# Studies on Catalytic Methods for Aerobic Oxidative Functionalization

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## Contents

# Chapter 1. General Introduction



## 1.1 Introduction

Oxidative transformations are fundamental subjects, and hence oxidations have been extensively used in laboratories and industries.[1] However, oxidations are among the most problematic process. Traditionally, oxidations of organic compounds are performed with stoichiometric amounts of inorganic oxidants, notably chromium (VI) reagent. Unfortunately, one or more equivalents of these oxidizing agents, which are often hazardous or toxic, are required, and also generate copious amounts of heavy-metal waste. As an alternative, monooxygen donors are available as milder oxidants such as peracides, metallorganic peroxides, organic hydroperoxides, and hydrogen peroxide. In catalytic oxidations using these oxidants, there are generally characterized by good activity and selectivity at moderate temperature, but monooxygen donors are not exempt from specific drawbacks of various natures. Thus, there is a need for the invention of clean, safe oxidation procedures. Molecular oxygen is an ideal oxidant, but aerobic oxidation is often difficult to control and sometimes results in combustion, and the reaction is performed with a low conversion to avoid over-oxidation. Therefore, the development of an efficient and highly selective aerobic oxidation method remains an important challenge from economic and environmental aspects.[2,3]

The aim of this doctoral dissertation is to explore efficient and environmentally benign methods for aerobic oxidative transformation of amines, alkanes, and oxidative esterification of aldehydes with alcohols. Before discussing these aerobic oxidations in detail, a general introduction and outline of this thesis will be given in this section.

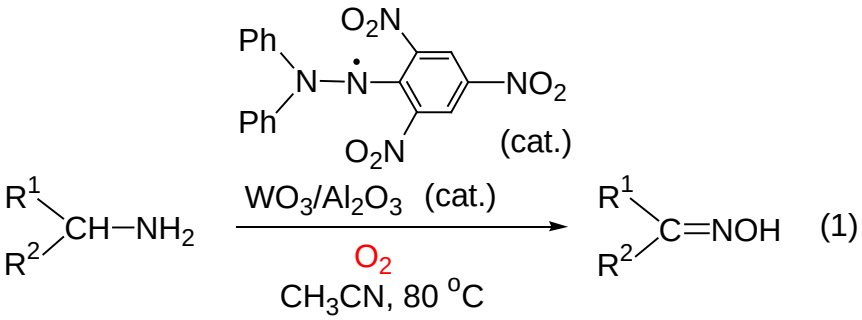
## 1.2 Aerobic Oxidation of Amines

Since catalytic oxidation of amines is of importance from enzymatic[4] and synthetic aspects,[5] various methods have been explored; however, useful methods for oxidation of amines are limited because of sensitiveness of amines. Using peroxides as oxidants, various transition-metal-catalyzed oxidative transformations of amines have been explored. Tertiary amines are converted to *N*-oxides.[6] Secondary amines can be oxidized to either nitrones[7] or imines.[8] Primary amines are oxidized to nitroso intermediates, which are converted to various compounds, such as nitro compounds[9] and oximes.[10] Catalytic oxidation of primary amines with hydrogen peroxide gives oximes along with by–products such as nitroalkanes, carbonyl compounds, and imines.[10]

Aerobic oxidation under mild conditions is one of the current challenging topics in view of environmental and economical aspects;[2,3] however, aerobic oxidative transformations of amines are limited to few reactions, which include ruthenium catalyzed oxidative cyanation of tertiary amines,[11] transition metal catalyzed oxidative transformation of secondary amines to imines,[12] that of primary amines to nitriles,[13] and flavin catalyzed oxidative transformation of secondary amines to nitrones.[14] There is no efficient method for aerobic oxidative transformation of primary amines to oximes. The reported method employing a heterogeneous catalyst such as $SiO_2$-gel at higher temperature (>150 °C) gave oximes only in low yields.[15]

Oximes are useful intermediates for the synthesis of commodity products, fine chemicals, medicines, and biologically active compounds.[16] Oximes are usually synthesized by condensation of aldehydes or ketones with hydroxylamine. Hydroxylamine is a toxic and thermally unstable product, and not negligible formation of ammonium salts cannot avoid after the reaction using its salts.

I aimed at exploring an efficient and environmentally benign method for aerobic oxidative transformation of primary amines to oximes. In chapter 2 describes a highly selective and efficient catalytic method for oxidative transformation of primary amines to oximes by employing 1,1-diphenyl-2-picrylhydrazyl (DPPH) and tungsten oxide/alumina ($WO_3/Al_2O_3$) as the catalyst, and molecular oxygen as the terminal oxidant (eq. 1). Various alicyclic and aliphatic amines can be converted to their corresponding oximes in excellent yields. The aerobic oxidation of secondary amines gives the corresponding nitrones. The key step of the present oxidation is a fast electron transfer from the primary amine to DPPH followed by proton transfer to give the α-aminoalkyl radical intermediate, which undergoes reaction with molecular oxygen and hydrogen abstraction to give α-aminoalkylhydroperoxide. Subsequent reaction of the peroxide with $WO_3/Al_2O_3$ gives oximes. Aerobic oxidative transformation of cyclohexylamines to cyclohexanone oximes is important as a method for industrial production of ε-caprolactam, a raw material for Nylon 6.




(1)

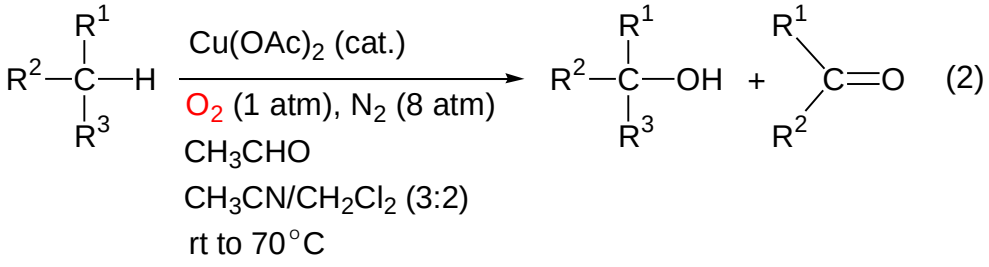
## 1.3 Aerobic Oxidation of Alkanes

The catalytic oxidative functionalization of C–H bonds of alkanes is of importance in synthetic, industrial, and biological aspects.[17,18] Development of a new method for selective and efficient aerobic oxidation of alkanes under mild conditions is an important goal.[19] During the course of simulation of the function of cytochrome P-450, Murahashi et al. found that ruthenium-catalyzed oxidation of various substrates can be performed highly efficiently.[20] Ruthenium[21a] and other transition metal[21b]-catalyzed oxidative functionalization of C–H bonds of alkanes with *tert*-butylhydroperoxide[21] or peracetic acid[21a] proceed highly efficiently. Peracetic acid is a highly reactive reagent for catalytic oxidation[22] of alkanes and alkenes; however, its availability and stability is problem. Therefore, a method for generation of peracetic acid in situ from acetaldehyde and molecular oxygen and immediately used as an oxidizing reagent has been explored. Thus, ruthenium catalyzed aerobic C–H functionalization of β-lactams[23] and alkanes[24] has been performed in the presence of acetaldehyde.

Copper is contained in metalloenzymes that plays an important role in biological dioxygen metabolism; however, the copper-catalyzed oxidative functionalization of C–H bonds of alkanes is limited to a few cases.[25-27] Copper catalyzed aerobic oxidative C–H functionalization of hydrocarbons has been performed in the presence of acetaldehyde using copper catalysts such as $Cu(OH)_2$[25] and $CuCl_2$/18-crown-6.[26] Typically a combination of $CuCl_2$ with 18-crown-6 was found to be highly effective catalyst for the oxidation of cyclohexane with molecular oxygen in the presence of acetaldehyde.[26]

I aimed at looking for simpler and more efficient catalytic system for the oxidation of alkanes. In chapter 3 describes a specific copper complex derived from copper acetate in acetonitrile is a convenient and highly useful catalyst for aerobic oxidative functionalization of non-activated hydrocarbons (eq 2). Various cyclic alkanes, *n*-alkane and alkyl aromatics can be converted into the corresponding alcohols and ketones in

excellent yields. This simple and useful catalytic system seems to involve metal-based and radical-based reactions. In this system acetonitrile acts not only as a solvent but also a ligand to generate and stabilize Cu(I) species, thus offering a new possibility for selective C–H functionalization of unreactive hydrocarbons.



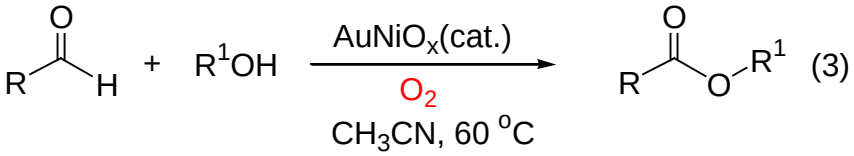
(2)

## 1.4 Aerobic Oxidative Esterification of Aldehydes with Alcohols

Esters are very useful chemical intermediates in terms of atom economy and versatility that can be helpful in further transformation. Esterification is one of the fundamental transformations in organic synthesis and widely used in laboratories and industries.[28] Esterification of aldehydes with alcohols is an attractive method for synthesis of esters, because aldehydes are readily available raw materials on a commercial scale. Several facile and selective esterification reactions have been reported.[29] Further, since Haruta et al. discovered that Au nanoparticles catalyze aerobic oxidation reactions,[30] several Au-nanoparticle-based catalysts for the aerobic esterification of aldehydes[31] or alcohols[32] have been reported.

I aimed at finding a catalytic method for direct aerobic oxidative esterification of aldehydes with alcohols under mild and neutral conditions in view of both economic and environmental aspects. In chapter 4 presents aerobic oxidative esterification of aldehydes with alcohols to give esters under mild and neutral reaction conditions in the presence of supported gold–nickel oxide nanoparticle catalyst ($AuNiO_x$) (eq 3). The oxidative esterification of various aldehydes and alcohols affords the corresponding

esters highly efficiently. The $AuNiO_x$ nanoparticles have a core shell structure, with Au nanoparticle at the core with its surface covered by highly oxidized $NiO_x$. The reaction mechanism proposed for the oxidative esterification of aldehydes involves the formation of hemiacetal as a key intermediate. A condensation reaction between aldehyde and an alcohol results in the formation of hemiacetal, which undergoes oxidative dehydrogenation to give esters.




(3)

Aerobic oxidative esterification of methacrolein in methanol to methyl methacrylate (MMA) is an important industrial method for the production of polymethyl methacrylate (PMMA). Direct procedure for the aerobic oxidative esterification of methacrolein with methanol to yield MMA has been performed using the $AuNiO_x$ catalyst.

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(32)(a) Hayashi, T; Inagaki, T; Itayama, N; Baba, H. *Catal. Today*. **2006**, *117*, 210–213. (b) Nielsen, I. S.; Taarning, E.; Egeblad, K.; Madsen, R.; Christensen, C. H. *Catal. Lett.* **2007**, *116*, 35–40. (c) Oliveira, R. L.; Kiyohara, P. K.; Rossi, L. M. *Green Chem.* **2009**, *11*, 1366–1370. (d) Casanova, O.; Iborra, S.; Corma, A. *J. Catal.* **2009**, *265*, 109–116. (e) Miyamura, H.; Yasukawa, T.; Kobayashi, S. *Green Chem.* **2010**, *12*, 776–778. (f) Costa, V. V.; Estrada, M.; Demidova, Y.; Prosvirin, I.; Kriventsov, V.; Cotta, R. F.; Fuentes, S; Simakov, A.; Gusevskaya, E. V. *J. Catal.* **2012**, *292*, 148–156. (g) Kotionova, T; Lee, C.; Miedziak, P.; Dummer, N. F.; Willock, D. J.; Carley, A. F.; Morgan, D. J.; Knight, D. W.; Taylor, S. H.; Hutchings, G. *J. Catal. Lett.* **2012**, *142*, 1114–1120.

# Chapter 2. Oxidation of Primary Amines to Oximes with Molecular Oxygen using 1,1-Diphenyl-2-picrylhydrazyl and $WO_3/Al_2O_3$ as Catalysts

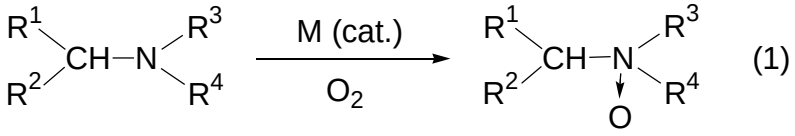


## 2.1 Introduction

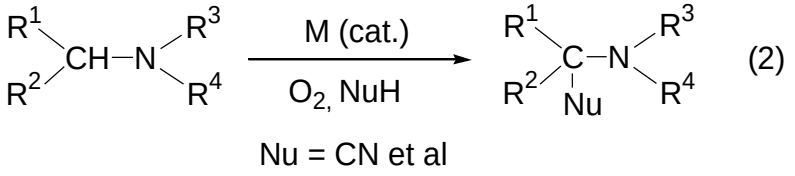
Catalytic oxidation of amines is of fundamental importance from both bioorganic and synthetic aspects.[1,2] Therefore, various methods have been reported. However, useful methods for catalytic oxidation are limited, because the selective oxidation of amines is extremely difficult as a result of amine sensitivity. Using peroxides as oxidants, various transition-metal-catalyzed oxidative transformations of amines have been explored. Tertiary amines are converted to *N*-oxides.[3] Secondary amines can be oxidized to either nitrones[4] or imines.[5] Primary amines are

oxidized to nitroso intermediates, which are converted to various compounds, such as nitro compounds[6] and oximes.[7]

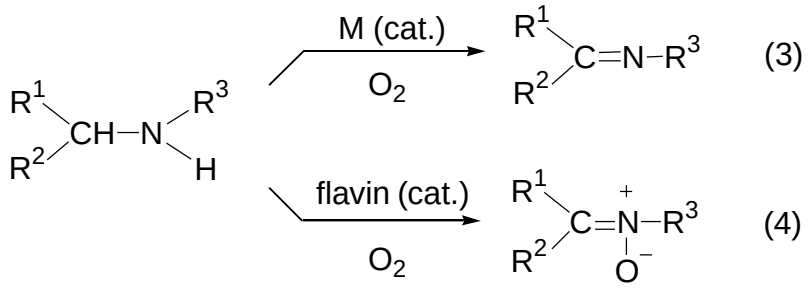
In the catalytic oxidation of amines, the use of molecular oxygen as an environmentally benign terminal oxidant under mild conditions is extremely important in view of environmental, economical, and synthetic aspects;[8] however, few catalytic aerobic oxidative transformations have been reported.[9] Aerobic catalytic oxidation of tertiary amines with transition-metal catalysts proceeds to give *N*-oxides (eq 1).[10]



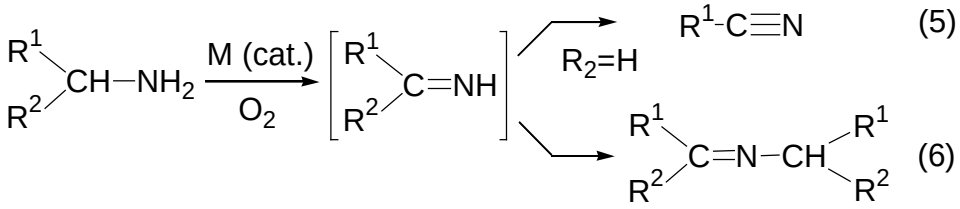

Aerobic catalytic oxidative transformations of tertiary amines by α-C–H activation adjacent to nitrogen gives the corresponding α-substituted products such as aminonitriles (eq 2).[2c,11]



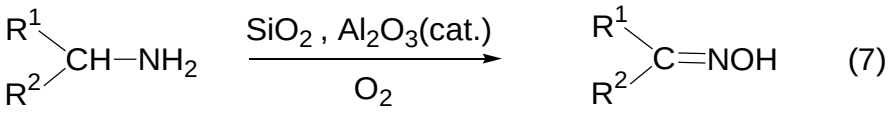

Aerobic catalytic oxidative transformations of secondary amines give either imines or nitrones selectively, depending on the reaction conditions employed. Thus, transition-metal-catalyzed aerobic catalytic oxidation of secondary amines gives imines (eq 3).[12] In contrast, flavin-catalyzed aerobic oxidation of secondary amines selectively gives nitrones (eq 4).[13]



Aerobic catalytic oxidation of primary amines gives the corresponding imine intermediates that undergo either extensive dehydrogenation to give nitriles (eq 5)[14] or addition of the starting amine to give N-substituted imines (eq 6).[15] In particular, benzylamines undergo oxidative dimerization to give the corresponding imines with[15] or without[16] catalysts.




Primary amines can be oxidized to oximes. Catalytic oxidative transformation of primary amines with oxidants such as hydrogen peroxide have been reported with transition-metal catalysts.[7] However, aerobic catalytic oxidative transformations are limited to a few reactions. Vapor-phase aerobic oxidations in the presence of $SiO_2$-gel or $\gamma$-$Al_2O_3$ catalyst (eq 7)[17a] and a polyoxometal catalyst[17b] at extremely high temperatures give the corresponding oximes in low yields and with low selectivity. Titanium oxide catalyzed aerobic oxidation of cyclohexylamine occurs with low conversion.[17c]




Oximes are useful intermediates for the synthesis of commodity products, fine chemicals, medicines, and biologically active compounds (Figure 1).[18] Oximes are usually synthesized by condensation of aldehydes or ketones with hydroxylamine, which is toxic and thermally unstable. Hydroxylamine is a toxic and thermally unstable product, and not negligible formation of ammonium salts cannot avoid after the reaction using its salts. Therefore, we aimed to explore an efficient and environmentally benign method for aerobic oxidative transformation of primary amines to oximes.

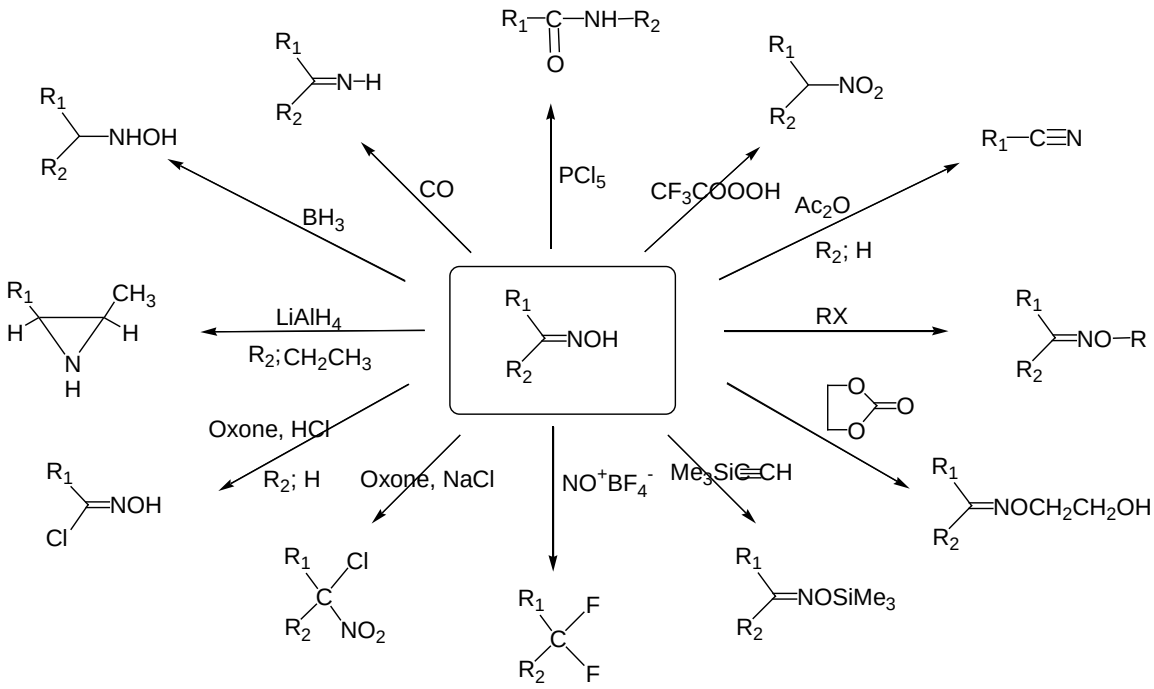
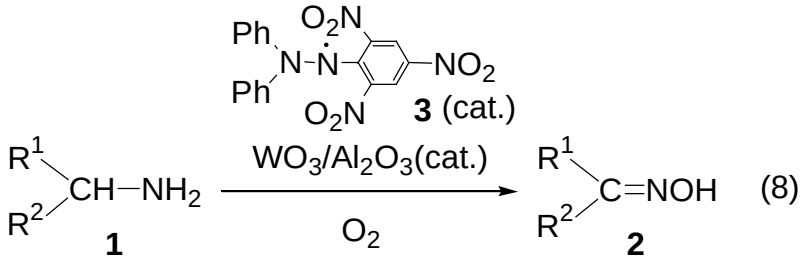



**Figure 1.** Derivatives of the oxime compound

After many attempts, we discovered a highly selective and efficient method for oxidative transformation of primary amines (**1**) to oximes (**2**) by employing 1,1-diphenyl-2-picrylhydrazyl (DPPH; **3**) catalyst, a tungsten oxide/alumina ($WO_3/Al_2O_3$) cocatalyst, and molecular oxygen as the terminal oxidant under mild conditions (eq 8). To our knowledge, this is the first description of an aerobic catalytic oxidation using DPPH as an organocatalyst. DPPH has been employed as a standard substrate for ESR spectroscopy[19a] and as a radical scavenger;[19b] however, it has never been used as an organic catalyst for organic synthesis.




(8)

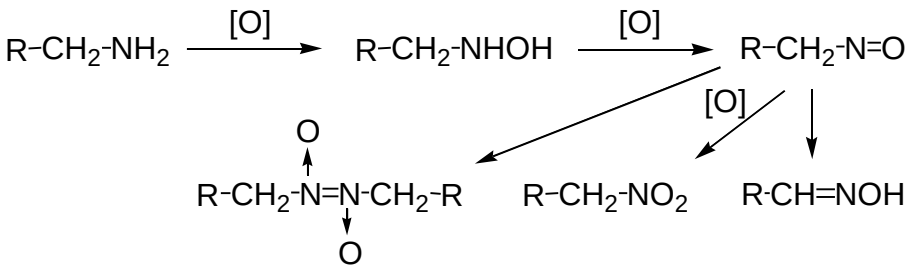
## 2.2 Results and Discussion

### 2.2.1 DPPH-Catalyzed Oxidative Transformation of Primary Amines with Molecular Oxygen.

Catalytic oxidative transformation of primary amines into oximes with hydrogen peroxide have been reported using various transition metal catalysts such as sodium salt of tungstic acids,[7a,b] peroxotungstophosphate,[7c] methyltrioxorhenium (MTO),[7d] $Mo(O)(O_2)L'L''(L'=H_2O$, L"=hexa-methylphosphoramide),[7e] titanium silicate,[7f,g,h] and vanadium silicate;[7j] However, these catalytic oxidations of primary amines with hydrogen peroxide gives oxime along with many by-products such as nitroalkanes, carbonyl compounds, nitriles and *N*-alkylimines.

Reaction of transition metal such as V, Mo, W, and Ti with hydrogen peroxide gives metal hydroperoxy or peroxy species, of which peroxygens have an electrophilic nature with respect to hydrogen peroxide. Oxygen transfer from these species to a nitrogen atom takes place readily to perform oxygenation of amines. The oxygenation of primary amines may give hydroxylamines, which undergo further oxidation to nitroso compounds. Nitroso compounds are reactive intermediates, which undergo further oxidation to nitro compound, condensation with amine to azo compounds, and nitroso alkanes possessing α-hydrogens undergo prototypic rearrangement to give oximes (Scheme 1).[2b]

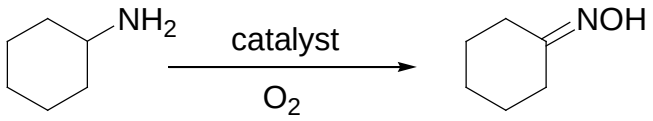
**Scheme 1.** Oxidation of primary amines.



Aerobic catalytic oxidation of primary amines using transition-metal catalysts usually gives either nitriles[14] or *N*-alkylimines[15] as shown in eqs 5 and 6. Furthermore, dehydration of aldoximes at higher temperature gives nitriles.[20] We attempted to discover a method for aerobic oxidative transformation of primary amines to oximes using transition-metal catalysts. However, all attempts failed. The aerobic oxidation of cyclohexylamine in the presence of a transition-metal catalyst such as $TiO(acac)_2$, $VO(acac)_2$, $FeCl_3$, $Co(acac)_2$, $CuCl_2$, $MoO_2(acac)_2$, $RuCl_2(PPh_3)_3$, $Na_2WO_4$, $WO_3$, and $WO_3/Al_2O_3$ gave no oxime, and a complex mixture of nitriles, *N*-alkylimines, and carbonyl compounds was obtained.

We next examined the aerobic oxidation of primary amines using various organocatalysts. 2,2,6,6-Tetramethylpiperidine-*N*-oxyl (TEMPO) has been used as a highly efficient catalyst for the aerobic oxidation of various substrates such as alcohols.[21] *N*-Hydroxyphthalimide (NHPI) is also an excellent catalyst for aerobic oxidation of a broad range of organic substrates such as alkanes and alkyl aromatics.[22] Flavin is an efficient catalyst for the aerobic oxidation of secondary amines to nitrones.[13] All attempts at the aerobic oxidation of primary amines using the organocatalysts mentioned above failed. The aerobic oxidations for cyclohexylamine in the presence of such catalysts are summarized in Table 1. Combining catalysts such as TEMPO with $RuCl_2(PPh_3)_3$[21] and NHPI with $Co(acac)_2$ [22] showed excellent catalytic activity for the aerobic oxidation of alcohols or hydrocarbons. However, these catalysts showed no effective activity (entries 1 and 2). It is noteworthy that when $WO_3/Al_2O_3$ was used instead of $RuCl_2(PPh_3)_3$ and $Co(acac)_2$, the oxime was obtained in low yields (entries 3 and 4). $WO_3/Al_2O_3$ alone is not effective (entry 5).

**Table 1.** The activity of catalysts for the aerobic oxidative transformation of cyclohexylamine **1a**[a]

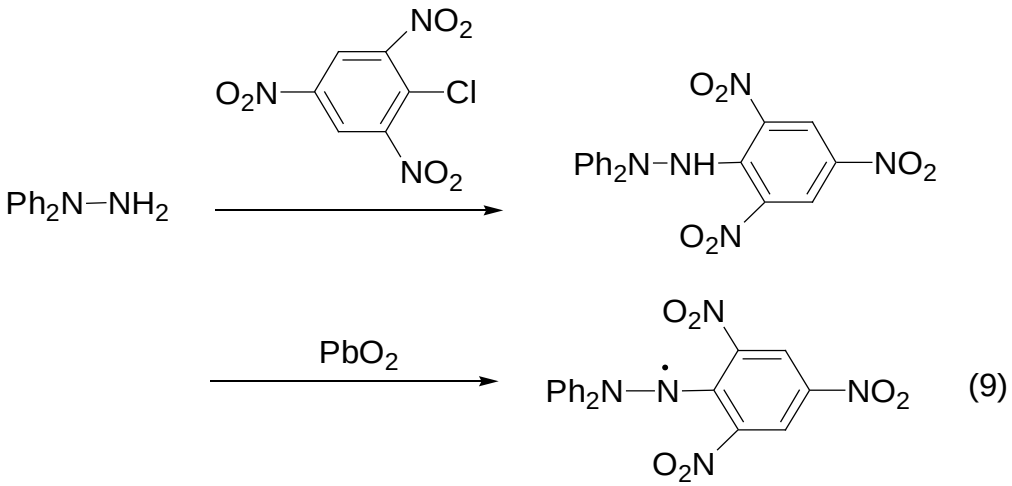



**1a** **2a**

| entry | catalyst | conversion of amine **1a** (%)[b] | selectivity for oxime **2a** (%)[b] |
|---|---|---|---|
| 1[c] | TEMPO - $RuCl_2(PPh_3)_3$ | 21 | 0 |
| 2[d] | NHPI - $Co(acac)_2$ | 36 | 0 |
| 3 | TEMPO - $WO_3/Al_2O_3$ | 4 | 2 |
| 4 | NHPI - $WO_3/Al_2O_3$ | 7 | 3 |
| 5 | $WO_3/Al_2O_3$ | 7 | 0 |
| 6 | DPPH | 21 | 3 |
| 7 | DPPH - $WO_3/Al_2O_3$ | 59 | 95 |

[a] Reaction conditions: **1a** (5 mmol), organocatalyst (2.5 mol%), $WO_3/Al_2O_3$ (W: 1 mol%) in acetonitrile (3 mL), $O_2$ ($O_2/N_2$=7/93 v/v, 5 MPa) at 80 °C for 4 h. [b] Determined by GC analysis using an internal standard. [c] TEMPO (3 mol%)- $RuCl_2(PPh_3)_3$ (1 mol%). [d] NHPI (10 mol%)- $Co(acac)_2$ (0.5 mol%).

DPPH is well-known as a stable radical and has been used as an ESR standard,[19a] polymerization inhibitior,[19b] and monitor of chemical reactions involving radicals.[19c–d] However, it has never been used as an organocatalyst for organic synthesis. DPPH can be readily prepared by oxidation of 1,1-diphenyl-2-picrylhydrazine, which is prepared from diphenylhydrazine and picryl chloride (eq 9).[23]




(9)

Therefore, we examined the catalytic activity of DPPH. The reaction with DPPH alone gave cyclohexanone and polymeric compounds in addition to a small amount of cyclohexanone oxime (entry 6). The combination of DPPH and $WO_3/Al_2O_3$ was found to give an excellent result (entry 7). Thus, the reaction of cyclohexylamine (**1a**) in the presence of DPPH (2.5 mol%)–$WO_3/Al_2O_3$ (W; 1 mol%) in acetonitrile at 80 °C under molecular oxygen ($O_2/N_2$ = 7/93 v/v, 5 MPa, outside flammability limits) for 4 h gave cyclohexanone oxime (**2a**) with 95% selectivity and 59% conversion. No decomposition or deterioration of DPPH was observed under the reaction conditions. Molecular oxygen diluted with nitrogen ($O_2/N_2$ = 7/93 v/v, 5 MPa), which corresponds to air diluted with molecular nitrogen, was used outside flammability limits using an autoclave at all times. In industry pure oxygen cannot be used, and air diluted with molecular nitrogen is used. This is such a case. This method is convenient for a large-scale closed system and also for a flow system. Oxidation with molecular oxygen (1 atm, balloon) gave excellent results; therefor, this method is convenient for laboratory organic synthesis.

We examined the catalytic activity of cocatalysts. Representative results are shown in Table 2. DPPH alone exhibited low catalytic activity for the aerobic oxidation of amines to oximes (entry 1). Amines were converted to the carbonyl compound and a mixture of unidentified byproducts. $WO_3/Al_2O_3$, $WO_3/ZrO_2$, Ti (Oi-Pr)$_4$, TiO(acac)$_2$, and $Nb_2O_5$ proved to be excellent cocatalysts for the aerobic oxidation of **1a** (entries 2, 3, and 10–12), while $WO_3/TiO_2$, $TiO_2$, and titanium silicate-1 (TS-1) showed low catalytic activity (entries 4, 8, and 9). Tungsten catalysts such as $WO_3$, $Na_2WO_4 \cdot 2H_2O$ and $W(OC_2H_5)_6$ and other transition-metal catalysts such as $MoO_3/Al_2O_3$, $MoO_2(acac)_2$, $Na_2MoO_4 \cdot 2H_2O$, $Mo(CO)_6$, $V_2O_5$, VO(acac)$_2$, Fe(acac)$_3$, Co(acac)$_2$, and $RuCl_2(PPh_3)_3$ showed poor catalytic activity (entries 5–7, and 13–21).

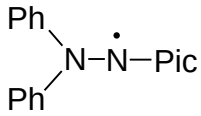
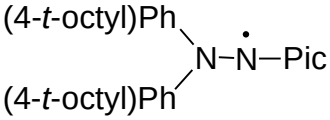
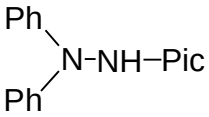
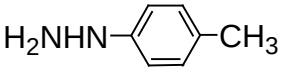
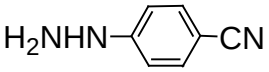
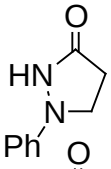
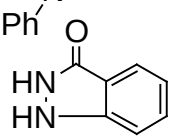
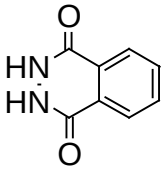
Next, we examined the catalytic activity of the hydrazyl radical, hydrazine, and hydrazide in combination with $WO_3/Al_2O_3$. Representative results are summarized in Table 3. DPPH and its derivatives, such as 1,1-bis(4-*tert*-octylphenyl)-2-picrylhydrazyl (DOPH) and 1,1-diphenyl-2-picrylhydrazine (DPPH–H), showed high catalytic activity (entries 1–3). Hydrazide compounds, such as *p*-methylphenylhydrazine and hydrazide compounds, such as 1-phenyl-3-pyrazolidone can be used as catalysts (entries 4 and 6). 4-Hydrazino-benzonitrile, 1,2-dihydroindazol-3-one, benzoic hydrazine, *N,N′*-dibenzoylhydrazine, and phthalhydrazide showed low catalytic activity (entries 5, 7–10). It is noteworthy that, with the exception of DPPH, DOPH, and DPPH–H, the organic catalysts undergo decomposition and deterioration under the reaction conditions. Therefore, DPPH is the best catalyst because of its high catalytic activity, stability, and ease of handling.

**Table 2.** Aerobic catalytic oxidative transformation of cyclohexyl amine **1a**; catalytic activity of cocatalysts[a]

| entry | transition-metal catalyst | conversion of amine **1a** (%)[b] | selectivity for oxime **2a** (%)[b] |
|---|---|---|---|
| 1 | none | 21 | 3 |
| 2 | $WO_3/Al_2O_3$ | 59 | 95 |
| 3 | $WO_3/ZrO_2$ | 63 | 86 |
| 4 | $WO_3/TiO_2$ | 22 | 64 |
| 5 | $WO_3$ | 15 | 6 |
| 6 | $Na_2WO_4$ | 13 | 5 |
| 7 | $W(OC_2H_5)_6$ | 3 | 0 |
| 8 | $TiO_2$ | 36 | 90 |
| 9 | TS-1 | 14 | 93 |
| 10 | $Ti(O\textit{i}Pr)_4$ | 67 | 88 |
| 11 | $TiO(acac)_2$ | 61 | 89 |
| 12 | $Nb_2O_5$ | 50 | 80 |
| 13 | $MoO_3/Al_2O_3$ | 15 | 4 |
| 14 | $MoO_2(acac)_2$ | 17 | 2 |
| 15 | $Na_2MoO_4 \cdot 2H_2O$ | 19 | 0 |
| 16 | $Mo(CO)_6$ | 17 | 0 |
| 17 | $V_2O_5$ | 33 | 2 |
| 18 | $VO(acac)_2$ | 21 | 1 |
| 19 | $Fe(acac)_3$ | 6 | 44 |
| 20 | $Co(acac)_2$ | 5 | 0 |
| 21 | $RuCl_2(PPh_3)_3$ | 4 | 19 |

[a] Reaction conditions: **1a** (5 mmol), DPPH (2.5 mol%), co-catalyst (metal: 1 mol%) in acetonitrile (3 mL), $O_2$ ($O_2/N_2$=7/93 v/v, 5 MPa) at 80 °C for 4 h. [b] Determined by GC analysis using an internal standard.

**Table 3.** Effect of organocatalyst on the organocatalyst–$WO_3/Al_2O_3$ catalyzed aerobic oxidative transformation of cyclohexylamine **1a**[a]

| entry | organocatalyst | conversion of amine **1a** (%)[b] | selectivity for oxime **2a** (%)[b] |
|---|---|---|---|
| 1 |  | 59 | 95 |
| 2 |  | 62 | 96 |
| 3 |  | 41 | 96 |
| 4 |  | 32 | 87 |
| 5 |  | 19 | 83 |
| 6 |  | 30 | 80 |
| 7 |  | 18 | 86 |
| 8 | $PhCONHNH_2$ | 16 | 88 |
| 9 | PhCONHNHCOPh | 2 | 83 |
| 10 |  | 0 | 0 |

[a]Reaction conditions: **1a** (5 mmol), organocatalyst (2.5 mol%), $WO_3/Al_2O_3$ (W: 1 mol%) in acetonitrile (3 mL), $O_2$ ($O_2/N_2$=7/93 v/v, 5 MPa) at 80 °C for 4 h. [b] Determined by GC analysis using an internal standard. Pic=picryl

The solvent effect of the aerobic oxidation of primary amine catalyzed by DPPH–$WO_3/Al_2O_3$ is very important. Representative results are shown in Table 4. Acetonitrile and *N*,*N*-dimethylformamide (DMF) were the best solvents among those examined (entries 1 and 2). Nitriles such as propionitrile and benzonitrile and amides such as *N*, *N*-dimethylacetamide and *N*, *N*-dimethylpropionamide also gave high conversions. However, slight formation of *N*-alkylformamide derived from primary amines when using DMF was observed under the reaction conditions. The reactions in nonpolar solvents, such as toluene, showed low conversions (entry 3). Use of a protic solvent such as methanol, *tert*-butyl alcohol, and $H_2O$ resulted in low conversions (entries 4–6).

**Table 4.** Effect of solvent on the DPPH–$WO_3/Al_2O_3$ catalyzed aerobic oxidative transformation of cyclohexylamine **1a**[a]

| entry | solvent | conversion of amine **1a** (%)[b] | selectivity for oxime **2a** (%)[b] |
|---|---|---|---|
| 1 | acetonitrile | 59 | 95 |
| 2 | *N,N*-dimethylformamide | 77 | 94 |
| 3 | tolene | 6 | 92 |
| 4 | methanol | 14 | 91 |
| 5 | *tert*-butyl alcohol | 9 | 93 |
| 6 | $H_2O$ | 5 | 83 |

[a] Reaction conditions: **1a** (5 mmol), DPPH (2.5 mol%), $WO_3/Al_2O_3$ (W: 1 mol%) in solvent (3 mL), $O_2$ ($O_2/N_2$=7/93 v/v, 5 MPa) at 80 °C for 4 h. [b] Determined by GC analysis using an internal standard.

The results of the influence of solvents polarity (ε) are shown in Figure 2. The dielectric constant of solvent in aerobic oxidation of amine plays an important role. The catalytic activity increased with dielectric constant in aprotic solvent, while using a protic solvent like alcohol or $H_2O$, such a correlation as that in aprotic solvent was not observed.

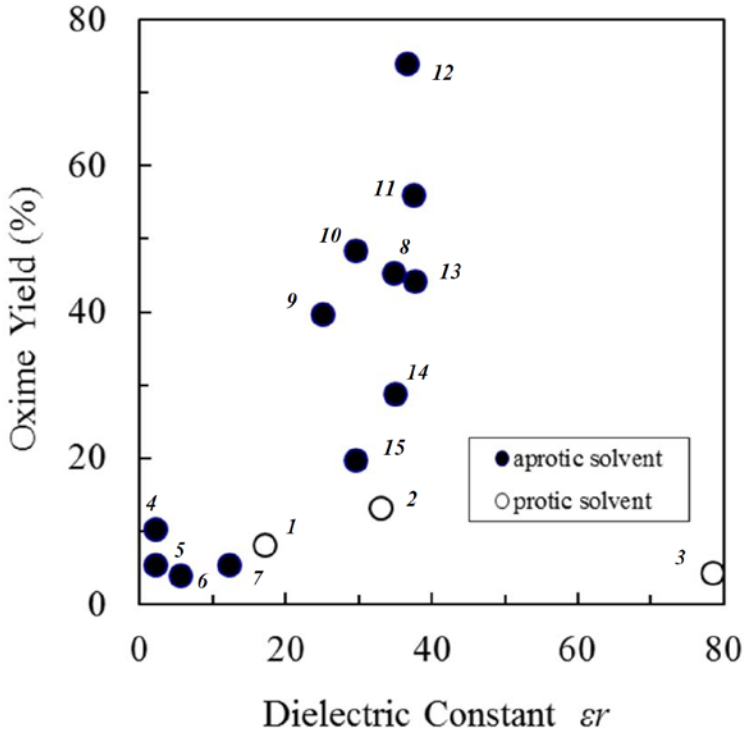
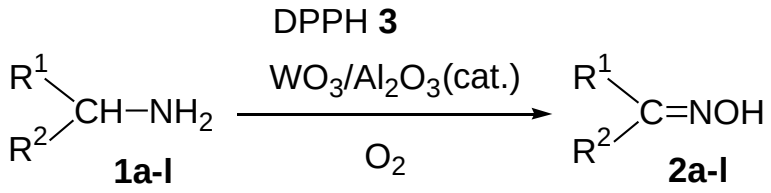



**Figure 2.** The correlation of the solvent's dielectric constant and cyclohexanone oxime **2a** yield for the DPPH–$WO_3/Al_2O_3$-catalysed aerobic oxidative transformation of cyclohexylamine **1a**. Parameters ε measured at standard temperature and pressure. Solvent; [1]*tert*-butyl alcohol, [2]methanol , [3]$H_2O$, [4]1,4-dioxane, [5]benzene, [6]chlorobenzene, [7]pridine, [8]nitrobenzene, [9] benzonitrile , [10]propionitrile, [11]acetonitrile, [12]*N,N*-dimethylformamide, [13]*N,N*-dimethylacetamide, [14]*N,N*-dimethylpropion amide, [15]hexamethyphosphoramide.

Representative results of the aerobic oxidation of primary amines in acetonitrile at 80 °C in the presence of the DPPH–$WO_3/Al_2O_3$ catalyst under molecular oxygen are summarized in Table 5. The oxidation of **1a** gave **2a** (90%) along with small amounts of nitrocyclohexane (4%), cyclohexanone (2%), and *N*-cyclohexylidene–cyclohexylamine (1%) (entry 1). In the gram scale reaction, cyclohexanone oxime was obtained in 85% isolated yield. No decomposition of DPPH was observed under the reaction conditions. The $WO_3/Al_2O_3$ catalyst was separated by filtration, after which tungsten was not observed in the filtrate by induced coupled plasma (ICP) analyses. The oxidation proceeded efficiently under an atmosphere pressure of molecular oxygen (1 atm, balloon) (entry 2). The reaction did not occur in the absence of molecular oxygen. A manometric measurement of oxygen uptake revealed that an equimolar amount of molecular oxygen was consumed for the oxidation of primary amines.

Alicyclic amines (**1b–1i**) were converted to the corresponding oximes (**2b–2i**) in excellent yields (entries 3–10). The reaction of aliphatic amines also gave their corresponding oximes in good yields. In a typical example, the oxidation of octylamine (**1k**) gave the corresponding oxime (**2k)** in 73% yield (entry 12). The reaction tolerates other oxidizing groups. Thus, the oxidation of 4-hydroxylcyclohexylamine (**1j**) proceeded chemoselectively to afford the corresponding oxime (**2j**) in 82% yield (entry 11). Oxidation of 5-hydroxylpentylamine (**1l**) proceeded chemoselectively (entry 13).

**Table 5.** The DPPH–$WO_3/Al_2O_3$-catalyzed aerobic oxidative transformation of primary amines to oximes[a]



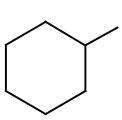
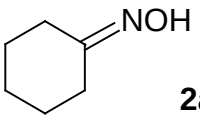
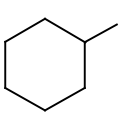
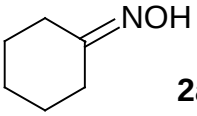
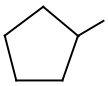
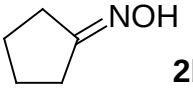
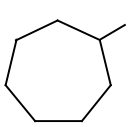
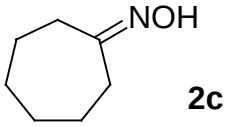
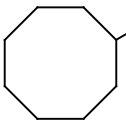
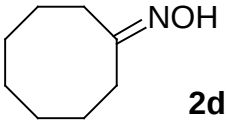
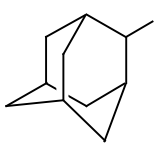
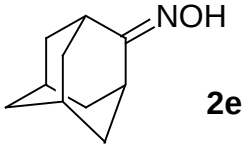
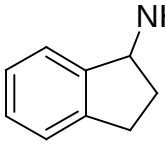
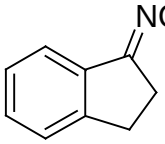
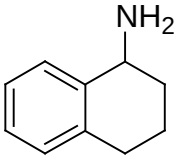
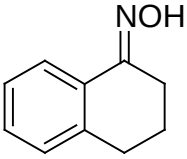
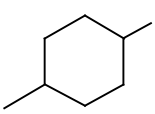
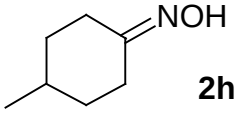
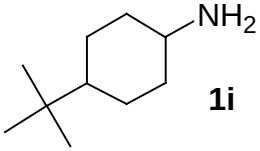
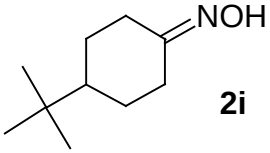
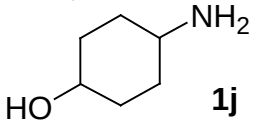
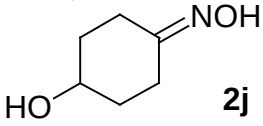

| entry | substrate | product | conversion (%)[b] / yield (%)[b] / time (h) |
|---|---|---|---|
| 1 |  **1a** |  **2a** | 98/90 (85)[c] /8 |
| 2[d] |  **1a** |  **2a** | 98/89/16 |
| 3 |  **1b** |  **2b** | 97/82/8 |
| 4 |  **1c** |  **2c** | 96/73/48 |
| 5[e] |  **1d** |  **2d** | 93/66/36 |
| 6 |  **1e** |  **2e** | 95/80/48 |

**Table 5.** (continued)

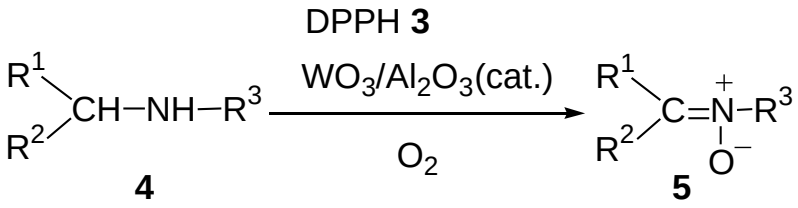
| entry | substrate | product | conversion (%)[b] / yield (%)[b] / time (h) |
|---|---|---|---|
| 7 |  **1f** |  **2f** | 90/72/48 |
| 8 |  **1g** |  **2g** | 87/63/48 |
| 9 |  **1h** |  **2h** | 97/85/8 |
| 10 |  **1i** |  **2i** | 98/75/16 |
| 11[e] |  **1j** |  **2j** | 97/82/48 |
| 12[e] | $CH_3(CH_2)_6CH_2NH_2$ **1k** | $CH_3(CH_2)_6CH{=}NOH$ **2k** | 94/73/36 |
| 13 | $HO(CH_2)_4CH_2NH_2$ **1l** | $HO(CH_2)_4CH{=}NOH$ **2l** | 95/75/48 |

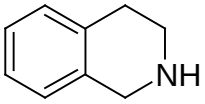
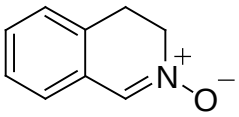
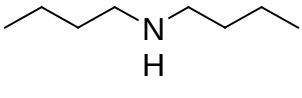
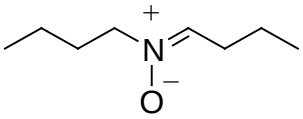
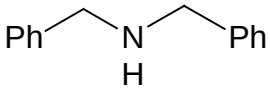
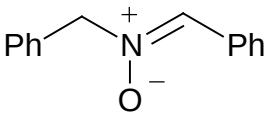
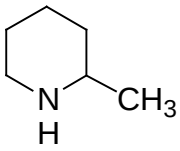
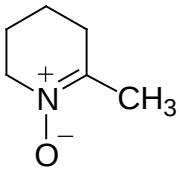
[a] Reaction conditions: primary amine (5 mmol), DPPH (5 mol%), $WO_3/Al_2O_3$ (W: 1 mol%) in acetonitrile (3 mL), $O_2$ ($O_2/N_2$=7/93 v/v, 5 MPa) at 80 °C. [b] Determined by GC analysis using an internal standard. [c] The isolated yield obtained from a gram-scale reaction is shown in parentheses. [d] $O_2$ atmosphere (1 atm, balloon) at 80 °C. [e] 10 mol% DPPH.

### 2.2.2 DPPH-Catalyzed Oxidative Transformation of Secondary Amines with Molecular Oxygen

The aerobic oxidation of secondary amines (**4**) gave their corresponding nitrones (**5**). Typically, the oxidation of 1,2,3,4-tetrahydroisoquinoline with molecular oxygen in the presence of DPPH–$WO_3/Al_2O_3$ catalyst in acetonitrile at 80 °C gave 3,4-dihydroisoquinoline *N*-oxide with 61% selectivity and 28% conversion, which are important precursors for synthesis of isoquinoline alkaloids (Table 6, entry 1). The low conversion of the starting amines is the result of the spin-trapping ability of nitrones.[24] A similar oxidation of dibutylamine gave *N*-butylidenebutylamine *N*-oxide with 72% selectivity (entry 2). Dibenzylamine and 2-methylpiperidine can also be converted into their corresponding nitrones; however, the selectivity of nitrones decreased at high conversion (entries 3 and 4). The reaction of tertiary amines such as *tert*-butylamine did not occur.

**Table 6.** The DPPH–$WO_3/Al_2O_3$-catalyzed aerobic oxidative transformation of secondary amines to nitrones[a]




| entry | substrate | product | conversion of amine (%)[b] | selectivity for nitrone (%)[b] |
|---|---|---|---|---|
| 1 |  |  | 28 | 61 |
| 2 |  |  | 5 | 72 |
| 3 |  |  | 4 | 37 |
| 4 |  |  | 4 | 36 |

[a] Reaction conditions: secondary amine (5 mmol), DPPH (5 mol%), $WO_3/Al_2O_3$ (W: 1 mol%) in acetonitrile (3 mL), $O_2$ ($O_2/N_2$=7/93 v/v, 5 MPa) at 80 °C for 8 h. [b] Determined by GC analysis using an internal standard.

Stability and recyclability is a key issue in catalysis. The DPPH–$WO_3/Al_2O_3$ catalyst can be reused without loss of catalytic activity or selectivity. After the reaction, the $WO_3/Al_2O_3$ could be easily separated from the reaction mixture by filtration, and the isolated $WO_3/Al_2O_3$ was reused. Kugelrohr distillation (100 °C, 30 mmHg) gave the solvent, the product, and the DPPH (**3**) residue. The recovered **3** was reused directly. The results obtained in a stability study of DPPH–$WO_3/Al_2O_3$-catalyzed aerobic oxidation of **1a** are shown in Table 7. The yield of cyclohexanone oxime was maintained at a similar value for at least three rounds of recycling.

**Table 7**. Recycling of the DPPH–$WO_3/Al_2O_3$ catalyst for the aerobic oxidation of cyclohexylamine **1a**[a]

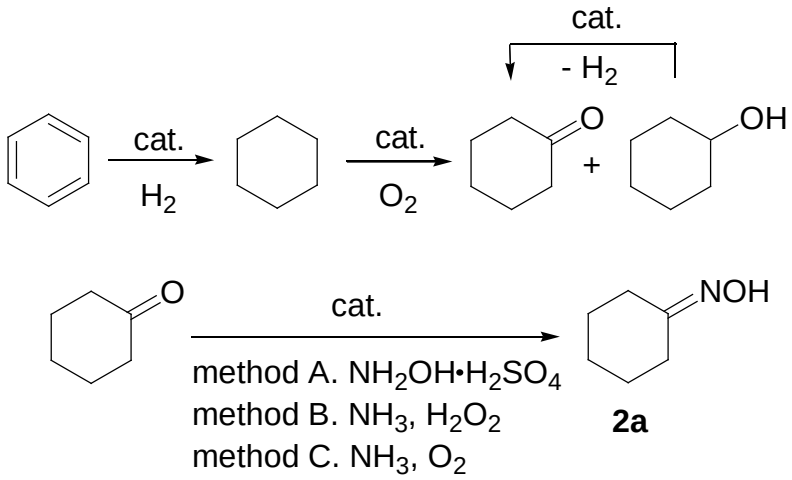
| cycle | conversion of amine **1a** (%)[b] | yield of oxime **2a** (%)[b] |
|---|---|---|
| 1 | 98 | 90 |
| 2 | 97 | 91 |
| 3 | 99 | 90 |

[a]Reaction conditions: **1a** (5 mmol), DPPH (5 mol%), $WO_3/Al_2O_3$ (W: 1 mol%) in acetonitrile (3 mL) under $O_2$ ($O_2/N_2$=7/93 v/v, 5 MPa) at 80 °C for 8 h. [b] Determined by GC analysis using an internal standard.

### 2.2.3 Evaluation of the Production of Cyclohexanone Oxime.

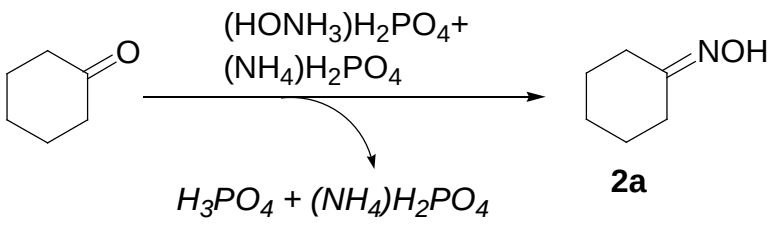
Oximes are usually synthesized by condensation of aldehydes or ketones with hydroxylamine, which is toxic and thermally unstable. Cyclohexanone oxime is an intermediate for the industrial production of ε-caprolactam, a precursor to Nylon 6. In the traditional route the Beckmann rearrangement of cyclohexanone oxime to ε-caprolactam is performed in the presence of fumic sulfuric acid (oleum). Once the ε-caprolactam salt of sulfuric acid is formed, $NH_3$ is supplied to neutralize the mixture, thus producing ε-caprolactam and ammonium sulfate. To overcome the above-mentioned problems, solid acid catalysts such as zeolite have been developed for vapor-phase Beckmann rearrangement of cyclohexanone oxime. The classic industrial route for cyclohexanone oxime is oximation of cyclohexanone with hydroxylamine sulfate, the sulfuric acid liberated being neutralized by ammonia, with coproduction of large amounts of ammonium sulfate[25] (method A; Raschig process) as shown in Scheme 2.

**Scheme 2.** Conventional route to cyclohexanone oxime **2a** from benzene



In order to reduce the formation of ammonium salts several modifications to the Raschig process have been introduced. Among them the better results were obtained by substituting $H_2$ for $SO_2$ as a reducing agent, as in the new process of DSM/Stamicarbon HPO process and BASF HSO process, as shown in Schemes 3 and 4, respectively. [25c] The HPO process involves oxidizing ammonia to obtain nitric acid ion, subjecting the obtained nitric acid ion to reduction with hydrogen in the presence of palladium as a catalyst using a phosphoric acid/monoammonium phosphate buffer solution to produce a phosphoric acid salt of hydroxylamine, and reacting the produced phosphoric acid salt of hydroxylamine with cyclohexanone. Also, the HSO process involves oxidizing ammonia in the presence of a platinum-containing catalyst to obtain NO, subjecting the obtained NO to reduction with hydrogen in the presence of a platinum-containing catalyst using an ammonium hydrogensulfate/ammonium sulfate buffer solution to produce hydroxylammonium sulfate, and reacting the produced hydroxylammonium sulfate with cyclohexanone which is advantageous in that the pH value is maintained at a certain level because the buffer solution is allowed to circulate between the cyclohexanone oxime production system and the hydroxylamine salt production system, so that by-production of ammonium sulfate can be prevented. However, the process has the following disadvantages, 1) High purity raw materials are needed; 2) the step of recovering the catalyst and the step of recycling the buffer solution are complicated; 3) the ammonia-based selectivity for the hydroxylamine salt is as low as about 60%.

**Scheme 3.** DSM/Stamicarbon HPO process

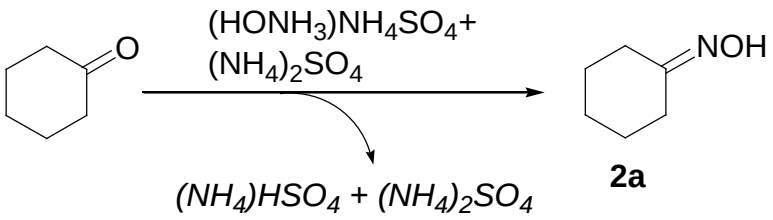



recycle:

$HNO_3 + 3H_2 + H_3PO_4 + (NH_4)H_2PO_4$

$\longrightarrow (HONH_3)H_2PO_4+(NH_4)H_2PO_4 + 2H_2O$

**Scheme 4.** BASF HSO process




recycle:

$4NH_3 + 5O_2 \longrightarrow 4NO + 6H_2O$

$2(NH_4)HSO_4 + 2(NH_4)_2SO_4 + 2NO + 3H_2$

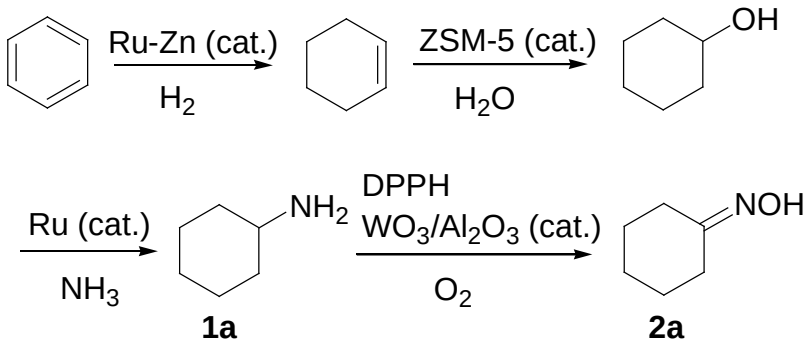
$\longrightarrow 2(HONH_3)NH_4SO_4 + 2(NH_4)_2SO_4$

Various other methods for the synthesis of cyclohexanone oxime from cyclohexanone have been developed. Ammoximation of cyclohexanone with ammonia and hydrogen peroxide catalyzed by titanium silicate-1 (TS-1) (Scheme 1: method B; EniChem process)[26a] and ammoximation with ammonia and molecular oxygen using $SiO_2$-$Al_2O_3$ and $Co^{II}Co^{III}$AlPO-36 (Scheme 1: method C)[26b,c] were explored. Method B is advantageous not only in that a difficult reagent (e.g., a hydroxylamine salt) which can be obtained only by a method involving complicated steps is not needed, but also in that ammonium sulfate is not by-produced. However, the method has a problem that hydrogen peroxide, which is expensive, is needed. The method C gives the corresponding oximes in low yield and with low selectivity.

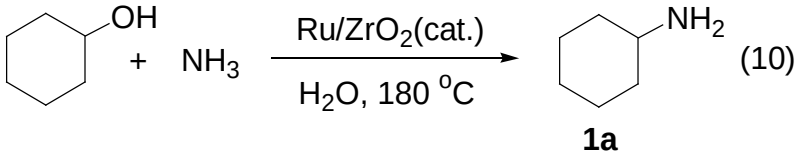
These methods require cyclohexanone, which is supplied by aerobic oxidation of cyclohexane, giving a mixture of cyclohexanone and cyclohexanol (K/A oil) with 70–80% selectivity and very low conversion (3–6%), which generated large amounts of organic acids as byproducts, requiring facilities for incineration of the waste liquid and treatment of the waste gas.[27]

The present method for aerobic catalytic oxidative transformation of cyclohexylamine to cyclohexanone oxime is compatible with the methods mentioned above by combining the following simple catalytic reactions starting from benzene, as shown in Scheme 5.

**Scheme 5.** Proposal route to cyclohexanone oxime **2a** from benzene




Thus, cyclohexylamine can be obtained by ruthenium-catalyzed amination of cyclohexanol in high selectivity.[28] We examined the amination of cyclohexanol using various supported ruthenium catalyst. The $Ru/ZrO_2$ catalyst was found to give an excellent result (eq 10). Thus, the reaction of cyclohexanol and $NH_3$ in the presence of 5wt% $Ru/ZrO_2$ in $H_2O$ at 180 ˚C under nitrogen (5 MPa) for 2 h gave cyclohexylamine with 99% selectivity and 89% conversion. The $Ru/ZrO_2$ catalyst can be reused without loss of catalytic activity or selectivity. The yield of cyclohexylamine was maintained at a similar value for at least ten rounds of recycling.



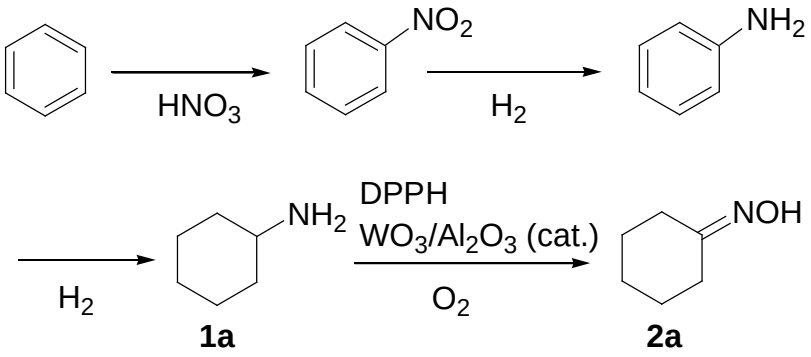

(10)

Cyclohexanol is produced by partial hydrogenation of benzene to cyclohexene over a ruthenium–zinc catalyst,[29] followed by hydration of cyclohexene in the presence of a high-silica zeolite catalyst (ZSM-5).[30] The conversion of benzene is at least 50%, and the selectivity of the

cyclohexene is at least 80%. The only remaining product is cyclohexane. Synthesis of cyclohexanol using hydration reaction is a simple process, with a conversion per pass between 10% and 15%, selectivity of at least 99% and almost no side-reaction products. The yield of carbon in which cyclohexane that can be utilized effectively was added is nearly 100%, the theoretical consumption of $H_2$ is reduced by one-third, and the amount of waste that requires treatment has been reduced to one-tenth that of the conventional process. This process has been applied industrially by Asahi Kasei Chemicals in 1990.[29,30]

These combined processes, that is, partial hydrogenation of benzene, hydration of cyclohexene, amination of cyclohexanol, and aerobic oxidation of cyclohexylamine, would be a useful method for the production of cyclohexanone oxime, a precursor of ε-caprolactam. Production of cyclohexanone oxime can be performed with high selectivity, using a simple apparatus, by a simple operation with less consumption of hydrogen, and with no need for use of a difficult reagent, such as a hydroxylamine salt. The method of the present invention is commercially very advantageous. DPPH-catalyzed aerobic oxidation of cyclohexylamine (obtained from aniline) can be also an attractive alternative route, as shown scheme 6. It is noteworthy that recently attractive approaches to **2a** have been explored, including NHPI-catalyzed nitrosation of cyclohexane with *tert*-butyl nitrite followed by treatment with triethylamine[31a] and chemoselective hydrogenation of 1-nitro-1-cyclohexene.[31b]

**Scheme 6.** Proposal route to cyclohexanone oxime **2a** from benzene via aniline



### 2.2.4 Mechanistic Aspects of the DPPH-$WO_3/Al_2O_3$ Catalyzed Aerobic Oxidation of Primary Amines

We investigated the effect of variables on kinetic factors for the DPPH–$WO_3/Al_2O_3$-catalyzed aerobic oxidation of cyclohexylamine. The effect of the DPPH and $WO_3/Al_2O_3$ concentrations on catalytic performance was examined. As shown in Figure 3a, a linear increase was observed with respect to the DPPH concentration in the range of 1–7.5 mol%. On the other hand, with respect to the effect of the $WO_3/Al_2O_3$ concentration, no significant increase in rate was observed above a W concentration of 0.5 mol% (Figure 3b). A kinetics study showed a first-order relationship for the amount of DPPH catalyst and a zero-order dependence of the reaction rate on the amount of $WO_3/Al_2O_3$ catalyst (W; 0.5–2 mol%).

The effect of reaction temperature in the range 60–110 °C on catalytic performance was investigated. A temperature of 80 °C was found to be optimal for the DPPH–$WO_3/Al_2O_3$-catalyzed aerobic oxidation of **1a**. Lower temperatures afforded a decrease in activity, and higher temperatures resulted in low selectivity. The conversion of **1a** increased exponentially with temperature, while the selectivity of the oxime **2a** decreased (Figure 4). The dependence of the initial rate of oxidation on temperature determined the activation energy of the reaction. The initial rate for the DPPH–$WO_3/Al_2O_3$-catalyzed aerobic oxidation of **1a** vs. the reaction temperature can be readily fitted to the familiar expression $k = A \exp(-E_a/RT)$ to give an activation energy ($E_a$) of 69.8 kJ/mol (Figure 5).

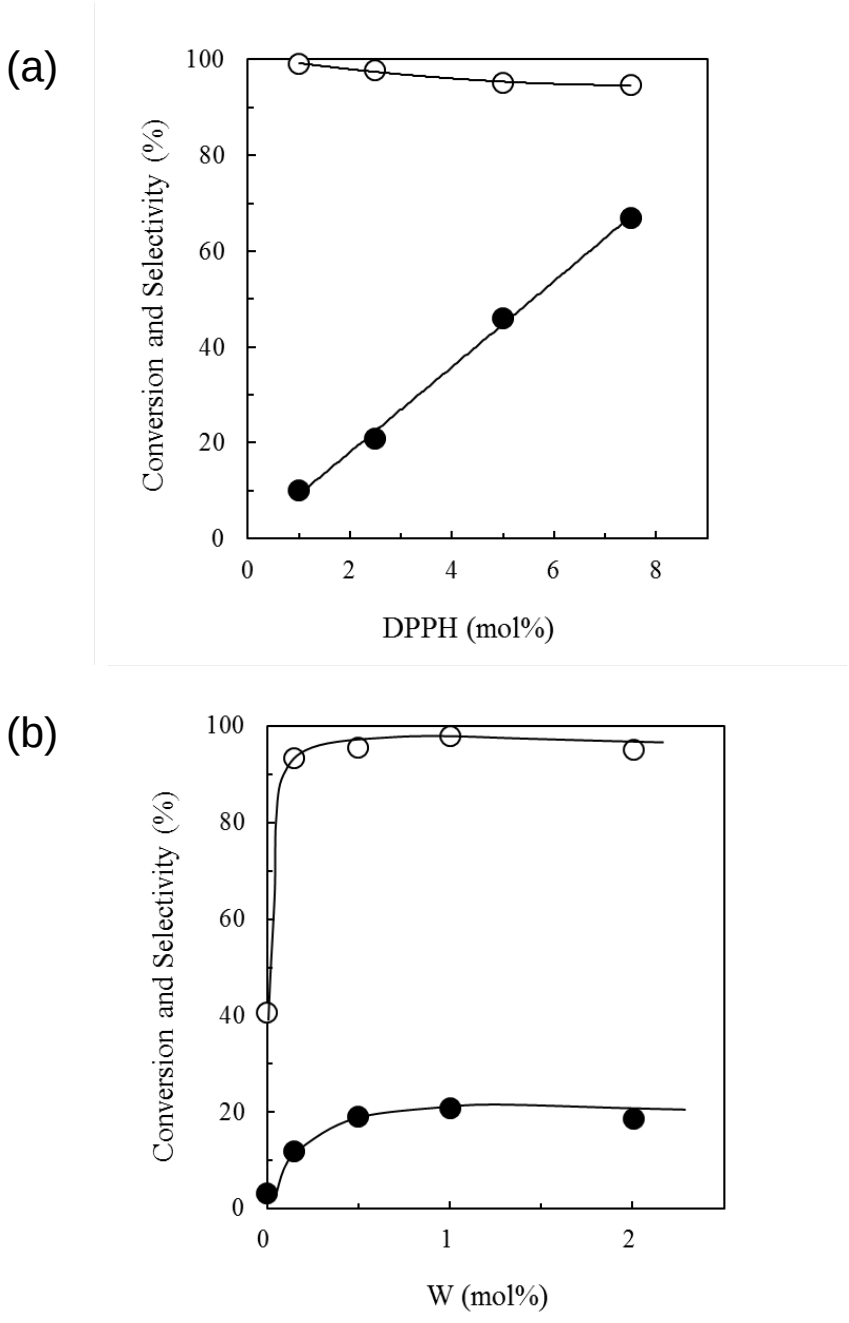



**Figure 3.** Effect of DPPH and $WO_3/Al_2O_3$ concentrations on the DPPH–$WO_3/Al_2O_3$-catalyzed aerobic oxidation of cyclohexylamine **1a** to cyclohexanone oxime **2a:** (a) different concentration of DPPH with $WO_3/Al_2O_3$ (W: 1 mol%); (b) different concentration of $WO_3/Al_2O_3$(W) with DPPH (2.5 mol%). Symbols: (●) **1a** conversion, (○) **2a** selectivity. Conditions: **1a** (5 mmol), DPPH (1–7.5 mol%), $WO_3/Al_2O_3$ (W: 0–2 mol%) in acetonitrile (3 mL), $O_2$ ($O_2/N_2$ = 7/93 v/v, 5 MPa) at 80 °C for 2 h.

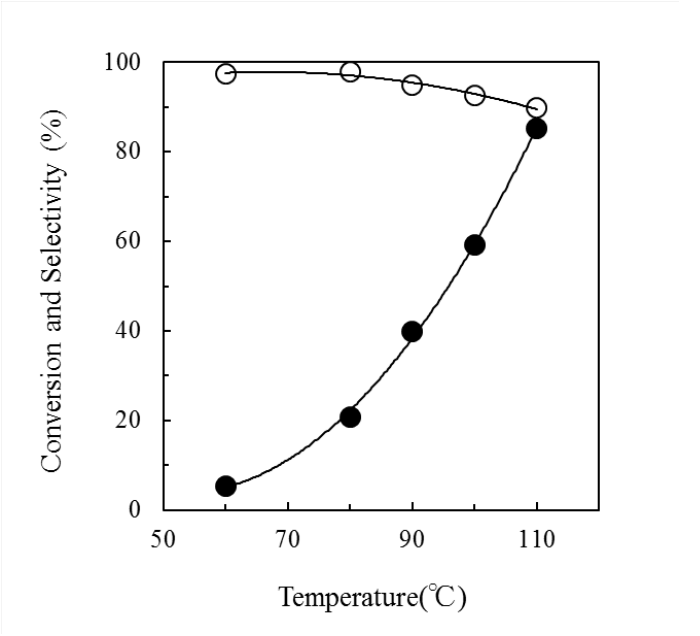



**Figure 4.** The effect of reaction temperature for the DPPH-$WO_3/Al_2O_3$-catalysed for aerobic oxidation of cylohexylamine **1a** to cyclohexanone oxime **2a**. Symbols: (●) **1a** conversion, (○) **2a** selectivity. Conditions: **1a** (5 mmol), DPPH (2.5 mol%), $WO_3/Al_2O_3$ (W: 1 mol%) in acetonitrile (3 mL), $O_2$ ($O_2/N_2$=7/93 v/v, 5 MPa) at 60-110 °C for 2 h.

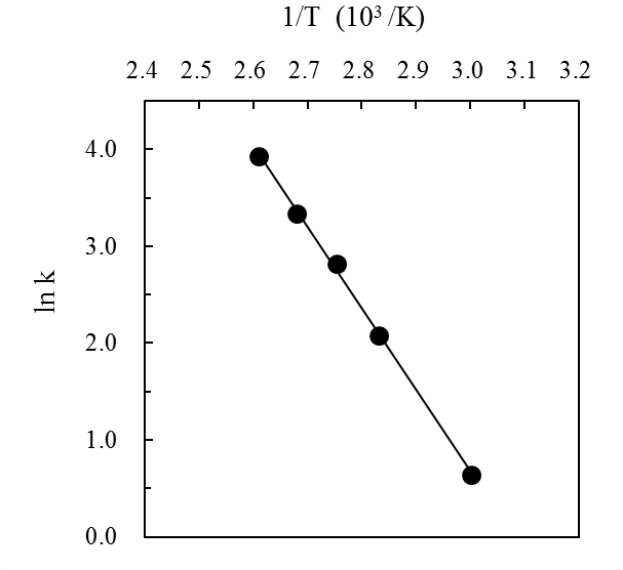



**Figure 5.** The correlation of initial rate and the temperature (60-110 °C) for the DPPH-$WO_3/Al_2O_3$ -catalyzed aerobic oxidation of cyclohexylamine **1a**.

The time course plotted for the aerobic oxidation of **1a** over DPPH–$WO_3/Al_2O_3$ catalyst at 80 °C showed that the conversion increased linearly with time during the initial 3 h of the reaction, and then the rate became slower. The initial conversion rate at 80 °C was calculated on the basis of the fraction after 1 h based on Figure 6 to be 12 g $h^{-1}$ (g of DPPH)$^{-1}$.

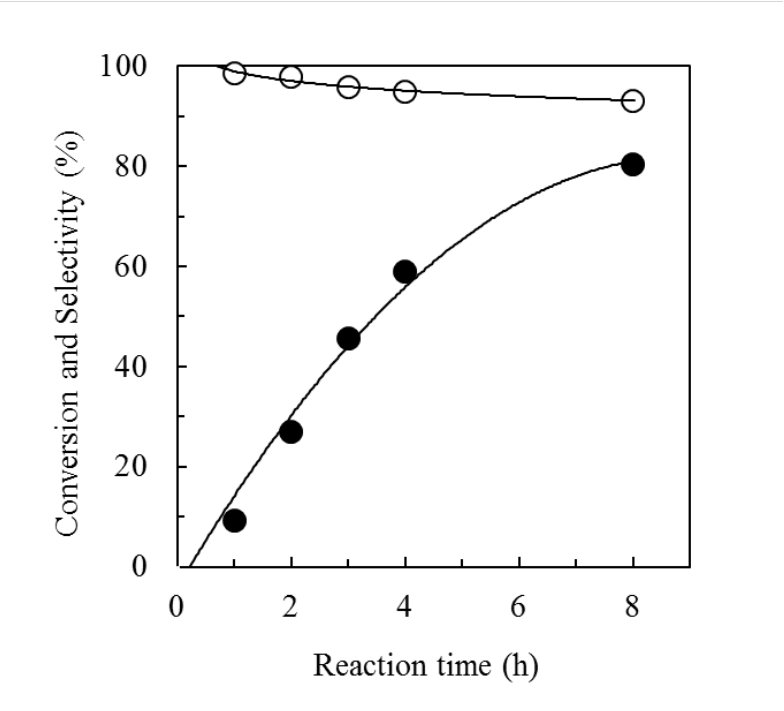



**Figure 6.** Time course for aerobic oxidation of cylohexylamine **1a** to cyclohexanone oxime **2a** over the DPPH-$WO_3/Al_2O_3$ catalyst. Symbols: (●) **1a** conversion, (○) **2a** selectivity. Conditions: **1a** (5 mmol), DPPH (2.5 mol%), $WO_3/Al_2O_3$ (W: 1 mol%) in acetonitrile (3 mL), $O_2$ ($O_2/N_2$=7/93 v/v, 5 MPa) at 80 °C.

The influence of oxygen pressure on catalytic performance for the aerobic oxidation of **1a** with the use of the DPPH–$WO_3/Al_2O_3$ catalyst at 80 °C was investigated using the $O_2/N_2$ (7/93 v/v) gas mixture between 3 and 10 MPa. The catalytic activity increased considerably upon going from low to high pressure, while the selectivity of **2a** decreased. The best results were obtained under 5 MPa of $O_2/N_2$ (7/93 v/v) (Figure 7).

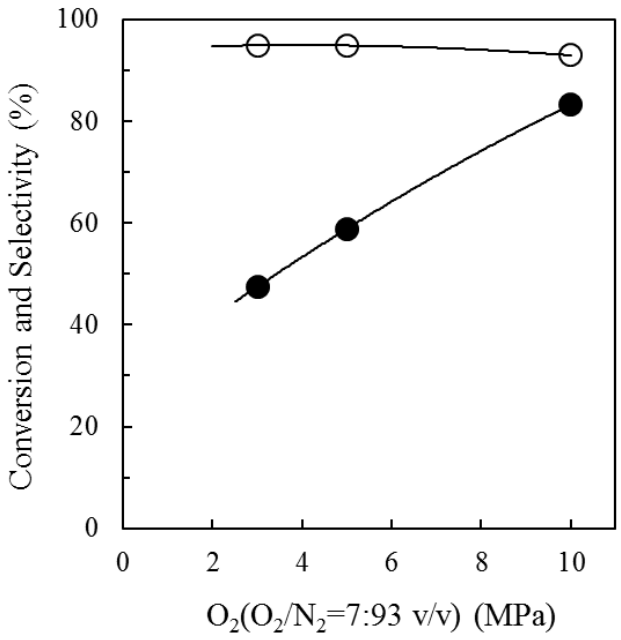
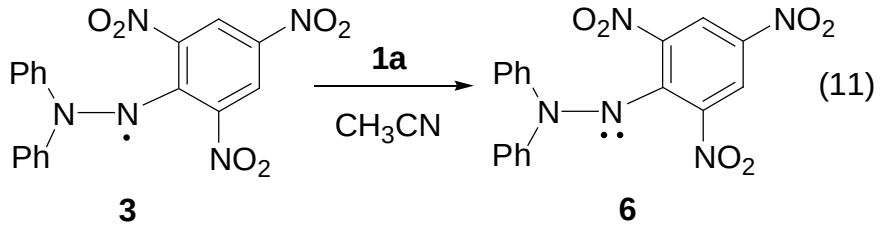



**Figure 7.** Effect of oxygen pressure on catalytic performance for aerobic oxidation of cylohexylamine **1a** to cyclohexanone oxime **2a** over DPPH-$WO_3/Al_2O_3$ catalyst. Symbols: (●) **1a** conversion, (○) **2a** selectivity. Conditions: **1a** (5 mmol), DPPH (2.5 mol%), $WO_3/Al_2O_3$ (W: 1 mol%) in acetonitrile (3 mL), $O_2$ ($O_2/N_2$=7/93 v/v, 3-10 MPa) at 80 °C for 4 h.

Next, we investigated the stoichiometric reaction of DPPH **3** with amine **1a** (eq 11). The electron transfers from **1a** to DPPH proceeded in an instant to give the DPPH anion (**6**). A solution of **3** in acetonitrile was allowed to react with an equimolar of **1a** under nitrogen at 25 °C; the color of the reaction mixture changed immediately from purple to brown, and the UV-vis absorption at 520 nm characteristic of **3** was not observed (Figure 8). Amine **1a** was converted to a mixture of unidentified high-boiling products.




**3** **6** (11)

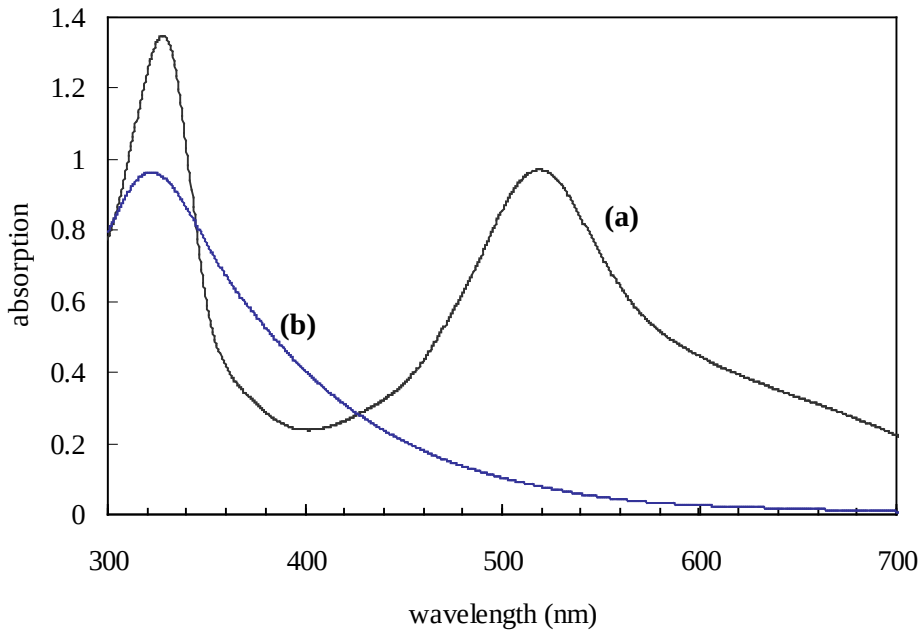
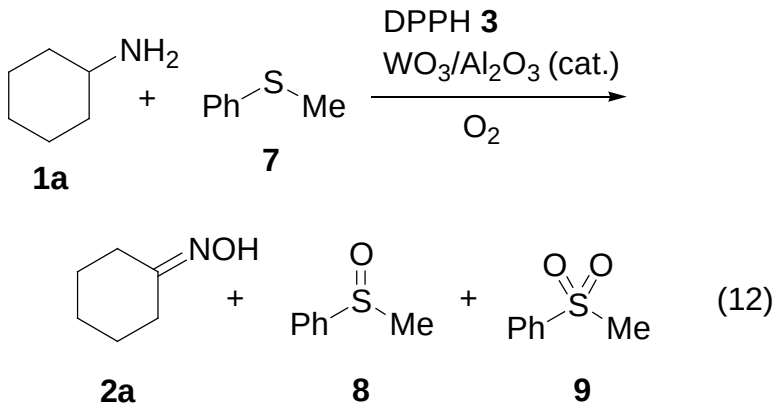



**Figure 8.** The UV-vis spectra. (a) DPPH in acetonitrile; (b) Reaction mixture of DPPH and cyclohexylamine **1a** in acetonitrile.

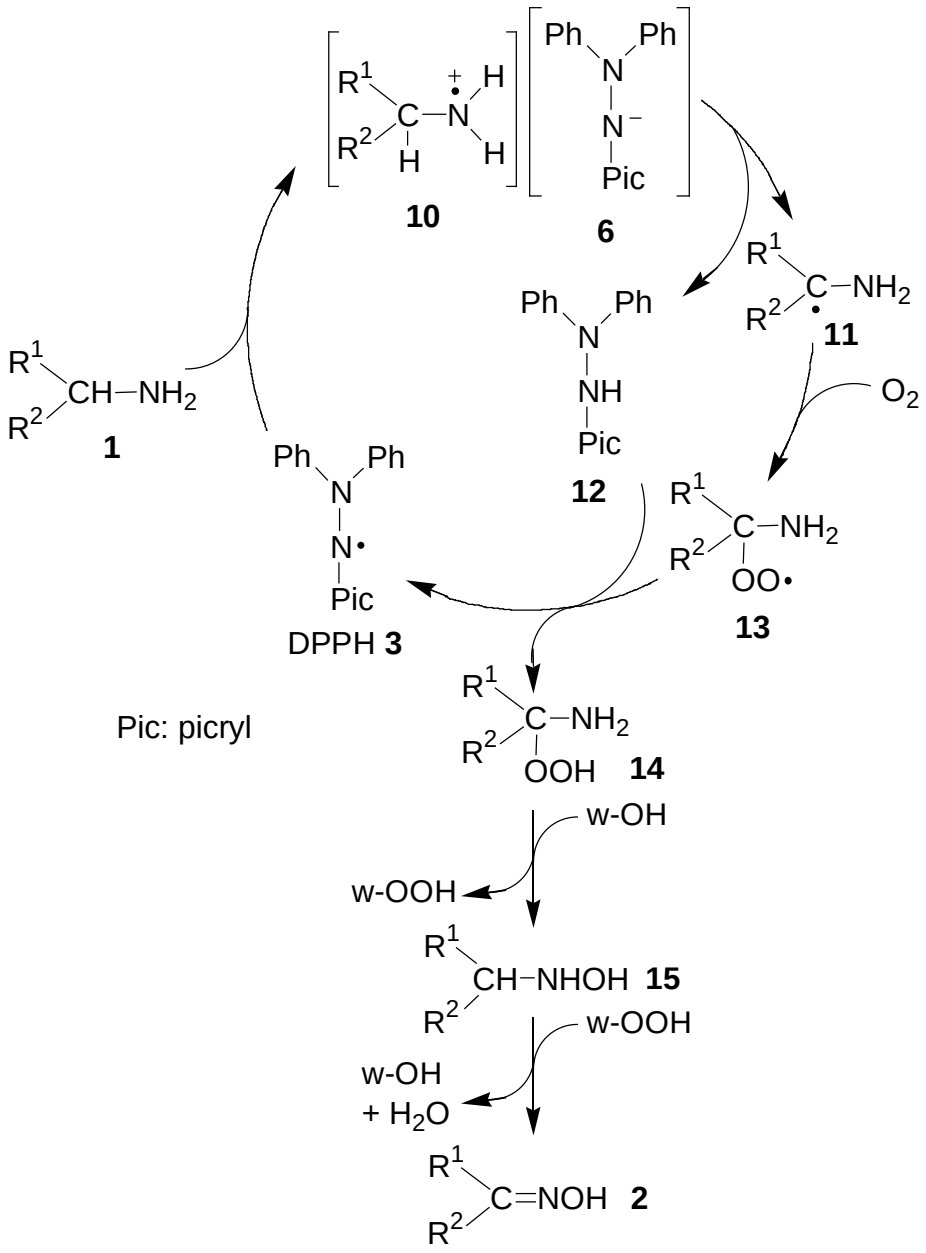
A Competitive reaction of primary amines and sulfides was performed with the aim of preserving the reactive oxygen species generated by the DPPH–$WO_3/Al_2O_3$ catalyst system (eq 12). The aerobic oxidation of a mixture of amine **1a** and thioanisole (**7**) (1/1) in the presence of DPPH (5 mol%)–$WO_3/Al_2O_3$ catalyst in acetonitrile at 80 °C for 8 h gave the oxime **2a** (16% yield at 99% conversion of **1a**), sulfoxide (**8**) (40% yield at 58% conversion of **7**), and sulfone (**9**) (16% yield at 58% conversion of **7**), respectively. Control experiments showed that the oxidation product of **7** could not be detected in the absence of **1a**. Oxidation of sulfides can be achieved with peroxides such as hydrogen peroxide in the presence of various transition metals.[32] Oxygen transfer from peroxy metal species to a sulfur atom takes place to give sulfoxides and sulfones. Apparently, hydroperoxy or peroxo tungsten species, which are electrophilic oxygen species, are generated by the DPPH–$WO_3/Al_2O_3$ catalyst system.



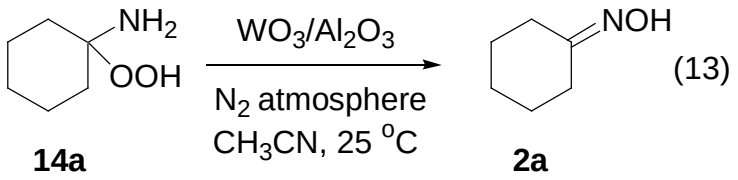

(12)

The reaction can be rationalized by assuming the mechanism shown in Scheme 7. Initially, fast electron transfer from primary amine **1** to **3** occurs to give a complex of an aminium cation radical (**10**) and DPPH anion (**6**).[33] Fast electron transfers from the amine to DPPH were observed by the UV-Vis spectral experiment. The aminium cation radical **10** thus formed undergoes deprotonation in the cage to give DPPH–H (**12**) and an α-aminoalkyl radical (**11**). The latter undergoes a reaction with molecular oxygen to afford an α-aminoalkylperoxy radical (**13**), which undergoes abstraction of hydrogen from DPPH–H (**12**) to give an α-aminoalkyl hydroperoxide (**14**) and regenerate **3** to complete the catalytic cycle. It is noteworthy that as shown in Table 1, aerobic oxidation of cyclohexylamine does not take place with usual radical initiators such as TEMPO and NHPI. The unique property of DPPH is probably the result of the ability of DPPH to promote a fast electron transfer to amines. It is unlikely that the radical **11** is formed by direct hydrogen abstraction of DPPH from the amine **1**. The reaction of alkyl hydroperoxide **14** with tungsten oxide/alumina ($WO_3/Al_2O_3$) gives hydroxylamine (**15**) and tungstate hydroperoxide w–OOH, where w may be $WO_3^-$, $WO_4^-$, or $WO_6^-$.[34] Further oxidation of **15** with w–OOH followed by dehydration would give **2** to complete the catalytic cycle.

**Scheme 7.** Proposed mechanism for DPPH–$WO_3/Al_2O_3$-catalyzed aerobic oxidation of primary amines **1** to oximes **2**.



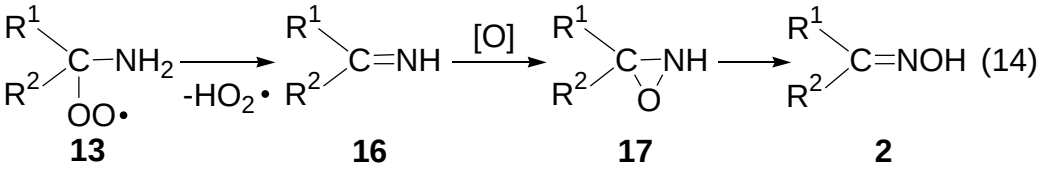
Indeed, when 1-hydroperoxycyclohexylamine (**14a**), which was prepared from cyclohexanone, ammonia, and hydrogen peroxide,[35] was allowed to react with the $WO_3/Al_2O_3$ catalyst at room temperature under nitrogen atmosphere, oxime **2a** was obtained in 75% yield (eq 13). It is noteworthy that the same reaction in the absence of the catalyst $WO_3/Al_2O_3$ gave cyclohexanone in 90% yield. It has been reported that **14a** undergoes decomposition to give **2a** in the presence of the catalyst $Na_2WO_4$ in EtOH.[35]




**14a** **2a** (13)

This one-step reaction is of considerable industrial interest, as it provides an alternative route to cyclohexanone oxime; therefore a mechanistic study has been conducted. Hermans reported an alternative pathway from α-aminoperoxyl radical **13** to oxime **2** on the basis of computational treatment through various quantum-chemical methods.[36] As shown in eq 14, elimination of HOO· radical from **13** would give imine **16** and subsequent oxidation of **16** gives oxazirane **17**, which undergoes rearrangement to give oxime **2**. It is very difficult to distinguish these two pathways after the formation of **13**; however, the pathway shown in Scheme 7 seems to be reasonable. The present aerobic oxidation is unique to DPPH, and no reaction takes place with the usual radical initiators such as TEMPO and NHPI, indicating that the direct α-CH hydrogen abstraction from primary amines to give α-aminoalkyl readical **11** seems unlikely. In the presence of $WO_3/Al_2O_3$ alone and without DPPH, no oxime was formed. It was claimed that HOO· elimination from **13** proceeds more quickly than hydrogen abstraction from amines; however, in the present catalytic system hydrogen abstraction from DPPH–H (**12**) would proceed more quickly in comparison with the hydrogen abstraction from the starting amine. The oxidation of unstable intermediate imine **16** with HOO· species to give oxazirane **17** would be difficult. Even if oxazirane **17** is formed from imine **16** under the reaction conditions, highly

selective formation of oxime **2** (90% yield) from **17** would be very difficult, because there has been no report on the selective rearrangement of **17** to **2**. Furthermore, neither the amination product of **17** with the starting amine nor amides derived from rearrangement of **17** could be detected among the products. Oxazirane **17** is a very active amination reagent[37] and also undergoes rearrangement to amides.[38]




## 2.3 Conclusion

Efficient and selective aerobic oxidative transformation of primary amines to oximes proceeds with high efficiency under mild conditions in the presence of the catalyst 1,1-diphenyl-2-picrylhydrazyl (DPPH) and the cocatalyst tungsten oxide/alumina ($WO_3/Al_2O_3$). Various alicyclic and aliphatic amines can be converted to their corresponding oximes in excellent yields. The aerobic oxidation of secondary amines gives the corresponding nitrones. In the DPPH–$WO_3/Al_2O_3$ system, DPPH acts as an electron transfer mediator, and an alkylhydroperoxide intermediate is transformed into an oxime by the $WO_3/Al_2O_3$ cocatalyst. This strategy provides an efficient and environmentally benign method for the synthesis of oximes. The principle of aerobic oxidation using DPPH will be particularly important for exploring further aerobic catalytic oxidations.

## 2.4 Experimental Section

**General Methods.** All the amines (**1a-l**) were commercially available and were used without further purification. 1,1-Diphenyl-2-picrylhydrazyl (DPPH), 1,1-diphenyl-2-picrylhydrazine (DPPH-H), 1,1-bis(4-*tert*-octylphenyl)-2-picrylhydrazyl (DOPH), N-hydroxyphthalimide (NHPI), 2,2,6,6-tetramethyl piperidine-N-oxyl (TEMPO), and all other reagents were obtained from commercial suppliers. GC measurements were carried out with a Shimadzu GC-14B gas chromatograph (FID) equipped with a DB-1701 glass capillary column (0.25 mm x 30 m). GC-MS analyses were performed on a Hewlett Packard 6890 Plus-5973N mass spectrometer equipped with a DB-1701 glass capillary column (0.25 mm x 30 m). $^{1}H$, $^{13}C$ NMR-spectra were recorded on a JEOL α 400 ($^{1}H$, 400 MHz; $^{13}C$, 100 MHz). Chemical shifts were expressed in parts per million downfield from tetramethylsilane. HRMS analyses were performed on a time-of-flight mass spectrometer equipped with an ESI sours (Waters, Synapt G2). The known compounds **2a–2i**, and **5** were identified by comparison of the $^{1}H$ and $^{13}C$ NMR spectra with those of the authentic samples obtained from the commercially available compounds or the compound prepared according to the literature.

**Preparation of $WO_3/Al_2O_3$.** The $WO_3/Al_2O_3$ catalyst was prepared by sol-gel method. Aluminium *sec*-butoxide (10 g, 0.41 mol) was placed in a beaker, and then an aqueous solution of $(NH_4)_{10}W_{12}O_{41}\cdot 5H_2O$ (100 mL, 2.2 x $10^{-2}$ M) was added with vigorous stirring. The resultant gel-like material was dried in vacuo at 110 ˚C for overnight and then calcined at 400 ˚C for 4 h to afford $WO_3/Al_2O_3$ as a white powder. The content of tungsten was determined to be 21.8 wt% by X-ray fluorescence (XRF) analysis (Rigaku RIX-3000), and the surface area was determined to be 360 $m^2g^{-1}$ by BET method (Quantachrome Instruments AUTOSORB 1-AG).

**General Procedure for the Catalytic Oxidation of Primary Amines to Oximes with Molecular Oxygen.** A stainless steel autoclave (120 mL) equipped with a magnetic stirring bar was charged with a mixture of DPPH (**3**) (98.6 mg, 0.25 mmol), $WO_3/Al_2O_3$[19] (42 mg, W: 0.05 mmol), amine (5 mmol), and tetradecane (internal standard for GC analysis, 0.25 mmol) in

acetonitrile (3 mL). The autoclave was pressurized to 5 MPa with an oxygen-nitrogen mixture (7/93 v/v), and the mixture was stirred (600 rpm) at 80 ˚C for 8 h. The reaction mixture was subjected to GC-analysis using tetradecane as an internal standard. The products were also isolated and purified by columm chromatography on silica gel with EtOAc and petroleum ether as eluent and identified by the usual methods, i.e., NMR, HRMS, etc.

**Cyclohexanone oxime (2a).** (Table 5, entries 1 and 2) White solid; $^{1}$H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.22 (1H, s), 2.51 (2H, t, J = 6.2 Hz), 2.21 (2H, t, J = 6.2 Hz), 1.63–1.62 (6H, m); $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm) 160.6, 32.1, 26.8, 25.8, 25.5, 24.4; HRMS (ESI) calcd for $C_6H_{11}NO$ $[M + H]^+$ 114.0919, found 114.0922. Mp 89–90 ˚C.

**Cyclopentanone oxime (2b).** (Table 5, entry 3) White solid; $^{1}$H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.36 (1H, s), 2.46 (2H, t, J = 7.0 Hz), 2.37 (2H, t, J = 6.8 Hz), 1.84–1.73 (4H, m); $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.3, 30.8, 27.1, 25.1, 24.5; HRMS (ESI) calcd for $C_5H_9NO$ $[M + H]^+$ 100.0762, found 100.0757. Mp 56–57 ˚C.

**Cycloheptanone oxime (2c).** (Table 5, entry 4) Colorless oil; $^{1}$H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.38 (1H, s), 2.58 (2H, t, J = 6.0 Hz), 2.38 (2H, t, J = 5.7 Hz), 1.71–1.56 (8H, m); $^{13}$C NMR ($CDCl_3$) δ (ppm) 164.3, 33.7, 30.4, 30.3, 28.5, 27.5, 24.5; HRMS (ESI) calcd for $C_7H_{13}NO$ $[M + H]^+$ 128.1075, found 128.1069.

**Cyclooctanone oxime (2d).** (Table 5, entry 5) White solid; $^{1}$H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.23 (1H, s), 2.45 (2H, t, J = 6.3 Hz), 2.29 (2H, t, J = 6.6 Hz), 1.81–1.71 (4H, m), 1.54–1.50 (6H, m); $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm) 164.0, 33.1, 27.2, 26.8, 26.6, 25.3, 24.6, 24.4; HRMS (ESI) calcd for $C_8H_{15}NO$ $[M + H]^+$ 142.1232, found 142.1226. Mp 40–42 ˚C.

**2-Adamantanone oxime (2e).** (Table 5, entry 6) White solid; $^{1}$H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.94 (1H, s), 3.58 (1H, s), 2.56 (1H, s), 2.00–1.82 (12H, m); $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.7, 38.8, 37.4, 36.5, 36.2, 28.7, 27.8; HRMS (ESI) calcd for $C_{10}H_{15}NO$ $[M + H]^+$ 166.1232, found 166.1224 . Mp 165–166 ˚C.

**Indan-1-one oxime (2f).** (Table 5, entry 7) White solid; $^{1}$H NMR (400 MHz, DMSO-$D_6$) δ (ppm) 10.83 (1H, s), 7.55 (1H, d, J = 7.8 Hz), 7.34 (2H, dd, J = 12.0, 4.3 Hz), 7.25 (1H, t, J =

7.2 Hz), 2.99 (2H, t, J = 6.7 Hz), 2.80–2.76 (2H, m); $^{13}$C NMR (100 MHz, DMSO-$D_6$) δ (ppm) 160.9, 147.6, 136.5, 129.6, 126.7, 125.6, 120.5, 27.8, 25.5; HRMS (ESI) calcd for $C_9H_9NO$ $[M + H]^+$ 148.0762, found 148.0772. Mp 145–146 ˚C.

**Tetralone-1-oxime (2g).** (Table 5, entry 8) White solid; $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.41 (1H, s), 7.89 (1H, d, J = 4.5 Hz), 7.29–7.25 (1H, m), 7.22–7.14 (2H, m), 2.83 (2H, t, J = 6.7 Hz), 2.77 (2H, t, J = 6.1 Hz), 1.92–1.85 (2H, m); $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.3, 139.8, 130.4, 129.2, 128.63, 126.5, 124.0, 29.8, 23.9, 21.3; HRMS (ESI) calcd for $C_{10}H_{11}NO$ $[M + H]^+$ 162.0919, found 162.0915. Mp 101–103 ˚C.

**4-Methylcyclohexanone oxime (2h).** (Table 5, entry 9) Yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.20 (1H, s), 3.29–3.22 (1H, m), 2.38 (1H, d, J = 12.9 Hz), 2.10 (1H, dt, J = 19.7, 6.8 Hz), 1.89–1.75 (3H, m), 1.70–1.58 (1H, m), 1.22–1.06 (2H, m), 0.95 (3H, d, J = 6.6 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm) 160.4, 34.8, 33.6, 31.9, 31.4, 23.7, 21.5; HRMS (ESI) calcd for $C_7H_{13}NO$ $[M + H]^+$ 128.1075, found 128.1071.

**4-*tert*-Butyl-cyclohexanone oxime (2i).** (Table 5, entry 10) White solid; $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.83 (1H, s), 3.36 (1H, d, J = 16.3 Hz), 2.43 (1H, dd, J = 13.8, 2.3 Hz), 2.06 (1H, td, J = 12.2, 3.9 Hz), 1.95–1.91 (2H, m), 1.69 (1H, td, J = 13.7, 5.0 Hz), 1.26–1.16 (3H, m), 0.87 (9H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm) 160.8, 47.5, 32.4, 31.9, 27.5, 26.3, 24.3; HRMS (ESI) calcd for $C_{10}H_{19}NO$ $[M + H]^+$ 170.1545, found 170.1535. Mp 135–136 ˚C.

**4-Hydroxy-cyclohexanone oxime (2j).** (Table 5, entry 11) White solid; $^1$H NMR (400 MHz, $CD_3OD$) δ (ppm) 4.86 (2H, s), 3.89–3.85 (1H, m), 2.94–2.88 (1H, m), 2.42–2.36 (1H, m), 2.25–2.10 (2H, m), 1.93–1.88 (2H, m), 1.60–1.49 (2H, m); $^{13}$C NMR (100 MHz, $CD_3OD$) δ (ppm) 160.0, 68.8, 35.4, 34.0, 29.2, 21.5; HRMS (ESI) calcd for $C_6H_{11}NO_2$ $[M + H]^+$ 130.0868, found 130.0860. Mp 80–82 ˚C.

**Octanal oxime (2k).** (Table 5, entry 12) White solid; $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm)7.99 (1H, s), 6.71 (1H, t, J = 5.5 Hz), 2.37 (2H, td, J = 7.5, 5.4 Hz), 1.48 (2H, dd, J = 14.8, 7.2 Hz), 1.31–1.29 (8H, m), 0.88 (3H, t, J = 7.0 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm) 152.9,

31.7, 29.3, 28.9, 26.0, 25.0, 22.6, 14.0; HRMS (ESI) calcd for $C_8H_{17}NO$ $[M + H]^+$ 144.1388, found 144.1380. Mp 58–59 ˚C.

**5-Hydroxylpentanal oxime (2l).** (Table 5, entry 13) White solid; $^1H$ NMR (400 MHz, $CD_3OD$) δ (ppm) 6.65 (1H, t, J = 5.5 Hz), 4.85 (2H, s), 3.57 (2H, t, J = 6.2 Hz), 2.37 (2H, td, J = 7.3, 5.5 Hz), 1.58–1.55 (4H, m); $^{13}C$ NMR (100 MHz, $CD_3OD$) δ (ppm) 152.8, 62.5, 33.3, 25.6, 23.6; HRMS (ESI) calcd for $C_5H_{11}NO_2$ $[M + H]^+$ 118.0868, found 118.0862. Mp 85–86 ˚C.

**General Procedure for Oxidation of Primary Amines under Molecular Oxygen (1 atm balloon). Cyclohexanone Oxime.** To a 25 mL side-armed round-bottomed flask equipped with a magnetic stirring bar was a mixture of DPPH (98.6 mg, 0.25 mmol), $WO_3/Al_2O_3$ (42 mg, W: 0.05 mmol), cyclohexylamine (**1a**) (495 mg, 5 mmol), and tetradecane (internal standard, 50 mg, 0.25 mmol) in acetonitrile (3 mL) was charged. The reaction mixture was stirred under molecular oxygen (1 atm, balloon) at 80 ˚C for 16 h.

**Product Isolation.** Typically, a mixture of cyclohexylamine (**1a**) (0.99 g, 10 mmol), DPPH (197.2 mg, 0.5 mmol) and $WO_3/Al_2O_3$ (84 mg, W: 0.1 mmol) in acetonitrile (6 mL) was placed in a closed 316-L stainless steel autoclave (200 mL), and stirred (600 rpm) at 80 ˚C for 8 h under an oxygen-nitrogen mixture (5 MPa, 7/93; v/v). The reaction mixture was diluted with acetonitrile and dried over $MgSO_4$. The resulting mixture was filtered, and the solvent was removed in vacuo. Kugelrohr distillation of the crude product (100 ˚C, 30 mmHg) afforded cyclohexanone oxime (**2a**) as a white solid (0.96 g, 85% yield).

**Measurement of the Oxygen Uptake for the Aerobic Oxidation of Primary Amines.** A 25 mL side-armed round-bottomed flask equipped with a magnetic stirring bar and a ball condenser connected to a gas burette with a balloon filled with $O_2$ (1atm) was charged with a mixture of DPPH (98.6 mg, 0.25 mmol, 5 mol%), $WO_3/Al_2O_3$ (42 mg, W: 0.05 mmol, 1 mol%), cyclohexylamine (495 mg, 5 mmol) in acetonitrile (3 mL). The reaction mixture was stirred under molecular oxygen at 80ºC. The absorption of $O_2$ was monitored for 30 min. After 16 h, the absorption of $O_2$ was stopped, and 4.9 mmol of $O_2$ was consumed.

**General Procedure for the Catalytic Oxidation of Secondary Amines to Nitrones with Molecular Oxygen.** As a typical example, the aerobic oxidation of 1,2,3,4-tetrahydroisoquinoline (**4**) is described. A stainless steel autoclave (120 mL) equipped with a magnetic stirring bar was charged with a mixture of DPPH (**3**) (98.6 mg, 0.25 mmol), $WO_3/Al_2O_3$ (42 mg, W: 0.05 mmol), 1,2,3,4-tetrahydroisoquinoline (**4**) (666 mg, 5 mmol), and tetradecane (internal standard for GC analysis, 50 mg, 0.25 mmol) in acetonitrile (3 mL). The autoclave was pressurized to 5 MPa with an oxygen-nitrogen mixture (7/93 v/v), and the mixture was stirred (600 rpm) at 80 ˚C for 8 h. The reaction mixture was analyzed GC-analysis using tetradecane as an internal standard. 3,4-Dihydroisoquinoline *N*-oxide (**5**) was obatined with 61% selectivity at 28% conversion.

**3,4-Dihydroisoquinoline *N*-Oxide (5).**[13a] White solid; $^1$H-NMR (500 MHz, $CDCl_3$) δ (ppm) 3.20 (2H, t, J =7.78 Hz), 4.12 (2H, dt, J =0.92 and 7.3 Hz), 7.12–7.15 (1H, m), 7.22–7.23 (1H, m), 7.28–7.30 (2H, m), 7.77 (1H, s); $^{13}$C-NMR (126 MHz, CDCh) δ (ppm) 27.7, 57.9, 125.4, 127.2, 127.6, 128.3, 129.4, 130.0, 134.1; MS (CI) m/z 148 (M+ $H^+$).

**Recycling of the Catalyst.** The first run was carried out under the same reaction conditions describes in the general procedure for aerobic oxidation under $O_2/N_2$(7/93, 5 MPa). After the reaction, the spent $WO_3/Al_2O_3$ could be easily separated from the reaction mixture by a filtration, and the isolated $WO_3/Al_2O_3$ was reused. Kugelrohr distillation (100 ˚C, 30 mmHg) gave the solvent and the product, and the residue of DPPH **3** was reused. These recycling procedures were repeated three times in the same manner as in the first run. The amount of tungsten in the leaching solution was estimated by analysis of an inductively coupled plasma (ICP) emission spectra (Rigaku JY138).

**Competitive Reaction of Cyclohexylamine and Thioanisole for the DPPH–$WO_3/Al_2O_3$-Catalyzed Aerobic Oxidation.** A mixture of DPPH (**3**) (98.6 mg, 0.25 mmol, 5 mol%), $WO_3/Al_2O_3$ (42 mg, W: 0.05 mmol, 1 mol%), cyclohexylamine (**1a**) (0.25 g, 2.5 mmol), thioanisole (**8**) (0.31 g, 2.5 mmol) and tetradecane (internal standard for GC analysis, 50 mg, 0.25 mmol) in acetonitrile (3 ml) was stirred under an oxygen-nitrogen mixture (7/93 v/v, 5 MPa) at

80 ˚C for 8 h. The reaction mixture was analyzed GC-analysis using tetradecane as an internal standard and the products were identified by GC-MS.

**Aerobic oxidation Reaction of α-Hydroperoxyclohexylamine with $WO_3/Al_2O_3$ Catalyst.** A mixture of $WO_3/Al_2O_3$ (42 mg, W: 0.05 mmol) and α-hydroperoxy cyclohexylamine (**15a**) (0.66 g, 5 mmol), which was prepared from cyclohexanone, $NH_3$, and $H_2O_2$ according to the literature procedure in acetonitrile (10 mL) was stirred for 3 h at room temperature. The reaction mixture was analysed by GC-analysis and iodimetry titration. The products were identified by GC-MS.

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# Chapter 3. Copper-Catalyzed Aerobic Oxidative Functionalization of C-H Bonds of Alkanes in the presence of Acetaldehyde under Mild Conditions



## 3.1 Introduction

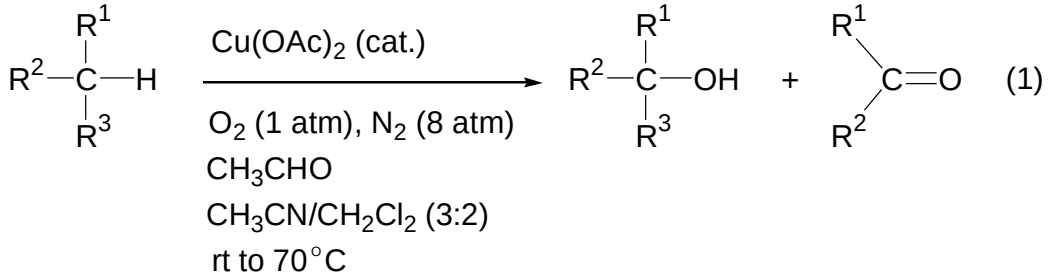
The catalytic oxidative functionalization of C–H bonds of alkanes is of importance in synthetic, industrial, and biological aspects.[1,2] Development of a new method for selective and efficient aerobic oxidation of alkanes under mild conditions is an important goal.[3] During the course of simulation of the function of cytochrome P-450, we found that ruthenium-catalyzed oxidation of various substrates can be performed highly efficiently.[4] Ruthenium[5a] and other transition metal[5b]-catalyzed oxidative functionalization of C–H bonds of alkanes with *tert*-butylhydroperoxide[5] or peracetic acid[5a] proceeds readily. Peracetic acid is a highly reactive reagent for catalytic oxidation[6] of alkanes and alkenes; however, its availability and stability is problem. Therefore we explored a method for generation of peracetic acid in situ from acetaldehyde and molecular oxygen and immediately used as an oxidizing reagent. Thus, ruthenium catalyzed aerobic C–H functionalization of β-lactams[7] and alkanes[8] has been

performed in the presence of acetaldehyde.

Copper is contained in metalloenzymes that plays an important role in biological dioxygen metabolism; however, the copper-catalyzed oxidative functionalization of C-H bonds of alkanes is limited to a few cases.[9,10] We wish to report that copper catalyzed aerobic oxidative C–H functionalization of hydrocarbons can be performed in the presence of acetaldehyde at 70 ˚C highly efficiently.

The catalytic activity of metal salts for the oxidation of cyclohexane with molecular oxygen (1 atm) in the presence of acetaldehyde has been examined. The representative results for the oxidation of cyclohexane with molecular oxygen (1atm) in the presence of acetaldehyde are summarized in Table 1. Iron powder[11] and chlorinated phthalocyanine iron (II) complex (**1**)[12] are effective catalysts. $RuCl_3$[11] and ruthenium porphyrine complex Ru(TPFPP)(CO) (**2**)[8] are also effective catalysts. Concerning copper catalysts, the combined use of a copper salt and an electron-donating ligand such as $Cu(OH)_2$[13] increases the catalytic activity remarkably. A combination of $CuCl_2$ with 18-crown-6 was found to be highly effective catalyst.[9a]

We looked for simpler and more efficient catalytic system for the oxidation of alkanes and found that the specific copper complex derived from copper acetate in acetonitrile is a convenient and highly useful catalyst for aerobic oxidative functionalization of non-activated hydrocarbons (eq 1).



(1)

## 3.2 Results and Discussion

### 3.2.1 Copper-Catalyzed Oxidative Transformation of Alkanes with Molecular Oxygen in the presence of Acetaldehyde.

A combination of $Cu(OAc)_2$ and acetonitrile gave a higher turnover number among copper salts examined. Copper(II) salts such as $CuCl_2$, $CuBr_2$, $Cu(OAc)_2$, and copper(I) salts such as CuOAc, CuCN, and $[Cu(CH_3CN)_4](PF_6)$ showed almost similar activity. It is noteworthy that even Cu(0) powder can be used similarly as a catalyst for the present oxidation in the presence of acetonitrile. Cu(0) powder was dissolved immediately to become a colorless solution, similar to the reaction using Cu(I) and Cu(II) salts. These results imply that all copper salts, Cu(II), Cu(I), and Cu(0), despite its valency, would be converted into the same colorless Cu(I) species like $[Cu(CH_3CN)_m(X)]$ (X=Cl, Br, OAc, etc.,) in acetonitrile under the reaction conditions.[14] Since Cu(II), Cu(I), and Cu(0) seem to be equally effective, we selected $Cu(OAc)_2$ as a precursor for a reactive species which is stable and can be handled easily.

When acetonitrile was used as a sole solvent, the reaction system becomes two phases, resulting in slower oxidation. For assistance of substrate solubility, the $CH_3CN/CH_2Cl_2$ (3:2) mixed solvent system is preferable for the oxidation reaction. Other nitriles such as *t*-BuCN and $C_6H_5CN$ are less effective. Pyridine can be also used instead of acetonitrile.

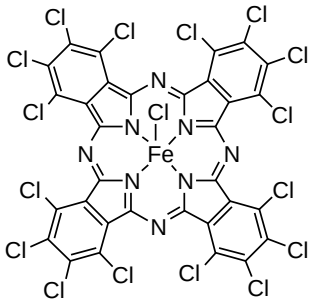
The reaction of cyclohexane with molecular oxygen (1 atm, balloon) at room temperature in the presence of $Cu(OAc)_2$ and acetaldehyde (1 equiv.) in $CH_3CN/CH_2Cl_2$ gave a mixture of cyclohexanol and cyclohexanone in 51% yield based on acetaldehyde with TON (turn over number of the catalyst) 207 (Table 1, entry 7). The method is convenient to laboratory organic synthesis. In industry pure oxygen cannot be allowed to use, and air diluted with molecular nitrogen is used. Therefore, we carried out the oxidation of cyclohexane at 70 ˚C under molecular oxygen (1 atm $O_2$ diluted of 8 atm $N_2$) outside flammability limits using autoclave at all times. This method is convenient for the large scale closed system and also for flow system. In the

oxidation of poorly reactive alkanes, we adopted alkane excess conditions, in which acetaldehyde was used up to 2.5 mol% based on each alkane to prevent any over-oxidation of the products.

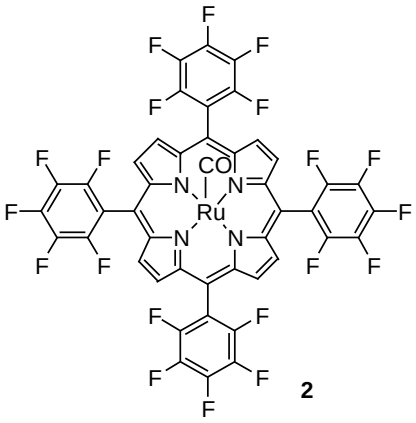
**Table 1.** Catalytic activity of metal complexes for oxidation of cyclohexane with molecular oxygen in the presence of acetaldehyde.[a]

| entry | catalyst | yield (%)[c] | | | TON[d] |
|---|---|---|---|---|---|
| | | alcohol | ketone | total | |
| 1[a] | Fe[e] | 2.6 | 2.9 | 5.5 | 22 |
| 2[a] | Fe(Pc-$Cl_{16}$) (**1**)[f] | 11 | 11 | 22 | 88 |
| 3[a] | $RuCl_3$•n$H_2O$[e] | 1.7 | 3.4 | 5.1 | 20 |
| 4[a] | Ru(TPFPP)(CO) (**2**)[g] | 2.1 | 6.5 | 8.6 | 35 |
| 5[a] | $Cu(OH)_2$[h] | 1.3 | 1.7 | 3.0 | 12 |
| 6[a] | $CuCl_2$/18-crown-6 (**3**)[i] | 7.9 | 7.5 | 15 | 62 |
| 7[b] | $Cu(OAc)_2$/acetonitrile | 22 | 29 | 51 | 207 |

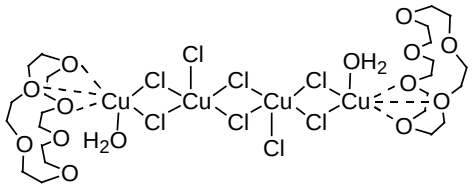
[a]Cyclohexane (40 mmol), catalyst (0.010 mmol), $CH_3CHO$ (4.0 mmol), $CH_3CN$ (5 mL), $CH_2Cl_2$ (4 mL), $O_2$ (1 atm), room temperature, 24 h. [b]Cyclohexane (40 mmol), $Cu(OAc)_2$ (0.0025 mmol), $CH_3CHO$ (1.0 mmol), $CH_3CN$ (3 mL), $CH_2Cl_2$ (2 mL), $O_2$ (1 atm), room temperature, 24 h. [c]Determined by GC analysis based on acetaldehyde. [d]Results are given in mole of products formed per mol of catalyst. [e]Ref 11. [f]Ref 12. [g]Ref 8. [h]Ref 13. [i]Ref 9a.




**1**



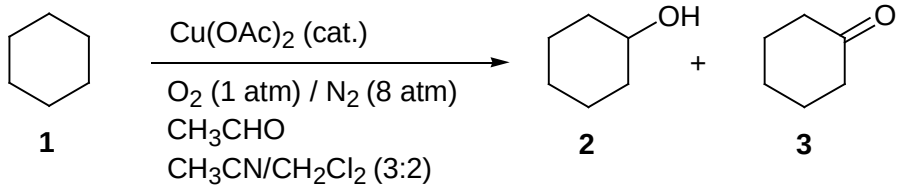

**2**




**3**

The results of the control experiments were shown in Table 2. The copper-catalyzed aerobic oxidation of cyclohexane at 70 ˚C gave cyclohexanol and cyclohexanone in 72% total yield based on acetaldehyde with TON of 25,000 (entry 1). The yield of acetic acid based on consumed acetaldehyde is 104%. When the oxidation was carried out at 40 ˚C, a similar result was obtained (entry 4). It is noteworthy that the oxidation took place without the copper catalyst (entries 3 and 6), although the total yields of cyclohexanol and cyclohexanone became lower. In the absence of acetaldehyde no oxidation takes place (entries 2 and 5).

**Table 2.** Control experiments for $Cu(OAc)_2$-catalyzed oxidation of cyclohexane with molecular oxygen in the presence of acetaldehyde.[a]

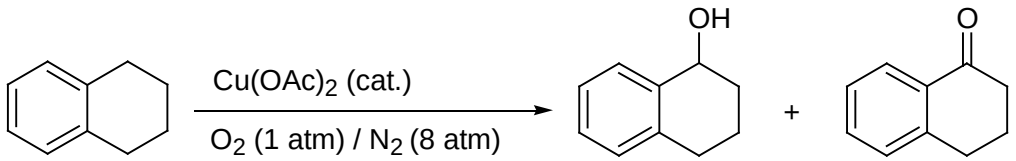



| entry | catalyst | aldehyde | temp. ($^oC$) | time (h) | 2+3 yield (%) based on aldehyde | 2+3 yield (%) based on alkane | TON[b] |
|---|---|---|---|---|---|---|---|
| 1 | $Cu(OAc)_2$ | $CH_3CHO$ | 70 | 10 | 72 | 1.6 | 25000 |
| 2 | $Cu(OAc)_2$ | - | 70 | 10 | - | 0 | 0 |
| 3 | - | $CH_3CHO$ | 70 | 10 | 34 | 0.8 | - |
| 4 | $Cu(OAc)_2$ | $CH_3CHO$ | 40 | 24 | 64 | 1.5 | 22000 |
| 5 | $Cu(OAc)_2$ | - | 40 | 24 | - | 0 | 0 |
| 6 | - | $CH_3CHO$ | 40 | 24 | 8 | 0.2 | - |

[a]Substrate (80 mmol), $Cu(OAc)_2$ (0.00005 mmol), $CH_3CHO$ (2 mmol), $CH_3CN$ (6 mL), $CH_2Cl_2$ (4 mL), $O_2/N_2$ (1 atm/8 atm), 70 ˚C. [b]Based on acetaldehyde. [c]Results are given in mole of products formed per mol of catalyst.

The oxidation of tetraline showed a different behavior. The reaction of tetraline in the presence of $Cu(OAc)_2$ and acetaldehyde at 40 ˚C and 70 ˚C gave the oxidation products with extremely high TON and reasonable yield based on acetaldehyde (Table 3, entries 1 and 4), respectively. It is noteworthy that the copper-catalyzed reaction took place in the absence of acetaldehyde at 70 ˚C (entry 2). The aerobic oxidation did not occur in the absence of $Cu(OAc)_2$ (entries 3 and 6). These results indicate that the copper-catalyzed autoxidation takes place for tetraline predominantly. The oxidative functionalization of benzylic C–H bonds seems to occur readily.

**Table 3.** Control experiments for $Cu(OAc)_2$-catalyzed oxidation of tetraline with molecular oxygen in the presence of acetaldehyde.[a]




**4** **5** **6**

| entry | catalyst | aldehyde | temp. (°C) | time (h) | 5+6 yield (%) based on aldehyde | 5+6 yield (%) based on alkane | TON[b] |
|---|---|---|---|---|---|---|---|
| 1 | $Cu(OAc)_2$ | $CH_3CHO$ | 70 | 5 | 78 | 1.8 | 28000 |
| 2 | $Cu(OAc)_2$ | - | 70 | 5 | - | 2.1 | 32000 |
| 3 | - | $CH_3CHO$ | 70 | 5 | 0 | 0 | - |
| 4 | $Cu(OAc)_2$ | $CH_3CHO$ | 40 | 5 | 97 | 2.4 | 39000 |
| 5 | $Cu(OAc)_2$ | - | 40 | 5 | - | 0 | 0 |
| 6 | - | $CH_3CHO$ | 40 | 5 | 0 | 0 | - |

[a]Substrate (80 mmol), $Cu(OAc)_2$ (0.00005 mmol), $CH_3CHO$ (2 mmol), $CH_3CN$ (6 mL), $CH_2Cl_2$ (4 mL), $O_2/N_2$ (1 atm/8 atm), 70 ˚C. [b]Based on acetaldehyde. [c]Results are given in mole of products formed per mol of catalyst.

Representative results for the copper-catalyzed oxidation of alkanes are summarized in Table 4. Cyclic alkanes such as cyclohexane, cyclooctane, and methylcyclohexane were oxidized efficiently to give the corresponding oxidation products in 72–96% yields with TON of > 25,000 (entries 1–4). The product distribution of the oxidation of methylcyclohexane showed that the relative reactivity of the C–H bonds is in the order of tertiary > secondary >> primary. Poorly reactive *n*-alkanes such as *n*-heptane and *n*-decane were also oxidized (entries 5 and 6). Alkyl aromatics bearing a benzylic C–H bond such as ethylbenzene, indane, and tetraline were converted into the corresponding alcohols and ketones in excellent yields (entries 7–9).

**Table 4.** $Cu(OAc)_2$-catalyzed oxidation of alkanes with molecular oxygen in the presence of acetaldehyde.[a]

| entry | substrate | time (h) | yield (%)[b] | | | TON[c] |
|---|---|---|---|---|---|---|
| | | | alcohol | ketone | total | |
| 1 | cyclohexane | 10 | 40[d] | 32[c] | 72 | $2.5x10^4$ |
| 2 | cyclohexane | 12 | 54[d] | 42[e] | 96 | $3.3 x10^4$ |
| 3 | cyclooctane | 24 | 8[f] | 74[g] | 82 | $2.9 x10^4$ |
| 4 | methylcyclohexane | 8 | 51[h] | 27[i] | 78 | $2.7 x10^4$ |
| 5 | *n*-heptane | 16 | 13[j] | 66[k] | 79 | $2.7 x10^4$ |
| 6 | *n*-decane | 10 | 15[l] | 60[m] | 75 | $2.6 x10^4$ |
| 7 | ethylbenzene | 8 | 33[n] | 60[o] | 93 | $3.3 x10^4$ |
| 8 | indane | 4 | 34[p] | 50[q] | 84 | $2.9 x10^4$ |
| 9 | tetraline | 5 | 34[r] | 44[s] | 78 | $2.8 x10^4$ |

[a]Substrate (80 mmol), $Cu(OAc)_2$ (0.00005 mmol), $CH_3CHO$ (2 mmol), $CH_3CN$ (6 mL), $CH_2Cl_2$ (4 mL), $O_2/N_2$ (1 atm/8 atm), 70 °C. [b]Based on acetaldehyde. [c]Results are given in mole of products formed per mol of catalyst. [d]Cyclohexanol. [e]Cyclohexanone. [f]Cyclooctanol. [g]Cyclooctanone. [h]1-, 2-, 3-, 4-Methylcyclo- hexanol (92:3:4:1). [i]2-, 3-, and 4-Methylcyclohexanone (35:45:20). [j]2-, 3-, and 4-Heptanol (39:38:23). [k]2-, 3-, and 4-Heptanone (37:40:23). [l]2-, 3- and (4+5)-Decanol (25:27:48). [m]2-, 3- and (4+5)-Decanone (15:25:60). [n]1-Phenylethanol. [o]Acetophenone. [p]1-Indanol. [q]1-Indanone. [r]1,2,3,4-Tetrahydro-1-naphthol. [s]1-Tetralone.

### 3.2.2 Mechanistic Aspects of the Cupper-catalyzed Aerobic Oxidation of Alkanes in the presence of Acetaldehyde

In order to gain insight into the mechanism of the $Cu(OAc)_2$-catalyzed oxidation of alkanes with acetaldehyde in $CH_3CN/CH_2Cl_2$, the relative reaction rates of the oxidation of four substituted toluenes (X-$C_6H_4$Me, X = *p*-Me,H, *p*-Cl, and *m*-Cl) were determined by the GLC analysis of the products. The rate data correlate well ( $\gamma$=0.991) with the Hammett linear free-energy relationship with use of $\sigma^+$ values. The $\rho$ value was –1.38 close to the values of –1.43 for the aerobic oxidation with $CuCl_2$-18-crown-6 catalyst in $CH_2Cl_2$[9a] and ca. –1.6 for cytochrome P-450[15] suggesting that the intermediate similar to metal-oxo species exists in the present oxidation, as shown in Figure 1.

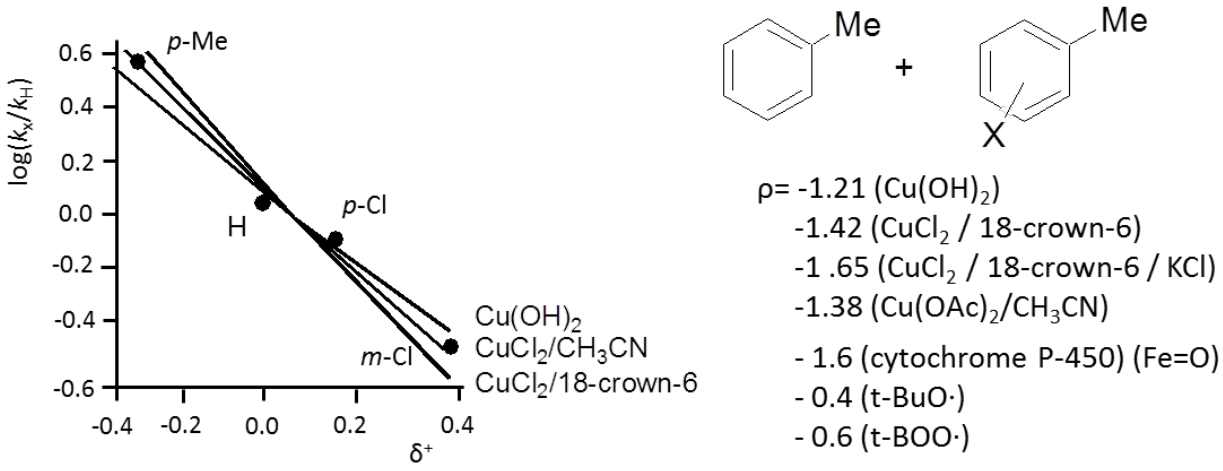



**Figure 1.** Hammett correlation of copper-catalyzed aerobic oxidation of substituted toluenes in the presence of acetaldehyde.

Further, the intermolecular deuterium isotope effect ($k_H/k_D$) on the oxygenation of cyclohexanes at room temperature was determined to be 2.4 by GLC analysis of the products obtained from the competitive reaction of cyclohexane and cyclohexane-$d_{12}$, suggesting that hydrogen abstraction by reactive radical species such as hydroxyl radical OH• is not involved (Figure 2).[16]

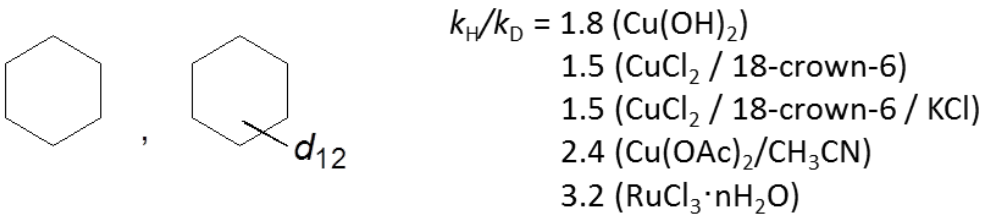



**Figure 2.** Isotope effects of the oxygenation of cyclohexane.

To determine the key valency of copper species, initial reaction rates with $Cu^{II}$, $Cu^{I}$, and $Cu^{0}$ complexes were examined for the oxidation of cyclohexane (Figure 3). The reaction with $Cu^{I}(OAc)$ started faster than that with $Cu^{II}(OAc)_2$ and $Cu^{0}$ powder in the initial period, indicating that $Cu^{I}$ is an important role to generate reactive species. Cu(I) species is unstable compared to Cu(II) and Cu(0) in common organic solvents, however, potentially labile Cu(I) ion can be stabilized by solvation with acetonitrile. Actually, in the present oxidation system, a remarkable color change of the solution was observed despite the use of Cu(II) (blue), Cu(I) (colorless), and Cu(0) (reddish powder), where a colorless solution was obtained in several minutes in the beginning of the reaction. Apparently, the equilibrium between Cu(0), Cu(I), and Cu(II) in acetonitrile is shifted to colorless Cu(I) species solvated by acetonitrile, like $[Cu(CH_3CN)_4]^{+}$, regardless of copper salts used, leading to a similar final product.

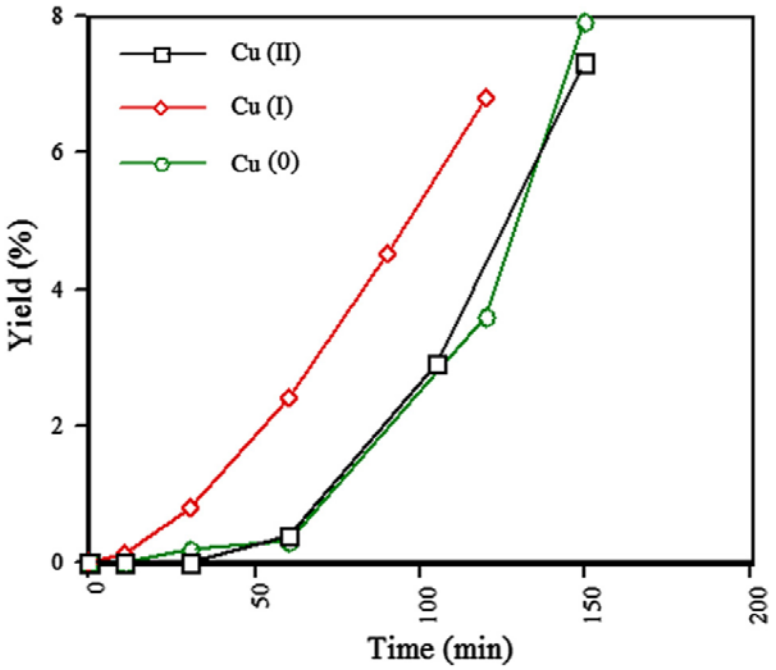
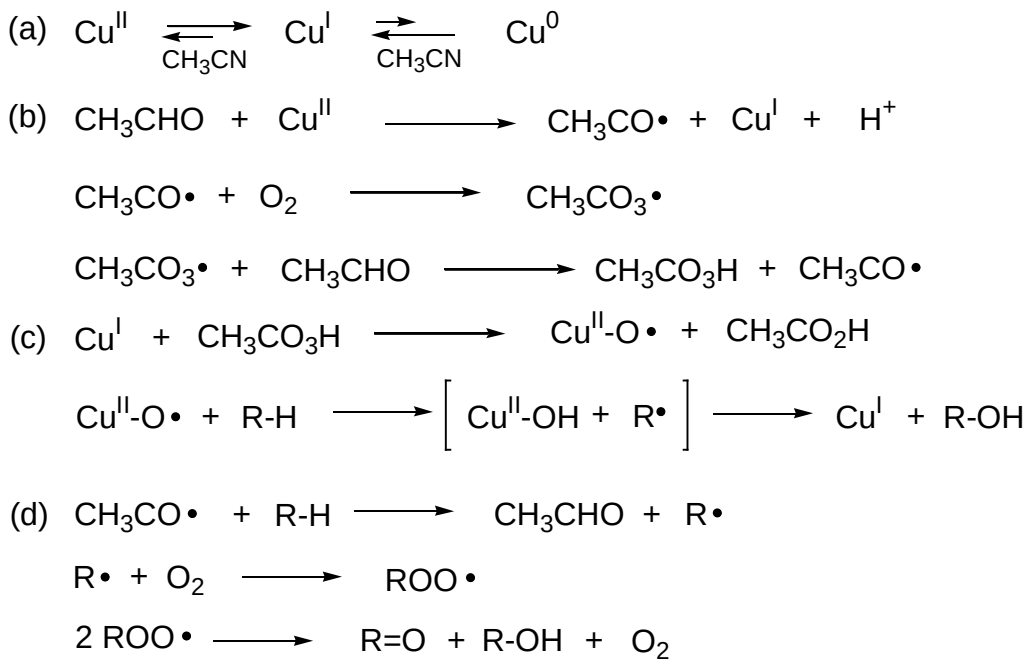



**Figure 3.** Time course (initial period) for the aerobic oxidations of cyclohexane catalyzed by Cu(II), Cu(I), and Cu(0) compounds. Cyclohexane (40 mmol), benzaldehyde (1.0 mmol), Cu cat. $(Cu(ClO_4)_2 \cdot 6H_2O$, $[Cu(CH_3CN)_4](ClO_4)$, and Cu powder) (0.0025 mmol), $CH_3CN$ (3 mL), $CH_2Cl_2$ (2 mL), $O_2$ (1 atm), room temperature.

Although it is premature to discuss the reaction mechanism of the copper catalyzed oxidative functionalization with molecular oxygen at the present stage, the mechanism can be rationalized by assuming Scheme 1, which includes both metal-based and radical-based reactions. In the present system, copper ion in acetonitrile seems to exist as Cu(I) species (Scheme 1a). The autoxidation of acetaldehyde is initiated easily in the presence of the copper catalyst to form acyl radical, which undergoes reaction with $O_2$ and abstract hydrogen from the second molecule of acetaldehyde or alkane to produce $CH_3CO_3H$ (Scheme 1b).[17] The reaction of peracetic acid with Cu(I) species would give copper-oxo speices,[18] which undergoes hydrogen abstraction from

alkane, and oxygen rebound to give the corresponding alcohol (Scheme 1c). The alcohol is oxidized to the corresponding ketone under the reaction conditions. The acyl radical thus formed undergoes hydrogen abstraction from alkanes to give an alkyl radical which undergoes reaction with molecular oxygen, giving an alkylperoxyl radical. Termination would give ketones and alcohols (Scheme 1d). Leitner et al. demonstrated that selective oxidation of alkanes with molecular oxygen and acetaldehyde in compressed carbon dioxide proceeds highly efficiently, where alkylperoxy radical plays a key role.[3a] In the copper-catalyzed aerobic oxidation of benzylic C–H bond the copper-promoted formation of acyl radical and Scheme 1d would occur.

**Scheme 1.** Proposed mechanism for aerobic oxidation of alkanes. (a) Formation of Cu(I) species in $CH_3CN$. (b) Copper-promoted autoxidation of acetaldehyde to give peracetic acid. (c) Formation of copper-oxo species followed by oxidation of alkanes. (d) Acylperoxyl radical-mediated oxidation.



Combination of the palladium-catalyzed oxidation of ethylene, which is obtained readily from shale gas, with molecular oxygen (Wacker reaction) and the present copper-catalyzed oxidation of alkanes with molecular oxygen in the presence of acetaldehyde would provide a powerful and atom-economical strategy for the oxidative functionalization of hydrocarbons $R_2CH_2$ with molecular oxygen to give oxidation products (Scheme 2).

**Scheme 2.**

$$H_2C{=}CH_2 + 1/2\ O_2 \xrightarrow{Pd\ (cat.)} CH_3CHO$$

$$R_2CH_2 + CH_3CHO + 3/2\ O_2 \xrightarrow{Cu\ (cat.)} R_2CO + CH_3CO_2H + H_2O$$

overall

$$R_2CH_2 + H_2C{=}CH_2 + 2\ O_2 \longrightarrow R_2CO + CH_3CO_2H + H_2O$$

## 3.3 Conclusion

The aerobic copper-catalyzed oxidation of alkanes with an equivalent of acetaldehyde can be performed highly efficiently in acetonitrile/$CH_2Cl_2$ at 70 ˚C without using any expensive ligand as the results of copper based and radical based reactions. In this system acetonitrile acts not only as a solvent but also a ligand to generate and stabilize Cu(I) species, thus offering a new possibility for selective C–H functionalization of unreactive hydrocarbons.

## 3.4 Experimental Section

**General Methods.** All the alkanes were commercially available and were used without further purification. $Cu(OAc)_2$, acetaldehyde, acetonitrile, dichloromethane, and all other reagents were obtained from commercial suppliers. GC measurements were carried out with a Shimadzu GC-14B gas chromatograph (FID) equipped with a DB-1701 glass capillary column (0.25 mm x 30 m). GC-MS analyses were performed on a Hewlett Packard 6890 Plus-5973N mass spectrometer equipped with a DB-1701 glass capillary column (0.25 mm x 30 m).

**General Procedure for the Catalytic Oxidation of Alkanes with Molecular Oxygen in the presence of acetaldehyde.** High-pressure oxidation reactions were performed in a high pressure system with a constant stream of 1 atm of $O_2$. A glass autoclave (96 mL) with hastelloy attachment (Hyper-glass cylinder HPG96-3, Taiatsu Techno Corporation, Japan) with a glass inner reaction vessel was charged with reaction solutions. A autoclave equipped with a magnetic stirring bar was charged with a mixture of substrate (80 mmol), $Cu(OAc)_2$ (0.00005 mmol), acetaldehyde (2 mmol) and tetradecane (internal standard for GC analysis, 0.25 mmol) in acetonitrile (3 mL) and dichloromethane (4 mL). The autoclave was pressurized to 1 atm of $O_2$ diluted with 8 atm of $N_2$, and the mixture was stirred at 70 ˚C. The reaction mixture was analyzed GC-analysis using tetradecane as an internal standard and the products were identified by GC-MS.

**Cyclohexanol:** m/z = 57 (100), 82 (46), 67 (26), 44 (24), 41 (22).

**Cyclohexanone:** m/z = 55 (100), 42 (76), 98 (M+, 45), 41 (38), 39 (36), 69 (33), 70 (26).

**Cyclooctanol:** m/z = 57 (100), 41 (44), 68 (44), 67 (42), 82 (40), 81 (33), 55 (29), 44 (24), 43 (24), 56 (21).

**Cyclooctanone:** m/z = 98 (100), 55 (81), 41 (75), 42 (75), 84 (49), 82 (44), 83 (42), 56 (39), 27 (32), 39 (30).

**1-Methylcyclohexanol:** m/z = 71 (100), 43 (34), 58 (26).

**2-Methylcyclohexanol:** m/z = 57 (100), 68 (78), 81 (74), 96 (66), 71 (51), 55 (45), 41 (38), 67 (30), 44 (25), 39 (21).

**3-Methylcyclohexanol:** m/z = 71 (100), 96 (71), 81 (65), 57 (42), 55 (38), 41 (34), 44 (22), 42 (20).

**4-Methylcyclohexanol:** m/z = 57 (100), 58 (53), 81 (47), 96 (35), 41 (35), 70 (34), 55 (31), 29 (20).

**2-Methylcyclohexanone:** m/z = 68 (100), 41 (93), 55 (79), 56 (73), 69 (62), 112 (M+, 59), 39 (56), 42 (55), 27 (48), 84 (34).

**3-Methylcyclohexanone:** m/z = 69 (100), 41 (58), 42 (53), 56 (49), 55 (42), 39 (41), 27 (35), 112 (M+, 26).

**4-Methylcyclohexanone:** m/z = 55 (100), 112 (M+, 41), 41 (39), 56 (34), 83 (25), 57 (21), 70 (20).

**2-Heptanol:** m/z = 45 (100), 27 (17), 43 (14).

**3-Heptanol:** m/z = 59 (100), 69 (70), 41 (35), 87 (31), 31 (22).

**4-Heptanol:** m/z = 55 (100), 73 (71), 43 (33).

**2-Heptanone:** m/z = 43 (100), 58 (55), 27 (20).

**3-Heptanone:** m/z = 57 (100), 29 (69), 27 (41), 85 (30), 41 (25), 72 (20), 114 (M+, 13).

**4-Heptanone:** m/z = 43 (100), 71 (85), 114 (M+, 14).

**2-Decanol:** m/z = 45 (100), 43 (23), 41 (21).

**3-Decanol:** m/z = 59 (100), 69 (68), 55 (31), 41 (24).

**4-Decanol:** m/z = 55 (100), 73 (44), 97 (32), 43 (30).

**5-Decanol:** m/z = 69 (100), 83 (82), 87 (66), 55 (65), 41 (43), 101 (37), 29 (21), 43 (21).

**2-Decanone:** m/z = 58 (100), 43 (85), 71 (38), 59 (28), 41 (27).

**3-Decanone:** m/z = 57 (100), 72 (58), 41 (26), 29 (25), 127 (25), 43 (25).

**4-Decanone:** m/z = 43 (100), 71 (48), 58 (41), 41 (37), 113 (35), 86 (28), 27 (24).

**5-Decanone:** m/z = 43 (100), 58 (98), 57 (87), 41 (66), 71 (63), 85 (62), 29 (58), 99 (50), 27 (34), 55 (23).

**1-Phenylethanol:** m/z = 107 (100), 79 (88), 122 (M+, 60), 43 (52), 77 (44), 51 (21), 78 (20).

**Acetophenone:** m/z = 105 (100), 77 (87), 51 (38), 120 (M+, 30).

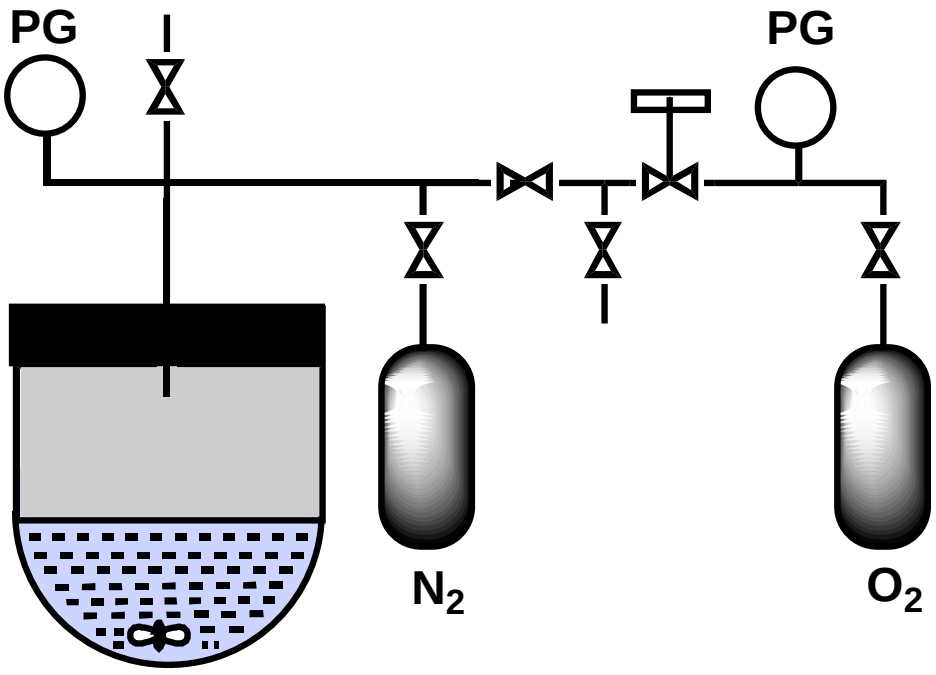
**1-Indanol:** m/z = 133 (100), 134 (M+, 58), 115 (32), 116 (31), 105 (22).

**1-Indanone:** m/z = 104 (100), 132 (M+, 98), 103 (42), 78 (30), 77 (24), 131 (23), 51 (21).

**1,2,3,4-Tetrahydro-1-naphthol:** m/z = 130 (100), 120 (89), 91 (76), 119 (67), 129 (45), 105 (36), 147 (34), 115 (31), 148 (M+, 28), 51 (21).

**1-Tetralone:** m/z = 118 (100), 90 (63), 146 (M+, 62).

***The batch reaction apparatus***



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# Chapter 4. Aerobic Oxidative Esterification of Aldehydes with Alcohols by Gold–Nickel Oxide Nanoparticle Catalysts with a Core-Shell Structure

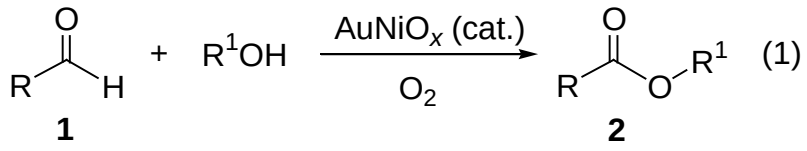


## 4.1 Introduction

Esterification, one of the most fundamental transformations in organic synthesis, is widely used in laboratories and industries.[1] Esterification of aldehydes with alcohols is an attractive method for the synthesis of esters because aldehydes are readily available raw materials on a commercial scale. Although several facile and selective esterification reactions have been reported,[2] the development of a catalytic method for the direct oxidative esterification of aldehydes with alcohols under mild and neutral conditions in the presence of molecular oxygen as the terminal oxidant is highly desirable for both economic and environmental aspects.

Since Haruta et al. discovered that Au nanoparticles can catalyze aerobic oxidation reactions,[3] Au-catalyzed oxidation reactions have been widely investigated. Efforts are being

directed at achieving highly selective oxidation using molecular oxygen.[4] Several Au-nanoparticle-based catalysts for the aerobic esterification of aldehydes[5] or alcohols[6] have been reported. In this paper, we report a highly selective and efficient catalytic method for the oxidative esterification of aldehydes with alcohols that employs supported gold–nickel oxide ($AuNiO_x$) nanoparticles as the catalyst and molecular oxygen as the terminal oxidant (Scheme 1).




As an example, the aerobic catalytic esterification of methacrolein **1a** with methanol to form methyl methacrylate (MMA; **2a**) was investigated under neutral conditions. The monomer MMA is mainly used to produce acrylic plastics such as poly(methyl methacrylate) (PMMA) and other polymer dispersions used in paints and coatings. MMA can be manufactured in numerous ways from $C_2$–$C_4$ hydrocarbon feed stocks (Figure 1).[7] Currently, MMA is mainly produced via the acetone cyanohydrin process, but there are problems in handling the resulting ammonium bisulfate waste and toxic hydrogen cyanide. Some manufacturers use isobutene or *tert*-butanol as the starting material, which is sequentially oxidized first to methacrolein and then to methacrylic acid, which in turn is esterified with methanol. Recently, an environmentally benign procedure based on the use of molecular oxygen and a Pd–Pb catalyst has been developed for the direct oxidative esterification of methacrolein with methanol to yield MMA.[8] This work was an important milestone in the aerobic oxidative esterification of aldehydes, as it put forth a clean and efficient method of forming carboxylic esters. However, the existing synthetic methods still suffer from several disadvantages; methods for successful catalytic oxidative esterification are limited as selective oxidation of methacrolein is extremely difficult because of the instability of α,β-unsaturated aldehydes. Therefore, the development of an efficient and highly selective catalytic system based on the above reaction remains a challenge.

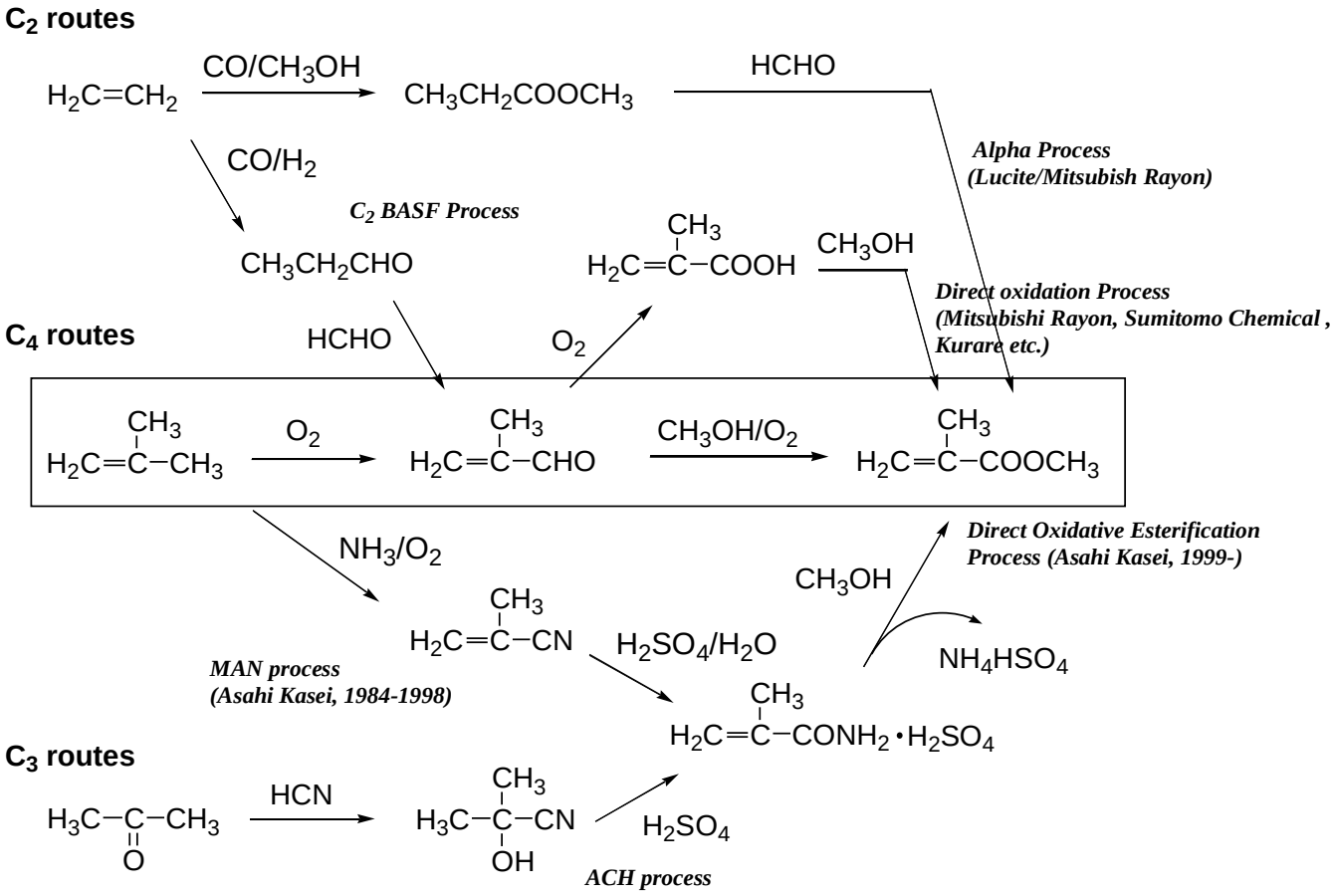



**Figure 1.** MMA production routes based on $C_2$–$C_4$ hydrocarbon feedstock

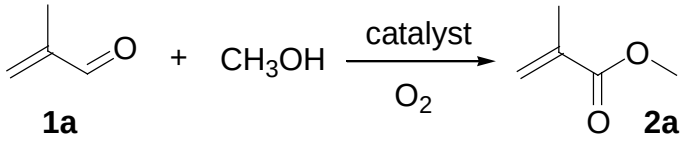
## 4.2 Results and Discussion

### 4.2.1 $AuNiO_x$-Catalyzed Oxidative Esterification of Aldehydes in Alcohols with Molecular Oxygen.

Table 1 summarizes the activity of various catalysts used in the aerobic esterification of **1a** with methanol. The activity of previously reported Pd catalysts was investigated first.[8] When 2.5 wt% $Pd/SiO_2–Al_2O_3$ was used, **2a** could not be obtained in satisfactory yields (entry 1) because the decarboxylation of **1a** resulted in the formation of large amounts of propylene and $CO_2$ as by-products. When oxidative esterification was carried out by the addition of $Pb(OAc)_2$ to the reaction mixture, decarboxylation was inhibited, and the selectivity to **2a** improved to 84% (entry 2). The active species in the above reaction was found to be the intermetallic compound $Pd_3Pb_1$. During oxidative esterification in the presence of methanol, the excess methanol is oxidized to form methyl formate (MF) as a by-product (0.2 moles of MF per mole of MMA). The turnover number (TON) of the catalyst, defined as the total number of moles of the product **2a** formed per mole of the Pd-catalyst, was determined to be 61. Attempts to carry out esterification of **1a** to **2a** in the presence of other Pd-based catalysts were unsuccessful. We then turned our attention to nickel oxide. Nickel peroxide is known to be highly oxidizing and can stoichiometrically oxidize various alcohols.[9] The catalytic aerobic oxidation of alcohols was possible after the recent development of catalysts such as Ni–Al hydrotalcite and nanosized $NiO_2$ powder.[10] In the field of electronic materials, research is being conducted on NiO–M (M: Ni, Pd, Pt, Au, Ag, Cu) composite film to quicken the light-absorption response of Ni oxide film used as an electrochromic material. The metal doped into Ni oxide is supposed to act as a positive hole and improves the speed of oxidative coloring by converting Ni oxide into a higher oxidation state.[11] Nickel peroxide was also found to participate in oxidative esterification of aldehydes with alcohols.[12] We examined the relationship between the chemical form and reactivity and

developed a new catalytic system of composite nanoparticles composed of NiO and Au active species.

**Table 1.** Catalytic activity for aerobic oxidative esterification of methacrolein **1a** with methanol.[a]




**1a** **2a**

| entry | catalyst | conversion of aldehyde **1** (%)[b] | selectivity for ester **2** (%)[b] |
|---|---|---|---|
| 1[c] | $Pd/SiO_2$-$Al_2O_3$ | 20 | 40 |
| 2[c] | $PdPb/SiO_2$-$Al_2O_3$ | 34 | 84 |
| 3 | $AuNiO_x/SiO_2$-$Al_2O_3$-MgO | 58 | 98 |
| 4 | $AuNiO_x/SiO_2$-$Al_2O_3$ | 63 | 97 |
| 5 | $AuNiO_x/SiO_2$-$TiO_2$ | 29 | 96 |
| 6 | $Au/SiO_2$-$Al_2O_3$-MgO | 14 | 91 |
| 7 | $Au/SiO_2$-$Al_2O_3$ | 17 | 79 |
| 8 | $Au/SiO_2$-$TiO_2$ | 6 | 89 |
| 9 | $AuNi/SiO_2$-$Al_2O_3$-MgO | 12 | 89 |

[a]Reaction conditions: **1a** (15 mmol), catalyst (Au: 0.1 mol%) in methanol (10 mL), $O_2$ ($O_2/N_2$ = 7:93 v/v, 3 MPa) at 60 °C for 2 h. [b] Determined by GC analysis using an internal standard. [c] Pd-based catalyst (Pd: 0.5 mol%).

Au and NiO were supported on $SiO_2$–$Al_2O_3$–MgO (average particle size of 60 μm) by co-precipitation. The amounts of Au and Ni in the supported nanoparticle were determined to be 0.9 and 1.1 wt% respectively, by inductively coupled plasma-atomic emission spectroscopy (ICP-AES). Thus, the reaction of **1a** in the presence of $AuNiO_x/SiO_2$–$Al_2O_3$–MgO in methanol at 60 °C under an oxygen-nitrogen mixture (7:93 (v/v), 3 MPa, outside flammability limits) for 2 h gave **2a** with 98% selectivity and 58% conversion (entry 3). Based on the moles of MMA formed per mole of the Au-catalyst, the TON of the supported nanoparticle catalyst was determined to be 621, and its activity was approximately 10 times that of the Pd–Pb catalyst.

Moreover, reduced by-product (MF) formation was observed in this case (0.007 moles of MF formed per mole of MMA). Oxidative esterification was found to proceed with high efficiency even when $SiO_2$–$Al_2O_3$ and $SiO_2$–$TiO_2$ were used as carriers (entries 4 and 5). The catalyst supported with only Au nanoparticles showed lower activity and selectivity than the supported $AuNiO_x$ catalyst (entries 6–8). The activity and selectivity of the Au–Ni catalyst, prepared by reduction of the $AuNiO_x$ catalyst under $H_2$ atmosphere at 400 °C for 3 h, was greatly decreased (entry 9). When 1 wt% Au–1 wt% $MO_x/SiO_2$–$Al_2O_3$–MgO (M: Cr, Mn, Fe, Co, Cu, Zn, Ga, Ge, Nb, In, Sn, Nb, Ta, and Pb) was used in oxidative esterification, similar effects to that of the $AuNiO_x$ catalyst could not be obtained. The oxidative esterification activity of the $AuNiO_x$ catalyst showed a strong dependence on the Au and NiO composition in the supported nanoparticle. The maximum activity was observed for 20 mol% of Au (Figure 1).

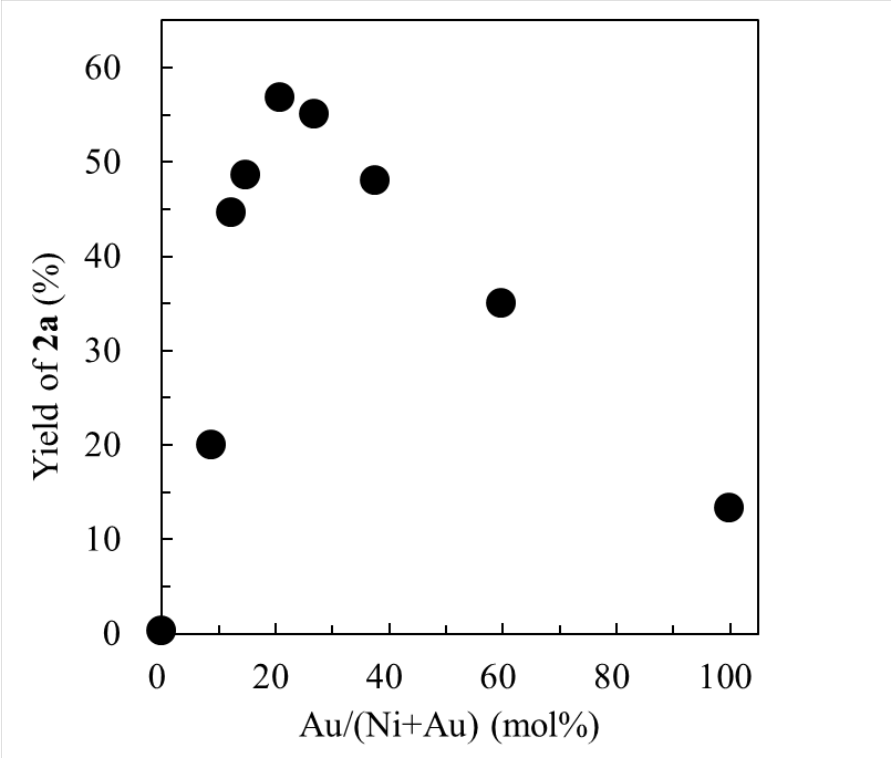
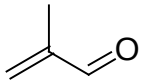
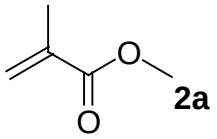
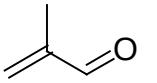
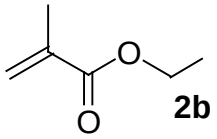
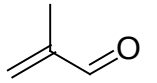
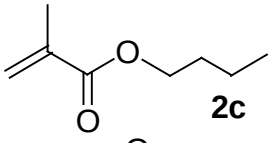
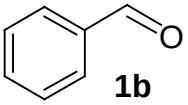
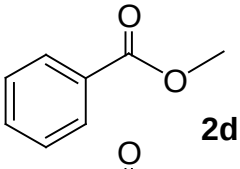
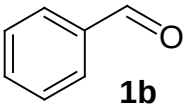
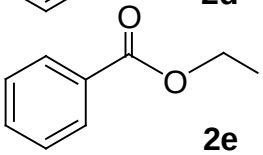



**Figure 1.** Yield of methyl methacrylate **2a** for oxidative esterification of methacrolein **1a** in methanol over catalysts with various Au/Ni compositions.

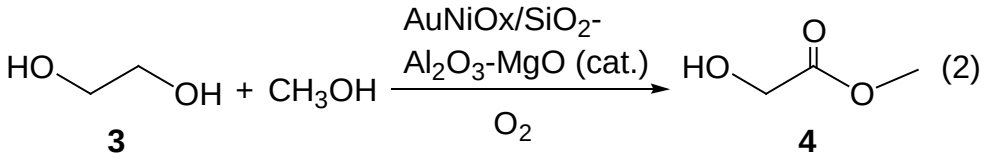
Next, oxidative esterification of various aldehydes and alcohols was carried out by using the $AuNiO_x$ catalyst (Table 2). When oxidative esterification of **1a** was carried out in the presence of $AuNiO_x/SiO_2–Al_2O_3–MgO$ in methanol at 80 °C, under an oxygen-nitrogen mixture (7:93 (v/v), 3 MPa) for 1 h, **2a** was obtained with 98% selectivity and 62% conversion (entry 1). The conversion of benzaldehyde **1b** to methyl benzoate **2d** was highly efficient (entry 4). When oxidative esterification of **1a** and **1b** was carried out using ethanol and *n*-butanol in place of methanol, the corresponding esters (**2b**, **2c**, and **2e**) were obtained with high selectivity but with lower conversion efficiencies than those in the case of using methanol (entries 2, 3, and 5).

**Table 2.** $AuNiO_x$-catalyzed aerobic oxidative esterification of aldehydes with alcohols[a]

| entry | aldehyde | alcohol | product | conversion (%) [b] / selectivity (%) [b] |
|---|---|---|---|---|
| 1 |  **1a** | methanol |  **2a** | 62/98 |
| 2 |  **1a** | ethanol |  **2b** | 11/97 |
| 3 |  **1a** | *n*-butanol |  **2c** | 15/97 |
| 4 |  **1b** | methanol |  **2d** | 61/97 |
| 5 |  **1b** | ethanol |  **2e** | 10/97 |

[a]Reaction conditions: aldehyde (15 mmol), $AuNiO_x/SiO_2–Al_2O_3–MgO$ (Au: 0.1 mol%) in alcohol (10 mL), $O_2$ ($O_2/N_2$ = 7:93 v/v, 3 MPa) at 80 °C for 1 h. [b] Determined by GC analysis using an internal standard..

The oxidative esterification of alcohols to afford the corresponding esters was also highly efficient. When oxidative esterification of ethylene glycol **3** was carried out in methanol at 90 °C, under an oxygen-nitrogen mixture (7:93 (v/v), 3 MPa) for 4 h, methyl glycolate **4** was obtained with 95% selectivity and 39% conversion (Scheme 2). Thus, methyl glycolate **4** is a useful intermediate for polyglycolic acid (PGA), which is applicable for beverage bottles or drilling chemicals that have attracted attention in the development of shale gas.




### 4.2.2 Characterization of Catalyst and Reaction Mechanism

Spherical particles of the $AuNiO_x$ catalyst that are uniformly distributed on the carrier can be seen in the transmission electron microscopy (TEM) images (Figure 2a, b). The particles have a diameter of 2–3 nm (number-average particle diameter: 3.0 nm). High-magnification images revealed a lattice of Au (111) particles with a d-spacing of 2.36 Å. Elemental analysis of individual particles by energy-dispersive X-ray (EDX) spectroscopy showed the presence of Ni and Au in the particles. The average Ni/Au atomic ratio of the nanoparticles was 0.82 (100 units used for calculation). As shown in Figures 2c–d, EDX analysis was performed on the scanning transmission electron microscopy (STEM) image of the nanoparticles. The results showed that the Ni/Au atomic ratio was 0.73 at the center of the particle (measurement point 1) but 2.95 at the edge of the particle (measurement point 2). Trace amounts of Ni were detected in areas that did not contain the particle (measurement point 3). Based on the composition profile observed in the direction of the scan, Ni appears to be more widely distributed than Au. Thus, Ni was distributed on the Au particles as well as around the edges of the particles. Hence, the

nanoparticles were assumed that the surface of the Au particles is covered by Ni without alloy formation. However, TEM/STEM images of the Ni shell around the Au particles could not be obtained.

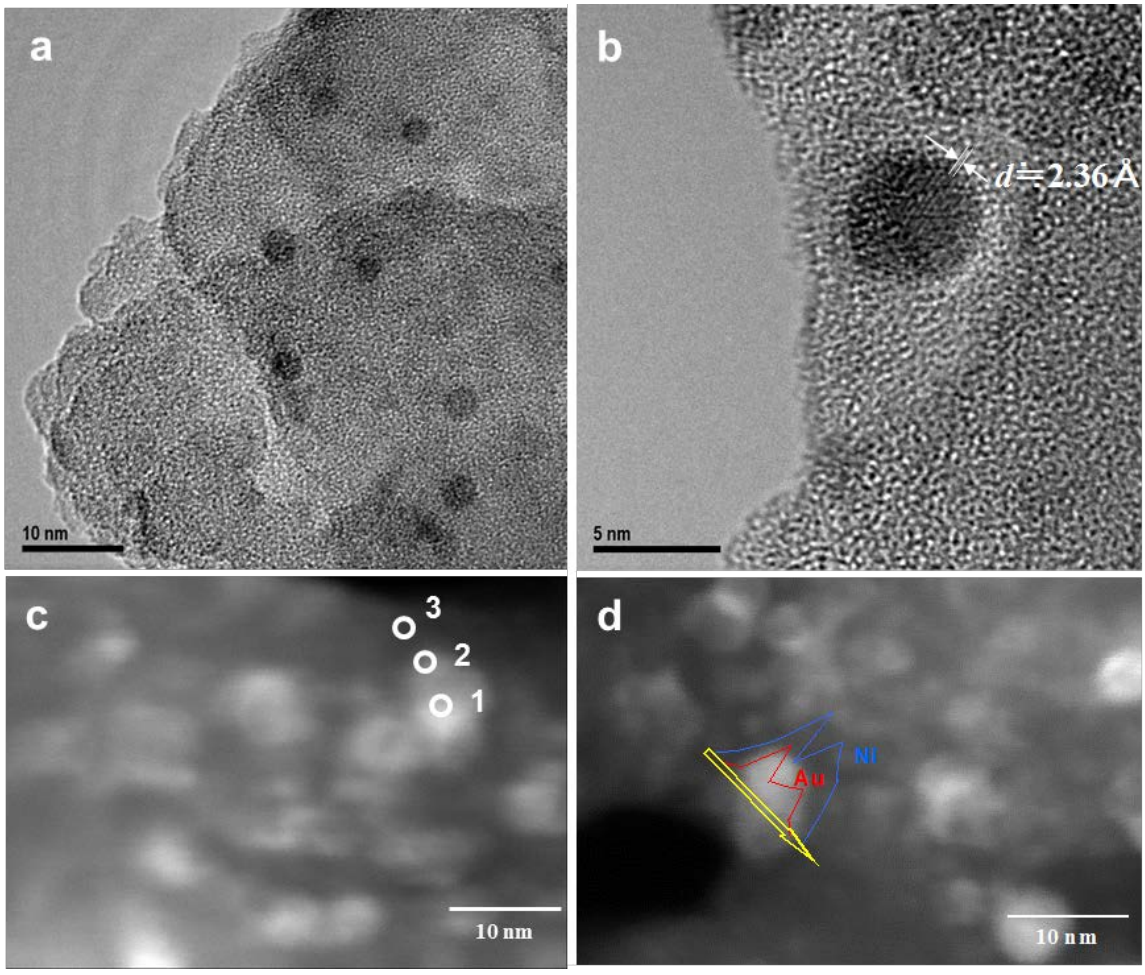



**Figure 2.** Typical transmission electron microscopy images (a, b) and scanning transmission electron microscopy–energy-dispersive X-ray compositional analyses (c; point analyses, d; line analyses) of $AuNiO_x/SiO_2–Al_2O_3–MgO$ catalyst.

A broad diffraction peak attributable to $Au^0$ was observed in X-ray diffraction (XRD) patterns. The absence of diffraction peaks due to Ni suggested that Ni existed as a noncrystalline phase (Figure 3). The Au 4f and Ni 2p XPS spectra confirmed the oxidation states of Au and Ni to be 0 and +2, respectively (Figure 4).

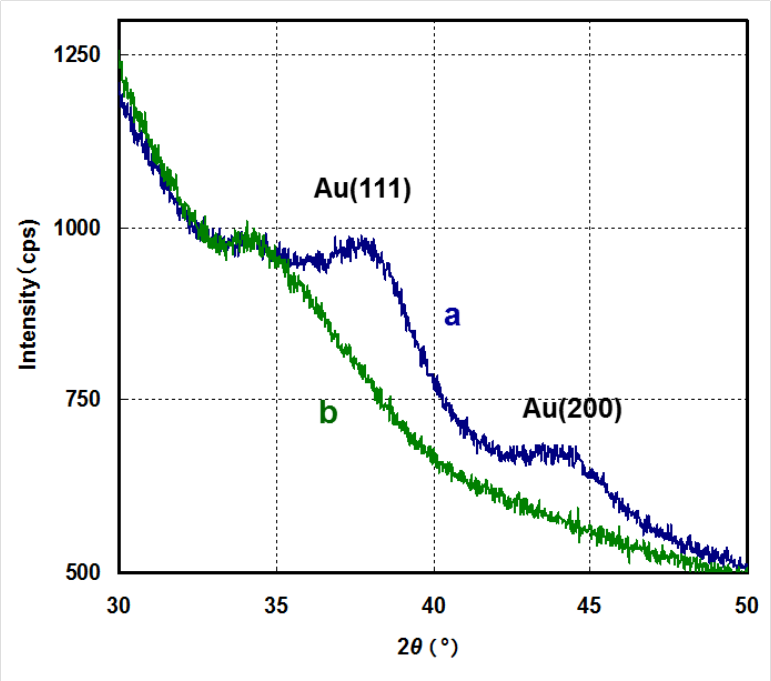



**Figure 3.** X-ray diffraction of (a) $AuNiO_x/SiO_2–Al_2O_3–MgO$ and (b) $NiO/SiO_2–Al_2O_3–MgO$.

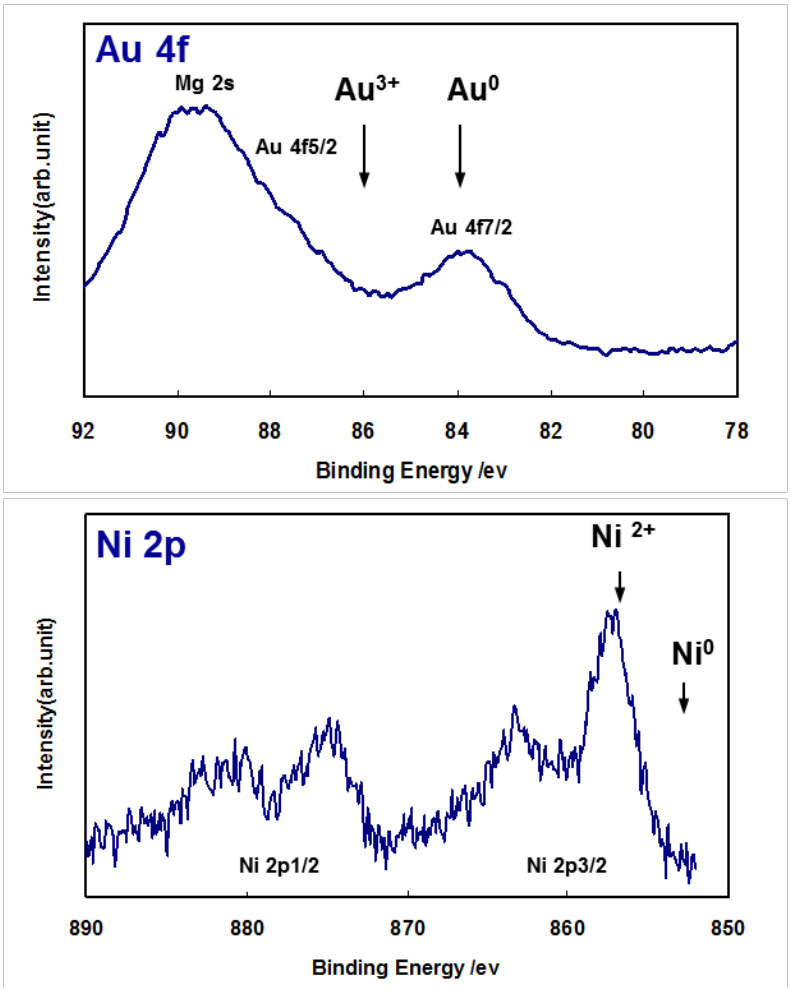



**Figure 4.** X-ray photoelectron spectroscopy (Au4f and Ni2p spectra) characterization of $AuNiO_x/SiO_2–Al_2O_3–MgO$ catalyst.

When the variation in the electronically excited state was examined using ultraviolet-visible (UV-vis) spectroscopy, no surface plasmon absorption peak, as observed in the case of the Au catalyst, originated from the Au nanoparticles (~ 530 nm) in the case of the $AuNiO_x$ catalyst (Figure 5). The $AuNiO_x$ catalyst was brown in color and showed a broad absorption peak in the wavelength region 200–800 nm. The spectrum pattern and color of the catalyst were similar to those of $NiO_x/SiO_2–Al_2O_3–MgO$, synthesized by the oxidation of $NiO/SiO_2–Al_2O_3–MgO$ using NaOCl. Thus, it can be deduced that the surface electronic state of the $AuNiO_x$ catalyst differs from that of the Au-only catalyst as Ni was present in a highly oxidized state.

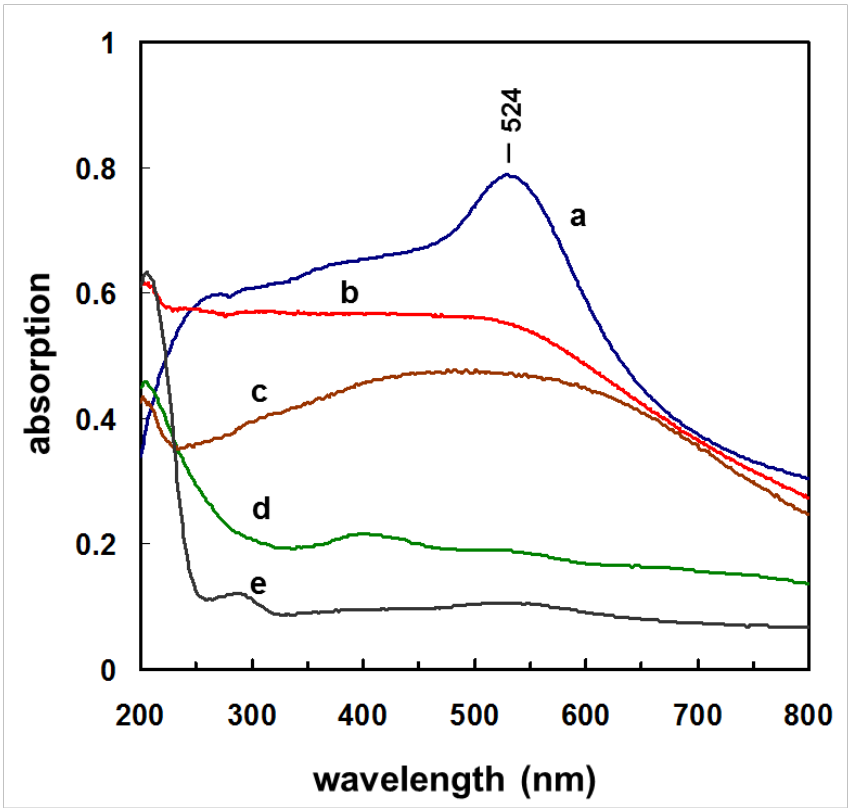



**Figure 5.** Ultraviolet-visible spectra of (a) $Au/SiO_2–Al_2O_3–MgO$, (b) $AuNiO_x/SiO_2–Al_2O_3–MgO$, (c) $NiO_2$ $/SiO_2–Al_2O_3–MgO$, (d) $NiO/SiO_2–Al_2O_3–MgO$, and (e) $SiO_2–Al_2O_3–MgO$.

The representative fourier transform-infrared (FT-IR) spectra of CO adsorbed on the catalysts are shown in Figure 6. The Au catalyst showed an intense band attributed to $Au^0$–CO, at 2058 $cm^{-1}$.[13] In contrast, the $AuNiO_x$ catalyst only showed a weak signal attributed to $Ni^{2+}$–CO, at 2111 $cm^{-1}$.[14] No peak corresponding to $Au^0$–CO could be observed.

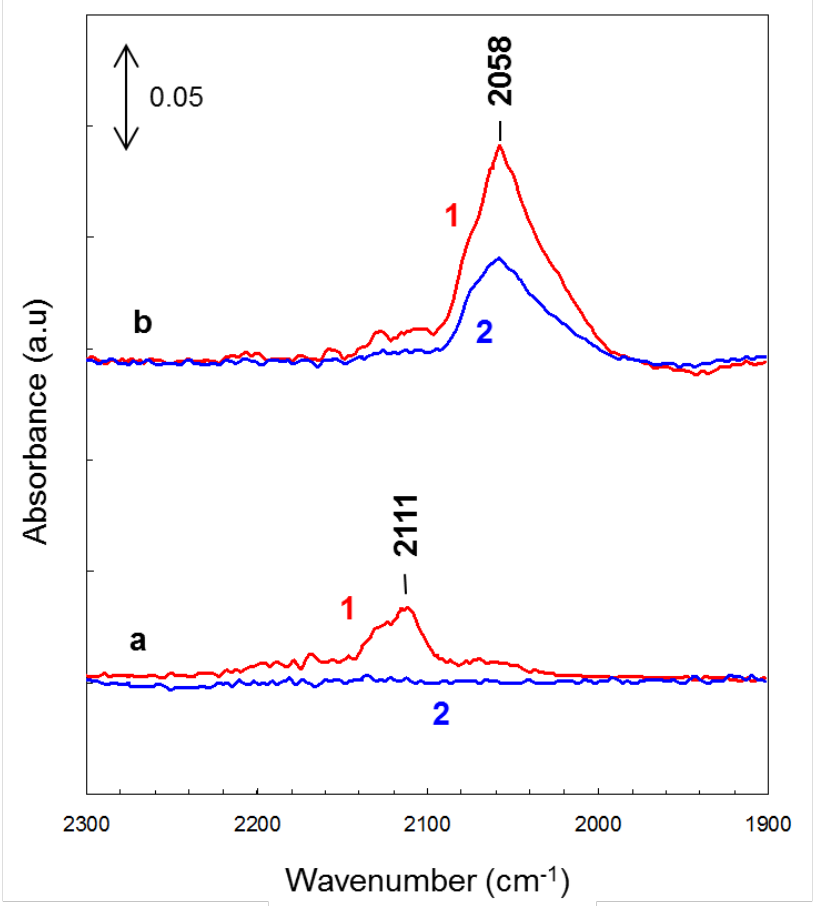
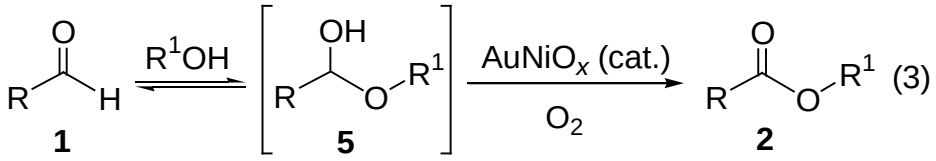



**Figure 6.** Fourier transform-infrared spectra for the adsorbed species of CO on $AuNiO_x/SiO_2$-$Al_2O_3$-MgO (a) and Au/$SiO_2$-$Al_2O_3$-MgO (b) at 15 °C. Spectra 1 and 2 were obtained after adsorption CO then evacuation of the cell for 5 min and 20 min, respectively.

Based on these results, the $AuNiO_x$ nanoparticle was assumed to have a core shell structure with Au nanoparticle at the core with its surface covered by highly oxidized $NiO_x$. The reaction mechanism proposed for the oxidative esterification of aldehydes involves the formation of hemiacetal **5** as a key intermediate. A condensation reaction between **1** and an alcohol results in the formation of **5**, which undergoes oxidative dehydrogenation to give **2** (Scheme 3).




### 4.2.3 Industrial Catalyst and Catalytic Life Test

Stability and long life are the key requirements of an effective catalyst. We precisely controlled the distribution of $AuNiO_x$ nanoparticles in the catalyst to decrease any loss of metals and to achieve high activity. Loss of metals from catalyst can occur because of detachment or abrasion under reaction. Figure 7 shows the results of linear analysis on a particle cross section of a sample obtained by embedding $AuNiO_x/SiO_2–Al_2O_3–MgO$ in a resin followed by polishing using electron probe microanalysis (EPMA). The $AuNiO_x$ layer was sharply distributed in a region within a 10-μm depth from the catalyst surface layer, and $AuNiO_x$ was shifted by submicron from the surface of the catalyst to inside.

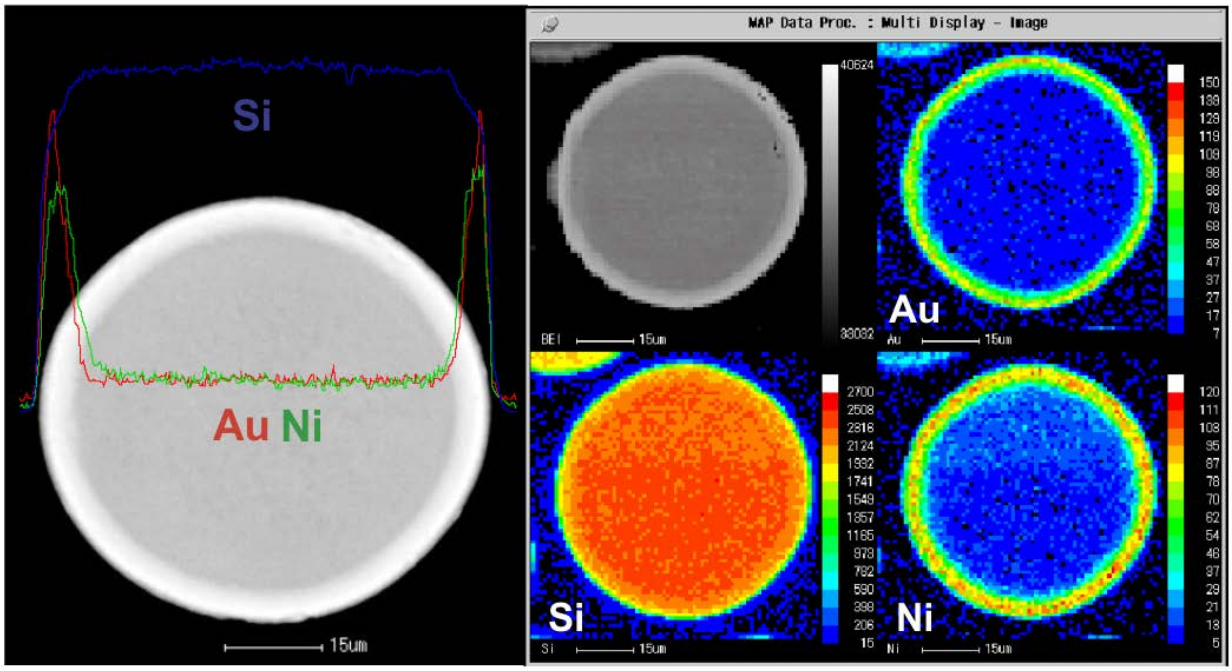



**Figure 7.** Electron probe microanalysis spectra and elemental mapping measured for a single particle of $AuNiO_x/SiO_2–Al_2O_3–MgO$.

Details on the chemical state of Ni were investigated by using two-crystal high-resolution X-ray fluorescence (HRXRF) spectroscopy analysis. HRXRF has an extremely high energy-resolution capacity, and the chemical state can be analyzed from the energy state (chemical shift) or shape of the obtained spectrum. In particular, in the k spectrum of *3d* transition metal elements, a chemical shift or change in shape occurs because of a change in the valance or electronic state; a difference in the chemical state can be considered even though the valence is the same. The HRXRF results showed that Ni from the $AuNiO_x$ catalyst can be considered to be in a high-spin bivalent state. The difference from the Ni Kα spectrum clearly shows that its chemical state is different from single NiO (Table 3). $NiO/SiO_2–Al_2O_3–MgO$ also showed a spectrum different from that for NiO powder. Thus, the Ni component of the $AuNiO_x$ catalyst

may form a composite with Au. In addition, free NiO may form a composite oxide or solid solution by reacting with metal component in the carrier.

**Table 3.** Two-crystal high-resolution X-ray fluorescence NiKα spectra of $AuNiO_x$/catalyst. [a] Full Width at Half Maximum. [b] Asymmentry Index

| Sample | Chemical Shft: ΔE (eV) | FWHM[a] (ev) | AI[b] |
|---|---|---|---|
| $AuNiO_x/SiO_2$-$Al_2O_3$-MgO | 0.332 | 3.487 | 1.463 |
| $NiO/SiO_2$-$Al_2O_3$-MgO | 0.311 | 3.521 | 1.464 |
| $NiO/SiO_2$ | 0.325 | 3.277 | 1.391 |
| NiO | 0.344 | 3.249 | 1.396 |
| Ni metal | 0.000 | 2.881 | 1.157 |

The catalytic life of $AuNiO_x/SiO_2$–$Al_2O_3$–MgO was evaluated by using a continuous-flow reaction apparatus (Figure 8). When the conversion efficiency of the reaction was maintained at approximately 60%, **2a** was obtained with high selectivity (96–97%). No decrease in the catalyst activity or selectivity was observed over a period of 1000 h. Furthermore, Au leaching was negligible during prolonged reactions. The concentration of metal in the reaction mixture was determined to be less than 2.5 ppb by ICP-AES. TEM observation of the catalyst after the reaction showed no sintering of the $AuNiO_x$ nanoparticles. The TEM/STEM-EDX, UV-vis, and FT-IR results confirmed that the core-shell structure of $AuNiO_x$ was preserved.

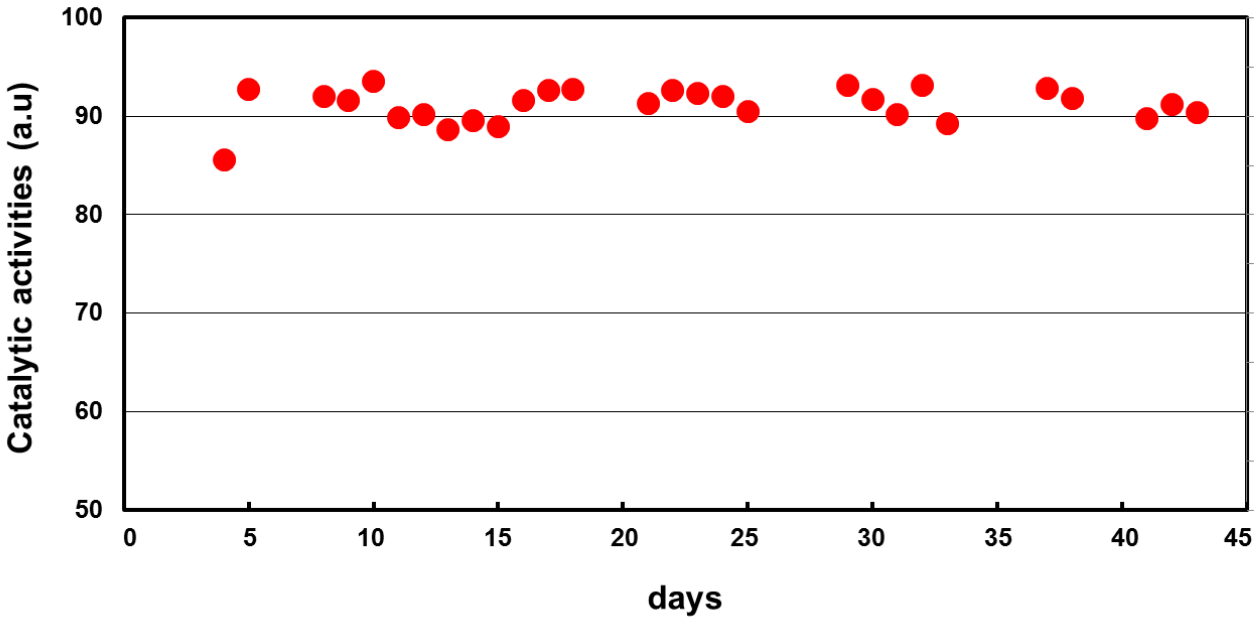
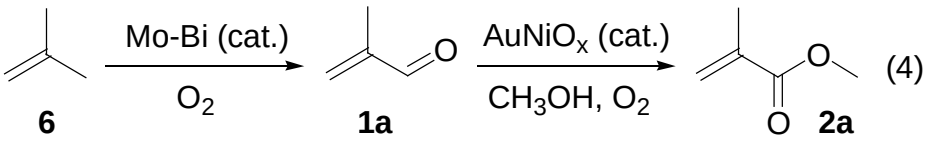



**Figure 8.** Catalytic life test using a continuous-flow reaction apparatus.

Evaluation of the catalyst life of Au/$SiO_2$–$Al_2O_3$–MgO showed that the activity decreased over time. After a reaction for 1000 h, the Au catalyst showed widening of the pore diameter of the carrier and sintering of Au. In the case of Au$NiO_x$/$SiO_2$–$Al_2O_3$–MgO, $NiO_x$ was found to be present on the carrier unlike the Au$NiO_x$ nanoparticles, and HRXRF confirmed that $NiO_x$ formed a composite compound or solid solution by reacting with the metal component of the carrier. The chemical stability of the carrier was assumed to be increased because of its action in stabilizing the Si–Al bridge structure. Stabilization of the carrier structure and anchor effect of NiO controlled the growth of the Au$NiO_x$ nanoparticles and thus made it possible to greatly increase the catalyst life compared to that of the monometallic Au catalyst.

### 4.2.4 Practical Applicability

The practical applicability of this catalytic system was verified in a 100,000 ton/year MMA production plant. Thus, isobutene **6** was oxidized in the gaseous phase using a Mo–Bi catalyst to synthesize **1a**. Subsequent oxidative esterification of **1a** in the presence of methanol using the $AuNiO_x$ catalyst produced **2a** (Scheme 4). This process confirmed the high selectivity, high activity, and long life of the $AuNiO_x$ catalyst. This catalyst would help in saving energy and resources, in addition to being highly economical (Figure 9).




(4)

**Figure 9.** Direct oxidative esterification process for MMA production.

## 4.3 Conclusion

Oxidative esterification of aldehydes with alcohols proceeds with high efficiency in the presence of molecular oxygen, on supported gold–nickel oxide ($AuNiO_x$) nanoparticle catalysts. The method is environmentally benign because it requires only molecular oxygen as the terminal oxidant and gives water as the side product. The $AuNiO_x$ nanoparticles have a core-shell structure, with the Au nanoparticles at the core and the surface covered by highly oxidized $NiO_x$. This strategy provides an efficient and environmentally benign method for the synthesis of esters. The oxidation will be particularly important for exploring further aerobic catalytic oxidations.

## 4.4 Experimental Section

**General Methods.** The aldehyde **1a, b** and alcohol **3** were purchased from Wako Pure Chemical Industries, Ltd. and used after purification. $HAuCl_4$ and $Pd/SiO_2–Al_2O_3$ were purchased from N.E. CHEMCAT Corporation. $Ni(NO_3)_2·6H_2O$, $Pb(OAc)_2$, methanol, ethanol and *n*-butanol were purchased from Wako Pure Chemical Industries, Ltd. $NiO_2·nH_2O$ was purchased from Sigma-Aldrich Corporation. All other reagents were obtained from commercial suppliers. GC measurements were carried out using a Shimadzu GC-14B gas chromatograph (FID) equipped with a DB-1701 glass capillary column (0.25 mm × 30 m). GC-MS analyses were performed on a Hewlett Packard 6890 Plus-5973N mass spectrometer equipped with a DB-1701 glass capillary column (0.25 mm × 30 m). The known products **2a**–**2e** and **4** were identified by comparison of GC and GC-MS spectra with those of the authentic samples obtained from the commercially available compounds. The amounts of Au and Ni in the leaching solution were estimated using inductively coupled plasma- atomic emission spectroscopy (ICP-AES).

**Methyl methacrylate (2a).** (Table 2, entry 1) m/z = 41 (100), 69 (63), 39 (37), 100 (M+, 27).

**Ethyl methacrylate (2b).** (Table 2, entry 2) m/z = 69 (100), 41 (96), 329 (35), 39 (28), 86 (20), 114 (M+, 12).

**Butyl methacrylate (2c).** (Table 2, entry 3) m/z = 41 (100), 69 (97), 87 (77), 56 (52), 39 (49), 29 (31), 27 (22).

**Methyl benzoate (2d).** (Table 2, entry 4) m/z = 105 (100), 77 (62), 136 (M+, 39), 51 (25).

**Ethyl benzoate (2e).** (Table 2, entry 5) m/z = 105 (100), 77 (41), 122 (31), 150 (M+, 22).

**Methyl glycolate (4).** m/z = 31 (100), 59 (52), 29 (28), 61 (24), 33 (23), 90 (M+, 16).

**Catalyst Preparation.** The $AuNiO_x/SiO_2–Al_2O_3–MgO$ catalyst was prepared by co-precipitation. $SiO_2–Al_2O_3–MgO$ (300 g, Si/Al/Mg: 83/8/9 mol%, surface area (SA): 149 $m^2/g$) was dispersed in water (1000 mL), and $Ni(NO_3)_2·6H_2O$ (16.35 g) and 1.3 mol/L $HAuCl_4$ (12 mL) were then added with vigorous stirring for 30 min at 90 °C. The resultant material was

dried in vacuum at 110 °C overnight and then calcined at 450 °C for 5 h to afford $AuNO_x/SiO_2–Al_2O_3–MgO$ as a brown powder. The Au and Ni contents were determined to be 0.9 and 1.1 wt% respectively, by ICP-AES.

**General Procedure for the Catalytic Oxidative Esterification of Aldehydes with Alcohols in the presence of Molecular Oxygen**. A stainless-steel autoclave (120 mL) equipped with a magnetic stirring bar was charged with a mixture of $AuNiO_x/SiO_2–Al_2O_3–MgO$ (328 mg, Au: 0.015 mmol, Ni: 0.06 mol), methacrolein (15 mmol), and tetradecane (internal standard for GC analysis, 0.25 mmol) in methanol (10 mL). The autoclave was pressurized to 3 MPa with an oxygen–nitrogen mixture (7:93 v/v), and the mixture was stirred (600 rpm) at 60 °C for 2 h. The reaction mixture was monitored by GC using an internal standard, and the products were identified by GC-MS.

**Characterization of the Catalyst.** The amounts of Au and Ni in the catalyst were determined by ICP-AES using a Thermo Fisher Scientific Model IRIS Intrepid III XDL instrument. Catalyst samples were prepared by weighing out the supporting material into a Teflon decomposition vessel, adding nitric acid and hydrogen fluoride, and heating and decomposing the sample in a microwave decomposition system (Milestone General Model ETHOS-TC). This was followed by evaporation to dryness over a heater, addition of nitric acid and hydrochloric acid to the precipitated residue, heating under an applied pressure with the microwave decomposition system, and using a fixed amount of the resulting pure decomposition product as a test liquid. Quantification was carried out by ICP-AES using an internal standard, and the Au and Ni contents in the catalyst were determined by subtracting a simultaneously determined blank value and calculating the supported amounts and atomic ratio.

Transmission electron microscopy (TEM)/scanning transmission electron microscopy (STEM) measurements were performed with a JEOL Model 3100 FEF microscope operating at 300 kV. The Au–Ni particles were identified using energy-dispersive X-ray (EDX) spectroscopy. The samples were prepared by crushing the particle along with its support using a mortar and pestle, followed by dispersion in ethanol. After ultrasonic cleaning for approximately 1 min, the

powder was dropped onto a molybdenum microgrid and air-dried to obtain TEM/STEM samples. Data analysis software Digital Micrograph™ from Gatan was used for TEM and STEM image analyses (length measurement, Fourier transform analysis), and NORAN System SIX from Thermo Fisher Scientific was used for EDS data analyses (mapping image processing, compositional quantification, and calculation).

X-ray diffraction (XRD) measurements of the catalyst were carried out on a Rigaku RINT 2500 diffractometer using monochromated Cu Kα radiation at 40 kV and 30 mA. The catalyst sample was prepared by uniformly spraying the sample onto a nonreflective sample plate and fixing it with neoprene rubber.

X-ray photoelectron spectroscopy (XPS) experiments were conducted on a Thermo Electron ESCALAB 250 spectrometer using an Al Kα excitation source (15 kV, 10 mA) from 0–1100 eV. The oval surface region considered for the analysis was approximately 1 $mm^2$. Narrow scans of Au4f, Ni2p were carried out over the analysis region.

Ultraviolet-visible (UV-vis) measurements were carried out on a Jasco V-550 spectrometer with an integrating sphere unit and a powder sample holder. Spectra were obtained over the wavelength range 200–800 nm at a scanning speed of 400 nm/min. The samples were prepared by crushing the catalyst in an agate mortar and pestle, and the powder was placed in the sample holder for spectral measurements.

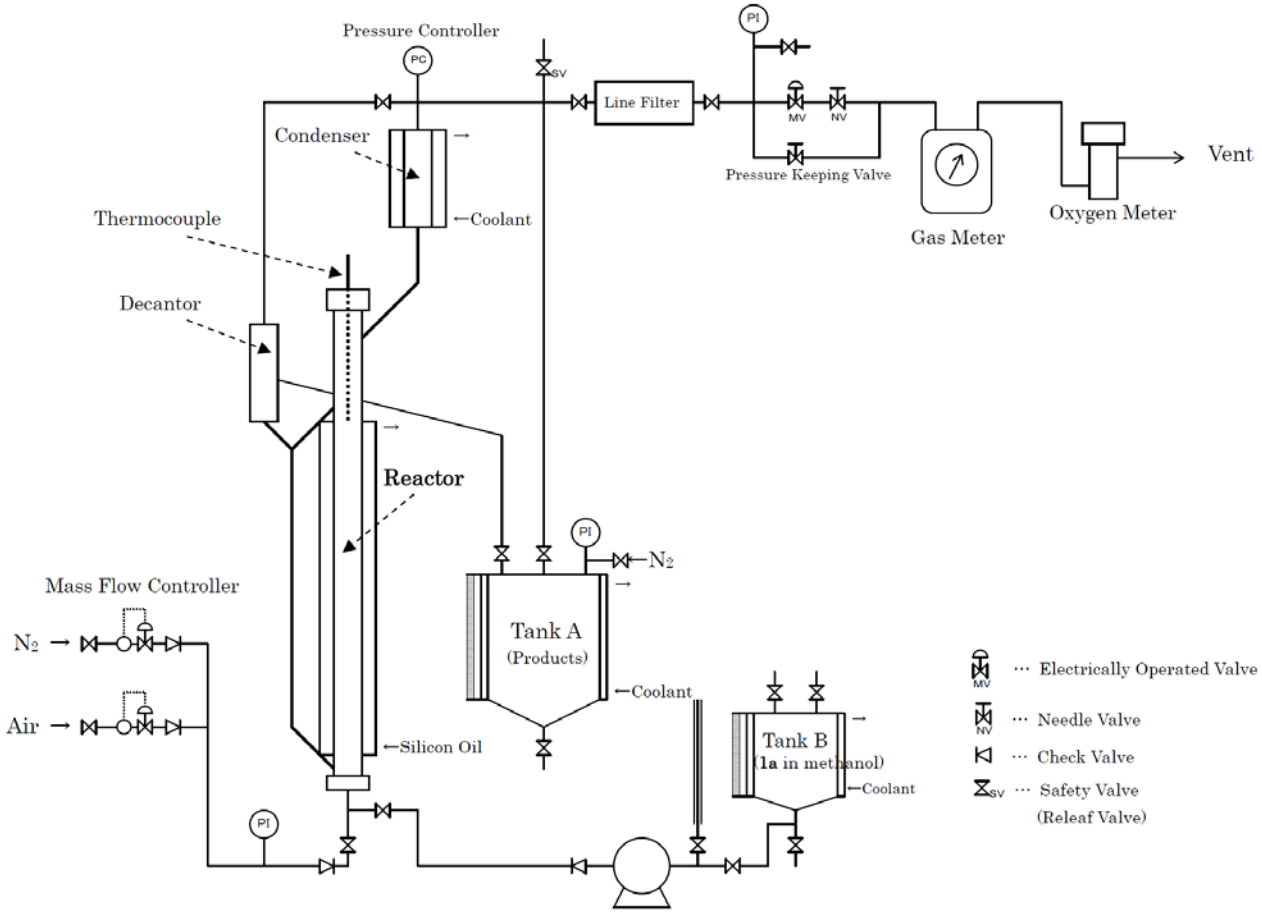
Fourier transform-infrared (FT-IR) spectra were recorded on a Shimadzu FTIR-8000 spectrometer. A cell with KBr windows was connected to a conventional vacuum system. Before CO adsorption, the catalyst samples were degassed at 350 °C for 1 h. Then CO (3cc) was introduced into the cell at 15 °C and hold for 30 min. Afterward the sample was evacuated and spectra were recorded.

Electron-probe microanalysis (EPMA) was performed on a Shimadzu Model 1600 microanalyzer at an accelerating voltage of 15 kV. The Ni and Au concentrations in the depth direction from the outer surface were determined from electron-reflected images and X-ray

analysis (Ni wavelength: 14.5829, analyzing crystal: RAP; Au wavelength: 5.8419, analyzing crystal: PET).

**Catalytic Life Test.** The catalytic life of $AuNiO_x/SiO_2–Al_2O_3–MgO$ was evaluated by using a continuous-flow reaction apparatus. The catalyst was packed in a 1.2-L stirring-type stainless-steel continuous reactor provided with a catalyst separator. A 37 wt% solution of **1a** in methanol was then continuously fed into the reactor at 0.6 L/h, and the reaction was carried out by blowing air in the reactor at 80 °C and 0.5 MPa until the exiting $O_2$ concentration became 4 vol% (equivalent to the oxygen partial pressure of 0.02 MPa). Then, the mixture was stirred (stirrer tip speed: 4 m/s). The reaction product was continuously extracted from the reactor outlet by overflow; the reactivity was investigated by GC analysis, and the products were identified by GC-MS.

***The continuous-flow reaction apparatus***



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(12) The reaction of **1a** (15 mmol) in the presence of $NiO_2 \cdot nH_2O$ (0.3 g) in methanol at 80 °C under an oxygen-nitrogen mixture (7:93 (v/v), 3 MPa) for 2 h gave a trace of **2a** (1.5 μmol).

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## List of Publications

### I. Journal

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後藤 英明, 鈴木 賢：平成 22 年度 旭化成グループ表彰 有功賞特級： 直メタ法 MMA 後段革新触媒の開発と導入

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