KAPITEL 6 / *CHAPTER 6* [6]

THE POTENTIAL OF N-HYDROXYPHTHALIMIDE FOR THE LARGE-SCALE CH-OXIDATIONS

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Introduction

The CH-oxidations with molecular oxygen are among most promising industrial processes because allow to convert hydrocarbons to various useful chemicals, primarily to alcohols and carbonyls under environmentally-friendly conditions. Accordingly, the development of facile and efficient systems for aerobic oxidations under mild conditions attracts attention of many [1, 2] in order to replace classic inorganic oxidants such as manganese dioxide, [3] chromic, [4] nitric, [5, 6] sulfuric [7, 8] acids, "Periana-Catalytica" system, [9, 10] “biomimetic” oxidants like Gif or GoAgg type reagents [11, 12], iodine reagents [13, 14]. At the large scale these oxidations either are difficult to control or the utilization of hazardous agents result in a large amount of toxic waste. In contrast, oxygen is an ideal reagent because of its availability, low price, production of water as byproduct and therefore economic viability for large-scale oxidations. However, considering that the oxidation of organic compounds by ground state O_2 is a very slow process at room temperature there is a need to use a catalyst [15].

During recent decades, a convenient catalytic approaches were developed using *N*-hydroxyphthalimide (NHPI)[16], which was broadly applied for CH-functionalizations of organic substrates[17, 18]. It attracted a great attention because of its non-toxic nature, simple preparation, low price, and high activity towards different types of organic substrates [19], especially alkanes [20-22], alcohols [23] and alkyl aromatics [24]. NHPI and a number of its derivatives[25-28] catalyze the free-radical aerobic oxidations by participation in the hydrogen atom transfer (HAT) processes [29-31] through the formation of highly electrophilic phthalimido-*N*-oxyl radical (PINO), which subsequently abstracts hydrogen from a substrate RH as illustrated in Figure 1. Under the oxidative conditions thus formed carbon-centered radicals $R^{\bullet}$ effectively react with oxygen leading to oxygen-containing products [20].

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[6] ***Authors:*** *Zhuk Tatyana, Babkina Valeriia*

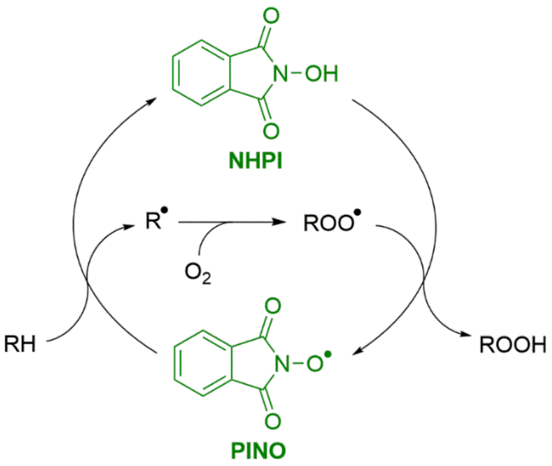


Figure 1. The mechanism of hydrocarbon oxidation in the presence of NHPI.

The reaction of intermediate peroxyl-radicals ROO$^•$ with NHPI propagates the formation of PINO and thus completing the catalytic cycle. High positional selectivities ordinate from remarkable electrophility of the PINO that maximizes the contribution of polar factors in HAT transition structures [32]. To initiate the formation of PINO [32] NHPI is often used together with various redox promoters such as hydroperoxides, Co(II) salts [21, 33], as well as Cu, Fe, Mn, Ni and other metal ions of variable valence [22, 34-41]. Some organic compounds, such as azo compounds, quinones, aldehydes also promote the reaction [29, 42-48].

The PINO abstracts hydrogen up to 20 times faster than the peroxyl-radicals ROO$^•$ that are involved in autocatalytic aerobic oxidations [16]. Such reactivity also can be explained by polar effects because of higher electrophilic character of PINO compared to the peroxyl radicals. At the same time, NHPI is a good hydrogen donor and is able to trap peroxyl-radicals before they undergo fast termination and, as a result, NHPI promotes the radical chain propagation more efficiently than observed in traditional aerobic oxidations. This is especially important, because such catalysis increases the selectivity of the process with respect to the target product as the by-products often form at the chain termination stage. All above factors lead to an increase in the oxidation rate with NHPI [16]. Here, we will mostly cover the aerobic oxidations of alkanes and alkyl aromatic hydrocarbons that are of great industrial importance and where NHPI-based catalysis have clear industrial perspectives.

6.1. Oxidations of alkanes and cycloalkanes

The CH-oxidations of saturated hydrocarbons by radicals is a promising methodology but require harsh reaction conditions which causes overreactions [9, 49] or utilization of toxic oxidants. Radical approaches based on HAT are in demand and promising because of their ability to activate inert C–H bonds under mild conditions relatively easily. This allows to introduce a greater variety of functional groups and increases tolerance to them. Moreover, sometimes it can enhance the reactivity compared to the methods based on traditional transition metal catalysis [50].

Due to a short lifetime of common oxygen-centered radicals, their efficiency in hydrocarbon oxidations varies and is most successful for moderately stable radicals [51-53]. Stable under ambient conditions 2,2,6,6-tetramethylpiperidine *N*-oxyl, commonly known as TEMPO, is an alternative NO-centered radical for aerobic oxidations [54]. However, the utilization of TEMPO is problematic because of its superior stability and therefore lesser reactivity than PINO. The difference in reactivity between TEMPO and PINO can be found, in turn, in the bond dissociation energy (BDE) of the O–H bond in the respective hydroxylamine derivatives where this value in NHPI is 369 [31, 55] (375) [56] kJ/mol, while only 292 kJ/mol in TEMPOH [57, 58]. Thus, based on these values, hydrogen abstraction by TEMPO will be highly endothermic and it can act as autoxidation inhibitor. On the contrary, hydrogen abstraction by PINO is thermoneutral or mildly exothermic, because NHPI has an O–H bond energy very close that in alkyl hydroperoxides (378 kJ/mol)[59]. Thus, the generation of the *N*-oxyl radicals such as PINO still needs the presence of radical initiators such as quinones, metal salts or peroxides [60]. Electrochemical way of PINO generation is also possible, but its decomposition under such conditions limits its applications[61].

Cycloalkanes as common petrochemical products are inexpensive starting materials. For example, cyclohexane (**1**) is the precursor of adipic acid (**3**) that is widely used for the preparation of a variety of polymers. The current process for the production of **3** consists of two steps [62]. At the first step **1** is oxidized by air to a mixture of cyclohexanone (**2**) and cyclohexanol (**4**), known as KA-oil followed by the oxidation with HNO_3. The main problem of this method is the environmental issues, which still require solution. The discovery that cycloalkanes can be efficiently oxidized under an oxygen atmosphere in the presence of NHPI provided an excellent alternative [16]. The process for the direct aerobic oxidation of **1** to **3** by using NHPI together with suitable metal salts as co-catalysts was under evaluation for further large-scale applications [63]. The oxidation of cyclic hydrocarbons in the presence of NHPI allows to carry the reaction at a considerably lower temperature and with high selectivity to desirable products [64, 65]. There is a small variety of solvents that can be used in oxidation reactions due to the limited solubility of NHPI [66] and where acetic acid (AcOH), acetonitrile, and benzonitrile are most common. For example, **2** and **3** were obtained with selectivities of 32 and 38%, respectively as the main products of the oxidation of **1** in AcOH at 100 °C in the NHPI/Co(II) system (Fig. 2). It should be noted that the selectivity of **2** in NHPI/Co(III) system in acetonitrile reaches 78% at 75 °C. In contrast, **3** was obtained with selectivity of 77%, as the main product of the reaction with NHPI/Mn(III) in acetic acid at 100 °C [20]. Thus, the type of the catalyst and the solvent allows to observe different reaction selectivity [22].

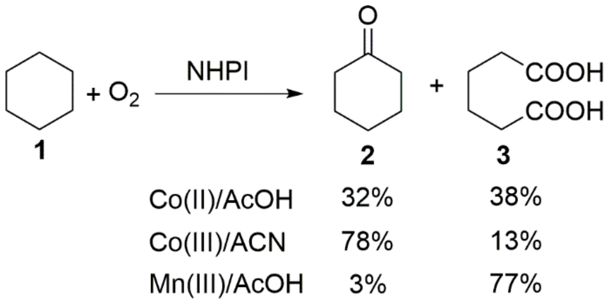


Figure 2. Direct aerobic oxidation of cyclohexane (1) in different systems.

Cyclooctane oxidation in the presence of NHPI/Co(III) gives a mixture of cyclooctanone, cyclooctane-1,4-dione and suberic acid with selectivities of 50%, 16% and 16%, respectively [20]. Simultaneous utilization of $Co(NO_3)_2$ and $Mn(NO_3)_2$ gives good results at lower temperatures [67, 68].

The generalized scheme of the oxidation of cycloalkanes in Co/Mn system is shown in Figure 3 with **1** as an example. The cobalt salt activates the molecular oxygen in the initiation phase that is especially effective and Mn(II) is needed for the cleavage of intermediate cyclohexanone, where Mn(III) forms from Mn(II) by oxidation with peroxyl radicals or by a redox reaction with Co(III). The key CC cleavage occurs through the formation of the α-keto radicals by oxidation of the enol followed by the reaction of α-keto radicals with oxygen and fragmentation of the cycle *en route* to **3** [67, 69].

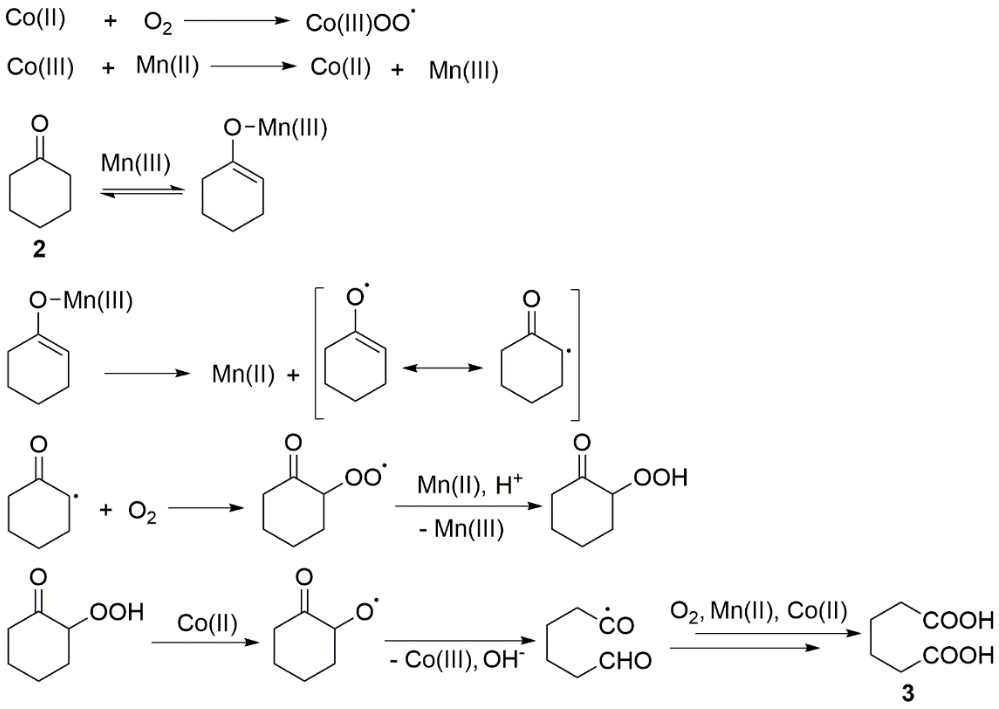


Figure 3. The mechanism of the oxidation of cyclohexanone (2) to adipic acid (3) catalyzed by $Co(NO_3)_2$ and $Mn(NO_3)_2$.

As proper solvent is needed to ensure a complete solubility of the polar organocatalyst Ishii's suggested to use a lipophilic derivative of NHPI (4-lauryloxycarbonyl-*N*-hydroxyphthalimide, **5**) in order to perform the reaction directly in cyclohexane (**1**) that gave good yield of cyclohexanone (**2**) (selectivity 61%) (Fig. 4) [29].

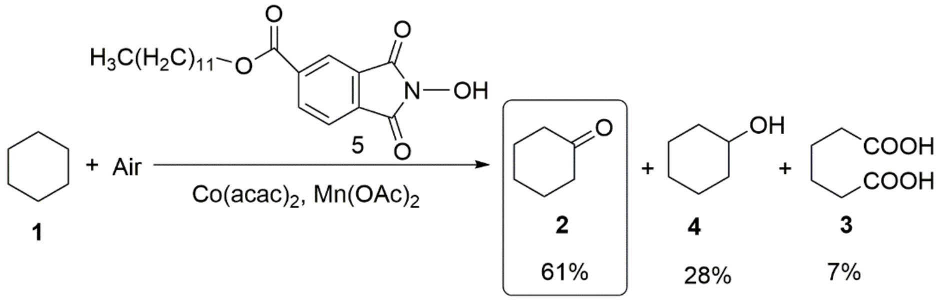
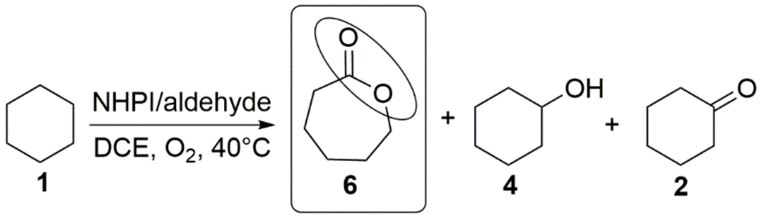


Figure 4. Aerobic oxidation of cyclohexane (1) in the presence of lipophilic NHPI derivative.

The one of the main problems associated with NHPI catalysis is instability of both NHPI and PINO at the temperatures above 80 °C where decomposition into phthalimide, phthalic anhydride [70, 71] or inactive trimers [72] is observed. Another problem is the decomposition of NHPI in polar solvents that affects the PINO reactivity and its decay rate. Accordingly, in the solvents with a high Gutmann donor numbers, which characterize the solvent nucleophilicity [73], the decay rate of PINO is low. This is due to the formation of complexes between PINO and solvent since the dipole moment of PINO and its electrophilicity are high [66, 71, 74, 75]. In this way, with an increase of the solvent donor number, the PINO solvation rises, that prevents its spontaneous decay [76].

Consequently, because of decomposition the large amounts (typically up to 10%) of NHPI are usually applied to increase conversions. However, when the NHPI amount is increased to a certain value depending on the solvent the conversion and selectivity are acutely lowered [33, 77, 78]. It should be noted that in any case NHPI is a sacrificial catalyst as it decomposes during the catalytic reaction and, in most cases, cannot be recovered or recycled [79].

ε-Caprolactone (**6**) is a monomer used in the production of highly specialized polymers and is produced at large scale as a precursor to caprolactam. Also, **6** is a monomer for the production of popular synthetic biodegradable polymer polycaprolactone [80-82]. Caprolactone is currently produced industrially by the Baeyer-Villiger oxidation of cyclohexanone with peracetic acid in two steps, i.e., the oxidation of cyclohexane (**1**) to cyclohexanone (**2**) followed by Baeyer-Villiger oxidation to **6** [83-87]. However, the direct oxidation of cyclohexane to ε-caprolactone was not achieved despite these two reactions separately are well-studied. An interesting property of aldehydes is their very high autoxidation rates with long propagation chains even at room temperature and atmospheric pressure. As a result aldehydes often are used in the co-oxidation processes [88]. It has been found that selective direct aerobic oxidation of cyclohexane (**1**) into **6** is possible with NHPI and aldehyde as the co-oxidative additive and promoter in dichloroethane (DCE). The results showed that the most effective promotors are 3-chloro-benzaldehyde (3-Cl-PhCHO), 4-fluoro-benzaldehyde (4-F-PhCHO), and benzaldehyde (PhCHO) (Fig. 5) [44].

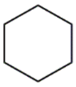
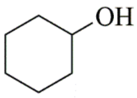
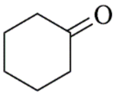
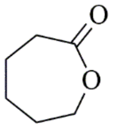
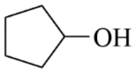
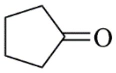
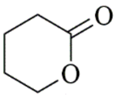
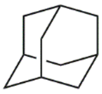
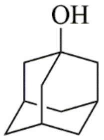
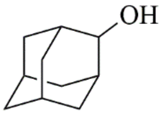
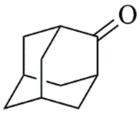
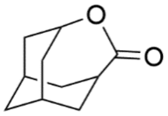


3-Cl-PhCHO	85%	2%	3%
4-F-PhCHO	80%	6%	7%
PhCHO	77%	6%	9%

Figure 5. The selective oxidation of cyclohexane (1) into ε-caprolactone (6).

The oxidation of other alkanes was carried out under the same conditions. As shown in the Table 1, cycloalkanes were predominantly converted to the corresponding lactones.

Table 1. NHPI/PhCHO-promoted aerobic oxidation of various alicycles[44].

Entry	Substrate	Products (Select., %)
1		 (6)  (9)  (77)
2		 (30)  (26)  (40)
3		 (89)  (2)  (2)  (5)

Suggested process has rather complex radical chain mechanism. The reaction is initiated by the autoxidation of aldehyde to form acyl radical, followed by formation of acylperoxyl radical, which oxidizes NHPI to PINO. In addition, the oxidation of aldehyde by PINO can also proceed and it happens much faster than the initial autoxidation. The acyl peroxyl radical species and PINO gave cyclohexane radical *via* HAT. Then cyclohexane radical reacts with acyl peroxyl radical to produce cyclohexanone and cyclohexanol, and then cyclohexanone is further oxidized to **6** under the same reaction conditions (Fig. 6) [44, 89].

The new metal-free direct aerobic oxidations of alkanes with NHPI achieved in highly polar trifluoroacetic acid as a media and HNO_3 or $NaNO_2$ as promoters [90] where adipic acid was obtained with up to 90% selectivities and 45% preparative yields (Fig. 7). The $NHPI/HNO_3/TFA/O_2$ system is quite convenient as TFA and unreacted starting material are easily recovered from the reaction mixture by distillation [90].

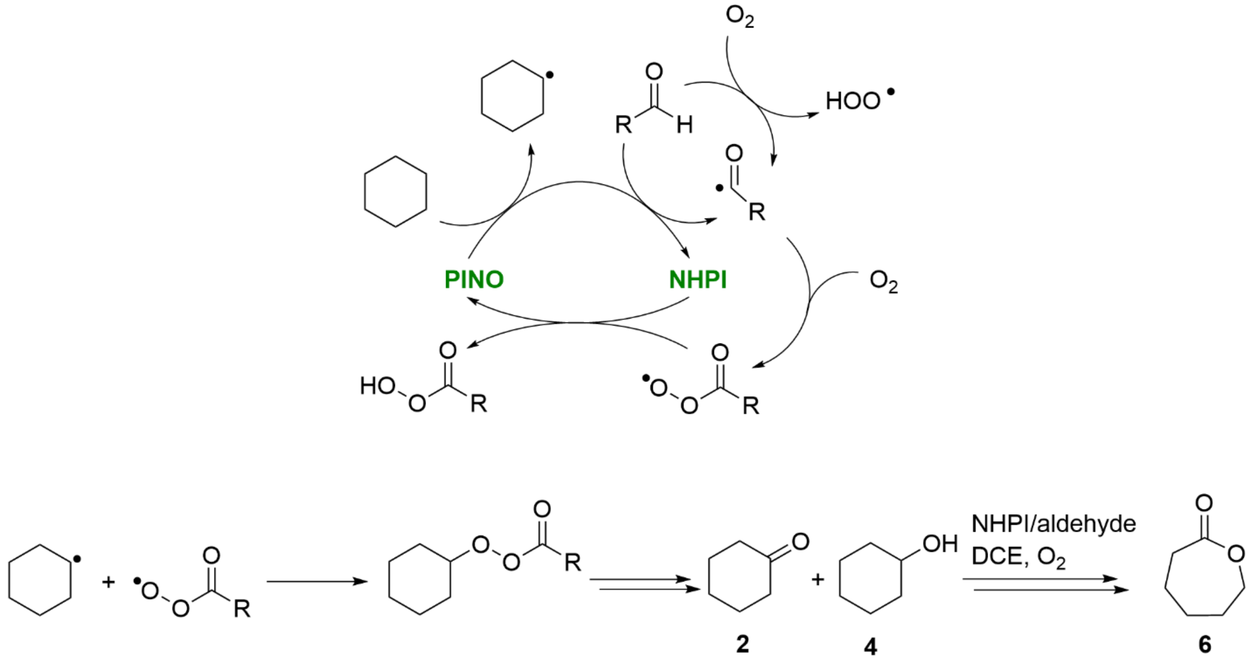


Figure 6. The mechanism of aerobic oxidation of cyclohexane (1) into ε-caprolactone (6) by NHPI/aldehyde/O_2.

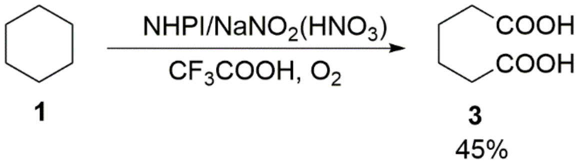


Figure 7. The aerobic oxidation of cyclohexane by NHPI/TFA/O_2/$NaNO_2$(HNO_3).

The other important issue is the oxidations of lower alkanes such as methane, ethane, and isobutene (**7**). It should be noted that although saturated hydrocarbons easily react with radicals, the selectivities of their conversion are rather low [91]. Many different oxygen radicals are used in the radical transformations of alkanes. For example, the hydroxyl radicals, which are often used in such conversions, are extremely reactive and selectivities of the C–H substitutions are low [91]. NHPI provides a solution as the aerobic oxidation of isobutane (**7**) in the presence of NHPI/$Co(OAc)_2$ system in benzonitrile gives *tert*-butyl alcohol (**8**) in high yield (81%) along with acetone (**9**) (14%). However, under the same conditions 2-methylbutane (**10**) predominantly give acetone and acetic acid *via* the C–C bond cleavage (Fig. 8) [16].

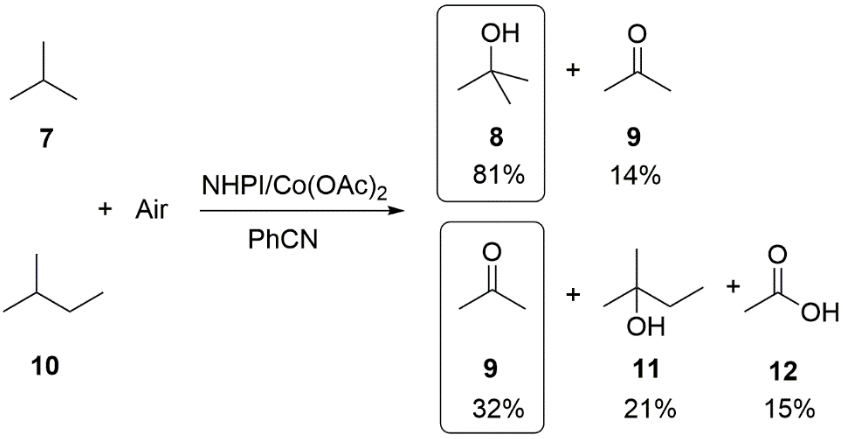


Figure 8. The oxidation of isobutane (7) and 2-methylbutane (10) by air in the presence of NHPI.

6.2. Oxidation of polycyclic compounds

Diamondoids are useful models in the development of hydrocarbon oxidation methods as eliminations and fragmentations in most cases are avoided and the positional selectivity, i.e., the 3°/2°-substitutional ratios are characteristic [92]. Additionally, the diamondoid cages are quite sensitive to polar effects where the polarization of the cage through the tertiary CH positions is much more favorable than through the secondary positions [93]. Observed sensitivity makes diamondoids especially useful model hydrocarbons in studying the reactivity towards such highly electrophilic radical as PINO [20, 44, 90, 94] and NO_3-radical [95, 96]. The importance of oxidation of adamantane (**13**) is superior because its derivatives found many applications in medicine [97-100] and material sciences [101, 102]. The 2°CH bonds in alkanes are usually stronger than 3°CH that is not true for adamantane where the BDEs are similar [103]. As a result the radical CH substitutions in diamondoids usually are not very selective as the mixture of 3°/2°-products forms [92]. A large variety of radicals such as halogen [104, 105], halosubstituted alkyl [106-108], peroxyl [109, 110], alkoxyl [106] have been tested on adamantane and high positional selectivities were never been achieved. The utilization of NHPI as a source of electrophilic PINO in the oxidation of **13** is promising as it yields minimal amounts of secondary substitution products[91]. The oxidation of **13** was carried out in the NHPI/Co(acac)$_2$ system under O_2 atmosphere and gave only trace amounts of ketone **15**, but alcohols **14** and **16** were dominant (Fig. 9) [111].

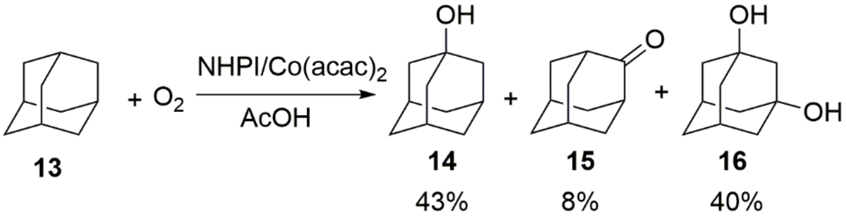


Figure 9. The oxidation of adamantane 13 in the presence of NHPI.

The oxidation of 1-hydroxyadamantane (**14**) in NHPI/Co(acac)$_2$ system exclusively gives the tertiary substituted products **16** and **17** (Fig.10) with selectivities approaching the respective reactions with charged electrophiles [112-115] and dioxiranes [116-118]. Recent attention to polysubstituted adamantanes is determined by their applications as pyramidal building blocks for the construction of 3D rigid scaffolds, in particular for biomolecular modeling [119-121], metal-organic frameworks (MOFs) [122, 123], and polymers [124-129]. Furthermore, adamantine polyhydroxyl derivatives are of especial interest in view of functional materials design [130].

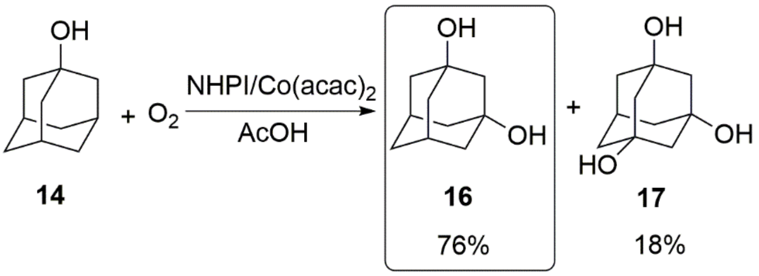


Figure 10. The oxidation of 1-hydroxyadamantane (14) in the presence of NHPI

Oxidation of **13** is also possible under the metal-free conditions. For instance, the oxidation in the presence of a catalytic amounts of NHPI at 80 °C and tetra-*n*-butylammonium bromide (TBAB) in PhCF$_3$ with small amount of H$_2$O gave **14** and **16** in 60% and 23% selectivities under satisfactory conversions of starting material (up to 73%) (Fig. 11) [94]. It should be noted that the reaction is very sensitive to water content as no acceleration by TBAB was observed in the absence of H$_2$O [94]. It is assumed that the TBAB acts as a surfactant to generate reversed micelles in a mixed solvent of PhCF$_3$ and H$_2$O and additionally promotes the decomposition of the resulting hydroperoxides to alkoxyl radicals [131-133].

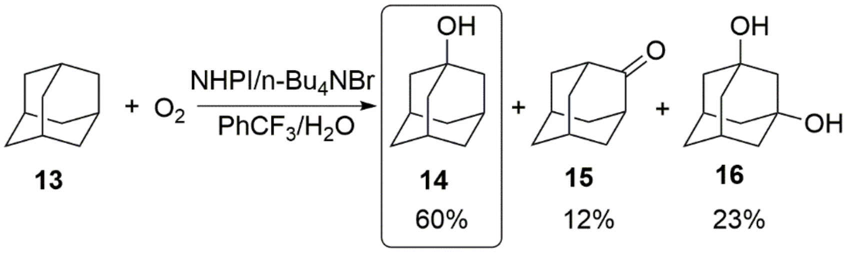


Figure 11. The oxidation of adamantane (13) in the presence of NHPI under metal-free conditions.

With strong oxidants, such as nitric acid or cerium (IV) ammonium nitrate (CAN), the products resulting from nucleophilic capture of carbocations formed from the oxidation of intermediate alkyl radicals were found. For example, adamantane (**13**) has been successfully converted into the corresponding amide **17** in NHPI/CAN system in the presence of ethyl cyanide (EtCN) (Fig. 12) [134].

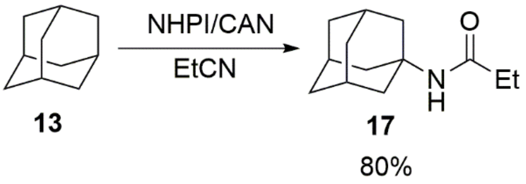


Figure 12. The amidation of adamantane (13) in the NHPI/CAN system.

The mechanism of this reaction is shown in Figure 13. At first, NHPI reacts with CAN to form PINO, which abstracts a hydrogen atom from adamantane to generate the adamantyl radical, which undergoes the one-electron oxidation by Ce(IV) to form respective carbocation. The latter is trapped by EtCN, followed by reaction with H_2O to produce amide **17** after hydrolysis[134].

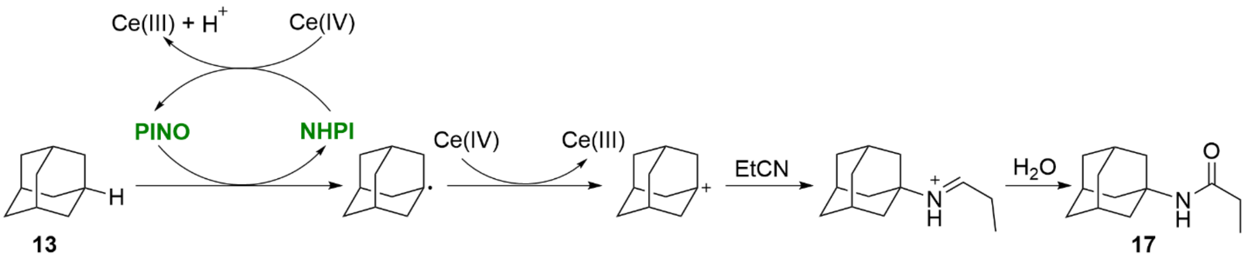


Figure 13. The mechanism of reaction in the presence of NHPI/CAN system.

Cyano-group is a key function in a variety of natural products and pharmaceuticals [135, 136]. Nitriles can easily be converted to carboxylic acids, esters, amines, or amides [137]. Furthermore, they can be used in [3+2] cycloadditions to form heterocycles such as tetrazoles and oxadiazolines [138, 139]. Direct cyanation of **13** is also possible with NHPI, CAN, *p*-toluenesulfonyl cyanide (TsCN) and Li_2CO_3 in DCE at 75 °C with 77% selectivity of **18** (Fig. 14). TsCN serves as the electrophilic cyanide source [137]. This method also allows to synthesize efficiently a series of substituted cyano-adamantanes and tolerates many functional groups.

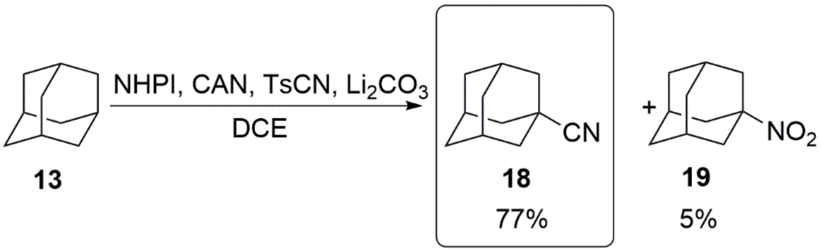


Figure 14. The cyanation of adamantane (13) in the presence of NHPI and TsCN.

The radical mechanism of the direct cyanation (Fig. 15) consist of three steps. Firstly, the formation of PINO from its precursor NHPI followed by HAT takes place. Thus formed adamantyl radical is trapped by TsCN to give a desired product. It should be noted that the use of CAN also can lead to the formation of considerable amounts of 1-nitroadamantane (**19**). This by-product is formed by reduction of Ce(IV) → Ce(III), thus generating HNO_3, which itself is able to generate PINO releasing NO_2-radical that recombines with the adamantyl radical. The use of carbonate such as Li_2CO_3 inhibits the formation of **19** by eliminating HNO_3 [137].

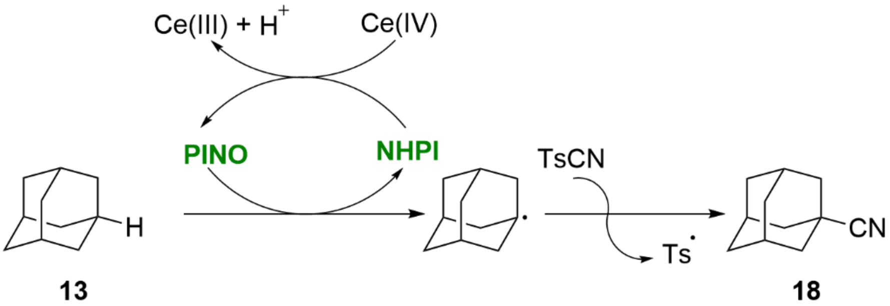


Figure 15. The mechanism of cyanation of adamantane (13) in the presence of NHPI and TsCN.

The new approach to metal-free direct aerobic oxidations of alkanes in trifluoroacetic acid with NHPI as catalyst and HNO_3 as promoter has also been used for adamantane (**13**) and diamantane (**20**) to give, respectively, 1-hydroxyadamantane

(**14**) and 1-hydroxydiamantane (**21**) with up to 90% selectivities (Fig. 16) [90].

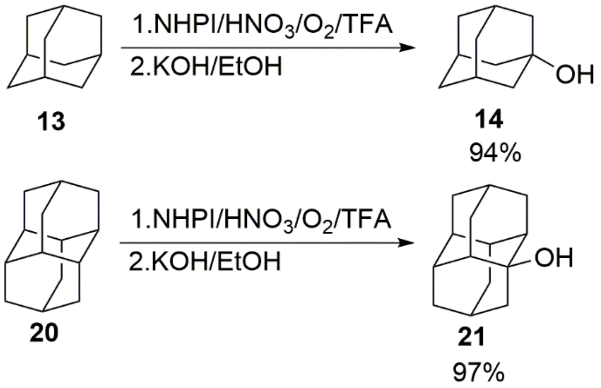


Figure 16. The aerobic oxidation of 13 and 20 with NHPI/TFA/O_2/HNO_3.

It should be noted that this method has also been used for 3-oxadiamantane (**22**), which generally is low reactive towards electrophiles [140]. Notable, the oxidation of **22** occurs only in the presence of NHPI in TFA allowing to prepare and isolate 1-hydroxy-3-oxadiamantane (**23**), 6-hydroxy-3-oxadiamantane (**24**), 11-hydroxy-3-oxadiamantane (**25**), 9-hydroxy-3-oxadiamantane (**26**) and ketone (**27**), which is difficult to make otherwise (Fig. 17). Note, that **26** is beneficial for surface depositions because the apical diamondoid derivatives are characterized by superior surface affinities [141].

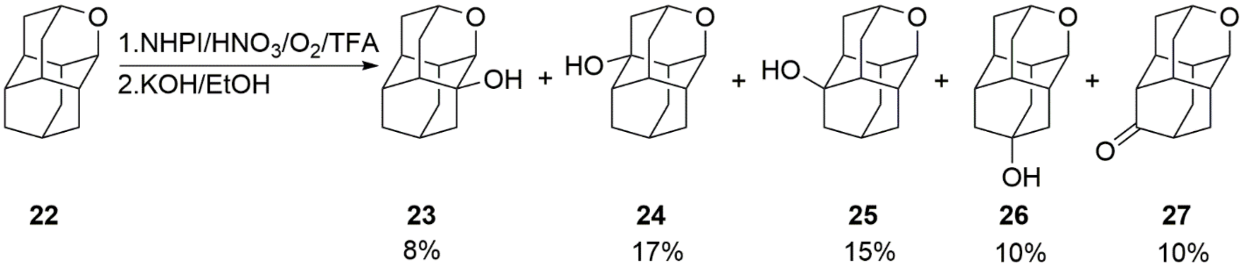


Figure 17. The aerobic oxidation of 22 with NHPI/TFA/O_2/HNO_3.

6.3. Oxidation of alkylaromatic compounds

Aerobic oxidations of cumene (**28**), toluene (**32**), *p*-xylene (**35**) are among key processes in manufacturing of, respectively, cumene hydroperoxide, benzoic and terephthalic acids. The use of NHPI for catalytic oxidations may result in a considerable improvement in energy consumption and reduction of environmental damages relative to the processes that industry currently uses [16].

The cumene hydroperoxide is used for the synthesis of phenol via the Hock process and as an oxidizing agent of propylene in Sumitomo PO-only process [142]. The autoxidation of **28** at temperatures lower than 100 °C is too slow and upon increasing the temperature, the conversion increases but the selectivity decreases [143]. The new catalytic systems are developed to produce the target hydroperoxides with higher selectivity and conversion at lower temperatures [143]. The one example is the use of NHPI which allows to conduct the reactions at temperatures lower than 100 °C, namely 75 °C [144] or even at room temperature [29]. The aerobic oxidation of cumene in NHPI/aldehyde system at 25 °C allows to obtain the corresponding hydroperoxide (**29**) with 81% selectivity (Fig. 18) [143]. In this case, aldehyde initiates the radical chain, generating PINO. Moreover, it has been found that high amounts of aldehyde adversely affect the selectivity of the process where high selectivities were achieved with a decrease in the amount of aldehyde up to 10% molar ratio with respect to the cumene [143].

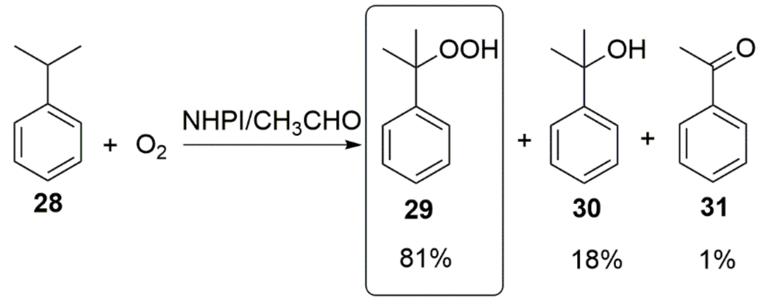
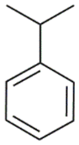
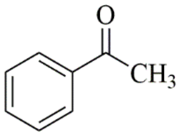
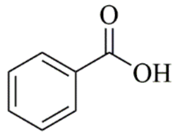
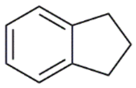
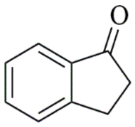
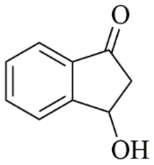
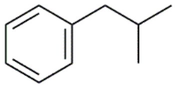
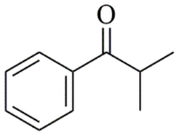
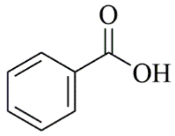
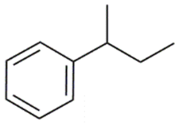
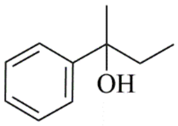
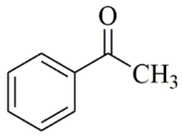
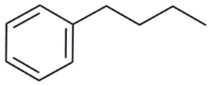
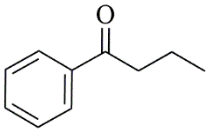
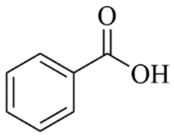


Figure 18. Aerobic oxidation of cumene (28) utilizing NHPI/aldehyde system.

The new approach to metal-free oxidation of benzylic positions by molecular O_2 is based on NHPI covalently anchored to the surface of diamond nanoparticles (DH) as a selective heterogeneous catalyst [42]. These particles were pre-functionalized using chemical and thermal treatments. The most important advantage of DH is the inertness of its surface to radicals. The aerobic oxidation of benzylic positions and cyclic alkenes in the NHPI/DH system do not require any transition metals as the surface acts as a solid radical initiator [42]. As seen from Table 2, excellent to good selectivities were observed in most cases.

The oxidation of alkylaromatics such as ethylbenzene, isobutylbenzene, and indane were carried out with O_2 and NHPI/PhCHO-system were ketones and alcohols form (Table 3) [44]. It was found that promotors such as benzaldehyde and its substituted derivatives (4-methylbenzaldehyde, 4-tert-butylbenzaldehyde, 4-flurobenzaldehyde, 4-chloro-benzaldehyde and 3-chlorobenzaldehyde) were more

Table 2. Aerobic oxidation of benzylic positions in the presence NHPI/DH at 140ºC[42].

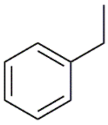
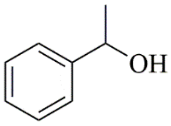
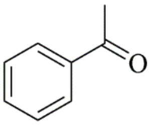
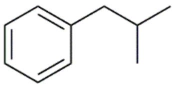
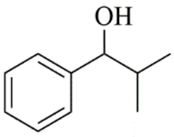
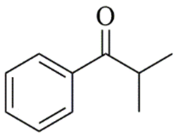
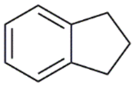
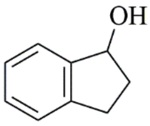
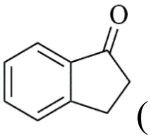
Substrate	Time (h)	Main products (selectivities, %)
	24	 (95)  (5)
	5	 (76)  (17)
	24	 (64)  (31)
	72	 (80)  (6)
	24	 (66)  (29)

efficient than aliphatic aldehydes such as acetaldehyde, heptanal and isobutyraldehyde. However, because of the lower price of these aliphatic aldehydes, they still remain the preferred choice for industry [44, 89].

The aerobic oxidation of toluene (**32**) was conducted in NHPI/Co(OAc)$_2$ system at room temperature and atmospheric pressure under O$_2$ with 96% selectivity to benzoic acid (**33**) (Fig. 19) [145].

There is the long-standing problem of the selectivity of producing benzaldehydes from toluene in the large-scale synthesis. The solution to this issue can be based on the combination NHPI/Co(OAc)$_2$ system with fluorinated solvents [146, 147]. The aerobic oxidation of toluene (**32**) in 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) at room temperature allows to obtain benzaldehyde with excellent selectivity (90%) and with 91% conversation (Fig. 20) [147].

Table 3. NHPI/PhCHO-promoted aerobic oxidation of various substrates[44].

Entry	Substrate	Products (Selectivities, %)	
1	n-C_8H_{18}	Octanol (40)	Octanone (56)
2		 (23)	 (68)
3		 (23)	 (68)
4		 (20)	 (72)

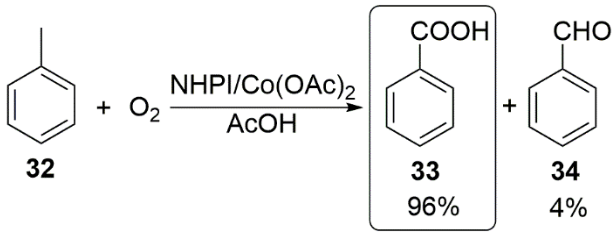


Figure 19. Aerobic oxidation of toluene (32) using NHPI/ Co(acac)$_2$.

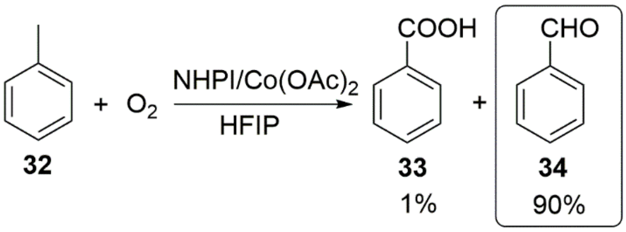
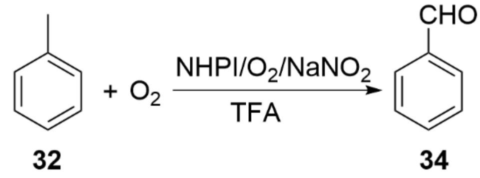


Figure 20. The aerobic oxidation of 32 by NHPI/Co(OAc)$_2$ in HFIP.

The NHPI-catalyzed and $NaNO_2$-promoted aerobic metal-free oxidations of toluene (**32**) in trifluoroacetic acid (TFA) gave benzaldehyde (**44**) in 35–38% preparative yield and with unprecedentedly high selectivity almost completely avoiding over-oxidations (98% conversion of **32**) (Fig. 21) [90].



32 **34**
38%

Figure 21. The aerobic oxidation of 32 by NHPI/TFA/O_2/HNO_3.

Another metal-free approach is based on the immobilization of NHPI on functionalized silica-coated magnetite nanoparticles through amide bond. This is novel-synthesized magnetic heterogeneous catalyst exhibited considerable activity in oxidative reactions of benzyl alcohols and hydrocarbons. Using 2 mmol 30% H_2O_2, the reaction gave benzaldehyde with 97% selectivity after 3 h at 80 °C (Fig. 22) [19].

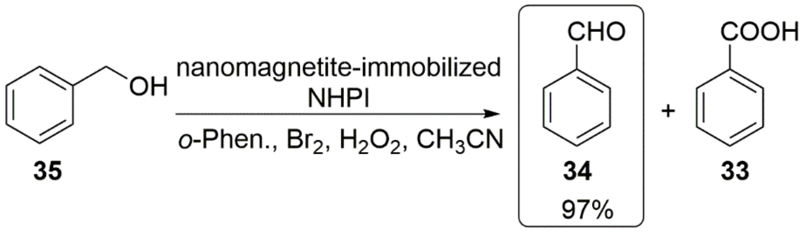
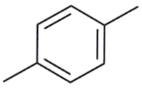
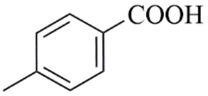
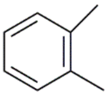
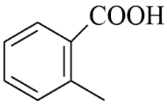
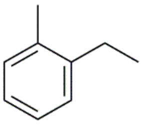
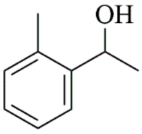
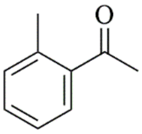
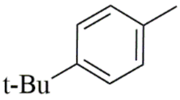
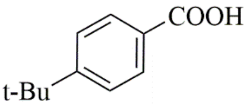
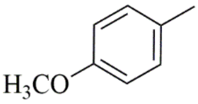
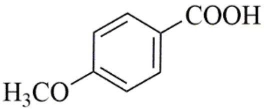
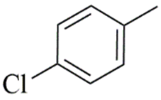
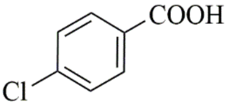
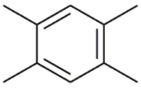
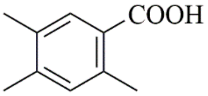


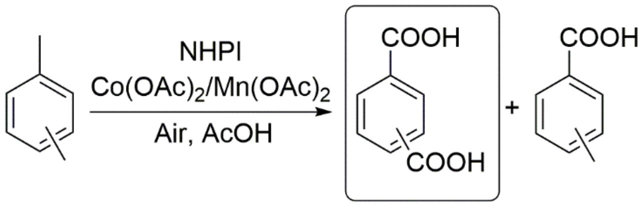
Figure 22. Aerobic oxidation of benzyl alcohol (35) using nanomagnetite-immobilizes NHPI.

Corresponding carbonyl-containing products were obtained from the starting materials with high yields. Furthermore, one of the most important advantages of this type of heterogeneous catalysts is simple and fast separation and recovery procedure using an external magnet [19].

In the case of aerobic oxidation of *p*-xylene with NHPI/$Co(OAc)_2$ only one methyl group is oxidized (Table 4). Terephthalic acid (**39**) is one of the largest bulk chemicals used in the production of polyester for clothing and plastics [148]. The production of **39** from *p*-xylene (**36**) with NHPI is possible only under harsh conditions at higher temperatures in a combination with Co and Mn salts as cocatalysts (Fig. 23), though, the oxidation of *p*-toluic acid requires milder condition. Thus, selective oxidation of only one methyl group in *p*-xylene is more profitable with NHPI.

Table 4. Aerobic oxidation of various alkylbenzenes at room temperature in the presence NHPI/$Co(OAc)_2$ [16].

Substrate	Time (h)	Products (yield, %)
	20	 (85)
	20	 (83)
	20	 (21)  (37)
	20	 (80)
	6	 (67)
	20	
	12	 (93)



36 para **39,** 84% **40,** 4%
37 meta **41,** 86% **42,** 7%
38 ortho **43,** 73% **44,** 6%

Figure 23. Aerobic oxidation of xylenes using NHPI and a combination of $Mn(OAc)_2$ and $Co(OAc)_2$.

Conclusion

N-Hydroxyphthalimide (NHPI) is an effective organocatalyst for the oxidation of C–H bonds of hydrocarbons due to ability to generate the highly elechtrophilic phthalimido-*N*-oxyl (PINO) radical. Typically, the presence of transitional-metal complexes as co-catalysts is necessary, however the metal-free approaches is currently underway as the principles of sustainable development requires the observation of the “green” chemistry standards. Based on numerous established approaches where PINO radical acts as a key reactant it is obviously clear that the NHPI is a highly promising catalyst for hydrocarbon functionalization in industrial as well as preparative levels. In particular, the utilization of various aldehydes in the metal-free aerobic NHPI-catalyzed oxidation of cycloalkanes and alkylaromatic compounds is very promising and currently studied intensively. In addition, the combination of highly polar solvents and the nitrogen-based oxidants as the initiators is effective for the oxidations of saturated hydrocarbons as well as alkylaromatics.