Review

Development of biomimetic catalytic oxidation methods and non-salt methods using transition metal-based acid and base ambiphilic catalysts

By Shun-Ichi MURAHASHI[*1,*2,†]

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Abstract: This review focuses on the development of ruthenium and flavin catalysts for environmentally benign oxidation reactions based on mimicking the functions of cytochrome P-450 and flavoenzymes, and low valent transition-metal catalysts that replace conventional acids and bases. Several new concepts and new types of catalytic reactions based on these concepts are described.

Keywords: biomimetic oxidation, ruthenium catalyst, flavin catalyst, oxidation of amines, sp^3 C–H activation, transition metal based acid and base ambiphilic catalyst

1. Introduction

New concepts regarding environmentally benign biomimetic oxidation catalysts and neutral redox catalysts that replace acids and bases are discussed, along with the development of a wide variety of catalytic reactions based on these concepts. These methods have been widely applied to the synthesis of biologically active substances and functional substances, and have contributed to some significant advances in industrial technology.

2. Biomimetic catalytic oxidation

Oxidation is one of the most fundamental reactions in organic synthesis. Owing to the need to develop forward-looking technology that is environmentally acceptable with respect to minimizing the formation of inorganic salts and the efficient, highly selective formation of end products, many aspects must be considered. The most attractive approach would be a biomimetic oxidation reaction that is analogous to metabolic processes that occur in living organisms. The development of innovative methods for systematically exploring new types of oxidation reactions would have many advantages. Indeed, we discovered novel biomimetic methods for catalytic oxidation reactions by simulating the functions of cytochrome P-450 and flavoenzymes *via* the use of metal catalysts or organocatalysts, and, as a result, we were able to develop some highly useful strategies that can be useful in this area.[1)]

2.1. Ruthenium catalyzed biomimetic cytochrome P-450-type oxidation reactions. Cytochrome P-450 has two major functions. One is the two-electron reduction of molecular oxygen by porphyrin followed by protonolysis to form an oxo iron species (Fe=O), and the other is the transfer of an oxygen atom to a substrate. We attempted to generate a middle-valent ruthenium oxo species, which could serve as an analogue for the oxo-iron species of cytochrome P-450 without the porphyrin moiety, although, at that time, high-valent oxo metal complexes were considered to be the active species for oxidation reactions. *N*-Methylamine derivatives were selected as substrates, because the oxidation of *N*-demethylation of tertiary *N*-methylamine is unique for cytochrome P-450 specific reactions and plays an important role in the metabolism of naturally occurring toxic tertiary *N*-methylamines. Fortunately, we discovered a novel cytochrome P-450 type of oxidation of tertiary *N*-methylamines that does not require porphyrin. Since then, unique cytochrome P-450 type selective oxidative transformations of various substrates have been explored.[1)]

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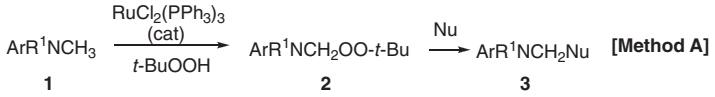
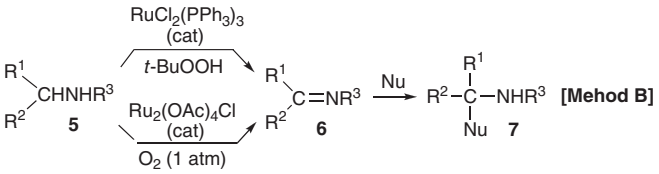


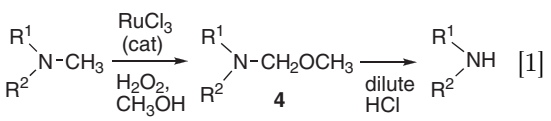
Scheme 1.



Scheme 2.

Ruthenium catalyzed oxidation of tertiary amines. In 1988 we discovered that a novel cytochrome P-450-type catalytic oxidation reaction can be carried out in the absence of porphyrins, using a ruthenium(II) phosphine catalyst.[2] Thus, the $RuCl_2(PPh_3)_3$-catalyzed oxidation of tertiary amines **1** with *t*-BuOOH gives the corresponding α-(*t*-butyldioxy)alkylamines **2** with high efficiency, as shown in Scheme 1.

The mechanism of this unique oxidation reaction was examined carefully through kinetics studies involving isotope effects. The ruthenium(II) complex reacts with *t*-BuOOH to give Ru(II)OO*t*-Bu, which is converted to the Ru=O species. C–H activation takes place by electron transfer and subsequent proton transfer to give the iminium ion complex. Nucleophilic attack of the second molecule of *t*-BuOOH gives the product **2**, water, and the regenerated Ru(II) species to complete the catalytic cycle. Similarly, the $RuCl_3$ catalyzed oxidation of tertiary amines with H_2O_2 in methanol gives the corresponding α-methoxy tertiary amines **4**.[3] The ruthenium catalyzed oxidation followed by hydrolysis of the oxidized products **2** and **4** gives the demethylated secondary amines chemo-selectively [Eq. 1]. The catalytic oxidation shown in Scheme 1 is highly useful for introducing a substituent at the α-position of tertiary amines [Method A]. The oxidation of tertiary amines provides a novel, biomimetic method for constructing the piperidine skeleton using an *N*-methyl group.[2]



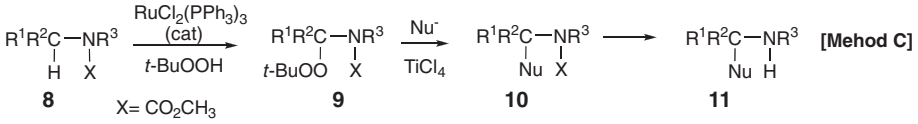
[1]

Ruthenium catalyzed oxidative transformation of secondary amines to imines. Based on the above mechanistic study, it is apparent that the same catalytic system could be used for the oxidative transformation of secondary amines into the corresponding imines **6**.[4] Indeed, the first catalytic oxidative transformation of secondary amines to imines was discovered as shown in Scheme 2.

The direct oxidative transformation of secondary amines was improved dramatically, because the reaction can be carreid out with molecular oxygen under mild conditions. Using a ruthenium bimetallic complex catalyst $Ru_2(OAc)_4Cl$, the oxidation of secondary amines could be performed in a highly efficient manner using molecular oxygen for the first time [Scheme 2].[5]

Substitution at the α-position of amines and amides. Substituents at the α position of amines and amides are of importance from the standpoint of the synthesis of biologically active nitrogen compounds. Generally, formation of a carbon–carbon bond at the α-position of an amine is achieved using carbon electrophiles. That is, *N*-protection of the amines with an electron-withdrawing group, lithiation with organolithium compounds to give α-carbanions, subsequent treatment with carbon electrophiles, and removal of the protecting group gives α-substituted amines. The limitation of this method is the difficulty in scaling-up the reaction because sensitive organolithium compounds are used in stoichiometric amounts.

The oxidative transformation of secondary amines to imines provides the first convenient general method for the synthesis of α-substituted amines, because the enantioselective addition of nucleophiles to imines has been established.[4,5] This is the second method for introducing a substituent at the α-position of amines [Method B] in addition to Method A, as shown in Scheme 2.

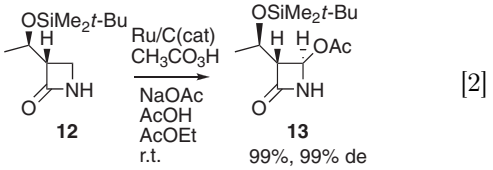


Scheme 3.

Ruthenium-catalyzed oxidation of amides and related compounds. The cytochrome P-450 type oxidation method of tertiary amines can be applied to the oxidations of amides and related compounds. Thus, the ruthenium-catalyzed oxidation of amide **8** with *t*-BuOOH under mild conditions gives the corresponding *t*-butyldioxyamide **9** as shown in Scheme 3.[6] It is important to note that α-substituted amides **11** can be obtained by the ruthenium-catalyzed oxidation of amide **8** to give product **9**, which can be treated with carbon nucleophiles [Method C] as shown in Scheme 3.[7]

This method can also be used for the selective oxidation of peptides. A novel catalytic backbone modification at the glycine residue of peptides was performed without backbone fragmentation.[8]

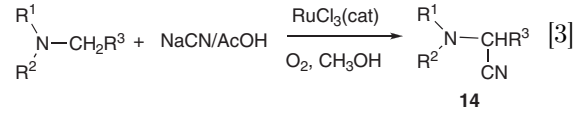
One of the most challenging topics in the oxidation of amides is the catalytic oxidation of β-lactams. We verified that the oxidation of β-lactams is effective, which has been a longstanding problem in pharmaceutical synthesis. Ruthenium-catalyzed oxidation with a reactive peracetic acid in a buffer solution was found to proceed under mild conditions.[6] Azetidinone **12** can be converted into the corresponding 4-acetoxyazetidinone **13** with extremely high stereoselectivity in a buffer solution (99%, 99%de).[6] The product is a versatile and common key intermediate for the synthesis of antibiotics such as carbapenems. Currently, 100,000 kg of **13** is produced per year by the pharmaceutical industry. It is noteworthy that this type of oxidation reaction does not proceed when RuO_2 and RuO_4 catalysts are used [Eq. 2].



[2]

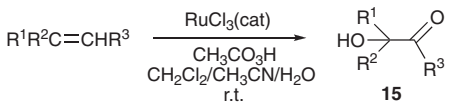
Since peracetic acid is produced by the cobalt-catalyzed aerobic oxidation of acetaldehyde, we examined ruthenium-catalyzed generation of peracetic acid from acetaldehyde under aerobic conditions and discovered that the $RuCl_3$ catalyzed oxidation of β-lactam **12** with molecular oxygen (1 atm) in the presence of acetaldehyde gave **13** in 91% yield.[9]

Direct oxidative transformation of tertiary amines with molecular oxygen. In the search for an environmentally benign and effective method for the direct oxidative transformation of tertiary amines with molecular oxygen, we aimed at the direct cyanation of tertiary amines by accomplishing two tasks at the same time; that is, (i) C–H activation by oxidation with molecular oxygen, and (ii) trapping of the iminium ion intermediate with a carbon nucleophile under oxidative conditions to give the carbon–carbon bond formation product. Indeed, we found that the ruthenium-catalyzed oxidative cyanation of tertiary amines with molecular oxygen in the presence of sodium cyanide gives the corresponding α-aminonitrile **14** in a higly efficient manner, which is a versatile intermediate for organic synthesis.[10] This is the first example of an aerobic, oxidative cross dehydrogenative coupling reaction induced by sp^3 C–H activation [Eq. 3].



[3]

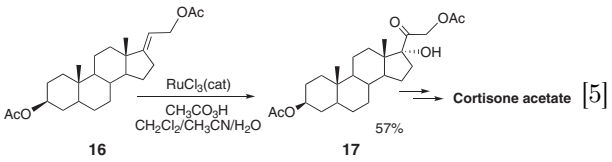
Oxidative transformation of alkenes to α-ketols. Direct oxidative transformation of an alkene to an α-ketol was discovered for the first time by the author, although epoxidation of the alkene is well known. Thus, the $RuCl_3$-catalyzed oxidation of alkenes with peracetic acid in an aqueous solution (CH_2Cl_2/CH_3CN/H_2O) affords the corresponding α-ketols **15** in high efficiency [Eq. 4].[11]



[4]

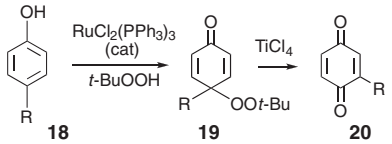
It is noteworthy that this oxidation is quite different from the oxidation with RuO_4. Furthermore, the introduction of an oxygen function to an alkene can be controlled by changing the metal catalysts. That is, the $RuCl_3$-catalyzed oxidation of alkenes gives α-ketols with Markovnikov selectivity,[11] while the $OsCl_3$-catalyzed oxidation gives α-ketols with anti-Markovnikov selectivity.[12]

The present method is particularly useful for the synthesis of biologically important compounds bearing α-ketol structures, such as cortizone acetate[11] and adriamycin acetate.[13] The ruthenium catalyzed stereoselective oxidative transformation of allyl acetate **16** to **17** is the key step in synthesis of cortisone acetate [Eq. 5].[11]



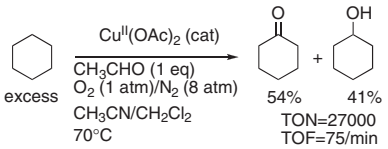
[5]

Oxidation of phenols. Oxidative transformation of phenols is of importance in view of the biological and synthetic inportance of such compounds; however, it suffers from non-selectivity. Selective oxidation of phenols is limited to those bearing bulky substituents at the 2 and 6 positions. We discovered that the $RuCl_2(PPh_3)_3$-catalyzed oxidation of *p*-substituted phenols **18** with *t*-BuOOH proceeds selectively to give the corresponding *t*-butyldioxydienone **19** without any substituent at the 2 and 6 positions [Eq. 6].[14] The reason why the ruthenium catalyzed reaction proceeds in a selective manner is due to the fast single electron transfer (SET) ability of ruthenium from a phenoxy radical to form the cationic intermediate, before radical coupling occurs. The dienones thus obtained are versatile synthetic intermediates. Typically, the treatment of dienones **19** with $TiCl_4$ at $-78\,^{\circ}C$ gives the corresponding 2-substituted quinone **20** selectively with high efficiency. The transformation of phenols can be applied to the one-pot synthesis of *cis*-fused octahydroanthraquinone by sequential migration and a Diels–Alder reaction.



[6]

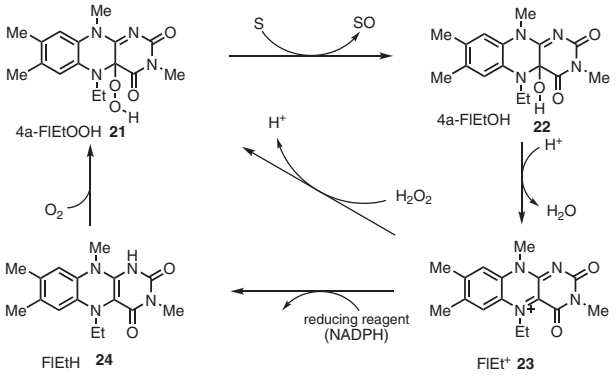
Oxidation of hydrocarbons. The catalytic oxidation of hydrocarbons remains as a challenging topic. The $RuCl_2(PPh_3)_3$ catalysed oxidation of hydrocarbons with *t*-BuOOH gives the corresponding ketones and alcohols with high efficiency.[15] The kinetic isotope effect and other studies indicated that the oxidation is not due to a BuO radical or a BuOO radical but rather, to the oxo ruthenium species.[15] As described before, peracetic acid is a more reactive reagent. The combination of a ruthenium catalyst with peracetic acid is an excellent system for the oxidation of non-activated hydrocarbons.[16] The method used for the *in situ* generation of peracetic acid from acetaldehyde and molecular oxygen can be used for the aerobic oxidation of non-activated hydrocarbons. The aerobic catalytic oxidation of non-activated hydrocarbons can be carried out using iron powder,[17] a ruthenium porphyrine catalysts,[18] and copper-crown ether catalysts[19] highly efficiently. In particular, the simple $Cu(OAc)_2$-acetonitrile catalytic system is convenient and useful for the aerobic oxidation of inactivated hydrocarbons as shown in Eq. 7.[20]



[7]

Simulating 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 with a 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 worked up easily and result in only *t*-butyl alcohol, acetic acid, water, respectively, as by-products and hence are widely used in laboratories and even in industry. The principle and mechanism of the reaction are now clearly understood, used widely, and extended to the design of more environmentally benign catalytic reactions using molecular oxygen under mild conditions.[1]

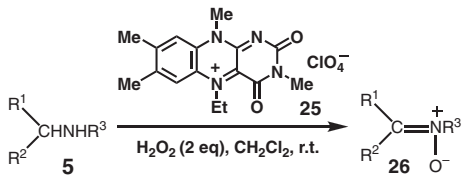
2.2. Flavin-catalyzed biomimetic oxidation reactions. In order to study the metabolic functions of metal enzymes and organic enzymes in a complementary manner, we initiated to study the oxidation mechanism of flavoenzymes. The flavoenzyme is a coenzyme in which riboflavin binds a dinucleotide to form flavin-adenine-dinucleotide (FAD). At that time, the mechanism of flavoenzymes was proposed as shown in Scheme 4 using 4a-hydroxy-5-ethylflavin as a model compound. The oxidation of a substrate (S) with hydroperoxyflavin **21** gives product SO and hydroxyflavin **22**, which eliminates water to form oxidized flavin **23**. Reduction of **23** with NADPH gives reduced flavin **24**, which then reacts with molecular oxygen to give **21** to complete the catalytic cycle. The transfer of oxygen from hydroperoxyflavin **21** to substrates has been verified; however, the catalytic recycling step, that is, the conversion of hydroxyflavin **22** to hydroperoxyflavin **21** was



Scheme 4.

ambiguous. In 1989 we examined the reactivity of 4a-hydroxy-5-ethylflavin **22** by stop-flow kinetics in order to identify biomimetic oxidation reactions that mimic the function of a flavoenzyme. We discovered that **22** undergoes a very fast pseudo-first order ionization ($k_1 = 3 \times 10^2\,M^{-1}s^{-1}$) to generate flavinium cation **23**. From this finding it was expected that **22** would undergo an S_N1-type reaction with aqueous hydrogen peroxide. Actually, the hydroperoxyflavin **21** was obtained from **22** in excellent yield. Based on this finding we discovered novel biomimetic flavin-catalyzed oxidation reactions with hydrogen peroxide.[21] This discovery constitutes a mile-stone for flavin-catalyzed oxidation reactions. We explored various flavin catalyzed oxidations using flavinium perchlorate **25** as a catalyst because of its stability and easy handling.

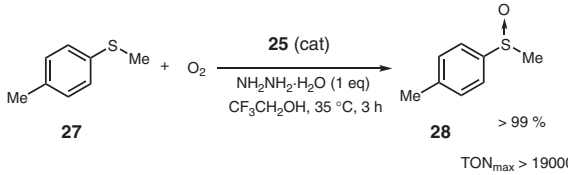
Flavin-catalyzed oxidation with hydrogen peroxide. The reaction of secondary amines **5** with a hydrogen peroxide solution in the presence of catalyst **25** results in efficient production of nitrones **26**. This was an unexpected and exciting result, because at that time, no method was available for the direct synthesis of nitrones from secondary amines [Eq. 8].



[8]

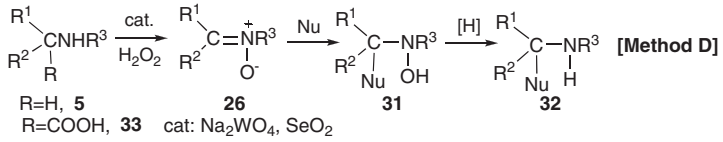
This catalytic system can be applied to the oxidative transformation of sulfides to sulfoxides.[21] The kinetics on the catalytic oxidation of methyl phenyl sulfide revealed that the rate-determining step is formation of flavinium cation ($\rho = -1.90$). Because of ease of designing a suitable chiral flavin catalyst, asymmetric catalytic oxidations of organic substrates can be carried out. Using a chiral flavin catalyst, the first asymmetric catalytic Baeyer–Villiger oxidation reaction was performed with an organocatalyst.[22]

Flavin-catalyzed aerobic oxidation reaction. We attempted to extend the flavin-catalyzed oxidation to a more environmentally benign oxidation reactions by using molecular oxygen in place of hydrogen peroxide. Based on the mechanism shown in Scheme 4, the crucial step for construction of flavin-catalyzed aerobic oxidation is the reduction of FlEt+ **23** to FlEtH **24** with an appropriate reducing agent that is analogous to NADPH. We turned out attention on the fact that hydrazine is the inhibitor of flavoenzymes, and we found that hydrazine hydrate can be used to replace NADPH as a reducing agent. We discovered that the oxidation of sulfides with molecular oxygen proceeds in the presence of a solution of flavin catalyst **25** and hydrazine hydrate in trifluoroethanol at room temperature.[23] Indeed, the flavin-catalyzed oxidation of sulfide **27** gave sulfoxide **28** cleanly and highly efficiently with an extremely high turn-over number (19,000). This is the first example of such an aerobic oxidation using an organic catalyst. Apparently, the flavinium cation intermediate reacts readily with hydrazine to give an adduct which undergoes β-elimination of the diazene to give the reduced flavin. Diazene can also be used for the reduction of the oxidized flavin **23** [Eq. 9].[23),24]

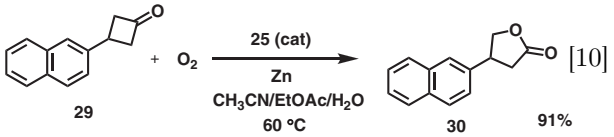


[9]

Our objective was a catalytic Baeyer–Villiger oxidation reaction with molecular oxygen under mild conditions, although Baeyer–Villiger oxidations are usually carried out *via* treatment with peroxides such as *m*-chloroperbinzoic acid. Using zinc as a reductant, the flavin-catalyzed oxidation of ketone **29** with molecular oxygen (balloon) in the presence of zinc gave the corresponding ester **30** in excellent yield.[25] The product was isolated by simple removal of coproduced insoluble $Zn(OH)_2$ by filtration. This aerobic flavin catalyzed B–V reaction can be highly useful in organic synthesis, because the chemo-selective oxidation of ketones can be performed in the presence of other reactive functionalities such as alkenes, alcohols, and sulfides [Eq. 10].



Scheme 5.



[10]

2.3. Tungstate catalyzed oxidative transformation of secondary amines to nitrones. We realized that the hydroperoxy flavin (FlOOH) has a unique cationic property of oxygen transfer. We simulated the function of the hydroperoxy flavin with a metal hydroperoxide (MOOH), and found that hydroperoxy tungstate is an excellent reagent for the oxidation of amines. The Na_2WO_4-catalyzed oxidation of secondary amines with hydrogen peroxide gave nitrone **26** in excellent yields.[26] For the synthesis of the unstable cyclic nitrones selenium dioxide is a more convenient catalyst.[27]

An important variation in nitrone synthesis is the Na_2WO_4-catalyzed decarboxylative oxidation of *N*-alkyl-α-amino acid **33**. The reaction proceeds smoothly under the similar conditions to give nitrone **26** regioselectively, as shown in Scheme 5.[28]

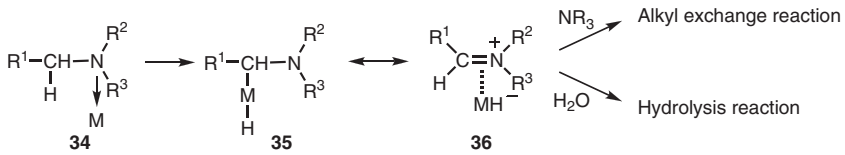
Nitrones are difficult to prepare and are typically prepared by either the stoichiometric oxidation of hydroxylamines with HgO or condensation of hydroxylamines with aldehydes. Therefore, the present biomimetic, single step synthesis of nitrones from secondary amines is carried out with a Na_2WO_4 catalyst, a SeO_2 catalyst [Method D], or a flavin catalyst [Eq. 8] and is highly useful, because nitrones are important reagents as 1,3-dipoles and spin trapping reagents. Furthermore, this method provides the fourth method for substitution at α to the nitrogen of secondary amines with a nucleophile [Method D]. The oxidation of secondary amines, followed by reactions with nucleophiles gives α-substituted *N*-hydroxyamine **31**, which is readily converted to amine **32**, as shown in Scheme 5. Typically, enantioselective iridium catalyzed hydrogenation gives a chiral *N*-hydroxylamine,[29] while diastereoselective[30] and enantioselective[31] addition of enolates gives chiral β-amino acids. Many biologically important nitrogen-containing compounds have been synthesized.[30),31]

3. Transition-metal-based Lewis acid, base, and ambiphilic catalysts

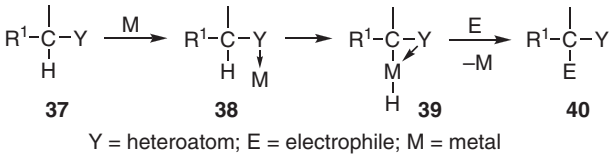
Strong Lewis acids and strong bases are often used for conventional organic transformations; however, stoichiometric amounts of these strong acids and bases are usually used. If it is possible to design transition-metal based redox Lewis acid catalysts, redox base catalysts, and ambiphilic catalysts, the reactions could be carried out catalytically and selectively under neutral conditions without the formation of any salts. Based on the new concept for sp^3 C–H activation induced by a hetero atom effect, we discovered that low-valent ruthenium, iridium, rhodium and rhenium hydride complexes can be used as redox Lewis acids and/or base catalysts. Using neutral catalysts, various environmentally benign catalytic reactions can be constructed.[32]

3.1. Transition metal catalyzed C–H activation of sp^3 C–H activation induced by α-heteroatom effect. Transition-metal complex-assisted C–H activation will open new opportunities for the catalytic formation of carbon–carbon bonds because of its potential to generate reactive carbon–metal complexes. The design of a catalytic reaction involving C–H activation followed by reaction with an electrophile would be important to provide an environmentally friendly non-salt process, which proceeds under neutral conditions.

The C–H activation of tertiary amines. In 1978 we discovered the palladium catalyzed alkyl group exchange reaction of tertiary amines and investigated the mechanism of this unique catalytic reaction.[33] C–H activation α to the nitrogen of tertiary amines was verified based on i) d-labeling experiments at the α- and β-positions, ii) racemization of the optically active amines, iii) product analysis,[33),34] although at that time, the concept of C–H activation was quite rare. The mechanism involves coordination of palladium to the nitrogen of tertiary amine **34**, followed by oxidative addition at the α-C–H bond to give iminium ion complex **36** as shown in Scheme 6. The reactions of intermediate **36** with a tertiary amine or



Scheme 6.

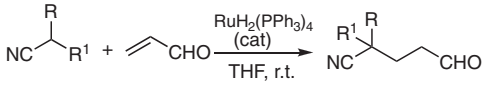


Scheme 7.

water give the alkyl exchange products[33] or hydrolysis products as shown in Scheme 6.[34] Such C–H activation occurs upon treatment with any type of low-valent transition metal and metal complexes.[1b] This is in sharp contrast to the reactions of primary and secondary amines, where N–H activation takes place to give an imine metal hydride complex as common intermediates.[35]

General concept for the sp^3 C–H activation by α-hetero atom effect. The concept of C–H activation of tertiary amines with a metal complex by an α-hetero atom effect led to the discovery of new methods for activating various organic substrates under neutral conditions as shown in Scheme 7. Coordination of a hetero atom (Y) to a low-valent metal complex (M) would increase both the basicity of the metal complex and the acidity of C–H bond adjacent to the heteroatom, and hence the oxidative addition of the metal to the α-C–H bond would occur to afford α-transition-metalated complex **39**. This concept has been extended to the α-C–H activation of pronucleophiles such as nitriles, isocyanates, carbonyl compounds, and trifluoromethylated compounds.[32]

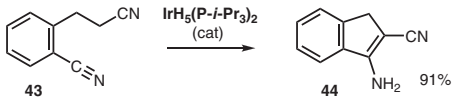
The C–H activation of nitriles. In 1989 we discovered that C–H activation of nitriles occurs readily when a $RuH_2(PPh_3)_4$ catalyst was employed.[36] We selected $RuH_2(PPh_3)_4$ as a catalyst, because ruthenium has a strong coordination ability towards hetero-atoms and a hydride is a small and labile ligand. When initiated by C–H activation, nitriles undergo various catalytic reactions, which include Aldol type reactions, Knoevenagel reactions, Michael additions, addition to acetylenes, and addition to imines, highly efficiently under neutral and mild conditions without salt formation.[37] These reactions proceed in a highly efficient manner, even in the case of base-sensitive substrates such as phenols, aldehydes, and propargyl groups [Eq. 11].[37]



[11]

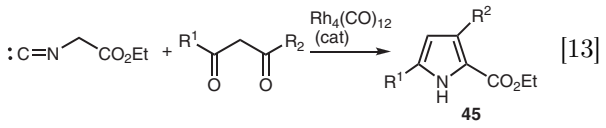
The mechanism of the catalytic Michael addition of nitriles has been clarified by isolation of the intermediate ruthenium complexes.[38] Coordination of the nitrile to the low-valent ruthenium complex, subsequent oxidative addition of the ruthenium to the α-C–H bond of nitrile would afford the C-bonded complex, which is then converted to the N-bonded complex. This complex subsequently undergoes a reaction with electrophiles.[38] It is noteworthy that the regioselective addition of nitriles to carbon–carbon triple bonds of terminal alkynes proceeds. Contrasting results were obtained depending on the presence of an α-substituent on the nitrile.[39]

Low-valent iridium hydride complex $IrH_2(i\text{-}PrP)_5$ was found to be an excellent catalyst for the activation of both C–H and carbon–nitrogen triple bonds of nitriles. The catalytic Thorpe–Ziegler reaction under neutral conditions gives cyanoenamines, which are versatile synthetic intermediates.[40] This method is preferable to the conventional method which requires stoichiometric amounts of strong bases, such as butyllithium [Eq. 12].



[12]

The C–H activation of isonitriles. The C–H activation of isonitriles gives the α-metalated intermediate. The rhodium or ruthenium-catalyzed addition of isonitriles to carbonyl compounds gives the corresponding α,β-unsaturated formamides.[41] Since rhodium is an excellent catalyst for decarbonylation reactions, the $Rh_4(CO)_{12}$-catalyzed reaction of isonitriles with 1,3-dicarbonyl compounds gives pyrroles regioselectively, based on the control of electronic and steric effects [Eq. 13].

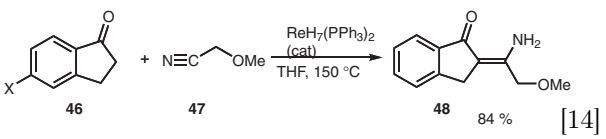


[13]

The C–H activation of carbonyl compounds. The most challenging transformation was the direct C–H activation of simple ketones, because carbonyl compounds coordinate to transition metals only weakly. Using more basic low valent ruthenium hydride complex $Cp^*RuH(PPh_3)_2$, the C–H activation of simple ketones and subsequent Michael addition takes place selectively under neutral conditions in an atom-economical manner.[32c)]

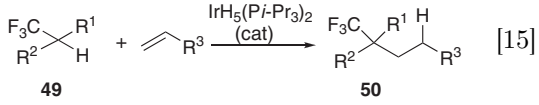
It is known that the α-C–H activation of substrates bearing a heteroatom takes place upon treatment with various transition metal complexes. Chemo-selective C–H activation induced by a heteroatom effect depends on the magnitude of the coordination ability of the metal towards the heteroatom. From the viewpoint of organic synthesis a catalyst that can activate carbonyl compounds in the presence of a nitrile is needed, although carbonyl compounds have a weaker coordination ability to a metal.

We discovered that rhenium complexes have such a unique property. Thus, the $ReH_5(P\textit{i}Pr_3)_2$-catalyzed reaction of carbonyl compounds with nitriles gives the corresponding (Z)-ketoenamines selectively.[42)] This is a clean and salt-free catalytic Blaise reaction and is advantageous compared to the conventional Blaise reaction, where the carbonyl compound is converted into the corresponding bromide, and then treated with zinc in a Reformatskii-type reaction. The addition of carbonyl compounds to a carbon–nitrogen triple bond can be carried out chemo-selectively in the presence of carbonyl compound. Actually, the rhenium catalyzed addition of lactones to nitriles in the presence of carbonyl compounds occurs chemo-selectively [Eq. 14].[42)]



[14]

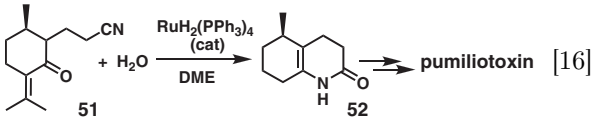
The C–H activation of trifluoromethylated compounds. Trifluoromethylated compounds play an important role in medicinal, agrochemical and material science; therefore, the development of a general method for the synthesis of these compounds would be highly desirable. However, it has, in the past, been difficult to achieve carbon–carbon bond formation *via* α-trifluoromethyl carbanions, because these carbanions spontaneously release fluoride species to produce 1,1-difluoroolefins. We discovered that $IrH_5(P\textit{i}\text{-}Pr_3)_2$-catalyzed reactions of trifluoromethylated compounds with alkenes afford alkylated products in an atom-economical and selective manner under neutral conditions without the formation of any defluorinated by-product [Eq. 15].[43)]



[15]

3.2. Low-valent ruthenium hydride complex as redox Lewis acid catalyst. The ruthenium hydride complex $RuH_2(PPh_3)_4$ functions as a transition metal-based base catalyst in the C–H activation of pronucleophiles. Importantly, we found that the $RuH_2(PPh_3)_4$ catalyst can also function as a Lewis acid catalyst. The coordination of ruthenium to nitriles perturbs the carbon–nitrogen triple bond, permitting the addition of a nucleophile.

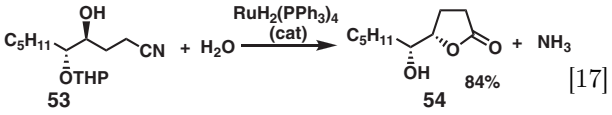
The conventional Lewis acid-promoted hydration of nitriles results in salt formation. In 1986, we discovered that the $RuH_2(PPh_3)_4$-catalysed hydration of nitriles proceeds highly efficiently upon treatment with only two equivalents of water under neutral conditions. This is a very important discovery, because this means that the $RuH_2(PPh_3)_4$ catalyst functions as a transition-metal based base catalyst and also as a transition-metal based Lewis acid catalyst. The hydration is useful and can be applied to the synthesis of biologically important compound such as pumiliotoxin C [Eq. 16].[44)]



[16]

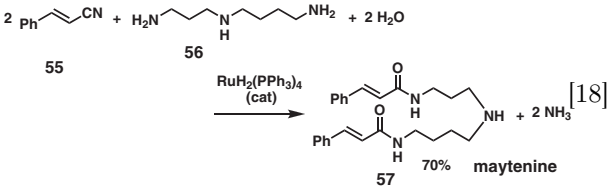
In order to investigate the mechanism, we switched the nucleophile from water to alcohols. As a result, we discovered a new type of esterification reaction, *i.e.* reactions of nitriles with alcohols. Thus, the $RuH_2(PPh_3)_4$-catalyzed reaction of alcohols with a nitrile in the presence of water under neutral conditions gives esters along with the evolution of ammonia. This is an environmentally friendly non-salt producing process. The synthesis of streptomycin griceus **54** is a typical example of such an ester synthesis [Eq. 17].[45)] It is noteworthy that as a closely related reaction, the $RuH_2(PPh_3)_4$-catalyzed reaction of alcohols gives esters along with the evolution of

molecular hydrogen by dehydrogenetive condensation.[46)]



[17]

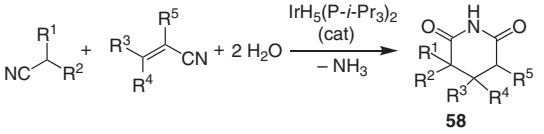
Extension of the ruthenium catalyzed reaction by changing the nucleophile from alcohols to amines led to the discovery of a new catalytic amidation reaction of nitriles with amines along with the evolution of ammonia. In the field of amide synthesis, a problem of continuing interest was the development of a general method for the conversion of amines into amides under neutral conditions without the formation of salts. The primary amine undergoes chemoselective amidation in the presence of a secondary amine. Chemo-selective synthesis of maytenine **57**, an important anti-bacterial compound was performed, because of the template effect of the metal, as shown in Eq. 18.[47)] Importantly, this method provides a highly useful route to the synthesis of polyesters and polyamides from dinitriles.



[18]

3.3. Acid and base ambiphilic catalysts. If a suitable catalyst is found that can simultaneously function both as a Lewis acid and base, the reaction could be carried out catalytically under neutral conditions without the formation of salts. According to the conventional method, Lewis acid promoted reactions and subsequent base promoted reactions cannot be carried out simultaneously because the reagents inactivate each other. However, if one can design an ambiphilic catalyst that functions as a Lewis acid catalyst and also as a base catalyst under neutral conditions, it would be possible to carry out sequential reactions catalytically without salt formation. We found that an iridium hydride complex $IrH_5(PPh_3)_2$ constitutes such an ideal catalyst.

The three-component reaction used in the synthesis of glutarimides, important precursors of certain types of pharmaceuticals, such as sedatives, was selected. The $IrH_5(PPh_3)_2$ catalyzed the reaction of nitriles with acrylonitriles in the presence of two equivalents of water at 150 °C in a sealed tube, giving high yields of glutarimides [Eq. 19]. According to the conventional method, glutarimide is prepared by the triton B-promoted Michael addition of a nitrile to an acrylonitrile to give a 1,3-dinitrile, followed by treatment with sulfuric acid in acetic acid, giving the product in about 4% over-all yield. Apparently, $IrH_5(PPh_3)_2$ functions both as a redox base catalyst and an acid catalyst, and the reaction occurs consecutively in the presence of the single $IrH_5(PPh_3)_2$ catalyst, without the formation of salts.[48)] Immobilized ruthenium and iridium catalysts are highly useful for combinatorial chemistry.



[19]

In summary, herein demonstrated is that low valent ruthenium, iridium, and rhodium rhenium hydride complexes can be used as transition-metal-based redox bases, Lewis acids, and ambiphilic catalysts. Using these catalysts, various pronucleophiles such as nitriles, carbonyl compounds, isonitriles, trifluoromethylated compounds undergo selective carbon–carbon bond formation upon treatment with nucleophiles or electrophiles under neutral conditions. These catalytic reactions have the potential to serve as environmentally benign catalytic processes in the future.

Acknowledgements

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Profile

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He received the Chemical Society of Japan Award in 1995, Docteur Honoris Causa, Université de Rennes in 1995, the Merck-Schuchart Lectureship in 1996, a Humboldt Research Award in 2002, a Special Award in Synthetic Organic Chemistry Japan in 2005, and The Japan Academy Prize in 2010. His current research interests are organometallic chemistry directed towards organic synthesis, biomimetic oxidation reactions, ruthenium chemistry, and non-salt, green processes by C–H activation.