

Contribution

Discovery of a carbon radical producing catalyst and its application to organic synthesis

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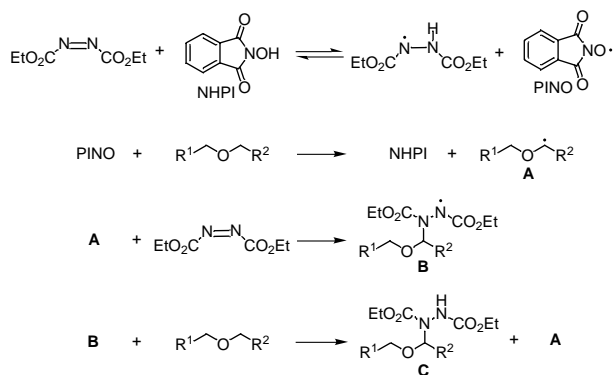
1. Introduction

Carbon radicals, typically exemplified by alkyl radicals, are highly reactive chemical species. Various methods for generating carbon radicals have been actively studied in recent years with wide applications to organic synthesis. Typical methods for the generation of alkyl radicals are by the reaction of alkyl halides with Bu_3SnH or $(\text{Me}_3\text{Si})_3\text{SiH}$ in the presence of radical initiators such as AIBN, the thermal decomposition of Barton esters or acyl peroxide, or one-electron oxidations by metal ions.¹⁾ However, all of these methods are stoichiometric reactions, which are suitable for small-scale laboratory use but difficult to apply to large-scale synthesis. There are industrial methods for the generation of alkyl radicals, such as the reaction of alkanes in the presence of a radical initiator or under photoirradiation. These methods are used for the autoxidation of alkanes. However, this auto-oxidation procedure requires harsh reaction conditions, carried out under high temperature. Under such temperature conditions, the C-H bond homolysis of alkanes occurs, as well as C-C bond homolysis, which has a lower bond energy than C-H bonds. Therefore, reaction selectivity is low and reaction efficiency is insufficient.²⁾ Until now, there has been no satisfactory general method for homolytic cleavage of the carbon-hydrogen bond of alkanes under mild conditions to selectively produce carbon radicals. In order to accomplish this, a new method for the generation of carbon radicals under mild conditions is required. Such a method will become an indispensable tool for organic synthesis.

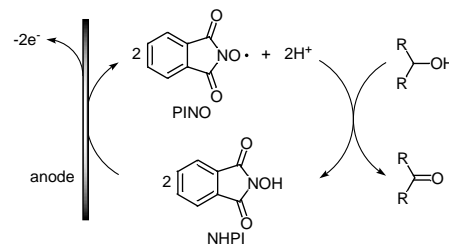
Recently, we found that phthalimide *N*-oxyl (PINO) radical, generated from *N*-hydroxyphthalimide (NHPI), abstracts a hydrogen atom from the carbon-hydrogen bond of various hydrocarbons including alkanes, alcohols, ethers, acetals, and aldehydes under mild conditions, and forms the corresponding carbon radical with high selectivity and high catalytic efficiency.³⁾ NHPI has been named a "Carbon Radical Producing Catalyst" (hereafter CRPC). Using a CRPC has enabled production of oxygen-containing compounds, such as ketones and carboxylic acids, from alkanes. This CRPC has also facilitated the addition of functional groups to alkanes, resulting in nitroalkanes, alkyl sulfonic acids, and oxyalkylates under mild conditions with high selectivity, both of which were difficult to accomplish previously. It has also become possible to produce dicarboxylic acids such as adipic acid, usually manufactured through nitric acid oxidation, by one-step oxidation of cyclohexane by molecular oxygen in good yield. Nitrous oxide (N_2O) is a compound having a global warming effect 300 times or higher than carbon dioxide, which is inevitably produced by the nitric acid oxidation method. Finding a method for manufacturing adipic acid without producing N_2O as a by-product is very important from the viewpoint of green chemistry. Reactions using CRPC are innovative methods for generating alkyl radicals from alkanes and will have a significant impact on the chemical industry. Some reactions using the CRPC method have already been industrialized.

2. Discovery of catalytic carbon radical generation method

Catalytic use of NHPI was first reported in 1977 by Grochowski and coworkers as an addition reaction of ether to diethyl azodicarboxylate (DEAD).⁴⁾ A detailed description of this reaction was not presented, and production of PINO was not experimentally proven. However, since the reaction did not progress under the presence of a radical scavenger, the reaction process was believed to proceed as shown in **Scheme 1**. The hydroxyimide group hydrogen atom of NHPI is added to DEAD, achieving an equilibrium between phthalimide *N*-oxyl (PINO) and added radical. The PINO produced at this step abstracts the hydrogen atom of the α -carbon to the ether oxygen, and provides a radical species **A**, which adds to DEAD resulting in the generation of an added radical species **B**. Radical species **B** abstracts the hydrogen atom from ether to yield adduct **C** and regenerates radical species **A**.



Scheme 1.

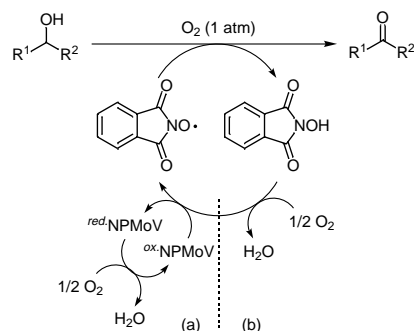


Scheme 2.

On the other hand, Masui *et al.* reported in 1983 that NHPI functions as a mediator for the electrolytic oxidation of secondary alcohols to ketones.⁵⁾ It is believed that PINO produced on an anode abstracts the hydrogen atom of the α -carbon of alcohols, thus catalyzing their oxidation to ketones (**Scheme 2**).

In the process of studying the oxidation reaction of alcohols with molecular oxygen using molybdovanado phosphate (NPMoV), having an average composition approximately expressed by $(\text{NH}_4)_5\text{H}_6\text{PV}_8\text{Mo}_4\text{O}_{40}$, we thought that use of only the NPMoV catalyst would not initiate the reaction, but that it would enhance the reaction if used in combination with NHPI (**Scheme 3**). We found that the reaction proceeds as expected (**path a**) and surprisingly discovered that NHPI catalyzed the oxidation of alcohols in the absence of NPMoV (**path b**). This oxidation occurred through the reaction of molecular oxygen (a triplet radical molecule) with NHPI to produce PINO, and then PINO abstracting the hydrogen atom from the alcohol to produce a ketone. In order to confirm PINO production from NHPI, NHPI was exposed to molecular oxygen in benzonitrile, and a triplet originating from PINO was observed by ESR as shown in **Fig. 1**.

It was revealed that PINO functions as a CRPC, selectively abstracting the hydrogen atom from the carbon-hydrogen bond of organic substrates under mild conditions to produce carbon radicals, and reverting itself to NHPI. Since carbon radicals are reactive chemical species, capturing them with various molecules, such as oxygen, allows the introduction of various functional groups. Various catalytic reactions using NHPI, as described below, include novel concepts that have not previously appeared in conventional synthetic organic approaches, and therefore, are significant breakthroughs in synthetic chemistry.



Scheme 3.

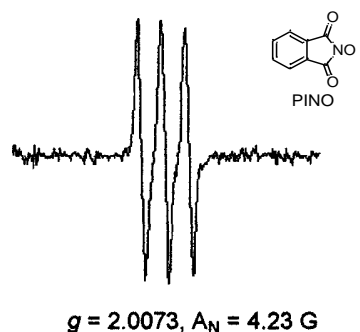


Figure 1. ESR spectrum of PINO

3. Oxidation of alkanes with molecular oxygen

Currently, over two million tons of adipic acid is manufactured worldwide annually as a raw material for 6,6-nylon through autoxidation of cyclohexane. The following two-step process is widely applied: cyclohexane is first converted to cyclohexanone/cyclohexanol (K/A oil) through air oxidation in the presence of a Co salt, followed by oxidation of the K/A oil by nitric acid to manufacture adipic acid.^{6a)} This method was developed by Du Pont in 1940 and, in principle, is still being used today. The first step of the reaction requires cleavage of C-H bonds (bond dissociation energy: 99.5 kcal mol⁻¹) which must be conducted using vigorous reaction conditions of 150 to 170 °C under high air pressure. In order to avoid side reactions, the conversion of cyclohexane must be controlled from 3 to 5%, making this method unsatisfactory in terms of reaction efficiency. Oxidation with nitric acid in the second step produces a large amount of N₂O as a by-product. Since N₂O is a substance that promotes global warming, a method for manufacturing adipic acid that does not use nitric acid for oxidation has been urgently sought by the industry. Along these lines, an oxidation reaction from cyclohexene to adipic acid, using hydrogen peroxide as an oxidant, has been reported and is attracting attention as a green route.^{6b)}

We found that cyclohexane is oxidized to adipic acid in one step with dioxygen (1 atm) by using NHPI combined with a small amount of Mn complex (**Eq. 1**).⁷⁾ Use of NHPI by itself hardly allows the oxidation to proceed. However, adding a small amount of Mn complex (0.5 mol%) yields adipic acid with high selectivity at conversion around 70%. In recent years, the oxidation of cyclohexane has been successfully carried out without solvents.⁸⁾ Since the NHPI catalyst is difficult to dissolve in nonpolar solvents such as cyclohexane, the oxidation of cyclohexane with air cannot be catalyzed efficiently without solvents. However, it was found that, by preparing a lipophilic NHPI derivative and using it as a catalyst, the oxidation of cyclohexane with air is catalyzed with extremely high catalytic efficiency without solvents (**Figure 2**).

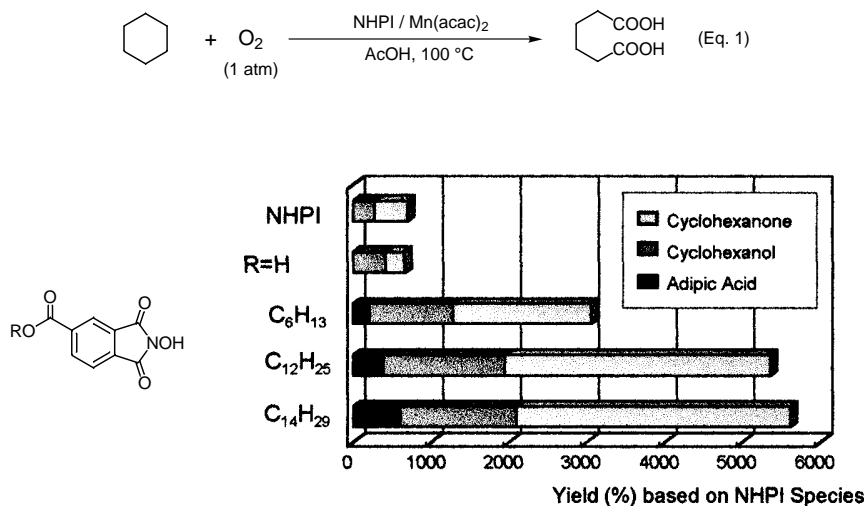
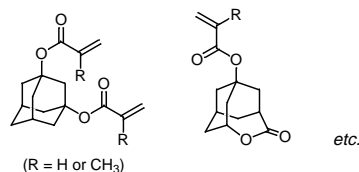
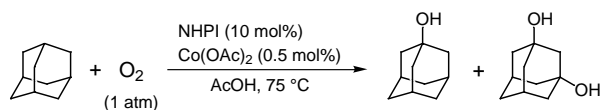


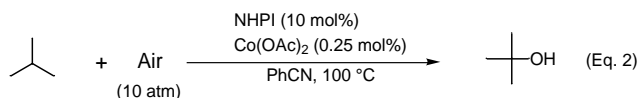
Figure 2. Oxidation of cyclohexane catalyzed by NHPI derivatives without solvent

Adamantane has a unique structure, and functionalized adamantanes are very useful as raw materials for high performance materials. Although many chemists have attempted oxidation of adamantane with molecular oxygen, none have obtained sufficient yields and selectivity for practical purposes. The oxidation of adamantane in the presence of the NHPI/Co catalyst system, molecular oxygen, and acetic acid at 75 °C, produced adamantanol at a yield of about 85% with a small amount of adamantanone (**Scheme 4**).⁹⁾ Selection of reaction conditions allows one to obtain mono-alcohols or diols with high selectivity. Acrylic acid and methacrylic acid esters derived from diols and triols synthesized by this method are manufactured into important raw material for photoresists.



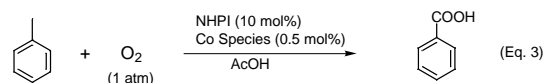
Scheme 4.

tert-Butyl alcohol, used as an additive for increasing gasoline octane number as well as a solvent, requires high purity and is industrially manufactured by the hydration of isobutene. A more rational method for producing *tert*-butyl alcohol may be by direct synthesis through oxidation of isobutane. The conventional autoxidation process of isobutane aims for synthesis of *tert*-butyl hydroperoxide. In this process, oxidation at around 200 °C under high air pressure (10 atm) produces *tert*-butyl hydroperoxide (about 75%), *tert*-butyl alcohol (about 21%), and acetone (about 2%) with a conversion of 8%.¹⁰ Oxidation of isobutane using NHPI/Co catalyst system in benzonitrile under high air pressure yields *tert*-butyl alcohol in 80% yield (Eq. 2).¹¹

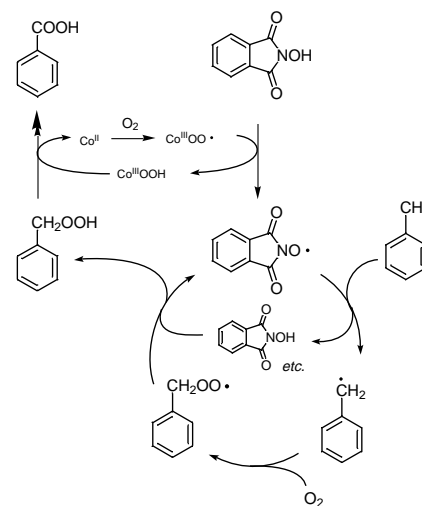


4. Oxidation of alkylbenzenes

Synthesis of carboxylic acids by oxidation of alkylbenzenes with molecular oxygen is an industrially important reaction. Oxidation of toluene is carried out in the presence of a Co catalyst at 130 to 160 °C under high air pressure. The conversion is 50% and benzoic acid is obtained with selectivity of around 80%.¹² By using a catalyst system consisting of NHPI and a small amount of Co(OAc)₂ with molecular oxygen at 1 atm and ambient temperatures, we successfully converted toluene to benzoic acid in good yield (81%), with only a small amount of benzaldehyde impurity (Eq. 3).¹³ Under these conditions, substitution of Co(III) instead of Co(II) failed to initiate the reaction, proving that the reaction is initiated by the Co(III)-oxygen complex generated from the Co(II) salt and oxygen (Scheme 5). Use of Co(III) does not generate the Co(III)-oxygen complex necessary for reaction initiation, therefore, no reaction occurs at room temperature. When the temperature is raised, Co(III) is gradually reduced to Co(II) by the substrate and Co(II) reacts with oxygen to form the Co(III)-oxygen complex, resulting in initiation of the reaction. Consequently, an induction period is observed when using Co(III). The fact that a hydrocarbon such as toluene can be catalytically oxidized by molecular oxygen at room temperature and atmospheric pressure has an important meaning for oxidation chemistry.



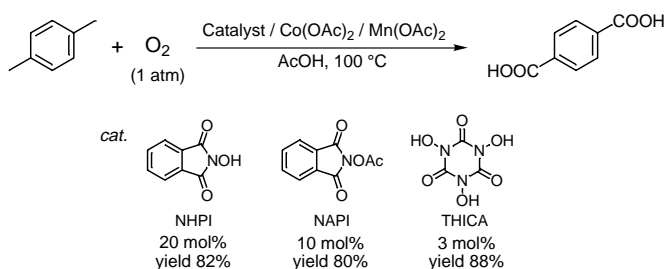
Co Species	Temp (°C)	Conv. (%)	Select. (%)
Co(OAc) ₂	25	84	96
Co(acac) ₂	25	74	96
Co(acac) ₃	25	no reaction	
Co(acac) ₃	100	92	99



Scheme 5.

Terephthalic acid is manufactured on a large scale because it is raw material for PET resin and the demand for it is expected to increase in the future. Currently, terephthalic acid is manufactured by autoxidation of *p*-xylene under high temperature and pressure conditions using Co/Mn/Br as catalysts. This method, developed by Amoco Corp., has problems such as dispersion of bromine into the gas phase and corrosion of the reaction vessel. Hence, it is desirable to develop a halogen-free catalyst system.

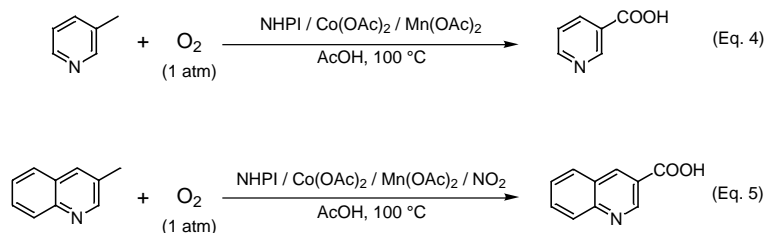
We developed a practical halogen-free oxidation with molecular oxygen for generating terephthalic acid from *p*-xylene by using NHPI catalysts (**Scheme 6**). Furthermore, *N*-acetoxyphthalimide (NAPI), prepared by addition of an acetoxy group to NHPI, also shows high catalytic activity similar to NHPI. We found that the amount of catalyst needed to produce the same amount of terephthalic acid is half of the amount required for NHPI if we used NAPI.¹⁴ In addition, we have recently found that trihydroxyiminocyanuric acid (THICA) has very high catalytic activity. In the oxidation of *p*-xylene catalyzed by NHPI, obtaining >80% yield of terephthalic acid in a one step process required 20 mol% of catalyst, whereas with the THICA catalyst, only 3 mol% was required to give similar results.



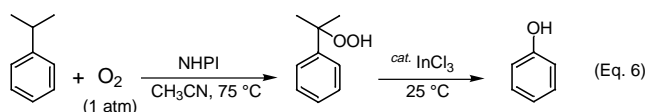
Scheme 6.

Carboxylic acids obtained by oxidation of side chains of alkyl heterocyclic compounds are widely used as an intermediate in pharmaceutical drug synthesis. For example, nicotinic acid obtained by oxidation of picoline is very important material for vitamin synthesis. At present, nicotinic acid is manufactured by oxidation of 5-ethyl-2-methylpyridine with nitric acid at high temperature and pressure. However, the production of a large amount of NO_x is a problem. While an autoxidation method for picoline using the Co/Mn/Br catalyst has been reported, the reaction conditions are harsh and selectivity is low.¹⁵

We conducted the oxidation of β -picoline in the presence of a catalytic amount of NHPI, a very small amount of Co(OAc)₂ and Mn(OAc)₂, oxygen under normal pressure, and acetic acid. As a result, a high yield of nicotinic acid was obtained (77%) (**Eq. 4**).^{16a} The reaction using NHPI/Co/Mn catalyst is a pollution-free reaction process that does not generate NO_x, and may prove to be industrially useful. On the other hand, 3-quinoline carboxylic acids derived from oxidation of 3-methylquinoline exist widely in nature, and there are many reports on their pharmacological activities. However, to date, heavy metal salts such as KMnO₄ and CrO₃ have been used as the oxidants. We found that addition of a small amount of NO₂ to the NHPI/Co/Mn catalyst system catalyzes the oxidation of 3-methylquinoline with molecular oxygen to give a good yield of quinoline carboxylic acid (75%) (**Eq. 5**).^{16b} Moreover, we have found that even if there are no transition metal salts, oxidation of quinolines with molecular oxygen can be carried out using the NHPI/NO₂ system. There have been no successful examples of oxidation of quinoline using molecular oxygen as an oxidant, and this present reaction is the first example thereof.



For industrial production of phenol, a two-step method is adopted as follows: cumene is autoxidized under weak alkali conditions, at 90 to 120 °C, and under the air compression (5 to 7 atm) and converted to cumene hydroperoxide (20-30% yield), after which the unreacted cumene is removed from the reaction solution, followed by concentration, and the concentrated product is treated with dilute sulfuric acid to convert it into phenol and acetone. This method is still employed as an industrial manufacturing method, even though it was established in the 1940's. However, the reaction efficiency for the first step is low. If the production efficiency of cumene to cumene hydroperoxide was increased, the reaction could be of more use. It was found that phenol can be obtained in a 77% yield through the use of the NHPI catalyst together with AIBN as the radical initiator in acetonitrile in the absence of transition metal salts, followed by the addition of a small amount of indium chloride to the reaction solution (Eq. 6).¹⁷⁾

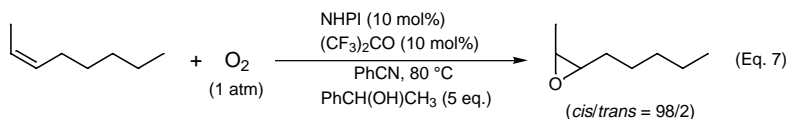


5. Oxidation of alkenes and alkynes with molecular oxygen

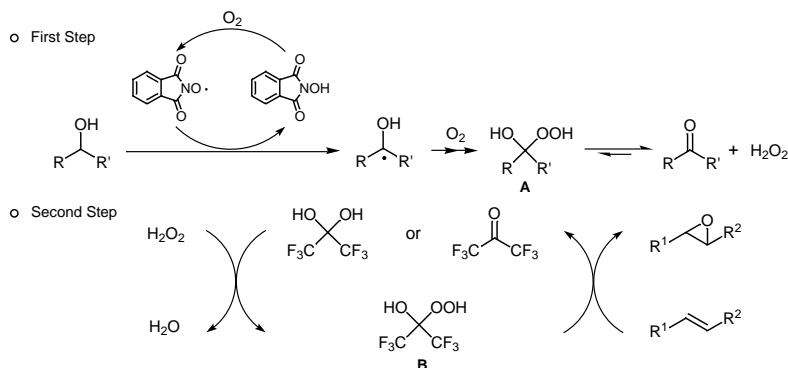
5.1 Production of hydrogen peroxide and epoxidation of alkenes

Epoxidation of alkenes, particularly propylene, using molecular oxygen as the oxidant, is practiced on an industrial scale. A popular method used is the Halcon process. This method comprises two steps, first ethylbenzene is autoxidized to produce ethylbenzene hydroperoxide and then, this is used as the oxidant for epoxidation by the Mo catalyst system.¹⁸⁾

Previously, we found that hydrogen peroxide and ketones are obtained by oxidation of secondary alcohols with molecular oxygen by NHPI catalysts.¹⁹⁾ Hydrogen peroxide produced by this reaction is used for epoxidation of alkenes. The reaction of 1-phenylethyl alcohol and *cis*-2-octene in an oxygen atmosphere under ambient pressures in the presence of a catalytic amount of NHPI and hexafluoroacetone (HFA) yields hydroperoxide by addition of the produced hydrogen peroxide to HFA. This is followed by production of the *cis*-epoxide by hydroperoxide acting as the true oxidant, in an 86% yield (Eq. 7).²⁰⁾ Generally, the epoxidation reaction of *cis*-olefins by molecular oxygen using aldehydes progresses *via* radical intermediates, resulting in a mixture of *cis*- and *trans*-epoxides.²¹⁾ Therefore, stereospecific epoxidation of *cis*-olefin by molecular oxygen is normally a difficult reaction.



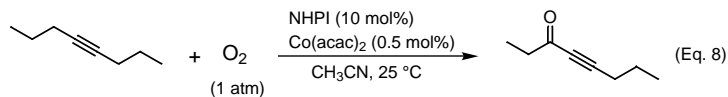
This epoxidation reaction comprises (i) production of hydrogen peroxide from an alcohol and oxygen *via* α -hydroxyhydroperoxide (**A**) catalyzed by NHPI, which is a radical reaction, and (ii) the epoxidation reaction of alkenes by α -hydroxyhydroperoxide (**B**) derived from hydrogen peroxide and HFA (**Scheme 7**). Oxidation of secondary alcohols by the NHPI catalyst can also be utilized as an excellent synthesis method of hydrogen peroxide.²²⁾



Scheme 7.

5.2 Introduction of oxygen to the propargylic position of alkynes

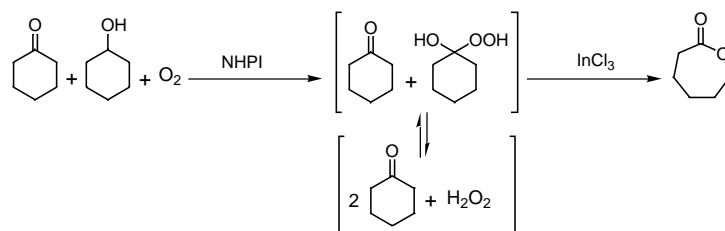
The dissociation energy for a C-H bond at the propargylic position in alkynes is about 85 kcal mol⁻¹, almost equal to that of the allylic position in alkenes (~87 kcal mol⁻¹).²³ Hence, it is expected that if alkynes are oxidized by molecular oxygen using the NHPI catalyst, the propargylic position will be selectively oxygenated to yield the corresponding α -alkynyl ketone. It is known that when 4-octyne is reacted with molecular oxygen in the presence of NHPI (10 mol%) and a trace amount of Co complex in acetonitrile, the reaction occurs at room temperature to yield 4-octyne-3-one in 75% yield (**Eq. 8**).²⁴ Alkynyl ketones are normally synthesized by a coupling reaction of a metal acetylide with an acylation agent. Reports of reactions introducing oxygen to the propargylic position are rare, and one example is an oxidation reaction by *tert*-BuOOH in the presence of a SeO₂ catalyst.²⁵ The reaction reported in this paper is the first successful example of oxygen introduction by molecular oxygen.



6. Oxidation of K/A oil with molecular oxygen

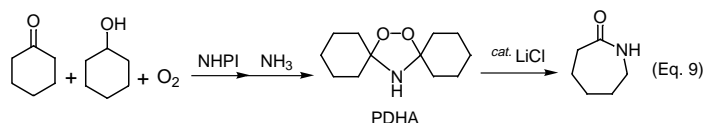
K/A oil, mixture of cyclohexanone with cyclohexanol is an important intermediate in the petrochemical industrial chemistry and is used as raw material for the production of adipic acid. The Baeyer-Villiger oxidation reaction converts cycloalkanones to lactones. A catalytic Baeyer-Villiger oxidation reaction using molecular oxygen as the oxidant has not been reported. ϵ -Caprolactone is manufactured by Baeyer-Villiger oxidation of cyclohexanone with peracetic acid. If the synthesis of ϵ -caprolactone can be accomplished without using peracetic acid, instead by catalytic Baeyer-Villiger oxidation of K/A oil using molecular oxygen, it is likely to become a very useful reaction since the use of hazardous peracetic acid can be avoided.

We have shown that NHPI acts as an efficient catalyst for the aerobic oxidation of secondary alcohols. The NHPI-catalyzed oxidation of secondary alcohols gives ketones and hydrogen peroxide through the formation of α -hydroxyhydroperoxide as an intermediate.¹⁹ Thus, by utilizing the oxidation of secondary alcohols with molecular oxygen in K/A oil, we produced hydrogen peroxide *in situ*, and used this as the oxidant for the Baeyer-Villiger oxidation. This reaction produces ϵ -caprolactone by first converting the cyclohexanol within K/A oil into hydrogen peroxide and cyclohexanone by aerobic oxidation. This is followed by Baeyer-Villiger oxidation of cyclohexanone by hydrogen peroxide and InCl₃ (**Scheme 8**).²⁶ Indium trichloride is a Lewis acid which is stable in water and can be reused if recovered after the reaction.



Scheme 8.

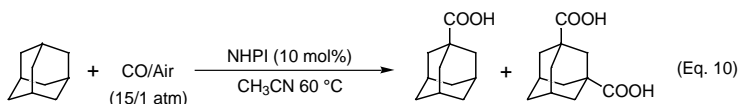
Peroxydicyclohexylamine (PDHA) is produced with good selectivity by aerobic oxidation of K/A oil in ethyl acetate and in the presence of catalytic amounts of NHPI, followed by treatment with ammonia gas (Eq. 9). It is known that PDHA is easily converted to ε-caprolactam in good yield. This reaction is a novel method that uses molecular oxygen for the synthesis of a ε-caprolactam precursor and is very interesting because it produces no ammonium sulfate as a reaction by-product.



7. Addition of functional groups to alkanes using NHPI catalyst

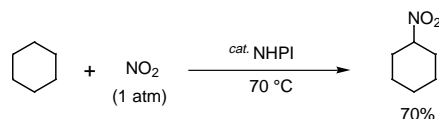
7.1 Introduction of CO to adamantane

Radical carboxylation of adamantanes by a CO/O₂ system using NHPI as a catalyst was achieved with relatively high selectivity. Reaction of adamantane in the presence of NHPI (10 mol%) and CO/air (15/ 1 atm) at 60 °C yielded adamantane carboxylate together with a small amount of oxidation products with 56% selectivity (conversion was 75%) (Eq. 10).²⁷⁾ Carbonylation reactions of saturated hydrocarbons by carbon monoxide are difficult. Therefore, few reports of catalytic radical carbonylation of alkanes have been reported. A few reports of reactions using persulfuric acid or light irradiation can be found in the literature.²⁸⁾

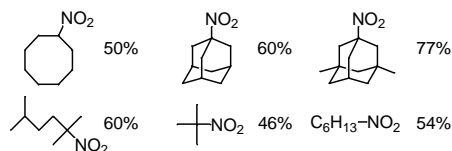


7.2 Catalytic nitration and sulfoxidation of alkanes

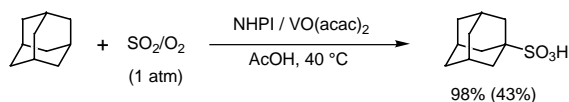
Nitration and sulfoxidation reactions of aromatic compounds are established reactions. However, a good general method for nitration and sulfoxidation of alkanes has not been developed. Nitration of alkanes is also an important reaction industrially, and is carried out at temperatures as high as 250-400 °C using nitric acid or NO₂ as the nitrating agent. However, at such high temperatures, cleavage of carbon-carbon bonds can also occur. Thus, the selectivity of the nitration reaction is very poor. For example, nitration of cyclohexane by NO₂ at 240 °C gives nitrocyclohexane in, at most, 16% yield.²⁹⁾ We reacted cyclohexane with NO₂ in the presence of a catalytic amount of NHPI and oxygen and found that the reaction went smoothly at 70 °C and nitrocyclohexane was obtained in 70% yield (Scheme 9). In addition, the catalyst can be collected almost quantitatively by simple filtration after the reaction.³⁰⁾ We have also successfully performed this nitration reaction using nitric acid in place of NO₂ as the nitrating agent.³¹⁾



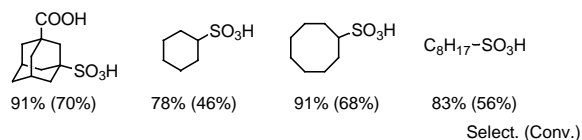
Scheme 9.



There are only a few reported studies on the sulfoxidation of alkanes. In one example, alkanes were irradiated by light in the presence of SO₂/O₂. However, the reactions efficiency was low and no further developments were reported. We found that reaction of adamantane with a very small amount of VO(acac)₂, using the NHPI catalyst in an SO₂/O₂ atmosphere, gives a good yield of adamantane sulfonic acid (**Scheme 10**). In addition, it was also found that this reaction is catalyzed only by VO(acac)₂. Moreover, lower alkanes such as propane are efficiently sulfoxidated by this method at room temperature.³²

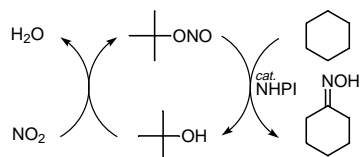
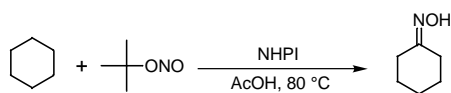


Scheme 10.



7.3 Oximation reaction of alkanes

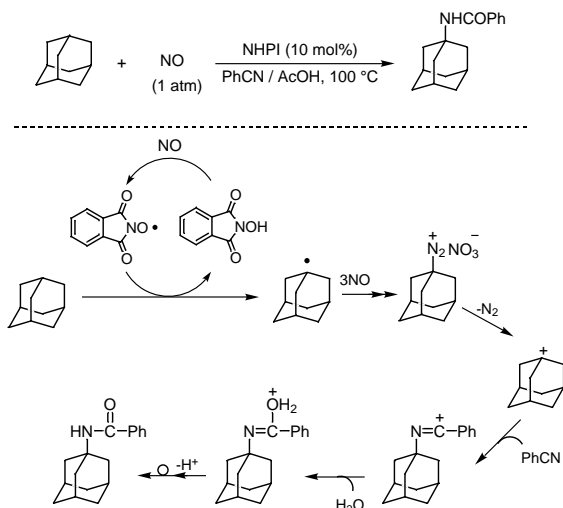
Cyclohexanone oxime is a major raw material for the production of 6-nylon. It is manufactured by oxidation of cyclohexane to produce cyclohexanone, followed by reaction with a hydroxylamine salt. However, this method has its drawbacks since a large amount of ammonium sulfate is produced as a by-product. We found that the reaction of cyclohexane with *tert*-butyl nitrite and acetic acid under an atmosphere of argon at 80 °C produces cyclohexanone oxime in one step (**Scheme 11**). This is a novel method for oxime synthesis which does not produce ammonium sulfate as a by-product. In addition, by making a one-step synthesis of cyclohexanone oxime possible, this is expected to become a breakthrough synthetic method. Moreover, this reaction has a very high atom efficiency since *tert*-butyl nitrite can be synthesized easily from *tert*-butyl alcohol and NO₂, and *tert*-butyl alcohol is regenerated in the reaction and can be continuously reused.



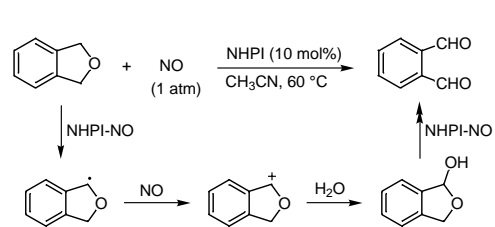
Scheme 11.

7.4 Generation of alkyl cations from alkanes using the NHPI catalyst

Nitrogen monoxide (NO) is a diatomic molecule which exists as a radical. If PINO can be produced by abstracting the hydrogen atom from NHPI, as is possible for molecular oxygen, it can be applied as a new synthesis reaction of NO. We attempted a reaction of adamantane in the presence of the NHPI catalyst, NO, and benzonitrile containing a small amount of acetic acid, and obtained *N*-1-adamantyl benzamide with a 65% yield (**Scheme 12**).^{33a)} In addition, we found that the reaction of phthalane with NO in acetonitrile gives phthalaldehyde (**Scheme 13**).^{33b)} Phthalaldehyde is generally synthesized by making tetrabromo-*o*-xylene from *o*-xylene followed by hydrolysis.³⁴⁾ No example of phthalaldehyde synthesis directly from phthalane is known. In this reaction, a carbocation is formed as the intermediate and water acts as the nucleophile resulting in hemiacetal formation. The hemiacetal further undergoes a similar reaction process and is oxidized to make phthalaldehyde.

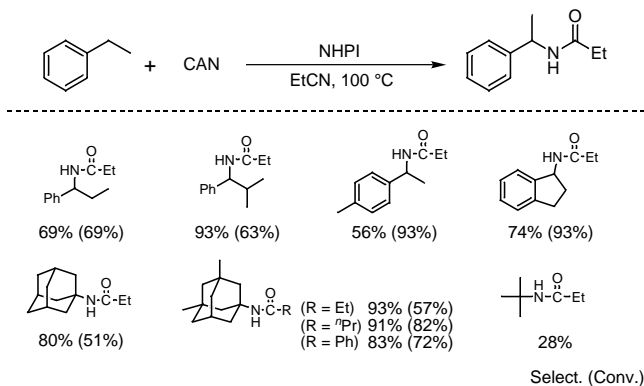


Scheme 12.



Scheme 13.

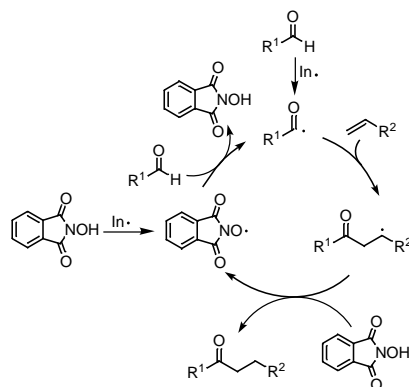
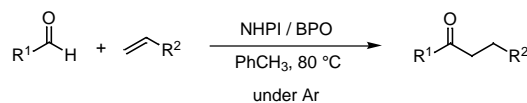
We found that alkyl cations can be formed from one-electron oxidations of generated alkyl radicals using the NHPI catalyst by cerium ammonium nitrate (CAN) (**Scheme 14**). It is clear that this reaction progresses with PINO produced by a reaction between NHPI and CAN. Under these conditions, the Ritter reaction at the benzylic position, which has to date been difficult, has now become possible with this methodology.³⁵⁾



Scheme 14.

7.5 Use as a polarity - reversal catalyst

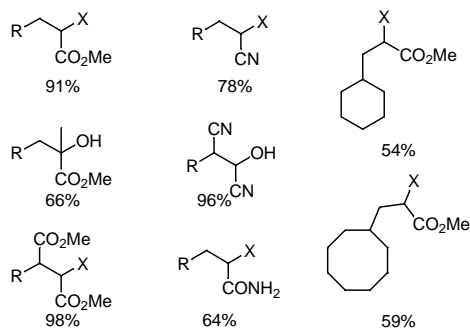
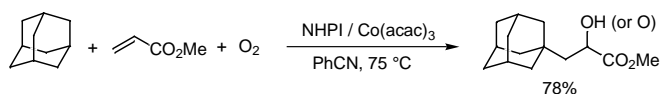
Reaction of aldehydes with alkenes, using BPO as an initiator, under an atmosphere of argon, a catalytic amount of NHPI, and toluene gives the corresponding ketone in good yield. The reaction progresses in a radical-like manner and, as shown in **Scheme 15**, functions as a polarity - reversal catalyst.³⁶⁾ An addition radical, generated by the addition of acyl radicals to alkenes, has a nucleophilic property and hence, abstracts the hydrogen atom from NHPI more easily than from an aldehyde, resulting in the smoother progression of the chain reaction.



Scheme 15.

8. C-C bond forming reaction based on the generation of a catalytic carbon radical

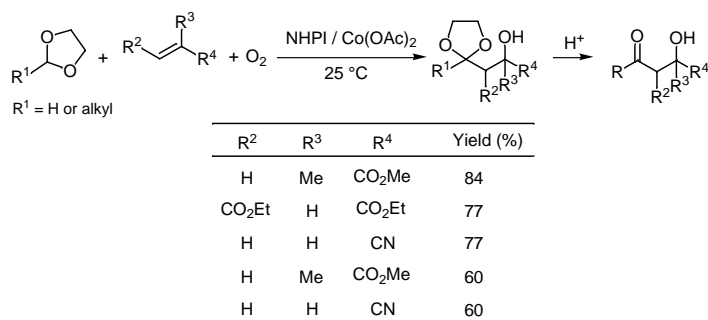
Radical coupling reactions are very useful methods in organic synthesis for forming C-C bonds. We have found that it is possible to generate alkyl radicals from alkanes using the NHPI/O₂ system. Thus, to capture the generated radical by an olefin, we examined the reaction of alkanes with α,β -unsaturated esters using the NHPI/O₂ system. Adamantane was reacted with methyl acrylate in the presence of the NHPI/Co(acac)₃ catalyst system and normal air. We found that a three-component coupling product with molecular oxygen is obtained in good yield following addition of the generated adamantyl radical to the double bond of methyl acrylate (**Scheme 16**).³⁷⁾ This reaction is regarded as the oxyalkylation of alkenes and a novel type of radical coupling reaction, in that oxygen is introduced simultaneously with C-C bond formation.



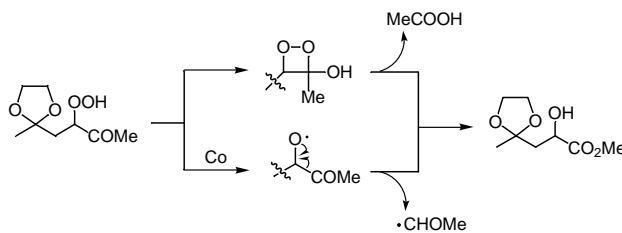
R : 3,5-dimethyladamantyl, X : =O or -OH

Scheme 16.

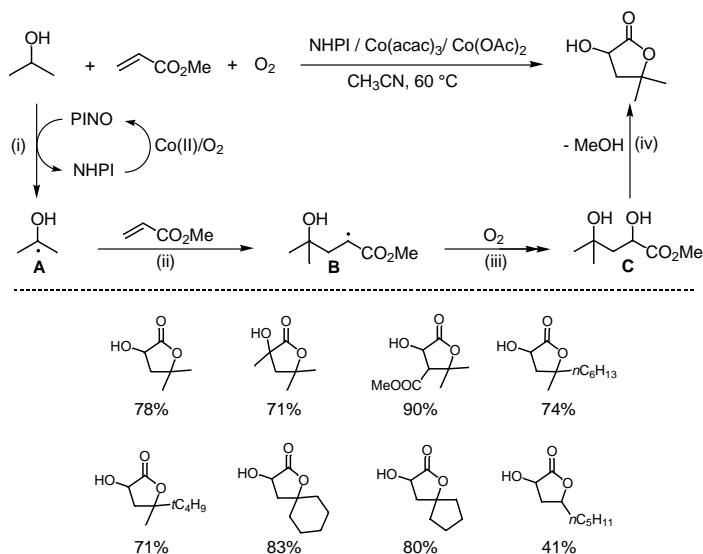
We reacted 1,3-dioxolane with methyl acrylate using the NHPI/O₂ system and the reaction progressed well at room temperature to yield the corresponding β -hydroxyacetal (**Scheme 17**). The acetal site of the coupling product can easily be converted to the corresponding ketone upon treatment with acid. This reaction is the addition reaction of acyl radical equivalents to alkenes, and is useful for the oxyalkylation reaction of alkenes.³⁸⁾



Scheme 17.



As shown above, the NHPI/O₂ system allows for production of α -hydroxy carbon radicals from alcohols. Therefore, we attempted to capture generated α -hydroxy carbon radicals with α,β -unsaturated esters, and found that it is possible to synthesize α -hydroxy- γ -lactones which, to date, have been difficult to synthesize by other methods. The reaction of isopropanol with methyl acrylate in the presence of a catalytic amount of NHPI and Co salt produced α -hydroxy- γ,γ -dimethyl- γ -butyrolactone (**Scheme 18**). In this reaction, (i) the hydrogen atom is abstracted from the alcohol in the presence of oxygen by the NHPI/Co(II) system to produce α -hydroxy carbon radicals (**A**), (ii) **A** is added to methyl acrylate to yield **B**, then (iii) oxygen is introduced and diol **C** is formed, and (iv) intramolecular cyclization occurs to convert it to lactone.³⁹⁾



Scheme 18.

9. Acknowledgments

We acknowledge that these studies were carried out in collaboration with co-workers at Kansai University. These studies were supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, JSPS Research for the Future Program of Japan Society for the Promotion of Science, and Daicel Chemical Co.

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