

***N*-hydroxyphthalimide (NHPI) organocatalyzed aerobic oxidations: advantages, limits and industrial perspectives**

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1. Introduction

N-hydroxyphthalimide (NHPI) is an efficient organocatalyst, capable to promote free-radical processes *via* Hydrogen Atom Transfer (HAT) reactions.

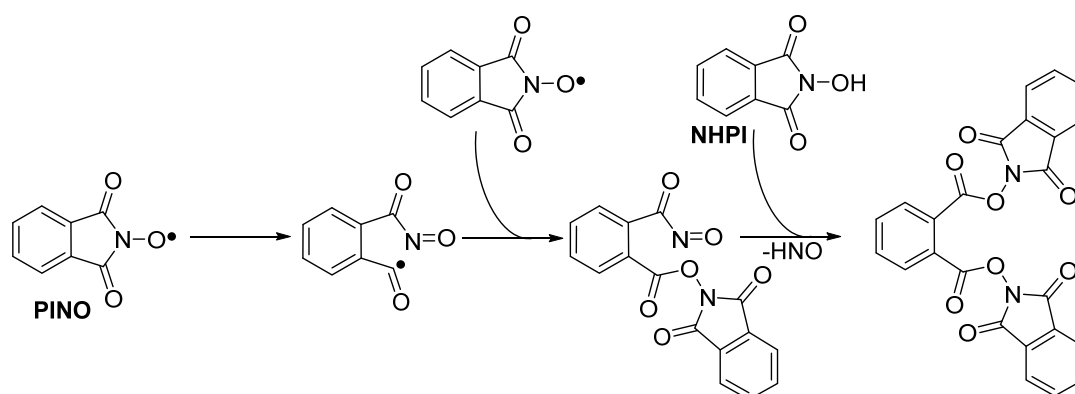
The first catalytic use of NHPI was reported in 1977 by Grochowski and co-workers for the addition of ethers to diethyl azodicarboxylate and the oxidation of 2-propanol to acetone [1]. A few years later, Masui proposed the use of NHPI as a mediator for the electrolytic oxidation of alcohols to ketones [2]. In both cases, the authors suggested the formation of the phthalimide *N*-oxyl (PINO) radical as a key intermediate, being responsible of the catalytic cycle by abstracting hydrogen atoms from activated C-H bonds. However, PINO production in the reaction medium was not experimentally proven until 1995 when, thanks to the pioneering work of Ishii *et al.*, a triplet signal, originating from PINO, was detected by Electron Spin Resonance (ESR) technique, after exposing NHPI to molecular oxygen [3]. With this work, regarding the oxidation of alkanes and alcohols, Ishii initiated the relatively recent history of oxidations catalyzed by NHPI.

Since then, and thanks to the investigation of the reaction mechanisms involving NHPI, mainly conducted by Ishii and the partnership of Minisci's and Pedulli's groups, the potentiality of this organocatalyst has been significantly extended.

In the last two decades, hundreds of papers reported the use of NHPI for promoting the homogeneous selective oxidation of a wide range of organic substrates (including alcohols, ketones, ethers, amines, amides, silanes, alkynes, alkenes, alkanes and alkyl aromatics) and the one-pot free-radical synthesis of complex molecules, involving directly or indirectly molecular oxygen [4].

In spite of the great interest that NHPI is attracting from scientific community and industrial companies, its concrete use for scaled productions is still limited to few examples. The reasons rely onto three, partially interconnected, obstacles which need to be overcome for the final launch of this organocatalyst.

- i. Even if NHPI could be considered a cheap, non-toxic molecule, as it is easily produced by the reaction between phthalic anhydride and hydroxylamine, its cost would significantly affect the overall economy of the process, if the final product is not of high added value and/or the homogeneous catalyst is not completely recovered from the reaction medium and efficiently recycled. For this reason, till now, this *N*-hydroxy derivative has found industrial application only in small-medium scale productions.
- ii. The polar character of this molecule often requires the use of polar co-solvents to ensure its complete solubilization. This aspect not only effects the productivity and consequently, once again, the economy of the process, but it also raises important environmental issues. New smart-designed lipophilic derivatives analogous to NHPI need to be developed to solve this problem.
- iii. It has been demonstrated how PINO may undergo self-decomposition, following a first-order self-decay under classical reaction conditions (Scheme 1) [5].

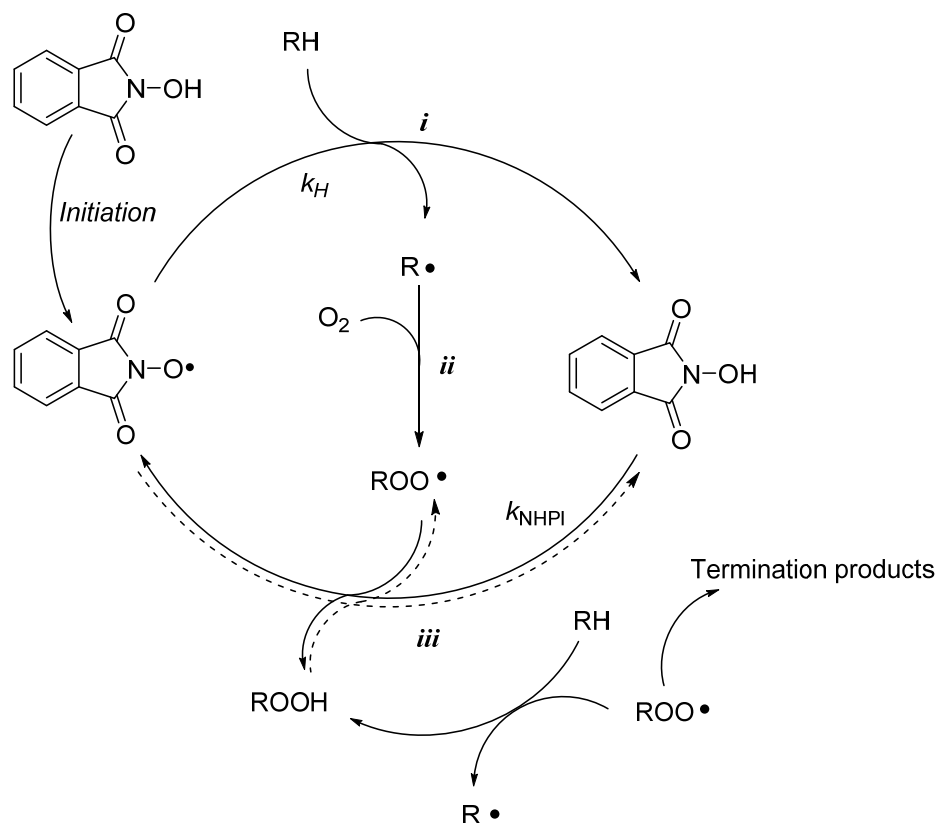


Scheme 1. Self-decomposition of PINO

This phenomenon results important when operating at temperatures higher than 80 °C, so that the activation of NHPI under mild conditions becomes a crucial aspect to be considered.

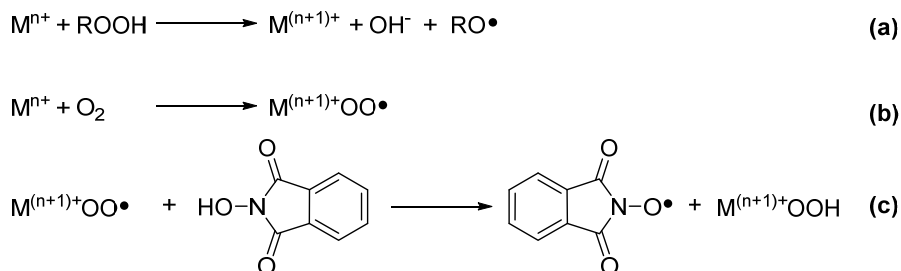
2. Chemistry and Catalysis

The catalytic cycle promoted by the NHPI/PINO system is reported in Scheme 2. Once generated in situ from NHPI (*Initiation*), PINO undergoes hydrogen abstraction from a generic C-H bond, forming once again NHPI and a carbon centered radical (path *i*). The latter reacts with molecular oxygen, leading to the corresponding peroxy radical (path *ii*), which in turn is quickly trapped by NHPI to form the hydroperoxide and a new molecule of PINO (path *iii*).



Scheme 2. The catalytic cycle of NHPI in the aerobic oxidation of organic substrates.

PINO generation being a key step of the overall process, in most cases the use of NHPI was proposed in combination with different co-catalysts or initiators. Several examples report the beneficial effect of transition metal salts and complexes for this purpose [4]. In this context, the main role of metal salts (including Mn, Co, Cu, V and Fe salts) is not only to accelerate the classical autoxidation reaction, by promoting the decomposition of the intermediate hydroperoxides (Scheme 3a), but also to bind oxygen (Scheme 3b), leading to the formation of PINO radical without requiring thermal treatment (Scheme 3c).

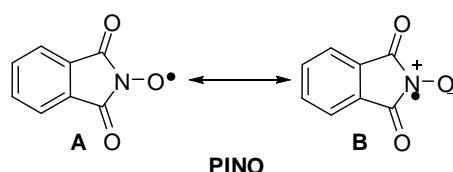


Scheme 3. Radical chain initiation by means of metal (M) salts.

Eco-friendly standards, including the demand for highly selective transformations, have pushed towards the development of metal-free NHPI-mediated protocols, especially for large scale productions, as in the case of the aerobic oxidation of hydrocarbons. So far, the activation of NHPI was obtained by means of aldehydes, quinones, nitric oxides, enzymes and by irradiation in the presence of organic photo-mediators [6].

The high efficiency of NHPI in initiating and propagating the classical free-radical autoxidation chain finds its explanation in the concomitant manifestation of three favorable distinct effects. This particular and unique behavior justifies the increased attention that NHPI has attracted in the last two decades.

Enthalpic Effect. In 2003, Pedulli's group determined the Bond Dissociation Enthalpy (BDE) of the O-H bond in NHPI by means of ESR radical equilibration technique [5]. The measured value of 88.1 kcal/mol (in acetonitrile, MeCN), about 18 kcal/mol higher than the corresponding O-H bond in the *N*-hydroxy 2,2,6,6-tetramethylpiperidine (TEMPO-H), clearly indicated that the carbonyl groups directly bonded to the nitrogen atom strongly increase the BDE values. In fact, the carbonyl group, with its electron-withdrawing character, reduces the importance of the mesomeric structure **B** of the nitroxyl radical (Scheme 4). As a consequence, the radical results to be less stabilized and the corresponding O-H BDE increases.



Scheme 4. PINO resonance structures.

First key point: from a thermochemical point of view, path *i* in Scheme 2 may be in many cases exothermic or only slightly endothermic.

Polar Effect. In the same work [5], Pedulli and co-workers also measured the k_H value, referred to path *i*, for a wide range of substrates, demonstrating that the HAT reaction promoted by PINO is always faster than the corresponding hydrogen abstraction reaction by means of generic peroxy radicals, occurring in classical non-catalyzed autoxidation process. This behavior cannot be ascribed to enthalpic effects, as the O-H BDE values in NHPI and generic hydroperoxides are similar, but instead to a polar effect, due to a more pronounced electrophilic character of the PINO radical relative to the peroxy one.

Second key point: PINO behaves as good catalyst for the hydrogen atom abstraction from C-H bonds (path *i*)

Entropic Effect. To complete the rationalization of the catalytic cycle reported in Scheme 2, Peduli *et al.* also determined the kinetic constant for the hydrogen atom abstraction from NHPI by peroxy radicals (k_{NHPI} in path *iii*). The unexpected fairly high value obtained ($k_{\text{NHPI}} = 7.2 \times 10^3 \text{ M}^{-1}\text{s}^{-1}$) [5] revealed the potential of the NHPI/PINO system. PINO shows high catalytic efficiency in the hydrogen atom abstraction (path *i*). NHPI behaves as good hydrogen donor, trapping peroxy radicals before they undergo fast termination and prolonging the propagation chain (path *iii*). This latter aspect justifies the need to operate in solution.

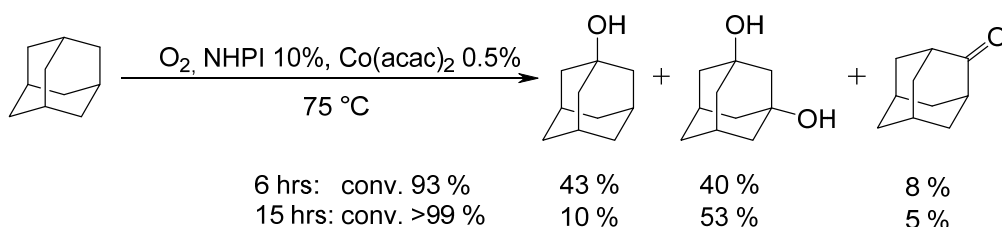
Third key point: NHPI guarantees high selectivity to the catalyzed oxidation process under homogeneous conditions.

3. Process Technology

3.1 Oxidation of adamantane to adamantanols.

The unique structure of adamantane justifies the interest for selective functionalization of this molecule, in order to develop enhanced functional materials. In particular, selective synthesis of mono-alcohols or diols represents the first step for the production of photoresist materials, *via* esterification of the hydroxyl groups with acrylic and methacrylic acids [7].

The selective oxidation of adamantane to adamantanols with molecular oxygen has found practical application by using NHPI catalysis. The reaction has been proposed and patented by Ishii in collaboration with Daicel Chemical Company [8], and consists of the aerobic oxidation of adamantane in chlorobenzene or acetic acid, at temperatures ranging from 75 to 85 °C for 7 h, in the presence of 10%mol of NHPI and 0.5%mol of different metal salts, including $\text{Co}(\text{acac})_2$, $\text{Co}(\text{OAc})_2$, $\text{VO}(\text{acac})_2$ and V_2O_5 (Scheme 5).

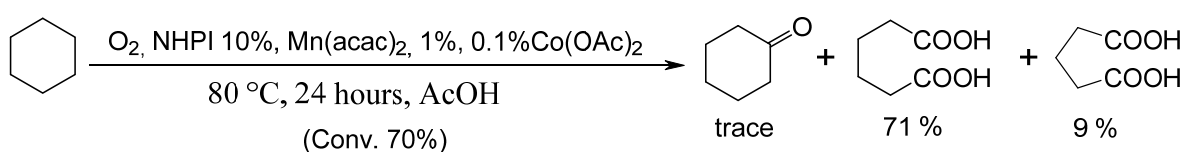


Scheme 5. Aerobic oxidation of adamantane catalyzed by NHPI.

Claimed conversion is higher than 90%, with a selectivity for alcohols depending on the co-catalyst of choice. Adamantanol production using this technology is commercialized at Daicel Arai plant in Japan.

3.2. Oxidation of cyclohexane to adipic acid

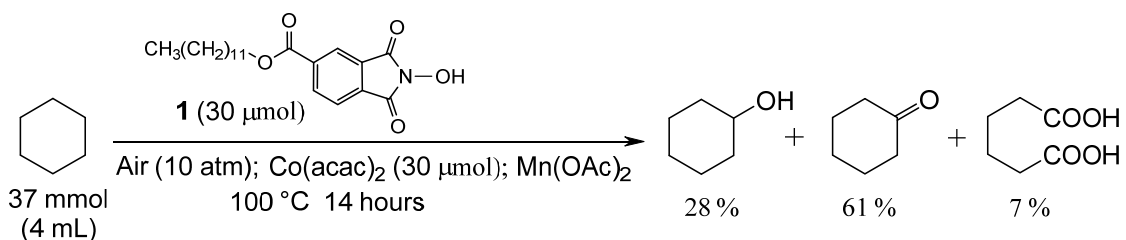
Ishii and Daicel Chemical Company also patented a method for the direct aerobic oxidation of cyclohexane to adipic acid by using NHPI in combination with small amounts of $\text{Mn}(\text{acac})_2$ and $\text{Co}(\text{OAc})_2$ as co-catalysts (Scheme 6) [9].



Scheme 6. Aerobic oxidation of cyclohexane to adipic acid catalyzed by NHPI.

While traces of cobalt salts seem to play a key role in reducing the induction period and accelerating the radical chain (Scheme 3), $\text{Mn}(\text{II})$ guarantees a higher selectivity for adipic acid, by promoting the enolization of cyclohexanone and activating the α -carbonyl position towards oxidation [10]. The reaction occurs in acetic acid (AcOH) at $80\text{ }^\circ\text{C}$ for 24 h.

As previously disclosed, the solvent is necessary to guarantee a complete solubility of the polar organocatalyst. However, in 2001 Ishii proposed the use of 4-lauryloxycarbonyl-*N*-hydroxyphthalimide (**1**), a lipophilic version of NHPI, in order to perform the reaction directly in neat cyclohexane [11] (Scheme 7).



Scheme 7. Aerobic oxidation of cyclohexane in the presence of lipophilic NHPI.

Since 2009 the process has been under evaluation at pilot scale, for further commercial application, by Daicel, in Aboshi (Japan).

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 relevant efforts to the development of NHPI based industrial processes with low environmental impact.

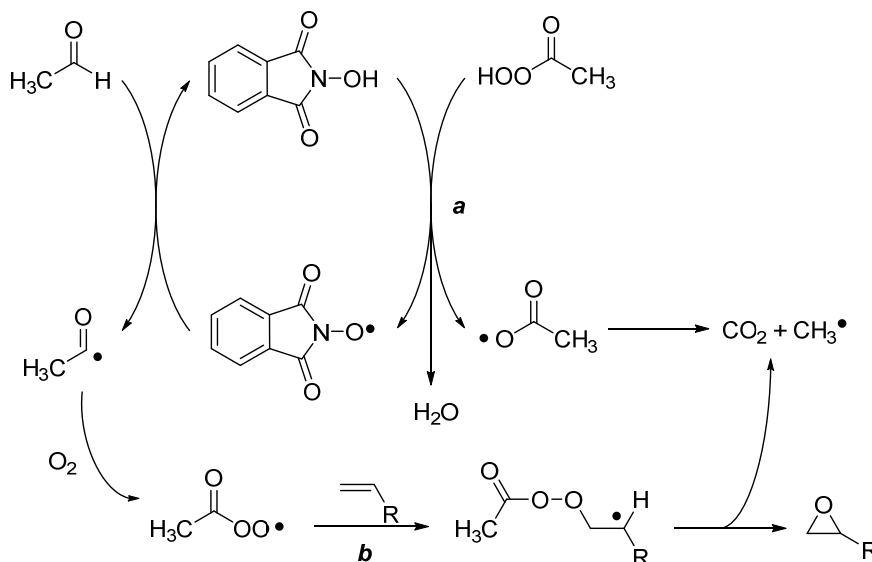
3.3 Epoxidation of olefins.

In 2006, our research group proposed the selective epoxidation of α -olefins by combining, at room temperature and in MeCN, stoichiometric amounts of acetaldehyde with catalytic quantities of NHPI under oxygen atmosphere [12].

Following the catalytic mechanism reported in Scheme 8, we demonstrated the role of peracetic acid, generated in situ, in promoting the formation of PINO by undergoing molecule induced homolysis with NHPI (path *a*), while the acyl peroxy radical resulted to be the effective epoxidising agent (path *b*).

The process was successfully applied to the synthesis of propylene oxide in MeCN [13].

The major drawback of this protocol consists into the long reaction times usually required in order to achieve high conversions (24-48 h). For this reason, in 2012 we started a collaboration for realizing an aerobic epoxidation catalyzed by NHPI under continuous-flow conditions by means of a new technology designed, manufactured, and developed by prof. Biørsvik (University of Bergen) and Fluens Synthesis Company: the multijet oscillating disk (MJOD) reactor [14]. A flowchart of this reactor applied to the our process is reported in Fig. 1.



Scheme 8. Reaction mechanism for epoxidation of olefins.

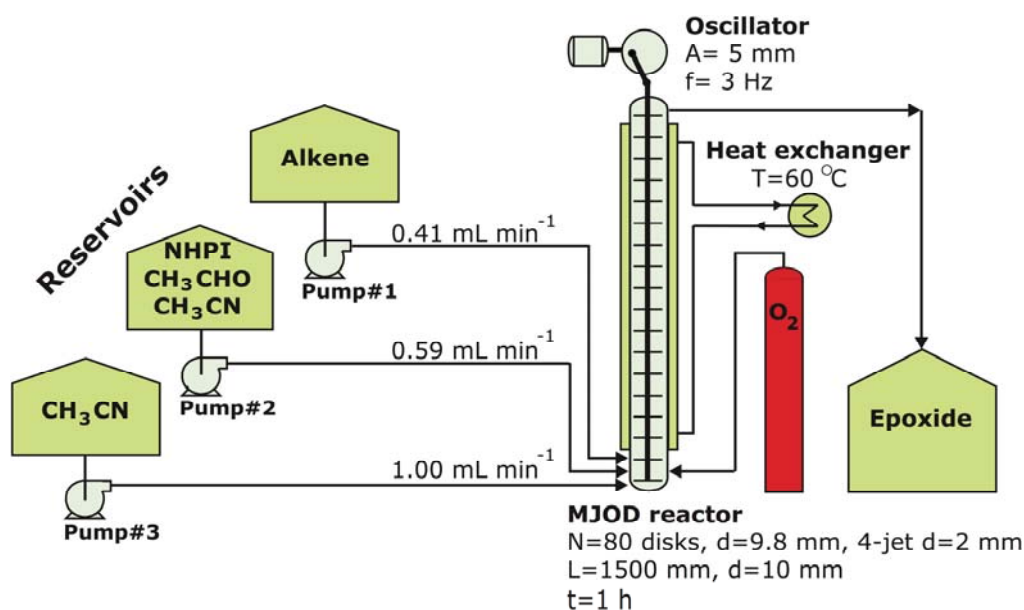


Figure 1. Process flowchart of NHPI-catalyzed epoxidation in MJOD millireactor system.

Due to the advantageous reactor net volume versus the heating/cooling surface ratio of the MJOD reactor tube, an exceptionally good heat transfer capacity is achieved. Moreover, extremely good mixing of the components is obtained by the oscillation of the disks, resulting in an excellent mass transfer capacity. This properties are usually combined with a with a substantially increased reaction rate.

For all the olefins investigated under continuous-flow conditions we obtained high conversions and yields (~80%) of the desired epoxides. Moreover, the process was substantially accelerated, shortening the residence time from 24–48 h (batch process) to only 1–4 h, with a standard production of about 80 g/day, which makes this protocol appealing for applications in pharmaceutical industry.

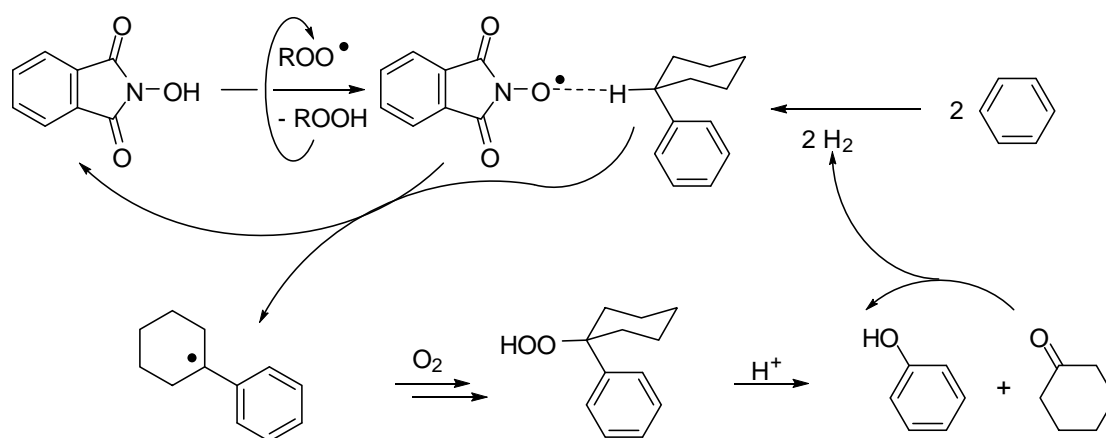
3.4 Oxidation of alkylaromatics to corresponding hydroperoxides

Aerobic selective oxidation of alkylaromatics, including cumene (CU), ethylbenzene (EtB), and cyclohexylbenzene (CyB), to the corresponding hydroperoxides represents a key step for several large-scale productions, including the Hock process for the synthesis of phenol (see chapter 2) [15] and the Shell SM/PO process for the production of propylene oxide (PO) and styrene monomer (SM) [16].

In this context, the NHPI-catalysed oxidation approach has been widely investigated as an alternative route to the classical autoxidation process, due to the evident opportunity to increase conversion and selectivity in the hydroperoxide, according to the catalytic cycle reported in Scheme 2. In particular, autoxidation of CU usually requires high temperatures in order to favour partial homolytic

decomposition of the hydroperoxide for prolonging the propagation phase of the radical chain. The use of NHPI would allow to operate under milder conditions, that is temperatures lower than 100 °C, limiting the formation of secondary products deriving from termination, such as cumyl alcohol and above all acetophenone.

The last decade has been characterized by a huge amount of patent applications in this field. Sheldon and Degussa (now Evonik) first reported in 2001 the NHPI-catalysed oxidation of a wide range of alkyl aromatics at 100°C, in the absence of co-solvent and initiators [17]. A particular attention was devoted to the oxidation of CyB [18]. Analogous to CU, the corresponding hydroperoxide could be converted to phenol and cyclohexanone, but in this case the dehydrogenation of the ketone could lead to the formation of a second molecule of phenol [19]. This process has attracted the interest of Exxon Mobil, which developed, with a series of patent applications, a protocol for the direct synthesis of phenol and cyclohexanone starting with the direct synthesis of CyB from benzene and H₂ via hydroalkylation [20]. This approach is completely waste-free, since the stoichiometric amount of H₂ required for the hydroalkylation is afforded by dehydrogenation of cyclohexanone formed after hydroperoxide cleavage (Scheme 9).



Scheme 9. Oxidation of cyclohexylbenzene.

More in general Exxon Mobil significantly contributed to the process engineering of the NHPI-catalysed oxidation of alkylaromatics, for example suggesting a procedure according to which water and NHPI-deactivating organic acid impurities are stripped from a portion of the reaction medium that is continuously removed from and after stripping returned to the reaction zone [21].

In 2009 Fierro and Repsol Quimica S.A. reported the beneficial effect of combining NHPI with ppm amounts of NaOH for the synthesis of hydroperoxides [22], with the dual effect of promoting the

formation of PINO in the absence of transition metal salts, and of neutralizing the acidic by-products of the reaction. This approach resulted particularly effective for increasing conversion and selectivity in the oxidation of secondary alkylaromatics [23].

In all the above mentioned approaches, the reactions are conducted in neat solution of hydrocarbons and, for this reason, at temperatures higher than 100 °C, in order to guarantee complete solubilization of NHPI. However, as previously disclosed, these harsh operating conditions favor the self-decomposition of the catalyst, partially limiting the applicability at industrial scale.

The results of our investigation in this field, in collaboration with Polimeri Europa (now Versalis S.p.A., Eni Group) has convinced us that the presence of variable amounts of polar co-solvents was crucial to operate under homogenous and mild conditions (< 80 °C). We also proposed the possible use of tiny amounts of acetaldehyde to initiate the radical chain even at ambient temperature [24], according to the molecule-induced mechanism already reported in Scheme 8 (path *a*). Initiation was necessary when trying to convert the less reactive secondary alkylaromatics, such as EtB [25], but we found that no initiator was required for the NHPI-catalysed selective oxidation of CU to the corresponding hydroperoxide (CHP). This approach was successfully applied also to the oxidation of CyB [28]. A complete design of the oxidation process should include an efficient recovery and recycle of the catalyst. A possible overall approach is reported in Fig. 2 [27].

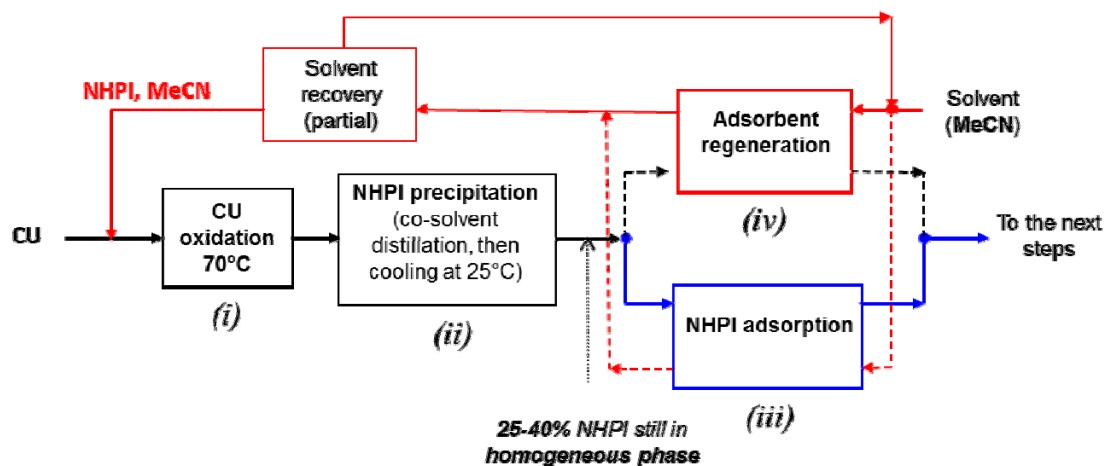


Figure 2. Process scheme for the NHPI-catalyzed oxidation of cumene.

Hydroperoxide formation in the reaction medium progressively increases the solution polarity, with a consequent increased solubility of NHPI, so that a variable amount of NHPI still remains in solution, the quantity depending on the converted starting material. In 2009 Exxon Mobil claimed the possibility

to exploit the acidic characteristics of NHPI by removing the catalyst via basic aqueous extraction or treatment of the effluent with a solid sorbent having basic properties (such as metal oxides and ionic exchange basic resins) [29]. However, we verified that this approach could be negatively affected by limitations in the recovery phase of the catalyst from the water solution or adsorbing bed, requiring the use of acidic solutions [27]. Moreover, NHPI can be hydrolysed under basic conditions [30].

For this reason we claimed a different approach, consisting in the physical adsorption of NHPI onto non-basic solid beds, such as A26(Cl) [26,31]. A26(Cl) guaranteed the reversibility of the adsorption process, allowing the recovery of the catalyst by washing the resin with the polar co-solvent used in the oxidation step (Fig. 2, path *iv*). Fig. 3 reports the adsorption/desorption cycles of NHPI onto A26(Cl).

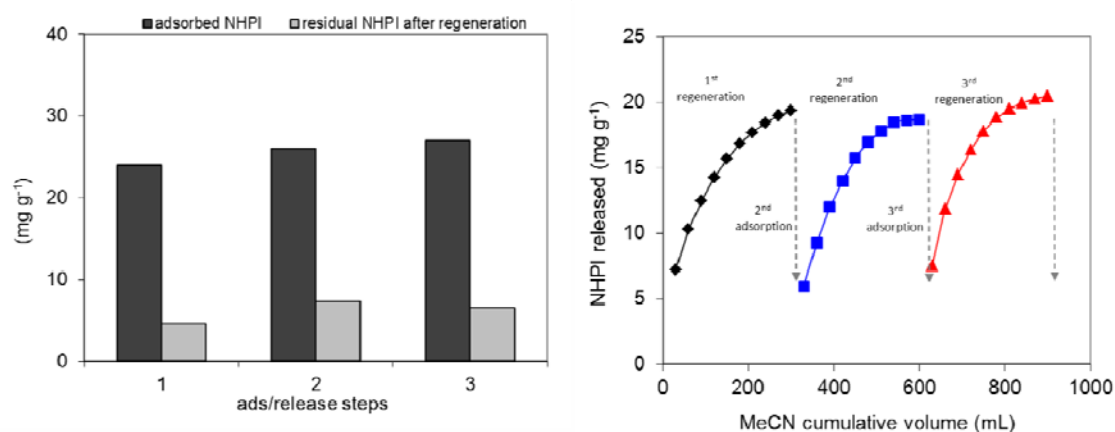
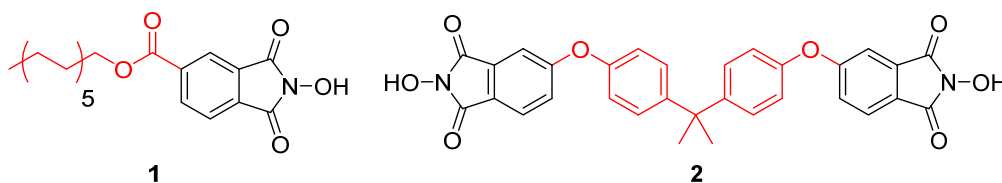


Figure 3. Adsorption of NHPI on A26(Cl) (mg of catalyst adsorbed per gram of A26(Cl) – Fig.3a) and regeneration of the adsorbing bed using MeCN. CU/CHP = 1.85/1 (mol/mol) (Fig.3b). Initial NHPI concentration: 2mg mL⁻¹.

4. New Developments

All the above mentioned protocols are limited by the low solubility of NHPI in apolar mediums. Ishii first opened the way for a possible solution of the problem, by suggesting the introduction of lipophilic chains onto the aromatic ring of the *N*-hydroxy derivative [9]. Nevertheless, the proposed catalyst **1** suffers from a major limitation, if used in processes which require a high control of selectivity. The carboxylic group, thanks to which the alkyl tail is linked to the NHPI moiety, affects the NO-H BDE due to its electron-withdrawing character, and increases the value by 0.7 kcal/mol, so that the efficiency of **1** as hydrogen donor is expected to be significantly reduced. In fact, the process requires a lower NO-H BDE value, when the selective conversion to hydroperoxides is desired [32].

In this context, we have very recently proposed catalyst **2** (Scheme 10), as a suitable lipophilic catalyst for the aerobic oxidation of CU and other alkyl aromatics to the corresponding hydroperoxides [33].



Scheme 10. Ishii's catalyst **1** and new organocatalyst **2**.

Our results confirmed for **2** a catalytic efficiency analogous to that observed for NHPI, and higher with respect to Ishii's catalyst **1**, for producing hydroperoxides. Even if this solution did not allow to completely remove the polar co-solvent, it was possible to operate with reduced amounts of MeCN and to run CU oxidations under homogeneous conditions even at 45°C, which cannot be realized in the presence of 1% NHPI catalyst. As expected, the new conditions led to an increment of CHP selectivity.

Acknowledgements

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5. References

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