Ruthenium catalyzed biomimetic oxidation in organic synthesis inspired by cytochrome P-450

Shun-Ichi Murahashi*[a] and Dazhi Zhang[ab]

Received 4th May 2008
First published as an Advance Article on the web 16th June 2008
DOI: 10.1039/b706709g

Simulation of the function of cytochrome P-450 with low valent ruthenium complex catalysts leads to the discovery of biomimetic, catalytic oxidation of various substrates selectively under mild conditions. The reactions discussed in this *tutorial review* are simple, clean, and practical. The principle of these reactions is fundamental and gives wide-scope and environmentally benign future practical methods.

1. Introduction

Oxidation is one of the most fundamental reactions in organic synthesis.[1] Owing to the current needs to develop forward-looking technology that is environmentally acceptable with respect to negligible formation of inorganic salts and efficient, highly selective formation of products, many aspects must be considered in the search for new catalytic oxidation reactions. The most attractive approach would be the biomimetic oxidation reaction that is closely related to the metabolism of living things. The metabolism is governed by various enzymes such as cytochrome P-450 and flavoenzymes. The metabolic routes of oxidation of a wide variety of amine compounds are of importance, because these are closely related to the metabolism of living things; however, when this chemistry was started in late 1970s, there was no general method for oxidative transformation of amine compounds under mild reaction conditions. The simulation of the functions of these enzymes with metal complex catalysts or organocatalysts should provide novel biomimetic methods for catalytic oxidations, and hence highly useful strategies for organic synthesis can be explored.[2,3] In order to find original method for exploring a new type of oxidation reaction systematically, this strategy seems to be the attractive future way. Indeed, the biomimetic catalytic oxidations were discovered to proceed with high efficiency using transition metal-catalysts and organo-catalysts.[2–7] Here, we focus on the simulation of the function of cytochrome P-450 with low valent ruthenium complex catalysts with peroxides or molecular oxygen. Cytochrome P-450 has two major functions. One is the activation of molecular oxygen with porphyrin to generated oxo iron(IV) porphyrin (Fe=O), and the other is its oxygen atom transfer to substrates.[8] The porphyrin moiety is required for two-electron reduction of molecular oxygen to generate hydroperoxy iron species, which undergoes protonolysis to give oxo iron Fe(IV)=O species. Similar oxo iron species has been generated from iron porphyrin and oxidizing reagents such as iodosylbenzene.[9]

We tried to generate the middle-valent ruthenium oxo species, which may correspond to oxo-iron species, although at that time high-valent oxo metal complexes such as RuO_4 were considered to be active species for oxidation reactions. As a target substrate

[a] *Department of Chemistry, Okayama University of Science, Ridai-cho, 1-1, Okayama, 700-0005, Japan. E-mail: murahashi@high.ous.ac.jp; Fax: +81 (0)86 256 4292; Tel: +81 (0)86 256 9513*
[b] *Department of Organic Chemistry, School of Pharmacy, Second Military Medical University, Shanghai, 200433, P. R. China. E-mail: zhangdzh@hotmail.com*

Shun-Ichi Murahashi

Shun-Ichi Murahashi received his PhD from Osaka University under the guidance of Prof. I. Moritani before spending two years as postdoctoral fellow in Prof. Ronald Breslow's group at Columbia University. He joined the faculty of Osaka University and was appointed full professor in 1979. In 2001, he moved to Okayama University of Science. His current research is focused on OMCOS chemistry, biomimetic oxidation, ruthenium chemistry, non-salt green process by C–H activation.

Dazhi Zhang

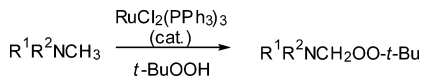
Dazhi Zhang is currently an associate professor in the Second Military Medical University (P. R. China) His research interests are organic synthesis and medicinal chemistry. He worked in Prof. Longqin Hu's group (RU) and Prof. Katritzky's group (UF) in USA as a postdoc. He is currently working in Prof. Shun-Ichi Murahashi's group at Okayama University of Science as a visiting researcher.

N-methyltertiaryamines were selected, because oxidative *N*-demethylation of *N*-methyltertiaryamines is a unique cytochrome P-450 specific reaction and plays an important role in the demethylation of very toxic naturally occurring *N*-methyltertiaryamines. Another reason is that we just found first C–H activation α to the nitrogen of tertiary amines.[10] Fortunately, novel cytochrome P-450 type oxidation of tertiary *N*-methylamines without using porphyrins was discovered.[11] Since then unique cytochrome P-450 type selective oxidative transformations of various substrates have been carried out easily. The methods developed are highly useful for organic synthesis and give an important clue to find the sp^3 C–H activation α to nitrogen. These are now very important current topics.

This review describes how a series of novel cytochrome P-450 type catalytic oxidation reactions have been explored systematically and also the usefulness of these reactions for organic synthesis and industry and designing environmentally benign methods.

2. Ruthenium catalyzed oxidation of tertiary amines

The oxidation of tertiary methylamines was investigated first, because the substrate is suitable to find cytochrome P-450 specific oxidation reaction. It was found that using low valent ruthenium(II) phosphine complex catalyst the novel cytochrome P-450 type catalytic oxidation reaction can be carried out without using porphyrins.[11] Thus, the $RuCl_2(Ph_3)_3$-catalyzed oxidation of tertiary amines **1** with *t*-BuOOH gives the corresponding α-(*t*-butyldioxy)alkylamines **2** highly efficiently as shown in Scheme 1.

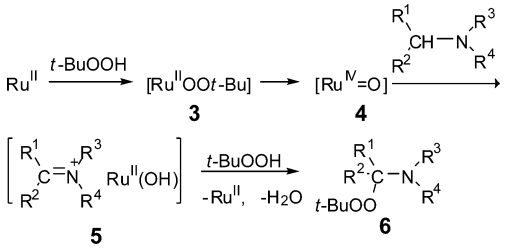


Scheme 1

This result is in contrast to the usual catalytic oxidation of tertiary amines to give *N*-oxides. The formation of α-(*t*-butoxy)alkylamines **2** is quite similar to the reaction of cytochrome P-450.

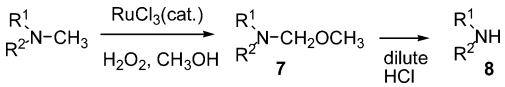
The mechanism of the oxidation reaction has been examined carefully. The results of kinetics and isotope effects are summarized in Table 1. The relative reaction rates of the oxidation of five substituted *N*,*N*-dimethylanilines ($XC_6H_4NMe_2$) with *t*-BuOOH were determined. The rate data correlate well with the Hammett linear free energy relationship with use of σ values. The ρ value is −0.84, indicating a cationic intermediacy in the rate determining step. The isotope effects were also determined. The intramolecular deuterium isotope effect (k_H/k_D) in the ruthenium-catalyzed oxidation of *N*-methyl-*N*-(trideuteriomethyl)aniline is 3.53. The intermolecular isotope effect in the oxidation of *N*,*N*-dimethylaniline is 1.64. These numbers are close to those observed for the oxidation with cytochrome P-450 (1.6–3.1 and 1.0–1.1),[12] but are slightly larger, suggesting that the cleavage of the C–H bond proceeds *via* an intermediate having more radical character.

The reaction can be rationalized by assuming the cytochrome P-450 type mechanism as shown in Scheme 2. The ruthenium(II) complex undergoes the reaction with *t*-BuOOH to give Ru(II)OO*t*-Bu **3**, which is converted to the Ru=O species **4** by cleavage of the O–O bond by protonolysis. Electron transfer and subsequent proton transfer results in the iminium ion complex **5**. Nucleophilic attack of the second molecule of *t*-BOOH on **5** would give the product **6**, water, and the Ru(II) species to complete the catalytic cycle.



Scheme 2

The generation of oxo-ruthenium species with other oxidizing reagents has been examined in order to extend this oxidation reaction. The combination of $RuCl_3$ with H_2O_2 gives similar results. Thus, the $RuCl_3$ catalyzed oxidation of tertiary amines with H_2O_2 in methanol gives the corresponding α-methoxytertiaryamines **7** with high efficiency as depicted in Scheme 3.[13] This method is useful with regards to its simple operation, mild reaction conditions, and high efficiency. The reaction mechanism has been examined. The Hammett treatment gives ρ value of −3.26. The intra- and intermolecular deuterium isotope effects are 3.47 and 3.72, respectively (Table 1). Accordingly, the ruthenium(III) complex reacts with H_2O_2 to give oxoruthenium(V) complex, which undergoes electron transfer and proton transfer from tertiary amines to afford iminium ion-hydroxy ruthenium complex. The nucleophilic attack of MeOH gives the α-methoxytertiaryamine **7**, water, and Ru(III) to complete the catalytic cycle.



Scheme 3

Table 1 Catalytic oxidation of *N*-methyltertiaryamines

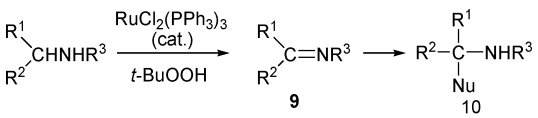
Entry	Catalyst	Oxidizing agent	Y	*H*	k_H/k_D[a]	k_H/k_D[b]	Ref.
1	$RuCl_2(PPh_3)_3$	*t*-BuOOH	OO-*t*-C_4H_9	−0.84	3.53	1.64	11
2	$RuCl_3$	H_2O_2	OCH_3	−3.60	3.47	3.72	13
3	$RuCl_3$	O_2	CN	−3.35	2.40	2.62	31
4	$RuCl_3$	H_2O_2	CN	−3.61	4.06	3.74	32
5	Cytochrome P-450	O_2	(OH)	−0.74	1.6–3.1	1.0–1.1	25

[a] Intramolecular. [b] Intermolecular.

Catalytic demethylation of *N*-methyltertiaryamines has never been performed; however, the ruthenium catalyzed oxidation followed by hydrolysis of the oxidation products **2** and **7** gives the demethylated secondary amines chemoselectively. Actually, the demethylation of *N*-methyl *N*-ethylaniline gives *N*-ethylaniline chemoselectively. This is the first synthetically practical method for *N*-demethylation of tertiary methylamines. These methods are convenient for demethylation of naturally occurring tertiary amines, and the secondary amines thus formed are convenient synthetic intermediates.

3. Ruthenium catalyzed oxidative transformation of secondary amines to imines

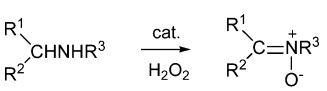
According to the mechanism shown in Scheme 2, secondary amines should be oxidized to the corresponding imines. That is, the electron transfer from secondary amine to oxo-ruthenium species **4** would lead to the iminium ion complex **5** (R^4 = H), which decomposes at this stage to give the product of imines, the Ru species, and water to complete the catalytic cycle. Indeed, the same catalytic system can be used for the conversion of secondary amines to the corresponding imines **9** with high efficiency.[14] This is the first catalytic oxidative transformation of secondary amines to imines. The reaction is particularly useful for the synthesis of cyclic imines and azadienes, because such imines are hardly accessible. Typically, the reaction of 3,4-dihydroisoquinolines **11** with *t*-BuOOH in the presence of $RuCl_2(PPh_3)_3$ catalyst at room temperature gives the corresponding imine **12**, which is an important precursor for synthesis of isoquinoline alkaloid. This provides a convenient general method for synthesis of α-substituted amines **10**, because addition of various nucleophiles to the carbon–nitrogen double bonds of imines **9** can be carried out selectively (Scheme 4).[15]



Scheme 4

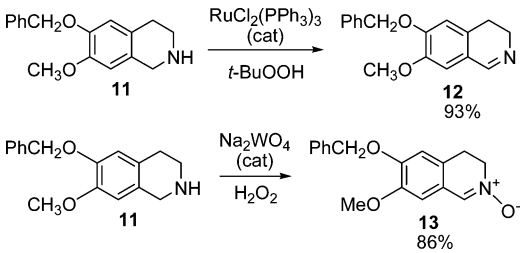
Recently Choi and Doyle reported similar $Rh_2(cap)_4$ catalyzed oxidative transformation of secondary amines to imines with *t*-BuOOH.[16]

The simulation of the function of flavoenzyme with transition metal catalysts or flavin catalyst leads to find the oxidative transformation of secondary amines to nitrones as shown in Scheme 5.[2,3] Thus, the oxidation of secondary amines with H_2O_2 in the presence of flavinium catalyst,[17] Na_2WO_4 catalyst,[18] and SeO_2 catalyst,[19] gives nitrones efficiently.



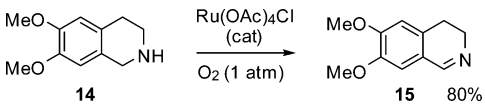
Scheme 5

Amines are sensitive substrates, and their oxidation can be carried out easily; however, selective oxidation is extremely difficult. Generation of clean active oxidizing species would lead to selective oxidation reaction. Secondary amines can be converted to either imines or nitrones by selecting the catalytic system cleanly. Typically, the ruthenium catalyzed oxidation of the amine **11** with *t*-BuOOH gives the imines **12** in 93% yield, while the tungstate–catalyzed oxidation of the same amine **11** with H_2O_2 gives the nitrone **13** in 86% yield (Scheme 6).



Scheme 6

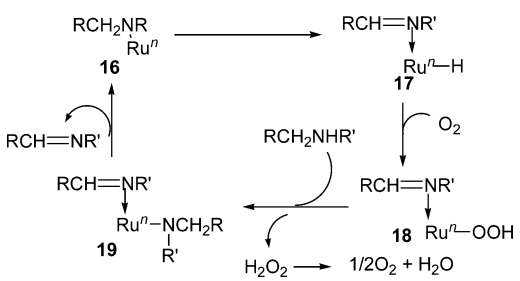
Recently the oxidative transformation of secondary amines was improved dramatically, because the reaction can be carreid out with molecular oxygen under mild conditions. Using ruthenium bimetallic complex catalyst $Ru_2(OAc)_4Cl$, the aerobic oxidation of secondary amines **14** in toluene at 50 °C under O_2 (1 atm) gives imine **15** in 80% isolated yield[20] (Scheme 7).



Scheme 7

The reaction can be rationalized by assuming the mechanism shown in Scheme 8. The initial coordination of secondary amines (RCH_2NHR') to $Ru_2(OAc)_4Cl$ gives **16** by ligand exchange reaction, subsequent β-hydride elimination gives the ruthenium hydride species **17**. The attack of molecular oxygen to the Ru–H of **17** affords a ruthenium hydroperoxide **18**. Such oxidation of the metal hydride with molecular oxygen to give M–OOH species was demonstrated for the first time in the asymmetric oxypalladation reactions of allyl phenols.[21] Addition of a secondary amine to **18** would give **19**, which leads to the imines and **16**.

It is noteworthy that Backvall *et al*. reported interesting aerobic dehydrogenative oxidation of secondary amines by

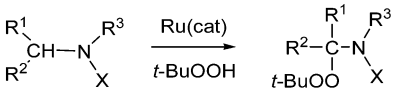


Scheme 8

biomimetic catalytic system. The ruthenium catalyzed aerobic oxidation in the presence of excess of electron-rich quinones proceeds at 110 °C.[22]

4. Ruthenium catalyzed oxidation of amides

The oxidation of the C–H bond at the α position of amides is of importance in view of the xenobiotic amino compounds and is one of the most attractive strategy for the synthesis of biologically active nitrogen compounds. Cytochrome P-450 enzymes catalyze specific oxidation reaction; however, the oxidation of amides is limited to the electrochemical process. The cytochrome P-450 type oxidation of tertiary amines can be applied to the oxidation of amides. Thus, the ruthenium-catalyzed oxidations of amides with *t*-BuOOH under mild conditions gives the corresponding *t*-butyldioxyamides as shown in Scheme 9.[23]



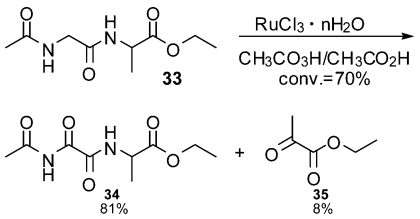
Scheme 9

Various *N*-protected secondary amines can be converted into the corresponding α-(*t*-butyldioxy)amides **20**. Particularly, the oxidation of cyclic amides, which have some resistance to the oxidation, proceeds efficiently. The oxidation of 1-(methoxycarbonyl)pyrrolidine **21** gives the corresponding oxidized product **22** in 60% yield. The *t*-butyldioxy amides of tetrahydroisoquinolines **23** (91%), **24** (98%), **25** (97%), and the indol **26** (92%), which are important intermediates for synthesis of natural products, are obtained highly efficiently from the corresponding amides.

The oxidation of proteins and peptides is of interest in view of aging and diseases. Oxidative modification of peptides is a useful tool for altering chemical and biological properties. However, there is no report on catalytic backbone modification of peptides except for the modification by the side-chain scission at the serine and threonine residue. Using the cytochrome P-450 type oxidation reaction, a novel catalytic backbone modification at the glycine residue of peptides is performed without backbone fragmentation. Typically, the catalytic oxidation of Ac-Gly-Ala-OEt **33** with peracetic acid in the presence of $RuCl_3$ catalyst in acetic acid gives Ac-NHCOCO-Ala-OEt **34** (81% yield), which is obtained by the oxidation at the C^{α} position of the glycine residue, and ethyl pyruvate **35** (8%), obtained by the oxidation at the C^{α} position of the alanine residue followed by hydrolysis.[24] The product ratio of the oxidation of the glycine residue and the alanine residue is 10 to 1 (Scheme 10).

5. Ruthenium catalyzed oxidation of β-lactams

One of the most challenging topics in the oxidation of amides is the catalytic oxidation of β-lactams, because β-lactams are highly strained unstable molecules, and are readily decomposed under acidic or basic conditions and oxidation conditions.



Scheme 10

Many attempts were in vain. Even the oxidation with oxo-ruthenium species derived from *t*-BuOOH was not successful. The ruthenium catalyzed oxidation with the more reactive peracetic acid in a buffer solution was discovered to proceed under mild conditions highly efficiently.[23] The obtained acetoxylated products are useful key intermediates for synthesis of antibiotics. Thus, 5% ruthenium on charcoal-catalyzed oxidation of azetidinones with peracetic acid in acetic acid in the presence of sodium acetate at room temperature gives the corresponding 4-acetoxy-2-azetidinones **28–30** in high yields as shown in Table 2.[23] It is noteworthy that these oxidation reactions do not occur with RuO_2 and RuO_4 catalysts.

Importantly, (1′*R*,3*S*)-3-[1′-(tertbutyldimethylsilyloxy)ethyl]azetidin-2-one **31** can be converted to the corresponding 4-acetoxyazetidinone **32** with extremely high stereoselectivity (99%, 99% de, Scheme 11). The product is a versatile and common key intermediate for the synthesis of antibiotics such as carbapenems. Now, 100 000 kg of the compound **32** is produced per year in the industry.

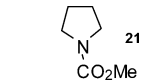
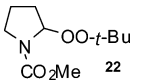
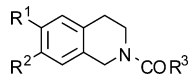
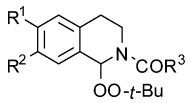
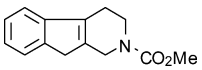
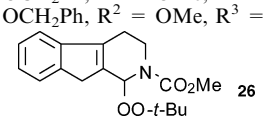
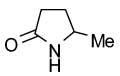
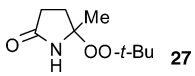
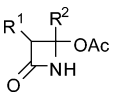
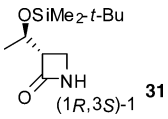
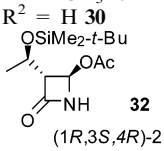
Interestingly similar oxidation of β-lactams can be carried out using $OsCl_3$ catalyst.[25] This is the first example of the C–H activation with osmium catalyst. For the oxidative transformation of **31** to **32** various oxidizing reagents such as mcpba (73%) and methyl ethyl ketone peroxide (70%) can be used in addition to CH_3CO_3H (92%).

Furthermore the oxidation of β-lactams can be carried out with molecular oxygen. In industry, peracetic acid is produced by the cobalt catalyzed aerobic oxidation of acetaldehyde. So it is expected that if peracetic acid is generated from the ruthenium catalyzed aerobic oxidation of acetaldehyde, one pot synthesis of the azetidinone **32** can be constructed by the ruthenium catalyzed aerobic oxidation of **31** in the presence of acetaldehyde. Indeed, the $RuCl_3$ catalyzed oxidation of β-lactam **31** with molecular oxygen (1 atm) in the presence of acetaldehyde and sodium carboxylate gives the corresponding 4-acetoxyl β-lactams **32** in 91% yields.[26] Various carboxylic acids can be introduced at the 4 position of the strained four-menbered iminium ion intermediate, giving 4-substitued β-lactams (Scheme 12).

6. Substitution at α-C–H bonds of amines and amides

The substituent at α position of amines and amides is of importance in view of synthesis of biologically active nitrogen compounds. Generally, introduction of a carbon–carbon bond at the α position of amines has been performed with carbon electrophiles.[27] That is, *N*-protection of the amines with an electron-withdrawing group Z, lithiation with organolithium

Table 2 Ruthenium catalyzed oxidation of amides and β-lactams

Substrate	Method[a]	Product	Yield (%)
 **21**	A	 **22**	60
			
	A	R^1 = H, R^2 = H, R^3 = OMe **23**	91
	A	R^1 = OCH_2Ph, R^2 = OMe, R^3 = Me **24**	98
	A	R^1 = OCH_2Ph, R^2 = OMe, R^3 = OMe **25**	97
	A	 **26**	92
	A	 **27**	80
			
	A	a: R^1 = H, R^2 = H **28**	94
	A	b: R^1 = H, R^2 = CH_3 **29**	86
	A	c: R^1 = H, R^2 = H **30**	82
 **31** (1*R*,3*S*)-1	B	 **32** (1*R*,3*S*,4*R*)-2	99

[a] A: *t*-BuOOH/$RuCl_2(PPh_3)_3$, B: CH_3CO_3H/Ru–C.

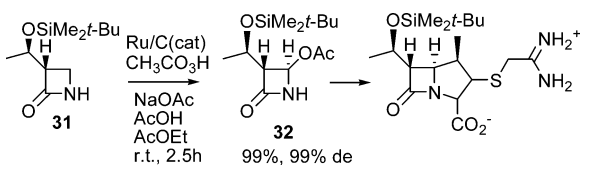
compounds to give carbanions, subsequent treatment with carbon electrophiles, and removal of the protecting group Z gives α-substituted amines.[27] The limitation of this method is the difficulty in the scale-up of the reaction.

In contrast, α-substituted amides **38** can be obtained by the ruthenium-catalyzed oxidation of amides **36**, followed by the reactions of the oxidized product **37** with carbon nucleophiles (Scheme 13).[28]

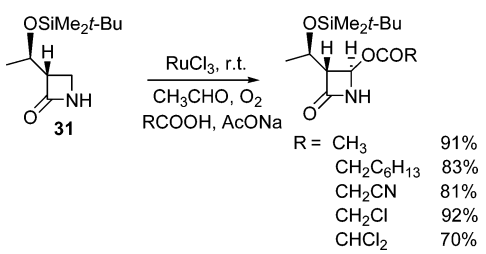
The oxidation reaction of tertiary amines shown in Scheme 1 provides a novel, biomimetic method for construction of the piperidine skeleton from *N*-methylhomoallylamine by means of an olefin-iminium ion cyclization reaction, likewise the biological transformation of (+)reticuline to (−)scoulerine. This is the first demonstration of the construction of the piperidine structure using *N*-methyl group. The oxidation of *N*-methyl-*N*-(3-heptenyl)aniline **39** followed by treatment with hydrogen chloride solution gives *trans*-1-phenyl-3-propyl-4-chloropiperidine **40** (77%) as shown in Scheme 14.[23] Similarly *cis*-4a-hydroxy-2-phenyldecahydroisoquinoline **42** is obtained from *N*-methyl-2-(1-cyclohexyl)ethylaniline **41** selectively by the oxidation followed by treatment with an aqueous CF_3CO_2H solution (oxidation 85%, cyclization 44%).[23]

Furthermore the present reaction provides an efficient method for the construction of the quinoline skeleton. Thus, *cis*-fused tricyclic amine **43** is obtained by the oxidation of *N*,*N*-dimethylaniline with H_2O_2 followed by treatment with 1,3-cyclohexadiene (oxidation 67%, cyclization 91%, Scheme 15).[13]

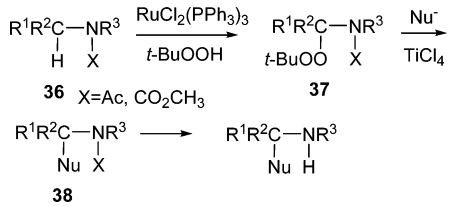
The most important synthetic utilization of *t*-butyldiosy amides **37** is the carbon–carbon bond formation α to the nitrogen. Typically, the $TiCl_4$ promoted reaction of **22** with silyl enol ether at −78 °C gives keto amide **44** in 81% yield (Scheme 16).[28]



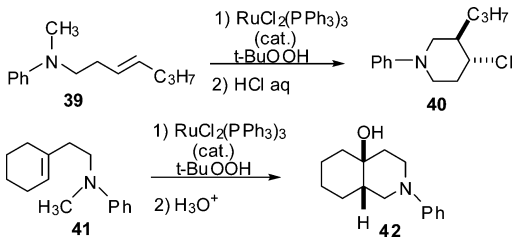
Scheme 11



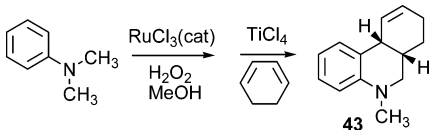
Scheme 12



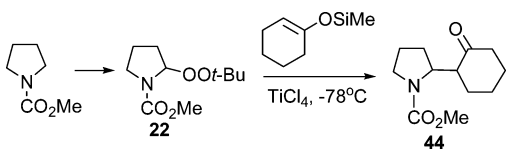
Scheme 13



Scheme 14

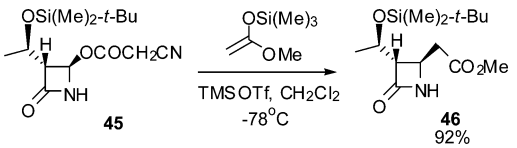


Scheme 15



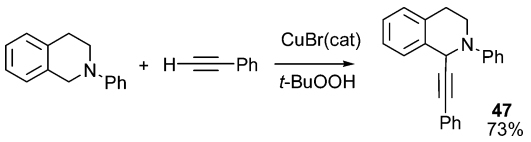
Scheme 16

Of course, the oxidation product of azetidinone undergoes carbon–carbon bond formation at the α-position. Thus the compounds **45**, which has a better leaving group of $OCOCH_2CN$ than acetate, undergoes reaction with ketene silyl acetal at −78 °C, giving 4-methoxycarbonylmethyl β-lactam **46** stereoselectively in 92% yield (Scheme 17).[26]



Scheme 17

Recently, Li *et al*. discovered interesting series of carbon–carbon bond formation at the α-position of cyclic tertiary amines by the CuBr catalyzed oxidation with *t*-BuOOH together with treatment with various pro-nucleophiles including alkynes (Scheme 18),[29a] nitromethanes,[29b] malonates,[29c] indoles,[29d] and naphthols[29e] as summarized in Table 3. Typically, the reaction of tetrahydroisoquinoline with phenylacetyrene gives **47** in 73% yield.[29a] Li *et al*. call this reaction as cross-dehydrogenative coupling reactions. The reaction can be rationalized by assuming that the CuBr catalyzed oxidation of tertiary amines with *t*-BuOOH would give iminium ion intermediate likewise the ruthenium catalyzed oxidation, followed



Scheme 18

by the CuBr promoted reaction with pro-nucleophiles. Indeed, the temperature at which the reactions are run correlates well with the ease of activation of pronucleophiles.

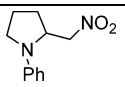
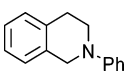
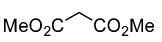
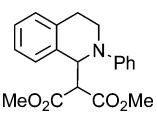
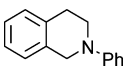
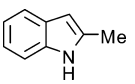
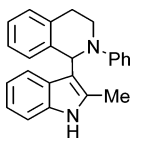
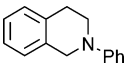
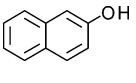
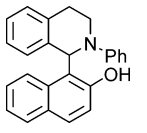
Doyle *et al*. reported unique dirhodium caprolactamate ($Rh_2(cap)_4$) catalyzed oxidative carbon–carbon bond formation of tertiary amines upon treatment with *t*-BuOOH in the presence of siloxyfuranes (Scheme 19).[30]

7. Direct oxidative transformation of tertiary amines with molecular oxygen

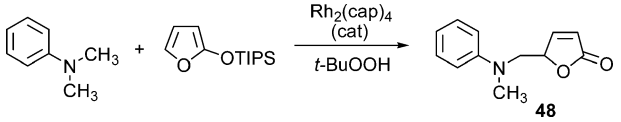
In the search for an environmentally benign and effective method for direct oxidative transformation of tertiary amines with molecular oxygen, the trap of the iminium ion intermediates **49** with carbon nucleophiles without isolation of the oxidation products **50** is the most attractive way as shown in Scheme 20. We aimed at direct cyanation of tertiary amines by accomplishing two tasks at the same time; that is, (1) C–H activation by oxidation with environmentally benign oxidant of molecular oxygen, and (2) trapping of the iminium ion intermediate **49** with a carbon nucleophile under oxidative conditions to give the carbon–carbon bond formation product **51** as shown in Scheme 20.

We found that ruthenium-catalyzed oxidative cyanation of tertiary amines with molecular oxygen in the presence of sodium cyanide gives the corresponding α-aminonitriles **52** highly efficiently (Scheme 21).[31] This is the first example of aerobic, catalytic method for carbon–carbon bond formation under oxidation conditions, and the method is environmentally benign and highly useful for organic synthesis.

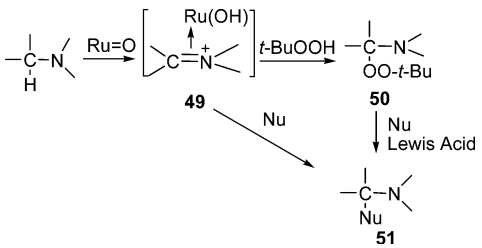
Table 3 Copper catalyzed oxidative cross-coupling[a]

Substrate		Product	Yield (%)
	$MeNO_2$		53
			74
			80
			63

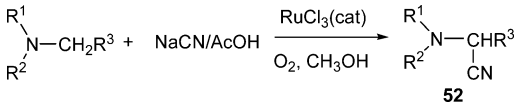
[a] Conditions: CuBr, *t*-BuOOH, NuH.



Scheme 19

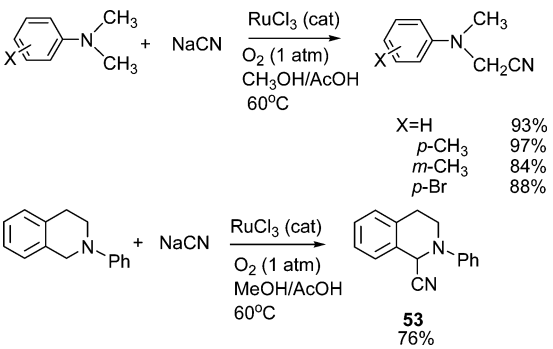


Scheme 20



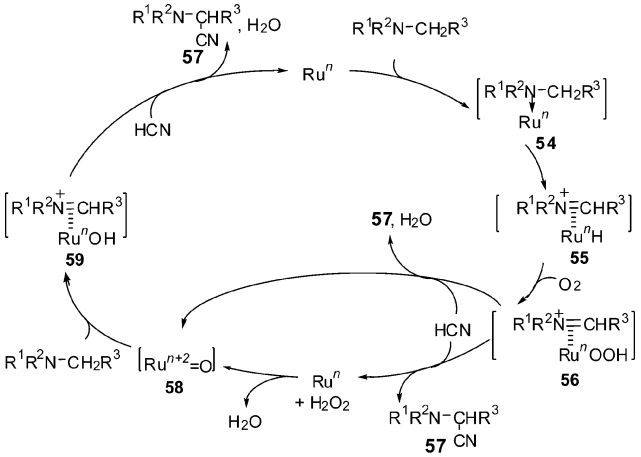
Scheme 21

Typically, the reaction of *N*,*N*-dimethylaniline with sodium cyanide in the presence of $RuCl_3$ catalyst (5 mol%) and acetic acid in methanol under molecular oxygen (1 atm, balloon) at 60 °C for 2 h gives *N*-methyl-*N*-phenylaminoactonitrile as shown in Scheme 22. The reaction can be applied to various tertiary amines. The cyanation takes place selectively at the C-1 position of *N*-phenyl 1,2,3,4-tetrahydroisoquinoline, affording the corresponding α-cyanated compound **53** in 76% yield.



Scheme 22

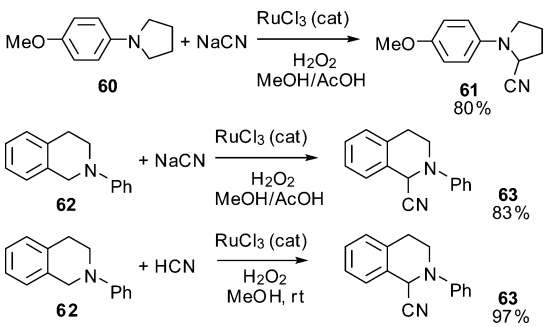
This is a simple catalytic reaction; however, the mechanism is not so simple and very interesting to be solved. The Hammett treatment of the cyanations of *para*-substituted *N*,*N*-dimethylanilines gives ρ value of −3.35 as shown in Table 2.[31a] The intra- and intermolecular deuterium isotope effects for the oxidative cyanation of *N*,*N*-dimethylanilines and its deuterated derivatives are 2.40 and 2.62, respectively. Noteworthy is that the intramolecular deuterium isotope effect for the para-substituted *N*-methyl-*N*-trideuteriomethylanilines (*p*-X-$C_6H_4N(Me)CD_3$, *p*-MeO, *p*-Me, H, *p*-Br) are 4.2, 3.1, 2.4, 1.1, respectively, indicating that electron transfer from the amine to the ruthenium would take place at the initial step.[31] One mole of molecular oxygen is consumed for the oxidation of two moles of tertiary amines. The reaction can be rationalized in terms of the mechanism shown in Scheme 23.



Scheme 23

The low valent ruthenium species Ru^n would coordinate to tertiary amine to give **54**.[10] Electron transfer and subsequent hydrogen transfer from the amine to the ruthenium results in the formation of iminium-ion–ruthenium hydride complex **55**. The ruthenium hydride species **55** undergoes the reaction with molecular oxygen to form an iminium ion Ru^nOOH complex **56**. Such oxidation of a metal hydride M–H species with molecular oxygen to give M–OOH species has been clearly demonstrated in the asymmetric oxypalladation of allylphenols,[21] and later in the ruthenium catalyzed reactions.[32] Subsequent reaction of the iminium ion-ruthenium–RuOOH complex **50** with HCN, which is generated from NaCN and acetic acid under the reaction conditions, gives α-aminonitrile **57**, Ru^n, and H_2O_2. The reaction of Ru^n with H_2O_2 thus formed would form $Ru^{n+2}{=}O$ species **58**, which undergoes reaction with another tertiary amine to give iminium ion intermediate **59** by electron transfer and subsequent hydrogen transfer. The iminium ion intermediate **59** is trapped with cyanide to afford α-aminonitriles **57**, Ru^n, and water to complete the catalytic cycle. Alternatively **58** can be generated for **56** directly.

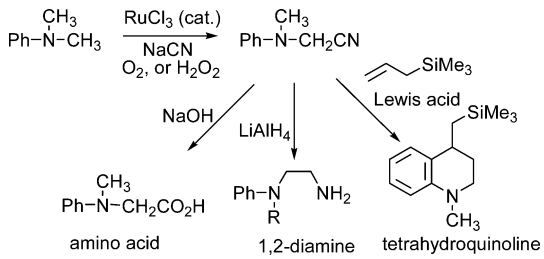
According to the mechanism of the aerobic oxidative cyanation shown in Scheme 23, the oxidative cyanation of tertiary amines with H_2O_2 should take place, giving α-aminonitriles **57**. Indeed, the $RuCl_3$-catalyzed oxidation of tertiary amines with H_2O_2 in the presence of cyanide gives the corresponding α-aminonitriles highly efficiently (Scheme 24).[33] Various



Scheme 24

tertiary amines such as pyrrolidine derivatives **60**,[33] and tetrahydroisoquinoline derivative **62** can be converted to the corresponding α-aminonitrile **61** and **63**, respectively. Noteworthy is that the oxidative cyanation also proceeds in the presence of hydrogen cyanide as shown in Scheme 24.

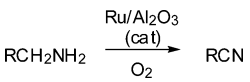
α-Aminonitriles thus obtained are versatile intermediates for organic synthesis,[31b,34] because these compounds exhibit valuable reactivity. The nitrile functionality can be hydrolyzed to produce α-amino acids, and nucleophilic addition to the nitrile group provides α-amino aldehydes, α-aminoketones, α-aminoalcohols, and 1,2-diamines (Scheme 25).



Scheme 25

It is noteworthy that Li *et al*. reported similar aerobic CuBr catalyzed oxidative coupling of tetrahydroisoquinoline with nitroalkanes.[35]

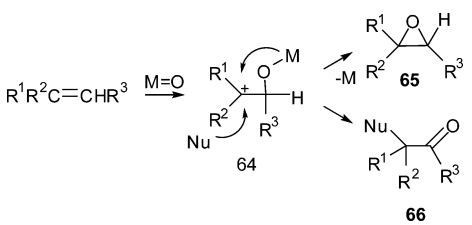
The oxidative transformation of primary amines to the corresponding nitriles is performed readily upon treatment with molecular oxygen in the presence of heterogeneous catalyst of Ru/Al_2O_3 in $PhCF_3$ at 100 °C (Scheme 26).[36]



Scheme 26

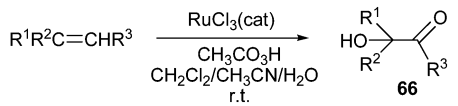
8. Oxidative transformation of alkenes to α-ketols

One of the typical functions of cytochrome P-450 is the epoxidation of alkenes. Many methods for selective efficient epoxidations of alkenes have been reported;[37] however, there is no space to describe them here. Therefore only ruthenium specific unique oxidative transformation of alkenes to α-ketols is described. In the cytochrome P-450 type oxidation, the cationic intermediate **64** has been postulated as a key intermediate.[38] If one could trap the intermediate **64** with nucleophiles such as water and β-metal hydride (MH) elimination takes place, a new type of catalytic oxidation of alkenes is expected to be constructed (Scheme 27).



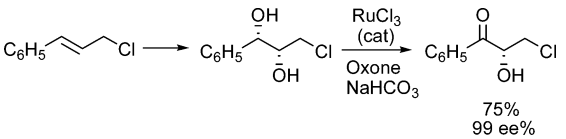
Scheme 27

In fact, novel oxidative transformation of alkene to α-ketol was discovered. Thus, the $RuCl_3$ catalyzed oxidation of alkenes with peracetic acid in an aqueous solution (CH_2Cl_2–CH_3CN–H_2O) under mild conditions affords the corresponding α-ketols highly efficiently (Scheme 28).[39]



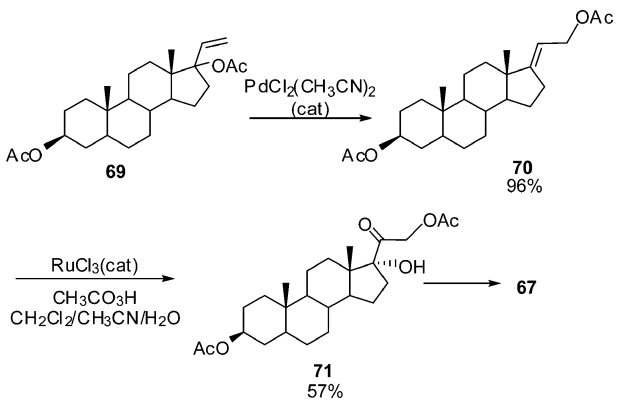
Scheme 28

Noteworthy is that this oxidation is quite different from the oxidation with RuO_4. For example the present oxidation of 1-methylcyclohexene gives the corresponding α-ketol, while the oxidation with RuO_4, which is generated catalytically from $RuCl_3$-$NaIO_4$, gives the corresponding keto-acid.[40] The α-ketol **66** is formed directly according to Scheme 27 rather than the two-step reaction, that is, dihydroxylation[39] followed by mono-oxidation. It is noteworthy that the two-step synthesis of chiral α-ketols is carried out by asymmetric dihydroxylation followed by regioselective mono-oxidation upon the treatment with $RuCl_3$/oxone/$NaHCO_3$ system (Scheme 29).[41]

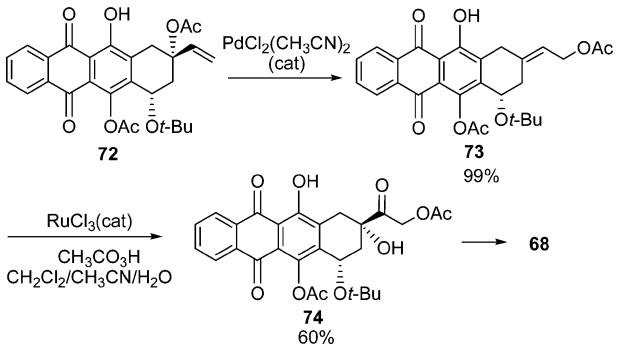


Scheme 29

The present method is particularly useful for synthesis of biologically important compounds bearing α-ketol structures. The synthesis of cortisone acetate **67** and adriamycin acetate **68** were successfully carried out using this method as a key step. The common key strategy for synthesis of α-ketols from allyl acetates is as follows; the palladium catalyzed rearrangement of allyl acetates followed by the ruthenium catalyzed oxidative transformation of allyl acetates to α-ketols. In case of synthesis of cortisone acetate **67**, the ruthenium catalyzed oxidative transformation of **70** to **71** proceeds stereoselectively in 57% yield (Scheme 30).[40] Similarly, the oxidation of the acetate **73** gives the α-ketol intermediate **74** stereoselectively (60%) (Scheme 31).[42]

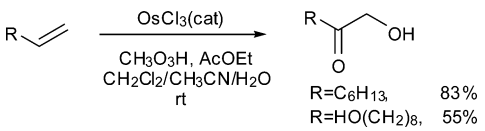


Scheme 30



Scheme 31

It is important that the regioselectivity of the introduction of oxygen functions to alkenes can be controlled by changing of metal catalysts. That is, the ruthenium catalyzed oxidation gives α-ketols with Markovnikov selectivity, while the osmium catalyzed oxidation gives the product with anti-Markovnikov selectivity. Thus, the oxidation of alkenes with peracetic acid in the presence of $OsCl_3$ catalyst in CH_2Cl_2–CH_3CN–H_2O gives the α-ketal.[43] The alcohols tolerate the reaction, and the reaction is quite different from the OsO_4 catalyzed reaction to give 1,2-diols (Scheme 32).[44]



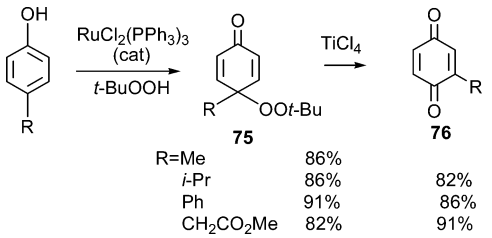
Scheme 32

9. Oxidation of phenols

Many excellent methods for catalytic oxidation of alcohols with molecular oxygen under mild reaction conditions[45] and dehydrogenative oxidation reactions[46] have been explored, there is no space to describe these results here; therefore, the ruthenium specific unique oxidation of phenols is described.[47]

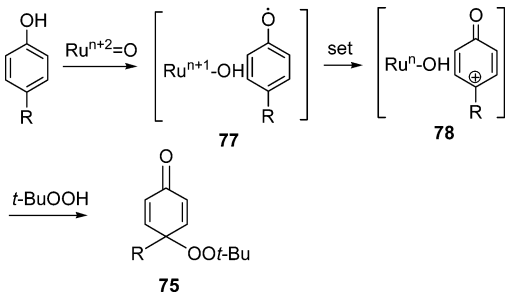
Oxidative transformation of phenols is of importance in view of its biological and synthetic aspects; however, oxidation of phenols proceeds non-selectively, giving a variety of side reaction products derived from radical coupling and over-oxidation. Selective oxidations of phenols are limited to those bearing bulky substituents at their 2 and 6 positions. We discovered that $RuCl_2(PPh_3)_3$ catalyzed oxidation of *p*-substituted phenols with *t*-BuOOH proceeds selectively to give the corresponding *t*-butyldioxydienone **75** without bearing any substituent at the 2 and 6 positions as shown in Scheme 33.[47]

The reason why this reaction proceeds selectively with ruthenium catalyst. The hydrogen abstraction of phenol with ruthenium oxo species derived from $RuCl_2(PPh_3)_3$ and *t*-BuOOH would afford a phenoxy radical–RuOH intermediate **77**. The electron transfer from the phenoxy radical to ruthenium would give the cationic intermediate **78**, which undergoes nucleophilic reaction with the second molecule of *t*-BuOOH, to give *t*-butyldioxy product **75**, water, and the ruthenium(II) complex to complete the catalytic cycle. Selective formation of **75** is due to very fast single electron transfer (SET) ability of ruthenium to



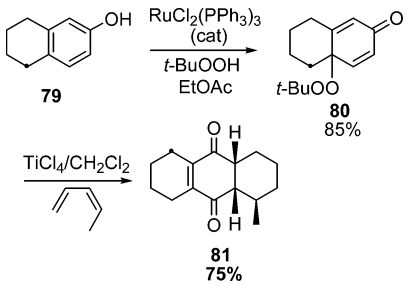
Scheme 33

phenoxy radical **77** to form the cationic intermediate **78**, before radical coupling occurs (Scheme 34).



Scheme 34

The dienones thus obtained are versatile synthetic intermediates. Typically, treatment of **75** with $TiCl_4$ at −78 °C gives the corresponding 2-substituted quinone selectively with high efficiency as shown in Scheme 33. An additional application of the transformation of phenols is illustrated by sequential migration Diels–Alder reaction. One pot synthesis of *cis*-fused octahydroanthraquinone **81** (75%) indicates great promise for further synthetic application (Scheme 35).

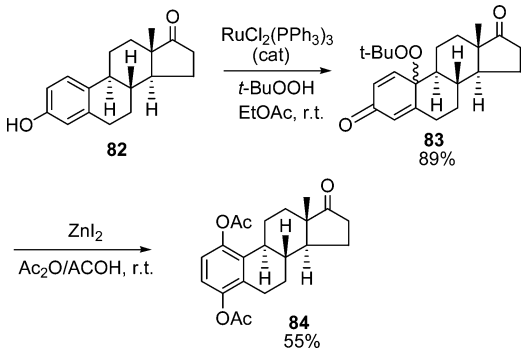


Scheme 35

The isolation and structure determination of metabolic products from drugs is particularly important in view of evaluation of medicines. In this aspect the oxidation of female hormone and isolation of the related compounds is interesting. The oxidation of female hormone of estrone **82** gives a diastereomeric mixture of the peroxide **83** (56 : 44) (89%), which corresponds to the metabolic product, is converted to the diacetate **84** upon treatment with ZnI_2 in 55% yield (Scheme 36).[47]

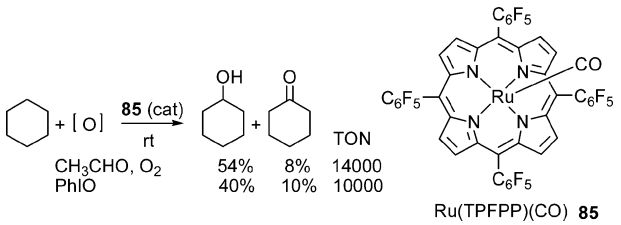
10. Oxidation of hydrocarbons

The catalytic oxidation of hydrocarbon remains as a challenging topic. Oxidation of hydrocarbons is one of the typical functions of cytochrome P-450. The ruthenium complex with perfluorinated



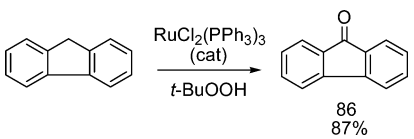
Scheme 36

porphyrin **85** is the most effective and robust catalyst. The ruthenium porphyrin **85** catalyzed oxidation of cyclohexane with molecular oxygen and acetaldehyde[48] or PhIO[49] gives a mixture of cyclohexanol and cyclohexanone with very high turnover numbers and high yields as shown in Scheme 37.



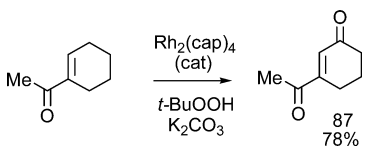
Scheme 37

The oxidation of hydrocarbons with ruthenium catalysts bearing a simple non-porphyrin ligand is practical in the synthetic aspects. The ruthenium catalyzed oxidation of hydrocarbons with *t*-BuOOH gives the corresponding ketones and alcohols highly efficiently. $RuCl_2(PPh_3)_3$ is an excellent catalyst for oxidation of the benzylic position of hydrocarbons. Typically, the catalytic oxidation of fluorene gives fluorenone in 87%.[50] The mechanism of this reaction has been clarified. The kinetic results, isotope effects, and other studies indicate that the oxidation is not due to BuO radical or BuOO radical but due to the oxo ruthenium species derived from low valent ruthenium and *t*-BuOOH (Scheme 38).[50]



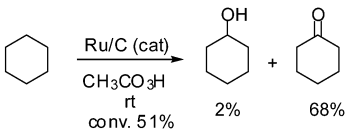
Scheme 38

It is noteworthy that the benzylic and allylic positions of hydrocarbons are oxidized selectively by the dirhodium caprolactamate catalyzed oxidation with *t*-BuOOH (Scheme 39).[51]



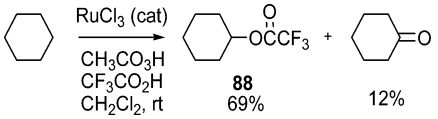
Scheme 39

As described before, CH_3CO_3H is a more reactive reagent than *t*-BuOOH, the combination of ruthenium catalyst with CH_3CO_3H is the excellent system for the oxidation of non-activated hydrocarbons. The ruthenium on charcoal catalyzes the oxidation of cyclohexane with CH_3CO_3H, giving the corresponding cyclohexanone in 68% yield (Scheme 40).[50]



Scheme 40

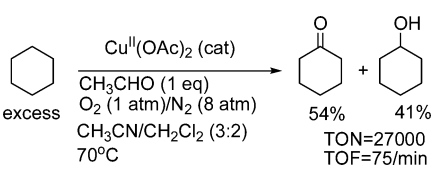
Furthermore, if the oxidation is carried out in trifluoroacetic acid, the catalytic activity increases dramatically. Typically, the $RuCl_3$ catalyzed oxidation of cyclohexanone in the presence of trifluoroacetic acid in ethyl acetate gives the corresponding ester **88** in 69% in addition to cyclohexanone (12%, (Scheme 41). The total yield of the oxidation products becomes to 81%.[52]



Scheme 41

The method for generation of peracetic acid from acetaldehyde and molecular oxygen *in situ* as described in the oxidation of β-lactams[36] can be used for aerobic oxidation of non-activated hydrocarbons. The ruthenium catalyzed oxidation in the presence of acetaldehyde can be carried out with molecular oxygen (1 atm) at room temperature.

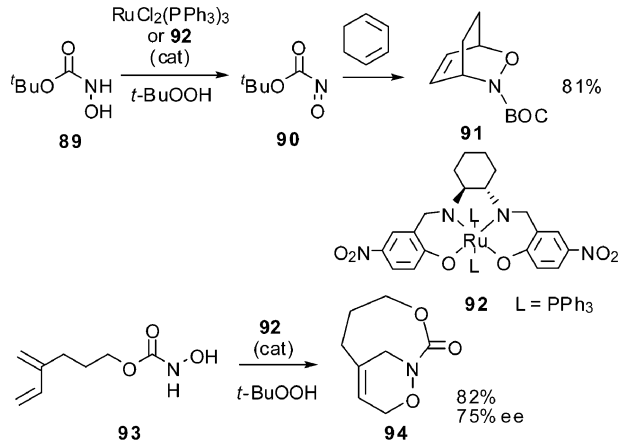
In order to pursue more efficient catalytic system, much study has been conducted. As a search to find a simple and efficient catalytic system for the oxidation of hydrocarbons, a combination of $Cu(OAc)_2$ and acetonitrile was found to be convenient and useful catalyst for the aerobic oxidation of unactivated hydrocarbons. Typically, the oxidation of cyclohexane with molecular oxygen (1 atm of O_2 diluted with 8 atm of N_2) in the presence of acetaldehyde and $Cu(OAc)_2$ catalyst in CH_3CN–Cl_2Cl_2 (3 : 2) at 70 °C in autoclave proceeds efficiently (95% based on CH_3CHO) with extremely high turnover number (27 000) (Scheme 42).[53]



Scheme 42

11. Oxidation of hydroxamic acid

The biomimetic oxidation will explore new types of highly useful methods for organic transformation.



Scheme 43

Acyl nitroso compounds are efficient hetero-dienophiles in the [4 + 2]-cycloaddition reaction with 1,3-diene to produce 3,6-dihydro-1,2-oxazines. Whiting reported ruthenium catalyzed oxidation of *tert*-butyl-*N*-hydroxyl formate **89** to the corresponding nitrosoformate **90** using *t*-BuOOH. Reactions run in the presence of cyclohexadiene resulted in high yield of cycloadduct **91** (Scheme 43).[54]

Intramolecular version of the cycloaddition gives high enantioselectivity.[55] For these reactions, H_2O_2 is also used in place of *t*-BuOOH.

12. Conclusions

The simulation of the function of cytochrome P-450 with ruthenium catalysts resulted in the discovery of various novel and selective catalytic oxidation reactions that are simple, clean, and practical. In combination of low valent ruthenium catalyst with an oxidant such as *t*-butyl hydroperoxide, acetaldehyde-molecular oxygen (peracetic acid), and hydrogen peroxide has been used as clean oxidizing reagents. The biomimetic oxidation reactions presented here can be work up easily and result in only *t*-butanol, acetic acid, water as by-products and hence are widely used in laboratory and even in industry. The principle and the mechanism of the reaction are now clearly understood, and the design for more environmentally benign catalytic reactions can be constructed using molecular oxygen under mild conditions. This is a challenging topic and the key to extend the chemistry of C–H activation. We hope this review will give an impact to design future environmentally benign catalytic oxidation reactions.

References

1. (*a*) *Modern Oxidation Methods*, ed. J. E. Backvall, Wiley-VCH, Weinheim, 2004; (*b*) R. A. Sheldon and J. K. Kochi, *Metal catalyzed Oxidations of Organic Compounds*, Academic Press, New York, 1981; (*c*) M. Hudlucky, *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, 1990.
2. S.-I. Murahashi, *Pure Appl. Chem.*, 1992, **64**, 403.
3. S.-I. Murahashi, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2443.
4. S.-I. Murahashi and N. Komiya, in *Biomimetic Oxidations Catalyzed by Transition Metal Complexes*, ed. B Munier, Imperial College Press, London, 2000, p. 563.
5. (a) S.-I. Murahashi and N. Komiya, *Modern Oxidation Methods*, ed. J.-E. Backvall, Wiley-VCH, Weinheim, 2004, p. 165.
6. S.-I. Murahashi and N. Komiya, *Ruthenium in Organic Synthesis*, ed. S.-I. Murahashi, Wiley-VCH, Weinheim, 2004, p. 53.
7. T. Naota, H. Takaya and S.-I. Murahashi, *Chem. Rev.*, 1998, **98**, 2599.
8. (*a*) R. Sato and T. Omura, *Cytochrome P-450*, Kodansha, Tokyo, 1978; (*b*) T. J. McMurry and J. T. Groves, *Cytochrome P-450: Structure, Mechanism and Biochemistry*, ed. P. R. Ortiz de Montellano, Plenum, New York, 1986, p. 3.
9. J. T. Groves, T. E. Nemo and R. S. Myers, *J. Am. Chem. Soc.*, 1979, **101**, 1032.
10. (*a*) S.-I. Murahashi, T. Hirano and T. Yano, *J. Am. Chem. Soc.*, 1978, **100**, 348; (*b*) S.-I. Murahashi and T. Watanabe, *J. Am. Chem. Soc.*, 1979, **101**, 7429.
11. S.-I. Murahashi, T. Naota and K. Yonemura, *J. Am. Chem. Soc.*, 1988, **110**, 8256.
12. D. C. Heimbrook, R. I. Murray, K. D. Egeberg, S. G. Sligar, M. W. Nee and T. C. Bruice, *J. Am. Chem. Soc.*, 1984, **106**, 1514.
13. S.-I. Murahashi, T. Naota, N. Miyaguchi and T. Nakato, *Tetrahedron Lett.*, 1992, **33**, 6991.
14. S.-I. Murahashi, T. Naota and H. Taki, *J. Chem. Soc., Chem. Commun.*, 1985, 613.
15. Reviews, (*a*) S. Kobayashi and H. Ishitani, *Chem. Rev.*, 1999, **99**, 1069; (*b*) G. K. Friestad and A. K. Mathies, *Tetrahedron*, 2007, **63**, 2541.
16. H. Choi and M. P. Doyle, *Chem. Commun.*, 2007, 745.
17. (*a*) H_2O_2 oxidation, S.-I. Murahashi, T. Oda and Y. Masui, *J. Am. Chem. Soc.*, 1989, **111**, 5002; (*b*) O_2 oxidation, Y. Imada, H. Iida, S. Ono and S.-I. Murahashi, *J. Am. Chem. Soc.*, 2003, **125**, 2865.
18. (*a*) S.-I. Murahashi, H. Mitsui, T. Shiota, T. Tsuda and S. Watanabe, *J. Org. Chem.*, 1990, **55**, 1736; (*b*) S.-I. Murahashi, T. Shiota and Y. Imada, *Org. Synth.*, 1991, **70**, 265; (*c*) S.-I. Murahashi, Y. Imada and H. Ohtake, *J. Org. Chem.*, 1994, **59**, 6170.
19. S.-I. Murahashi and T. Shiota, *Tetrahedron Lett.*, 1987, **28**, 2383.
20. S.-I. Murahashi, Y. Okano, H. Sato, T. Nakae and N. Komiya, *Synlett*, 2007, **11**, 1675.
21. (*a*) T. Hosokawa, T. Uno. T. Inui and S.-I. Murahashi, *J. Am. Chem. Soc.*, 1981, **103**, 2318; (*b*) T. Hosokawa and S.-I. Murahashi, *Acc. Chem. Res.*, 1990, **23**, 49.
22. S. M. Samec, A. H. Ell and J.-E. Backvall, *Chem.–Eur. J.*, 2005, **11**, 2327.
23. S.-I. Murahashi, T. Naota, T. Kuwabara, T. Saito, H. Kumobayashi and S. Akutagawa, *J. Am. Chem. Soc.*, 1990, **112**, 7820.
24. S.-I. Murahashi, A. Mitani and K. Kitao, *Tetrahedron Lett.*, 2000, **41**, 10254.
25. S.-I. Murahashi, T. Saito, T. Naota, H. Kumobayashi and S. Akutagawa, *Tetrahedron Lett.*, 1991, **32**, 2145.
26. S.-I. Murahashi, T. Saito, T. Naota, H. Kumobayashi and S. Akutagawa, *Tetrahedron Lett.*, 1991, **32**, 5991.
27. P. Beak, A. Basu, D. J. Gallagher, Y. S. Park and S. Thayumanavan, *Acc. Chem. Res.*, 1996, **29**, 552.
28. T. Naota, T. Nakato and S.-I. Murahashi, *Tetrahedron Lett.*, 1990, **31**, 7475.
29. (*a*) Z. Li and C.-J. Li, *J. Am. Chem. Soc.*, 2004, **126**, 11810; (*b*) Z. Li and C.-J. Li, *J. Am. Chem. Soc.*, 2005, **127**, 3672; (*c*) Z. Li and C.-J. Li, *Eur. J. Org. Chem.*, 2005, 3173; (*d*) Z. Li and C.-J. Li, *J. Am. Chem. Soc.*, 2005, **127**, 6968; (*e*) Z. Li, S. Bohle and C.-J. Li, *Proc. Natl. Acad. Sci. U. S. A.*, 2006, 9828.
30. A. J. Catino, J. M. Nicols, B. J. Nettles and M. P. Doyle, *J. Am. Chem. Soc.*, 2006, **128**, 5648S.
31. (*a*) I. Murahashi, N. Komiya, H. Terai and T. Nakae, *J. Am. Chem. Soc.*, 2003, **125**, 15312; (*b*) See also, highlight: M. North, *Angew. Chem., Int. Ed.*, 2004, **43**, 4126.
32. (*a*) K. Yamaguchi, K. Mori, T. Mizugaki, K. Ebitani and K. Kaneda, *J. Am. Chem. Soc.*, 2000, **122**, 7144; (*b*) K. Yamaguchi and N. Mizuno, *Angew. Chem., Int. Ed.*, 2002, **41**, 4538.
33. S.-I. Murahashi, N. Komiya and H. Terai, *Angew. Chem., Int. Ed.*, 2005, **44**, 6931.
34. D. Enders and J. P. Solvock, *Chem. Soc. Rev.*, 2000, **29**, 359.
35. O. Basle and C.-J. Li, *Green Chem.*, 2007, **9**, 1047.
36. K. Yamaguchi and N. Mizuno, *Angew. Chem., Int. Ed.*, 2003, **42**, 1480.

37. Reviews: (*a*) H. Adolfsson, *Modern Oxidation Methods*, ed. J. E. Backvall, Wiley-VCH, Weinheim, 2004, p. 21; (*b*) D. Chatterjee, *Coord. Chem. Rev.*, 2008, **252**, 176; (*c*) B. C. Lane and K. Burgess, *Chem. Rev.*, 2003, **103**, 2457.
38. (*a*) D. Ostovic and T. C. Bruice, *J. Am. Chem. Soc.*, 1989, **111**, 6511; (*b*) T. G. Traylor and A. R. Miksztal, *J. Am. Chem. Soc.*, 1987, **109**, 2770.
39. P. H. J. Carlsen, T. Katsuki, V. S. Martin and K. B. Sharpless, *J. Org. Chem.*, 1981, **46**, 3936.
40. S.-I. Murahashi, T. Saito, H. Hanaoka, Y. Murakami, T. Naota, H. Kumobayashi and S. Akutagawa, *J. Org. Chem.*, 1993, **58**, 2929.
41. (*a*) B. Prietker, *Org. Lett.*, 2004, **6**, 289; (*b*) B. Prietker, *J. Org. Chem.*, 2004, **69**, 8287.
42. T. Hotopp, H.-J. Gutke and S.-I. Murahashi, *Tetrahedron Lett.*, 2001, **42**, 3343.
43. S.-I. Murahashi, T. Naota and H. Hanaoka, *Chem. Lett.*, 1993, 1767.
44. R. A. Johnson and K. B. Sharpless, *Catalytic Asymmetric Synthesis*, ed. I Ojima, VCH, Weinheim, 1993, p. 227.
45. Reviews: (*a*) M. J. Schultz and M. S. Sigman, *Tetrahedron*, 2006, **62**, 8227; (*b*) S. S. Stahl, *Angew. Chem., Int. Ed.*, 2004, **43**, 3400; (*c*) I. E. Marko, P. R. Giles, M. Tsukazaki, A. Gautier, R. Dumeunier, K. Doda, F. Philippart, I. Chelle-Regnault, J.-L. Mutonkole, S. M. Brown and C. J. Urch, in *Transition Metals for Organic Synthesis*, ed. M Beller and C Bolm, Wiley-VCH, 2nd edn, 2004, vol. 2, p. 437; (*d*) I. W. C. E. Arends and R. Sheldon, in *Modern Oxidation Methods*, ed. J. E. Backvall, Wiley-VCH, 2004, p. 83; (*e*) T. Matsumoto, M. Ueno, N. Wang and S. Kobayashi, *Chem.–Asian J.*, 2008, **3**, 196.
46. Reviews: (*a*) J. Piera and J. E. Backvall, *Angew. Chem., Int. Ed.*, 2008, **47**, 2; (*b*) J. S. M. Samec, J. E. Backvall, P. G. Anderson and P. Brandt, *Chem. Soc. Rev.*, 2006, **35**, 237; (*c*) S.-I. Murahashi and T. Naota, *Adv. Met. Org. Chem.*, 1994, **3**, 225.
47. S.-I. Murahashi, T. Naota, N. Miyaguchi and S. Noda, *J. Am. Chem. Soc.*, 1996, **118**, 2509.
48. S.-I. Murahashi, T. Naota and N. Komiya, *Tetrahedron Lett.*, 1995, **36**, 8059.
49. J. T. Groves, M. Bonchio, T. Carofiglio and K. Shalyaev, *J. Am. Chem. Soc.*, 1996, **118**, 8961.
50. S.-I. Murahashi, N. Komiya, Y. Oda, T. Kuwabara and T. Naota, *J. Org. Chem.*, 2000, **65**, 9186.
51. A. C. Catino, R. E. Forslund and M. P. Doyle, *J. Am. Chem. Soc.*, 2004, **126**, 13622.
52. N. Komiya, S. Noji and S.-I. Murahashi, *Chem. Commun.*, 2001, 65.
53. (*a*) S.-I. Murahashi, N. Komiya, Y. Hayashi and T. Kumano, *Pure Appl. Chem.*, 2001, **73**, 311; (*b*) N. Komiya, T. Naota, Y. Oda and S.-I. Murahashi, *J. Mol. Catal. A: Chem.*, 1997, **117**, 21; (*c*) S.-I. Murahashi, Y. Oda and T. Naota, *J. Am. Chem. Soc.*, 1992, **114**, 7913.
54. (*a*) K. R. Flower, A. P. Lightfoot, H. Wan and A. Whiting, *Chem. Commun.*, 2001, 1812; (*b*) K. R. Flower, A. P. Lightfoot, H. Wan and A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2058; (*c*) J. A. K. Howard, G. Hyanshenko, H. A. Sparkes and A. Whiting, *Dalton Trans.*, 2007, 2108.
55. C. P. Chow and K. J. Shea, *J. Am. Chem. Soc.*, 2005, **127**, 3678.