Aerobic Oxidation of Alkylaromatics using a Lipophilic *N*-Hydroxyphthalimide: Overcoming the Industrial Limit of Catalyst Solubility

Manuel Petroselli,^[a] Paola Franchi,^[b] Marco Lucarini,^[b] Carlo Punta,^{*[a]} and Lucio Melone^{*[a]}

Received: March 3, 2014 Revised: May 13, 2014 Published online on July 14, 2014

Introduction

The liquid-phase aerobic oxidation of hydrocarbons (HC) is a key process of the chemical industry because it is the first step toward the synthesis of a large variety of advanced materials and fine chemicals. For this reason, in recent years, intensive research efforts have pursued the development of new reliable oxidative transformations capable of combining high chemical efficiency with minimization of both waste production and energy consumption.

In this context, *N*-hydroxyimides, the most representative of which is *N*-hydroxyphthalimide (NHPI, 1), are effective organocatalysts for the oxidation of organic substrates by using dioxygen as the final oxidant.^[1–5] In the oxidative process, NHPI leads to the formation of the corresponding phthalimide *N*oxyl (PINO) radical, which represents the key intermediate of the catalytic cycle, activating a generic C–H bond by hydrogen abstraction (Scheme 1).

Despite relevant academic research activity devoted to the development of NHPI-catalyzed processes, including its application for promoting innovative organic syntheses,^[6-10] the use of this catalyst in real industrial processes is yet to be realized.

Indeed, in the last decade, several research groups^[11-21] and a few leading companies^[22,23] have focused their efforts on pro-

 [a] Dr. M. Petroselli, Dr. C. Punta, Dr. L. Melone Department of Chemistry, Materials, and Chemical Engineering "G. Natta" Politecnico di Milano, Piazza Leonardo da Vinci 32 I-20133 Milano (Italy) Fax: (+ 39) 0223993180 E-mail: carlo.punta@polimi.it lucio.melone@polimi.it

[b] Dr. P. Franchi, Prof. M. Lucarini Department of Chemistry "G. Ciamician" University of Bologna, Via San Giacomo 11 I-40126 Bologna (Italy)



Scheme 1. Catalytic activity of 1 in the aerobic oxidation of organic substrates.

moting aerobic oxidations of alkylaromatics (namely, cumene (CU), ethylbenzene (EtB), and cyclohexylbenzene (CHB)) to the corresponding hydroperoxides by mediation of NHPI catalysis. In these processes, catalyst **1** exhibits its potential as a good hydrogen donor, trapping peroxyl radicals to the corresponding hydroperoxides; thus preventing fast termination (Scheme 1). However, in a recent paper, we pointed out the two main drawbacks that could hinder the scale up of these processes: the low solubility of polar **1** in liquid HC, which would require a polar cosolvent to obtain homogeneous solutions, and the need for an effective process for the recovery and recycling of the catalyst.^[24] Both of these aspects derive

from the necessity to operate under homogeneous conditions to guarantee high selectivity for hydroperoxides, which, in turn, depend on the concentration of the hydrogen donor in solution. In the same report, we suggested a possible route to overcome the limit of catalyst recovery. It consisted of treatment of the reaction mixture with non-basic resins, which were capable of adsorbing 1 through physical interactions. The adsorbing solids can be, in turn, regenerated by washing with a polar solvent, which allows complete recovery of the catalyst.

Nevertheless, the use of large amounts of cosolvent remains a non-negligible aspect that negatively influences the economic and environmental impact of the overall process. Reports in the literature show how liquid-phase oxidation of HC catalyzed by 1 can be conducted in the absence of cosolvent, only if the operating temperature is higher than 100 °C.^[14,25] Under these conditions, despite the low solubility of 1, the process proceeds, at least in the initial stages, mainly through the classical uncatalyzed autoxidation mechanism. The formation of products (peroxides, alcohols, ketones) contributes to an increase of the polarity of the reaction mixture with time. This event progressively favors solubilization of 1, which becomes more actively involved in the oxidation process and finally exploits its catalytic action. This approach is unsuitable for application in the industrial oxidation of alkylaromatics. First, the use of 1 is convenient only if it allows the reaction to operate under milder conditions than those of the classical Hock process to guarantee high selectivity to the desired product. Moreover, the stability of the catalyst cannot be warranted at high temperature. Finally, the design of an industrial process based on feeding solid 1 directly to the oxidation units is a challenging task.

The simplest way to overcome the limit of catalyst solubility consists of the design and production of lipophilic catalysts by means of easy and cheap synthetic pathways. The first approach in this direction was followed by Ishii and co-workers,^[26,27] who reported the synthesis and use of **2** (Figure 1), which was a NHPI unit prepared by starting from trimellitic anhydride with a lipophilic tail that was eventually fluorinated and attached to the aromatic ring through esterification. This catalyst was successfully used for the aerobic oxidation of cycloalkanes at high temperature and pressure (100 °C, air at 10 atm; 1 atm = 101325 Pa); a process that did not require a high control of selectivity. However, we envisioned that derivative **2** could suffer from some drawbacks when applied to

the selective hydroperoxidation of alkylaromatics, and thus, limiting its effective industrial applicability. It has been shown that the presence of a carboxylic group affects the NO–H bond dissociation energy (BDE) by increasing its value, and consequently, reducing the efficiency of **2** as a hydrogen donor.^[28] Moreover, the presence of the ester group does not guarantee complete stability of the catalyst during the steps of the industrial process, in particular, during the oxidative phase, and thus, reducing the possibility of recovering the catalyst.

On the basis of these observations, we decided to investigate alternative solutions to the industrial use of **1** and analogues of catalyst **2**, according to the following criteria: 1) the catalyst had to have an unaffected NO–H BDE compared with **1** to guarantee at least similar catalytic performances; 2) the catalyst had to operate under homogeneous conditions with significantly reduced amounts of cosolvent compared with that of pristine **1**, and at process temperatures not higher than 70 °C; and 3) the catalyst had to be synthesized starting from industrially available and cheap precursors.

Herein, we report the synthesis, characterization, and use of a new lipophilic NHPI catalyst (**3**; Figure 1), which fulfils all of the above-described requirements. The experiments, supported by DFT calculations and EPR spectroscopy, confirmed the active role of substituents on the aromatic ring in determining the NO–H BDE values, and consequently, the efficiency of catalysis.

Results and Discussion

Synthesis of catalysts

Compound **2** was prepared by following a two-step optimized version of a previously reported procedure (Scheme 2a).^[26] First, dodecyl alcohol was treated with trimellitic anhydride at 0 °C for 4 h. The resulting crude product was mixed with an excess of hydroxylamine hydrochloride and reacted for 1 h in a microwave reactor. The final product was isolated in 90% yield after purification by flash chromatography.

Compound **3** was quantitatively obtained by simply reacting an excess of hydroxylamine hydrochloride (in anhydrous pyridine under reflux for 1 h in a microwave reactor) with 4,4'-(4,4'-isopropylidenediphenoxy)bis(phthalic anhydride), which isa commercially available and cheap precursor obtained frombisphenol A (Scheme 2 b). The purification of crude product by



Figure 1. Structures of Ishii's lipophilic catalyst (2), the catalyst considered herein (3), and model compounds (4-8).

flash chromatography on silica gel afforded the desired catalyst in 93% yield with respect to the starting anhydride.

Substituent effect on NO-H BDE

The efficiency of the catalytic cycle reported in Scheme 1 depends on a compromise between two main factors. From one point of view, hydrogen atom abstraction from the C–H bond of the substrate by PINO occurs at acceptable rates only if the BDE value of the formed NO–H bond (88.1 kcal mol⁻¹; 1 cal = 4.18 J) is higher or similar to that of the cleaved C–H bond.^[28-30] On the other hand, as already stressed, the same NO–H bond has to be weak enough to ensure 1 can operate as a hydrogen atom donor towards peroxyl radicals to favor the formation of the corresponding hydroperoxides over the production of termination products.

Because the synthesis of lipophilic *N*-hydroxyphthalimides involves the functionalization of the aromatic ring of 1, we decided to conduct a preliminary investigation by EPR spectroscopy into how the presence of substituents could influence the NO–H BDE of 2 and 3 with respect to 1.

Nitroxide radicals derived from **2** and **3** were generated in acetonitrile (ACN) at room temperature by photolysis with UV light in the presence of about 10% of di-*tert*-butyl peroxide. The EPR spectrum of **2** was interpreted on the basis of the coupling of the unpaired electron with the nitrogen nucleus (a(N) = 4.55 G) and one proton (0.3 G). These values are almost the same as those values previously reported for the model compound **4**.^[28]

The EPR spectrum of **3**, reported in Figure 2a, was interpreted on the basis of coupling of the unpaired electron with the nitrogen nucleus (a(N) = 4.86 G) and one proton (0.72 G). No evidence for the formation of a biradical species was obtained.

Determination of the BDEs of ring-substituted NHPIs was achieved by using the EPR radical equilibration technique.^[31] This technique consists of measuring the equilibrium constant, K_{eqr} for the hydrogen atom transfer reaction between the aryl-substituted NHPIs, an appropriate reference compound (the BDE of which is already known), and the corresponding radicals. In the present case, the reference derivative used was 1, the BDE (88.1 kcalmol⁻¹) of which has been already measured.^[30]

The BDEs for the aryl-substituted NHPIs were calculated, with the assumption that the entropic term could be neglected, by means of Equation (1) from K_{eq} and the known BDE of **1**.



Scheme 2. Schematic procedure for the synthesis of compounds 2 (a) and 3 (b).



Figure 2. EPR spectra obtained by photolysis with UV light of a solution in ACN containing 10% di-*tert*-butyl peroxide and **3** (20 mm) in the absence (a) and in the presence (b) of NHPI 30 mm.

$$BDE(2 \text{ or } 3) = BDE(1) - RT \ln(K_{eq})$$
(1)

For example, the EPR spectrum obtained by photolysis of a solution of **3** and **1** in ACN is reported in Figure 2b; this shows the simultaneous presence of signals of nitroxides derived from **3** and **1**. From analysis of the experimental spectra, it was possible to determine the concentration ratio of the two radicals, and thus, the strength of the O–H bond as 88.8 kcal mol⁻¹ for compound **2** and 88.0 kcal mol⁻¹ for compound **3**.

It has been already shown that, in the aryl-substituted NHPIs, the O–H BDEs increase by increasing the electron-withdrawing properties of the substituent.^[28] This was confirmed by the increase of $0.7 \text{ kcal mol}^{-1}$ measured in the O–H BDE,

> upon going from **1** to hydroxylamine **2** with an electron-withdrawing acetyl group on the aromatic ring. This effect is relatively small, but is expected to have a non-negligible impact on the efficiency of the catalytic process.

> Catalyst **3** is instead characterized by a BDE value very close to that of **1**. A smaller value was re

ported for model compound **6** (87.3 kcal mol⁻¹).^[28] We suppose that the phenoxy substituent in **3** reduces the electron-donating ability of the oxygen atom with respect to a methoxy group, leading to a compensation between mesomeric and inductive effects, and thus, to a BDE value close to that of **1**.

This picture was further confirmed by measuring a(N) of different nitroxide radicals. BDE values of the hydroxylamines were found to roughly correlate with nitrogen coupling of the corresponding nitroxide radicals.^[30] Larger values of O–H BDE in the hydroxylamines and lower values of a(N) in the corresponding radicals are both the result of the presence of electronegative groups, which decrease the importance of polar mesomeric structures that describe the nitroxide moiety, in which the unpaired electron is localized on nitrogen. Inspection of the a(N) values reported in Table 1 shows this is also the case for the investigated nitroxide; the smallest (4.55 G) and largest (4.94 G) values are those measured with derivatives **2** and **6**, respectively.

We also measured, by EPR spectroscopy, the rate, $k_{\rm H'}$ by which the nitroxide radical derived from **3** abstracted the tertiary benzylic hydrogen atom from CU. In the EPR kinetic studies, the nitroxide radical was initially produced photochemically from **3** and di-*tert*-butyl peroxide (10% by volume) in deoxygenated solutions in *tert*-butylbenzene and the decay of the

Table 1. O–H BDE values of NHPI derivatives and hyperfine splitting constants of the corresponding <i>N</i> -oxyl radicals measured in ACN.				
Compound	<i>a</i> (N) [G]	<i>a</i> (other) [G]	BDE [kcal mol ⁻¹]	
1	4.76	0.50 (2H)	88.1 ^[a]	
2	4.55	0.30 (1 H)	88.8	
3	4.86	0.72 (1 H)	88.0	
4	4.55	0.35 (1 H)	88.9 ^[b]	
6	4.94	0.83 (1 H), 0.14 (4 H)	87.3 ^[b]	

[a] Ref. [30]. [b] Ref. [28].

radical was monitored in the presence of increasing amounts of CU. When the pseudo-first-order rate constant (k_{EPR}) was plotted as a function of the substrate concentration (see Figure SI04 in the Supporting Information), the second-order rate constants, $k_{\rm H}$, were determined from the slopes of these plots as 2.44 Lmol⁻¹s⁻¹ at 300 K. This value is very similar to that measured with **1** (3.25 Lmol⁻¹s⁻¹),^[30] as expected by the measured values of O–H BDE.

We also ran DFT calculations on 1 and other model molecules (compounds 3–7; Figure 1). Derivative 4, with a methyl ester moiety on the ring, was considered in place of 2, to reduce the computational costs. Despite the lower level of theory used (B3LYP/6-311G(d,p)), simulations in the gas phase provided theoretical BDE values for 1 and 6 that were in good agreement with the values reported in the literature, as shown in Table 2. As expected, the NO–H BDE values for 4 and 5 were higher than that calculated for 1. Once again, this behavior can be ascribed to the presence of an electron-withdrawing carbonyl substituent on the ring. On the contrary, compounds **6** and **7**, with alkoxy moieties in the *para* position, revealed BDE values even lower than that observed for **1**.

Theoretical calculations were also performed in the liquid phase, by using IEFPCM, to simulate conditions closer to those of experimental ones (Table 2). Both ACN and toluene, the latter was chosen as a representative alkylaromatic, were used to reproduce environments with different polarities. Geometry optimization was run by coordinating a solvent molecule to

Table 2. NO–H BDE values of NHPI model molecules calculated in ACN and toluene (integral equation formalism variant of the polarizing continuum model (IEFPCM)) and corresponding experimental values obtained by EPR spectroscopy in ACN.

Compound	BDE calculated [kcal mol ⁻¹] gas phase ACN		1] toluene
1	81.9 ^[a]	87.5	-
3	81.3	87.0	-
4	82.3	88.7	83.7
5	82.4	-	-
6	81.2 ^[a]	-	-
7	81.1	87.0	82.3

[a] For a comparison with BDE calculated values (gas phase) reported in the literature, see: for 1: Refs. [32] (82.52 kcalmol⁻¹) and [33] (83.3 kcalmol⁻¹); for 1 and 6: Ref. [34] (80.8 kcalmol⁻¹).

the investigated compound to better simulate eventual hydrogen bonding. Following this approach, the theoretical value obtained for **1** in ACN was consistent with that experimentally determined by EPR spectroscopy in the same solvent, as previously reported.^[28,29] Also, in this case, compound **4** had a higher NO–H BDE value with respect to **1** and **7**. Calculations performed in toluene provided BDE values lower than those obtained in ACN. These results are not surprising upon considering that, in toluene, the NO–H bond is not involved in intermolecular hydrogen bonding. A comparison between **4** and **7** showed the same trend of BDE values.

These results confirmed our original doubts on considering trimellitic anhydride as a possible precursor of lipophilic NHPI derivatives. We anticipated poor results for the aerobic oxidation of alkylaromatics when mediated by **2**. At the same time, the results also suggested that NHPI derivatives with alkyloxyl chains could represent the ideal compromise of combining good solubility in HCs with good catalytic efficiency.

Aerobic oxidation of alkylaromatics

Initial experiments were performed to find the solubility limits of NHPI in CU, EtB, and CHB in the presence of ACN as a cosolvent at 70 °C. According to our previous works,^[18,19] this temperature could be considered as a good compromise of the need to obtain significant energy savings, good process yields with the reduced formation of byproducts, and the importance of preserving the catalyst from decomposition. Table 3 reports the maximum HC/ACN ratio (v/v) at which **1** (1 or 2 mol% with respect to the HC) could be found completely in solution. It is interesting to observe that, in all cases, about 25% of the total volume of the reaction mixture was due to the cosolvent in the presence of 1% **1**. A higher concentration of **1** could not be reached without increasing the volume of cosolvent. Thus, at 2% **1**, the cosolvent volumetric percentage increased to about 33%.

On the contrary, as expected, the oxidation process in the presence of **3** could be performed with reduced volumes of cosolvent and higher concentrations of catalyst. As reported in Table 4, it was possible to increase the concentration of **3** up to 5% (corresponding to 10% of N–OH equivalents) at 70°C, by maintaining a CU/ACN ratio (2.5:1; Table 4, entry 2) comparable with that measured by using **1** at 1% (Table 3, entry 1).

Table 3. Minimum volume of ACN for the complete solubilization of 1 in different HCs (5 mL) at 70 $^\circ$ C.					
Entry		HC [mmol]	1 [mol %]	ACN [mL]	HC/CAN ^[a]
1	CU	35.9	1	1.75	2.86:1 (25.9)
2	CU	35.9	2	3.0	1.67:1 (37.5)
3	EtB	40.8	1	1.5	3.33:1 (23.1)
4	EtB	40.8	2	2.75	1.81:1 (35.6)
5	CHB	29.96	1	1.5	3.33:1 (23.1)
6	CHB	29.96	2	2.5	2.00:1 (33.3)

[a] Volumetric percentages of ACN are reported in parentheses.

Moreover, a homogeneous solution of **3** at 5% could also be obtained at 25°C with a CU/ACN ratio equal to 2:1. For comparison with another derivative that also contained two NO–H moieties, we synthesized compound **8** (Figure 2), which was

Table 4. Minimum volume of ACN for the complete solubilization of 3 in CU (5 mL) at 70 $^\circ\text{C}.$					
Entry		HC [mmol]	3 [mol%]	ACN [mL]	HC/CAN ^[a] (v/v)
1	CU	35.9	2	1.5	3.33:1 (23.1)
2	CU	35.9	5	2.0	2.50:1 (28.6)
3 ^[a]	CU	35.9	5	2.5	2.0:1 (33.3)
4 ^[b]	CU	35.9	2	6.5	0.77:1 (56.5)

[a] Volumetric percentages of ACN are reported in parentheses. [b] 25 °C. [c] Compound ${\bf 8},$ 70 °C.

previously reported in the literature.^[35,36] Unsurprisingly, this molecule required much more cosolvent than **3**: at 70 °C and with 2% **8**, the CU/ACN ratio was only 0.77:1 (Table 4, entry 4).

We further proceeded in our investigation by running oxidations of CU in the presence of **1** (1%), **2** (1%), and **3** (0.5%, corresponding to 1% of NO–H equivalents) at 70 °C for 6 h. Considering the solubility limit of **1** in CU at 70 °C (Table 3, entry 1), we performed these experiments by using a CU/ACN volumetric ratio of 2.67, which was very close to the saturation limit. α , α '-Azobisisobutyronitrile (AIBN, 0.5%) was used for a more reliable comparison of the data because random induction times can be observed if operating in the absence of initiator.^[24] The experiments were performed in triplicate. The data reported in Figure 3 (CU conversion and cumyl hydroperoxide (CHP) yield) are mean values \pm standard deviation.

In accordance with computational calculations and EPR spectroscopy measurements of the corresponding BDEs, compound **2** was less efficient than both **1** and **3**. In the presence of **2**, we observed a CU conversion of 34% with a CHP selectivity of 92%. With **1**, the CU conversion increased to 42% (selectivity: 92%), which means a 20% improvement in productivity, and similar values were obtained for **3** (conversion: 41%; selectivity: 94%).



Figure 3. Comparison of the performance [conversion (**m**) and CH yield (**m**)] of 1 (1%), **2** (1%), and **3** (0.5%) during the aerobic oxidation of CU. O_2 (1 atm), 70 °C for 6 h, AIBN initiator (0.5%).

Encouraged by these data, we decided to take advantage of the higher solubility of **3** to investigate the effects of nitroxyl concentration in the aerobic oxidation of CU at 70 °C. It is well known that the conversion rate of the substrate depends on the PINO radical concentration, according to Equation (2), in which the $k_{\rm H}$ value depends on the specific substrate (RH).

$$PINO + RH \xrightarrow{k_{H}} R^{\bullet} + NHPI$$
(2)

The CU conversion, CHP and cumyl alcohol (CA) yields, and the selectivity in CHP versus the molar percentage of **3**, operating under two different CU/ACN volumetric ratios (2.67, Figure 4a, and 6.67, Figure 4b), are reported in Figure 4. The first ratio (2.67) reproduces the conditions under which no more than 1% of **3** can be dissolved at 70 °C. The second ratio (6.67) shows a notable reduction in the amount of cosolvent. The oxidations were performed in flasks of the same volume (25 mL) and magnetic stirring speed (700 rpm) to ensure a comparable gas–liquid interface area for all experiments.

According to the above-reported considerations, increasing amounts of catalyst contributed toward improving the catalytic performances of the process under both solvent conditions. In particular, moving from 0.5 to 1% of **3** (corresponding to double the number of NO–H equivalents) for CU/ACN = 2.67 at 70 °C, it was possible to increase the conversion to 47.1%, with also a significant change of selectivity in CHP (from 94 to 96%). It is important to highlight once again that the analogous oxidation with 2% NHPI cannot be performed in the same medium. Other intriguing data were obtained by work-



Figure 4. Effect of the amount of **3** in the aerobic oxidation of CU at different CU/ACN ratios: a) CU/ACN = 2.67:1 (v/v); b) CU/ACN = 6.67:1 (v/v). The total volume (CU + ACN) was kept constant and equal to 6.9 mL. O₂ (1 atm), 6 h, 70 °C, AIBN initiator (0.5%). Symbols: **a** conversion; \diamond CHP yield; **a** CA yield; **b** CHP selectivity.

ing with reduced volumes of ACN (CU/ACN=6.67). In this case, a higher concentration of **3** was extremely beneficial, both in terms of conversion and selectivity. Interestingly, the CU conversion and CHP yield curves reached a plateau at higher concentrations of **3** (>0.5%). In this case, the conversion value with 1% of **3** was 39.6%, which was a lower value

than that obtained at CU/ACN = 2.67. However, the apparently lower performance reported in Figure 4b should be ascribed to the higher mass of CU to be converted and not to a minor efficiency of the catalyst, as detailed in the Supporting Information.

Recently, we investigated the use of aldehydes as sacrificial initiators for the peroxidation of alkylaromatics.^[18,19] Aldehydes may generate PINO radicals, even at room temperature, through the formation of the corresponding peracetic acid under an oxygen atmosphere and consequent molecule-induced homolysis with 1 (Scheme 3).^[37-39]

In line with our previous works, we decided to perform the oxidation of CU, EtB, and CHB by using propionaldehyde as the initiator and comparing the performances of 1 and 3 at 70 °C. In the case of CU and CHB (Table 5, entries 1–4 and 5–6), we worked with a HC/ACN ratio (2.67:1) close to the solubility limits of 1 % 1.

In the case of EtB, we decided to perform experiments with EtB/ACN = 1:1 (Table 5, entries 7–10), to

maintain the same conditions as those investigated in our previous paper,^[24] and EtB/ACN = 2.67:1 (Table 5, entries 11 and 12). Surprisingly, using propionaldehyde (5%), we observed different performances of the two catalysts. Indeed, CU oxidation performed with 1% **1** gave a conversion of about 28% (Table 5, entry 1), whereas the corresponding experiment with 0.5% **3** afforded a conversion of 40% (Table 5, entry 2). This

value is similar to those obtained with AIBN (0.5%) for both 1 (42%; Table 5, entry 3) and 3 (41%; Table 5, entry 4). Moreover, different behavior observed for 1 and 3 with propionaldehyde as the initiator was also observed for the oxidation of CHB (Table 5, entries 5 and 6) and EtB (Table 5, entries 7–12).

The CU oxidation kinetics reported in Figure 5 provide better evidence for the differences observed between the two organocatalysts in the presence of propionaldehyde. Analogous results

for **1** and **3** were observed during the oxidation of CU at 70 °C with CU/CAN \ll 1 (\approx 0.07:1), as illustrated in Figure SI05a in the Supporting Information. Once again, the corresponding experiments performed with AIBN as the initiator did not show remarkable differences (Figure SI05b in the Supporting Information).

Table 5. Alkylaromatic oxidation with 1 or 3. ^[a]						
Entry	HC/CAN ^[b] (v/v)	HC [mmol]	Catalyst ([%])	Conv. [%]	Selectivity HP ^[c] [%]	
1	CU/ACN = 2.67:1 (27.3)	35.90	1 (1)	28.1	83.3	
2	CU/ACN = 2.67:1 (27.3)	35.90	3 (0.5)	40.2	88.4	
3 ^[d]	CU/ACN = 2.67:1 (27.3)	35.90	1 (1)	42.0	92.3	
4 ^[d]	CU/ACN = 2.67:1 (27.3)	35.90	3 (0.5)	41.0	93.9	
5	CHB/ACN = 2.67:1 (27.3)	29.96	1 (1)	16.9	97.0	
6	CHB/ACN = 2.67:1 (27.3)	29.96	3 (0.5)	21.3	98.0	
7 ^[e]	EtB/ACN = 1:1 (50)	40.80	1 (2)	13.4	91.0	
9	EtB/ACN = 1:1 (50)	40.80	3 (1)	12.8	93.8	
8 ^[e,f]	EtB/ACN = 1:1 (50)	40.80	1 (5)	13.5	93.0	
10	EtB/ACN = 1:1 (50)	40.80	3 (2.5)	20.0	90.0	
11	EtB/ACN = 2.67:1 (27.3)	40.80	1 (1)	9.6	92.1	
12	EtB/ACN = 2.67:1 (27.3)	40.80	3 (0.5)	11.5	93.1	

[a] Conditions: O₂ (1 atm), 6 h, 70 °C. Initiator: Propionaldehyde (5%). [b] Volumetric percentages of ACN are reported in parentheses. [c] Selectivity is referenced to the corresponding hydroperoxide product. [d] AIBN 0.5%. [e] From Ref. [24]. [f] Heterogeneous at 70 °C.

One possible explanation for these results could be found in the different mechanisms followed by the two initiators to promote free radical processes. AIBN generates radicals by thermal autodecomposition, with kinetics depending on the reaction temperature. The AIBN half-life ($t_{1/2}$), defined as the time for the concentration of the initiator to decrease to one half of its original value, is reported to be 4.8 h at 70 °C.^[40] This value



Scheme 3. Transition state for the molecule-induced homolysis of NHPI by peracids.

guarantees continuous initiation of radical chains for the duration of the process and hides possible differences in the catalytic activity of **1** and **3**. On the contrary, propionaldehyde initiation proceeds through molecule-in-



Figure 5. CU oxidation with 1 (1%, open symbols) or 3 (0.5%, filled symbols). Conditions: CU (5 mL, 4.32 g, 35.9 mmol) and ACN (1.9 mL; CU/ $ACN = 2.67:1 \ v/v$) under O₂ (1 atm) for 6 h, $T = 70 \ ^{\circ}C$, propionaldehyde initiator (5%). Symbols: \blacksquare , \square : CU conversion; ④, \bigcirc : CHP selectivity.

duced homolysis; a process that is expected to be over within the initial phases of the reaction. Under these conditions, potential differences between 1 and 3 can be manifested. The higher conversion and selectivity observed in this case would suggest a higher capacity for 3 to maintain the radical chain. This kinetic aspect will be the subject of future investigations.

To further exploit the opportunity to develop more sustainable oxidation processes, we verified the applicability of **3** (0.5%) at a temperature lower than 70°C. The results obtained at 45 and 70°C, with propionaldehyde as the initiator, are reported in Figure 6 for two CU/ACN volumetric ratios (2.67:1 and 6.66:1). Interestingly, although a lower temperature usually causes a decrease in productivity, only a modest reduction in CU conversion was observed upon changing from 70 (about 42%) to 45°C (37%) in the case of CU/ACN = 2.67. Analogous results were obtained for CU/ACN = 6.67 (33% at 70°C and 27% at 45°C). As expected, a decrease in temperature led to an increase in CHP selectivity. In both cases, homogeneous solutions were obtained at 45°C. Indeed, it was not possible to



Figure 6. CU conversion at different CU/ACN volumetric ratios (2.67:1 and 6.67:1) and temperatures [45 (\blacksquare) and 70 C (\blacksquare)] with **3** (0.5%) and propional-dehyde (5%) as initiator. The total volume (CU + ACN) was kept constant and equal to 6.9 mL. The selectivity in CHP is reported in parentheses.

achieve this result at the same temperature with 1% 1, even with CU/ACN = 2.67.

The beneficial effects provided by changing the concentration of **3** during CU oxidation were also observed at 45° C (Figure 7). Complete homogeneous solutions were also obtained with 1% catalyst, with consequent higher conversions and selectivity in CHP. Similar results were obtained during the oxidation of EtB (45 and 70°C) at different concentrations of **3** (Figure Sl06 in the Supporting Information)



Figure 7. Effect of the amount of **3** on the aerobic oxidation of CU at 45 °C. Conditions: CU (5 mL, 4.32 g, 35.9 mmol) and ACN (1.9 mL; CU/ACN = 2.67:1 v/v) under O₂ (1 atm) for 6 h, propionaldehyde initiator (5%). Symbols: • conversion; \diamond CHP yield; \blacktriangle CA yield; \blacklozenge CHP selectivity.

Conclusions

A new lipophilic catalyst (3), obtained from 4,4'-(4,4'-isopropylidenediphenoxy)bis(phthalic anhydride) was reported. By EPR spectroscopy, it was shown that 3 had a NO-H BDE value very close to that of 1, whereas Ishii's catalyst (2) was characterized by a higher BDE value; this negatively affected its efficiency as a hydrogen donor. Experimental EPR data were supported by DFT calculations performed in both the gas and liquid phases. Aerobic oxidation of three different alkylaromatics (CU, EtB, and CHB), performed at 70 °C in the presence of AIBN (0.5%) and variable amounts of 3, allowed the corresponding hydroperoxides to be obtained with similar catalytic performances, but a significant reduction in the amounts of cosolvent compared with NHPI-catalyzed processes. Catalyst 2 was less efficient with respect to both 1 and 3, and afforded lower conversions and selectivity. When operating with propionaldehyde (5%) in place of AIBN as a sacrificial initiator, compound 3 showed better catalytic performances than 1. By overcoming the solubility limits of 1, catalyst 3 was successfully used at higher concentrations, with reduced amounts of cosolvent, and at lower temperatures (45°C); in all cases, thus positively affecting the selectivity of the process.

The aspects investigated herein could be useful for developing selective oxidative industrial transformations with a more rational use of chemical resources, reduced energetic costs, and low secondary product formation; this is in agreement with the requirement for the sustainable management of chemical processes and restrictive environmental policies.

Experimental Section

General

All reagents were purchased from commercial sources and used without further purification unless otherwise stated. 4,4'-(4,4'-lso-propylidenediphenoxy)bis(phthalic anhydride) was purified as described in the following section. Compound **8** was synthesized according to a procedure reported in the literature.^[36] THF and pyridine (99.8%) were dried with CaH₂ before use.

¹H and ¹³C NMR spectra were recorded at room temperature with a Bruker Avance-400 NMR spectrometer. Conversions and yields for CU, EtB, and CHB were determined by HPLC analysis (reversedphase column; ACN/MeOH/H₂O, 35/5/60), with the addition of 2phenylethanol as an internal standard, and confirmed by ¹H NMR spectroscopy. EPR spectra were recorded at room temperature by using an ELEXYS E500 spectrometer equipped with an NMR gaussmeter for calibration of the magnetic field and a frequency counter for the determination of *g* factors.

Catalyst preparation

4,4'-(4,4'-Isopropylidenediphenoxy)bis(phthalic anhydride) was purified by recrystallization from acetic anhydride. Dianhydride (5 g; commercially provided as yellowish flakes) was dispersed in acetic anhydride (40 mL) and heated at reflux at 139 °C for 1 h in a microwave reactor with automatic control of the power (Micro-SYNTH Labstation; Milestone Inc., USA). After cooling to room temperature, pure crystals were recovered by filtration on filter paper and extensively washed with cold diethyl ether to remove any remaining acetic anhydride. The white crystals were dried under vacuum and stored in a desiccator until next use.

Synthesis of 2: An anhydrous solution of dodecyl alcohol (10 mmol, 2.25 mL) in THF (20 mL) was added dropwise (\approx 30 min) to an anhydrous solution of trimellitic anhydride chloride (10 mmol, 2.106 g) and anhydrous pyridine (4 mL; 99.8%) in THF (20 mL) under magnetic stirring at 0 °C. The mixture was stirred at $0\,^\circ C$ for 6 h and then at RT overnight. After filtration of the white precipitate, the resulting liquid phase was evaporated under vacuum to give a white solid. The solid was dissolved in pyridine (40 mL) without further purification and reacted with hydroxylamine hydrochloride (50 mmol, 3.48 g) in a microwave for 1 h under reflux. Evaporation of the solvent under vacuum and washing of the mixture with 0.1 M HCl (4×100 mL) at 0 °C led to a white solid, which was purified by chromatography on silica gel with CHCl₃/ MeOH (9:1; v/v) as the eluent (R_f : 0.76; orange spot if the TLC plate was exposed to NH₃). Yield: 90%; ¹H NMR (400 MHz, [D₆]acetone): $\delta =$ 8.44 (d, 1 H), 8.31 (s, 1 H), 7.96 (s, 1 H), 4.40 (t, 2 H), 1.83 (q, 2 H), 1.6-1.2 (m, 18H), 0.88 ppm (t, 3H).

Synthesis of **3**: Purified 4,4'-(4,4'-isopropylidenediphenoxy)bis-(phthalic anhydride) (2.60 g, 5 mmol) was added to anhydrous pyridine (30 mL) in a 50 mL two-necked flask. After adding an excess of hydroxylamine hydrochloride (30 mmol, 2.85 g), the mixture was heated under reflux (119 °C) for 1 h in a microwave reactor. After cooling, pyridine was removed in vacuum to give a viscous orange product, which was dissolved in ethyl acetate (150 mL). The organic phase was extensively washed with 0.5 m HCl (100 mL, 3×) and water (100 mL, 3×) to remove residual pyridine and finally dried with anhydrous sodium sulfate. Evaporation of the solvent gave a pale-yellow foam, which was purified by chromatography on silica gel with CHCl₃/MeOH 9:1 (v/v) as the eluent. ($R_{\rm f}$: 0.54; orange spot if TLC plate was exposed to NH₃). Yield: 93%; ¹H NMR (400 MHz, [D₆]DMSO): δ = 10.77 (s, 2H), 7.80 (d, 2H), 7.34 (d, 4H), 7.29 (d, 2H), 7.24 (s, 2H), 7.08 (d, 4H), 1.69 ppm (s, 6H).

Oxidation experiments

The minimum volumes of ACN required for the complete dissolution of 1 and 3 in different HCs were obtained by adding the required amount of catalyst to a two-necked round-bottomed flask equipped with a condenser containing the HC (5 mL). The mixture was heated to 70 °C by using an oil bath. Small volumes of ACN (100 μ L) were injected into the flask every 2 min with a calibrated syringe until complete disappearance of the solid fraction was observed.

Aerobic oxidations were performed in a 25 mL two-necked roundbottomed flask equipped with a condenser and containing the HC (5 mL; CU=35.90 mmol; CHB=29.96 mmol; EtB=40.80 mmol), ACN (1.9 mL; CU/ACN=2.67:1 (v/v)), and appropriate amount of catalyst, as reported in Tables 1–5. Either AIBN (0.5%) or propionaldehyde (5%) were used as the initiators. The solution was stirred for 6 h at 700 rpm with a magnetic stirrer bar at the selected temperature (45 or 70 °C) under an oxygen atmosphere. For CU/ACN = 6.67:1 (v/v), 6 mL of the HC and 0.9 mL of ACN were used.

EPR analysis

EPR spectra were recorded by using a Bruker ELEXYS E500 spectrometer equipped with an NMR gaussmeter for the calibration of the magnetic field and a frequency counter for the determination of *g* factors. Relative radical concentrations for the determination of K_{eq} were determined by comparison of the digitized experimental spectra with those obtained by computer simulations. In these cases, an iterative least-squares fitting procedure based on the systematic application of the Monte Carlo method was performed to obtain experimental spectral parameters of the two species, including their relative intensities.^[41]

Nitroxide radicals were produced photochemically by UV light from an unfiltered 500 W high-pressure Hg lamp.

Computational Methods

Ab initio and density functional calculations were performed by using the Gaussian 03 program package^[42] and Gaussview as the interface program. The optimization of all derivatives of NHPI was performed at the B3LYP/6-311G(d,p) level of theory, whereas the solvent effects were described by using the IEFPCM at the B3LYP/6-311G level of theory. The NO–H BDE values, both in the gas phase and in solution, were calculated by using a nonisodesmic work reaction (e.g., NHPI→PINO+H). Zero-point energy (ZPE) was included in each result.

Acknowledgements

Financial support from Versalis S.p.A is gratefully acknowledged. L.M. and C.P. thank MIUR for continual support of their free-radical (PRIN 2010–2011, project 2010PFLRJR_005) and organic (FIRB-Future in Research 2008, project RBFR08XH0H_001) chemistry. M.L. and P.F. thank the University of Bologna for financial support.

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