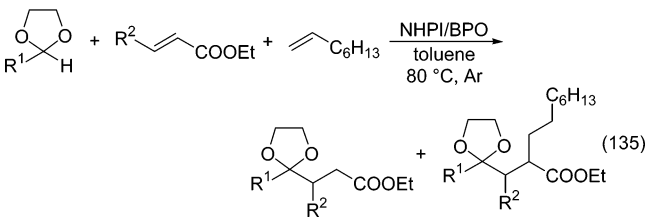
Table 48. Reactions of Methyl Acrylate with Various Alcohols Catalyzed by NHPI[a]

Alkene	Aldehyde	Yield (%)
	C_4H_9CHO	80
	C_4H_9CHO	72
	C_4H_9CHO	43
	Dioxolane	Polymerized
	Dioxolane	74
	Dioxolane	41
	Dioxolane	46
	2-Methyldioxolane	80
	2-Phenyldioxolane	No-reaction

[a] Alkenes (2 mmol), aldehydes (15 mmol) or oxolanes (30 mmol), NHPI (0.2 mmol), and BPO (0.2 mmol) were stirred in toluene (1 mL) at 80 °C under Ar (1 atm).

As shown in Table 48, the reaction also takes place with masked aldehydes such as 1,3-dioxolanes.

An interesting three-component reaction was also made possible by using dioxolane, an electron-poor olefin, and an electron-rich one (eq 135).



(135)

Free radical substitution on aromatic rings is another way to make C−C bonds. The Minisci reactions[192] are a well-developed class of homolytic free radical sustitutions. The

Table 49. Acylation of Heteroaromatic Bases by Aerobic Oxidation of Aldehydes, R-CHO, Catalyzed by NHPI[a]

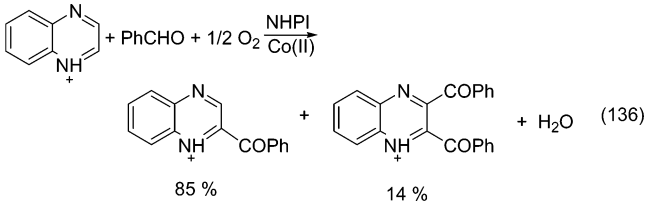
heterocycle	R-CHO	conversion (%)	products selectivity (%)
quinoline	Ph	50	2-acyl (34); 4-acyl (41); 2,4-diacyl (22)
lepidine	Ph	15	2-acyl (98)
quinoxaline	Ph	86	2-acyl (85); 2,3-diacyl (14)
quinoxaline[b]	*t*-Bu	100	2-acyl (45); 2-*t*-Bu (52)
quinoxaline	*t*-Bu	100	2-acyl (26); 2-*t*-Bu (72)
quinoxaline	*n*-C_6H_{13}	91	2-acyl (77); 2,3-diacyl (14)
quinoxaline	cyclohexyl	100	2-acyl (43); 2,3-diacyl (32); 2-acyl-3-cyclohexyl (12)
quinazoline	*n*-C_6H_{13}	100	3H-quinazolin-4-one (96)
quinazoline	Ph	100	3H-quinazolin-4-one (98)
pyrazine	*n*-C_6H_{13}	85	2-acyl (96)
pyrazine	Ph	82	2-acyl (97)
pyrimidine	*n*-C_6H_{13}	14	4-acyl (98)
4-cyanopyridine[c]	Ph	100	2-acyl (96)

[a] 3 mmol of the heterocycle, 3 mmol of CF_3COOH, 15 mmol of aldehyde, 0.3 mmol of NHPI, 0.005 mmol of $Co(acac)_2$, and 0.01 mmol of $Co(OAc)_2 \cdot 4H_2O$ in 8 mL of PhCN with air at 70 °C for 12 h. [b] 20 °C. [c] CH_3CN instead of PhCN as solvent.

Friedel−Crafts alkylation and acylation reactions are of little utility when applied to heterocyclic aromatic bases, but substitution of protonated heterocycles by nucleophilic carbon centered radicals is quite successful.

Thus, in the presence of NHPI, we have realized two new processes for the free radical substitution of protonated heteroaromatics.

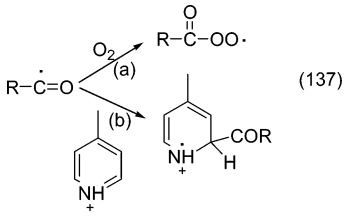
In the first process, we have acylated the heteroaromatic bases by using aldehydes in the presence of NHPI, air, and Co(II) as cocatalysts (eq 136).[193]



(136)

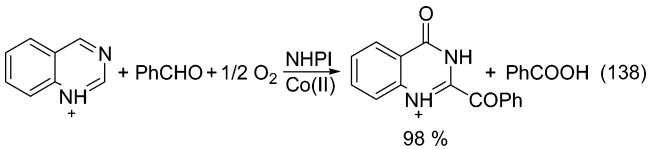
The acyl radicals arising from hydrogen abstraction from aldehydes by PINO led to aromatic substitution (eq 137b). This substitution was favored relative to the competitive aerobic oxidation reaction (eq 137a) by keeping the O_2 concentration low (Scheme 43).

Scheme 43. Competitive Reactions of Acyl Radicals with Oxygen and Protonated Heteroaromatic Bases



(137)

This reaction is generally applicable for aldehydes and bases (Table 49), with the exception only of quinazoline, which gives no acylation, but instead gives only 3-H-quinazolin-4-one as the sole reaction product (eq 138).



(138)

Analogous attempts to achieve carbamoylation of heteroaromatic bases gave poor conversions, indicating that the carbamoyl radical formed during the aerobic oxidation of formamide with NHPI/Co(II) catalysis reacted much faster with oxygen than with the bases.

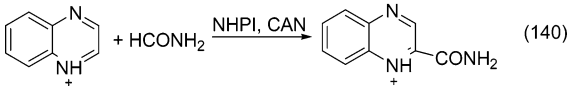
Table 50. Carbamoylation of Heteroaromatic Bases by Oxidation of Formamide with CAN Catalyzed by NHPI[a]

heterocycle	conversion (%)	selectivity (%)
quinoxaline[b]	100	100 (2)
quinoline	78	95 (2); 5 (4)
4-methylquinoline	66	100 (2)
2-methylquinoline	18	100 (4)
isoquinoline	78	100 (1)
4-cyanopyridine	57	100 (2)
pyrazine	62	100 (2)
quinazoline	52	100 (2)

[a] 2.5 mmol of the heterocycle, 5 mmol of CAN, 2.5 mmol of NHPI, and 5 mmol of CF_3COOH in 10 mL of $HCONH_2$ at 70 °C for 6 h. [b] 5 mmol of H_2SO_4 was used instead of CF_3COOH.

Thus, in a second process, we considered generating the PINO radical anaerobically using CAN as an alternative oxidant (eq 139), and indeed, when the NHPI catalyzed oxidation of formamide by CAN was carried out under N_2 in the presence of protonated heteroaromatic bases, selective carbamoylation of the heterocyclic ring was observed (eq 140). The results are shown in Table 50.[194]

(139)



(140)

Since the reaction does not occur in the absence of NHPI, it appears clear that the role of PINO is to generate the carbamoyl radical by a classical hydrogen-transfer reaction (eq 141).

$$H\text{-}CONH_2 + PINO \rightarrow {}^{\bullet}CONH_2 + NHPI \quad (141)$$

CAN has a 2-fold function: it generates the PINO radical and participates in the rearomatization of the radical adduct between the carbamoyl radical and the heteroaromatic base. Thus, 2 equiv of Ce(IV) per mole of base are necessary.

8. Conclusions

This review gives a general overview of the reactions catalyzed by *N*-hydroxyphthalimide and related compounds. It focuses on processes ranging from commercial production chemicals, such as adipic and terephthalic acid, to fine

chemicals such as those discussed in the sections on C−N and C−C bond formation.

Great emphasis is given to C−H bond activation reactions, which are involved in processes of wide interest. NHPI catalysis has opened a large window in this challenging field, and many aspects still need further investigation, especially those related to the actual effectiveness of the catalyst in the various reaction conditions under which it it has been used. The main limitation of every NHPI related system, although they are more efficient for some selected transformations, is connected to the intrinsic nature of the transient nitroxyl radical, which has a limited shelf-life despite the nature of the groups surrounding the CO−N(OH)−CO functionality.

To the best of our knowledge, no systematic study has been made yet of the stability of the *N*-hydroxyimides under conditions relevant to NHPI catalysis, especially in acidic media such as those more suitable for the activation of alkanes such as cyclohexane. This is also the case for the related nitroxyl radicals, for which it is clear that higher temperatures favor decomposition.

Moreover, all of the tentatively proposed methods for modifying NHPI to facilitate recycling (for example, by immobilizing it in a polymer matrix or by making it soluble in ionic liquids) deserve particular attention, but in our opinion, the high costs of these modifications limit their application to the synthesis of fine chemicals. The big game remains an efficient and cheap catalyst which will make the oxidations of cyclohexane to adipic acid and of *p*-xylene to terephthalic acid much more cost-effective and environmentally friendly processes. And at present, in the class of *N*-hydroxyimides, simple NHPI is the catalyst which has the best cost/effectiveness ratio.

Other issues which need to be addressed concern the metal cocatalyst used with NHPI in the reactions. In particular, a deeper systematic investigation of both the nature of the metals themselves and their ligands should allow the design of systems with a better activation of oxygen in synergy with the chemical behavior of NHPI and PINO radicals.

Although only a few examples have been reported so far, metal-free processes using an external cocatalyst such as bromine, anthraquinones, and/or suitable promoters allow relatively low temperature transformations and appear to be very interesting.

The effectiveness of NHPI catalyzed autoxidation reactions is due to two factors: (1) the PINO radical is more reactive in C−H bond hydrogen abstraction than is the peroxyl radical, and (2) NHPI has the ability to quench the peroxyl radical as shown in eq 18. As has been shown by Pedulli and others, this process is very sensitive to the hydrogen donor ability of the solvent, which has a detrimental effect on the peroxyl scavenging process: it raises the concentration of these radicals and lowers the chain length of the chain processes, thus producing a negative overall effect on the progress and selectivity of the autoxidation.

Extending the pioneering study done by Pedulli and coworkers should yield a better understanding of the chemistry connected to this process, which would allow more effective planning of processes with high conversion and high selectivity.

For systems involving alkoxyl radicals, such studies on the solvent effect would also be welcome because increasing our understanding of this effect on the alkoxyl radical + NHPI reactions ought to allow us to better treat the chemistry in the way we intend.

In conclusion, to widen its applicability and gain a more mature understanding of NHPI catalysis, we need not only the great efforts made in the past decade by the Ishii group and other prominent researchers in the synthetic aspects of this catalyst system, but also a fuller exploration of its physical chemistry aspects. This is required for more systematic planning of new synthetic processes and to have a better overview of the advantages and limitations of this very important kind of catalysis.

In the last 5 years, our contribution in collaboration with Prof. Minisci and Prof. Pedulli's group has followed somewhat this philosophy: the development of new synthetic processes is to be based upon a mechanistic understanding of the chemical aspect on which this catalysis is based. This is in line with Prof. Minisci's motto "understanding chemistry for making chemicals".

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10. References

(1) Sheldon, R. A. *Pure Appl. Chem.* **2000**, *72*, 1233.
(2) Dyker, G., Ed. *Handbook of C-H Transformations*; Wiley-VCH: Weinheim, 2005.
(3) Walling, C. In *Active Oxygen in Chemistry*; Foote, C. S., Valentie, J. S., Greenberg, A., Liebman, J. F., Eds.; Chapman & Hall: Glasgow, 1995; p 24.
(4) Suresh, A. K.; Sharma, M. M.; Sridhar, T. *Ind. Eng. Chem. Res.* **2000**, *39*, 3958.
(5) Salem, L. *Electrons in Chemical Reactions. First Principles*; Wiley-Interscience: New York, 1982.
(6) Simandi, L. L., Ed. *Dioxygen Activation and Homogeneous Catalytic Oxidation*; Elsevier: Amsterdam, 1991. Parshall, G. W.; Ittel, S. D. *Homogeneous Catalysis*, 2nd ed.; Wiley: New York, 1992. Barton, D. H. R., Martell, A. E., Sawyer, D. T., Eds. *The Activation of Dioxygen and Homogeneous Catalytic Oxidation*; Plenum: New York, 1993. Sheldon, R. A.; Kochi, J. K. *Metal-catalyzed Oxidations of Organic Compounds*; Academic: New York, 1981.
(7) Bäckvall, J.-E., Eds. *Modern Oxidation Methods*; Wiley-VCH: Weinheim, 2004.
(8) Centi, G.; Trifirò, F.; Cavani, F. *Selective Oxidation by Heterogeneous Catalysis*; Kluwer Academic/Plenum: New York, 2001. Sheldon, R. A., van Bekkum, H., Eds. *Fine Chemicals through Heterogeneous Catalysis*; Wiley-VCH: Weinheim, 2001.
(9) Schreiner, P. R.; Fokin, A. A. *Chem. Rec.* **2004**, *3*, 247.
(10) Fokin, A. A.; Schreiner, P. R. *Adv. Synth. Catal.* **2003**, *345*, 1035.
(11) Fokin, A. A.; Schreiner, P. R. *Chem. Rev.* **2002**, *102*, 1551.
(12) Sheldon, R. A. *J. Chem. Technol. Biotechnol.* **1997**, *68*, 381.
(13) Punniyamurthy, T.; Velusamy, S.; Iqbal, J. *Chem. Rev.* **2005**, *105*, 2329.
(14) Meunier, B.; de Visser, S. P.; Shaik, S. *Chem. Rev.* **2004**, *104*, 3947.
(15) Adam, W.; Saha-Möller, C. R.; Ganeshpure, P. A. *Chem. Rev.* **2001**, *101*, 3499.
(16) Ishii, Y.; Sakaguchi, S. *Catal. Surv. Jpn.* **1999**, *3*, 27. Ishii, Y.; Sakaguchi, S.; Iwahama, T. *Adv. Synth. Catal.* **2001**, *343*, 393.
(17) Gambarotti, C.; Punta, C.; Recupero, F. *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons: Weinheim, 2005; http://dx.doi.org/10.1002/047084289X.rn00598.
(18) Minisci, F.; Recupero, F.; Pedulli, G. F.; Lucarini, M. *J. Mol. Catal. A* **2003**, *63*, 204. Minisci, F.; Punta, C.; Recupero, F. *J. Mol. Catal. A* **2006**, *251*, 129.

(19) Ishii, Y.; Sakaguchi S. In *Modern Oxidation Methods*; Bäckvall, J.-E., Eds.; Wiley-VCH: New York, 2004; p 119.
(20) Sheldon, R. A.; Arends, I. W. C. E. *Adv. Synth. Catal.* **2004**, *346*, 1051.
(21) Karakurt, A.; Dalkara, S.; Ozalp, M.; Ozbey, S.; Kendi, E.; Stables, J. P. *Eur. J. Med. Chem.* **2001**, *36*, 421.
(22) Grochowski, E.; Boleslawska, T.; Jurczak, J. *Synthesis* **1977**, 718.
(23) Masui, M.; Ueshima, T.; Ozaki, S. *Chem. Commun.* **1983**, 479.
(24) Masui, M.; Hara, S.; Ueshima, T.; Kawaguchi, T.; Ozaki, S. *Chem. Pharm. Bull.* **1983**, *31*, 4209.
(25) Masui, M.; Rosomi, K.; Tsuchida, K.; Ozaki, S. *Chem. Pharm. Bull.* **1985**, *33*, 4798.
(26) Masui, M.; Hara, S.; Ozaki, S. *Chem. Pharm. Bull.* **1986**, *34*, 975.
(27) Masui, M.; Kawaguchi, T.; Ozaki, S. *Chem. Commun.* **1985**, 1484.
(28) Masui, M.; Kawaguchi, T.; Yoshida, S.; Ozaki, S. *Chem. Pharm. Bull.* **1986**, *34*, 1837.
(29) Foricher, J.; Furbringer, C.; Pfoertner, K. EP Patent 0198351, 1986. Foricher, J.; Furbringer, C.; Pfoertner, K. U.S. Patent 5,030,739, 1991.
(30) Ishii, Y.; Nakayama, K.; Takeno, M.; Sakaguchi, S.; Iwahama, T.; Nishiyama, Y. *J. Org. Chem.* **1995**, *60*, 3934.
(31) *Focus on Catalysts*, 2004, Issue 1, January 2004, p 7.
(32) The Minister of Education, Culture, Sports, Science and Technology of Japan in 2003 awarded "The Third Green and Sustainable Chemistry Award" to Prof. Ishii and the Daicel Chemical Company for their efforts relevant to the development of NHPI based industrial processes with low environmental impact.
(33) Koshino, N.; Saha, B.; Espenson, J. H. *J. Org. Chem.* **2003**, *68*, 9364.
(34) Ueda, C.; Noyama, M.; Ohmori, H.; Masui, M. *Chem. Pharm. Bull.* **1987**, *35*, 1372.
(35) Cai, Y.; Koshino, N.; Saha, B.; Espenson, J. H. *J. Org. Chem.* **2005**, *70*, 238.
(36) Lemaire, H.; Rassat, A. *Tetrahedron Lett.* **1964**, 2245. Mackor, A.; Wajer, Th. A. J. W.; De Boer, T. *Tetrahedron* **1968**, *24*, 4542.
(37) Amorati, R.; Lucarini, M.; Mugnaini, M.; Pedulli, G. F.; Minisci, F.; Recupero, F.; Fontana, F.; Astolfi, P.; Greci, L. *J. Org. Chem.* **2003**, *68*, 1747.
(38) Malatesta, V.; Ingold, K. U. *J. Am. Chem. Soc.* **1981**, 103, 3094. Jenkins, T. C.; Perkins, M. J.; Siew, N. P. Y. *J. Chem. Soc., Chem. Commun.* **1975**, 880.
(39) Aurich, H. G. In *The Chemistry of Amino, Nitroso, Nitro Compounds and of their Derivatives*; Patai, S., Ed.; Wiley: Chichester, 1982; Chapter 14.
(40) Chatgilialogu, C.; Malatesta, V.; Ingold, K. U. *J. Phys. Chem.* **1980**, *84*, 3597.
(41) Gorgy, K.; Lepretre, J.-C.; Saint-Aman, E.; Einhorn, C.; Einhorn, J.; Marcadal, C.; Pierre, J.-L. *Electrochim. Acta* **1998**, *44*, 385.
(42) Annunziatini, C.; Baiocco, P.; Gerini, M. F.; Lanzalunga, O.; Sjögren, B. *J. Mol. Catal. B: Enzym.* **2005**, *32*, 89.
(43) Koshino, N.; Cai, Y.; Espenson, J. H. *J. Phys. Chem. A* **2003**, *107*, 4262.
(44) Bordwell, F. G.; Liu, W.-Z. *J. Am. Chem. Soc.* **1996**, *118*, 10819.
(45) Annunziatini, C.; Gerini, M. F.; Lanzalunga, O.; Lucarini, M. *J. Org. Chem.* **2004**, *69*, 3431.
(46) Hussain, S. A.; Jenkins, T. C.; Perkins, M. J. *Tetrahedron Lett.* **1977**, *36*, 3199.
(47) Cohen, A. D.; Zeng, B.-B.; King, B. S.; Toscano, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 1444.
(48) Baciocchi, E.; Gerini, M. F.; Lanzalunga, O. *J. Org Chem.* **2004**, *69*, 8963.
(49) Minisci, F.; Punta, C.; Recupero, F.; Fontana, F.; Pedulli, G. F. *Chem. Commun.* **2002**, *7*, 688.
(50) Coseri, S.; Mendenhall, G. D.; Ingold, K. U. *J. Org. Chem.* **2005**, *70*, 4629.
(51) Mihailović, M. Lj.; Čeković, Ž.; Lorenc, Lj. Oxidations with Lead Tetraacetate. In *Organic Synthesis by Oxidation with Metal Compounds*; Mijs, W. J., De Jonge, C. R. H. I., Eds.; Plenum Press: New York, 1986; p 758.
(52) Mahoney, L. R.; DaRooge, M. A. *J. Am. Chem. Soc.* **1970**, *92*, 4063.
(53) Russell, G. A.; Williamson, R. C. *J. Am. Chem. Soc.* **1964**, *86*, 2357.
(54) Pratt, D. A.; DiLabio, G. A.; Mulder, P.; Ingold, K. U. *Acc. Chem. Res.* **2004**, *37*, 334.
(55) Avila, D. V.; Ingold, K. U.; Lusztyk, J.; Green, W. H.; Procopio, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 2929.
(56) Snelgrove, D. W.; Lusztyk, J.; Banks, J. T.; Mulder, P.; Ingold, K. U. *J. Am. Chem. Soc.* **2001**, *123*, 469.
(57) Shaik, S.; de Visser, P. S.; Wu, W.; Song, L.; Hiberty, P. C. *J. Phys. Chem. A* **2002**, *106*, 5043.
(58) Howard, J. A. In *Peroxyl Radicals*; Alfassi, Z., Ed.; Wiley & Sons: Chichester, 1997.
(59) Marchai, A.; Douglas, G. K.; Bakac, A.; Espenson, J. H. *J. Phys. Chem. A* **1991**, *95*, 4440.
(60) Howard, J. A. In *Free Radicals*; Kochi, J. K., Ed.; Wiley & Sons: New York, 1973; Volume 2, Charter 12. Howard, J. A.; Scaiano, J. In *Landolt Börnstein Numerical Data and Functional Reactions in Science and Technology*; Fischer, H., Ed.; Sprinter-Verlag: Berlin, 1984; Volume 3, Subvolume d.
(61) Ingold, K. U. *Acc. Chem. Res.* **1969**, *2*, 1.
(62) Lucarini, M.; Pedulli, G. F.; Valgimigli, L. *J. Org. Chem.* **1998**, *63*, 4497.
(63) Hermans, I.; Vereecken, L.; Jacobs, P. A.; Peeters, J. *Chem. Commun.* **2004**, 1140.
(64) Thomas, J. R. *J. Am. Chem. Soc.* **1967**, *89*, 4872.
(65) Bottle, S. E.; Chand, U.; Micallef, A. S. *Chem. Lett.* **1997**, 857. Johnston, L. J.; Tencer, M.; Scaiano, J. C. *J. Org. Chem.* **1986**, *51*, 2806.
(66) Matsui, S.; Fujita, T. *Catal. Today* **2001**, *71*, 145.
(67) Matyjaszewski, K., Davis, T. P., Eds. *Handbook of Radical Polymerization*; John Wiley & Sons: New York, 2002.
(68) Cornejo, J. J.; Larson, K. D.; Mendenhall, G. D. *J. Org. Chem.* **1985**, *50*, 5382.
(69) Hermans, I.; Nguyen, T. L.; Jacobs, P. A.; Peeters, J. *ChemPhysChem* **2005**, *6*, 637.
(70) Ravens, D. A. S. *Trans. Faraday Soc.* **1959**, *55*, 1768. Kamiya, Y.; Nakajima, T.; Sakoda, K. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 519.
(71) Shimizu, A.; Tanaka, K.; Ogawa, H.; Matsuoka, Y.; Fujimori, M.; Nagamori, Y.; Hamachi, H.; Rimura, K. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1993.
(72) Wang, J.-R.; Liu, L.; Wang, Y.-F.; Zhang, Y.; Deng, W.; Guo, Q.-X. *Tetrahedron Lett.* **2005**, *46*, 4647.
(73) Sawatari, N.; Yokota, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2001**, *66*, 7889.
(74) Baucherel, X.; Gonsalvi, L.; Arends, I. W. C. E.; Ellwood, S.; Sheldon, R. A. *Adv. Synth. Catal.* **2004**, *346*, 286.
(75) Tong, X.; Xu, J.; Miao, H. *Adv. Synth. Catal.* **2005**, *347*, 1953.
(76) Dobies, O.; Benson, S. W. *J. Phys. Chem. A* **1997**, *101*, 6030.
(77) Shibamoto, A.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2002**, *43*, 8859.
(78) Sakaguchi, S.; Kato, S.; Iwahama, T.; Ishii, Y. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1240.
(79) Finn, M.; Friedline, R.; Suleman, N. K.; Wohl, C. J.; Tanko, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 7578.
(80) Holmes, J. L. *Int. J. Mass Spectrom. Ion Processes* **1992**, *118*−*119*, 381.
(81) Recupero, F.; Bravo, A.; Bjørsvik, H.-R.; Fontana, F.; Minisci, F.; Piredda, M. *J. Chem. Soc., Perkin Trans. 2* **1997**, 2399.
(82) Ishii, Y.; Kato, S.; Iwahama, T.; Sakaguchi, S. *Tetrahedron Lett.* **1996**, *37*, 4993.
(83) Minisci, F.; Fontana, F.; Zhao, L. H.; Banfi, S.; Quici, S. *Tetrahedron Lett.* **1994**, *35*, 8033.
(84) Matsunaka, K.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **1999**, *40*, 2165.
(85) Yoshino, Y.; Hayashi, Y.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1997**, *62*, 6810.
(86) Tashiro, Y.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *Adv. Synth. Catal.* **2001**, *343*, 220.
(87) Saha, B.; Koshino, N.; Espenson, J. H. *J. Phys. Chem. A* **2004**, *108*, 425.
(88) Partenheimer, W. *Catal. Today* **1995**, *25*, 69.
(89) Shibamoto, A.; Sakaguchi, S.; Ishii, Y. *Org. Process Res. Dev.* **2000**, *4*, 505.
(90) Michael, J. P. *Nat. Prod. Rep.* **1997**, *14*, 605. Jones, G. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 5, pp 167.
(91) Cain, C. K.; Planpin, J. N.; Sam, J. *J. Org. Chem.* **1955**, *20*, 466. Ladner, D.W. *Synth. Commun.* **1986**, *16*, 157.
(92) Sakaguchi, S.; Shimamoto, A.; Ishii, Y. *Chem. Commun.* **2002**, 180.
(93) Fritz-Langhals, E.; Kunath, B. *Tetrahedron Lett.* **1998**, *39*, 5955.
(94) Rajabi, F.; Clark, J. H.; Karimi, B.; Macquarrie, D. J. *Org. Biomol. Chem.* **2005**, *3*, 725.
(95) Einhorn, C.; Einhorn, J.; Marcadal, C.; Pierre, J.-L. *Chem. Commun.* **1997**, 447.
(96) Einhorn, C.; Einhorn, J.; Marcadal, C.; Pierre, J.-L. *J. Org. Chem.* **1999**, *64*, 4542.
(97) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726.
(98) Cho, S.-H.; Cheong, M.-S.; Jung, K.-D.; Kim, C.-S.; Han, S.-H. *Appl. Catal. A: Gen.* **2004**, *267*, 241.
(99) Yang, G.; Ma, Y.; Xu, J. *J. Am. Chem. Soc.* **2004**, *126*, 10542.
(100) Yang, G.; Zhang, Q.; Miao, H.; Tong, X.; Xu, J. *Org. Lett.* **2005**, *7*, 263.
(101) Minisci, F.; Recupero, F.; Gambarotti, C.; Punta, C.; Paganelli, R. *Tetrahedron Lett.* **2003**, *44*, 6919.
(102) Schmieder-van de Vondervoort, L.; Bouttemy, S.; Heu, F.; Weissenbock, K.; Alsters, P. L. *Eur. J. Org. Chem.* **2003**, *3*, 578.
(103) Wentzel, B. B.; Donners, M. P. J.; Alsters, P. L.; Feiters, M. C.; Nolte, R. J. M. *Tetrahedron* **2000**, 7797.

(104) Patai, S., Ed. *Chemistry of Peroxides*; Wiley-Interscience: New York, 1983.
(105) Hock, H.; Lang, B. *Chem. Ber.* **1944**, *77*, 257.
(106) Ishii, Y.; Iwahama, T.; Sakaguchi, S.; Nakayama, K.; Nishiyama, Y. *J. Org. Chem.* **1996**, *61*, 4520.
(107) (a) Walling, C.; Padwa, A. *J. Am. Chem. Soc.* **1963**, *85*, 1593. (b) Walling, C.; Wagner, P. I. *J. Am. Chem. Soc.* **1964**, *86*, 3368.
(108) Minisci, F.; Recupero, F.; Cecchetto, A.; Gambarotti, C.; Punta, C.; Paganelli, R. *Org. Process Res. Dev.* **2004**, *8*, 163.
(109) Boger, D. L.; Coleman, R. S. *J. Org. Chem.* **1986**, *51*, 5436.
(110) Volyi, I.; Janssen, A. G.; Mark, H. *J. Phys. Chem.* **1945**, *49*, 461.
(111) Aoki, Y.; Sakaguchi, S.; Ishii, Y. *Adv. Synth. Catal.* **2004**, *346*, 199.
(112) Aoki, Y.; Hirai, N.; Sakaguchi, S.; Ishii, Y. *Tetrahedron* **2005**, *61*, 10995.
(113) Arends, I. W. C. E.; Sasidharan, M.; Kühnle, A.; Duda, M.; Jost, C.; Sheldon, R. A. *Tetrahedron* **2002**, *58*, 9055.
(114) Jordan, W.; Barneveld, H.; van Gerlich, O.; Kleine-Boymann, M.; Ullrich, J. *Ullmann's Encyclopedia of Industrial Chemistry*; VCH: Weinheim, 1991; Vol. A19, p 307.
(115) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 5th ed.; Wiley-Interscience Publications: New York, 2001; pp 1514.
(116) Iwahama, T.; Sakaguchi, S.; Nishiyama, Y.; Ishii, Y. *Tetrahedron Lett.* **1995**, *36*, 6923.
(117) Iwahama, T.; Yoshino, Y.; Keitoku, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2000**, *65*, 6502.
(118) Oakley, M. A.; Woodward, S.; Coupland, K.; Parker, D.; Temple-Heald, C. *J. Mol. Catal. A* **1999**, *150*, 105.
(119) Brandi, P.; Galli, C.; Gentili, P. *J. Org. Chem.* **2005**, *70*, 9521.
(120) Denisov, E. T.; Denisova, T. *Handbook of Antioxidants: Bond Dissociation Energies, Rate Constants, Activation Energies, and Enthalpies of Reactions*; CRC Press: Boca Raton, FL, 2000.
(121) Denisov, E. T.; Khursan, S. L. *Russ. J. Phys. Chem.* **2000**, *74*, Suppl 3, S491.
(122) Minisci, F.; Recupero, F.; Cecchetto, A.; Gambarotti, C.; Punta, C.; Faletti, R.; Paganelli, R.; Pedulli, G. F. *Eur. J. Org. Chem.* **2004**, 109.
(123) Viehe, H. G.; Janausek, Z.; Mereny, R.; Stella, L. *Acc. Chem. Res.* **1985**, *18*, 148.
(124) Baiocco, P.; Barreca, A. M.; Fabbrini, M.; Galli, C.; Gentili, P. *Org. Biomol. Chem.* **2003**, *1*, 191.
(125) McMillen, D. F.; Golden, D. M. *Annu. Rev. Phys. Chem.* **1982**, *33*, 493.
(126) Amati, A.; Dosualdo, G.; Fontana, F.; Minisci, F.; Bjørsvik, H.-R. *Org. Process Res. Dev.* **1998**, *2*, 261.
(127) Figiel, P. J.; Sobczak, J. M.; Ziolkowski, J. J. *Chem. Commun.* **2004**, 244.
(128) Figiel, P. J.; Sobczak, J. M. *Pol. J. Chem.* **2001**, *75*, 869.
(129) Kim, S. S.; Rajagopal, G. *Synth. Commun.* **2004**, *34*, 2237.
(130) Astolfi, P.; Brandi, P.; Galli, C.; Gentili, P.; Gerini, M. F.; Greci, L.; Lanzalunga, O. *New J. Chem.* **2005**, *29*, 1308.
(131) Messerschmidt, A. *Multi-Copper Oxidases*; World Scientific: Singapore, 1997.
(132) Cantarella, G.; Galli, C.; Gentili, P. *New J. Chem.* **2004**, *28*, 366.
(133) Fukuda, O.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2001**, *42*, 3479.
(134) Mokaya, R.; Poliakoff, M. *Nature* **2005**, *437*, 1243.
(135) Walling, C.; Clark, R. T. *J. Am. Chem. Soc.* **1974**, *96*, 4530.
(136) Van Sickle, D. E.; Mayo, F. R.; Arluck, R. M. *J. Am. Chem. Soc.* **1965**, *87*, 4824.
(137) Mayo, F. R. *Acc. Chem. Res.* **1968**, *1*, 193.
(138) Ishii, Y.; Iwahama, T.; Sakaguchi, S.; Nakayama, K.; Nishiyama, Y. *J. Org. Chem.* **1996**, *61*, 4520.
(139) Ozaki, S.; Hamaguci, T.; Tsuchida, K.; Kimata, Y.; Masui, M. *J. Chem. Soc., Perkin Trans. 2* **1989**, 951.
(140) Hara, T.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2001**, *66*, 6425.
(141) Punta, C.; Rector, C. L.; Porter, N. A. *Chem. Res. Toxicol.* **2005**, *18*, 349.
(142) Iwahama, T.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* **1999**, 727. Iwahama, T.; Sakaguchi, S.; Ishii, Y. *Heterocycles* **2000**, *52*, 693.
(143) Iwahama, T.; Hatta, G.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* **2000**, 163.
(144) Jørgensen, K. A. *Chem. Rev.* **1989**, *89*, 431.
(145) Minisci, F.; Gambarotti, C.; Pierini, M.; Porta, O.; Punta, C.; Recupero, F.; Lucarini, M.; Veronica, M. *Tetrahedron Lett.* **2006**, *47*, 1421.
(146) Utimoto, K.; Miwa, M.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 4277. Smith, A. B., III; Levenberg, P. A.; Suits, J. Z. *Synthesis* **1986**, 184. Karpf, M.; Huguet, J.; Dreiding, A. S. *Helv. Chim. Acta* **1986**, *65*, 13. Tam, S. T.-K.; Klein, R. S.; De Las Heras, F. G.; Fox, J. J. *J. Org. Chem.* **1979**, *44*, 4854. Sayo, N.; Azuma, K.-I.; Mikawa, K.; Nakai, T. *Tetrahedron Lett.* **1984**, *25*, 565.
(147) Jargstorff, C.; Wille, U. *Eur. J. Org. Chem.* **2003**, 3173.
(148) Eikawa, M.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1999**, *64*, 4676.
(149) d'Acunzo, F.; Baiocco, P.; Galli, C. *New J. Chem.* **2003**, *27*, 329.
(150) Karimi, B.; Rajabi, J. *Org. Lett.* **2004**, *6*, 2841.
(151) Iwahama, T.; Yoshino, Y.; Keitoku, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2000**, *65*, 6502.
(152) Chen, Y.; Wang, G. *Tetrahedron Lett.* **2001**, *42*, 4955.
(153) Karimi, B.; Rajabi, J. *Synthesis* **2003**, *15*, 2373.
(154) Burkey, T. J.; Castelhano, A. L.; Griller, D.; Lossing, F. P. *J. Am. Chem. Soc.* **1983**, *105*, 4701.
(155) Cecchetto, A.; Minisci, F.; Recupero, F.; Fontana, F.; Pedulli, G. F. *Tetrahedron Lett.* **2002**, *43*, 3605.
(156) Baciocchi, E.; Bietti, M.; Gerini, M. F.; Lanzalunga, O. *J. Org. Chem.* **2005**, *70*, 5144.
(157) Minisci, F.; Punta, C.; Recupero, F.; Fontana, F.; Pedulli, G. F. *J. Org. Chem.* **2002**, *67*, 2671.
(158) Wang, J.-R.; Liu, L.; Wang, Y.-F.; Zhang, Y.; Deng, W.; Guo, Q.-X. *Tetrahedron Lett.* **2005**, *46*, 4647.
(159) Iwahama, T.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **1998**, *39*, 9059.
(160) Kanabus-Kaminska, J. M.; Hawari, J. A.; Griller, D.; Chatgilialoglu, C. *J. Am. Chem. Soc.* **1987**, *109*, 5267.
(161) Minisci, F.; Recupero, F.; Punta, C.; Guidarini, C.; Fontana, F.; Pedulli, G. F. *Synth. Lett.* **2002**, *7*, 1173.
(162) Tayama, O.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *Eur. J. Org. Chem.* **2003**, 2286.
(163) Minisci, F.; Porta, O.; Recupero, F.; Gambarotti, C.; Paganelli, R.; Pedulli, G. F.; Fontana, F. *Tetrahedron Lett.* **2004**, *45*, 1607.
(164) Singh, H.; Tedder, J. M. *J. Chem. Soc. B* **1964**, 4737.
(165) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001.
(166) Albright, L. F. *Chem. Eng.* **1966**, *73*, 149. Markofsky, S. B. In *Ullman's Encyclopedia of Industrial Organic Chemicals*; Elvers, B., Hawkins, S., Eds.; Wiley-VCH: Weinheim, 1999; Vol. 6, pp 3487. Albright, L. F. In *Kirk-Othmer Encyclopedia of Chemical Technology*; Kroschwite, J. I., Howe-Grant, M., Eds.; Wiley-VCH: New York, 1995; Vol. 17, pp 68.
(167) Ishii, Y.; Sakaguchi, S.; Nishiwaki, Y.; Kitamura, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 222.
(168) Sawatari, N.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2003**, *44*, 2053.
(169) Sakaguchi, S.; Eikawa, M.; Ishii, Y. *Tetrahedron Lett.* **1997**, *38*, 7075. Eikawa, M.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1999**, *64*, 4676.
(170) Sakaguchi, S.; Hirabayashi, T.; Ishii, Y. *Chem. Commun.* **2002**, 516.
(171) Hirabayashi, T.; Sakaguchi, S.; Ishii, Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 1120.
(172) Weissermel, K.; Arpe, H.-J. *Industrial Organic Chemistry*, 4th ed.; Wiley-VCH: Weinheim, 2003.
(173) Giese, B. In *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: Oxford, 1986. Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon: Oxford, 1991; Vol. 4, p 715. Motherwell, W. B.; Crich, D. *Free-Radical Reactions in Organic Synthesis*; Academic Press: London, 1992. Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Synthesis*; Wiley: Chichester, 1995. Parsons, A. F. *An Introduction to Free Radical Chemistry*; Blackwell Science: Oxford, 2000. Chatgilialoglu, C.; Renaud, P. In *General Aspects of the Chemistry of Radicals*; Alfassi, Z. B., Eds.; Wiley: Chichester, 1999. Renaud, P., Sibi, M. P., Eds. *Radicals in Organic Synthesis*; Wiley-VCH: Weinheim, 2001.
(174) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996.
(175) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177−194.
(176) Kato, S.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1998**, *63*, 222.
(177) Hara, T.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2001**, *66*, 6425.
(178) Iwahama, T.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* **2000**, 613.
(179) Munoz, H.; Tamariz, J.; Jiminez, R.; Mora, G. G. *J. Chem. Res. (S)* **1993**, 68. Laurent-Robert, H.; Le Roux, C.; Dubac, J. *Synlett* **1998**, 1138.
(180) Li, S.; Vert, M. In *Degradable Polymers*; Scott, G., Gilead, D., Eds.; Chapman & Hall: London; 1995; pp 43.
(181) Puthuraya, K.; Oomura, Y.; Shimizu, N. *Brain Res.* **1985**, *332*, 165.
(182) Hoffman, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 94.
(183) Kagayama, T.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2005**, *46*, 3687.
(184) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, 99, 1991.
(185) Punniyamurthy, T.; Bhatia, B.; Iqbal, J. *J. Org. Chem.* **1994**, *59*, 850.
(186) Braun, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 24.
(187) Hirano, K.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2002**, *43*, 3617.

(188) Tsujimoto, S.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* **2001**, 2352.
(189) Kharasch, M. S.; Urry, W. H.; Kuderna, B. M. *J. Org. Chem.* **1949**, *14*, 239.
(190) Roberts, B. P. *Chem. Soc. Rev.* **1999**, *28*, 25.
(191) Tsujimoto, S.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2003**, *44*, 5601.
(192) Minisci, F. *Synthesis* **1973**, 1. Minisci, F. *Top. Curr. Chem.* **1976**, *62*, 1. Minisci, F.; Vismara, E.; Fontana, F. *Heterocycles* **1989**, *28*, 489. Minisci, F.; Vismara, E.; Fontana, F. *J. Heterocycl. Chem.* **1990**, *27*, 79. Porta, O.; Minisci, F. In *Handbook of C-H transformation*; Dyker, G., Ed.; Wiley-VCH: New York, 2005; Vol. 1, p 212.
(193) Minisci, F.; Recupero, F.; Cecchetto, A.; Punta, C.; Gambarotti, C.; Fontana, F.; Pedulli, G. F. *J. Heterocycl. Chem.* **2003**, *40*, 325.
(194) Minisci, F.; Recupero, F.; Punta, C.; Gambarotti, C.; Antonietti, F.; Fontana, F.; Pedulli, G. F. *Chem. Commun.* **2002**, 2496.

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