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New types of catalytic oxidations in organic synthesis

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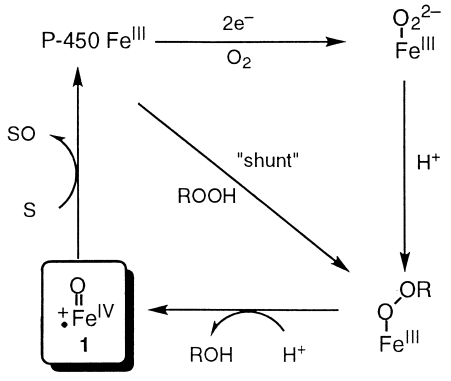
Abstract

Simulation of the enzymatic function of cytochrome *P*-450 with transition metal complex catalysts has resulted in finding biomimetic and catalytic oxidations of amines, amides, β-lactams, alcohols, phenols and hydrocarbons by using ruthenium catalyst and peroxide. Further study revealed that the catalytic formation of peracids in situ from aldehydes and molecular oxygen enables the aerobic oxidation of β-lactams, alcohols, alkanes and ketones in the presence of metal catalyst under mild conditions. © 1998 Elsevier Science B.V. All rights reserved.

1. Introduction

Oxidation is one of the most fundamental reactions in organic synthesis, and a number of stoichiometric and catalytic reactions have been reported [1–5]. However, practical and selective methods are limited to the oxidations of substrates bearing reactive functional groups, and catalytic oxidations of unactivated substrates such as amides and alkanes remains a challenging topic. In living organisms selective oxidations are achieved under mild conditions by enzymes such as methane monooxygenase (MMO) [6], cytochrome *P*-450 [7,8] and flavoenzymes [9]. Cytochrome *P*-450 catalyzes the oxidation of various organic compounds in many living organisms, from plants to mammals, and has attracted particular attention, because of its strong oxidation ability.

Cytochrome *P*-450 has two major functions. One is the activation of molecular oxygen by iron porphyrin to generate oxo-iron porphyrin, the other is its oxygen atom transfer to the substrates. The porphyrin moiety is required for the generation of hydroperoxy iron porphyrin species, which undergoes protonolysis to give oxo-iron(IV) (**1**) species as shown in Scheme 1. Simulation of these enzymatic functions with transition metals has been tried extensively. The shunt process is often used for the oxidation of organic substrates, because oxo-metal porphyrin species can be formed readily upon treatment with oxygen donors such as iodosyl benzene and hypochlorites [4,5,10].



Scheme 1. Oxidation with cytochrome *P*-450. S=substrate.

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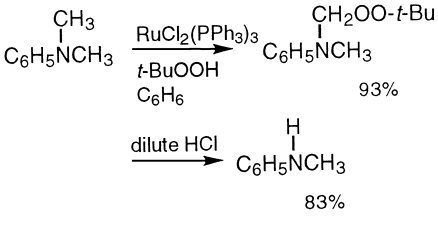
According to the shunt process, oxo-metal complexes can be also generated without porphyrins. In order to generate oxo-metal complexes, which correspond to oxo-iron(IV) species, we have investigated low valent ruthenium complexes extensively from many aspects [11,12]. Novel cytochrome *P*-450 type oxidations of amines, amides, β-lactams, alcohols, phenols, and unactivated alkanes without using porphyrins have been developed. In this paper, we would like to report these oxidations which have led to new synthetic methodologies.

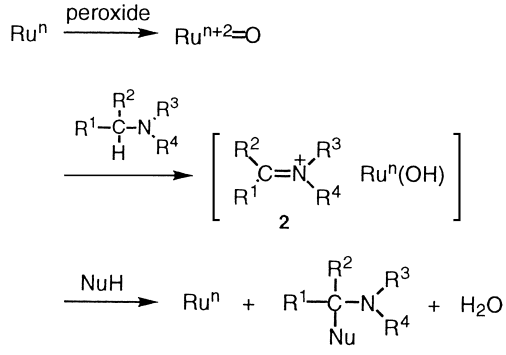
2. Oxidation of amines

Oxidative *N*-demethylation of *N*-methylamines is one of the important *P*-450 specific reactions, and several model reactions using iron-porphyrins have been reported [13]. Our systematic studies on the simulation of enzymatic function of metabolism of amines with transition metal catalyst resulted in finding novel cytochrome *P*-450 type oxidation behavior with tertiary amines without using porphyrins. Thus, the ruthenium-catalyzed oxidation of tertiary amines with *tert*-butyl hydroperoxide gives the corresponding α-(*t*-butyldioxyalkyl)amines highly efficiently Eq. (1)[14]. This is in contrast to the usual catalytic oxidation of tertiary amines with peroxides to give *N*-oxides.



(1)

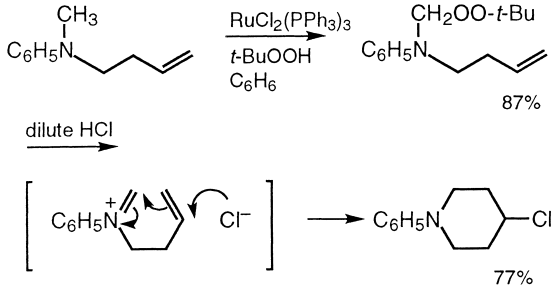
The relative reaction rates of the oxidation of five substituted *N*,*N*-dimethylanilines with *t*-BuOOH correlate well with the Hammett linear free energy relationship with use of σ values. The ρ value is −0.84, which is similar to the value (−0.74) with *P*-450, indicating cationic intermediacy at the rate-determining step. The observed intra- and intermolecular isotope effects (3.53 and 1.64) for the oxidation of *N*,*N*-dimethylanilines are larger than the values obtained for *P*-450 *N*-demethylations (1.6–3.1 and 1.0–1.1), suggesting that the C–H bond breaking in the present reaction proceeds with more radical character. These



Scheme 2.

kinetic data show that the reaction can be rationalized by assuming the cytochrome *P*-450 type mechanism shown in Scheme 2. A ruthenium(II) complex reacts with *t*-BuOOH to give an oxo-ruthenium(IV) species. Thus, the reaction of the Ru(II) complex with *t*-BuOOH yields $Ru^{II}OO$-*t*-Bu, which is transformed into the Ru^{IV}=O complex by cleavage of the O–O bond. Electron transfer and subsequent proton transfer results in forming the iminium ion complex **2**. Nucleophilic attack of *t*-BuOOH to **2** gives the product, water, and the Ru^{II} species to complete the catalytic cycle.

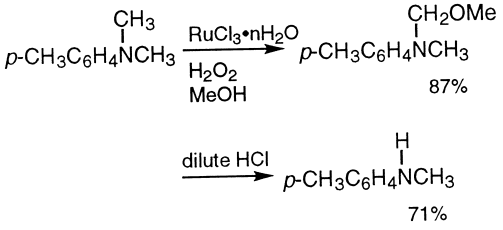
Selective *N*-demethylation of tertiary methyl amines is performed by the present ruthenium-catalyzed oxidations with *t*-BuOOH and subsequent hydrolysis with an aqueous HCl solution Eq. (1). The present reaction provides a novel, biomimetic method for construction of the piperidine skeleton from *N*-methylhomoallylamine via olefin–iminium ion cyclization reactions Eq. (2).



(2)

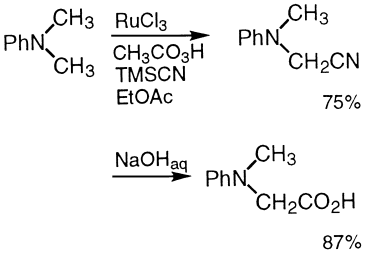
Based on Scheme 2, both generation of the oxo-ruthenium species using other oxidizing reagents and trapping of the iminium ion intermediate **2** with other nucleophiles can be expected. Indeed, catalytic systems that satisfy these two points have been explored.

The ruthenium-catalyzed oxidation of tertiary methylamines with hydrogen peroxide in the presence of methanol gives the corresponding α-methoxymethylamines with high efficiency Eq. (3)[15].



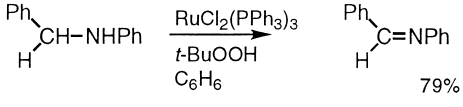
(3)

Iminium ion intermediate **2** in Scheme 2 can be considered to trap directly with carbon nucleophiles. Indeed, ruthenium-catalyzed oxidation of amines and amides with peracetic acid in the presence of trimethylsilyl cyanide gives the corresponding α-cyano derivatives efficiently Eq. (4)[16]. The direct oxidative cyanation of tertiary amines opens a new and efficient approach to the synthesis of *N*,*N*-dialkyl-α-amino acid derivatives upon subsequent hydrolysis reactions Eq. (4).



(4)

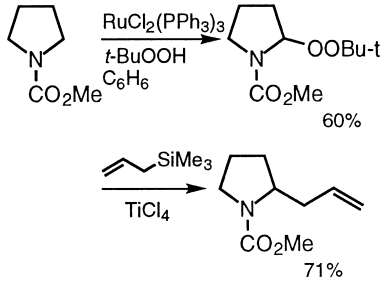
Considering Scheme 2, the oxidation of secondary amines (R^4=H) is expected to give imines. Indeed, the ruthenium-catalyzed oxidation of secondary amines with *t*-BuOOH affords the corresponding imines efficiently Eq. (5)[17]. This is the first catalytic oxidative transformation of secondary amines into imines.



(5)

3. Oxidation of amides and β-lactams

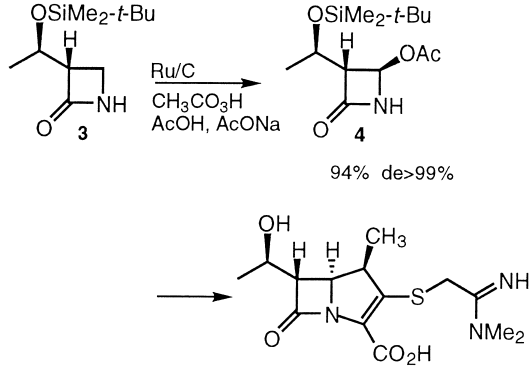
Cytochrome *P*-450 catalyzes specific oxygenation of amides; however, the selective oxidation of amides is limited to an electrochemical process [18]. The catalytic system using ruthenium catalyst and *tert*-butylhydroperoxide was found to be efficient for the oxidation of amides into α-*t*-butyldioxyamides. Typically, the oxidation of 1-(methoxycarbonyl)pyrrolidine gave 2-*t*-butyldioxy compounds Eq. (6)[19].



(6)

tert-Butyldioxyamides thus obtained undergo substitution reactions with various nucleophiles to give α-substituted amides. Therefore, we now have a method for the transformation of amides into the corresponding α-substituted amides. The most important transformation of α-*tert*-butyldioxyamides is the formation of a carbon–carbon bond at the position α to the nitrogen atom. Titanium(IV)-promoted reactions of α-*tert*-butyldioxypyrrolidine with allyltrimethylsilane gave α-allylamide in 71% yield Eq. (6)[20].

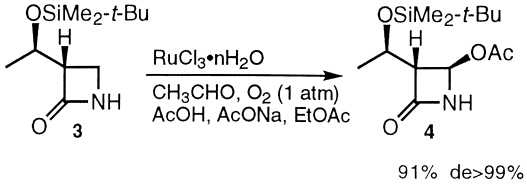
One of the most interesting oxidation of amides is the catalytic oxidation of β-lactams. However, it has remained a challenging topic since β-lactam has the ring strain of four-membered rings. We found that the treatment of β-lactams with peracetic acid in acetic acid in the presence of low valent ruthenium catalysts and sodium acetate at room temperature gives the corresponding 4-acetoxy β-lactams highly efficiently Eq. (7)[19]. 4-Acetoxy azetidinone is an important precursor of various β-lactam antibiotics such as thienamycine and carbapenems.



(7)

Ruthenium-catalyzed oxidation of (1′R,3S)-3-[1′-(*tert*-butyldimethylsilyloxy)ethyl]azetidin-2-one **3** with peracetic acid gives the corresponding 4-acetoxyazetidinone **4** with extremely high diastereoselectivity (94% yield, 99% de) Eq. (7). This is a versatile and key intermediate for the synthesis of important antibiotics and is now produced industrially.

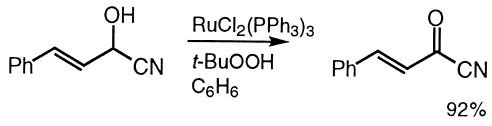
The ruthenium-catalyzed oxidation of β-lactams can be achieved efficiently using peroxides such as peracetic acid; however, peroxides are not always available. We therefore examined catalytic formation of peracids in situ from aldehydes and molecular oxygen, because it is well known that peracetic acid can be prepared upon treatment of acetaldehyde with molecular oxygen in the presence of cobalt catalyst [2]. Based on this idea, we discovered that ruthenium-catalyzed transformation of β-lactams into the corresponding 4-acetoxy β-lactams can be also performed readily upon treatment with molecular oxygen in the presence of acetaldehyde and carboxylic acid [21]. This aerobic oxidation has the same efficiency as the ruthenium-catalyzed oxidation with peracetic acid Eq. (8).



(8)

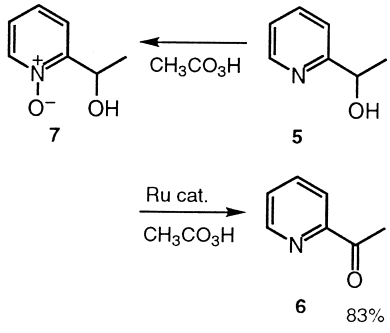
4. Oxidation of alcohols

Ruthenium-catalyzed oxidation of alcohols has been carried out with various oxidizing agents. In particular, the oxidative transformation of primary and secondary alcohols by tetrapropylammonium perruthenate (TPAP)/*N*-methylmorpholine *N*-oxide (NMO) is an excellent method [22]. Considering the results mentioned above, our catalytic system seems to be applicable for the oxidation of alcohols. Indeed, the $RuCl_2(PPh_3)_3$-catalyzed reaction of secondary alcohols with *t*-BuOOH gives ketones under mild conditions [23,24]. This oxidation can be applied to the transformation of cyanohydrins into acyl cyanides [23], which are versatile synthetic intermediates such as acylating reagents Eq. (9). The reaction of alcohols



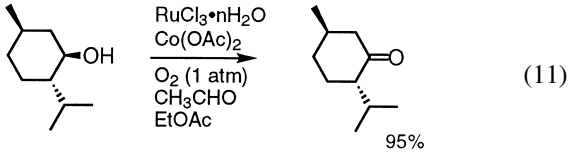
(9)

with peracetic acid in the presence of $RuCl_3$ catalyst also gave the corresponding ketones with high efficiency Eq. (10)[25]. The utility of the present reaction has been demonstrated by the selective oxidation of nitrogen-containing hydroxy compounds. Thus, the Ru/C-catalyzed oxidation of 1-(2-pyridyl)ethanol (**5**) with peracetic acid gave 2-acetylpyridine (**6**) chemoselectively Eq. (10). This is in contrast to the oxidation of **5** with peracetic acid itself, giving the corresponding *N*-oxide (**7**) preferentially Eq. (10).

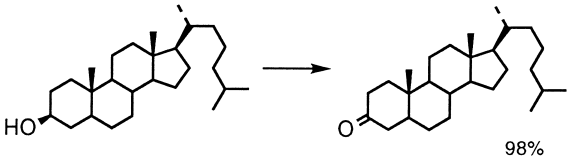


(10)

Considering the high reactivity of oxo-ruthenium complexes toward alcohols, the aerobic oxidation of alcohols in the presence of aldehydes under mild conditions seems feasible. However, under these conditions, the oxidation does not occur because the formation of peracids is prevented by strong coordination of alcohol to the ruthenium. Therefore, we examined catalysts which are known to form peracetic acid from acetaldehyde and molecular oxygen and have no strong coordination ability toward alcohols. We have found a novel, general, and efficient method for the aerobic oxidation of alcohols by using a ruthenium–cobalt bimetallic catalyst. The oxidation of alcohols is performed at room temperature with molecular oxygen (1 atm) in the presence of an aldehyde and $RuCl_3$–$Co(OAc)_2$ bimetallic catalyst Eqs. (11) and (12)[26]. Various aliphatic and aromatic secondary alcohols can be oxidized at room

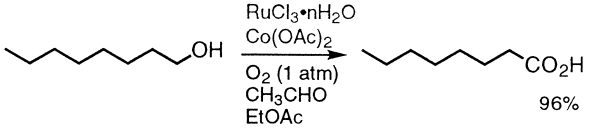


(11)



(12)

temperature under O_2 atmosphere (1 atm). Since most of the reactions proceed highly efficiently, the products can be readily isolated simply by removal of acetic acid and the catalyst through washing. Primary alcohols are oxidized to the corresponding carboxylic acids smoothly Eq. (13). The present aerobic oxidation can be rationalized by assuming the following

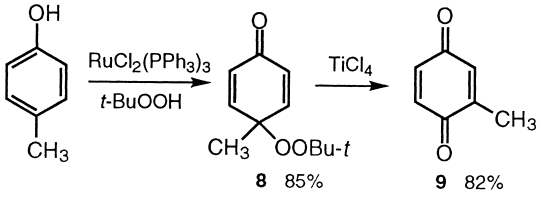


(13)

two sequential pathways: (i) formation of peracids by a cobalt-mediated radical chain reaction of aldehydes with molecular oxygen and (ii) ruthenium-catalyzed oxidation of alcohols with the peracids thus formed (Scheme 3).

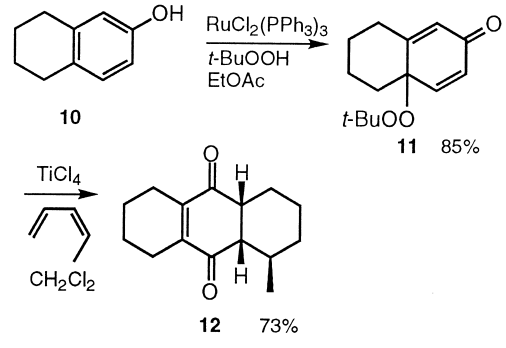
5. Oxidation of phenols

Oxidative transformation of phenols is of importance in view of its biological and synthetic aspects. However, the oxidation of phenols generally lacks selectivity because of coupling reactions caused by phenoxyl radicals, and selective oxidation of phenols is limited to phenols bearing substituents at 2- and 6-positions. During the course of our study, we have found a biomimetic method for selective oxidation of phenols. The oxidation of *p*-substituted phenols with *t*-BuOOH in the presence of $RuCl_2(PPh_3)_3$ catalyst gives 4-(*tert*-butyldioxy)-4-alkylcyclohexadienones **8** Eq. (14)[27]. The present reaction is an efficient method for the

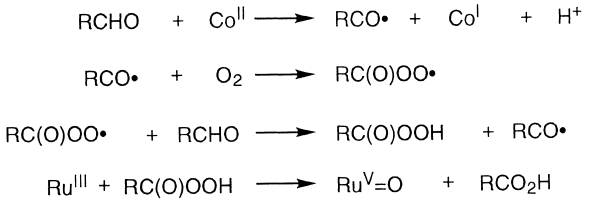


(14)

selective oxidation of the phenols that have no substituents at the 2- and 6-positions. Selective formation of **8** is due to the fast single electron transfer to ruthenium from the phenoxy radical, which is formed from the hydrogen abstraction by oxo-ruthenium, to form the cationic intermediate before radical coupling occurs. 4-(*tert*-Butyldioxy)-4-alkylcyclohexadienones thus obtained are versatile synthetic intermediates. For example, $TiCl_4$-promoted transformation of **8** gives 2-substituted quinones **9** which are rearrangement products of alkyl groups Eq. (14). Interestingly, sequential migration-Diels–Alder reactions of *tert*-butyldioxy dienone **11** in the presence of *cis*-1,3-pentadiene gave *cis*-fused octahydroanthraquinone **12** stereoselectively Eq. (15). The two-step synthesis of **12** from **11** shows great promise for further synthetic applications.



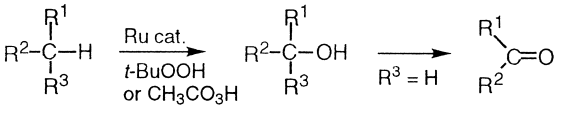
(15)



Scheme 3.

6. Oxidation of alkanes

Direct oxidation of hydrocarbons is also one of the typical reactions of cytochrome *P*-450 [7,8]. The oxo-ruthenium species (Ru=O) generated from low valent ruthenium and peroxides can be used for the oxidation of alkanes [28–30]. Actually, the oxidations of hydrocarbons with either $RuCl_2(PPh_3)_3$/*t*-BuOOH [31] or Ru/peracetic acid [32] have been reported to give the corresponding ketones and alcohols in good yields Eq. (16). Typically, ruthenium-catalyzed oxidations of cyclohexane with peroxide give cyclohexanone along with small amount of cyclohexanol efficiently Eq. (17).



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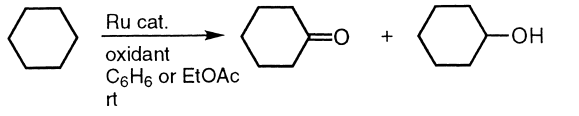
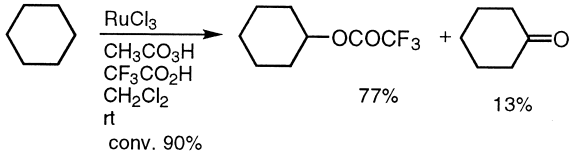


$RuCl_2(PPh_3)_3$ –*t*-BuOOH	conv. 41%	47%	7%
Ru/C–CH_3CO_3H	conv. 62%	67%	1%

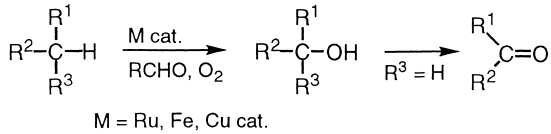
(17)

Assuming the reaction of oxo-ruthenium species, we expected more reactive species will be generated in the presence of strong acid such as trifluoroacetic acid. Indeed, the $RuCl_3{\cdot}nH_2O$-catalyzed oxidation of cyclohexane in trifluoroacetic acid and dichloromethane (5:1) with peracetic acid gives cyclohexyl trifluoroacetate in 77% Eq. (18)[32].



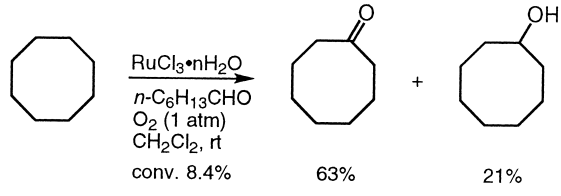
(18)

The catalytic oxidation of alkanes with molecular oxygen under mild conditions is especially a rewarding goal, since direct functionalization of unactivated C–H bonds in saturated hydrocarbons usually requires drastic conditions such as high pressure and high temperature. As shown in Eq. (16), we have found that a low valent ruthenium catalyst/peroxide system is efficient for the biomimetic oxidation of hydrocarbons. Furthermore, the oxo-metal species can be generated by the reaction of a low valent transition metal complex with molecular oxygen in the presence of an aldehyde. As a consequence of continuous study on the development of efficient aerobic oxidation reactions, we found that ruthenium catalysts are effective for the oxidation of alkanes with molecular oxygen in the presence of acetaldehyde Eq. (19)[33]. Furthermore, we found that even iron [33] and copper [34–36] catalysts are efficient for the oxidation of non-activated hydrocarbons at room temperature under 1 atm of molecular oxygen Eq. (19). Actually, $RuCl_3{\cdot}nH_2O$, iron powder, and $Cu(OH)_2$ have proven to be effective



(19)

catalysts, although $Fe(OAc)_3$, $FeCl_3$, $RuCl_2(PPh_3)_3$, and $Cu(OAc)_2$ can be also used. Aldehydes such as acetaldehyde and heptanal are effective. Typically, $RuCl_3{\cdot}nH_2O$, Fe, and $Cu(OH)_2$-catalyzed oxidations of cyclooctane, adamantane, and indane with molecular oxygen in the presence of an aldehyde give the corresponding alcohols and ketones selectively Eqs. (20)–(22).



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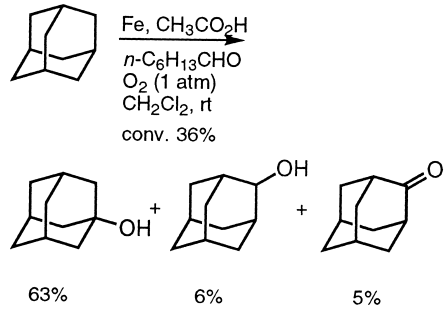

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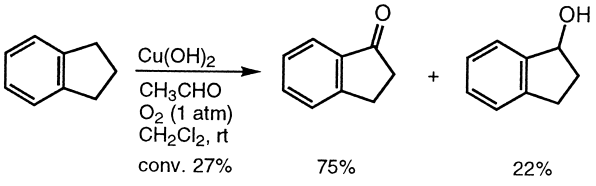

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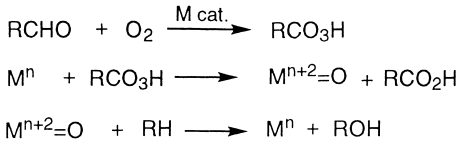
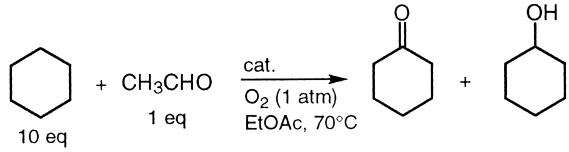


Scheme 4.

These aerobic oxidations can be rationalized by assuming the sequence shown in Scheme 4. The metal-catalyzed radical chain reaction of an aldehyde with molecular oxygen affords the corresponding peracid. The formation of peracetic acid was confirmed by ^{1}H NMR analysis. The reaction of metal catalyst with peracids thus formed would give an oxo-metal intermediate. Hydrogen abstraction of alkanes with the oxo-metal is followed by oxygen transfer to afford the corresponding alcohols. The alcohols are further oxidized to the corresponding ketones under these conditions. Recently, similar iron [37,38], cobalt [39], and vanadium [40]-catalyzed aerobic oxidations of alkanes with aldehydes were reported.

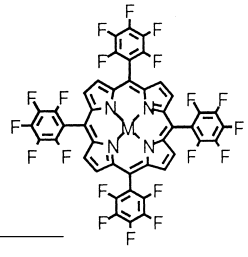
Generation of the oxo-metal porphyrin using an aldehyde and O_2 in place of single oxygen atom donors was examined, and we found that metalloporphyrins bearing meso-pentafluorophenyl groups are highly efficient catalysts for the aerobic oxidation of alkanes with acetaldehyde Eq. (23). Haber et al. reported alkane oxidations by using molecular oxygen and propanal in the presence of metalloporphyrins such as Fe(TTP)Cl, Mn(TTP)Cl, and Co(TTP) (TTP=tetra(*p*-tolyl)porphyrin), which have electron-donating group at each *meso*-aryl position; however, the catalytic activities in these reactions are not so high [41]. Perhalogenated iron- and manganese- porphyrins having ligands such as Fe(TPFPP)Cl, Mn(TPFPP)Cl, and Fe(TPFPPβ-Cl_8)Cl (TPFPP= tetrakis(pentafluorophenyl)porphyrin, TPFPPβ-Cl_8= tetrakis(pentafluorophenyl)-β-octachloroporphyrin) are generally known to be efficient catalysts for the oxidation of alkanes and alkenes with oxidants such as iodosyl benzene and molecular oxygen [4,5]. We found that a novel Ru(TPFPP)(CO) (**13**) complex is an efficient catalyst for the aerobic oxidation of alkanes using acetaldehyde Eq. (23)[42]. Furthermore, Mn(TPFPP)Cl (**14**) and Co(TPFPP) (**15**) were also found to be effective catalysts Eq. (20)[42]. The efficiency of the present catalytic reaction has been demonstrated by extremely high



cat. M =				turnover number
Ru^{II}(CO):	Ru(TPFPP)(CO)(**13**)	54%	8.1%	1.41×10^4
Mn^{III}(Cl):	Mn(TPFPP)Cl (**14**)	61%	9.4%	1.59×10^4
Co^{II} :	Co(TPFPP) (**15**)	64 %	11%	1.70×10^4

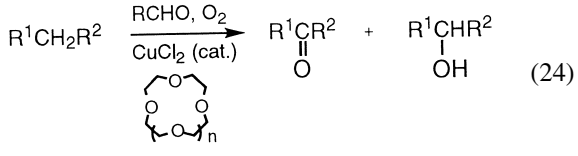
(based on acetaldehyde)

(23)



turnover numbers in the aerobic oxidation of cyclohexane, which is most important in view of its industrial application. Thus, **13**, **14**, and **15**-catalyzed oxidation of cyclohexane with molecular oxygen in the presence of acetaldehyde gave cyclohexanone and cyclohexanol in 62–75% yields based on acetaldehyde and turnover numbers of 14 100–17 000 Eq. (23).

In the copper-catalyzed oxidation of alkanes, the catalytic activity of copper salts is in the order of $Cu(OH)_2$>$Cu(OAc)_2$>>$Cu(OCOCF_3)_2$>$CuCl_2$, indicating that a copper salt bearing a more basic or an electron donating ligand is suitable for the present oxidation. Divalent copper ions form the most stable complexes with ligands amongst all the metals of the second half of the first transition series. So we thought that crown ethers could be used as an electron donating ligand for the copper catalysts, although transition metals usually do not make a stable complex with crown ethers. As a consequence of this study we found that the combination of a copper complex and a crown ether shows high catalytic activity for the present aerobic oxidation of alkanes with acetaldehyde Eq. (24)[35,36].



(24)

The efficiency of the present catalysts is highlighted by extremely high turnover numbers in the aerobic oxidation of cyclohexane. Actually, the oxidation of cyclohexane in the presence of $CuCl_2$ (2.50×10^{-3} mol%) and 18-crown-6 (2.50×10^{-3} mol%) and acetaldehyde at 70°C under O_2 atmosphere (1 atm) gave cyclohexanone (61% yield based on acetaldehyde) and cyclohexanol (10%) with turnover number of 16 200 Eq. (25).

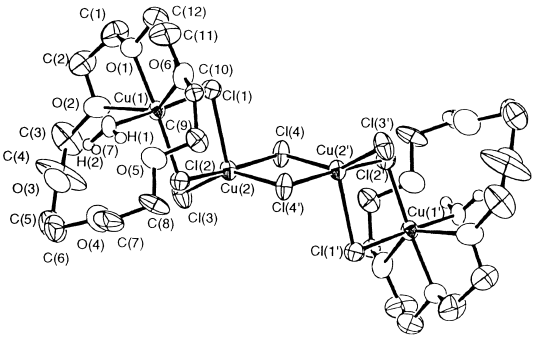
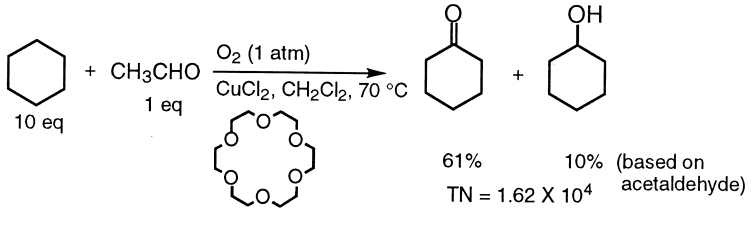
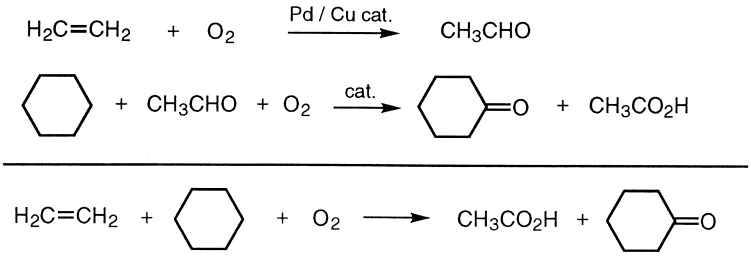


Fig. 1. The X-ray crystal structure of $[(CuCl_2)_4(18\text{-crown-}6)_2(H_2O)_2]$ (**16**). Hydrogen atoms on carbons are omitted for clarity. Atoms related by inversion center are primed.

Although stable transition metal complexes of crown ethers are rarely isolated, we succeeded in the isolation of copper crown ether complex. When $CuCl_2$ was allowed to react with 18-crown-6 in CH_2Cl_2-ether at room temperature, a 4:2 complex of $CuCl_2$ and 18-crown-6, $[(CuCl_2)_4(C_{12}H_{24}O_6)_2(H_2O)_2]$ (**16**) was obtained as a brown crystal. The structure of **16** was determined by X-ray crystal analysis as shown in Fig. 1. The complex **16** consists of tetrameric $(CuCl_2)_4$, two crown ethers and two H_2O molecules. The centrosymmetric molecule contains copper atoms in two distinct coordination geometries: the central pair of copper ions have 4+1 coordination, while the outer pair has a distorted-octahedral geometry. Each outer copper ion is hexacoordinate with three oxygen atoms of the crown ether, two bridged chlorine atoms and one oxygen atom of H_2O. Importantly, this complex is as highly efficient a catalyst as the combined use of $CuCl_2$ and 18-crown-6, indicating that ligation of crown ether is significant for the catalytic activity.



(25)

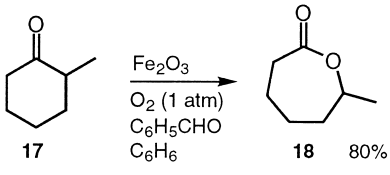


Scheme 5.

Cobalt-catalyzed aerobic oxidation of cyclohexane has been used commercially, however, the total yield of cyclohexanone and cyclohexanol is quite low. Our oxidation reaction provides a powerful industrial strategy for the synthesis of cyclohexanone by combination of Wacker Oxidation of ethylene with the present metal-catalyzed oxidation of cyclohexane (Scheme 5).

7. Baeyer-Villiger type oxidation of ketones

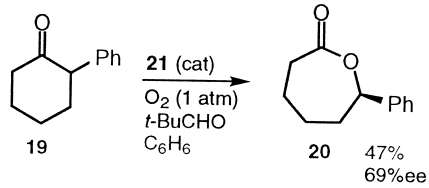
A precise mechanistic study on the iron-catalyzed oxidation of alkanes led to the discovery of a highly efficient Baeyer-Villiger oxidation of ketones with molecular oxygen (1 atm) in the presence of Fe_2O_3 catalyst and benzaldehyde Eq. (26)[43]. For example, Fe_2O_3-catalyzed

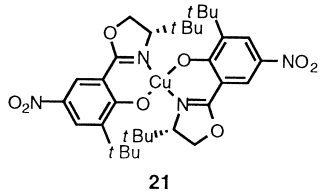


(26)

oxidation of 2-methylcyclohexane (**17**) with molecular oxygen (1 atm) in benzene in the presence of benzaldehyde at room temperature gave the corresponding lactone (**18**) efficiently Eq. (26). Both cyclic and acyclic ketones were converted to the corresponding lactones or esters highly efficiently.

The Baeyer-Villiger oxidations of ketones have been performed by using various peroxides such as peracids, hydrogen peroxide, and bis(trimethylsilyl)-peroxide; however, catalytic Baeyer-Villiger oxidations of ketones with molecular oxygen are limited to few cases [44–47]. Mukaiyama et al. reported that the oxidation of ketones by combined use of molecular oxygen and aldehydes proceeds efficiently in the presence of nickel(II) complexes coordinated with 1,3-diketone such as bis(dipivaloylmethanato)nickel-(II) [48,49]. Copper [50], heteropolyoxometalates [51], and hydrotalcite [52] have also been shown to be good catalysts, although Bayer-Villiger oxidation of ketones using molecular oxygen and benzaldehyde can occur in the absence of metal catalyst [53]. Recently, an asymmetric Baeyer-Villiger oxidation of **19** with molecular oxygen was reported with Cu^{II} catalyst **21** Eq. (27)[54].

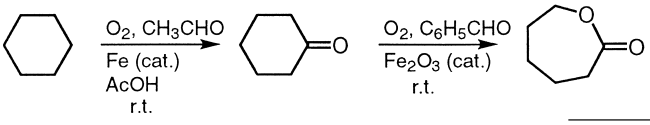




(27)

As described in Section 6, the iron(0)-catalyzed oxidation of cyclohexane with molecular oxygen in the presence of acetaldehyde and a catalytic amount of acetic acid gives cyclohexanone highly efficiently. Under the reaction conditions the Bayer-Villiger oxidation of cyclohexanone to, ε-caprolactone does not occur. In contrast, in the present Fe_2O_3-catalyzed reaction the oxidation of cyclohexane does not occur. We wish to emphasize that completely different cat-

alytic systems, that is, the aerobic oxidation of alkanes to ketones and the aerobic oxidation of ketones to lactones have been explored by using iron catalysts. Interestingly, sequential iron-catalyzed oxidations of cyclohexane with molecular oxygen give, ε-caprolactone highly efficiently, as shown in Eq. (28).



(28)

8. Conclusion and perspectives

Owing to the current need to develop forward-looking technology that is environmentally acceptable with respect to, for example, negligible formation of inorganic salts and efficient, highly selective formation of products, many aspects must be considered in the search for new catalytic oxidation reaction. The most attractive approach is biomimetic oxidation that is closely related to the metabolism of living organisms. Simulation of the function of cytochrome *P*-450 with transition metal catalysts such as ruthenium, iron, and copper has resulted in the discovery of biomimetic reactions for selective oxidations of amines, amides, β-lactams, alcohols, phenols, ketones, and even non-activated hydrocarbons using peroxides and molecular oxygen/aldehyde under mild conditions. These reactions are practically useful, because the oxidation itself is catalytic, selective, and highly efficient. The most important point is that such catalytic reactions are much more environmentally friendly and are expected to be widely used processes in the future. If our working hypothesis is correct, we will find further important strategies for synthesis of fine chemicals, drugs, and others important compounds.

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