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# **STUDIES ON THE SYNTHESIS OF** $\beta$ -LACTAMS AND $\alpha$ -KETOLS BY USING **TRANSITION METAL-COMPLEX** CATALYSTS

1996

# General Introduction

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**Publication List** 

Acknowledgment

STUDIES ON THE SYNTHESIS OF LACTAMS AND G-KETOLS BY USING TRANSITION METAL-COMPLEX CATALYSTS

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The catalysis of organic reactions by means of transition metal complexes has become a major synthetic tool both in the laboratory and in the chemical industry. Catalysis have often played important roles in opening new areas of organic chemistry. In this thesis, the author focused mainly on the catalysis leading to desired target molecules specifically and studied the development of efficient catalysis for the synthesis of some biologically active compounds.

Since discovery of thienamycin (1a) bearing novel  $\beta$ -thioenamine chromophore from fermentation broth of the soil microorganism, Streptmyces cattleya, by the Merck research group,<sup>1</sup> much effort has been conducted for the synthesis of the carbapenem family of compounds and the derivatives<sup>2</sup> because of their excellent broad antibacterial activity, the low fermentation yield, and unique framework. In 1984, the Merck group also reported the synthesis of the 1 $\beta$ -methyl analogue (1b),<sup>3</sup> which exhibited greater stability and resistance to deactivation by renal dipeptidase-1 and still retained the excellent broad antibacterial spectrum. Among those various reported processes for the synthesis of carbapenem antibiotics, a synthetic approach via (1'R, 3R, 4R)-4-acetoxy-3-[1'-[(tertbutyldimethylsilyl)oxy]ethyl]azetidin-2-one (2) or its derivatives as an intermediate is considered to be especially advantageous, because various types of carbon chains can be readily introduced into 2 by substitution of the acetoxy group with nucleophiles. Thus, the attention was focused to how construct the 4-acetoxyazetidin-2-one (2) with desired stereochemistry.

The author shows a possibility in the retrosynthetic analysis of the target molecule 2. This synthetic strategy involves two substantial problems to be overcome; effective asymmetric hydrogenation of  $\alpha$ -substituted  $\beta$ -ketoesters with excellent stereoselectivities and subsequent novel oxidation reaction of  $\beta$ -lactam at C-4 position.

# **General Introduction**





Recent dramatic progress in both fields of asymmetric hydrogenation performed by BINAP chemistry<sup>4</sup> and transition metal catalyzed oxidation of amines<sup>5</sup> encouraged the author to overcome these problems. First, in order to get desired stereochemistry, the author employed the BINAP-Ru(II) complexes catalyzed asymmetric hydrogenation of  $\alpha$ substituted *B*-ketoesters.



As described in Chapter 1, novel diastereo- and enantio-selective hydrogenation of α-substituted β-ketoesters via dynamic kinetic resolution by BINAP-Ru(II) complexes was performed.<sup>6</sup> Asymmetric hydrogenation of carbonyl compounds is significantly important for the synthesis of optically active secondary alcohols. In this decade, Noyori and Takaya established the excellent chiral recognition ability of BINAP-Ru(II) complexes in homogenous hydrogenation of a wide variety of carbonyl compounds.<sup>7</sup> On the other hands, in usual kinetic resolution processes, one enantiomer is obtained in 50% yield maximally and the enantiomeric excess is affected by the extent of conversion. However, racemic compounds may be converted to one major stereoisomer under certain conditions, where the chemical yield can be 100% and the enantiomeric excess is independent of conversion. Thus, chiral lability of  $\alpha$ -substituted  $\beta$ -ketoesters, coupled with the high chiral recognition ability of the BINAP-Ru(II) complexes, has stimulated the author to study the possibility of stereoselective hydrogenation by using dynamic stereomutation. The author investigated the stereoselective hydrogenation of  $\alpha$ acylaminomethyl \beta-ketoesters based on this principle and found that the catalytic reaction promoted by  $\operatorname{Ru}_2\operatorname{Cl}_4((R)-\operatorname{binap})_2$ •NEt<sub>3</sub> forms almost one isomer among the four possible



stereoisomer. The present stereoselective hydrogenation provides the considerable precurser of 2 having desired stereochemistry. Hydrolysis of 6, cyclization and subsequent protection of the secondary alcohol with tert-butyldimethylsilyl group gave the optically active  $\beta$ -lactam 7 without difficulty.

5

This is the first example of an ideal asymmetric catalysis performed by BINAP-Ru (II) complexes. These high syn selections were considered to be caused by the sterically restricted transition state as visualized as follows. This procedure has been applied to the industrial production of syn-(2S, 3R)-6 in a scale of 100 ton per year.



X = Halogen, H, H<sub>2</sub> or Solvent  $\bigcirc P_P = BINAP$ 



Representative examples for the preparation of 2 include oxidation of 4-carboxy-2-azetidinone 8a, 8b with lead tetraacetate,<sup>8</sup> electrochemical oxidation of 7, 8b,<sup>9</sup> treatment of 4-silyloxy-2-azetidinone 9 with acetic anhydride,<sup>10</sup> and Baeyer-Viliger oxidation of 4-acethyl-2-azetidinone 10.<sup>11</sup> In order to introduce an acetoxy group to the 4-position of the  $\beta$ -lactam skeleton according to any of above described methods, it is necessary to prepare an  $\beta$ -lactam baring a specific substituent at the 4-position of the  $\beta$ -lactam. Hence, these conventional processes are not regarded as advantageous in industrial technologies. Thus, the author attempted to develop a novel transformation reaction.



Recently, the use of oxo metal complexes to effect catalytic oxidation has become increasingly important and these recent developments in the area of the oxidation of biological active compounds have attracted considerable attention.<sup>12</sup> Ruthenium and osmium are unique elements in the periodic table to exhibit octavalency and to cover the entire range of eleven oxidation states, inclusively VIII to -II, theoretically available to a transition metal. The group VIII transition metal complexes catalyzed reactions can be effectively employed in the synthesis of a variety of natural products. However, little use has been made of its variety in organic synthetic chemistry. The well known complex is the tetroxide (RuO4 and OsO4) but these are very powerful oxidizing agents and which are rather non-selective oxidant.<sup>13</sup> On the contrary to the tetroxide, the author

has focused his attention on the low valent oxo metal species because of their diversity and still unknown abilities.

Described in Chapter 2 is a novel ruthenium-catalyzed oxidation of  $\beta$ -lactams with peroxides<sup>14</sup>. The introduction of a substituent into C-H bond adjacent to nitrogen of amides such as  $\beta$ -lactams with metal complex catalysis is one of the most attractive strategies.<sup>15</sup> Cytochrome P-450 enzymes which play an important role in the metabolism of amines, catalyze specific oxygenation of amides,<sup>16</sup> but biomimetic oxidation for selective oxidation of  $\beta$ -lactams is limited to electrochemical process.<sup>17</sup> Indeed, these processes are not enough to succeed in solving those problems in the transformation of  $\beta$ -lactams. During the course of systematic study on the simulation of enzymatic function with metal complex catalysts, Murahashi *et al.* have found novel cytochrome P-450 type oxidation of amines with *t*-butyl hydroperoxide under mild reaction conditions gives the corresponding *t*-butyldioxy amines and proposed the formation of oxoruthenium species as a key intermediate.<sup>5</sup>

Ruthenium-catalyzed oxidation with *t*-butyl hydroperoxide can not be applied to the oxidation of  $\beta$ -lactams under the same reaction conditions because of the more specific reaction conditions for the oxidation of  $\beta$ -lactams due to the higher strain of the four-membered acyliminium ion intermediates. The author investigated the improvement of these reactions. Oxidation of  $\beta$ -lactams can be performed by the ruthenium-catalyzed oxidation with peroxides such as peracetic acid as follows.



Thus, the author has found that the ruthenium-catalyzed oxidation of  $\beta$ -lactams with peroxides such as peracetic acid in acetic acid gives the corresponding 4-acetoxy  $\beta$ -lactams. This is the first example of the ruthenium-catalyzed oxidation of C-H bond





adjacent to nitrogen of amide. Especially, oxidation of 7 under the present reaction conditions gives 2 in excellent yield. Diastereoselectivity of 2 obtained is determined to be up to 99%. This preferential formation is due to the steric interaction between the side chain at C-3 position of B-lactam and acetoxy group at C-4 position.



Described in Chapter 3 is a novel osmium-catalyzed oxidation of β-lactams with peroxides.<sup>18</sup> Osmium-catalyzed transformation of olefins is an attractive and highly useful method in organic synthesis.<sup>19</sup> Asymmetric dihydroxylation reaction of alkenes is a representative success by using osmium tetroxide and chiral amine complex catalyst system.<sup>20</sup> The author has engaged in a systematic study on the effects of various transition metal complexes for the oxidation of  $\beta$ -lactams with peroxides and found that the osmium-catalyzed oxidation of β-lactams with peracetic acid gives the corresponding 4-acetoxy β-lactams in good to excellent yields under mild reaction conditions.



This is the first example of the osmium-catalyzed activation of C-H bond neighboring nitrogen of amide. Also, in this case, oxidation of 7 gives 2 in excellent yield in the similar manner to the ruthenium-catalyzed oxidation. Furthermore, under the present reaction conditions, unprotected  $\beta$ -lactam 11 can be converted into the corresponding a mixture of 12a and 12b (4:1) in moderate yield without over oxidation of secondary alcohol on its side chain.



The present oxidation is different from the osmium tetroxide catalyzed oxidation and can be rationalized by assuming an intermediacy of oxoosmium species, which may have a similar function to oxoruthenium complexes.

Described in Chapter 4 is the ruthenium-catalyzed oxidation of  $\beta$ -lactams with molecular oxygen and aldehydes.<sup>21</sup> For the oxidation of  $\beta$ -lactams, peroxides such as peracetic acid have been used. However, these peroxides are not always available and sometimes contain undesirable matalials such as diacylperoxides. Therefore, the author studied on the effect of peroxide more precisely in order to get insight into the active species of the present oxidation reaction. As the results, the author found a convenient method for the oxidation of  $\beta$ -lactams without using peroxides. The rutheniumcatalyzed oxidation of  $\beta$ -lactams with molecular oxygen in the presence of acetaldehyde and acetic acid gives the corresponding 4-acetoxy  $\beta$ -lactams in excellent yields, where air can be used for the oxidation of  $\beta$ -lactams.



Furthermore, the present oxidation reaction provides various 4-acyloxy B-lactams such as 4-methoxyacetoxy- (2b), 4-cyanoacetoxy- (2c), 4-chloroacetoxy- (2d), and 4dichloroacetoxy- $\beta$ -lactam (2e) in good to excellent yields, which are useful intermediates because of their higher reactive leaving groups.<sup>22</sup>

In recent years there has been considerable speculation concerning the nature of the active oxidant in iron-containing enzymes (cytochrome P-450), which mediate incorporation of molecular oxygen into a variety of organic compounds.<sup>23</sup> Some reports on the ruthenium-catalyzed oxidation of organic compounds using molecular oxygen have been published.<sup>24</sup> The oxidation of organic compounds by molecular oxygen has a long history, but this is the first example of the ruthenium-catalyzed activation of C-H bonds

cat., 
$$O_2$$
,  $CH_3CHO$   
OH, AcONa, 40 °C



adjacent to nitrogen of B-lactams with molecular oxygen in the presence of an aldehyde. The present reaction gives a great contribution to the synthesis of carbapenem antibiotics from the industrial point of view. The methodology described herein accomplishes a new approach to the construction of a versatile key intermediate for synthesis of carbapenem antibiotics. The present process is now industrially operating on 50 ton/year scale.

Finally, described in Chapter 5 is the ruthenium-catalyzed oxidative transformation of alkenes to  $\alpha$ -ketols with peracetic acid and simple synthesis of cortisone acetate.

Conversions of olefins to oxygenated derivatives via a wide variety oxidative transformations constitute prime examples of the broad synthetic utility of metal-catalyzed oxidation reactions. a-Ketols are important synthetic intermediates and also partial structures of various biologically active compounds such as cortisone acetate  $(13)^{25}$  and adriamycin acetate (14).<sup>26</sup>



In chapters 3-5, the author describes details of a novel cytochrome P-450 typeoxidations of  $\beta$ -lactams. In these reactions, non-porphyrin oxo-ruthenium species generated from low valent ruthenium and peroxide undergo cytochrome P-450 type reactions. One of the typical function of cytochrome P-450 is epoxidation of alkenes, where cationic intermediate 15 has been postulated as a key intermediate.27



If one could trap the intermediate 15 with nucleophiles such as water, a new type of catalytic oxidation of alkenes can be performed. Indeed, the author found that novel oxidative transformation of olefins to  $\alpha$ -ketols proceeds highly efficiently. Thus, low valent ruthenium-catalyzed oxidation of alkenes with peracetic acid in an aqueous solution under mild conditions gives the corresponding  $\alpha$ -ketols.<sup>28</sup>

Furthermore, the author demonstrated the efficiency of the present reaction by synthesis of cortisone acetate (13), which is a valuable anti-inflammatory agent. In conclusion, the development of transition metal-complex catalysis has brought about striking innovations to synthetic chemistry and, especially, to industrial chemistry, giving us a new methodology for the creation of target molecules. Since catalysis plays an important role in organic synthesis, ever-increasing effort of research and development in this field is expected to contribute toward further improvement of health science.

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In this decade there has been spectacular progress in homogenous asymmetric catalysis performed by transition metal complexes utilizing optically active phosphine ligands.<sup>1</sup> Among those investigated the atropisomeric 2,2'-bis(diphenylphosphino)-1, 1'-binaphthyl (BINAP) and their family of compounds<sup>2</sup> exhibit extremely high chiral recognition ability and broad applicability in various transition metal-catalyzed asymmetric reactions.<sup>3</sup> Especially, the development of asymmetric homogeneous hydrogenation promoted by BINAP-Ru (II) complex catalysts becomes one of the glorious chapters of synthetic organic chemistry.4





On the other hands, kinetic resolution of racemic compounds is one of the significant method to get the optically active compounds;<sup>8</sup> however, the yields of the

Chapter 1. Diastereo- and Enantio-selective Hydrogenation via Dynamic Kinetic Resolution Promoted by **BINAP-Ru** (II) Complexes

# Introduction





For example, BINAP-Ru (II) dicarboxylate complexes,  $Ru(binap)(O_2CR)_2$  (R = CH<sub>3</sub>, CF<sub>3</sub>), catalyze hydrogenation of a variety of functionalized olefins with a high degree of enantioselectivity.<sup>5</sup> By contrast the activity towards enantioselective hydrogenation of functionalized ketones is discouragingly poor.<sup>6</sup> Recently halogencontaining complexes with the empirical formula  $RuX_2(binap)$  (X = Cl, Br or I) or Ru<sub>2</sub>Cl<sub>4</sub>(binap)<sub>2</sub>•NEt<sub>3</sub> have opened a new generation for homogenous asymmetric hydrogenation of a wide variety of functionalized ketones represented by β-keto esters.<sup>7</sup>

desired chiral product do not exceed 50%. By contrast, as outlined in Scheme I, if the racemization of the enantiomers  $1\alpha$  and  $1\beta$  could be rapid enough with respect to the hydrogenation giving 2, then when the rates of the reaction of  $1\alpha$  and  $1\beta$  are substantially different, the hydrogenation would form one isomer selectively among the four possible stereoisomeric hydroxy esters. This second-order stereoselective transformation, if feasible, constitutes an ideal asymmetric catalysis which, in theory, is capable of converting a racemic starting material in 100% yield to a single chiral product possessing

Scheme 1



stereodefined vicinal asymmetric centers. Thus, the chiral lability of  $\alpha$ -substituted  $\beta$ -ketoesters, coupled with the high chiral recognition ability of the BINAP-Ru(II) complexes<sup>2-7</sup>, has stimulated the author to investigate the possibility of stereoselective hydrogenation utilizing stereomutation. The author investigated diastereo- and enantio-selective hydrogenation based on this principle, and found that BINAP-Ru(II) complex catalyzed hydrogenation allows efficient dynamic kinetic resolution of certain  $\alpha$ -substituted  $\beta$ -ketoesters to lead to the corresponding alcoholic compounds in high enantiomeric and diastereomeric excess.<sup>9</sup> This is the first example of an ideal asymmetric catalysis performed by BINAP-Ru(II) complexes.

# **Results and Discussion**

The efficiency and sense of the diastereo- and enantio-selective synthesis of the  $\alpha$ -substituted  $\beta$ -ketoesters is highly influenced by the substrate structures and the reaction conditions. A series of racemic keto esters 1 was subjected to homogeneous

hydrogenation using (R)- or (S)-BINAP-Ru(II) complex catalysts under high hydrogen pressure at 25-50 °C. Representative results are summarized in Table 1. Thus, the BINAP-Ru (II) complex catalyzed hydrogenation of 2-alkylated β-ketoester such as ethyl 2-methyl-3-oxobutanoate (1a) proceed with high stereoselectivity with respect to the C-3 position, but no appreciable resolution is seen, resulting in a 50:50 mixture of ethyl (2R, 3R)-3-hydroxy-2-methylbutanoate syn-2a and ethyl (2S, 3R)-3-hydroxy-2methylbutanoate anti-2a (entry 1).<sup>10</sup> Actually, hydrogenation of the methyl ester 1a catalyzed by Raney nickel modified by (R,R)-tartaric acid gave methyl (2S,3R)-3hydroxy-2-methylbutanoate (56.7% ee) and the 2R, 3R isomer (64.4% ee) in a 3.6:1 ratio.<sup>10b</sup> Under the present reaction conditions, the syn and anti isomers are not interconvertible. On the contrary to this result, functional perturbation of the substrates leads clear differentiation of syn and anti transition states as shown in Table I (entry 2-8). Using ethanol containing (R)-BINAP-Ru complex, ethyl 2-chloro-3-oxobutanoate (1b) was hydrogenated with slightly sifted syn diastereoselectivity to give a 60:40 mixture of syn-hydroxy ester 2b (92% ee) and anti-hydroxy ester 2b (82% ee) in high yields (entry 2). A dramatic advance in diastereoselection was observed in the hydrogenation of 1b using dichloromethane as a solvent. Thus, the reaction in dichloromethane proceeded in great increase of diastereoselectivity to give a 90:10 mixture of syn-2b (95% ee) and anti-2b (71% ee) but conversion was low (entry 3). Furthermore, an amide or carbamate group present in certain acyclic substrates exhibited remarkable syn directivity, leading to threonine type products in excellent ee's and high yields. For instance, hydrogenation of ethyl 2-acetamido-3-oxobutanoate (1c) in the presence of  $Ru_2Cl_4((S))$ tol-binap)•NEt<sub>3</sub> in dichloromethane gave a protected L-threonine, sy n-2c (99% ee), and allothreonine, anti-2c, with 99:1 selectivity.<sup>11</sup> Also, the syn and anti isomers are not reversible under the present reaction conditions. There are remarkable solvent effects in this reaction and high diastereoselectivity was obtained in dichloromethane (entry 4) than in methanol (entry 5). The reaction in methanol proceeded more rapidly but resulted in decrease of diastereoselectivity to give a 71:29 mixture of threonine (95% ee) and allothreonine derivatives (ee was not determined). The N-acylthreonine methyl ester obtained can be converted easily to optically active threonine by acid mediated hydrolysis. Although there have been reported many processes for the synthesis of optically active threonine,<sup>11</sup> this is the first example of asymmetric synthesis of optically active threonine from a racemic starting material performed by BINAP-Ru complex catalysis.



Table 1. Hydrogenation of α-Substituted β-Ketoesters Promoted by BINAP-Ru(II) complexes<sup>a</sup>

					H <sub>2</sub>	temp.	conv.ª	l	products
entry	sub.	cat."	S/C <sup>c</sup>	solv.	atm	°C	%	synlanti <sup>d</sup>	%,ee (syn, anti) <sup>d</sup>
1	1a	(R)-A	200	MeOH	80	25	100	50 / 50	98, 98 (2S,3R; 2R,3R)
2	1b	(R)-A	200	EtOH	30	25	100	60 / 40	92, 82 <sup>8</sup>
3	1b	(R)-A	100	CH <sub>2</sub> Cl <sub>2</sub>	100	50	37	90 / 10	95, 71 <sup>g</sup>
4	1c	( <b>R</b> )-A	440	CH <sub>2</sub> Cl <sub>2</sub>	100	50	100	99 / 1 <sup>e</sup>	99, $(2S, 3R)$
5	1c	( <b>R</b> )-A	200	EtOH	70	25	100	71 / 29 <sup>e</sup>	95, (2 <i>S</i> ,3 <i>R</i> )
6	1d	( <b>R</b> )-A	400	CH <sub>2</sub> Cl <sub>2</sub>	40	25	100	99/1 <sup>e</sup>	97, $(2S, 3R)$
7	1d	(R)-A	400	MeOH	100	25	100	85 / 15 <sup>e</sup>	80, (2S, 3R)
8	1d	(S)- <b>B</b>	400	CH <sub>2</sub> Cl <sub>2</sub>	100	25	100	98 / 2 <sup>h</sup>	90, (2 <i>R</i> ,3 <i>S</i> )
9	1e	(R)-A	200	CH <sub>2</sub> Cl <sub>2</sub>	100	50	100	94 / 6 <sup>f</sup>	98, 93 (2 <i>S</i> ,3 <i>R</i> ; 2 <i>R</i> ,3 <i>R</i> )
10	1e	(S)-A	200	CH <sub>2</sub> Cl <sub>2</sub>	70	50	100	93/7	98, (2R, 3S)
11	1e	(R)-A	200	MeOH	100	50	100	56 / 44 <sup>f</sup>	94, 94 (2 <i>S</i> ,3 <i>R</i> ; 2 <i>R</i> ,3 <i>R</i> )
12	1f	(R)-A	200	CH <sub>2</sub> Cl <sub>2</sub>	70	35	73	88 / 12	92, (2S, 3R)
13	1g	(R)-A	200	CH <sub>2</sub> Cl <sub>2</sub>	100	45	98	70 / 30	90, 89 (2 <i>S</i> ,3 <i>R</i> )

<sup>a</sup>Reaction was carried out according to the general procedure described in experimental section. <sup>b</sup>Catalyst: A: Ru<sub>2</sub>Cl<sub>4</sub>(binap)<sub>2</sub>•NEt<sub>3</sub>, B: Ru<sub>2</sub>Cl<sub>4</sub>(tol-binap)<sub>2</sub>•NEt<sub>3</sub>. <sup>c</sup>Substrate/catalyst mole retio. <sup>d</sup>The relative and absolute configurations and the ee's were determined by combination of HPLC and <sup>1</sup>H NMR (400 MHz) analysis of the alcholic products or their MTPA esters and rotation mesurment. Details of the analysis are described in experimental section. <sup>e</sup>Derivatization of natural threonine and allothreonine. <sup>f</sup>The stereochemistry was determined by <sup>1</sup>H NMR (400 MHz) analysis after conversion to 2,2,4-trimethyl-5-benzamidomethyl-1,3-dioxane by NaBH4 reduction followed by acetonidation: cis isomer,  $J_{4,5} = 3.1$  Hz; trans isomer,  $J_{4,5} = 9.5$  Hz. <sup>g</sup>The absolute configuration was not determined. <sup>h</sup>The absolute configuration was determined by derivatization of D-threonine.

As visualized in the structures 3 and 4, the unique stereoselection is resulted from efficient kinetic discrimination of the enantiomers,  $1\alpha$  and  $1\beta$ , where the ester group is acting as trigger inducing diastereoselective hydrogenation. The transition state leading to the syn products may be stabilized by hydrogen bonding between CONH and ester OR<sup>2</sup>. Such an effect, consistent with the solvent influence, is inaccessible with other substituents and, consequently, enantiomers  $1\alpha$  and  $1\beta$  are hydrogenated at comparable rates with equally efficient catalyst/substrate chirality transfer. Thus the solvent effect on the diastereoselectivity agrees with this view.





Especially, by using complex  $Ru_2Cl_4((R)-binap)_2 \cdot NEt_3$  as a catalyst, excellent results have been attained in the diastereo- and enantioselective hydrogenation of the 2amidomethyl substrate 1e-1g to the syn- $\beta$ -hydroxy esters 2e-2g, which is an important starting material with the desired stereochemistry at C-2 and C-3 positions for synthesis of carbapenem antibiotics.<sup>12</sup> Thus, the hydrogenation of methyl 2-benzamidomethyl-3oxobutanoate (1e) performed by the complex  $Ru_2Cl_4((R)-binap)_2 \cdot NEt_3$  in dichloromethane at 50  $^{\circ}$  under 100 atm of hydrogen gave methyl (2S.3R)-2benzamidomethyl-3-hydroxybutanoate (2e) in 88% de and 98% ee.

> X = Halogen, H, H<sub>2</sub> or Solvent  $\bigcirc P = BINAP$

Representative results are given in Table I. The solvent effect in this reaction is remarkable, and the reaction in a protic solvent such as methanol decreased diastereoselectivity (56:44) (entry 11). Furthermore, this high syn selection is due to the sterically restricted transition state as visualized in structures **5** and **6**.

Thus the author has realized stereoselective hydrogenation utilizing kinetic discrimination of rapidly equilibrating enantiomers.<sup>13</sup> The absolute configuration at C-3 position is governed by the handedness of the chirality of BINAP ligand, while the C-2 configuration is dependent on the substrate structure. The obtained **2e** was converted to (1'R, 3S)-3-[1'-[(*tert*-butyldimethylsilyl)oxy]ethyl]azetidin-2-one (**9**) according to Scheme 2. Hydrolysis of**2e**and subsequent neutralization with triethylamine in acetonitril gave <math>(2S, 3R)-2-aminomethyl-3-hydroxybutanoic acid (**7**) in 92% yield. Cyclization of **7** assisted with dibenzothiazole disulfide and triphenylphosphine gave (1'R, 3S)-3-(1'-hydroxyethyl)azetidin-2-one (**8**). Reaction of **8** with *tert*-butyldimethyl-silyl chloride in the presence of imidazole in toluene at 0 °C gave **9** in 90% yield, the absolute configuration of hydrogenated product **2e** was confirmed to be 2S, 3R by comparison with the authentic data.<sup>14</sup> This procedure has been applied to the industrial production of **9** in a scale of 100 ton per year.

# Scheme 2



All these hydrogenations of keto esters proceed in the keto form in which the ester function is acting as the donor trigger. Because methyl 2,2-dimethyl-3-oxobutanoate was smoothly hydrogenated by BINAP-Ru catalysts to give the corresponding alcoholic product (96% ee in methanol; 88% ee in dichloromethane) and the general sense of asymmetric induction is observed in C-3 position.<sup>15</sup> The high level *syn* selection achieved with amide substrates is held not to be a result of NHCO-directed hydrogenation of prochiral enols of type **10**.



Furthermore, the C-2 absolute configuration in the products is not consistent with the empirical stereochemical consequence observed with related the enamide substrate 11. This is supported by the facts as follows. Hydrogenation of the deoxy analogue 11 with  $\operatorname{RuBr}_2((R)$ -binap) in methanol under 100 atm of hydrogen gave (2*R*)-12 in 85% optical yield.<sup>16</sup> In contrast, hydrogenation of 2-acetamide substrates 1c and 1d with  $\operatorname{Ru}_2\operatorname{Cl}_4((R)$ -binap)\_2•NEt<sub>3</sub> produced the products with (*S*)-configuration at C-2 position.



Thus ideal dynamic kinetic resolution of  $\alpha$ -substituted  $\beta$ -ketoesters has been accomplished, and possible reasons for this are considered as follows: (1) racemization of the substrates is sufficiently faster than hydrogenation, (2) stereochemical control by chirality on BINAP-Ru(II) catalyst is efficient, and (3) the cyclic intermediate of the substrates supported with intermolecular hydrogen bond differentiates clearly between the *syn* and *anti* transition states. Chirality of BINAP ligand is controlling the facial selectivity at the carbonyl function, whereas the cyclic transition state determines the



relative reactivities of the enantiomeric substrates. Overall, one of four possible diastereomeric transition states is selected to realize a high level of enantio- and diastereoselective formation of the  $\alpha$ -substituted  $\beta$ -hydroxyesters.

# **Experimental Section**

General. <sup>1</sup>H NMR spectra were recorded on a JEOL PMX-60 SI (<sup>1</sup>H, 60 MHz), a JEOL JNM-GSX 270 (1H, 270 MHz; 13C, 67.9 MHz), and a BRUKER AM-400 (1H, 400 MHz; 13C, 100 MHz) spectrometers; chemical shifts (d) were expressed in parts per million relative to tetramethylsilane (TMS) as an internal reference or phosphoric acid as an external reference. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet, m, multiplet and b, broad. IR spectra were recorded on a Hitachi 215 spectrometer, a JASCO IR-810, and a Shimadzu FTIR-4100 spectrometers. Mass spectra were obtained on a JEOL JMX-DX 303 mass spectrometer and a HITACHI M-80B spectrometer. Elemental analyses were performed on a Yanagimoto MT-2 CHN corder. Mass spectra were measured on a Hitachi Model RSM-4 mass spectrometer. Exact mass spectra were measured on a JEOL Model JMS-DX-303 mass spectrometer. All melting points were measured on a Yanagimoto micro melting point apparatus. HPLC analyses were performed on a JASCO TRI ROTAR-VI system with a JASCO UVIDEC-100-VI UV detector by using a 250 mm x 4.6 mm analytical column packed with Chiralpack AS (Daicel Chemical Industry, Ltd.), COSMOSIL 5SL, and Develosil 100-3. Gas chromatographic (GLC) analyses were conducted on a Shimazu GC-9A (capillary column: NEWTRABOND-1, 0.25 mm I. D. x 30 m) or on a HITACHI 263-80 ( capillary column: PEG-HT, 0.25 mm I. D. x 25 m) or on a HP 5890A (capillary column: HP-1, 0.25 mm I. D. x 25 m) equipped with a flame ionization detector. Thin layer chromatography (0.2 mm) for analyses was carried out with silica gel 60 PF254 (Merk). Preparative thin layer chromatography (1.5 mm) was made of silica gel 60 PF254 (Merck) and activated at 120 °C for 2 h. Optical rotations were measured on a JASCO DIP-360 polarimeter.

Materials. All manipulations involving air- and moisture-sensitive organametallic compounds were carried out with the standard Schlenk technique under nitrogen or argon atmosphere purified by passing it through a BASF-Catalyst R3-11 column. (R)-(+)- and (S)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl [(R)-(+)and (S)-(-)-BINAP] and (R)-(+)- and (S)-(-)-2,2'-bis(di-p-tolylphosphino)-1,1'-

binaphthyl [(R)-(+)- and (S)-(-)-tol-BINAP] were prepared according to the literature methods.<sup>2</sup> [Ru(COD)Cl]<sub>2</sub> was synthesized according to the literature procedure.<sup>17</sup> Oxygen-free dry solvents were prepared as follows: dichloromethane, benzene, toluene, xylene, hexane, dimethylformamide and ether were distilled under nitrogen from calcium hydride; dichloromethane was alternatively dried over P2O5; methanol and ethanol were dried over the corresponding magnesium alkoxides; tetrahydrofuran was dried over 70% sodium bis(2-methoxyethoxy)aluminium hydride in toluene; triethylamine was distilled from BaO. Imidazole, triphenylphosphine, dibenzothiazoldisulfide, tert-butyldimethylsilvl chloride,  $(\pm)$ -ethyl 2-methyl-3-oxobutanoate and  $(\pm)$ -ethyl 2-chloro-3-oxobutanoate are commercially available (Aldrich). (*R*)- $\alpha$ -Methoxy- $\alpha$ -(trifluoromethyl)-phenylacethyl chloride ((R)-MTPACl) was prepared by the reaction with (R)- $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)phenylacetic acid and thionyl chloride. β-Keto ester substrates were prepared by the known procedures. (±)-Ethyl 2-benzamindo-3-oxobutanoate and (±)ethyl 2-acetamindo-3-oxobutanoate.<sup>18</sup> (±)-Methyl 2-benzamidomethyl-3-oxobutanoate, (±)-methyl 2-acetamidomethyl-3-oxobutanoate and (±)-methyl 2-ethoxycarbamidomethyl-3-oxobutanoate. All ketonic substrates were purified by recrystallization or distillation before use.

# Preparation of Catalysts

NMR (161 MHz, CDCl<sub>3</sub>)  $\delta$  ppm: 12.92 (d, J = 41.1 Hz).

Preparation of Di[2,2'-bis(diphenylphosphino)-1,1'-binaphthyl]tetrachlorodiruthenium Triethylamine  $[Ru_2Cl_4((R)-(+)-binap)_2 \cdot NEt_3]$ : To 100 ml of toluene were added 1 g (3.56 mmoles) of [RuCl<sub>2</sub>(COD)]n, 2.66 g (4.27 mmoles of (R)-(+)-binap, and 1.5 g of triethylamine in a nitrogen atmosphere, and the mixture was heat-refluxed for 10 hours. The solvent was removed from the reaction mixture by distillation under reduced pressure, and the residual solid was dissolved in methylene chloride, followed by filtration through Celite. The filtrate was concentrated to dryness to obtain 3.7 g of the entitled compound as a deep brown solid. Elemental Analysis for C94H79Cl4NP4Ru2: Calcd. (%): C. 66.79; H 4.71; N 0.83. Found (%): C, 66.62; H, 4.97; N, 0.52. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ ppm: 1.30-1.50 (t, 6H, NCH<sub>2</sub>CH<sub>3</sub>), 3.05-3.30 (q, 4H, NCH<sub>2</sub>CH<sub>3</sub>). 6.40-8.60 (m, 32H; Ar-H). <sup>31</sup>P

Preparation of Di[2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl]tetrachlorodiruthium Triethylamine [Ru<sub>2</sub>Cl<sub>4</sub>((S)-(-)-tol-binap)<sub>2</sub>•NEt<sub>3</sub>]: To 100 ml of toluene were added 1 g (3.56 mmoles) of [RuCl<sub>2</sub>(COD)]<sub>n</sub>, 2.89 g (4.27 mmol)

of (*S*)-(-)-tol-binap, and 1.5 g of triethylamine in a nitrogen atmosphere, and the mixture was heat-refluxed for 10 hours. The solvent was removed from the reaction mixture by distillation under reduced pressure, and the residual solid was dissolved in methylene chloride, followed by filtration through Celite. The filtrate was concentrated to dryness to obtiain 3.9 g of the entitled compound as a deep brown solid. Elemental Analysis for  $C_{102}H_{95}Cl_4NP_4Ru_2$ : Calcd. (%): C, 67.96; H, 5.31; N, 0.78. Found (%): C, 67.69; H, 5.60; N, 0.55. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  ppm: 1.30-1.50 (t, 6H, NCH<sub>2</sub>CH<sub>3</sub>), 2.39-2.58 (s, 24H, CH<sub>3</sub> x 4), 3.05-3.30 (q, 4H, NCH<sub>2</sub>CH<sub>3</sub>). 6.40-8.60 (m, 32H, Ar-H). <sup>31</sup>P NMR (161 MHz, CDCl<sub>3</sub>)  $\delta$  ppm: 13.22 (d, *J* = 40.1 Hz).

General Procedure for Determination of the Enantiomeric Excesses and the Absolute Configurations of Hydroxy Esters. The ee's of hydrogenation products were determined by HPLC analysis of them or their (*R*)-MTPA esters. In the preparation of the MTPA esters, no noticeable kinetic resolution of chiral alcohols took place. In most cases, the peaks of the diastereomers gave base-line separation. The relative configurations (rel configns) and absolute configurations were determined, directly or after converting to the known compounds, by comparison of the <sup>1</sup>H NMR spectra, HPLC behavior of the synthetic and authentic materials, or the rotation values with those reported in the literatures.

Hydrogenation of Ethyl 2-methyl-3-oxobutanoate  $[(\pm)-1a]$  by Ru<sub>2</sub>Cl<sub>4</sub>((*R*)-(+)-binap)<sub>2</sub>•NEt<sub>3</sub> as the Catalyst. A solution of ethyl 2-methyl-3-oxobutanoate (( $\pm$ )-1a) (1.0 g, 6.95 mmol) in degassed anhydrous methanol (5 mL) was placed in a 20-mL Schlenk tube. By using a cannula this was then mixed with solid Ru<sub>2</sub>Cl<sub>4</sub>((*R*)-(+)-binap)<sub>2</sub>•NEt<sub>3</sub> (58.6 mg, 0.035 mmol, S/C = 200) in another 20-mL Schlenk tube under nitrogen atmosphere and the resulting yellow solution was transferred into a 100-mL stainless steel autoclave. After pressurizing hydrogen to 100 atm, the solution was stirred at 25 °C for 24 hours. After cooling the mixture to room temperature and releasing the hydrogen pressure, the solvent of the light brown solution was removed under reduce pressure. 400 MHz <sup>1</sup>H NMR analysis of the residue showed 100% conversion. The crude product was distilled to give a mixture of ethyl (2*S*,3*R*)-3-hydroxy-2-methylbutanoate (2a) and the (2*S*,3*R*)-isomer (2a) (860 mg, 85% yield): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) d 1.18 and 1.19 (two sets of d, *J* = 7.25 and 6.30 Hz, 3H, CH<sub>3</sub>CHOH), 1.23 and 1.26 (two sets of d, *J* = 6.6 and 6.9 Hz, 3H, CH<sub>3</sub>CHCO), 1.28 (t, *J* = 7.30 Hz, 3H, CH<sub>3</sub>CH<sub>2</sub>), 2.45 (quintet, *J* = 7.3 Hz, 0.5H,

CHCH<sub>3</sub>) and 2.50 (dq, J = 7.3, 4.0 Hz, 0.5 H, CHCH<sub>3</sub>), 2.63 and 2.74 (two sets of bd, J = 4.6Hz and 5.6 Hz, 1H, OH), 3.88 (m, 0.5H, CHOH), 4.07(m, 0.5H, CHOH), 4.17 and 4.18 (two sets of q, J = 7.3 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>); bp 115-120°C/25 mmHg. The syn / anti ratio was analyzed by GC method to be 50:50 (column, PEG-20M; injection temp, 140°C; column temp, 110°C; tR of anti-(2R,3R)-2a, 38.5 min; tR of syn-(2S, 3R)-2a, 42.1 min). An aliquot of the product (10.6 mg, 72.6 µmol) was dissolved in toluene (0.7 mL). To this solution was added (R)-1-(1-naphthyl)ethyl isocyanate (Aldrich, 21.5 mg, 109 µmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene pyridine (2.0 µL, 13.4umol) and the mixture was kept at 24°C for 12 hours. To this was added water (1 mL) and the mixture was extracted by 2 mL portions of ether. The combined organic layers were washed with 1N HCl solution (3 mL), water (3 mL), brine (3 mL), and dried over anhydrous sodium sulfate. Filtration and evaporation of the solvent gave a crude oil, which was chromatagraphed on silica gel by using a 1:1 mixture of ether and hexane as eluent to give the corresponding carbamates (23.4 mg, 94% yield). The diastereomer ratio was determined by HPLC analysis (column, YMC 003-3 SIL, YMC 002-3 SIL, and Develosil 100-3; eluent, 1:2 ether-hexane mixture; flow rate, 0.8 mL/min; detection, UV-254 nm; t<sub>R</sub> of 41.3, 42.6, 46.0 and 47.5 for (2R,3S)-(R)-isomer, (2S,3R)-(R)-isomer, (2R,3R)-(R)-isomer and (2S,3S)-(R)-isomer. Thus, the (R)-BINAP-based hydrogenation syn product has 2S, 3R configuration in 98% ee, and anti product has 2R, 3R configuration in 98% ee. All peaks were assigned by coinjection of a 91:9 mixture of ethyl (2R, 3R)-3-hydroxy-2-methylbutanoate and (2S, 3R)-isomer, and 93:7 mixture of ethyl (2S, 3S)-3-hydroxy-2-methylbutanoate and (2R, 3S)-isomer, prepared from the known method.<sup>20</sup>

Hydrogenation of Ethyl 2-acetamido-3-oxobutanoate  $[(\pm)-1c]$  with  $Ru_2Cl_4((R)-(-)-binap)_2 \cdot NEt_3$  as the Catalyst. A solution of  $(\pm)-1c$  (2.90 g, 0.12 mmol) in degassed anhydrous dichloromethane (100 mL) was placed in a 200-mL Schlenk tube and degassed under reduced pressure. By using a cannula this was then mixed with solid  $Ru_2Cl_4((R)-binap)_2 \cdot NEt_3$  (582 mg, 0.33 mmol) in another 200-mL Schlenk tube under nitrogen and the resulting yellow solution was transferred into a 500-mL stainless steel autoclave. After pressurizing hydrogen to 100 atm, the solution was stirred at 50 °C for 24 hours. The hydrogen pressure was released, and the solvent was removed under reduced pressure. The conversion was 100% and the *synlanti* ratio was estimated to be 99:1 by GC analysis (column, HP-1; injection temp, 250 °C; column temp,

50-200 °C (4 °C/min); tR of anti isomer 2c, 21.4 min; tR of syn isomer 2c, 21.4 min; detection TCI). The residue was purified by silica gel column chromatography using a mixture of hexane-isopropanol as an eluent to give the methyl (2S, 3R)-2-acetamido-3hydroxybutanoate (26.0 g, 90% yield); mp 98-99 °C; [α]<sub>D</sub><sup>20</sup> -1.96 (c 1.02, ethanol); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  1.22 (d, J = 6.4 Hz, 3H, CH<sub>3</sub>CH), 2.08 (s, 3H, CH<sub>3</sub>CO), 2.14-2.42 (b, 1H, OH), 3.77 (s, 3H, -OCH<sub>3</sub>), 4.31-4.36 (m, 1H, CHOH), 4.60 (dd, J = 2.5, 8.85 Hz, 1H, CHNH), 6.29-6.31 (b, 1H, NH). A aliquot of the product (50 mg, 0.28 mmol) was dissolved in pyridine (0.5 ml). To this solution was added (R)- $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)phenylacetyl chloride ((R)-MTPACl) (100 mg, 0.40 mmol) and the mixture was kept at room temperature for 17 hours. To this was added ether (4 mL) and water (2 mL) and the mixture was vigorously stirred for 15 min. The aqueous layer was extracted with two 4 mL portions of ether and the combined the organic layers were successively washed with a 1N hydrogen chloride solution (5 mL), 1 N sodium hydroxide solution (5 mL), water (5 mL), and brine (5 mL). Drying over anhydrous sodium sulfate, evaporation of the solvent under reduced pressure afforded the (R)-MTPA esters (98 mg) in 90% yield, HPLC analysis of which indicated 99% ee in favor of (2S, 3R)-isomer (column, Senshu Pack NO2-1251; eluent, hexane-THFmethanol = 850:150:1; flow rate, 1.0 mL/min; detection, UV-254 nm;  $t_R$  24.1, 26.4, 35.1 and 37.5 min for the MTPA ester of syn-(2S,3R)-2c, syn-(2R,3S)-2c, anti-(2R,3R)-2c and anti-(2S,3S)-2c. The peak assignment was done by comparison of authentic (R)and (S)-MTPA esters of 2c and (2S, 3S)-N-acetyl-allo-threonine methyl ester, prepared from (2S, 3R)-threonine methyl ester (Kokusan Chemical) by N-acetylation (acetyl chloride, triethylamine, dichloromethane, 0°C, 3 h, 60% yield), cyclization (thionyl chloride, benzene, 0-30 °C, 1 h, 100% yield), and hydrolysis (sodium hydrogen carbonate, water, 25 °C, 12 h, 80% yield). The absolute configuration of the major hydrogenation product was confirmed, after converting to threonine (10% HCl at 100°C), by sign of rotation ( $[\alpha]_D^{24}$  -27.8° (c 1.05, H<sub>2</sub>O); lit.  $[\alpha]_D^{26}$  -28.3° (c 1.05, H<sub>2</sub>O) for (2S, 3R)-(-)-threonine.<sup>21</sup>

Hydrogenation of Ethyl 2-benzamido-3-oxobutanoate  $[(\pm)-1d]$  with  $Ru_2Cl_4((S)-(-)-tol-binap)_2 \cdot NEt_3$  as the Catalyst. A solution of ethyl 2benzamido-3-oxobutanoate  $[(\pm)-1d]$  (30.0 g, 0.12 mol) in degassed anhydrous dichloromethane (100 mL) was placed in a 200-mL Schlenk tube. By using a cannula this was then mixed with solid Ru<sub>2</sub>Cl<sub>4</sub>((S)-(-)-tol-binap)<sub>2</sub>•NEt<sub>3</sub> (540 mg, 0.30 mmol, S/C = 400) in another 200-mL Schlenk tube under nitrogen atmosphere and the resulting vellow solution was transferred into a 500-mL stainless steel autoclave. After pressurizing hydrogen to 100 atm, the solution was stirred at 25 °C for 80 hours. After cooling the mixture to room temperature and releasing the hydrogen pressure, the solvent of the light brown solution was removed under reduce pressure. The conversion was 100% and the synlanti ratio was estimated to be 98:2 by GC analysis [t<sub>R</sub>: anti-isomer, 28.7 min; syn-isomer, 36.6 min], and enantiomeric excess of the major product was confirmed to be 98% ee by HPLC analysis of their (R)-MTPA esters according to the same conditions of analysis of 2c. The residue was purified by silica gel column chromatography and pure sample of (2R, 3S)-ethyl 2-benzamido-3-hydroxybutanoate (2d) was obtained by recrystallization from a 2:1 mixed solvent of benzene and diethyl ether; mp 85-86.5 °C;  $[\alpha]_D^{25}$  -29.5° (c 3.225, CHCl<sub>3</sub>), Absolute configuration was dettermined as follows: 3.6 g of pure ester was refluxed in 10% HCl solution to give a uniform solution. The solution was allowed to stand under ice-cooling for 1 hour, followed by filtration to remove crystals of benzoic acid. The filtrate was concentrated to dryness and the residue was dissolved in 10 mL of water. After adjusting to a pH of 7.0 with 28% aqueous ammonia, the precipitate was recrystallized from a 1:2 mixture of water and ethanol to give 1.2 g (71% yield) of D-threonine [(2R,3S)-2-amino-3hydroxybutanoate]; mp 250-251 °C;  $[\alpha]_D^{25}$  +28.0° (c 1.85, H<sub>2</sub>O), lit.<sup>21</sup>;  $[\alpha]_D^{26}$  +28.4° (c 1.2, H<sub>2</sub>O); <sup>1</sup>H NMR (D<sub>2</sub>O, 400 MHz)  $\delta$  1.25 (d, J = 6.78 Hz, 3H, CH<sub>3</sub>CH), 3.35 (d, J= 4.86 Hz, 1H, NH<sub>2</sub>CHCO<sub>2</sub>H), 4.18 (dq, *J* = 4.86, 6.78, 1H, CHOH).

Hydrogenation of Methyl 2-benzamidomethyl-3-oxobutanoate  $[(\pm)$ -1e]. (1) To a mixture of  $(\pm)$ -methyl 2-benzamidomethyl-3-oxobutanoate  $(\pm)$ -1e (2.50 g, 10.0 mmol), and Ru<sub>2</sub>Cl<sub>4</sub>((R)-(+)-binap)<sub>2</sub>•NEt<sub>3</sub> (84.5 mg, 0.05 mmol, S/C=200 mol/mol) was added dry dichloromethane (17.5 ml) under nitrogen. The resulting mixture was transferred into a 100-mL autoclave and stirred under an initial hydrogen pressure of 100 atm at 50 °C for 20 hours to conduct a hydrogenation reaction. Conversion (100%) of 2e and the ratio of syn-2e and anti-2e (94:6, 88% de) were determined by HPLC analysis of the orange yellow reaction mixture on a Develosil 60-5 (4.6 mm x 250 mm) column [eluent: hexane-chloroform-methanol = 90:10:2; detect: U.V.254 nm; t<sub>R</sub>: 18.8 (1e), 36.2 (syn-2e), 49.2 (anti-2e); flow rate: 2.0 ml/min]. The solvent was removed from the reaction mixture by evaporation, and the residue was purified by silica gel column chromatography using a mixed solvent of hexane and ethyl acetate (7:3) as an

eluant to obtain 2.25 g (90% yield) of methyl (2S, 3R)-2-benzamidomethyl-3hydroxybutonoate (2S, 3R)-2e (98% ee) and 0.12 g (4% yield) of methyl (2R, 3R)-2benzamidomethyl-3-hydroxybutonoate (2R, 3R)-2e (93% ee). Enantiomeric excess of (2S, 3R) and (2R, 3R)-2e was measured by HPLC analysis of the obtained on esterification of the above compounds with 1.5 equivalent of (R)-(+)- $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)phenylacetyl chloride [(R)-MTPACl] in the presence of triethylamine (2.0 equiv) under the following conditions: Develosil 100-3 (4.6 mm x 250 mm) column [eluant: hexane-THF-methanol = 1000/100/1; detect: U.V.254 nm; t<sub>R</sub>: 25.1, 26.4, 31.9 and 38.5 min for the (R)-MTPA esters of syn-(2S, 3R)-2e, syn-(2R, 3R)-2e, anti-(2R,3R)-2e and anti-(2S,3S)-2e, syn-2e; 98% ee, anti-2e; 93% ee; flow rate: 1.0 ml/min], syn-(2S, 3R)-2e; a colorless oil; IR (neat) 3350, 2975, 1740, 1650, 1605, 1580, 1540, 1495, 1380, 1315, 1200, 1180, 1100, 1040 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$ 1.30 (d, J = 6.25 Hz, 3H, -CH<sub>3</sub>), 2.84-2.86 (m, 1H), 3.73 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 3.71-3.77 (m, 1H), 3.58-3.91 (m, 1H), 4.09-4.14 (m, 1H), 7.02 (b, 1H, NH), 7.41-7.80 (m, 5H); Anal. Calcd for C13H17NO4: C, 62.12; H, 6.92; N, 5.67. Found: C, 62.10; H, 6.98; N, 5.66. anti-(2R, 3R)-2e; a colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.26 (d, J = 6.25 Hz, 3H), 2.60-2.64 (m, 1H), 3.57-3.62 (m, 1H), 4.00-4.03 (m, 1H), 3.73 (s, 3H), 4.08-4.14 (m, 1H), 7.27 (b, 1H), 7.41-7.80 (m, 5H). (2) To a mixture of (±)-methyl 2-benzamidomethyl-3-oxobutanoate (±)-1e (2.50 g, 10.0 mmol), and Ru<sub>2</sub>Cl<sub>4</sub>((R)-(+)-binap)<sub>2</sub>•NEt<sub>3</sub> (84.5 mg, 0.05 mmol, S/C 200 mol/mol) was added dry methanol (17.5 ml) under nitrogen. The resulting mixture was transferred into a 100-mL autoclave and stirred under an initial hydrogen pressure of 100 atm at 50 °C for 20 hours to conduct a hydrogenation reaction. Conversion (100%) of 2e, the ratio of syn-2e and anti-2e (56:44, 12% de) and enantiomeric excesses [syn-(2S, 3R)-2e (94% ee), anti-(2R,3R)-2e (94% ee)] were determined by HPLC analysis according to above described conditions. The absolute configuration of the major hydrogenated product was butyldimethylsilyl)oxy)ethyl]-azetidin-2-one (9) and comparison of authentic physical data (<sup>1</sup>H NMR, <sup>13</sup>C NMR and IR) of 9; abs confign of (2S, 3R)-isomer (2e), rotation (9: synthetic,  $[\alpha]_D^{25}$  -69.8° (c 1.02, CHCl<sub>3</sub>); lit.<sup>14</sup>  $[\alpha]_D$  -74.4° (c 1.05, CHCl<sub>3</sub>). The absolute configuration of (2R, 3R)-isomer (2e) was determined, after converting to (2R,3S)-isomer (thionyl chloride, benzene, 0-30 °C; sodium hydrogen carbonate, water, 25 °C, 16 h), by HPLC analysis of the (R)-MTPA esters.

Hydrogenation of Ethyl 2-acetamidomethyl-3-oxobutanoate  $[(\pm)-1f]$ . To a mixture of  $(\pm)$ -ethyl 2-acetamodomethyl-3-oxobutanoate  $(\pm)$ -1f (2.01 g, 10.0 mmol), and Ru<sub>2</sub>Cl<sub>4</sub>((R)-(+)-binap)<sub>2</sub>•NEt<sub>3</sub> (84.5 mg, 0.05 mmol, S/C 200 mol/mol) was added dry dichloromethane (18.0 ml) under nitrogen. The resulting mixture was transferred into a 100-mL autoclave and stirred under an initial hydrogen pressure of 70 atm at 35 °C for 17 hours to conduct a hydrogenation reaction. Conversion (100%) of 1f and the ratio of syn-2f and anti-2f (88:12, 76% de) were determined by HPLC analysis of the orange yellow reaction mixture on a COSMOSIL 5C-18 (4.6 mm x 250 mm) column [eluant:  $CH_3CN-H_2O = 10:90;$  detect: U.V.210 nm;  $t_R: 19.63$  (1f), 14.05 (syn-2f), 10.01 (anti-2f); flow rate: 0.8 ml/min]. The solvent was removed from the reaction mixture by evaporation, and the residue was purified by silica gel column chromatography using a mixed solvent of hexane and iso-propanol (7:3) as an eluant to obtain 0.96 g (48% yield) of ethyl (2S, 3R)-2-acetamidomethyl-3-hydroxybutonoate (2S, 3R)-2f (92%ee). Enantiomeric excess of (2S, 3R)-2f was measured by HPLC analysis of the obtained on esterification of the above compound with 1.5 equiv of (R)-MTPACI in the presence of triethylamine (2.0 equiv.) under the following conditions: A-002-3 S-3 120A column (4.6 mm x 250 mm) produced by Yamamura Kagaku Kenkyusho K. K. [eluant: hexanetetrahydrofuran-methanol = 800:200:1; detect: U.V.254 nm; t<sub>R</sub>: 18.2 and 22.7min for the (R)-MTPA esters of syn-(2S, 3R)-2f and syn-(2R, 3R)-2f, syn-2f; 92% ee; flow rate: 1.0 ml/min]. syn-(2S, 3R)-2f; a colorless oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 1.25 (d, J = 6.30 Hz, 3H, -CH<sub>3</sub>), 1.29 (t, J = 7.10 Hz, 3H, -CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 2.10 (s, 3H, -CH<sub>3</sub>), 2.47 (m, 1H), 3.36 (m, 1H), 3.87-3.95 (m, 3H), 4.13-4.21 (m, 2H), 6.13 (b, 1H, NH).

Hydrogenation of Ethyl 2-ethoxycarbamidomethyl-3-oxobutanoate  $[(\pm)-1g]$ . To a mixture of  $(\pm)$ -ethyl 2-ethoxycarbamidomethyl-3-oxobutanoate  $(\pm)-1g$ (2.31 g, 10.0 mmol), and Ru<sub>2</sub>Cl<sub>4</sub>((R)-(+)-binap)<sub>2</sub>•NEt<sub>3</sub> (84.5 mg, 0.05 mmol, S/C 200 mol/mol) was added dry dichloromethane (18.0 ml) under nitrogen. The resulting mixture was transferred into a 100-mL autoclave and stirred under an initial hydrogen pressure of 75 atm at 45°C for 20 hours to conduct a hydrogenation reaction. Conversion (100%) of 1g and the ratio of syn-2g and anti-2g (70:30, 40% de) were determined by HPLC analysis of the orange yellow reaction mixture on a COSMOSIL 5SL (4.6 mm x 250 mm) column [eluant: hexane-chloroform-methanol = 90:10:2; detect: U.V.210 nm;  $t_R$ : 16.60 (1g), 34.05 (syn-2g), 40.51 (anti-2g); flow rate: 2.0 ml/min]. The solvent was

removed from the reaction mixture by evaporation, and the residue was purified by silica gel column chromatography using a mixed solvent of hexane and *iso*-propanol (8:2) as an eluant to obtain a mixture of 1.63 g (70% yield) of *syn*-(2*S*, 3*R*)-2g (90% ee) and *anti*-(2*R*, 3*R*)-2g (89% ee). Enantiomeric excess of (2*S*, 3*R*)-2g and (2*R*, 3*R*)-2g were measured by HPLC analysis of the obtained on esterification of the above mixture with 1.5 equiv of (*R*)-MTPAC1 in the presence of triethylamine (2.0 equiv) under the following conditions: A-002-3 S-3 120A column (4.6 mm x 250 mm) produced by Yamamura Kagaku Kenkyusho K. K. [eluant: hexane-tetrahydrofuran-methanol = 1000:100:1; flow rate: detect: U.V.254 nm; t<sub>R</sub>: 22.3, 24.1, 28.9 and 34.5 min for the (*R*)-MTPA esters of *syn*-(2*S*,3*R*)-2g, *syn*-(2*R*,3*R*)-2g, *anti*-(2*R*,3*R*)-2g and *anti*-(2*S*,3*S*)-2g, *syn*-2g; 90% ee, *anti*-2g; 89% ee; 1.0 ml/min]. (2*S*, 3*R*)-2g; a colorless oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  1.25-1.30 (m, 9H), 2.51 (m, 1H), 3.45 (m, 1H), 3.66 (m, 1H), 4.05 (b, 1H), 4.17 (m, 4H), 5.37 (b, 1H, NH).

Preparation of  $(\pm)$ -Methyl 2-benzamidomethyl-3-oxobutanoate (1e): A 10 L side-armed round-bottomed flask equipped with a thermometer, a mechanical stirrer and a pressure equalizing dropping funnel connected to a three way stopcock was charged with 681 g (5.63 mol) of benzamide and chloroform (5 L). The mixture was stirred at 40-50 °C and aqueous 35% formaldehyde solution (438 g, 5.64 mol) was added dropwise over a period of 1 hour. After additional 1 hour refluxing, the resulting mixture was cooled to room temperature and then chloroform was separated. The chloroform layer was concentrated to about 2 L and which was crystallized below 5 °C over night. The precipitate was collected by filtration and dried under reduced pressure to give 680 g ( 4.50 mol) of (N-hydroxymethyl)benzamide in 80% yield, which was suspended in diisopropyl ether (6.80 L). 526 g (4.50 mol) of thionyl chloride was added to the mixture at 0°C over a period of 1 hour and the resulting mixture was stirred for 2 hours. Filtration gave 649 g (3.83 mol) of (N-chloromethyl)benzamide in 85% yield. A 10 L side-armed round-bottomed flask equipped with a thermometer, a mechanical stirrer and a pressure equalizing dropping funnel connected to a three way stopcock was charged with 153 g (3.83 mol) of sodium hydride (60% oil dispersion) and 3.24 L of THF under nitrogen stream. The mixture was stirred at 10°C and 666 g (5.74 mol) of methyl acetacetate in THF (1.30 L) was added dropwise over a period of 2.0 hours. The resulting mixture was stirred for additional 1 hour at room temperature, cooled to 10 °C and then 649 g (3.83 mol) of (N-chloromethyl)benzamide in THF (1.94

L) was added dropwise for 2 hours and stirred additional for 2 hours. The reaction mixture was poured into brine (1.94 L) and THF layer was separated. Water layer was extracted twice with ethyl acetate (633 ml). The conbined organic layer was evaporated to dryness and recrystallization from a 1:1 mixture of ethyl acetate and hexane (2.40 L) at -20  $\degree$  gave 505 g (2.03 mol) of (±)-methyl 2-benzamidomethyl-3-oxobutanoate (1e) in 53% yield as colorless powder; mp 90  $\degree$ ; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  2.33 (s, 3H, CH<sub>3</sub>CO-), 3.78 (s, 3H, -OCH<sub>3</sub>), 3.88-3.99 (m, 3H), 6.75 (b, 1H, NH), 7.43-7.74 (m, 5H, aromatic).

Preparation of (2S, 3R)-2-Aminomethyl-3-hydroxybutanoic acid (7): A 200 mL side-armed round-bottomed flask equipped with a thermometer, a mechanical stirrer and a pressure equalizing dropping funnel connected to a three way stopcock was charged with 10.65 g (42.43 mmol) of methyl (2S,3R)-2-benzamidomethyl-3hydroxybutanoate (2e). 70 mL of a 10% hydrochloric acid aqueous solution was added dropwise at room temperature over a period of 30 min with vigorous stirring. The solution was heated at reflux for 4.5 hours and then allowed to cool to room temperature. The precipitated benzoic acid was filtered off, and the filtrate was washed twice with 100 ml portions of toluene. The aqueous layer was concentrated to dryness under reduced pressure to obtain 6.67 g of (2S, 3R)-2-aminomethyl-3-hydroxybutanoic acid hydrochloride, which was added 150 ml of acetonitrile. The resulting mixture was cooled to 0 °C assisted by ice-water bath, and 5.5 ml (39.35 mmol) of triethylamine was added dropwise keeping the temperature at 0 °C, followed by vigorous stirring at room temperature for 2 days. The precipitated powder was collected by filtration, washed with 100 ml of acetonitrile to give 4.84 g of (2S, 3R)-2-aminomethyl-3hydroxybutanoic acid in 92% yield as colorless powder; mp 171-172 ℃; IR (KBr) 3000, 1650 (COOH), 1590, 1520, 1460, 1405, 1365, 1340, 1300, 1200, 1115, 1100, 990, 935, 850 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz,  $D_2O$ )  $\delta$  1.27 (d, J = 6.39 Hz, 3H, CH3), 2.49 (dt, J = 6.21, 6.36 Hz, 1H), 3.24 (d, J = 6.36 Hz, 2H), 4.08 (dq, J = 6.21, 6.39 Hz, 100 Hz)1H); <sup>13</sup>C NMR (D<sub>2</sub>O, 100 MHz) δ 23.5 (CH<sub>3</sub>), 41.6 (CH<sub>2</sub>NH<sub>2</sub>), 55.2 (CHCO<sub>2</sub>H), 70.6 (CHOH), 181.1 (COOH); Anal. Calcd for C<sub>5</sub>H<sub>11</sub>NO<sub>3</sub>: C, 45.10; H, 8.33; N, 10.52. Found: C, 44.97; H, 8.51; N, 10.39.

**Preparation of** (1'R, 3S)-3-(1'-Hydroxy)ethylazetidin-2-one (8): A 500 mL side-armed round-bottomed flask equipped with a thermometer, a magnetic stirring bar and a pressure equalizing dropping funnel connected to a three way stopcock

was charged with 2.28 g (17.14 mmol) of (2S, 3R)-2-aminomethyl-3-hydroxybutanoic acid (7) and 342 mL of anhydrous acetonitrile under nitrogen atmosphere, and then 5.49 g (20.93 mmol) of triphenylphosphine and 6.84 g (20.61 mmol) dibenzothiazole disulfide were added into the mixture. A reaction was conducted with stirring at 55 to 60 °C for 20 hours. The resulting mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography using an 8:8:1 (by volume) mixture of dichloromethane, ethyl acetate and methanol as an eluant to obtain 1.88 g of (1'R,3S)-3-(1'-hydroxy)ethylazetidin-2-one (8) in 95% yield as colorless needles. Diastereomer excess was determined to 94.6% de by GLC analysis under following conditions: PEG-HT capillary column 25 m [injection temp.; 200 °C, initial temp.; 100 °C, final temp; 200 °C, program temp; 10°C/min, t<sub>R</sub>; 15.91 and 17.92 for (1'R, 3R)-8 and (1'R,3S)-8; mp 90.5-91.5 °C; IR (KBr) 3200, 1740 (NHC=O), 1460, 1400, 1380, 1350, 1320, 1220, 1145, 1100, 1075, 995, 980, 910 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 1.28 (d, J = 6.30 Hz, 3H, CH3), 2.10 (b, 1H, OH), 3.31 (ddd, J = 5.43, 5.30, 2.71 Hz, 1H), 3.36 (ddd, J = 5.23, 5.28, 2.71 Hz, 2H), 4.21 (dq, J = 6.30, 5.42 Hz, 1H), 5.82 (s, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 21.3 (CH<sub>3</sub>), 37.9 (CH<sub>2</sub>NH), 58.7 (CHCO), 64.8 (CHOH), 169.5 (CONH); Anal. Calcd for C5H9NO2: C, 52.16; H, 7.89; N, 12.17. Found: C, 52.21; H, 7.99; N, 11.98.

Preparation of (1'R, 3S)-3-[((1'-tert-Butyldimethylsilyl)oxy)ethyl]azetidin-2-one (9): A 50 mL side-armed round-bottomed flask equipped with a thermometer, a magnetic stirring bar and a pressure equalizing dropping funnel connected to a three way stopcock was charged with 15 ml of dry dimethylformamide, 3.88 g (33.73 mmol) of (1'R,3S)-3-(1'-hydroxy)ethylazetidin-2-one (8) and 2.41 g (35.43 mmol) of imidazole under nitrogen atmosphere. The mixture was stirred at room temperature and tert-butyldimethylsilyl chloride 5.34 g (35.43 mmol) in 10 mL of dry dimethylformamide was added to the mixture over a period of 30 min. The resulting mixture was stirred at room temperature for 20 hours, and then was poured into 100 ml of cold water. The precipitated were collected by filtration to give 6.96 g of (1'R, 3S)-3-[((1'-tert-butyldimethylsilyl)oxy)ethyl]azetidin-2-one (9) in 90% yield as colorless needles. Recrystallization from heptane gave pure sample of 9. Diastereomer excess was determined to be 98.2% de by GLC analysis under following conditions: PEG-HT capillary column 25 m [injection temp.; 200°C, initial temp.; 100°C, final temp; 200 °C, program temp; 10 °C/min, tR; 13.51 and 12.81 for (1'R,3R)-9 and (1'R,3S)-9: mp 1.02, CHCl<sub>3</sub>).

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67.5-68.0 °C; IR (KBr) 3200 (NH), 2950, 2920, 2880, 2850, 1745 (NHC=O), 1700, 1465, 1360, 1250, 1198, 1145, 1080, 1035, 950, 840 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  0.09 (s, 6H), 0.88 (s, 9H), 1.21 (d, J = 6.21 Hz, 3H, CH3), 3.21 (ddd, J = 6.21 Hz, J = 6.215.26, 5.08, 2.70 Hz, 1H), 3.30 (dd, J = 5.26, 5.08 Hz, 1H), 3.37 (dd, J = 5.26, 2.70 Hz, 1H), 4.20 (dq, J = 6.21, 5.26 Hz, 1H), 5.63 (s, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ -5.2 (CH<sub>3</sub>), -4.4 (CH<sub>3</sub>), 17.9 (CH<sub>3</sub>), 22.5 (C), 25.6 (CH<sub>3</sub>), 37.6 (CH<sub>2</sub>NH), 59.3 (CHCO), 65.2 (CHOH), 169.5 (CONH); Anal. Calcd for C11H23NO2: C, 65.63; H, 11.52; N, 6.96. Found: C, 65.91; H, 11.76; N, 6.71.  $[\alpha]_D^{25}$ -69.8 (c

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# Chapter 2. Ruthenium-Catalyzed Oxidation of $\beta$ -Lactams with Peroxides.

Oxidative transformations of organic compounds are basic reactions in organic chemistry, oxidation is extensively used in both of laboratory syntheses and industrial processes of fine organic chemicals. In these two decades the use of oxo metal complexes to effect catalytic oxidation has become increasingly important and these recent developments in the area of the oxidation of biological active compounds have lately attracted considerable attention. The catalytic reactions by the group VIII transition metal complexes can be effectively employed in the synthesis of a variety of natural products.1 Ruthenium is an unique element in the periodic table to exhibit octavalency and to cover the entire range of eleven oxidation states, inclusively VIII to -II. The well known complex is ruthenium tetroxide, RuO4, which is a very powerful oxidizing agent but a rather non-selective oxidant. On the contrary to this oxidation species, the author has focused his attention on the low valent oxoruthenium species, because of their diversity and potentiality.

Oxidation of the C-H bond adjacent to nitrogen of amides such as  $\beta$ -lactams with metal complex catalysts is one of the most attractive strategy for the synthesis of carbapenem antibiotics represented by thienamycin.<sup>2</sup> Cytochrome P-450 enzym, which plays an important role in the metabolism of amines,3 catalyzes specific oxygenation of amides,<sup>4</sup> however, biomimetic oxidation for selective oxidation of β-lactams is limited to electrochemical process.<sup>5</sup> As the result of the systematic study on the simulation of enzymatic function with metal complex catalysts,6 Murahashi et al. have found a novel cytochrome P-450 type oxidation of amines with t-butyl hydroperoxide under mild reaction conditions to give the corresponding t-butyldioxy amides (eq 1).7



In 1990, the author found that the ruthenium-catalyzed oxidation of  $\beta$ -lactams with peroxides such as peracetic acid in acetic acid gives the corresponding 4-acetoxy  $\beta$ lactams, which are the versatile key intermediates for the synthesis of carbapenem

# Introduction

$$\begin{array}{ccc} t. & \mathbb{R}^2 \mathbb{R}^3 \\ \hline DH & \mathbb{R}^4 - \mathbb{C} - \mathbb{N} - \mathbb{C} - \mathbb{R}^4 & (1) \\ t - Bu OO & O \end{array}$$

antibiotics.7 The present reaction gives a great contribution to the synthesis of carbapenem antibiotics from the industrial point of view. In this chapter, full details of ruthenium-catalyzed oxidation of  $\beta$ -lactams with peroxides are described with respects to scope, limitation, and mechanism.

# **Results and Discussion**

Ruthenium-catalyzed oxidation with t-butyl hydroperoxide can not be applied to the oxidation of  $\beta$ -lactams, since the oxidation of  $\beta$ -lactams requires more specific reaction conditions due to the high strain of the four-membered acyliminium ion intermediates. This catalytic system is effective for the oxidation of five or six membered cyclic amines and amides. Oxidation of β-lactams can be performed by the ruthenium-catalyzed oxidation reaction with peroxides such as peracetic acid as follows (eq.2).



The representative results of oxidation of  $\beta$ -lactams with peracetic acid are listed in Table 1. Direct  $\beta$ -acetoxylation of  $\beta$ -lactams can be performed by ruthenium-catalyzed oxidation in the presence of sodium acetate with peracetic acid in acetic acid. Thus, the ruthenium-catalyzed oxidation of azetidin-2-ones (1) with peracetic acid in acetic acid at room temperature gives 4-acetoxyazetidin-2-one (2) in 94% yield (entry 1). Importantly, (1'R,3S)-3-[1'-[(t-butyldimethylsilyl)oxy]ethyl]azetidin-2-one (8)<sup>9</sup> can be converted into (1'R, 3R, 4R)-4-acetoxy-3-[1'-[(t-butyldimethylsilyl)oxy]ethyl]azetidin-2-one (9) with extremely high diastereoselectivity in 99% yield (entry 5), which is a versatile key intermediate for the synthesis of thienamycin and other biologically active  $\beta$ -lactam antibiotics.<sup>10</sup> The diastereomeric excess of 9 was determined to be >99% by means of <sup>1</sup>H NMR and HPLC analyses. This preferential formation of trans-isomer is due to the steric effect of the substituents at C-3 position of  $\beta$ -lactams. Therefore, stereoselective synthesis of optically active 4-acetoxyazetidin-2-one 9 has been extensively studied.11 Electrochemical oxidation and oxidation with lead tetraacetate are representative results, but those have some disadvantages from the industrial point of view. Evans reported that effect clean  $\alpha$ -oxidation with the  $\beta$ -lactam 8 by the electrochemical methods was



product	yield, % <sup>a</sup>
OAc NH 2	94
OH3 OAC NH 4	86
	0
OFN Ph 7	68
P-BuMe2SIO	99
	0

OAC  

$$OAC$$
  
 $OAC$   
 $OA$ 

<sup>a</sup>Isolated yield. <sup>b</sup>%ee was determined by HPLC analysis using Chiralpack AS (Daicel Chemical Industry, Ltd.)

especially difficult because a peak potential of azetidin-2-one in cyclic voltametry is 0.3V higher than 2-pyrollidine.<sup>8b</sup> Oxidation of β-lactams without sodium acetate gives complex mixtures, and small amount of 4-acetoxy  $\beta$ -lactams were obtained. Sodium acetate is essential for the present oxidation reaction in order to avoid ring opening of  $\beta$ lactams and desilylation reaction. Steric effect at C-4 position is remarkable. Thus, in proportion to increasing steric hindrance at the C-4 position of the  $\beta$ -lactam skeleton, the acetoxylation goes from bad to worse (entries 1-3). The acetoxylation of N-tertbutyldimethyisilylated  $\beta$ -lactam of 8 does not proceed because of its steric hindrance. Furthermore, N-methylation, and N-ethylation of  $\beta$ -lactams retard the oxidation reaction (entry 6, 7). These results indicate that the generation of a tertiary four-membered acyliminiumion is considered to require more specific conditions. N-Benzylazetidin-2one (6) was readily oxidized to give N-benzoylazetidin-2-one (7) by oxidation at the benzylic position (entry 4). (4S)-4-Carboxy-azetidin-2-one (12) undergoes acetoxylation and subsequent decarboxylation to give  $\beta$ -acetoxy  $\beta$ -lactams 2 (entry 8). On the other hands, (4S)-4-methoxycarbonylazetidin-2-one (13) can be converted into 4acetoxy-4-methoxycarbonylazetidin-2-one (14) (entry 9) without decarboxylation under the same reaction conditions. These reactions are similar with the Kolbe type

entry	catalyst	solvent <sup>b</sup>	substrate/catalyst (molar ratio)	yield of $2 (\%)^d$
1	RuCl <sub>3</sub> •3H <sub>2</sub> O	А	20	70
2	RuBr <sub>3</sub>	В	10	62
3	Rul <sub>3</sub>	В	10	02
4	Ru(OAc) <sub>3</sub>	В	10	10
5	Ru(acac) <sub>3</sub>	В	20	43
6	Ru <sub>3</sub> (CO) <sub>12</sub>	B	10	58
7	RuCl <sub>2</sub> (cod)	B	10	15
8	Ru(NH3)6Cla	B	10	43
9	Ru(NO)Cla•HaO	B	10	50
10	BuCla(PPha)a	D	20	47
11	BuHo(PPho)	D	10	23
12	BuOc	B	10	45
13	RuO.	В	10	0
14	F% Du C	В	20	0
15	5% HU-C	A	$(3)^{c}$	94
15	1% Hu-graphite	A	$(3)^{c}$	61

Table 2. Catalytic Activity of Various Ruthenium Complexes for the Oxidation of Azetidin-2-one (1) with Peracetic Acid.<sup>a</sup>

<sup>a</sup>The reaction was carried out above described in the text. <sup>b</sup>Solvent A; AcOH, B; CH<sub>2</sub>Cl<sub>2</sub>-AcOH. <sup>c</sup>Numerals in parentheses are substrate/catalyst ratio by weight. <sup>d</sup>Isolated yield.

electrochemical oxidation reaction.<sup>4b</sup> The products thus formed, 2 and 14, were confirmed to be racemic by means of HPLC analysis using a chiral packed column.<sup>12</sup> These results suggest that the present acetoxylation undergoes via an acyliminium ion intermediate.

Ruthenium catalysts such as RuCl<sub>3</sub>·3H<sub>2</sub>O and 5% Ru on carbon are also effective Although peracetic acid is the best oxidant among examined, other peroxides such

for the oxidation of  $\beta$ -lactam 1 with peracetic acid as listed in Table 2. Amines, and phosphines are not effective ligands for the acetoxylation because self oxidation of the ligands was observed. Recovered Ru on carbon can be reused as catalyst; however, low activity was observed because of elution of ruthenium metal into the solvent. Twenty percent of the ruthenium metal was thawed into the solvent. This was quantitatively analyzed by Inductively Coupled Plasma Atomic Emission Spectroscopy. Importantly, RuO<sub>2</sub> and RuO<sub>4</sub> were sluggish catalysts for the present oxidation. In addition, attempts to drive the reaction to completion led to a complex mixture of products, presumably over oxidation occurred. These results suggest that oxoruthenium with similar function to cytochrome P-450 enzymes acts as an active species for this present oxidation reaction. Also, ruthenium complex containing a porphyline, such as 5,10,15,20-tetraphenyl-21H,23H-porphine ruthenium (II) carbonyl is ineffective under these reaction conditions. as m-chloroperbenzoic acid, and methyl ethyl ketone peroxide can be used for the acetoxylation of  $\beta$ -lactams (see Table 3). Also, PhI(OAc)<sub>2</sub>, and PhIO, obtained by the reaction of iodobenzene with peracetic acid, which are important for generation of metaloxo species<sup>13</sup>, are effective oxidants for the present oxidation reaction. Control of oxidation potential in order to maintain the ruthenium in the most active oxidation state below ruthenium tetroxide RuO4 (VIII) can be effected for example by the rate of addition of peroxides to the reaction system, because it will be appreciated that if the addition rate of the peroxide is increased to that at which the ruthenium is oxidized to its highest oxidation state, the reaction rate decreases abruptly. Thus, the peroxide must be added slowly to prevent the formation of ruthenium tetroxide.

The present oxidation can be rationalized as proceeding by a Cytochrome P-450 type mechanism.<sup>14</sup> As illustrated in Scheme 1, the ruthenium complex reacts with peracetic acid to give an oxoruthenium (V) species, which produces an acyliminium ion intermediate by abstraction of a hydrogen from β-lactams at C-4 position and subsequent electron transfer. Nucleophilic attack of acetic acid gives the corresponding  $\beta$ -acetoxy

entry	oxidant	catalyst <sup>a</sup>	oxidant/substrate (molar ratio)	yield of 9, % <sup>b</sup>
1	H <sub>2</sub> O <sub>2</sub>	A,B	2.0	0
2	Na <sub>2</sub> O <sub>2</sub>	В	4.0	trace
3	NaCIO	В	2.0	0
4	Ca(CIO) <sub>2</sub>	В	2.0	trace
5	t-BuOOH	A,B	2.0	trace
6	()-ООН	A,B	2.0	0
7	(t-BuO) <sub>2</sub> O	A,B	2.0	0
8	(()+0) <sub>2</sub>	A,B	2.0	0
9	CH <sub>3</sub> CO <sub>3</sub> H	А	2.0	99
10	mCPBA	A	2.0	68
11	(PhCO) <sub>2</sub> O <sub>2</sub>	A,B	2.0	0
12	PhCO <sub>3</sub> Bu-t	A,B	2.0	0
13	(CH(-)202	A,B	2.0	0
14	(C11H23CO)2O2	A,B	2.0	0
15	MEK peroxide <sup>c</sup>	А	2.0	78
16	O <sub>3</sub>	С	4.0	11
17	Me <sub>3</sub> N <sup>+</sup> →O <sup>-</sup>	В	2.0	0
18	(+N→O <sup>-V</sup>	В	2.0	15
19	PhI(OAc) <sub>2</sub>	В	2.0	88
20	PhIO	В	2.0	79
21	NalO <sub>4</sub>	В	2.0	trace
22	Na <sub>2</sub> H <sub>2</sub> IO <sub>6</sub>	В	2.0	trace
23	NaBO <sub>3</sub>	В	2.0	trace
24	Na <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	В	2.0	0
25	02	В	excess	0
26	oxone <sup>d</sup>	В	2.0	trace

Table 3. Effect of Various Oxidants for the Ruthenium-Catalyzed Oxydation of  $\beta$ -Lactam 8

<sup>*a*</sup>Catalyst A; 5% Ru-C, B; RuCl<sub>3</sub>•3H<sub>2</sub>O, C; Ru<sub>3</sub>(CO)<sub>12</sub> <sup>*b*</sup> Isolated yield. <sup>*c*</sup>Methyl ethyl ketone peroxide. <sup>*d*</sup>2KHSO<sub>5</sub>•KHSO<sub>4</sub>• K<sub>2</sub>SO<sub>4</sub>  $\beta$ -lactams, water, and ruthenium (III) species to complete the catalytic cycle. Peracetoxy group is not introduced at C-4 position of  $\beta$ -lactams because nucleophilicity of acetic acid is higher than that of peracetic acid.<sup>15</sup> The formation of a four-membered acyliminium ion has been confirmed by exclusive formation of the corresponding dichloroacetate upon oxidation of **8** in a mixture of AcOH and Cl<sub>2</sub>CHCO<sub>2</sub>H (1:1) (eq. 3).



Scheme 1. Catalytic Cycle of Ruthenium-Catalyzed Oxidation of β-Lactams with Peracetic Acid









of the corresponding carboxylic acid expressed as XCH<sub>2</sub>CO<sub>2</sub>H.

Table 4.	Relative	Ra	ate	e Co
of 8 with	AcOOH	in	a	mix

X in XCH <sub>2</sub> CO <sub>2</sub> H	
Br	
CI	
MeO	
PhCH <sub>2</sub>	
CH <sub>3</sub> CH <sub>2</sub>	

The description of these results is as follows. The present reaction may involve the formation of the acyliminium ion intermediate and oxoruthenium (V) species act as a two-electron oxidant. Introduction of substituents at C-4 position of  $\beta$ -lactams are subject to the strength of nucleophilicity of the corresponding carboxylic acid. Also, much effort has been conducted for the mechanistic investigation of the reactivity of Nacyliminium ions toward nucleophiles.<sup>16</sup> Zaugg and Martin distinguish between i) the formation of N-acyliminium ion is the rate-determining step and ii) the reaction of Nacyliminium ion with the nucleophile is the rate-determining step.<sup>17</sup> When the reaction was strongly influenced by the reactivity of the nucleophile, the latter case could be employed. Thus, these results could imply that the nucleophilic reaction with acetic acid is the rate-limiting step.

In conclusion, the development of oxo-metal complex catalysis by means of transition metal complex catalysts has brought about striking innovations to synthetic chemistry and, especially, industrial chemistry, giving us a new methodlogy of the

Furthermore, the formation of acyliminium ion intermediate can be understood by the results of the oxidation of 8 in a mixture of AcOH and XCH<sub>2</sub>CO<sub>2</sub>H (10:1). The relative ratio of k<sub>X</sub>/k<sub>H</sub> was obtained by means of <sup>1</sup>H NMR analysis as summarized in Table 4. As shown in Figure 1, introduction of acyloxy groups such as CICH<sub>2</sub>CO<sub>2</sub>-, MeOCH<sub>2</sub>CO<sub>2</sub>-, PhCH<sub>2</sub>CO<sub>2</sub>-, and CH<sub>3</sub>CH<sub>2</sub>CO<sub>2</sub>-group is deeply dependent on pka value

onstants for the Ruthenium-Catalyzed Oxidation ture of AcOH and XCH<sub>2</sub>CO<sub>2</sub>H (10:1).

pka value	$k_{\rm X}$ / $k_{\rm H}$ <sup>a</sup>
2.9	0.428
2.9	0.409
3.5	0.219
4.3	0.124
4.9	0.041

<sup>a</sup>Relative rate constants (k<sub>X</sub>/k<sub>H</sub>) were determined by <sup>1</sup>H NMR analysis (270 MHz).

creation of the target molecules. Since oxidation reaction plays an important role in organic chemistry, ever-increasing efforts of research and development in this field are expected to contribute toward further improvement of human life. Now, the ruthenium-catalyzed oxidation of the  $\beta$ -lactam with peracetic acid is industrially operating on 50 ton scale/year since 1992.

# **Experimental Section**

General. <sup>1</sup>H NMR spectra were recorded on a JEOL PMX-60 SI (<sup>1</sup>H, 60 MHz), a JEOL JNM-GSX 270 (<sup>1</sup>H, 270 MHz; <sup>13</sup>C, 67.9 MHz), and a BRUKER AM-400 (<sup>1</sup>H, 400 MHz; <sup>13</sup>C, 100 MHz) spectrometers. IR spectra were recorded on a Hitachi 215 spectrometer, a JASCO IR-810, and a Shimadzu FTIR-4100 spectrometers. Mass spectra were obtained on a JEOL JMX-DX 303 mass spectrometer and a HITACHI M-80B spectrometer. Elemental analyses were performed on a Yanagimoto MT-2 CHN corder. Mass spectra were measured on a Hitachi Model RSM-4 mass spectrometer. Exact mass spectra were measured on a JEOL Model JMS-DX-303 mass spectrometer. All melting points were measured on a Yanagimoto micro melting point apparatus. HPLC analyses were performed on a JASCO TRI ROTAR-VI system with a JASCO UVIDEC-100-VI UV detector by using a 250 mm x 4.6 mm analytical column packed with Chiralpack AS (Daicel Chemical Industry, Ltd.). Optical rotations were measured on a JASCO DIP-360 polarimeter.

**Materials.** Acetic acid, anhydrous sodium acetate, dichloroacetic acid, bromoacetic acid, chloroacetic acid, methoxyacetic acid, phenylacetic acid, propionic acid, and azetidin-2-one were commercially available and used without further purification. All ruthenium compounds were commercially available (Aldrich) and without further purification. RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub>,<sup>17</sup> and RuH<sub>2</sub>(PP<sub>3</sub>)<sub>4</sub><sup>18</sup> were prepared by according to the literatures. PhI(OAc)<sub>2</sub>, and PhIO were prepared by the known method. 30% peracetic acid in EtOAc was a gift from Daicel Chemical Industry Ltd., and another oxidants were commercially available and without further purification. 4-*tert*-Butylazetidin-2-one (**5**) was prepared by cycloaddition of the corresponding olefins with chlorosurfonyl isocyanate.<sup>19</sup> N-Benzylazetidin-2-one (**6**),<sup>20</sup> (1'R,3S)-3-[1'-[(*tert*-butyldimethyl-silyl)oxy]ethyl]azetidin-2-one (**8**), and (4S)-4-benzyloxycarbonylazetidin-2-one (**15**)<sup>21</sup> were prepared by according to the literature's procedure. (1'R,3S)-N-*tert*-Butyldimethylsilyl-3-[1'-[(*tert*-butyldimethylsilyl)oxy]ethyl]azetidin-2-one was prepared

by the reaction of 8 with *tert*-butyldimethylsilyl chloride in the presence of triethylamine. (4S)-4-Carboxyazetidin-2-one (12) was prepared by the hydrogenolysis of (4S)-4-benzyloxycarbonylazetidin-2-one (15) by using 5% Pd on charcoal in toluene at room temperature. (4S)-4-Methoxycarbonylazetidin-2-one (13) was prepared by the esterification of carboxylate 12 with diazomethane.

General Procedure for the Ruthenium-Catalyzed Oxidation of  $\beta$ -Lactams with Peracetic acid. A 20 mL three-necked round-bottomed flask equipped with a thermometer, a magnetic stirring bar and a pressure equalizing dropping funnel connected to a three-way stopcock was charged with  $\beta$ -lactam (0.2 mmol), ruthenium trichloride (0.01 mmol, 5 mol%), anhydrous sodium acetate (0.2 mmol) and acetic acid (2 mL) under argon atmosphere. The mixture was stirred at room temperature and 30% solution of peracetic acid in EtOAc (0.44 mmol) was added dropwise over a period of 2 h. After stirring for 12 h, the reaction mixture was poured into water (80 mL) and extracted with an appropriate solvent. The extract was washed with NaHCO<sub>3</sub> solution and brine and dried over MgSO<sub>4</sub>. The solvent was removed under reduced presser, and purification by column chromatography on SiO<sub>2</sub> with appropriate eluents gave the corresponding 4-acetoxy- $\beta$ -lactam. The representative results according to general procedure were shown in Table 1.

**4-Acetoxyazetidin-2-one (2):** The reaction was carried out according to the general procedure. Extraction with EtOAc (200 mL) and purification by column chromatography on SiO<sub>2</sub> (hexane/ EtOAc, 2/1) gave **2** in 94% (preparation from **1**), and 82%.yield(preparation from **12**). colorless oil; IR (neat) 3250 (NH), 3020, 2970, 1765 (ester C=O), 1740 (β-lactam C=O), 1410, 1380, 1240, 1110, 1043, 990, 960 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 2.13 (s, 3H, -OCOCH<sub>3</sub>), 3.00 (ddd, J = 15.3, 1.4, 0.5 Hz, 1H, -HCHCH(OAc)--), 3.26 (ddd, J = 15.3, 4.1, 0.5 Hz, 1H, -HCHCH(OAc)--), 5.84 (dd, J = 4.1, 1.4 Hz, 1H, -HCHCH(OAc)--), 7.02 (b, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 20.7 (COCH<sub>3</sub>), 44.9 (CH<sub>2</sub>), 73.0 (CH), 165.6 (NHC=O), 170.9 (OC=O); Anal. Calcd for C<sub>5</sub>H<sub>7</sub>NO<sub>3</sub>: C, 46.51; H, 5.47; N, 10.58. Found: C, 46.71; H, 5.56; N, 10.84.

**4-Methylazetidin-2-one (3):** A mixture of DL- $\beta$ -amino-n-butanoic acid (2.58 g, 25 mmol), triphenylphosphine (7.87 g, 30 mmol), carbon tetrachloride (7.70 g, 50 mmol), triethylamine (3.03 g, 30 mml), and acetonitril (250 mL) was stirred for 6 h at room temperature under argon atmosphere. The solvent was removed by reduced

pressure, and the resulting mixture was purified by column chromatography on SiO2 (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc/MeOH, 8/8/1) to give 3 (1.72g, 81% yield) as colorless oil: IR (neat) 3250 (NH), 2975, 1740 (C=O), 1420, 1380, 1360, 1280, 1200, 1060, 965, 905, 800 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz)  $\delta$  1.35 (d, J = 5.9 Hz, 3H, -CH<sub>3</sub>), 2.52 (dd, J = 2.4, 14.9 Hz, 1H, -CH<sub>2</sub>-), 3.10 (dd, J = 4.9, 14.9 Hz, 1H, -CH<sub>2</sub>-), 3.78 (ddq, J = 2.4, 4.9, 5.9 Hz, 1H, -NCHCH<sub>3</sub>), 6.61 (b, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 67.9 MHz) δ 21.2 (CH<sub>3</sub>), 43.8 (CH<sub>2</sub>), 44.9 (-CHN-), 168.3 (C=O); Anal. Calcd for C<sub>4</sub>H<sub>7</sub>NO: C, 56.44; H, 8.29; N, 16.46. Found: C, 56.32; H, 8.27; N, 16.31.

4-Acetoxy-4-methylazetidin-2-one (4): The reaction was carried out according to the general procedure. Extraction with EtOAc (200 mL) and purification by column chromatography on SiO<sub>2</sub> (hexane/ EtOAc, 2/1) gave 4 in 86% yield. Colorless oil; IR (neat) 3350 (NH), 1750 (ester C=O), 1720 (β-lactam C=O), 1360, 1265, 1165, 1020 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 1.83 (s, 3H, -CCH<sub>3</sub>), 2.07 (s, 3H, OCOCH<sub>3</sub>), 3.00 (d, J = 14.9 Hz, 1H, -HCHCCH<sub>3</sub>(OAc)-), 3.17 (d, J = 14.9 Hz, 1H, -HCHCCH<sub>3</sub>(OAc)-), 7.17 (b, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 67.9 MHz) δ 21.5 (CCH<sub>3</sub>), 22.9 (OCOCH<sub>3</sub>), 51.0 (CH<sub>2</sub>), 84.7 (NHC(OAc)CH<sub>3</sub>), 165.1 (NHC=O), 170.8 (OC=O); Anal. Calcd for C<sub>6</sub>H<sub>9</sub>NO<sub>3</sub>: C, 50.35; H, 6.34; N, 9.79. Found: C, 50.22; H, 6.08; N, 9.71.

N-Benzoylazetidin-2-one (7): The reaction was carried out according to the general procedure. Extraction with EtOAc (200 mL) and purification by column chromatography on SiO<sub>2</sub> (hexane/ EtOAc, 3/2) gave 7 in 68% yield as a colorless oil. IR (neat) 3250, 2980, 1800 (C=O), 1660 (C=O), 1600, 1580, 1500, 1450, 1320, 1200, 1110, 1080, 960 cm<sup>-1; 1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz)  $\delta$  3.11 (dd, J = 5.6, 5.4 Hz, 2H, CH<sub>2</sub>), 3.78 (dd, J = 5.6, 5.4 Hz, 2H,CH<sub>2</sub>), 7.43-7.99 (m, 5H, aromatic H).

(1'R, 3R, 4R)-4-Acetoxy-3-[1'-[(tert-buthyldimethylsilyl)oxy]ethyl]azetidin-2-one (9): The reaction was carried out according to the general procedure. 5% Ruthenium on charcoal (3% weight/weight to substrate) was used as catalyst. Extraction with hexane (200 mL) and evaporation gave pure 9 in 99% yield as a colorless needles. mp 108.5 °C; IR (KBr) 3190 (NH), 2940, 2850, 1780 (ester C=O), 1750 (β-lactam C=O), 1240, 1160, 1140, 1080, 1040, 940 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 0.08 (s, 3H, SiCH<sub>3</sub>), 0.09 (s, 3H, SiCH<sub>3</sub>), 0.88 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.27 (d, J = 6.4 Hz, 3H, -(t-BuMe<sub>2</sub>SiO)CHCH<sub>3</sub>), 2.11 (s, 3H, -OCOCH<sub>3</sub>), 3.19 (dd, J = 3.5, 1.3 Hz, COCH), 4.23 (dq, J = 3.5, 6.4 Hz, -(t-BuMe<sub>2</sub>SiO)CHCH<sub>3</sub>), 5.84 (d, J = 1.3 Hz,

Found: C, 59.27; H, 10.36; N, 5.88.

CHNH), 6.40 (b, 1H, NH). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 67.9 MHz) δ -5.2 (SiCH<sub>3</sub>), -4.3 (SiCH<sub>3</sub>), 17.9 (SiC(CH<sub>3</sub>)<sub>3</sub>), 20.8 (-(t-BuMe<sub>2</sub>SiO)CHCH<sub>3</sub>), 22.3 (OCOCH<sub>3</sub>), 25.7 (SiC(CH<sub>3</sub>)<sub>3</sub>), 64.0 (CH), 65.2 (-(t-BuMe<sub>2</sub>SiO)CHCH<sub>3</sub>), 75.2 (CH(OAc)), 166.4 (NHC=O), 171.2 (OCOCH<sub>3</sub>). Anal. Calcd for C<sub>13</sub>H<sub>25</sub>NO<sub>4</sub>Si: C, 54.32; H, 8.77 N, 4.87. Found: C, 54.15.; H, 8.55; N, 4.96.  $[\alpha]_D^{25}$  +51.2 (c 1.00, CHCl<sub>3</sub>).

# (1'R, 3S)-3-[1'-[(tert-Butyldimethylsilyl)oxy]ethyl]-N-methyl-

azetidin-2-one (10): To a mixture of NaH (0.4 g, 10 mmol), and THF (20 mL) was added dropwise a solution of  $\beta$ -lactam 8 (2.29 g, 10 mmol) in THF (20 mL) with stirring at 0 °C. After stirring for 1 h at 0 °C, MeI (0.62 mL, 10 mmol) was added dropwise to the mixture. After keeping the resulting mixture at room temperature under stirring for 3 h, reaction mixture was poured into the water. Extraction with EtOAc and evaporation by reduced pressure gave 10 (563 mg, 24% yield) as a colorless oil: IR (neat) 2970, 2930, 2900, 2850, 1760 (β-lactam C=O), 1640, 1460, 1400, 1380, 1330, 1260, 1240, 1140, 1120, 1090, 1070, 1020, 940 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 0.07 (s, 3H, SiCH<sub>3</sub>), 0.08 (s, 3H, SiCH<sub>3</sub>), 0.87 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.17 (d, J = 6.1 Hz, 3H, -(t-BuMe<sub>2</sub>SiO)CHCH<sub>3</sub>), 2.80 (s, 3H, -NCH<sub>3</sub>), 3.14 (ddd, J = 5.1, 4.2, 2.2 Hz, 1H, H-3), 3.19 (dd, J = 5.1, 4.9 Hz, 1H, cis-H-4), 3.27 (dd, J = 4.9, 2.2 Hz, 1H, trans-H-4),4.20 (dq, J = 4.2, 6.1 Hz, -(t-BuMe<sub>2</sub>SiO)CHCH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 67.9 MHz)  $\delta$  -5.0 (SiCH<sub>3</sub>), -4.3 (SiCH<sub>3</sub>), 17.9 (SiC(CH<sub>3</sub>)<sub>3</sub>), 22.6 (-(t-BuMe<sub>2</sub>SiO)CHCH<sub>3</sub>), 25.7 (SiC(CH<sub>3</sub>)<sub>3</sub>), 28.3 (NCH<sub>3</sub>), 42.9 (CH), 58.1 (CH<sub>2</sub>), 65.2 (-(t-BuMe<sub>2</sub>SiO)CHCH<sub>3</sub>), 168.6 (NHC=O); Anal. Calcd for C12H25NO2Si: C, 59.22; H, 10.36; N, 5.76.

(1'R, 3S)-3-[1'-[(tert-Butyldimethylsilyl)oxy]ethyl]-N-ethylazetidin-2-one (11): To a mixture of NaH (0.4 g, 10 mmol), and THF (20 mL) was added dropwise a solution of  $\beta$ -lactam 8 (2.29 g, 10 mmol) in THF (20 mL) with stirring at 0 °C. After stirring for 1 h at 0 °C, EtI (0.80 mL, 10 mmol) was added dropwies to the mixture. After keeping the resulting mixture at room temperature under stirring for 3 h, reaction mixture was poured into the water. Extraction with EtOAc and evaporation by reduced pressure gave 11 (538 mg, 21% yield) as a colorless oil: IR (neat) 2970, 2940, 2900, 2860, 1750 (β-lactam C=O), 1480, 1460, 1410, 1380, 1260, 1240, 1150, 1070, 1020, 960 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 0.06 (s, 3H, SiCH<sub>3</sub>), 0.07 (s, 3H, SiCH<sub>3</sub>), 0.87 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.14 (t, J = 7.3 Hz, 3H, -CH<sub>2</sub>CH<sub>3</sub>), 1.18 (d, J = 6.4 Hz, 3H,  $-(t-BuMe_2SiO)CHCH_3)$ , 3.10 (ddd, J = 5.1, 4.2, 2.4 Hz, 1H, H-3), 3.19 (dd, J = 5.1, 4.9 Hz, 1H, *cis*-H-4), 3.23 (q, J = 7.3 Hz, 2H, -CH<sub>2</sub>CH<sub>3</sub>), 3.27 (dd, J = 4.9, 2.4 Hz, 1H, *trans*-H-4), 4.20 (dq, J = 4.2, 6.4 Hz, -(*t*-BuMe<sub>2</sub>SiO)CHCH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 67.9 MHz)  $\delta$  -4.9 (SiCH<sub>3</sub>), -4.3 (SiCH<sub>3</sub>), 12.7 (CH<sub>3</sub>), 18.0 (SiC(CH<sub>3</sub>)<sub>3</sub>), 22.7 (-(*t*-BuMe<sub>2</sub>SiO)CHCH<sub>3</sub>), 25.7 (SiC(CH<sub>3</sub>)<sub>3</sub>), 36.1 (CH<sub>2</sub>), 40.2 (CH<sub>2</sub>), 57.0 (CH), 65.2 (-(*t*-BuMe<sub>2</sub>SiO)CHCH<sub>3</sub>), 168.1 (NHC=O); Anal. Calcd for C<sub>13</sub>H<sub>27</sub>NO<sub>2</sub>Si: C, 60.66; H, 10.58; N, 5.44. Found: C, 60.56; H, 10.44; N, 5.55.

**4-Acetoxy-4-methoxycarbonylazetidin-2-one** (14): The reaction was carried out according to the general procedure. Extraction with EtOAc (200 mL) and purification by column chromatography on SiO<sub>2</sub> (hexane/ EtOAc, 2/1) gave 14 in 59% yield. Colorless oil, IR (neat) 3300 (NH), 3030, 1784 (ester C=O), 1750 (β-lactam C=O), 1439, 1371, 1304, 1246, 1196, 1141, 1105, 1041, 978, 916 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 2.17 (s, 3H, OCOCH<sub>3</sub>), 3.26 (dd, J = 14.9, 0.7 Hz, 1H,-HCH-), 3.33 (dd, J = 14.9, 2.4 Hz, 1H,-HCH-), 3.83 (s, 3H, -CO<sub>2</sub>CH<sub>3</sub>), 7.02 (b, 1H, NH). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 67.9 MHz) δ 20.5 (COCH<sub>3</sub>), 49.4 (COCH<sub>2</sub>), 53.6 (OCH<sub>3</sub>), 80.4 (NHC(OAc)CO<sub>2</sub>CH<sub>3</sub>), 163.9 (NHC=O), 167.5 (CO<sub>2</sub>CH<sub>3</sub>), 170.9 (OC=O); exact mass calcd for C<sub>7</sub>H<sub>9</sub>NO<sub>5</sub> 187.0481, found 187.0489; [α]<sup>23</sup>D -5.88 (c 1.12, CHCl<sub>3</sub>).

Catalytic Activity of Various Ruthenium Complexes for the Oxidation of  $\beta$ -Lactam 1 with Peracetic Acid. A 20 mL three-necked roundbottomed flask equipped with a thermometer, a magnetic stirring bar and a pressure equalizing dropping funnel connected to a three-way stopcock was charged with azetidin-2-one (1) (0.2 mmol), a catalyst (1-10 mol%), anhydrous sodium acetate (0.2 mmol) and acetic acid (2 ml) under argon atmosphere. The mixture was stirred at room temperature and 30% solution of peracetic acid in ethyl acetate (0.44 mmol) was added dropwise over a period of 2 h. After stirring for 12 h, the reaction mixture was poured into water (80 mL) and extracted three times with 100 mL of EtOAc. The extract was washed with saturated aqueous NaHCO<sub>3</sub> solution, and brine and dried over MgSO<sub>4</sub>. The solvent was removed under reduced presser, and purification by column chromatography on SiO<sub>2</sub>.(hexane/EtOAc, 2/1) gave 4-acetoxyazetidin-2-one (2). The representative results were listed in Table 2.

Effect of Various Oxidants for the Ruthenium-Catalyzed Oxidation of  $\beta$ -Lactam 8. A 20 mL three-necked round-bottomed flask equipped with a thermometer, a magnetic stirring bar and a pressure equalizing dropping funnel connected to a three-way stopcock was charged with (1'R, 3S)-3-[1'-[(tert-butyldimethylsilyl)oxy]- ethyl]azetidin-2-one (8) (1.0 mmol), a catalyst [A: 5 % Ru-Carbon (5 mol%), B: RuCl<sub>3</sub>· 3H<sub>2</sub>O (5 mol%), C: Ru<sub>3</sub>(CO)<sub>3</sub> (5 mol%)], anhydrous sodium acetate (1.0 mmol) and acetic acid (2 mL) under argon atmosphere. The mixture was stirred at room temperature and 30% solution of peracetic acid in EtOAc (2.2 mmol) was added dropwise over a period of 2 h. After stirring for 12 h, the reaction mixture was poured into water (80 mL) and extracted three times with 100 mL of hexane. The combined extract was washed with saturated aqueous NaHCO<sub>3</sub> solution, and brine and dried over MgSO<sub>4</sub>. The solvent was removed under reduced presser, and purification by column chromatography on SiO<sub>2</sub>.(hexane/EtOAc, 5/1) gave (1'*R*,3*R*,4*R*)-4-acetoxy-3-[1'-[(*tert*butyldimethylsilyl)oxy]ethyl]-azetidin-2-one (9). The representative results were listed in Table 3.

Preparation of (1'R, 3R, 4R)-3-[1'-[(t-Butyldimethylsilyl)oxy]ethyl]-4-dichloroacetoxyazetidin-2-one (15). A 20 mL three-necked round-bottomed flask equipped with a thermometer, a magnetic stirring bar and a pressure equalizing dropping funnel connected to a three-way stopcock was charged with  $\beta$ -lactam 8 (229 mg, 1.0 mmol), RuCl<sub>3</sub>·3H<sub>2</sub>O (13 mg, 5 mol%), anhydrous sodium acetate (41 mg, 0.5 mmol), dichloroacetic acid (12.9 g, 100 mmol), and acetic acid (6.0 g, 100 mmol) under argon atmosphere. The mixture was stirred at room temperature and 30% solution of peracetic acid in EtOAc (0.56 g, 2.2 mmol) was added dropwise to the mixture over a period of 2 h. After stirring for 12 h, the reaction mixture was poured into water (100 mL) and extracted twice with hexane (100 mL). The combined extracts were washed with saturated aqueous NaHCO<sub>3</sub> solution (100 mL), brine (50 mL) and dried over MgSO<sub>4</sub>. Evaporation of the solvent gave 9i as a colorless needles; mp 118 °C; IR (KBr) 3150 (NH), 2960, 2940, 2860, 1790, 1765 (ester C=O), 1740 (amide C=O), 1470, 1380, 1300, 1260, 1150, 1080, 1040, 1010, 940 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 0.07 (s, 3H, SiCH<sub>3</sub>), 0.08 (s, 3H, SiCH<sub>3</sub>), 0.87 (s, 9H,  $-C(CH_3)_3$ ), 1.28 (d, J = 6.4 Hz, 3H, -CH(OTBDMS)CH<sub>3</sub>), 3.32 (dd, *J* = 3.3, 1.2 Hz, 1H, C<sub>3</sub>-H), 4.25 (dq, *J* = 3.3, 6.4 Hz, 1H, -CH(OTBDMS)CH<sub>3</sub>), 5.96 (s, 1H, -C=OCHCl<sub>2</sub>), 6.00 (d, J = 1.2 Hz, 1H, C<sub>4</sub>-H), 6.50 (br, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ -5.2 (SiCH<sub>3</sub>), -4.3 (SiCH<sub>3</sub>), 18.1 (-C(CH<sub>3</sub>)<sub>3</sub>), 22.5 (-CH(OTBDMS)CH<sub>3</sub>), 25.6 (-C(CH<sub>3</sub>)<sub>3</sub>), 64.1 (-CHCl<sub>2</sub>), 64.2 (-CH(OTBDMS)CH<sub>3</sub>), 66.3 (C<sub>3</sub>), 78.5 (C<sub>4</sub>), 165.6 (NHC=O), 166.6 (-OC=OCHCl<sub>2</sub>). Anal. Calcd for C13H23NO4SiCl2: C, 43.93; H, 6.53; N, 3.94; Cl, 19.70. Found: C, 43.90; H, 6.83; N, 4.02; Cl, 19.58.  $[\alpha]_D^{28.5}$  +34.4 (*c* 1.00, CHCl<sub>3</sub>).

Competitive Reaction for the Oxidation of 8 in a Mixture of AcOH and XCH2CO2H (10:1). A 20 mL three-necked round-bottomed flask equipped with a thermometer, a magnetic stirring bar and a pressure equalizing dropping funnel connected to a three-way stopcock was charged with  $\beta$ -lactam 8 (1.0 mmol), RuCl<sub>3</sub>. 3H2O (0.05 mmol, 5 mol%), anhydrous sodium acetate (1.0 mmol), XCH2CO2H (10 mmol), and acetic acid (100 mmol) under argon atmosphere. The mixture was stirred at room temperature and 30% solution of peracetic acid in EtOAc (1 mmol) was added dropwise to the mixture over a period of 2 h. After stirring for 12 h, the reaction mixture was poured into water (100 mL) and extracted twice with hexane (100 mL). The combined extracts were washed with saturated aqueous NaHCO3 solution (100 mL), brine (50 mL) and dried over MgSO4. The solvent was removed under reduced pressure. Relative rate constants of kx/kH were determined by means of <sup>1</sup>H NMR (proton relaxation time is adjusted to 30 sec.) analyses of the obtained reaction mixture. The representative results were summarized in Table 4 and visualized in Figure 1.

(1'R, 3R, 4R)-4-Bromoacetoxy-3-[1'-[(t-butyldimethylsilyl)oxy]ethyl]azetidin-2-one (16): The reaction was carried out according to above described competitive reaction procedure. Bromoacetic acid (1.39 g, 10 mmol) was used. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 0.06 (s, 3H, SiCH<sub>3</sub>), 0.08 (s, 3H, SiCH<sub>3</sub>), 0.87 (s, 9H, -C(CH<sub>3</sub>)<sub>3</sub>), 1.26 (d, J = 6.3 Hz, 3H, -CH(OTBDMS)CH<sub>3</sub>), 3.24 (dd, J = 3.4, 1.2 Hz, 1H, C<sub>3</sub>-H), 3.86 (s, 2H, -C=OCH<sub>2</sub>Br), 4.23 (dq, J = 3.4, 6.3 Hz, 1H, -CH(OTBDMS)CH<sub>3</sub>), 5.92 (d, J = 1.2 Hz, 1H, C<sub>4</sub>-H), 6.49 (br, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 67.9 MHz) δ -5.2 (SiCH<sub>3</sub>), -4.3 (SiCH<sub>3</sub>), 17.9 (-C(CH<sub>3</sub>)<sub>3</sub>), 22.3 (-CH(OTBDMS)CH<sub>3</sub>), 25.0 (-CH<sub>2</sub>Br), 25.7 (-C(CH<sub>3</sub>)<sub>3</sub>), 63.8(-CH(OTBDMS)CH<sub>3</sub>), 65.6 (C<sub>3</sub>), 76.8 (C<sub>4</sub>), 165.9 (NHC=O), 167.5 (-OC=OCH<sub>2</sub>Cl).

(1'R, 3R, 4R)-4-Chloroacetoxy-3-[1'-[(t-butyldimethylsilyl)oxy]ethyl]azetidin-2-one (17): The reaction was carried out according to above described competitive reaction procedure. Chloroacetic acid (0.95 g, 10 mmol) was used. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) & 0.07 (s, 3H, SiCH<sub>3</sub>), 0.08 (s, 3H, SiCH<sub>3</sub>), 0.87 (s, 9H,  $-C(CH_3)_3$ ), 1.27 (d, J = 6.3 Hz, 3H,  $-CH(OTBDMS)CH_3$ ), 3.24 (dd, J = 6.3 Hz, 3H,  $-CH(OTBDMS)CH_3$ ), 3.24 (dd, J = 6.3 Hz, 3H,  $-CH(OTBDMS)CH_3$ ), 3.24 (dd, J = 6.3 Hz,  $-CH(OTBDMS)CH_3$ ),  $-CH(OTBDMS)CH_3$ )),  $-CH(OTBDMS)CH_3$ )),  $-CH(OTBDMS)CH_3$ )),  $-CH(OTBDMS)CH_3$ )) 3.3, 1.2 Hz, 1H, C<sub>3</sub>-H), 4.10 (s, 2H, -C=OCH<sub>2</sub>Cl), 4.24 (dq, J = 3.3, 6.3 Hz, 1H, -CH(OTBDMS)CH<sub>3</sub>), 5.94 (d, J = 1.2 Hz, 1H, C<sub>4</sub>-H), 6.44 (br, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) & -5.2 (SiCH<sub>3</sub>), -4.3 (SiCH<sub>3</sub>), 17.9 (-C(CH<sub>3</sub>)<sub>3</sub>), 22.3 (-CH(OTBDMS)CH<sub>3</sub>), 25.7 (-C(CH<sub>3</sub>)<sub>3</sub>), 40.5 (-CH<sub>2</sub>Cl), 63.8(-CH(OTBDMS)CH<sub>3</sub>),

# 65.6 (C<sub>3</sub>), 76.8 (C<sub>4</sub>), 166.0 (NHC=O), 167.5 (-OC=OCH<sub>2</sub>Cl).

acetoxyazetidin-2-one (18): The reaction was carried out according to above described competitive reaction procedure. Methoxyacetic acid (0.90 g, 10 mmol) was used. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz)  $\delta$  0.07 (s, 3H, SiCH<sub>3</sub>), 0.09 (s, 3H, SiCH<sub>3</sub>),  $0.87 (s, 9H, -C(CH_3)_3), 1.26 (d, J = 6.4 Hz, 3H, -CH(OTBDMS)CH_3), 3.22 (dd, J = 0.87 (s, 9H, -C(CH_3)_3), 1.26 (d, J = 0.4 Hz, 3H, -CH(OTBDMS)CH_3), 3.22 (dd, J = 0.4 Hz, -CH(OTBDMS)CH_3)), 3.22 (dd, J = 0.4 Hz, -CH(OTBDMS)CH_3)))$ 3.4, 1.2 Hz, 1H, C<sub>3</sub>-H), 4.07 (s, 2H, -C=OCH<sub>2</sub>O-), 4.22 (dq, J = 3.4, 6.4 Hz, 1H,  $C_{1'}$ -**H**), 5.94 (d, J = 1.2 Hz, 1H,  $C_{4}$ -**H**), 6.44 (br, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 67.9) MHz) δ -5.18 (SiCH<sub>3</sub>), -4.35 (SiCH<sub>3</sub>), 17.91 (-C(CH<sub>3</sub>)<sub>3</sub>), 22.30 (-CH(OTBDMS)CH<sub>3</sub>), 25.68 (-C(CH<sub>3</sub>)<sub>3</sub>), 59.49 (-CH<sub>2</sub>OCH<sub>3</sub>), 63.89 (-CH(OTBDMS)CH<sub>3</sub>), 65.46 (C<sub>3</sub>), 69.53 (-CH<sub>2</sub>OCH<sub>3</sub>), 75.66 (C<sub>4</sub>), 166.05 (NHC=O), 170.51 (-OC=OCH<sub>2</sub>CH<sub>3</sub>).

(1'R, 3R, 4R)-3-[1'-[(t-Butyldimethylsilyl)oxy]ethyl]-4-phenylacetoxyazetidin-2-one (19): The reaction was carried out according to above described competitive reaction procedure. Phenylacetic acid (1.36 g, 10 mmol) was used. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) & 0.04 (s, 3H, SiCH<sub>3</sub>), 0.06 (s, 3H, SiCH<sub>3</sub>), 0.85 (s, 9H,  $-C(CH_3)_3$ ), 1.23 (d, J = 6.4 Hz, 3H,  $-CH(OTBDMS)CH_3$ ), 3.18 (dd,  $J=3.6, 1.2 \text{ Hz}, 1\text{H}, C_3-\text{H}), 3.66 (s, 2\text{H}, -C=OCH_2Ph), 4.20 (dq, J = 3.4, 6.4 \text{ Hz}, 1\text{H}), 4.20 (dq, J = 3.4, 6.4 \text{ Hz}, 1\text{H})$ -CH(OTBDMS)CH<sub>3</sub>), 5.86 (d, J = 1.2 Hz, 1H, C<sub>4</sub>-H), 6.48 (br, 1H, NH), 7.24-7.36 (m, 5H, aromatic); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 67.9 MHz) δ -5.2 (SiCH<sub>3</sub>), -4.3 (SiCH<sub>3</sub>), 17.9 (-C(CH<sub>3</sub>)<sub>3</sub>), 22.3 (-CH(OTBDMS)CH<sub>3</sub>), 25.6 (-C(CH<sub>3</sub>)<sub>3</sub>), 41.1 (C=OCH<sub>2</sub>Ph), 64.0 (-CH(OTBDMS)CH<sub>3</sub>), 65.3 (C<sub>3</sub>), 75.7 (C<sub>4</sub>), 127.4 (aromatic), 128.7 (aromatic), 129.2 (aromatic), 133.1 (aromatic), 166.4 (NHC=O), 171.9 (-OC=OCH<sub>2</sub>CH<sub>3</sub>).

carbonyloxyazetidin-2-one (20): The reaction was carried out according to above described competitive reaction procedure. Propionic acid (0.74 g, 10 mmol) was used. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 0.06 (s, 3H, SiCH<sub>3</sub>), 0.08 (s, 3H, SiCH<sub>3</sub>), 0.87 (s, 9H,  $-C(CH_3)_3$ , 1.16 (t, J = 7.6 Hz, 3H,  $CH_2CH_3$ ), 1.26 (d, J = 6.4 Hz, 3H, -CH(OTBDMS)CH<sub>3</sub>), 2.37 (q, J = 7.6 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 3.18 (dd, J = 3.7, 1.2 Hz, 1H, C<sub>3</sub>-H), 4.22 (dq, J = 3.7, 6.4 Hz, 1H, C<sub>1</sub>-H), 5.84 (d, J = 1.2 Hz, 1H, C<sub>4</sub>-H), 6.44 (br, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 67.9 MHz) δ -5.15 (SiCH<sub>3</sub>), -4.31 (SiCH<sub>3</sub>), 8.77 (-CH<sub>2</sub>CH<sub>3</sub>), 17.94 (-C(CH<sub>3</sub>)<sub>3</sub>), 22.32 (-CH(OTBDMS)CH<sub>3</sub>), 25.62 (-C(CH<sub>3</sub>)<sub>3</sub>),

# (1'R, 3R, 4R)-3-[1'-[(t-Butyldimethylsilyl)oxy]ethyl]-4-methoxy-

# (1'R, 3R, 4R)-3-[1'-[(t-Butyldimethylsilyl)oxy]ethyl]-4-ethyl-

27.43 (-CH2CH3), 64.01 (-CH(OTBDMS)CH3), 65.15 (C3), 75.15 (C4), 166.44 (NHC=O), 174.70 (-OC=OCH<sub>2</sub>CH<sub>3</sub>).

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# Chapter 3. Osmium-Catalyzed Oxidation of $\beta$ -Lactams with Peroxides.

# Introduction

The oxidation of organic substrates by using oxometal reagents, such as permanganate,1 manganese(IV) oxide,2 chromyl compounds,3 selenium(IV) oxide,4 ruthenium tetroxide,<sup>5</sup> and osmium tetroxide<sup>6</sup> are well known to organic chemists. These reagents have traditionally played an important role in organic synthsis because of their ability for selective oxygen transfer to a wide range of substrates under mild reaction conditions. Thus, a variety of oxometal complex-catalyzed oxidations have been developed for selective oxidations that can be carried out in both fields of laboratory and industry. Therefore, osmium tetroxide has been extensively used in organic chemistry as an oxidizing agent or catalyst to transformation of olefins into syn-1,2-diols as depicted in eq. 1.7 Particularly, asymmetric syn-dihydroxylation of olefins using osmium tetroxide gave excellent results.8

$$\begin{array}{c} R^2 \\ R^1 \\ R^4 \end{array} \xrightarrow{OsO_4} \\ R^2 \\ R^1 \\ R^4 \end{array} \xrightarrow{HOOH} \\ R^2 \\ R^1 \\ R^4 \end{array} (1)$$

Oxidation of  $\beta$ -lactams is of importance in view of synthesis of carbapenem and thiopenem antibiotics.<sup>9</sup> The author found that osmium-catalyzed oxidation of  $\beta$ -lactams with peroxides gives 4-acetoxy  $\beta$ -lactams highly efficiently (eq. 2).<sup>10</sup> This is the first example of the osmium-catalyzed oxidation of C-H bonds adjacent to the nitrogen of  $\beta$ lactams.



This oxidation reaction is different from the osmium tetroxide catalyzed oxidation, and can be considered to cytocrome P-450 type oxidation involving the oxoosmium species in similar manner to that of ruthenium-catalyzed oxidation.<sup>11</sup> It could be regarded that the present reaction will give a new advancement and development to organic chemistry concerning with osmium complexes.

osmium-catalyzed reactions.

The effect of oxidants has been examined for the oxidation of  $\beta$ -lactam 4. As shown in Table 2, peracetic acid was found to be the most effective oxidant among those examined, and other oxidants such as methyl ethyl ketone peroxide, m-chloroperbenzoic

# **Results and Discussion**

The osmium trichloride catalyzed oxidation of  $\beta$ -lactams with peracetic acid in acetic acid proceeds highly efficiently under mild reaction conditions. The oxidation of azetidin-2-one (1) is the representative result. To a mixture of 1 (0.20 g, 2.8 mmol), anhydrous sodium acetate (0.23 g, 2.8 mmol), OsCl<sub>3</sub> (17 mg, 2 mol%) in acetic acid (2 ml) was added a 30% solution of peracetic acid in ethyl acetate (1.56 g, 6.2 mmol) dropwise with stirring at room temperature over a period of 2 h. After stirring for 3 h, the reaction mixture was poured into water and extracted with ethyl acetate. To decompose excess peracetic acid, the combined organic layer was washed with aqueous 5% sodium sulfite solution (20 ml) and dried over magnesium sulfate. Evaporation followed by column chromatography on silica gel (hexane/ethyl acetate, 1/1) gave 4acetoxyazetidin-2-one (2) (0.28 g, 2.2 mmol, 78%). The representative results of the formation of 4-acetoxyazetidin-2-ones are shown in Table 1. Various azetidin-2-ones (entries 1-6) can be converted into the corresponding 4-acetoxyazetidin-2- ones in good yields. The oxidation of (4S)-4-carboxyazetidin-2-one (3) gave racemic 2 accompanied by decarboxylation (entry 3). It is noteworthy that the Kolbe type electrolysis of 4carboxyazetidin-2-one gives  $\beta$ -lactam 2.<sup>12</sup> Importantly, (1'R, 3S)-3-[1'-[(tbutyldimethylsilyl)oxy]ethyl]azetidin-2-one (4)<sup>13</sup> can be readily converted into (1'R, 3R, 4R)-4-acetoxy-3-[1'-[(t-butyldimethylsilyl)oxy]ethyl]azetidin-2-one (5) (entry 5), which is a versatile key intermediate for the synthesis of thienamycin and other important carbapenem antibiotics.<sup>9</sup> The <sup>1</sup>H NMR and HPLC analyses show that the diastereomeric excess of 5 is over 99%. The preferential formation of the trans-isomer is due to the steric interaction between the acetoxy group and the substituent at C-3 position. Actually, the oxidation of (1'R, 3S)-3-[1'-(hydroxy)ethy] azetidin-2-one (6) afforded a mixture of trans-7 and cis-8 (ca. 4:1) (entry 6). On the other hands, the ruthenium-catalyzed oxidation of hydroxy lactam 6 gave a complex mixture, because the hydroxy group is also oxidized under the reaction conditions. Therefore, osmium catalysis could be considered to be more chemoselective than ruthenium catalysis. This result is an example of the differences between the ruthenium-catalyzed reactions and the

entry	substrate	products <sup>b</sup>	yield, <sup>c</sup> %
1	NH 1	OAc NH 2	78
2	O NH	OAC CH <sub>3</sub> OH	76
3	NH 3	NH 2	77
4	NH O	OAC CO <sub>2</sub> CH <sub>3</sub>	48
<i>t</i> -	Bu(CH <sub>3</sub> ) <sub>2</sub> SiO	t-Bu(CH <sub>3</sub> ) <sub>2</sub> SiO OAc OH 5	92
5		HO HO HO DAG	43 <sup>d</sup>

Table 1. Conversion of Azetidin-2-ones into 4 Acoto

<sup>a</sup>The reaction was carried out as described in the text. <sup>b</sup>The structure of the product has been determined on the basis of analytical and IR, NMR, and mass spectral data. <sup>c</sup>Isolated yield. <sup>d</sup>A mixture of two diastereomers (7:8, 4:1)

entry	oxidant <sup>b</sup>	yield, <sup>c</sup> %
1	CH <sub>3</sub> CO <sub>3</sub> H	92
2	<i>m</i> CPBA <sup><i>d</i></sup>	73
3	PhI(OAc) <sub>2</sub>	70
4	PhIO	67
5	MEKP <sup>e</sup>	70

<sup>a</sup>To a mixture of 4 (200 mg, 0.87 mmol), OsCl<sub>3</sub> (1~3 mol %), anhydrous AcONa (72 mg, 0.87 mmol) in AcOH (2 ml) was added an oxidant (1.91 mmol) dropwise with stirring at room temperature over a period of 2h. <sup>b</sup>2.2 equivalents were used. <sup>c</sup>Isolated yield of (4b). <sup>d</sup>mCPBA; m-chloroperbenzoic acid. <sup>e</sup>MEKP; methyl ethyl ketone peroxide.

oxidation reaction.

of catalytic amount and stoichiometric of OsO<sub>4</sub>.

of β-lactams with tert-butyl peracetate.<sup>14</sup>

**Table 2.** Effect of Various Oxidants for the Oxidation of  $\beta$ -Lactam 4<sup>*a*</sup>.

acid, PhIO, and PhI(OAc)<sub>2</sub> gave good results. Oxidants such as t-BuOOH, H<sub>2</sub>O<sub>2</sub>, NaOCl, PhCO<sub>3</sub>-t-Bu, and N-methylmorpholin N-oxide are ineffective for the present

Osmium trichloride has proved to be the most effective catalyst, although other osmium complexes such as  $Os_3(CO)_{12}$ ,  $Os(NH_4)_2Cl_2$ , and  $OsH_2Cl_6$  are ineffective. It is noteworthy that no reaction takes place upon treatment with peracetic acid in the presence

It is noteworthy that cobalt complexes such as  $CoCl_2$ ,  $Co(OAc)_2$ , and  $Co(acac)_2$ can be utilized as catalysts under the same reaction conditions, although their catalytic activity is not so high. The oxidations of  $\beta$ -lactams of 1, 3, and 4 by using cobalt dichloride (10 mol%) as a catalyst gave the corresponding 4-acetoxyazetidin-2-ones in 62%, 11%, and 41% yields, respectively. The reaction mechanism is considered to involve acyloxy radical derived from homolytic cleavage of O-O bond of peracetic acid performed by cobalt complexes in a similar manner to the cupper-catalyzed acetoxylation

The present oxidation is different from the  $OsO_4$  catalyzed oxidation<sup>7</sup>, and can be rationalized by assuming an intermediacy of oxoosmium (V) species, which may have a similar function to oxoruthenium (IV) complexes.<sup>11</sup> However, it is recognized that the mechanism of the osmium-catalysis is different from that of ruthenium-catalysis. In the ruthenium-catalyzed reaction, the intermediacy of an acyliminium ion could be explained by the exclusive formation of (1'R, 3R, 4R)-4-dichloroacetoxy-3-[1'-[(t-butyldimethylsilyl)oxy]ethyl]azetidin-2-one (9) upon oxidation of  $\beta$ -lactam 4 in a mixture of dichloroacetic acid and acetic acid (1:1) (eq.3).



On the other hands, the osmium-catalyzed oxidation of  $\beta$ -lactam 4 gives a mixture of 4-dichloroacetoxy  $\beta$ -lactam (9) and 4-acetoxy  $\beta$ -lactam (5) (2:1) (eq 4).



Furthermore, in order to dissolve the discrepancy between the rutheniumcatalyzed reaction and the osmium-catalyzed reaction, competitive reactions upon oxidation of 4 were carried out in a 1:10 mixture of  $XCH_2CO_2H$  (ClCH<sub>2</sub>CO<sub>2</sub>H, MeOCH<sub>2</sub>CO<sub>2</sub>H, PhCH<sub>2</sub>CO<sub>2</sub>H, and CH<sub>3</sub>CH<sub>2</sub>CO<sub>2</sub>H) and CH<sub>3</sub>CO<sub>2</sub>H. Relative rate constants of kX/kH were obtained by means of <sup>1</sup>H NMR analysis as shown in Table 3.

**Table 3.** Relative Rate Constants for the Osmium-Catalyzed Oxidation of **4** with AcOOH in a mixture of AcOH and XCH<sub>2</sub>CO<sub>2</sub>H (10:1).

X in XCH <sub>2</sub> CO <sub>2</sub> H	pka value	k <sub>X</sub> / k <sub>H</sub> (x 10)	
		Osmium	Ruthenium
CI	2.9	0.952	4.09
MeO	3.5	0.889	2.19
PhCH <sub>2</sub>	4.3	0.931	1.24
CH <sub>3</sub> CH <sub>2</sub>	4.9	0.704	0.41



Figure 1. A Comparison of Ru and Os Catalysts in the Competitive Oxidation Reactions of  $\beta$ -Lactam 4.

In case of the ruthenium-catalyzed reaction, a remarkable pKa dependence was observed as illustrated in Figure 1. In contrast, the osmium-catalyzed reaction under the same reaction conditions gave, independent the pKa values of XCH2CO2H, a 1:10 mixture of XCH<sub>2</sub>CO<sub>2</sub>-lactam and CH<sub>3</sub>CO<sub>2</sub>-lactam. It could be suggested that the osmium catalyst has a radical character and the reaction proceeds via a radical intermediate.<sup>15</sup> Thus, oxoruthenium complex undergoes two-electron oxidation to give a four-membered acyliminium ion; however, oxoosmium species abstracts the hydrogen atom from the  $\beta$ -lactam at C-4 position to give a radical intermediate tightly coupled with osmium. Solvolysis reaction with acetic acid takes place with replacement of 4-acetoxy  $\beta$ -lactam from the complex to give osmium (III) species and water. It is supported that in the competitive reaction the cobalt-catalyzed oxidation reaction, which has a strong radical character, shows the same tendency to the osmium-catalyzed oxidation reaction. Thus, the product distribution is dependent on the concentrations of XCH2CO2H and CH<sub>3</sub>CO<sub>2</sub>H. The catalytic cycle is thus completed as illustrated in Scheme 1.





In conclution, the osmium complex reacts with peracetic acid to give an oxoosmium (V) species, which undergoes abstraction of a hydrogen atom from β-lactams at C-4 position to give a radical intermediate tightly coupled with osmium. Finally, the solvolysis reaction with acetic acid gives the corresponding β-acetoxy β-lactams, water, and osmium (III) species. Ruthenium catalysis and osmium catalysis have some similarities, but the differences arise from the choice of reaction media. These effects are of considerable importance interms of the known and possible redox chemistry of the metal-oxo species.

General. <sup>1</sup>H NMR spectra were recorded on a JEOL PMX-60 SI (<sup>1</sup>H, 60 MHz), a JEOL JNM-GSX 270 (1H, 270 MHz; 13C, 67.9 MHz), and a BRUKER AM-400 (<sup>1</sup>H, 400 MHz; <sup>13</sup>C, 100 MHz) spectrometers. IR spectra were recorded on a Hitachi 215 spectrometer, a JASCO IR-810, and a Shimadzu FTIR-4100 spectrometers. Mass spectra were obtained on a JEOL JMX-DX 303 mass spectrometer and a HITACHI M-80B spectrometer. Elemental analyses were performed on a Yanagimoto MT-2 CHN corder. Mass spectra were measured on a Hitachi Model RSM-4 mass spectrometer. Exact mass spectra were measured on a JEOL Model JMS-DX-303 mass spectrometer. All melting points were measured on a Yanagimoto micro melting point apparatus. HPLC analyses were performed on a JASCO TRI ROTAR-VI system with a JASCO UVIDEC-100-VI UV detector by using a 250 mm x 4.6 mm analytical column packed with Chiralpack AS (Daicel Chemical Industry, Ltd.). Optical rotations were measured on a JASCO DIP-360 polarimeter.

procedure above described in Chapter 3.

# **Experimental Section**

Materials. Acetic acid, ethyl acetate, hexane, anhydrous sodium acetate, anhydrous magnesium sulfate, OsCl<sub>3</sub>•xH<sub>2</sub>O, Os<sub>3</sub>(CO)<sub>12</sub>, Os(NH4)<sub>2</sub>Cl<sub>2</sub>, OsH<sub>2</sub>Cl<sub>6</sub>, methyl ethyl ketone peroxide, m-chloroperbenzoic acid, PhIO, PhI(OAc), t-BuOOH, H<sub>2</sub>O<sub>2</sub>, NaOCl, PhCO<sub>3</sub>-t-Bu, N-methylmorpholin N-oxide, and azetidin-2-one were all commercially available and used without further purification. 4-Methylazetidin-2-one, (4S)-4-carboxyazetidin-2-one (3), (4S)-4-methoxycarbonylazetidin-2-one, (1'R,3S)-3-[1'-[(tert-butyldimethylsilyl)oxy]ethyl]azetidin-2-one (4), and (1'R,3S)-3-[1'-[(hydroxyoxy)ethyl]azetidin-2-one (6) were prepared by according to the literatur's

General Procedure for the Osmium-Catalyzed Oxidation of  $\beta$ -

Lactams with Peracetic acid. A 20 mL three-necked round-bottomed flask equipped with a thermometer, a magnetic stirring bar and a pressure equalizing dropping funnel connected to a three-way stopcock was charged with β-lactam (1.0 mmol), OsCl<sub>3</sub>. nH<sub>2</sub>O (0.01 mmol, 2 mol%), anhydrous sodium acetate (1.0 mmol) and acetic acid (2 mL) under argon atmosphere. The mixture was stirred at room temperature and 30% solution of peracetic acid in EtOAc (2.2 mmol) was added dropwise over a period of 2 h. After stirring for 3 h, the reaction mixture was poured into water (80 mL) and extracted with an appropriate solvent. To decompose excess peracetic acid, the combined extracts were washed with aqueous 5% sodium sulfite solution (20 mL), brine (50 mL), and dried over MgSO<sub>4</sub>. The solvent was removed under reduced pressure, and purification by column chromatography on SiO<sub>2</sub> with appropriate eluents gave the corresponding 4acetoxy  $\beta$ -lactam. The representative results are shown in Table 1.

4-Acetoxyazetidin-2-one (2): The reaction was carried out according to the general procedure. Extraction with EtOAc (200 mL) and purification by column chromatography on SiO<sub>2</sub> (hexane/EtOAc, 2/1) gave 4-acetoxy β-lactam 2 in 78% (starting from compound 1), and 77% yield (starting from compound 3). Colorless oil; IR (neat) 3250 (NH), 3020, 2970, 1765 (ester C=O), 1740 (β-lactam C=O), 1410, 1380, 1240, 1110, 1043, 990, 960 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 2.13 (s, 3H, -OCOCH<sub>3</sub>), 3.00 (ddd, J = 15.3, 1.4, 0.5 Hz, 1H,-HCHCH(OAc)-), 3.26 (ddd, J = 15.3, 4.1, 0.5 Hz, 1H, -HCHCH(OAc)-), 5.84 (dd, J = 4.1, 1.4 Hz, 1H, -HCHCH(OAc)-), 7.02 (b, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 20.7 (COCH<sub>3</sub>), 44.9 (CH<sub>2</sub>), 73.0 (CH), 165.6 (NHC=O), 170.9 (OC=O).

4-Acetoxy-4-methylazetidin-2-one: The reaction was carried out according to the general procedure. Extraction with EtOAc (200 mL) and purification by column chromatography on SiO<sub>2</sub> (hexane/EtOAc, 2/1) gave 4-acetoxy-4-methylazetidin-2one in 76% yield. Colorless oil; IR (neat) 3350 (NH), 1750 (ester C=O), 1720 (Blactam C=O), 1360, 1265, 1165, 1020 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>2</sub>, 270 MHz) δ 1.83 (s, 3H, -CCH<sub>3</sub>), 2.07 (s, 3H, OCOCH<sub>3</sub>), 3.00 (d, J = 14.9 Hz, 1H, -HCHCCH<sub>3</sub>(OAc)-), 3.17 (d, J = 14.9 Hz, 1H, -HCHCCH<sub>3</sub>(OAc)-), 7.17 (b, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 67.9 MHz) δ 21.5 (CCH<sub>3</sub>), 22.9 (OCOCH<sub>3</sub>), 51.0 (CH<sub>2</sub>), 84.7 (NHC(OAc)CH<sub>3</sub>), 165.1 (NHC=O), 170.8 (OC=O).

4-Acetoxy-4-methoxycarbonylazetidin-2-one: The oxidation of (4S)-4-methoxycarbonylazetidin-2-one was carried out according to the general procedure.

(c 1.08, CHCl<sub>3</sub>).

(OCOCH<sub>3</sub>).; [a]<sub>D</sub><sup>25</sup> +50.8 (*c* 0.98, CHCl<sub>3</sub>).

(1'R, 3R, 4R)-4-Acetoxy-3-[1'-(hydroxy)ethyl]azetidin-2-one (7) and (1'R, 3R, 4S)-4-Acetoxy-3-[1'-(hydroxy)ethyl]azetidin-2-one (8): The reaction was carried out according to the general procedure. Extraction with EtOAc (200 mL) and purification by column chromatography on SiO<sub>2</sub> (hexane/ EtOAc, 3/1) gave a mixture of 7 and 8 in 43% yield. The ratio of the mixture was determined by means of <sup>1</sup>H NMR analysis on crude reaction mixture (proton relaxation time was adjusted to 30 sec.). trans-7: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz)  $\delta$  1.36 (d, J = 6.5 Hz, 3H, -CH(OH)CH<sub>3</sub>), 2.15 (s, 3H, -OCOCH<sub>3</sub>), 3.25 (dd, J = 5.7, 1.3 Hz, 1H, -CHC=O), 4.24 (dq, J = 6.5, 5.7 Hz, 1H, -CH(OH)CH<sub>3</sub>), 5.84 (d, J = 1.3 Hz, 1H, -NHCH(OAc)-), 6.63 (b, 1H, NH). cis-8: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 1.44 (d, J = 6.4 Hz, 3H, -CH(OH) CH<sub>3</sub>), 2.20 (s, 3H, -OCOCH<sub>3</sub>), 3.41 (ddd, J = 9.4, 4.2, 2.4

Extraction with EtOAc (200 mL) and purification by column chromatography on SiO<sub>2</sub> (hexane/EtOAc, 2/1) gave 4-Acetoxy-4-methoxycarbonylazetidin-2-one in 48% yield. Colorless oil, IR (neat) 3300 (NH), 3030, 1784 (ester C=O), 1750 (β-lactam C=O), 1439, 1371, 1304, 1246, 1196, 1141, 1105, 1041, 978, 916 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 2.17 (s, 3H, OCOCH<sub>3</sub>), 3.26 (dd, J = 14.9, 0.7 Hz, 1H,-HCH-), 3.33 (dd, J = 14.9, 2.4 Hz, 1H,-HCH-), 3.83 (s, 3H, -CO<sub>2</sub>CH<sub>3</sub>), 7.02 (b, 1H, NH). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 67.9 MHz) & 20.5 (COCH<sub>3</sub>), 49.4 (COCH<sub>2</sub>), 53.6 (OCH<sub>3</sub>), 80.4 (NHC(OAc)CO<sub>2</sub>CH<sub>3</sub>), 163.9 (NHC=O), 167.5 (CO<sub>2</sub>CH<sub>3</sub>), 170.9 (OC=O); [α]<sub>D</sub><sup>23</sup> -7.04

# (1'R, 3R, 4R)-4-Acetoxy-3-[1'-[(tert-buthyldimethylsilyl)oxy]-

ethyl]azetidin-2-one (5): The reaction was carried out according to the general procedure. Extraction with hexane (200 mL) and purification by column chromatography on SiO<sub>2</sub> (hexane/ EtOAc, 5/1) gave 5 in 92% yield as a colorless needles; mp 108.5 °C; IR (KBr) 3190 (NH), 2940, 2850, 1780 (ester C=O), 1750 (β-lactam C=O), 1240, 1160, 1140, 1080, 1040, 940 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 0.08 (s, 3H, SiCH<sub>3</sub>), 0.09 (s, 3H, SiCH<sub>3</sub>), 0.88 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.27 (d, J = 6.4 Hz, 3H, -(t-BuMe<sub>2</sub>SiO)CHCH<sub>3</sub>), 2.11 (s, 3H, -OCOCH<sub>3</sub>), 3.19 (dd, J = 3.5, 1.3 Hz, COCH), 4.23 (dq, J = 3.5, 6.4 Hz, -(t-BuMe<sub>2</sub>SiO)CHCH<sub>3</sub>), 5.84 (d, J = 1.3 Hz, CHNH), 6.40 (b, 1H, NH).; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 67.9 MHz) δ -5.2 (SiCH<sub>3</sub>), -4.3 (SiCH<sub>3</sub>), 17.9 (SiC(CH<sub>3</sub>)<sub>3</sub>), 20.8 (-(*t*-BuMe<sub>2</sub>SiO)CHCH<sub>3</sub>), 22.3 (OCOCH<sub>3</sub>), 25.7 (SiC(CH<sub>3</sub>)<sub>3</sub>), 64.0 (CH), 65.2 (-(t-BuMe<sub>2</sub>SiO)CHCH<sub>3</sub>), 75.2 (CH(OAc)), 166.4 (NHC=O), 171.2 Hz, 1H, -CHC=O), 4.35 (dq, *J* = 9.4, 6.4 Hz, 1H, -CH(OH)CH<sub>3</sub>), 5.93 (d, *J* = 4.2 Hz, 1H, -NHCH(OAc)-), 6.63 (b, 1H, NH).

Catalytic Activity of Various Osmium Complexes for the Oxidation of  $\beta$ -Lactam (4) with Peracetic Acid: A 20 mL three-necked round-bottomed flask equipped with a thermometer, a magnetic stirring bar and a pressure equalizing dropping funnel connected to a three-way stopcock was charged with (1'*R*,3*S*)-3-[1'-[(*tert*buthyldimethylsilyl)oxy]ethyl]azetidin-2-one (4) (100 mg, 0.44 mmol), catalyst (2 mol%), anhydrous sodium acetate (36 mg, 0.44 mmol) and acetic acid (2 mL) under argon atmosphere. The mixture was stirred at room temperature and 30% solution of peracetic acid in EtOAc (246 mg, 0.97 mmol) was added dropwise over a period of 2 h. After stirring for 3 h, the reaction mixture was poured into water (80 mL) and extracted three times with 100mL of hexane. To decompose excess peracetic acid, the combined extracts were washed with aqueous 5% sodium sulfite solution (20 mL), brine (50 mL), and dried over MgSO<sub>4</sub>. The solvent was removed under reduced pressure, and purification by column chromatography on SiO<sub>2</sub>.(hexane/EtOAc, 5/1) gave (1'*R*,3*R*,4*R*)-4-acetoxy-3-[1'-[(*tert*-butyldimethylsilyl)oxy]ethyl]azetidin-2-one (**5**).

Effect of Various Oxidants for the Osmium-Catalyzed Oxidation of  $\beta$ -lactam (4): A 20 mL three-necked round-bottomed flask equipped with a thermometer, a magnetic stirring bar and a pressure equalizing dropping funnel connected to a three-way stopcock was charged with (1'*R*,3*S*)-3-[1'-[(*tert*-buthyldimethylsilyl)oxy]ethyl]azetidin-2-one (4) (100 mg, 0.44 mmol), catalyst (2 mol%), anhydrous sodium acetate (36 mg, 0.44 mmol) and acetic acid (2 mL) under argon atmosphere. The mixture was stirred at room temperature and 30% solution of peracetic acid in EtOAc (246 mg, 0.97 mmol) was added dropwise over a period of 2 h. After stirring for 3 h, the reaction mixture was poured into water (80 mL) and extracted three times with 100 mL of hexane. To decompose excess peracetic acid, the combined extracts were washed with aqueous 5% sodium sulfite solution (20 mL), brine (50 mL), and dried over MgSO<sub>4</sub>. The solvent was removed under reduced pressure, and purification by column chromatography on SiO<sub>2</sub>.(hexane/EtOAc, 5/1) gave (1'*R*,3*R*,4*R*)-4-acetoxy-3-[1'-[(*tert*-butyldimethylsilyl)oxy]ethyl]-azetidin-2-one (5). The representative results were listed in Table 2.

Competitive Reaction for the Oxidation of 4 in a 1:1 Mixture of Acetic acid and Dichloroacetic acid. A 20 mL three-necked round-bottomed flask equipped with a thermometer, a magnetic stirring bar and a pressure equalizing dropping funnel connected to a three-way stopcock was charged with  $\beta$ -lactam 4 (229 mg, 1.0 mmol), OsCl<sub>3</sub>·xH<sub>2</sub>O (6 mg, 2 mol%), anhydrous sodium acetate (41 mg, 0.5 mmol), dichloroacetic acid (1.29 g, 10 mmol), and acetic acid (0.6 g, 10 mmol) under argon atmosphere. The mixture was stirred at room temperature and 30% solution of peracetic acid in EtOAc (0.56 g, 2.2 mmol) was added dropwise to the mixture over a period of 2 h. After stirring for 3 h, the reaction mixture was poured into water (100 mL) and extracted twice with hexane (100 mL). To decompose excess peracetic acid, the combined extracts were washed with aqueous 5% sodium sulfite solution (20 mL), brine (50 mL), and dried over MgSO4. Evaporation of the solvent under reduced pressure gave a mixture of (1'R, 3R, 4R)-3-[1'-[(t-butyldimethylsilyl)oxy]ethyl]-4-dichloroacetoxyazetidin-2-one (9) and 5. Ratio of products was determined to be 2:1 (9:5) by mean of <sup>1</sup>H NMR analysis (proton relaxation time is adjusted to 30 sec.). Analytical sample of 9 was obtained by recrystallization from hexane. 9: Colorless needles; mp 118 °C; IR (KBr) 3150 (NH), 2960, 2940, 2860, 1790, 1765 (ester C=O), 1740 (amide C=O), 1470, 1380, 1300, 1260, 1150, 1080, 1040, 1010, 940 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 0.07 (s, 3H, SiCH<sub>3</sub>), 0.08 (s, 3H, SiCH<sub>3</sub>), 0.87 (s, 9H, -C(CH<sub>3</sub>)<sub>3</sub>), 1.28 (d, J = 6.4 Hz, 3H, -CH(OTBDMS)CH<sub>3</sub>), 3.32 (dd, J = 3.3, 1.2 Hz, 1H, C<sub>3</sub>-H), 4.25 (dq, J = 3.3, 6.4 Hz, 1H. -CH(OTBDMS)CH<sub>3</sub>), 5.96 (s, 1H, -C=OCHCl<sub>2</sub>), 6.00 (d, J = 1.2 Hz, 1H, C<sub>4</sub>-H), 6.50 (br, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ -5.2 (SiCH<sub>3</sub>), -4.3 (SiCH<sub>3</sub>), 18.1 (-C(CH<sub>3</sub>)<sub>3</sub>), 22.5 (-CH(OTBDMS)CH<sub>3</sub>), 25.6 (-C(CH<sub>3</sub>)<sub>3</sub>), 64.1 (-CHCl<sub>2</sub>), 64.2 (-CH(OTBDMS)CH<sub>3</sub>), 66.3 (C<sub>3</sub>), 78.5 (C<sub>4</sub>), 165.6 (NHC=O), 166.6 (-OC=OCHCl<sub>2</sub>). Anal. Calcd for C13H23NO4SiCl2: C, 43.93; H, 6.53; N, 3.94; Cl, 19.70. Found: C, 43.90; H, 6.83; N, 4.02; Cl, 19.58. [α]<sub>D</sub><sup>25.5</sup>+34.2 (*c* 1.00, CHCl<sub>3</sub>).

Competitive Reaction for the Oxidation of 4 in a Mixture of AcOH and XCH<sub>2</sub>CO<sub>2</sub>H (10:1). A 20 mL three-necked round-bottomed flask equipped with a thermometer, a magnetic stirring bar and a pressure equalizing dropping funnel connected to a three-way stopcock was charged with  $\beta$ -lactam 4 (1.0 mmol), OsCl<sub>3</sub>· 3H<sub>2</sub>O (0.02 mmol, 2 mol%), anhydrous sodium acetate (1.0 mmol), XCH<sub>2</sub>CO<sub>2</sub>H (10 mmol), and acetic acid (100 mmol) under argon atmosphere. The mixture was stirred at room temperature and 30% solution of peracetic acid in EtOAc (1 mmol) was added dropwise to the mixture over a period of 2 h. After stirring for 3 h, the reaction mixture was poured into water (100 mL) and extracted twice with hexane (100 mL). To

decompose excess peracetic acid, the combined extracts were washed with aqueous 5% sodium sulfite solution (20 mL), brine (50 mL), and dried over MgSO<sub>4</sub>. Evaporation of the solvent under reduced pressure gave a mixture of 4-acetoxy β-lactam 5 and 4-XCH<sub>2</sub>CO<sub>2</sub>-β-lactam. Relative rate constants of kX/kH were determined by means of <sup>1</sup>H NMR analysis (proton relaxation time is adjusted to 30 sec.). The representative results were summarized in Table 3 and visualized in Figure 1.

(1'R, 3R, 4R)-3-[1'-[(t-Butyldimethylsilyl)oxy]ethyl]-4-ethylcarbonyloxyazetidin-2-one: An analytical sample of the title azetidinine was obtained by column chromatography (silica gel, hexane/ethyl acetate, 5/1) followed by recrystallization from hexane to gave the title azetidinone as a colorless needles; mp 85  $\infty$ ; IR (KBr) 3150 (NH), 2930, 2860, 1780 (ester C=O), 1740 (amide C=O), 1460, 1380, 1260, 1160, 1130, 1070, 1040, 950, 830 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 0.06 (s, 3H, SiCH<sub>3</sub>), 0.08 (s, 3H, SiCH<sub>3</sub>), 0.87 (s, 9H,  $-C(CH_3)_3$ ), 1.16 (t, J = 7.6 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>), 1.26 (d, J = 6.4 Hz, 3H, -CH(OTBDMS)CH<sub>3</sub>), 2.37 (q, J = 7.6 Hz, 2H,  $CH_2CH_3$ ), 3.18 (dd, J = 3.7, 1.2 Hz, 1H,  $C_3$ -H), 4.22 (dq, J = 3.7, 6.4 Hz, 1H,  $C_1$ -**H**), 5.84 (d, J = 1.2 Hz, 1H, C<sub>4</sub>-**H**), 6.44 (br, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 67.9 MHz) δ -5.15 (SiCH<sub>3</sub>), -4.31 (SiCH<sub>3</sub>), 8.77 (-CH<sub>2</sub>CH<sub>3</sub>), 17.94 (-C(CH<sub>3</sub>)<sub>3</sub>), 22.32 (-CH(OTBDMS)CH<sub>3</sub>), 25.62 (-C(CH<sub>3</sub>)<sub>3</sub>), 27.43 (-CH<sub>2</sub>CH<sub>3</sub>), 64.01 (-CH(OTBDMS)CH<sub>3</sub>), 65.15 (C<sub>3</sub>), 75.15 (C<sub>4</sub>), 166.44 (NHC=O), 174.70 (- $OC=OCH_2CH_3).$ 

(1'R, 3R, 4R)-3-[1'-[(t-Butyldimethylsilyl)oxy]ethyl]-4-methoxyacetoxyazetidin-2-one: An analytical sample of the title azetidinone was obtained by column chromatography (silica gel, hexane/ethyl acetate, 5/1) followed by recrystallization from hexane to gave the title azetidinone as a colorless needles; mp 80 °C; IR (KBr) 3119 (NH), 2959, 2930, 1782 (ester C=O), 1761 (amide C=O), 1734, 1377, 1255, 1196, 1170, 1132, 1074, 1053, 972, 835 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 0.07 (s, 3H, SiCH<sub>3</sub>), 0.09 (s, 3H, SiCH<sub>3</sub>), 0.87 (s, 9H, -C(CH<sub>3</sub>)<sub>3</sub>), 1.26 (d, J = 6.4Hz, 3H, -CH(OTBDMS)CH<sub>3</sub>), 3.22 (dd, J = 3.4, 1.2 Hz, 1H, C<sub>3</sub>-H), 4.07 (s, 2H, -C=OCH<sub>2</sub>O-), 4.22 (dq, J = 3.4, 6.4 Hz, 1H, C<sub>1</sub>'-H), 5.94 (d, J = 1.2 Hz, 1H, C<sub>4</sub>-H), 6.44 (br, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 67.9 MHz) δ -5.18 (SiCH<sub>3</sub>), -4.35 (SiCH<sub>3</sub>), 17.91 (-C(CH<sub>3</sub>)<sub>3</sub>), 22.30 (-CH(OTBDMS)CH<sub>3</sub>), 25.68 (-C(CH<sub>3</sub>)<sub>3</sub>), 59.49 (-CH2OCH3), 63.89 (-CH(OTBDMS)CH3), 65.46 (C3), 69.53 (-CH2OCH3), 75.66 (C<sub>4</sub>), 166.05 (NHC=O), 170.51 (-OC=OCH<sub>2</sub>CH<sub>3</sub>).

# (1'R, 3R, 4R)-3-[1'-[(t-Butyldimethylsilyl)oxy]ethyl]-4-phenyl-

(aromatic), 133.1 (aromatic), 166.4 (NHC=O), 171.9 (-OC=OCH<sub>2</sub>CH<sub>3</sub>).

ethyl]azetidin-2-one: An analytical sample of the title azetidinone was obtained by column chromatography (silica gel, hexane/ethyl acetate, 5/1) followed by recrystallization from hexane gave the title azetidinone as a colorless needles; mp 109 °C; IR (KBr) 3200 (NH), 2960, 2940, 2850, 1780 (ester C=O), 1750 (amide C=O), 1470, 1380, 1300, 1260, 1140, 1080, 1040, 1010, 950 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 0.07 (s, 3H, SiCH<sub>3</sub>), 0.08 (s, 3H, SiCH<sub>3</sub>), 0.87 (s, 9H, -C(CH<sub>3</sub>)<sub>3</sub>), 1.27 (d, J = 6.3Hz, 3H, -CH(OTBDMS)CH<sub>3</sub>), 3.24 (dd, J = 3.3, 1.2 Hz, 1H, C<sub>3</sub>-H), 4.10 (s, 2H, -C=OCH<sub>2</sub>Cl), 4.24 (dq, J = 3.3, 6.3 Hz, 1H, -CH(OTBDMS)CH<sub>3</sub>), 5.94 (d, J = 1.2 Hz, 1H, C<sub>4</sub>-H), 6.44 (br, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ -5.2 (SiCH<sub>3</sub>), -4.3 (SiCH<sub>3</sub>), 17.9 (-C(CH<sub>3</sub>)<sub>3</sub>), 22.3 (-CH(OTBDMS)CH<sub>3</sub>), 25.7 (-C(CH<sub>3</sub>)<sub>3</sub>), 40.5 (-CH<sub>2</sub>Cl), 63.8(-CH(OTBDMS)CH<sub>3</sub>), 65.6 (C<sub>3</sub>), 76.8 (C<sub>4</sub>), 166.0 (NHC=O), 167.5 (-OC=OCH<sub>2</sub>Cl).

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acetoxyazetidin-2-one: An analytical sample of the title azetidinone was obtained by column chromatography (silica gel, hexane/ethyl acetate, 8/1) followed by recrystallization from hexane to gave the title azetidinone as a colorless needles; mp 61 °C; IR (KBr) 3200 (NH), 2950, 2850, 1780 (ester C=O), 1740 (amide C=O), 1460, 1370, 1320, 1250, 1130, 1070, 1000, 940, 830, 770 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 0.04 (s, 3H, SiCH<sub>3</sub>), 0.06 (s, 3H, SiCH<sub>3</sub>), 0.85 (s, 9H,  $-C(CH_3)_3$ ), 1.23 (d, J = 6.4Hz, 3H, -CH(OTBDMS)CH<sub>3</sub>), 3.18 (dd, J=3.6, 1.2 Hz, 1H, C<sub>3</sub>-H), 3.66 (s, 2H, -C=OCH<sub>2</sub>Ph), 4.20 (dq, J = 3.4, 6.4 Hz, 1H, -CH(OTBDMS)CH<sub>3</sub>), 5.86 (d, J = 1.2Hz, 1H, C4-H), 6.48 (br, 1H, NH), 7.24-7.36 (m, 5H, aromatic); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 67.9 MHz) δ -5.2 (SiCH<sub>3</sub>), -4.3 (SiCH<sub>3</sub>), 17.9 (-C(CH<sub>3</sub>)<sub>3</sub>), 22.3 (-CH(OTBDMS)CH<sub>3</sub>), 25.6 (-C(CH<sub>3</sub>)<sub>3</sub>), 41.1 (C=OCH<sub>2</sub>Ph), 64.0 (-CH(OTBDMS)CH<sub>3</sub>), 65.3 (C<sub>3</sub>), 75.7 (C<sub>4</sub>), 127.4 (aromatic), 128.7 (aromatic), 129.2

# (1'R, 3R, 4R)-4-Chloroacetoxy-3-[1'-[(t-butyldimethylsilyl)oxy]-

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# Chapter 4. Ruthenium-Catalyzed Oxidation of $\beta$ -Lactams with Molecular Oxygen and Aldehydes.

# Introduction

The oxidation of organic compounds by molecular oxygen has been investigated for a long time, which also marked the beginning of the modern area of chemistry.1 Although the oxidation reactions of organic compounds with molecular oxygen are generally highly exothermic, they do not readily undergo spontaneous combustion in air, largely owing to the relatively high activation energies. In other words, it is often difficult to interrupt the reaction at the short stage of the most thermodynamically stable products.

The metal complex catalysis plays an important role in the control of selective and partial oxidation of a variety of organic substrates.<sup>2</sup> Indeed, the catalytic oxidations can be effectively employed in the laboratory-scale synthesis and which play an important role in the petrochemical processes.<sup>3</sup> Thus, the metal complex catalyzed oxidation by use of molecular oxygen, which is an abundant natural source and a briefly available oxidant, could be regarded to one of the ideal processes from the industrial point of view.

In recent years there has been considerable speculation concerning the nature of the active oxidant in iron-containing enzymes (cytochrome P-450), which mediate the incorporation of molecular oxygen into a variety of organic compounds.<sup>4</sup> During the course of our systematic study on the simulation of enzymatic function with metal complex catalysts,<sup>5</sup> the author has found that the ruthenium-catalyzed oxidation of  $\beta$ lactams with peroxides such as peracetic acid in acetic acid gives the corresponding 4acetoxy  $\beta$ -lactams,<sup>6</sup> which are the versatile key intermediates for the synthesis of carbapenem antibiotics.7 Sometimes these peroxides are containing undesirable materials and not always available. Therefore, the author studied on the effect of peroxide more precisely in order to get insight of the active species of the present oxidation reaction. As the result, the author found a convenient method for the oxidation of  $\beta$ -lactams without using peroxides. Here, the author describes the ruthenium trichloride catalyzed oxidation of  $\beta$ -lactams with molecular oxygen in the presence of acetaldehyde, acetic acid and sodium acetate in ethyl acetate at 40  $^{\circ}$ C to give the corresponding 4-acetoxy  $\beta$ -lactams highly efficiently as depicted in eq. 1.8

Some reports on the ruthenium-catalyzed oxidation of organic compounds by using molecular oxygen have been published.<sup>9</sup> The oxidation of organic compounds by molecular oxygen has a long history, however, this is the first example of the rutheniumcatalyzed oxidation of C-H bonds adjacent to nitrogen of B-lactams with molecular oxygen in the presence of aldehyde as the co-oxidant. These reactions give a great contribution to the synthesis of carbapenem antibiotics from the industrial point of view.

The representative results of the formation of 4-acetoxy  $\beta$ -lactams are listed in Table 1. Acetoxylation of  $\beta$ -lactams at C-4 position can be performed by the ruthenium trichloride catalyzed oxidation in the presence of acetaldehyde and acetic acid with molecular oxygen in ethyl acetate at 40 °C. In particular, the oxidation of (1'R, 3S)-3- $[1'-[(t-butyldimethylsilyl)oxy]ethyl]azetidin-2-one (1)^{10}$  gives (1'R, 3R, 4R)-4-acetoxy-3-[1'-[(t-butyldimethylsilyl)oxy]ethyl]azetidin-2-one (2) in 91% isolated yield in the same manner with above described oxidation reaction utilizing peroxides.

Under the present reaction conditions the catalytic activity of various ruthenium complexes has been examined for the oxidation of 1. As shown in Table 2, RuCl<sub>3</sub>.  $3H_2O$  gave the best results and the catalytic activity is in the order of RuCl<sub>3</sub> > RuBr<sub>3</sub> >  $Ru(OAc)_3$  > 1% Ru-graphite >  $Ru_3(CO)_{12}$ . As ruthenium is oxidized from Ru (III), its color changes from dark brown to dark red violet. However, ruthenium tetroxide (VIII) exhibits no catalytic activity under the present reaction conditions. Thus these results could suggest the generation of low valent oxoruthenium species. In addition, osmium trichloride exhibits the catalytic activity for the oxidation of 1 under the same reaction conditions to give 2 in 84% yield.

Next, the effect of an aldehyde was also examined for the oxidation of 1. Acetaldehyde gives the best result (entry 1), and other aliphatic aldehydes such as propionaldehyde (entry 2), hexylaldehyde (entry 3), and isobutyraldehyde (entry 5) gave good results (see Table 3). On the other hands, after the reaction, aldehydes were oxidized to the corresponding carboxylic acids respectively. Available aldehydes for the



# **Results and Discussion**

entry	substrate	product	yield, % <sup>a</sup>
t-Bu(	Me) <sub>2</sub> SiO <i>t</i> -Bu(N	Me) <sub>2</sub> SiO	
1	0 NH	NH 2	91
2	O 3	OAc NH 4	88
3	O 5 CH3	CH <sub>3</sub> OAc NH	72
4	NH 7	NH 8	87
5	NH 9	CO <sub>2</sub> Me CO <sub>2</sub> Me CO <sub>2</sub> Me NH 10	63

Table 1. Conversion of β-Lactams into 4-Acetoxy β-Lactams with Molecular Oxygen.

<sup>a</sup>Isolated yield.

entry	catalyst	mol%	conv. yield of 2, %b
1	RuCl <sub>3</sub>	5	$94(91^d)$
2	RuBr <sub>3</sub>	5	88
3	Ru(OAc) <sub>3</sub>	5	83
4	Ru <sub>3</sub> (CO) <sub>12</sub>	5	62
5	Ru(NO)Cl <sub>2</sub>	5	51
6	Ru(TPP)(CO)-THF <sup>c</sup>	5	9
7	RuCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>3</sub>	5	8
8	Ru(acac) <sub>3</sub>	5	3
9	RuO <sub>2</sub>	5	0
10	1%Ru-graphite	5	78
11	5%Ru-carbon	5	56
12	5%Ru-Aluminum	5	31
13	OsCl <sub>3</sub>	2	84
14	CoCl <sub>2</sub>	10	23

<sup>a</sup>To the mixture of β-lactam 1 (2 mmol), AcOH (1 ml), anhydrous AcONa (0.5 mmol), EtOAc (20 ml) and catalyst (5 mol%) was added CH<sub>3</sub>CHO (4 mmol) all at once at 40°C under O<sub>2</sub> atmosphere and stirred for 3 h. <sup>b</sup>Conversion yields of  $\beta$ -lactam 2 were determined by <sup>1</sup>H NMR (270MHz) analysis. <sup>c</sup>Tetraphenylporphine ruthenium carbonyl 1 to 1 complex with THF. <sup>d</sup>Isolated yield.

Table 3. The Effect of Various Aldel of  $\beta$ -Lactam 1 with Molecular Oxyger

entry	aldehyde	time (h)	conv. yield of 2, % <sup>b</sup>
1	acetaldehyde	3	94(91 <sup>c</sup> )
2	propionaldehyde	5	88
3	hexylaldehyde	5	90
4	decylaldehyde	5	57
5	isobutyraldehyde	5	86
6	cyclohexancarboxyaldehyde	5	78
7	benzaldehyde	5	31 <sup>d</sup>

<sup>a</sup>The mixture of β-lactam 1 (2 mmol), AcOH (1 ml), AcONa (0.5 mmol), EtOAc(20 ml) and RuCl<sub>3</sub> (0.01 mmol, 5 mol%) was replaced with O<sub>2</sub> and then heated to 40 °C. Keeping the temperature at 40 °C, an aldehyde (4 mmol) was added to the mixture all at once. <sup>b</sup>Conversions were determined by <sup>1</sup>H NMR (270 MHz) analysis. <sup>c</sup>Isolated yield. <sup>d</sup>28 equivalents of benzaldehyde was used and oxygen was bubbled into the mixture at 40 °C.

Table 2. Catalytic Activity of Various Metal Complexes for the Oxidation of  $\beta$ -Lactam 1

hydes	for	the	Ruthenium-Catalyzed	Oxidation
na				

entry	solvent	conv. yield of 2, % <sup>b</sup>
1	EtOAc	94(91 <sup>c</sup> )
2	CH <sub>3</sub> CN	67
3	dioxane	24
4	THF	21
5	hexane	16
6	toluene	8
7	acetone	4
8	acetic acid	4
9	CH <sub>2</sub> Cl <sub>2</sub>	2
10	DMF	0
11	DMSO	0

**Table 4.** The Solvent Effect for the Ruthenium-Catalyzed Oxidation of  $\beta$ -Lactam 1 with Molecular Oxygen<sup>*a*</sup>.

<sup>*a*</sup>The mixture of  $\beta$ -lactam 1 (2 mmol), AcOH (1 ml), AcONa (0.5 mmol), a solvent (20 ml) and RuCl<sub>3</sub> (0.01 mmol, 5 mol%) was replaced with O<sub>2</sub> and then heated to 40°C. Keeping the temperature at 40°C, acetaldehyde (4 mmol) was added to the mixture all at once. After stirring for additional 3 h, usual workup was carried out. <sup>*b*</sup>Conversions were determined by <sup>1</sup>H NMR (270 MHz) analysis. <sup>*c*</sup>Isolated yield.

present reaction are limited to aliphatic aldehydes because unsaturated aldehyde such as benzaldehyde can be used as the co-oxidant but require more drastic conditions (entry 7). Thus, oxygen was bubbled into the reaction mixture at 40  $^{\circ}$ C and much amount of benzaldehyde, 28 equivalent aldehyde to the substrate, is need to proceed the reaction.

The effects of various solvents have been examined for the oxidation of 1 under the same reaction conditions. The representative results are summarized in Table 4. The solvent effect is remarkable. Ethyl acetate was found to be the best solvent for the present oxidation reaction, acetonitrile can be used, but solvents such as DMF and DMSO could not be used because of their strong coordination ability to the ruthenium catalysts. Although acetic acid is an effective solvent for the ruthenium-catalyzed oxidation of  $\beta$ lactams with peroxides, it is disadvantageous for the present oxidation reaction. Sodium acetate is indispensable as a buffer in order to prevent the side reactions such as  $\beta$ -lactam ring opening reaction and deprotection of silyl group.



Furthermore, we have investigated the safety operation of the present reaction from the industrial point of view and found that the application of air to the present reaction can be attained. Thus, the ruthenium-catalyzed oxidation of **1** in the presence of acetic acid, sodium acetate and *iso*-butyraldehyde in ethyl acetate with bubbling air at  $30^{\circ}$  give **2** in 88% yield. In order to increase efficiency of the present reaction, air bubbling is essential because of low concentration of oxygen in air. In this case, acetaldehyde is found to be a disadvantageous co-oxidant because it can be easily removed by air bubbling due to its high volatility.

Various acyloxy groups can be introduced at the C<sub>4</sub>-position of  $\beta$ -lactams. The representative results are summarized in Table 5. Thus, the ruthenium-catalyzed oxidation of 1 in the presence of propionaldehyde and propionic acid under the same reaction conditions gave (1'R, 3R, 4R)-3-[1'-[(tert-butyldimethylsilyl)oxy]ethyl]-4ethylcarbonyloxyazetidin-2-one (2b) in 83% yield. Furthermore, the present reaction provides various 4-acyloxy β-lactams such as 4-dichloroacetoxy (2i), 4-chloroacetoxy (2g), 4-bromoacetoxy (2h), and 4-cyanoacetoxy  $\beta$ -lactam (2f) in good to excellent yields. Thus, the treatment of 1 in the presence of chloroacetic acid instead of acetic acid under the same reaction conditions gave (1'R, 3R, 4R)-3-[1'-[(tert-butyldimethylsilyl)oxy]ethyl]-4-chloroacetoxyazetidin-2-one (2g) in 92% yield respectively. These 4-acyloxy β-lactams are considered to be more reactive and useful intermediates of various carbapenem antibiotics rather than 4-acetoxy  $\beta$ -lactam 2, because the reactivity of the leaving group roughly correlates with the acidity of the corresponding acid.<sup>11</sup> This is supported by the experiment that in the substitution reaction of 2 with ketene silyl acetal the yield is 72%, while the yield obtained by using 4-cyanoacetoxy  $\beta$ -lactam (2f) is 92%.



2c : R=CH2(CH2)3CH3  $2d: R=CH_2OCH_3$  $2e: R=CH_2C_6H_5$ 2f : R=CH2CN  $2g: R=CH_2CI$ 2h: R=CH2Br 2i: R=CHCl2 2j : R=CHBr<sub>2</sub> 2k : R=2,4-(NO<sub>2</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>

Table 5.	Ruthenium-Cataly	zed Acyloxylation	of B-Lactam 1	with Molecular	Oxygen
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entry	carboxylic acid	aldehyde	product	yield, %b
1	CH <sub>3</sub> CH <sub>2</sub> COOH	CH <sub>3</sub> CH <sub>2</sub> CHO	2b	83
2	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> CH <sub>2</sub> COOH	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> CH <sub>2</sub> CHO	2c	61
3	CH3OCH2COOH	CH <sub>3</sub> CHO	2d	74
4	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> COOH	CH <sub>3</sub> CHO	2e	83
5	CNCH <sub>2</sub> COOH	CH <sub>3</sub> CHO	2f	81
6	CICH <sub>2</sub> COOH	CH <sub>3</sub> CHO	2g	92
7	BrCH <sub>2</sub> COOH	CH <sub>3</sub> CHO	2h	78
8	Cl <sub>2</sub> CH <sub>2</sub> COOH	CH <sub>3</sub> CHO	2i	70 <sup>c</sup>
9	Br <sub>2</sub> CH <sub>2</sub> COOH	CH <sub>3</sub> CHO	2j	65 <sup>c</sup>
10	2,4-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> COOH	CH <sub>3</sub> CHO	2k	54 <sup>c</sup>

<sup>a</sup>The mixture of RuCl<sub>3</sub>•3H<sub>2</sub>O (5 mol%), carboxylic acid (10 mmol), AcONa (0.5 mmol), β-lactam 1 (2 mmol) and EtOAc (20 mL) was stirred under O<sub>2</sub> atmosphere at 40 °C. Keeping the temperature at 40 °C, an aldehyde (5 mmol) was added to the mixture all at once and the resulting mixture was stirred for 3 h. <sup>b</sup>Isolated yield. <sup>c</sup>Recrystalization from hexane.

When the substrate 1 was added to the solution which was obtained by treatment of acetaldehyde with molecular oxygen in the presence of ruthenium trichloride, the acetoxylation did not proceed. Kaneda et al reported that the cleavage of carbon carbon double bonds occurs upon treatment of olefins with ruthenium catalyst in the presence of molecular oxygen and acetaldehyde, and the formation of ruthenium tetroxide as a key intermediate was proposed.<sup>12</sup> However neither ruthenium dioxide (IV) nor ruthenium tetroxide (VIII) show catalytic activity for the present oxidation reaction. Therefore, the present process may involve the oxoruthenium species as active species.<sup>13</sup> What discrepancy is present between the present reaction and the former reaction? In this case of aerobic oxidation, two possible pathways can be considered to generate oxoruthenium species as shown in Scheme 1.

Firstly, the reaction of acetaldehyde with molecular oxygen promoted by ruthenium catalysts would give peracetic acid thus formed with ruthenium trichloride gives oxoruthenium species A.

β-lactams at the same time on its formation.





The treatment of ruthenium trichloride in the presence of acetaldehyde with molecular oxygen at 0 °C in CD<sub>3</sub>CN shows signals such as  $\delta$  2.00 ppm (d, J = 5.1 Hz, 3H, -CHCH<sub>3</sub>), and 5.05 ppm (q, J = 5.1 Hz, 1H, -OCH(O-)CH<sub>3</sub>), which can be assigned to paraacetaldehyde without observation of peracetic acid (s, 2.05 ppm in CD<sub>3</sub>CN). Also signals of peracetic acid and acetic acid monoperacetate, <sup>14</sup> which is a precursor of peracetic acid, are not detected under the reaction conditions. However the oxidation of 1 at 0 °C under the same reaction conditions readily proceeds to give 2. It is considered that peracetic acid would be immediately consumed for the oxidation of

Scheme 1. Catalytic Cycle of Ruthenium-Catalyzed Oxidation of  $\beta$ -Lactams with

Next, an alternative process involves the formation of metalacyclic intermediate **B** as observed for platinum and other complexes<sup>15</sup> and subsequent protonolysis of **B** gives oxoruthenium species A along with acetic acid. The following catalytic cycle could be completed analogously to the former reaction by use of peracetic acid.

It is noteworthy that the acetoxylation did not take place, when this reaction was carried out without a proton source such as acetic acid, and N-acylated products were obtained. The intermediacy of the four-membered acyliminium ion could be supported by the almost exclusive formation of 4-dichloroacetoxy  $\beta$ -lactam 2i upon oxidation of 1 in a mixture of acetic acid and dichloroacetic acid (1:1) under the same reaction conditions.

In conclusion, the development of oxo-metal complex catalysis by means of transition metal complex catalysts has brought about striking innovations to synthetic chemistry and, especially, industrial chemistry, giving us a new image of the creation of the target molecules. Since oxidation reaction plays an important role in organic chemistry, ever-increasing efforts of research and development in this field are expected to contribute toward further improvement of health science.

# **Experimental Section**

General. <sup>1</sup>H NMR spectra were recorded on a JEOL PMX-60 SI (<sup>1</sup>H, 60 MHz), a JEOL JNM-GSX 270 (1H, 270 MHz; 13C, 67.9 MHz), and a BRUKER AM-400 (<sup>1</sup>H, 400 MHz; <sup>13</sup>C, 100 MHz) spectrometers. IR spectra were recorded on a Hitachi 215 spectrometer, a JASCO IR-810, and a Shimadzu FTIR-4100 spectrometers. Mass spectra were obtained on a JEOL JMX-DX 303 mass spectrometer and a HITACHI M-80B spectrometer. Elemental analyses were performed on a Yanagimoto MT-2 CHN corder. Mass spectra were measured on a Hitachi Model RSM-4 mass spectrometer. Exact mass spectra were measured on a JEOL Model JMS-DX-303 mass spectrometer. All melting points were measured on a Yanagimoto micro melting point apparatus. HPLC analyses were performed on a JASCO TRI ROTAR-VI system with a JASCO UVIDEC-100-VI UV detector by using a 250 mm x 4.6 mm analytical column packed with Chiralpack AS (Daicel Chemical Industry, Ltd.). Optical rotations were measured on a JASCO DIP-360 polarimeter.

Materials. Ethyl acetate, hexane, CH<sub>3</sub>CN, dioxane, THF, toluene, acetone, CH2Cl2, DMF, DMSO, paraformaldehyde, acetaldehyde, acetic acid, propionic acid,

benzaldehyde, and crotonaldehyde were used by simple distillation.

General Procedure for the Ruthenium-Catalyzed Oxidation of the β-Lactams with Molecular Oxygen and Aldehydes. A 50 mL side-armed round-bottomed flask equipped with a magnetic stirring bar and a 50 mL gas burette was charged with RuCl<sub>3</sub>·3H<sub>2</sub>O (0.1 mmol, 5 mol%), anhydrous sodium acetate (0.5 mmol), and the  $\beta$ -lactam (2 mmol). After the atmosphere was surely replaced with oxygen, ethyl acetate (20 mL) and acetic acid (1 mL) were added to the mixture. The resulting mixture was heated to 40  $^{\circ}$ C with vigorously stirring. Keeping the temperature at 40  $^{\circ}$ C, acetaldehyde (5 mmol) was added to the mixture all at once. When oxygen absorption was stopped, the reaction mixture was powered into 10% Na2SO3 aqueous solution (80 mL) and extracted with two 100 mL portions of an appropriate solvent. The combined organic layer was washed with brine (100 mL), and dried over anhydrous magnesium sulfate. Evaporation of the solvents by reduced pressure followed by column chromatography on silica gel (hexane/ethyl acetate) gave the corresponding 4-acetoxy βlactam. Conversions of various  $\beta$ -lactams into the corresponding 4-acetoxy  $\beta$ -lactams are shown in Table 1.

(1'R, 3R, 4R)-4-Acetoxy-3-[1'-[(tert-butyldimethylsilyl)oxy]ethyl]azetidin-2-one (2): The oxidation of 1 was carried out according to the general procedure. Extraction with hexane (200 mL) and evaporation gave pure 2 in 91% isolated yield as a colorless needles; mp 108.5 °C; IR (KBr) 3190 (NH), 2940, 2850, 1780 (ester C=O), 1750 (β-lactam C=O), 1240, 1160, 1140, 1080, 1040, 940 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) & 0.08 (s, 3H, SiCH<sub>3</sub>), 0.09 (s, 3H, SiCH<sub>3</sub>), 0.88 (s, 9H,  $SiC(CH_3)_3$ , 1.27 (d, J = 6.4 Hz, 3H, -(*t*-BuMe<sub>2</sub>SiO)CHCH<sub>3</sub>), 2.11 (s, 3H, -OCOCH<sub>3</sub>),  $3.19 (dd, J = 3.5, 1.3 Hz, COCH), 4.23 (dq, J = 3.5, 6.4 Hz, -(t-BuMe_2SiO)CHCH_3),$ 5.84 (d, J = 1.3 Hz, CHNH), 6.40 (b, 1H, NH). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 67.9 MHz)  $\delta$  -5.2 (SiCH<sub>3</sub>), -4.3 (SiCH<sub>3</sub>), 17.9 (SiC(CH<sub>3</sub>)<sub>3</sub>), 20.8 (-(t-BuMe<sub>2</sub>SiO)CHCH<sub>3</sub>), 22.3

hexanoic acid, methoxyacetic acid, phenylacetic acid, cyanoacetic acid, chloracetic acid, dichloracetic acid, bromacetic acid, dibromacetic acid, 2,4-dinitrobenzoic acid, RuCl<sub>3</sub>•3H<sub>2</sub>O, RuBr<sub>3</sub>•3H<sub>2</sub>O, Ru(OAc)<sub>3</sub>, Ru<sub>3</sub>(CO)<sub>12</sub>, Ru(NO)Cl<sub>2</sub>, Ru(TPP)(CO)-THF, RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub>, Ru(acac)<sub>3</sub>, RuO<sub>2</sub>, RuO<sub>4</sub>, 1%Ru-graphite, 5%Ru-carbon, 5%Ru-aluminum, OsCl<sub>2</sub>.xH<sub>2</sub>O, CoCl<sub>2</sub>, anhydrous sodium acetate, oxygen (99.99%), and azetidin-2-one were all commercially available and used without further purification. Propionaldehyde, hexyl aldehyde, decyl aldehyde, isobutyraldehyde, cyclohexane carboxy aldehyde,

(OCOCH<sub>3</sub>), 25.7 (SiC(CH<sub>3</sub>)<sub>3</sub>), 64.0 (CH), 65.2 (-(*t*-BuMe<sub>2</sub>SiO)CHCH<sub>3</sub>), 75.2 (CH(OAc)), 166.4 (NHC=O), 171.2 (OCOCH<sub>3</sub>). Anal. Calcd for C<sub>13</sub>H<sub>25</sub>NO<sub>4</sub>Si: C, 54.32; H, 8.77 N, 4.87. Found: C, 54.15.; H, 8.55; N, 4.96.  $[\alpha]_D^{25}$  +51.2 (*c* 1.00, CHCl<sub>3</sub>).

**4-Acetoxyazetidin-2-one** (**4**): The oxidation of **3** was carried out according to the general procedure. Extraction with EtOAc (200 mL) and purification by column chromatography on SiO<sub>2</sub> (hexane/ EtOAc, 2/1) gave **4** in 88% (from **3**), and 87% isolated yield(from **7**). Colorless oil; IR (neat) 3250 (NH), 3020, 2970, 1765 (ester C=O), 1740 (β-lactam C=O), 1410, 1380, 1240, 1110, 1043, 990, 960 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 2.13 (s, 3H, -OCOCH<sub>3</sub>), 3.00 (ddd, J = 15.3, 1.4, 0.5 Hz, 1H, -HCHCH(OAc)-), 3.26 (ddd, J = 15.3, 4.1, 0.5 Hz, 1H, -HCHCH(OAc)-), 5.84 (dd, J = 4.1, 1.4 Hz, 1H, -HCHCH(OAc)-), 7.02 (b, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 20.7 (COCH<sub>3</sub>), 44.9 (CH<sub>2</sub>), 73.0 (CH), 165.6 (C=O); Anal. Calcd for C<sub>5</sub>H<sub>7</sub>NO<sub>3</sub>: C, 46.51; H, 5.47; N, 10.58. Found: C, 46.71; H, 5.56; N, 10.84.

4-Acetoxy-4-methylazetidin-2-one (6): The oxidation of 5 was carried out according to the general procedure. Extraction with EtOAc (200 mL) and purification by column chromatography on SiO<sub>2</sub> (hexane/ EtOAc, 2/1) gave 6 in 72% isolated yield. Colorless oil; IR (neat) 3350 (NH), 1750 (ester C=O), 1720 (β-lactam C=O), 1360, 1265, 1165, 1020 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 1.83 (s, 3H, -CCH<sub>3</sub>), 2.07 (s, 3H, OCOCH<sub>3</sub>), 3.00 (d, J = 14.9 Hz, 1H,-HCHCCH<sub>3</sub>(OAc)-), 3.17 (d, J = 14.9 Hz, 1H,-HCHCCH<sub>3</sub>(OAc)-), 7.17 (b, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 67.9 MHz) δ 21.5 (CCH<sub>3</sub>), 22.9 (OCOCH<sub>3</sub>), 51.0 (CH<sub>2</sub>), 84.7 (NHC(OAc)CH<sub>3</sub>), 165.1 (NHC=O), OC=O); Anal. Calcd for C<sub>6</sub>H<sub>9</sub>NO<sub>3</sub>: C, 50.35; H, 6.34; N, 9.79. Found: C, 50.22; H, 6.08; N, 9.71.

Catalytic Activity of Various Metal Complexes for the Oxidation of  $\beta$ -Lactam 1 with Molecular Oxygen and Acetaldehyde. A 50 mL side-armed round-bottomed flask equipped with a magnetic stirring bar and a 50 mL gas burette was charged with a catalyst (2 - 5 mol%), anhydrous sodium acetate (0.5 mmol), and  $\beta$ -lactam 1 (2 mmol). After the atmosphere was surely replaced with oxygen, ethyl acetate (20 mL) and acetic acid (1 mL) were added to the mixture. The resulting mixture was heated to 40 °C with vigorous stirring. Keeping the temperature at 40 °C, acetaldehyde (4 mmol) was added to the mixture all at once. After stirred for 3h, the reaction mixture was powered into 10% Na<sub>2</sub>SO<sub>3</sub> aqueous solution (80 mL) and extracted with two 100

mL portions of hexane . Yields of  $\beta$ -lactam 2 were determined by <sup>1</sup>H NMR analysis and obtained results were listed in Table 2.

Effect of Various Aldehydes for the Oxidation of β-Lactam 1 with Molecular Oxygen. A 50 mL side-armed round-bottomed flask equipped with a magnetic stirring bar and a 50 mL gas burette was charged with a catalyst (2 - 5 mol%), anhydrous sodium acetate (0.5 mmol), and  $\beta$ -lactam 1 (2 mmol). After the atmosphere was surely replaced with oxygen, ethyl acetate (20 mL) and acetic acid (1 mL) were added to the mixture. The resulting mixture was heated to 40 °C with vigorous stirring. Keeping the temperature at 40 °C, acetaldehyde (4 mmol) was added to the mixture all at once. After stirred for 3-5h, the reaction mixture was powered into 10% Na2SO3 aqueous solution (80 mL) and extracted with two 100 mL portions of hexane. Conversions were determined by <sup>1</sup>H NMR analysis and the obtained results were listed in Table 3. When the effect of benzaldehyde was attempted, the reaction was carried out as follows; Oxygen was bubbled into a mixture of RuCl<sub>3</sub>·3H<sub>2</sub>O (0.1 mmol, 5 mol%), benzaldehyde (5.7 mL), acetic acid (1 mL), anhydrous sodium acetate (0.5 mmol), the βlactam (2 mmol) and ethyl acetate (20 ml) at 40°C for 2 h. The resulting mixture was stirred under oxygen atmosphere at room temperature for 1 h. The reaction mixture was powered into 10% Na2SO3 aqueous solution (80 mL) and extracted with two 100 mL portions of hexane.

Solvent Effect for the Oxidation of  $\beta$ -Lactam 1 with Molecular Oxygen. A 50 mL side-armed round-bottomed flask equipped with a magnetic stirring bar and a 50 mL gas burette was charged with a catalyst (2 - 5 mol%), anhydrous sodium acetate (0.5 mmol), and  $\beta$ -lactam 1 (2 mmol). After the atmosphere was surely replaced with oxygen, a solvent (20 mL) and acetic acid (1 mL) were added to the mixture. The resulting mixture was heated to 40 °C with vigorous stirring. Keeping the temperature at 40 °C, acetaldehyde (4 mmol) was added to the mixture all at once. After stirring for additional 3h, the reaction mixture was powered into 10% Na<sub>2</sub>SO<sub>3</sub> aqueous solution (80 mL) and extracted with two 100 mL portions of hexane. Conversions of 1 into product 2 were determined by <sup>1</sup>H NMR analysis and the obtained results were listed in Table 4.

General Procedure for the Ruthenium-Catalyzed Acyloxylation of  $\beta$ -Lactam 1 with Molecular Oxygen and Aldehydes. A 50 mL side-armed round-bottomed flask equipped with a magnetic stirring bar and a 50 mL gas burette was charged with RuCl<sub>3</sub>·3H<sub>2</sub>O (0.1 mmol, 5 mol%), anhydrous sodium acetate (0.5 mmol),

and B-lactam 1 (458 mg, 2 mmol). After the atmosphere was surely replaced with oxygen, ethyl acetate (20 mL) and a carboxylic acid (10 mmol) were added to the mixture. The reaction mixture was heated to 40°C with vigorous stirring. Keeping the temperature at 40 °C, an aldehyde (4 mmol) was added to the mixture all at once. After stirring for 3 h, the reaction mixture was powered into 10% Na<sub>2</sub>SO<sub>3</sub> aqueous solution (80 mL) and extracted with two 100 mL portions of hexane. The combined hexane solution was washed with brine (100 mL), and dried over anhydrous magnesium sulfate. When oxygen absorption was stopped, the reaction mixture was powered into 10% Na2SO3 aqueous solution (80 mL) and extracted with two 100 mL portions of hexane. The combined hexane solution was washed with brine (100 mL), and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and followed by column chromatography on silica gel (hexane/ethyl acetate) gave the corresponding 4acyloxy  $\beta$ -lactam 2b-2k. The results of acyloxylations are listed in Table 5.

(1'R, 3R, 4R)-3-[1'-[(t-Butyldimethylsilyl)oxy]ethyl]-4-ethylcarbonyloxyazetidin-2-one (2b): The reaction was carried out according to general procedure for the ruthenium-catalyzed acyloxylation of substrate 1. Propionic acid and propionaldehyde were used. Column chromatography (silica gel, hexane/ethyl acetate, 5/1) followed by recrystallization from hexane gave 2b in 83% yield as a colorless needles; mp 85 °C; IR (KBr) 3150 (NH), 2930, 2860, 1780 (ester C=O), 1740 (amide C=O), 1460, 1380, 1260, 1160, 1130, 1070, 1040, 950, 830 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 0.06 (s, 3H, SiCH<sub>3</sub>), 0.08 (s, 3H, SiCH<sub>3</sub>), 0.87 (s, 9H, -C(CH<sub>3</sub>)<sub>3</sub>), 1.16  $(t, J = 7.6 \text{ Hz}, 3\text{H}, \text{CH}_2\text{CH}_3), 1.26 (d, J = 6.4 \text{ Hz}, 3\text{H}, -\text{CH}(\text{OTBDMS})\text{CH}_3), 2.37 (q, J)$ J = 7.6 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 3.18 (dd, J = 3.7, 1.2 Hz, 1H, C<sub>3</sub>-H), 4.22 (dq, J = 3.7, 6.4 Hz, 1H,  $C_{1'}$ -H), 5.84 (d, J = 1.2 Hz, 1H,  $C_4$ -H), 6.44 (br, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 67.9 MHz) δ -5.15 (SiCH<sub>3</sub>), -4.31 (SiCH<sub>3</sub>), 8.77 (-CH<sub>2</sub>CH<sub>3</sub>), 17.94 (-C(CH<sub>3</sub>)<sub>3</sub>), 22.32 (-CH(OTBDMS)CH<sub>3</sub>), 25.62 (-C(CH<sub>3</sub>)<sub>3</sub>), 27.43 (-CH<sub>2</sub>CH<sub>3</sub>), 64.01 (-CH(OTBDMS)CH<sub>3</sub>), 65.15 (C<sub>3</sub>), 75.15 (C<sub>4</sub>), 166.44 (NHC=O), 174.70 (-OC=OCH<sub>2</sub>CH<sub>3</sub>); Anal. Calcd for C<sub>14</sub>H<sub>28</sub>NO<sub>4</sub>Si: C, 55.78; H, 9.04; N, 4.65. Found: C, 55.73; H, 8.95; N, 4.72.  $[\alpha]_D^{28.5}$  +46.2 (c 0.98, CHCl<sub>3</sub>).

(1'R, 3R, 4R)-3-[1'-[(t-Butyldimethylsilyl)oxy]ethyl]-4-pentylcarbonyloxyazetidin-2-one (2c): The reaction was carried out according to general procedure for the ruthenium-catalyzed acyloxylation of substrate 1. Hexanoic acid and hexylaldehyde were used. Column chromatography (silica gel, hexane/ethyl acetate, Found: C, 59.72; H, 9.59; N, 4.14;  $[\alpha]_D^{23}$  +45.6 (*c* 0.99, CHCl<sub>3</sub>).

 $[\alpha]_D^{23}$  +34.0 (c 0.99, CHCl<sub>3</sub>).

5/1) followed by recrystallization from hexane gave 2c in 61% yield as a colorless needles; mp 60 °C; IR (KBr) 3300 (NH), 2953, 1786 (ester C=O), 1745 (amide C=O), 1470, 1460, 1377, 1340, 1251, 1157, 1107, 1078, 1035, 943, 837 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 0.06 (s, 3H, SiCH<sub>3</sub>), 0.08 (s, 3H, SiCH<sub>3</sub>), 0.88 (s, 9H, - $C(CH_3)_3$ , 0.90 (t, J = 6.8 Hz, 3H,  $-CH_2CH_3$ ), 1.25 (d, J = 6.1 Hz, 3H, -CH(OTBDMS)CH<sub>3</sub>), 1.32 (m, 4H), 1.64 (tt, J = 7.6, 7.3 Hz, 2H, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-), 2.34 (t, J = 7.3 Hz, 2H, -C=OCH<sub>2</sub>CH<sub>2</sub>), 3.17 (dd, J = 3.7, 1.2 Hz, 1H, C<sub>3</sub>-H), 4.22  $(dq, J = 3.7, 6.1 Hz, 1H, C_{1}-H), 5.84 (d, J = 1.2 Hz, 1H, C_4-H), 6.44 (br, 1H, NH);$ <sup>13</sup>C NMR (CDCl<sub>3</sub>, 67.9 MHz) δ -5.18 (SiCH<sub>3</sub>), -4.34 (SiCH<sub>3</sub>), 13.82, 17.90 (-C(CH<sub>3</sub>)<sub>3</sub>), 22.22, 22.28 (-CH(OTBDMS)CH<sub>3</sub>), 24.35, 25.68 (-C(CH<sub>3</sub>)<sub>3</sub>), 31.18, 34.03, 64.01 (-CH(OTBDMS)CH<sub>3</sub>), 65.14 (C<sub>3</sub>), 75.08 (C<sub>4</sub>), 166.43 (NHC=O), 174.04 (-OC=OCH<sub>2</sub>CH<sub>3</sub>); Anal. Calcd for C<sub>17</sub>H<sub>33</sub>NO<sub>4</sub>Si: C, 59.44; H, 9.69; N, 4.08.

# (1'R, 3R, 4R)-3-[1'-[(t-Butyldimethylsilyl)oxy]ethyl]-4-methoxy-

acetoxyazetidin-2-one (2d): The reaction was carried out according to general procedure for the ruthenium-catalyzed acyloxylation of substrate 1. Methoxyacetic acid and acetaldehyde were used. Column chromatography (Silica gel, hexane/ethyl acetate, 5/1) followed by recrystallization from hexane gave 2d in 74% yield as a colorless needles; mp 80 °C; IR (KBr) 3119 (NH), 2959, 2930, 1782 (ester C=O), 1761 (amide C=O), 1734, 1377, 1255, 1196, 1170, 1132, 1074, 1053, 972, 835 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 0.07 (s, 3H, SiCH<sub>3</sub>), 0.09 (s, 3H, SiCH<sub>3</sub>), 0.87 (s, 9H, - $C(CH_3)_3$ , 1.26 (d, J = 6.4 Hz, 3H, -CH(OTBDMS)CH<sub>3</sub>), 3.22 (dd, J = 3.4, 1.2 Hz, 1H, C<sub>3</sub>-H), 4.07 (s, 2H, -C=OCH<sub>2</sub>O-), 4.22 (dq, J = 3.4, 6.4 Hz, 1H, C<sub>1</sub>'-H), 5.94 (d, J = 1.2 Hz, 1H, C<sub>4</sub>-H), 6.44 (br, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 67.9 MHz)  $\delta$  -5.18 (SiCH<sub>3</sub>), -4.35 (SiCH<sub>3</sub>), 17.91 (-C(CH<sub>3</sub>)<sub>3</sub>), 22.30 (-CH(OTBDMS)CH<sub>3</sub>), 25.68 (-C(CH<sub>3</sub>)<sub>3</sub>), 59.49 (-CH<sub>2</sub>OCH<sub>3</sub>), 63.89 (-CH(OTBDMS)CH<sub>3</sub>), 65.46 (C<sub>3</sub>), 69.53 (-CH2OCH3), 75.66 (C4), 166.05 (NHC=O), 170.51 (-OC=OCH2CH3); Anal. Calcd for C14H27NO5Si: C, 52.97; H, 8.58; N, 4.42. Found: C, 53.14; H, 8.41; N, 4.52;

# (1'R, 3R, 4R)-3-[1'-[(t-Butyldimethylsilyl)oxy]ethyl]-4-phenyl-

acetoxyazetidin-2-one (2e): The reaction was carried out according to general procedure for the ruthenium-catalyzed acyloxylation of substrate 1. Phenylacetic acid and acetaldehyde were used. Column chromatography (Silica gel, hexane/ethyl acetate,

8/1) followed by recrystallization from hexane gave 2e in 83% yield as a colorless needles; mp 61 °C; IR (KBr) 3200 (NH), 2950, 2850, 1780 (ester C=O), 1740 (amide C=O), 1460, 1370, 1320, 1250, 1130, 1070, 1000, 940, 830, 770 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 0.04 (s, 3H, SiCH<sub>3</sub>), 0.06 (s, 3H, SiCH<sub>3</sub>), 0.85 (s, 9H, -C(CH<sub>3</sub>)<sub>3</sub>), 1.23 (d, J = 6.4 Hz, 3H, -CH(OTBDMS)CH<sub>3</sub>), 3.18 (dd, J=3.6, 1.2 Hz, 1H, C<sub>3</sub>-H), 3.66 (s, 2H, -C=OCH<sub>2</sub>Ph), 4.20 (dq, J = 3.4, 6.4 Hz, 1H, -CH(OTBDMS)CH<sub>3</sub>), 5.86 (d, J = 1.2 Hz, 1H, C<sub>4</sub>-H), 6.48 (br, 1H, NH), 7.24-7.36 (m, 5H, aromatic); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 67.9 MHz) δ -5.2 (SiCH<sub>3</sub>), -4.3 (SiCH<sub>3</sub>), 17.9 (-C(CH<sub>3</sub>)<sub>3</sub>), 22.3 (-CH(OTBDMS)CH<sub>3</sub>), 25.6 (-C(CH<sub>3</sub>)<sub>3</sub>), 41.1 (C=OCH<sub>2</sub>Ph), 64.0 (-CH(OTBDMS)CH<sub>3</sub>), 65.3 (C<sub>3</sub>), 75.7 (C<sub>4</sub>), 127.4 (aromatic), 128.7 (aromatic), 129.2 (aromatic), 133.1 (aromatic), 166.4 (NHC=O), 171.9 (-OC=OCH<sub>2</sub>CH<sub>3</sub>). Anal. Calcd for C19H29NO4Si: C, 62.78; H, 8.05; N, 3.86. Found: C, 62.71; H, 7.99; N, 3.88;  $[\alpha]_{D}^{28.5}$  +46.8 (c 0.99, CHCl<sub>3</sub>).

(1'R, 3R, 4R)-3-[1'-[(t-Butyldimethylsilyl)oxy]ethyl]-4-cyanoacetoxyazetidin-2-one (2f): The reaction was carried out according to general procedure for the ruthenium-catalyzed acyloxylation of substrate 1. Cyanoacetic acid and acetaldehyde were used. Column chromatography (Silica gel, hexane/ethyl acetate, 8/1) followed by recrystallization from hexane/ethyl acetate (1:1) gave 2f in 81% yield as an amorphous powder; mp 117 °C; IR (KBr) 3343 (NH), 2955, 2270 (C=N), 1774 (ester C=O), 1743 (amide C=O), 1473, 1375, 1334, 1258, 1192, 1161, 1076, 1043, 943, 837 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 0.06 (s, 3H, SiCH<sub>3</sub>), 0.08 (s, 3H, SiCH<sub>3</sub>), 0.87  $(s, 9H, -C(CH_3)_3), 1.27 (d, J = 6.4 Hz, 3H, -CH(OTBDMS)CH_3), 3.27 (dd, J = 3.2, J)$ 1.2 Hz, 1H, C<sub>3</sub>-H), 3.52 (s, 2H, -C=OCH<sub>2</sub>CN), 4.24 (dq, J = 3.2, 6.4 Hz, 1H, -CH(OTBDMS)CH<sub>3</sub>), 5.96 (d, J = 1.2 Hz, 1H, C<sub>4</sub>-H), 6.53 (br, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 67.9 MHz) δ -5.2 (SiCH<sub>3</sub>), -4.4 (SiCH<sub>3</sub>), 17.9 (-C(CH<sub>3</sub>)<sub>3</sub>), 22.3 (-CH(OTBDMS)CH<sub>3</sub>), 24.7 (C=OCH<sub>2</sub>CN), 25.7 (-C(CH<sub>3</sub>)<sub>3</sub>), 63.7(-CH(OTBDMS)CH<sub>3</sub>), 65.7 (C<sub>3</sub>), 77.3 (C<sub>4</sub>), 112.1 (-CH<sub>2</sub>C=N), 163.2 (NHC=O), 165.6 (-OC=OCH2CH3); Anal. Calcd for C14H24N2O4Si: C, 53.82; H, 7.75; N, 8.97. Found: C, 53.98; H, 7.69; N, 9.06.  $[\alpha]_D^{23}$  +42.4 (c 1.05, CHCl<sub>3</sub>).

(1'R, 3R, 4R)-4-Chloroacetoxy-3-[1'-[(t-butyldimethylsilyl)oxy]ethyl]azetidin-2-one (2g): The reaction was carried out according to general procedure for the ruthenium-catalyzed acyloxylation of substrate 1. Chloroacetic acid and acetaldehyde were used. Column chromatography (silica gel, hexane/ethyl acetate, N, 4.42; Cl, 10.66;  $[\alpha]_D^{23}$  +46.3 (*c* 1.06, CHCl<sub>3</sub>).

ethyl]azetidin-2-one (2h): The reaction was carried out according to general procedure for the ruthenium-catalyzed acyloxylation of substrate 1. Bromoacetic acid and acetaldehyde were used. Column chromatography (silica gel, hexane/ethyl acetate, 5/1) followed by recrystallization from hexane gave 2h in 78% yield as colorless needles; mp 107 °C; IR (KBr) 3323 (NH), 2959, 2930, 1782 (ester C=O), 1765 (amide C=O), 1743, 1446, 1273, 1255, 1186, 1169, 1155, 1136, 1107, 1074, 1049, 947, 837 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 0.06 (s, 3H, SiCH<sub>3</sub>), 0.08 (s, 3H, SiCH<sub>3</sub>), 0.87 (s, 9H,  $-C(CH_3)_3$ , 1.26 (d, J = 6.3 Hz, 3H,  $-CH(OTBDMS)CH_3$ ), 3.24 (dd, J = 3.4, 1.2 Hz, 1H, C<sub>3</sub>-H), 3.86 (s, 2H, -C=OCH<sub>2</sub>Br), 4.23 (dq, J = 3.4, 6.3 Hz, 1H, -CH(OTBDMS)CH<sub>3</sub>), 5.92 (d, J = 1.2 Hz, 1H, C<sub>4</sub>-H), 6.49 (br, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 67.9 MHz) δ -5.2 (SiCH<sub>3</sub>), -4.3 (SiCH<sub>3</sub>), 17.9 (-C(CH<sub>3</sub>)<sub>3</sub>), 22.3 (-CH(OTBDMS)CH<sub>3</sub>), 25.0 (-CH<sub>2</sub>Br), 25.7 (-C(CH<sub>3</sub>)<sub>3</sub>), 63.8(-CH(OTBDMS)CH<sub>3</sub>), 65.6 (C<sub>3</sub>), 76.8 (C<sub>4</sub>), 165.9 (NHC=O), 167.5 (-OC=OCH<sub>2</sub>Cl); Anal. Calcd for C13H24N2O4SiBr: C, 42.73; H, 6.63; N, 3.84; Br, 21.62. Found: C, 42.63; H, 6.40; N, 3.90; Br, 21.45.  $[\alpha]_D^{28.5}$  +40.4 (*c* 1.02, CHCl<sub>3</sub>). (1'R, 3R, 4R)-3-[1'-[(t-Butyldimethylsilyl)oxy]ethyl]-4-dichloro-

acetoxyazetidin-2-one (2i): The reaction was carried out according to general procedure for the ruthenium-catalyzed acyloxylation of substrate 1. Dichloroacetic acid and acetaldehyde were used. Recrystallization from hexane without using silica gel column chromatography gave 2i in 70% yield as colorless needles; mp 118 °C; IR (KBr)

5/1) followed by recrystallization from hexane gave 2g in 92% yield as a colorless needles; mp 109 °C; IR (KBr) 3200 (NH), 2960, 2940, 2850, 1780 (ester C=O), 1750 (amide C=O), 1470, 1380, 1300, 1260, 1140, 1080, 1040, 1010, 950 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 0.07 (s, 3H, SiCH<sub>3</sub>), 0.08 (s, 3H, SiCH<sub>3</sub>), 0.87 (s, 9H, - $C(CH_3)_3$ , 1.27 (d, J = 6.3 Hz, 3H, -CH(OTBDMS)CH<sub>3</sub>), 3.24 (dd, J = 3.3, 1.2 Hz, 1H, C<sub>3</sub>-H), 4.10 (s, 2H, -C=OCH<sub>2</sub>Cl), 4.24 (dq, J = 3.3, 6.3 Hz, 1H, -CH(OTBDMS)CH<sub>3</sub>), 5.94 (d, J = 1.2 Hz, 1H, C<sub>4</sub>-H), 6.44 (br, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) & -5.2 (SiCH<sub>3</sub>), -4.3 (SiCH<sub>3</sub>), 17.9 (-C(CH<sub>3</sub>)<sub>3</sub>), 22.3 (-CH(OTBDMS)CH<sub>3</sub>), 25.7 (-C(CH<sub>3</sub>)<sub>3</sub>), 40.5 (-CH<sub>2</sub>Cl), 63.8(-CH(OTBDMS)CH<sub>3</sub>), 65.6 (C<sub>3</sub>), 76.8 (C<sub>4</sub>), 166.0 (NHC=O), 167.5 (-OC=OCH<sub>2</sub>Cl); Anal. Calcd for C13H24N2O4SiCl: C, 48.58; H, 7.53; N, 4.36; Cl, 10.89. Found: C, 48.35; H, 7.36;

# (1'R, 3R, 4R)-4-Bromoacetoxy-3-[1'-[(t-butyldimethylsilyl)oxy]-

3150 (NH), 2960, 2940, 2860, 1790, 1765 (ester C=O), 1740 (amide C=O), 1470, 1380, 1300, 1260, 1150, 1080, 1040, 1010, 940 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 0.07 (s, 3H, SiCH<sub>3</sub>), 0.08 (s, 3H, SiCH<sub>3</sub>), 0.87 (s, 9H,  $-C(CH_3)_3$ ), 1.28 (d, J = 6.4 Hz, 3H, -CH(OTBDMS)CH<sub>3</sub>), 3.32 (dd, *J* = 3.3, 1.2 Hz, 1H, C<sub>3</sub>-H), 4.25 (dq, *J* = 3.3, 6.4 Hz, 1H, -CH(OTBDMS)CH<sub>3</sub>), 5.96 (s, 1H, -C=OCHCl<sub>2</sub>), 6.00 (d, J = 1.2 Hz, 1H, C<sub>4</sub>-H), 6.50 (br, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ -5.2 (SiCH<sub>3</sub>), -4.3 (SiCH<sub>3</sub>), 18.1 (-C(CH<sub>3</sub>)<sub>3</sub>), 22.5 (-CH(OTBDMS)CH<sub>3</sub>), 25.6 (-C(CH<sub>3</sub>)<sub>3</sub>), 64.1 (-CHCl<sub>2</sub>), 64.2 (-CH(OTBDMS)CH<sub>3</sub>), 66.3 (C<sub>3</sub>), 78.5 (C<sub>4</sub>), 165.6 (NHC=O), 166.6 (-OC=OCHCl<sub>2</sub>); Anal. Calcd for C13H23NO4SiCl2: C, 43.93; H, 6.53; N, 3.94; Cl, 19.70. Found: C, 43.90; H, 6.83; N, 4.02; Cl, 19.58;  $[\alpha]_D^{28.5}$  +34.4 (c 1.00, CHCl<sub>3</sub>).

(1'R, 3R, 4R)-3-[1'-[(t-Butyldimethylsilyl)oxy]ethyl]-4-dibromoacetoxyazetidin-2-one (2j): The reaction was carried out according to general procedure for the ruthenium-catalyzed acyloxylation of substrate 1. Dibromoacetic acid and acetaldehyde were used. Recrystallization from hexane without using silica gel column chromatography from hexane gave 2j in 65% yield as an amorphous powder; mp 105.5 °C; IR (KBr) 3437 (NH), 2926, 2854, 1788 (ester C=O), 1743 (amide C=O), 1250, 1182, 1138, 1074, 1039, 1001, 945, 839 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 0.07 (s, 3H, SiCH<sub>3</sub>), 0.09 (s, 3H, SiCH<sub>3</sub>), 0.87 (s, 9H, -C(CH<sub>3</sub>)<sub>3</sub>), 1.28 (d, J = 6.4Hz, 3H, -CH(OTBDMS)CH<sub>3</sub>), 3.28 (dd, J = 3.4, 1.2 Hz, 1H, C<sub>3</sub>-H), 4.25 (dq, J = 3.4, 6.4 Hz, 1H, -CH(OTBDMS)CH<sub>3</sub>), 5.82 (s, 1H, -C=OCHBr<sub>2</sub>), 5.99 (d, J = 1.2 Hz, 1H, C<sub>4</sub>-H), 6.49 (br, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 67.9 MHz) δ -5.2 (SiCH<sub>3</sub>), -4.3 (SiCH<sub>3</sub>), 17.9 (-C(CH<sub>3</sub>)<sub>3</sub>), 22.3 (-CH(OTBDMS)CH<sub>3</sub>), 25.7 (-C(CH<sub>3</sub>)<sub>3</sub>), 31.2 (-CHBr<sub>2</sub>), 63.8 (-CH(OTBDMS)CH<sub>3</sub>), 65.8 (C<sub>3</sub>), 78.0 (C<sub>4</sub>), 164.8 (NHC=O), 165.6 (-OC=OCHBr<sub>2</sub>); Anal. Calcd for C13H23NO4SiBr<sub>2</sub>: C, 35.22; H, 5.23; N, 3.16; Br, 35.63. Found: C, 35.39; H, 5.28; N, 3.31; Br, 35.87;  $[\alpha]_D^{28.5}$  +28.6 (c 0.99, CHCl<sub>3</sub>).

(1'R, 3R, 4R)-3-[1'-[(t-Butyldimethylsilyl)oxy]ethyl]-4-(2, 4-dinitrobenzoyl)azetidin-2-one (2k): The reaction was carried out according to general procedure for the ruthenium-catalyzed acyloxylation of substrate 1. 2,4-Dinitrobenzoic acid and acetaldehyde were used. Recrystallization from hexane without using silica gel column chromatography from hexane gave 2k in 54% yield as colorless needles; mp 148 °C; IR (KBr) 3449 (NH), 2990, 2860, 1790 (ester C=O), 1743 (amide C=O), 1724, 1604, 1550, 1352, 1280, 1248, 1159, 1130, 1066, 1006, 939, 833 cm<sup>-1</sup>; C, 49.32; H, 5.71; N, 9.51;  $[\alpha]_D^{23}$  -7.2 (*c* 1.09, CHCl<sub>3</sub>).

Preparation of (1'R, 3R, 4R)-3-[1'-[(t-Butyldimethylsilyl)oxy]ethyl]-4-methoxycarbonylmethylazetidin-2-one (11): A 100 mL three-necked round-bottomed flask equipped with a thermometer, a magnetic stirring bar and a pressure equalizing dropping funnel connected to a three-way stopcock was charged with CF<sub>3</sub>SO<sub>3</sub>SiMe<sub>3</sub> (0.62 g, 2.79 mmol), and CH<sub>2</sub>Cl<sub>2</sub> (40 mL) under argon atmosphere. The mixture was cooled to -68 °C assisted with a dry-ice acetone bath and the mixture of CH<sub>2</sub>Cl<sub>2</sub> (40 mL), 1-(trimethylsilyl)oxy-1'-methoxyethene (2.44 g, 16.71 mmol), and 4acyloxy β-lactam (2: 0.80 g, 2.79 mmol, 2f: 0.87 g 2.79 mmol) was added dropwise over a period of 3 h. After stirring for 2 h at -68 °C, the resulting mixture was allowed to room temperature and then stirred overnight. The reaction mixture was poured into water (80 mL) and extracted twice with EtOAc (50 mL). The extract was washed with NaHCO3 solution, brine and dried over MgSO4. The solvent was removed under reduced presser, and purification by column chromatography on SiO<sub>2</sub> by using a 2:3 mixture of hexane and EtOAc as the eluent gave the title compound. Isolated yields of 11 were 60% (0.50 g, 1.67 mmol, from 2) and 92% (0.75 g, 2.51 mmol, from 2f). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 0.08 (s, 6H, SiCH<sub>3</sub>x2), 0.88 (s, 9H, -C(CH<sub>3</sub>)<sub>3</sub>), 1.21  $(d, J = 6.1 \text{ Hz}, 3\text{H}, -CH(OTBDMS)CH_3), 2.56 (dd, J = 16.4, 9.6 \text{ Hz}, 1\text{H}, CH_{a}H_{b}CO_{2}$ -), 2.74 (dd, J = 16.4, 4.2 Hz, 1H,  $-CH_{a}H_{b}CO_{2}$ -), 2.81 (dd, J = 4.9, 2.2 Hz, 1H, -CHCO-), 3.72 (s, 3H, -OCH<sub>3</sub>), 3.97 (ddd, J = 9.6, 4.2, 2.2 Hz, 1H, -CHNH-), 4.19 (dq, J = 4.9, 6.1 Hz, 1H, -CH(OTBDMS)CH<sub>3</sub>), 6.03 (b, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 67.9 MHz) δ -5.0 (SiCH<sub>3</sub>), -4.3 (SiCH<sub>3</sub>), 17.9 (-C(CH<sub>3</sub>)<sub>3</sub>), 22.5 (-CH(OTBDMS)CH<sub>3</sub>), 25.7 (-C(CH<sub>3</sub>)<sub>3</sub>), 39.5 (-CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>), 46.8 (-CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>), 51.9 (-CHCONH-), 64.3 (-CH(OTBDMS)CH<sub>3</sub>), 65.4 (-CHNH), 167.7 (NHC=O),

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 0.09 (s, 3H, SiCH<sub>3</sub>), 0.10 (s, 3H, SiCH<sub>3</sub>), 0.90 (s, 9H,  $-C(CH_3)_3$ , 1.30 (d, J = 6.3 Hz, 3H,  $-CH(OTBDMS)CH_3$ ), 3.29 (dd, J = 2.9, 1.2 Hz, 1H, C<sub>3</sub>-H), 4.28 (dq, J = 2.9, 6.3 Hz, 1H, -CH(OTBDMS)CH<sub>3</sub>), 6.20 (d, J = 1.2 Hz, 1H, C<sub>4</sub>-H), 6.53 (br, 1H, NH), 7.94 (d, J = 8.6 Hz, 1H, aromatic C<sub>6</sub>-H), 8.57 (dd, J =8.6, 2.2 Hz, 1H, aromatic C<sub>5</sub>-H), 8.84 (d, J = 2.2 Hz, 1H, aromatic C<sub>3</sub>-H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 67.9 MHz) δ -5.2 (SiCH<sub>3</sub>), -4.3 (SiCH<sub>3</sub>), 17.9 (-C(CH<sub>3</sub>)<sub>3</sub>), 22.2 (-CH(OTBDMS)CH<sub>3</sub>), 25.7 (-C(CH<sub>3</sub>)<sub>3</sub>), 63.7 (-CH(OTBDMS)CH<sub>3</sub>), 65.9 (C<sub>3</sub>), 77.6 (C<sub>4</sub>), 119.8, 127.7, 131.2, 132.0, 148.0, 149.3 (aromatic carbon), 163.8 (NHC=O), 165.7 (-OC=O-); Anal. Calcd for C<sub>18</sub>H<sub>25</sub>N<sub>3</sub>O<sub>8</sub>Si: C, 49.19; H, 5.74; N, 9.57. Found:

171.6 (-OC=O-). Anal. Calcd for C14H27NO4Si: C, 55.78; H, 9.04; N, 4.65. Found: C, 55.58; H, 9.18; N, 4.53.

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Chapter 5. **Ruthenium-Catalyzed Oxidative Transformation** of Alkenes to *a*-Ketols with Peracetic Acid. Simple Synthesis of Cortisone Acetate.

Olefins are well known to particularly important building blocks in organic synthesis, and their conversions to oxygenated derivatives via a wide variety oxidative transformations constitute prime examples of the broad synthetic utility of metal-catalyzed oxidation reactions.  $\alpha$ -Ketols are one of the representative examples, and which are important synthetic intermediates and partial structures of various biologically active compounds such as cortisone acetate  $(1)^1$  and adriamycin acetate  $(2)^2$ . The methods for the synthesis of  $\alpha$ -ketols from enol ethers<sup>3</sup> and enolates<sup>4</sup> have been studied extensively; however, those from olefins are limited to the oxidations with KMnO<sub>4</sub>-CuSO<sub>4</sub>•5H<sub>2</sub>O<sup>5</sup> and with isobutylaldehyde/O2 in the presence of OsO4 and bis(3-methyl-2,4-pentanedionato)nickel(II) catalysts.6



Recently, we found that the ruthenium-catalyzed oxidation of amines and amides with peroxides proceeds highly efficiently to give the corresponding  $\alpha$ -oxygenated products.<sup>7,8</sup> In these reactions, non-porphyrin oxo-ruthenium species generated from low valent ruthenium and peroxide undergoes cytochrome P-450 type reactions. One of the typical function of cytochrome P-450 is epoxidation of alkenes, where cationic intermediate 3 has been postulated as a key intermediate (eq. 1).9

# Introduction



If one could trap the intermediate 3 with nucleophiles such as water, a new type of catalytic oxidation of alkenes can be performed. Indeed, the author found that novel oxidative transformation of olefins to  $\alpha$ -ketols proceeds highly efficiently. Thus, the low valent ruthenium-catalyzed oxidation of alkenes with peracetic acid in an aqueous solution under mild reaction conditions gives the corresponding  $\alpha$ -ketols (eq. 2).<sup>10</sup>



# **Results and Discussion**

The present oxidation can be applied to the oxidation of di- and tri-substituted alkenes generally. The representative results of the oxidation of alkenes are shown in Table 1. The oxidation of trans-4-octene (4) and indene (6) gave the corresponding  $\alpha$ ketols, 5-hydroxy-4-ocanone (5) in 59% and 2-hydroxy-1-indanone (7) in 54% yield, regioselectively. Acyclic and cyclic alkenes can be converted into the corresponding  $\alpha$ ketols in good yields. The oxidation of 1,3-cyclohexadiene (8) proceeds to give the  $\alpha$ ketol 9 regioselectively. Small amount of by-products, such as epoxides and 1,2-diols, can be removed readily by short chromatographic separation. The two-phase aqueous system is required for the present reaction. Without water, the cleavage of carboncarbon bonds of alkenes occurs to give carboxylic acids predominantly. Ruthenium trichloride has been found to be the best catalyst among those examined because of high solubility to water.

The oxidation is quite different from that promoted by ruthenium tetroxide.<sup>11</sup> Indeed, the oxidation of 1-methylcyclohexene (10) under the present reaction conditions gave 2-hydroxy-2-methylcyclohexanone (11) in 67% isolated yield, while the oxidation of the same substrate under the conditions where ruthenium tetroxide can be generated, gave 6-oxoheptanoic acid (91%). Furthermore, the oxidation of diphenylacetylene gave benzil in 73% yield, while the similar oxidation with ruthenium tetroxide gave benzoic acid. Importantly, allylic acetates can be oxidized to give the corresponding acetoxy  $\alpha$ ketols in good to excellent yields. The oxidation of allylic acetate 16 is the model case of the synthesis of adriamycin acetate (2). Particularly, the oxidation of 3-acetoxy-1-



<sup>b</sup>Isolated yield based on the starting olefin. <sup>c</sup>Single diastereomer.

<sup>a</sup>The product gives satisfactory IR, NMR, and Mass spectral data, and analysis.

cyclohexene (18) gave  $(2R^*, 3S^*)$ -3-acetoxy-2-hydroxycyclohexanone (19) chemo- and stereo-selectively. Similarly, the oxidation of *cis*-5-methoxycarbonyl-2-cyclohexenyl acetate  $(20)^{12}$  gave  $(2R^*, 3S^*, 5R^*)$ -3-acetoxy-2-hydroxy-5-methoxycarbonyl-1cyclohexanone (21) selectively. These reactions are highly useful for synthesis of sugars.

The oxidation of  $\alpha$ ,  $\beta$ -unsaturated carbonyl compounds such as methyl crotonate (22) gave the corresponding  $\alpha$ -ketols, indicating that direct oxidation with peracetic acid is not involved in these reactions. The oxidation of 22 with peracetic acid in the absence of the catalyst does not occur under the similar reaction conditions.



<sup>a</sup>(a) CH<sub>2</sub>=CHMgBr; (b) Ac<sub>2</sub>O, DMAP/pyridine; (c) PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub> (cat.); (d) RuCl<sub>3</sub> (cat.), CH<sub>3</sub>C O<sub>3</sub>H; (e) KOH; (f) NBA; (g) Ac<sub>2</sub>O; (h) Br<sub>2</sub>; (i) 2,4-(NO<sub>2</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>NHNH<sub>2</sub>; (j) CH<sub>3</sub>C OC O<sub>2</sub>H.

The efficiency of the present reaction has been demonstrated by the synthesis of cortisone acetate (1),<sup>13</sup> which is a valuable anti-inflammatory agent. Our strategy for the

synthesis of **1** is shown in Scheme 1. Epiandrosterone (**24**), which is commercially available, was converted into  $3\beta$ , 17 $\xi$ -diacetoxy-5 $\alpha$ -pregn-20-ene (**25**) (mp 152-153.5 °C) upon treatment with vinyImagnesium bromide followed by *N*, *N*dimethylaminopyridine and Ac<sub>2</sub>O in dry pyridine. Catalytic rearrangement of **25** with PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub> catalyst<sup>14</sup> in THF at room temperature gave  $3\beta$ , 21-diacetoxy-5 $\alpha$ -pregn-17(20)-ene (**26**) (mp 153-154.5 °C) in 92% yield. The present ruthenium-catalyzed oxidation of **26** proceeds stereoselectively to give 20-oxo-5 $\alpha$ -pregnane- $3\beta$ , 17 $\alpha$ , 21-triol 3, 21-acetate (**27**) (mp 202-203.5 °C, [ $\alpha$ ]<sub>D</sub> +28.0° (*c* 1.03, CHCl<sub>3</sub>)) in 57% yield. Hydrolysis of **27** followed by oxidation with *N*-bromoacetamide gave **28**. Acetylation followed by dehydrogenation gave **29** (mp 235-236 °C, [ $\alpha$ ]<sub>D</sub> +114° (c 0.245, acetone)),<sup>15</sup> which can be converted into **1** by microbial oxidation with *Rhizopus nigricans*.<sup>16</sup>

The reaction can be rationalized by assuming three pathways which involve direct formation of  $\alpha$ -ketols from alkenes (path A), formation of epoxides followed by ring opening (path B), and formation of 1,2-diols and subsequent oxidation (path C). The following control experiments for the oxidation of 5-decene exclude path B and path C: i) The oxidation of 5,6-decanediol under the reaction conditions gave 5,6-decanedione and pentanoic acid rather than the corresponding a-ketol. ii) cis- and trans-5,6-Epoxydecanes were recovered completely under the reaction conditions. Although it is premature to discuss the mechanism at the present stage, the reaction can be rationalized by assuming the following reaction pathways: The reaction of the Ru(III) complex with peracetic acid would give Ru(V)=O species,<sup>8</sup> which undergoes reaction with olefins to give cationic species 3. Nucleophilic attack of water before ring closure to give epoxide and subsequent  $\beta$ -elimination of ruthenium hydride species would give  $\alpha$ -ketols. The oxidation of cis-5-decene gave 6-hydroxy-5-decanone (30%) along with trans-5,6epoxydecane (5%) and cis-5, 6-epoxydecane (15%), suggesting the presence of intermediate 3 in this oxidation reaction. Actually, the oxidation of 2,3-dimethyl-2butene which has no  $\beta$ -hydrogen atom gave 2,3-dihydroxy-2,3-dimethylbutane exclusively.

# **Experimental Section**

**Materials.** (*Z*) 5-Decene was prepared by hydrogenation of 5-decyne with Lindlar catalyst. (*E*) 5-Decene was prepared by hydrogenation of 5-decyne with LiAlH<sub>4</sub>.

(Z) 5-Decene oxide and (E) 5-decene oxide were prepared by epoxidation of the corresponding (Z)-, and (E)-olefins with m-chroloperbenzoic acid. CH2Cl2, CH3CN, EtOAc, hexane, Et<sub>2</sub>O, MeOH, CHCl<sub>3</sub>, RuCl<sub>3</sub>•H<sub>2</sub>O, PdCl<sub>2</sub>(MeCN)<sub>2</sub>, 2,4dimethylaminopyridine, Ac2O, magnesium, vinyl magnesium bromide, Nbromoacetoamide, 1-hydroxy-3-methyl-2-butene, cyclopentanone, trans-4-octene, indene, 1-methyl-1-cyclohexene, 2,4,4-trimethyl-2-pentene, \beta-tetralon, estron, and epiandrosterone were all commercially available and used without further purification. Dry pyridine and triethylamine were obtained by distillation over CaH<sub>2</sub>. Preparation of diazomethane was carried out according to usual procedure. A 30% solution of peracetic acid was a gift from DAICEL Chemical Industries, Ltd. cis-5-Methoxycarbonyl-2cyclohexyl acetate<sup>12</sup> was prepared by the reported method.

General Procedure for the Ruthenium-Catalyzed Oxidation of Alkenes with Peracetic Acid. A 50 mL round-bottomed flask equipped with a magnetic stirring bar and a dropping funnel connected to a three-way stopcock was charged with alkene (5.0 mmol), CH2Cl2 (5 mL), CH3CN (5 mL), H2O (5 mL) and RuCl<sub>3</sub>·3H<sub>2</sub>O (0.039 g, 0.15 mmol). The mixture was stirred at room temperature and a 30% solution of AcOOH in EtOAc (3.8 g, 15 mmol) was added dropwise over a period of 2 h. After complete addition, the mixture was stirred for an additional 3 h at room temperature. Then, the reaction mixture was poured into 5% Na<sub>2</sub>SO<sub>3</sub> aqueous solution and extracted with CH2Cl2 (25 mL x 5). The combined extracts were washed with a saturated NaCl aqueous solution (25 mL) and dried over MgSO4. Removal of the solvent under reduced pressure followed by column chromatography on SiO2 or distillation gave  $\alpha$ -ketol.

4-Hydroxy-5-octanone (5): IR (neat) 3400 (OH), 2937, 1712 (C=O), 1470, 1406, 1381, 1284, 1246, 1203, 1122, 1082, 1055, 1026 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz)  $\delta 0.94$  (t, J = 7.5 Hz, 3H, -CH<sub>3</sub>), 0.97 (t, J = 7.3 Hz, 3H, -CH<sub>3</sub>), 1.40 (b, 1H, OH), 1.48 (m, 2H,  $-CH_2$ -), 1.66 (tq, J = 5.1, 7.3 Hz,  $-CH_2CH_2CH_3$ ), 1.72 (m, 2H, CH<sub>2</sub>), 2.45 (dt, J = 7.2, 5.1 Hz, -COCH<sub>2</sub>CH<sub>3</sub>), 4.18 (t, J = 3.5 Hz, 1H, -CH<sub>2</sub>CH(OH)-); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 67.9 MHz) δ 13.6 (CH<sub>3</sub>), 13.8 (CH<sub>3</sub>), 17.2 (CH<sub>2</sub>), 18.2 (CH<sub>2</sub>), 35.9 (CH<sub>2</sub>), 39.8 (CH<sub>2</sub>), 76.3 (-CH(OH)-), 212.5 (C=O); exact mass calcd for C<sub>8</sub>H<sub>16</sub>O<sub>2</sub> 144.1150, found 144.1183.

2-Hydroxy-1-indanone (7): IR (neat) 3450 (OH), 1720 (C=O), 1620, 1590, 1470, 1440, 1380, 1300, 1250, 1210, 1150, 1120, 1090, 1030, 990, 910 cm<sup>-1</sup>; calcd for C<sub>0</sub>H<sub>8</sub>O<sub>2</sub> 148.0524, found 148.0509.

C<sub>6</sub>H<sub>8</sub>O<sub>2</sub> 112.0524, found 112.0537.

9.44. Found: C, 65.78; H, 9.68.

Calcd for C<sub>8</sub>H<sub>16</sub>O<sub>2</sub>: C, 66.63; H, 11.18. Found: C, 66.23; H, 11.06.

(-C=O).

Preparation of 2-Hydroxy-2-vinyl-1,3,5-trihydronaphthalene: A 300 mL three-necked flask equipped with a mechanical stirrer, a dropping funnel connected to a three-way stopcock, and a reflux condenser connected to a three-way

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz)  $\delta$  3.01 (dd, J = 16.6, 5.1 Hz, 1H, -CH<sub>2</sub>-), 3.27 (b, 1H, OH), 3.56 (dd, J = 16.6, 7.8 Hz, 1H, -CH<sub>2</sub>-), 4.54 (dd, J = 7.8, 5.1 Hz, 1H, -CH(OH)-), 7.37-7.77 (m, 5H, aromatic); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 67.9 MHz) δ 35.2 (CH<sub>2</sub>), 74.3 (-CH(OH)-), 124.5, 126.8, 128.0, 134.1, 135.9, 151.0, 206.5 (C=O); exact mass

6-Hydroxy-2-cyclohexenone (9): IR (neat) 3406 (OH), 2895 (CH), 1685 (C=O), 1616, 1514, 1458, 1425, 1386, 1263, 1219, 1157, 1103, 1068, 1035, 891, 829, 721 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 1.88-2.54 (m, 4 H, -CH<sub>2</sub>- x 2), 3.70 (br, 1 H, OH), 4.20 (dd, J = 13.7, 5.6 Hz, 1 H, -CH(OH)-), 6.12 (ddd, J = 9.8, 3.7, 1.8 Hz, 1 H), 7.02 (m, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 68 MHz) δ 25.7 (CH<sub>2</sub>CH(OH)), 31.3 (CH=CHCH<sub>2</sub>), 72.9 (COCH(OH)), 127.0, 152.0, 200.4 (C=O); exact mass calcd for

2-Hydroxy-2-methylcyclohexanone (11): IR (neat) 3439, 2942, 1713, 1451, 1373, 1312, 1254, 1165, 1134, 1165, 1134, 1080, 1030, 1020, 974, 949, 916, 829, 697, 664 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 1.40 (s, 3 H, CH3), 1.60-1.80 (m, 4 H), 2.12 (m, 2 H), 2.50 (m, 2 H), 3.93 (br, 1 H, OH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 68 MHz) δ 214.3, 76.4, 42.1, 37.8, 27.9, 25.1, 23.0; Anal. Calcd for C7H12O2: C, 65.58; H,

2-Hydroxy-2,4,4-trimethyl-3-pentanone (13): mp 54 °C; IR (KBr) 3491 (OH), 3022, 2874, 1697 (C=O), 1485, 1456, 1388, 1370, 1263, 1224, 1194, 1155, 1059, 1005, 966, 937 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 1.29 (s, 9H, - $C(CH_3)_3$ , 1.46 (s, 6H, - $C(OH)(CH_3)_2$ ), 3.50 (b, 1H, OH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 67.9) MHz) δ 27.0 (C(CH<sub>3</sub>)<sub>3</sub>), 27.9 (CH<sub>3</sub>), 28.4 (CH<sub>3</sub>), 78.1 (-C(OH)), 218.6 (C=O); Anal.

3-Hydroxy-3-methyl-2-oxobutyl Acetate (15): IR (neat) 3504 (OH), 2982, 2940, 1731 (C=O), 1466, 1412, 1375, 1269, 1235, 1194, 1148, 1100, 1040, 993, 961, 851, 802, 662, 608 cm<sup>-1</sup>; <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>) δ 1.41 (s, 6 H, -CH<sub>3</sub> x 2), 2.17 (s, 3 H, CH<sub>3</sub>CO<sub>2</sub>-), 3.05 (br, 1 H, -OH), 5.02 (s, 2 H, -CH<sub>2</sub>OAc); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 68 MHz) δ 20.5, 26.7, 26.7, 64.7 (-C-O-), 76.5 (-C-O-), 170.6 (-CO<sub>2</sub>-), 207.7

stopcock was charged with THF solution of vinylmagnesium bromide (50 mL, 37.4 mmol) under argon atmosphere. The solution was stirred at 0  $^{\circ}$  C and  $\beta$ -tetralon (5.07 g, 34.7 mmol) in dry THF (10 mL) was added dropwise. After stirring for a half hour at the room temperature and a half hour at 40 °C, and then saturated aqueous NH<sub>4</sub>Cl (20 mL) was added at 0 °C. The resulting mixture was extracted with EtOAc (75 mL x 3), the conbined extracts were washed with 2% aqueous NaHCO<sub>3</sub> (75 mL) and H<sub>2</sub>O (75 mL), and dried over Na, SO<sub>4</sub>. After removal of the solvent column chromatography (SiO<sub>2</sub>, hexane/Et<sub>2</sub>O, 6:1) gave the title compound (1.24 g, 21%) as yellow oil: <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$  1.76-3.22 (m, 6 H, -CH<sub>2</sub>- x 3), 5.09 (dd, J = 1.2, 10.7 Hz, 1 H, *cis*-H of -CH=CH<sub>2</sub>), 5.30 (dd, J = 1.2, 17.3 Hz, 1 H, trans-H of -CH=CH<sub>2</sub>), 6.03 (dd, J =10.7, 17.3 Hz, 1 H, -CH=CH<sub>2</sub>), 7.02-7.22 (m, 4 H, ArH x 4); <sup>13</sup>C NMR (68 MHz, CDCl<sub>3</sub>) § 26.1 x 2, 34.2, 41.8, 71.2(-C-O-), 112.6 (-C=CH<sub>2</sub>), 125.9, 126.0, 128.7, 129.4, 134.1, 135.3, 144.2 (-C=CH<sub>2</sub>).

Preparation of 2-Acetoxy-2-vinyl-1,3,5-trihydronaphthalene: 2-Hydroxy-2-vinyl-1,3,5-trihydronaphthalene (1.24 g, 7.1 mmol), 2,4-dimethylaminopyridine (0.037 g, 0.30 mmol), Ac<sub>2</sub>O (1.4mL, 15.0 mmol), and dry triethylamine (1.5 mL, 10.7 mmol) were stirred over night under argon atmosphere at room temperature. The reaction mixture was poured into cooled H<sub>2</sub>O, and then extracted with EtOAc (50 mL x 3), combined extracts were washed with 2N-HCl (70 mL), a saturated aqueous NaHCO<sub>3</sub> (70 mL), and a saturated aqueous NaCl (70 mL), and dried over Na<sub>2</sub>SO<sub>4</sub>. After removal of the solvent the residue was distilled to give the title compound (1.13 g, 74%) as yellow oil: <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>) δ 1.94 (s, 3 H, CH<sub>3</sub>CO<sub>2</sub>-), 2.44-2.54 (m, 2 H, -CH<sub>2</sub>-), 2.80-2.88 (m, 2 H, -CH<sub>2</sub>-), 3.15-3.31 (m, 2 H, -CH<sub>2</sub>-), 5.18 (d, J =11.0 Hz, 1 H, cis-H of -CH=CH<sub>2</sub>-), 5.21 (d, J = 17.6 Hz, 1 H, trans-H of -CH=CH<sub>2</sub>-), 6.19 (dd, J = 11.0, 17.6 Hz, 1 H, -CH=CH2), 7.04-7.24 (m, 4 H, ArH x 4); <sup>13</sup>C NMR (68 MHz, CDCl<sub>3</sub>) δ 22.0, 26.0, 31.7, 39.3, 80.7 (-C-O-), 114.5 (-C=CH<sub>2</sub>), 125.9, 126.0, 128.5, 129.2, 133.8, 135.2, 140.4 (-C=CH<sub>2</sub>), 170.1 (-CO<sub>2</sub>-).

2-(2-Acetoxyethylidenyl)-1,3,4-trihydronaphthalene (16): 2-Acetoxy-2-vinyl-1,3,5-trihydronaphthalene (1.13 g, 5.2 mmol), PdCl<sub>2</sub>(MeCN)<sub>2</sub> (0.11 g, 0.43 mmol), and dry THF (52.4 mL) were stirred over night under argon atmosphere at room temperature. After removal of the solvent the mixture was washed by Et<sub>2</sub>O on florisil. After removal of the solvent the residue was distilled to give 16 (0.16 g, 14%) as yellow oil: 'NMR (270 MHz, CDCl<sub>3</sub>) δ 2.03 (s, 3 H, CH<sub>3</sub>CO<sub>2</sub>-), 2.44-2.57 (m, 2 H,

equatorial H x 2), 2.82 (d, J=6.7 Hz, 1 H, axial H), 2.85 (d, J=6.7 Hz, 1 H, axial H),  $3.48(s, 1 H, 1 H \text{ of -CH}_2)$ ,  $3.60(s, 1 H, 1 H \text{ of -CH}_2)$ , 4.65(dd, J = 7.3, 11.7 Hz, 2)H, -CH<sub>2</sub>OAc), 5.53 (m, J = 7.3 Hz, 1 H, -C=CH-), 7.00-7.16 (m, 4 H, ArH x 4); <sup>13</sup>C NMR (270 MHz, CDCl<sub>3</sub>) δ 21.1, 30.0, 60.7, 76.9 (-C-O-), 117.1 (-C=CH-), 126.3, 126.6, 127.8, 128.4, 135.2, 137.5, 142.3 (-C=CH-), 171.0 (-C=O).

2-(1-Acetoxy-2-oxoethyl)-2-hydroxy-1,3,4-trihydronaphthalene (17): IR (neat) 3490 (OH), 3021, 2934, 1750 (C=O), 1730 (C=O), 1603, 1497, 1455. 1410, 1373, 1267, 1233, 1163, 1111, 1069, 1028, 972, 928, 907, 851, 797, 754, 731 cm<sup>-1</sup>; <sup>1</sup>H NMR (270 MHz, CDCl<sub>2</sub>) δ 1.91-2.13 (m, 2 H, -CH<sub>2</sub>-), 2.16 (s, 3H, CH<sub>2</sub>CO<sub>2</sub>-), 2.79 (dd, J = 2.0, 16.8 Hz, 1 H, 1H of -CH<sub>2</sub>-), 2.86-3.06 (m, 2 H, -CH<sub>2</sub>-), 3.26 (d, J =16.8 Hz, 1 H, 1H of -CH<sub>2</sub>-), 5.08 (s, 2 H, -CH<sub>2</sub>OAc), 7.06-7.26 (m, 4 H, ArH x4); <sup>13</sup>C NMR (68 MHz, CDCl<sub>3</sub>) δ 20.5, 24.6, 31.0, 38.4, 65.3 (-C-O-), 77.7 (-C-O-), 126.3, 126.4, 128.7, 129.7, 132.2, 134.9, 170.6 (-CO<sub>2</sub>-), 207.2 (-C=O); mass spectrum (FAB) m/z 249 (M<sup>+</sup>+1); HRMS calcd for  $C_{14}H_{16}O_4$  249.113, found 249.114 (M<sup>+</sup>+1).

 $(2R^*, 3S^*)$ -3-Acetoxy-2-hydroxycyclohexanone (19): mp 161-165 °C; IR (KBr) 3395 (OH), 2957, 1730 (C=O), 1452, 1435, 1379, 1240, 1111, 1062, 1036, 976, 939, 916, 884, 837 cm<sup>-1</sup>; <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>) δ 1.49-1.84 (m, 2 H, -CH2-), 2.00-2.12 (m, 1 H, 1H of -CH2-), 2.13 (s, 3 H, CH3CO2-), 2.21-2.28 (m, 1 H, 1H of -CH<sub>2</sub>-), 2.31-2.44 (m, 1 H, 1H of -CH<sub>2</sub>-), 2.60 (dddd, J = 2.2, 2.2, 4.4, 14.2Hz, 1 H, H<sup>6</sup>(ax) of -CH<sub>2</sub>C(=O), 3.65 (d, J = 3.9 Hz, 1 H, -OH), 4.18 (dd, J = 2.5, 10.0 Hz, 1 H, -CHOH), 4.75 (ddd, J = 4.6, 10.0, 11.2 Hz, 1 H, -CHOAc); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 68 MHz) δ 20.6, 21.1, 29.1, 38.4, 77.2 (-COAc), 78.6 (C(OH)(C=O)), 170.3 (-CO<sub>2</sub>-), 207.1 (-C=O); HRMS calcd for C<sub>8</sub>H<sub>12</sub>O<sub>4</sub> 172.074, found 172.073.

(2R\*, 3S\*, 5R\*)-3-Acetoxy-2-hydroxy-5-methoxycarbonyl-1cyclohexanone (21): IR (neat) 3426, 2957, 1459, 1304, 1242, 1101, 1044, 1022, 978, 951, 928, 872, 829 cm<sup>-1</sup>; <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$  1.95 (ddd, J = 3.0, 4.0, 12.0 Hz, 1 H of CH<sub>3</sub>CO<sub>2</sub>CHCH<sub>2</sub>), 2.11 (s, 3 H, CH<sub>3</sub>CO<sub>2</sub>), 2.53 (m, 1 H, 1 H of CH<sub>3</sub>CO<sub>2</sub>CHCH<sub>2</sub>), 2.63-2.86 (m, 3 H, COCH<sub>2</sub>CH), 3.65 (br, 1 H, OH), 3.74 (s, 3 H, CO<sub>2</sub>CH<sub>3</sub>), 4.22 (d, J = 11 Hz, 1 H, CHOH), 4.81 (ddd, J = 4.5, 10.0, 11.0 Hz, 1 H, CH<sub>3</sub>CO<sub>2</sub>CH); <sup>13</sup>C NMR (68 MHz, CDCl<sub>3</sub>) δ 20.9, 31.8, 37.7, 40.6, 52.5, 75.0, 78.1, 170.1, 172.3, 205.2; HRMS calcd for C<sub>10</sub>H<sub>15</sub>O<sub>6</sub> 231.0869, found 231.085.

Methyl 2-Hydroxy-3-oxo-butanoate (23): mp 133-134 °C; IR (KBr) 3360 (OH), 2966, 1749 (ester C=O), 1716 (C=O), 1437, 1363, 1334, 1265, 1184, 1097,

1039, 979, 912, 831, 794, 702 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 1.53 (br, 1 H, OH), 2.50 (s, 3 H, COCH<sub>3</sub>), 3.47 (s, 3 H, CO<sub>2</sub>CH<sub>3</sub>), 5.32 (s, 1 H, COCH(OH)); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 68 MHz) δ 26.9 (COCH<sub>3</sub>), 53.3 (CO<sub>2</sub>CH<sub>3</sub>), 83.5 (COCH(OH)), 168.0 (CO<sub>2</sub>CH<sub>3</sub>), 204.7 (CH<sub>3</sub>CO); HRMS calcd for C<sub>5</sub>H<sub>8</sub>O<sub>4</sub> 132.0423, found 132.0416.

Preparation of 3β,17ξ-Diacetoxy-5α-pregn-20-ene (25): A 100 mL three-necked round-bottomed flask equipped with a magnetic stirring bar, a dropping funnel connected to a three-way stopcock, and a reflux condenser connected to a threeway stopcock was charged with epiandrosterone (24) (3.00 g, 10.3 mmol) in dry THF (25 mL) under argon atmosphere. The solution was stirred with cooling in an ice bath and a 1.0 M solution of vinyl magnesium bromide in THF (35 mL, 35 mmol) was added dropwise. After stirring for 0.5 h at the room temperature and an additional 0.5 h at 40 °C, the reaction was quenched by adding saturated aqueous NH<sub>4</sub>Cl (20 mL). Then, the mixture was extracted with EtOAc (50 mL x 3). The combined extracts were washed successively with 2% aqueous NaHCO3 solution (50 mL) and saturated NaCl aqueous solution (50 mL), and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvent gave crude 3β-acetoxy-17ξ-hydroxy-5α-pregn-20-ene (2.88 g). A mixture of 3β-acetoxy-17ξ-hydroxy-5α-pregn-20-ene prepared above, N, N-dimethylaminopyridine (0.10 g, 0.75 mmol), Ac2O (3.5 mL, 36.6 mmol), and dry pyridine (5.0 mL) was stirred overnight under argon atmosphere at room temperature. The reaction mixture was poured into cold H<sub>2</sub>O and extracted with EtOAc (50 mL x 3). The combined extracts were washed successively with 2M HCl (50 mL), saturated aqueous NaHCO3 solution (50 mL) and a saturated aqueous NaCl (50 mL), and dried over anhydrous Na2SO4. After removal of the solvent column chromatography (SiO<sub>2</sub>, hexane/EtOAc, 15:1) gave **25** (1.50 g, 36%) as a colorless solid: mp 152-153.5 °C;  $[\alpha]^{23.5}$  +19.9° (c 1.04, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub> 270 MHz) δ 0.53-2.56 (m, 22 H, -CH<sub>2</sub>- x 9 + -CH- x 4), 0.83 (s, 3 H, -CH<sub>3</sub>), 0.90 (s, 3 H, -CH<sub>3</sub>), 1.99 (s, 3 H, CH<sub>3</sub>CO<sub>2</sub>-), 2.01 (s, 3 H, CH<sub>3</sub>CO<sub>2</sub>-), 4.67 (tt, J = 4.9, 9.8 Hz, 1 H, -CHOAc), 5.01 (dd, J = 0.9, 17.6 Hz, 1 H, trans H of -CH=CH<sub>2</sub>), 5.21 (dd, J = 0.9, 11.0 Hz, 1 H, cis H of -CH=CH<sub>2</sub>), 5.85 (ddd,  $J = 1.1, 11.0, 17.6 \text{ Hz}, 1 \text{ H}, -CH=CH_2$ ; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 68 MHz)  $\delta$  12.2, 14.7, 20.6, 21.4, 21.6, 24.0, 27.4, 28.4, 31.6, 32.2, 33.0, 34.0, 35.5, 35.8, 36.7, 44.7, 47.1, 47.4, 54.0, 73.6 (-C-O-), 91.7 (-C-O-), 114.3 (-C=CH<sub>2</sub>), 139.5 (-C=CH<sub>2</sub>), 170.0 (-CO<sub>2</sub>-), 170.6 (-CO<sub>2</sub>-).

110.6, 158.2, 170.6 (-CO<sub>2</sub>-), 171.1 (-CO<sub>2</sub>-).

**Preparation of 3** $\beta$ , 21-Diacetoxy-5 $\alpha$ -pregn-17-ene (26): Acetate 26 was prepared by stirring 25 (1.30 g, 3.23 mmol), PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub> (0.040 g, 0.16 mmol), and dry THF (20 mL) overnight at room temperature under argon atmosphere. Evaporation of the solvent and column chromatography on a short Florisil with Et<sub>2</sub>O gave **26** (1.20 g, 92%) as a colorless solid; mp 153-154.5 °C;  $[\alpha]^{24}_{D}$  +19.3°(c 1.03, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 0.64-2.45 (m, 22 H, -CH<sub>2</sub>- x 9 + -CH- x 4), 0.76 (s, 3 H, -CH<sub>3</sub>), 0.84 (s, 3 H, -CH<sub>3</sub>), 2.01 (s, 3 H, CH<sub>3</sub>CO<sub>2</sub>-), 2.04 (s, 3 H, CH<sub>3</sub>CO<sub>2</sub>-), 4.52 (d, J = 6.2 Hz, 1 H, 1 H of -CH<sub>2</sub>(OAc)CH=C-), 4.54 (d, J = 6.8 Hz, 1 H, 1 H of -CH<sub>2</sub>(OAc)CH=C-), 4.68 (tt, J = 5.3, 10.7 Hz, 1 H, -CHOAc), 5.15 (dd, J = 6.2, 6.8 Hz, 1 H, -CH=C-); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 68 MHz) δ 12.2, 18.7, 21.1, 21.1, 21.4, 26.3, 27.5, 28.5, 31.8, 34.0, 35.3, 35.6, 35.7, 36.8, 44.3, 44.7, 54.0, 54.6, 62.3 (-C-O-),

Preparation of  $3\beta$ , 21-Diacetoxy-17 $\alpha$ -hydroxy-5 $\alpha$ -pregnan-20-one (27): The oxidation of 26 (1.10 g, 2.74 mmol) was carried out according to the general procedure. After removal of the solvent column chromatography (SiO<sub>2</sub>, hexane/EtOAc, 15:1) gave 27 (0.68 g, 57%) as a colorless solid: mp 202-203.5 °C;  $[\alpha]^{22}$  +28.0° (c 1.03, CHCl<sub>3</sub>); IR (KBr) 3490 (OH), 2942, 2870, 2850, 1748 (C=O), 1730 (C=O), 1713 (C=O), 1450, 1440, 1410, 1370, 1262, 1237, 1173, 1150, 1134, 1111, 1096, 1082, 1046, 1028, 909, 895, 847, 781, 670, 656, 608, 536, 457 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 0.67 (s, 3 H, -CH<sub>3</sub>), 0.83 (s, 3 H, -CH<sub>3</sub>), 0.70-2.75 (m, 22 H, -CH<sub>2</sub>- x 9+ -CH- x 4), 2.01 (s, 3 H, CH<sub>3</sub>CO<sub>2</sub>-), 2.16 (s, 3 H, CH<sub>3</sub>CO<sub>2</sub>-), 4.68 (tt, J = 5.4, 10.7 Hz, 1 H, -CHOAc), 4.82 (d, J = 17.6 Hz, 1 H, 1 H of -CH<sub>2</sub>OAc), 5.78 (d, J = 17.6 Hz, 1 H, 1 H of -CH<sub>2</sub>OAc); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 68 MHz) δ 12.2, 14.7, 20.5, 20.8, 21.4, 23.6, 27.4, 28.5, 30.4, 32.1, 34.0, 34.8, 35.5, 35.6, 36.8, 44.7, 48.5, 51.1, 53.8, 67.9 (-C-O-), 73.6 (-C-O-), 90.3 (-C-O-), 170.5 (-CO<sub>2</sub>-), 170.7 (-CO<sub>2</sub>-), 205.1 (-C=O).

**Preparation of 3** $\beta$ , 17 $\alpha$ , 21-Trihydroxy-5 $\alpha$ -pregnan-20-one: A 20 mL three-necked round-bottomed flask equipped with a magnetic stirring bar, a dropping funnel connected to a three-way stopcock, and a reflux condenser connected to a threeway stopcock was charged with 27 (0.65 g, 1.49 mmol) in MeOH-CH<sub>2</sub>Cl<sub>2</sub> (1/1=v/v, 20 mL). The solution was stirred and a solution of KOH (0.33 g, 5.96 mmol) in MeOH-CH<sub>2</sub>Cl<sub>2</sub> was added dropwise. After stirring for 3 h at room temperature and an additional 1 h at 40 °C, 5% aqueous KOH solution (10 mL) was added. The reaction mixture was extracted with EtOAc (50 mL x 3). The combined extracts were washed

successively with 2M HCl (100 mL), saturated aqueous NaHCO3 solution (50 mL) and saturated aqueous NaCl solution (50 mL), and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvent under reduced pressure followed by column chromatography (SiO<sub>2</sub>, hexane/EtOAc, 4:1) gave  $3\beta$ ,  $17\alpha$ , 21-trihydroxy- $5\alpha$ -pregnan-20-one (0.34 g, 66%) as a colorless solid: mp 176-178 °C;  $[\alpha]^{24}_{D}$  +41.5° (c 0.99, EtOH); IR (KBr) 3410 (OH), 2928, 2859, 1709 (C=O), 1638, 1468, 1451, 1385, 1136, 1097, 1082, 1040 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>3</sub>OD, 270 MHz) δ 0.66 (s, 3 H, -CH<sub>3</sub>), 0.81 (s, 3 H, -CH<sub>3</sub>), 0.67-2.70 (m, 22 H,  $-CH_2 - x 9 + -CH - x 4$ ), 2.10 (s, 1 H, -OH), 3.07 (s, 1 H, -OH), 3.59 (tt, J = 5.2, 10.4 Hz, 1 H, -CHOH), 4.28 (d, J = 19.7 Hz, 1 H, 1H of -CH<sub>2</sub>OH), 4.65 (d, J = 19.7 Hz, 1 H, 1H of -CH<sub>2</sub>OH); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 68 MHz) δ 13.5, 16.3, 22.9, 25.5, 30.7, 32.8, 32.9, 34.3, 35.8, 37.5, 37.8, 39.1, 39.7, 47.1, 50.0, 53.0, 56.3, 68.6 (-C-O-), 72.6 (-C-O-), 91.4 (-C-O-), 214.3 (-C=O).

Preparation of  $17\alpha$ , 21-Dihydoxy- $5\alpha$ -pregnane-3, 20-dione (28): The mixture of 3β, 17α, 21-trihydroxy-5α-pregnan-20-one (0.328 g, 0.94 mmol), MeOH (10 mL), dry pyridine (0.5 mL), H<sub>2</sub>O (0.5 mL), and N-bromoacetamide (0.520 g, 3.76 mmol) were stirred overnight at room temperature. Allyl alcohol and 2M HCl were added to decompose excess oxidant. After separation of the organic layer followed by removal of the solvent, column chromatography (SiO<sub>2</sub>, hexane/EtOAc, 3:1) gave 28 (0.150 g, 46%) as a colorless solid: mp 204.5-205 °C; IR (KBr) 3480 (OH), 2948, 2928, 2865, 1705 (C=O), 1445, 1389, 1273, 1233, 1128, 1092, 1074, 1048, 1036 cm<sup>-</sup> <sup>1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 0.69 (s, 3 H, -CH<sub>3</sub>), 1.02 (s, 3 H, -CH<sub>3</sub>), 0.75-3.08 (m, 22 H,  $-CH_2 - x 9 + -CH - x 4$ ), 3.06 (t, J = 4.6 Hz, 1 H,  $-CH_2OH$ ), 4.30 (dd, J = 4.6, 19.5 Hz, 1 H, 1H of  $-CH_2(C=O)OH$ , 4.66 (dd, J = 4.6, 19.5 Hz, 1 H, 1H of - $CH_2(C=O)OH$ ; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 68 MHz)  $\delta$  11.4, 15.1, 20.9, 23.8, 28.8, 30.3, 31.8, 34.6, 35.4, 35.7, 38.1, 38.5, 44.6, 46.6, 48.8, 50.7, 53.4, 67.4 (-C(C=O)OH), 89.2 (-*C*(C=O)OH), 211.8 (-C=O), 212.3 (-C=O).

Preparation of 21-Acetoxy-17α-hydoxy-4-pregnene-3,20-dione (29): A mixture of 28 (0.140 g, 0.40 mmol), dry pyridine (1 mL), and acetic anhydride (0.5 mL) was stirred for 2 h at room temperature. The resulting mixture was poured into ice-water and the resulting precipitate was collected by filtration to give crude  $17\alpha$ , 21-diacetoxy-5 $\alpha$ -pregnane-3, 20-dione acetate (0.160 g). The acetate (0.160 g) and glacial acetic acid (5 mL) were chilled in an ice bath, and bromine (0.150 g, 0.94 mmol) in glacial acetic acid (2 mL) were added dropwise for 30 min. After stirring for an

additional 1 h, 2,4-dinitrophenylhydrazine (0.142 g, 0.50 mmol) was added in one portion. Then the mixture was heated for 15 min at 60°C under nitrogen atmosphere. After addition of 5% HCl (15 mL) the resulting precipitate was collected by filtration and washed with water to give the crude hydrazone as a brown powder. To a solution of hydrazone in CHCl<sub>3</sub> (10 mL), pyruvic acid (8 mL), water (0.1 mL), and 3.21 M hydrobromic acid in glacial acetic acid (0.8 mL) were added dropwise at room temperature. The mixture was heated at 60°C under nitrogen atmosphere. The resulting mixture was poured into ether (50 mL) and washed successively with saturated Na<sub>2</sub>CO<sub>3</sub> aqueous solution, 5% NaOH aqueous solution, and water, and dried over Na<sub>2</sub>SO<sub>4</sub>. Evaporation and column chromatography (SiO<sub>2</sub>, hexane/EtOAc, 10/1) gave **29** (0.067 g, 43%) as a colorless solid: mp 235-236 °C;  $[\alpha]^{31}_{D}$  +114° (c 0.245, acetone) [lit<sup>15</sup> mp 235-238 °C;  $[\alpha]^{24}_{D}$  +114° (c 0.224, acetone)]; IR (KBr) 3400 (OH), 2950, 2925, 1740 (C=O), 1720 (C=O), 1680, 1380, 1280, 1240, 1040 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 0.72 (s, 3 H, -CH<sub>3</sub>), 0.93-1.16 (m, 2 H), 1.17 (s, 3 H, -CH<sub>3</sub>), 1.30-2.10 (m, 13 H), 2.17 (s, 3 H, -OCOCH<sub>3</sub>), 2.25-2.50 (m, 4 H), 2.73 (m, 1 H), 2.80 (br, 1 H, -OH), 4.85 (d, J = 17.5 Hz, 1 H, 1H of -CH<sub>2</sub>-OAc), 5.08 (d, J = 17.5Hz, 1 H, 1H of -CH<sub>2</sub>-OAc), 5.74 (s, 1H, -COCH=C); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 68 MHz) δ 14.4, 17.4, 20.5, 20.7, 23.6, 30.1, 32.0, 32.8, 33.9, 34.8, 35.7, 35.7, 38.6, 48.3, 50.5, 53.3, 68.0, 89.9, 123.9, 170.6 (-CO<sub>2</sub>-), 199.6 (-C=O), 205.2 (-C=O). Anal. Calcd for C<sub>23</sub>H<sub>32</sub>O<sub>5</sub>: C, 71.09; H, 8.31. Found: C, 70.88; H, 8.49.

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# Chapter 1.

"Selective Hydrogenation via Dynamic Kinetic Resolution." Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. J. Am. Chem. Soc. 1989, 111, 9134.

# Chapter 2.

Akutagawa, S. J. Am. Chem. Soc. 1990, 112, 7820. Naota, T.; Kumobayashi, H. is to be published.

# Chapter 3.

"Osmium-Catalyzed Oxidation of B-Lactams with Peroxides." Murahashi, S.-I.; Saito, T.; Naota, T.; Kumobayashi, H.; Akutagawa, S. Tetrahedron Lett. 1991, 32, 2145.

# Chapter 4.

"Ruthenium-Catalyzed Oxidation of B-Lactams with Molecular Oxygen and Aldehydes." Murahashi, S.-I.; Saito, T.; Naota, T.; Kumobayashi, H.; Akutagawa, S. Tetrahedron Lett. 1991, 32, 5991.

# Chapter 5.

"Ruthenium-Catalyzed Oxidative Transformation of Alkenes to  $\alpha$ -Ketols with Peracetic acid. Simple Synthesis of Cortison Acetate." Murahashi, S.-I.; Saito, T.; Hanaoka, H.; Murakami, Y.; Naota, T.; Kumobayashi, H.; Akutagawa, S. J. Org. Chem. 1993, 58, 2929.

# **Publication List**

1) "Ruthenium-Catalyzed Oxidation of Amides and Lactams with Peroxides." Murahashi, S.-I.; Naota, T.; Kuwabara, T.; Saito, T.; Kumobayashi, H.;

2) "Ruthenium-Catalyzed Oxidation of β-Lactams." Murahashi, S.-I.; Saito, T.;

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