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Biomimetic oxidation in organic synthesis using transition metal catalysts

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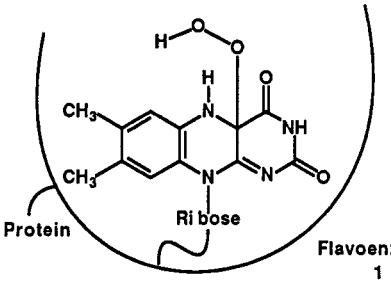
Abstract–Simulation of the function of hepatic flavoenzyme and Cytochrome P-450 with transition metal-complex catalysts results in finding biomimetic, catalytic oxidations of amines, amides, alkenes, and hydrocarbons.

1. INTRODUCTION

In my group, a systematic study has been conducted in aiming at finding a new methodology by using transition metal catalysts. Among several subjects I am concerning, I focus on the recent work on the activation of amine compounds with metal complexes. This work is based on the concept that simulation of the function of enzymes with metal complex catalysts (synzyme) will provide novel synthetic methodologies. Metabolism of amines is promoted by various enzymes such as hepatic flavoenzyme and Cytochrome P-450. Simulation of the functions of these enzymes with metal complex catalysts will provide novel biomimetic methods for the catalytic oxidation of amines, and hence highly useful strategies for organic synthesis can be explored.

2. SIMULATION OF HEPATIC FLAVOENZYME

Hepatic flavoenzyme (**1**) undergoes oxygen atom transfer from molecular oxygen to substrates. The key intermediate of the flavoenzyme is highly reactive hydroperoxyflavins. The reaction of hydroperoxyflavins with substrates gives oxidized products and hydroxyflavins. We recently found that hydroxyflavins undergo facile substitution reaction with hydrogen peroxide to give hydroperoxyflavins. Therefore, biomimetic flavin -catalyzed oxidation with hydrogen peroxide has been discovered (ref. 1). Typically, the reaction of secondary amines with hydrogen peroxide in the presence of flavin catalysts such as flavinium perchlorate (**2**) gives nitrones (**3**) highly efficiently (eq 1). This single-step transformation to nitrones is similar to the



$$R^1R^2CHNHR^3 \xrightarrow[\text{Flavin (cat)}]{H_2O_2} R^1R^2C{=}\overset{+}{N}R^3\,(O^-) \qquad (1)$$

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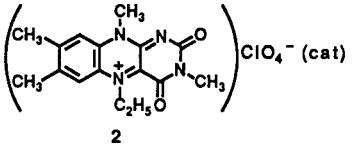
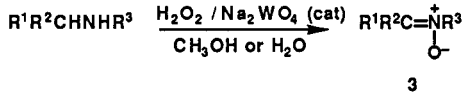


enzymatic reaction and is highly useful, because nitrones are versatile synthetic intermediates. Considering the reactivity of hydroperoxyflavins, metal hydroperoxides (M-OOH) are expected to have similar reactivity, and hence the reactivity of metal hydroperoxides towards amines was examined extensively. To date little attention has been paid to metal hydroperoxides, however metal hydroperoxides can be generated either upon treatment of metals (M) with hydrogen peroxide or by oxidation of metal hydrides (M-H) with molecular oxygen (ref. 2).

2.1 Tungstate-catalyzed oxidation of secondary amines

We discovered that secondary amines are oxidized cleanly with tungstate hydroperoxide to give nitrones. Thus, the treatment of secondary amines with three molar equivalents of a 30% hydrogen peroxide solution in

the presence of 1 mol% of sodium tungstate in either methanol or water at 0 °C under nitrogen gives the corresponding nitrones in good to moderate yields (eq 2) (ref. 3).



(2)

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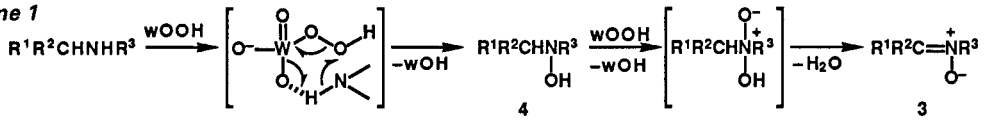
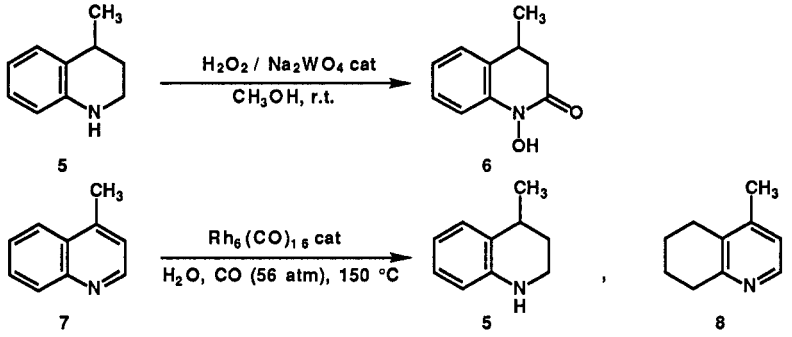
The present reaction can be rationalized by assuming Scheme I. The oxidation with tungstate hydroperoxide w-OOH, where w may be WO_3^-, WO_4^-, WO_6^- (ref. 4), gives N-hydroxylamines (**4**), which undergo further oxidation followed by dehydration to give nitrones (**3**).

Scheme 1

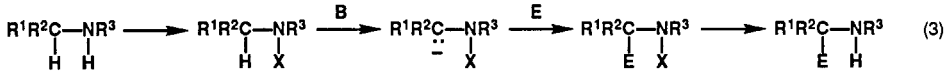


The tungstate-catalyzed reaction can be used for the oxidation of various substrates (ref. 5). Typically, the oxidation of tetrahydroquinolines provides a convenient method for the synthesis of cyclic hydroxamic acid. For example, the treatment of 4-methyl-1,2,3,4-tetrahydroquinoline (**5**) with H_2O_2 gave pure **6**, which shows antibacterial activity, in 83% yield after recrystallization. It should be commented that the substrate (**5**) can be obtained selectively by $Rh_6(CO)_{16}$-catalyzed water gas-shift reaction (ref. 6) of **7** in 91% yield, although, $Rh_6(CO)_{16}$-catalyzed hydrogenation gave **8** predominantly.



2.2 Substitution at the α-position of secondary amines

The present oxidation provides powerful strategies for organic synthesis. The most important synthetic evaluation of the present oxidation is the substitution at the α-position of amines. The available methods are limited to few ones, that is, protection of N-H bond, deprotonation of α-C-H bond with strong base, reaction with electrophiles (E), and removal of the protection (eq 3) (ref. 7). Our reaction may provide an alternative method for the substitution α to the nitrogen of amines; that is, oxidation of secondary amines, reaction of nitrones thus obtained with nucleophiles, and catalytic reduction (eq 4) (ref. 3a). Various nucleophiles can be



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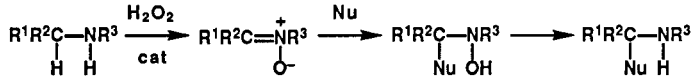
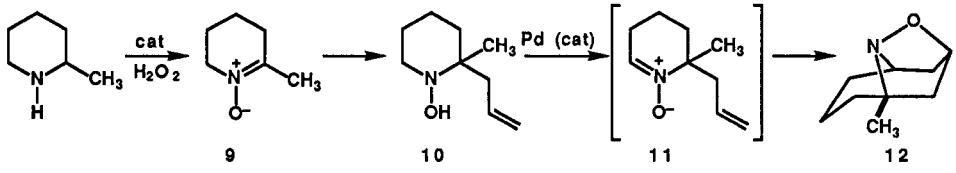
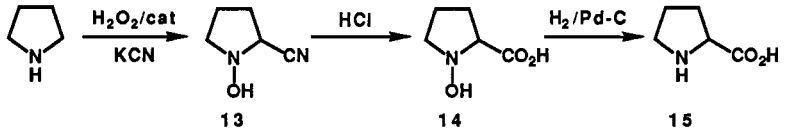


(4)

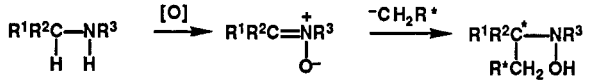
used to introduce substituents in place of electrophiles. Simple example of alkylation α to the nitrogen of amines is the synthesis of the precursor of pellefirine alkaloid (**12**). The reaction of nitrone (**9**) (ref. 8) with allylmagnesium bromide, followed by palladium-catalyzed oxidation (ref. 9) of hydroxylamine (**10**) gives nitrone (**11**), which undergoes intramolecular 1,3-dipolar cycloaddition to give adduct (**12**).



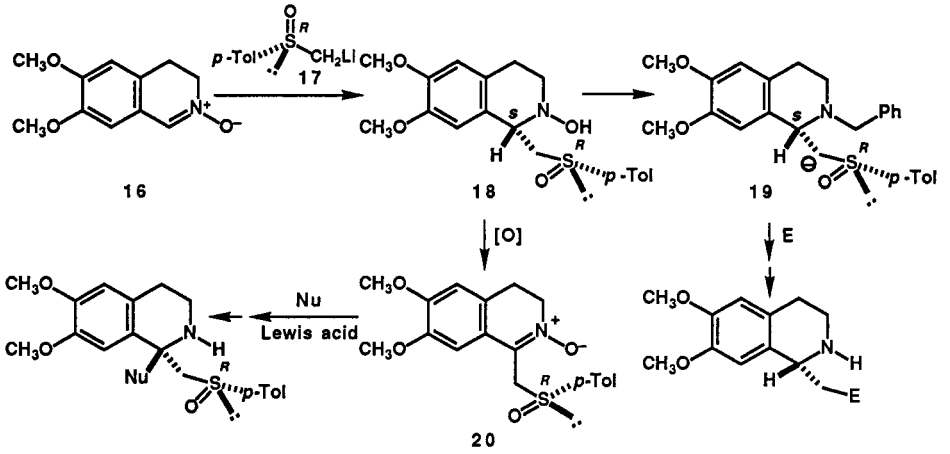
Nucleophiles are not limited to Grignard reagents. Introduction of cyanide provides short-step syntheses of N-hydroxy amino acids and amino acids from secondary amines (ref. 10). Typically, *N*-hydroxy-2-cyanopyrrolidine (**13**) (72%) is obtained without isolation of 1-pyrroline *N*-oxide. Hydrolysis of **13** gives biologically active N-hydroxy amino acid (**14**) (93%), which is hardly accessible. Further, catalytic hydrogenation of **14** gives proline (**15**) (93%).



The asymmetric induction at the α-position of amines is of importance in view of synthesis of biogenic amines as well as chiral amine ligands. Various optically active nucleophiles can be utilized to introduce asymmetry *via* enantio face differentiation of nitrones (eq 5). Attractive nucleophiles are optically active α-

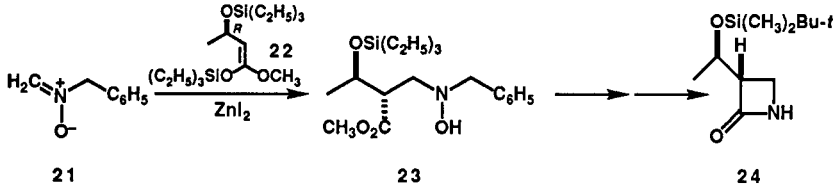


sulfinyl carbanion, which can be obtained readily by using asymmetric oxidation of sulfides with chiral titanium catalysts (ref. 11) or our chiral flavin catalysts (ref. 1, 12). Typically, the reaction of nitrone (**16**) with optically active (*R*)-α-sulfinyl carbanion (**17**) gives (S_C,R_S)-hydroxylamine (**18**) stereoselectively (ref. 13). Reduction of **18** with Raney nickel gives (*R*)-(+)-Salsolidine. Further treatment of **18** with benzyl bromide, tin hydride, and LDA gives (S_C,R_S)-α-sulfinyl carbanion (**19**), which undergo reactions with various electrophiles to give optically active α-substituted amine compounds. Optically active α,α-



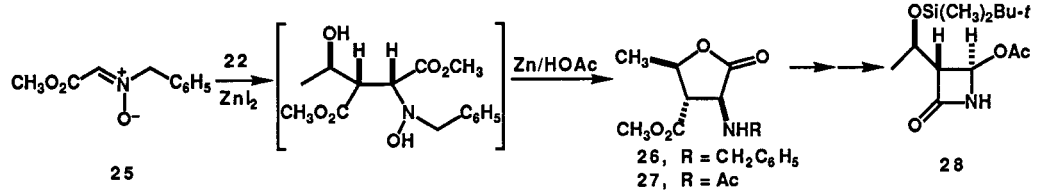
disubstituted N-hydroxylamines are hardly accessible; however, these compounds can be prepared simply by repeating the present reaction. For example, the oxidation of **18** gives optically active nitrone (**20**), which undergoes diastereoselective Lewis acid promoted nucleophilic reactions to give optically active α,α-disubstituted hydroxylamines (ref. 13).

Optically active β-amino acids are of importance in view of synthetic key intermediates of β-lactams and antagonists. The Lewis acid promoted reaction of nitrones with ketene silyl acetals gives N-hydroxy β-amino acids stereoselectively (ref. 14). Typically, zinc iodide promoted reaction of nitrone (**21**) with (*R*)-ketene silyl acetal (**22**), which is derived by using either asymmetric catalytic hydrogenation (ref. 15) or microbiological process, gave *anti* N-hydroxylamine (**23**) selectively (de>99.5%). β-Lactam (**24**) is readily prepared from **23**.



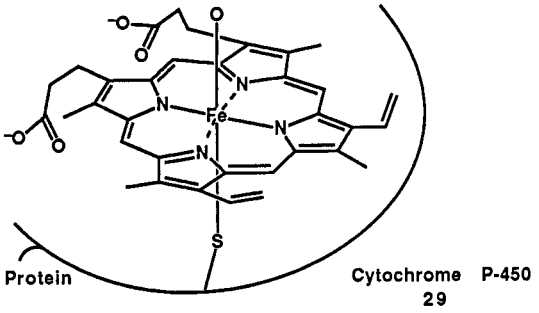
Further, the reaction of nitrone (**25**) with pure (*R*)-ketene silyl acetal (**22**) in CH_2Cl_2 in the presence of ZnI_2 at -78°C followed by treatment with zinc in acetic acid gave aminolacton (**26**) (mp 90.5-91.5°C) (de > 99.5%)

(60%) (ref. 14). Compound **26** was readily converted to the compound **27** (ref. 16), which is the precursor of 4-acetoxy azetidinone (**28**).

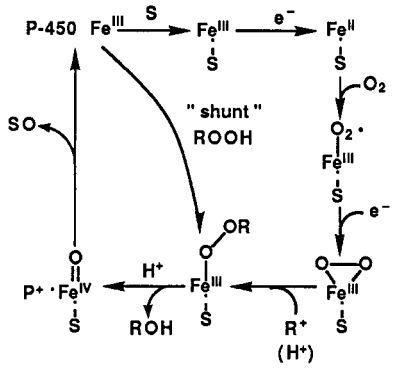


3. SIMULATION OF CYTOCHROME P-450

Cytochrome P-450 (**29**) has two major functions. One is the activation of molecular oxygen by porphyrin to generate oxo iron(IV) porphyrin, the other is its oxygen atom transfer to the substrates. The porphyrin moiety is required for the generation of hydroperoxy iron species, which undergoes protonolysis to give oxo iron(IV) species as shown in Scheme 2. However "shunt process" is often used for the oxidation of organic substrates, because oxo iron(IV) species can be formed readily upon treatment with oxygen donors such as alkylperoxides and iodosylbenzene (ref. 17). According to the "shunt process", oxo metal complexes can be generated without using porphyrins. In order to generate oxo metal complexes, which corresponds to oxo iron(IV) species, we chose low-valent ruthenium complexes, because we have been investigated low valent ruthenium complexes extensively from many aspects (ref. 18).



Scheme 2



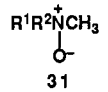
3.1 Ruthenium-catalyzed oxidation of *tert*-amines

3.1.1 The oxidation with t-butyl hydroperoxide

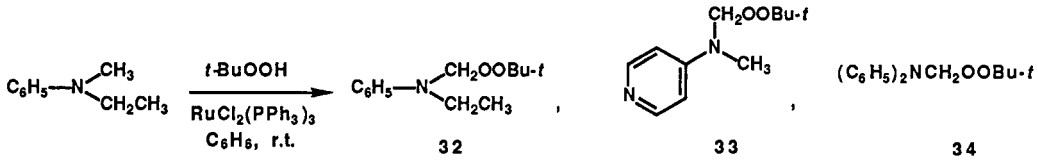
Oxidative N-demethylation of amines is one of the important P-450 specific reactions, and several model reactions using iron-porphyrins have been reported (ref. 19). We found that novel Cytochrome P-450-type oxidation of tertiary amines can be performed without using porphyrins. Thus, the ruthenium-catalyzed oxidation of tertiary amines with *t*-butyl hydroperoxide gives the corresponding α-(*t*-butyldioxy)alkylamines (**30**) highly efficiently (eq 6) (ref. 20). This is in contrast to the usual catalytic oxidation of tertiary amines

$$R^1R^2NCH_3 \xrightarrow[RuCl_2(PPh_3)_3\ (cat)]{t\text{-BuOOH}} \underset{\mathbf{30}}{R^1R^2NCH_2OOBu\text{-}t} \qquad (6)$$

with peroxides to give *N*-oxides (**31**). Typically, the reaction of *N*-ethyl-*N*-methylaniline with *t*-butyl



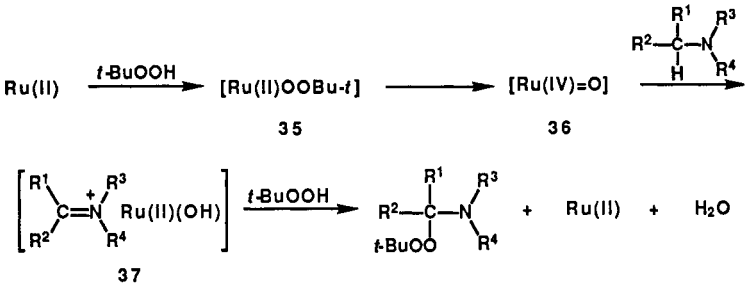
hydroperoxide in the presence of 3 mol% of $RuCl_2(PPh_3)_3$ gives peroxide (**32**) (78%), where N-methyl group is oxidized chemoselectively. Benzylic and allylic carbon-hydrogen bonds and carbon-carbon double



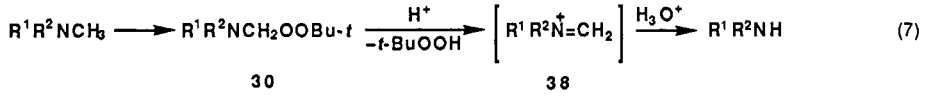
bonds tolerate the reaction, and *t*-butyldioxyamines (**33**) and (**34**) are obtained in 72% and 83% yields, respectively.

In order to gain insight into the mechanism of the oxidation, relative rates of the oxidation of five substituted *N,N*-dimethylanilines 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, which indicates cationic intermediacy at the rate-determining step. The intramolecular deuterium isotope effect (k_H/k_D) of the ruthenium-catalyzed oxidation of *N*-methyl-*N*-(trideuteriomethyl)aniline is determined to be 3.53. Furthermore, the intermolecular isotope effect is determined to be 1.64 by the NMR analysis of the demethylated products of the competitive reaction of *N,N*-dimethylaniline and *N,N*-bis(trideuteriomethyl)aniline. The observed isotope effects (3.53 and 1.64) are larger than the values observed for Cytochrome P-450 N-demethylation (1.6-3.1 and 1.0-1.1). The reaction is rationalized by assuming the Cytochrome P-450-type mechanism shown in Scheme 3. Ruthenium(II) complex reacts with *t*-butyl hydroperoxide to give oxo ruthenium(IV) species. Thus, the reaction of Ru(II) complex with *t*-butyl hydroperoxide would give Ru(II)OOBu-*t* (**35**), which undergoes cleavage of O-O bond to give Ru(IV)=O complex (**36**). Electron transfer followed by proton transfer would give iminium ion complex (**37**). Nucleophilic attack of *t*-BuOOH to **37** gives the product of peroxide, water, and Ru(II) species to complete the catalytic cycle.

Scheme 3



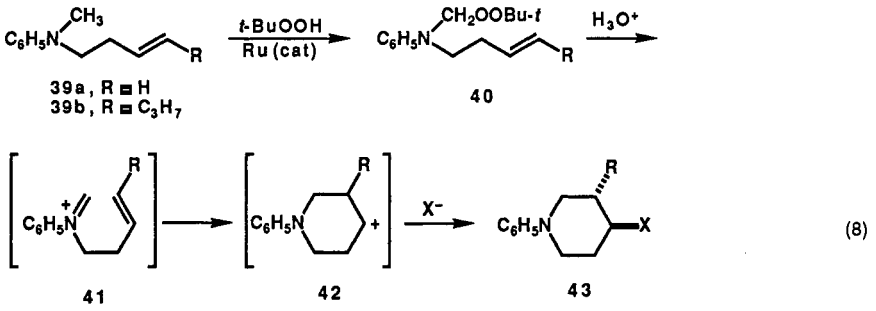
N-Demethylation of tertiary amines is the typical function of Cytochrome P-450. Selective N-demethylation of tertiary methylamines is performed by the present ruthenium-catalyzed oxidation and subsequent hydrolysis of α-*t*-butyldioxyamine (**30**) with an aqueous HCl solution *via* iminium ion (**38**) (ref. 20).



(7)

Typically, N-demethylation of *N*-methyl-*N*-ethylaniline can be performed readily to give *N*-ethylaniline. This is the first synthetically practical method for the N-demethylation of tertiary methylamines, although few catalytic (ref. 19) and stoichiometric reactions (ref. 21) have been reported.

The present reaction provides a novel, biomimetic method for the construction of piperidine skeletons from *N*-methylhomoallylamines (**39**) *via* olefin-iminium ion cyclization reaction (eq 8). The ruthenium-catalyzed oxidation of *N*-methyl-*N*-(3-butenyl)aniline (**39a**) gave the peroxide (**40a**) (87%), which was converted to 1-phenyl-4-chloropiperidine (**43a**) (77%) upon treatment with a 2 M HCl solution at room temperature. Cyclization of the peroxide (**40**) bearing a substituted 3-butenyl group gave *trans*-3,4-disubstituted piperidines stereoselectively. Thus, *trans*-1-phenyl-3-propyl-4-chloropiperidine (**43b**) was obtained from (**39b**) (oxidation 76%; cyclization 55%). These cyclizations can be rationalized by assuming the formation of iminium ion (**41**) by protonation of **40** and subsequent elimination of *t*-BuOOH. Nucleophilic attack of an alkene gives cation (**42**), which is trapped by nucleophile X^- from the less hindered side.



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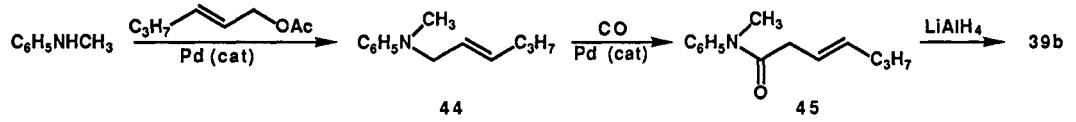
Homoallylamines (**39**) are hardly accessible substrates; however we found a convenient method for the synthesis of homoallylamines from allyl alcohols recently. Actually, the palladium-catalyzed carbonylation of *tert*-allylamine (**44**) which are derived from palladium-catalyzed amination of allyl acetates, gives β, γ-

unsaturated amides (**45**) (ref. 22). This is one of the first example of the insertion of CO into carbon-nitrogen bonds.



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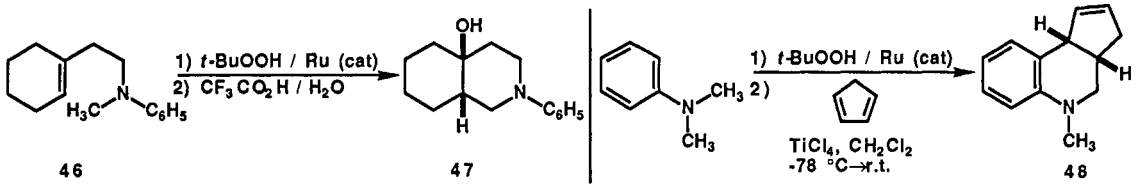
The present biomimetic method can be applied for organic synthesis. The reaction of cyclic amines (**46**) gives fused bicyclic amines (**47**). Furthermore, when dienes are used as nucleophiles to trap such iminium

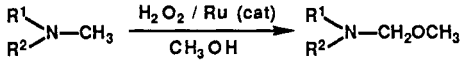


46 47 48

ion intermediates, various cyclized products are obtained. Selective formation of tetrahydroquinoline derivatives (**48**) (80%) from *N,N*-dimethylaniline and cyclopentadiene is such an example.

3.1.2 The oxidation with hydrogen peroxide

On considering the Scheme 3, generation of the oxo ruthenium species (**36**) by using other oxidizing reagents and the trap of the iminium ion intermediate (**37**) with other nucleophiles can be expected. Indeed, we succeeded in finding a catalytic system which satisfies these points. Thus, we found that ruthenium trichloride-catalyzed oxidation of tertiary amines with hydrogen peroxide gives α-methoxymethylamines (**49**) (ref. 23). Actually, the treatment of **50** with a 30% H_2O_2 solution at room temperature in CH_3OH in the



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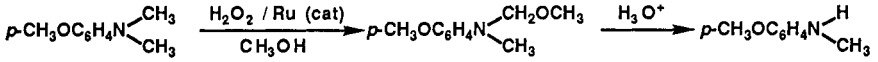
presence of 1 mol% of $RuCl_3 \cdot nH_2O$ catalyst gave the corresponding α-methoxymethylamine (**51**) in 87% yield. The Hammett treatment showed that the ρ value is −3.26. The intramolecular and intermolecular isotope effects were determined to be 3.47 and 3.72, respectively. These data show that the active ruthenium



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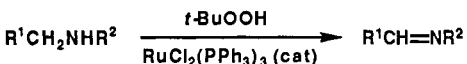
species of this reaction is less reactive in comparison with that derived from $RuCl_2(PPh_3)_3$ and *t*-BuOOH. The α-methoxymethylamines thus obtained undergo facile hydrolysis and titanium promoted cyclization reactions. One pot reaction of *N,N*-dimethylanisidine (**50**) gave demethylated amine (**52**) in 71% yield.

3.2 Ruthenium-catalyzed oxidation of secondary amines

By using the same catalytic system, secondary amines can be converted into the corresponding imines (**53**) highly efficiently (eq 10) (ref. 24). This is the first catalytic oxidative transformation of secondary amines to imines. The treatment of secondary amines with two equivalents of *t*-butyl hydroperoxide in benzene in the presence of $RuCl_2(PPh_3)_3$ catalyst at room temperature gives the corresponding imines in high yields. Our reaction provides the second method for the substitution α to the nitrogen of amines by using nucleophiles. That is, the oxidation of secondary amines gives imines, which react with various nucleophiles (eq 11). Asymmetric additions of nucleophiles to imines are well known.



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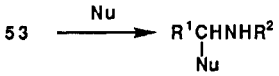
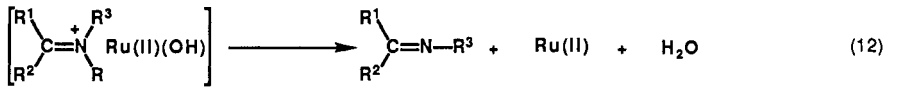


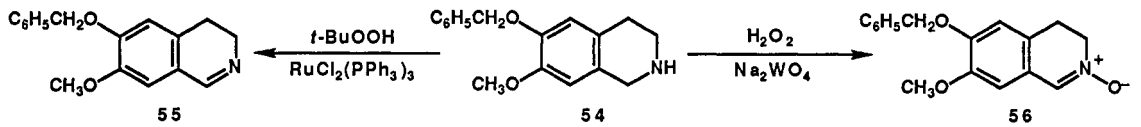
(11)

The mechanism of the present oxidation of secondary amines is quite similar to that of tertiary amines as shown in eq 12. Electron transfer to oxo ruthenium(IV) species (**36**), followed by proton transfer would give iminium ion complex (**37**) (R=H), which undergoes decomposition to give the product imine, Ru(II) species, and water to complete catalytic cycle. In the case of the oxidation of tertiary amines, the iminium ion complex (**37**) (R≠H) is stable to be attacked by the second molecule of *t*-butyl hydroperoxide to give *t*-butyldioxyamines.



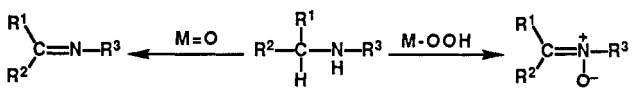
37 (R = H) (12)

We are now in a position to be able to prepare either imines or nitrones from secondary amines by changing the catalytic system utilized. Typically, the ruthenium-catalyzed oxidation of amine (**54**) with *t*-BuOOH gives imine (**55**) (93%), while the tungstate-catalyzed oxidation of the same amine with hydrogen peroxide gives nitrone (**56**) (86%). The contrast formations of nitrones and imines are due to the different



55 54 56

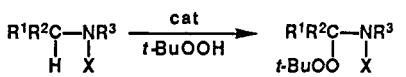
oxidizing species. The oxidation of secondary amines with hydroperoxy metal complexes (M-OOH) gives nitrones, while the oxidation with oxo metal complexes (M=O) gives imines (eq 13). This is the first result that shows different reactivities between MOOH species and M=O species.



(13)

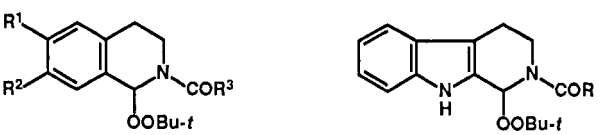
3.3 Ruthenium-catalyzed oxidation of amides

Cytochrome P-450 enzymes catalyze specific oxygenation of amides; however, the biomimetic method for selective oxidation of amides is limited to an electrochemical process (ref. 25). We have found that using the same catalytic system, amides (**57**) can be converted into *t*-butyldioxyamides (**58**) highly efficiently as shown in eq 14 (ref. 26). Typically, the oxidation of 1-(methoxycarbonyl)pyrrolidine (**59**) gave 2-*t*-



57 58 (14)

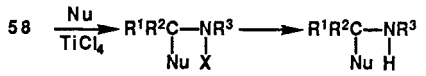
X = Ac, CO_2CH_3



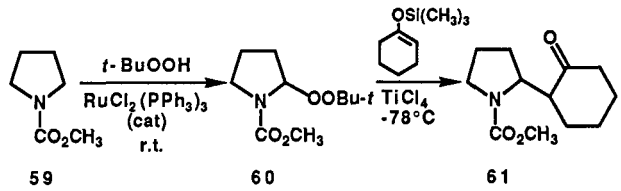
62a, R¹, R²= H, R³= OCH_3 (91%)
62b, R¹, R²= OCH_3, R³= OCH_3 (97%)

63, R = OCH3 (92%)

butyldioxy compound (**60**) (60%). The *t*-butyldioxyamides of isoquinolines (**62**) and indoles (**63**) thus obtained are important synthetic intermediates. *t*-Butyldioxyamides (**58**) thus obtained undergo substitution reactions with various nucleophiles to give α-substituted amides (**64**). Therefore, we have now the third method for the transformation of amines to the corresponding α-substituted amines (eq 15) (ref. 27). Thus, the oxidation of N-protected amines with *t*-butyl hydroperoxide gives α-*t*-butyldioxyamides, which undergo substitution reactions with nucleophiles to give α-substituted amides. Hydrolysis of the amides gives the corresponding α-substituted amines. The most important transformation of α-*t*-butyldioxyamides is the



64 (15)

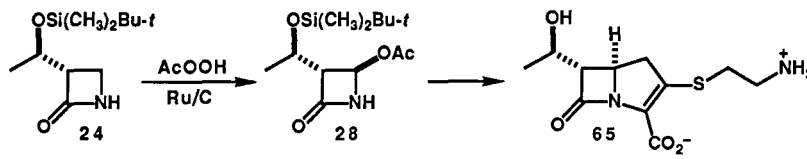


carbon-carbon bond formation at the α-position of amides. Typically, the transformation of the pyrrolidine amide (**59**) to α-*t*-butyldioxypyrrolidine (**60**) followed by titanium promoted reaction with silyl enol ether at –78 °C gives ketoamide (**61**) (81%).

3.4 Ruthenium and osmium-catalyzed oxidations of β-lactams

3.4.1 Oxidation with peracetic acid

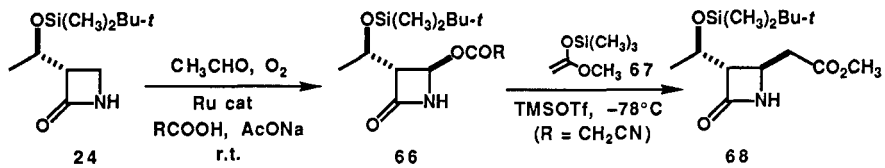
One of the most interesting oxidation of amides is the catalytic oxidation of β-lactams. Modification of the catalytic system is required because of the ring strain of four-membered rings. We found that the treatment of β-lactams with peracetic acid in acetic acid in the presence of low valent ruthenium catalysts and sodium acetate at room temperature gives the corresponding 4-acetoxy β-lactams highly efficiently (ref. 26). 4-Acetoxy azetidinone (**28**) is an important precursor of various β-lactam antibiotics such as thienamycine (**65**). Addition of a peracetic acid solution to a solution of **24** at room temperature in the presence of ruthenium on charcoal gives **28** (99%) with >99% diastereoselectivity.



We have found that osmium trichloride-catalyzed oxidation of β-lactams with peracetic acid in acetic acid proceed at room temperature highly efficiently (ref. 28). This reaction is different from the OsO_4-catalyzed oxidation, and can be rationalized by assuming an intermediacy of oxo osmium(V) species, which may have a similar function to oxo ruthenium complexes (ref. 20).

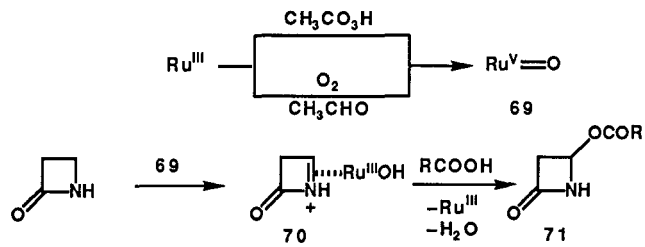
3.4.2 Oxidation with acetaldehyde and molecular oxygen

The ruthenium-catalyzed oxidation of β-lactams requires peroxides such as peracetic acid and methyl ethyl ketone peroxide. However, these peroxides are not always available and sometimes contain undesirable materials; therefore we examined the formation of peroxides *in situ* from aldehydes and molecular oxygen in the presence of catalysts. It is well known that peracetic acid, for example, can be prepared upon treatment of acetaldehyde with molecular oxygen in the presence of cobalt salts. We discovered that ruthenium-catalyzed oxidation of β-lactams with molecular oxygen can be performed in the presence of acetaldehyde and an acid and sodium acetate highly efficiently (ref. 29). For example, 4-acetoxy (**28**) and 4-cyanoacetoxy β-lactams (**66**, R=CH_2CN) are obtained in 91% and 81% yields, respectively. The TMSOTf promoted reaction of 4-cyanoacetoxy β-lactam (**66**, R=CH_2CN) with ketene silyl acetal (**67**) affords 4-methoxycarbonylmethyl β-lactam (**68**) (92%) stereoselectively.



As shown in Scheme 4, the active species of the present oxidation seems to be oxo ruthenium(V) species (**69**). The reaction of ruthenium with either peracetic acid or acetaldehyde and molecular oxigen gives oxo ruthenium species (**69**), which undergoes hydrogen abstraction of the C_4-H of β-lactam, followed by electron transfer to give acyliminium ion (**70**). Nucleophilic reaction with an acid gives **71**.

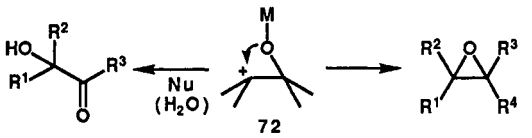
Scheme 4



If our proposed mechanisms are correct, we are now in a position to be able to have oxo ruthenium species without using porphyrins by i) *t*-butyl hydroperoxide/$RuCl_2(PPh_3)_3$, ii) $H_2O_2/RuCl_3$, iii) peracetic acid/Ru, and iv) acetaldehyde-O_2/Ru. By using these catalytic systems, Cytochrome P-450 type oxidations can be carried out with various substrates. I show two such typical reactions here.

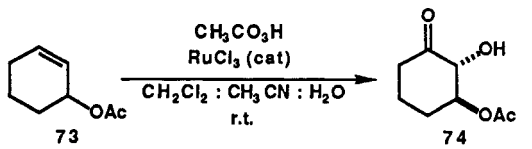
3.5 Ruthenium-catalyzed oxidation of alkenes

In the Cytochrome P-450 promoted epoxidation of alkenes, the cationic complex (**72**) is postulated as a key intermediate. If one could trap **72** with certain nucleophiles before ring close, new types of oxidation reactions can be explored. Indeed, we discovered a convenient method for the transformation of alkenes to



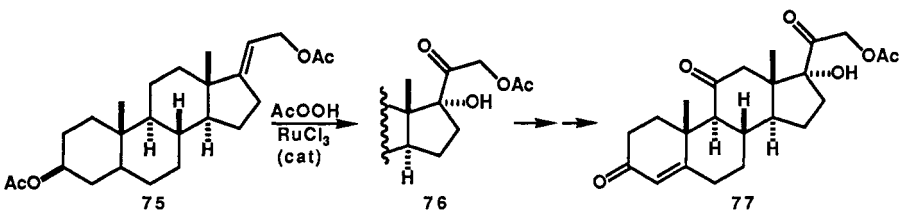
72

ketols. Typically, the oxidation of allyl acetate (**73**) with peracetic acid in a mixture of dichloromethane, acetonitrile, and water (1:1:1) in the presence of 3 mol% of ruthenium trichloride at room temperature gives



73 74

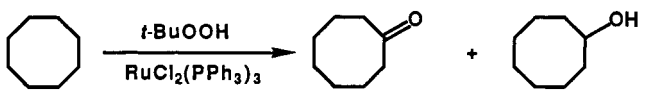
ketol (**74**) (70%) stereoselectively. α-Ketols are important partial structures of biologically active compounds such as cortisone and adriamycin. The ruthenium-catalyzed oxidation was applied for the synthesis of cortisone acetate, steroid hormone (**77**) from epiandrosterone. The key step is the diastereoselective ruthenium-catalyzed oxidation of allyl acetate (**75**) with peracetic acid. The ketol (**76**) obtained is readily converted into cortexolone, which undergoes microbiological oxidation to give cortisone acetate.



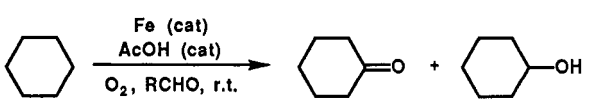
75 76 77

3.6 Oxidation of hydrocarbons

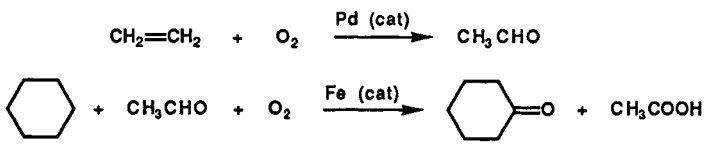
Direct oxidation of hydrocarbons is also one of the typical reaction of Cytochrome P-450. Our catalytic system is expected to be used for the oxidation of alkanes (ref. 30, 31). Actually, the treatment of hydrocarbons with either *t*-butyl hydroperoxide/$RuCl_2(PPh_3)_3$ or peracetic acid/Ru gives the corresponding ketones in good yields along with alcohols. The simple system which is closely related to the Cytochrome P-450 is the iron-catalyzed oxidation of alkanes with molecular oxygen. We found that alkanes can be oxidized



with molecular oxygen in the presence of aldehyde and iron powder at room temperature to give ketones along with alcohols. Typically, cyclohexane can be converted into cyclohexanone (66%) and cyclohexanol (29%) readily.



This reaction provide a powerful industrial strategy for synthesis of cyclohexanone from cyclohexane by combination of the Wacker oxidation reaction.



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