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Lipophilic N-hydroxyphthalimide Catalysts for the Aerobic Oxidation of Cumene: Towards Solvent-Free Conditions ... and Back

Manuel Petroselli,[a] Lucio Melone,[a] Massimo Cametti[a*] and Carlo Punta[a*]

Abstract: A new class of lipophilic *N*-hydroxyphthalimides catalysts designed for the aerobic oxidation of cumene in solvent-free conditions were synthesized and tested. The specific strategy proposed for the introduction of lipophilic tails on the NHPI moiety leads to lipophilic catalysts which, while completely preserving the activity of the precursor, allow to conduct the catalytic oxidation in neat cumene for the very first time. The corresponding cumyl hydroperoxide is obtained in good yields (28-52%) and high selectivity (95-97%), under mild conditions. Importantly, the presence of a polar solvent is no longer required to guarantee the complete solubilization of the catalyst. On the other hand, the oxidation conducted in neat cumene unearths the unexpected necessity of using small amounts of acetonitrile in order to fully promote the hydrogen atom transfer process and prevent the catalyst from detrimental hydrogen bond (HB) driven aggregation.

Introduction

Research on alkyl C-H bond activation via hydrogen atom transfer (HAT), an important route for the synthesis of high added value molecules and materials, is experiencing a renewed interest. The selective C-H bond oxidation represents the most straightforward and versatile strategy for this purpose,[1] favoring the direct oxygenation,[2] amination[3], desaturation,[4] or halogenation[5] of a wide range of substrates. However, this approach implies a demanding task, that of combining high reactivity with high chemo-selectivity. The design of new homogeneous catalysts capable both to promote C(sp^3)-H oxidation and limit, or better avoid the formation of side products is thus highly desirable.

In this context, *N*-hydroxyphthalimide (NHPI) homogeneous catalysis has found a starring role and has been particularly exploited for promoting the aerobic oxidation of different organic substrates. [6,7]

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NHPI's catalytic action occurs following a well-known free-radical mechanism (Scheme 1). Briefly, in an initiation step the phthalimide *N*-oxyl (PINO) radical is generated from NHPI (*i*). PINO is then capable to undergo HAT from suitable C-H bonds, promoting the formation of a carbon centered radical (*ii*). The latter reacts with O_2 under diffusion control, leading to the corresponding peroxyl radical (*iii*). The cycle is finally closed by a second molecule of NHPI which, acting also as a good hydrogen donor, favors the propagation of the radical chain with the formation of hydroperoxide and a new PINO unit (*iv*), while delaying the termination reaction.

The catalytic efficiency is ascribed to the favorable synergy among enthalpic, polar, and entropic effects. The bond dissociation energy (BDE) of the O-H group in the NHPI moiety (88.1 kcal/mol)[8] renders *path i* in many cases exothermic or thermo-neutral. At the same time, the higher electrophilic character of PINO radical compared to the peroxyl one favors the stabilization of the transition state for HAT reaction of *path ii*.[8] Finally, the relatively high value of k_{NHPI} (7.2 x 10^3 $M^{-1}s^{-1}$)[8] guarantees the efficiency of the propagation chain, which results in high selectivity towards hydroperoxides, when operating under proper conditions.

For this reason, NHPI has been also widely investigated for the selective oxidation of alkyl aromatics to the corresponding hydroperoxides.[9-12] Our group recently focused on this topic as well, proposing both a new initiation system, capable to generate PINO at low temperatures, and an unique approach for the recovery of the catalyst.[13,14]

NHPI catalysis has been always performed in polar solvents, in order to guarantee the complete solubilization of the polar catalyst, especially at room temperature. As a consequence, the reactivity of this derivative in non-polar mediums is unknown, and till now experimentally undetermined, while the huge efforts devoted to the synthesis of more active derivatives seem not to consider such detrimental aspect.[15,16]

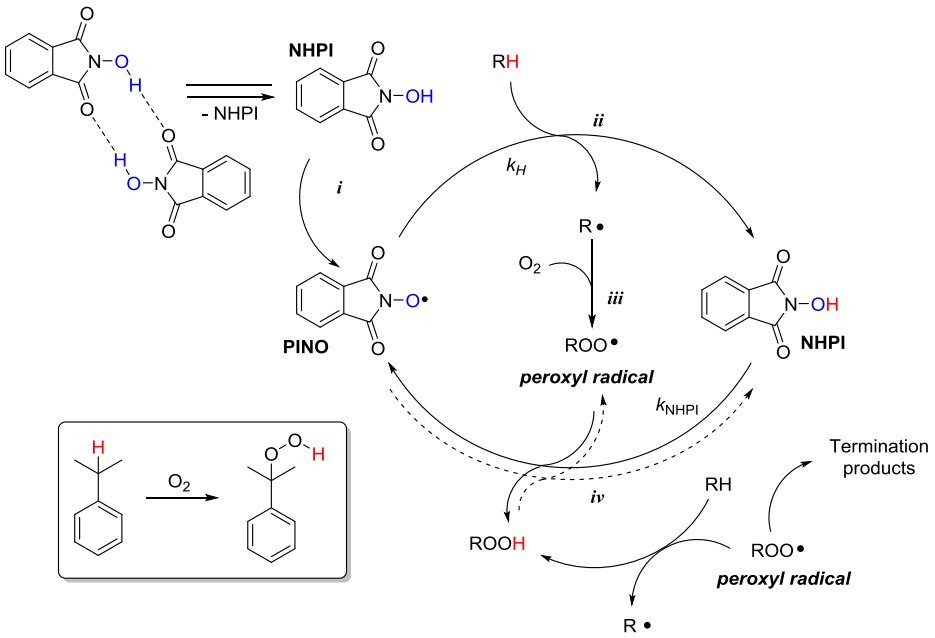
The possible route to overcome this limitation would require the design of new lipophilic NHPIs. Ishii first opened this way, by suggesting the introduction of lipophilic chains onto the aromatic ring of the *N*-hydroxy derivative.[17] Nevertheless, we recently demonstrated that the proposed Ishii's catalyst **1** (Scheme 2), when used in processes which require a high control of selectivity in hydroperoxide, is far from ideal.[18]

Indeed, not only its solubility is still low under mild conditions, in spite of its higher lipophilic character, but the carboxylic group, by which the alkyl tail is linked to the NHPI moiety, also affects the NO-H BDE due to its electron-withdrawing character, determining a value increase of 0.7 kcal/mol. As a result, the efficiency of **1** as hydrogen donor is significantly reduced.

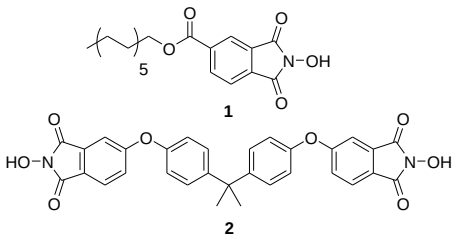
In the same work, we proposed catalyst **2** (Scheme 2) as a suitable lipophilic alternative to **1** for the aerobic oxidation of alkyl aromatics. The catalyst **2** showed an O-H BDE analogous to that of NHPI and a similar reactivity. This solution did not

allow to completely remove the polar co-solvent, but it was possible to run cumene (CU) oxidations under homogeneous conditions even at 45 °C with 1% of **2**, drastically reducing the $CU/MeCN_{(v/v)}$ ratio up to 2.67. Under the same solvent composition, NHPI resulted almost completely insoluble. As expected, the new conditions also led to an increment in cumyl hydroperoxide (CHP) selectivity.

Following this proof of concept, we herein report on the design and synthesis of a new class of lipophilic NHPI derivatives, reaching the final goal of achieving catalysts completely soluble in neat CU even at room temperature.



Scheme 1. General improved catalytic mechanism for NHPI-mediated aerobic oxidation of hydrocarbons



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

Results and Discussion

Synthesis of the new lipophilic NHPI catalysts

The general multi-step procedure for the synthesis of the new lipophilic NHPI catalysts is summarized in Scheme 3.

In a first step, 4-nitrophthalonitrile (**3**) was reacted with phenols bearing different substituents on the *ortho* and/or *para* positions (**4a-e**). **4a** was selected in order to reproduce the mono-functional derivative analogous to the double-NHPI compound **2**. **4b**, which presents a halogen in *para* position, could open the route to further substitution, while **4c-e** progressively increase the lipophilic character of the tail.

The second step consisted into the hydrolysis of compounds **5a-e** to the corresponding phthalic acid derivatives **6a-e**,.[19]

Finally, the closure of the cycle to the corresponding *N*-hydroxy phthalic derivatives occurred following a two-step procedure previously reported. The **7a-e** intermediates were obtained by reacting substrates **6a-e** with acetic anhydride in microwave at 140 °C for just 1 h.[20] The crude anhydride products were then let to react, without further purification, in microwave with hydroxylamine hydrochloride,[18] leading to the formation of **8a-e** potential catalysts, with 85% yield after purification.

Solubility tests

The effect of lipophilic tails on the solubility of **8a-e** in CU was investigated in detail. Table 1 reports the minimum amount of MeCN required for having 4 % mol of each *N*-hydroxy derivative completely solubilized, when added to 0.5 ml of CU. NHPI, **1**, and **2** were also investigated for comparison.

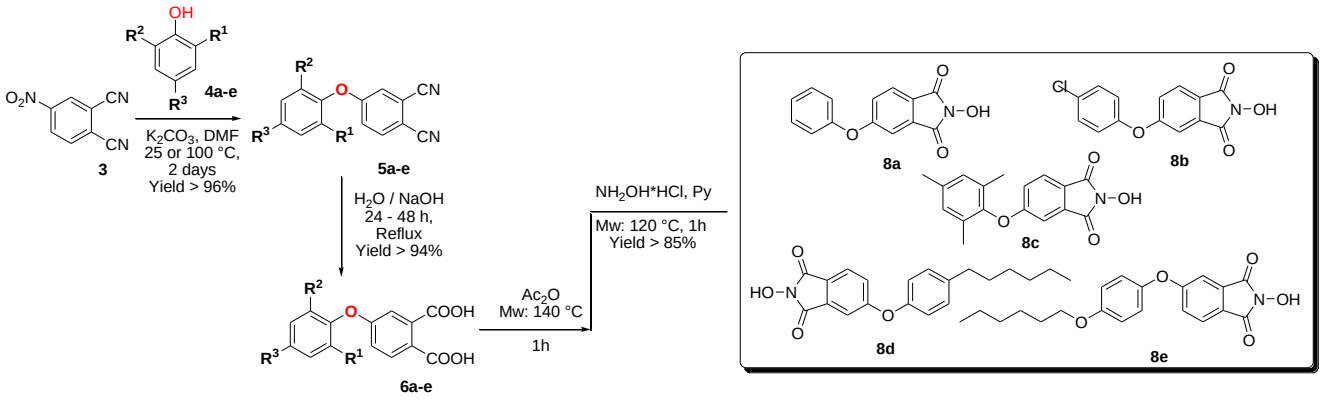
Table 1. Solubilization of *N*-hydroxy derivatives in CU at room temperature by addition of the minimum quantity of MeCN as co-solvent.[a)]

Entry	Compound	MeCN	
		Volume (µl)	% v/v
1	NHPI	1375	73
2	**1**	250	33
3[b)]	**2**	175	26
4	**8a**	175	26
5	**8b**	275	36
6	**8c**	350	41
7	**8d**	/	/
8	**8e**	65	12

[a)] General conditions: 0.5 mL of CU (3.6 mmol) added with 4% mol of selected compound at 25 °C. [b)] 2% of catalyst **2** was added.

As expected, while NHPI requires a huge amount of MeCN (73% v/v) to remain in solution (entry 1), the presence of the lipophilic chain in catalyst **1** induces a considerable increase of solubility in CU (entry 2), with a consequent significant decrease

of the required amount of polar co-solvent (33% v/v). An even lower quantity of MeCN (26% v/v) was required for the complete solubilization of **2** (entry 3). In this case, as derivative **2** bears two equivalents of NHPI moieties, a 2% mol was used, in order to compare the different catalysts in terms of real NHPI units' concentration in CU. The same trend, with an analogous volume of MeCN required, was confirmed by testing the solubility of 4% position of the phenolic ring. For this reason, we synthesized NHPI derivatives **8d** and **8e**, bearing 4-hexylphenoxy and 4-hexyloxylphenoxy substituents respectively, which resulted to be much more soluble in CU (entries 7 and 8). In particular, it was possible to completely solubilize 4% mol **8d** in neat CU even at room temperature, while compound **8e** required the addition of 12% of MeCN.



Scheme 3. Multi-step procedure for the synthesis of the new lipophilic NHPIs.

of compound **8a**, the half-unit of the corresponding catalyst **2** (entry 4), while **8b** showed a behavior analogous to catalyst **1** (entry 5).

Unexpectedly, compound **8c**, which should exhibit a higher lipophilic character due to the presence of three methyl groups on the phenolic ring, required a relatively high volume of MeCN (41% v/v) (entry 6). We hypothesized that the presence of the methyl groups could negatively affect the possible π-staking interactions with cumene, deleting the beneficial effects of an increased lipophilic character.

Table 2. Minimum temperatures for complete solubilization of catalysts in neat cumene.[a)]

Entry	Compounds	Catalyst amount		Minimum Temperature
		mmol	% mol	°C
1	NHPI	0.14	4%	> 140
2	**1**	0.14	4%	63-65
3	**1**	0.036	1%	52-53
4	**2**	0.072	2%	> 140
5	**8a**	0.14	4%	> 140
6	**8b**	0.14	4%	> 140
7	**8c**	0.14	4%	123-126
8	**8d**	0.14	4%	28-29
9	**8e**	0.14	4%	47-50
10	**8e**	0.036	1%	34-37

[a)] General conditions: 0.5 mL of CU (3.6 mmol) added with reported % mol of selected compounds at 28 °C, and slowly heated up to the temperature of complete solution homogeneity.

As a consequence, we opted to vacate the ortho positions of the phenol substituents and to increase the lipophilic character of *N*-hydroxy compounds by introducing alkyl chains in *para*

This trend was confirmed by determining the minimum temperature required for a complete solubilization in neat cumene (Table 2). As expected, NHPI could not be dissolved even by heating up to 140 °C (entry 1), and the same result was also observed both for the previously reported catalyst **2** (entry 4), and for the new derivatives **8a** and **8b** (entries 5 and 6, respectively), while just a slight decrease of the minimum temperature was measured for compound **8c** (entry 7).

On the contrary, Ishii's lipophilic catalyst **1** reached a complete solubilization at 63-65 °C (entry 2), once again confirming the beneficial effect of introducing a lipophilic tail on the NHPI unit. In this case, a minimum temperature of 52-53 °C was also measured when operating with 1% of the catalyst (entry 3), which simulates the standard oxidation conditions.[12]

However, as already observed in Table 1, the best result was obtained for compound **8d**, which resulted the unique derivative completely soluble in neat CU at room temperature (entry 9). The analogous derivative **8e**, whose importance will be discussed in depth in the next sections, also showed a high solubility, with minimum temperature ranges of 47-50 °C (entry 9) and 34-37 °C (entry 10) with 4% and 1% catalyst/CU mol ratio respectively. These values are in any case significantly lower than those reported for Ishii's catalyst **1** (entries 2 and 3), testifying the higher lipophilic character of derivative **8e**.

Cumene oxidation catalyzed by 8d

The solubility observed for compound **8d** allowed to conduct a solvent-free oxidation of alkylaromatics catalyzed by *N*-hydroxyphthalimide derivatives (Table 3) for the very first time. Propionaldehyde (5% mol) was used as suitable initiator,[21-23] being able to promote PINO generation even at low temperatures by molecule-induced homolysis,[24] via *in situ* formation of the corresponding peracid (Scheme 4). Under these reaction conditions, 18% of CU was converted to CHP, with a selectivity of 97%, while by operating in the absence of **8d**, only 2 % of conversion was observed (entry 2).

Table 3: Solvent-free aerobic oxidation of cumene catalyzed by new lipophilic NHPIs.[a)]

Entry	Initiator	Catalyst		Temp.	MeCN	Conversion	CHP Selectivity
		Compound	% mol	(°C)	(μL)	(%)	(%)
1	CH_3CH_2CHO (5%)	**8d**	2%	45	-	18	97
2	CH_3CH_2CHO (5%)	**/**	/	45	-	2	79
3	CH_3CH_2CHO (5%)	**8d**	2%	70	-	23	95
4	AIBN (2%)	**8d**	2%	70	-	43	96
5	AIBN (2%)	**/**	/	70	-	20	69
6[b)]	CH_3CH_2CHO (5%)	**2**	1%	45	300	27	97
7[c)]	CH_3CH_2CHO (5%)	**8d**	2%	45	10.000	15	89
8[c)]	CH_3CH_2CHO (5%)	**NHPI**	2%	45	10.000	18	81
9	CH_3CH_2CHO (5%)	**8d**	2%	45	25	28	97
10	CH_3CH_2CHO (5%)	**8d**	2%	70	25	30	95
11	AIBN (2%)	**8d**	2%	70	25	45	96
12	CH_3CH_2CHO (5%)	**8d**	2%	45	100	32	94
13	CH_3CH_2CHO (5%)	**8e**	2%	45	-	19	97
14	CH_3CH_2CHO (5%)	**8e**	2%	45	25	28	96
15	AIBN (2%)	**8e**	2%	70	-	52	95
16	AIBN (2%)	**8e**	2%	70	25	54	95

[a)] General Reaction Conditions: Cumene (2 mL, 14.3 mmol), O_2 (1 atm), **8d** or **8e**, 6 h, Conversion and selectivity were obtained by ^{1}H-NMR with internal standard. [b)] see ref. 18. [c)] 5 mmol of cumene were reacted in 10 mL of MeCN. Difference among independent measurements are within 2%.

An increase of temperature up to 70 °C resulted in just a slight increment in CU conversion (23%, entry 3). We assumed that this low temperature effect could be associated to the nature of the initiator, which could be quickly oxidized and consumed at higher temperatures. For this reason, we repeated the reaction at 70 °C in the presence of AIBN (entry 4), and in this case we found a significantly higher conversion (43%), preserving the selectivity of the process.

While confirming the catalytic activity of **8d**, the conversions obtained using propionaldehyde as initiator were under our expectations, based on the comparison with our previous work on **2** (see entry 6). In order to shade light on this behavior, we compared the catalytic efficiency of the new lipophilic derivative **8d** with that of NHPI, by conducting the oxidation of CU in MeCN (entries 6 and 7). The results revealed a comparable reactivity between **8d** and NHPI, and thus we initially supposed that the poor conversion observed at 45 °C in neat CU could be ascribed to the different polarity of the reaction medium. Indeed, an increase of the polarity of the reaction medium could lead to the stabilization of the transition state in the HAT reaction of *path ii* (Scheme 1), resulting in higher catalytic performances.

Seemingly pointing to the above hypothesis, a significantly higher conversion (28%) was observed by performing the same reaction with the addition of 25 μl of MeCN to the oxidation solution (entry 9). An analogous beneficial effect was also observed at 70 °C (comparison between entries 3 and 10), when operating with propionaldehyde initiator. With AIBN no differences were observed (entries 4 and 11).

Notably, however, oxidations carried out in the presence of a higher amount of MeCN in solution (100 μl, entry 12), do not show any further increase in CU conversion, thus a simple solvent polarity effect should be ruled out, and another explanation sought.

As, from a structural point of view, the NHPI moiety possesses both hydrogen bond (HB) acceptor (C=O) and donor (N-OH) groups, catalyst **8d** might display self-complementary and, thus, the tendency to aggregate into dimers (or higher HB adducts) when dissolved in low polarity media (see Scheme 4).

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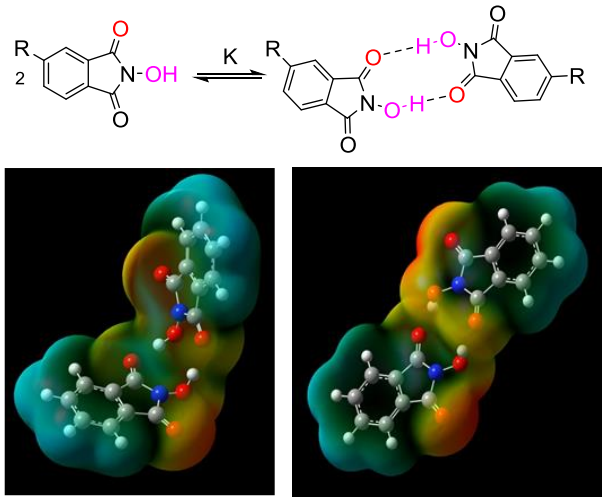

Scheme 4. Top: HB driven self-association into dimeric species for a NHPI derivative in apolar medium; Bottom: Electrostatic potential surface (ESP) for the two most stable dimers of NHPI, calculated in gas phase at 298 K (B3LYP/6-311G(d,p)). See ESI (Section Computational Study) for further information.

As **8d** is employed in neat cumene, an eventually forming dimeric species (or a higher aggregate), might hamper the HAT mechanism as described in *path ii* of Scheme 1, being the NO-H bond directly involved in the self-aggregation process. DFT calculations performed in the gas phase for NHPI could provide an initial tentative guess at the dimeric structure that could be found in apolar solution. Interestingly, calculated HB $O_{donor}\cdots O_{acceptor}$ distances (ca. 2.75 Å) are similar to the HB distance found in the only X-ray determined structure of NHPI (ca. 2.68 Å).[25]

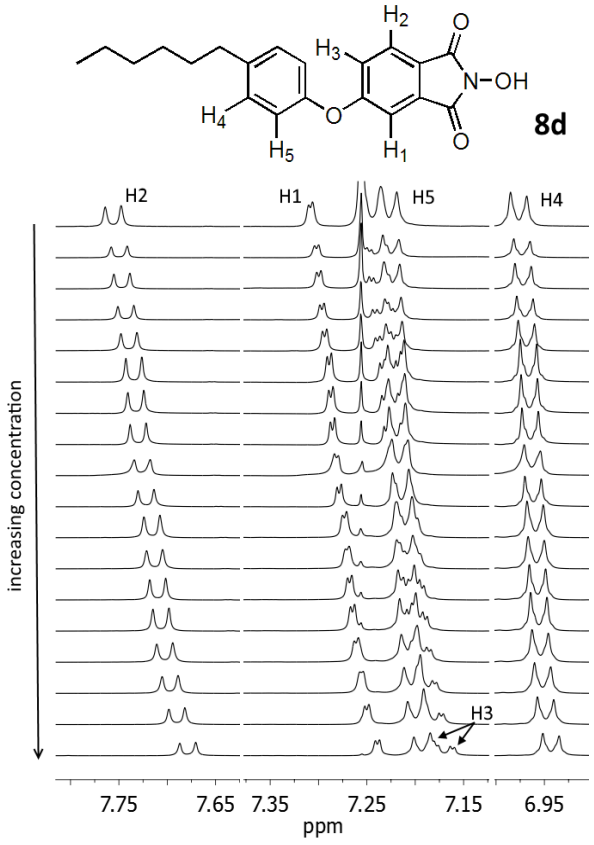

Figure 1. ^{1}H-NMR spectra of **8d** in $CDCl_3$ at 305 K at different concentrations ranging from 0.5 to 9.2 x 10^{-3} M, from bottom to top

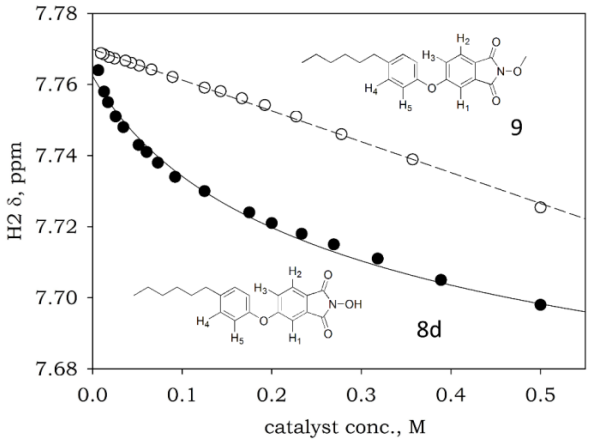

Figure 2. Plot of the chemical shift, δ, of the aromatic H2 signal belonging to the NHPI moiety in **8d** (●) and **9** (○), versus their molar concentration, measured in $CDCl_3$ at 305K

In order to verify the possibility of aggregation, we first investigated whether any concentration dependent effect on the ^{1}H-NMR spectrum of **8d** could be observed in $CDCl_3$.

The results of this experiment are shown in Figure 1 where the spectra of **8d** at different concentrations are reported. A significant downfield shift of all the signals in the aromatic region can be seen. Plot of the chemical shift, δ, of the aromatic H2 signal belonging to the NHPI moiety in **8d** versus its molar concentration is shown in Figure 2 (●). Also, we synthesized compound **9** (Figure 2), analogous to **8d** but for its N-OMe group which lacks any HB donating capability. Being **9** incapable to form any dimeric HB adducts, it represents an optimal model compound for comparison with **8d**.

The data clearly point to a self-association process for **8d** and they can be fitted by non-linear least square methods with a binding isotherm based on a 1:1 association model which affords a self-association constant K equal to 2.3 ± 0.2 M^{-1} (see Fig. SI 31). Model compound **9**, instead, under the same experimental conditions, shows a markedly different behavior, *i.e.*, a linear decrease of the δ of the H2 signal of **9** (see Figure 2 ○ data points). This strongly confirms the validity of our initial hypothesis: **8d** can indeed self-associate into HB dimeric adducts at high concentrations.

Small though the determined K value might appear, it can be easily demonstrated that under the oxidation reaction conditions (catalyst concentration ca. 0.145 M, Table 3) it results in a significant association, with the monomeric species reduced to ca. 70% of the total catalyst concentration (see Fig SI 36). Ishii's catalyst, **1**, soluble in $CDCl_3$, was also tested and it was found to behave similarly to **8d** (K equals 3.3 ± 0.2 M^{-1}, see Fig. SI 33).

As catalyst **8d,** in the present work, succeeds in operating in neat cumene, we were interested in studying the same self-association phenomenon under conditions which could be as similar as possible to those employed in the real catalytic process. Thus, we repeated the above dilution experiment in toluene-d_8[26] and the results are reported in Figure 3, where a plot of the chemical shift of the H2 signal of the NHPI moiety in 8**d** versus its molar concentration is shown (● data points). It appears evident that the monotonic behavior displayed in $CDCl_3$ is now replaced by a more complex profile. Indeed, by dilution an initial upfield shift in the high concentration regime is observed, followed by a downfield shift in the low concentration regime (minimum at ca. 0.025 M). Again, self-association is the likely explanation for observed data.[27] We speculate that at low concentration of **8d**, an initial dimeric HB-driven species forms, similarly to what occurs in $CDCl_3$, while at higher concentration, due to the low polarity of toluene solvent, larger aggregates start to appear. The same experiment performed in a toluene:MeCN mixture (95:5) shows only nominal changes of **8d** signals δ upon its dilution (see Figure SI 37).

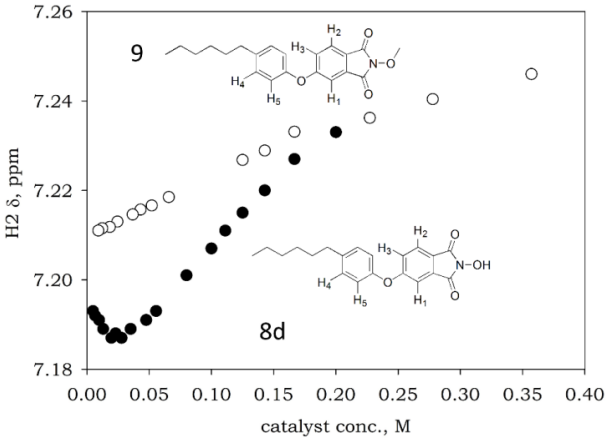

Figure 3. Plot of the chemical shift, δ, of the aromatic H2 signal belonging to the NHPI moiety in **8d** (●) and **9** (○) versus their molar concentration, measured in toluene-d_8 at 305 K

Again, the comparison with the model compound **9** (○ data points) substantiates our hypothesis concerning the nature of the adduct formed in the low concentration regime, which is most likely HB driven. As to the linear behavior of the chemical shift of the H2 signal in model **9**, observed in both toluene-d_8 and in $CDCl_3$, it can be explained as due to a non-specific and inefficient aggregation of the compound probably due to π-stacking interactions.[28] Additional confirmation of the aggregation tendency of compound **8d** can be also obtained by ATR-IR and fluorescence studies (See ESI - Section *ATR-IR* and *Fluorescence analysis*).

Cumene oxidation catalysed by 8e

By conducting the aerobic oxidation of CU at 70 °C in the presence of **8d**, we observed the formation of tiny amounts of side products clearly derived from degradation of the catalyst. We assumed that they could be associated to the partial oxidation onto the benzyl position of the catalyst, in spite of the high molar ratio between CU and **8d** and of the higher reactivity of the tertiary benzyl C-H bond in CU respect to that of the secondary one in **8d**. In order to verify this hypothesis and to identify the possible oxidation products, we promoted an oxidation of **8d** in the absence of CU under drastic conditions (in MeCN and at 70 °C, using an equivalent amount of AIBN as radical initiator). At the end of the reaction, 82% of the initial catalyst was converted, as determined by ^{1}H-NMR analysis (entry 1, Table 4). As expected, the oxidation products derived from the conversion of benzyl C-H to a mixture of the corresponding alcohol, hydroperoxide and ketone (see Fig. SI 41 and 43).

Even if the oxidation of **8d** under the standard reaction conditions in neat CU occurs to a small extent, and negligibly affects the catalytic efficiency, we set up to overcome this potential limit by designing the analogous compound **8e**, where an oxygen atom is inserted between the phenolic ring and the alkyl chain. While the solubility of the new catalyst in CU appeared just slightly lower, as previously discussed (see entry 8, Table 1, and entries 9 and 10, Table 2), **8e** resulted to be much more resistant to direct oxidation, with only 12% of conversion (see Fig. SI 47). due to the attack on the α-position to the oxygen atom (entry 2, Table 4).

We tested **8e** as catalyst in the solvent-free oxidation of cumene at 45 °C, with 5% of propionaldehyde, and we observed analogous results to those obtained with **8d**, in terms of both CU conversion and CHP selectivity (entry 13, Table 3). Also in this case, the addition of tiny amounts of MeCN (25 µL) resulted in a significant increase in CU conversion, from 18% to 28% (entry 14, Table 3), confirming one more time the activation role of the polar solvent at lower temperatures.

By moving up to 70 °C, with 2% AIBN as initiator, we obtained the highest conversion (52 %), with a selectivity in hydroperoxide of 95% (entries 15 and 16, Table 3). Even under these reaction conditions, we did not observe any oxidation products deriving from the catalyst, and this confirms the quality of the catalyst design.

Table 4. Stability of catalysts **8d** and **8e** to oxidation conditions.[a)]

Entry	Catalyst	Conversion[b)] (%)
1	**8d**	82
2	**8e**	12

[a)] MeCN (2 ml), catalyst (0.29 mmol), O_2 (1 atm), 6 h. Initiator: AIBN (0.29 mmol). [b)] Conversion determined by ^{1}H-NMR analysis (See ESI). Difference among independent measurements are within 2% based on three different experiments.

Conclusions

NHPI homogeneous catalysis for oxidative processes has revealed to be a promising system for several applications, especially for the selective aerobic oxidation of alkylaromatics to the corresponding hydroperoxides. However, as of yet this approach suffered from the necessity to use high amounts of co-solvent, due to the polar character of the NHPI molecule and solubility issues. Despite significant efforts in the last decade devoted to work out this problem, most of the proposed solutions were not able to consider both aspects of solubility and reactivity. In this context, this work opens the way to a new class of

lipophilic NHPI catalysts, bearing alkyl aromatic tails on the NHPI moiety. The new catalysts are designed to improve their solubility in apolar media while maintaining unaltered the NO-H BDE value of the NHPI moiety, and thus preserving the catalytic efficiency in terms of conversion and selectivity in hydroperoxides. The new catalysts allowed, for the first time, to perform solvent-free oxidations of alkylaromatics under mild conditions (45 °C and atmospheric pressure), obtaining good yields, high selectivity in hydroperoxides and a higher productivity in comparison with previously reported processes.

While the use of a polar co-solvent is thus no longer required with our novel lipophilic catalysts, this work also uncovers an intrinsic limit to the implementation of solvent free conditions. Indeed, a detailed study on catalyst **8d** reveals its tendency towards HB-driven aggregation in low polarity solvents, as demonstrated by ^{1}H-NMR investigation, also confirmed by ATR-IR and fluorescence spectroscopy. This finding allowed us to rationalize those data which showed, under certain experimental conditions, a lower than expected catalytic efficiency (entry 1, Table 1), but more generally, it shows that the addition of tiny amounts of MeCN to the reaction medium is necessary to allow the catalytic system to show its full potential.

Finally, catalyst stability under the reaction conditions has been also investigated. The partial oxidation of **8d** on the benzyl position suggests the use of the analogous 4-(*p*-hexyloxylphenoxy)-*N*-hydroxyphthalimide **8e**, which maintains a high solubility in cumene, reproduces the catalytic efficiency of **8d** in terms of yield, selectivity and productivity, but importantly is not converted during the oxidation process.

In conclusion, compounds **8d** and **8e** resulted to be the most soluble *N*-hydroxy catalysts ever reported, in particular compound **8e** features a higher chemical stability and HAT efficiency with respect to compound **1.**

Experimental Section

General Methods

All chemicals, reagents and solvents were obtained from commercial sources and were used without further purification, if not mentioned otherwise. Catalysts **1** and **2** were synthesised following the procedure reported in the literature [12] ^{1}H-NMR spectra of the products were recorded at 305 K with a Bruker Avance-400 MHz NMR spectrometer (Bruker, Billerica, MA, USA). ESI-MS mass spectra were collected on a Bruker Esquire 3000+ with electrospray ionization source and ion-trap detector. The samples were analyzed by direct infusion of suitable solutions (methanol) in the spectrometer source. The IR spectra reported in ESI were obtained by a Varian 640 high-performance ATRIR spectrometer. The fluorescence maps reported in ESI were obtained by a spectrofluorometer Fluorolog® (See ESI for further information). The NMR studies of the aggregation of NHPIs were conducted in $CDCl_3$ and toluene-d_8; more details, are reported in the ESI. The melting points were measured on a Büchi 535 apparatus. Flash column chromatography was performed by using 40–63 μm silica gel packing; the eluent was chosen in order to move the desired components to *R*f 0.35 on analytical TLC.

Synthesis of the catalysts

General procedure for the synthesis of 5a-c*:* In a round-bottom flask of 50 ml, 4-phthalonitrile **3** (1 g, 5.78 mmol), phenol 4a-c (5.78 mmol, 544 mg, 743 mg, and 787 mg, respectively), K_2CO_3 (1.6 g, 11.56 mmol) were dissolved in DMF (20ml). The solution was stirred at room temperature for 2 days. The solution was diluted in 150 ml of water and cooled at 0 °C overnight, obtaining a pink-white solid precipitate. Average yield: 94%.

4-phenoxyphthalonitrile (5a): ^{1}H-NMR (400 MHz, DMSO-d6) δ 8.09 (d, 1H), 7.75 (s, 1H), 7.51 (t, 2H), 7.38 (dd, 1H), 7.32 (t, 1H), 7.20 (d, 2H). ^{13}C-NMR (400 MHz, DMSO-d6) δ 161.52, 154.28, 136.78, 131.13, 126.29, 123.17, 122.46, 120.79, 117.18, 116.35, 115.84, 108.65.
4-(p-chlorophenoxy)phthalonitrile (5b): ^{1}H-NMR (400 MHz, DMSO-d6) δ 8.11 (d, 1H), 7.81 (s, 1H), 7.55 (d, 2H), 7.45 (dd, 1H), 7.25 (d, 2H). ^{13}C-NMR (400 MHz, DMSO-d6) δ 161.16, 153.24, 136.78, 130.97, 130.21, 123.32, 122.83, 122.67, 117.24, 116.30, 115.79, 109.07.
4-(2,4,6-trimethylphenoxy)phthalonitrile (5c): ^{1}H-NMR (400 MHz, DMSO-d6) δ 8.03 (d, 1H), 7.54 (s, 1H), 7.14 (dd, 1H), 7.01 (s, 2H), 2.27 (s, 3H), 2.00 (s, 6H). ^{13}C-NMR (400 MHz, DMSO-d6) δ 161.22, 147.46, 136.94, 135.96, 130.45, 130.25, 120.97, 120.01, 117.35, 116.41, 115.90, 107.82, 20.82, 16.09.

General procedure for the synthesis of 5d and 5e: In a round-bottom flask of 50 ml, 4-phthalonitrile **3** (1 g, 5.78 mmol), 4-hexylphenol (**4d**, 1.05 g, 5.78 mmol) or 4-(p-hexyloxyl)phenol (**4e**, 1.12g, 5.78 mmol), K_2CO_3 (1.6 g, 11.56 mmol) were dissolved in DMF (20ml) and stirred at 100 °C for 24 hours. The solution was diluted with 50 ml of water and extracted with ethyl acetate. The organic layer was washed with water (3 x 15 ml), dried with Na_2SO_4, filtered and concentrated in vacuum. **5d** (1.67 g of pure pink-white solid) and **5e (**1.72 light brown solid) were obtained (93% yield in both cases).

4-(p-hexylphenoxy)phthalonitrile (5d): ^{1}H-NMR (400 MHz, DMSO-d6) δ 8.07 (d, 1H), 7.70 (s, 1H), 7.35 (dd, 1H), 7.31 (d, 2H), 7.10 (d, 2H), 2.61 (t, 2H), 1.59 (m, 2H), 1.29 (m, 6H), 0.86 (t, 3H). ^{13}C-NMR (400 MHz, DMSO-d6) δ 164.14, 163.88, 163.46, 152.80, 140.17, 131.87, 130.67, 125.93, 122.43, 120.67, 111.62, 34.91, 31.52, 31.35, 28.76, 22.48, 14.37
4-(p-hexyloxylphenoxy)phthalonitrile (5e): ^{1}H-NMR (400 MHz, DMSO-d6) δ 8.06 (d, 1H), 7.68 (s, 1H), 7.32 (dd, 1H), 7.13 (d, 2H), 7.04 (d, 2H), 3.97 (t, 2H), 2.07 (m, 2H), 1.42 (m, 2H), 1.31 (m, 4H), 0.88 (t, 3H). ^{13}C-NMR (400 MHz, DMSO-d6) δ 162.41, 156.97, 147.09, 136. 67, 122.31, 122.22, 121.67, 117.06, 116.54, 116.36, 115.84, 108.05, 68.41, 31.45, 29.12, 25.65, 22.52, 14.32.

General procedure for the synthesis of 6a-c: In a round-bottom flask of 100 ml, **5a-c** (5.7 mmol, 1.25 g, 1,46 g, and 1.44 g, respectively) and sodium hydroxide (4.5g, 113.28 mmol) were dissolved in 30 ml of water. The solution was stirred for 24 hours at reflux. The solution was diluted with 80 ml of water and HCl conc. was added until pH 1-2. The resulting solution was cooled at 0 °C for 12 hours. A white solid was obtained and filtered, obtaining a minimum yield in 4a-c of 94%.

4-phenoxyphthalic acid (6a): ^{1}H-NMR (400 MHz, DMSO-d6) δ 13.01 (s, 2H), 7.76 (d, 1H), 7.46 (t, 2H), 7.24 (t, 1H), 7.11 (m, 4H). ^{13}C-NMR (400 MHz, DMSO-d6) δ 168.88, 167.91, 159.78, 155.46, 136.92, 131.83, 130.87, 126.31, 125.33, 120.44, 119.22, 116.96. MS (ESI): m/z = 281.0 $[M+Na]^+$.
4-(p-chlorophenoxy)phthalic acid (6b): ^{1}H-NMR (400 MHz, DMSO-d6) δ 13.01 (s, 2H), 7.78 (d, 1H), 7.50 (d, 2H), 7.16 (m, 4H). ^{13}C-NMR (400 MHz, DMSO-d6) δ 168.77, 167.91, 159.29, 154.50, 136.92, 131.86, 130.70, 129.14, 126.84, 122.11, 119.53, 117.34. MS (ESI): m/z = 315.0 $[M+Na]^+$.
4-(2,4,6-trimethylphenoxy)phthalic acid (6c): ^{1}H-NMR (400 MHz, DMSO-d6) δ 13.01 (s, 2H), 7.74 (d, 1H), 7.01 (s, 2H), 6.88 (m, 2H), 2.28 (s, 3H), 2.02 (s, 6H). 13C-NMR (400 MHz, DMSO-d6) δ 169.17, 167.83, 159.78, 148.06, 137.31, 135.31, 132.07, 130.46, 130.27, 124.85, 115.99, 113.93, 20.81, 16.16. MS (ESI): m/z = 323.1 $[M+Na]^+$.

Synthesis of 6d: In a round-bottom flask of 250 ml, **5d** (3.27g, 10.74 mmol) and NaOH (8.59g, 215 mmol) were dissolved in 60 ml of water. The solution was refluxed for 2 days under stirring, and the diluted with additional 80 ml of water. HCl 37% (v/v) was added until a white precipitate was formed. The resulting solution was cooled at 0 °C for 12

hours to favor the product precipitation. The white solid was finally filtered (3.08 g, 86 % yield) and used without further purification for the next synthetic step.

4-(p-hexylphenoxy)phthalic acid (6d): ^{1}H-NMR (400 MHz, DMSO-d6) δ 13.01 (s, 2H), 7.75 (d, 1H), 7.27 (d, 2H), 7.08 (dd, 1H), 7.04 (m, 3H), 2.58 (t, 2H), 1.57 (m, 2H), 1.28 (m, 6H), 0.85 (t, 3H). ^{13}C-NMR (400 MHz, DMSO-d6) δ 164.14, 163.88, 163.46, 152.80, 140.17, 131.87, 130.67, 125.93, 122.34, 120.67, 111.62, 34.91, 31.52, 31.35, 28.76, 22,48, 14.37. MS (ESI): m/z = 365.1 $[M+Na]^+$.

Synthesis of 6e: In a round-bottom flask of 250 ml, **5e** (1.73g, 5.4 mmol) and NaOH (4.32g, 108 mmol) were dissolved in 100 ml of water. The solution was refluxed for 2 days under stirring. Work up was analogous to that reported for compound **6d**. A green solid was finally filtered (1.77g, 92%) and used without further purification for the next synthetic step.

4-(p-hexyloxylphenoxy)phthalic acid (6e): ^{1}H-NMR (400 MHz, DMSO-d6) δ 13.01 (s, 2H), 7.75 (d, 1H), 7.09-6.99 (m, 6H), 3.97 (t, 2H), 1.72 (m, 2H), 1.43 (m, 2H), 1.32 (m, 4H), 0.89 (t, 3H). ^{13}C-NMR (400 MHz, DMSO-d6) δ 169.05, 167.81, 160.89, 156.40, 148.19, 137.02, 131.81, 125.47, 122.09, 118.16, 116.35, 115.87, 68.37, 31.46, 29.15, 25.65, 22.52, 14.23. MS (ESI): m/z = 359 $[M+H]^+$, m/z = 381.1 $[M+Na]^+$.

General procedure for the synthesis of 8a-e: In a two-neck round-bottom flask of 50 ml, **6a-e** (5.3 mmol, 1.38 g, 1. 56 g, 1.58 g, 1.83 g, and 1.91 g, respectively) were dissolved in acetic anhydride (30 ml) and heated at 140 °C for 1 hour in a microwave reactor with automatic control of the power (Micro-SYNTH Labstation; Milestone Inc. USA). The solution was concentrated under reduced pressure (60 °C and < 20 mbar), obtaining derivatives **7a-e**. In the same two-necks round-bottom flask containing **7a-e**, pyridine (30 ml) and hydroxylamine hydrochloride (3.7 g, 53.3 mmol) were added. The mixture was heated at 120 °C for 1 hour in the microwave reactor. The resulting orange solution was evaporated under reduce pressure (60 °C, > 10 mbar), washed with a solution of diluted HCl and extracted with ethyl acetate (3 x 15 ml). The organic layer was washed with water, dried with Na_2SO_4 anhydrous, filtered and evaporated under vacuum. All the catalysts resulted in a yellow solid. **8a-c** were purified by flash chromatography (eluent hexane/ethyl acetate 1/1). **8d-e** were purified by crystallization, dissolving them in the minimum quantity of toluene and adding hexane until the formation of a pale yellow solid. In all cases a minimum yield of 85 % was observed.

4-(phenoxy)-N-hydroxyphthalimide (8a): ^{1}H-NMR (400 MHz, DMSO-d6) δ 10.77 (s, 1H), 7.83 (d, 1H), 7.52 (t, 2H), 7.33 (m, 2H), 7.25 (s, 1H), 7.19 (d, 2H). ^{13}C-NMR (400 MHz, DMSO-d6) δ 164.11, 163.84, 163.08, 155.07, 131.91, 131.01, 125.95, 125.82, 122.93, 122.68, 120.74, 112.01. MS (ESI): m/z = 278.0 $(M+Na)^+$, m/z = 532.6 $(2M+Na)^+$.

4-(p-chlorophenoxy)-N-hydroxyphthalimide (8b): ^{1}H-NMR (400 MHz, DMSO-d6) δ 10.75 (s, 1H), 7.84 (d, 1H), 7.54 (d, 2H), 7.36 (dd, 1H), 7.31 (s, 1H), 7.22 (d, 2H). ^{13}C-NMR (400 MHz, DMSO-d6) δ 164.03, 163.76, 162.56, 154.10, 131.94, 130.82, 129.66, 125.94, 123.37, 122.99, 122.40, 112.46. MS (ESI): m/z = 312.0 $(M+Na)^+$.

4-(2,4,6-trimethylphenoxy)-N-hydroxyphthalimide (8c): ^{1}H-NMR (400 MHz, DMSO-d6) δ 10.68 (s, 1H), 7.79 (d, 1H), 7.13 (dd, 1H), 7.03 (m, 3H). ^{13}C-NMR (400 MHz, DMSO-d6) δ 164.15, 163.95, 162.89, 148.01, 135.65, 132.19, 130.36, 126.11, 122.02, 119.88, 109.36, 20.81, 16.14. MS (ESI): m/z = 320.1 $(M+Na)^+$.

4-(p-hexylphenoxy)-N-hydroxyphthalimide (8d): ^{1}H-NMR (400 MHz, DMSO-d6) δ 10.72 (s, 1H), 7.82 (d, 1H), 7.31 (m, 3H), 7.21 (s, 1H), 7.09 (d, 2H). ^{13}C-NMR (400 MHz, DMSO-d6) δ 164.14, 163.88, 163.46, 152.80, 140.17, 131.87, 130.67, 125.93, 122.34, 120.67, 111.62, 34.91, 31.52, 31.35, 28.76, 22.48, 14.37. MS (ESI): m/z = 340.1 $(M+H)^+$, m/z = 362.1 $(M+Na)^+$, mp = 89.4 °C.

4-(p-hexyloxylphenoxy)-N-hydroxyphthalimide (8e): ^{1}H-NMR (400 MHz, DMSO-d6) δ 10.76 (s, 1H), 7.81 (d, 1H), 7.27 (dd, 1H), 7.18 (s, 1H), 7.14 (d, 2H), 7.05 (d, 2H), 3.99 (t, 2H), 1.73 (m, 2H), 1.43 (m, 2H), 1.33 (m, 4H), 0.89 (t, 3H). ^{13}C-NMR (400 MHz, DMSO-d6) δ 164.15,164.09, 163.90, 156.71, 147.84, 131.86, 125.88, 122.27, 121.80, 116.48, 111.06, 68.41, 31.46, 29.13, 25.65, 22.52, 14.34. MS (ESI): m/z = 356.1 $[M+H]^+$, m/z = 378.1 $[M+Na]^+$, mp = 87.4 °C.

Procedure for the synthesis of 9: In a round-bottom flask of 50 ml, compound **8d** (300 mg, 0.884 mmol) was dissolved in 15 ml of acetone. NaOH (36 mg, 0,884 mmol) was added and, after sonication, the mixture was diluted with water to obtain a homogeneous red clear solution. Finally, CH_3I (1.53 g, 10.6 mmol) was added in five aliquots, one each hour. After 5 hours, the resulting colorless solution was concentrated under reduced pressure, leading to the precipitation of a yellow solid, which was filtered and purified by flash chromatography column (hexane/ethyl acetate 4/1) obtaining 304 mg of pure **9** (97 % yield).

4-(p-hexyloxylphenoxy)-N-methoxyphthalimide (9): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.70 (d, 1H), 7.24 (d, 1H), 7.20 (dd, 1H), 7.17 (d, 2H), 6,92 (d, 2H), 3.98 (t, 3H), 2,56 (t, 2H), 1.57 (m, 2H), 1.27 (m, 6H), 0.83 (t, 3H). ^{13}C-NMR (400 MHz, $CDCl_3$) δ 164.29, 163.03, 162.98, 152.33, 140.53, 131.36, 130.24, 125.64, 122.41, 121.81, 120.34, 111.80, 65.84, 35.34, 31.69, 31.47, 28.97, 22.59, 14.07. MS (ESI): m/z = 354.1 $[M+H]^+$, m/z = 376.1 $[M+Na]^+$, 391.8 $[M+K]^+$

Tests of Solubility

Determination of the minimum volume of MeCN to be added for complete solubilization in cumene: The minimum volumes of MeCN required for the complete solubilization of each catalyst in CU were obtained by adding the required amount of catalyst (4% mol respect to CU) to a two-neck round-bottom flask containing CU (0.5 ml). The mixture was stirred for 5 min at room temperature. Fixed volumes of MeCN (25µl) were injected into the flask with a calibrated syringe every 5 minutes, until complete solubilization of the catalyst was observed.

Determination of the minimum temperature for complete solubilization in cumene: In a two-neck round-bottomed flask, the selected amount of each catalyst (generally 4% mol) was added to 0.5 ml of cumene (3.6 mmol). The mixture was put in an oil bath under stirring at room temperature. The temperature was increased of 5 °C every 20 minutes, until complete solubilization of the catalyst was observed.

Cumene aerobic oxidations

General procedure for cumene oxidations in MeCN under diluted conditions: Aerobic oxidations were performed in a 50 mL two-necked round-bottom flask equipped with a condenser and containing CU (0.6g, 5 mmol), MeCN (10 ml), and an appropriate amount of catalyst, as reported in Table 3. Either AIBN (2% mol) or propionaldehyde (5% mol) were used as initiators. The solution was stirred for 6 h at 850 rpm with a magnetic stirrer bar at the selected temperature (45 or 70 °C) under an oxygen atmosphere.

General procedure for oxidations in neat cumene: Aerobic oxidations were performed in a 50 mL two-necked round-bottom flask equipped with a condenser and containing CU (1.7g, 14.3 mmol), and an appropriate amount of catalyst, as reported in Table 3. Either AIBN (2% mmol) or propionaldehyde (5% mmol) were used as initiators. Variable amounts of MeCN were also added, as indicated in Table 3. The solution was let to react for 6 h under magnetic stirring (850 rpm), at the selected temperature (45 or 70 °C), under an oxygen atmosphere.

Computational Methods

Ab initio and density functional calculations were performed by using the Gaussian 09 program package [29] and Gaussview as the interface program. The optimizations of all derivatives of NHPI was performed at the B3LYP/6-311G(d,p) level of theory. The electrostatitic potential

surface (ESP) was calculated and generated at B3LYP/6-311G(d,p) level of theory. Zero point energy (ZPE) was included in each result

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Keywords *N*-hydroxyphthalimide; aerobic oxidation; homogeneous catalysis; solvent-free; hydrogen atom transfer.

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[26] Toluene and cumene can be considered very similar in terms of their capacity to solvate NHPI derivatives such as **8d** and **9**.

[27] The observed behavior prevents any precise determination of the association constant pertaining to the HB adduct formation, which however can be estimated to be of the same order of magnitude of that observed in $CDCl_3$.

[28] In principle, this behaviour, that is the signal drift observed as the concentration is varied, could be also considered as due to the change of the solvent inherent dielectric constant due to the addition of increasing quantities of **9** or **8d**. In any case, whether this could be a valid consideration or not, this phenomenon does not weaken the validity of the proposed thesis relative to the formation of HB dimers and higher aggregates for **8d**.

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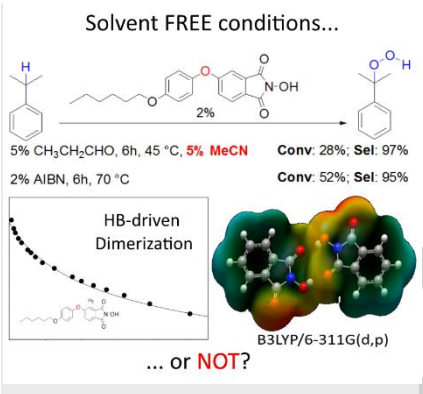
FULL PAPER

Novel lipophilic *N*-hydroxyphthalimides catalysts allowed firstly to conduct catalytic oxidation of neat cumene for the very first time, and secondly to discover the limits of solvent free conditions wherein hydrogen bond (HB) driven aggregation of the catalyst occurs.



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