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Review

Challenges and opportunities for N-hydroxyphthalimide supported over heterogeneous solids for aerobic oxidations

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ABSTRACT

Organocatalysis, in combination with, or as an alternative to the use of metals, is attracting increasing interest as a sustainable route to promote selective transformations. In this context, *N*-hydroxyphthalimide (NHPI) has found ample application as an effective organocatalyst capable to promote the aerobic oxidation of a wide range of organic substrates, including saturated and unsaturated hydrocarbons, alcohols, amines and sulphides among others. However, most of these transformations required the use of NHPI dissolved in solution, with consequent limits in the scale-up of the process. Leaving aside the reviews of NHPI as organocatalyst in homogeneous phase, the present review describes the strategies reported to support or anchor NHPI on a wide range of insoluble solids, thus converting this homogeneous organocatalyst into a heterogeneous system, with the consequent advantages related to the ease of separation and recovery of the catalyst from the reaction medium, its recyclability and the possibility to develop continuous flow reactions. After a brief introductory section, a detailed description of the catalytic mechanism is here presented, also providing a comparison between NHPI and 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) radical, and by highlighting the main challenges associated to NHPI heterogenization. The critical description of the heterogeneous solutions is organized according to the nature of the support, focusing on metal–organic frameworks (MOFs), organic polymers, carbon-based materials, and inorganic supports, while the growing use of NHPI-containing photocatalysts is presented separately. In the final section, we outline the main achievements on the use of NHPI heterogeneous catalysis and provide our views for future developments in the area.

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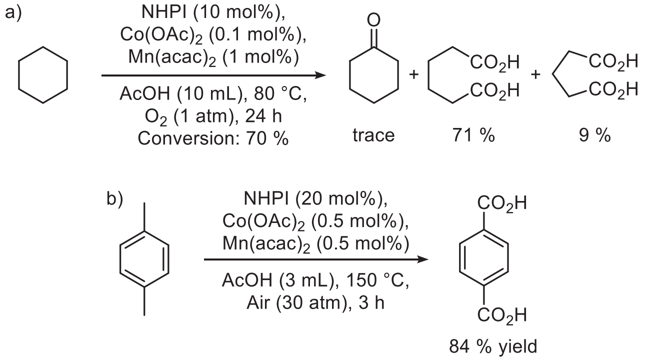
1. Introduction

N-hydroxyphthalimide (NHPI) is an organocatalyst which is attracting a growing interest in the field of C-H bond activation [1]. Initially reported by Grochowsky in 1977 [2] and subsequently studied by Masui [3–7], NHPI proved to be effective in mediating a wide range of free-radical transformations via hydrogen atom transfer (HAT) processes. Despite a few works reporting its use for the formation of carbon–carbon, carbon–nitrogen, and carbon-silicon bonds, NHPI has found its main application in the promotion of aerobic oxidation reactions [8]. A fundamental contribution to this field was made by Ishii and co-workers, who first reported the use of NHPI for promoting the aerobic oxidation of alcohols and hydrocarbons to the corresponding carbonylic and/or carboxylic derivatives [9]. Starting from their pioneering work, in the last decades, the interest in NHPI has grown considerably not only in the academy, but also in the industry, with the development of two pilot plants for the conversion of cyclohexane to adipic acid and of *p*-xylene to terephthalic acid (Scheme 1) [10].

As for most organocatalysts, the literature concerning NHPI mainly refers to its application under homogeneous conditions. However, due to the high lipophilic character of substrates such as hydrocarbons, polar co-solvents (*e.g.* acetonitrile, benzonitrile, acetic acid) are usually necessary for the complete solubilization of the highly polar NHPI molecule [11]. Nevertheless, the use of toxic and hazardous media entails both ecological and economical drawbacks.

For this reason, researchers working on this topic shifted their attention toward greener catalytic systems for the development of NHPI-based solvent-free processes. The most common adopted strategies for the solubilization of NHPI into apolar hydrocarbons are: i) the derivatization of the NHPI unit to increase its lipophilic character [12–15]; ii) the inclusion of NHPI into micelles or aggregates [16,17]; iii) the use of polar additives in the reaction mixture [18,19].



Scheme 1. Ishii's processes for the production of a) adipic acid and b) terephthalic acid, through the NHPI-promoted oxidation of hydrocarbons.

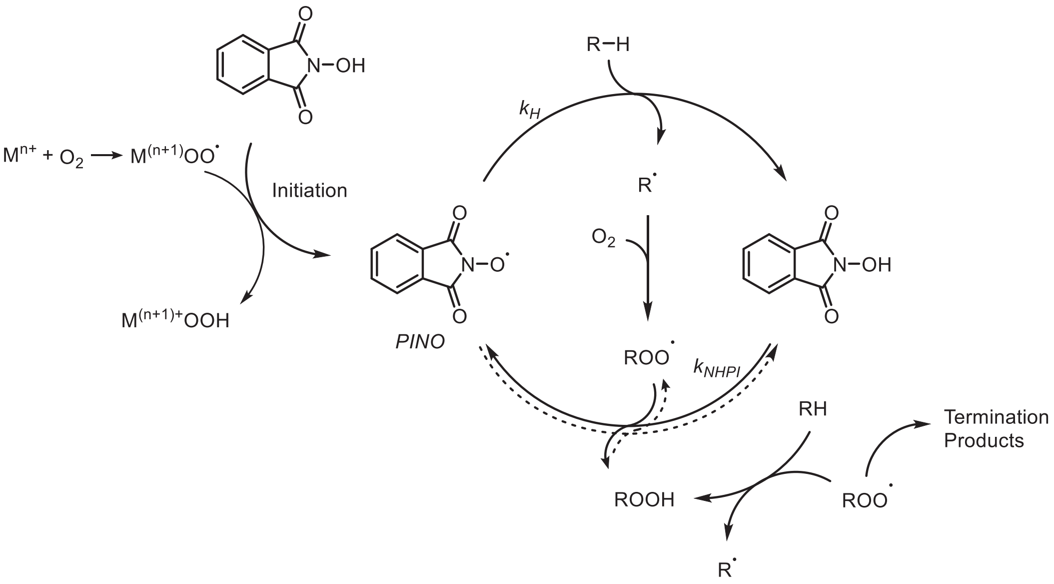
Despite these works represent a remarkable step forward in the design of increasingly sustainable NHPI-based processes, they still suffer from the major limitations arising from working under homogeneous conditions such as the recovery, the purification, and the reuse of the catalyst.

After a detailed description of the NHPI-mediated catalytic mechanism (Section 2), also providing a comparison between NHPI and 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) radical (Section 3), and highlighting the main challenges associated to NHPI heterogenization (Section 4), the present review focusses on the various strategies and supports which have been developed to move from NHPI-based homogeneous oxidation catalysis to heterogeneous solutions (Section 5). Through a critical analysis of the literature, the goal of the authors is to trace useful guidelines for the development of new NHPI-based heterogeneous catalysts. For the sake of clarity, this section has been organized as a function of the material used as NHPI support. More specifically, the list includes metal–organic frameworks (MOFs), organic polymers, silicas, carbon-based materials, zeolites, and clays. Furthermore, we have included two additional sections, one describing the use of heterogeneous catalysts, such as hydrotalcites, metal oxides, and polyoxometalates (POMs), in combination with NHPI (Section 6), and one reviewing the use of NHPI-based photocatalysts (Section 7). In each of these sections, the general structure of each support is briefly described, highlighting its advantages and limitations for the development of active and stable heterogeneous catalysts. After the description of the state of the art of heterogenized NHPI on different supports, a comparison of the most active heterogeneous solutions is provided. Special emphasis has been placed on highlighting both the strengths and weaknesses of each catalytic system, with the perspective of possible industrial processes development. Finally, the conclusion and outlook section (Section 8) summarizes the main achievements obtained in the field together with future directions for further development.

Even if the use of NHPI in homogeneous as well as in heterogeneous media was partly reviewed for oxidation reactions in 2021 [20], to the best of our knowledge this is the first exclusive review focused on summarizing the various strategies used to covalently anchor NHPI on solid supports and to provide a far more general view on the overall performance of NHPI-based heterogeneous solids as catalysts for oxidation reactions.

2. Reaction mechanism

Transition metal salts play a unique role in promoting autooxidation reactions [21]. Their use as cocatalysts in NHPI-mediated oxidations has been widely investigated [22]. The commonly accepted catalytic cycle for NHPI-mediated aerobic oxidation reactions in solution is illustrated in Scheme 2 [23,24]. The role of transition metals is to favor phthalimide-N-oxyl (PINO) generation from NHPI in the initiation step of the mechanism. Metal ions can bind molecular oxygen and form a metal-peroxyl radical which



Scheme 2. Generally accepted mechanism for the NHPI-mediated aerobic oxidation of C-H bonds.

then reacts with NHPI to efficiently generate the PINO radical. After that, PINO radical abstracts a hydrogen atom from the target substrate forming a carbon-centered radical and regenerating NHPI. The carbon radical reacts with molecular oxygen at a near diffusion rate, yielding the corresponding peroxyl radical. This is quickly trapped by NHPI to give a hydroperoxide molecule and to close the catalytic cycle. The superior performance of the NHPI/PINO system over the uncatalyzed autoxidation process relies on the high efficiency of NHPI as a hydrogen atom donor and that of PINO as a hydrogen atom acceptor.

Kinetic studies revealed that the HAT process from the target substrate to PINO (k_H) is from 20 to 200 times faster than that promoted by a peroxyl radical, thanks to a strong polar effect by which the transition state is stabilized. Moreover, the rate in the trapping of the peroxyl radical by NHPI (k_{NHPI}) is 4 orders of magnitude higher than that promoted by another substrate molecule [24]. Therefore, the introduction of NHPI allows for the prolongation of the propagation chain and the prevention of early termination reactions compared to the non-catalyzed autoxidation. For this reason, when NHPI is used alone high selectivity in hydroperoxides is usually observed.

In NHPI-mediated oxidation reactions, cobalt cocatalysts are most usually employed as they display higher oxophilicity compared to other transition metals, so that they bind molecular oxygen with higher efficiency [25]. Nonetheless, iron, copper, and manganese species are also widely used.

In addition to that, metal salts are well-known to promote the decomposition of hydroperoxides to give alkoxyl or peroxyl radicals (eqs. (1) and (2).

$$M^{n+} + ROOH \rightarrow M^{(n+1)+} + HO^- + RO^\cdot \quad (1)$$

$$M^{n+} + ROOH \rightarrow M^{(n-1)+} + HO^- + ROO^\cdot \quad (2)$$

Alkoxyl radicals can in turn abstract a hydrogen atom from a substrate molecule (eq. 3) or undergo a β-scission reaction (eq. 4), yielding an alcohol or a carbonyl derivative, respectively.

$$RO^\cdot + H - R \rightarrow ROH + R^\cdot \quad (3)$$

$$R_1R_2R_3CO^\cdot \rightarrow R_1R_2C = O + R_3^\cdot \quad (4)$$

Hence, transition metal salts are usually added when overoxidation products are targeted (*viz.* alcohols, aldehydes, ketones, and carboxylic acids) [26].

It should be emphasized that all the processes just described take place properly when both the substrate and the catalyst are in solution. Despite the lack of specific mechanistic insights, it can be assumed that the behavior of NHPI in heterogeneous conditions differs from that in solution, as typically observed for other radicals on surfaces or within reaction cavities. Specifically, radicals are much less mobile and diffuse much slower due to the interaction with solid surfaces or confinement.

In the case of anchored or strongly supported systems, it can even be assumed that NHPI is immobilized. Under these conditions, the chain length of the propagation steps of the radical reaction mechanism becomes comparatively much shorter than in homogeneous solution, due to the restricted diffusion of reagents and NHPI. Eventually, the chain length can be limited to only few products molecules formation, limiting the effect of the catalyst, and implying that the formation of almost every product molecule would require its own activation step. This short chain mechanism can be easily brought on experimentally by removing the solid containing NHPI and allowing the reaction to progress in the absence of it. What is frequently observed in heterogenized NHPI is that the reaction stops immediately very soon after NHPI removal, thus proving the need of having NHPI "available" for the entire course of the reaction.

Clearly, mechanistic studies are very informative regarding the chain length and the degree of confinement of the radical reaction inside the support pores.

3. Comparison between NHPI and TEMPO catalysts.

To deeply understand the challenges related to the design of efficient heterogeneous NHPI-based catalysts an insight into the catalytic mechanism is necessary.

The hydrogen abstracting/donating properties of PINO and *N*-oxyl radicals, in general, strongly depend on their bond dissociation enthalpies (BDEs), defined as the difference between the energies of an N-oxyl and the corresponding *N*-hydroxy forms. Indeed, the homolytic cleavage of a C-H bond from the substrate proceeds

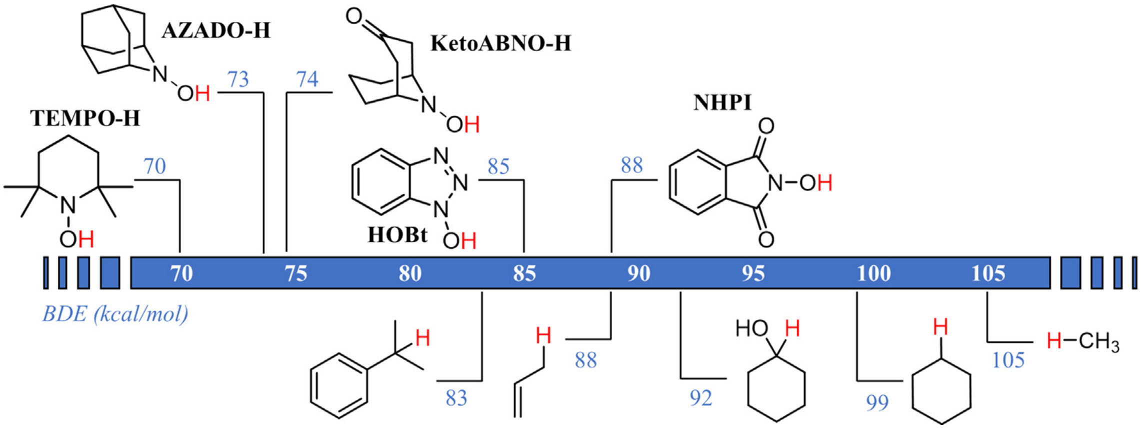


Fig. 1. BDE of NO-H and C-H bonds for a selected library of N-hydroxy species and hydrocarbons.
Abbreviations: TEMPO-H: N-hydroxy-2,2,6,6-tetramethylpiperidine; AZADO-H: N-hydroxy azaadamantane; KetoABNO-H: N-hydroxy azaadamantanone; HOBt: N-hydroxybenzotriazole.

at an acceptable rate only if its BDE is lower, or at least comparable, to that of the *N*-oxyl species employed. Fig. 1 summarizes the BDEs of a selected list of substrates in comparison to that of N-hydroxy compounds [27–29].

Among the reported *N*-hydroxy compounds, NHPI possesses the highest BDE of the NO-H, whose experimental value is 88.1 kcal/mol. This value is about 15–20 kcal/mol higher than that observed for aminoxyl radicals such as the TEMPO and the 2-azaadamantane-N-oxyl (AZADO). Pedulli *et al.* demonstrated that this difference is ascribable to the conjugation of the two carbonyl groups to the NO-H bond in NHPI [24]. This conjugation with carbonyl groups stabilizes the neutral form and destabilizes the radical form of NHPI, resulting in a redistribution of the electron density of the NO-H moiety. The overall result is an increase in the BDE which makes the hydrogen atom abstraction by PINO more favorable than that by TEMPO for enthalpic reasons, allowing activation of a wider variety of organic substrates with NHPI than with TEMPO.

Although considering the BDE alone is not sufficient to fully rationalize the reactivity of an *N*-oxyl radical, that still represents an essential tool for understanding its behavior. For example, Li *et al.* reported a computational study on the electrocatalytic oxidation of benzyl alcohol promoted by a series of *N*-oxyl radicals in which a correlation between the mechanism involved in the reaction and the BDE of the organocatalyst was established [30]. The authors found that for *N*-oxyl species having a BDE smaller than 74 kcal/mol the reaction likely proceeds through an ionic mechanism, whereas a radical mechanism is involved for those having a BDE larger than 79 kcal/mol. *N*-oxyl radicals with BDE in the range of 74 and 79 kcal/mol might be able to react through both mechanisms. Furthermore, these differences in NO-H BDE values make TEMPO an inhibitor of free radical processes by acting as radical scavenger, while PINO efficiently promotes radical chains, as previously discussed. This substantial difference in catalytic mechanism allows to understand why the several efficient heterogeneous solutions already developed in the case of TEMPO, as the examples in the literature well demonstrate [31], cannot be automatically transferred to NHPI catalysis. In particular, as previously discussed, a key aspect in NHPI-mediated catalytic cycle is the HAT to peroxyl radicals, in order to guarantee high selectivity of the overall process. The efficiency of this step is strictly correlated to the hydrogen atom donor concentration and therefore, this aspect should be considered when designing the process of NHPI heterogenization.

On the other hand, we should here highlight how the use of TEMPO as oxidation catalyst is mainly limited to alcohols, while PINO can promote HAT from a wide variety of substrates, from activated C-H bonds, such as those at the benzylic or allylic positions, to the relatively unreactive ones in alkanes [32–39]. The general scope of this catalyst justifies once more all the efforts for designing efficient heterogeneous solutions.

4. Challenges in NHPI heterogenization

One general trend in catalysis is the heterogenization of successful homogeneous molecular catalysts by adsorption, incorporation, or grafting of an analogous of the homogeneous catalyst conveniently functionalized to favor interactions with the insoluble support. Heterogenization of homogenous catalysts results in several advantages from the process point of view, including an easy separation from the reaction mixture, allowing the reuse of the material, a high activity derived from the immobilized system, well-defined active sites, and the possibility to implement continuous flow processes. Several requirements must be met by switching to a heterogeneous system, the most important being the long-term stability of the immobilized moiety, which must not degrade and maintain a high turnover number (TON). In cases where the heterogenization process makes use of porous materials having internal pores and channels, there is an additional feature to be noted. Indeed, product selectivity can be modulated or controlled in confined reaction spaces (*i.e.*, the internal voids of porous solids), in comparison to homogeneous systems. This control derives from the restricted diffusion (*cage effect*) and selectivity in the absorption of substrates over products due to the difference in polarity between the internal cavities and the bulk solvent.

Following the seminal studies by Ishii and coworkers showing the excellent catalytic activity of NHPI combined with transition metal ions to promote aerobic oxidation in a large variety of organic functional groups, there has been a large interest in developing insoluble solids in which NHPI can somehow maintain or even enhance its activity.

In heterogenized catalysts, the solid support can play various roles going from purely passive support, just providing high surface area and insolubility to recover the catalyst, to an active role cooperating within the reaction mechanism. In some cases, a synergistic effect of the support with the incorporated active site has been established. Since NHPI activation is favored by transition metals, the support may also contain metal sites promoting this specific step.

5. Heterogeneous NHPI catalysts

Before an in-depth revision of all the above-mentioned types of materials employed for the development of heterogeneous NHPI-based catalysts, which will consider their inherent and intrinsic physicochemical properties, some general comments can be drawn. One of the main purposes of catalyst heterogenization is to facilitate catalyst recovery and its reuse in batch reactions or to implement continuous flow processes. It must be reminded here that most industrial chemical processes employ a heterogeneous catalyst at least in one of their steps. In addition, heterogenization can be beneficial to enhance the stability of the PINO radical by preventing its auto-decomposition [1].

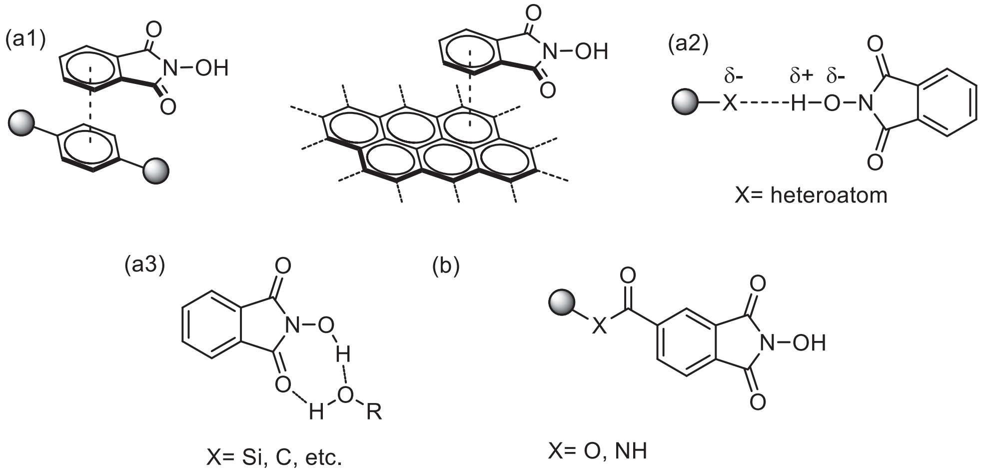
As commented in the introduction, Ishii and co-workers reported the use of NHPI together with a variety of transition metal salts, especially Co(II) ones, as one of the most effective approaches to promote the aerobic oxidations of a large variety of substrates. Thus, an ideal heterogeneous NHPI-based catalytic system should contain both the NHPI unit and the transition metal ion in such a way that the presence of O_2 triggers the occurrence of the general reaction mechanism involving PINO radicals. With this aim in mind, several general approaches using different supports have been reported. For example, a series of studies have proposed the use of NHPI adsorbed on transition metal-containing solids such as MOFs, metal oxides, POMs, clays, and hydrotalcites. Other reports have proposed the use of metal-loaded supports, such as silicas, to adsorb NHPI, while some studies have described an intermediate approach, where NHPI is supported on the solid, while the transition metal ions are added to the solution. Finally, some studies have reported the use of heterogeneous solids having transition metal ions as active sites, but using NHPI in homogeneous phase. Regardless of the good activity achieved in some cases upon heterogenization of either NHPI or the transition metal ions, the applicability of these catalytic systems at industrial scale is hampered due to the difficulty of recovering the soluble component from the reaction mixture for its re-use in a new catalytic cycle.

Another important point to be considered during the heterogenization of the NHPI/transition metal system is the possibility to support the NHPI moiety. The term heterogenization, referring to NHPI not present in the liquid phase, applies to covalently anchoring as well as strong (physi/chemi)sorption of NHPI on solids. In general, NHPI can be heterogenized on a solid support through adsorption or by covalent anchoring strategies (Scheme 3). NHPI adsorption on a solid can be easily performed by mixing the solid support with a solution containing the NHPI followed by solvent removal. NHPI interactions with the solid include van der Waals forces, dipole–dipole or hydrogen bonds of the support involving both carbonyls and N-OH groups of the NHPI molecule. Consequently, the reaction medium can favor, or not, NHPI leaching to the reaction medium. For example, NHPI with its large dipole moment (>4 Debye) is poorly soluble in nonpolar hydrocarbons such as cyclohexane. This situation is favorable for the aerobic oxidations of liquid hydrocarbons under solvent-free conditions. In contrast, the use of relatively polar solvents such as acetonitrile as reaction medium can promote the partial dissolution of the NHPI in the reaction mixture, and for this reason, the use of less polar ones, such as chlorobenzene, is more convenient. Scheme 3 shows a common strategy to anchor NHPI over solid supports by establishing ester or amide covalent bonds. Further, it is expected that the catalytic stability of these solids should be relatively higher due to the strength of the covalent bond and the lack of leaching or shuttling NHPI to the solution compared to adsorption by van der Waals forces indicated in Scheme 3 (a1, a2 and a3).

Covalent anchoring of NHPI requires adequate derivatives having suitable functional groups peripheral to the hydroxyimide active site. There are some commercially available derivatives such as 4-hydroxy, 4-amino, and 4-carboxy- NHPI derivatives that can be used for this purpose. Alternatively, organic synthesis can be used to prepare non-commercially available NHPI analogues, the drawback being that multistep synthesis, which can limit the final NHPI derivative yield. As an example, *N,N'*-dihydroxypyromellitimide (NDHPI) was used as starting material for the covalent attachment of an NHPI derivative. The synthesis uses one of the carboxylic anhydride moieties to fix the molecule on the solid, and the second anhydride is converted to the *N*-hydroxy group and used as NHPI to promote oxidation reactions. This example illustrates the large variety of possibilities that can be developed to attach covalently the hydroxyimide moiety to a solid support.

5.1. MOFs as supports

MOFs are porous highly crystalline materials [40] made by the combination of metal ions (or clusters) and organic ligands, and they represent a very promising platform for catalysts heteroge-



Scheme 3. Schematic illustration of NHPI interactions with the support through (a1) Van der Waals, (a2) dipole–dipole, and (a3) hydrogen bonds. b) Covalent anchorage of NHPI on a solid support through ester or amide bonds.

Table 1
Summary of MOFs used to entrap NHPI exhibiting activity as heterogeneous catalysts for aerobic oxidations.

Material	Substrate	Con.(%) / Sel. (%)	Major product	General remarks	Ref.
Fe(BTC)	Benzylamine	98/90	N-benzylidene benzylamine	-Solvent-free -Retained crystallinity and porosity -Retained activity after two runs	[56]
Fe(BTC)	Styrene and styrene derivatives (4-Me, 4-F, 4-Cl, 4-OMe, 3-NO_2)	2–60/63–99	Benzaldehyde and derivatives	-Retained crystallinity and porosity -Retained activity after two runs	[57]
Fe(BTC)	Cyclooctane	71/61	Ol/One mixture (1:8)	-Solvent-free	[58]
	Cyclododecane	23/85	Ol/One mixture	-Retained crystallinity and porosity	
	n-octane	7/88	Mixture of 2-, 3-, and 4-ones	-Retained activity after two runs (on cyclooctane)	
	Ethylbenzene	17/92	Ol/One mixture	-Minor leaching effect Fe(III) < 0.1 ppm	
Fe(BTC)	Cyclooctene	9/95	Cyclooctene oxide	-Solvent-free	[59]
	Cycloheptene	13/77	Ol/One mixture (1:2)	-Retained crystallinity and porosity	
	Cyclohexene	12/97	Ol/One mixture (2:3)	-Retained activity after three runs (on cyclooctene)	
	Cyclopentene	6/97	Ol/One mixture (1:18)	-Hot filtration test revealed no leached species	
Co-MOF-74 [Co_2(dobdc)]	Toluene	16/34	Benzoic acid	-Solvent-free - Coordinatively unsaturated metal centers -Retained crystallinity and porosity	[60]
Co(BTT)	Cyclooctane	48/78	Ol/One mixture	-Solvent-free	[61]
	Tetralin	41/93	Ol/One mixture	-Coordinatively unsaturated metal centers	
	Diphenylmethane	20/99	Benzophenone		
	Ethylbenzene	7/99	Acetophenone		
Co(BTC)	α-isophorone	37/82	Ketoisophorone	-Solvent-free	[62]
	Indan	49/91	Indanone	-Retained crystallinity and porosity	
	Tetralin	65/97	α-Tetralone	- Minor decrease in conversion (3 %)	
	Fluorene	54/93	Fluoren-9-one	and retained selectivity on the 3rd reuse	
	Cyclohexene	55/82	2-Cyclohexen-1-one	(on α-isophorone) –No metal leaching	
TJU-68-NHPI	1-phenylethanol	99/100	Acetophenone	Used ten cycles with no decay in activity	[63]
TJU-68-NDHPI	1-phenylethanol	99/100	Acetophenone	Used ten cycles with no decay in activity	[63]

Abbreviations: BTC: 1,3,5-benzenetricarboxylate; dobdc: 2,5-dihydroxy-1,4-benzenedicarboxylate; BTT: 1,3,5-benzenetristetrazole; TJU: Tongji University.

nization [41–44]. MOFs can provide not only the internal space for catalyst adsorption but also active metal sites which could avail NHPI activation (*i.e.*, PINO formation). Accordingly, the present section describes those reports in which NHPI has been entrapped within the MOFs cavities and employed as a heterogeneous catalyst to promote aerobic oxidations of organic substrates (Table 1). Studies where NHPI is not directly adsorbed into a MOF but rather just added in solution as a cocatalyst are not covered in the present review and readers are suggested to look elsewhere [45–55].

The approach based on entrapping the NHPI within the MOF cavities to obtain NHPI@MOF solids, and to study their heterogeneous catalytic activity, is advantageous and at the same time challenging. As described in detail in the introduction, this review aims not only to exploit the potentials of NHPI as cocatalysts in combination with purposely designed MOFs, but also to solve the key issue of NHPI recovery and recycling, while preserving its catalytic efficiency in terms of conversion and high selectivity in target products.

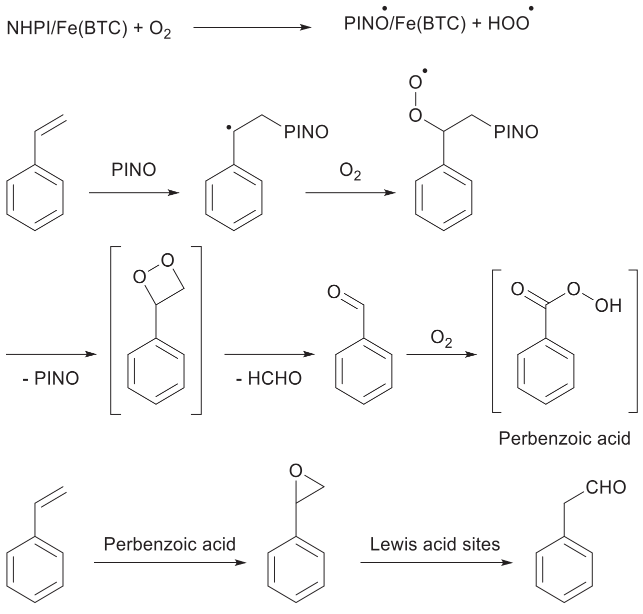
In this context, Garcia and co-workers made extensive contributions and reported for the first time a strategy to entrap NHPI within the MOF cavities of Fe(BTC). This MOF, also known as Basolite F300, is commercially available and it is constituted by the assembly of the trianionic form BTC with Fe(III) ions. At variance with other MOFs containing the same ligand, the structure of Fe (BTC) remains elusive due to its poor crystallinity [64]. This notwithstanding, it has been characterized in terms of pore dimension (ca. 22 Å) and BET surface of 1500 m^2 /g [65]. NHPI incorporation within the Fe(BTC) was confirmed by observing a decrease in MOF surface area from about 840 to 24 m^2/g [57,59]. Attempts to characterize the composite by Fourier-transformed infrared spectroscopy (FT-IR) or Raman spectroscopy did not show any significant spectroscopic change with respect to Fe(BTC) with the exception of a background increase of the fluorescence of the NHPI/Fe(BTC) solid seen by Raman spectroscopy. Interestingly, the catalytic activity of NHPI@Fe(BTC) outperforms analogous MOF catalysts based on $Cu_3(BTC)_2$ or $Al_2(BDC)_3$ (BDC: 1,4-benzenedicarboxylate) for the solvent-free oxidation of benzylamine to *N*-benzylidene benzylamine at 100 °C in the presence of O_2 [56]. This result is quite unexpected and deserves an additional comment. It was in fact reported on how the NHPI-catalyzed oxidation of primary and secondary amines (including benzylamines) under homogenous conditions could not be pursued, in spite of the fact that the amino group is a more effective electron-releasing substituent than the hydroxyl group [66]. The failure of NHPI to activate primary and secondary amines was attributed to the deactivation caused by the addition of the amino group to the NHPI carbonyl. For this reason, amine group protection by acetylation before running the oxidation was required. In the case of NHPI@Fe(BTC), the NHPI decomposition seems to be inhibited and the catalyst can develop its pro-oxidant activity. Furthermore, a synergistic effect between NHPI and the MOF, when the former is adsorbed within the latter, was observed. These observations highlight the importance for catalysis of having NHPI molecules close to iron metal nodes. In addition, the activity of NHPI@Fe(BTC) is comparable to that Au(1 %)/CeO_2, Au(1 %)/TiO_2, Pd(5 %)/C, Pt(0.2 %)/TiO_2 but the selectivity of the noble metal-based catalysts is lower due to consecutive overoxidation processes that occur with supported noble metals.

The NHPI@Fe(BTC) catalyst could be reused, maintaining its catalytic activity as well as its crystallinity and porosity, as revealed by powder X-ray diffraction (XRD) and N_2 absorption measurements. Hot filtration test and iron leaching revealed that most of the observed activity derives from the NHPI@Fe(BTC) solid, although partial autoxidation and minor leaching of Fe(III) were noticed. The role of Fe(III) in promoting PINO formation is evident, but not deeply investigated.

The NHPI@Fe(BTC) can be efficiently applied to the oxidation of a variety of primary and secondary benzyl amines to their corresponding imines. The use of tribenzyl amines resulted in the formation of *N*-benzylidene benzylamine (71 %) together with dibenzylamine (24 %). In contrast, and not surprisingly by considering the HAT driving mechanism, the NHPI@Fe(BTC) is not active for the oxidation of aniline. Attempts to oxidize piperidine or *n*-hexylamine resulted in catalyst dissolution possibly due to the stronger Lewis basicity of the media.

In another work of the same group, NHPI@Fe(BTC) catalyst was employed for the selective aerobic oxidation of styrene to benzaldehyde (Scheme 4) under different conditions [57]. Without the use of co-solvent, the catalytic system proved to be unselective giving a mixture of styrene epoxide, benzaldehyde, and phenylacetaldehyde, and a conversion of ca. 10 % after 2 h. For comparison, the use of $Fe(NO_3)_3$ as cocatalyst resulted in the formation of unidentified polymeric material. Under the same conditions, but in toluene (0.250 mL styrene in 4 mL of toluene) the reaction turned to be completely selective (>99 %) toward benzaldehyde, although with 3.5 % conversion after 3 h. It is interesting to note that if the reaction is maintained for a more prolonged period of time, styrene oxide is detected (25 % after 6 h) as secondary and preferential reaction product, reasonably arising from the formation of peracids generated from the corresponding primary aldehydes, in the reaction conditions employed. The recovered NHPI@Fe(BTC) catalyst retained its efficiency and selectivity after two reaction cycles, and power XRD analysis demonstrated the structural stability of Fe(BTC) after three consecutive runs. The versatility of the catalyst was tested towards the oxidation of styrene derivatives showing an increased conversion (up to 60 %) for substrates bearing halogens in the *para* position (eg. -F, -Cl), along with poorer selectivity, and observing that the presence of electron donating groups facilitated the addition of PINO to the C = C double bond.

The reaction mechanism proposed that the addition of the PINO radicals to the C = C double bond may lead to a carbon-centered radical in the benzylic position. This, in turn, reacts with molecular O_2 leading to the formation of peroxyl radicals which, intramolecularly, form a dioxetane intermediate, releasing PINO. A [2 + 2] *cyclo*-reversion of the aryl dioxetane would then afford benzaldehyde (Scheme 4). The formation of traces of phenylacetaldehyde was proposed to occur by the interaction of the epoxide with Fe(III) as Lewis acid sites.



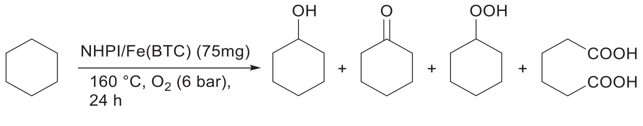
Scheme 4. Proposed mechanism for the aerobic oxidation of styrene by NHPI@Fe(BTC).

In another study, NHPI@Fe(BTC) was also reported for the aerobic oxidation of cyclic alkanes under solvent-free conditions and atmospheric pressure [58]. In this context, the conversion of cyclooctane was studied and the MOF-based system was compared with different heterogeneous supports such as silica, zeolites, and mesoporous silica [67]. After 4 h, NHPI@Fe(BTC) exhibited 17 % conversion (94 % selectivity alcohol plus ketone (ol + one), which extends to a remarkable 71 % conversion (with a diminished selectivity to ca. 64 %) after 24 h. These data confirm the efficiency of NHPI@Fe(BTC) system, especially if compared to the results obtained with the mixtures of $Fe(acac)_3$ (acac: acetylacetonate) or $Fe(NO_3)_3$ with NHPI (at the same metal/NHPI molar ratio as with NHPI@Fe(BTC)) as homogeneous catalysts. Furthermore, NHPI@Fe(BTC) was more active with respect to analogous solids in which NHPI was adsorbed on high surface area silica containing Fe or Co oxides, zeolites, or mesoporous silica. The higher activity of the NHPI@Fe(BTC) was attributed to the higher porosity and surface area of the Fe(BTC) solid together with the presence of isolated μ-Fe_3O clusters on the solid network which consist of coordinatively unsaturated sites. In this line, the lower activity of aluminosilicates or silicas having dispersed Fe^{3+} in their structure was ascribed to the presence of ill-defined iron oxide clusters with lower coordinatively unsaturated sites with respect to Fe(BTC).

Notably, Fe(BTC) MOF was also investigated to determine whether preferential adsorption of reagents over products could occur and the results showed that in MOF dispersed in acetonitrile at room temperature adsorbs 10 times higher amount of cyclooctane compared to cyclooctanol. Once again, this preferential adsorption is essential for driving the selectivity of the process. The NHPI@Fe(BTC) catalyst maintains its activity after two consecutive reuses. In addition, Fe(BTC) crystallinity was retained after reuses as revealed by XRD, and no iron leaching was found.

Although cyclooctane was found to be a suitable substrate, NHPI@Fe(BTC) was not able to reach similar conversions for cyclohexane oxidation under atmospheric pressure at 120 °C. Higher reaction temperature and oxygen pressure (160 °C / 6 bar O_2) were necessary to promote cyclohexane oxidation, achieving 6 % conversion after 24 h (72 % selectivity ol/one) (Scheme 5) [67]. To put this result into context, a previous work using Fe-MIL-101 as catalyst and *t*-butylhydroperoxide (TBHP) as oxidant reported a conversion of 38 % and selectivity of 83 % to the ol/one products at 70 °C [68]. Considering the economic cost and risks associated with the use of TBHP compared to O_2, the combination of NHPI@Fe(BTC) with O_2 to promote cyclohexane oxidation could be preferable from an industrial point of view. At the same time, the high temperature employed is probably not compatible with the thermal stability of NHPI. Reusability data for cyclohexane oxidation under these harsh conditions would have been important to determine catalyst stability.

The versatility of NHPI@Fe(BTC) finds also application in the aerobic oxidation of cycloalkenes under solvent-free conditions at atmospheric O_2 pressure [59]. Interestingly, cyclooctene oxidation



Scheme 5. Aerobic oxidation of cyclohexane catalysed by NHPI/Fe(BTC) system.

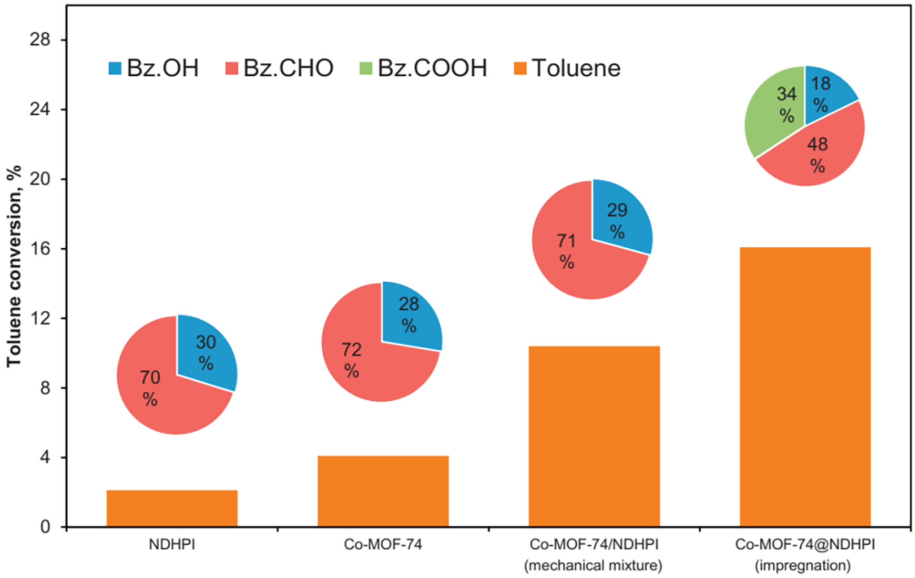


Fig. 2. Toluene conversion and product selectivity (circle histograms) were obtained after 2 h of oxidation at 100 °C using various catalysts. Reproduced with permission from ref. [60]. Copyright 2018 Elsevier.

with NHPI@Fe(BTC) resulted in higher selectivity towards cyclooctene oxide (95%) compared to Fe(acac)$_3$/NHPI as a homogeneous system (64%). This observation highlights the role of the MOF cavities in avoiding oxidation at the allylic position, and hints at the importance of substrate accumulation within the pores, as the above-mentioned reaction is clearly favored at higher local substrate concentrations. The hot filtration test confirmed the heterogeneity of the reaction, and the catalyst could be reused three consecutive times without a significant change in catalytic activity, while maintaining its crystallinity as revealed by powder XRD.

The reaction scope was further extended to cycloheptene, cyclohexene, and cyclopentene. These substrates were less reactive than cyclooctene and an increase in oxygen pressure was required to achieve some conversion (6–13%). Interestingly, for the series of cyclic olefins, the selectivity towards epoxide diminishes as the number of carbon decreases due to the favored allylic oxidation towards ol/one compounds, as the carbocycle becomes smaller [59]. A similar trend, *i.e.* mixture of epoxides and allylic oxidation was observed when using other substituted cyclohexenes, such as 1-methylcyclohexene, *(S)*-pinene, and *(S)*-limonene.

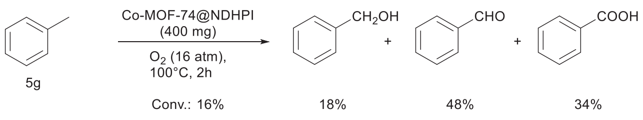
Logar *et al.* [60] reported the use of NDHPI, a bis-NHPI derivative, entrapped within the Co-MOF-74 and the resulting solid activity was tested in the solvent-free aerobic oxidation of toluene. Co-MOF-74 [Co$_2$(dobdc)] is a Co(II) honeycomb framework possessing large 1D channels [69]. The Co(II) centers, found in a distorted octahedral environment, are connected through the ligands into mono-dimensional chains with C-3 symmetry. Each ligand carboxylate binds two different metal ions and so does each hydroxyl group on the ring. This metal–ligand connectivity gives rise to large channels, whose accessible volume occupies ca. 49 % of the total cell volume [52].

NDHPI@Co-MOF-74 was characterized by FT-IR spectroscopy and powder XRD with evidence pointing to an effective inclusion of the organic derivative in the MOF, estimated to be of ca 5 wt% as seen by thermogravimetric analysis (TGA). In addition, isothermal N$_2$ adsorption measurements revealed a decrease of surface area and pore volume for NDHPI@Co-MOF-74 (736 m^2/g, 0.2 cm^3/g) with respect to the pristine Co-MOF-74 (1197 m^2/g, 0.4 cm^3/g). Isothermal adsorption of toluene also confirmed a decrease of uptake from 34 to 24 wt% upon NDHPI loading of the MOF.

NDHPI@Co-MOF-74 exhibited superior activity (Fig. 2, 16 %) with respect to their separated constituents (<4 %), as well as to their physical mixture (ca. 10 %) in the oxidation of toluene under high O$_2$ pressure (Scheme 6). It should be noted that benzoic acid was only observed as a product when using NDHPI@Co-MOF-74 and the formation of this aromatic acid was taken as evidence of the higher reactivity of benzaldehyde within NDHPI@Co-MOF-74. It might be speculated that this effect could be ascribed to a preferential adsorption of this partially oxidized substrate within the MOF, leading to an increased local concentration. The integrity of NDHPI@Co-MOF-74 after the reaction was confirmed by XRD and FT-IR spectroscopy, however, no tests on its reusability were conducted.

In a related study, NHPI was entrapped within the micropores of a cobalt-based MOF [Co(DMA)$_6$]$_3$-[(Co$_4$Cl)$_3$(BTT)$_8$(H$_2$O)$_{12}$]$_2$12H$_2$O (DMA: N,N-dimethylacetamide) (Fig. 3), named Co-BTT. The system exhibited good activity for the aerobic oxidation of cycloalkanes and benzylic compounds [61]. Single crystal-XRD analysis indicated that the MOF is built upon square planar μ_4-Cl-centered [Co(II)$_4$Cl]$^{7+}$ secondary building units (Fig. 3), which are connected with each other through the planar trigonal ligands. Each Co(II) ion is octahedrally coordinated to four different ligands, the central chloride ion and a water molecule. The above-described metal–ligand connectivity results in a 3D framework (Fig. 3), resembling a truncated octahedron with square and hexagonal faces, which is anionic and thus requires the presence of solvated Co(II) ions within the large pores to reach electroneutrality of the material. The void space of the framework without considering the counter cations is ca. 66.7 % of the total cell volume [52].

One of the important features of Co-BTT is the presence of coordinatively unsaturated metal sites, which can be generated by the thermal release of the coordinated water molecules present in the



Scheme 6. Aerobic oxidation of toluene catalysed by NDHPI@Co-MOF-74.

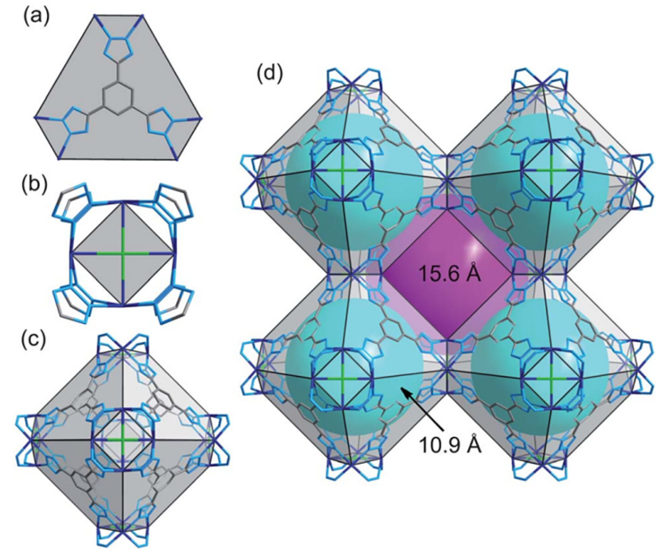
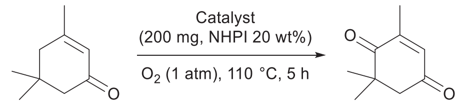


Fig. 3. a) BTT ligand connected with six neighboring M^{2+} ions constructing the 3-connected node and hexagonal face. b) Four M^{2+} ions bridged by eight tetrazolate rings forming the 8-connected node and square face. c) a sodalite-like cage constructed from six $[M_4Cl]^{7+}$ units and eight BTT linkers located at its square and hexagonal faces, respectively. d) a cube of eight cages, each of which is connected with six adjacent cages through its square faces. The void cavity inside the cages and the one formed by connecting eight such cages are displayed as cyan and magenta spheres, respectively. Reproduced with permission from ref. [61]. Copyright 2012 Royal Society of Chemistry. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

as–synthesized material. The NHPI@Co-BTT can promote the aerobic oxidation of several hydrocarbons including ethylbenzene, diphenylmethane, tetralin, and cyclooctane. The highest conversions were observed for cyclooctane (48 %) and tetralin (41 %) after 29 h at 120 °C under 1 atm O_2, with the corresponding ketone as final product in selectivity of 78 % and > 93 %, respectively. Ethylbenzene showed less conversion (7 % after 9 h), while toluene was unreactive under these conditions. In spite of the relatively lower activity of NHPI@Co-BTT compared to NHPI@Fe(BTC), described before, its higher product selectivity towards the desired ol/one products makes this MOF a preferable solid catalyst. One important aspect of this work related to the solvated metal ions present within the MOF pores, whose fate after NHPI adsorption and role in the catalytic performance of the NHPI@Co-BTT was not studied and remains to be addressed.

Another work related to NHPI@MOF system was reported by Tang et al. [62] Nine different MOF systems, based on the combination of Cu(II), Co(II) and Mn(II) with pyridine-2,6-dicarboxylic (H_2PDA), BTC or pyridine-2,4,6-tricarboxylate (H_3PTC) as organic ligands were investigated. The higher activity of Co(II)-based MOFs was observed compared to their analogous Cu(II) or Mn(II)-based MOFs in the allylic oxidation of α-isophorone (α-IP) into ketoisophorone (KIP) (Table 2). For the most active NHPI/Co-BTC catalyst, the hot filtration test and inductively coupled plasma (ICP) measurements confirmed that the catalyst worked under heterogeneous conditions and that no metal ions were dissolved in the reaction mixture. Moreover, no significant changes in the conversion of α-IP or in the selectivity of KIP were observed after three consecutive runs. Finally, the versatility of the NHPI@Co(BTC) as heterogeneous catalyst was also investigated for aerobic allylic oxidation of other carbocycles. For instance, tetralin, indane, fluorene, and cyclohexene were oxidized to their corresponding carbonyl compounds in conversions>49 % and with a selectivity ranging from 81.9 % to 97.2 %. These comparative studies are extremely useful to better highlight the role of the metal centers, as well as the different MOF architectures on their catalytic performance.

Table 2
Aerobic oxidation of α-IP catalyzed by a series of Cu, Co, and Mn-based MOFs.[a]



Entry	Catalyst	Conversion [%]	KIP Selectivity [%]
1	NHPI/Cu(PTC)	35.0	66.5
2	NHPI/Cu(BTC)	23.1	80.0
3	NHPI/Cu(PDA)	20.7	82.1
4	NHPI/Co(PTC)	38.5	72.7
5	NHPI/Co(BTC)	36.6	81.7
6	NHPI/Co(PDA)	30.9	69.7
7	NHPI/Mn(PTC)	36.9	54.2
8	NHPI/Mn(BTC)	29.7	78.8
9	NHPI/Mn(PDA)	28.1	58.2
10	–	0.86	86.7

[a] Reaction conditions: α-IP (10 mmol), catalyst (200 mg), 110 °C, 5 h. The products were analyzed by GC.

Recently, two MOF catalysts, TJU-68-NHPI and TJU-68-NDHPI were synthesized under solvothermal conditions as shown in Fig. 4 [63]. This approach conveniently provided the anchoring of NHPI over MOF structure with a high density of nitroxyl radical centers. The activity of TJU-68-NHPI and TJU-68-NDHPI was evaluated in the aerobic oxidation of secondary alcohols to their respective ketones at 80 °C in CD_3CN with *t*-butyl nitrite as cocatalyst. Under these conditions, TJU-68-NHPI and TJU-68-NDHPI afforded 99% yields of acetophenone in the aerobic oxidation of 1-phenylethanol. The activity of these solids in the absence of oxygen was negligible. The yield of acetophenone was 8% in the presence of only *t*-butyl nitrite under similar conditions. Under identical conditions, the activity of H_2L_{NOH} and H_2L_{2NOH} (Fig. 4) led to 42% and 36% yields of acetophenone, respectively, while yields increased up to 76% with H_2L_{NOH} + $ZrCl_4$ and to 82% with H_2L_{2NOH} +- $ZrCl_4$. These control experiments clearly prove the superior performance of TJU-68-NHPI and TJU-68-NDHPI catalysts because of the NHPI anchoring to the ligands within the frameworks. Besides, TJU-68-NHPI and TJU-68-NDHPI solids were also used for ten cycles for the aerobic oxidation of 1-phenylethanol, with no decay in their activity. In addition, powder XRD characterization of the reused TJU-68-NHPI and TJU-68-NDHPI solids showed similar patterns to those observed for the original catalysts. Interestingly, these catalytic systems have also been demonstrated to be efficient in promoting the aerobic oxidation of primary alcohols and benzylic hydrocarbons for a broad range of substrates, with high conversions and selectivity.

Overall, the current state of the art shows the advantages on using MOFs as NHPI supports for efficient heterogeneous catalysts in the aerobic oxidation of organic substrates. Considering the high tunability of MOF composition and structures [70–74], more examples exploiting the opportunities of combining MOFs with NHPI derivatives are to be expected. For example, studies have shown that electron-withdrawing groups in the ligands could increase the Lewis acidity at the metal centers. This effect, in some cases, has been shown to lead to a considerable increase of the catalytic activity for aerobic oxidations [75] or Lewis-acid catalyzed reactions [76]. Thus, it is expected that the use of these MOFs with increased Lewis acidity could increase NHPI adsorption and/or favor its activation through polarization of the N-OH bond. Furthermore, the use of MOFs with Lewis acidic open metal sites together with NHPI entrapped within their cavities could be employed to promote tandem reactions. Similarly, other works have shown that the use of mixed-metals exhibit superior activity

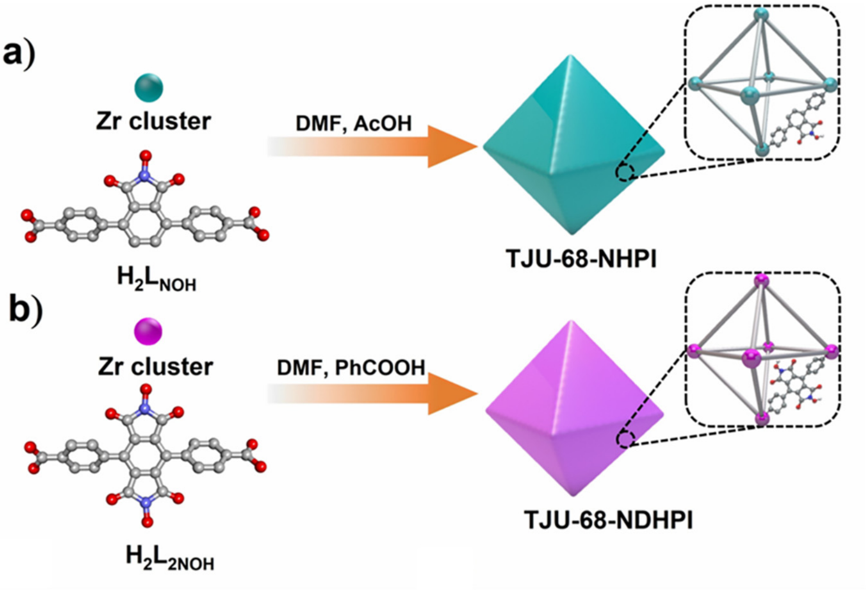


Fig. 4. Synthesis of (a) TJU-68-NHPI and (b) TJU-68-NDHPI. Reproduced with permission from ref. [63]. Copyright 2021 Wiley.

for O_2 activation, and this knowledge could be exploited to increase the activity and selectivity of NHPI@MOF systems.

Another important property of MOFs that can be further exploited to favor aerobic oxidation is the polarity of the internal voids. In this context, the development of MOFs with hydrophobic character can increase the preferential adsorption of hydrocarbons close to the active centers with respect to the more polar oxidized products. This behavior could result in an increase in product selectivity by diminishing overoxidation. Hydrophobicity can also be used to increase NHPI adsorption and, thus, to minimize its leaching into solution.

Additionally, NHPI derivatives could be directly used as organic ligands for building the MOF architecture. This approach would offer some advantages compared to simple NHPI adsorption into the MOF system, despite the intrinsic difficulty which pertains to the structural modification of the NHPI moiety itself [77]. On one hand, it would favor their dispersion within the MOF network. Moreover, the MOF cavities will be free to accommodate reagents and products favoring diffusion and resulting in higher catalytic activity. Since confinement of the radical chain reaction inside restricted pores allows considerable control of the product distribution by applying polarity and geometrical factors, and considering the wide range of pore sizes, void geometries, and possible substituents in MOF chemistry, these tools should be applied to show control on the product selectivity by operation of shape selectivity and polarity effects, all features which are not possible in the homogeneous phase.

5.2. Polymers as supports

Traditionally, organic polymers have been used as preferred supports in heterogeneous catalysis [78]. Hence, an alternative strategy for achieving heterogenization of NHPI-based catalytic systems consists on the covalent modification of the polymeric backbone. This approach may present advantages with respect to the physical inclusion of NHPI. However, some limitations of this strategy include: i) only a few NHPI derivatives suitable for simple straightforward covalent linking are commercially available; ii) additional groups on the NHPI aromatic ring could affect the BDE value, and thus the reactivity; iii) the lability of the *N*-hydroxylimido moiety imposes significant restrictions on the reaction conditions that can be employed for polymer functionalization, thus limiting the possible pathways; iv) concomitant functionalization of a polymeric support with the NHPI unit and the access to active metal centers might be difficult.

Table 3 lists the studies reported using polymers functionalized with NHPI combined with metal salts to promote aerobic oxidations of organic compounds. We feel to remark once again that

Table 3
Summary of polymeric systems used as heterogeneous NHPI catalysts for aerobic oxidations.

Material	Substrate	Con. (%) / Sel. (%)	Major product	General remarks	Ref.
Polymer pSt/NHPI	Toluene	56/86	Benzoic acid	10 % conversion drop after the first reuse, then stable for additional 6 runs	[79]
Polymer GMA/MMA-NHPI	Ethylbenzene	20/76	Acetophenone	Reusable up to 6 consecutive runs	[80]
Polymer Cu(II)-APP	Cyclohexylbenzene	43/90	Cyclohexylbenzene hydroperoxide	Used for five cycles with no decay in its activity	[81]
CPS-NHPI	1-phenylethanol	40/100	acetophenone	No stability data were reported	[82]
$NHPI_{30}$-co-S_{63}-co-DVB_7	4-methoxytoluene	23/-	4-methoxybenzyl alcohol, 4-methoxybenzaldehyde, and 4-methoxybenzoic acid	No stability data were reported	[83]

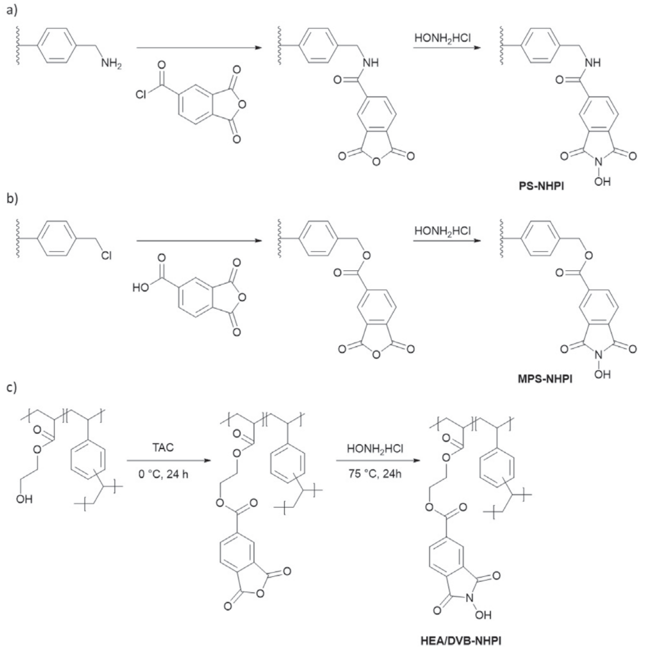
Abbreviations: pSt: polystyrene; GMA: glycidyl methacrylate; MMA: methyl methacrylate; APP: azo-bridged Cu(II) porphyrin polymer; CPS: crosslinked pSt; co-S-co-DVB: copolymer of styrene and divinylbenzene as monomers.

the use of a polymeric system that could act simultaneously as support of the NHPI and the transition metal to develop fully heterogeneous catalysis should be ideally preferred, but this is not the case for the examples reported in the literature.

From a synthetic point of view, a straightforward solution is exemplified by recent works involving the use of aminomethyl- or chloromethyl-pSt [84], and 2-hydroxyethylacrylate-divinylbenzene copolymer (HEA-DVB) [85]. Scheme 7 shows the synthetic procedures for the covalent derivatization of the three polymeric materials. Amide or ester bonds are generated in the first step, where the trimellitic anhydride derivative (an acid chloride or a carboxylic acid) is fixed to the polymer, followed by treatment with NH_2OH, which leads to the formation of the *N*-hydroxyl moiety. FT-IR spectroscopy and elemental analysis confirmed both the formation of the corresponding amide and ester bonds, and the presence of the *N*-hydroxylimido moieties into the three solid supports. Quantitative estimation of the percentage of grafted NHPI indicates 0.81, 1.65 and 2.06 mmol NHPI/g for pSt-NHPI, MPS-NHPI (MPS: commercial pSt) and HEA/DVB-NHPI, respectively.

The catalytic efficiency of these functionalized supports was tested in the aerobic oxidation of toluene, *p*-methoxytoluene, and *p*-methoxystyrene. Solvent-free reaction conditions, at 80 °C and 1 atm oxygen, required the presence of $Co(OAc)_2$ as well as azobisisobutyronitrile (AIBN) as radical initiator to shorten the induction period. The observed low conversions reported (<3 %) compared to control experiments, along with indications of partial polymeric support degradation, highlight the difficulties which this approach entails, especially in terms of degree of polymer functionalization and stability, as well as regarding the actual availability of the active sites.

The use of porous organic polymers (POPs) might have advantages with respect to the use of unstructured materials, such as an increased surface area and porosity, and a better dispersion of the active centers within the polymeric network. This is the case reported by Jianlan *et al.*, where a NHPI-pSt porous polymer was prepared by using high surface area silica as template [79]. The multistep synthesis of the polymeric framework (Scheme 8) starts with the functionalization of silica gel particles (125 μm) through a coupling reaction with (3-mercaptopropyl)trimethoxysilane (MPMS). This approach allowed the surface modification of the silica particles by the introduction of mercapto groups which, upon treatment with AIBN, acted as initiating radical centers for graft polymerization of polystyrene (pSt/SiO_2). Subsequently, the silica matrix was etched away upon dispersion of the pSt/SiO_2 composite material into aqueous HF solution. Finally, chloromethylation of the pendant phenyl rings, reaction with trimellitic anhydride, and treatment with hydroxylamine hydrochloride yielded the desired NHPI-decorated porous polystyrene (pSt/NHPI). The success of each synthetic step was determined by FT-IR spectroscopy, scanning electron microscopy (SEM), and elemental analysis which also indicated a 2.23 mmol_NHPI/g loading. TGA analysis showed a notable thermal stability of the heterogeneous system, which started to decompose only above 380 °C. Moreover, isothermal N_2 adsorption indicated a BET surface area for pSt/NHPI ca. 250 m^2/g, with a predominance of mesopores (85.8 %) over micro- and macropores.

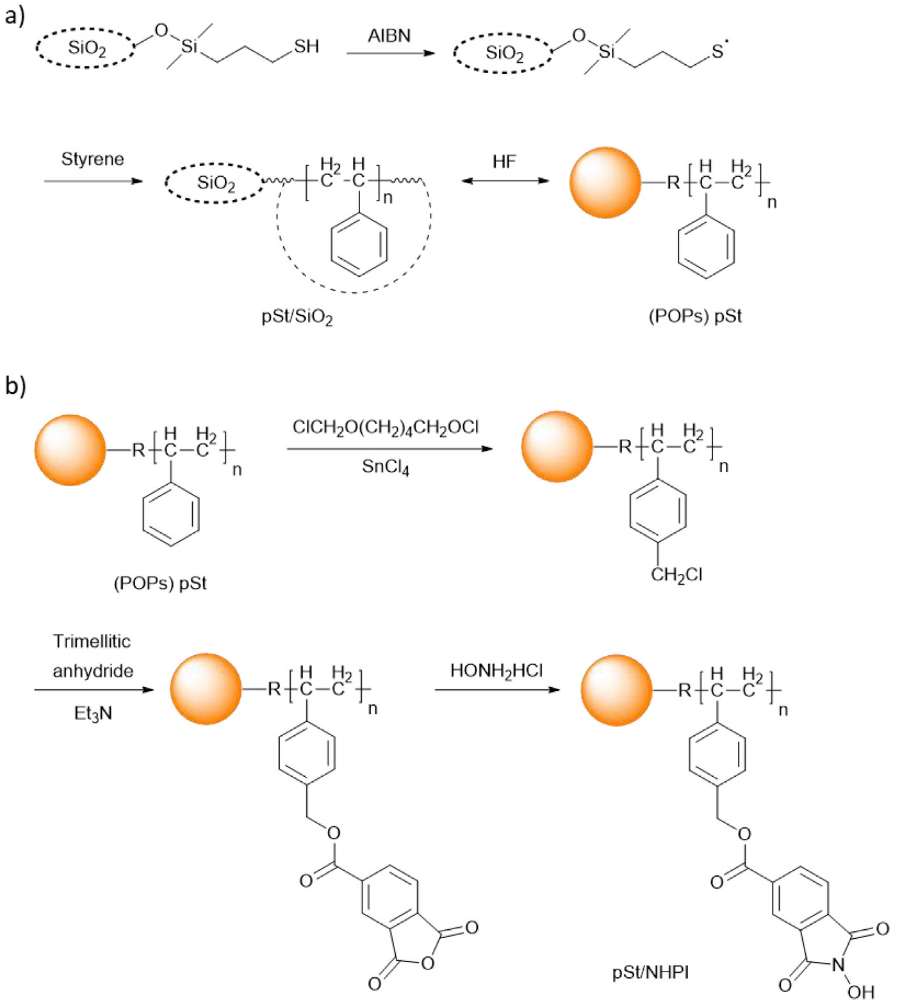


Scheme 7. Covalent immobilization of NHPI onto a) (aminomethyl)polystyrene, b) (chloromethyl)polystyrene, and c) HEA/DVB polymer. TAC: trimellitic anhydride acid chloride.

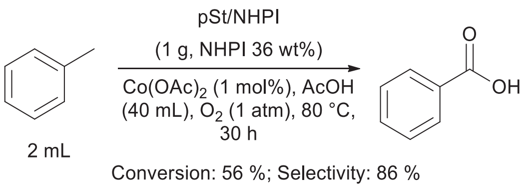
The pSt/NHPI solid resulted in an efficient activity for the selective toluene oxidation to benzoic acid under mild reaction conditions. The pSt/NHPI catalytic system provided 56% conversion with 86% selectivity (Scheme 9). Reuse of the catalyst showed a decreased efficiency after the second run (conversion drops to 44 %), which then remained unchanged for up to seven cycles. No reasons for this activity drop were given, although probably the presence of acetic acid as solvent could favor the hydrolysis or self-degradation of NHPI. Importantly, control experiments using pSt/NHPI or $Co(OAc)_2$ alone showed no significant activity, while a mixture of NHPI, Co(II) ions and pSt/SiO_2, a material with a different pore size distribution, led to lower conversions. This finding illustrates the effect of direct functionalization of the polymer and the role of porosity of the polymeric support. This study also extended the investigation to a series of transition metal cations as potential cocatalysts, compared to Co(II). The catalytic activity was found to decrease in the following order of $Co(OAc)_2 > MnSO_4 > Fe(acac)_2 > CuCl_2$. Notably, this activity trend replicates that of the standard reduction potentials (E°/V) for the redox couples Co^{3+}/Co^{2+} (1.84 V), Mn^{3+}/Mn^{2+} (1.51 V Fe^{3+}/Fe^{2+} (0.77 V) and Cu^{2+}/Cu^{+} (0.15 V).

Another aspect worth mentioning is related to the solubility of the transition metal salt within the reaction media. In this regard, in a related study using NHPI covalently grafted on polymer microsphere made of glycidyl- and methyl-methacrylate co-polymeric microspheres (GMA/MMA) (synthesis shown in Scheme 10) [80], the order of activity for the aerobic oxidation of ethylbenzene was found to be: $Co(OAc)_2 > CoCl_2 > Mn(OAc)_2 > CuCl_2$. The higher solubility of $Co(OAc)_2$ in acetic acid, used as solvent under the reported conditions, was considered responsible for the higher activity observed. Interestingly, the same study found that the activity of $Mn(OAc)_2$ decreased over time becoming lower than that of $CuCl_2$. This observation was explained by assuming overoxidation pathways of Mn(II) to Mn(V) by O_2, which diminishes the ability of manganese ions to cycle between the active Mn^{2+}/Mn^{3+} states.

The incorporation of the metal center into an organic polymeric structure is also an option. In the field of aerobic oxidations, metalloporphyrins have been proposed as biomimetic catalysts for the oxidation of organic compounds, and porphyrin-based MOFs were developed too [86–89]. Thus, conjugated polyporphyrin polymers are promising candidates for heterogeneous oxidation systems as they would not need additional metal salts in solution. For example, azo-bridged Cu(II)-based porphyrin polymer was prepared by co-polymerization of meso-tetra(4-aminophenyl) and meso-tetra (4-nitrophenyl)-Cu(II) porphyrins (Cu^{II}-APP) (Scheme 11). The activity of the resulting polymer porphyrin was evaluated as cata-



Scheme 8. a) preparation of the (pops)pst. b) immobilization of nhpi onto (pops)pst.

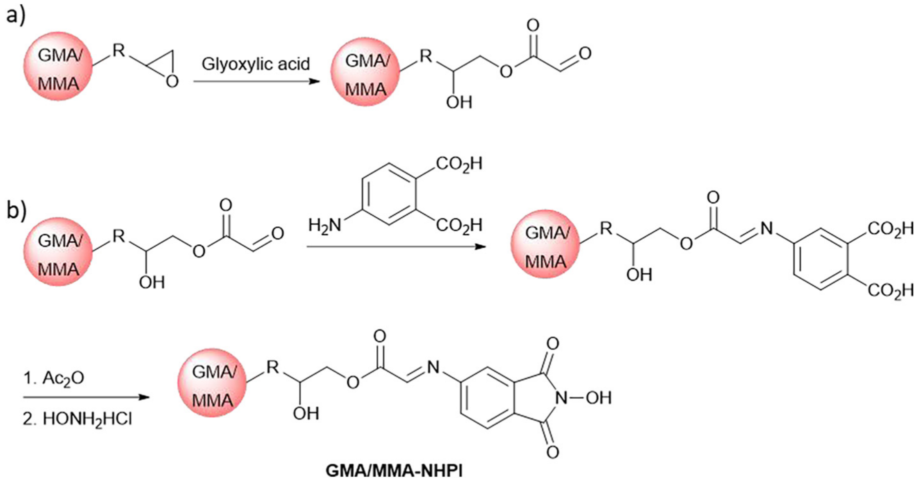


Scheme 9. Aerobic oxidation of toluene to benzoic acid catalysed by pSt/NHPI.

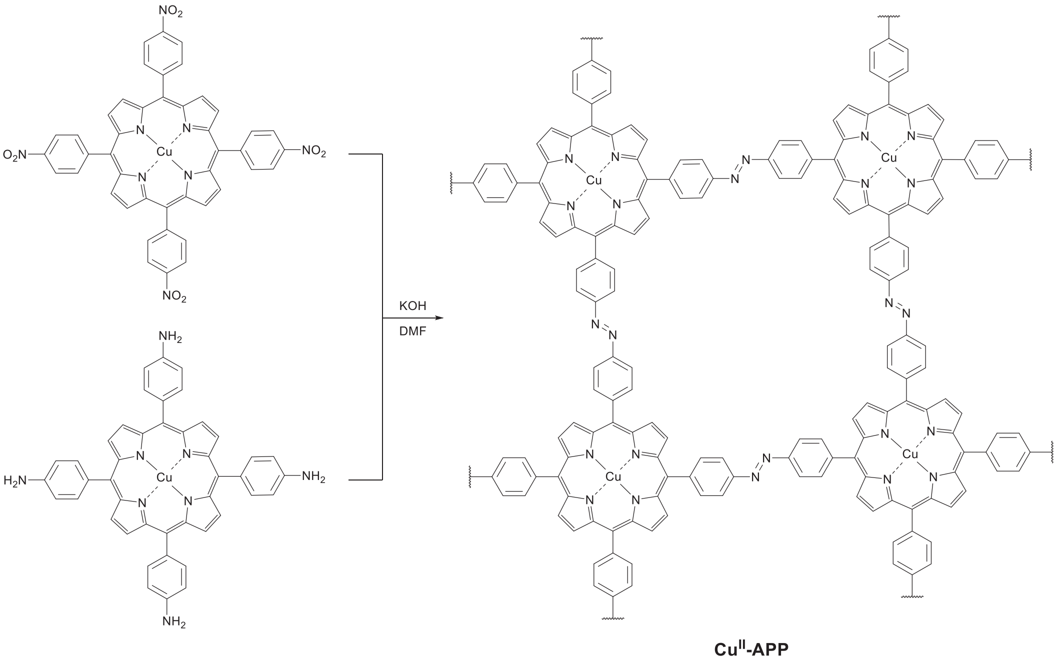
lyst together with unsupported NHPI cocatalyst for the aerobic oxidation of cyclohexylbenzene [81]. Field emission scanning electron microscopy (FE-SEM) and high-resolution transmission electron microscopy (HR-TEM) revealed that the Cu^{II}-APP material was constituted of porous circular particles of about 20–40 nm with a large density of nanopores on the surface. N_2 adsorption measurements showed BET surface area of 217 m^2/g, a total pore volume of 0.18 cm^3/g, and the presence of pore diameters of 1.2 and 1.9 nm. TGA analysis revealed that Cu^{II}-APP is stable at temperatures below 150 °C, while above this temperature azo bond decomposition occurs and, finally porphyrin ring degrades at a temperature of about 350 °C.

Cu^{II}-APP exhibited a two-fold higher conversion (ca. 24 %) than the corresponding monomers (10–12 %) in the aerobic oxidation of cyclohexylbenzene under solvent-free conditions. This higher activity was ascribed by the authors to a beneficial effect of the porous structure which facilitated the interaction between O_2, the Cu(II) active centers, and the substrate. The small size of the polymer nanoparticles (NPs) would surely increase the kinetics of substrate permeation within the solid support, but also, the conjugated structure of Cu^{II}-APP might facilitate electron and energy transfer processes related to the activation of O_2. The catalytic activity of this solid was tested under solvent-free conditions in chlorobenzene as solvent. The conversion was 2.3 % and ca. 9.5 % at 80 °C and at 90 °C respectively after 8 h, with selectivity to the hydroperoxide in the range of 95–97 %. In contrast, the conversion was increased to ca. 35 % with a concomitant decrease in selectivity to around 91 %. Under the optimized reaction conditions, the conversion was 43.3 % at 90 °C after 8 h with selectivity towards cyclohexylbenzene hydroperoxide of about 89.6 %. Importantly, the performance of this heterogeneous solid was higher than $CuCl_2$ under the same experimental conditions. On the other hand, the use of NHPI as catalyst exhibited 12.1 % conversion.

The Cu^{II}-APP solid was recovered and maintained its activity for five cycles with no decay. The structural integrity was confirmed by FT-IR. However, it was noted that NHPI recovery was severely



Scheme 10. a) Functionalization of GMA/MMA microspheres with glyoxylic acid. b) synthesis of the NHPI covalently anchored onto GMA/MMA polymer.



Scheme 11. Schematic representation of the synthesis of Cu^{II}-APP.

lower after each cycle (ca. 60 %) and this finding was associated to its degradation during the catalytic reaction. As commented earlier in the introduction, precautions should be taken, especially in terms of working temperature, to prevent NHPI degradation.

In another work, NHPI was immobilized on crosslinked pSt microspheres (CPS-NHPI), as shown in Fig. 5, by first anchoring 4-carboxyphthalic anhydride and then converting the anhydride into the corresponding *N*-hydroxy derivative. The activity of the resulting CPS-NHPI in combination with $VO(acac)_2$, $Co(OAc)_2$, $CoCl_2$ and $Mn(OAc)_2$ was evaluated for the aerobic oxidation of 1-phenylethanol at 75 °C [82]. Among the catalysts screened for this oxidation, the best performing system was CPS-NHPI with $VO(acac)_2$, which reached 40% conversion of 1-phenylethanol to acetophenone with complete selectivity under these conditions. The order of activity of these metal salts with CPS-NHPI was $VO(acac)_2 > Co(OAc)_2 > CoCl_2 > Mn(OAc)_2$. However, no data on catalyst stability in terms of reusability and characterization of recovered CPS-NHPI were reported.

Recently, a series of copolymer materials having different proportions of monomers like 4-vinyl-diisopropyl phthalate ester (10–90 mol%), divinylbenzene (1–11 mol%), and styrene were prepared by radical copolymerization [83]. As shown in Fig. 6, diisopropyl ester functionalities were transformed into NHPI units attached to the polymer network (NHPI-S-DVB). The catalytic performance of this solid with Co(II) acetate cocatalyst was investigated in the aerobic oxidation of *p*-methoxytoluene. Among the various reaction conditions, a maximum conversion of 23% was achieved for $NHPI_{30}$-co-S_{63}-co-DVB_7 solid at 80 °C. Although this solid showed oxidation activity, the catalyst underwent deactivation during the reaction by the opening of the imide ring, leading to the formation of carboxyl groups by releasing hydroxylamine molecules as evidenced by FT-IR spectroscopy. Even if the deacti-

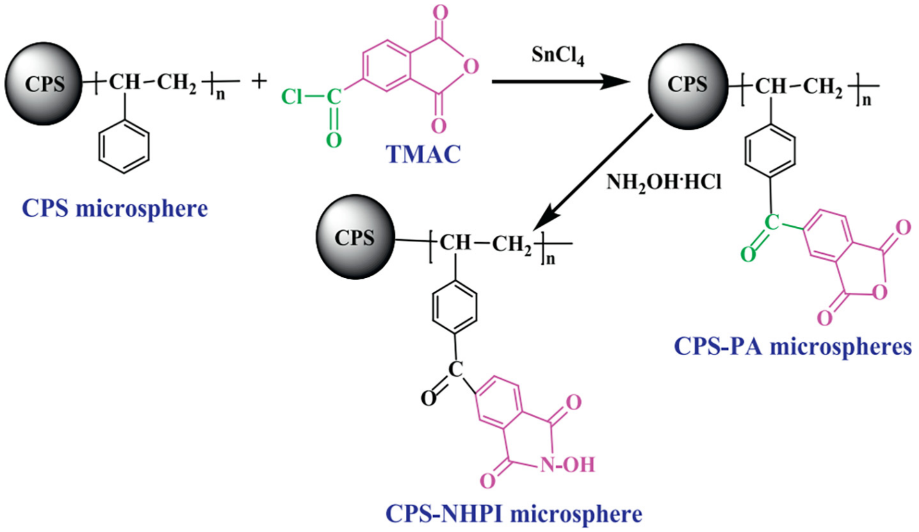


Fig. 5. Chemical route to prepare CPS-NHPI microspheres. TMAC: trimellitic anhydride acid chloride; CPS-PA: crosslinked pSt-phthalic anhydride. Reproduced with permission from ref. [82]. Copyright 2018 Elsevier.

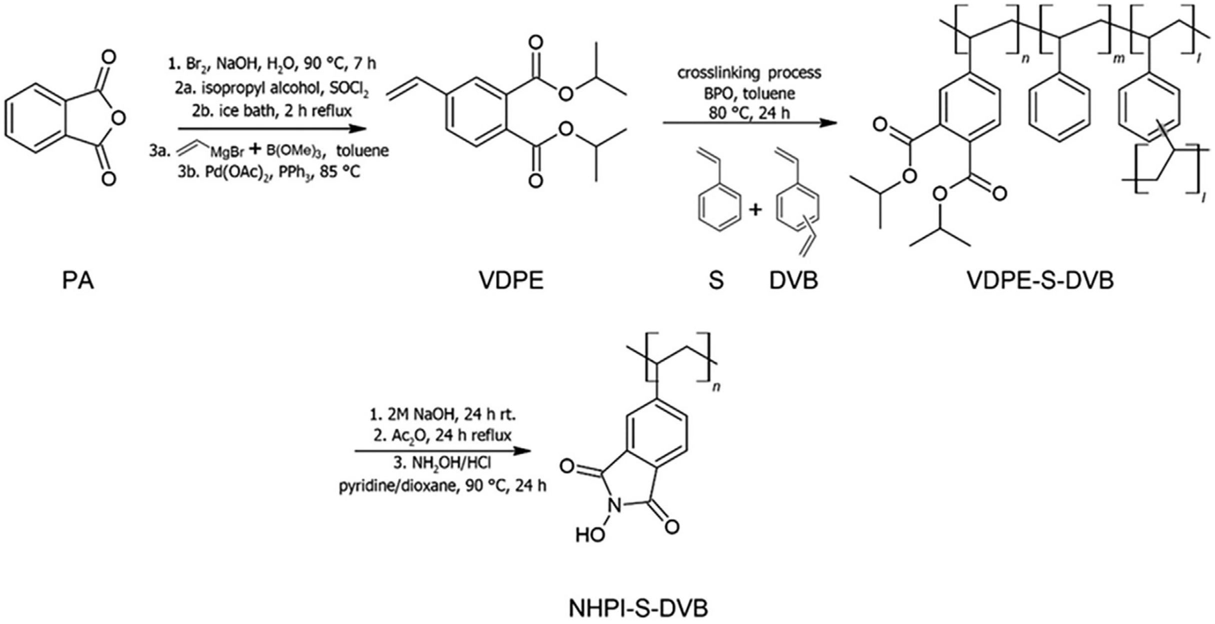


Fig. 6. Synthetic route for novel NHPI-containing copolymer catalysts. PA: phthalic anhydride; VDPE: 4-vinyldiisopropyl-phtalate ester; S: styrene; DVB: divinylbenzene. Reproduced with permission from ref. [83]. Copyright 2021 MDPI.

vated catalyst was regenerated, no activity data for the recovered catalyst was reported.

Synthetic polymers offer many possibilities regarding the nature of the monomer, degree of crosslinking and molecular size. Simultaneous attachment of a metal could avoid the need to add a soluble salt together with the polymer. These tools can be used to prepare a wide range of heterogeneous NHPI-based solid catalysts in which the reaction environment can also experience differences in polarity and even geometrical restriction. In addition, the polymer can have also acid or basic sites that can provide multifunctional materials adequate for tandem and cascade reactions. At present, as shown in the present section, there is still much room for designing new NHPI-functionalized polymers to promote oxidations of a wide range of organic substrates.

5.3. Silicas as supports

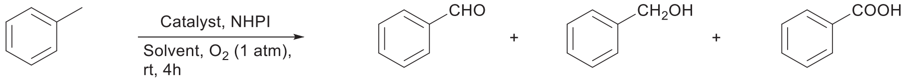
Due to the stability of silicas under a wide range of conditions, silica-based materials have been frequently employed as high surface area supports. Silicas offer good chemical and thermal stability and allow their easy recovery when used as heterogeneous catalysts under batch conditions and can also be employed as packed beds for continuous flow operation. In the area of heterogeneous catalysts using NHPI as promoter for aerobic oxidations, silicas have been employed to support metal active centers or NHPI derivatives. As commented in the section dealing with polymers, for the sake of applicability it would be convenient to develop fully heterogeneous systems in which the NHPI derivative as well as the transition metal are supported on the silica particles. Table 4 pro-

Table 4
Summary of silica-NHPI heterogeneous solid catalysts for aerobic oxidations.

Material	Substrate	Con. (%) / Sel. (%)	Major product	General remarks	Ref.
CoO_x/SiO_2, NHPI	Toluene	91.2/68.8	benzaldehyde	Reused catalyst retained 60 % of the initial activity due to Co leaching	[90]
Silica-Schiff base Co-Mn complex, NHPI	4-tert-butyltoluene	43.7/62.7	4-tert-butylbenzaldehyde	Reused for four cycles with no decrease in conversion/ selectivity	[91]
Aminopropylsilica functionalized with NHPI	Toluene	18[a]	benzaldehyde	No stability data were reported	[92]
SiO_2/Al_2O_3 -APTMS-BPK-Co, NHPI	Ethylbenzene	64/82	acetophenone	Seven times reused with no decay in its activity	[93]
SiO_2/Al_2O_3 -APTMS-BPK-Mn, NHPI	Ethylbenzene	46/69	acetophenone	Five times reused with no decay in its activity	[94]
Fe_3O_4@SiO_2-APTMS/CC/Met@Co(II)	Ethylbenzene	86.7/98	acetophenone	Catalyst was reusable and deactivated after 9th cycle	[95]
NHPI-loaded silica	Cyclohexane	38[a]	cyclohexanone	Activity dropped after one use	[96]
SiO_2-APTES-PMDA-NOH, $Co(OAc)_2$	Ethylbenzene	63.8/79	acetophenone	Used four cycles with no decrease in conversion/selectivity	[97]

Abbreviations: APTMS-BPK: aminopropyltrimethoxysilane-bipyridylketone; CC: cyanuric chloride; Met@Co(II): metformin-cobalt complex; APTES: 3-aminopropyltriethoxysilane; PMDA: pyromellitic dianhydride. [a]Value corresponds to yield.

Table 5
Aerobic oxidation of toluene on CoOx catalysts.[a]



Entry	Catalyst	Solvent	Conversion [%][a]	Selectivity [%][b]		
				Benzaldehyde	Benzyl alcohol	Benzoic acid
1	–	HFIP	0.0	–	–	–
2	CoO_x/SiO_2 only	HFIP	0.0	–	–	–
3	NHPI only	HFIP	0.6	41.7	14	44.3
4	SiO_2	HFIP	0.0	–	–	–
5	Co_3O_4	HFIP	7.0	62.1	23.4	1.9
6	CoO_x/SiO_2	HFIP	91.2	68.8	8.4	20.3
7	MnO_x/SiO_2	HFIP	26.0	62.3	30.7	1.7
8	CeO_x/SiO_2	HFIP	1.0	36.4	14.4	15.5
9	CoO_x/SiO_2	Acetic acid	75.2	3.2	0.5	93.5
10	CoO_x/SiO_2	Acetonitrile	23.8	21.5	2.2	71.8
11	CoO_x/SiO_2	Ethanol	1.3	2.2	0.0	97.8
12	CoO_x/SiO_2^c	HFIP	92.2	69.7	9.5	19.2
13	CoO_x/SiO_2^d	HFIP	55.5	65.1	30.3	3.6

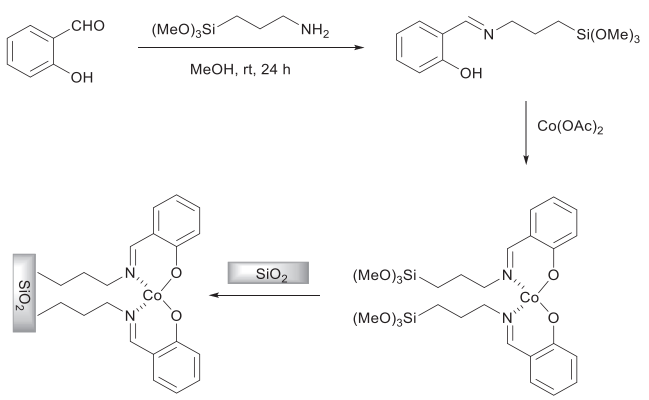
[a] Reaction conditions: toluene (0.50 mmol), supported oxide catalyst (2 mmol/g, 0.005 g), NHPI (0.05 mmol), O_2 (99.9%, 0.1 MPa), solvent (1 mL), 4 h.
[b]The composition of reaction mixture was analysed by GC-FID.
[c]Toluene (100 mmol), catalyst (2 mmol/g, 1.0 g), NHPI 10 mmol), O_2 (99.9%, 0.1 MPa), solvent (200 mL).
[d]Catalyst recycled from entry 12.

vides the overall view of the reported silica-NHPI-based heterogeneous solid catalysts for aerobic oxidations along with their stability data.

In a series of studies, silica particles have been used as support of active species, such as periodate [98] transition metal oxides, transforming them into active co-catalysts for the aerobic oxidation of hydrocarbons in the presence of unsupported NHPI [91]. In one of these studies, CoO_x impregnated on SiO_2 exhibited high catalytic activity for toluene oxidation in the presence of NHPI at atmospheric oxygen pressure [90]. The use of analogous catalysts based on CeO_x/SiO_2, $MnO_{x,}$ or unsupported Co_3O_4 resulted in lower conversions (Table 5). Importantly, the use of hexafluoropropan-2-ol (HFIP) as solvent increased the toluene conversion and benzaldehyde selectivity. In contrast, the use of other solvents such as acetic acid, acetonitrile, or ethanol led to a high production of benzoic acid. The use of 2,2,2-trifluoroethanol as solvent resulted into a selectivity in the benzaldehyde intermediate with respect to the use of HFIP and the non-fluorinated solvents. Similarly, as previously observed in homogeneous phase, it was proposed that the hydrogen bond formation between HFIP and benzaldehyde limits the overoxidation to benzoic acid. The enhanced toluene conversion with HFIP was proposed to be related to the easy activation of molecular O_2 hydrogen bonds. The reused catalyst only retains 60 % of the initial activity, a fact that was mainly attributed to the occurrence of cobalt leaching. Thus, it was proposed that a co-precipitation or ion exchange method could increase catalyst stability by stronger interaction of cobalt species with the silica surface.

In another example, a series of cobalt and manganese oxides at different loading degrees were supported by consecutive two incipient wet impregnation method on previously formed hexagonal mesoporous silica (HMS). HMS were prepared from tetraethylorthosilicate (TEOS) and dodecylamine as template (DDA) by calcination at 550 °C [91]. Among all the samples, a bimetallic Co (4 wt%) and Mn (4 wt%) supported on HMS (645 m^2/g BET, 0.77 cm^3/g pore volume, mesopores 2.4–2.9 nm) exhibited enhanced catalytic activity (43.7% conversion) for the aerobic oxidation of 4-*tert*-butyltoluene using unsupported NHPI as cocatalyst. XRD analysis of this solid revealed the formation of Co_3O_4 particles with average size of about 15.8 nm, while peaks attributable to manganese oxide were not observed due to the good dispersion of these manganese oxide NPs that should have a size below the detection limit. UV–Vis spectra revealed that the main cobalt species are present in the form of Co_3O_4 while the manganese co-exists in the forms of MnO, Mn_2O_3, and Mn_3O_4. Catalyst stability was assessed by observing a slight cobalt (0.28 wt%) and manganese (0.39 wt%) leaching and catalyst retained its efficiency up to 5 consecutive runs. The almost coincident UV–Vis spectra between fresh and reused catalysts were taken as evidences to support the stability of the supported metal species. Overall, this work shows the possibility to develop bimetallic silica-based catalyst to promote aerobic oxidations by NHPI while more insights are required to clarify the role of metal oxides during the catalytic process.

One of the interesting properties of silicas is their easy and reliable surface functionalization via condensation reaction between surface silanol groups and organic molecules or metal complexes bearing alkoxy silanes. In the field of catalysis by NHPI, a couple of papers have reported the use of SiO_2 to covalently anchor a Schiff cobalt complex that was further used as heterogeneous catalysts for aerobic oxidations using unsupported NHPI as cocatalyst [99,100]. Scheme 12 shows the preparation of a trimethoxysilyl Schiff base Co(II) complex and grafting to the surface of a mesoporous silica matrix. Characterization of the resulting solid by FT-IR spectroscopy, TGA, and atomic absorption spectroscopy revealed the silica functionalization with a cobalt complex loading of 0.3 mmol/g.



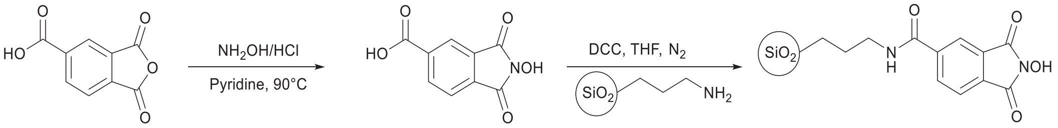
Scheme 12. Schematic representation of the synthesis of silica-Schiff base Co(II) complex (SSb-Co).

The Schiff cobalt complex grafted to mesoporous silica exhibited good to excellent catalytic activity for the aerobic oxidation of benzylic, aliphatic alcohols, and oxidation of ethylbenzene derivatives. Hot filtration test proved that the catalyst operates under heterogeneous conditions, and reusability was assessed up to five runs.

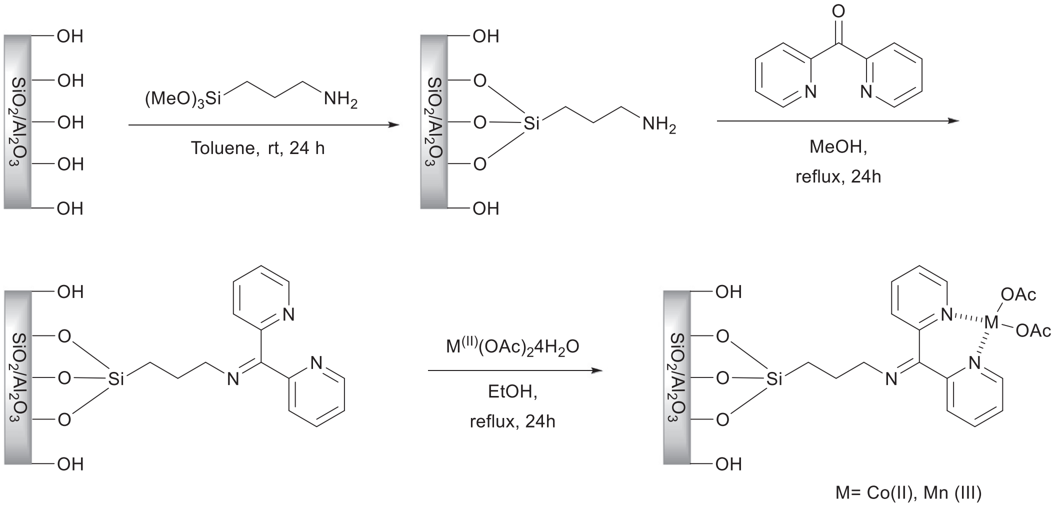
More interestingly, the same authors combined the Schiff cobalt complex anchored to mesoporous silica (Scheme 13) with other mesoporous aminopropylsilica (AMPS) functionalized with NHPI moieties [92]. The catalyst resulted to be active for the aerobic oxidation of toluene derivatives using acetic acid as solvent and atmospheric oxygen pressure. The hot filtration test proved the system to work in the heterogeneous phase. However, information on its stability and reuse data are lacking.

Similarly, a couple of studies reported the use of a Co(II) [93] or Mn(III) [94] Schiff base complex covalently grafted onto SiO_2-Al_2O_3 matrix (Scheme 14) as selective and reusable heterogeneous catalyst for aerobic oxidations in the presence of unsupported NHPI.

In particular, the catalytic systems were applied to the oxidation of ethylbenzene to acetophenone, cyclohexene to 2-cyclohexene-1-one as well as for the oxidative deprotection of oximes to their corresponding carbonyl compounds. Control experiments using Mn(II) supported on SiO_2-Al_2O_3 show poor activity and, thus, the good SiO_2/Al_2O_3-APTMS-BPK-Mn catalytic activity was proposed to arise from the heterogeneous Mn(III) Schiff complex. Both catalysts could be reused several times without significant loss of activity, and neither Co(III) nor Mn(IV) underwent leaching from the solid to the liquid phase. The cobalt catalyst



Scheme 13. Schematic representation of the anchoring of the NHPI core onto AMPS.



Scheme 14. Schematic representation of the preparation process of SiO_2/Al_2O_3-APTMS-BPK-M (M: Co or Mn) catalysts.

exhibited higher activity than the manganese one for the oxidation of ethylbenzene, but lower activity for the oxidation of oximes. Regardless of the proposed different redox properties of Co(II) and Mn(II) and the different abilities of these complexes to decompose the organic hydroperoxides, more experimental and theoretical evidences are required to gain a deeper understanding of the activity of these solids to promote the aerobic oxidation of organic compounds by O_2 in the presence of NHPI as cocatalyst.

More recently, a recoverable magnetic catalyst based on a Fe_3O_4 core and a SiO_2 shell covalently functionalized on the surface with APTMS was employed as support of a metformin-cobalt complex to obtain Fe_3O_4@SiO_2-APTMS/CC/Met@Co(II) material [95]. The activity of this catalyst was tested in combination with unsupported NHPI for the aerobic oxidation of ethylbenzene and cyclohexene showing high conversion and almost complete selectivity to the corresponding ketones (>98%). However, the catalyst activity underwent significant deactivation for ethylbenzene conversion (86.7 to 23 %) and for cyclohexene conversion (from 94.1 to 65.4 %) during reuse until it largely inactivated after the 9th cycle. Thus, more efforts should be made for the development of a magnetically recoverable and stable catalyst based on SiO_2. In addition, a less synthetically demanding catalyst preparation would be also recommendable.

In another study, Jacobs and co-workers developed a metal-free heterogeneous catalyst based on NHPI impregnated on commercial silicas from different sources for the autoxidation of cyclohexane by molecular O_2 [96]. The ultimate goal of this work was to screen several silicas as support of NHPI. The activity of the different NHPI-loaded silicas was ranked based on O_2 consumption during cyclohexane oxidation. The use of silica or NHPI alone did not result in any O_2 consumption, thus highlighting the importance of the NHPI dispersion in an appropriate silica support to observe a catalytic effect. In contrast to a common observation when using silicas as heterogeneous catalysts, the activity of the NHPI-loaded silicas cannot be correlated as a function of the BET surface and the micro- and/or mesopores distribution.

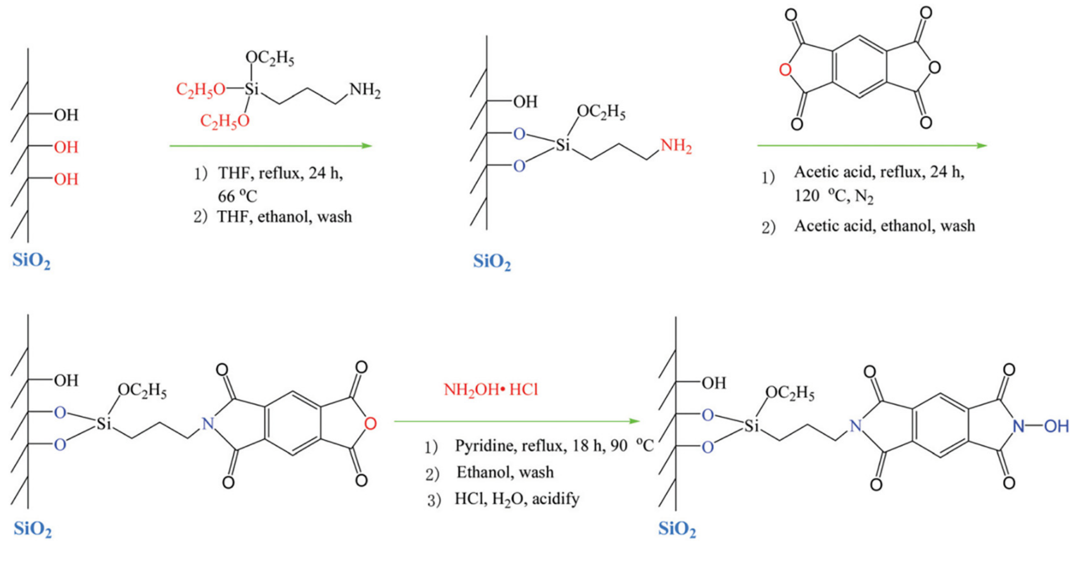
Importantly, it was concluded that the dominant key factor controlling catalytic activity is the Si distribution, the higher population of hydroxyl groups on the surface of the silica gels tends to deactivate the catalyst. In addition, the presence of alumina in the silica gels increases the polarity, inactivating silicas. The heterogeneity of the reaction was confirmed by performing the hot filtration test. The presence of an induction period was attributed to the time required to produce a minimum amount of hydroperoxides and to the leaching of a small fraction of NHPI (3 wt% respect to the initial loading) to the liquid phase. The catalyst drops its activity after one use, due to the adsorption of oxygenated hydrocarbons, such as adipic acid to the free silanol groups present in the fresh catalyst, as revealed by FT-IR spectroscopy. After the first cycle, the activity of the catalyst was maintained for consecutive reuses. The relatively high yield of cyclohexanone with respect to cyclohexane hydroperoxide was attributed to the ability of PINO to convert the organic hydroperoxide to ketone by abstraction of a second H-atom.

In a recent work, NHPI was covalently linked to SiO_2 (SiO_2-APTES-PMDA-NOH) by means of a precursor of PMDA as symmetric aromatic dianhydride and APTES as linking molecule (Scheme 15) [97]. The covalent grafting of NHPI was confirmed by FT-IR spectroscopy and TGA measurements. SiO_2-APTES-PMDA-NOH catalyst exhibited a grafting density of 0.70 $mmol_{N-OH}\ g^{-1}_{silica}$. The catalytic performance of SiO_2-APTES-PMDA-NOH was evaluated in the aerobic oxidation of ethylbenzene in the presence of $Co(OAc)_2$ in acetic acid medium at 90 °C. Under these conditions, the conversion of ethylbenzene was 63.8 % with 79 % selectivity to acetophenone, while other byproducts like benzoic acid (5.9 %), benzaldehyde (0.3 %) and 1-phenylvinyl acetate (14.6 %) were also observed. In contrast, the catalytic activity of $Co(OAc)_2$ and SiO_2-APTES-PMDA-NOH alone resulted into 2.8 and 0.4 % of conversions, respectively. On the other hand, SiO_2-APTES-PMDA-NOH was used for four cycles with no decrease in both the conversion of ethylbenzene and the selectivity of acetophenone. These results indicate that the structural integrity is retained without the detachment of NHPI from SiO_2.

It is interesting to highlight how, in contrast to what observed for NHPI/MOFs systems, examples in which both transition metals and NHPI are simultaneously attached on silicas are still limited. In fact, Table 4 shows examples where either the transition metal is attached to the silica through a metal–ligand complex, or a NHPI unit has been anchored on the silica surface through APTES, while examples of simultaneous attachment, are still missing.

5.4. Carbons as supports

Traditionally, carbonaceous materials have been among the preferred solids for the development of heterogeneous catalysts for both academic and industrial applications [101–105]. Some of



Scheme 15. Proposed synthetic route of the catalyst SiO_2-APTES-PMDA-NOH. Reproduced with permission from ref. [97].

their important physicochemical properties for catalysis include their high thermal and chemical stability, high surface area and good adsorption capacity. Importantly, the physicochemical properties of the carbonaceous materials can be easily tuned by chemical and/or thermal treatments. During the XXth century, activated carbon obtained from biomass has been a clear example of sustainable support and has been widely used in the chemical industry. The field of carbonaceous materials has been continuously growing with the discovery of additional carbon allotropes [106–111]. Therefore, there is an increasing interest in developing carbon supports for heterogeneous catalysis exhibiting superior activity. Table 6 summarizes the activity and stability reported for NHPI supported over carbon-based materials for the oxidation reaction.

In this context, Garcia and co-workers have reported catalytic activity of NHPI covalently anchored to the hydroxylated surface of D NPs as metal-free catalyst for the aerobic oxidations of hydrocarbons including benzylic compounds and cyclic olefins [112]. Since D NPs are produced in explosive detonation they have become widely available on a multigram scale for a number of applications. The resulting diamond blend from detonation is constituted by a core of crystalline sp^3 carbon network doped with nitrogen atoms (2.5 %) and a shell of amorphous carbon with graphitic domains and some oxygen and nitrogen functional groups. The reader is referred to an existing review on the preparation and use of D NPs for catalytic applications [118].

Scheme 16 illustrates the preparation of a NHPI derivative covalently grafted to previously purified and surface hydroxylated commercial D NPs (NHPI/D), which was submitted to a Fenton treatment followed by hydrogen annealing. The aim of this chemical and thermal treatment is the removal of soot matter embedding the D NPs as well as surface functionalization with hydroxyl groups. The covalent tethering of the NHPI was confirmed by in-depth characterization of the D NPs via X-ray photoelectron spectroscopy (XPS), magic angle spinning ^{13}C NMR, FT-IR spectroscopy, and TGA. For comparison purposes, analogous functionalization treatment was employed for the preparation of NHPI covalently anchored to activated carbon (AC) and multiwalled carbon nanotubes (MWCNTs). In all cases, NHPI loading on the carbon support was estimated to be 4 %.

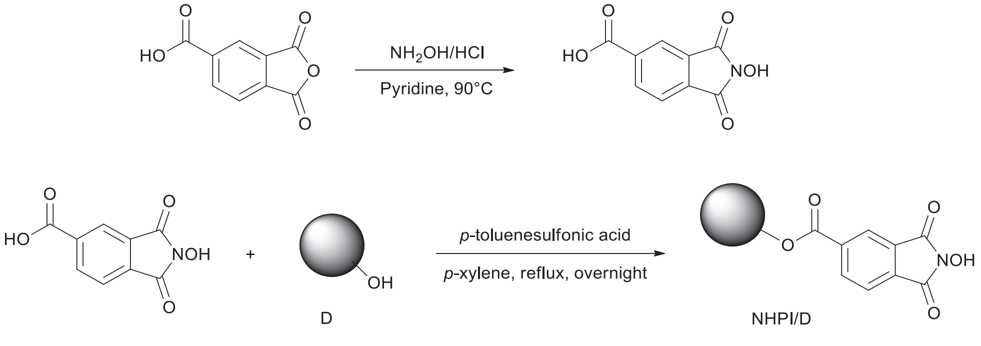
The high activity of NHPI/D NPs was ascribed to the inertness of the D support that facilitates the reaction of hydroperoxyl radicals as free species in the solution with the organic substrates via a chain radical reaction. These hydroperoxyl radicals were characterized by electron paramagnetic resonance spectroscopy using *N-tert*-butyl-α-phenylnitrone as a spin trap. In contrast, the catalytic activity of NHPI supported on AC and MWCNTs was negligible, a fact that was attributed to the presence of oxygen functional groups within the sp^2 carbon network that may quench the radical species. Commercial NHPI or its carboxylic derivative as homogeneous organocatalysts were comparatively much less active to NHPI/D NPs. This observation was explained considering the long lifetime of PINO radicals present on the inert D support, allowing the efficient promotion of the hydrocarbon oxidation through a radical chain mechanism. Further, NHPI/D was reused three consecutive times for the aerobic oxidation of butylbenzene, observing only a small decrease in its activity. Characterization of the three-times used catalyst by FT-IR spectroscopy and TGA revealed the partial oxidation of the catalyst and the presence of adsorbed organic molecules (12 wt%). These observations were considered as evidence to justify the partial activity loss. A TON of 20,600 (based on the NHPI loading) was estimated for the selective aerobic oxidation of isobutylbenzene to benzoic acid at its full conversion.

In addition to the use of D NPs as supports, another study has reported that polymeric g-C_3N_4 is also a suitable support to adsorb NHPI to obtain g-C_3N_4/NHPI and reported as a reusable metal-free catalyst for aerobic oxidations [113]. The g-C_3N_4 was prepared by heating melamine at 3 °C/min up to 550 °C for 4 h in a muffle furnace. XRD, FT-IR spectroscopy, and SEM were used to confirm the

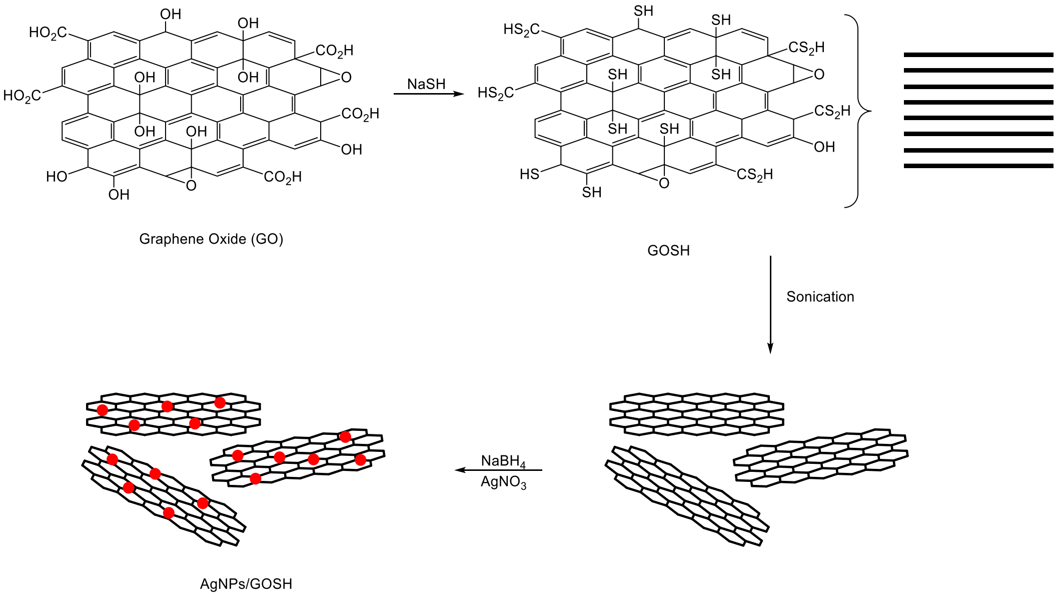
Table 6
Summary of NHPI supported on carbon solids as heterogeneous catalysts for oxidation reactions.

Material	Substrate	Con. (%) / Sel. (%)	Major product	General remarks	Ref.
NHPI/D	Isobutylbenzene	95/92	Benzoic acid	Used for three cycles; NHPI degraded after three uses.	[112]
g-C_3N_4/NHPI	α-IP	74.8/44.4	KIP	Used three cycles and no decay in activity	[113]
Co_3O_4/rGO, NHPI	Ethylbenzene	84.1/96.2	Acetophenone	Used for five cycles with a slight decay in activity	[114]
Ag NPs/GOSH	Benzyl alcohol	61/58	Benzaldehyde	Five cycles reused with a gradual decay in activity.	[115]
NHPI-HCMS	1-Phenylethanol	42/96	acetophenone	Used six cycles without any decay in conversion/selectivity	[116]
NHPI-NPCS	Ethylbenzene	45/72	acetophenone	Activity retained for nine cycles.	[117]

Abbreviations: D: diamond; g-C_3N_4: graphitic carbon nitride; rGO: reduced graphene oxide; GOSH: thiolated graphene oxide; HCMS: hydrothermal carbon microspheres; NPCS: nanosized porous carbon spheres.



Scheme 16. Synthesis of NHPI/D NPs.



Scheme 17. Preparation procedure of Ag NPs/GOSH catalyst preparation.

formation of g-C_3N_4. The catalyst can promote the aerobic oxidation of allylic positions of compounds such as α-IPand cyclohexene as well as benzylic compounds such as tetralin, indane, fluorene, and toluene. Among the various conditions tested for the optimization, the oxidation of α-IP with g-C_3N_4/NHPI afforded 74.8 % conversion with the selectivity to KIP of 44.4 % at 130 °C after 5 h. Further, the catalyst retained its stability for three cycles without any decay in its activity. It would have been important to compare the activity of NHPI/g-C_3N_4 with other related solids to rank its activity under the same reaction conditions. Regarding the reaction mechanism, it was proposed that g-C_3N_4 is activated upon heating and leads to an electron jump from the valence band to the conduction band. Then, this electron may react with O_2 and form $O_2^{\cdot-}$ that further can react with NHPI leading to the formation of PINO and then, several steps were proposed for the oxidation of the organic substrates. However, there is no spectroscopic evidences of this proposed reaction mechanism involving the thermal generation of an excited electronic state and, thus, further studies are required to obtain insights about the use of NHPI/g-C_3N_4 to understand the observed catalytic activity.

In another comparative study, Co_3O_4 NPs supported on rGO showed higher catalytic activity with respect to analogous catalysts based on AC or graphite powder for the aerobic oxidation of ethylbenzene using NHPI as cocatalyst [114]. Further, NHPI resulted to be a better initiator in terms of conversion and selectivity with respect to the use of dibenzoyl peroxide (BPO), TEMPO, and AIBN although more insights are required to understand the reasons for this higher activity. The catalyst can be reused up to five times with only a slight decrease in catalytic activity. XRD and SEM-energy dispersive X-ray spectroscopy (SEM EDX) of the five-times used catalyst confirm its stability although it would be recommendable to verify if graphene prevents aggregation of Co_3O_4 NPs. It is well-known in the literature that the use of different carbonaceous materials, even if prepared under the same conditions, frequently determines different metal NP size distribution and sometimes different metal loading, and these two parameters strongly affect the observed catalytic activity. To highlight convincingly the advantage of using rGO as support, the activity of Co_3O_4/rGO (23 nm average particle size and 35.8 wt% of Co_3O_4) catalyst should have been compared with samples of the same cobalt loading and cobalt average particle size distribution deposited on AC and graphite, while the study did not pay sufficient attention to these parameters. Thus, more studies are required to understand the origin of the higher activity observed.

In another study, Ag NPs supported on thiolated rGO (Scheme 17) exhibited higher catalytic activity with respect to

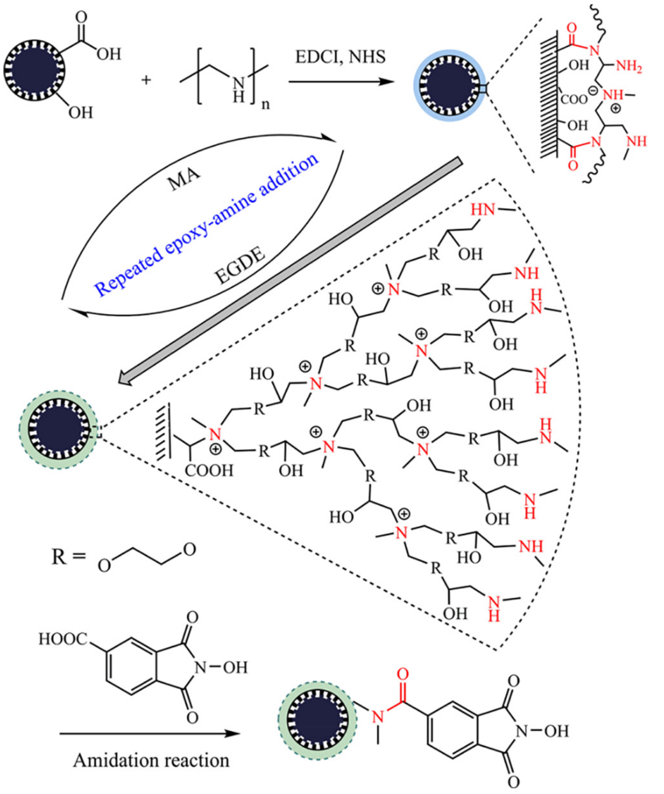


Fig. 7. Synthesis of NHPI-HCMS solid catalyst. Abbreviations: EDCl: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride; NHS: N-hydroxysuccinimide; MA: methylamine; EDGE: ethylene glycol diglycidyl ether. Reproduced with permission from ref. [116]. Copyright 2021 American Chemical Society.

the use of GO or rGO for the aerobic oxidation of benzyl alcohol using NHPI as cocatalyst [115]. The higher activity of the thiolated catalyst compared to other systems employing rGO or GO as supports, could be mainly due to the stabilization of small Ag NPs by thiol groups, allowing its reuse for five consecutive runs without significant loss of catalytic activity. As generally observed in catalysis by metal NPs, this work shows that the smaller the metal NP, the higher its catalytic activity.

Recently, a reusable and metal-free catalyst consisting of HCMS covalently attached to NHPI (NHPI-HCMS) was prepared and its activity was tested in the aerobic oxidation of 1-phenylethanol in acetic acid at 90 °C [116]. The covalent attachment of NHPI to HCMS was performed by grafting a hyperbranched polyquaternary amine through ring-opening reactions using diglycidyl ether, and subsequent amidation with 4-carboxy-NHPI (Fig. 7). Under the reported conditions, NHPI-HCMS promoted a 42 % conversion with 96 % selectivity to acetophenone. In contrast, the activity of NHPI with similar loading as in the case of NHPI-HCMS provided 18 % conversion with 55 % selectivity to acetophenone. These experimental catalytic data clearly support the superior performance of the heterogeneous catalytic system. Furthermore, NHPI-HCMS was used for six cycles without observing any decrease in the conversion/selectivity. In addition, reused NHPI-HCMS showed no chemical and morphological modifications by FT-IR and SEM analyses respectively, with respect to the original catalyst.

Extending further this strategy, the same group has prepared NPCSs with < 100 nm from soluble starch as carbon source and NHPI was covalently anchored on it through a sequence of processes involving polyamidamine dendrimer-based quaternization and amidate modification with 4-carboxyl-NHPI to give (NHPI-NPCS). (Fig. 8) [117]. These dendrimeric NPCSs make it possible to load 6.09 mmol/g of NHPI which is a remarkably high value. The catalytic performance of NHPI-NPCS was studied in the aerobic oxidation of ethylbenzene to acetophenone in acetic acid at 95 °C. Under these optimized experimental conditions, the activity of NHPI-NPCS was 45 % conversion of ethylbenzene and 72 % selectivity to acetophenone. In contrast, 18 % conversion of ethylbenzene with 21 % selectivity to acetophenone was observed with NPCS without NHPI under identical conditions. These data indicate the synergistic effect derived from the combination of NHPI and quaternized dendrimer structure in NHPI-NPCS solid. Furthermore, NHPI-NPCS solid retained its activity for nine cycles with no decay either in conversion or selectivity. The dendrimeric nature of NPCS is also retained after nine cycles. These catalytic and stability data firmly confirm the robust nature of NHPI-NPCS in promoting aerobic oxidation reactions. This solid was also used for the aerobic oxi-

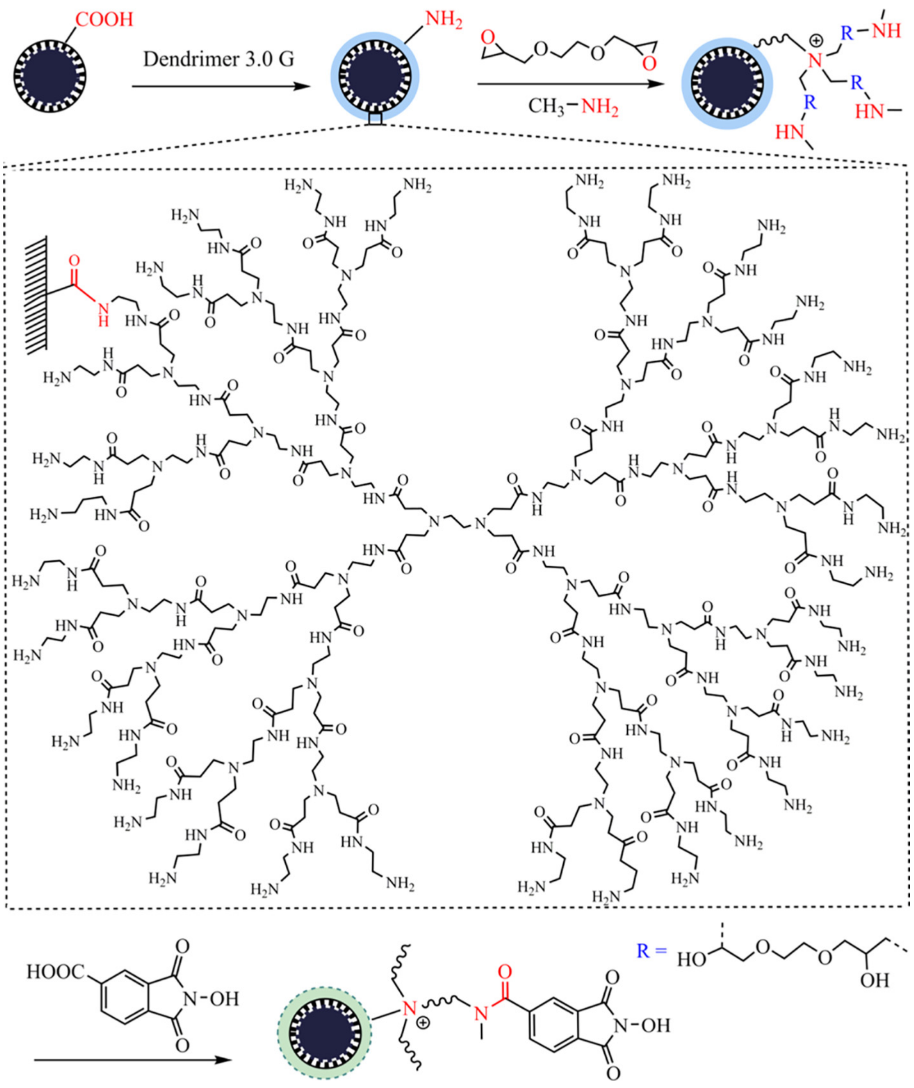


Fig. 8. Various synthetic steps in the immobilization of NHPI over NPCS to obtain NHPI-NPCS. Reproduced with permission from ref. [117]. Copyright 2022 American Chemical Society.

dation of other benzylic hydrocarbons with conversions ranging between 30 and 48 % and selectivity of 67–76 %.

In summary, the current state of the art shows that despite the large variety of active carbons and carbon allotropes, the number of examples in which NHPI has been attached covalently to the carbon support is still limited.

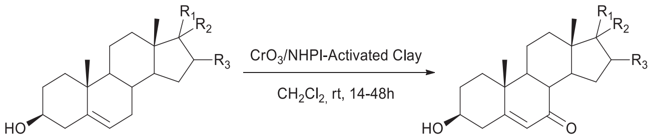
Interestingly, it has been shown that the high activity of D NPs partially arises from its surface inertness while the use of g-C_3N_4 may act as a source of electrons upon heating to initiate the reaction.

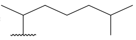
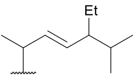
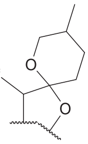
Furthermore, since AC has a very large surface area and is a well-known support for transition metal and transition metal oxide NPs, the still limited number of examples of heterogeneous carbon supported NHPI catalysts is somehow unexpected. Hydrophobicity and high specific surface area, together with material availability are major features that can be exploited to develop novel advanced solutions.

5.5. Zeolites as supports

Zeolites are a class of microporous crystalline aluminosilicate minerals with the general formula $M_{x/n}[(AlO_2)_x(SiO_2)_y]\cdot mH_2O$. Zeolites are widely applied in the chemical industry as exchangers, adsorbents, or catalysts, among other uses. In one example combining zeolites and NHPI, nanozeolite NaY was employed to covalently support an NHPI derivative, and further used in the oxidation of hydrocarbons and benzyl alcohols using H_2O_2 as oxidant [119]. In particular, a high activity was achieved with zeolite ZSM-5 as support. Also, ZSM-5 exchanged with various transition metals has been reported as catalyst for the aerobic oxidation of cyclohexane using NHPI as cocatalyst [120]. Control experiments showed that at the same metal loading the activity of the heterogeneous metal-ZSM-5 catalyst resulted higher respect to the use of the metal salt precursor. The most active catalyst of the series was Co(II)/ZSM-5 followed by Mn(II)/ZSM-5 and with lower activity Zn(II)/ZSM-5, Fe(III)/ZSM-5 and Ni(II)/ZSM-5. The higher activity of Co(II) and Mn(II) was attributed to the ability of these metals to undergo reversible one-electron transfer as key step of the aerobic oxidation mechanism using NHPI as cocatalyst. In the case of Mn(II) the easy two-electron oxidation to O = Mn(V) may hamper the one-electron transfer redox cycle that occurs in the case of Co(II)/Co(III). The Co(II)/ZSM-5 can be used for five consecutive uses with gradual conversion decrease from 28.4 to 22.4 %, attributed to the observation of cobalt leaching. Although the leaching value around 0.01 wt% of the initial amount was low, it could however correspond to the most active sites.

Table 7
Aerobic oxidation of different steroids using the CrO_3/NHPI-activated bentonite system.[a]



Entry	Substrate	Yield [%]
1	R_3 = H, R_1,R_2 = O	67
2	R_1,R_3 = H, R_2 = $COCH_3$	54
3	R_1,R_3 = H, R_2= 	52
4	R_1,R_3 = H, R_2=  Et	40
5	R_1 = H, R_2,R_3=  O O	58

[a]Reaction conditions: substrate (5 mmol), Catalyst (5.8 g, 8 mmol CrO_3 content), RT.

5.6. Clays as supports

Besides zeolites, clays have also been commonly used as supports. Bentonite or activated clay is a mineral with the general formula as $Na_{0,5}Al_{2,5}Si_{3,5}O_{10}(OH)_2\cdot(H_2O)$. One of the few existing examples using clays in combination with NHPI to promote aerobic oxidations has shown that CrO_3 and NHPI impregnated on activated clay can promote the selective allylic oxidation of Δ^5-sterols introducing an allylic ketone group with moderate yields (40–67%; Table 7) [121]. The mild conditions employed during the reaction avoid the oxidation of a 3β-hydroxyl group present in the sterol structure and, therefore, the use of protecting groups is not required. A decrease in catalytic activity of about 15 % was observed upon catalyst reuse. It should be noted that the used catalyst was recovered by filtration and submitted to thermal treatment at 120 °C for 4–6 h. Thus, it was proposed that the decrease in catalytic activity was due to the presence of adsorbed reagents or products blocking the active sites. More studies are required to exploit the potential use of clay-supported NHPI systems for the aerobic oxidations.

6. Heterogeneous catalysis using NHPI as cocatalyst

As commented previously, the main purpose of the present review is to critically discuss the development of heterogenized NHPI solids and their use as catalysts for oxidation reactions. Aiming in this direction, there are numerous studies in which solid catalysts, such as hydrotalcites, metal-oxides, and POMs have been used in combination with dissolved NHPI as a cocatalyst. It should be noted that given the poor solubility of NHPI in common solvents and its adsorption on solid surfaces, these studies can be taken as precedents for the development of heterogenized NHPI catalysts. Thus, the following sections summarize these studies, bridging the field of homogeneous and heterogeneous NHPI catalysis.

6.1. Hydrotalcites as supports

Other common types of layered inorganic support [122] used in chemical industry are hydrotalcites. These are layered double hydroxides (LDHs) of di-and trivalent ions with brucite structure. The proportion of the trivalent ions can be 30 % or lower and their presence introduces a positive charge in the layer that must be compensated by the presence of anions in the required proportion loaded in the intergallery space. The main characteristics of this type of materials to be employed as catalysts include low cost, reliable synthesis, and large flexibility in the nature of the di- and trivalent cations as well as the charge compensating anions. Table 8 provides a list of examples using LDH-based solids as heterogeneous solid catalysts with NHPI as a cocatalyst for oxidation reactions.

In one of the earlier studies, Cu(II)-Al(III) hydrotalcite showed good catalytic activity for the allylic oxidation of cyclic olefins using NHPI as a cocatalyst and TBHP as oxidant [123]. More interestingly, a cobalt porphyrin was intercalated between the layers of a ZnAl hydrotalcite (CoTPP-Zn_2Al-LDH) by the simple addition of zinc and aluminum salts to a slightly basic aqueous solution of sodium CoTPP (pH: 8.5) [124]. Thus, the obtained material was used as reusable catalyst in the presence of NHPI for the aerobic oxidation of different primary and secondary alcohols in moderate

Table 8
LDH-based solid catalysts with NHPI as a cocatalyst for aerobic oxidations.

Material	Substrate	Con. (%) / Sel. (%)	Major product	General remarks	Ref.
Cu(II)-Al(III) LDH+ NHPI cocatalyst	α-IP	68/81.8	KIP	Used five cycles with no loss in activity	[123]
CoTPP-Zn_2Al-LDH+ NHPI cocatalyst	cyclohexanol	91/99	cyclohexanone	Reused five times with no loss in activity	[124]
CoTPP-Zn_2Al-LDH+ NHPI cocatalyst	Ethylbenzene	90/99	acetophenone	Five times reused with no activity decay.	[125]
Co_2Al-LDO+ NHPI cocatalyst	Ethylbenzene	52.4/92.3	acetophenone	Activity retained for six cycles with no decrease in conversion/selectivity	[126]

CoTPP: tetrasulfonic phenylporphyrin; LDO: layered double oxide.

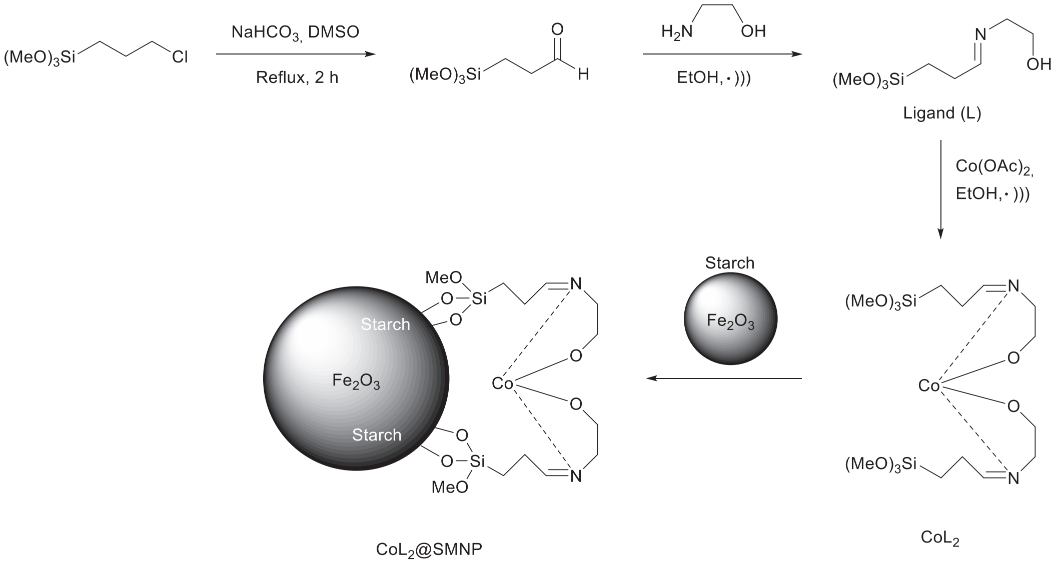
to high conversions. The selectivity to aldehyde was around 70%, while to ketones was always 99%.

Later, the same group has shown that CoTPP-Zn_2Al-LDH exhibits higher activity in terms of conversion and selectivity than their analogous based on Cu, Fe, and Mn for the aerobic oxidation of ethylbenzene in the presence of NHPI [125]. As commented before, the high activity of the CoTPP LDH was mainly attributed to the ability of Co(II) to react with O_2 forming a Co(III)OO$^{\cdot}$ radical, to the high reduction potential of Co(III) to Co(II), as well as to the stability of this redox pair during the catalytic cycle. Interestingly, CoTPP-Zn_2Al-LDH showed higher activity than the unsupported CoTPP complex as catalyst. Additional experiments showed that the use of CoTPP with NaOH or Na_2CO_3 further increases the activity of the unsupported catalyst. Thus, a synergistic effect between CoTPP intercalated in the LDH and the basic character of LDH resulted in a catalyst with enhanced activity. The CoTPP LDH was reused five times without loss of activity and the structural stability was revealed by powder XRD, with absence of cobalt leaching. The catalyst also showed the ability to selectively oxidize a large variety of benzylic compounds to their carbonyl derivatives. In the case of the oxidation of ethylbenzene with different substituents, the observed negative slope indicates the higher reactivity of the ethylbenzene derivatives bearing electron donor groups. Overall, this work shows the feasibility of developing active, reusable, and stable bifunctional catalysts based on CoTPP and LDH for the selective aerobic oxidation of ethylbenzene derivatives with NHPI and O_2.

In a recent work, a series of Co-based solids has been prepared from Co_2Al-LDHs through calcination at different temperatures, leading to the formation of Co_2Al-LDO [126]. The catalytic performance of the resulting solids was examined in the aerobic oxidation of ethylbenzene to acetophenone. Among the various reaction conditions screened, the use of Co_2Al-LDO(250) prepared at 250 °C showed the highest conversion of ethylbenzene (52.4 %) with high selectivity to acetophenone (92.3 %) when using NHPI in solution in trifluorotoluene at 100 ℃. In contrast, Co_2Al-LDO (250) without NHPI showed <5 % conversion under identical conditions. Further, the activity of NHPI alone as catalyst exhibited 14.6 % conversion with 72.6 % selectivity to acetophenone. These results suggest that the superior activity of Co_2Al-LDO(250) in combination with NHPI is due to its high specific surface area and high density of Co^{2+} sites on the surface. The catalyst retained its activity for six cycles with no decay in its conversion/selectivity.

6.2. Metal oxides-based catalysts

Beyond silicas, other metal oxides offer many advantages for their use as catalysts. Metal oxides can exhibit good thermal and chemical stability as well as high surface area, and the possibility to give rise to mesoporous materials. The area is still mostly unexplored and only a few studies employing metal oxides have been reported to develop heterogeneous catalysts for aerobic oxidations using NHPI. In one of these examples, the possibility to develop magnetically separable catalysts to facilitate their reusability was

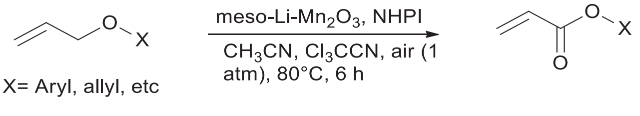


Scheme 18. Preparation procedure of CoL_2@SMNP.

shown [127]. In particular, a cobalt Schiff base was covalently anchored to the surface of magnetic Fe_2O_3 NPs coated with starch by using alkyl trimethoxy silane route (Scheme 18) to obtain CoL_2@SMNP (SMNP: starch coated maghemite NPs). This solid was used as stable and reusable nanocatalyst (10–15 nm particle size) achieving medium to good yields for the aerobic oxidation of benzyl alcohols and alkylaromatics using NHPI as cocatalyst under mild reaction conditions. As examples, the aerobic oxidation of benzyl alcohol to benzaldehyde resulted in 97 % yield at 70 °C, while ethylbenzene was converted to acetophenone in 97% yield at the same temperature. The activity of CoL_2@SMNP was retained for five cycles.

Other possibilities that metal oxides offer for the development of catalysts with enhanced activity include doping with other metals or even non-metals. Using this strategy, CeO_2 nanocrystals doped with copper resulted in a heterogeneous catalyst with increased catalytic activity for the aerobic oxidation of benzylamines to their corresponding imines in the presence of NHPI [128]. An optimized $Ce_{0.95}Cu_{0.05}O_2$ catalyst was prepared by hydrothermal synthesis at basic pH using Ce(IV) and Cu(II) salts as metal precursors. The Cu-doped CeO_2 was characterized by several techniques, for example, XRD of the solid showed that Cu-doping into CeO_2 lattice induces a shift of the (1 1 1) diffraction peak to lower angles, indicating a lattice parameter increase that may be attributed to the generation of oxygen vacancies and/or Ce^{3+} in the lattice. Besides, the estimated crystal size of CeO_2 (19.3 nm) decreases upon Cu doping up to 13.7 nm, which may be a consequence of the restricted CeO_2 growth by Cu ions in the crystal lattice. XPS also showed a similar proportion of Cu(0)/Cu(I) and Cu(II), while Ce(IV) predominates ($\sim$80 %) with respect to Ce(III) ions. The Cu-doped CeO_2 showed enhanced catalytic activity with respect to the undoped one, which can be ascribed to the efficient PINO generation as revealed by FT-IR spectroscopy measurements. The doping Cu^{2+}/Cu^{+} was proposed to be responsible for NHPI activation to PINO, with Cu(II) which could be regenerated by O_2 and/or Ce^{4+}. Aerobic oxidation of benzylamine using $Ce_{0.95}Cu_{0.05}O_2$ was 97.8% conversion after 48 h at 110 °C. In contrast, CeO_2 afforded 31.4% conversion under similar experimental conditions. Regardless of the occurrence of some copper leaching upon catalyst reuse for four cycles, this work opens new routes for the development of stable and efficient doped metal oxides for aerobic oxidations with NHPI as cocatalyst.

In a related work, a lithium-impregnated mesoporous Mn_2O_3 solid exhibited high catalytic activity, when combined with NHPI, for the selective aerobic oxidation of allyl ethers to acrylate ester derivatives (Scheme 19) under mild conditions [129]. As an example, diallyl ether was oxidized to its respective ketone, as shown in Scheme 19, in 92 % yield under these conditions. Incorporation of lithium into Mn_2O_3 lattice may increase the basicity of the solid. However, in the present case, the origin of the catalytic activity improvement remains unclear. Besides, the catalyst only retains about 60 % of its initial activity after the fourth run and some manganese leaching occurs. Regardless of these observations, the study shows the potential use of doping with lithium and probably with other alkaline or alkaline earth ions as strategy for the development of cost-effective catalysts.



Scheme 19. Aerobic oxidation of allyl ethers to the corresponding acrylates using *meso*-Li-Mn_2O_3 catalyst.

6.3. POMs

In general, POMs are a particular class of metal–oxygen anionic clusters constituted by early transition metals such as Mo, W, and V with high oxidation states. These solids are frequently prepared by hydro- or solvothermal methods via Bronsted acid-base condensation-addition processes of two or more oxyacid salts. POMs and heteropolyacids offer many advantages for catalytic applications due to their structural versatility at an atomic or molecular level, leading to the formation of ten basic structures with unique and tunable physicochemical and redox properties [130].

In this context, a series of studies have shown the potential use of POMs as catalysts to promote aerobic oxidations using NHPI as cocatalyst. For example, a particular nanosized and porous POM, Keplerate, with a $Mo_{72}V_{30}$-based cluster ($Na_8K_{16}(VO)(H_2O)_5[K_{10} \subset [(Mo)Mo_5O_{21}(H_2O)_3(SO_4)]_{12}(VO)_{30}(H_2O)_{20}]\cdot 150H_2O$, Fig. 9), exhibited good activity as heterogeneous catalyst for the aerobic oxidation of benzyl alcohol to benzaldehyde and oxidation of benzylic hydrocarbon to its corresponding ketone with turnover frequency values between 43 and 400 h^{-1} [131]. The $Mo_{72}V_{30}$ showed superior activity with respect to the use of other metal salt precursors or analogous Keplerate-based catalysts, thus highlighting the role in the structure of $Mo_{72}V_{30}$-based cluster to promote the reaction. In addition, modification of the Keplerate $Mo_{72}V_{30}$-based cluster with organic cations, such as 1-methyl-3-octadecaneimidazolium or dioctadecyldimethylammonium, resulted in a decrease of activity due to the partial blockage of the active centers by these organic molecules. Interestingly, the use of TEMPO instead NHPI resulted in much lower activity, a fact attributed to the steric hindrance of methyl groups of TEMPO although other reasons may also influence the observed activity, also considering that TEMPO inhibits free-radical processes. Keplerate $Mo_{72}V_{30}$-based cluster retains over 90 % of the catalytic activity of the fresh material after the fifth use for benzyl alcohol oxidation and the solid maintains its integrity as revealed by XRD, FT-IR, and UV–Vis spectroscopic measurements. Hot filtration test and the negligible metal leaching indicated by ICP (<1ppm Mo, V) confirm the heterogeneity of the process. Regarding the reaction mechanism, the strong inhibition of the reaction in the presence of 2,6-di-*tert*-butyl-4-methylphenol was taken as an evidence for the occurrence of a radical reaction pathway, which could somehow

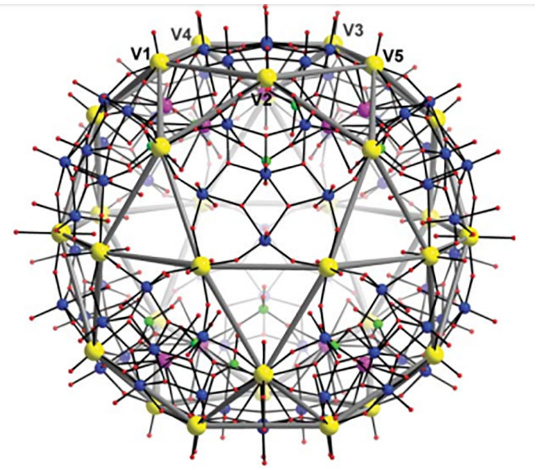


Fig. 9. Ball-and-stick representation of the V_{30} structural motif (view approximately perpendicular to the anion's C5 axis; Mo-blue, V-yellow, K-purple, S-green, O-red. Reproduced with permission from ref. [132]. Copyright 2005 Royal Society of Chemistry. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

explain the lower activity observed with TEMPO. The catalyst can perform the aerobic oxidation of benzyl alcohol and 1-phenylethanol with TON values of 4920 and 5850, respectively.

In a similar fashion, the same authors employed the Keplerate $Mo_{72}V_{30}$-based cluster as stable and reusable heterogeneous catalyst for the synthesis of a variety of benzimidazoles using benzyl alcohols [133]. Again, the $Mo_{72}V_{30}$ showed superior activity (99% yield) with respect to the use of other metal salt precursors or analogous Keplerate-based catalysts, although more insights are required to understand the reasons behind this higher activity. Regarding the reaction mechanism it was proposed that the role of the catalyst was to promote two aerobic oxidations in the presence of the catalyst, NHPI, and O_2. Regardless the absence of control experiments, it is likely to suppose that the catalyst promotes the aerobic oxidation of NHPI to PINO and the acid centers of the catalyst may participate in the condensation of the benzaldehyde with the 1,2-diaminobenzene as in analogous reports [134]. Thus, this work can serve as an example of the possibility of using active POM as multifunctional catalyst to promote tandem oxidation-cyclocondensation reactions involving aerobic oxidations and Lewis-acid catalyzed reactions.

In a related study, a 2D porous POM framework with the formula $Gd_4(H_2O)_{26}[WZn[Cu(H_2O)]_2(ZnW_9O_{34})_2]{\cdot}24H_2O$ (CZJ-11) and a related 3D porous POM $Gd_4(H_2O)_{24}[WZn[Cu(H_2O)]_2(ZnW_9O_{34})_2]{\cdot}11H_2O$ (CZJ-12) obtained by partial dehydration of CZJ-11 showed high catalytic activity for the aerobic oxidation of aliphatic alcohol in the presence of NHPI and tetramethylammonium bromide (TMAB) as cocatalyst and electron-transfer mediator, respectively to afford 96% yield [135].

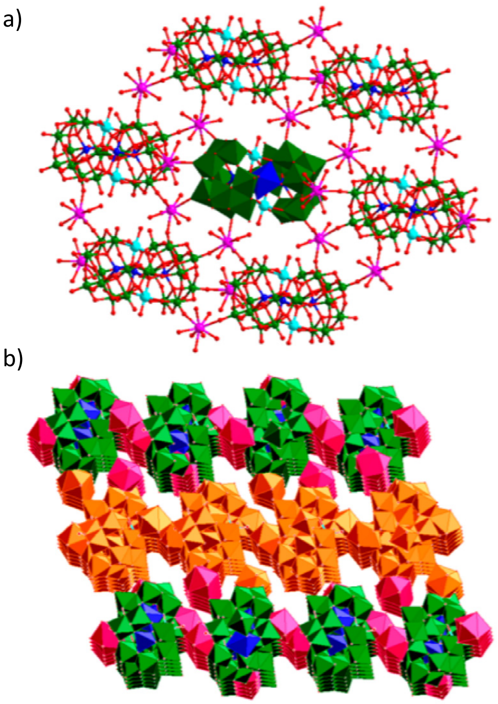
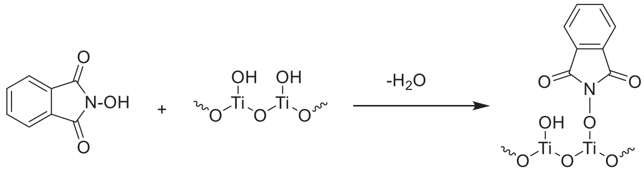


Fig. 10. (a) A view of the connections between $[WZn[Cu\text{-}(H_2O)]_2(ZnW_9O_{34})_2]^{12-}$ polyanions and Gd^{3+} ions in the 2D lamellar network of CZJ-11, in which one polyanion is highlighted in polyhedral model. (b) Packing pattern of CZJ-11 (the central lamellar network is highlighted as orange polyhedra). Color: Cu, cyan; W, green and yellow green; Gd, purple; Zn, blue; O, red. Reproduced with permission from ref. [135]. Copyright 2017 American Chemical Society. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)



Scheme 20. Illustration of $NHPI\text{-}TiO_2$ formation.

These solids exhibit redox active accessible and redox-active Cu (II) sites in the sandwich-type POM cluster $[WZn[Cu\text{-}(H_2O)]_2(ZnW_9O_{34})_2]^{12}$. Fig. 10 shows both 2D and 3D POM solids. These 2D and 3D POMs perform similarly and with higher activity and stability with respect to other related catalysts such as copper (II) perchlorate, molecular $[WZn[Cu(H_2O)]_2(ZnW_9O_{34})_2]^{12}$ or copper or iron tetraphenylporphyrins.

More evidence, however, to understand the proposed role of TMAB as electron-transfer mediator improving the electron transfer efficiency of the catalytic cycle would be recommendable. It should be noted that TMAB is commonly used as phase transfer catalyst rather than electron shuttle. Catalyst recycling indicates that the recovered 3D POM retains most of its initial crystallinity compared to the 2D analogue. This work showed the possibility of developing porous inorganic frameworks with enhanced activity and stability for aerobic oxidations of low-reactive primary aliphatic alcohols to their corresponding carboxylic acids.

7. Heterogeneous NHPI photocatalysts

In addition to thermal catalysis in which the activation energy is supplied by heat, some studies have also been investigated on the possibility of using heterogenized NHPI as visible-light-driven photocatalysts for oxidation reactions by molecular O_2. In most cases solid photocatalysts such as TiO_2 [136,137], $\alpha\text{-}Fe_2O_3$ [138], CdS [139], $Pd/BiVO_4$ [140], $AgI/BiVO_4$ [141], MIL-125(Ti) coated melamine-based polymer [142], or $g\text{-}C_3N_4$ [143] have been modified with NHPI as cocatalyst. In this context, recently, NHPI was attached to the TiO_2 surface (Scheme 20) [144]. The structural integrity and the covalent anchoring of NHPI over TiO_2 was confirmed by powder XRD, UV–Visible spectra, TEM, HRTEM, and XPS techniques. The resulting activity of the $NHPI\text{-}TiO_2$ conjugate was tested as visible light photocatalyst in the selective oxidation of amines into imines with atmospheric O_2 using blue LED irradiation. Among the various experimental conditions tested, $NHPI\text{-}TiO_2$ was able to promote the aerobic oxidation of benzylamine to its corresponding imine, reaching 73 % conversion with 98 % selectivity after 30 min in acetonitrile in the presence of TEMPO as cocatalyst. Control and quenching experiments clearly indicated that superoxide anion radical is primarily the main reactive oxygen species involved in this oxidation reaction. Furthermore, the scope of $NHPI\text{-}TiO_2$ photocatalytic oxidation was also studied for a wide range of substituted benzyl amines achieving more than 90 % conversion and 90 % selectivity to their respective imines under the optimized reaction conditions. Although this system exhibited high substrate scope, catalyst stability by providing reusability data were not reported. Also, characterization data of the reused solids were not provided and, therefore, information about catalyst stability is missing.

8. General remarks and conclusions

NHPI is probably one of the most relevant examples of organocatalyst for aerobic oxidation reactions. As commented in the introduction, NHPI-based oxidations, although benefiting from the presence of transition metals, can occur in their absence. Compared to conventional catalysts based on transition metals, organocatalysis has the advantage of sustainability, better use of natural resources, and lower environmental impact, generating a lower number of residues.

The present review aims to demonstrate, by an extensive search in the existing literature, that immobilization of NHPI by adsorption or covalent anchoring to insoluble solid materials may yield useful heterogeneous catalysts which can be easily separated from the reaction mixture and reused several times, reaching higher accumulated TON values, or implemented in continuous flow processes. Future research goals should be aimed at improving the catalytic activity of supported NHPI while increasing its stability and reusability, and at gaining selectivity on the product distribution. These objectives can be achieved by using appropriate supports, tuning their properties such as particle morphology and size, as well as pore geometry and dimensions. Research aimed at controlling surface polarity and preferential product absorption can eventually lead to avoid over-oxidation and to increase the yield of the desired products. At the moment, the role of the support has been mostly limited to ensuring NHPI recovery without paying attention to other potential benefits that could derive from an appropriate selection and we expect exciting developments in these regards in the following years.

The overview of the current state of the art shows that these NHPI-containing heterogeneous systems have been mostly used for oxidation at the benzylic position of aromatic hydrocarbons, and benzylic alcohol oxidation. Clearly, the scope of heterogenized NHPI catalysts must be considerably expanded, initially, at least, evaluating those substrates that are known to be effectively oxidized by NHPI under homogeneous conditions. Also, the increase in the number of NHPI derivatives used as actual constituents of the solid supports should be considered as an important part in the evolution of this research. Information on the reaction mechanism for heterogenized NHPI should also deserve more attention, and more detailed studies to determine the role of NHPI catalyst, either as initiator of long oxidation chains or as real catalyst participating in the formation of each product molecule, should be carried out in the future. Intermediate situations with short oxidation chains occurring within the pores or near the surface of the support are also possible, highlighting the importance to assess the chain length. Quenching studies can serve the purpose to estimate this chain length and to determine the reactive intermediates.

Finally, an appropriate design of the dimensions, polarity, and other properties of the reaction environment in which NHPI triggers the oxidation reaction should be also looked for. Confinement and polarity effects have appeared as powerful tools to control product distributions in otherwise unselective aerobic oxidation reactions. In this regard, considering the versatility in the synthesis of MOFs, we encourage the community to overcome these difficulties in the development of NHPI analogs, designed as organic functional linkers in which the catalytic properties of NHPI will be directly embedded into the material structural constituents.

Also, steps towards scaling up of heterogeneous NHPI oxidation, life cycle assessment, and techno-economic feasibility in comparison with current industrial processes based on metals are important missing information which needs to be gathered and that would lead heterogenized NHPI catalysts forward, eventually towards industrial implementation.

Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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