REVIEW

Innovation of Hydrocarbon Oxidation with Molecular Oxygen and Related Reactions

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Abstract: An innovation of the aerobic oxidation of hydrocarbons through catalytic carbon radical generation under mild conditions was achieved by using *N*-hydroxyphthalimide (NHPI) as a key compound. Alkanes were successfully oxidized with O_2 or air to valuable oxygen-containing compounds such as alcohols, ketones, and dicarboxylic acids by the combined catalytic system of NHPI and a transition metal such as Co or Mn. The NHPI-catalyzed oxidation of alkylbenzenes with dioxygen could be performed even under normal temperature and pressure of dioxygen. Xylenes and methylpyridines were also converted into phthalic acids and pyridinecarboxylic acids, respectively, in good yields. The present oxidation method was extended to the selective transformations of alcohols to carbonyl compounds and of alkynes to ynones. The epoxidation of alkenes using hydroperoxides or H_2O_2 generated *in situ* from hydrocarbons or alcohols and O_2 under the influence of the NHPI was demonstrated and seems to be a useful strategy for industrial applications. The NHPI method is applicable to a wide variety of organic syntheses *via* carbon radical intermediates. The catalytic carboxylation of alkanes was accomplished by the use of CO and O_2 in the presence of NHPI. In addition, the reactions of alkanes with NO_2 and SO_2 catalyzed by NHPI provided efficient methods for the synthesis of nitroalkanes and sulfonic acids, respectively. A catalytic carbon-carbon bond forming reaction was achieved by allowing carbon radicals generated *in situ* from alkanes or alcohols to react with alkenes under mild conditions.

Keywords: dioxygen; hydrocarbons; *N*-hydroxyphthalimide; oxidation; radicals

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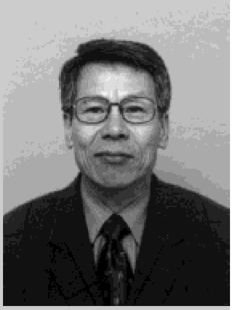


Yasutaka Ishii was born in Osaka, Japan, in 1941, graduated from Kansai University (Department of Engineering) in 1964. He received his Ph.D. degree under the supervision of Prof. Masaya Ogawa. In 1967, he was appointed assistant professor at Kansai University. He was a postdoctoral fellow at Colorado State University in 1980–1981. Since 1990 he has a full professor at Kansai University. He has received the Japan Petroleum Institute Award for Distinguished Papers in 1987, Divisional Award (Organic Synthesis) of the Chemical Society of Japan in 1999, and Award of the Synthetic Organic Chemistry, Japan (Yu-uki Gosei Kagaku Kyokai) in 1999. His current research interests include the development of practical oxidation reactions using molecular oxygen and hydrogen peroxide, homogeneous catalysis, petrochemistry, organometallic chemistry directed towards organic synthesis.

Satoshi Sakaguchi was born in 1970 in Nishinomiya, Japan, completed his undergraduate study and graduate study for his master degree at Kansai University in 1993 and 1995, respectively. He joined Kansai University, Faculty of Engineering, as a research associate in 1995. He received his Ph.D. from Kansai University in 2001. His Ph.D. studies on the development of innovative catalytic oxidation and nitration methods of hydrocarbons were carried out under the direction of Prof. Yasutaka Ishii.

Takahiro Iwahama was born in 1972 in Osaka, Japan, received his bachelor's degree (1994) and master's degree (1996) from Kansai University. After working in industry for one year, he did his Ph.D. work as research assistant under the tutelage of Prof. Yasutaka Ishii being the thesis advisor at Kansai University in 1997–2000. In 2000, he joined Daicel Chemical Industries, Ltd. as a researcher, where his work is focused on the development of novel aerobic oxidation reactions and catalytic carbon-carbon bond forming reactions.

1 Introduction

Prior to the utilization of hydrocarbons as raw materials in industrial chemistry, organic substrates were oxidized with inorganic oxidizing agents like chromium and manganese oxides, halogen and nitric acid but only rarely with molecular oxygen, since the organic compounds needed at that time were pharmaceuticals and synthetic dyes materials. In parallel with the development of the petrochemical industry, a wide range of oxygen-containing molecules including alcohols, aldehydes, ketones, epoxides and carboxylic acids became necessary to supply the starting materials for producing, in particular, plastics and synthetic fiber materials for polyamides, polyesters, and polycarbonates, etc. For instance, ethylene oxide, acrolein, acrylic acid, and methacrolein, are produced by the vapor-phase partial oxidation of lower alkenes like ethylene, propylene and butenes,[1] while acetic acid, K/A oil (a mixture of cyclohexanone and cyclohexanol), benzoic acid, terephthalic acid, and phenol accompanied with acetone are manufactured by the liquid-phase catalytic oxidation of alkanes like butane, cyclohexane, and alkylbenzenes, etc.[2] Liquid-phase aerobic oxidation, which is generally referred to as autoxidation, is extensively practiced in industry worldwide, although the efficiency of this oxidation methodology is not necessarily so high.[2a,3] As a result, nitric acid is still widely used as a useful oxidizing agent for manufacturing carboxylic acids like adipic acid, nicotinic acid, and pyromellitic acid, etc.[2a,4] Nowadays, however, environmentally unacceptable traditional oxidation methods using metal oxides, halogen and nitric acid are being replaced by cleaner oxidation methods.

Although the partial aerobic oxidation of alkanes leading to alcohols and carbonyl compounds has considerable potential from both ecological and economical viewpoints, current oxidation technology is not fully feasible as it incurs extensive oxidative cleavage or concomitant combustion of alkanes. The most important liquid-phase oxidation methods include the transformation of *p*-xylene to terephthalic acid and cyclohexane to K/A oil.[2a] However, the reaction conditions are often harsh, the reagent mixture is corrosive (Cr^- or Br^-), and the reaction is often unselective. Therefore, it is apparent that selective transformation of hydrocarbons, especially saturated hydrocarbons like alkanes, to valuable oxygenated compounds constitutes an extremely important area of contemporary industrial chemistry. Today, over 90% of organic chemicals are derived from petroleum whose main components are saturated hydrocarbons. Thus, considerable research effort has been made for the development of the selective oxidation of alkanes with molecular oxygen, leading to alcohols, ketones, and carboxylic acids.[5,6] A number of catalytic oxida-

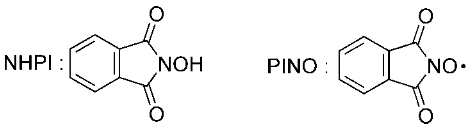


Figure 1. Structures of NHPI and PINO.

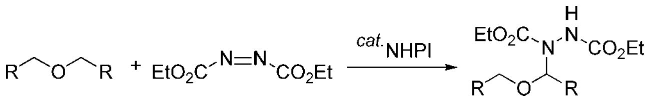
tions of alkanes with dioxygen by transition metals in the presence of reducing agents such as aldehydes have appeared in the literature, but these oxidations may be limited to laboratory-scale synthesis.[6] In recent years, there has been a growing demand for the development of fundamentally new and environmentally benign catalytic systems for hydrocarbons that are operative on an industrial scale under moderate conditions in the liquid-phase with a high degree of selectivity.

Recently, we have developed an innovative strategy for the catalytic carbon radical generation from hydrocarbons by a phthalimide *N*-oxyl (PINO) radical generated *in situ* from *N*-hydroxyphthalimide (NHPI) (Figure 1) and molecular oxygen in the presence or absence of a cobalt ion under mild conditions. The carbon radicals derived from a variety of hydrocarbons under the influence of molecular oxygen lead to oxygenated products like alcohols, ketones, and carboxylic acids in good yields. This account is focused on a novel methodology for the functionalizations, including oxygenation, nitration, sulfoxidation, epoxidation, carboxylation and oxyalkylation, of hydrocarbons through the catalytic carbon radical generation. In particular, we describe in detail the NHPI-catalyzed aerobic oxidations of alkanes which are very important in industry worldwide.

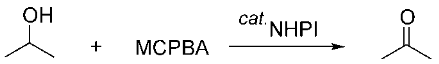
2 Discovery of NHPI as Carbon Radical Producing Catalyst from Alkanes

2.1 Historical Background

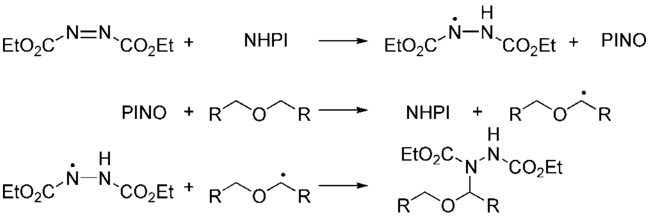
The first report on the use of NHPI as a catalyst in organic synthesis in the literature goes back to the addition of ethers to diethyl azodicarboxylate (DEAD) reported by Grochowski and coworkers in 1977 (Equation 1).[7] The reaction is also promoted even in the absence of NHPI at higher temperature. They assumed the formation of phthalimide *N*-oxyl (PINO) from a mixture of NHPI, DEAD, and ether as an intermediate, and that the PINO abstracts the hydrogen atom of the ethers to form 1-alkoxyalkyl radicals that add to DEAD (Scheme 1). The radical character of this reaction was demonstrated by its failure to proceed in the presence of a radical inhibitor. In the cited paper, they demonstrated the oxidation of 2-propanol to acetone with MCPBA by the presence of NHPI (Equation 2).



(1)

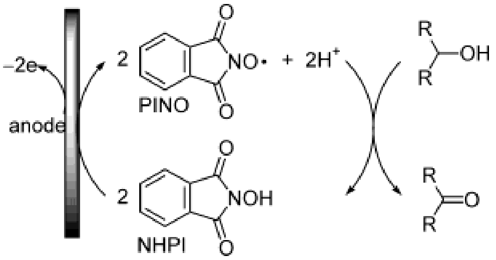


(2)

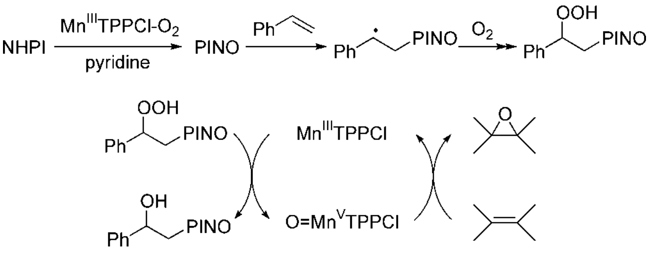


Scheme 1. Proposed pathway for the reaction of ether with DEAD catalyzed by NHPI.

In 1983, Masui et al. carried out a pioneering work on the synthetic application of NHPI as mediator in electrochemical oxidation of secondary alcohols to ketones, and showed that PINO formed by an electrochemical oxidation of NHPI abstracts selectively hydrogen atoms from the alcohols leading to ketones (Scheme 2).[8] After this first use of NHPI as a mediator in the electrochemical oxidation of alcohols, they applied the method to the oxidation of benzylic compounds, olefins, amides, lactams, and acetals to obtain the corresponding oxygen-containing compounds like alcohols, ketones, and imides.[9]



Scheme 2. Electrolytic oxidation of alcohols mediated by NHPI.

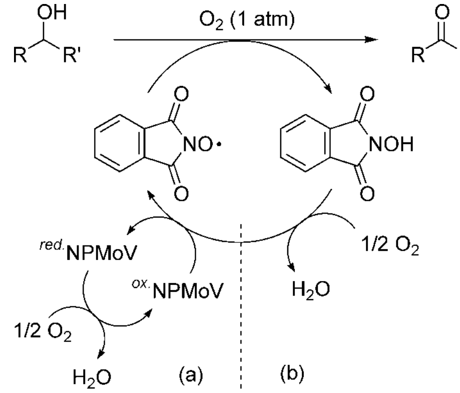


Scheme 3. Epoxidation catalyzed by Mn-TPPCl using hydroperoxides generated from NHPI, styrene, and O_2.

Furthermore, NHPI was used as the hydroperoxide source for the Mn-porphyrin catalyzed epoxidation of alkenes with dioxygen (Scheme 3).[10] The Mn(III)TPPCl-pyridine-O_2 system is reported to induce the generation of PINO from NHPI.

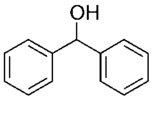
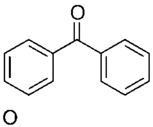
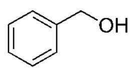
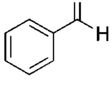
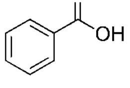
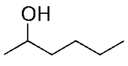
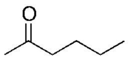
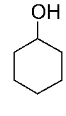
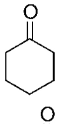
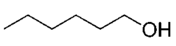
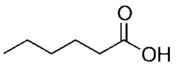
2.2 Catalysis of NHPI in Aerobic Oxidation

Since 1990, we have been investigating various heteropolyoxometalate-catalyzed oxidations of organic compounds using dioxygen as a terminal oxidant. Among the heteropolyoxometalates, a mixed-addenda vanadomolybdophosphate (NPMoV) whose composition is approximately indicated as $(NH_4)_5H_6PV_8Mo_4O_{40}$ proved to be an efficient catalyst for the selective dehydrogenation of amines to Schiff-base imines and phenols to quinones with molecular oxygen (Equation 3).[11] Unfortunately, this catalyst exhibits no activity for the dehydrogenation of aliphatic secondary alcohols to ketones with O_2. However, if the NPMoV is capable of abstracting the hydrogen atom from the hydroxyimide moiety of NHPI, we can envisage the oxidation of alcohols through the generation of PINO under non-electrolytic conditions by a multi-catalytic system consisting of NPMoV, NHPI, and dioxygen (Scheme 4, path a). Careful performance of the oxidation of alcohols by this catalytic system led to an innovative aerobic oxidation system of organic compounds through the *in situ* generation of PINO from NHPI with O_2 under non-electrochemical conditions (Scheme 4, path b). Thus, a variety of alcohols under atmospheric dioxygen could be converted into ketones or carboxylic acids by the use of NHPI as the catalyst (Table 1).[12] The generation of PINO from NHPI under aerobic conditions was confirmed by the ESR measurements.[13] On exposing NHPI in benzonitrile to dioxygen at 80 °C, an ESR signal attributed to PINO as a triplet signal having hyperfine splitting (hfs) by the nitrogen atom (g = 2.0074, AN = 4.3 G) was observed (Figure 2). No ESR signal appeared under argon. The g-value and hyperfine splitting constants observed here were consistent with those (g = 2.0073, AN = 4.23 G) of PINO reported previously.[14] This observation suggested that the hy-



Scheme 4. Generation of PINO from NHPI under non-electrolytic conditions.

Table 1. Oxidation of various alcohols catalyzed by NHPI with O_2.[a]

Run	Alcohol	Products (Yield [%])
1		 (88)
2		 (40)  (21)
3		 (49)
4		 (56)
5[b]		 (80)

[a] Alcohols (5 mmol) were allowed to react with dioxygen (1 atm) in the presence of NHPI (10 mol%) in PhCN (10 mL) at 100 °C for 5 h.

[b] Reaction was conducted at 75 °C for 20 h in CH_3CN.

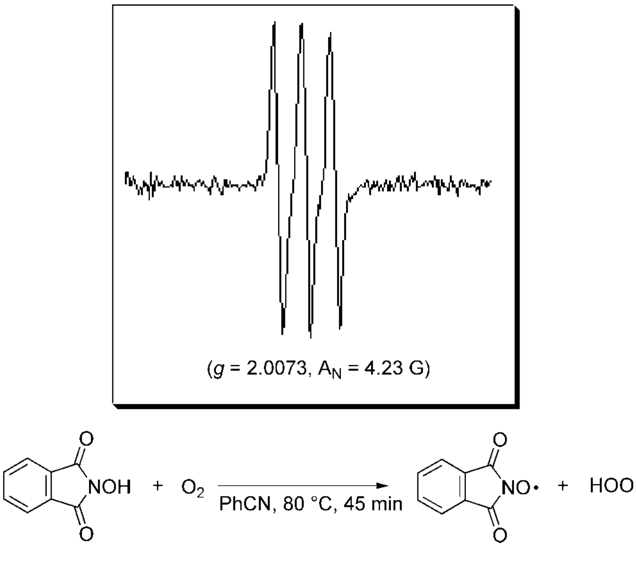
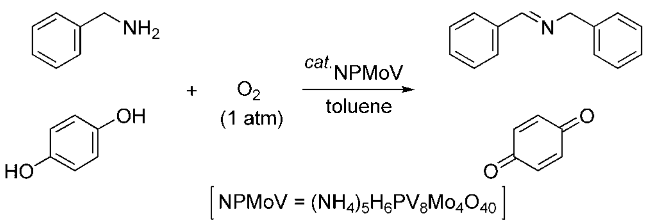


Figure 2. ESR spectrum of the phthalimide *N*-oxyl radical (PINO) under dioxygen.



(3)

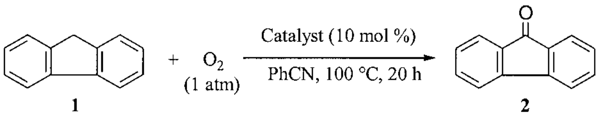
drogen atom anchored to the *N*-hydroxy moiety in NHPI is easily abstracted by molecular oxygen to form PINO which can abstract the α-hydrogen of alcohols to give ketones.

3 NHPI-Catalyzed Aerobic Oxidation

3.1 Oxidation of Benzylic Compounds

In order to know the features of NHPI catalysis, aerobic oxidation of hydroaromatic compounds like fluorene (**1**) was examined by the use of NHPI and its homologues as catalyst (Table 2).[12] Treatment of **1** with dioxygen (1 atm) in the presence of NHPI (10 mol %) in benzonitrile at 100 °C for 20 h gave fluorenone (**2**) in 80% yield. The oxidation using AIBN as a radical initiator instead of NHPI resulted in a low yield of **2**. The NHPI analogues, *N*-hydroxysuccinimide (NHSI) and *N*-hydroxymaleimide (NHMI), were also found to promote the oxidation while TEMPO was inactive.

Table 2. Oxidation of fluorene (**1**) in the presence of various catalysts with O_2.[a]



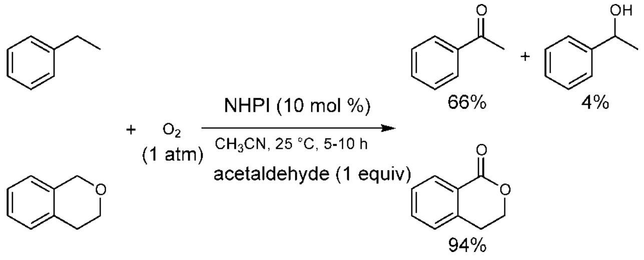
1 **2**

Run	Catalyst	Yield [%]
1	NHPI	80
2	-	trace
3	NHSI[b]	62
4	NHMI[c]	41
5	AIBN	10
6	TEMPO[d]	n.d.

[a] Fluorene (2 mmol) was allowed to react with O_2 (1 atm) in the presence of catalyst (10 mol%) in PhCN (5 ml) at 100 °C for 20 h.
[b] NHSI: *N*-hydroxysuccinimide.
[c] NHMI: *N*-hydroxymaleimide.
[d] TEMPO: 2,2,6,6-tetramethylpiperidine-1-oxyl.

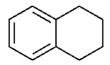
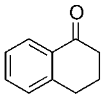
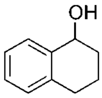
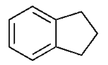
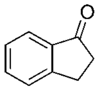
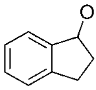
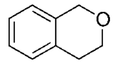
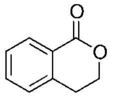
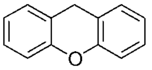
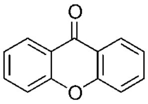
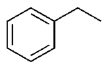
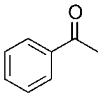
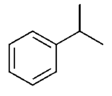
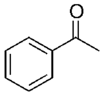
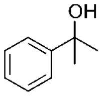
Various hydroaromatic and benzylic compounds under dioxygen in the presence of NHPI afforded the corresponding ketones and alcohols in good yields (Table 3). It is interesting that oxygen-containing hydroaromatic compounds like isochromane and xanthene were easily oxygenated to 1-isochromanone and xanthone in high yields.

After our finding of NHPI catalysis in the aerobic oxidation, Einhorn et al. reported the oxidation of these substrates with O_2 at room temperature in the presence of NHPI and acetaldehyde (Equation 4), and they concluded that the active species is the PINO formed by the reaction of NHPI with an acetylperoxy radical (Scheme 5).[15] They prepared chiral *N*-hydroxyimides and used them as catalyst of the asymmetric oxidation of indanes to give indanones in low % ee (Figure 3).[16]

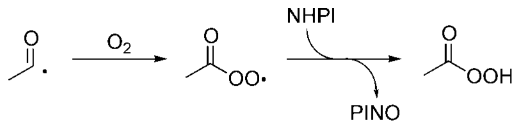


(4)

Table 3. Oxidation of various benzylic compounds with O_2.[a]

Run	Substrate	Products (Yield [%])
1		 (37)  (13)
2		 (42)  (7)
3		 (83)
4		 (99)
5		 (34)
6		 (64)  (8)

[a] Reactions were performed under the similar conditions as described in Table 2.



Scheme 5. Formation of PINO by reaction of NHPI with the acetylperoxy radical.

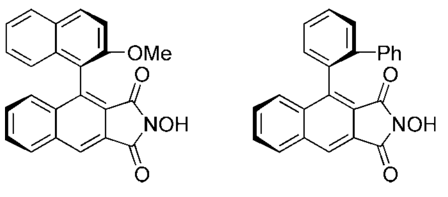


Figure 3. Chiral *N*-hydroxyimides prepared by Einhorn et al.

3.2 Alkane Oxidations with Molecular Oxygen

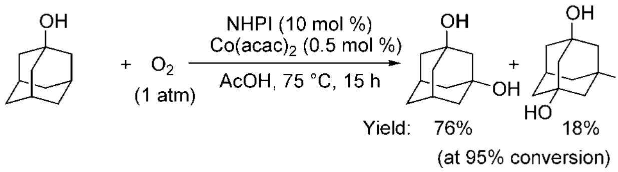
During the past several decades, a number of catalytic systems has been developed for the oxidation of alkanes with dioxygen in the presence of reducing agents, e.g., H_2, metals, aldehydes, etc., under mild conditions.[5,6,17–21,28,29] In 1981 Tabushi et al. reported the oxidation of adamantane to 1- and 2-adamantanols by the Mn(III)porphyrin/Pt/H_2 system under a dioxygen atmosphere at room temperature.[18] Barton developed a family of systems, the so-called Gif systems, for aerobic oxidation and oxidative functionalization of alkanes under mild conditions using Fe and Zn as reductants.[19a,21b] Alkane oxidation using aldehydes as reducing agents was reported by Murahashi et al., who attempted the aerobic oxidation of cyclohexane and adamantane by ruthenium or iron catalysts in the presence of acetaldehyde.[21a-21c] There have been several reports on the photo-oxidations of alkanes with O_2 catalyzed by polyoxotungstates,[22] heteropolyoxometalates,[23] and $FeCl_3$.[24] Shul'pin et al. carried out the vanadium-catalyzed oxidation of alkanes to alcohols, ketones, and hydroperoxides by O_2 in combination with H_2O_2.[25] Lyon and Ellis reported that halogenated metalloporphyrin complexes are efficient catalysts for the oxidation of isobutane with dioxygen.[26] Mizuno et al. have shown that heteropolyanions containing Fe catalyze the aerobic oxidation of cyclohexane and adamantane into the corresponding alcohols and ketones.[27] A Ru(III)-EDTA system,[30] Ru-substituted polyoxometalate,[31] and $[Co(NCMe)_4](PF_6)_2$ [32] have been reported to catalyze the aerobic oxidation of cyclohexane and adamantane. However, effective and selective methods for the catalytic oxygenation of alkanes with dioxygen still remain a major challenge.

3.2.1 Effect of Transition Metal Salts on NHPI-Catalyzed Oxidation of Adamantanes

Although benzylic hydrocarbons could be efficiently oxidized to the corresponding oxygenated compounds with dioxygen (1 atm) in the presence of NHPI, the oxygenation of alkanes like adamantane was difficult to carry out in higher conversions. To improve the conversion of the adamantane oxidation by NHPI, the effect of transition metal salts was examined, since transition metal salts such as cobalt and manganese assist the redox decomposition of alkyl hydroperoxides to alkoxy radicals which facilitate the chain transfer reaction in the alkane autoxidation (Equation 5).[5a,5d,33] It was found that the NHPI-catalyzed aerobic oxidation of adamantane is considerably accelerated by adding a small amount of a Co salt.[13,34,35] Thus, the oxidation of adamantane (**3**) in the presence of NHPI (10 mol %) and $Co(acac)_2$ (0.5 mol %) in acetic acid under dioxygen (1 atm) for 6 h produced 1-adamantanol (**4**) (43%), 1,3-adamantanediol (**6**) (40%), and 2-adamantanone (**5**) (8%) (Table 4). Interestingly, $VO(acac)_2$ and $MoO_2(acac)_2$, which are rarely employed in aerobic oxidation, were also good additives, while the effect of manganese salts was moderate compared with that of Co salts.

$$\begin{aligned} \mathrm{ROOH} + \mathrm{M}^{n} &\longrightarrow \mathrm{RO}\bullet + \mathrm{M}^{n+1} + {}^{-}\mathrm{OH} \\ \mathrm{ROOH} + \mathrm{M}^{n+1} &\longrightarrow \mathrm{ROO}\bullet + \mathrm{M}^{n} + \mathrm{H}^{+} \end{aligned} \tag{5}$$

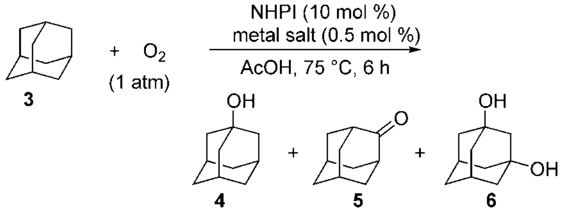
There have been a few reports on the catalytic hydroxylation of adamantane with dioxygen in the presence of aldehydes.[21] Mizuno et al. reported that the aerobic oxidation of adamantane by the PW_9-Fe_2Ni heteropolyanion without any reducing agents gives 1-adamantanol and 2-adamantanone at 29% conversion.[27a]



(6)

It is worth noting that the oxidation led to adamantanediol (**6**) in high selectivity, because the diol is rarely produced by conventional oxidation. Hirobe obtained **6** in 25% yield by the oxidation of adamantane using a Ru complex with 2,6-dichloropyridine *N*-oxide as the oxidant.[36] In the stepwise hydroxyla-

Table 4. Aerobic oxidation of adamantane (**3**) catalyzed by NHPI combined with metal salts.[a]



Run	Metal salt	Conv. [%]	Yield [%][b] 4	5	6
1	-	17	52	-	4
2	$Co(acac)_2$	93	43	8	40
3	$Co(OAc)_2$	99	21	6	54
4	$Mn(acac)_3$	68	56	6	31
5	$VO(acac)_2$	95	32	7	54
6	$MoO_2(acac)_2$	85	54	6	31
7	$Fe(acac)_3$	19	63	-	-
8	$Cu(OAc)_2$	36	64	6	8

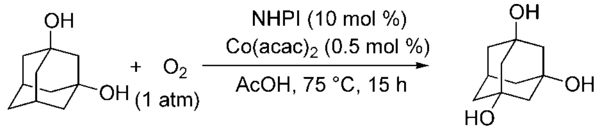
[a] Adamantane (3 mmol) was allowed to react with dioxygen (1 atm) in the presence of NHPI (10 mol%) and metal salt (0.5 mol%) in AcOH (8 mL) at 75 °C for 6 h.

[b] Based on converted starting material.

Table 5. Relative reactivity of the 3-hydrogen to the 2-hydrogen of adamantane.

Run	Method	3-H/2-H	Ref.
1	NHPI/Co(acac)$_2$	31	[34]
2	Autoxidation	3.8–5.4	[18b,37]
3	Fe(TPP)OAc-Zn	0.4	[19e]
4	PW$_9$-Fe$_2$Ni	10	[27a]
5	Mn(TPP)Cl/Pt/H$_2$	17	[18b]
6	Fe/AcOH/CH$_3$CHO	20	[21a]
7	[ZnRu(III)$_2$(OH)(ZnW$_9$O$_{34}$)$^{11-}$	>110	[31]

tion of adamantane by the NHPI/Co(acac)$_2$ system, the diol and triol were obtained in high selectivity (Equation 6 and Equation 7). These alcohols are now manufactured as important components of photoresist polymer materials on an industrial scale by Daicel Chemical Company.



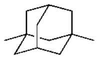
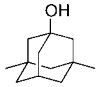
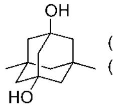
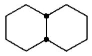
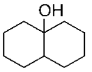
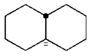
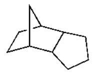
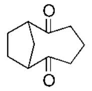
Yield: 85%
(at 46% coversion)

(7)

The ratio of the oxidation products of tertiary C-H bonds to secondary C-H bonds by the NHPI system was compared with that by other oxidation systems (Table 5).[37] The relative reactivity of the tertiary C-H bond to the secondary C-H bond in the oxidation by NHPI/Co(II) was 31:1. This value is considerably higher than that attained by the conventional autoxidation. The preferential oxidation of the tertiary C-H bond over the secondary bond may be attributed to the electron-deficient character of PINO which is a key radical species in the NHPI-catalyzed oxidation.

Table 6 shows the oxidation of several polycyclic alkanes by the NHPI/Co system. 1,3-Dimethyladamantane and *cis*-decalin were successfully hydroxylated, while tetrahydrodicyclopentadiene (THDCP) afforded the diketone, bicyclo[5.2.1]decane-2,6-dione, rather than alcohols.

Table 6. Oxidation of various polycyclic alkanes.[a]

Run	Substrate	Conv. [%]	Products (Yield [%][b])	
1		99	 (47)	 (37)
2[c]		99	(23)	(64)
3[d,e]		97	 (56) [*trans*/*cis* = 78/22]	
4 [d]		49	(32) [*trans*/*cis* = 78/22]	
5[d,f]		80	 (54)	
6[d,f,g]		39	(98)	

[a] Substrates (2 mmol) were allowed to react with dioxygen (1 atm) in the presence of NHPI (10 mol %) and Co(acac)$_2$ (0.5 mol %) in AcOH at 75 °C for 6 h.

[b] Based on converted starting material.

[c] 15 h.

[d] PhCN was used as the solvent.

[e] 60 °C.

[f] 65 °C.

[g] VO(acac)$_2$ was used in place of Co(acac)$_2$.

3.2.2 Direct Conversion of Cyclohexane to Adipic Acid

Adipic acid, which is used as a raw material for nylon-6,6 and polyester, is the most important acid of all of the aliphatic dicarboxylic acids manufactured at present. The current production of adipic acid consists of a two-step oxidation process involving the aerobic oxidation of cyclohexane in the presence of a soluble Co catalyst at 150–170 °C to a K/A oil and the nitric acid oxidation of the K/A oil to adipic acid.[2a,38] The drawbacks of this process are that the oxidation in the first step must be operated in 3–6% conversion of cyclohexane to keep a high yield (80%) of the K/A oil, and that the nitric acid oxidation evolves a large amount of undesired global-warming nitrogen oxides, in particular N$_2$O. Therefore, the direct conversion of cyclohexane to adipic acid with molecular oxygen has long been sought after as a desirable and promising method in industrial chemistry worldwide.[39]

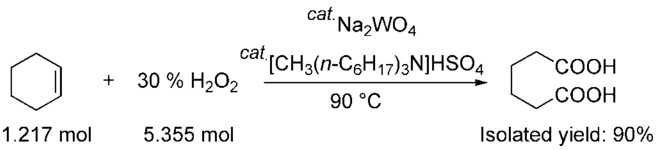
Table 7 shows representative one-step oxidations of cyclohexane to adipic acid in reported patents and the literature.[40] Tanaka et al. succeeded in achieving conversion of cyclohexane to adipic acid under

Table 7. Reports for autoxidation of cyclohexane to adipic acid with dioxygen.

Catalysts ([mol %])	Additive	Conditions	Conv. [%]	Yield [%][a]	Ref.
Co(OAc)$_2$ (2)	Acetaldehyde	O$_2$ (30 atm), 95 °C	88	73	[40a]
Co(OAc)$_2$ (2.5)	Cyclohexanone	O$_2$ (1.7 atm), 75 °C	53	58	[40b]
Co(OAc)$_2$ (9.5)	2-Butanone/H$_2$O	O$_2$ (20 atm), 95 °C	94	75	[40c]
Co(OAc)$_2$ (5), ZrO(OAc)$_2$ (1.3)	Peracetic acid	Air (20 atm), 90 °C	28	81	[40d]
Co(OAc)$_2$ (8)	Cyclohexanone	O$_2$ (20 atm), 100 °C	85	77	[40e]
Co(OAc)$_2$ (4.8), Fe(OAc)$_2$ (0.7)	Cyclohexanone	O$_2$ (20 atm), 95 °C	71	77	[40f]
Co(OAc)$_2$ (0.5), Cr(OAc)$_3$ (0.06)	Cyclohexanone	Air (100 atm), 105 °C	15	75	[40g]
Co(OAc)$_2$ (0.6)	Acetaldehyde	50% O$_2$ (14 atm), 105 °C	21	88	[40h]

[a] Based on converted starting material.

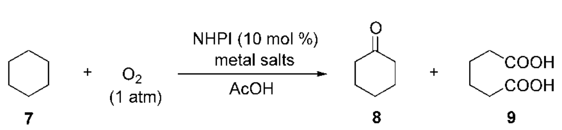
30 atm of O_2 by the use of a higher concentration of Co(III) acetate combined with acetaldehyde or cyclohexanone which serves as promoter.[40a] Recently, Noyori and coworkers have reported the oxidation of cyclohexene to adipic acid with aqueous hydrogen peroxide by a polyoxometalate having a phase-transfer function as an alternative clean route (Equation 8).[41]



(8)

An important application of the NHPI-catalyzed aerobic oxidation of alkanes is the direct conversion of cyclohexane to adipic acid. The oxidation of cyclohexane (**7**) to adipic acid (**9**) was examined by the use of a combined catalyst of NHPI with Co and Mn ions (Table 8).[42] A typical oxidation is as follows: an acetic acid solution containing cyclohexane **7**, NHPI (10 mol %) and $Mn(acac)_2$ (1 mol %) was placed in a two-necked flask equipped with a balloon filled with O_2 (1 atm), and the mixture was stirred at 100 °C for 20 h. After esterification of the reaction mixture, adipic acid (**9**) was obtained in 73% yield at 73% conversion. Interestingly, when the NHPI/Co/Mn system was employed as the catalyst, the oxidation proceeded smoothly even at 80 °C. By using air instead of pure O_2, the present oxidation becomes much more useful as a practical method. With this in mind, the oxidation of **7** under 20 atm of air pressure was examined to form **9** in 64% yield (60% conversion). On the other hand, oxidation using the NHPI/$Co(OAc)_2$ system in acetic acid resulted in a mixture of cyclohexanone (**8**) and adipic acid (**9**). Oxidation by the NHPI/Co system in acetonitrile gave rise to **8** in good selectivity, but the same oxidation using the NHPI/Mn system did not take place.[13] The oxidation by the NHPI/Co system in acetonitrile provides an alternative direct route to cyclohexanone, although the autoxidation of cyclohexane leads to a mixture of K/A oil consisting of cyclohexanol as a main product.[2a,38]

Table 8. Oxidation of cyclohexane (**7**) with dioxygen catalyzed by NHPI.[a]



Run	Metal salts (mol %)	Time [h]	Temp. [°C]	Conv. [%]	Yield [%][b] 8	9
1	-	6	100	<1	trace	n.d.
2	$Mn(acac)_2$ (0.5)	6	100	36	20	46
3	$Mn(acac)_3$ (0.5)	6	100	44	3	77
4	$Mn(acac)_2$ (1.0)	20	100	73	trace	73
5	$Mn(acac)_2$ (0.5) $Co(OAc)_2$ (0.05)	24	80	63	trace	69
6[c]	$Mn(acac)_2$ (0.1) $Co(OAc)_2$ (0.05)	24	80	60	8	64
7	$Co(OAc)_2$ (0.5)	6	100	40	36	34
8[d]	$Co(OAc)_2$ (0.5)	6	75	13	78	13

[a] Cyclohexane (3 mmol) was allowed to react with dioxygen (1 atm) in the presence of NHPI (10 mol%) and metal salts in AcOH (7.5 mL).
[b] Based on converted starting material.
[c] Reaction was carried out under air (20 atm).
[d] CH_3CN was used as the solvent.

The present catalytic system can be extended to the oxidation of large-membered cycloalkanes to afford the corresponding dicarboxylic acids (Table 9). Cyclooctane, cyclodecane, and cyclododecane were oxidized to suberic acid, sebacic acid and dodecanedioic acid, respectively.

Table 9. Oxidation of various cycloalkanes with dioxygen catalyzed by NHPI in the presence of $Mn(acac)_2$.[a]

Substrate	Conv. [%]	Products (Yield [%][b])	
Cyclooctane	83	Cyclooctanone (2)	Suberic acid (53)
Cyclodecane	90	Cyclodecanone (2)	Sebacic acid (55)
Cyclododecane	81	Cyclododecanone (3)	Dodecanedioic acid (68)

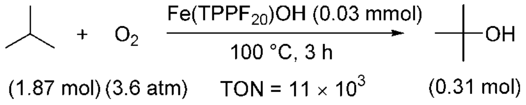
[a] Reaction was performed under the similar conditions as described in Table 8.
[b] Yield based on converted starting material.

General Procedure for Oxidation of Cyclohexane in Preparative Scale

An acetic acid (250 mL) solution of cyclohexane (8.4 g, 0.1 mol), NHPI (10 mol %, 1.63 g), and $Mn(acac)_2$ (1 mol %, 250 mg) was placed in a pear-shaped flask. The flask, attached to a condenser, was equipped with a balloon filled with O_2. **Caution:** *A balloon filled with O_2 can be hazardous, even with a small-scale reaction.* The mixture was stirred at 100 °C for 20 h. After removal of the solvent under reduced pressure, acetonitrile (100 mL) was added to the reaction mixture to give a white solid. After filtration adipic acid was obtained; yield: 3.62 g (25%).

3.2.3 Oxidation of Lower Alkanes

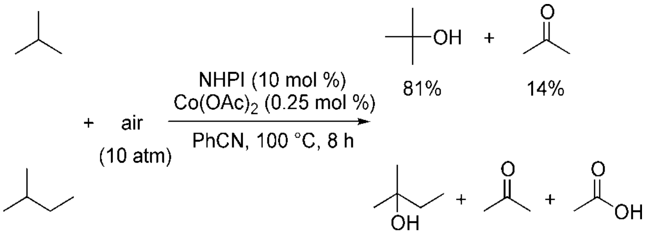
The autoxidation of lower alkanes such as isobutane is now carried out to mainly obtain *tert*-butyl hydroperoxide.[43] Halogenated metalloporphyrin complexes are reported to be efficient catalysts for the aerobic oxidation of isobutane (Equation 9).[26,44] Recently, Shul'pin et al. have explored the transformation of lower alkanes such as methane and ethane to the corresponding oxygenated products by a vanadium/pyrazine-2-carboxylic acid/H_2O_2/O_2 system.[25a] Fujiwara et al. have reported the partial oxidation of methane by vanadium and copper catalysts in trifluoroacetic acid with $K_2S_2O_8$ as the oxidant.[45]



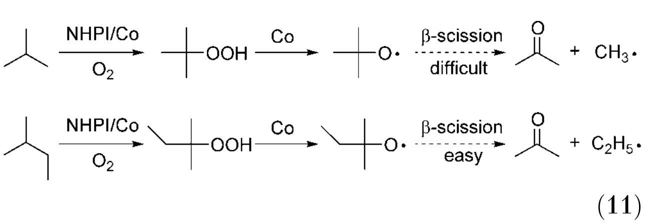
(9)

$TPPF_{20}$ = 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin

The oxidation of isobutane by air (10 atm) under the influence of NHPI (10 mol %) and $Co(OAc)_2$ (0.25 mol %) in benzonitrile at 100 °C (oil bath temperature) for 8 h produced *tert*-butyl alcohol in high yield (81%) along with acetone (14%) (Equation 10).[46] 2-Methylbutane was converted into the carbon-carbon bond cleaved products, acetone and acetic acid, rather than the alcohols, as principal products. These cleaved products seem to be formed *via β*-scission of an alkoxy radical derived from the decomposition of a hydroperoxide by Co ions. The extent of the *β*-scission is known to depend on the stability of the radicals released from the alkoxy radicals.[47] It is thought that the *β*-scission of a *tert*-butoxy radical to acetone and a methyl radical occurs with more difficulty than that of a 2-methylbutoxy radical to acetone and an ethyl radical. As a result, isobutane produces *tert*-butyl alcohol as the principal product, while 2-methylbutane affords mainly acetone and acetic acid (Equation 11).



(10)



(11)

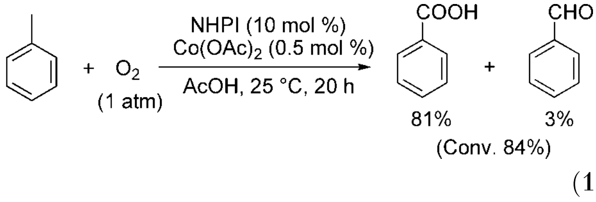
3.3 Oxidation of Alkylbenzenes

Aerobic oxidation of alkylbenzenes is a promising subject in industrial chemistry. Many bulk chemicals such as terephthalic acid, phenol, benzoic acid, etc. are manufactured by homogeneous liquid-phase oxidations with O_2.[2,48] The largest-scale liquid-phase oxidation is the conversion of *p*-xylene to terephthalic acid which is chiefly used as polyethylene terephthalate polymer material.[2a] *m*-Xylene is also commercially oxidized to isophthalic acid. Benzoic acid derived from the oxidation of toluene is an important raw material in the production of various pharmaceuticals and pesticides. Cumene hydroperoxide, the precursor of phenol and acetone, and ethylbenzene hydroperoxide, an oxidant for the epoxidation of propylene to propylene oxide, are also manufactured by the aerobic oxidation of isopropylbenzene and ethylbenzene, respectively.[2a,5a] These oxidation processes are usually operated at higher temperatures and pressures of air. A great deal of effort has been made to develop the homogeneous oxidations of alkylbenzenes with better selectivity under milder conditions. We have now achieved the first successful oxidation of a variety of alkylbenzenes with O_2 by the use of NHPI as the catalyst under mild conditions.

3.3.1 Aerobic Oxidation of Toluenes under Ambient Conditions

Currently, the oxidation of toluene is commercially practiced in the presence of a catalytic amount of cobalt(II) 2-ethylhexanoate under a pressure of 10 atm of air at 140–190 °C.[49] We first succeeded in the oxidation of toluene under normal pressure of dioxygen at room temperature by the use of a combined catalyst of NHPI and Co(II) species. The fact that the toluene was oxidized with dioxygen through the catalytic process in high yield under ambient conditions is very important from ecological and technical viewpoints as a promising strategy in oxidation chemistry.

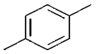
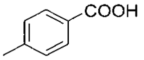
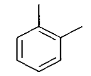
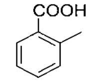
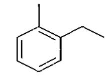
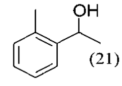
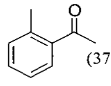
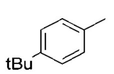
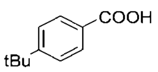
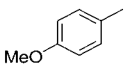
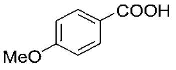
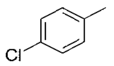
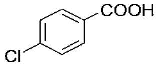
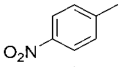
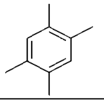
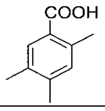
As a typical example, the oxidation of toluene in the presence of NHPI (10 mol %) and $Co(OAc)_2$ (0.5 mol %) in acetic acid under an atmosphere of O_2 at 25 °C for 20 h afforded benzoic acid and benzaldehyde in 81% and 3% yields, respectively (Equation 12).[50] This finding suggests that an efficient cleavage of a C-H bond having the bond dissociation energy (BDE) of 88 kcal/mol (corresponding to the BDE of toluene) is possible at room temperature by the use of NHPI catalyst. However, when Co(III) was employed in place of Co(II), no reaction took place at all at room temperature.



(12)

Representative results for the NHPI-catalyzed aerobic oxidation of various alkylbenzenes in the presence of $Co(OAc)_2$ in acetic acid under ambient conditions are listed in Table 10.

Table 10. Aerobic oxidation of various alkylbenzenes at room temperature.[a]

Run	Substrate	Time [h]	Conv. [%]	Product (Yield [%])
1		20	95	 (85)
2		20	93	 (83)
3[b]		20	82	 (21)  (37)
4		20	95	 (91)
5[b]		6	89	 (80)
6		20	71	 (67)
7		20	No reaction	
8		12	>99	 (93)

[a] Substrates (3 mmol) were allowed to react in the presence of NHPI (10 mol %) and $Co(OAc)_2$ (0.5 mol %) in AcOH (5 mL) under dioxygen (1 atm) at 25 °C.

[b] CH_3CN was used as the solvent.

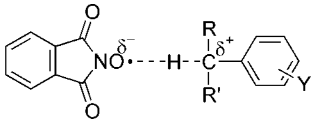


Figure 4. Transition state for the reaction of PINO with substituted benzenes.

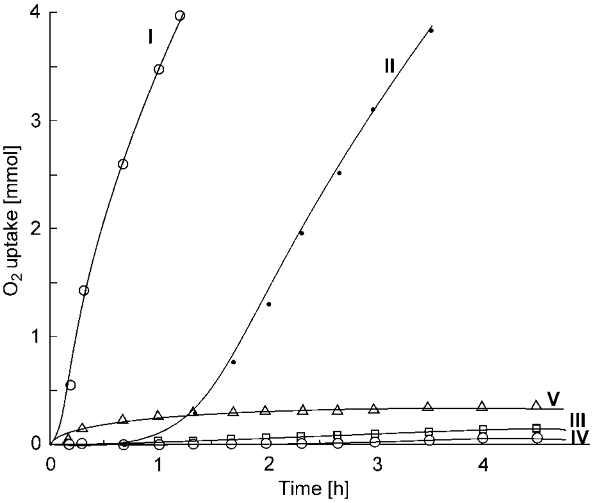
Both *p*- and *o*-xylenes were selectively oxidized to *p*- and *o*-toluic acids without the formation of dicarboxylic acids. *o*-Ethyltoluene underwent selective oxidation to form a mixture of the corresponding alcohol and ketone in which the ethyl moiety was selectively functionalized. It is of interest to examine the effect of substituents on the aromatic ring in the oxidation of substituted toluenes. *p*-Methoxytoluene was more rapidly oxidized than the toluene itself, while *p*-chlorotoluene was oxidized at a relatively slow rate. An electron-donating substituent anchoring to toluene stabilizes the partial positive charge on the benzylic carbon atom in the transition state for the abstraction of a benzylic hydrogen atom by PINO possessing an electrophilic character (Figure 4).[51] Therefore, the oxidation of toluenes having electron-donating groups by the NHPI catalyst is facilitated. Indeed, *p*-nitrotoluene substituted by a strong electron-withdrawing nitro group was not oxidized at all under these conditions. Recently, various substituted NHPI derivatives were prepared, and the effect of these substituted NHPI's on the aerobic oxidation of ethylbenzene was studied by Nolte et al.[52] They reveal that the electron-withdrawing fluorine substituent enhances the catalytic activity of NHPI to lead to the acceleration of the oxidation rate of ethylbenzene at the early stage, while the NHPI substituted by a methoxy group decreases the oxidation rate.

General Procedure for Oxidation of Toluene under Ambient Conditions

An acetic acid (5 mL) solution of toluene (276 mg, 3 mmol), NHPI (10 mol %, 48.9 mg) and $Co(OAc)_2$ (0.5 mol %, 3.7 mg) was placed in a two-necked flask equipped with a balloon filled with O_2. The mixture was stirred at 25 °C. After 20 h, evaporation of the solvent followed by flash chromatography on silica gel afforded benzoic acid as a white solid; yield: 296 mg (81%).

3.3.2 Mechanistic Consideration of Aerobic Oxidations by NHPI/Co System

The combined catalyst of NHPI with Co species led to a dramatic enhancement of the oxidation rate of alkanes. The effect of the Co species on the NHPI-catalyzed aerobic oxidation of alkanes was investigated. The absorption rates of dioxygen during the oxidation of ethylbenzene by several catalytic systems were measured using a constant-pressure absorption apparatus.[13] Figure 5 shows the time-dependence curves of the O_2 uptake in the oxidation of ethylbenzene under atmospheric pressure (1 atm) at 80 °C. It is interesting to compare the O_2 uptake by NHPI/



Conditions: ethylbenzene (10 mmol) was allowed to react with dioxygen (1 atm) in AcOH (25 mL) at 80 °C.

I) NHPI (10 mol %), $Co(acac)_2$ (0.5 mol %)

II) NHPI (10 mol %), $Co(acac)_3$ (0.5 mol %)

III) NHPI (10 mol %)

IV) $Co(acac)_2$ (0.5 mol %)

V) AIBN (5 mol %), $Co(acac)_2$ (0.5 mol %)

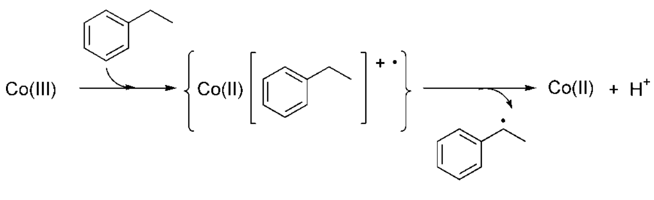
Figure 5. Time dependence curves of O_2 uptakes for the oxidation of ethylbenzene under atmospheric pressure of dioxygen by various catalysts.

Co(II) with that by the NHPI/Co(III) system. No induction period was observed in the O_2 uptake by the NHPI/Co(II) system, while with the NHPI/Co(III) system the O_2 uptake was initiated after about 1.5 h. In the oxidations of ethylbenzene by NHPI plus $Co(acac)_2$, or $Co(acac)_3$ alone, almost no O_2 uptake was observed. The oxidation results from an AIBN/$Co(acac)_2$ system were almost the same as those for $Co(acac)_2$ except for the O_2 uptake by radicals generated from AIBN in the early stage of the reaction. This indicates that NHPI serving as a radical producing catalyst is essentially different from AIBN serving as a radical initiator. The isotope effect during the present oxidation was estimated by measuring the O_2 uptake by ethylbenzene and ethylbenzene-d_{10}. The observed isotope effect, k_H/k_D, was approximately 3.74. In addition, the same oxidation in the presence of hydroquinone (1 mol %) did not occur at all.

$$\text{NHPI} + O_2 \xrightarrow[\text{PhCN, 80 °C, }\mathbf{<10\ min}]{Co(OAc)_2} \text{PINO} \qquad (13)$$

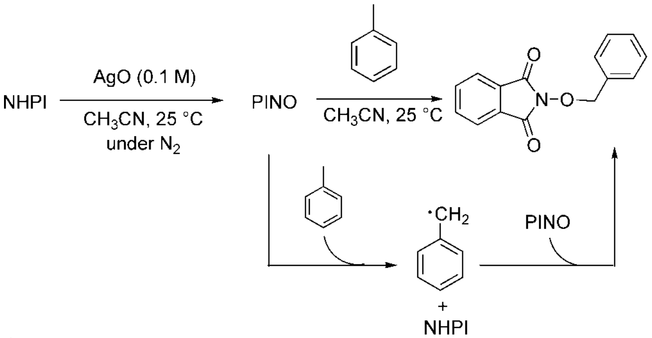
$$\begin{aligned} L_2Co(II) + O_2 &\rightleftharpoons L_2Co(III)\text{-}OO\cdot \\ L_2Co(III)\text{-}OO\cdot + L_2Co(II) &\rightleftharpoons L_2Co(III)\text{-}OO\text{-}Co(III)L_2 \\ L_2Co(III)\text{-}OO\cdot + \text{NHPI} &\rightleftharpoons L_2Co(III)\text{-}OOH + \text{PINO} \end{aligned} \qquad (14)$$

In order to gain further insight into the role of the Co species, ESR measurements were carried out. In Section 2.2, we mentioned the ESR signal of the PINO obtained by exposing the NHPI to O_2 at 80 °C for 45 min. Interestingly, the generation of PINO from NHPI was remarkably accelerated in the presence of a Co(II) salt. When a benzonitrile solution of NHPI containing a small amount of $Co(OAc)_2$ was exposed to dioxygen at 80 °C, the ESR signal of the PINO was immediately observed (Equation 13).[42] However, no ESR signal was obtained when a Co(III) species was added in place of Co(II) under the same conditions. In addition, PINO was observed during the oxidation of toluene by the NHPI/Co(II) system under ambient conditions.[50] A labile dioxygen complex such as superoxocobalt(III) or peroxocobalt(III) complexes is known to be formed by the complexation of Co(II) with O_2 and assists the formation of PINO from NHPI (Equation 14).[53] Since no cobalt-oxygen complex is generated from the Co(III) and O_2, the NHPI/Co(III) system does not catalyze the oxidation of toluene under ambient conditions as shown in Section 3.3.1. At higher temperatures, however, Co(III) ions are gradually reduced to Co(II) ions by organic substrates such as toluene and cyclohexane *via* a one-electron transfer process.[54] In fact, the oxidation of ethylbenzene by the NHPI/Co(III) system was initiated after a lapse of 1.5 h (Figure 5). The induction period observed here, therefore, would correspond to the time needed to reach a threshold concentration of Co(II) by the one-electron transfer to Co(III) from ethylbenzene (Scheme 6).



Scheme 6. One-electron transfer to Co(III) in the oxidation of ethylbenzene by NHPI/$Co(acac)_2$.

It is reported that PINO can be easily generated upon treating NHPI with a one-electron oxidant like AgO or $Pb(OAc)_4$.[55] Thus, PINO was generated from NHPI and AgO according to the literature procedure. When toluene was added to this solution, the ESR signal attributed to PINO immediately disappeared, and the coupling product of PINO with the benzyl radical was obtained (Scheme 7).[56] This indicates that the PINO radical can abstract a hydrogen atom from toluene even at room temperature to form a benzyl radical which then couples with another molecule of PINO.



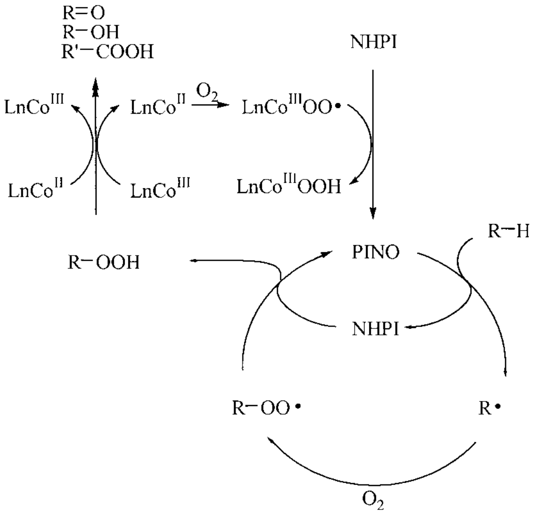
Scheme 7.

On the basis of these observations, a plausible reaction pathway for the aerobic oxidation of alkanes by NHPI combined with Co(II) is illustrated in Scheme 8.

The *in situ* generation of PINO from NHPI by the action of the cobalt(III)-oxygen complex is a key step in the present oxidation. The next step involves the hydrogen atom abstraction from alkanes by PINO to form alkyl radicals. Trapping the resulting alkyl radicals by dioxygen provides peroxy radicals which are eventually converted into oxygenated products through alkyl hydroperoxides.

3.3.3 Production of Terephthalic Acid by Aerobic Oxidation of *p*-Xylene

Terephthalic acid (TPA) as well as dimethyl terephthalate (DMT) have recently become much more important as raw material for polyethylene tere-

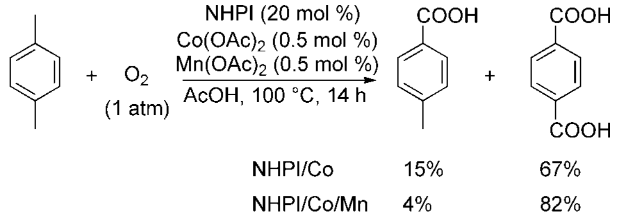


Scheme 8. Plausible reaction pathway for the aerobic oxidation of alkanes catalyzed by NHPI combined with Co(II).

phthalate.[57] In 1999, *ca.* 17 million tons of TPA were manufactured worldwide and its production has been estimated to increase at a minimum growth rate of 10% annually by the year 2002.

Until the 1980's, the following four-step process developed by Witten and modified by Hercules and Dynamit-Nobel (Witten-Hercules process) had been mainly operated to produce DMT.[2a,57] The first step is the conversion of *p*-xylene (PX) to *p*-toluic acid (PTA). It then passes to an esterification step to form methyl *p*-toluate which is subjected to further oxidation to monomethyl terephthalate, followed by esterification to DMT. From the 1990's, these processes were changed to the aerobic one-stage oxidation of PX to TPA by the combined use of cobalt and manganese salts in the presence of bromide as a promoter in acetic acid at 175–225 °C under 15–30 atm of air, followed by hydrogenation of the crude TPA to remove 4-carboxybenzaldehyde (4-CBA) by a Pd catalyst.[57–59] This process was developed by Scientific Design and Amoco Ltd. (Amoco process). Currently, about 70% of TPA produced worldwide is based on the Amoco process, and almost all of the new plants adopt this method. However, there are several disadvantages in the Amoco process: (i) significant combustion of acetic acid used as the solvent to CO and CO_2; (ii) use of the highly corrosive bromide ion which calls for the use of vessels lined with expensive metals like titanium; (iii) contamination of 4-CBA in crude TPA which necessitates elaborate hydrogenation and recrystallization procedures in manufacturing the purified TPA required for PET. Therefore, a new oxidation system for the production of TPA is desired to overcome these disadvantages. Partenheimer recently published a review devoted to the aerobic oxidation of alkylbenzenes, especially PX, using the Co/Mn/Br system.[59] Higashijima has developed an aerobic oxidation of PX to TPA catalyzed by Ru-substituted heteropolyanions in H_2O.[60]

We examined the aerobic oxidation of *p*-xylene (PX) to terephthalic acid (TPA) by the NHPI catalyst to elaborate a halogen-free catalytic system.[61] The oxidation of PX with dioxygen (1 atm) in the presence of catalytic amounts of NHPI (20 mol %) and $Co(OAc)_2$ (0.5 mol %) in acetic acid at 100 °C for 14 h produced TPA in 67% yield and *p*-toluic acid (PTA) (15%) together with small amounts of 4-CBA, 4-carboxybenzyl alcohol, 1,4-diacetoxymethylbenzene, and 4-acetoxymethylbenzoic acid as well as several unidentified compounds in 1–2% yields, respectively, at over 99% conversion (Equation 15). We found that the yield of TPA is improved to 82%, when $Mn(OAc)_2$ (0.5 mol %) is added to the NHPI/$Co(OAc)_2$ system. The synergistic effect of Co and Mn salts in the aerobic oxidation of alkylbenzenes has been well documented.[59,62,63] From a practical point of view, it is important to note that the aerobic oxidation of PX under air (30 kg/cm^2) by the NHPI/Co/Mn system was completed within 3 h at 150 °C to form TPA in 84% yield (Equation 16). Both *o*- and *m*-xylenes were also successfully converted into the corresponding dicarboxylic acids, isophthalic acid and phthalic acid, respectively, in high yields.



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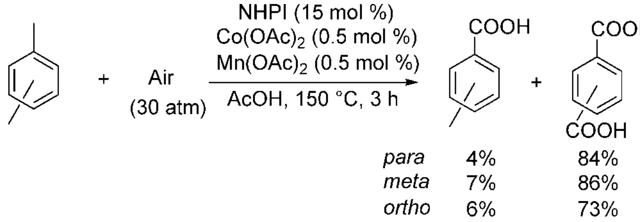
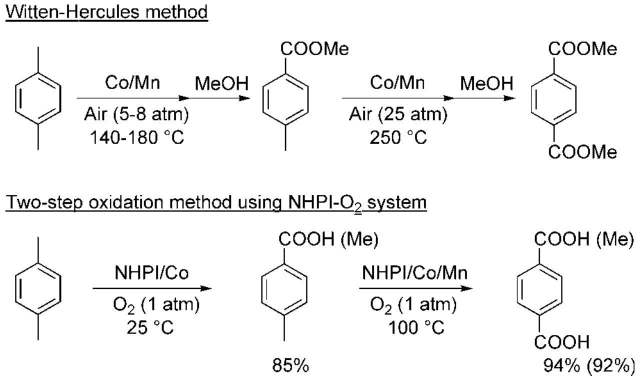


(16)

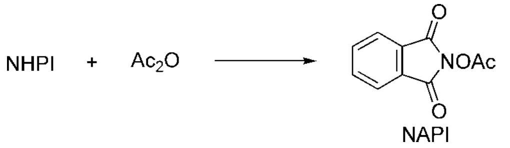
In a previous section, we showed that the aerobic oxidation of PX to *p*-toluic acid (PTA) can be carried out even at room temperature. The conversion of PX into TPA through the oxidation of PX to PTA at room temperature provides a two-step oxidation method which is thought to be an alternative to the Witten-Hercules procedure that manufactures dimethyl terephthalate (DMT) from PX (Scheme 9). PTA or methyl *p*-toluate was allowed to react under dioxygen (1 atm) in the presence of NHPI (10 mol %), $Co(OAc)_2$ (0.5 mol %) and $Mn(OAc)_2$ (0.5 mol %) in AcOH at 100 °C for 14 h to give TPA or monomethyl terephtha-



Scheme 9. Production of TPA combined with oxidation of PX at room temperature.

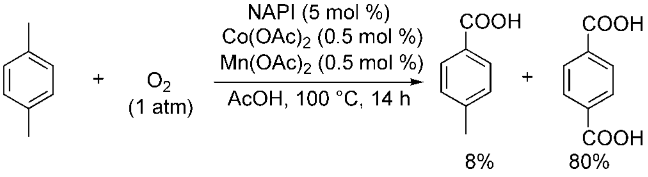
late in 94% or 92% yields, respectively, along with a small amount (<1%) of 4-CBA. It is noteworthy that the oxidation proceeded smoothly even by the use of 5 mol % of NHPI forming TPA in 86% yield. Treatment of PTA under pressure of air (30 atm) at 150 °C afforded TPA in excellent yield within 3 h.

As shown in Equation 15, *ca.* 20 mol % of NHPI must be used to obtain TPA in satisfactory yield (over 80%), because NHPI gradually decomposes to inert phthalimide and phthalic anhydride during the oxidation. If the NHPI used can be reduced by a simple modification, the present oxidation would be more desirable. Our efforts to reduce the amount of the NHPI led us to the discovery of an efficient catalyst, *N*-acetoxyphthalimide (NAPI), which can be easily prepared by the reaction of NHPI with acetic anhydride (Equation 17). Surprisingly, PX was oxidized to TPA in high yield (80%) even by the use of 5 mol % of NAPI, $Co(OAc)_2$ (0.5 mol %), and $Mn(OAc)_2$ (0.5 mol %) (Equation 18).



(17)

Figure 6 shows the time-dependence curves for the aerobic oxidation of PX catalyzed by NAPI or NHPI combined with $Co(OAc)_2$. In contrast to the oxidation of PX by NHPI where PX was completely consumed within 1 h, the oxidation of PX by NAPI proceeded more slowly. This observation suggests that the oxidation of PX at the early stage of the reaction triggered the decomposition of NHPI to phthalimide and phthalic anhydride. Although it is rather difficult to explain the effect of NAPI in this oxidation, NAPI was found to be gradually hydrolyzed to NHPI by water present in acetic acid as well as the water resulting during the oxidation. Therefore, NAPI may be resistant to the rapid decomposition to phthalimide or phthalic anhydride at the early stage of the reaction where violent chain reactions take place.



(18)

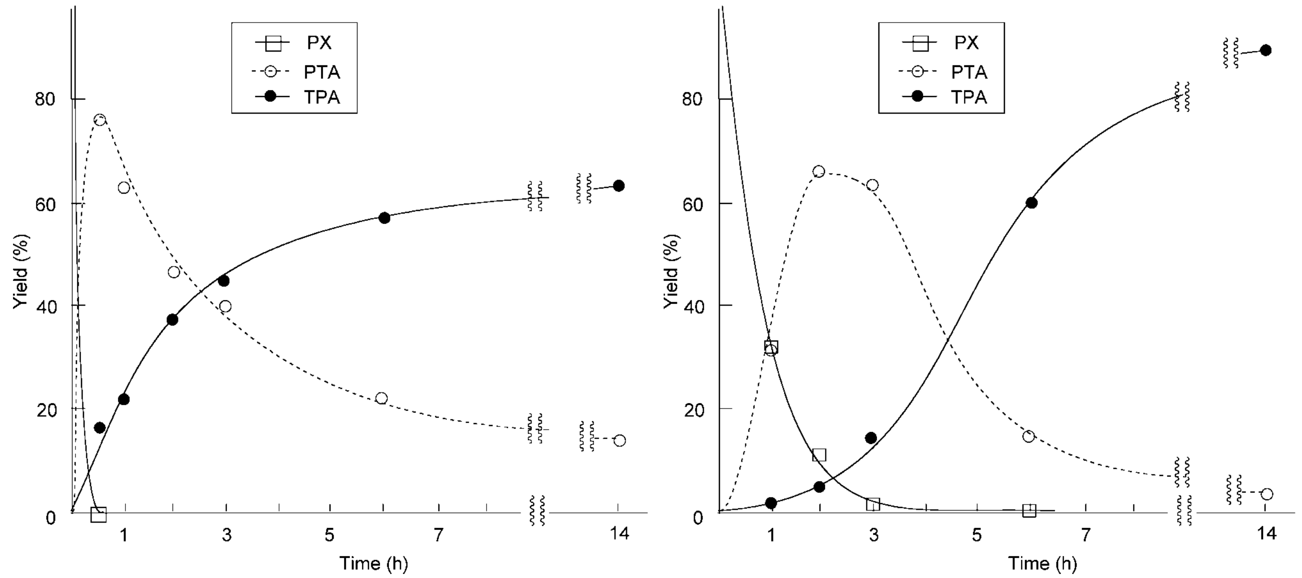


Figure 6. Time dependence cruves for the aerobic oxidation of PX by the NHPI/Co system (*left*) or the NAPI/Co system (*right*).

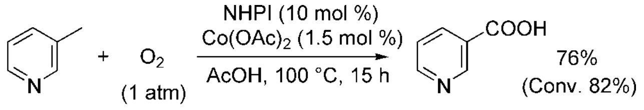
General Procedure for Oxidation of *p*-Xylene under Pressure of Air

To a 50-mL autoclave made of sus-304 with a Teflon vessel-liner, NHPI (15 mol %, 48.9 mg), $Co(OAc)_2$ (0.5 mol %, 2.5 mg), $Mn(OAc)_2$ (0.5 mol %, 2.6 mg), acetic acid (3 mL) and then *p*-xylene (212 mg, 2 mmol) were added. The autoclave was pressurized to 30 atm with air. The mixture was stirred at 150 °C (oil bath temperature) for 3 h. After the reaction, the autoclave was cooled in water, and then the residual air was ventilated. A white precipitate including terephthalic acid was filtered off under vacuum, and washed with acetic acid several times to give almost pure terephthalic acid; yield: 279 mg (84%).

3.4 Practical Oxidation of Methylpyridines

Pyridinecarboxylic acids are useful and important intermediates in pharmaceutical syntheses. Although the synthesis of these carboxylic acids by the aerobic oxidation of alkylpyridines is straightforward, the oxidation is usually difficult to carry out selectively owing to their low reactivities.[59,64,65] In general, pyridinecarboxylic acids are prepared by the oxidation of alkylpyridines with nitric acid or by the hydrolysis of pyridinecarboxamides derived from pyridinecarbonitrile.[66]

The aerobic oxidation of β-picoline catalyzed by NHPI to nicotinic acid was examined.[67] Nicotinic acid is used as a precursor of vitamin B_3 and is commercially manufactured on a large scale by nitric acid oxidation of 5-ethyl-2-methylpyridine.[66a] The oxidation of β-picoline in the presence of NHPI (10 mol %) and $Co(OAc)_2$ (1.5 mol %) under dioxygen (1 atm) at 100 °C for 15 h in acetic acid afforded nicotinic acid in 76% yield at 82% conversion (Equation 19). This is the first successful oxidation of picolines with O_2 under mild conditions. According to the recent literature, nicotinic acid is obtained in *ca.* 50% yield at 52% conversion by the oxidation of β-picoline in the presence of $Co(OAc)_2$ and $Mn(OAc)_2$ using LiCl as a promoter under air (16 atm) at 170 °C.[65]



(19)

A remarkable rate enhancement of the oxidation was observed by adding $Mn(OAc)_2$ to the NHPI/$Co(OAc)_2$ system (Table 11). The reaction by the NHPI/Co/Mn system at 150 °C under air (20 atm) was completed within 2 h to produce nicotinic acid in 89% yield.

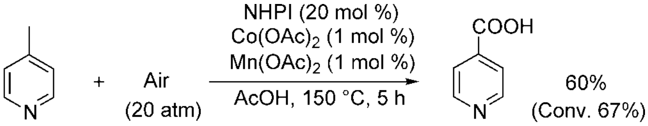
Table 11. Effect of $Mn(OAc)_2$ on aerobic oxidation of β-picoline by NHPI/$Co(OAc)_2$.[a]

Run	$Co(OAc)_2$ [mol %]	$Mn(OAc)_2$ [mol %]	Conv. [%]	Yield [%]
1	0.1	-	5	4
2	0.1	0.1	48	41
3	0.1	0.5	72	65
4[b]	0.5	0.1	91	89

[a] β-Picoline (2 mmol) was allowed to react with dioxygen (1 atm) in the presence of NHPI (10 mol %), $Co(OAc)_2$ and $Mn(OAc)_2$ in AcOH (7 mL) at 100 °C for 15 h.

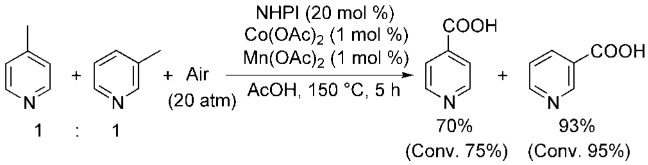
[b] The reaction was carried out under air (20 atm) at 150 °C

In contrast to the oxidation of β-picoline by the NHPI/Co/Mn system where nicotinic acid was formed in good yield, γ-picoline was oxidized with some difficulty under these conditions to form 4-pyridinecarboxylic acid in low yield (22%). After optimization of the reaction conditions, 4-pyridinecarboxylic acid was obtained by the use of NHPI (20 mol %), $Co(OAc)_2$ (1 mol %) and $Mn(OAc)_2$ (1 mol %) in 60% yield at 67% conversion (Equation 20).



(20)

Interestingly, the oxidation of γ-picoline was considerably accelerated by the copresence of β-picoline. For instance, when a 1:1 mixture of β-picoline and γ-picoline under 20 atm of air was oxidized, nicotinic acid and 4-pyridinecarboxylic acid were formed in 93% and 70% yields, respectively (Equation 21). This shows that radical intermediates such as $3\text{-ArCH}_2\text{OO}^\bullet$ and $3\text{-ArCH}_2\text{O}^\bullet$ (where Ar is a pyridinyl moiety) generated from β-picoline serve as chain-transfer agents to facilitate the generation of $4\text{-ArCH}_2^\bullet$ from γ-picoline.



(21)

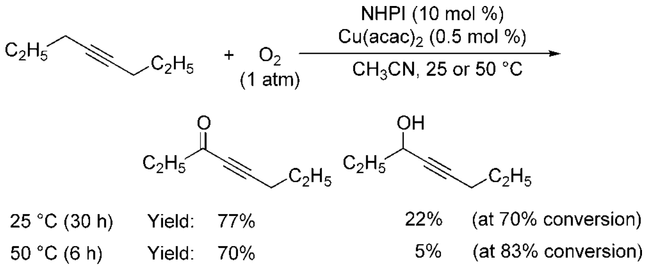
General Procedure for Oxidation of β-Picoline

To a solution of NHPI (10 mol %, 32.6 mg), $Co(OAc)_2$ (1.0 mol %, 5.0 mg) and $Mn(OAc)_2$ (0.1 mol %, 0.5 mg) in acetic acid (7 mL) in a pear-shaped flask was added β-picoline (186 mg, 2 mmol). The flask, attached to a condenser, was equipped with a balloon filled with O_2 (1 atm), and then the mixture was stirred at 100 °C for 15 h. After the reaction, the solvent was removed under reduced pressure to afford a brown solid. To remove NHPI and metals, the solids thus obtained were dissolved in a small amount of methanol or DMSO, and the solution was refluxed and then cooled in an ice bath. To the solution was added excess acetonitrile to give a pure white solid, 3-pyridinecarboxylic acid; yield: 172 mg (70%).

3.5 Preparation of Acetylenic Ketones *via* Alkyne Oxidation

α,β-Acetylenic carbonyl compounds, ynones, are important intermediates in organic synthesis, since further elaboration of ynones can lead to highly valuable compounds such as heterocyclic compounds,[68] α,β-unsaturated ketones,[69] cyclopentenones,[70] *C*-nucleosides,[71] and chiral pheromones,[72] etc. Several methods have been described for the synthesis of conjugated acetylenic ketones; a coupling reaction of acetylenides with activated acylating reagents such as acid chloride or anhydrides.[73] On the other hand, the selective oxidation of alkynes to ynones is carried out by the use of CrO_3/TBHP,[74] CrO_3(pyridine)$_2$,[75] Na_2CrO_4/acetic anhydride,[75] and SeO_2/TBHP systems,[76] but these oxidations are not fully successful.[77]

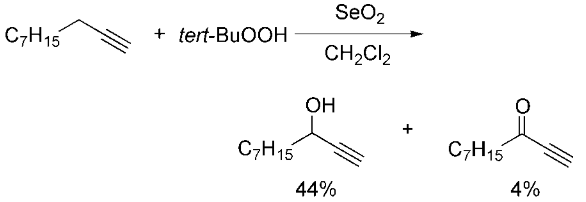
An alternative approach for preparing ynones is the oxygenation of the propargylic C-H bonds of alkynes with dioxygen, since the bond dissociation energies of the propargyl C-H bonds (87 ± 2 kcal/mol for 2-pentyne) are approximately equal to those of the benzylic C-H bonds of alkylbenzenes (88 ± 1 kcal/mol for toluene).[78] However, the conventional oxidation of alkynes with dioxygen at higher temperature (around 150 °C) results in undesired over-oxidation products like carboxylic acids. The aerobic oxidation of alkylbenzenes by the NHPI catalyst could be effected even at room temperature as mentioned in Section 3.3. The NHPI-catalyzed oxidation of alkynes at lower temperature is expected to suppress undesired side reactions. We aimed at applying the NHPI/O_2 system to the selective oxygenation of alkynes to ynones.[79]



(22)

Treatment of 4-octyne with dioxygen (1 atm) under the influence of NHPI (10 mol %) and Cu(acac)$_2$ (0.5 mol %) in acetonitrile at room temperature for 30 h gave 4-octyn-3-one (77%) and 4-octyn-3-ol (22%) at 70% conversion (Equation 22). The same reaction at 50 °C was almost completed after 6 h to give the ynone in 70% yield based on 83% conversion. This oxidation would offer a facile catalytic method for the preparation of conjugated ynones from alkynes.

It is reported that 1-decyne, upon treatment with TBHP in the presence of SeO_2, leads to the acetylenic alcohol, 1-decyn-3-ol, rather than the ynone, 1-decyn-3-one (Equation 23).[76] However, the present aerobic oxidation of 4-octyne formed the ynone in preference to the ynol, because the NHPI/Cu(II) system can also promote the oxidation of acetylenic alcohols to ketones. The reaction of 1-octyn-3-ol under dioxygen (1 atm) in the presence of NHPI and Cu(acac)$_2$ afforded 1-octyn-3-one in 95% yield based on 57% conversion (Equation 24).



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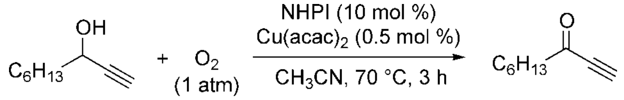
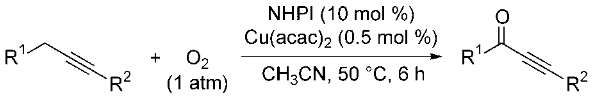


(24)

The NHPI-catalyzed oxidation of various alkynes afforded α,β-acetylenic carbonyl compounds in moderate to good yields (Table 12). Symmetrical alkynes gave the corresponding ynones in good yields, while unsymmetrical alkynes resulted in 1:1 regioisomeric mixtures.[74,75] The CrO_3-catalyzed oxidation of 3-decyne with TBHP is reported to produce

Table 12. Aerobic oxidation of several alkynes to ynones.[a]



Run	R^1	R^2	Conv. [%]	Yield [%][b]
1[c]	CH_3	C_2H_5	93	81
2[d]	C_4H_9	C_5H_{11}	89	75
3[c]	C_3H_7	C_2H_5	92	70[e]
4[d]	C_4H_9	CH_3	94	70
5[c,d]	C_5H_{11}	H	50	80

[a] Alkynes (3 mmol) were allowed to react with dioxygen (1 atm) in the presence of NHPI (10 mol %) and Cu(acac)$_2$ (0.5 mol %) in CH_3CN (5 mL) at 50 °C for 6 h.

[b] Based on converted starting material.

[c] 20 h.

[d] 70 °C.

[e] A 1:1 regioisomeric mixture was obtained.

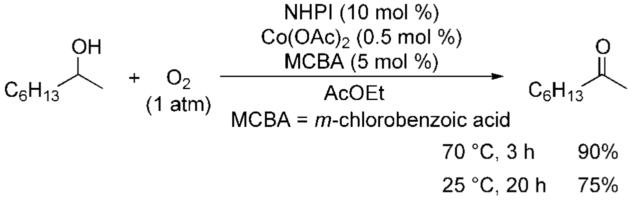
only 3-decyn-2-one. However, 2-octyne could be oxidized regioselectively to form 2-octyn-4-one in which the internal propargyl hydrogen was exclusively oxidized.

3.6 Oxidation of Alcohols

The oxidation of alcohols to the corresponding carbonyl compounds is a frequently used transformation in organic synthesis.[80] There have been many catalytic methods for the aerobic oxidation of alcohols to the corresponding carbonyl compounds.[81,82] However, some of these oxidations are carried out in the presence of a reducing agent such as an aldehyde which is eventually converted into carboxylic acid, or they are severely limited to some reactive alcohols such as benzylic and allylic alcohols. Recently, a few aerobic oxidations involving non-activated alcohols have appeared, although expensive metal catalysts such as Ru and Pd must be employed to effect the oxidation.[83] In 1996, Markó and coworkers developed an efficient aerobic oxidation system of aliphatic alcohols using an inexpensive $CuCl_2$/phenanthroline catalyst combined with azodicarboxylate.[84] Quite recently, reusable heterogeneous catalysts consisting of Ru or Pd have been reported by Kaneda[85] and Uemura,[86] respectively. Sheldon and coworkers have succeeded in the aerobic oxidation of alcohols by a water-soluble Pd catalyst.[87]

3.6.1 Oxidation of Secondary and Primary Alcohols

As described in the preceding sections, we are now able to oxidize alkanes by the NHPI/Co(II) system with dioxygen under mild conditions. This catalytic system is expected to promote the aerobic oxidation of the hydroxy functions of alcohols to carbonyl functions. We first examined the oxidation of secondary alcohols using the NHPI/$Co(OAc)_2$ system.[88,89] The oxidation of 2-octanol in ethyl acetate at 70 °C in the presence of NHPI (10 mol %) and $Co(OAc)_2$ (0.5 mol %) under dioxygen (1 atm) produced 2-octanone in quantitative yield. We discovered that benzoic acids such as *m*-chlorobenzoic acid (MCBA) enhance the oxidation of alcohols to carbonyl compounds. 2-Octanol was converted into 2-octanone with O_2 even at room temperature by adding a catalytic amount of MCBA to the NHPI/$Co(OAc)_2$ system (Equation 25). To the best of our knowledge, the aerobic oxidation of aliphatic alcohols at room temperature has been reported only by Ley et al. who used $[Bu_4N]^+[RuO_4]^-$ assisted by 4 Å molecular sieves (Equation 26).[83b]



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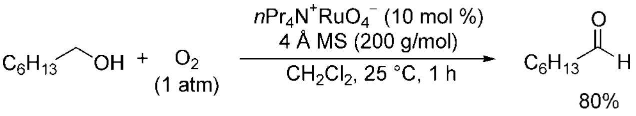


(26)

Figure 7 shows the oxidation of secondary and primary alcohols under ambient conditions by the NHPI/$Co(OAc)_2$/MCBA system. Aromatic and cyclic alcohols afforded the corresponding ketones in good to quantitative yields. Primary alcohols were also oxidized to carboxylic acids in good yields, although MCPBA was added instead of MCBA. Lauryl alcohol led to lauric acid, which is used as a surfactant source, in 66% yield. In the present oxidation, which proceeds through a free radical process, primary alcohols were rapidly converted into carboxylic acids without isolation of aldehydes, because the hydrogen atom abstraction from aldehydes to afford acyl radicals takes place more easily than that from alcohols to furnish α-hydroxyalkyl radicals.[5a] The present method was extended to the oxidation of allylic alcohols.

The oxidation can be rationalized by a path involving the formation of an α-hydroxy hydroperoxide as an intermediate shown in Scheme 10. By UV-VIS measurements on a solution containing MCBA, NHPI, and $Co(OAc)_2$, it was found that the MCBA reacts with the $Co(OAc)_2$ to form a Co-MCBA complex whose new band appears at 570 nm, and that the Co-MCBA complex promotes the decomposition of the hydroperox-

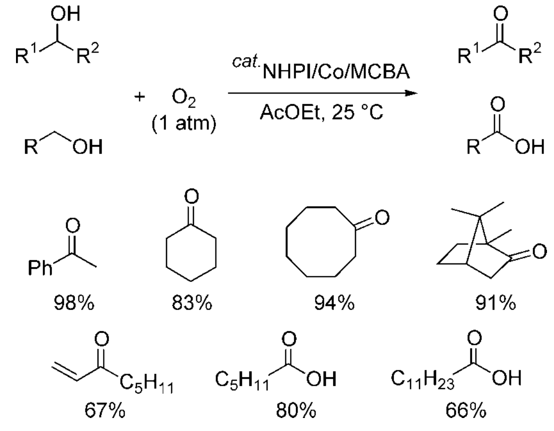
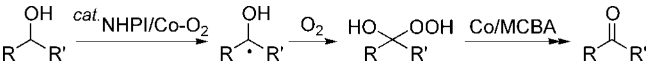
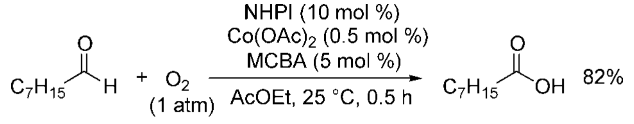


Figure 7. Aerobic oxidation of alcohols by the NHPI/Co/MCBA system.

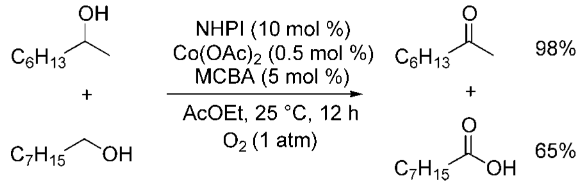


Scheme 10. Reaction pathway for the oxidation of secondary alcohols.

ide. The decomposition rate of cumyl hydroperoxide by $Co(OAc)_2$ was compared with that by the Co-MCBA system, and the latter induced the decomposition much more rapidly than the former. Since the decomposition rate of hydroperoxides in the autoxidation of alkanes is well known to be an important factor to determine the overall reaction rate,[5a,5d,33] the aerobic oxidation of secondary alcohols by the NHPI/$Co(OAc)_2$ system is facilitated by the addition of the MCBA. Primary alcohols are also converted into carboxylic acids through a similar reaction pathway to that for secondary alcohols. The oxidation of 1-octanal gave octanoic acid in 82% yield after as little as 0.5 h (Equation 27). It is interesting to carry out the competitive oxidation of a 1:1 mixture of a primary alcohol and a secondary alcohol. Although the oxidation of 2-octanol alone gave 2-octanone in 75% yield after 20 h, the same oxidation in the presence of 1-octanol resulted in a higher yield of the ketone even after 12 h (Equation 28). Acyl and/or acylperoxy radicals generated from the primary alcohol during the oxidation seem to assist not only the formation of an α-hydroxy radical from the secondary alcohol but also the regeneration of PINO from NHPI.[90]



(27)

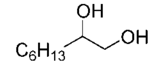
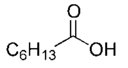
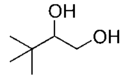
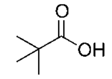
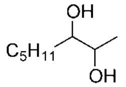
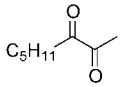
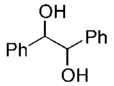
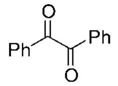
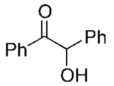
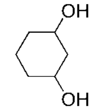
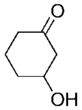
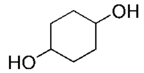
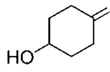
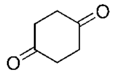
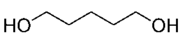
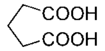


(28)

3.6.2 Oxidation of Diols

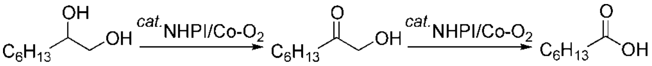
In contrast to oxidations of diols with stoichiometric oxidants like $NaIO_4$ and $Pb(OAc)_4$,[91] or hydrogen peroxide[92] which are often used in organic synthesis, there has been little work so far of the oxidation of diols with dioxygen in spite of their importance.[93] Recently, Uemura and coworkers have reported the $Pd(OAc)_2$-catalyzed lactonization of α,ω-primary diols with dioxygen in the presence of pyridine and 3 Å molecular sieves[94] We have also developed an oxidative cleavage of aliphatic and cyclic 1,2-diols with O_2 to furnish aldehydes and dialdehydes, respectively, by $Ru(PPh_3)_3Cl_2$ on active carbon.[95]

Table 13. Oxidation of various diols with dioxygen.[a]

Diol	Conv. [%]	Products (Yield [%])			
	80		(70)		
	89		(71)		
	96		(86)		
	97		(84)		(12)
	80		(80)		
	88		(72)		(16)
	80		(66)		

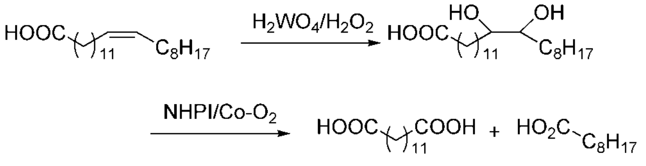
[a] Diols (3 mmol) were allowed to react with molecular oxygen (1 atm) in the presence of NHPI (10 mol %), $Co(acac)_3$ (1 mol %) in CH_3CN (5 mL).

The oxidation of 1,2-octanediol with dioxygen catalyzed by NHPI combined with $Co(acac)_3$ afforded a one-carbon less oxidized product, heptanoic acid, in 70% yield at 80% conversion (Table 13).[89] A precursor to heptanoic acid was found to be an α-ketol, since 1-hydroxy-2-octanone was obtained as a principal product at the limited stage of the reaction (Scheme 11). In fact, an independent oxidation of the α-ketol led to the carboxylic acid in good yield. Woodward and coworkers have applied the NHPI-catalyzed oxidation to the carbon-carbon bond cleavage of diols to carboxylic acids (Equation 29).[96]



Scheme 11.

Unlike 1,2-diols, internal *vic*-diols such as 2,3-octanediol were selectively oxidized to diketones such as 2,3-octanedione rather than cleaved to carboxylic acids. The conversion of *vic*-diols to diketones is usually performed by oxidation with metal oxidants such as $AgCO_3$[97] and permanganate,[98] and by a TEMPO-NaOCl system under electrochemical conditions[99] or by a catalytic method using heteropolyoxometalates and H_2O_2.[100] Interestingly, 1,3- and 1,4- diols were selectively converted into the corresponding hydroxy ketones rather than the diketones. An α,ω-diol such as 1,5-pentanediol afforded the dicarboxylic acid in good yield. The present reaction provides an alternative and useful route to dicarboxylic acids from diols and dioxygen.



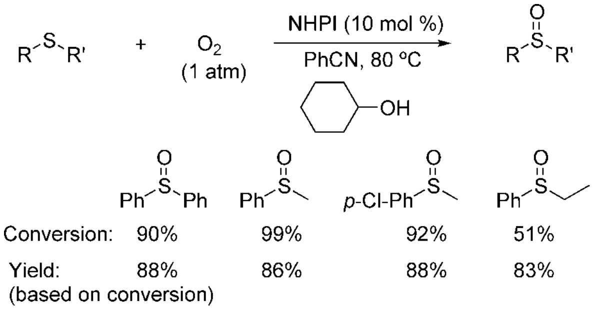
(29)

General Procedure for Oxidation of 2-Octanol

An acetonitrile (5 mL) solution of 2-octanol (391 mg, 3 mmol), NHPI (10 mol %, 48.9 mg), $Co(OAc)_2$ (0.5 mol %, 3.7 mg) and *m*-chlorobenzoic acid (5 mol %, 23 mg) was placed in a two-necked flask equipped with a balloon filled with O_2. **Caution:** *A balloon filled with O_2 can be hazardous, even with a small-scale reaction.* The mixture was stirred at 25 °C for 20 h. Removal of the solvent under reduced pressure gave a clear liquid, which was then purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 5/1) to give 2-octanone; yield: 288 mg (75%).

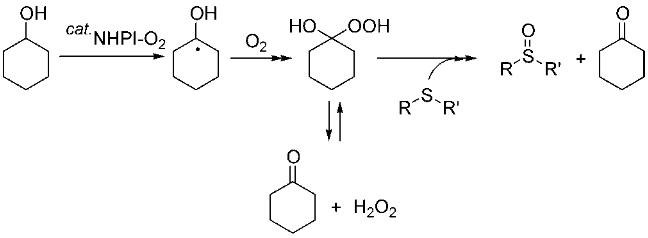
3.7 Selective Oxidation of Sulfides to Sulfoxides

In the aerobic oxidation of secondary alcohols, we showed that α-hydroxy hydroperoxides are formed as precursors to ketones. Our attention is focused on the utilization of *in situ*-generated hydroperoxides as mild oxidants of organic compounds. The NHPI-catalyzed aerobic oxidation of sulfides in the presence of alcohols like cyclohexanol gave the corresponding sulfoxides in high selectivities (Equation 30).[101] As an example, diphenyl sulfide was allowed to react with dioxygen (1 atm) in the presence of NHPI and cyclohexanol in benzonitrile at 80 °C, giving diphenyl sulfoxide in 88% yield at 90% conversion. Mukaiyama et al. explored an asymmetric sulfoxidation of aromatic sulfides under the influence of aldehydes and dioxygen using optically active Mn-diketonate complexes as the catalyst.[102]



(30)

An outline of the present oxidation of sulfides is illustrated in Scheme 12. Cyclohexanone reacts with the resulting H_2O_2 to give the α-hydroxy hydroperoxide which may exist in equilibrium with H_2O_2 and ketone in the reaction medium.[103] The actual oxidizing reagent in the present oxidation is considered to be the hydroperoxide, because the oxidation of diphenyl sulfide with H_2O_2 in the presence of cyclohexanone gave the sulfoxide in higher yield (89%), but the same oxidation in the absence of cyclohexanone formed the sulfoxide in poor yield.

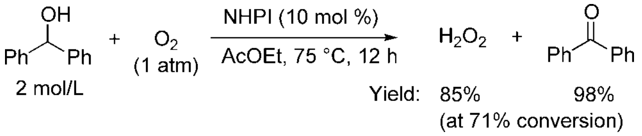


Scheme 12.

3.8 Production of Hydrogen Peroxide by Aerobic Oxidation of Alcohols

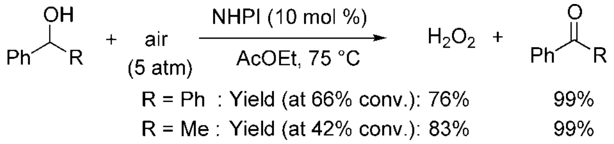
Hydrogen peroxide is the most important oxidant for bleaching in industry. Recently, H_2O_2 has become more and more popular as an environmentally friendly oxidant that remains as only water after the oxidation.[104] Current technology for the production of H_2O_2 is based on the autoxidation of anthrahydroquinones, which is known as the AO process.[104,105] The anthraquinones formed are reduced to the original hydroquinones with hydrogen. This process, therefore, leads to the net formation of H_2O_2 from gaseous hydrogen and oxygen. In addition to the AO process, the autoxidation of secondary alcohols is a powerful candidate for the production of H_2O_2 *via* the formation of α-hydroxy hydroperoxides.[104b,106] For instance, the autoxidation of 1-phenylethanol produces H_2O_2 and acetophenone (Arco process), although the oxidation must be carried out under relatively severe conditions (~160 °C, 10–20 atm of air or O_2). After the isolation of H_2O_2, the resulting mixture containing acetophenone is subjected to hydrogenation to form the original alcohol.

The aerobic oxidation of alcohols, especially benzylic alcohols such as benzhydrol and 1-phenylethanol, under the influence of NHPI catalyst was found to produce H_2O_2 *via* the formation of α-hydroxy hydroperoxides in good yields.[107] When benzhydrol (40 mmol) was reacted with O_2 (1 atm) in the presence of NHPI (10 mol%) in ethyl acetate at 75 °C for 12 h, H_2O_2 was obtained in 85% yield along with benzophenone (98%) (Equation 31). This indicates that the present oxidation permits a practical production of H_2O_2 on an industrial scale.



(31)

The employment of air instead of pure oxygen is important for economical and safety reasons. It is noteworthy that the reaction proceeded smoothly even under 1 atm of air. When the same oxidation was conducted under 5 atm of air, H_2O_2 was produced in 76% yield at 66 % conversion (Equation 32). By the use of 1-phenylethanol, H_2O_2 was formed in satisfactory yields along with acetophenone, although the oxidation rate was slower than that of benzhydrol.



(32)

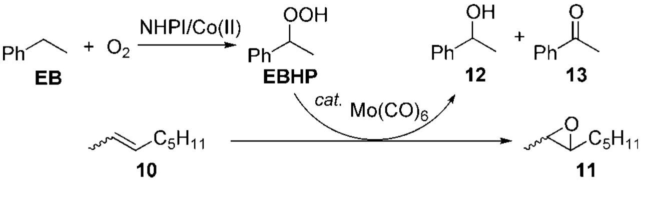
3.9 Epoxidation of Alkenes using Molecular Oxygen as Terminal Oxidant

The epoxidation of alkenes using dioxygen *via* a catalytic process is a challenging subject in the field of oxidation chemistry. Much effort has been devoted to the epoxidation of alkenes with dioxygen using transition metals as catalysts.[5d,5e,6a,108–115] In recent years, alkenes have been successfully epoxidized by the use of a combined system of dioxygen with a reducing reagent such as aldehyde catalyzed by metal complexes and heteropolyoxometalates.[109–112] For instance, β-diketonate complexes of Ni, V, and Fe are reported to catalyze efficiently the epoxidation of alkenes with dioxygen in the presence of an aldehyde, alcohol, or acetal as a reducing agent under mild conditions.[109j] On the other hand, Ru-porphyrin complex[113] and Ru-substituted polyoxometalate, $\{[WZnRu_2(OH)(H_2O)](ZnW_9O_{34})_2\}^{11-}$,[114] catalyze the epoxidation of alkenes without any reducing agent.

3.9.1 Epoxidation of Alkenes using Hydrocarbons as Hydroperoxide Sources

Although there has been long-standing interest in the epoxidation of alkenes with alkyl hydroperoxides generated *in situ* from hydrocarbons and dioxygen, only one report has appeared on the epoxidation of alkenes using cumene and dioxygen catalyzed by heteropolyoxometalates.[115] Difficulties in the epoxidation by hydrocarbons and O_2 different from that by aldehydes and O_2 are attributed to the following reasons: (i) autoxidation of hydrocarbons takes place very slowly, at least two orders of magnitude slower than that of aldehydes, (ii) as a result, the epoxidation using hydrocarbons must be carried out under severe reaction conditions, (iii) the epoxidizing ability of alkyl hydroperoxides is considerably lower than that of peracids or acylperoxy radicals derived from aldehydes.[5a] Therefore, stepwise-procedures are commonly utilized in epoxidations using alkyl hydroperoxides. The Halcon process involves the aerobic oxidation of ethylbenzene to α-hydroperoxyethylbenzene and the Mo-catalyzed epoxidation of propylene with the hydroperoxide obtained above.[116] Consequently, the development of an epoxidation system with the hydroperoxide derived from ethylbenzene and dioxygen is very attractive from the synthetic and industrial view points.

In the NHPI-catalyzed oxidation of hydrocarbons, oxygen-containing compounds such as alcohols and ketones are formed through alkyl hydroperoxides as transient intermediates. If the alkyl hydroperoxides generated *in situ* from hydrocarbons can be utilized as the oxidant, it would be possible to epoxidize alkenes with a hydrocarbon and dioxygen. Thus, our attention was focused on the epoxidation of alkenes with alkyl hydroperoxides generated *in situ* by the NHPI-catalyzed oxidation of hydrocarbons such as ethylbenzene with dioxygen (Scheme 13). We attempted the epoxidation of 2-octene (**10**) with ethylbenzene (EB) and O_2 (1 atm) in the presence of NHPI (10 mol %), $Co(OAc)_2$ (0.1 mol %), and $Mo(CO)_6$ (5 mol %) at 60 °C. The reaction gave 2,3-epoxyoctane (**11**) in moderate yield (Table 14).[117] A significant improvement of the epoxidation was achieved by adding a small amount of 4 Å molecular sieves (MS-4Å) to the reaction system. When tetralin (TL) was employed instead of EB, the epoxide was obtained in high yield (86%, based on 67% conversion of 2-octene). It is very interesting to note that the present epoxidation was induced even at room temperature. Up to now, the conversion of these hydrocarbons into the hydroperoxides was difficult at room temperature. Usually, Mo(VI) complexes exhibit potent catalytic activity in the epoxidation of alkenes with alkyl



Scheme 13. Epoxidation pathway for alkenes using EBHPO generated *in situ* from EB in the presence of NHPI, $Co(acac)_2$, and $Mo(CO)_6$.

Table 14. Epoxidation of 2-octene (**10**) to 2,3-epoxyoctane (**11**) with dioxygen in the presence of hydrocarbons using NHPI, $Co(OAc)_2$, and $Mo(CO)_6$ as catalysts.[a]

Run	Hydrocarbon	Temp. [°C]	Conv. [%]		Yield [%][b]		
			10	EB or TL	**11**	**12**	**13**
1	Ethylbenzene(EB)	60	67	10	61	65	25
2[c]	EB	60	81	12	70	71	19
3	Tetralin(TL)	50	67	25	86	62	30
4	TL	25	31	11	97	72	21

[a] 2-Octene (4 mmol) was allowed to react with dioxygen (1 atm) in the presence of NHPI (10 mol %), $Co(OAc)_2$ (0.1 mol %), $Mo(CO)_6$ (5 mol %) and hydrocarbon in PhCN (2 mL) for 12 h. EB (40 mmol) and TL (20 mmol) were used, respectively.

[b] Based on converted starting material.

[c] 4 Å MS (200 mg) was added.

hydroperoxides,[118] but the activity of $MoO_2(acac)_2$ in the present epoxidation was low due to the retardation of the formation of hydroperoxides from the hydrocarbons by the NHPI/O_2 system.

Inspection of Table 15 shows that the present reaction system is applicable to the epoxidation of various alkenes in high yields. Although the metal-catalyzed epoxidation of *cis*-alkenes using an aldehyde and O_2 affords a mixture of *cis*- and *trans*-epoxides (Equation 33),[119] the present epoxidation of *cis*-2-octene proceeded in stereospecific manner to give *cis*-2,3-epoxyoctane in almost complete stereoselectivity. In the present system, the real epoxidizing agent is a peroxomolybdenum species generated from Mo(VI) and the hydroperoxide such as α-hydroperoxyethylbenzene (EBHP) from a hydrocarbon such as EB and O_2 by the action of NHPI.[120] The terminal alkene, 1-octene, was epoxidized to 1,2-epoxyoctane in moderate conversion.

Table 15. Epoxidation of various alkenes with dioxygen in the presence of EB or TL catalyzed by NHPI, $Co(OAc)_2$ and $Mo(CO)_6$.[a]

Run	Alkene	Temp. [°C][b]	Conv. [%][b]	Yield [%][b],[c]
1	*trans*-2-Octene	60 (60)	78 (71)	88 (79)[d]
2	*cis*-2-Octene	50 (60)	83 (75)	87 (71)[e]
3	1-Octene	60(70)	38 (37)	80 (81)
4[f]	Cyclohexene	60	80	74
5[f]	Cyclooctene	60	89	83
6	*trans*-2-Hexen-1-ol	60	79	65
7[g],[h]	*trans*-2-Hexen-1-ol	60	97	92

[a] Alkenes (4 mmol) and EB (40 mmol) or TL (20 mmol) were allowed to react with dioxygen (1 atm) in the presence of NHPI (10 mol %), $Co(OAc)_2$ (0.1 mol %), $Mo(CO)_6$ (5 mol %) and 4 Å MS (200 mg) in PhCN (2 mL) for 14 h.

[b] The results using EB are in parentheses.

[c] Based on converted starting material.

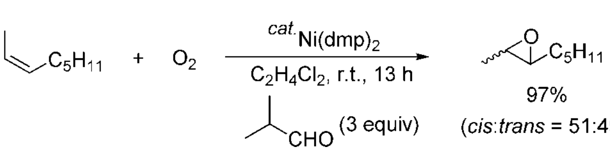
[d] *trans/cis* = >99/1.

[e] *cis/trans* = 99/1 for TL, 94/6 for EB.

[f] TL (40 mmol) was used.

[g] $VO(acac)_2$ (0.5 mol %) was used instead of $Mo(CO)_6$ and $Co(OAc)_2$.

On the other hand, epoxidation of the allylic alcohol, *trans*-2-hexen-1-ol, to the epoxy alcohol was realized in high yield by using the NHPI/$VO(acac)_2$ system. The epoxidation of allylic alcohols with TBHP by V(V) complexes is known to result in epoxides in higher yields than those by Mo(VI) complexes.[118] In the present reaction, $VO(acac)_2$ acts not only as the epoxidation catalyst of alkenes with the hydroperoxide, but also as the catalyst for the generation of PINO from NHPI.

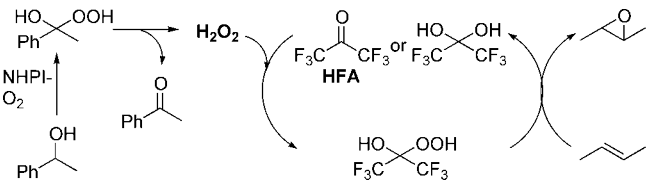


(33)

3.9.2 Epoxidation of Alkenes with Hydrogen Peroxide Generated *in situ* from Alcohols and O_2

In a preceding section, we showed that EBHP generated *in situ* from EB is converted into 1-phenylethanol after the epoxidation of alkenes. In the Halcon process, the resulting 1-phenylethanol during the epoxidation of propylene is dehydrogenated into styrene.[116] However, when the demands of propylene oxide and the styrene are not balanced in the market, the formation of the co-product harbors an economical disadvantage.[121] If 1-phenylethanol can be reused as a hydroperoxide source for the epoxidation of alkenes, it is expected to compensate for this disadvantage.

As shown in Section 3.8, treatment of 1-phenylethanol with dioxygen in the presence of NHPI produced hydrogen peroxide efficiently. We envisaged the hexafluoroacetone (HFA)-catalyzed epoxidation of alkenes utilizing H_2O_2 obtained *in situ* by the NHPI-catalyzed aerobic oxidation of alcohols (Scheme 14). A hydroperoxide derived from HFA and H_2O_2 has been reported to epoxidize various alkenes in fair to good



Scheme 14. Epoxidation pathway for alkenes using H_2O_2 generated *in situ* from alcohols in the presence of NHPI and hexafluoroacetone (HFA).

yields.[122,123] This epoxidation system seems to be an interesting industrial strategy, for it does not require the storage and transportation of explosive H_2O_2.[124] In addition, the resulting ketones can be easily reduced to the original alcohols.

2-Octene was allowed to react under O_2 (1 atm) in the presence of 1-phenylethanol under the influence of catalytic amounts of NHPI (10 mol %) and HFA (10 mol %) in benzonitrile at 80 °C for 24 h, giving 2,3-epoxyoctane in 73% yield based on 90% conversion (Equation 34).[125] The present example is the first epoxidation with H_2O_2 generated *in situ* from alcohols and O_2 without any metal catalysts. Among the alcohols examined, benzhydrol was the best source for H_2O_2 formation (Table 16). The use of 2-propanol as H_2O_2 source reduced the yield of the epoxide because of the difficulty of the abstraction of the α-hydrogen atom from 2-propanol compared with that from 1-phenylethanol. As a consequence, the α-hydrogen abstraction from the 2-propanol by the PINO takes place in competition with the allylic hydrogen abstraction from 2-octene to result in a reduction of the yield of epoxide. In the electrochemical oxidation using NHPI as the mediator, Masui et al. reported that the allylic oxidation of olefins occurs more easily than the dehydrogenation of alcohols such as 2-propanol and cyclohexanol to ketones.[126] Hence, benzhydrol and 1-phenylethanol whose α-hydrogen is more easily abstracted than those of 2-propanol and cyclohexanol are a good choice as the H_2O_2 source in the present epoxidation.

Table 16. Effect of alcohols on the epoxidation of 2-octene (**10**) to 2,3-epoxyoctane (**11**) with dioxygen catalyzed by NHPI and HFA.[a]

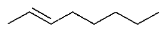
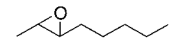
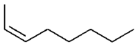
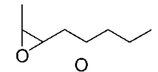
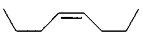
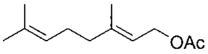
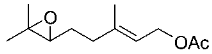
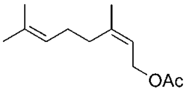
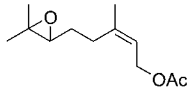
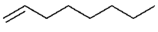
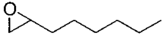
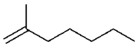
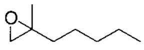
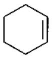
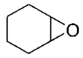
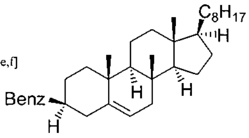
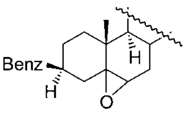
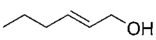
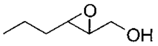
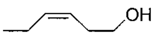
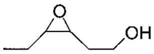
Run	Alcohol	Conv. [%]	Yield [%][b]
1	2-Propanol	58	42
2	Benzylalcohol	84	71
3	1-Phenylethanol	90	73
4[c]	Benzhydrol	94	90

[a] 2-Octene (3 mmol) was allowed to react with dioxygen (1 atm) in the presence of NHPI (0.3 mmol), HFA (0.3 mmol) and alcohol (15 mmol) in PhCN (6 mL) at 80 °C for 24 h.

[b] Based on converted starting material.

[c] Reaction was carried out for 18 h.

Table 17. Epoxidation of various alkenes with dioxygen in the presence of benzhydrol catalyzed by NHPI and HFA.[a]

Run	Substrate	Conv. [%]	Product [%][b]	
1		93		93 (99/1)
2[c]		90		80 (99/1)
3		94		86 (2/98)
4		96		83 (1/99)
5		88		81
6		89		83
7[d,e]		80		90
8[e,f]		83		84
9[e]		78		80
10[e,f]		72		83 (75/25)
11[g]		82		87
12[g]		90		82

[a] Reaction was performed under the similar conditions as described in Table 16.

[b] Parentheses show the ratio of *trans/cis*.

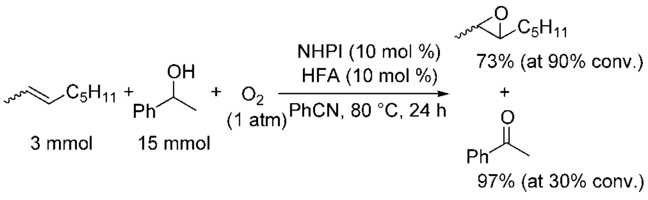
[c] 1-Phenylethanol was used instead of benzhydrol.

[d] 90 °C.

[e] Trifluorotoluene was used as a solvent.

[f] NHPI (20 mol %) was used.

[g] Reaction was conducted in the presence of $Co(OAc)_2$ (0.05 mol %) at 50 °C in trifluorotoluene as the solvent.



(34)

The epoxidation of various alkenes using benzhydrol or 1-phenylethanol and dioxygen is listed in Table 17. The epoxidation of *cis*- and *trans*-2-octenes, and *cis*-4-octene proceeded in a stereospecific manner to form *cis*- and *trans*-2,3-epoxyoctanes, and *cis*-4,5-epoxyoctane, respectively, in high yields. Geranyl and neryl acetates afforded the corresponding epoxides in which the double bonds remote from their acetoxy groups were epoxidized in high regioselectivity. It is noteworthy that the epoxidation of terminal olefins such as 1-octene and 2-methyl-1-heptene, which undergo the oxidation with more difficulty than internal olefins, produced epoxides in satisfactory yields. Cholesteryl benzoate gave the 5,6-α-epoxide in preference to the 5,6-β-epoxide in a ratio of 75/25, which is comparable to that from the epoxidation by MCPBA.[127] In contrast, this epoxidation by the Mn complex/aldehyde/O_2 system is reported to result in the epoxide in a ratio of α/β = 18/82.[128]

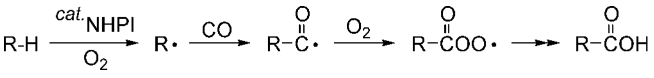
trans-2-Hexen-1-ol was easily epoxidized to the epoxy alcohol in high yield, although a very small amount of $Co(OAc)_2$ (0.05 mol %) must be added to the reaction system in order to perform the reaction at lower temperature (50 °C). Similarly, *cis*-3-hexen-1-ol was epoxidized in a stereoselective manner to form the corresponding *cis*-epoxy alcohol in good selectivity.

4 Carboxylation of Alkanes with CO and O_2

Carbonylation as well as carboxylation of alkanes with carbon monoxide (CO) are challenging subjects in organic synthesis.[129] There have been several important discoveries including the Rh-catalyzed photocarbonylation of alkanes by Tanaka[130,131] and the carboxylation of methane with CO/O_2 using Pd/Cu[132] or $RhCl_3$[133] catalysts by Fujiwara and Sen et al. The carbonylation of adamantanes under the influence of Lewis acid and superacids is also reported.[134,135]

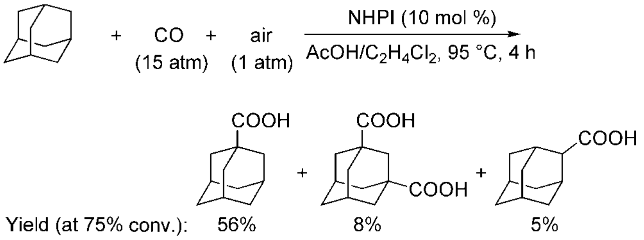
Following the first report on the free-radical mediated carbonylation by Coffmann et al. in 1952,[136] this type of reaction was not investigated for a long time, probably because the reaction must be conducted under extremely high CO pressure (200–300 atm).[137] In 1990, Ryu performed a successful free-radical carbonylation of alkyl halides with CO mediated by tributyltin hydride.[129e,138] Sen et al. disclosed a free-radical carboxylation of methane to acetic acid by the use of peroxydisulfate as a radical source.[139] Benzophenone-[140] and polyoxotungstate-photocatalyzed[141] as well as mercury-photosensitized[142] carbonylations of cyclohexane afford cyclohexanecarbaldehyde. Our interest was directed to the trapping of alkyl radicals generated from alkanes under the influence of NHPI catalyst by CO followed by O_2 leading to carboxylic acids (Scheme 15).[143]

The carboxylation of adamantane under CO/air (15/1 atm) in the presence of NHPI (10 mol %) in a mixed solvent of acetic acid and 1,2-dichloroethane at 95 °C for 4 h afforded 1-adamantanecarboxylic acid, 1,3-adamantanedicarboxylic acid, 2-admantanecarboxylic acid, and several oxygenated products such as 1-adamantanol and 2-adamantanone, but 1-adamantanecarbaldehyde was not formed at all (Equation 35). The selectivity of these products depended markedly on the reaction conditions. Increasing the oxygen concentration increased the formation of oxygenated products.



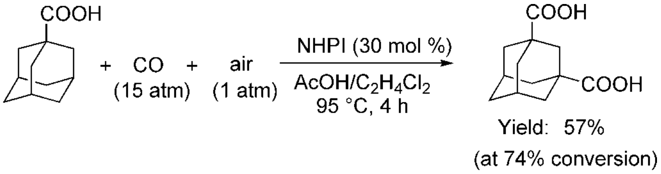
$$R\text{-}H \xrightarrow[O_2]{cat.\,NHPI} R\cdot \xrightarrow{CO} R\text{-}\overset{O}{\overset{\|}{C}}\cdot \xrightarrow{O_2} R\text{-}\overset{O}{\overset{\|}{C}}OO\cdot \longrightarrow R\text{-}\overset{O}{\overset{\|}{C}}OH$$

Scheme 15. Carbonylation of alkanes with CO and O_2 catalyzed by NHPI.



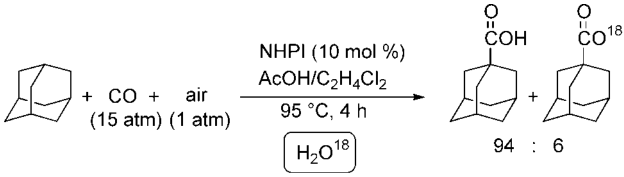
(35)

The present strategy was successfully applied to the preparation of adamantanedicarboxylic acid, which is an interesting monomer in polymer chemistry, through a stepwise procedure (Equation 36), although the dicarboxylic acid is difficult to obtain by the conventional method. Similarly, 1,3-dimethyladamantane and *endo*-tricyclo[5.2.1.0]decane were carboxylated to the respective mono- and dicarboxylic acids.

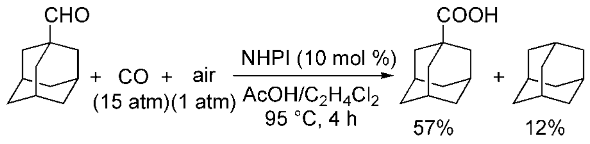


(36)

In order to clarify whether the present carboxylation proceeds through a radical process or not, hydroquinone (0.1 mol %) was added to the reaction system. The reaction was found to be completely inhibited. In addition, the carboxylation of adamantane in the presence of H_2O^{18} produced no labeled-products, meaning no participation of the acyladamantyl cation as an intermediate in this carbonylation (Equation 37). For the reaction of adamantanecarbaldehyde under CO/air, it was found that the decarbonylation from adamantanecarbaldehyde takes place under the conditions employed (Equation 38).



(37)



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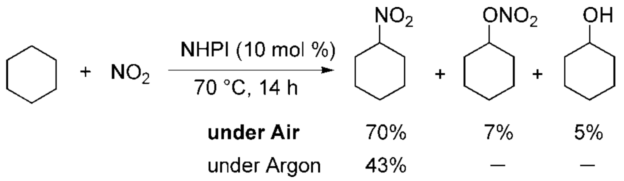


(39)

5 Utilization of NO_x in Organic Synthesis

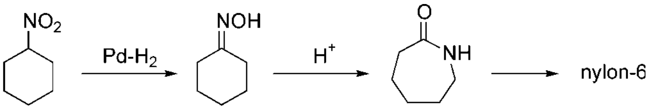
5.1 First Catalytic Nitration of Alkanes using NO_2

Nitration of lower alkanes such as methane and ethane with nitric acid or nitrogen dioxide is industrially practiced to produce nitroalkanes.[144,145] However, a major problem in current industrial nitration is that the reaction must be run at fairly high temperature (250–400 °C), because of the difficulty of the C-H bond homolysis by NO_2.[144] Under such high temperatures, higher alkanes undergo not only homolysis of the C-H bonds but also cleavage of the C-C skeleton. Hence, the nitration is limited to lower alkanes.[145] The nitration of propane results in all of the possible nitroalkanes, i.e., nitromethane, nitroethane, 1-nitropropane, and 2-nitropropane.[144,146] Therefore, the catalytic nitration of alkanes under mild conditions would offer a promising and superior alternative.

Since NO_2 is a paramagnetic molecule, the generation of PINO from NHPI by the action of NO_2 in analogy with O_2 is expected. Indeed, when NO_2 was added to NHPI in benzene at room temperature, an ESR signal attributable to PINO was instantly observed as a triplet.

As a typical result, the nitration of cyclohexane with NO_2 by NHPI without any solvent under air (1 atm) proceeded smoothly even at 70 °C to give nitrocyclohexane (70% based on NO_2 used) and cyclohexyl nitrite (7%) along with a small amount of an oxygenated product, cyclohexanol (5%) (Equation 39).[147]

It is important that the NHPI-catalyzed nitration is conducted under air, since NO generated in the course of the reaction can be reoxidized to NO_2 by O_2. In the absence of air, the yield of nitrocyclohexane decreased to 43%. After the nitration, the NHPI catalyst can be separated from the reaction mixture by simple filtration and reused repeatedly. Nitrocyclohexane is easily reduced to cyclohexanone oxime. Therefore, our nitration provides an alternative practical route to cyclohexanone oxime, which is a raw material for ε-caprolactam leading to nylon-6 (Scheme 16).[148,149,150]



Scheme 16.

The results of the nitration of other alkanes are shown in Table 18. The reaction of cyclooctane afforded nitrocyclooctane in relatively good yield. The present method can be applied to the nitration of aliphatic alkanes. From hexane, a 3:53:44 regioisomeric mixture of 1-nitrohexane, 2-nitrohexane, and 3-nitrohexane was obtained in 54% yield. In the nitration of substituted alkanes such as isobutane and 2,5-dimethylhexane, the tertiary positions were selectively nitrated.

Scheme 17 shows the reaction sequence for the conventional vapor-phase nitration of alkanes by NO_2.[145] In the present nitration of alkanes by NO_2 under air catalyzed by NHPI, the NO formed is reoxidized by O_2 to NO_2 which can be reused in the nitra-

Table 18. NHPI-catalyzed nitration of alkanes with NO_2.[a]

Run	Alkane	**Products**	Method	Yield [%]
1	Cyclooctane	Nitrocyclooctane	A	50
2	Hexane	1-Nitrohexane, 2-Nitrohexane, 3-Nitrohexane	A	54[b]
3	Isobutane	2-Nitro-2-methylpropane	B	46
4	2,5-Dimethylhexane	2-Nitro-2,5-dimethylhexane	C	60
5	Adamantane	Nitroadamantane	C	66
6	1,3-Dimethyladamantane	1-Nitro-3,5-dimethyladamantane	C	70

[a] Method A: Alkanes (5 mL) were allowed to react with NO_2 (2.5 mmol) in the presence of NHPI (0.6 mmol) under air (1 atm) at 70 °C for 14 h. Yields were based on NO_2 used. Method B: Reaction was carried out using a glass autoclave. Isobutane (2 mL) was allowed to react with NO_2 (2.5 mmol) in the presence of NHPI (0.6 mmol) under air (1 atm) in $PhCF_3$ (3 mL) at 70 °C for 14 h. Method C: Alkanes (3 mmol) were allowed to react with NO_2 (3.3 mmol) in the presence of NHPI (0.6 mmol) under air (1 atm) in $PhCF_3$ (5 mL) at 70 °C for 14 h. Yields were based on alkanes used.

[b] A 3:53:44 regioisomeric mixture of 1-nitrohexane, 2-nitrohexane and 3-nitrohexane was obtained.

$$2\,R{-}H + 3\,NO_2 \longrightarrow 2\,R{-}NO_2 + H_2O + NO$$

$$\begin{aligned}
R{-}H + NO_2 &\longrightarrow R\cdot + HNO_2\\
HNO_2 &\longrightarrow \cdot OH + NO\\
R{-}H + \cdot OH &\longrightarrow R\cdot + H_2O\\
R\cdot + NO_2 &\longrightarrow R{-}NO_2
\end{aligned}$$

Scheme 17. Nitration pathways for alkanes by NO_2.

$$3\,R{-}H + 4\,NO_2 + O_2 \longrightarrow 3\,R{-}NO_2 + HNO_3 + H_2O$$

$$\begin{aligned}
NHPI + NO_2 &\longrightarrow PINO + HNO_2\\
R{-}H + PINO &\longrightarrow R\cdot + NHPI\\
R\cdot + NO_2 &\longrightarrow R{-}NO_2\\
3\,HNO_2 &\longrightarrow HNO_3 + H_2O + 2NO\\
2\,NO + O_2 &\longrightarrow 2\,NO_2
\end{aligned}$$

Scheme 18. A possible nitration pathway for alkanes by NO_2/air catalyzed by NHPI.

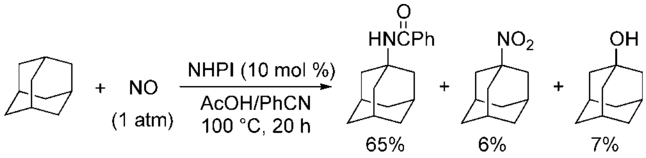
tion. Because of the complexities of the present nitration system, it seems rather difficult to delineate a detailed reaction path, but a plausible pathway is shown in Scheme 18.

The hydrogen atom abstraction from the hydroxyimide group of NHPI is induced by NO_2 to form PINO, a key radical species. The PINO abstracts the hydrogen atom from an alkane to give an alkyl radical which is readily trapped by NO_2 to form a nitroalkane. It has been reported that the formed HNO_2 is converted into HNO_3, H_2O, and NO which is easily oxidized to NO_2 under air.[151] Indeed, when the reaction mixture was extracted with water after the reaction, the aqueous phase was acidic, probably because of the formation of HNO_3. The most promising feature of the NHPI-catalyzed nitration of alkanes by NO_2 is that the nitration can be conducted under air at moderate temperature. Owing to the higher concentration of NO_2 than air, the alkyl radicals formed can react selectively with NO_2 rather than with O_2 to give nitroalkanes in preference to oxygenated products. The conventional nitration is difficult to carry out in air, because the nitration must be carried out at high temperature (250–400 °C). Under these temperatures, the resulting alkyl radicals react not only with NO_2 but also with O_2 to provide a complex mixture of products.[145b] By the use of the NHPI catalyst, the highly selective nitration of higher alkanes with NO_2/air under mild conditions was realized for the first time.

5.2 Reaction of NO with Organic Compounds

In recent years, much attention has been paid to nitric oxide (NO), a molecule having a free radical character, in the fields of biochemistry and medical science.[152,153] However, its application to synthetic organic chemistry is quite limited because of the sparse information available on the chemical behavior of NO and the difficulty incurred in controlling its reactivity. Recently, Yamada et al. have reported that NO can be used as a nitrogen source for the synthesis of nitrogen-containing compounds such as 2-nitrosocarboxamides[154] and nitroalkenes.[155] In addition, it has been shown that amines,[156] phenothiazines,[157] and dienes[158] react with NO in the presence or absence of dioxygen. We have now found a novel utilization of NO in organic synthesis.[159,160]

The reaction of adamantane with NO (1 atm) in the presence of NHPI (10 mol %) in a mixed solvent of benzonitrile and acetic acid at 100 °C for 20 h afforded 1-*N*-adamantylbenzamide in substantial yield along with a small amount of nitroadamantane (Equation 40).[159] The present reaction provides a novel and alternative modified Ritter-type reaction, although there are a few reports on the transformation of adamantane to the amide by means of the anodic oxidation[161] or nitronium tetrafluoroborate.[162]



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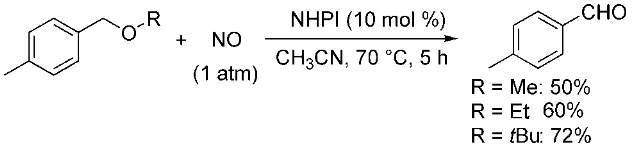
On the other hand, benzyl ethers reacted with NO in the presence of the NHPI catalyst to afford the corresponding aromatic aldehydes (Equation 41 and Figure 8).[160] The reaction of 4-methoxymethyltoluene catalyzed by NHPI (10 mol %) under NO (1 atm) for 5 h led to *p*-tolualdehyde in 50% yield. *tert*-Butoxymethyltoluene was transformed into the aldehyde in 72% yield. *tert*-Butyl benzyl ethers were found to be converted into the corresponding aldehydes in good yields.



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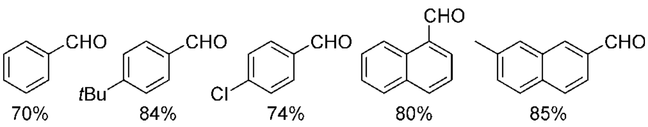
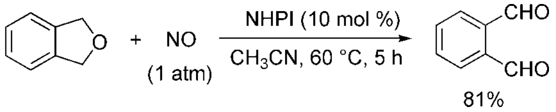


Figure 8. Alkdehydes synthesized by reaction of ethers with NO.

The most important application of this procedure is the transformation of ethers to benzenedicarbaldehydes, which are attractive starting materials in pharmaceutical synthesis. There have been few reports on practical methods for these dialdehydes so far.[163] 1,3-Dihydro-2-benzofuran, 1,3-di-*tert*-butoxymethyl-, and 1,4-dimethoxymethylbenzenes were converted into the respective dialdehydes in good yields (Equation 42 and Equation 43). Of the various indirect procedures to obtain dialdehydes, hydrolysis of α,α,α',α'-tetrabromoxylenes is usually used, although the preparation of bromides is troublesome.[164] Therefore, the present procedure provides a very convenient and direct route to benzenedicarbaldehydes.



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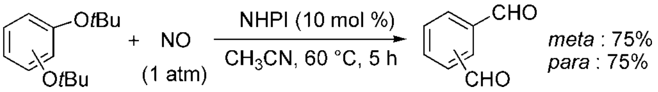
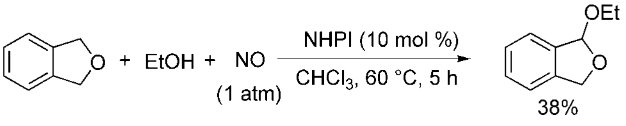


(43)

Mechanistically, the reactions of adamantane and ethers with NO are rationally explained by considering the formation of carbocations as transient intermediates (Scheme 19). The generation of PINO from NHPI in the presence of NO was confirmed by ESR measurements.[159] On the other hand, Suzuki has suggested the formation of a cationic species *via* a diazonium nitrate in the nitration of alkenes with NO.[165] The nucleophilic attack of the benzonitrile and water to the adamantyl and benzylic cations would result in the amide and aldehyde, respectively. Indeed, an intermediate carbocation generated from phthalane by the NHPI/NO system has been trapped by a nucleophile such as alcohol (Equation 44).[160]



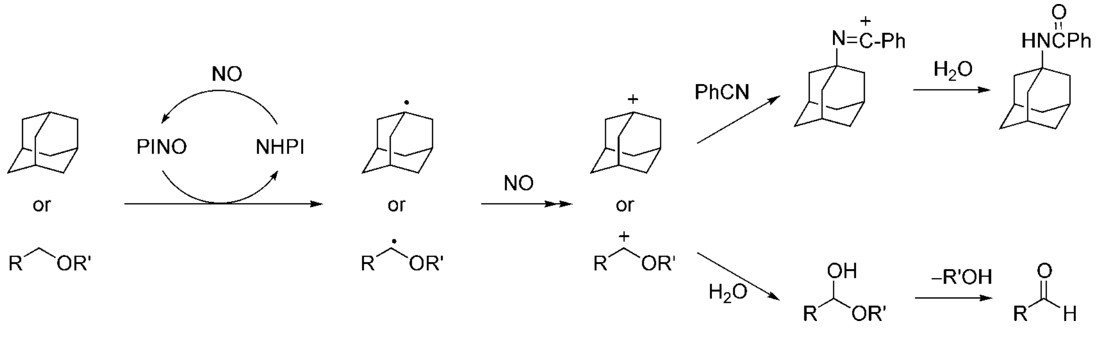
(44)

General Procedure for Reaction of Phthalane with NO

To a solution of phthalane (120 mg, 1 mmol) in acetonitrile (5 mL) in a three-necked flask was added NHPI (10 mol %, 16.3 mg). The flask was cooled to −78 °C to freeze the solvent, degassed under vacuum, and then filled with Ar gas. Next, the frozen solvent was melted at room temperature and refrozen to reiterate the evacuation-Ar purge procedure. This series of operations was repeated three times, and then NO was added to the reaction vessel. The reaction mixture was allowed to react under an atmospheric pressure of NO at 60 °C for 5 h. After solvent was removed under vacuum, *o*-phthalaldehyde was isolated by flash chromatography with chloroform on silica gel; yield: 108 mg (81%).

6 Sulfoxidation of Alkanes Catalyzed by Vanadium

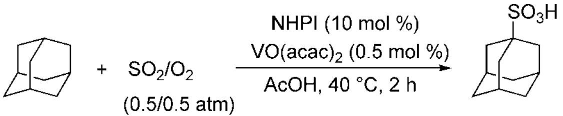
The sulfoxidation of aromatic hydrocarbons has been extensively studied, but work on the sulfoxidation of saturated hydrocarbons to alkanesulfonic acids remains at a less satisfactory level. The Strecker reaction using alkyl halides, preferably alkyl bromides, and alkali metal or ammonium sulfides, is commonly used for the synthesis of alkanesulfonic acids.[166] Another procedure, the oxidation of thiols with bromine in the presence of water or hydrogen peroxide and acetic acid, has been reported.[167] Attempts to realize the sulfoxidation of alkanes with SO_2 and O_2 have not been fully studied in spite of their importance, probably because of the difficulty of selective cleavage of the C-H bond in alkanes. Only a few reactions are reported for the sulfoxidation of alkanes such as cyclohexane *via* a radical process using a mixture of SO_2 and O_2 by means of the photo- and peroxide-initiated techniques.[168] However, the efficiency of the sulfoxidation by these methods is at an insufficient level. Therefore, if alkanes can be sulfoxidated catalytically by SO_2/O_2 without irradiation with light or initiation by a peroxide, such a method would have enormous synthetic potential and provide a very attractive route to alkanesulfonic acids. The direct sulfoxidation of alkanes using SO_2 and O_2 was found to be efficiently



Scheme 19. Reaction of adamantane or ethers with NO through the formation of carbocations as transient intermediates.

catalyzed by a vanadium species in the presence or absence of NHPI.[169]

The reaction of adamantane with a mixture of SO_2 and O_2 (0.5/0.5 atm) in the presence of NHPI (10 mol %) and $VO(acac)_2$ (0.5 mol %) in acetic acid at 40 °C for 2 h produced 1-adamantanesulfonic acid in 95% yield based on 65% conversion. Smith obtained the same product in 15% yield by the photosulfoxidation of adamantane with SO_2/O_2 in the presence of H_2O_2.[170] Surprisingly, 1-adamantanesulfonic acid was produced with high selectivity and at moderate conversion even in the absence of the NHPI (Equation 45).



Catalyst	Yield
NHPI/$VO(acac)_2$	95% (at 65% conv.)
$VO(acac)_2$	98% (at 43% conv.)

(45)

In order to assess the potential of various metal ions in this sulfoxidation, a series of first-row transition metal salts, $TiO(acac)_2$, $Cr(acac)_3$, $Mn(acac)_3$, $Fe(acac)_3$, $Co(acac)_2$, $Ni(OAc)_2$, and $Cu(OAc)_2$ was tested. It is interesting to note that no sulfoxidation was induced by these metal salts other than vanadium ions.[171] From a survey of vanadium compounds, $VO(acac)_2$ and $V(acac)_3$ were found to be efficient catalysts (Table 19). $VO(acac)_2$ promoted the reaction even at room temperature affording the sulfonic acid in 81% yield based on 64% conversion after 24 h. When a small amount of hydroquinone was added to the present reaction system, no reaction took place. This indicates that a radical chain process is involved in the present catalytic sulfoxidation.

A variety of alkanes was successfully sulfoxidated by a mixture of SO_2 and O_2 giving the corresponding alkanesulfonic acids in high selectivities (Figure 9). Adamantane having either an electron-withdrawing or electron-donating group was sulfoxidated in good selectivity in a range of *ca.* 60–80 % conversion. The aliphatic hydrocarbon, octane, afforded a mixture of 2-, 3-, and 4-octanesulfonic acids.

The sulfoxidation of alkanes seems to proceed *via* the following reaction steps (Scheme 20). The sulfoxidation may be initiated by one-electron transfer from an alkane to a V(V) species generated *in situ* from $VO(acac)_2$ and O_2 to form an alkyl cation radical which readily liberates a proton to form an alkyl radical. The V(IV) species is reported to undergo disproportionation to V(V) and V(III) in the oxidative polymerization of diphenyl disulfide by the vanadium ion under a dioxygen atmosphere.[172] In addition, α-hydroxycarbonyl compounds are oxidized to α-dicarbonyl compounds by $VOCl_3$ and $VO(acac)_2$ under an oxygen atmosphere.[173] The resulting radical is trapped by SO_2 and then O_2 to generate an alkanesulfonylperoxy radical which is finally converted into an alkanesulfonic acid through the well-known reaction path.[174]

Table 19. Sulfoxidation of adamantane with SO_2/O_2 by vanadium catalyst.[a]

Run	Catalyst	Ratio of SO_2/O_2 [atm]	Conv. [%]	Yield [%][b]
1	$VO(acac)_2$	0.5/0.5	43	98
2	-	0.5/0.5	no reaction	
3[c]	$VO(acac)_2$	0.5/0.5	no reaction	
4[d]	$VO(acac)_2$	0.5/0.5	64	81
5	$V(acac)_3$	0.5/0.5	50	94
6[d]	$VO(acac)_2$	0.67/0.33	54	98

[a] Adamantane (2 mmol) was allowed to react under 1 atm of SO_2/O_2 (*ca.* 2 L) in AcOH (10 mL) in the presence of vanadium catalyst (0.5 mol %) at 40 °C for 2 h.
[b] Based on converted starting material.
[c] In the presence of hydroquinone (1 mol %).
[d] 25 °C, 24 h.

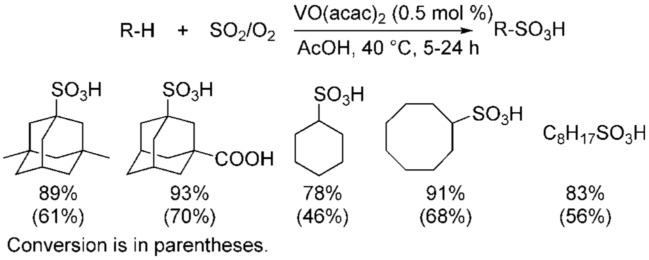
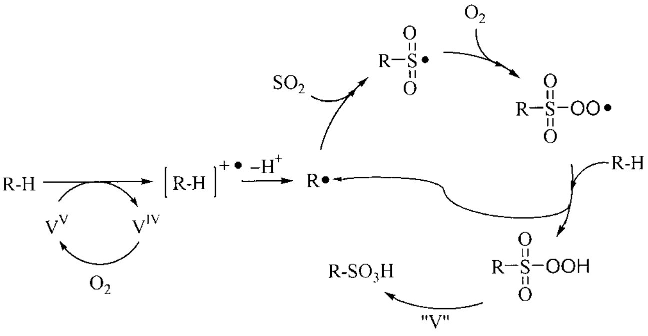


Figure 9. Sulfoxidation of various alkanes catalyzed by $VO(acac)_2$.



Scheme 20. A possible reaction pathway for the vanadium-catalyzed sulfoxidation.

General Procedure for Sulfoxidation of Adamantane

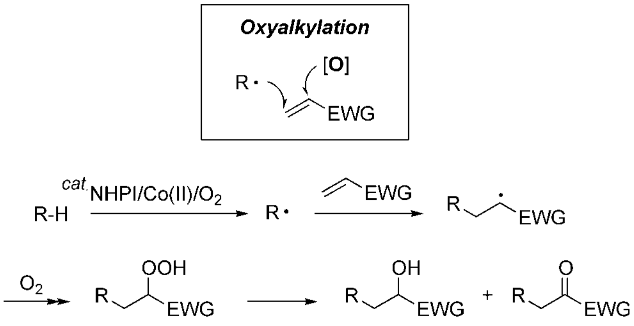
An acetic acid solution (5 mL) of adamantane (272 mg, 2 mmol), $VO(acac)_2$ (0.5 mol %, 2.7 mg) was placed in a pear-shaped flask equipped with a balloon filled with SO_2 (0.5 atm) and O_2 (0.5 atm). The mixture was stirred at 40 °C for 2 h and then extracted with ethyl acetate. The aqueous layer was concentrated by evaporation, and the solid obtained was recrystallized carefully with ethyl acetate to give 1-adamantanesulfonic acid; yield: 182 mg (42%).

7 Carbon-Carbon Bond Forming Reaction *via* Catalytic Carbon Radicals Generation from Various Organic Compounds Assisted by NHPI

Reactions of carbon radicals with alkenes, which can lead to the formation of new carbon-carbon bonds, are of major synthetic interest in organic chemistry, because of many advantages of the reactions over ionic processes.[175] Nowadays, numerous methods for the generation of carbon radicals and their inter- or intramolecular additions to alkenes for the synthesis of fine chemicals and natural products have been developed.[175,176] For instance, reactions of alkyl halides with tributyltin hydride or tris(trimethylsilyl)silane[177] and the thermal decomposition of Barton esters[178] are the most common methodologies for the generation of alkyl radicals. Although the peroxide- and photo-initiated reactions are often used as practical synthetic means, major problems of these methods are the lack of selectivity, generality and efficiency of the reaction.[175] Therefore, the carbon-carbon bond forming reaction through the carbon radical generation from alkanes is a worthwhile target in free radical chemistry.

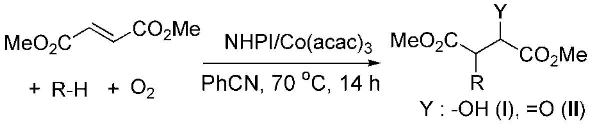
7.1 Oxyalkylation of Alkenes with Alkanes and Dioxygen

The NHPI-catalyzed aerobic oxidation of alkanes proceeds through the formation of alkyl radicals as mentioned previously. If alkyl radicals generated from alkanes could add to alkenes smoothly, it would provide a powerful strategy for the construction of a C-C bond in which alkanes can be directly used as alkyl sources. Furthermore, since the generation of PINO from NHPI is performed under a dioxygen atmosphere, we can envisage the concomitant introduction of both an alkyl group and an oxygen function to alkenes. This new type reaction may be regarded as a catalytic oxyalkylation of alkenes, which has not yet fully succeeded. Our approach to oxyalkylation is illustrated in Scheme 21. The reaction involves an alkyl radical generation by the NHPI/Co/O_2 system and the addition of the resulting alkyl radical to an alkene to form an adduct radical which is readily trapped by O_2.



Scheme 21. Catalytic oxyalkylation of alkenes with alkanes and O_2.

We attempted the oxyalkylation of methyl acrylate with 1,3-dimethyladamantane under dioxygen catalyzed by NHPI combined with a Co species.[179] As expected, the reaction of methyl acrylate with 1,3-dimethyladamantane under a mixed gas of O_2 (0.5 atm) and N_2 (0.5 atm) catalyzed by NHPI (20 mol %) in the presence of $Co(acac)_3$ (1 mol %) in acetonitrile at 75 °C for 16 h gave about a 7:3 mixture of oxyalkylated products, methyl 3-(3,3'-dimethyladamantyl)-2-hydroxypropionate and methyl 3-(3,3'-dimethyladamantyl)-2-oxopropionate in 91% yield (Figure 10). To the best of our knowledge, this is the first successful simultaneous introduction of alkyl and oxygen functions to alkenes through a catalytic process.[180] Fukunishi reported the peroxide-initiated simple radical addition of 1,3-dimethyladamantane to maleate and fumaronitrile affording the adduct.[181] Dimethyl fumarate served as a good acceptor to form the corresponding adducts in excellent yields. It is noteworthy that acrylonitrile and fumaronitrile led to alcohols in high selectivity. Further oxidation of the resulting alcohols to ketones may be suppressed by the cyano group with its strong electron-withdrawing character. Other alkanes also gave oxyalkylated adducts in good yields (Equation 46).



R-H =		
	Adamantane	78% (**I**/**II**=71:29)
	Methylcyclohexane	68% (**I**/**II**=71:29)
	Cyclohexane	54% (**I**/**II**=70:30)
	Cyclooctane	59% (**I**/**II**=78:22)

(46)

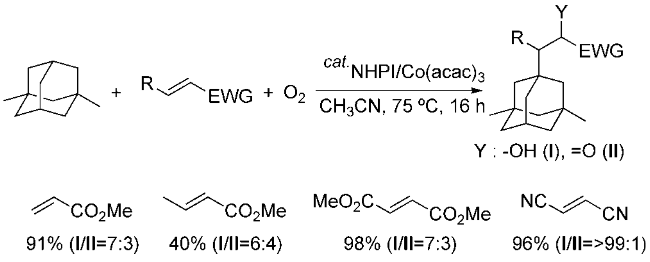


Figure 10. Oxyalkylation of several alkanes with 1,3-dimethyladamantane and O_2.

7.2 Synthesis of α-Hydroxy-γ-lactones by Addition of α-Hydroxy Carbon Radicals to Unsaturated Esters

α-Hydroxy-γ-lactones are very attractive as valuable synthetic precursors to compounds such as α,β-butenolides having potent biological activities,[182] efficient food intake-control substances,[183] and monomers of biodegradable polymers as well as fine chemicals.[184] However, there are few practical methods for the synthesis of these lactones.[185]

The same strategy of the oxyalkylation of alkenes with alkanes and O_2 could be extended to the reaction of alkenes with alcohols and O_2 leading to α-hydroxy-γ-lactones.[186] The reaction of 2-propanol with methyl acrylate under a dioxygen atmosphere in the presence of NHPI (10 mol %) combined with $Co(OAc)_2$ (0.1 mol %) and $Co(acac)_3$ (1 mol %) afforded α-hydroxy-γ,γ-dimethyl-γ-butyrolactone in 78% yield. Mori et al. prepared the same lactone *via* three steps from isobutene and trichloroacetaldehyde in 14% yield.[185a]

This new method for the construction of α-hydroxy-γ-lactones was quite general for a variety of alcohols and α,β-unsaturated esters (Figure 11). The preparation of α-hydroxy-γ-spirolactones from cyclic alcohols is especially notable, because these spirolactones were very difficult to synthesize up to now. The reaction can be explained by Scheme 22: (i) *in situ* generation of an α-hydroxy carbon radical from an alcohol assisted by NHPI/Co(II)/O_2, (ii) the addition of the radical to methyl acrylate, (iii) trapping of the adduct radical by O_2, (iv) the intramolecular cyclization to give α-hydroxy-γ-butyrolactone. From the viewpoints of low-cost material, reaction efficiency, and reaction simplicity, the present reaction provides an innovative approach to α-hydroxy-γ-lactones which have considerable industrial potential.

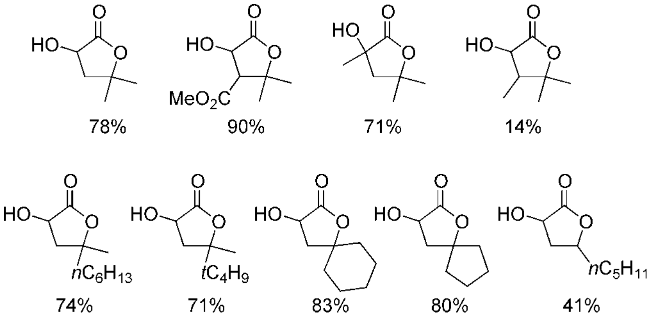
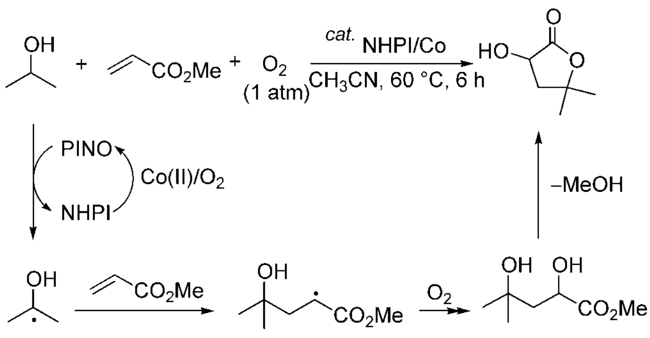


Figure 11. Synthesis of α-hydroxy-γ-lactones by reaction of alcohols with various alkenes.



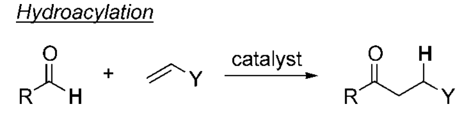
Scheme 22. Radical addition of 2-propanol to methyl acrylate under O_2 catalyzed by NHPI and $Co(acac)_2$.

General Procedure for Reaction of 2-Propanol with Methyl Acrylate

To a solution of 2-propanol (30 mmol), NHPI (48.9 mg, 0.3 mmol), $Co(OAc)_2 \cdot 4\,H_2O$ (0.7 mg, 0.003 mmol), and $Co(acac)_3$ (10.7 mg, 0.03 mmol) in acetonitrile (0.5 mL) in a two-necked flask equipped with a balloon filled with O_2 (1 atm) was added methyl acrylate (258 mg, 3 mmol). The mixture was vigorously stirred at 60 °C for 5 h. After the reaction, rotary evaporation of the solvent and unreacted alcohol followed by flash chromatography on silica gel (*n*-hexane/ethyl acetate = 1/1) afforded dihydro-3-hydroxy-5,5-dimethyl-2(3*H*)-furanone as a colorless liquid; yield: 304 mg (78%).

7.3 Hydroxyacylation of Alkenes using 1,3-Dioxolanes and Dioxygen

Addition of aldehydes through cleavage of the aldehydic carbon-hydrogen bond to terminal alkenes is known as hydroacylation (Equation 47).[187] If the concomitant introduction of acyl and hydroxy moieties to alkenes, which is referred to as hydroxyacylation, can be achieved by a cascade reaction, it would provide a novel route to β-hydroxy carbonyl compounds (Equation 48). β-Oxycarbonyl arrays constitute important structural subunits in a variety of natural and unnatural materials and in key intermediates leading to pharmaceuticals.[188] There is one report on the hydroxyacylation of acrylates with acyl radicals derived from aldehydes using dioxygen as a hydroxy source assisted by a cobalt(II) Schiff-base complex, but the attempt was not fully successful due to the decarbonylation from the acyl radicals as well as the reaction of the acyl radicals with O_2 leading to carboxylic acids which caused undesired side reactions.[189] To overcome these drawbacks, we employed 1,3-dioxolanes, masked aldehydes, as the acyl source.[190]



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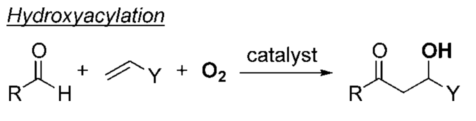
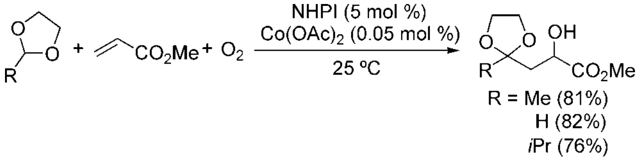
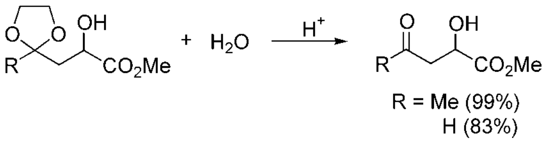


(48)

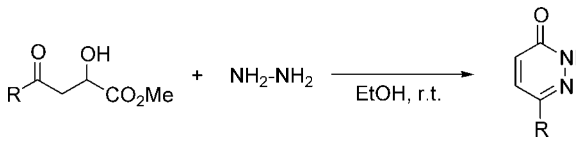
Since α,α-dioxaalkyl radicals corresponding to acyl radical equivalents are expected to be generated from 1,3-dioxolanes by the use of the NHPI/O_2 system, the apparent hydroxyacylation of methyl acrylate using several 1,3-dioxolanes and O_2 was examined (Equation 49).[191,192] A mixture of 2-methyl-1,3-dioxolane and methyl acrylate was allowed to react under O_2 (1 atm) in the presence of NHPI (5 mol %) and a small amount of $Co(OAc)_2$ (0.05 mol %) at room temperature for 3 h. As expected, the apparent hydroxyacylation based on the concomitant introduction of a dioxaalkyl radical and a hydroxy group to the carbon-carbon double bond was achieved to form the β-hydroxy ketal in 81% yield. The dioxolane moiety could be easily deprotected under acidic conditions in quantitative yield (Equation 50). Interestingly, the present strategy provides a useful method for the introduction of formyl and hydroxy groups to alkenes. The reaction of 1,3-dioxolane, masked formaldehyde, with methyl acrylate followed by deprotection of the dioxolane moiety, produced the adduct in good yield. In general, the direct use of formaldehyde in organic synthesis is restricted owing to its intractability. α-Hydroxy esters obtained by the present reaction are reported to be valuable precursors for the synthesis of attractive compounds possessing a variety of pharmacological properties, e.g., pyridazinones and alkaloid epibatidines (Equation 51).[193]



(49)



(50)



(51)

8 Conclusions

The achievement of highly efficient and selective transformations of hydrocarbons to useful chemical substances is an ambitious goal in synthetic chemistry. Fortunately, we have been able to open up a new vista in organic synthesis and to confirm the catalytic method for the carbon radical generation from a C-H bond of a wide variety of compounds by the use of *N*-hydroxyphthalimide (NHPI) which serves as a radical producing catalyst. By employing NHPI as the catalyst, a novel aerobic oxidation of alkanes, which surpasses the conventional autoxidations in conversion and selectivity, has been achieved under mild conditions. This oxidation method provides entry to a diverse array of significant oxygen-containing compounds. In particular, a success in the direct conversion of cyclohexane to adipic acid with dioxygen in high conversion and selectivity has greatly benefited the chemical industry as an environmentally benign process, because the current production of adipic acid *via* nitric acid oxidation causes the evolution of nitrogen oxides, serious air-polluting materials. In addition, the finding that the NHPI catalyzes the aerobic oxidation of alkylbenzenes even at room temperature is notable. The epoxidation of alkenes by *in situ* generated hydroperoxides or hydrogen peroxide has been explored for the first time. This new methodology was applicable to the functionalization of alkanes to afford nitroalkanes, alkanesulfonic acids, and carboxylic acids by allowing them to react with NO_2, SO_2/O_2 and CO/O_2, respectively. Finally, a new type of reaction for the concomitant introduction of alkanes and O_2 to alkenes, which is referred to as catalytic oxyalkylation of alkenes, has been established. α-Hydroxy-γ-lactones, which are very difficult to synthesize by conventional methods, are easily prepared by the reaction of alcohols, alkenes and O_2 under the influence of the NHPI catalyst. The same strategy could be applied to the reaction of 1,3-dioxolanes, masked aldehydes, alkenes and dioxygen to form three-component coupling products with introduced oxygen functions.

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