Catalysis Surveys *from Japan* 3 (1999) 27–35

A new strategy for alkane oxidation with O_2 using N-hydroxyphthalimide (NHPI) as a radical catalyst

Yasutaka Ishii and Satoshi Sakaguchi

Department of Applied Chemistry, Faculty of Engineering & High Technology Research Center, Kansai University, Suita, Osaka 564-8680, Japan
E-mail: ishii@ipcku.kansai-u.ac.jp

A practical catalytic method to convert alkanes into the corresponding oxygen-containing compounds with O_2 under mild conditions using N-hydroxyphthalimide (NHPI) in the presence or absence of a transition metal was developed. Thus, cyclohexane was successfully converted into adipic acid in good conversion and selectivity by a combined catalytic system consisting of NHPI and $Mn(acac)_2$. Lower alkane such as isobutane was converted into t-butyl alcohol (83%) under 10 atm of air by NHPI-$Co(OAc)_2$ system. Alkylbenzene such as toluene was oxidized to benzoic acid in high yield (81%) under normal temperature and pressure of dioxygen in the presence of a catalytic amount of NHPI and $Co(OAc)_2$. ESR measurements showed that phthalimide-N-oxyl generated from NHPI under dioxygen atmosphere is a key species in this oxidation and functions as a radical catalyst.

Keywords: oxidation, oxygen, alkane, N-hydroxyphthalimide, radical catalyst

1. Introduction

During the last decade, there have been major advances in the oxidation of saturated hydrocarbons by molecular oxygen [1–4]. However, effective and selective methods for the catalytic functionalization of hydrocarbons still remain a major challenge in both synthetic and industrial chemistry. In particular, the selective transformation of alkanes to oxygen-containing compounds such as alcohols, ketones and carboxylic acids with molecular oxygen is a very important reaction as the fundamental technology in the chemical industry worldwide [5]. The importance of the utilization of molecular oxygen as an oxidant is driven both by its abundance and low cost and by its potential to be a more environmentally friendly oxidant which results in no-waste technologies.

In the course of our study to develop the aerobic oxidation of alkanes, we found a novel methodology for the oxidation of alkanes with molecular oxygen catalyzed by N-hydroxyphthalimide (NHPI) which functions as a radical catalyst.

The present paper will review our recent work on the aerobic oxidation of a variety of alkanes by dioxygen (O_2) using NHPI as the catalyst.

2. Discovery of radical catalyst, N-hydroxyphthalimide (NHPI)

Homogeneous liquid-phase oxidation of hydrocarbons using molecular oxygen as an oxidant is commonly referred to as autoxidation and divided into three categories [2,3,6]:

(i) Radical-initiated aerobic oxidation.
A typical example is the autoxidation of isobutane to t-butyl hydroperoxide initiated by a radical initiator such as t-butyl peroxide or by oxygen itself.

(ii) Base-catalyzed aerobic oxidation.
Hydrocarbons such as fluorene having acidic hydrogen are oxidized by dioxygen in the presence of a base like t-BuOK.

(iii) Transition metal-catalyzed aerobic oxidation.
Cyclohexane and xylenes are oxidized by dioxygen under the influence of Co and/or Mn salts.

We now propose a new type of autoxidation using a radical catalyst classified as the category (iv).

(iv) Radical-catalyzed aerobic oxidation.
This type of aerobic oxidation of alkanes has first been successfully achieved by using NHPI which serves as the radical catalyst.

Although NHPI is a commercially available compound, it can be prepared very easily by the reaction of phthalic anhydride, which is manufactured in a large scale as bulk chemicals, with hydroxylamine. The treatment of NHPI with $Pb(OAc)_4$ forms phthalimide-N-oxyl (PINO) whose ESR signal appears at $g = 2.0073$ as a triplet signal having $A_N = 0.423$ mT (figure 1) [7].

Nitroxyl radicals as exemplified by 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) are known to promote the oxidation of alcohols and amines via oxoammonium salts in the presence of an appropriate oxidizing agent [8]. Semmelhack et al. have developed the electrochemical oxidation of alcohols to the corresponding carbonyl compounds using TEMPO as a mediator [9]. N-hydroxyphthalimide, NHPI, has first been used in 1977 by Grochowski et al. as a catalyst for the addition of ethers to azodicarboxylate and for the oxidation of isopropanol with mCPBA [10]. Masui et al. have reported that the NHPI acts as an efficient electron carrier for the electrochemical oxidative dehydrogenation of secondary alcohols to the corresponding ketones (scheme 1) [11].

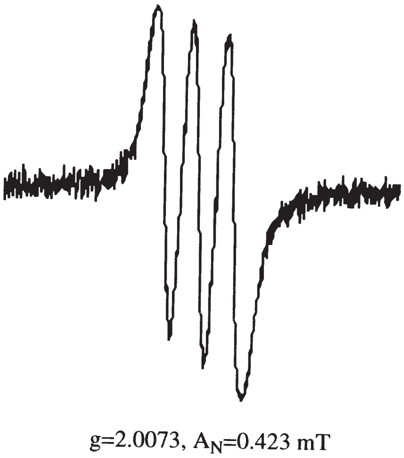
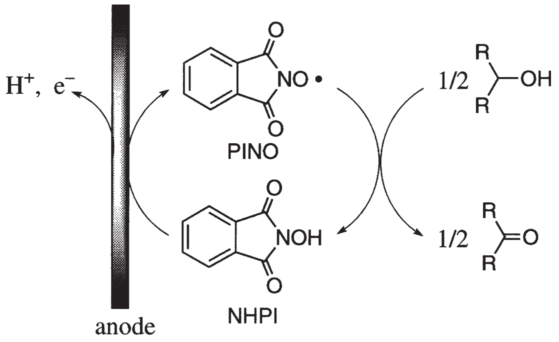


Figure 1. ESR spectrum of phthalimide-N-oxyl (PINO).



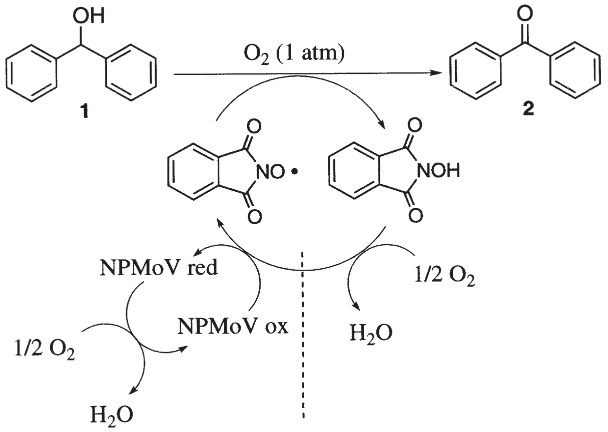
Scheme 1. Electrolytic oxidation of alcohols mediated by NHPI.

On the other hand, we have shown that a mixed-addenda vanadomolybdophosphate (NPMoV) whose composition is approximately indicated as $(NH_4)_5H_6PV_8Mo_4O_{40}$ (anhydrous salt) catalyzes the selective dehydrogenation of amines to Schiff-base imines and of phenols to quinones with O_2, but aliphatic alcohols were difficult to oxidize to the corresponding carbonyl compounds [12]. We thought that if the hydrogen atom anchored to the N-hydroxy moiety of the NHPI can be abstracted by the NPMoV and the reduced NPMoV can be reoxidized by dioxygen to the original NPMoV, PINO is possibly generated under non-electrolytic conditions.

Thus, we tried the oxidation of alcohols by O_2 in the presence of a catalytic amount of NHPI and NPMoV. As expected, benzhydrol (**1**) was oxidized to benzophenone (**2**) in quantitative yield. Surprisingly, in this oxidation, we found that **1** was smoothly oxidized by NHPI alone even under non-electrolytic conditions to give **2** in good yield (scheme 2) [13].

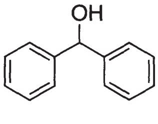
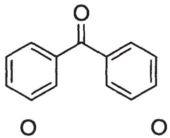
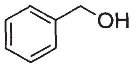
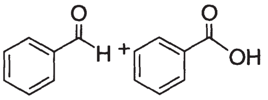
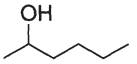
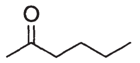
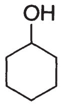
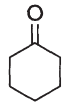
Similarly, a variety of alcohols were converted into ketones or carboxylic acids by the NHPI under atmospheric dioxygen (table 1).

This fact shows that PINO, which is a key species in this reaction, is easily generated from NHPI by O_2. In fact, when the NHPI in benzonitrile is exposed to O_2 at 80 °C for 45 min, the ESR signal attributed to the PINO was observed as a triplet, as shown in figure 1. This observation suggests that the hydrogen atom bonded to the hydroxy moiety of the NHPI can be abstracted by molecular oxygen, and the resulting PINO acts as a radical catalyst which abstracts the α-hydrogen of alcohols to form ketones.



Scheme 2. Aerobic oxidation of alcohols catalyzed by NHPI.

Table 1
Aerobic oxidation of various alcohols catalyzed by NHPI.[a]

Substrate	Conv. (%)	Product(s)	Yield (%)
	89		88
	62		40+21
	54		49
	80		56

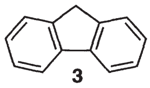
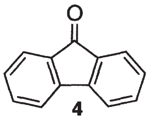
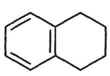
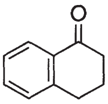
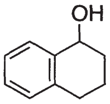
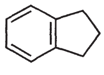
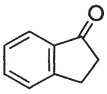
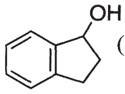
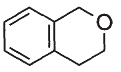
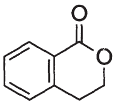
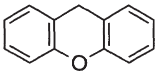
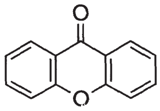
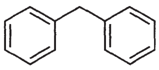
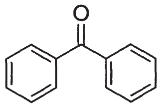
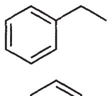
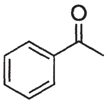
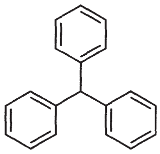
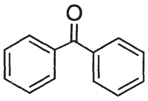
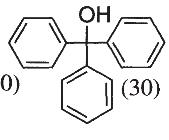
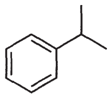
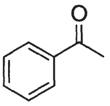
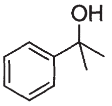
[a] Alcohols (5 mmol) were allowed to react with dioxygen (1 atm) in the presence of NHPI (0.5 mmol) in benzonitrile (10 ml) at 100 °C for 5 h.

3. NHPI-catalyzed oxidation of alkanes with molecular oxygen

3.1. Oxidation of hydroaromatic and benzylic compounds

In order to evaluate the features of NHPI catalysis, the oxidation of fluorene (**3**) was examined under various reaction conditions. These results are listed in table 2. Treatment of **3** in the presence of 10 mol% of NHPI with respect to **3** in benzonitrile solution at 100 °C for 20 h gave an oxidized product, fluorenone (**4**), in 80% yield. After the oxidation, NHPI was almost recovered unchanged. In the absence of NHPI, the reaction produced a trace amount of **4**. When NHPI analogs N-hydroxysuccinimide (NHSI)

Table 2
Aerobic oxidation of benzylic derivatives catalyzed by NHPI.[a]

Run	Substrate	Catalyst	Products (yield (%))[b]
1	 **3**	NHPI	 **4** (80)
2	**3**	—	**4** (trace)
3	**3**	NHSI[c]	**4** (62)
4	**3**	NHMI[d]	**4** (41)
5	**3**	TEMPO[e]	**4** (0)
6		NHPI	 (37)  (13)
7		NHPI	 (42)  (7)
8		NHPI	 (83)
9		NHPI	 (99)
10		NHPI	 (73)
11		NHPI	 (34)
12		NHPI	 (20)  (30)
13		NHPI	 (64)  (8)

[a] Substrate (2 mmol) was allowed to react with dioxygen (1 atm) in the presence of NHPI (0.2 mmol) in benzonitrile (5 ml) at 100 °C for 20 h.

[b] GLC yields.

[c] NNHSI: N-hydroxysuccimide.

[d] NHMI: N-hydroxymaleimide.

[e] TEMPO: 2,2,6,6-tetramethylpiperidine-1-oxy.

and N-hydroxymaleimide (NHMI) were employed instead of NHPI, **3** was oxidized to **4** in 62% and 41% yields, respectively. However, TEMPO, which acts as an efficient catalyst for the oxidation of alcohols with O_2 in the presence of cupric chloride [14], had no catalytic activity.

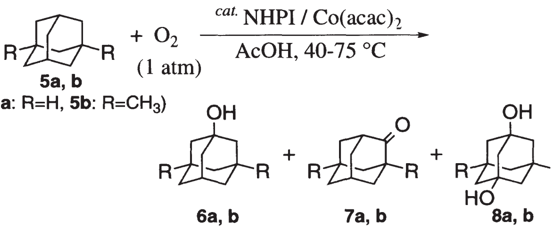
Various hydroaromatic and benzylic compounds were allowed to react in the presence of NHPI (10 mol%) under these reaction conditions. Like **3**, tetraline and indane were oxygenated by this system, giving 1-tetralone and 1-indanone, respectively, with small amounts of the corresponding alcohols. It is interesting that oxygen-containing substrates such as isochromane and xanthene were smoothly oxygenated to give rise to 1-isochromanone and xanthone in 83% and 99% yields, respectively.

In the same manner as hydroaromatic compounds, benzylic hydrocarbons were also oxygenated by the NHPI-O_2 system. For diphenylmethane and ethylbenzene, the corresponding ketones were obtained rather than alcohols. In the oxidation of triphenylmethane, triphenylethanol was obtained along with benzophenone. However, in the case of isopropylbenzene, with its tertiary carbon, demethylation took place in preference to hydroxylation to give acetophenone (64%). Einhorn et al. have reported the NHPI-catalyzed oxidation of similar substrates by O_2 in the presence of an aldehyde [15].

3.2. Oxidation of adamantanes

Although there have been a few reports on the catalytic hydroxylation of adamantane (**5a**) using O_2 as the ultimate oxidant, the direct hydroxylation of **5a** with O_2 in the absence of any reducing agents such as aldehyde is very difficult to carry out in higher conversion and selectivity [16,17].

By using the NHPI as the catalyst, **5a** and **5b** were first successfully converted into hydroxy adamantanes by the direct hydroxylation with O_2 under mild conditions (equation (1)) [18].



5a, b
(**5a**: R=H, **5b**: R=CH_3)
6a, b **7a, b** **8a, b**

(1)

The results for oxidation of **5a** under several conditions are summarized in table 3. The oxidation of **5a** in the presence of a catalytic amount of NHPI (10 mol%) and Co(acac)$_2$ (0.5 mol%) in acetic acid under dioxygen atmosphere (1 atm) at 75 °C for 6 h produced adamantan-1-ol (**6a**) (43%), admantane-1,3-diol (**8a**) (40%) and 2-adamantanone (**7a**) (8%). It is worth noting that the present oxidation led to diol **8a** in relatively high selectivity, because **8a** is rarely produced by conventional aerobic oxidations [19–21]. Hirobe et al. reported that the oxidation of **5a** by 2,6-dichloropyridine N-oxide catalyzed by a Ru complex leads to **8a** in 25% [22]. Leaving out Co(acac)$_2$ from the catalytic system led to a significant decrease in the conversion of **5a**. Replacing Co(acac)$_2$ with Co(OAc)$_2$ resulted in the complete conversion of **5a** to oxygenated products. It is interesting to note that VO(acac)$_2$ and MoO$_2$(acac)$_2$, which are rarely employed in aerobic oxidation as catalysts, promote the hydroxylation of **5a** to **6a** and **8a** in good yields. Fe(acac)$_3$ and Cu(acac)$_2$ were inefficient in this oxidation. The oxidation of **5a** in air under these con-

Table 3

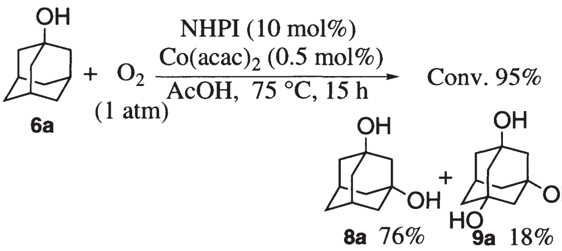
Aerobic oxidation of adamantane (**5a**) catalyzed by NHPI combined with metal salts.[a]

Run	Metal salt	Time	Conv.	Select. (%)		
		(h)	(%)	**6a**	**7a**	**8a**
1	$Co(acac)_2$	6	93	43	8	40
2	–	6	17	52	–	–
3	$Co(OAc)_2$	6	>99	21	6	54
4	$Mn(acac)_3$	6	68	56	6	31
5	$VO(acac)_2$	6	95	32	7	54
6	$MoO_2(acac)_2$	6	85	54	6	31
7	$Fe(acac)_3$	6	19	63	–	–
8	$Cu(OAc)_2$	6	36	64	6	8
9[b]	$Co(acac)_2$	10	73	56	14	25

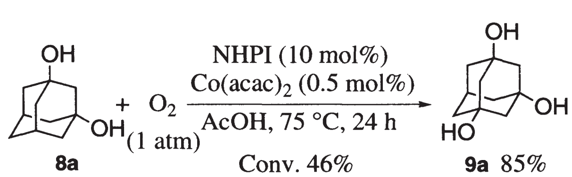
[a] **5a** (3 mmol) was allowed to react with dioxygen (1 atm) in the presence of NHPI (0.3 mmol) and transition metal salt (0.015 mmol) in acetic acid (8 ml) at 75 °C.

[b] Under air atmosphere.

ditions afforded **6a** (56%), **7a** (14%) and **8a** (25%) in 73% conversion. In contrast to the oxidation of hydroaromatic compounds where NHPI was recoverd unchanged, most of NHPI was found to be converted into phthalimide after the oxidation of **5a** by the NHPI/$Co(acac)_2$ system. The reaction phthalimide could be reconverted into NHPI by treating it with hydroxylamine. To obtain diol and triol, the hydroxylation of **5a** and **8a** under these conditions gave **8a** and adamantane-1,3,5-triol (**9a**), respectively, in high selectivities (equations (2) and (3)). 1,3-dimethyladamantane (**5b**) was also oxidized with O_2 by the NHPI/$Co(acac)_2$ system to give 3,5-dimethyladamantan-1-ol (**6b**) in 47% yield and diol, **8b**, in 37% yield.



(2)



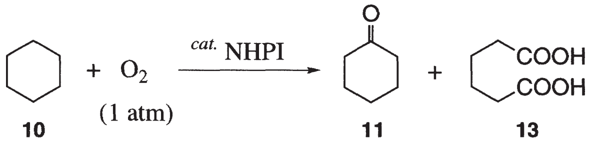
(3)

3.3. Aerobic oxidation of cyclohexane

The oxidation of cyclohexane (**10**) to a cyclohexanone (**11**)/cyclohexanol (**12**) mixture (K/A oil) is the first step in the two-step process for the production of adipic acid (**13**). Although there are several variants of this oxidation, the principal method is the autoxidation of **10** in the presence of a metal catalyst such as Co or Mn salt [23]. An alternative cyclohexane oxidation uses a higher concentration of Co(II) acetate under oxygen pressure (20–30 atm) [24,25].

Table 4

Aerobic oxidation of cyclohexane (**10**) catalyzed by NHPI combined with transition metals.[a]



Run	Additive	Time	Temp.	Conv.	Select. (%)	
	(mol%)	(h)	(°C)	(%)	**11**	**13**
1	–	6	100	<1	Trace	N.d.
2	$Co(acac)_2$ (0.5)	6	100	45	32	38
3	$Mn(acac)_2$ (0.5)	6	100	44	3	77
4	$Mn(acac)_2$ (1.0)	20	100	73	Trace	73
5	$Mn(acac)_2$ (0.5) $Co(acac)_2$ (0.05)	24	80	63	Trace	69
6[b]	$Mn(acac)_2$ (0.1) $Co(acac)_2$ (0.05)	24	80	60	8	64

[a] **10** (3 mmol) was allowed to react with dioxygen (1 atm) in the presence of NHPI (0.3 mmol) and transition metals (0.015 mmol) in acetic acid (7.5 ml) for 6 h at 100 °C.

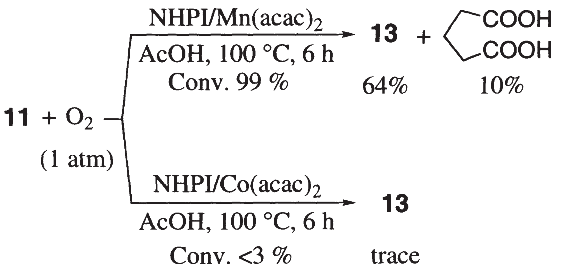
[b] Air (20 kg·cm^{-2}).

However, the homogeneous catalytic oxidations of **10** using these methods have several problems, i.e., oxidative attack on the C–H bonds is slow and requires vigorous reaction conditions. To overcome these limitations, a new catalyst for selective oxidation with O_2 must be identified. The selective oxidation of **10** to K/A oil, therefore, is one of the most challenging and promising targets in oxidation chemistry.

The oxidation of **10** with O_2 using NHPI under selected conditions is shown in table 4. The oxidation of **10** under 1 atm of O_2 in the presence of NHPI (10 mol%) and $Co(acac)_2$ (0.5 mol%) in acetic acid at 100 °C for 6 h afforded **11** (32%) and **13** (38%) at 45% conversion along with a small amount of glutaric acid (up to 5%) and cyclohexyl acetate (up to 2%) [26]. In the similar way as the oxidation of adamantane **5a**, **10** was oxidized with difficulty to give a trace of **11**. Similar effects of $Co(acac)_2$ on the oxidation of **10** were observed. $Mn(acac)_2$, which is often used as a catalyst for autoxidation, was also effective in this transformation. It is attractive that the addition of $Mn(acac)_2$ brought about adipic acid **13** rather than cyclohexanone **11** in high selectivity (77%). The oxidation of **10** by the use of 1 mol% of $Mn(acac)_2$ gave **13** in 73% yield at 73% conversion. When a very small amount of a Co(II) species was added to the NHPI/Mn(II) system, **10** was smoothly oxidized to **13** even at 80 °C. It is very important to employ air instead of oxygen as the oxidant to carry out the present oxidation in industrial scale. With this in mind, the oxidation of **10** using the NHPI/Mn(II)/Co(II) system was examined under 20 kg/cm^2 of air in acetic acid for 24 h. The reaction gave **13** (64%) and **11** (8%) in 60% conversion.

It is interesting to make clear the effect of Co and Mn salts on the NHPI-catalyzed oxidation of **10**, since the effect of Mn(II) on the oxidation of **10** by the present system is in contrast to that of manganese derivatives shown by

Tanaka [25] and Schulz [27], who reported that Co, Cr and Zn salts are good catalysts for the conversion of **10** to **13**, while Mn salts have poor catalytic activity. It was found that the oxidation of cyclohexanone **11** by NHPI (10 mol%) in the presence of $Mn(acac)_2$ (0.5 mol%) in acetic acid at 100 °C for 6 h produced **13** (64%), glutaric acid (10%) and succinic acid (5%). However, the same oxidation of **11** using $Co(acac)_2$ instead of $Mn(acac)_2$ resulted in the recovery of the starting **11** (equation (4)). This observation suggests that an unreactive species which acts as an inhibitor in the aerobic oxidation of **11** may be formed. In fact, a mixture of Co(II), **11**, and NHPI was allowed to react in acetic acid under O_2 at 100 °C for 3 h to give a dark-brown complex which appears a mixture of some cobalt complexes. The aerobic oxidations of **10** and **11** using this complex were examined, but both substrates were recovered unchanged.



(4)

It is interesting to compare the reaction rate in the oxidation of **10** by the NHPI/Mn(II) system with that by the NHPI/Mn(II)/Co(II) system. Figure 2 shows the O_2 uptakes for the oxidation of **10** by both systems.

Since the oxidation of **10** by the NHPI/Mn(II)/Co(II) proceeded faster than that by the NHPI/Mn(II), an important role of the Co(II) species was thought to reduce the induction period of the oxidation of **10**.

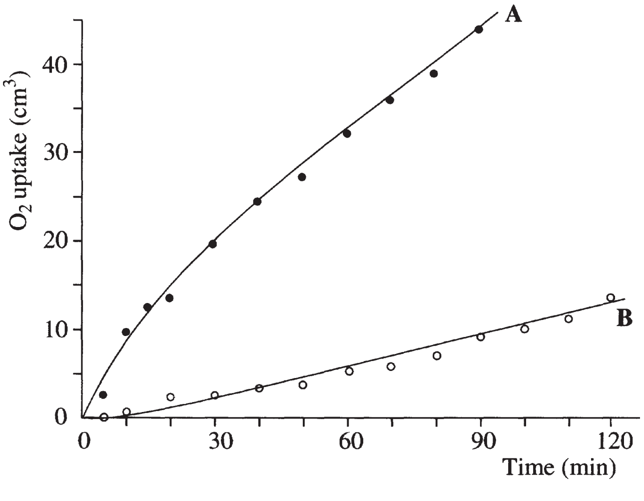


Figure 2. Time courses of O_2 uptakes during the aerobic oxidation of cyclohexane (**10**) by various catalytic systems. Conditions: **10** (10 mmol) was allowed to react with dioxygen (1 atm) in acetic acid (25 ml) at 80 °C. (A) NHPI (1 mmol), $Co(acac)_2$ (0.01 mmol), $Mn(acac)_2$ (0.1 mmol); (B) NHPI (1 mmol), $Mn(acac)_2$ (0.1 mmol).

Table 5
Aerobic oxidation of various cycloalkanes catalyzed by NHPI combined with $Mn(acac)_2$.[a]

Substrate	Temperature (°C)	Conv. (%)	Dicarboxylic acid (select. (%))
Cyclooctane (**14**)	100	83	**16** (53)
Cyclodecane (**17**)	100	90	**19** (55)
Cyclododecane (**20**)	70	81	**22** (68)

[a] Substrate (3 mmol) was allowed to react with molecular oxygen (1 atm) in the presence of NHPI (0.3 mmol) and $Mn(acac)_2$ (0.03 mmol) in acetic acid (7.5 ml) for 14 h.

To extend the present oxidation to large-membered cycloalkanes, the oxidation of several cycloalkanes with O_2 was examined using the NHPI/$Mn(acac)_2$ system (table 5).

Like **10**, cyclooctane (**14**) and cyclodecane (**17**) were oxidized to cyclooctanone (**15**) and cyclodecanone (**18**), and suberic acid (**16**) and sebacic acid (**19**), respectively. Cyclododecane (**20**) was easily oxidized even at 70 °C to give dodecanedioic acid (**22**) and a small amount of cyclododecanone (**21**). These results show that the present NHPI-catalyzed aerobic oxidation can be applied to the production of cyclic ketones and dicarboxylic acids, which are very important chemicals, derived from a variety of large-membered cycloalkanes.

3.4. Aerobic oxidation of isobutane to *t*-butyl alcohol

The conversion of lower alkanes to carbonyl compounds is one of the important and fundamental transformations in industrial chemistry. For instance, butane and isobutane are currently converted into acetic acid and *t*-butyl hydroperoxide, respectively, by homogeneous liquid-phase oxidation with molecular oxygen using a cobalt salt [28]. These oxidations, however, are carried under severe reaction conditions, higher temperature (150–250 °C) and oxygen or air pressure (10–30 atm) [29]. As a consequence, the oxidation must be practiced in a lower conversion of alkanes to prevent the formation of undesired side products. Recently, Lyons and Ellies showed that halogenated metalloporphyrin complexes are efficient catalysts for the direct oxygenation of acyclic alkanes with O_2 under relatively mild conditions (i.e., at around 100 °C, and 6.8 atm of O_2) [30].

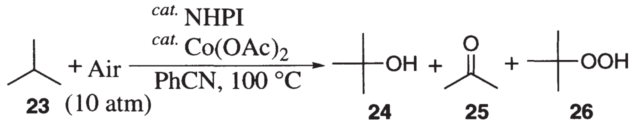
The representative results for the oxidation of isobutane (**23**) with air catalyzed by NHPI under various reaction conditions are given in table 6 [31].

The oxidation of **23** by air (10 atm) under the influence of NHPI (10 mol%) in benzonitrile at 100 °C produced *t*-butyl hydroperoxide (**26**) as a major product together with small amounts of *t*-butyl alcohol (**24**) and acetone (**25**).

Interestingly, the oxidation of **23** with air by NHPI was markedly enhanced by adding a slight amount of $Co(OAc)_2$ (0.25 mol%) to result in **24** in higher yield (81%) and **25** (14%). But $Mn(acac)_2$ had only a slight effect for the present oxidation. It is noteworthy that **24** was obtained in satisfactory yield even under 5 atm of air. The oxidation at 80 °C gave **24** (63%), **25** (8%) and **26** (6%). When the amount of NHPI was reduced to a half, **24** was obtained in

Table 6

Oxidation of isobutane (**23**) with O_2 catalyzed by NHPI combined with $Co(OAc)_2$.[a]



Run	NHPI (mol%)	$Co(OAc)_2$ (mol%)	Temperature (°C)	Yield (%) 24	25	26
1	10	0	100	3	4	8
2	10	0.25	100	81	14	0
3	0	0.25	100	2	<1	0
4[b]	10	0.25	100	66	16	0
5	10	0.25	80	63	8	6
6[c]	10	0.25	50	32	5	5
7	5	0.25	100	63	11	0
8[d]	10	0.25	100	No reaction		
9[e]	10	0.25	100	21	22	0

[a] **23** (5 mmol) was allowed to react in the presence of NHPI and $Co(OAc)_2$ under a pressure of air (10 atm) in benzonitrile (10 ml) for 8 h.

[b] Pressure of air was 5 atm.

[c] Reaction was carried out for 48 h.

[d] 2,4-di-*tert*-butyl-*p*-cresol (1 mol%) was added.

[e] Acetic acid (10 ml) was used as the solvent.

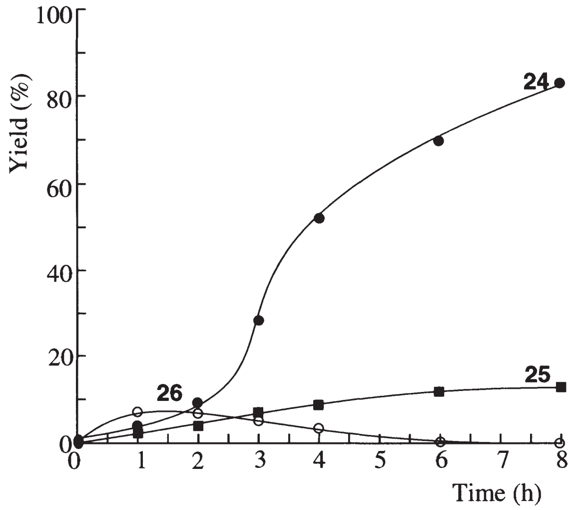
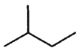
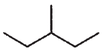
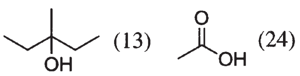
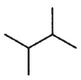
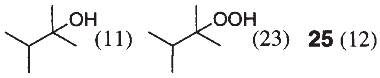


Figure 3. Time courses for the oxidation of isobutane (**23**) with O_2 catalyzed by NHPI combined with $Co(OAc)_2$ in PhCN at 100 °C.

Table 7

Oxidation of several alkanes with O_2 catalyzed by NHPI combined with $Co(OAc)_2$.[a]

Substrate	Products (yield (%))
	 (21) **25** (32) (15)
	 (13) (24)
	 (11) (23) **25** (12)

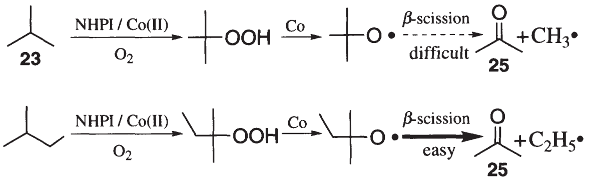
[a] Substrate (5 mmol) was allowed to react in the presence of NHPI (0.5 mmol) and $Co(OAc)_2$ (0.00125 mmol) under a pressure of air (10 atm) in benzonitrile (10 ml) at 100 °C for 8 h.

63% yield. Surprisingly, **23** was oxidized even at 50 °C by the present catalytic system, although a somewhat longer reaction time is needed. In contrast to the oxidation of cycloalkanes where acetic acid serves as a good solvent, the oxidation of **23** in acetic acid resulted in a considerable amount of cleaved products.

Figure 3 shows the changes of products, **24**, **25** and **26**, with the reaction time for the oxidation of **23**. This indicates that *t*-butyl hydroperoxide **26** is the primary product during the early stage of oxidation.

The NHPI-catalyzed aerobic oxidation of several lower alkanes was examined (table 7). Methyl-substituted alkanes, such as 2-methybutane and 3-methylpentane, were oxidized under air pressure of 10 atm in the presence of NHPI and $Co(OAc)_2$ in benzonitrile at 100 °C to afford carbon–carbon bond cleaved products, acetone and acetic acid, as principal products in preference to the corresponding alcohols. In the oxidation of 2,3-dimethylbutane, 1,1,2-trimethyl propyl hydroperoxide (23%) was obtained as the major product.

Alkyl hydoperoxides by metal ions, such as $FeSO_4$, brought about carbon–carbon bond cleaved products through the β-scission of alkyl radical intermediates; the extent of the β-scission depends on the structure of the resulting alkoxy radicals [32]. Since the *t*-butoxy radical is more stable than the *t*-pentyloxy radical, it is thought that **23** produced alcohol **24** as the principal product, while 2-methylbutane gave cleaved products, acetone and acetic acid (equation (5)).



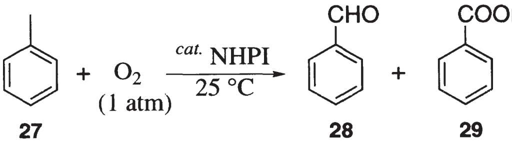
(5)

3.5. Oxidation of alkylbenzenes under ambient conditions

The selective catalytic oxidation of alkylbenzenes with O_2 is a very important reaction for the production of bulk chemicals such as benzoic acid and terephthalic acid. For example, the oxidation of toluene is currently carried out in the presence of a catalytic amount of cobalt(II) 2-ethylhexanoate under a pressure of 10 atm of air at 140–190 °C [33]. If the direct aerobic oxidation of alkylbenzenes can be done under normal pressure and temperature, it will vastly contribute to industrial chemistry from technical, economical and environmental aspects, since undesired reactions due to the higher pressure and temperature will be minimized. However, there is yet no way to carry out such oxidations under ambient conditions.

The oxidation of toluene (**27**) in the presence of NHPI and $Co(OAc)_2$ (0.5 mol%) in acetic acid under an atmosphere of O_2 at ambient temperature (up to 25 °C) for 20 h afforded benzaldehyde (**28**) and benzoic acid (**29**) in

Table 8
Aerobic oxidation of toluene (**27**) catalyzed by NHPI at 25 °C under various conditions.[a]



Run	Metal salts	Solv.	Conv. (%)	Yield (%)	
				28	**29**
1	$Co(OAc)_2$	AcOH	84	2	81
2	$Co(OAc)_2$	CH_3CN	52	5	45
3	$Co(acac)_2$	AcOH	74	3	71
4	$Co(acac)_2$	CH_3CN	<1	N.d.	N.d.
5	$Co(acac)_3$	AcOH	No reaction		

[a] Substrate (3 mmol) was allowed to react in the presence of NHPI (0.3 mmol) and transition metal salts (0.015 mmol) in solvent (5 ml) under an oxygen atmosphere (1 atm) at 25 °C for 20 h.

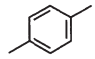
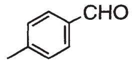
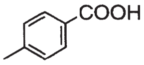
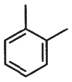
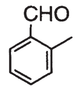
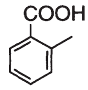
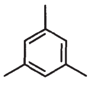
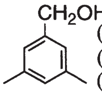
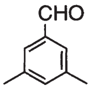
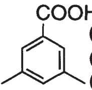
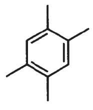
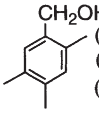
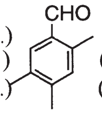
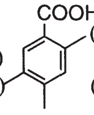
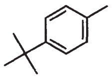
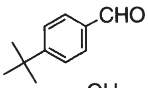
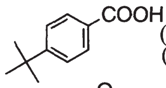
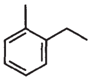
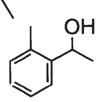
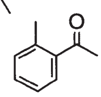
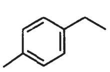
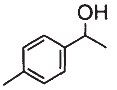
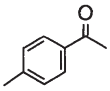
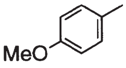
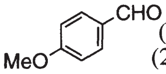
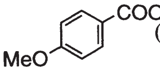
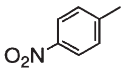
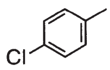
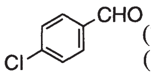
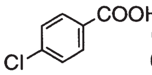
2% and 81% yields, respectively (table 8). To our best knowledge, this is the first example of the catalytic oxidation of **27** by O_2 at room temperature. This finding is of great industrial importance, as it leads to development of a practical process which enables the aerobic oxidation of **27** under ambient conditions. The oxidation of **27** in acetonitrile resulted in **29** in a lower yield. When $Co(acac)_2$ was used in place of $Co(OAc)_2$, **27** was oxidized to **29** in 71% yield. But this reaction did not proceed at all in acetonitrile. These results show that the NHPI-catalyzed aerobic oxidation of **27** is advantageously assisted by $Co(OAc)_2$ in acetic acid [34]. However, the oxidation did not entirely take place when $Co(acac)_3$ was employed in place of $Co(acac)_2$.

In order to obtain further information on the role of Co(II) species in the present reaction, ESR measurements were carried out under similar conditions to those for the oxidation of **27**. Although an acetonitrile solution of NHPI and **27** was exposed to a dioxygen atmosphere, no ESR signal was observed over 10 h. However, when a very small amount of $Co(OAc)_2$ was added to this solution under ambient conditions, an ESR signal based on the PINO radical was observed at $g = 2.0073$ as a triplet signal. No signal appeared when $Co(acac)_3$ was added in place of $Co(OAc)_2$ in the solution. These observations suggest that the complexation of Co(II) with O_2 to generate a labile dioxygen complex such as superoxocobalt(III) or μ-peroxocobalt(III) complex is present during the oxidation step. Such cobalt–oxygen species are reported to be easily formed by the one-electron reduction of O_2 using Co(II) (equation (6)) [35].

$$\begin{aligned} &\mathrm{LnCo^{II}} + \mathrm{O_2} \rightleftharpoons \underset{\text{superoxocobalt (III)}}{\mathrm{LnCo^{III}\text{–}O\text{–}O\bullet}} \\ &\mathrm{LnCo^{III}\text{–}O\text{–}O\bullet} + \mathrm{LnCo^{II}} \rightleftharpoons \underset{\mu\text{-peroxocobalt (III)}}{\mathrm{LnCo^{III}\text{–}O\text{–}O\text{–}Co^{III}Ln}} \end{aligned} \qquad (6)$$

Therefore, it is reasonable to assume that such cobalt species assist in the generation of a PINO radical from NHPI under ambient conditions. On the contrary, since a cobalt-oxygen complex cannot be generated from the Co(III) with O_2, the oxidation of **27** by the NHPI-$Co(acac)_3$ system did not occur. When the above reaction was carried out by adding a small amount of benzaldehyde, however, **27** was oxidized to **29** in 43% yield at 48% conversion, because the Co(III) species is reduced with benzaldehyde to a Co(II) ion [27].

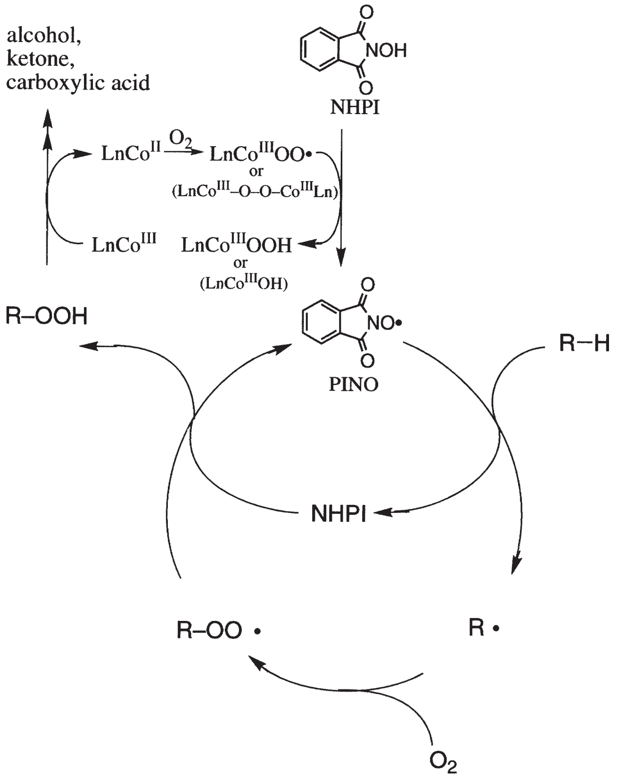
Table 9
Aerobic oxidation of various alkylbenzenes catalyzed by NHPI combined with $Co(OAc)_2$ in CH_3CN or AcOH at 25 °C.[a]

Run	Substrate	Conv. (%)	Products (yield (%))					
1		94^b 95^c		(3) (2)		(83) (85)		
2		70^b 93^c		(3) (2)		(63) (83)		
3		73^b 73^c $81^{c,d}$		(2) (2) (2)		(23) (26) (21)		(46) (39) (51)
4	 **4**	$98^{b,e}$ $39^{c,e}$ $100^{c,f}$	 **5**	(n.d.) (11) (n.d.)	 **6**	(5) (17) (n.d.)	 **7**	(93) (6) (93)
5		83^b 95^c		(4) (2)		(77) (91)		
6		82^b 61^c		(21) (21)		(37) (25)		
7		87^b 75^c		(12) (17)		(47) (31)		
8		$89^{b,g}$ $26^{c,g}$		(9) (20)		(80) (0)		
9		No reaction^b No reaction^c						
10		47^b 71^c		(7) (3)		(40) (67)		

[a] Substrate (3 mmol) was allowed to react in the presence of NHPI (0.3 mmol) and $Co(OAc)_2$ (0.015 mmol) in solvent (5 ml) under an oxygen atmosphere (1 atm) at 25 °C for 20 h.
[b] CH_3CN was used as the solvent.
[c] AcOH was used as the solvent.
[d] 30 h.
[e] 3 h.
[f] 12 h.
[g] 6 h.

Table 9 shows the representative results for the oxidation of alkylbenzenes with O_2 by the NHPI-$Co(OAc)_2$ under ambient conditions.

p-xylene was selectively oxidized to p-toluic acid in good yields in both acetic acid and acetonitrile, while o-xylene in acetonitrile was converted into o-toluic acid



Scheme 3. A plausible reaction path for the aerobic oxidation of alkanes catalyzed by NHPI combined with Co(II).

in a somewhat lower yield (63%). Although the oxidation of mesitylene was expected to take place more easily than that of **27**, the oxidation proceeded slowly to form 3,5-dimethylbenzoic acid and 3,5-dimethylbenzaldehyde as main products. In contrast, durene was oxidized to 2,4,5-trimethylbenzoic acid in good yield. *o*-ethyltoluene, having different alkyl substituents on the benzene ring, underwent the oxidation exclusively at the ethyl moiety to form 1-(2′-methylphenyl)ethanol and 2′-methylacetophenone in 21 and 37% yields. 4-methylanisole was smoothly oxidized in acetonitrile to give 4-methoxybenzoic acid (80%), but in acetic acid, the oxidation stopped at 26% conversion. This is believed to be due to the formation of a phenol derivative, which inhibits the radical reaction, based on hydrolysis of anisole by acetic acid. *p*-nitrotoluene substituted by an electron withdrawing substituent was not oxidized under these conditions.

A plausible reaction pathway for the aerobic oxidation of alkanes by the combined use of NHPI and $Co(OAc)_2$ is illustrated in scheme 3.

The generation of PINO by the reaction of the NHPI with the cobalt(III)–oxygen complex under ambient conditions would be the most important step in the present oxidation. The next step in the oxidation involves the hydrogen abstraction from RH by the PINO to form R· which is readily trapped by dioxygen to provide ROO· followed by ROOH and eventually the formation of alcohols, ketones and/or carboxylic acids.

4. Concluding remarks

We now find a novel radical-catalyzed aerobic oxidation method of alkanes using NHPI as a catalyst. This method will provide a possibility of a new industrial technology for the aerobic oxidation of a variety of organic substrates. In particular, since no-waste technology will become more important in the future as worldwide environmental policies, the direct conversion of cyclohexane to adipic acid with dioxygen (air) in high conversion and selectivity is noteworthy as nitric acid free oxidation which makes it possible to avoid the evolution of nitrogen oxides, serious air polluting materials. In addition, the reaction can be applied to the production of various oxygen-containing bulk and fine chemicals such as benzoic acid, *tert*-butyl alcohol, and adamantanols under mild conditions.

Acknowledgement

This work was supported by Daicel Chemical Industries Ltd., and Research for the Future program JSPS, and Grant-in-Aid for Scientific Research from Monbusho, Japan.

References

[1] C.L. Hill, *Activation and Functionalization of Alkanes* (Academic Press, New York, 1989).
[2] (a) R.A. Sheldon and J.K. Kochi, *Metal-Catalyzed Oxidation of Organic Compounds* (Academic Press, New York, 1981);
(b) R.A. Sheldon, Chem. Tech. 24 (1994) 38.
[3] L.I. Simandi, *Catalytic Activation of Dioxygen by Metal Complexes* (Kluwer Academic, Dordrecht, 1992).
[4] D.H.R. Barton, A.E. Martell and D.T. Sawyer, eds., *The Activation of Dioxygen and Homogeneous Catalytic Oxidation* (Plenum, New York, 1993).
[5] G.W. Parshall and S.D. Ittel, *Homogeneous Catalysis*, 2nd Ed. (Wiley, New York, 1992).
[6] (a) Y. Kamitani, *Yuki Sanka Han-no* (Oxidation of Organic Compounds) (Gihodo, Tokyo, 1973);
(b) T. Matsuura, *Sanso Sanka Han-no* (Oxygenation Reaction) (Maruzen, Tokyo, 1977).
[7] A. Mackor, Th.A.J.W. Wajer and Th. de Boer, Tetrahedron 24 (1968) 1623.
[8] (a) J.A. Cella, J.A. Kelly and E.F. Kenehan, J. Org. Chem. 40 (1975) 1860;
(b) T. Inokuchi, S. Matsumoto, T. Nishiyama and S. Torii, J. Org. Chem. 55 (1990) 462;
(c) J.P. Freeman et al., eds., *Organic Synthesis Coll.*, Vol. 8 (Wiley, New York, 1993) p. 367.
[9] M.F. Semmelhack, C.S. Chou and D.A. Corites, J. Am. Chem. Soc. 105 (1983) 4492.
[10] E. Grochowski, T. Boleslawska and J. Jurczak, Synthesis (1977) 718.
[11] M. Masui, T. Ueshima and S. Ozaki, J. Chem. Soc., Chem. Commun. (1983) 479.
[12] S. Fujibayashi, K. Nakayama, M. Hamanmoto, S. Sakaguchi, Y. Nishiyama and Y. Ishii, J. Molec. Catal.: A Chemical 110 (1996) 105.
[13] (a) Y. Ishii, K. Nakayama, M. Takeno, S. Sakaguchi, T. Iwahama and Y. Nishiyama, J. Org. Chem. 60 (1995) 3934;
(b) Y. Ishii, J. Molec. Catal.: A Chemical 117 (1997) 123;
(c) T. Iwahama, S. Sakaguchi, Y. Nishiyama and Y. Ishii, Tetrahedron Lett. 38 (1995) 6923.

[14] M.F. Semmelhack, C.R. Scmid, D.A. Cortes and C.S. Chou, J. Am. Chem. Soc. 106 (1984) 3374.

[15] C. Einhorn, J. Einhorn, C. Maracadal and J.-L. Pierre, Chem. Commun. (1997) 47.

[16] N. Mizuno, M. Tateishi, T. Hirose and M. Iwamoto, Chem. Lett. (1993) 2137.

[17] J.E. Lyons, P.E. Ellis Jr. and H.K. Myers Jr., J. Catal. 155 (1995) 59.

[18] Y. Ishii, S. Kato, T. Iwahama and S. Sakaguchi, Tetrahedron Lett. 37 (1996) 4993.

[19] D.H.R. Barton, J. Boivin, M. Gastiger, J. Morzycki, R.S. Hay-Motherwell, W.B. Motherwell, N. Ozbalik and K.M. Schwartzentruber, J. Chem. Soc., Perkin Trans. 1 (1986) 947.

[20] P. Battioni, J.F. Bartori, P. Leduc, M. Fortecave and D. Mansuy, J. Chem. Soc., Chem. Commun. (1987) 791.

[21] S.-I. Murahasi, Y. Oda and T. Naota, J. Am. Chem. Soc. 114 (1992) 7913.

[22] H. Ohtake, T. Higuchi and M. Hirobe, J. Am. Chem. Soc. 114 (1992) 10660.

[23] G.W. Parshall and S.D. Ittel, *Homogeous Catalysis*, 2nd Ed. (Wiley, New York, 1992) p. 246.

[24] (a) J.W.M. Steeman, S. Kaarsemaker and P. Hoftyzer, J. Chem. Eng. Sci. 14 (1961) 139;
(b) S.A. Miller, Chem. Process Eng. (London) 50 (1969) 63.

[25] K. Tanaka, Chem. Tech. (1974) 555.

[26] (a) Y. Ishii, T. Iwahama, S. Sakaguchi, K. Nakayama and Y. Nishiyama, J. Org. Chem. 61 (1996) 4520;
(b) T. Iwahama, K. Shoujo, S. Sakaguchi and Y. Ishii, Org. Proc. Res. & Dev. 2 (1998) 255.

[27] A. Onopchenko and J.G.D. Schulz, J. Org. Chem. 38 (1973) 3729.

[28] J.I. Kroschwitz and M. Howe-Grant, eds., *Kirk–Othmer Encyclopedia of Chemical Technology*, 4th Ed. (Wiley, New York, 1990).

[29] D.E. Winlker and G.W. Hearne, Ind. Eng. Chem. 53 (1961) 655.

[30] (a) J.E. Lyons, P.E. Eillis Jr. and H.K. Myers, J. Catal. 155 (1995) 59;
(b) J.E. Lyons and P.E. Ellis Jr., Catal. Lett. 8 (1991) 45;
(c) P.E. Ellis Jr. and J.E. Lyons, Coord. Chem. Rev. 105 (1990) 181;
(d) P.E. Ellis Jr. and J.E. Lyons, J. Chem. Soc., Chem. Commun. (1989) 1187;
(e) P.E. Ellis Jr. and J.E. Lyons, Catal. Lett. 3 (1989) 389.

[31] S. Sakaguchi, S. Kato, T. Iwahama and Y. Ishii, Bull. Chem. Soc. Jpn. 71 (1998) 1237.

[32] (a) J.D. Bacha and J.K. Kochi, J. Org. Chem. 30 (1965) 3272;
(b) F.D. Greene, M.L. Savitz, F.D. Osterholts, H.H. Fau, W.H. Smith, and P.M. Zanet, J. Org. Chem. 28 (1963) 55.

[33] G.W. Parshall and S.D. Ittel, *Homogeous Catalysis,* 2nd Ed. (Wiley, New York, 1992) p. 255.

[34] Y. Yoshino, Y. Hayashi, T. Iwahama, S. Sakaguchi and Y. Ishii, J. Org. Chem. 62 (1997) 6810.

[35] (a) F. Basolo, R.D. Jones and D.A. Summerville, Chem. Rev. 79 (1979) 139;
(b) R.S. Drago, J.P. Cannady and K.A. Leslie, J. Am. Chem. Soc. 102 (1980) 6014;
(c) E.C. Niederhoffer, J.H. Timmons and A.E. Martell, Chem. Rev. 84 (1984) 137;
(d) J.J.Bozell, B.R. Hames and D.R. Dimmel, J. Org. Chem. 60 (1995) 2398.