N-Hydroxyphthalimide (NHPI)/Lead Tetraacetate, a Peculiar System for the Phthalimide-*N*-Oxyl (PINO) Radical Generation

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Abstract: The development of efficient catalytic system for selective organic transformation is currently one of the challenging tasks in synthetic organic chemistry. In recent years, *N*-hydroxyphthalimide (NHPI) has been recognized as a valuable catalyst for the aerobic oxidation of various organic compounds under mild conditions. The generation of the phthalimide-*N*-oxyl (PINO) radicals from its precursor NHPI, can be achieved by using different ways including electrochemical, enzymatic and chemical methods. Among all of these methods, the use of lead tetraacetate for the PINO radicals' generation seems to be the most peculiar, several kinetic and mechanistic "anomalies" for this catalytic system being reported.

Keywords: *N*-hydroxyphthalimide (NHPI), phthalimide-*N*-oxyl (PINO), lead tetraacetate, reaction mechanism, catalyst.

I. INTRODUCTION

One of the biggest concerns nowadays is linked to the high level of the global pollution caused by old-fashioned industrial processes. Researchers have now focused to develop new "*environmentally-friendly*" technologies able to replace the older ones. One of the most common processes used in industry refers to the oxidation of various organic substrates. Clean and inexpensive oxidation methods are feasible research targets when using molecular oxygen as the oxidant. However, there is a serious limitation of this approach, because despite of the oxygen's diradical character, it cannot be used to oxidize strong C-H bonds, as in alkanes. To overcome this impediment, an adequate catalyst should be employed. A new organocatalyst, *N*-hydroxyphthalimide (NHPI), has recently been introduced as an effective catalyst towards a large variety of organic substrates. NHPI is easily prepared by the reaction of phthalic anhydride and hydroxylamine [1]. The general consensus is that the oxidation process occur *via* intermediate phthalimide-*N*-oxyl (PINO) radical, able to abstract a hydrogen atom from the organic substrate [2-6], forming a new carbon centered radical, reacting easily with dioxygen to give ultimately oxygenated compounds, Scheme **1**.

The generation of the PINO radicals from its precursor NHPI, can be achieved by using various methods, including the well-known "Ishii catalytic system" which implies the use of Co(II) or Mn(II) salts [7]. Due to metallic toxicity and high expense, in the last years, researchers have been concentrated on developing nonmetallic systems, which becomes frequently used. These metal free systems to generate NHPI includes compounds such as α,α-azoisobutyronitrile [8], peracids [9], dioxirane [10], NO_2 [11], anthraquinones [12], and other. The use of NHPI has become now more frequently in industry as well, due to its numerous advantages. Thus, many patents founded now materialization in industrial processes, in 2001, the Daciel Chemical Company in
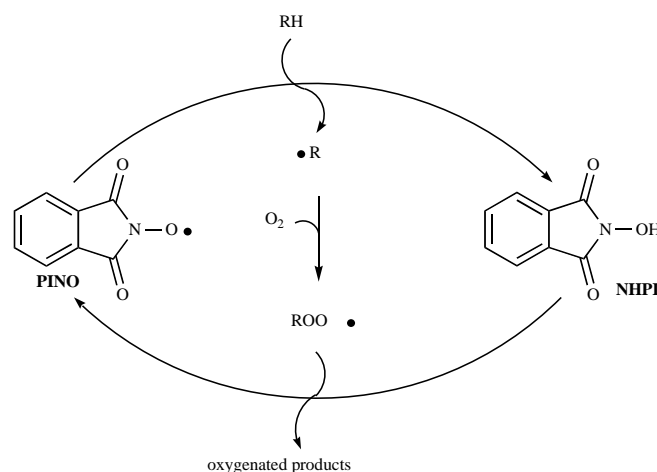

Scheme 1. The schematization of oxidation of RH substrate by PINO radical.

troduced at a large scale the synthesis of dihydroxyadamantane. Adipic acid and terephthalic acid, another chemicals produced in large quantity in industry are ready to be obtain into more environmentally friendly technologies by using NHPI, avoiding the use of previous expensive titanium reactors, cheaper stainless steel material being used instead. The use of NHPI is useful as well for the in situ production of epoxidizing agents and for the oxidation of the KA oil (cyclohexanol/cyclohaxeanone mixture) in order to obtain a valuable intermediate for the preparation of caprolactone or caprolactam.
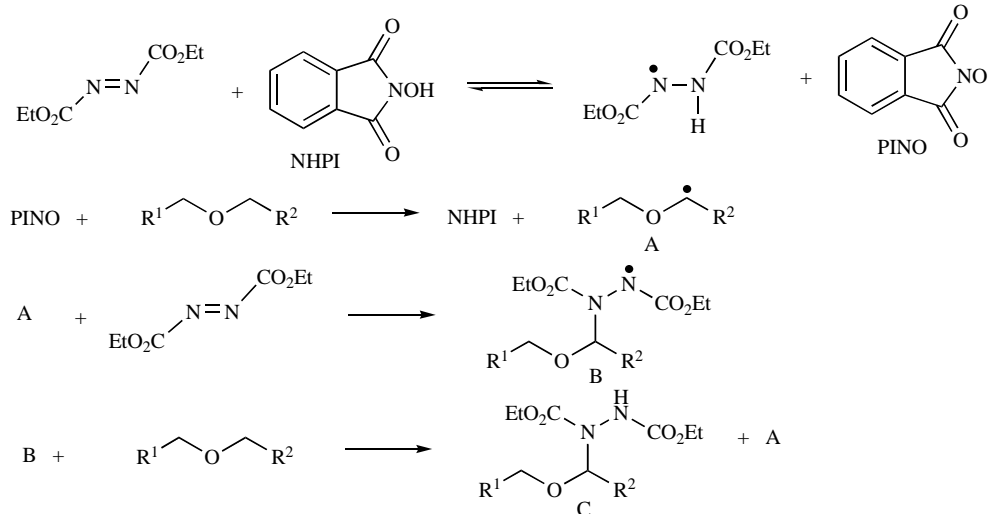
II. HISTORICAL BACKGROUND

NHPI/Pb(OAc)$_4$ system, was shown to produce PINO radical as early as 1964 by Lemaire and Rassat [13], using EPR spectroscopy, Scheme **2**. PINO presents a triplet signal with a hyperfine coupling constant in *t*-BuOH of $a_N = 4,36$ G, which is smaller than the constants of other nitroxyl radicals [3]. The *g*-factor in PINO is larger than that of other nitroxyl radicals; one explanation could be due to the presence of acyl groups linked to the nitrogen atom.

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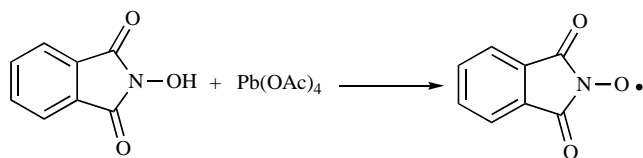
Scheme 2. NHPI/Pb(OAc)$_4$ reaction for PINO radical generation.

The first report on the catalytic use of NHPI, was in 1977 by Grochowski and coworkers as an addition reaction of ether to diethyl azodicarboxylate, Scheme **3** [14].

reactions with PINO, founded in acetonitrile and acetic acid were attributed to the formation of a hydrogen bond intermediate complex, Scheme **4**, adjacent with the quantum mechanical tunneling phenomenon [4].

III. NHPI/PB(OAC)$_4$ SYSTEM CONTRIBUTION AT DEVIATIONS FROM CLASSICAL MECHANISMS

Baciocchi *et al.* [15] employed the NHPI/Pb(OAc)$_4$ system to generate PINO radicals in acetonitrile (CH$_3$CN) and

Scheme 3. The use of NHPI in the reaction of ethers with azodicarboxylate (DEAD) [14].

Koshino [4] reported that the molar absorptivity of PINO generated from NHPI/Pb(OAc)$_4$ in acetic acid, is 1.36 x 10^3 L mol^{-1} cm^{-1} at λ_{max} 382 nm, (ε_{382} = 1360 L mol^{-1} cm^{-1}) (Fig. (**1**)).

Scheme 4. The hydrogen bond complex formation between PINO radical and organic substrates [4].

react with 4-X-substituted *N,N*-dimethylanilines, at 25 ^{o}C. The corresponding *N*-methylanilines were formed, but for this reaction, only low yields were obtained (up to 20 % referred to the starting material). Interestingly, the authors [15] claimed that for this process the hydrogen transfers from the N-CH$_3$ group to PINO *"does not occur by a classical free radical hydrogen abstraction mechanism (as suggested for the PINO reactions with benzylic C-H bonds)"*. Baciocchi *et al.* [15] proposed for this process a two-step mechanism (Scheme **5**) involving a reversible electron transfer from the substrate to PINO in the first step, that is supported by inter- and intramolecular deuterium kinetic isotope effects.

The cross-coupling product of PINO and α-aminomethyl radical formed by the PINO-induced hydrogen abstraction from the N-Me group of the substrate (path c, Scheme **5**) was detected by authors [15], only before the reaction work-up, otherwise this adduct can react with small quantities of water present in the solvent, forming a carbinolamine which decomposes into the *N*-methylaniline (path f, Scheme **5**) and CH$_2$O. In another study, Baciocchi *et al.* [16], investigate the reactivity of the PINO toward the OH bond of a series of substituted phenols, Scheme 6, PINO radical generation be-
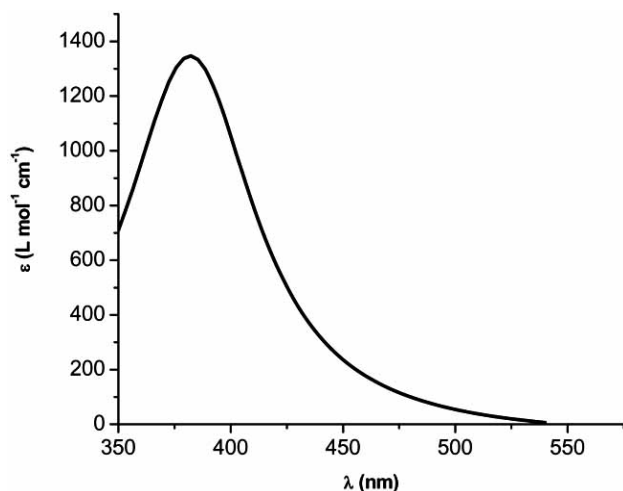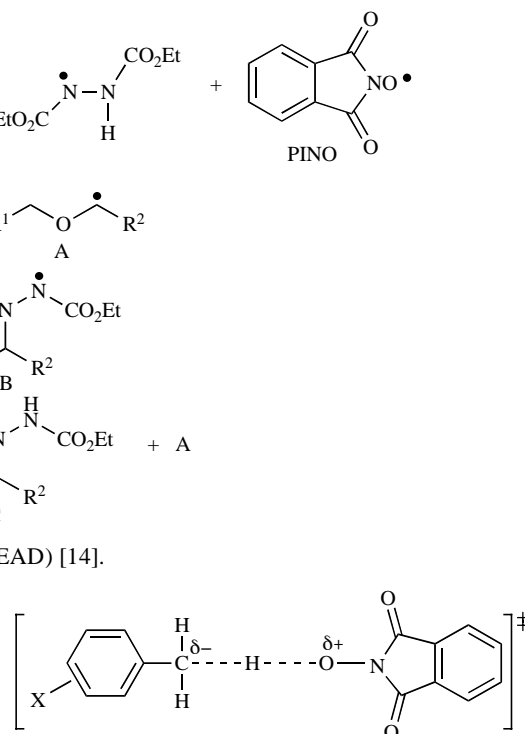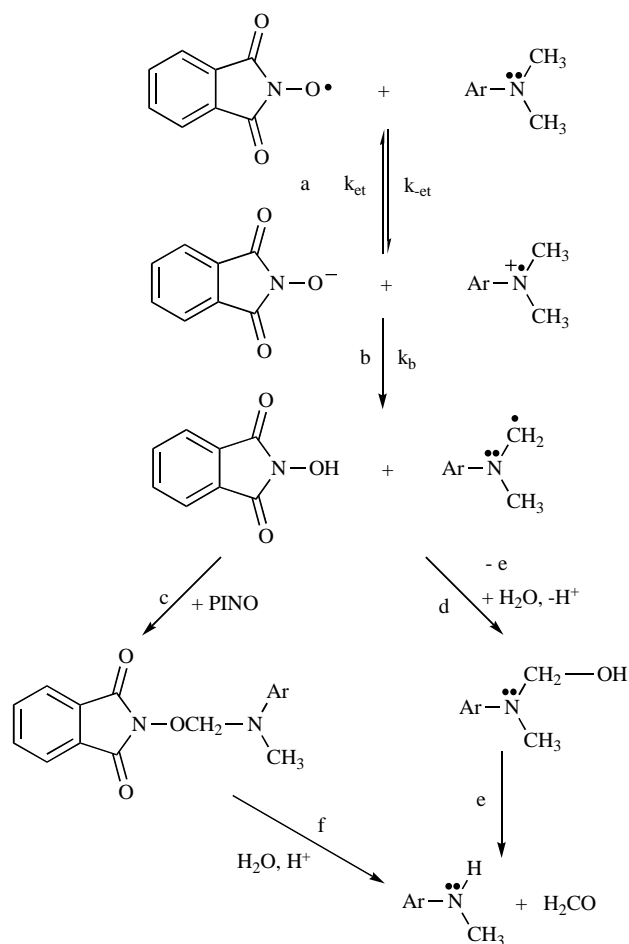

Fig. (1). Spectrum of PINO radical in acetic acid.

The above-mentioned authors, [4] investigate the reactions of PINO with substituted toluenes, benzaldehydes, and benzyl alcohols, presenting the PINO's reactivity with these species in terms of polar effects (Hammett analysis) and kinetic isotope effects. The differences between the rate constants for the *p*-xylene, benzaldehyde and benzyl alcohol

**Scheme 5.** (15) PINO radical reaction mechanism with 4-X-substituted *N,N*-dimethylanilines.

ing achieved by the reaction between NHPI and Pb(OAc)$_4$ in CH$_3$CN.

To simplify the analysis of the complex reaction mixture obtained, Bacciocchi *et al.* [16] used a substituted phenol, such as 2-*tert*-butyl-4-methylphenol as substrate. It was found that the major product for this reaction it that coming from the cross-coupling of PINO with phenoxyl radical, Scheme **7**.

Based on the cross-coupled product formed in the above-mentioned reaction, Baciocchi *et al.* [16] acquiesce to the Mayer and his associate opinion [17, 18] that "*a reaction*
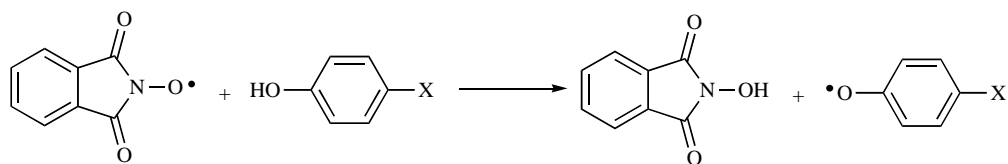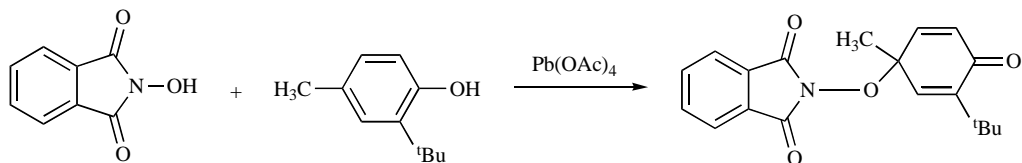
between an oxyl radical and phenol can be better seen as proton coupled electron transfer (PCET) rather than as classical hydrogen atom transfer (HAT)". In a PCET reaction a hydrogen-bonded complex is first formed between the reactants, and the electron and the proton are transferred through different orbitals.
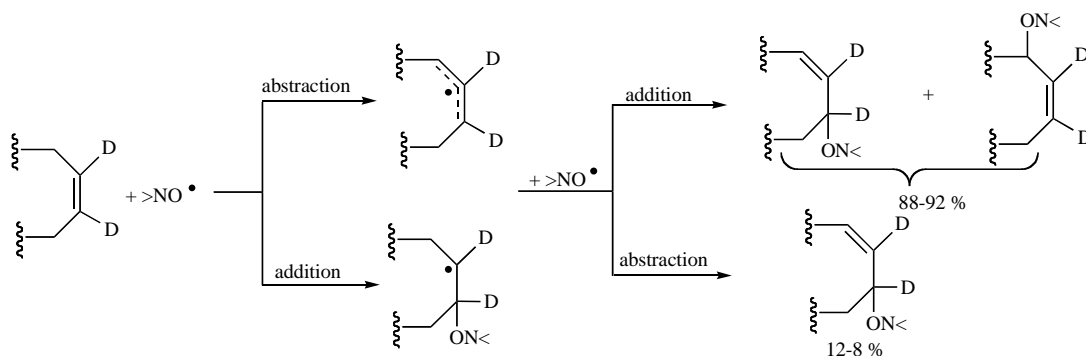
IV. NHPI/PB(OAC)$_4$ SYSTEM IN REACTION WITH ALKENES

Our previous work, [19, 20] was devoted distinguishing between abstraction-addition and addition-abstraction mechanisms, as the first step of the reaction of aminoxyl (nitroxyde), iminoxyl, and imidoxyl radicals with alkenes. We have used 2,2,6,6-tetramethyl-4-piperidine-*N*-oxyl (TEMPO), di-*tert*-butyliminoxyl and PINO (generate by using *tert*-alkoxyl radicals and lead tetraacetate) radicals, in reaction with dideuterated alkenes, such as: 1,2-dideuterio-cyclohexene, 1,2-dideuterio-cyclooctene, and *trans*-3,4-dideuterio-hex-3-ene. In all cases, except the NHPI/Pb(OAc)$_4$ system, only mono >NO-substituted alkenes were produced, and 88-92 % of monoadducts were formed by the initial abstraction of an allylic H-atom, followed by capture of the allylic radical by a second >NO•. The remained 12-8 % product appeared to be formed by the initial addition of >NO• to the double bound and than the H-atom abstraction by a second >NO•, Scheme **8**.

Exceptionally, for the NHPI/Pb(OAc)$_4$ – alkene reaction system, the reaction pathway is much more different. Due to the strong influence of the lead tetraacetate, this can form initially a complex with the π double bond electrons from the olefinic substrate, and than induces a double route for the reaction mechanism, radical-nonradical and the major reaction product is represented by the saturated diadduct, Scheme **9**. The influence is even more pronounced in the case of acyclic alkenes, when the reaction products founded are a mixture of unsaturated and saturated diadducts, Scheme **10** [21].

V. NEW REACTION PROTOCOL INVOLVING NHPI/PB(OAC)$_4$ SYSTEM

The crucial importance of this subject and the questionable points which are still in debate is a good reason to design a protocol to solve these ambiguities. There are at least two deficiencies regarding the previous work in this area:


Scheme 6. PINO reaction with *para*-substituted phenols.

Scheme 7. The cross-coupling product between PINO radical and 2-*tert*-butyl-4-methylphenol.

Scheme 8. Addition-abstraction and abstraction-addition reaction mechanisms involved in the alkene reactions with nitroxyl radicals.
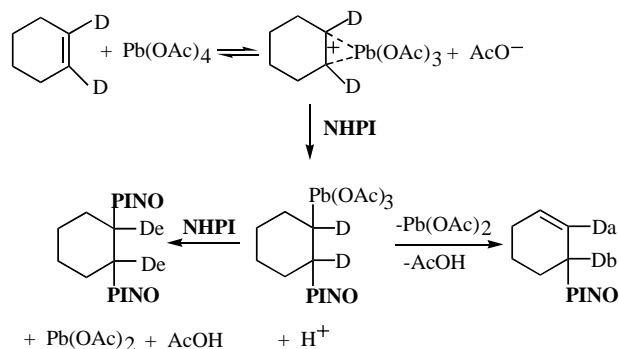

Scheme 9. NHPI/Pb(OAc)$_4$ reaction mechanism with 1,2-dideuterio-cyclohexene.

a) The high (and constant) percentage of abstraction-addition raises the disturbing possibility that abstraction-addition is the only operative reaction mechanism. That is, the 88-92 % value might be due to some artifact such as a systematic ^{2}H NMR peak integration error or incorporation of the deuterium into more than just the two vinylic positions [20].

b) The intervention of some form of Pb(IV) in the NHPI / alkene / Pb(OAc)$_4$ reaction introduces two quite different channels for product formation, viz., radical and non-radical reactions [20]. A similar phenomenon may occur with other substrates and may provide an explanation for a puzzling kinetic anomaly in the literature. Thus, Minisci *et al.* [22] reported that NHPI and a cobalt salt in aerated acetonitrile oxidized benzyl alcohol quantitatively to benzaldehyde without the formation of significant amounts of benzoic acid. However, Espenson and coworkers [5] using the NHPI / Pb(OAc)$_4$ system later reported that the rate constant for reaction of PINO with benzyl alcohol (5.65 M^{-1} s^{-1}) was *lower* than the rate constant for PINO's reaction with benzaldehyde 10.6 M^{-1} s^{-1}, implying that a clean conversion of benzyl alcohol to benzaldehyde would not be possible. More recently, Pedulli and coworkers [3] reported a much higher rate constant for the reaction of PINO with benzyl alcohol (28.3 M^{-1}s^{-1}) which would be consistent with Minisci's observations [3]. On the other hand, Espenson has recently reported [23] that the rate constants for H atom abstraction by PINO from *p*-xylene and toluene using
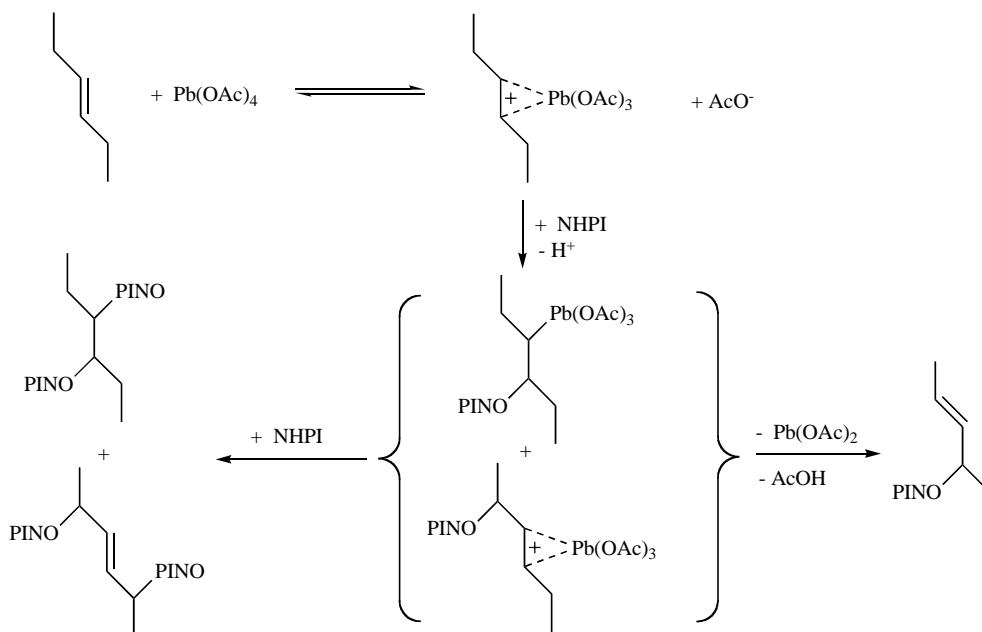
Scheme 10. NHPI/Pb(OAc)$_4$ reaction mechanism with *trans*-3-hex-ene.
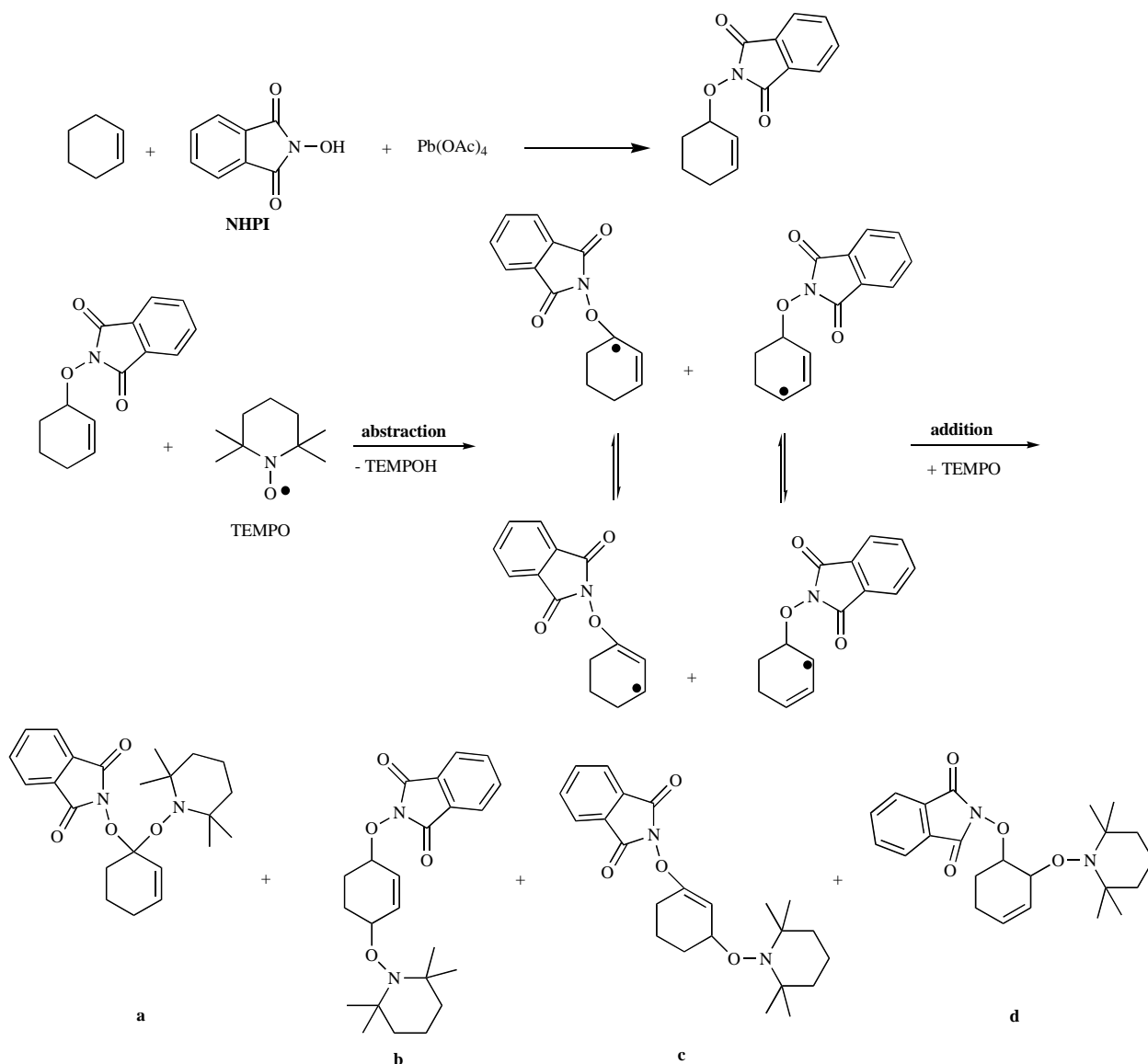
Scheme 11. The abstraction-addition mechanism.

NHPI/Co (III) were "slightly different" from those obtained using NHPI/Pb(OAc)₄.

In order to solve these questions we can propose a new protocol, that it, the synthesis of the cyclohexene – PINO monoadduct, it's separation and purification, followed in the second step, by a reaction with a persistent radical (TEMPO), to generate a mixture of disubstituted products.

The two possible routes for the reaction, (abstraction-addition and addition-abstraction) would generate, different products, specific for every proposed mechanism, see Schemes **11** and **12**. The compounds **c** and **d** are common for the both mechanisms. The compounds **a**, **b** are specific only for the abstraction-addition mechanism, while **e** and **f** are specific only for the addition-abstraction mechanism.

The ¹H NMR and ¹³C NMR of the crude reaction mixtures and for every purified product will clearly indicate whether both mechanisms are truly presents, or indeed, the abstraction-addition is the only operative mechanism in-

volved in this process. The relative importance of two mechanisms of formation of products can be determined by integration of the characteristic signals.

VI. CONCLUSIONS

NHPI catalysis has opened a large door to the activation and functionalization of a wide range of organic substrates being a useful choice for both industry and organic syntheses labs [24-30]. Although there are used many cocatalysts together with NHPI to generate the active free radical species, PINO the use of metals is still abundant. A major drawback of using metals beside the polluting issues, concern the unsolved questions of catalytic mechanisms and strong influences exerted on the organic substrate. Thus, Espenson recently reported [23]: "*when Co (III) was used to generate PINO, we obtained slightly different rate constants of hydrogen abstraction reactions, even under argon atmosphere. Probably, Co (II) takes part in subsequent reactions*". Lead

addition

+ TEMPO

+ TEMPO

abstraction

- TEMPOH

TEMPO

+

+

e

d

c

f
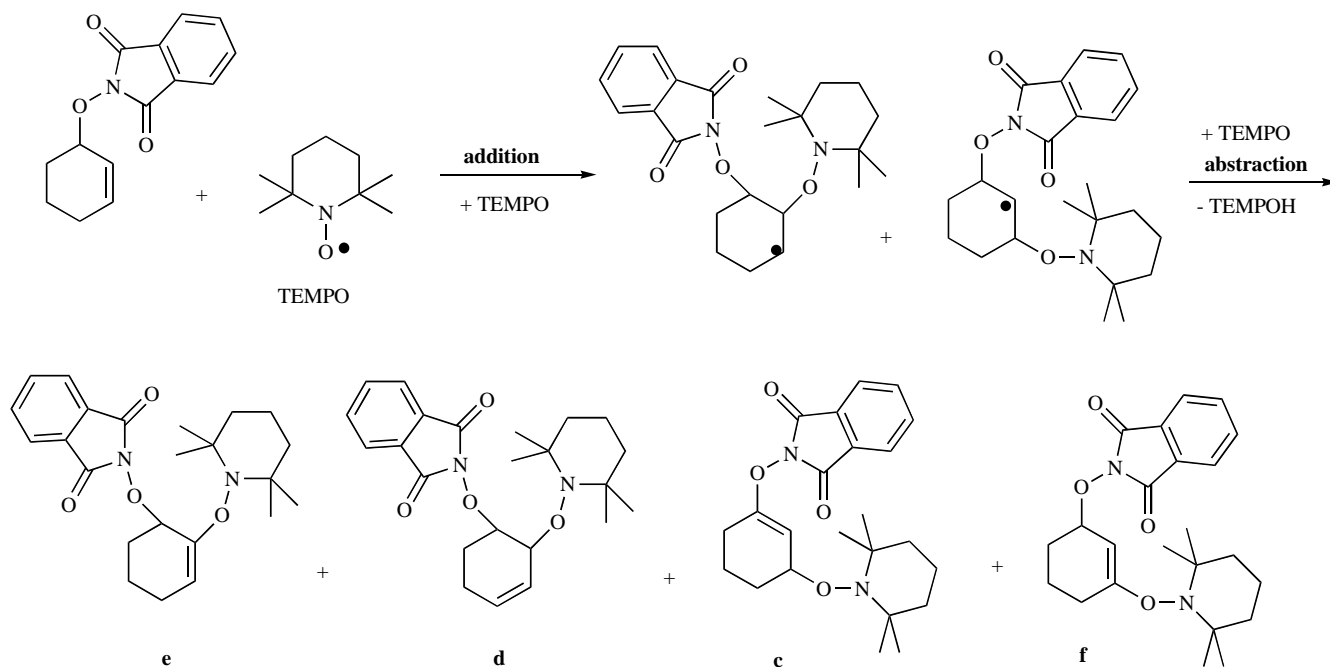
Scheme 12. The addition-abstraction mechanism.

tetracetate, provide even more confusing details when is used to generate PINO radicals. Clearly, the NHPI / Pb(OAc)$_4$, method for generating PINO radicals should be treated with caution until these (and other) anomalies have been sorted out.

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