Title	Study on Development of Hydroxyapatite-Bound Metal Complex Catalysts in Organic Syntheses
Author(s)	森, 浩亮
Citation	大阪大学, 2003, 博士論文
Version Type	VoR
URL	https://hdl.handle.net/11094/2630
rights	
Note	

Study on Development of Hydroxyapatite-Bound Metal Complex Catalysts in Organic Syntheses

Kohsuke MORI

Division of Chemical Engineering
Department of Chemical Science and Engineering
Graduate School of Engineering Science
Osaka University
2003

Study on Development of Hydroxyapatite-Bound Metal Complex Catalysts in Organic Syntheses

Kohsuke MORI

Division of Chemical Engineering
Department of Chemical Science and Engineering
Graduate School of Engineering Science
Osaka University
2003

Preface

This dissertation is a collection of the author's studies, which have been carried out under the supervision of Professor Kiyotomi Kaneda at the Division of Chemical Engineering, Department of Chemical Science and Engineering, Graduate School of Engineering Science, Osaka University from 1998 to 2003.

The present thesis deals with the design of high-performance hydroxyapatite-bound transition metal complex catalysts for various types of oxidation and carbon-carbon bond-forming reactions. Currently, the catalysis of nanostructured heterogeneous catalysts has received considerable attention because of their unique functions that cannot be attained with homogeneous catalysts.

Development of novel catalysts with high selectivity and economically favored reaction rate has been of a grate importance in both academic and industrial fields. Transition metal complexes, in which both steric and electronic properties can be tuned up by varying the active metal center and/or organic ligands, have been developed to greatly contribute toward making the arsenal of powerful synthetic methods. However, they are often faced with a number of disadvantages such as thermal instability and difficulties associated with corrosions of reaction wall. In view of the current interest in establishment of ecologically acceptable chemical processes, there is an increasing emphasis on the development of heterogeneous catalysts for organic synthesis. Therefore, the author tried to create high-performance heterogeneous catalysts using hydroxyapatite, having promising ability as a macroligand for catalytically active centers.

The preparation protocol of solid catalysts using hydroxyapatites will provide an attractive route for the design of nanostructured catalysts at the atomic and molecular levels. The author strongly believes that this study on the development of hydroxyapatite-bound transition metal complex catalysts can offer significant contributions in achieving the simple and clean organic syntheses in the 21st century.

Contents

Chapter I

General Introduction

1. Preliminary

Ever-growing demand for energy and raw materials of mankind is gradually pushing natural resources to their limits, giving rise to more environmental problems. In this regard, chemistry has played a contradictory role, although it represents one of the most successful and diverse sectors of manufacturing industries in many regions of the world. The range of chemical products is enormous, and they make invaluable contributions to our quality of life. However, these manufacturing processes also lead to millions of tons of waste. As a consequence, the role of chemistry is not generally accepted by public; chemistry is actually considered by many as the cause of the pollutions. Hence, so-called "green chemistry" becomes increasingly important, with the objective to create new products, processes, and services that achieve societal, economic, and environmental benefits [1].

Traditionally, fine and specialty chemicals have been produced predominantly via classical organic syntheses employing toxic and/or hazardous stoichiometric reagents. Many of these processes were developed simply to maximize product yield disregarding the environmental influences of inorganic waste and toxic by-products formed during the reaction. In acid catalyzed reaction, for example, most of the waste is generated during the separation stage of the process when a water quench and neutralization results in the formation of large volumes of salts waste. Increasing waste disposal costs are adding to the environmental and the societal costs of an increasingly hostile public towards chemical waste [2]. Therefore the drive toward cleaner technologies brought about by public, legislative and corporate pressure provides new and exciting opportunities for catalysis and catalytic processes [3].

Transition metal complexes are powerful catalysts for organic synthesis, for when the suitable ligands are associated with the metal center, they can offer chemo-, regio-, stereo-, and enantioselectivity under mild reaction conditions [4]. The use of homogeneous transition metal catalysts on an industrial scale, however, is faced with the number of disadvantages such as losses of expensive metal, difficulties associated with corrosion, and plating out on the reaction wall [5]. Also, this procedure often generates large volumes of waste eluent and devours a lot of energy. The efficient use of solid catalysts that stay in a separate phase to the organic compounds can go a long way to achieving these goals through simpler processes, less waste and reusable catalysts.

Heterogeneously-catalyzed processes are widely used in large-scale petrochemical processes [6], but the development of better catalysts in fine, specialty and pharmaceutical chemicals manufacturing processes has been hindered by the presence of numerous kinds of active sites and also by the low concentration of active sites. These factors have precluded a rational improvement of these systems, hence the empirical nature of heterogeneous catalysis. Catalysis is primarily a molecular phenomenon, and it must involve surface organometallic intermediates and/or transition states. Thus, one must be able to construct a well-defined active site, test its catalytic performance, and assess a structure-activity relationship, which will be used, in turn—as in homogeneous catalysis—to design better catalysts. By the transfer of the concepts and tools of molecular organometallic chemistry to solid surfaces, surface organometallic chemistry can generate well-defined active species by understanding the reaction of organometallic complexes with the support, which can be considered as a rigid ligand [7]. This new approach to heterogeneous catalysis can bring molecular insight into the design of new catalysts and even allow the discovery of new reactions. After more than a century of existence, heterogeneous catalysis can still be improved and will play a crucial role in solving current problems of the chemical processes. It offers an answer to economical and environmental issues faced by industry in the production of fine and pharmaceutical molecules.

2. Background

2-1. Hybrid-Heterogeneous Catalysts

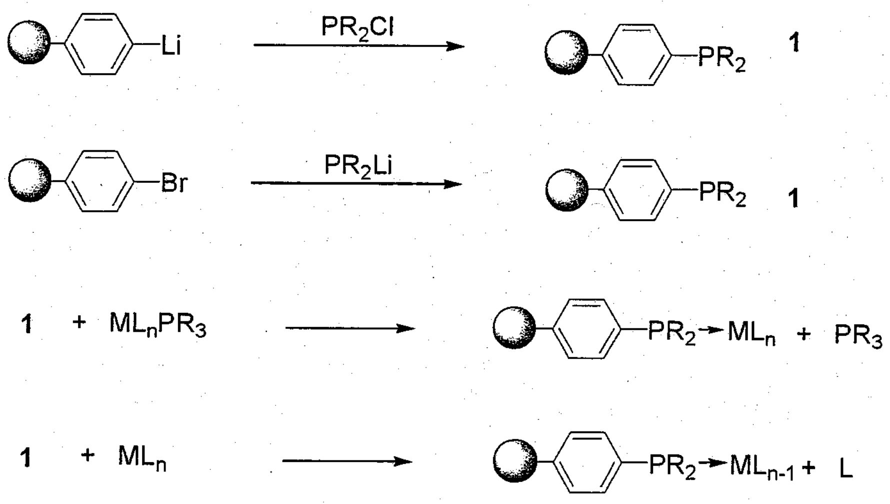
The development of heterogeneous catalysts with well-defined surface structure that enable rapid and selective chemical transformations and can be separated completely from the product is a paramount challenge [8]. These hybrid-catalysts can be synthesized by a number of methods: (i) adsorption of the organic species into the pores of support; (ii) construction of the organic molecule piece by piece within the confines of cavities of the support (the "ship-in-bottle" technique); (iii) attachment of the desired functionality to the support by covalent bond formation; (iv) direct synthesis into the final composite material (isomorphous substitution in framework position) [9]. The types of solid used can be organic, e.g., polymers, or inorganic, e.g., silica and alumina.

In the following, fundamental background on hybrid-heterogeneous catalysts, including synthesis, characterization, and their catalytic performances are reviewed. As target reactions, the author mainly focused on the selective oxidation and carbon-carbon bond-forming reactions.

2-1-1. Polymer-Supported Metal Phosphine Complexes

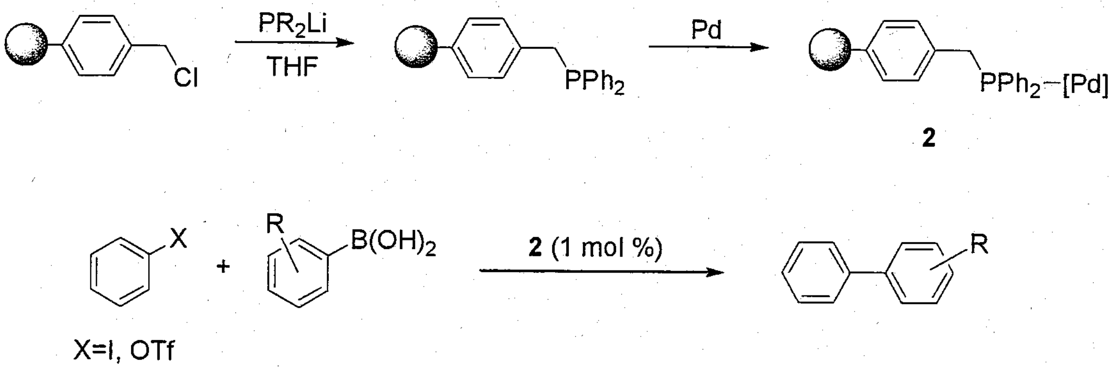
Polystyrene is one of the most popular organic polymeric materials used in synthesis due to its inexpensiveness, ready availability, mechanical robustness, chemical inertness, and facile functionalization [10]. The simplest ways to prepare a polymer-immobilized phosphine ligand is direct reaction of a functionalized polymer such as bromopolystyrene or Merrifield's resin with a derivative of the desired ligand. This route has been employed many times and is often still preparative method of choice. The commercial availabilities of polystyrene resins in a variety of cross-linked densities, particle size, and types permit investigation of these variables on catalytic performances. Simple ligands such as 1 are easily prepared from bromostyrene by initial lithiation of the support to form lithated polystyrene and the reaction with PPh_2Cl. An alternative way to introduce phosphines is by replacing brominated or chloromethylated resins with $LiPR_2$ or KPR_2. Attachment of metals to phosphine-derivatized polymer support is often achieved via a phosphine substitution reaction or direct formation of the phosphine complex by reaction with an organometallic precursor (Scheme 1).

Scheme 1



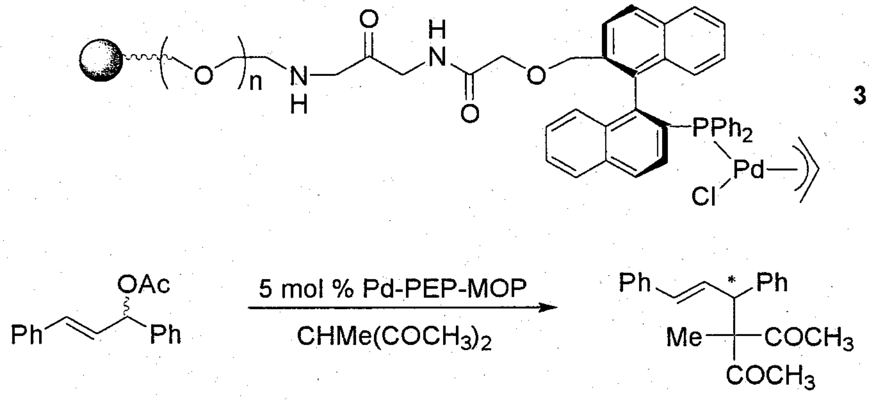
Jang has reported the use of polymer-bound palladium catalyst **2** in the Suzuki coupling reaction of a number of organoboranes with iodobenzene and aryl triflates, with the polymer-supported catalyst being prepared from Merrifield resin in two steps (Scheme 2) [11].

Scheme 2



The obtained results were good with isolated yields of the coupling products in the range 78-96 %. Catalytic activity was at least comparable to homogeneous $Pd(PPh_3)_4$, and in some cases was significantly improved. The catalyst was reused more than 10 times with no decrease in activity, showing the huge utility of these supported catalysts.

Uozumi et al. reported the amphiphlic resin-supported MOP ligands PEP-MOP were prepared on a polystyrene glycol-polystyrene graft copolymer for asymmetric allylic substitution (Figure 1) [12]. Treating this amphiphlic resin-supported MOP ligands with $[PdCl(\eta_3\text{-}C_3H_5)]_2$ gave the corresponding supported catalysts **3**. Up to 84 % ee was obtained by using this catalyst in the asymmetric allylic substitution of 1,3-diphenyl-2-propenyl acetate with 3-methyl-2,4-pentanedione in aqueous media.



3

Figure 1. Amphiphlic catalysts for asymmetric allylic substitution

A number of polystyrene (PS)-supported ruthenium complexes have been reported to catalyze olefin metathesis reactions [13]. Blechert reported the synthesis of the permanently immobilized olefin metathesis catalysts **4**, as shown in Figure 2 [14]. This was used to catalyze olefin metathesis reactions of diallyl malonic acid diethyl ester, giving RCM product quantitatively for 40 min. The catalyst was recycled four times without loss of the catalytic activity. With the soluble catalyst **5** this reaction is complete in less than 5 min, which clearly suggests that fast metathesis reactions are diffusions controlled when the immobilized catalysts is employed.

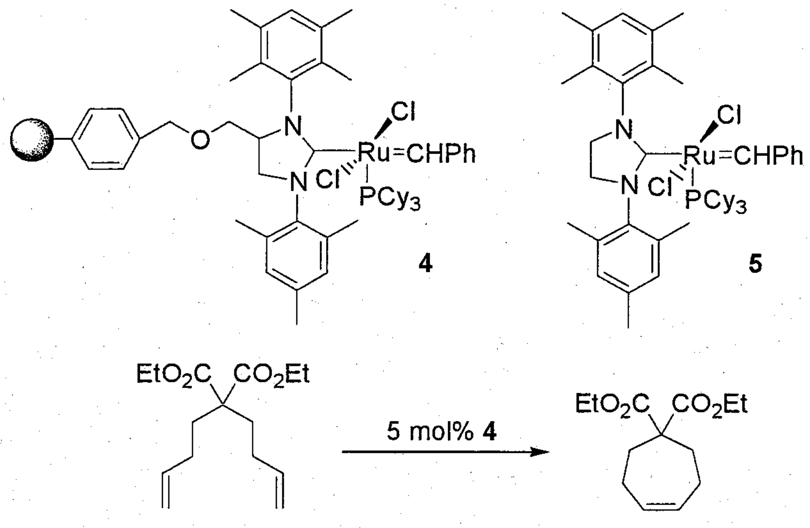


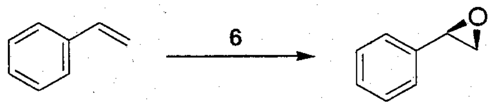
Figure 2. PS-supported ruthenium complex catalysts for olefin metathesis reaction

2-1-2. Organic-Inorganic Hybrid Catalysts

Binding of a ligand to a solid support via a covalent bond has become the most often employed method of heterogenization of a transition metal complex catalyst [15]. Clearly the supports and/or homogeneous complexes must be functionalized in such a way as to be effect immobilization. However, the linking to the inorganic support often leads to detrimental change of catalytic performances. Immobilization without covalent bonds frequently avoids the chemical modification of the homogeneous catalyst, and several strategies were reported to date. The complex can be encapsulated within a pore of a zeolite or embedded into a mesoporous silicate [16]. It is also possible to immobilize a cationic or anionic complex by ion pairing with an anionic and cationic solid [17]. Another strategy involves the use of a thin layer of a suitable solvent containing the homogeneous catalyst onto a solid with a high surface area [18]. In any case of immobilization, the support materials need to be thermally, chemically, and mechanically stable during the reaction processes. Moreover, the structure of the support needs to be such that the active sites are well dispersed on its surface and that these sites are easily accessible [19]. Generally, this requires the support to have a reasonably high surface area (typically > 100 m^2g^{-1}) and appropriate pore size (i.e., > 20 Å) to allow easy diffusion of the reactants to the active sites [20]. Inorganic supports such as silica, zeolite, alumina, zirconia, ZnO, clay, etc., generally meet these criteria rather than organic polymers.

For example, Kim *et al.* reported a salen complex immobilized on the surface of mesoporous MCM-41 in a step-by-step manner (Figure 3) [21]. Reaction of (3-aminopropyl) trimethoxysilane with MCM-41 molecular sieves gave the modified MCM-41 with a free amino group, which was used to connect the salen ligand. A multifunctional group aldehyde 2,6-diformyl-4-*tert*-butylphenol was attached to MCM-41 through imine bond formation. Subsequent routine chemistry furnished the immobilized salen complex **6**. In the asymmetric epoxidation of styrene using *m*-CPBA/NMO as oxidants, the corresponding epoxide was obtained in 89% ee at 92% conversion (Scheme 3). In comparison, 84 % ee at 97 % conversion was observed when the homogeneous catalyst was used.

Scheme 3



Contemporaneously, Kim *et al.* also immobilized the chiral (salen)Mn complexes by direct ion-exchange with Na^+-type MCM-41 (Figure 4) [22]. The heterogenized chiral (salen)Mn complexes 7 exhibited relatively high enantioselectivity for epoxidation of styrene using *m*-CPBA/NMO as oxidant system, as compared with the homogeneous counterparts. This improvement of ee was explained by steric restriction of the olefin's approach to the catalytic site in the mesopores. Moreover, the immobilized (salen)Mn complexes were stable during the reaction without any leaching. The catalytic activity and selectivity were not changed after three reuses in the epoxidation of styrene.

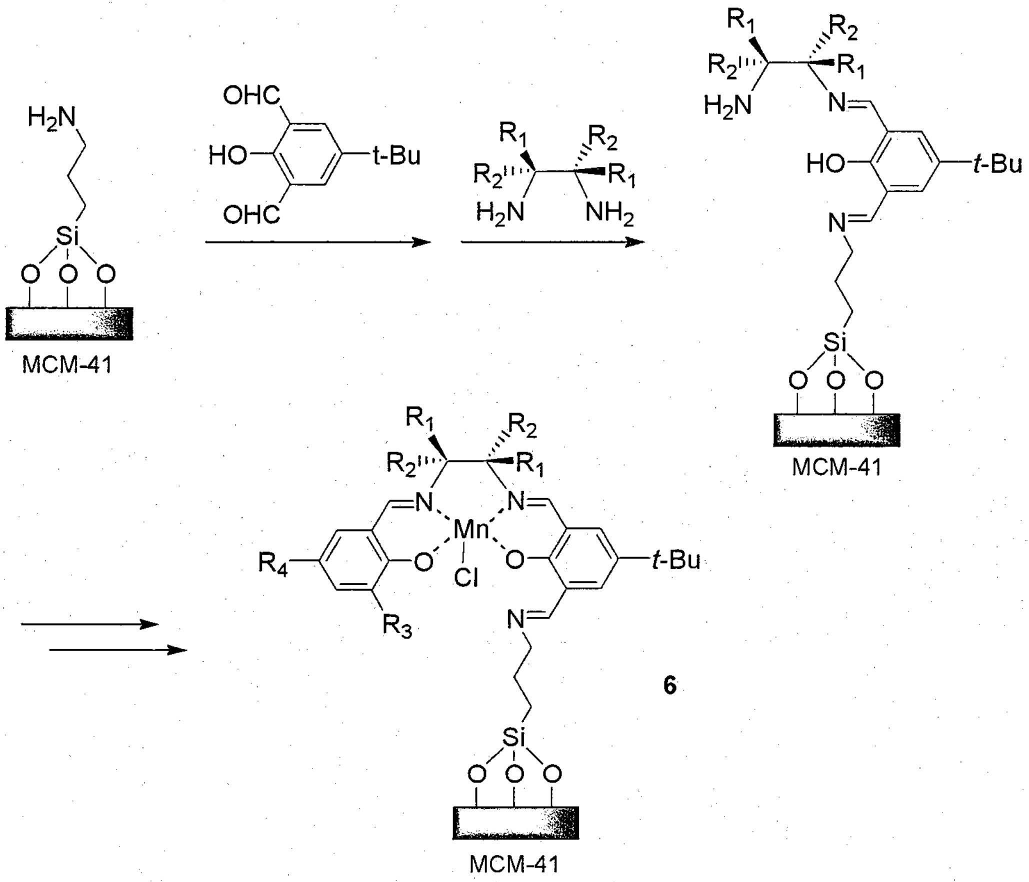
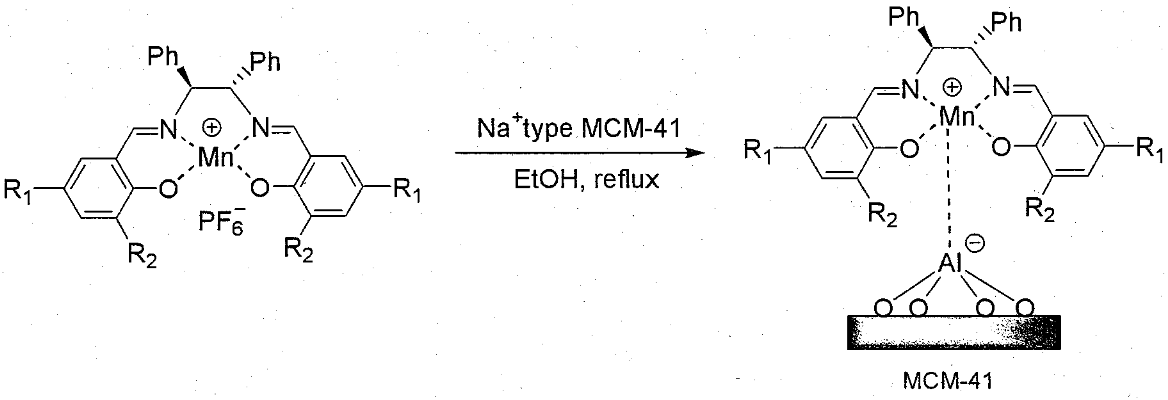


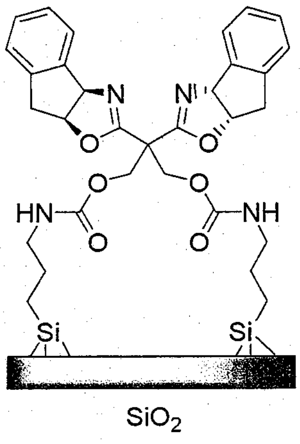
Figure 3. Salen Mn complexes immobilized on mesoporous MCM-41



7

Figure 4. Salen Mn complexes immobilized on mesoporous MCM-41by direct ion exchange

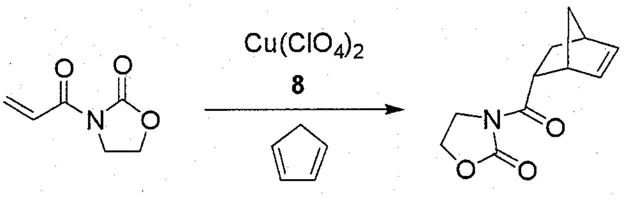
Recently, Lemaire studied the Diels-Alder reaction catalyzed by chiral bis(oxazoline) Cu complex immobilized on silica surface (Figure 5) [23]. The catalytic performance of the silica-grafted **8** was examined for asymmetric Diels-Alder reaction of 3-acryoyl-2-oxazolidinone with cyclopentadiene (Scheme 4). The heterogenized catalyst could be efficiently recycled when $Cu(ClO_4)_2 \cdot 6H_2O$ was used as the metal precursor. The catalytic activity did not diminish after four cycles. To obtain the best result, the silanol groups of this silica catalyst were protected by trimethylsilyl groups, and thus 92 % ee was obtained. These results, although not quite as good as those of the homogeneous system, are better than any achived so far with heterogeneous bis(oxazoline) ligands in Diels-Alder reaction. Moreover, this system has the advantage of being compatible with air humidity.



8

Figure 5. Chiral bis(oxazoline) Cu complex immobilized on silica

Scheme 4

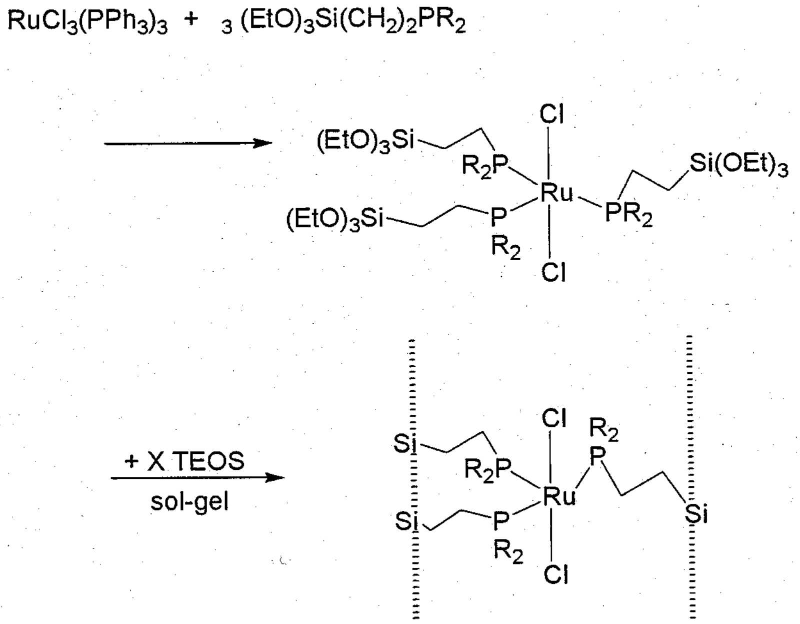


2-1-3. Sol-Gel Processed Interphase Catalysts

With the aim to develop high-performance heterogenized homogeneous catalysts, the concept of "interphase catalysts" has recently been introduced [24]. An interphase is defined as a region within a material in which a stationary and mobile component penetrates each other on a molecular level. The stationary phase is composed of an inert matrix, flexible spacer, and an active center, whereas the mobile phase consists of a solvent or dissolved reactants. In the ideal interphase, the reactive center is uniform, well-defined, and highly mobile. Rigid but highly porous materials can as well serve as supporting matrix afforded that sufficiently long spacers lead to a satisfactory mobility of the reactive centers. However, conventional supported catalysts are faced with the major disadvantages such as leaching, poor selectivity, and restricted accessibility. On the contrary, an interphase system combines many advantages of homogeneous (high activity, selectivity, reproducibility) and heterogeneous (easy separation and recovery of the catalyst from the reaction mixture) catalysis. For the preparation of interphase catalysts, the sol-gel process is a powerful tool [25]. Suitable polysiloxane networks (hybrid polymers) are synthesized under low-temperature conditions. Si-multaneous co-condensation of T-silyl-functionalized metal complexes or ligands with various alkoxysilanes provide materials in which, in the case of ideal interphase, the reactive centers are nearly homogeneously distributed across a chemically and thermally inert carrier matrix.

Sol-gel derived ruthenium catalysts for the synthesis of *N,N*-dimethylformamide (DMF) from supercritical carbon dioxide were reported by the group of Baiker [26]. As ligands, T-silyl-functionalized phosphines of the type of $Ph_2P(CH_2)_2Si(OEt)_3$ and $Me_2P(CH_2)Si(OMe)_3$ were employed. Co-condensation with TEOS produced the ruthenium (II) catalysts **9** (Figure 6). The structural characterization by means of ^{31}P and ^{29}Si NMR, EXAFS, XRD, TEM, and nitrogen physisorption showed that prepared gels had micro- to mesopores and that the organometallic complexes were immobilized as monomer. Under the required reaction conditions, both candidates were stable and able to produce DMF with

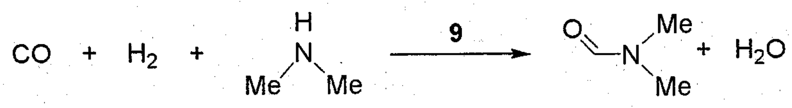
100 % selectivity; a maximum turnover number (TON) of 110,800 corresponding to a TOF of 1860 h^{-1} (Scheme 5). Leaching of active species from the catalysts was negligible, because the filtrate exhibited no catalytic activity in subsequent activity test.



9

Figure 6. Synthesis of sol-gel derived ruthenium (II) catalysts.

Scheme 5



An attractive topic is the nondestructive immobilization of cobalt Schiff base complexes [27]. As an example, in a first step a cobalt (salen) compound was obtained by reaction of cobalt acetate with a solution of aminopropyltriethoxysilane and salicylaldehyde. Then the silyl-modified salen complex was poly-co-condensed with TEOS to give **10** (Figure 7). The polysiloxane **10** was characterized by FT-IR, UV-vis, XPS, ICP-MS, EPR, BET, TGA, and laser ablation studies. Oxidation of ethylbenzene to acetophenone was carried out in DMSO at 130 °C under an oxygen atmosphere in the presence of pyridine and potassium *tert*-butoxide. After 72 h, the conversion achieved a value of 99.9 % (Scheme 6). Leaching of cobalt analyzed with ICP in the filtrate amounted to < 0.1 wt %.

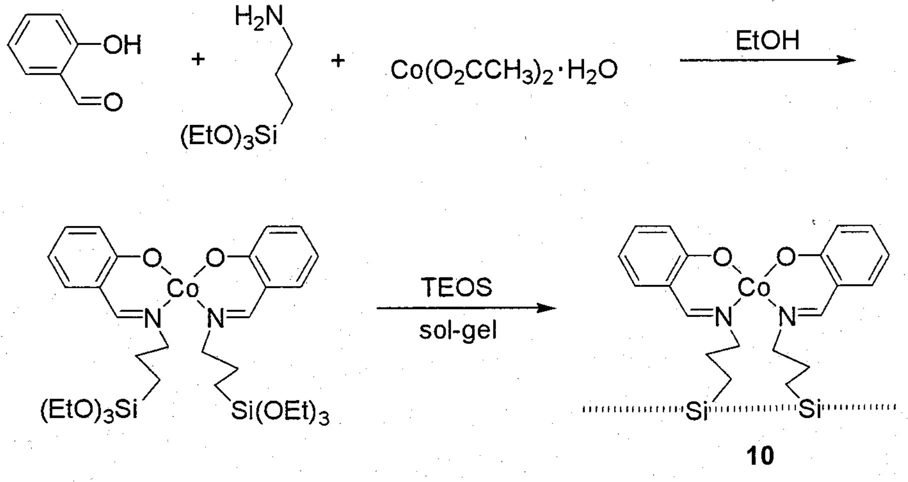
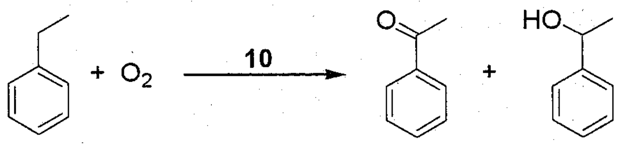


Figure 7. Immobilization of cobalt Schiff base complexes.

Scheme 6



2-1-4. Immobilized Nanoparticles

Nanoscale transition metal particles are gaining increasing attention in the field of catalysis, nanoelectronics, and material science because of their existence on the borderline molecular states with discrete quantum energy levels [28]. However, the application of liquid suspensions of metal nanoparticles in catalysis is limited due to the difficulties of the products separation and catalysts recycling. Several method and supports have been investigated for the immobilization of metal nanoparticles. Transition metal nanoparticles can be either adsorbed on inorganic supports or chemically bonded to polymeric materials.

Liu reported the immobilization of Pd, Pt, or Rh colloids stabilized by PVP)poly-vinyl-pyloridone on silica [29]. The metal nanoparticles are deposited by adsorption of the protective polymers/metal complex on silica and this adsorption was due to hydrogen bonds formed between polymers and the hydroxyl functions of silica. With the same procedure, Au or Pd nanoparticles dispersed within the pores of mesoporous silica or in the interlamellar space of silicates such as montmorillonite and kaolinite have been reported [30].

Hirai [31] and Toshima [32] grafted Pt and Rh colloids onto polyacrylamide gel having aminoethylgroup. The immobilization is achieved by formation of amide bonds by reaction of ester function of protecting polymer with amine function of the gel (Figure 8). According to TEM analysis, the grafted nanoparticles remains unchanged during the immobilization process.

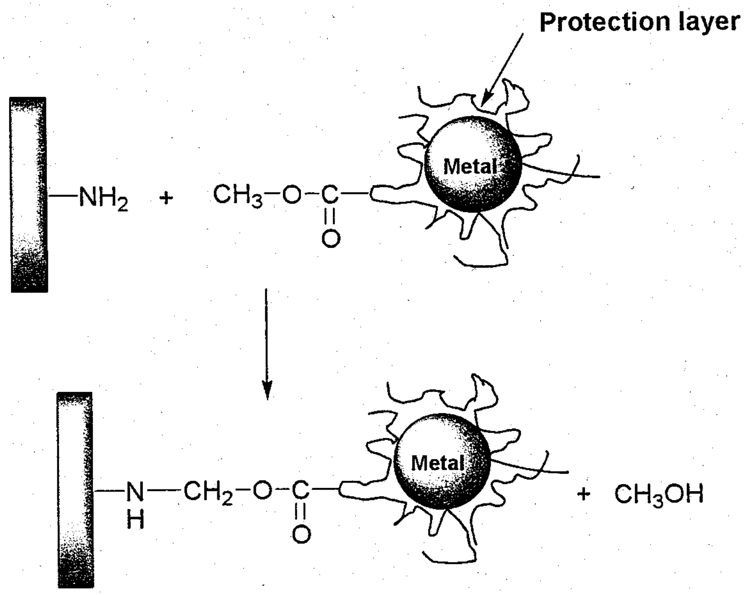


Figure 8. Immobilization of Pt and Rh colloids onto polyacrylamide gel.

Akashi et al. prepared transition metal nanoparticles covalently bonded to the support through protecting polymer [33]. The supports used were polystyrene microspheres with surface-grafted PNIPAAm (Figure 9). This synthetic procedure consists of the reduction of H_2PtCl_6 in the presence of the microspheres. Thus, PNIPAAm chains will stabilize and maintain dispersed Pt nanoparticles on the surface of the polystyrene microsphere.

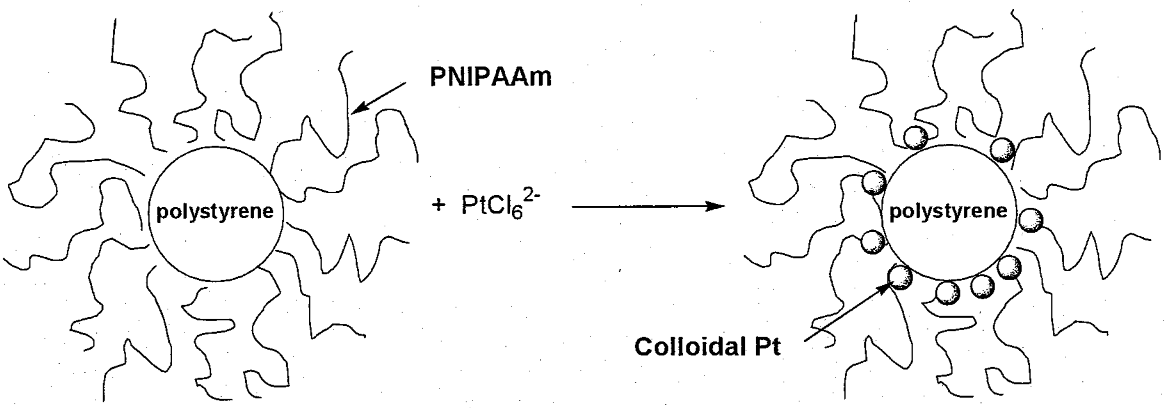


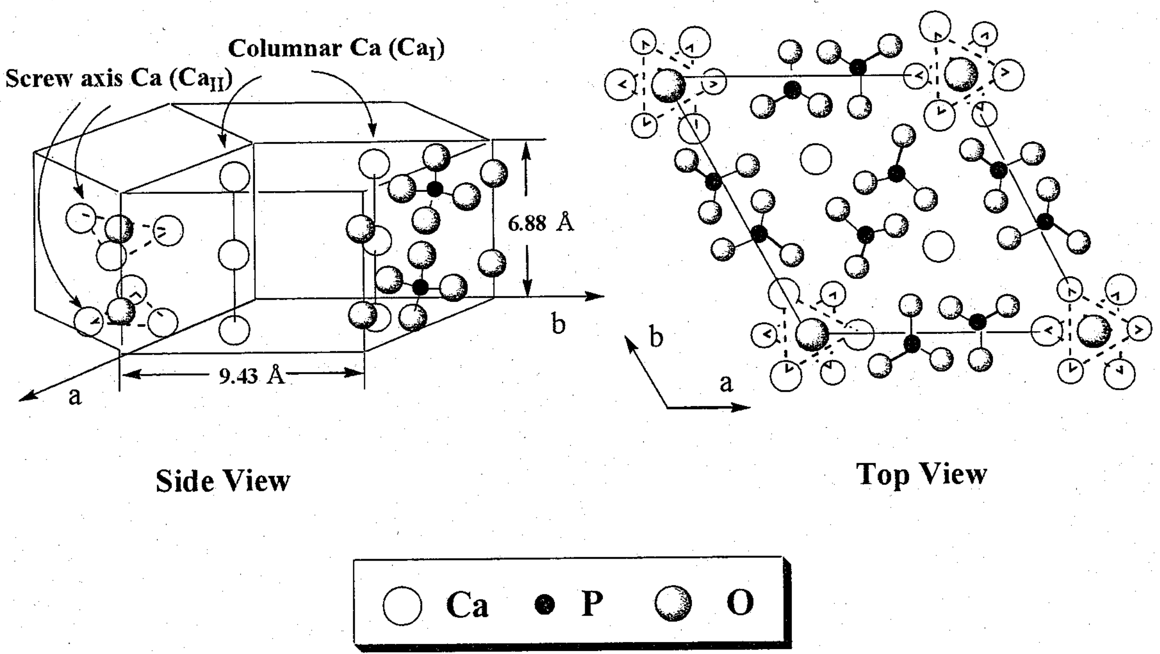
Figure 9. Pt colloids supported on polystyrene microspheres.

2-2. Properties of Apatite Compounds

The apatite and related calcium phosphates have been of considerable interest to biologists, mineralogists, and inorganic and industrial chemists for many years [34]. The reasons for this are clear: the apatite form the mineral component of bones and teeth, and the more acid calcium phosphates are probably also involved in mineralization process; apatites and other calcium phosphates are increasingly used as biocompatible materials for bone replacement or for the coating of bone phosphorous, particularly phosphates for the production of fertilizers; and they are used as phosphorous in fluorescent light tubes. The great versatility of apatites in accepting a large variety of substitutional ions complicates their study, but also presents considerable interest in its own right.

The detailed structures of the apatite compounds have been well established by both X-ray [35] and neutron diffraction studies [36], and most recently the application of atomic force microscopy has been reported [37]. Stoichiometric calcium hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$] has a hexagonal structure constructed from columns of Ca and O atoms which are parallel to the hexagonal axis with lattice constants of a = 9.418 and c = 6.884 Å

[38] (Figure 10). Three oxygen atoms from each PO_4 tetrahedron are shared by one column, with the fourth oxygen atom attached to a neighboring column. The hexagonal unit cell of calcium hydroxyapatite contains ten cations located on two sets of non-equivalent sits, four on site I (Ca_I) and six on site II (Ca_{II}). The calcium ions on site I are aligned in columns, while those on site II are in equilateral triangles centered on the screw axes. The site I cations are coordinated to six oxygen atoms belonging to different PO_4 tetrahedra and also to three, relatively distant, oxygen atoms. The site II cations are found in cavities in the walls of the channels formed between the cations and O atoms. The hydroxygroups are situated in these channels and probably form an approximately triangular coplanar arrangement with the Ca ions [39].



Side View

Top View

Figure 10. Structure of Hydroxyapatite

Hydroxyapatites have several unique characteristics, which makes them worthy of consideration as nanostructured materials. The chemical composition of hydroxyapatites can be also modified from the stoichiometric form, $Ca_{10}(PO_4)_6(OH)_2$ (Ca/P = 1.67), to the nonstoichiometric Ca-deficient form without significant changes in the crystallographic structure. Nonstoichiometric hydroxyapatites have the formula $Ca_{10-Z}(HPO_4)_Z(PO_4)_{6-Z}(OH)_{2-Z}$ $(0 < Z \leq 1,\ 1.5 \leq Ca/P < 1.67)$, in which the charge deficiency due to the lack of Ca^{2+} in the lattice is compensated by both H^+ introduction and OH^- removal [40]. The Ca-deficient hydroxyapatites function as acid catalyst [41], while stoichiometric hydroxyapatite has base properties [42]. The selectivity of alcohol dehydrogenation and dehydration over hydroxyapatite catalysts has been reported to be controlled by this stoichiometry [43]. Hydroxyapatite can be prepared cheaply from readily available materials. They have relatively high surface areas, 60-100 m^2/g, and high heat resistance (stable up to 1173 K) due to their nonporous structure. Another notable characteristic of this material is flexibility in its elemental composition, as expressed follows [44].

$$\mathbf{M_{10}(ZO_4)_6X_2}$$

where M : Ca, Pb, Cd, Sr, Ni, Eu, Al, Y, La, Ce, Na, K. etc.
Z : P, As, V, Cr, Si, C, Al, S, Re, etc.
X : OH, F, Cl, Br, I, O, N, CO_3, H_2O, □(vacancy), etc.

Suzuki and co-workers have concluded that the divalent cations possessing ionic radii within the radius of Ca_I (1-1.05 Å) and Ca_{II} (0.9-1.3 Å) as well as higher electronegativity than that of Ca^{2+} can be readily accommodated into the apatite framework [45]. One more important feature is cation exchange abilities [46]. Various kinds of transition metal cations can be readily accommodated into the apatite framework via cation exchange process, which have a high potentiality for the function as the catalytically active center. These many advantages makes the hydroxyapatites attractive as catalysts and catalyst supports, even though, few excellent applications has been studied so far [47].

3. Purpose of This Thesis

Recent interest in evolution of environmentally-benign organic synthesis has evoked a renewed interest in developing heterogeneous catalysts that maintain high activity and selectivity. Creation of a stable and well-defined active center on solid surface is a promising protocol for designing more efficient hybrid-catalysts that bridge the gap between homogeneous and heterogeneous catalysis. To date, most of these attempts have been directed toward the anchoring of metal complex catalysts on various insoluble supports. These catalysts, however, have often encountered diminishing of catalytic activity in comparison with homogeneous analogues together with their limited stability towards metal leaching.

The main purpose of this thesis is to design new types of the hybrid-catalysts based on hydroxyapatites (HAP) for attaining "green organic synthesis". The choice of hydroxyapatite is motivated by the following advantages: i) well-defined monomeric active species can be precisely created on their surface based on multiple functionalities, ii) active species are immobilized rigidly on hydroxyapatite surface, which can help to overcome the problems toward metal leaching iii) neutral nature avoids side-reactions arising from acid-base properties of support itself. Thus, hydroxyapatite serves as a promising macroligand for catalytically active center. The use of hydroxyapatite facilitates catalyst/product separation and recycling of catalysts, and which also provides unique catalytic functions including site isolation of well-defined active species, cooperative action by several sites, and steric control of a reaction intermediate. Furthermore, the designing of the prominent heterogeneous catalysts can allow large-scale operations, contributing to the increasing demands for environmentally-friendly chemical processes.

4. Outline of This Thesis

The present thesis deals with the studies on the catalyst design of the hydroxyapatite-bound transition metal complexes toward green organic syntheses. The strategies of the design of nanostructured hydroxyapatites are illustrated in Figure 11.

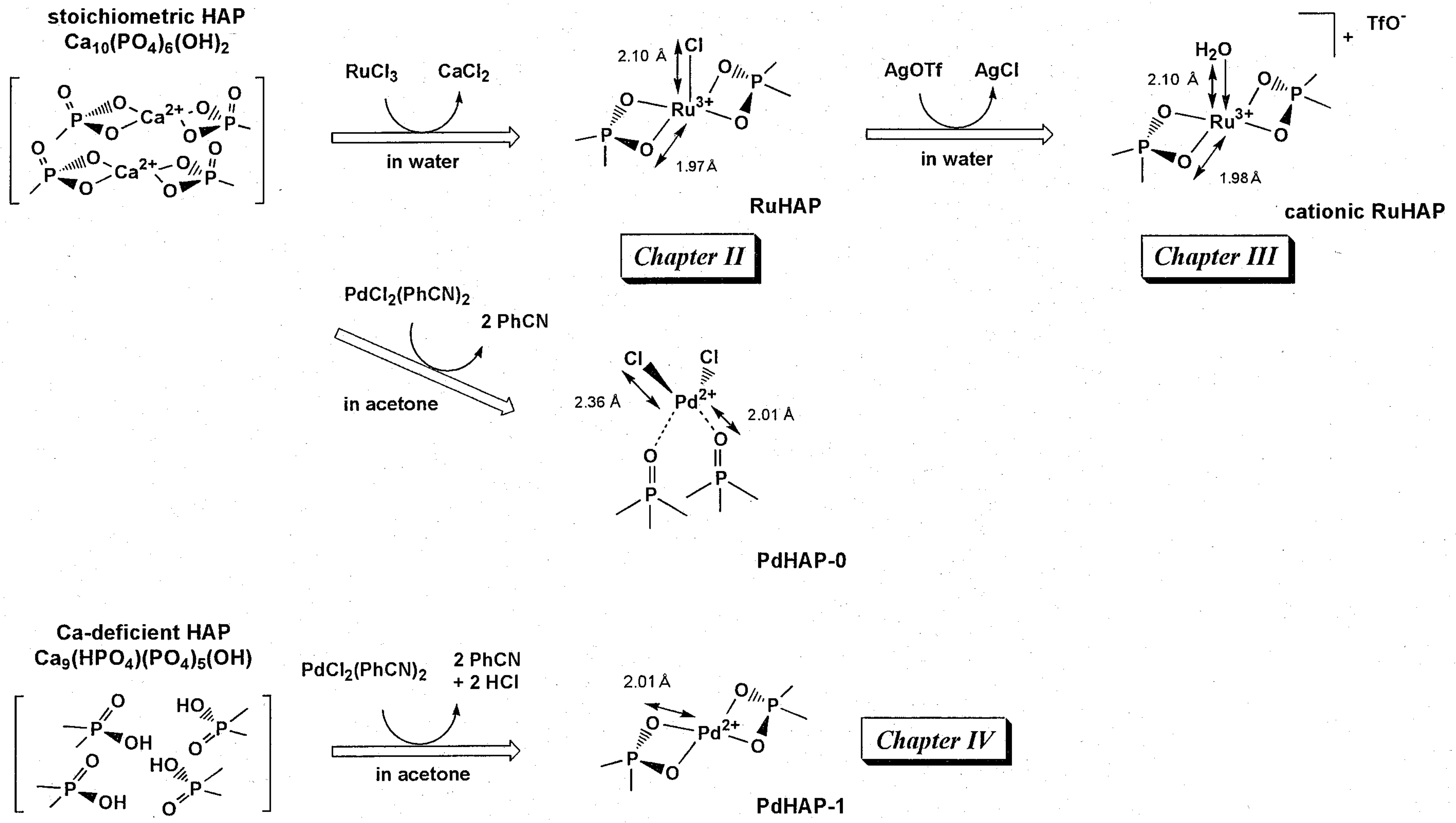
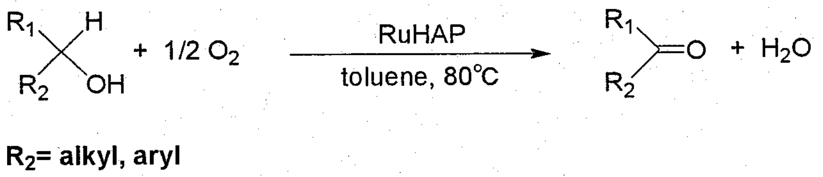
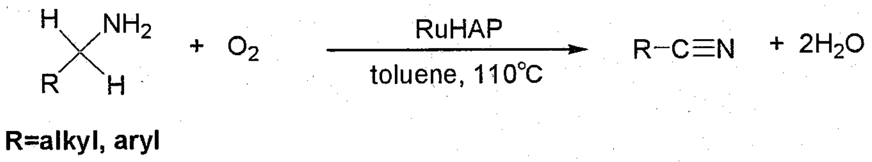


Figure 11. Strategies for design of hydroxyapatite catalysts

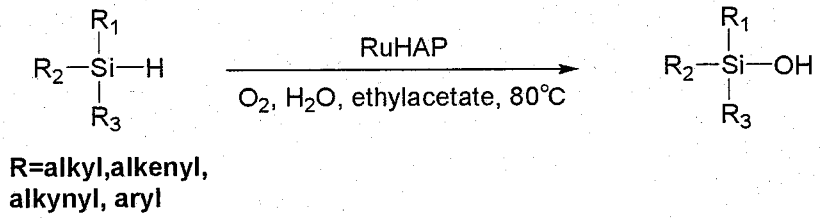
In the next Chapter, the author prepared hydroxyapatite-bound Ru complex based on cation-exchange ability by treatment of stoichiometric hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$, with an aqueous $RuCl_3$ solution. An equimolar substitution of Ru^{3+} for Ca^{2+} occurred on the surface of hydroxyapatite, which gave a monomeric Ru^{3+} species surrounded by oxygen and chlorine atoms (RuHAP). This RuHAP could efficiently catalyze the oxidation of alcohols and amines using molecular oxygen as a sole oxidant (eqs. 1 and 2). Moreover, this RuHAP catalyst was applicable to the oxidation of silanes to silanols in the presence of H_2O and O_2 (eq. 3).



(eq. 1)

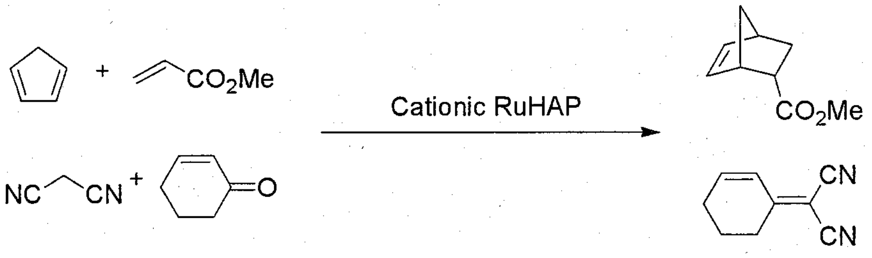


(eq. 2)



(eq. 3)

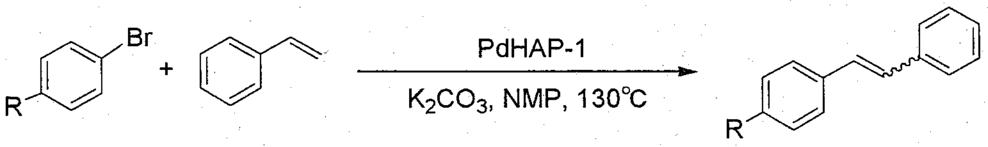
Description in Chapter III is the synthesis of hydroxyapatite-bound cationic Ru complexes. The simple surface modulation of the neutral RuHAP using AgX ($X=SbF_6^-$ and TfO^-) afforded cationic Ru species with potentially vacant coordination sites. The obtained cationic RuHAPs exhibited Lewis acid property, promoting Diels-Alder and aldol reactions with high efficiencies (eqs. 4 and 5). No Ru leaching was detected even under aqueous conditions, and then the catalyst was recyclable. Furthermore, the present Ru catalyst showed unique catalytic functions including acid-base bifunctional catalysis and steric control of a reaction intermediate.



(eq.4)

(eq.5)

In Chapter IV, new classes of hydroxyapatite-bound Pd complex (PdHAP-1), which was synthesized with nonstoichiometric hydroxyapatite $Ca_9(HPO_4)(PO_4)_5(OH)$, is described. The PdHAP-1 exhibited high catalytic activity for the Mizoroki-Heck reactions (eq. 6), and was shown to give a remarkably high TON of up to 47,000 in the reaction of bromobenzene with styrene. Moreover, the PdHAP-1 catalyst was also applicable to the Suzuki-Miyaura coupling reaction of chloroarenes bearing electron-withdrawing substituents in the presence of TBAB (tetrabuthylammonium bromide) and a small amount of water.



(eq.6)

Finally, the author summarizes overall conclusions of the present thesis. The scopes for the extensive design of the hydroxyapatite-bound metal complex catalysts are also mentioned.

References

[1] (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice;* Oxford University Press, 1998. (c) Clark, J. H. *Green Chem.* **1999**, *1*, 1. (d) Sheldon, R. A. *Green Chem.* **2000**, *2*, G1. (e) Anastas, P. T.; Bartlett, L. B.; Kirchhoff, M. M.; Williamson, T. C. *Catal. Today* **2000**, *55*, 11. (f) *Nanotechnology in Material Science*, Mitura, S. Ed.; Elsevier: Amsterdam, 2000. (g) *Nanomaterials in Catalysis*, Lu, G. Q. Eds.; *Catal. Today*, *68*, **2001**.

[2] Sheldon, R. A. *Chemtech* **1994**, *24*, 38.

[3] Clark, J. H.; Rhodes, C. N. RSC *Clean Technology Monographs*, Clark, J. H. Ed.; Chambering, 2000.

[4] (a) Heck, R. F. *Palladium Reagents in Organic Syntheses*, Academic Press: London, 1985. (b) Tsuji, J. *Palladium Reagents and Catalysts*, Wiley: Chichester, 1995. (c) Trost, B. M. *Angew. Chem. Int. Ed.* **1995**, *34*, 259. (d) *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann, W. A., Eds., VCH: Weinheim, 1996. (e) Beller, M.; Riermeir, T. H. In *Transition Metals for Organic Syntheses*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1996.

[5] Wijngaarden, R. J.; Kronberg, A.; Westerterp, K. R. *Industrial Catalysis*; Wiley-VCH: Weinheim, 1997.

[6] Knözinger, H.; Weitkamp, J. *Handbook of Heterogeneous Catalysis*; Ertle, G., Knözinger, H., Weitkamp, J., Eds.; Wiley-VCH: Weinheim, 1997.

[7] (a) Gates, B. C. *Chem. Rev.* **1995**, *95*, 511. (b) Basset, J.-M.; Lefebre, F.; Santini, C. *Coord. Chem. Rev.* **1998**, *178-180*, 1703. (c) Iwasawa, Y. *Prep. Solid Catal.* **1999**, 427. (d) Bergbreiter, D. E. *Med. Res. Rev.* **1999**, *19*, 439. (e) Copéret, C.; Chabanas, M.; Saint-Arroman, R. P.; Basset, J.-M. *Angew. Chem. Int. Ed.* **2003**, *42*, 156.

[8] (a) De Vos, D. E.; Dams, M.; Sels, B. F.; Jacobs, P. A. *Chem Rev.* **2002**, *102*, 3615. (b) Wight, A. P.; Davis, M. E. *Chem Rev.* **2002**, *102*, 3589.

[9] Arends, I. W. C. E.; Sheldon, R. A. *Applied Catalysis A: General* **2001**, *212*, 175.

[10] Leadbeater N. E.; Marco, M. *Chem Rev.* **2002**, *102*, 3217. (b) McNamara, C. A.; Dixon, M. J.; Bradly, M. *Chem Rev.* **2002**, *102*, 3275.

[11] Jang, S. *Tetrahedron Lett.* **1997**, *38*, 1793.

[12] Uozumi, Y.; Danjyo, H.; Hayashi, T. *Tetrahedron Lett.* **1998**, *39*, 8303.

[13] (a) Nguyen, S. T.; Grubbs, R. H.; *J. Organomet. Chem.* **1995**, *497*, 195. (b) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3074. (c) Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 9858. (d) Dowden, J.; Savovi, J. *Chem. Commun.* **2001**, 37.

[14] Schürer, S. C.; Gesseler, S.; Bushman. N.; Blechert, S. *Angew. Chem. Int. Ed.* **2000**, *39*, 3898.

[15] Song, C. E.; Lee, S.-G. *Chem Rev.* **2002**, *102*, 3495.

[16] (a) Miller, M. M; Sherrington, D. C. *J. Catal.* **1995**, *152*, 377. (b) De Vos, D. E.; Parton, R. F. *J. Incl. Phen. Mol. Recogn. Chem.* **1995**, *21*, 185.

[17] (a) Bianchini, C.; Burnaby, D. G.; Evans, J.; Frediani, P.; Meli, A.; Oberhauser, W.; Psaro, R.; Sordelli, L.; Vizza, F. *J. Am. Chem. Soc.* **1999**, *121*, 5961. (b) de Rege, F. M.; Morita, D. K.; Ott, K. C.; Tumas, W.; Broene, R. D. *Chem. Commun.* **2000**, 1797.

[18] Kakkar, A. K. *Chem Rev.* **2002**, *102*, 3579.

[19] Price, P. M.; Clark, J. H.; Macquarrie, , D. J. *J. Chem. Soc., Dalton Trans.* **2000**, 101.

[20] (a) Vankelecom, I. F. J.; Jacobs, P. A. In *Catalyst Immobilization on Inorganic Supports*; De Vos, D. E., Vankelecom, I. F. J., Jacobs, P. A. Eds.; Wiley-VCH: Weinheim, 2000. (b) Shuttleworth, S. J.; Allin, S. M.; Sharama, P. K. *Synthesis* **1997**, 1217. (c) Bergbreiter, D. E. In *Organic polymers as a Catalyst Recovery Vehicle in Chiral Catalyst Immobilization and Recycling*; De Vos, D. E., Vankelecom, I. F. J., Jacobs, P. A. Eds.; Wiley-VCH: Weinheim, 2000.

[21] Kim, G. J.; Shin, J. H. *Tetrahedron Lett.* **1999**, *40*, 6827.

[22] (a) Kim, G. J.; Kim, S. H. *Catal. Lett.* **1999**, *57*, 139. (b) Kim, G. J. *React. Kinet. Catal. Lett.* **1999**, *67*, 295.

[23] Rechavi, D.; Lemaire, M. *Org. Lett:* **2001**, *3*, 2493.

[24] (a) Linder, E.; Schneller, T.; Auer, F.; Mayer, H. A. *Angew. Chem. Int. Ed.* **1999**, *38*, 2155. (b) Linder, E.; Kemmler, M.; Schneller, T.; Mayer, H. A. *Inorg, Chem.* **1995**, *34*, 5489. (c) Lu, A.-L.; Lindner, E.; Mayer, H. A. *Chem Rev.* **2002**, *102*, 3543.

[25] (a) Baiker, A.; Grunwaldt, J. D.; Muller, C. A.; Schmid, L. *Chimia* **1998**, *52*, 517. (b) Huesing, N.; Schubert, U. *Angew. Chem. Int. Ed.* **1998**, *37*, 23. (c) Moreau, J. J. E.; Man, M. W. C. *Coord. Chem. Rev.* **1998**, *180*, 1073. (d) Schubert, U. *New. J. Chem.* **1994**, *18*, 1049.

[26] (a) Kroecher, O.; Koeppel, R. A.; Baiker, A. *Chem. Commun.* **1996**, 1497. (b) Kroecher, O.; Koeppel, R. A.; Froeba. M.; Baiker, A. *J. Catal.* **1998**, *178*, 284.

[27] Murphy, E. F.; Schmid, L.; Buergi, T.; Maciejewski, M.; Baiker, A.; Guenther, D.; Schneider, M. *Chem. Mater.* **2001**, *13*, 1296.

[28] (a) *Clusters and Colloids: From Theory to Applications* Schmid, G. Ed.; VCH, Weinheim, 1994. (b) *Nanoparticles and Nanostructured Filems* Fendler, J. H. Ed.; Wiley-VCH, Weinheim, 1998. (c) Finke, R. G. In *Metal Nanoparticles: Synthesis, Characterization and Applications*; Feldheim, D. L., Foss, C. A., Jr., Eds.; Marcel Dekker: New York, 2002.

[29] (a) Wang, Y.; Liu, H.; Huang, Y. *Polym. Adv. Technol.* **1996**, *7*, 634. (b) Wang, Q.; Liu, H.; Wang, H. *J. Coloid Interface Sci.* **1997**, *190*, 380.

[30] (a) Shi, H.; Zhang, L.; Cai, W. *Mater. Res. Bull.* **2000**, *35*, 1689. (b) Szûcs, A.; Berger, F.; Dékány, I. *Colloid Surf., A* **2000**, *174*, 387.

[31] (a) Hirai, H.; Ohtaki, M.; Komiyama, M. *Chem. Lett.* **1986**, 269. (b) Hirai, H.; Ohtaki, M.; Komiyama, M. *Chem. Lett.* **1987**, 149.

[32] (a) Toshima, N.; Ohtaki, M.; Teranishi, T. *React. Polym.* **1991**, *15*, 135. (b) Ohtaki, M.; Toshima, N.; Komiyama, M. Hirai, H. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1433.

[33] (a) Suzuki, K.; Yumura, T.; Mizuguchi, M., Tanaka, Y.; Chen, C.-W.; Akashi, M. *J. Appl. Polym. Sci.* **2000**, *77*, 2678. (b) Chen, C.-W.; Chen, M. -Q; Serizawa, T.; Akashi, M. *Chem. Commun.* **1998**, 831. (c) Chen, C.-W.; Serizawa, T.; Akashi, M. *Chem. Mater.* **1999**, *11*, 1381.

[34] (a) Elliott, J. C. *Structure and Chemistry of the Apatites and Other Calcium*

Orthophosphates: Elsevier, Amsterdam, 1994. (b) Cihlář, J.; Trunec, M. *Biomaterials* **1996**, *17*, 1905. (c) Suzuki, T.; Hatsushika, T.; Hayakawa, Y. *J. Chem. Soc., Farady Trans. 1* **1981**, *77*, 1059.

[35] (a) Ji, H.; Marquis, P. M. *J. Matr. Sci. Lett.* **1991**, *10*, 132. (b) Landis, W. J.; GlimCher, M. J. *J. Ultrastruct. Res.* **1978**, *63*, 188.

[36] Kay, M. I.; Young, R. A.; Posner, A. S. *Nature* **1964**, *204*, 2050.

[37] Siperko, L. M.; Landis, W. J. *Appl. Phys. Lett.* **1992**, *61*, 2611.

[38] (a) Corbridge, D. E. C. *Studies in Inorganic Chemistry 10, Phosphorous, An Outline of its Chemistry, Biochemistry, and Technology*: 4th Ed., Elsevier, Amsterdam, 1994. (b) Corbridge, D. E. C. *Topics in Phosphorous Chemistry*: Griffith, E. J., Grayson, M. Eds.; Interscience: New York, 1966.

[39] Corbridge, D. E. C. *The Structural Chemistry of Phosphorous*: Elsevier, Amsterdam, 1974.

[40] Neuman, W. F.; neuman, M. W. *Chem. Rev.* **1953**, *53*, 1045.

[41] (a) Bett, J. A. S.; Christner, L. G.; Hall. W. K. *J. Am. Chem. Soc.* **1967**, *89*, 5535. (b) Kibby, C. L.; Hall, W. K. *J. Catal.* **1973**, *29*, 144. (c) Kibby, C. L.; Lande, S. S.; Hall, W. K. *J. Am. Chem. Soc.* **1972**, *94*, 214. (d) Kibby, C. L.; Hall, W. K. *J. Catal.* **1973**, *31*, 65. (e) Kibby, C. L.; Hall, W. K. In *The chemistry of Biosurfaces*: Vol 2, Hair, M. L. Ed.; Dakker, New York, 1972.

[42] Izumi, Y.; Kadoya, M.; Abe, H.; Ito, H.; Tada, A. C. *Chem. Lett.* **1982**, 425.

[43] Bowman, R. S.; Piasecky, L. J. U. S. Patent 3, **1964**, 149082.

[44] (a) Klement, R.; Haselbeck, H. Z. *Analo. Allg. Chem.* **1965**, *336*, 113. (b) Schwarz, H. *Analo. Allg. Chem.* **1968**, *356*, 29.

[45] (a) Suzuki, T.; Hatsushika, T.; Mitake, M. *J. Chem. Soc., Farady Trans. 1* **1982**, *78*, 3605. (b) Suzuki, T. Zyosui Gijutsu **1989**, *15*, 41.

[46] (a) Suzuki, T.; Ishigaki, K.; Mitake, M. *J. Chem. Soc., Farady Trans. 1* **1984**, *80*, 3157. (b) Mitake, M.; IshigaKi, K.; Suzuki, T. *J. Solid. State Chem.* **1986**, *61*, 230.

[47] (a) Sugiyama, S.; Minami, T.; Hayashi, H.; Tanaka, M.; Shigemoto, N.; Moffat, J. B. *J. Chem. Soc., Faraday Trans.* **1996**, *92*, 293. (b) Sebi, S.; Tahir, R.; Nazih, R.; Boulaajaj, S. *Appl. Catl.* A **2001**, *218*, 25. (c) Xiao, F.-S.; Sun, J.; Meng, X.; Yu, R.; Yuan, H.; Jiang, D.; Qiu, S.; Xu, R. *Appl. Catl.* A **2001**, *207*, 267.

Chapter II

Hydroxyapatite-Bound Ruthenium Complex as Highly Efficient Heterogeneous Catalyst for Aerobic Oxidations

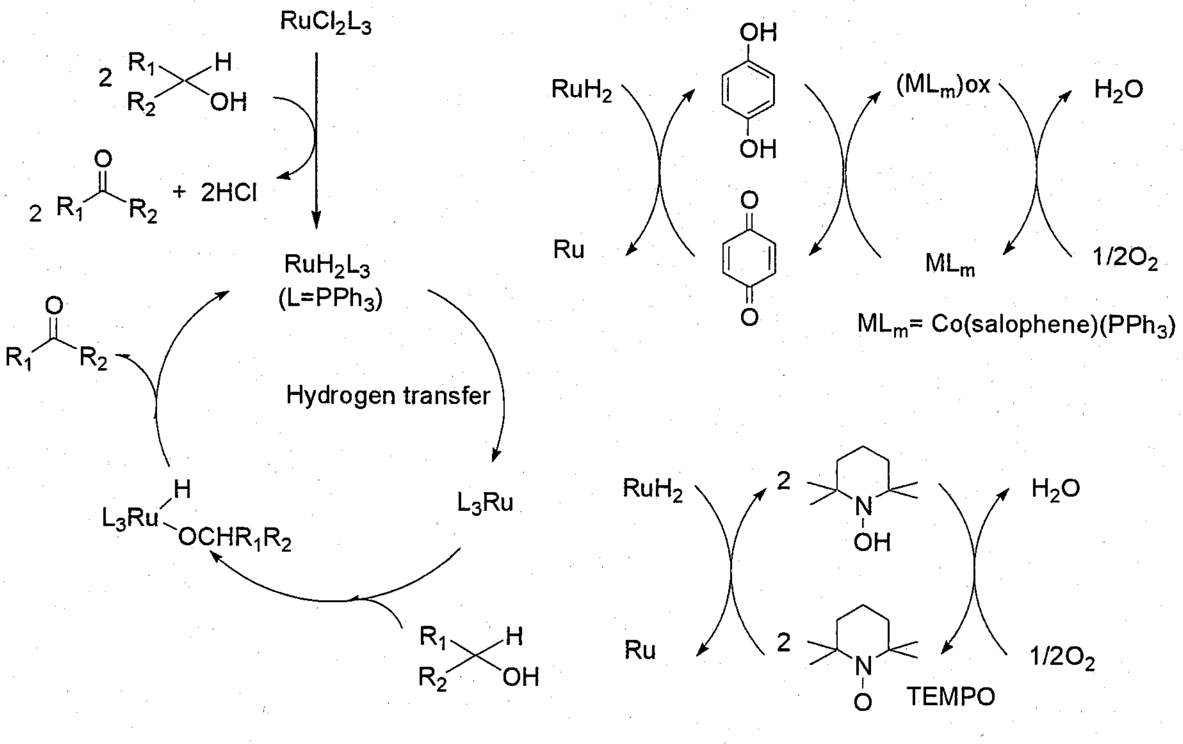
II-1. Aerobic Oxidation of Alcohols Catalyzed by Hydroxyapatite-Bound Ruthenium Complex

1. Introduction

The selective oxidation of alcohols to the corresponding carbonyl compounds plays a crucial role both in industrial and academic areas [1]. Many oxidizing reagents such as hypochloride [2], chromium (VI) oxide [3], permanganate [4], ruthenium(VIII) oxide [5], and dichromate [6] have been employed to effect this transformation, but these stoichiometric oxidants possess the serious disadvantages that they are expensive and/or toxic, and produce equimolar amounts of deoxygenated wastes. Because of the increasing demand for development of environmentally-benign oxidation processes in organic chemistry, much attention has been directed toward the development of a catalytic protocol in combination with molecular oxygen (O_2) or air as a primary oxidant, which is readily available, inexpensive, nontoxic, and would produce water as the sole by-product [7]. This "green method" for converting alcohols into carbonyl compounds on an industrial scale, remains an important challenge of synthetic chemistry.

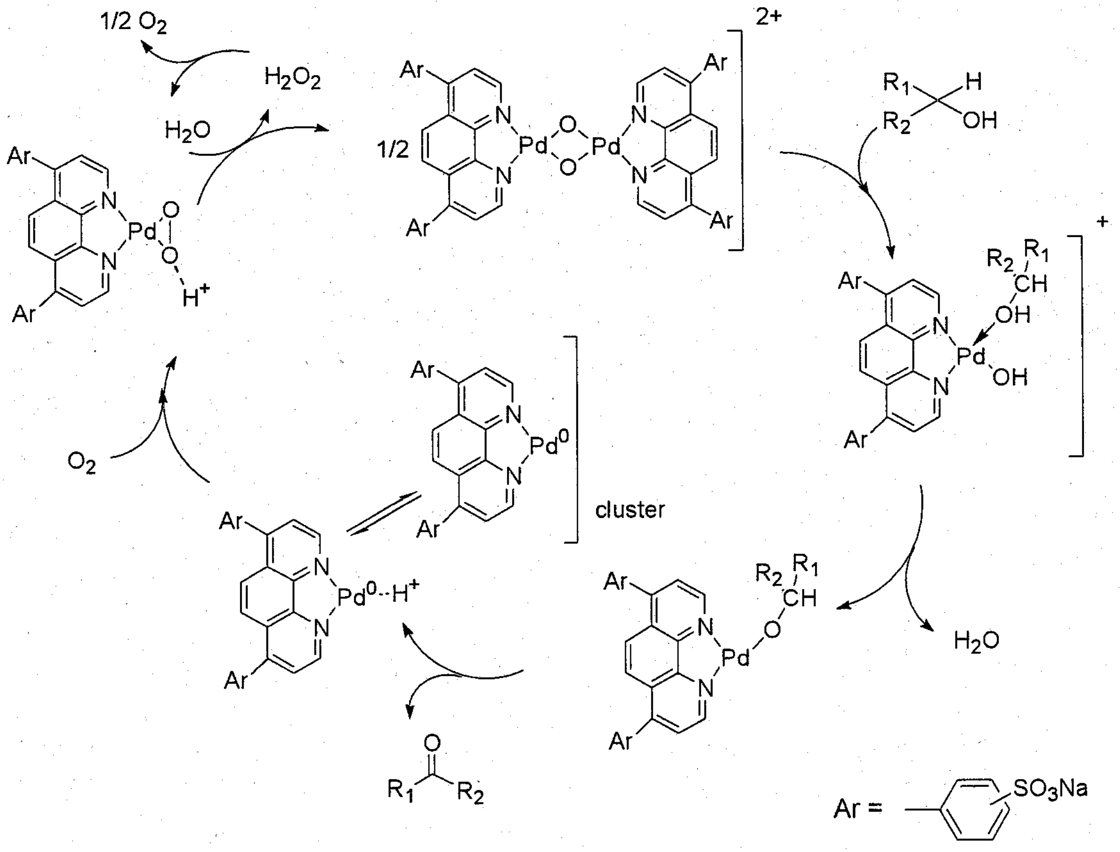
A number of methods for metal-catalyzed aerobic oxidations of alcohols, both homogeneous and heterogeneous, have been developed. Especially ruthenium compounds have been thoroughly investigated as catalysts. For example, $RuCl_3$ [8], $RuCl_2(PPh_3)_3$ [9], hydrated RuO_2 [10], $Ru_2O_6(py)_4$ (py=pyridine) [11], $[Ru_3O(O_2CR)_6L_3]^n$ (R=CH_3, C_2H_5; L=H_2O, PPh_3) [12], and Ru-hydrotalcite [13] have proved to be efficient catalysts for the oxidation of alcohols using molecular oxygen. Unfortunately, these systems require relatively large amounts of catalyst and their scope was generally limited to activated alcohols, *i.e.* benzylic and allylic ones. On the other hand, Ru/CeO_2 [14], tetrapropylammonium perruthenate (TPAP), either as such [15] or supported on polystyrene [16] or MCM-41 [17], and Ru/Co-hydrotalcite [18] exhibited enhanced activity and could be applicable to non-activated aliphatic alcohols. Bäckvall *et al.* have established $RuCl(OAc)(PPh_3)_3$

/hydroquinone/Co(salophen)(PPh_3) system from the biomimetic approach [19], in which hydroquinone-benzoquinone redox cycle would facilitate an electron-transfer to re-oxidize ruthenium hydride species. Similar catalytic system using low-valent ruthenium complexes like $RuCl_2(PPh_3)_3$ in combination with hydroquinone-K_2CO_3 [20], 2,2',6,6'-tetramethylpiperidine *N*-oxyl [21], and Cs_2CO_3 [22] have been also developed to affect this transformation (Scheme 1). Most recently, Mizuno *et al.* have reported the effective aerobic oxidation of both activated and nonactivated alcohols containing sulfur, nitrogen, and carbon-carbon double bonds with dioxygen or in air by ruthenium on alumina as a heterogeneous catalyst [23].



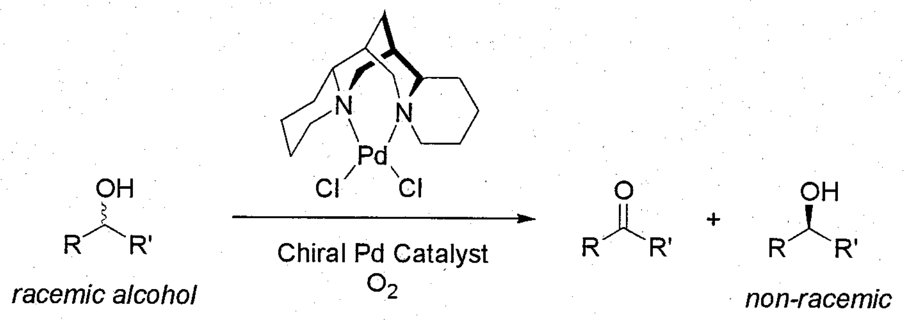
Scheme 1. Possible Hydrogen Transfer Mechanism of Ru-Catalyzed Aerobic Alcohol Oxidation

In recent years many research groups have extensively investigated palladium-catalyzed aerobic alcohol oxidations. The first successful system that did not require chlorinated solvents or copper salts for reoxidation of reduced palladium(0) was reported in 1977 by Schwartz [24]. This method involved a simple $PdCl_2/NaOAc$-catalyzed reaction in ethylene carbonate at ambient temperature, but full conversion was reached after ca. 100 hours. Twenty years later, Peterson and Larock have described the aerobic oxidation of alcohols using $Pd(OAc)_2$-$NaHCO_3$ in DMSO solvent [25]. In both cases, ethylene carbonate and DMSO acted both as the solvent and the ligand for a smooth reoxidation of Pd(0). Soon afterward, better results were reported by Uemura *et al.* who carried out the reaction in toluene and obtained full conversion in 2 hours with 5 mol% catalyst [26]. In this non-coordinating solvent, however, the use of a ligand such as pyridine is indispensable to maintain the catalytic activity without concomitant precipitation of palladium black. Sheldon



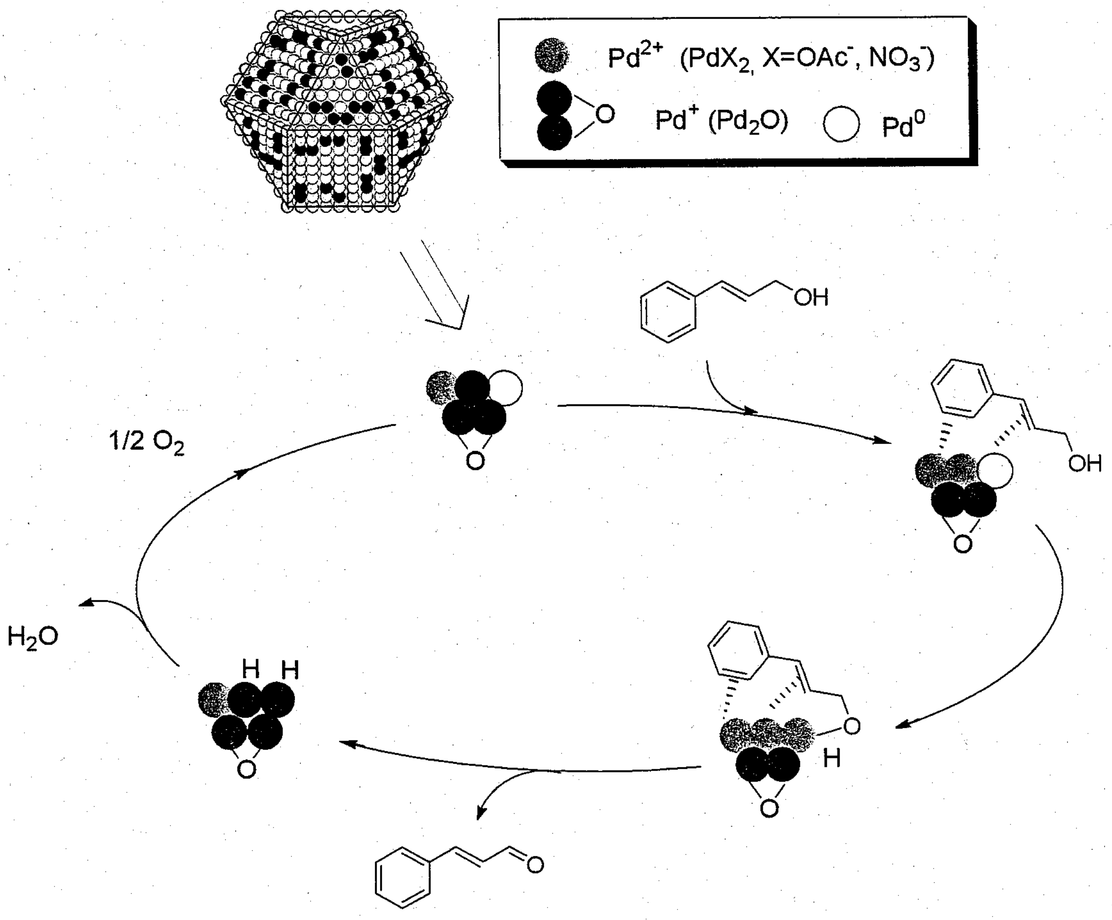
Scheme 2. The Catalytic Cycle Proposed for Alcohol Oxidation with the Aqueous-Soluble Phen*Pd(II) Catalyst.

et al. reported a quite sophisticated catalytic system for aerobic oxidation in water [27]. A water-soluble Pd^{2+}-bathophenanthoroline disulfonate (PhenS*Pd^{2+}) is a stable and reusable catalyst for a diverse array of alcohols in biphasic water-alcohol conditions (Scheme 2). Most recently, Sigman, as well as Ferrein and Stolta, discovered that the combination of a Pd(II) salt and (-)-sparteine effectively catalyzed the aerobic oxidative kinetic resolution of secondary alcohols (Scheme 3) [28]. This reaction gives moderate to good k_{rel} values for various benzylic alcohols.



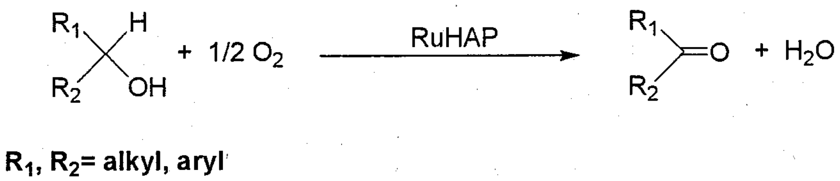
Scheme 3. Pd((-)-sparteine)Cl$_2$-Catalyzed Oxidative Kinetic Resolution of Secondary Alcohols using Molecular Oxygen.

Independently, Kaneda *et al.* have been developed the effective aerobic oxidation of allylic alcohols to the corresponding α,β-unsaturated aldehydes catalyzed by $Pd_4Phen_2CO(OAc)_4$ complex [29] and $Pd_{561}Phen_{60}(OAc)_{180}$ giant cluster [30]. They have postulated that multiple interactions between the allylic alcohols and the paired site of the Pd atoms at the surface of the Pd cluster play a definitive role in the above oxidation (Scheme 4). Furthermore, new type of palladium-grafted hydroxyapatite (PdHAP) have been prepared by Kaneda *et al.*, which can effectively promote alcohol oxidation, displaying a remarkable high TON of up to 236,000 [31]. Besides ruthenium and palladium, a few other metals, *e.g.* copper [32], osmium [33], cobalt [34], and vanadium [35], have also been shown to catalyze aerobic alcohol oxidations. However, most reported systems require relatively large quantities of catalyst (5-10 mol %), high O_2 pressure (10-20 bar), and additives to complete the catalytic cycle.



Scheme 4. A Possible Reaction Mechanism of Oxidation of Cinnamyl Alcohol Catalyzed by the Ensemble Pd Site of the 8-shell Pd Nanoclusters Surface.

In this chapter, the author designed the hydroxyapatite-bound ruthenium complex (RuHAP) as an effective heterogeneous catalyst for the aerobic oxidation of various alcohols including allylic, benzylic, aliphatic, and heteroatom-containing ones. This heterogeneous catalyst has advantages not only of using O_2 as an oxidant, but also of simple work-up procedure and reusability of the catalyst, over other homogeneous ones. The author descrived a preparation of the RuHAP on the basis of the characterization using physicochemical methods and its unique catalysis for the alcohol oxidation.



2. Experimental

2-1. General

^{1}H- and ^{13}C-NMR spectra were obtained on JEOL GSX-270 or JNM-AL400 spectrometers at 270 or 400 MHz in $CDCl_3$ with TMS as an internal standard. Infrared spectra were obtained with a JASCO FTIR-410. Elemental analysis was carried out by Perkin Elmer 2400CHN. Analytical GLC was performed by Shimadzu GC-8A PF with flame ionization detector equipped with KOCL 3000T, Silicon SE-30, and OV-17 columns. Powder X-ray diffraction patterns were recorded using Philips X'Pert -MPD with Cu Kα radiation. XPS were measured on Shimadzu ESCA-KM using MgKα radiation. Ru K-edge X-ray absorption spectra were recorded at room temperature in a transmission mode at the EXAFS facilities installed on the beam line BL01B1 station attached to Si (311) monochromator at SPring-8 of JASRI, Harima, Japan. The EXAFS data were normalized by fitting the background absorption coefficient around the energy region higher than the edge about 35-50 eV with the smoothed absorption of an isolated atom. Fourier transformation (FT) of k^3-weighted normalized EXAFS data was performed over the $3.5\ \text{Å} < k/\ \text{Å}^{-1} < 12\ \text{Å}$ range to obtain the radial structure function. CN (coordination number of scatters), *R* (distance between an absorbing atom and scatterer), and Debye-Waller factor were estimated by curve-fitting analysis with the inverse FT of the $0.8 < R/\ \text{Å} < 2.8$ range assuming single scattering. Data reductions were performed with the FACOM M-780 computer system of the Data Processing Center of Kyoto University. [36]

$(NH_4)_2HPO_4$ and $Ca(NO_3)_2 \cdot 4H_2O$ were purchased from Wako Pure Chemical as a special grade. $RuCl_3 \cdot nH_2O$ was obtained from N. E. Chemcat. Alcohols as substrate and solvents were purchased from Wako Pure Chemical, Tokyo Kasei, and Aldrich, and purified by the standard procedures prior to experiments. All of the oxidation products are well known compounds. Their identities were confirmed by comparison with infrared spectra, elemental analyses, and NMR spectra.

2-2. Synthesis of Hydroxyapatite-Bound Ruthenium Complex

A stoichiometric calcium hydroxyapatite of Ca/P=1.67 (HAP), $Ca_{10}(PO_4)_6(OH)_2$, was synthesized according to the literature procedure [37]. $(NH_4)_2HPO_4$ (40.0 mmol) was dissolved in deionized water (150 mL) and pH was adjusted to 11 with aqueous NH_3 solution. To a solution of $Ca(NO_3)_2{\cdot}4H_2O$ (66.7 mmol) in deionized water (120 mL) adjusted to pH 11 with aqueous NH_3 solution was added drop-wise over 30 min into the above solution with vigorous stirring at room temperature, and then the obtained milky solution was heated at 90 °C for 10 min. The precipitate was filtered, washed with deionized water, and dried at 110 °C, giving $Ca_{10}(PO_4)_6(OH)_2$ (Z = 0, HAP-0). The HAP (1.0 g) was stirred with 75 mL of a 2.67×10^{-2} M aqueous $RuCl_3.H_2O$ solution at 25 °C for 24 h. The obtained slurry was filtered, washed with deionized water and dried overnight at 110 °C, yielding 1.01 g of the RuHAP as a dark brown powder.

2-3. General Procedures for the Oxidation of Alcohols Catalyzed by Hydroxyapatite-Bound Ruthenium Complex

A typical procedure for the aerobic oxidation is as follows. Into a reaction vessel with a reflux condenser were placed RuHAP (0.2 g, Ru: 0.34 mmol), 1-phenylethanol (0.24 g, 2 mmol) and toluene (5 mL). The resulting mixture was stirred at 80 °C under 1 atm of O_2. The progress of reaction was monitored by GC analysis. After 2 h, 98 % yield of acetophenone was obtained.

2-4. Procedure of the Large-Scale oxidation of Benzyl Alcohol

Into a reaction vessel with a reflux condenser were placed benzyl alcohol (10.8 g, 100 mmol), RuHAP (0.2 g), and toluene (100 ml). The resulting mixture was stirred at 90 °C under 1 atm of O_2 for 24 h, benzaldehyde was produced in 98% GC yield. The organic layer was separated, followed by removal of solvent under a reduced pressure. The residue was then distilled to give pure benzaldehyde (9.6 g, 91 % yield).

2-5. Recycling of the Hydroxyapatite-Bound Ruthenium Complex for Alcohol Oxifation

The first run was carried out under the same reaction conditions as described in section **2-3**. After the oxidation, the spent RuHAP could be easily separated from the reaction mixture by a filtration and the isolated RuHAP was washed with deionized water prior to reuse. These recycling procedures were repeated three times in the same manner as identical conditions of the first run.

3. Results and Discussion

3-1. Characterization of Hydroxyapatite-Bound Ruthenium Complex

To gain insight into the structure of surface-bound Ru species of the RuHAP, detailed study were performed using physicochemical methods. The XRD peak positions of the RuHAP were similar to those of the parent HAP. From the elemental analysis, (Ru+Ca)/P ratio of the RuHAP was estimated to 1.67 (Ru content: 17.1wt%, 1.69 mmol·g^{-1}), which shows the occurrence of an equimolar substitution of Ru^{3+} for Ca^{2+} at the column of Ca and O atoms parallel to hexagonal axis [37]. The presence of chlorine was confirmed by XPS and EDX analyses; the atomic ratio of Ru to Cl was 1:1. The Ru K-edge XANES spectrum of the RuHAP resembles that of $RuCl_3$. In Fourier transform (FT) of k^3-weighted Ru K-edge EXAFS of the RuHAP, the lack of peaks around 3.5 Å indicates no Ru-Ru bond on the RuHAP in Figure 1(a). The inverse FT of main peaks was well fitted by the use of three Ru-O and single Ru-Cl shells, as summarized in Figure 1(b) and Table 1. The distance from Ru to the nearest four oxygen atoms, Ru-O(1), in the RuHAP is well consistent with a value of the RuO_2 (R=1.96 Å), and the Ru-Cl distance of 2.32 Å is close to that found in monochlororuthenium complexes [38]. Conclusively, the Ru species on the surface of the RuHAP exists as a monomeric Ru cation species surrounded by oxygen and chlorine and a proposed surface structure of the RuHAP is represented in Figure 1(c).

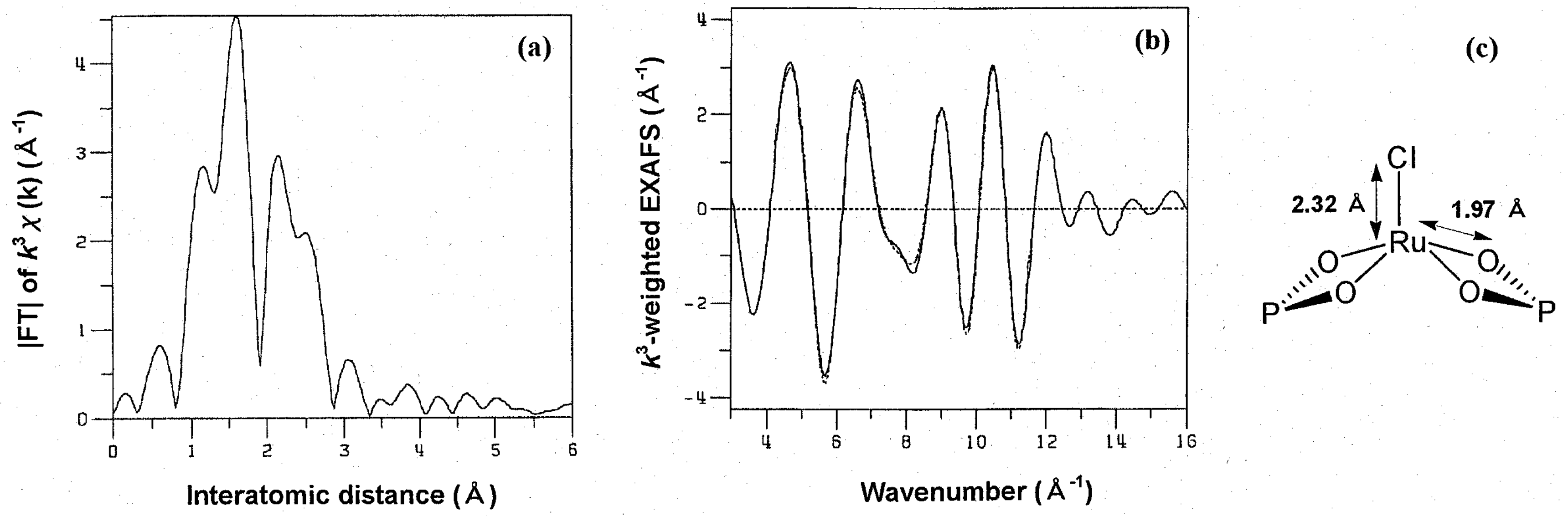


Figure 1. (a) FT magnitude of k^3-weighted EXAFS of the RuHAP, (b) inverse of FT of the peaks with the $0.8 < R/\text{Å} < 2.8$ range in part a, and (c) a proposed surface structure around Ru^{3+} of the RuHAP. The nearest oxygens around the Ru^{3+} are shown. The dotted line in part b shows the result of curve fitting analysis using three Ru-O and single Ru-Cl shell parameters.

The present simple preparation method using the cation-exchange ability of HAP can allow a strong protocol to create a monomeric metal species on the solid surface as a hybrid heterogeneous catalyst.

Table 1. Results of Curve-fitting Analysis for RuHAP [a]

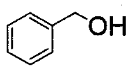
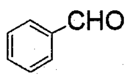
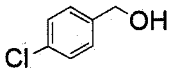
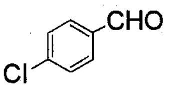
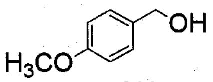
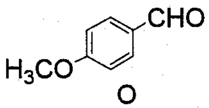
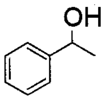
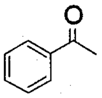
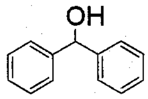
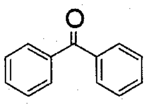
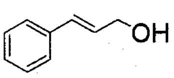
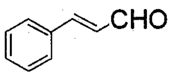
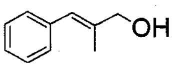
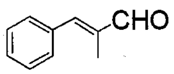
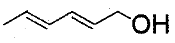
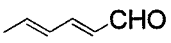
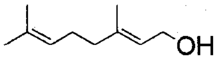
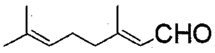
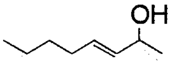
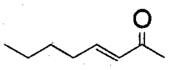
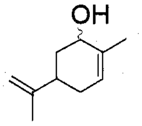
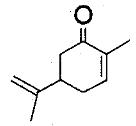
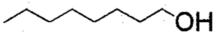
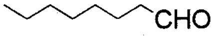
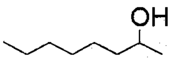
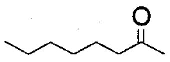
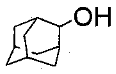
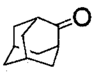
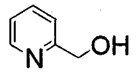
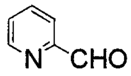
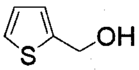
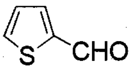
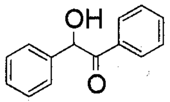
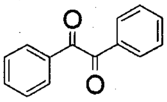
shell	C.N.[b]	R[c]/Å	σ^{d}/Å
Ru-O(1)	4.1	1.97	0.0067
Ru-O(2)	2.1	2.28	0.0008
Ru-O(3)	1.7	2.62	-0.0054
Ru-Cl	1.2	2.32	0.0010

[a] The region of 0.8-2.8 Å was inversely fourier transformed. [b] Coordination number. [c] Interatomic distance. [d] Difference between Debye-Waller factor of RuHAP and that of the reference sample.

3-2. Catalytic Performances for Aerobic Oxidation of Alcohols

To explore potential ability of the RuHAP, oxidation of alcohols using molecular oxygen as an oxidant were performed. As can be seen from Table 2, various alcohols smoothly oxidized in the presence of the RuHAP at 80 °C under 1 atm of O_2 atmosphere to give the corresponding carbonyl compounds in excellent yields. Especially, benzylic and allylic ones showed high reactivity for the oxidative dehydrogenation (entries 1-13). A 100 mmol-scale oxidation of benzyl alcohol was also performed to give 98% yield of benzaldehyde; the turn over number approached 290 after 24 h. It is notable that a *primary* aliphatic alcohol of 1-octanol was smoothly oxidized to afford 1-octanal without any formation of the corresponding carboxylic acid and ester (entry 14). When the reaction temperature was raised from 60 to 80 °C, 1-octanoic acid was obtained in 82% yield for 6 h without formation of the corresponding aldehyde. Moreover, this catalyst system was applicable to the oxidation of heterocyclic alcohols including nitrogen and sulfur atoms. For example, 2-pyridinemethanol and 2-thiophenemethanol gave the corresponding aldehydes in

Table 2. Oxidation of Various Alcohols Catalyzed by RuHAP Using O_2[a]

entry	substrate	product	time (h)	convn (%)[b]	yield (%)[b]
1			3	100	>99
2[c]			3	100	95
3[d]			48	20	17
4			3	100	>99
5			3	100	92
6			2	100	98
7			2	100	>99
8			1	100	99
9			2	100	95
10			4	99	99
11			3	99	85
12			5	93	91
13			6	83	80
14[e]			16	95	94
15			6	96	96
16[f]			4	100	95
17			10	100	>99
18			2	100	94
19			24	100	>99

[a] Reaction conditions: alcohol (2 mmol), RuHAP(0.2 g, Ru: 0.34 mmol), toluene (5 mL), 80 ℃, O_2 atmosphere. [b] Determined by GC using an internal standard technique. [c] Under 1 atm of air instead of O_2. [d] N_2 atmosphere. [e] The reaction temperature was lowered to 60 ℃ [f] Reaction conditions: alcohol (1 mmol), RuHAP (0.1 g, Ru:0.17 mmol).

high yields (entries 17 and 18). Generally, heterocyclic alcohols coordinate to metal and inactivate the catalysts. It is possible to synthesize dicarbonyl compounds, which is an important building block in organic synthesis, *via* the oxidation of α-hydroxyketones (entry 19). Even under air conditions in place of pure O_2, the above oxidations proceeded smoothly; a quantitative yield of benzaldehyde was obtained within 3 h (entry 2). Unfortunately, the reaction of cyclohexanol was significantly slow, resulting in the formation of only 34 % of the corresponding ketones. Important points concerning the use of heterogeneous catalysts are their lifetime and leaching of active species in solution, particularly for industrial and pharmaceutical applications of alcohol oxidation. The RuHAP catalyst could be reused with a retention of its high catalytic activity and selectivity; the yield of benzaldehyde in the case of benzyl alcohol could be kept over 93% during three recycling experiments. The Ru content between a fresh and spent RuHAP catalysts did not change and no Ru leaching in the filtrate was observed during the above recycles by ICP method whose detection limit is 24 ppb.

In the present RuHAP catalytic system, the competitive oxidation in an equimolar mixture of *p*-substituted benzyl alcohols gave a Hammett ρ value of -0.429, which is much smaller than -1.9 with ruthenium-oxo compounds, e.g. *cis*-$[(N_4)Ru^{VI}O_2]^{2+}$ [39], but is close to -0.431 with a stoichiometric reagent of a monomeric $RuCl_2(PPh_3)_3$ complex (Figure 1). These results suggest that the present RuHAP catalyst does not contain ruthenium-oxo species as the active oxidant. When an equimolar mixture of 1-octanol and 4-octanol was used as substrates, 95% of 1-octanal was selectively obtained together with 5% of 4-octanone (Figure 2) [21][40]. In the intramolecular competitive oxidation of 1,7-octanediol, the RuHAP catalyst gave chemoselectively 7-hydroxyoctanal in 81% yield (Scheme 5). The above high chemoselectivity for primary hydroxyl functions is not similar to that of bulk Ru catalysts such as RuO_2 and Ru/Al_2O_3, but to that of a monomeric $RuCl_2(PPh_3)_3$ complex. The author thinks that this catalytic behavior may be attributed to monomeric Ru cation species on the RuHAP surface.

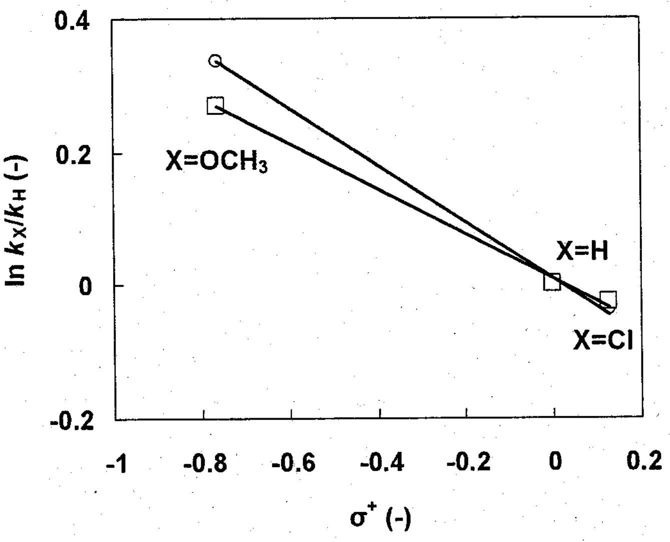


Figure 1. Hammett plots for the oxidation of *p*-substituted benzyl alcohols catalyzed by RuHAP (□) and $RuCl_2(PPh_3)_3$ (○). Reaction conditions: alcohol (1 mmol), Ru catalyst (0.17 mmol of Ru), toluene (5 mL), 60℃, O_2 atmosphere. Hammett ρ values for RuHAP (□) and $RuCl_2(PPh_3)_3$ were –0.429 and –0.431, respectively.

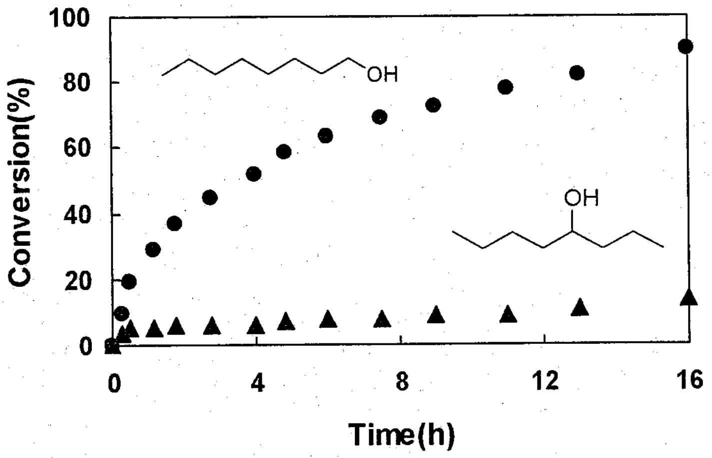
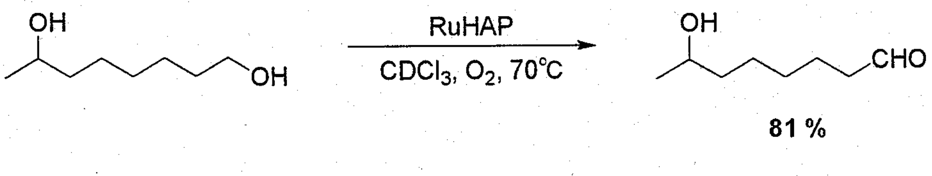


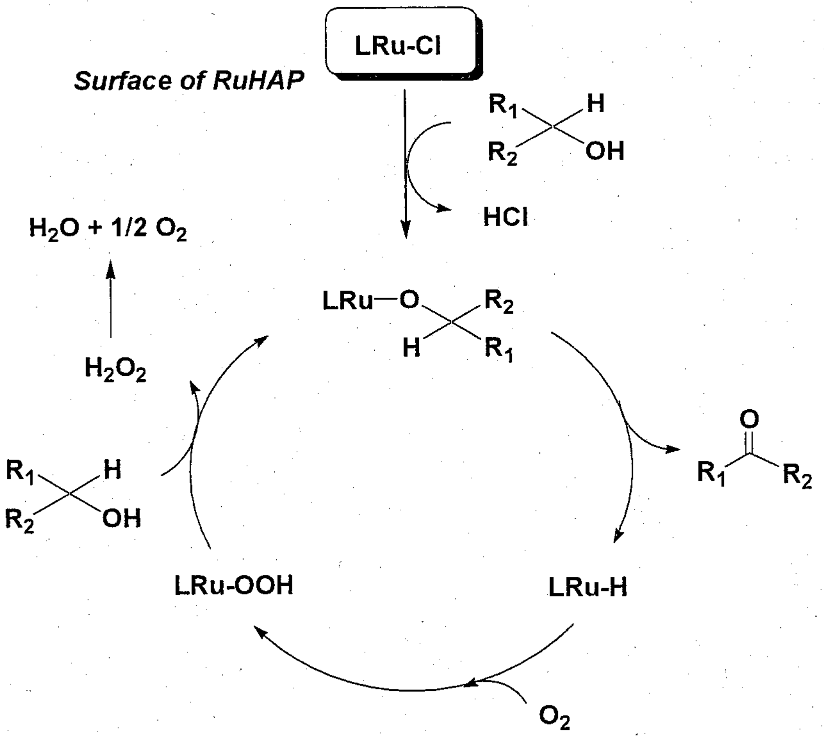
Figure 2. Competitive oxidation of 1-octanol (●) and 2-octanol (▲) using RuHAP. Reaction conditions: 1-octanol (1 mmol), 2-octanol (1 mmol),RuHAP (0.1 g, Ru: 0.17 mmol), toluene (5 ml), 60℃, O_2 flow.

Scheme 5.



3-3. Reaction Mechanism of the Aerobic Oxidation of Alcohols Catalyzed by Hydroxyapatite-Bound Ruthenium Complex

The above results of the Hammett ρ value and a preference for primary *versus* secondary hydroxyl groups suggest that the present RuHAP-catalyzed alcohol oxidation involves an alkoxy-ruthenium intermediate. Therefore, we propose a possible catalytic cycle using the RuHAP as follows (Scheme 6). The oxidation is initiated by a ligand-exchange between an alcohol and a Cl species of the RuHAP to give a Ru-alcoholate species [41], which undergoes the β-hydride elimination to produce the corresponding carbonyl compound and a Ru-hydride species. Reaction of the hydride species with O_2 affords a Ru-hydroperoxide species, followed by the ligand-exchange to regenerate the Ru-alcoholate species together with the formation of O_2 and H_2O. H_2O_2 is a more probable intermediate for the formation of O_2 and H_2O, but H_2O_2 in the reaction medium could not be detected.



Scheme 6. A Possible Alcohol Oxidation Mechanism Catalyzed by RuHAP

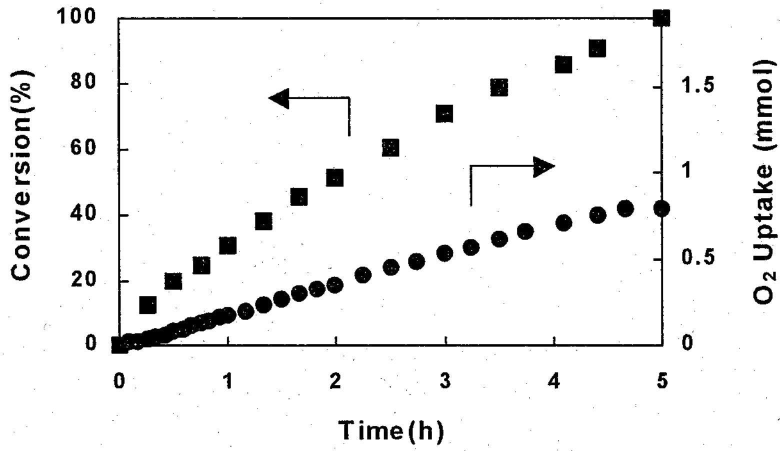
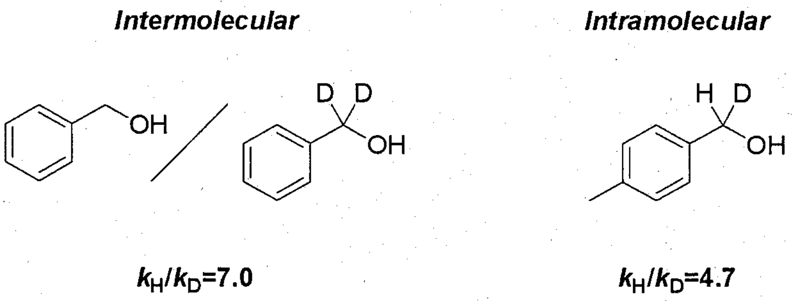


Figure 3. Time profile of O_2 uptake and benzyl alcohol conversion catalyzed by RuHAP. Reaction condition: alcohol (2 mmol), RuHAP (0.1 g :Ru: 0.3 mmol), toluene (5 ml), 60℃.

In the case of $RuCl_2(PPh_3)_3$, the catalytic cycle was not completed without hydroquinone [20] or 2,2',6,6'-tetramethylpiperidine *N*-oxyl [21]. It is notable that our RuHAP catalyst does not need the above additives for the catalytic aerobic oxidation. Further, the above mechanism can be well evidenced by the following experiments of benzyl alcohol: (i) Addition of a radical trap, 2,6-di-*tert*-butyl-*p*-cresol, to the reaction medium hardly influences the oxidation. (ii) One mole of H_2O was produced for every mole of benzaldehyde formation. (iii) In monitoring the O_2 uptake, two moles of benzaldehyde were equivalent to one mole of O_2 consumption (Figure 3). (iv) Under N_2 atmosphere, benzaldehyde was obtained only in a stoichiometric amount to Ru element on the RuHAP catalyst (Table 2, entry 3). Kinetics data of this alcohol oxidation could be well accommodated with a rate equation based on the Michaelis-Menten type model for the above proposed mechanism [42]. The initial rate (R_0) of the oxidation of benzyl alcohol could be express as $R_0=k_2[C]/\{1+k_2/(k_1[S])\}$, where [C] is the concentration of the RuHAP, [S] is the concentration of benzyl alcohol, and k_1 and k_2 are rate constants of an alcoholate formation and β-elimination step, respectively. From the O_2 uptake experiment, the reaction step of a Ru-hydride species with O_2 was very fast. The apparent activation energies for each steps were calculated to be 43.4 and 64.7 kJ·mol^{-1}, respectively. The β-elimination is a rate-determining step in the overall oxidation process because the k_H/k_D values of 7.0 and 4.7 were observed in the competitive oxidation of benzyl alcohol with benzyl-d_7 alcohol ($C_6D_5CD_2OH$) and the intramolecular kinetic isotope effect for the oxidation of *p*-methyl-α-deutero-benzyl alcohol (Scheme 7) [42]. This value is far smaller than those reported for the stoichiometric benzyl alcohol oxidations with ruthenium-oxo complexes, *e.g.* $[Ru^{IV}(tpy)(O)_2(CH_3CN)]^{2+}$ (k_H/k_D =12.1) [43], *cis*-$[(N_4)Ru^{VI}O_2]^{2+}$ (k_H/k_D =21) [44], $[(bpy)^2(py)Ru^{IV}(O)]^{2+}$ (k_H/k_D =50) [45], and $[Ru^{IV}(tpy)(CH_3CN)_2(O)]^{2+}$ (k_H/k_D =61.5), which also reveal that the present RuHAP catalyst does not contain ruthenium-oxo species as the active oxidant, as shown by Hammett plots.

Scheme 7


Intermolecular

Intramolecular

k_H/k_D=7.0

k_H/k_D=4.7

4. Conclusins

The author pioneered synthetic method of a novel heterogeneous ruthenium catalyst using hydroxyapatite based on their cation-exchange ability. An extensive characterization by means of XRD, XPS, EDAX, and Ru K-edge XAFS revealed that a monomeric Ru cation species could be uniformly fixed on the surface of hydroxyapatite. The RuHAP catalyst system has proven to be simple, clean, and general for aerobic alcohol oxidations and does not require any additives and co-catalysts to complete the catalytic cycle, which is dominated by the formation of a monomeric Ru species as the phosphate complex on the RuHAP surface. No Ru leaching was observed during oxidations and then the Ru catalyst was recyclable, which demonstrates that the hydroxyapatite serves as a suitable macroligand for the catalytically active Ru center.

The above hydroxyapatite-bound ruthenium complex catalyst were further applicable to a wide range of functional group transformations such as amine and silane oxidations under atmospheric O_2 pressure, as described in the following Sections.

References

[1] (a) Hill, C. L. *Advances in Oxygenated Processes*; Baumstark, A. L., ed.; JAI Press, Inc.: London, 1988; Vol. 1, p. 1. (b) Hudlucky, M. *Oxidations in Organic Chemistry*; ACS Monograph Series; American Chemical Society: Washington, DC, 1990. (c) Parshall, G.W.; Ittel, S. D. *Homogeneous Catalysis*; 2nd Ed., John-Wiley & Sons, Inc.: New York, 1992. (d) Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press: London, 1981. (f) *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I. Eds.; Pergamon: Oxford, England, 1991.

[2] Stevens, R. V.; Chapman, K. T.; Weller, H. N. *J. Org. Chem.* **1980**, *45*, 2030.

[3] Holum, J. R. *J. Org. Chem.* **1961**, *26*, 4814.

[4] Menger, F. M.; Lee, C. *Tetrahedron Lett.* **1981**, *22*, 1655.

[5] Berkowitz, L. M.; Rylander, P. N. *J. Am. Chem. Soc.* **1958**, *80*, 6682.

[6] Lee, D. G; Spitzer, U. A. *J. Org. Chem.* **1970**, *35*, 3589.

[7] (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice;* Oxford University Press, **1998**. (c) Clark, J. H. *Green Chem.* **1999**, *1*, 1. (d) Sheldon, R. A. *Green Chem.* **2000**, *2*, G1. (e) Anastas, P. T.;Bartlett, L. B.; Kirchhoff, M. M.; Williamson, T. C. *Catal. Today* **2000**, *55*, 11.

[8] Matumoto, M; Ito, S. *J. Chem. Soc., Chem. Commun.* **1981**, 907.

[9] Tang, R.; Diamond, S. E.; Neary, N.; Mares, F. *J. Chem. Soc., Chem. Commun.* **1978**, 562.

[10] Matsumoto, M.; Watanabe, N. *J. Org. Chem.* **1984**, *49*, 3436.

[11] Dengel, A. C.; El-Hendawy, A. M.; Griffith, W. P.; O'Mahoney, C. A.; Williams, D. J. . *J. Chem. Soc., Dalton Trans.* **1990**, *92*, 737.

[12] Bilgren, C.; Davis, S.; Drago, R. S. *J. Am. Chem. Soc.* **1987**, *109*, 3786.

[13] Kaneda, K.; Yamashita, T.; Matsushita, T.; Ebitani, K. *J. Org. Chem.* **1998**, *63*, 1750.

[14] Vocanson, F.; Guo, Y. P.; Namy, J. L.; Kagan, H. B. *Synthetic Commun.* **1996**, *28*, 2577.

[15] Markó, I. E.; Giles, P. R.; Tsukazaki, M.; Chellé-Regnaut, I.; Urch, C. J.; Brown, S. M. *J. Am. Chem. Soc.* **1997**, *119*, 12661.

[16] Hinzen, B.; Lenz, R.; Ley, S. V. *Synthesis* **1998**, 977.

[17] Bleloch, A.; Johnson, B. F. G; Ley, S. V.; Price, A. J. Shephard, D. S.; Thomas, A. W. *Chem. Commun.* **1999**, 1907.

[18] Matsushita, T.; Ebitani, K.; Kaneda, K. *Chem. Commun.* **1999**, 265.

[19] (a) Bäckvall, J,-E.; Chowdhury, R. L.; Karllsson, J. *J. Chem. Soc., Chem. Commun.* **1991**, 473. (b) Csjernyik, G; Ell, A. H.; Fadini, L.; Pugin, B.; Bäckvall, J,-E. *J. Org. Chem.* **2002**, *67*, 1657.

[20] Hanyu, A.; Takezawa, E.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **1998**, *39*, 5557.

[21] (a) Dijksman, A.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Commun.* **1999**, 1591. (b) Dijksman, A.; Marino-Gonzalez, A.; Payeras, A. M. I; Arends, I. W. C. E.; Sheldon, R. A. *J. Am. Chem. Soc.* **2001**, *123*, 6826.

[22] Lee, M.; Cheng, S. *Tetrahedron Lett.* **2000**, *41*, 7507.

[23] Yamaguchi, K.; Mizuno, N. *Angew. Chem. Int. Ed.* **2002**, *41*, 4538.

[24] Blackburn, T. F.; Schwarts. J. *J. Chem. Soc., Chem. Commun.* **1977**, 157.

[25] Peterson, K. P.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 3185.

[26] (a) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *Tetrahedron Lett.* **1998**, *39*, 6011. (b) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750. (c) Kakiuchi, N.; Nishimura, T.; Onoue, T.; Uemura, S. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 165. (d) Nishimura, T.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 2645. (e) Nishimura, T.; Maeda, Y.; Kakiuchi, N.; Uemura, S. *J. Chem. Soc., Parkin Trans. 1* **2000**, 4301. (f) Nishimura, T.; Kakiuchi, N.; Onoue, T.; Ohe, K.; Uemura, S. *J. Chem. Soc., Parkin Trans. 1* **2000**, 1915. (g) Nishimura, T.; Kakiuchi, N.; Inoue, M.; Uemura, S. *Chem. Commun.* **2000**, 1245.

[27] (a) ten Brink, G-J.; Arends, I. W. C. E.; Sheldon, R. A. *Science* **2000**, *287*, 1636. (b) ten Brink, G-J.; Arends, I. W. C. E.; Sheldon, R. A. *Adv. Synth. Catal.* **2002**, *344*, 355.

[28] (a) Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Am. Chem. Soc.* **2001**, *123*, 7475. (b) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2001**, *123*, 7725. (c) Mueller, J. A.; Jensen, D. R.; Sigman, M. S. *J. Am. Chem. Soc.* **2002**, *124*, 8202.

[29] Kaneda, K.; Fujie, Y.; Ebitani, K. *Tetrahedron Lett.* **1997**, *38*, 9023.

[30] (a) Ebitani, K.; Fujie, Y.; Kaneda, K. *Langmuir* **1999**, *15*, 3557. (b) Choi, K.-M.; Akita, T.; Mizugaki, T,; Ebitani, K.; Kaneda, K. *New. J. Chem.* **2003**, *27*, 324.

[31] Mori, K.; Yamaguchi, K; Hara, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2002**, *124*, 11572.

[32] (a) Markó, I. E.; Giles, P. R.; Tsukazaki, M.; Brown, S. M.; Urch, C. J. *Science* **1996**, *274*, 2044. (b) Markó, I. E.; Tsukazaki, M.; Giles, P. R.; Brown, S. M.; Urch, C. J. *Angew. Chem. Int. Ed.* **1997**, *36*, 2208. (c) Markó, I. E.; Gautier, A.; Chelle-Regnaut, I.; Giles, P. R.; Tsukazaki, M.; Urch, C. J.; Brown, S. M.; *J. Org. Chem.* **1998**, *63*, 7576. (d) Markó, I. E.; Giles, P. R.; Tsukazaki, M.; Chelle-Regnaut, I.; Gautier, A.; Brown, S. M.; Urch, C. J. *J. Org. Chem.* **1999**, *64*, 2433.

[33] (a) Döbler, C.; Mehtretter, G. M.; Sundermeier, U.; Eckert, M.; Militzer, H.-C.; Beller, M. *Tetrahedron Lett.* **2001**, *42*, 8447. (b) Shapley, P. A.; Zhang, N.; Allen, J. L.; Pool, D. H.; Liang, H.-C. *J. Am. Chem. Soc.* **2000**, *122*, 1079.

[34] Iwahama, T.; Sakaguchi, S.; Nishiyama, Y,; Ishii, Y. *Tetrahedron Lett.* **1998**, *36*, 6923.

[35] (a) Maeda, Y.; Kakiuchi, N.; Matsumura, S.; Nishimura, T.; Kawamura, T.; Uemura, S. *J. Org. Chem.* **2002**, *67*, 6718. (b) Maeda, Y.; Kakiuchi, N.; Matsumura, S.; Nishimura, T.; Kawamura, T.; Uemura, *Tetrahedron Lett.* **2002**, *42*, 8877.

[36] Tanaka, T; Yamashita, H.; Tsuchitani, R.; Funabiki, T.; Yoshida, S. *J. Chem. Soc., Faraday Trans.* **1988**, *84*, 2987.

[37] (a) Elliott, J. C. *Structure and Chemistry of the Apatites and Other Calcium Orthophosphates*; Elsevier: Amsterdam, 1994. (b) Sugiyama, S.; Minami, T.; Hayashi, H.; Tanaka, M.; Shigemoto, N.; Moffat, J. B. *J. Chem. Soc., Faraday Trans.* **1996**, *92*, 293.

[38] Joslin, F. L.; Mague, J. T.; Roundhill, D. M. *Organometallics* **1991**, *10*, 521.

[39] Chen, W,-C.; Yu, W.-Y.; Li, C.-K; Che, C.-M. . *J. Org. Chem.* **1995**, *60*, 6840

[40] Kanemoto, S.; Matsubara, S.; Takai, K.; Oshima, K.; Utimoto, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3607.

[41] Chatt, J.; Shaw, B. L.; Field, A. E. *J. Chem. Soc.* **1964**, 3466.

[42] Connors, K. A. *Chemical Kinetics, The Study of Reaction Rates in Solution*; VCH Publishers, Inc.: New York, 1990.

[43] Lebeau, E. L.; Meyer, T. J. *Inorg. Chem.* **1999**, *38*, 2174.

[44] Cheng, W.-C.; Tu, W.-Y.; Li, C.-K.; Che, C.-M. *J. Org. Chem.* **1995**, *60*, 6840.

[45] Roecker, L.; Meyer, T. J. *J. Am. Chem. Soc.* **1987**, *109*, 746.

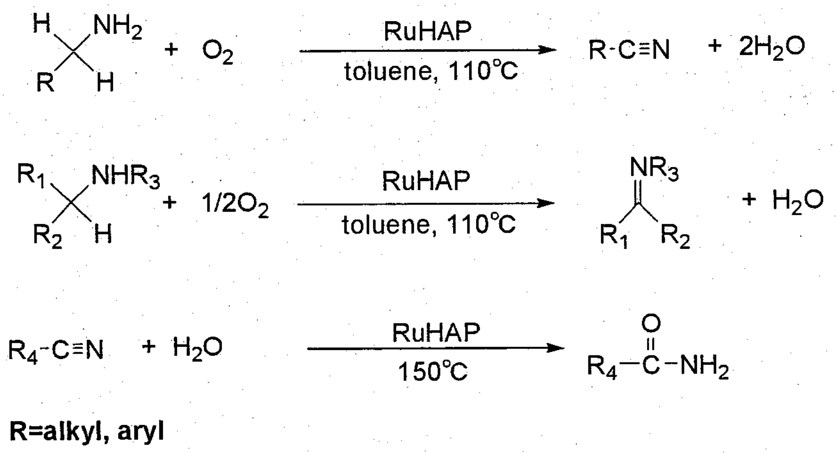
II-2. Oxidation of Primary Amines to Nitriles Catalyzed by Hydroxyapatite-Bound Ruthenium Complex using Molecular Oxygen

1. Introduction

Nitriles are key constituent in numerous natural products, and they also serve as versatile synthetic intermediates for pharmaceuticals, agricultural chemicals, dyes, and material sciences [1]. One of the most general methodologies for synthesis of alkylnitriles is a nucleophilic displacement of alkylhalides with inorganic cyanide ions, although the reaction is frequently accompanied by elimination of hydrogen halides especially with bulky alkylhalides [2]. Ammoxidation and Sandmeyer reaction are also well-known methods, but they require hazardous reagents and severe reaction conditions [3]. α,β-Unsaturated nitriles can be prepared via a Wittig reaction of the corresponding aldehyde with cyanoalkyl phosphonate [4]. However, it resulted in an unbiased mixture of *E*- and *Z*-isomeric nitriles. Nitrile synthesis by means of dehydration of amides or aldoximes with an appropreate nonmetal dehydrating agents such as P_2O_5 would be an alternative method [5]. However it suffer from serious disadvantages such as inconvenient preparation of the reagents, limited substrate scope, or incompatibility of sensitive functional groups under the reaction conditions.

With ever-growing environmental concern in organic reactions, there is a strong need for a preparative method of highly efficient nitrile synthesis. Direct oxidative dehydrogenation of *primary* amines is one powerful candidate for a clean nitrile synthesis. Many stoichiometric reagents in the above dehydrogenation have, however, been used [6], which often result in the production of a vast amount of environmental wastes [7]. Catalytic protocols using molecular oxygen as an oxidant are more desirable from the consideration of “green and sustainable chemistry” [8].

As described in Chapter II-1, the author has succeeded in creating a monomeric Ru^{3+} species on the surface of hydroxyapatite (RuHAP), which acts as a highly efficient heterogeneous catalyst for the aerobic oxidation of various alcohols. During the course of these studies, the author has also found that the aerobic oxidation of amines to the corresponding nitriles smoothly occurred in the presence of this RuHAP catalyst. Compared with other catalysts for this amine oxidation, the RuHAP system has many advantages as follows: (i) high catalytic activity for the oxidation of both aromatic and aliphatic amines under mild reaction conditions, (ii) a reusable heterogeneous catalyst, (iii) use of molecular oxygen as an ultimate oxidant, and (iv) applicability to the hydration of nitriles to amides.



2. Experimental

2-1. General

^{1}H- and ^{13}C-NMR spectra were obtained on JEOL GSX-270 or JNM-AL400 spectrometers at 270 or 400 MHz in $CDCl_3$ with TMS as an internal standard. Infrared spectra were measured with a JASCO FTIR-410. Elemental analysis was carried out by Perkin Elmer 2400CHN. Analytical GLC was performed by Shimadzu GC-8A PF with flame ionization detector equipped with KOCL 3000T, Silicon SE-30, and OV-17 columns.

$(NH_4)_2HPO_4$ and $Ca(NO_3)_2{\cdot}4H_2O$ were purchased from Wako Pure Chemical as a special grade. $RuCl_3{\cdot}nH_2O$ was obtained from N. E. Chemcat. Amines as substrate and solvents were purchased from Wako Pure Chemical, Tokyo Kasei, and Aldrich, and purified by the standard procedures prior to experiments. 4-(Aminomethyl)benzyl alcohol was synthesized according to the literature procedure [9]. All of the oxidation products are well known compounds. Their identities were confirmed by comparison with infrared spectra, elemental analyses, and NMR spectra.

2-2. Synthesis of Hydroxyapatite-Bound Ruthenium Complex

A calcium hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$, was synthesized according to the literature procedure [10]. 1.0 g of the calcium hydroxyapatite was stirred at 25 °C for 24 h in 75 mL of a 2.67×10^{-2} M aqueous $RuCl_3$ solution. The obtained slurry was filtered, washed with deionized water and dried overnight at 110 °C, yielding the RuHAP as a dark brown powder (Ru^{3+} content: 1.69 $mmol \cdot g^{-1}$). The surface structure of the present RuHAP was determined by means of XRD, XPS, EDAX, and Ru K-edge XAFS as described in Chapter 2-I.

2-3. General Procedures for the Oxidation of Amines Catalyzed by Hydroxyapatite-Bound Ruthenium Complex

A typical amine oxidation is as follows. Into a reaction vessel with a reflux condenser were successively placed the RuHAP (0.2 g, Ru: 6.5 mol%), *p*-xylene (15 mL), and *n*-dodecylamine (0.96 g, 5.2 mmol). The reaction mixture was stirred at 125 °C under atmospheric pressure of O_2. After 24 h, the RuHAP was separated by filtration and the organic layer was distilled to afford pure *n*-dodecanenitrile (0.88 g, 94% yield).

2-4. General Procedures for the Hydration of Nitriles Catalyzed by Hydroxyapatite-Bound Ruthenium Complex

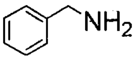
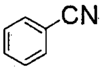
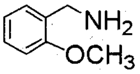
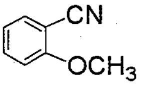
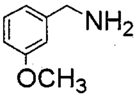
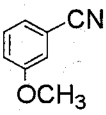
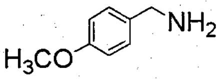
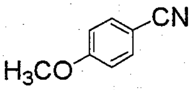
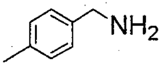
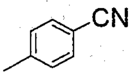
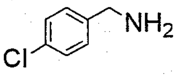
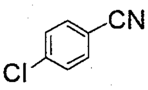
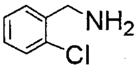
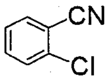
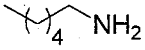
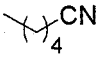
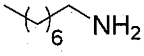
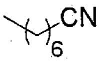
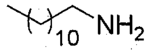
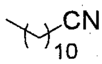
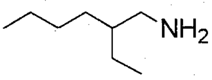
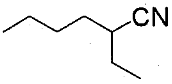
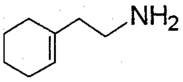
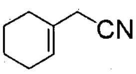
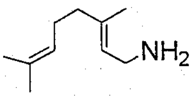
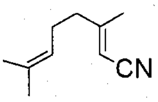
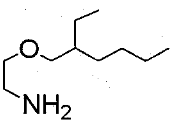
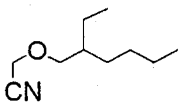
A typical hydration of nitriles is as follows. Into a stainless autoclave (100 mL) were successively placed the RuHAP (0.2 g, Ru: 6.5 mol%), H_2O (3 mL), and benzonitrile (0.103 g, 1 mmol). The reaction mixture was stirred at 150 °C under inert atmosphere. After 24 h, the RuHAP was separated by filtration and the filtrate was extracted with diethylether (25 mL x 3). Removal of the solvent under reduced pressure afforded pure benzamide (0.99 g, 94% yield).

3. Results and Discussion

3-1. Oxidation of Various Amines Catalyzed by Hydroxyapatite-Bound Ruthenium Complex

The results of oxidation of various *primary* amines catalyzed RuHAP in the presence of molecular oxygen are summarized in Table 1. Many benzylic amines were converted into the benzonitriles in high yields (entries 1-8). Notably, our RuHAP could oxidize aliphatic amines to the corresponding nitriles in high yields (entries 9-12). It is said that aliphatic amines give low yields of the nitriles in homogeneous Ru-catalyzed systems such as *trans*-[Ru^{VI}(tmp)(O_2)] [8a] (H_2tmp=5,10,15,20-tetramesitylporphyrin) and $RuCl_2(PPh_3)_3$ [8c] using molecular oxygen. Among the solvent examined, toluene and dichloromethane were good solvents, while acetonitrile gave slightly low yield. When an equimolar mixture of *n*-octylamine and 1-octanol was used as substrates, the oxidation of *n*-octylamine occurred exclusively to afford *n*-octanenitrile in 91% yield for 12 h without any oxidation products derived from 1-octanol (Figure 1). 1-Octanol alone was smoothly oxidized to afford 1-octanoic acid in 82% yield within 6 h under the same reaction conditions as described in Chapter II-1. Also, an intramolecular competitive oxidation of 4-(aminomethyl)benzyl alcohol afforded chemoselectively 4-cyanobenzyl alcohol in a quantitative yield because the amino function coordinates more strongly to a Ru center than the hydroxyl one (Scheme 1). 2-(1-Cyclohexenyl)ethylamine and geranylamine gave the allylic and vinylic nitriles in high yields without geometrical isomerization of double bonds, respectively (entries 13 and 14). As exemplified in Table 2, the RuHAP catalyst was applicable to the dehydrogenation of *secondary* amines [11]. Heterocyclic amines such as indole and 1,2,3,4-tetrahydroquinoline gave indole and quinoline in over 99 % yields, respectively (entries 1 and 2). In the case of dibenzylamine, *N*-benzylidenebenzylamine could be obtained in 91% yield (entry 5). Other *secondary* amines such as *N*-methylbenzylamine and *N*-ethylbenzylamine afforded the corresponding imines accompanied with benzaldehyde through the imine hydrolysis. Oxidation of *tertiary* amines did not proceed under the present conditions.

Table 1. Oxidation of *Primary* Amines Catalyzed by RuHAP in the Presence of O_2[a]

entry	substrate	product	time (h)	convn (%) [b]	yield (%) [b]
1			12	100	90 [c]
2			12	100	96
3[d]			12	100	97
4			12	92	90
5			12	100	97
6			12	100	96
7			12	95	95
8			12	100	>99
9			12	100	91
10			24	100	>99
11			24	100	>99
12			24	100	98
13			24	100	>99
14			12	100	81
15			24	100	94

[a] Reaction conditions: amine (1 mmol), RuHAP (0.1 g, Ru: 0.17 mmol), toluene (10 mL), 110°C, O_2 atmosphere. [b] Determined by GC using an internal standard technique.

[c] *N*-Benzylidenbenzylamine was also formed (10% yield). [d] Recycling experirment.

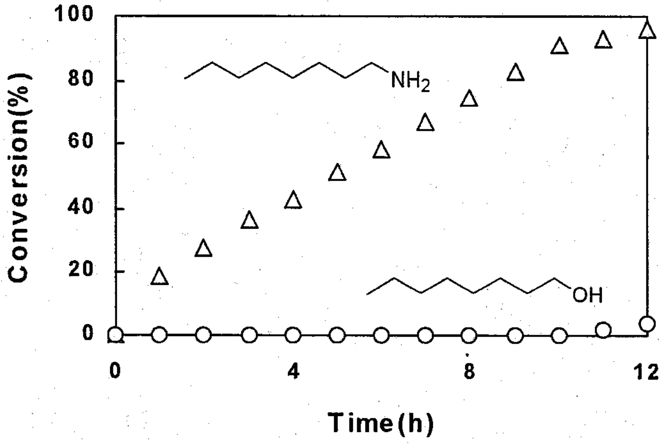


Figure 1. Competitive oxidation of *n*-octylamine (△) and 1-octanol(○) using RuHAP. Reaction conditions: *n*-octylamine (1 mmol), 1-octanol (1 mmol), RuHAP (0.1 g, Ru: 0.17 mmol), toluene (5 ml), 100°C, O_2 flow.

Scheme 1

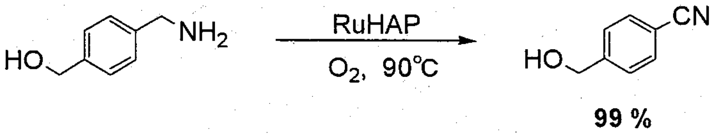
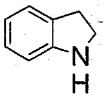
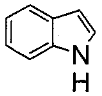
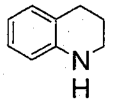
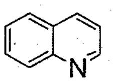
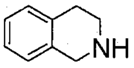
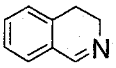
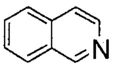
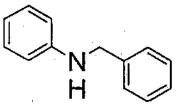
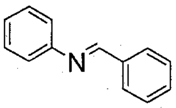
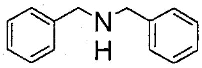
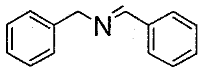


Table 2. Oxidation of *Secondary* Amines Catalyzed by RuHAP in the Presence of O_2[a]

entry	substrate	product	temp. (°C)	convn (%) [b]	yield (%) [b]
1			100	100	>99
2			80	100	>99
3		 	80	100	88, 11
4			110	100	>99
5[c]			130	98	91

[a] Reaction conditions: amine (1 mmol), RuHAP (0.1 g, Ru: 0.17 mmol), toluene (10 mL), O_2 atmosphere, 24 h. [b] Determined by GC using an internal standard technique.
[c] *p*-Xylene(10 ml) was used instead of toluene.

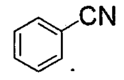
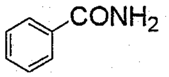
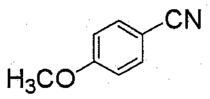
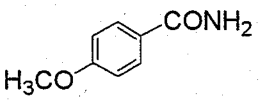
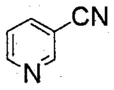
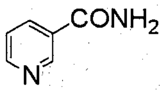
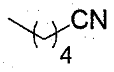
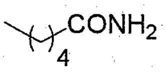
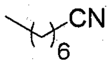
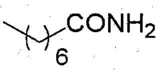
The spent RuHAP catalyst was easily separated from the reaction mixture and the ICP analysis of the filtrate showed that no leaching of the Ru species was observed during the above oxidation. In the oxidation of 4-methoxybenzylamine, the RuHAP was removed after 40 % conversion. The filtrate was further reacted at 110 °C for 12 h and no reaction was occurred, showing that the oxidation occurs on the surface of HAP. Moreover, this catalyst could be reused with retention of its high catalytic activity and selectivity; the yields of 2-methoxybenzonitrile in the case of 2-methoxybenzonitrile kept over 96 % during the four recycling experiments (Table 1, entry 3).

3-2. Hydration of Nitriles Catalyzed by Hydroxyapatite-Bound Ruthenium Complex

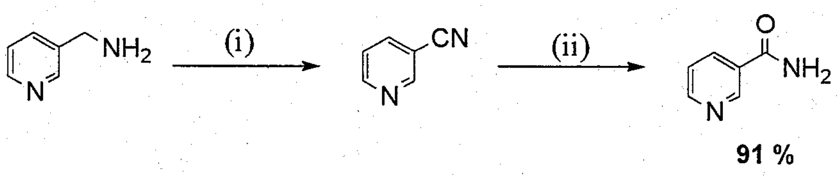
The preparation of amide is one of the most important synthetic transformations in organic synthesis, which is usually carried out in the laboratory using acid or base catalysis. A problem associated with this reaction is that it is often not possible to stop at the amide stage and further hydrolysis to the corresponding acid occurs. Recently, catalytic method using transition metal complexes have been reported, but they require extremely severe reaction conditions and the yield for aliphatic nitriles are often low. Consequently, with respect to the environmental concerns, there is a strong demand for a clean and highly efficient catalytic methodology for the conversion of nitriles to amides.

Interestingly, when water was used as a solvent instead of toluene, which was employed in the oxidation of amines, the RuHAP could also catalyze the hydration reaction of many nitriles, *i.e.*, *n*-hexanenitrile, *n*-octanenitrile, benzonitrile, 4-methoxybenzonitrile, and 3-cyanopyridine to afford excellent yields of the corresponding amides without any formations of carboxylic acids, respectively, as shown in Table 3. This hydration system using the RuHAP has advantages over other reported methods because of its simple and clean operation under neutral conditions and of a high reactivity for both aliphatic and aromatic nitriles [12]. Finally, the RuHAP catalyst could be applied to the one-pot synthesis of nicotinamide, a highly versatile intermediate of nicotinamide nucleotides, directly from 3-aminomethylpyridine, giving an excellent yield of a pure amide (Scheme 2).

Table 3. Hydration of Nitriles Catalyzed by RuHAP in the Presence of H_2O [a]

entry	substrate	product	convn (%) [b]	yield (%) [b]
1			100	90[c]
2			92	90
3			100	97
4			100	91
5			100	>99

[a] Reaction conditions: nitrile (1 mmol), RuHAP (0.1 g, Ru: 0.17 mmol), water (3 mL), 150°C, N_2 atmosphere, 24 h. [b] Determined by GC using an internal standard technique.



Scheme 2. Reaction conditions: (i) RuHAP (0.1 g), amine (10 mmol), 1,2-diethoxyethane (25 mL), O_2 atmosphere, 120 °C, 16 h, (ii) followed by adding water (5 mL), N_2 atmosphere, 150 °C, 48 h.

3-3. A Possible Reaction Mechanism

In the oxidation of various *para*-substituted benzylamines, the Hammett plot showed a negative ρ value, –0.137, which is close to that with a monomeric $RuCl_2(PPh_3)_3$, $\rho = -0.118$, as shown in Figure 3. These results suggest that the present RuHAP-catalyzed amine oxidation involves an amino-ruthenium intermediate. In addition, molar ratio of O_2 uptake to benzonitrile yield was 1:1. Addition of radical trap, 2,6-di-*tert*-butyl-*p*-cresol, to the reaction mixture hardly influences the oxidation. In consideration of the reaction mechanism of the

RuHAP-catalyzed aerobic alcohol oxidation, a most possible catalytic cycle for this amine oxidation are proposed in Scheme 3. Initially, a ligand exchange between an amine and a surface Cl moiety of the RuHAP gives a Ru–NHCH$_2$R species, followed by an elimination to produce a Ru-H species and an intermediate imine. Attack of molecular oxygen on the hydride species affords a Ru-OOH species, which reacts with the imine to produce a Ru–N=CHR species. The second dehydrogenation of the imine to nitrile proceeds *via* the similar path described in the above. H_2O_2 is a more probable intermediate for the formation of O_2 and H_2O, but H_2O_2 in the reaction medium could not be detected. The formation of imine as a reaction intermediate is supported by the fact that the RuHAP is able to catalyze the oxidation of *secondary* amines to the corresponding imines. In the nitrile hydration, the reaction of the surface Cl moiety with water yields a Ru-OH species, which attacks nucleophilically to a nitrile. A formed iminol intermediate, Ru–N=C(OH)R [12b], subsequently undergoes a ligand exchange with water to give the amide accompanied with the Ru-OH species.

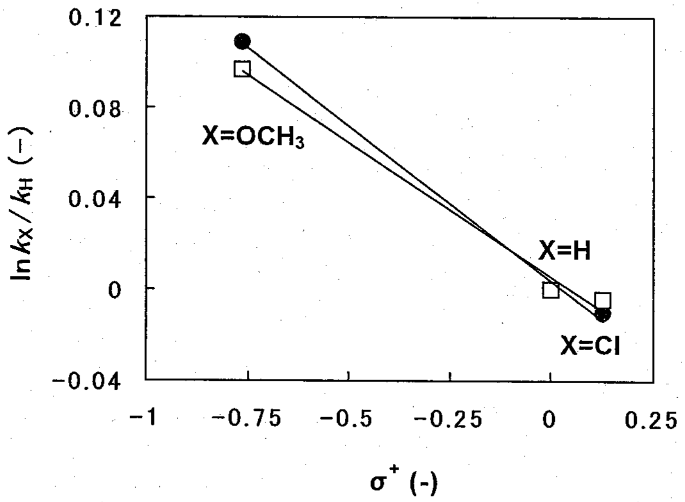
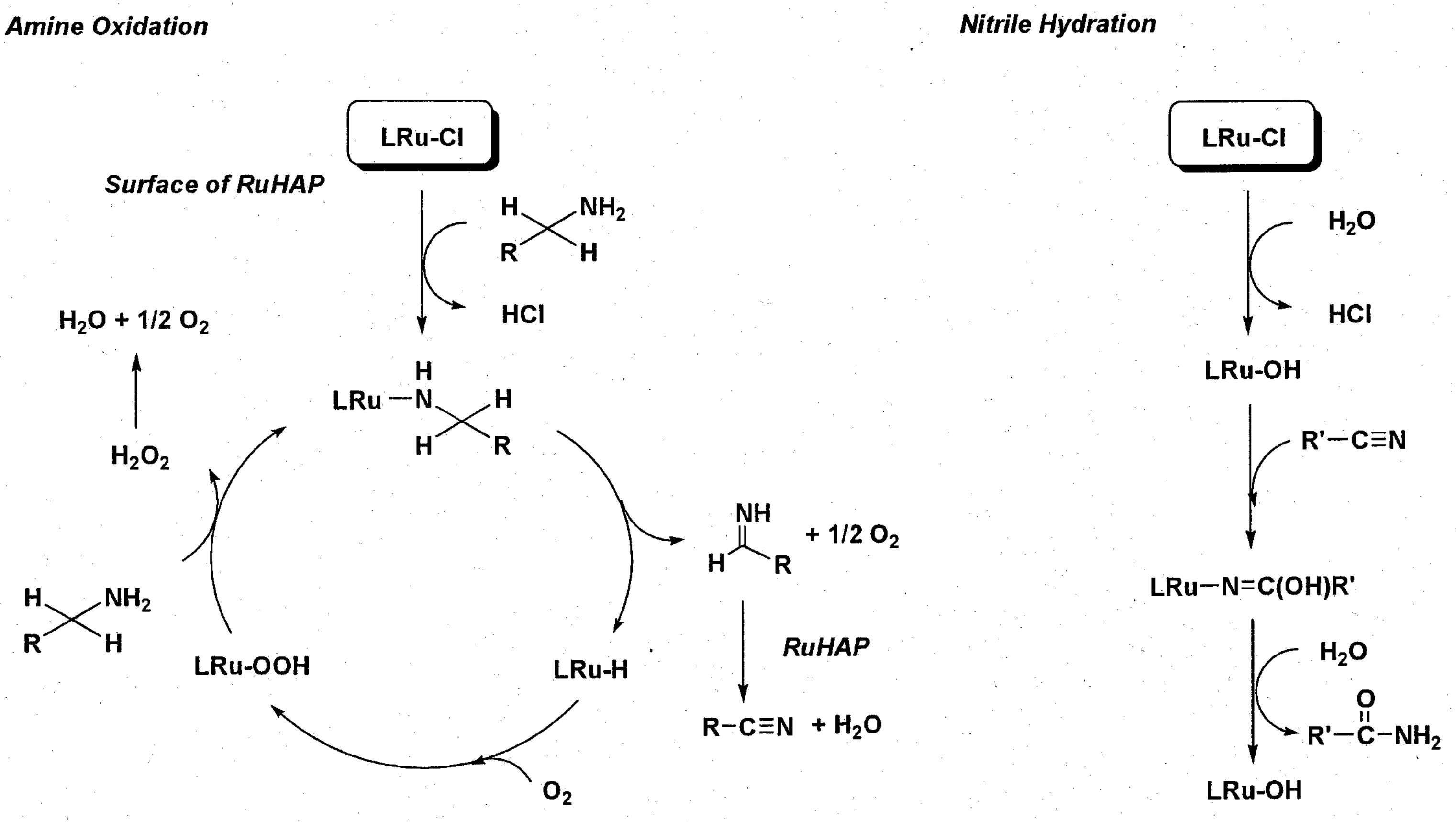


Figure 2. Hammett plots for the oxidation of *p*-substituted benzyl amines catalyzed by RuHAP (●) and $RuCl_2(PPh_3)_3$ (□). Reaction conditions: amine (1 mmol), Ru catalyst (0.34 mmol of Ru), toluene (5 mL), 80°C, O_2 atmosphere. Hammett ρ values for RuHAP and $RuCl_2(PPh_3)_3$ were −0.137 and −0.118, respectively.



Scheme 3. Possible Reaction Mechanism Catalyzed by RuHAP

4. Conclusions

In conclusion of Chapter II-2, the RuHAP efficiently catalyzed the oxidation of many *primary* and *secondary* amines using molecular oxygen, and could be further extended for the nitrile hydration. In both inter- and intramolecular competition experiments, the RuHAP system displayed a preference for amine *versus* alcohols. No leaching of the Ru species in the reaction solution was observed, which allows the hydroxyapatite catalyst to be recycled with retention of its high catalytic activity and selectivity. This protocol can be readily applied to large-scale process with high efficiency, making it an economical and an environmentally benign process for the preparation of nitriles.

References

[1] (a) Friedrich, K.; Wallenfels, K. The Chemistry of the Cyano Group; Rappaport, Z., Ed.; Wiley-Interscience Publisher: New York, 1970; p67. (b) Fatiadi, A. J. Preparation and Stnthetic Applications of Cyano Compounds; Patai, S., Rappaport, Z., Eds.; Wiley: New York, 1983; p1057. (c) Miller, J. S.; Manson, J. L. *Acc. Chem. Res.* **2001**, *34*, 563.

[2] (a) Kiefel, M. J. *Comprehensive OrganicFunctinal Group Transformations;* Katrizky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Wiley: New York, 1983; p1057. (b) Kukushkin, V, Y.; Tudela, D.; Pombeiro, A. J. L. *Coord. Chem. Rev.* **1996**, *156*, 333.

[3] *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I. Eds.; Pergamon: Oxford, England, 1991.

[4] For example, see: Magunus, P.; Scott, D. A.; Filding, M. R. *Tetrahedron Lett*, **2001**, *42*, 751.

[5] (a) Jung, M. E.; Long-Mei, Z. *Tetrahedron Lett*, **1983**, *24*, 4533. (b) Arrieata, A.; Aizpurua, J. M.; Palomo, C. *Tetrahedron Lett*, **1984**, *25*, 4533. (c) Kim, S.; Yi, K. Y. *Tetrahedron Lett*, **1986**, *27*, 1925. (d) Hendrickson, J. B.; Hussoin, M. S. *J. Org. Chem.*, **1987**, *52*, 4139. (e) Fukuzawa, S.-I.; Yamaishi, Y.; Furuya, H.; Terao, K.; Iwasaki, F. *Tetrahedron Lett*, **1997**, *38*, 7203.

[6] (a) Capdevielle, P.; Lavigne, A.; Maumy, M. *Synthesis*, **1989**, 453. (b) George, M. V.; Balachandran, K. S. *Chem. Rev.*, **1975**, *75*, 491. (c) Lee, J. B.; Parkin, C.; Shaw, M. J.; Hampson, N. A.; MacDonald, K. I. *Tetrahedron*, **1973**, *29*, 751.

[7] (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice;* Oxford University Press, **1998**. (c) Clark, J. H. *Green Chem.* **1999**, *1*, 1. (d) Sheldon, R. A. *Green Chem.* **2000**, *2*, G1. (e) Anastas, P. T.;Bartlett, L. B.; Kirchhoff, M. M.; Williamson, T. C. *Catal. Today* **2000**, *55*, 11.

[8] Example of catalytic amine oxidation are as follows (a) Bailey, A. J.; James, B. R. *Chem. Commun.*, **1996**, 2343. (b) Yamazaki, S.; Yamazaki, Y. *Bull. Chem. Soc. Jpn.*, **1990**, *63*, 301. (c) Porta, F.; Crotti, C.; Cenini, S. *J. Mol. Catal.*, **1989**, *50*, 333. (d) Cenini, F. Porta and M.

Pizzottio, *J. Mol. Catal.*, 1982, **15**, 297.

[9] Lee, T. R.; Niu, J.; Lawrence, D. S. *J.Biol. Chem.*, **1995**, 270, 5375.

[10] (a) Elliott, J. C. *Structure and Chemistry of the Apatites and Other Calcium Orthophosphates*; Elsevier: Amsterdam, 1994. (b) Sugiyama, S.; Minami, T.; Hayashi, H.; Tanaka, M.; Shigemoto, N.; Moffat, J. B. *J. Chem. Soc., Faraday Trans.* **1996**, *92*, 293.

[11] Example of secondary amine oxidation are as follows (a) Jansen, A. B, A.; Johnson, J. M.; Surtees, J. R. *J. Chem. Soc.* **1964**, 5573. (b) Pratt, E. F.; McGovern, T. P. *J. Org. Chem.*, **1964**, *29*, 1540. (c) Giethlem, B.; Schaus, J. M.; *Tetrahedron Lett*, **1997**, *38*, 8493. (d) Terent'ev, A. P.; Ban-lun', G.; Preobrazhenskaya, M. N. *J. Gen, Chem. USSR* **1962**, *32*, 173. (e) Kikugawa, Y.; Kawase, M. *Chem. Lett.* **1981**, 445. (f) Mukaiyama, T.; Kawana, A.; Fukuda, Y.; Matsuo, J. *Chem. Lett.* **2001**, 390. (f) Goti, A.; Romani, M. *Tetrahedron Lett*, **1994**, *35*, 6567. (g) Inada, A.; Nakamura, Y.; Morita, Y. *Chem. Lett.* **1980**, 1287. (h) Sundberg, R. J., *Chemistry of indoles*; Academic Press: New York, 1970.

[12] For examples of catalytic nitrile hydration: (a) Cobley, C. J.; van den Heuvel, M.; Abbadi and J. G. de Vries, A. *Tetrahedron Lett.* **2000**, *41*, 2467. (b) Kaminskaia, N. V.; Kostic, N. M.; *J. Chem. Soc., Dalton Trans.* **1996**, 3677. (c) Ghaffar, T.; Parkins, A. W. *Tetrahedron Lett.* **1995**, *36*, 8657. (d) Murahashi, S.-I.; Sasao, S.; Saito, E.; Naota, T. *J. Org. Chem.*, **1992**, *57*, 2521.

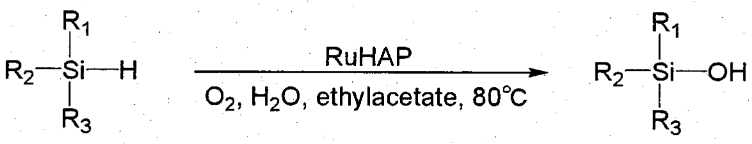
II-3. Oxidation of Organosilanes to Silanols Catalysed by Hydroxyapatite-Bound Ruthenium Complex in the Presence of Water and Molecular Oxygen

1. Introduction

Organosilicon compounds are of paramount importance as valuable building blocks [1], among which silanols have been prominently utilized in industry for the production of silicon-based polymeric materials [2] as well as in organic synthesis as reaction intermediates [3]. Especially noteworthy is that organosilanols have been recognized as an efficient organic donor in metal-catalyzed cross-coupling reactions [4]. Although the wide utility of silanols requires efficient preparative procedures for the compounds from readily available precursors, only a limited number of methods are available to date, including hydrolysis of halosilanes, stoichiometric oxidation of organosilanes, and reaction of siloxanes with alkali reagents [5]. These methods often result in the production of vast amounts of toxic wastes.

A more promising procedure is the catalytic insertion of oxygen atom into the Si-H bond of organosilanes, which have been carried out by some metals [6]. This protocol, however, is rather limited due to the fact that in generally produces mixture of the silanol and its undesirable disiloxane. Therefore, highly efficient catalytic transformation of silanes to the corresponding silanols is particularly attractive from both environmental and synthetic perspectives [7]. Recently, Chang et al. have reported the effective hydrolytic oxidation of silanes including alkynyl and alkenyl groups catalyzed by the $[RuCl_2(p\text{-cymene})]_2$ complex [8], but the use of homogenous catalyst often demonstrate limited practical utility due to difficulties in separation and recovery.

In Chapter II-1 and II-2, the author showed that monomeric Ru cation species could be uniformly introduced into hydroxyapatite surface based on cation-exchange ability. This hydroxyapatite-bound Ru complex (RuHAP) exhibits excellent catalytic performances for the aerobic oxidation of alcohols and *primary* and *secondary* amines, which is attributable to a monomeric Ru species as the phosphate complex on solid surfaces [9]. In the course of our ongoing studies for exploring practical organic transformations using the RuHAP, the author also found that oxidation of silanes occurred smoothly to give the corresponding silanols. The catalytic system described here is a powerful candidate for a promising synthetic protocol because of following advantages: (1) use of nonpolluting oxidants of water and molecular oxygen, (2) high selectivity and substrate tolerance, (3) stereospecific oxidation via inversion of the configuration of silanes, and (4) simple work-up procedure and easy recovery of catalyst.



**R=alkyl,alkenyl,
alkynyl, aryl**

2. Experimental

2-1. General

^{1}H- and ^{13}C-NMR spectra were obtained on JEOL GSX-270 or JNM-AL400 spectrometers at 270 or 400 MHz in $CDCl_3$ with TMS as an internal standard. Infrared spectra were measured with a JASCO FTIR-410. Elemental analysis was carried out by Perkin Elmer 2400CHN. Analytical GLC was performed by Shimadzu GC-8A PF with flame ionization detector equipped with KOCL 3000T, Silicon SE-30, and OV-17 columns.

$(NH_4)_2HPO_4$ and $Ca(NO_3)_2 \cdot 4H_2O$ were purchased from Wako Pure Chemical as a special grade. $RuCl_3 \cdot nH_2O$ was obtained from N. E. Chemcat. Silanes as substrate and solvents were purchased from Wako Pure Chemical, Tokyo Kasei, and Aldrich, and purified by the standard procedures prior to experiments. All of the oxidation products are well known compounds. Their identities were confirmed by comparison with infrared spectra, elemental analyses, and NMR spectra.

2-2. Synthesis of Hydroxyapatite-Bound Ruthenium Complex

A calcium hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$, was synthesized according to the literature procedure [10]. 1.0 g of the calcium hydroxyapatite was stirred at 25 °C for 24 h in 75 mL of a 2.67×10^{-2} M aqueous $RuCl_3$ solution. The obtained slurry was filtered, washed with deionized water and dried overnight at 110 °C, yielding the RuHAP as a dark brown powder (Ru^{3+} content: 1.69 $mmol \cdot g^{-1}$). The surface structure of the present RuHAP was determined by means of XRD, XPS, EDAX, and Ru K-edge XAFS as described in Chapter 2-I.

2-3. General Procedures for the Oxidation of Silanes Catalyzed by Hydroxyapatite-Bound Ruthenium Complex

Into a reaction vessel equipped with a reflux condenser were successively placed the RuHAP (0.2 g, Ru^{3+}: 0.2 mol %), ethyl acetate (50 mL), dimethylphenylsilane (100 mmol), and water (200 mmol). The reaction mixture was stirred at 80 °C under an atmospheric O_2 pressure. After 6 h, the RuHAP was separated by filtration and the organic layer was distilled to afford pure dimethylphenylsilanol (94% isolated yield).

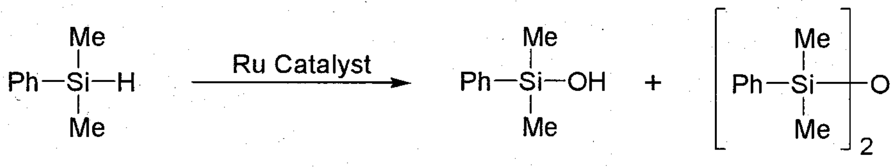
2-4. A Procedure for the Reaction of (+)-methylethylphenylsilane

The optically active (+)-methylethylphenylsilane (ee 98 %) was obtained from racemic methylethylphenylsilane by preparative HPLC (Daicel Chiralcel OJ-H×2, *n*-hexane, 1.0 mL/min, 0°C, 254 nm, $t_R s$=13.1 min). Into a reaction vessel equipped with a reflux condenser were successively placed the RuHAP (0.01 g), 1,4-dioxane (4 mL), 0.1 mol/L of (+)-methylethylphenylsilane in *n*-hexane solution (1 mL), and water (1 mmol). After the reaction mixture was stirred at 80 °C under O_2 atmosphere for 24 h, the RuHAP was separated by filtration. To the filtrate was added $LiAlH_4$ (0.3 mmol) solution in 1,4-dioxane (2 mL), followed by stirring at 90 °C for 24 h to afford (–)-methylethylphenylsilane (ee 97%, determined by HPLC, $t_R s$=14.2 min). It is known that the reduction of silanols using $LiAlH_4$ proceeds with a retention of stereochemistry [11].

3. Results and Discussion

3-1. Survey of Optimal Reaction Conditions for Silane Oxidation

Oxidations of dimethylphenylsilane (**1**) using various Ru catalysts were first examined under several conditions. The sterically exposed silane was chosen as a model substrate because its conversion to the corresponding silanol is highly sensitive to the reaction conditions, and condensation to disiloxane is a serious drawback [6]. As shown in Table 1, the RuHAP catalyst exhibited the highest activity and selectivity in the presence of water under atmospheric oxygen to afford the corresponding dimethylphenylsilanol (**2**) in 99% yield (entry 1). Water and molecular oxygen were indispensable components for attaining high silanol yields (entries 2 and 3). Among the solvents examined, ethyl acetate, acetonitrile, and DMF were excellent solvents,



1 **2** **3**

Table 1. Oxidation of Dimethylphenylsilane using Various Ru Catalysts [a]

entry	catalyst	H_2O (eq.)	atmosphere	convn. (%)[b]	Selectivity[b] **2:3**
1	**RuHAP**	**5**	**O_2**	**>99**	**>99:1**
2	RuHAP	—	O_2	>1	—
3	RuHAP	5	Ar	7	>99:1
4	Ru/carbon	5	O_2	97	73:27
5	RuO_2	5	O_2	84	70:30
6	Ru/Al_2O_3	5	O_2	66	64:36
7	$RuCl_2(PPh_3)_3$	5	O_2	94	56:44
8	$Pr_4N^+ \cdot RuO_4^-$	5	O_2	47	10:90
9[c]	$RuCl_3 \cdot nH_2O$	5	O_2	48	3:97

[a] Reaction conditions; dimethylphenylsilane (1 mmol), ethyl acetate (5 mL), catalyst (5 mol% of Ru relative to substrate), 80°C, 3 h. [b] Determined by GC using internal standard. [c] Acetonitrile was used as solvent.

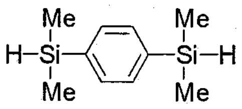
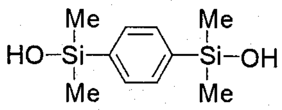
while *n*-heptane and toluene gave poor results with respect to both conversion and selectivity. Typical heterogeneous Ru catalysts such as Ru/carbon, RuO_2, and Ru/Al_2O_3 were found to be less effective under the same reaction conditions. The use of $Pr_4N^+ \cdot RuO_4^-$ and $RuCl_3 \cdot nH_2O$ led to the silanol condensation, giving an undesirable disiloxane (**3**). Neutral nature of the hydroxyapatite presumably avoids side-reactions arising from acid-base properties of support itself.

3-2. Oxidation of Various Silanes Catalyzed by Hydroxyapatite-Bound Ruthenium Complex

Oxidation results for a variety of silanes catalyzed by the RuHAP under optimal reaction conditions are summarized in Table 2. In our oxidation system, the corresponding silanols were obtained without any condensation products. For example, even a sterically exposed silane of triethylsilane was exclusively oxidized to give triethylsilanol in 92% yield (entry 5). As mentioned above, silanols containing small substituents are easily converted to the disiloxane due to heat, acid, or base instability, which is a crucial drawback in other reported synthetic procedures. The RuHAP catalyst was also applicable to the oxidation of silanes possessing alkynyl- and alkenyl groups to form the corresponding silanols in high yields (entries 8 and 9). In the cases of diphenylsilane and 1,4-bis(dimethylsilylbenzene), the silanediols were obtained in almost quantitative yields (entries 10-11). Sterically bulky silanes such as triphenylsilane and triisopropylsilane were hardly oxidized under the present system. The RuHAP catalytic system represents a highly suitable method for large-scale operations; a 100 mmol scale oxidation of (**1**) was completed within 6 h to provide 94 % of (**2**).

In the oxidation of dimethylphenylsilane, the catalyst was filtered off after ca. 50% conversion at the reaction temperature. The filtrate was further reacted at 80 °C for 3 h and then, no oxidation of dimethylphenylsilane occurred. Ru leaching in the filtrate was not observed by ICP analysis whose detection limit is 0.04 ppm. It can be said that this silane oxidation proceeds with heterogeneous Ru species. Furthermore, the RuHAP catalyst could be reused four times without loss of the high catalytic activity and selectivity (entries 2-5). The Ru K-edge XANES spectra of the recovered RuHAP catalyst was similar to that of the fresh one and the EXAFS analysis showed no Ru-Ru bond. These results support that the Ru species exist as a Ru^{3+} monomer even in the used RuHAP. No chlorine was confirmed by XPS analysis of the used RuHAP, whereas the atomic ratio of Ru to Cl was 1:1 in the fresh RuHAP. Hence, it was suggested that the Cl^- ligand of the RuHAP was exchanged with OH^- during the silane oxidation.

Table 2. RuHAP-Catalysed Oxidation of Silanes in the Presence of H_2O and O_2 [a]

entry	substrate	product	time (h)	convn. (%) [b]	yield (%) [b]
1	$PhMe_2SiH$	$PhMe_2SiOH$	3	100	99
2	Recycle 1		3	100	97
3	Recycle 2		3	100	98
4	Recycle 3		3	100	97
5	Recycle 4		3	100	98
6[c]	*t*-$BuMe_2SiH$	*t*-$BuMe_2SiOH$	24	89	89
7	Ph_2MeSiH	$Ph_2MeSiOH$	12	95	92
8	Et_3SiH	Et_3SiOH	6	93	92
9	$(n\text{-}Bu)_3SiH$	$(n\text{-}Bu)_3SiOH$	12	100	>99
10	$(n\text{-}C_6H_{13})_3SiH$	$(n\text{-}C_6H_{13})_3SiOH$	12	92	90
11	$Ph-\equiv-SiMe_2H$	$Ph-\equiv-SiMe_2OH$	14	92	92
12	$Ph-=-SiMe_2H$	$Ph-=-SiMe_2OH$	12	93	90
13	Ph_2SiH_2	Ph_2SiOH_2	9	100	98[d]
14			24	91	91[d]

[a] Reaction conditions; silane (1 mmol), ethyl acetate (5 mL), catalyst (0.05 g, Ru: 0.05 mmol), H_2O (5 mmol), 80°C, O_2 atmosphere. [b] Determined by GC analysis using internal standard technique. [c] H_2O (3 mmol), 70°C. [d] Isolated yield.

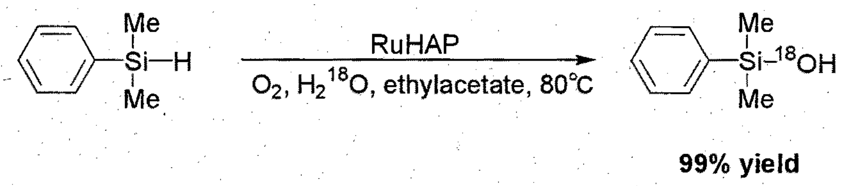
3-3. Oxidation of Optically Active Silane

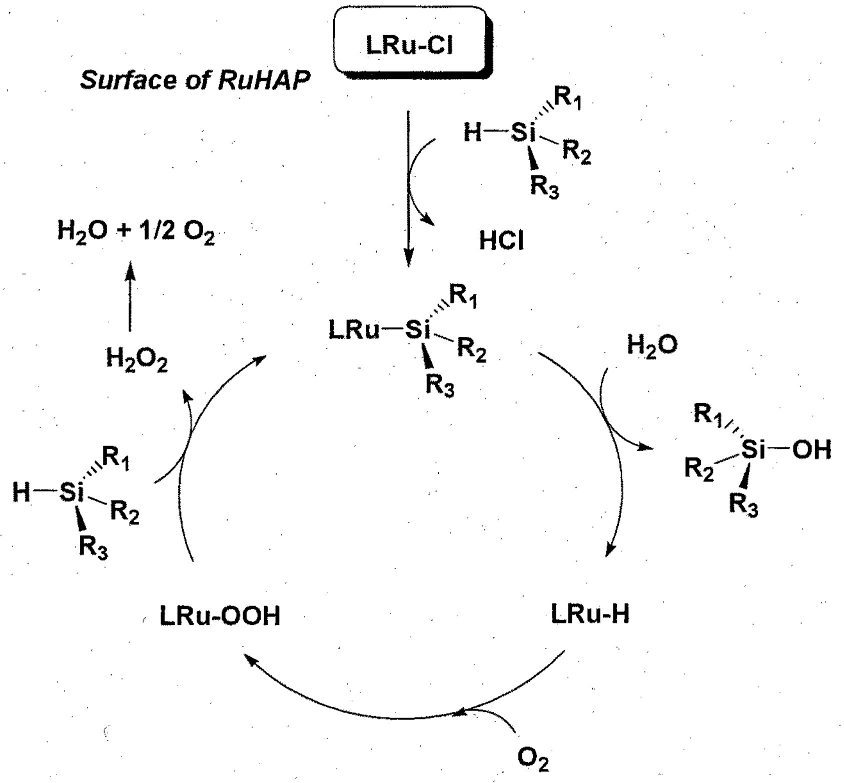
Growing interest has been shown in the synthesis of optically active silanols as useful synthetic intermediates for a variety of bioactive compounds [12]. For the stereoselective oxidation of optically active silanes with *retention* of configuration, only stoichiometric oxidants, *i.e.*, *m*-CPBA, dimethyldioxirane, and oxaziridines, have been reported to date [5b-d]. Significantly, the RuHAP-catalyzed oxidation of optically active silanes proceeded exclusively with *inversion* of the silicon configuration; the oxidation of (+)-methylethylphenylsilane in the presence of the RuHAP, followed by the reduction with $LiAlH_4$ afforded (–)-methylethylphenylsilane in 97% *ee*. Similar stereospecific oxidation has also been achieved by $[RuCl_2(p\text{-cymene})]_2$ complex, but the selectivity with the RuHAP was higher than that reported for the homogeneous Ru complex. Such prominent performance of the RuHAP might be due to the structurally robust monomeric active site on a solid surface, which provides strict steric control of the reaction intermediate.

3-4. A Possible Reaction Mechanism for Silane Oxidation

The RuHAP-catalyzed oxidation of **(1)** with isotopic $H_2{}^{18}O$ led to the selective formation of ^{18}O-labeled silanol in a quantitative yield (Scheme 1). The oxygen atom incorporated into silanol is not derived from molecular oxygen but from water. In addition, molar ratio of O_2 uptake to silanol **(2)** yield was 1:2. On the basis of these results, a plausible mechanism of this silane oxidation is proposed as follows (Scheme 2). Initially, the ligand exchange between a silane and a surface Cl moiety of the RuHAP gives a silyl-metal intermediate, which undergoes the nucleophilic attack of water to produce a corresponding silanol and a Ru-H species. The reaction of the hydride species with molecular oxygen affords a Ru-OOH species, followed by the ligand exchange with the silane to regenerate the silyl-metal intermediate together with the formation of O_2 and H_2O. H_2O_2 is a more probable intermediate for the formation of O_2 and H_2O, but H_2O_2. The inversion of the stereochemistry of silane in the oxidation shows that the nucleophilic attack of water occurs from the backside of a Ru-silicon bond [13]. Hydrolytic oxidation of silanes using the homogeneous $[RuCl_2(p\text{-cymene})]_2$ catalyst is moderately promoted under the oxygen atmosphere [8]. But, the above oxidation proceeds via the oxidative addition of silane to ruthenium, whereas the catalytic pathway of the RuHAP is initiated by the ligand exchange with silane. This unique activation of Si-H bond using the RuHAP is attributable to robust monomeric Ru^{3+} species generated on solid surfaces.

Scheme 1





Scheme 2. A Possible Silane Oxidation Mechanism Catalyzed by RuHAP

4. Conclusions

In summary of Charpter II-3, the author demonstrated that the RuHAP was found to offer an efficient heterogeneous catalyst system for the oxidation of silanes employing a combined oxidant of water and molecular oxygen. The oxidation proceeded selectively with functional group tolerance. For the steleoselective oxidation of optically active silane, *inversion* of configuration has been observed, in contrast to the previously reported stoichiometric oxidants. Moreover, the spent RuHAP catalyst was recyclable with retention of the high activity and selectivity. The present catalytic systems are therefore highly suitable for large-scale operations, meeting the increasing demands for environmentally-friendly chemical processes.

References

[1] (a) Ojima, I.; Li, Z.; Zhu, L. *Chemistry of Organic Silicon Compounds*; Rappoport, S., Apeloig, Y., Eds.; Wiley: New York, 1998; Chapter 29. (b) Colvin, E. W. *Silicon Reagents in Organic Synthesis*; Academic Press: London, 1988; p 7.

[2] Lickness, P. D. *Adv. Inorg. Chem.* **1995**, *42*, 147.

[3] (a) Chan, T. H.; Chen, L. M.; Wang, D.; Li. L.H. *Can. J. Chem.* **1993**, *71*, 60. (b) Takaku, K.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1994**, *35*, 6329. (c) Uehira, S.; Takaku, K.; Shinokubo, H.; Oshima, K. Synlett **1998**, 1096.

[4] (a) Hirabayashi, K.; Nishihara, Y.; Mori, A.; Hiyama, T.; *Tetrahedron Lett.* **1998**, *39*, 7893. (b) Hirabayashi, K.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T.; *Org. Lett.* **1999**, *1*, 299. (c) Denmark, S. E.; Wehrli, D. *Org. Lett.* **2000**, *2*, 565.

[5] (a) Rochow, E. G.; Gilliam, W. F. *J. Am. Chem. Soc.* **1941**, *63*, 798. (b) Adam, W.; Mello, R,; Curci, R. *Angew. Chem. Int. Ed.* **1990**, *29*, 890. (c) Seiburth, S. M.; Mu, W. *J. Org. Chem.* **1993**, *58*, 7584; (d) Cavicchioli, M.; Montanari, V.; Resnati, G, *Tetrahedron Lett.* **1994,** *35*, 6329. (e) Hirabayashi, K.; Mori, A.; Hiyama, T.; *Tetrahedron Lett.* **1997**, *38*, 461.

[6] (a) Adam, W.; Mitchell, C. M.; Saha-Möller, C. R.; Weichold, O. *J. Am. Chem. Soc.* **1999**, *121*, 2097. (b) Tan, H.; Yoshikawa, A.; Gordon, M. S.; Espenson, J. H. *Organometallics* **1999**, *18*, 4753 (c) Adam, W.; Saha-Möller, C. R.; Weichold, O. *J. Org. Chem.* **2000**, *65*, 2897. (d) Matarasso-Tchiroukhine, E. *J. Chem. Soc., Chem. Commun.* **1990**, *681* (e) Schubert, U.; Lorenz, C. *Inorg. Chem.* **1997**, *36*, 1258 (f) Shi, M.; Nicholas, K. M. *J. Chem. Res., Synop.* **1997**, 400. (f) Adam, W.; Garcia, H.; Mitchell, C. M.; Saha-Möller, C. R.; Weichold, O. *Chem. Commun.* **1998**, 2609. (g) Adam, W.; Corma, A.; Garcia, H.: Weichold, O. *J. Catal.* **2000**, *196*, 339.

[7] (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice;* Oxford University Press, **1998**. (c) Clark, J. H. *Green Chem.* **1999**, *1*, 1. (d) Sheldon, R. A. *Green Chem.* **2000**, *2*, G1. (e) Anastas, P. T.; Bartlett, L. B.; Kirchhoff, M. M.; Williamson, T. C. *Catal. Today* **2000**, *55*, 11.

[8] Lee, M.; Ko, S.; Shang, S. *J. Am. Chem. Soc.*, **2000**, *122*, 12011.

[9] (a) Yamaguchi, K.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2000**, *122*, 7144. (b) Mori, K.; Yamaguchi, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Chem. Commun.* **2001**, 461.

[10] (a) Elliott, J. C. *Structure and Chemistry of the Apatites and Other Calcium Orthophosphates*; Elsevier: Amsterdam, 1994. (b) Sugiyama, S.; Minami, T.; Hayashi, H.; Tanaka, M.; Shigemoto, N.; Moffat, J. B. *J. Chem. Soc., Faraday Trans.* **1996**, *92*, 293.

[11] Sommer, L. H.; Lyons, J. E. *J. Am. Chem. Soc.* **1969**, *91*, 7061.

[12] (a) Tacke, R.; Linoh, H.; Ernst, L.; Moser, U.; Mutschler, E.; Sarge, S.; Cammenga H. K.; Lambrecht, G *Chem, Ber.* **1987**, *120*, 1229. (b) Yamamoto, K.; Kawanami, Y.; Miyazawa, M. *J. Chem. Soc., Chem. Commun.* **1993**, 436. (c) Mori, A.; Toriyama, F.; Kajiro, H.; Hirabayashi, K.: Nishihara, Y.; Hiyama, T. *Chem. Lett.* **1999**, 549.

[13] Sommer, L. H.; Frye, C. L.; Parker, G A.; Michel, K. W. *J. Am. Chem. Soc.* **1964**, *86*, 3271.

Chapter III

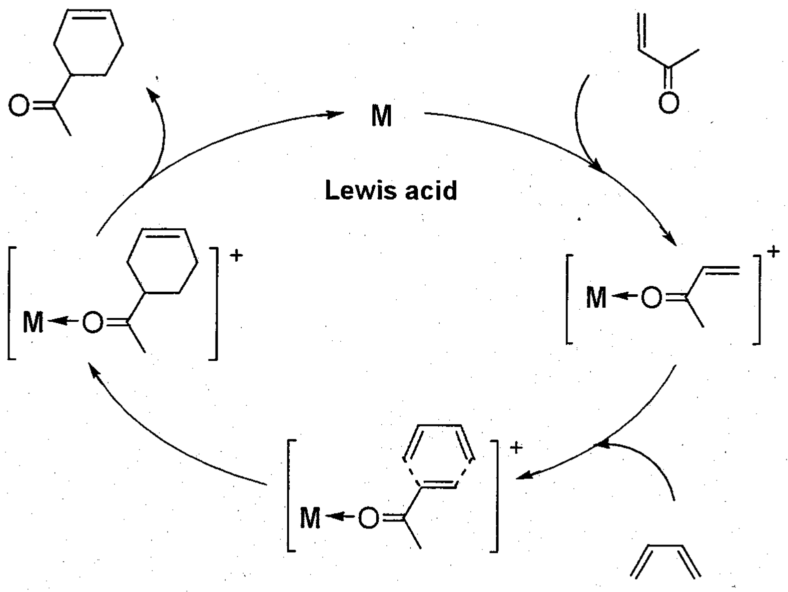
Carbon-Carbon Bond-Forming Reactions using Hydroxyapatite-Bound Cationic Ruthenium Complexes as Heterogeneous Lewis Acid Catalysts

1. Introduction

Lewis acid catalysis has attracted considerable interest in organic synthesis because of their unique properties across a diverse array of carbon-carbon bond-forming reactions [1]. The most conventional Lewis acids are the halide of B(III), Al(III), Ti(IV), and Sn(IV) [2]. However, these reagents generally require stoichiometric amounts in order to achieve maximum acceleration and must be used under strictly anhydrous conditions. The presence of even a small amount of water inhibits the reactions, because most Lewis acid immediately reacts with water rather than substrates. Therefore, the development of new types of Lewis acid catalyst is particularly important; society needs forward-looking technology, which is based on environmental acceptability [3].

The Diels-Alder reaction is a typical Lewis acid catalyzed process and a versatile tool for the synthesis of natural products in organic chemistry (Scheme 1) [4]. The reaction can proceeded with remarkable regio- and stereoselectivity up to four stereocenters can be created in one step in the formation of a six-membered ring. The rate enhancements by Lewis acids can be readily understood in terms of FMO theory, as illustrated in Figure 1 [5]. Upon coordination to a lone pair located on the Lewis-basic center of the dienophile, the catalytically active Lewis acid withdraws electron density and lowers the LUMO energy of the conjugated system. This improves the $\mathrm{HOMO_{diene}}$-$\mathrm{LUMO_{dienophile}}$ interaction. Recently, several attempts have been made to accomplish the reaction enantioselectively, by complexing traditional Lewis acids with chiral ligands and, subsequently, by using transition metal complexes, among which those of Co [6], Fe [7], Cu [8], Ru [9], Ti [10], and Pd [11] have proved to be interesting, often showing ee's in the 95 % range.

Murahashi et al. have discovered that the low-valent transition metal complexes act as redox Lewis acid catalysts for the α-C-H bond activations of amines, nitriles, and isonitriles [12]. The activation of α-C-H bonds is induced by the α-heteroatom effect; coordination of heteroatom (Y) of substrate to low-valent transition metal would increase both the basicity of the metal and acidity of the C-H bond adjacent to Y, resulting in oxidative



Scheme 1. Mechanism of Diels-Alder reaction catalyzed by Lewis acid

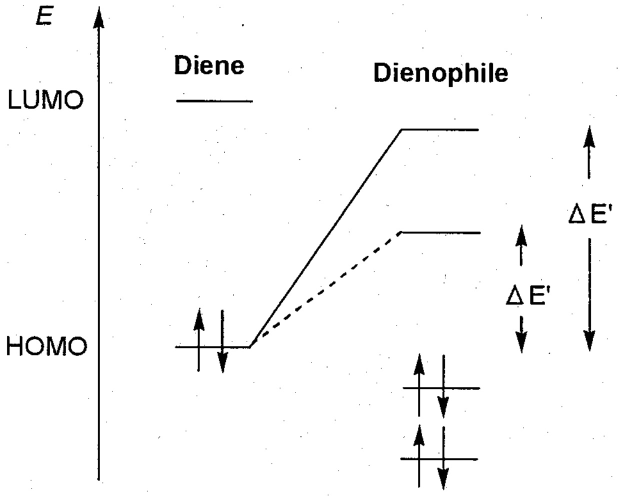
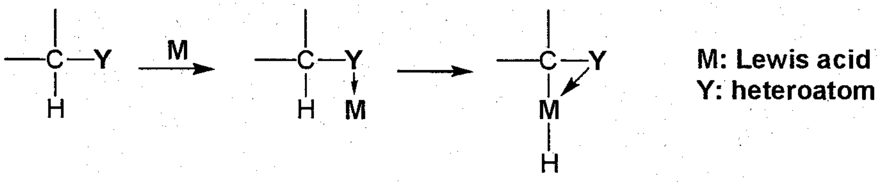


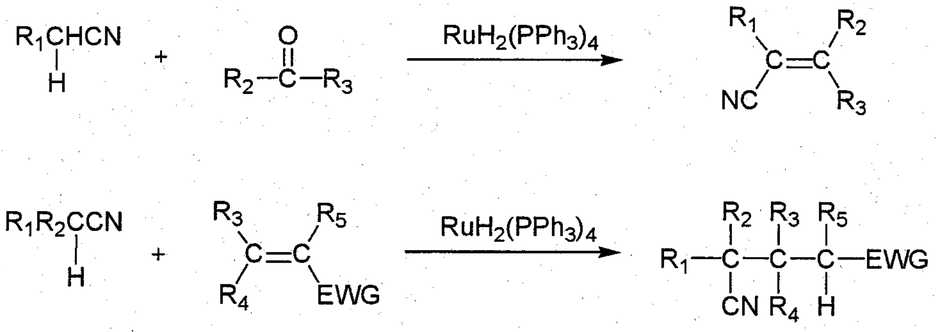
Figure 1. HOMO-LUMO arrangements for Lewis acid-catalyzed (broken line) and uncatalyzed (solid line) Diels-Alder reactions with normal electron demand.

addition of the metal into the α-C-H bond to afford α-metalated intermediate (Scheme 2)[13]. The generated α-metalated intermediate can be trapped with electrophiles to form a carbon-carbon bond at the α position. For example, the $RuH_2(PPh_3)_4$ complex has proved to be an effective catalyst for the activation of the α-C-H bond of nitriles. Upon treatment with carbonyl compounds or olefins bearing electron-withdrawing groups, catalytic aldol and Michael reactions could be performed under neutral and mild reaction conditions (Scheme 3) [14].

Scheme 2



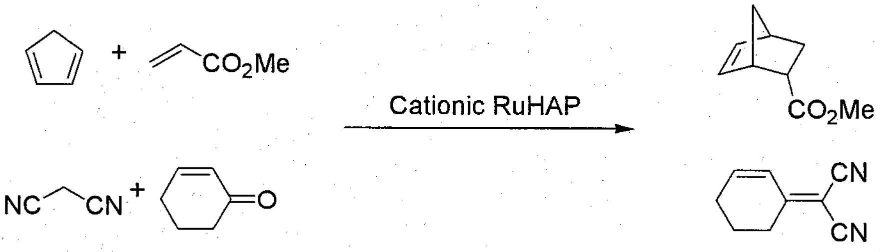
Scheme 3



In spite of these advantages of homogeneous metal complex catalysts, difficulties in recovering the expensive catalyst metals and ligands from the reaction mixtures severely limit their industrial applications. Attempts to overcome these problems have so far directed toward the anchoring of efficient soluble systems on insoluble matrices. These hybrid-catalysts, however, have been inadequate due to: i) inferior activities, as compared to homogeneous analogues, ii) tedious multi-step preparations, and iii) leaching of active components [15].

Other alternative strategy for design of the hybrid-catalysts focuses on the utilizing of hydroxyapatites (HAP), having promising ability as a macroligand for catalytically active centers [16]. As described in Chapter II, the author has successfully created a stable monomeric Ru phosphate complex on the surface of the hydroxyapatite (RuHAP) by using the cation-exchange method as a versatile catalyst with superior activity for the selective oxidation reactions, and possessing high reusability.

In this Chapter, a new type of hydroxyapatite-bound cationic Ru complexes with potentially vacant coordination sites were prepared by simple modulation of the neutral RuHAP using silver salts. By acting as a Lewis acid toward carbonyl and cyano groups, these cationic RuHAPs exhibited effective catalytic activities for Diels-Alder and aldol reactions under mild and neutral conditions. By utilizing the unique properties of the cationic RuHAPs, including acid-base bifunctional catalysis and steric control of a reaction intermediate, it is possible to develop efficient catalytic system which cannot be attained with homogeneous metal complex catalysts.



2. Experimental

2-1. General

^{1}H- and ^{13}C-NMR spectra were obtained on JEOL GSX-270 or JNM-AL400 spectrometers at 270 or 400 MHz in $CDCl_3$ with TMS as an internal standard. Infrared spectra were measured with a JASCO FTIR-410. Elemental analysis was carried out by Perkin Elmer

2400CHN. Analytical GLC was performed by Shimadzu GC-8A PF with flame ionization detector equipped with KOCL 3000T, Silicon SE-30, and OV-17 columns. Powder X-ray diffraction patterns were recorded using Philips X'Pert -MPD with Cu Kα radiation. XPS were recorded on Shimadzu ESCA-KM using MgKα radiation. Ru K-edge X-ray absorption spectra were recorded at room temperature in a transmission mode at the EXAFS facilities installed on the beam line BL01B1 station attached to Si (311) monochromator at SPring-8 of JASRI, Harima, Japan. The EXAFS data were normalized by fitting the background absorption coefficient around the energy region higher than the edge about 35-50 eV with the smoothed absorption of an isolated atom. Fourier transformation (FT) of k^3-weighted normalized EXAFS data was performed over the $3.5 \text{ Å} < k/\text{Å}^{-1} < 12 \text{ Å}$ range to obtain the radial structure function. CN (coordination number of scatters), R (distance between an absorbing atom and scatterer), and Debye-Waller factor were estimated by curve-fitting analysis with the inverse FT of the $0.8 < R/\text{Å} < 2.8$ range assuming single scattering. Data reductions were performed with the FACOM M-780 computer system of the Data Processing Center of Kyoto University.

$(NH_4)_2HPO_4$ and $Ca(NO_3)_2 \cdot 4H_2O$ were purchased from Wako Pure Chemical as a special grade. $RuCl_3 \cdot nH_2O$ was obtained from N. E. Chemcat. Substrate and solvents were purchased from Wako Pure Chemical, Tokyo Kasei, and Aldrich, and purified by the standard procedures prior to experiments. All of products are well known compounds. Their identities were confirmed by comparison with infrared spectra, elemental analyses, and NMR spectra.

2-2. Synthesis of Hydroxyapatite-Bound Cationic Ruthenium Complexes

A stoichiometric calcium hydroxyapatite of Ca/P=1.67 (HAP), $Ca_{10}(PO_4)_6(OH)_2$, was synthesized according to the literature procedure [17]. The HAP (1.0 g) was stirred with a 1.34×10^{-2} M aqueous $RuCl_3 \cdot nH_2O$ solution (75 mL) at room temperature for 24 h. The obtained slurry was filtered, washed with water and dried under vacuum, yielding the RuHAP as a dark brown powder (Ru content: 0.97 $mmol \cdot g^{-1}$). The cationic RuHAP-(**I**) and -(**II**) were synthesized *in situ* by treatment of the RuHAP (0.05 g) with aqueous solution of AgX (1.1

equiv. of Ru, X=SbF_6^-, TfO^-) at room temperature under argon atmosphere. After 5 h, the solution was removed, dried under vacuum and the solvent was added prior to the reaction. For XPS and XAFS analyses, sodium salts such as $NaSbF_6$ and NaOTf were used instead of silver salts to avoid an interference of insoluble AgCl.

2-3. A Typical Example for the Diels-Alder Reaction

Into a reaction vessel with the cationic RuHAP-(**I**) (0.05 g, Ru: 0.05 mmol) and nitromethane (5 mL) were placed cyclopentadiene (1 mmol) and methyl vinyl ketone (1.2 mmol) under Ar atmosphere, and then the resulting mixture was stirred at room temperature. The progress of the reaction was monitored by GC analysis. After 4 h, 92 % of 5-acetyl-2-norbornene (*endo:exo*=90:10) was obtained. The *endo:exo* ratio was determined by ^1H NMR spectroscopy.

2-4. A Typical Example for the Aldol Reaction of Nitriles

Into a reaction vessel with the cationic RuHAP-(**II**) (0.05 g, Ru: 0.05 mmol) and water (5 mL) were placed ethylcyanoacetate (1 mmol) and benzaldehyde (1.2 mmol) under Ar atmosphere, and then the resulting mixture was stirred at room temperature. The progress of the reaction was monitored by GC analysis. After 4 h, 99 % of (*E*)-ethyl 2-cyano-3-phenyl-2-propenoate was obtained. For the recycling experiment, the reaction mixture was centrifuged after the fresh run, and the liquid phase was decanted. The residual solid catalyst was again added to water and substrates, and reacted under identical conditions. The first, the second, and the third runs gave (*E*)-ethyl 2-cyano-3-phenyl-2-propenoate in 99, 97, and 97 % yields, respectively.

2-5. A Procedure of the Large-Scale Aldol Reaction of Nitriles

Into a reaction vessel with the cationic RuHAP-(**II**) (0.2 g, Ru: 0.2 mmol) and water (50 mL) were placed ethylcyanoacetate (100 mmol) and benzaldehyde (120 mmol) under Ar atmosphere, and then the resulting mixture was stirred at 50 °C. After 24 h, the catalyst was separated by filtration and the GC analysis of the filtrate showed a 94 % yield of (*E*)-ethyl 2-cyano-3-phenyl-2-propenoate. The filtrate was extracted with diethylether (30 mL x 3), and the organic layer was concentrated under reduced pressure to afford the 18.1 g of a pure product (90 % isolated yield).

3. Results and Discussion

3-1. Characterization of Hydroxyapatite-Bound Cationic Ruthenium Complexes

As described in Chapter II-1, the author has succeeded in creating a monomeric Ru^{3+} species on the surface of hydroxyapatite (RuHAP). Characterizations by means of elemental analysis, XPS, EDX, and Ru-K edge XAFS demonstrated that the occurrence of an equimolar substitution of Ru^{3+} for Ca^{2+} to generate a monomeric Ru^{3+} species surrounded by four oxygen and one chlorine atoms (Figure 2A). The cationic RuHAP-(**I**) and -(**II**) were prepared by treatment of the RuHAP, at room temperature under argon atmosphere, with aqueous solution of AgX (1.1 equiv. of Ru; X=SbF_6^- and TfO^-, respectively). The absence of chlorine was confirmed by XPS analysis of the cationic RuHAPs. The complete exchange of the Cl^- by SbF_6^- was confirmed by elemental analysis: the atomic ratio of Ru to Sb was ca 1:1. The Ru K-edge XANES spectrum was quite similar to that of the parent RuHAP, showing that the Ru species exists in the 3+ oxidation state. In the Fourier transform (FT) of k^3-weighted Ru K-edge EXAFS, there was no peak around 3.5 Å due to the presence of contiguous Ru sites (Figure 3B). The inverse FTs of the cationic RuHAPs were well fitted by replacing the Ru-Cl bond (2.32 Å) in the RuHAP with a Ru-O bond (2.10 Å) assignable to a weakly coordinated aqua ligand (Table 1, A and B). Consequently, a well-defined cationic Ru phosphate complex can be created on the hydroxyapatite surface, as illustrated in Figure 2B.

3-1. Diels-Alder Reaction Catalyzed by Hydroxyapatite-Bound Ruthenium Complex

As can be seen from Table 2, several Diels-Alder reactions were successfully accelerated by the use of the cationic RuHAP-(**I**) as an effective heterogeneous Lewis acid catalyst in nitromethane at room temperature. For example, reaction between cyclopentadiene and methyl vinyl ketone proceeded smoothly to afford 5-acetyl-2-norbornene in 92% yield

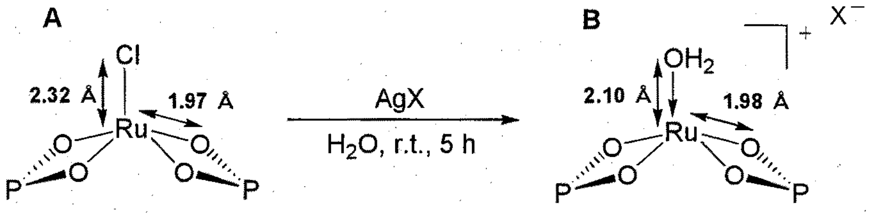


Figure 2. Proposed structures of (A) RuHAP, (B) cationic RuHAP-**(I)** and -**(II)** (**I**: X=SbF_6, **II**: X=OTf).

Table 1. Curve-fitting analysis for RuHAPs [a]

Sample	Shell	C.N.[b]	R (Å) [c]	Δ σ ($Å^2$) [d]
RuHAP**(A)**	Ru-O(1)	4.1	1.97	0.0067
	Ru-O(2)	2.1	2.28	0.0008
	Ru-O(3)	1.7	2.62	-0.0054
	Ru-Cl	1.2	2.32	0.0010
Cationic RuHAP**(B)**	Ru-O(1)	4.1	1.98	-0.0013
	Ru-O(2)	2.2	2.28	-0.0029
	Ru-O(3)	1.7	2.68	-0.0007
	Ru-O(4)	1.0	2.10	0.0093
Cationic RuHAP after treatment with ethylcyanoacetate**(C)**	Ru-O(1)	3.2	1.97	-0.0052
	Ru-O(2)	3.0	2.28	0.0088
	Ru-O(3)	1.7	2.61	-0.0040
	Ru-N(O)	1.1	2.10	0.0114

[a] Inverse FT were performed for the regions of 0.8-2.8 Å in Figure 2 (A), 0.8-2.9 Å in Figure 2 (B), and 0.8-2.8 Å in Figure 2 (C). [b] Coordination number. [c] Interatomic distance. [d] Difference between Debye-Waller factor of the RuHAP and that of the reference sample.

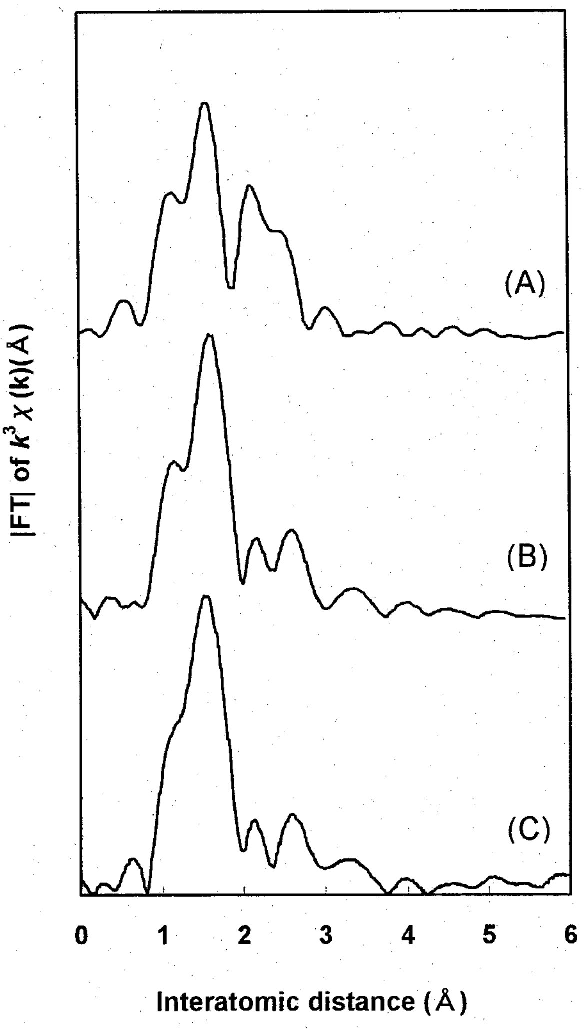
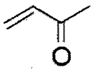
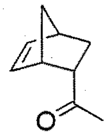
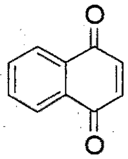
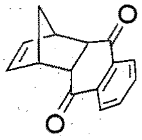
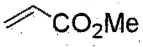
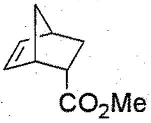
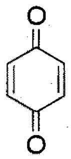
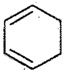
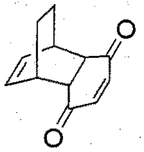
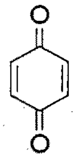
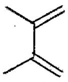
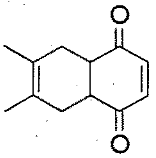
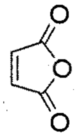
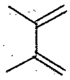
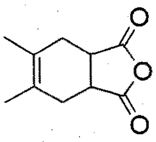


Figure 3. Fourier-transforms (FT) of k^3-weighted Ru K-edge EXAFS experimental data for (**A**) RuHAP, (**B**) cationic RuHAP-(**I**), and (**C**) cationic RuHAP-(**II**) after treatment with ethylcyanoacetate.

Table 2. RuHAP-(I)-Catalyzed Diels-Alder Reaction[a]

entry	dienophile	diene	product	time (h)	yield (%) [b]	endo/exo [c]
1				4	92	90/10
2[d]				4	82	91/9
3				4	91	100/0
4				5	92	91/9
5				6	89	100/0
6				6	83	—
7				6	93	—

[a] Reaction conditions: diene (1.2 mmol), dienophile (1 mmol), nitromethane (5 mL), cationic RuHAP-(I) (0.05 g, Ru: 0.05 mmol), room temperature.
[b] Determined by GC based on dienophile using an internal standard technique.
[c] Determined by ^1H NMR. [d] Cationic RuHAP-(II).

with a favorable *endo:exo* selectivity (entry 1). In a marked contrast to the homogeneous $[Ru^{III}(salen)(NO)H_2O]^+SbF_6^-$ complex, which is a representative example of the cationic Ru complex having the 3+ oxidation state, the RuHAP-(**I**) was applicable to a less reactive dienophile of methyl acrylate (entry 4). The RuHAP-(**II**) also acted as efficient catalyst for the Diels-Alder reaction, but the yield of the corresponding cycloadducts was slightly low (entry

2). This comparison reveals that the counterion structure affects catalysts efficiency. Among the solvents examined, nitromethane and 1,2-dichloromethane gave excellent results, while DMF and acetonitrile were poor solvents presumably because of coordination. It is generally known that product inhibition is a crucial drawback in traditional Al, Ti, or B based Lewis acid catalysis [2]. When the above reaction of cyclopentadiene with methyl acrylate was completed, two substrates were added and a new mixture was allowed to further react. The subsequent three reactions gave the corresponding cycloadduct over 92 % yields at essentially the same rates, showing that the present catalyst can keep its inherent activity during the successive reactions (Figure 4).

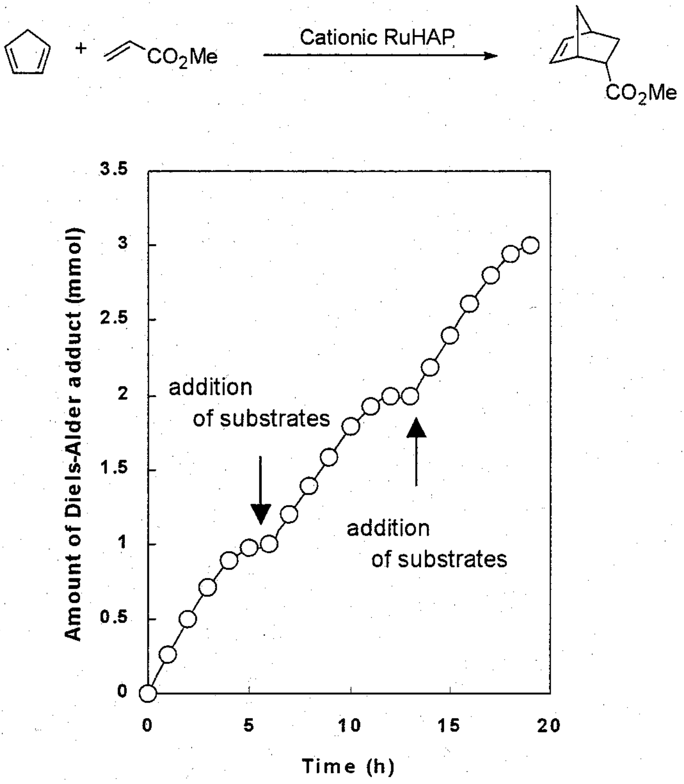
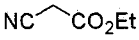
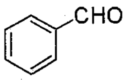
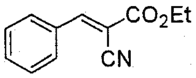
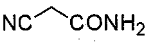
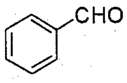
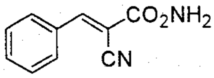
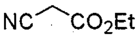
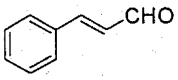
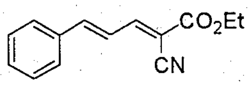
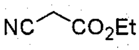
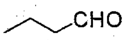
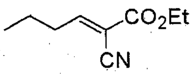
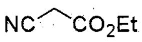
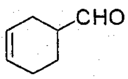
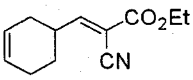
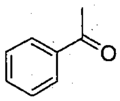
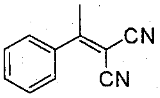
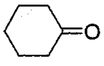
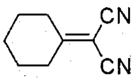
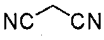
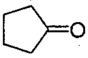
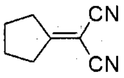


Figure 4. Time profile for the Diels-Alder reaction of cyclopentadiene with methylacrelate catalyzed by RuHAP. Reaction condition: methylacrelate (1 mmol), cyclopentadiene (1.2 mmol), cationic RuHAP-(II) (0.05 g :Ru: 0.1 mmol), nitromethane (5 ml), room temperature.

3-2. Aldol Reaction of Nitriles with Carbonyl Compounds Catalyzed by Hydroxyapatite-Bound Ruthenium Complex

From practical and environmental considerations, development of water-tolerant Lewis acid catalysts is particularly attractive [18]. The cationic RuHAP-(**II**) has proved to be a useful catalyst for the aldol reaction of nitriles with carbonyl compounds in water, affording the corresponding α, β-unsaturated nitriles in excellent yields [19]. Representative results are summarized in Table 3. Especially, bezylic aldehyde showed high reactivity for the aldol reaction, which could be performed at room temperature. The reaction of ketones as acceptors required high reaction temperature and longer reaction time. The effect of the counterion structure on catalytic activity was also observed; in the case of the RuHAP-(**I**), the yields of (*E*)-ethyl 2-cyano-3-phenyl-2-propenoate was slightly low (entry 2). The present catalyst exhibited a specific activity only toward nitriles as aldol donors; other active methylene compounds such as 2,4-pentanedione, dimethyl malonate, and nitroethane, whose pK_a values are similar to that of ethylcyanoacetate, did not yield aldol products under the above conditions (eq. 1). For example, in a competitive reaction of benzaldehyde between ethylcyanoacetate and 2,4-pentanedione, the cationic RuHAP-(**II**) gave 96 % yield of (*E*)-ethyl 2-cyano-3-phenyl-2-propenoate exclusively. In the RuHAP catalytic system, the reaction of less reactive nitriles such as benzyl cyanide hardly occurred. It is notable that treatment of α, β-unsaturated carbonyl compounds such as 2-cyclopenten-1-one and 2-cyclohexene-1-one with malononitrile gave the 1,2-addition products in high yields (eq. 2); attack of an enolate species on the carbonyl function exclusively occurred without the 1,4-addition. This phenomenon is quite distinct from that of the $Ru^{II}H_2(PPh_3)_4$-catalyzed reaction, whose products are predominantly a result of the 1,4-addition (eq. 3) [14b]. In terms of the HSAB principle, a trivalent Ru enolate species generated from the RuHAP may behave as a harder nucleophile than that from the divalent Ru one, which allows a favorable interaction with the carbonyl groups to enhance the 1,2-addition.

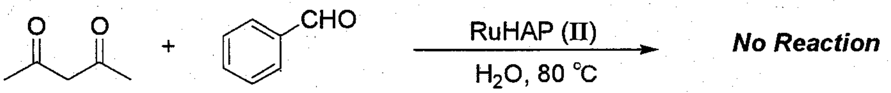
Table 3. RuHAP-(II)-Catalyzed Aldol Reaction of Nitriles with Carbonyl Compounds [a]

entry	donor	acceptor	product	time (h)[b]	conv. (%)[b]
1 2[c]				4 4	>99 78
3				4	>99
4[d]				8	95
5[d]				3	95
6[d]				5	92
7[e]				6	82
8[e]				3	>99
9[e]				5	>91

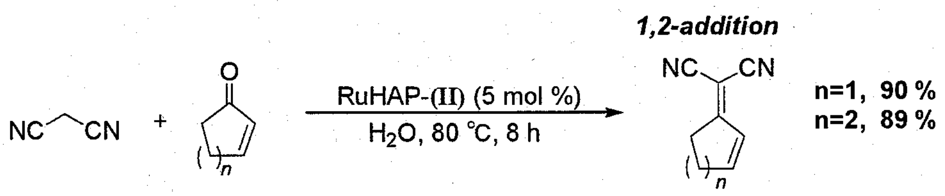
[a] Reaction conditions: nitrile (1.0 mmol), carbonyl compound (1.2 mmol), cationic RuHAP-(**II**) (0.05 g, Ru: 0.05 mmol), H_2O (5 mL), room temperature.

[b] Determined by GC based on nitrile using an internal standard technique.

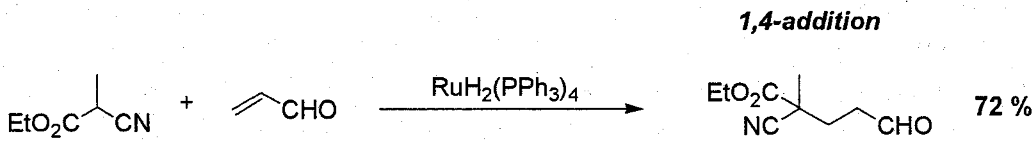
[c] Cationic RuHAP-(**I**). [d] 50°C. [e] 80°C.



(1)



(2)

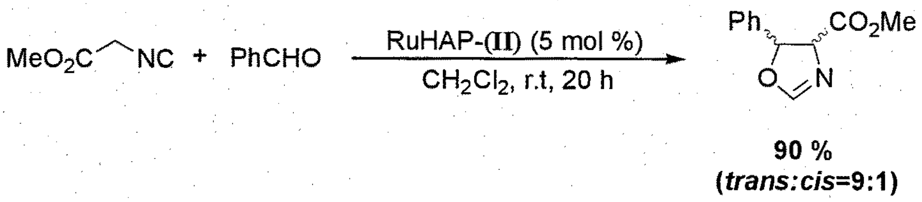


(3)

Furthermore, the present catalytic system is highly suitable for large-scale operations. A 100 mmol scale reaction of ethylcyanoacetate with benzaldehyde using 0.2 mol % of the Ru catalyst provided 94 % of (*E*)-ethyl 2-cyano-3-phenyl-2-propenoate within 24 h. More significantly, no Ru leaching even under aqueous conditions was detected by ICP analysis whose detection limit is 0.03 ppm. The recovered catalyst could be reused without loss of its activity; over 97% yields were attained for the three recycling reactions of ethylcyanoacetate with benzaldehyde.

3-3. A Possible Reaction Mechanism

For the aldol reaction of methyl isocyanoacetate with benzaldehyde, the cationic RuHAP-(**II**) gave the corresponding oxazoline in 90 % yield without any additives (eq.4), whereas analogous homogeneous cationic Ru^{3+} complex of the [Ru(salen)(NO)H_2O]$^+$SbF_6^- complex required a Hunig's base (*i*-Pr_2NEt) to complete the catalytic cycle [20]. Other cationic transition metal complexes such as [Pd(2,2'-bipyridyl)(CH_3CN)$_2$](BF_4)$_2$ and [Pd(2,6-bis(2-oxazolinyl)phenyl)] have been reported as effective catalysts for aldol reaction of isonitrile; however they also needs a suitable base. It is generally accepted that the base abstracts a proton of isonitriles coordinating to the metals.



(4)

The above results introduce me a hypothesis that the cationic RuHAP serves as an acid-base bifunctional catalyst for the aldol reactions. Hayashi and coworkers reported that silver and gold complexes in combination with a chiral ferrocene bis-phosphine ligand gave chiral oxazoline with good-to-excellent optical yields, when the ferrocene phosphine contains a suitable chiral tertiary amine side chain which can act as a base [21]. Therefore, the author has applied IR and XAFS spectroscopy to gain the detailed structural information about the

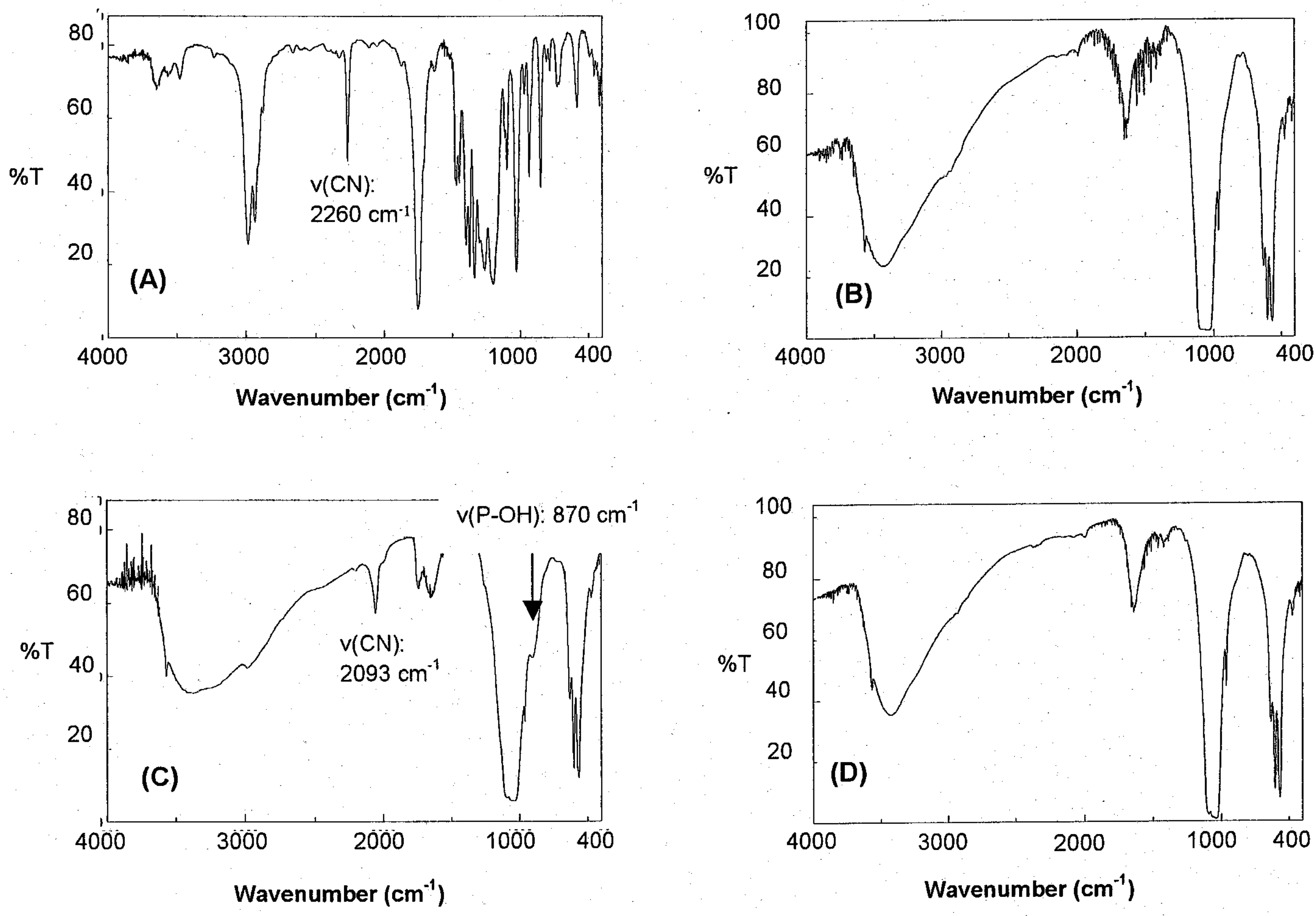


Figure 5. IR spectra of (A) ethylcyanoacetate (**3a**), (B) fresh cationic RuHAP (**II**), (C) after treatment of (B) with ethylcyanoacetate at 80 °C and desorbed under vacuum, and (D) after treatment of (C) with benzaldehyde and desorbed under vacuum

reaction intermediate on solid surface. The IR spectrum of the cationic RuHAP-(II), upon treatment with ethylcyanoacetate, showed a shift of the ν(CN) band toward 2093 cm^{-1} in comparison with the free cyano group at 2260 cm^{-1}, together with a new peak at 870 cm^{-1} assigned to the P-OH group of a HPO_4^{2-} ion on the hydroxyapatite surface (Figure 5C) [22]. In contrast, no interaction was observed in either parent RuHAP or HAP, which were inactive for the Diels-Alder and aldol reactions. Furthermore, treatment of the sample (C) with benzaldehyde resulted in the disappearance of these two bands, as shown in the spectrum of (D).

The FT-EXAFS analysis for the above treated sample indicated the decrease of the coordination number of the nearest neighboring Ru-O bond (1.98 Å) from 4 to 3, and the appearance of an additional second Ru-O bond (2.28 Å) attributable to a weak interaction between Ru and P-OH (Figure 3C, Table 1). These results are in agreement with the formation of a Ru-enolate species surrounded by three oxygen, as shown in Figure 6C.

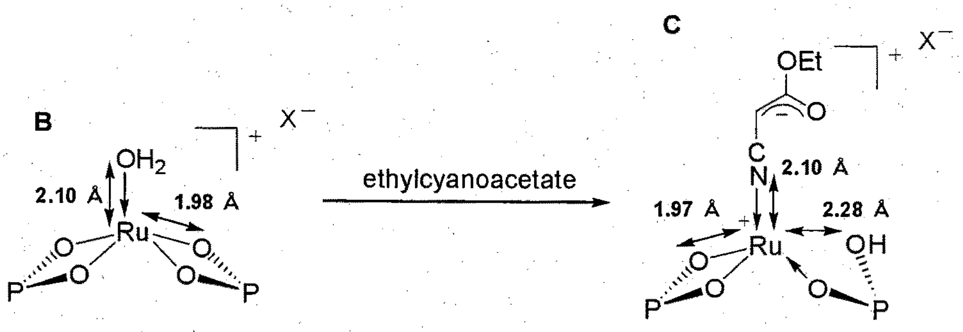
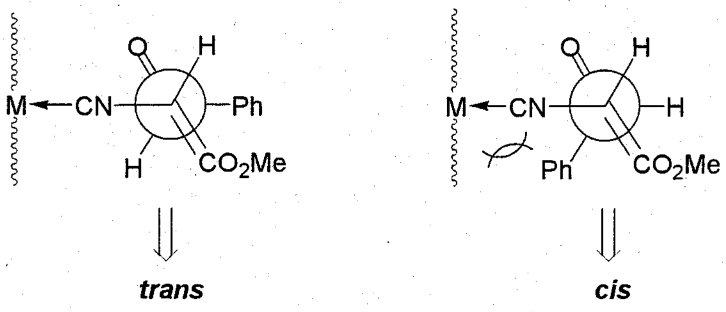
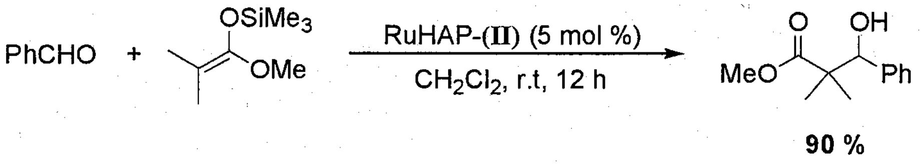


Figure 6. Proposed structures of (B) cationic RuHAP-**(II)**, and (C) Ru-enolate intermediate (X=OTf)

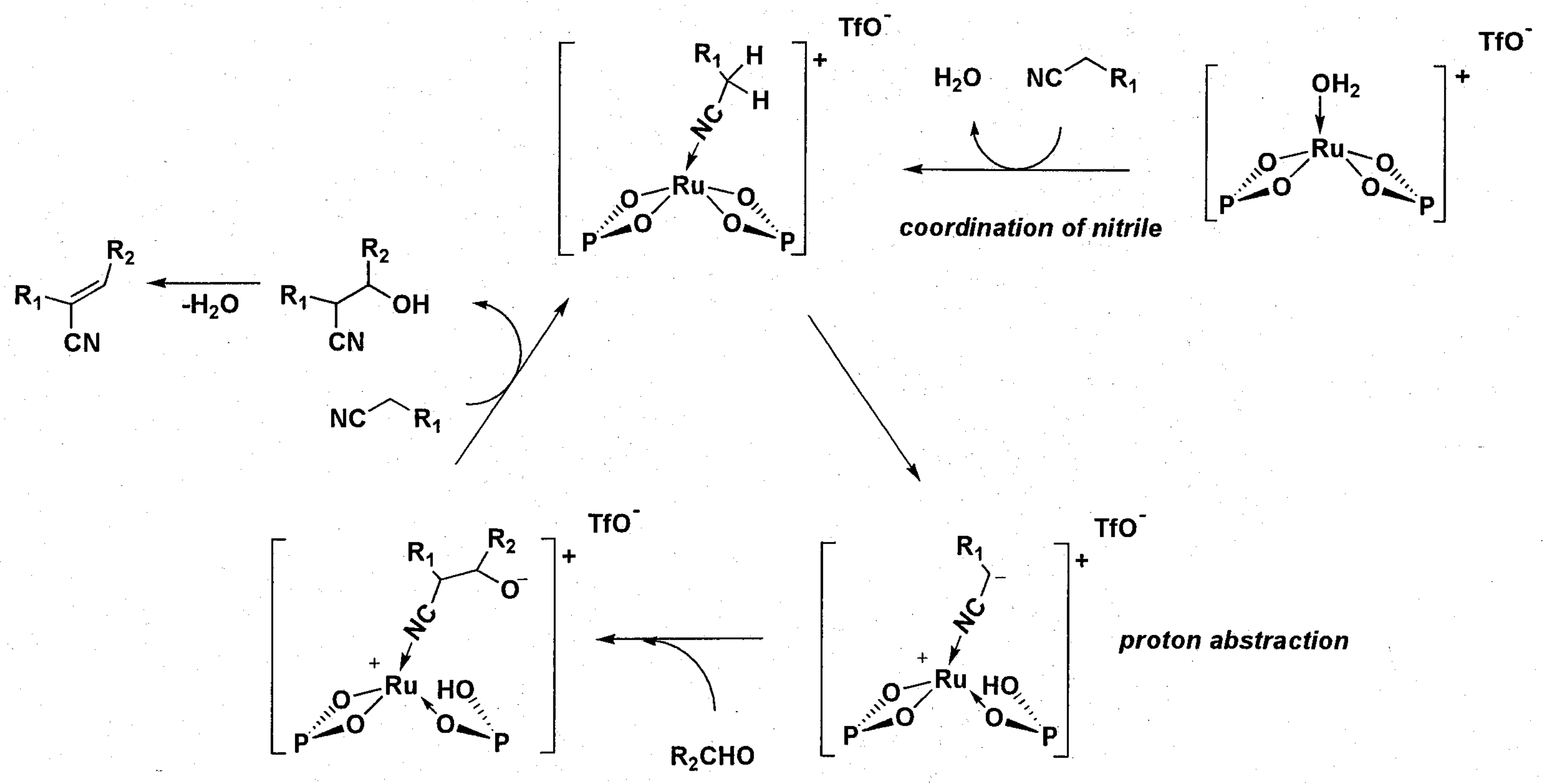
From the above results, it is reasonable to suggest that the cationic RuHAP-(II)-catalyzed aldol reaction using nitriles involves the Ru-enolate intermediate, which is generated thorough the cooperative catalysis between the cationic Ru species and the basic phosphate ligand; the former activates the nitrile as a Lewis acid, while the latter phosphate abstracts an acidic α-proton of the nitrile to generate enolate species. The Diels-Alder reaction can be induced by the Lewis acid site that originates from the cationic Ru species. Furthermore, the hydroxyapatite effectively serves as a suitable macroligand for the catalytically active Ru center, which allows strict steric control of the reaction intermediate. *Vide supra*, the high *trans* stereoselectivity of oxazoline (*trans:cis* =9:1), as compared with those of other homogeneous systems is ascribed to steric repulsion between the phenyl groups of benzaldehyde and the isocyano moiety bound to the Ru phosphate complex in *synclinal* configuration severely limits the formation of *cis*-isomer (Figure 7). The Mukaiyama-aldol reaction of ketene silyl acetal with aldehyde can also be catalyzed by RuHAP-**(II)** (eq.5). However, the reaction of sterically bulky silyl enol ethers derived from cyclohexenone, acetophenone, and propiophenone hardly occurred, probably because the formation of six-membered transition state is restricted owing to the steric congestion around the active site.

Figure 7





(5)



Scheme 4. A possible mechanism for the aldol reaction of nitriles with carbonyl compounds catalyzed by the cationic RuHAP-(II)

4. Conclusions

In summary of Chapter III, the author demonstrated that novel hydroxyapatite-bound cationic Ru complexes with potentially vacant coordination sites could be obtained by the simple surface modulation of the neutral RuHAP using AgX (X=SbF_6^- and TfO^-). These cationic RuHAPs exhibited Lewis acid property, promoting useful carbon-carbon bond-forming reactions such as Diels-Alder and aldol reactions with high efficiencies. No Ru leaching was detected even under aqueous conditions, and then the catalyst was recyclable. Characterization of surface organometallic intermediate by means of IR and XAFS measurement reveals that the RuHAP-catalyzed aldol reaction involves a cooperative catalysis between the cationic Ru species and the phosphate ligand on hydroxyapatite surface. Moreover, the hydroxyapatite effectively served as a suitable macroligand for the catalytically active Ru center, which provided unique catalytic functions arising from the strict steric control of a reaction intermediate.

References

[1] (a) *Selectivites in Lewis Acid Promoted Reactions*; Schinzer, D., Ed.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1989. (b) Santelli, M.; Pons, J.-M. *Lewis Acids and Selectivity in Organic Synthesis*; CRS Press: Boca Raton, FL, 1995. (c) *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: WeinHeim, 2000. (d) Hay, R. W. Lewis Acid Catalysis and the Reactions of Coordinated Ligands. In *Comprehensive Coordination Chemistry; Wilkinson*, G., Gillard, R. D., McCleverty, J. A., Eds.; Pergamon Press: Oxford, 1987; Vol 6. (e) Bosnich, B. *Aldrichimica Acta* **1998**, *31*, 76.

[2] (a)Yates, P.; Eaton, P. *J. Am. Chem. Soc.* **1960**, *82*, 4436. (b) Wassermann, A. *J. Chem. Soc.* **1942**, 618. (c) Mukaiyama, T. The directed Aldol Reactions. In *Organic Reactions*; Dauben, W. G., Ed.; John Wiley and Sons, Inc.: New York, 1982; Vol, 28. (d) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, *16*, 1295. (e) Hosomi, A.; Endo, M.; Sakurai, H.; *Chem. Lett.* **1976**, 941. (f) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 3716. (g) Cnfalone, P. N.; Huie, E. M. *Org. React.* **1988**, *36*, 1.

[3] (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice;* Oxford University Press, **1998**. (c) Clark, J. H. *Green Chem.* **1999**, *1*, 1. (d) Sheldon, R. A. *Green Chem.* **2000**, *2*, G1. (e) Anastas, P. T.;Bartlett, L. B.; Kirchhoff, M. M.; Williamson, T. C. *Catal. Today* **2000**, *55*, 11.

[4] (a) Ciganek, E. *Org. React.* **1984**, *32*, 1. (b) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187. (c) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon: Oxford, 1990. (d) Pindur, U.; Luts, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741.

[5] Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1976.

[6] (a) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007. (b) Huang, Y.; Iwama, T., Rawall, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 5950.

[7] (a) Corey, E. J.; Imai, N.; Zhang, H. *J. Am. Chem. Soc.* **1991**, *113*, 728. (b) Kündig, E.P.; Bouring E. P.; Bernardinelli, G *Angew. Chem. Int. Ed.* **1994**, *33*, 1856.

[8] (a) Evans, D. A.; Miller, S. J.; Letcka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6469. (b) Evans, D.

A.; Murry, J. A.; Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem. Int. Ed.* **1995**, *34*, 798. (c) Johaasen, M.; Jørgensen, K. A. *J. Org. Chem.* **1995**, *60*, 5757. (d) Jørgensen, K. A.; Johaasen, M.; Yao, S.; Audrian, H.; Thorhauge, *J. Acc. Chem. Res.* **1999**, *32*, 605. (e) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635.

[9] (a) Odenkirk, W.; Rheingold, A.-L.; Bosnich, B. *J. Am. Chem. Soc.* **1992**, *114*, 6392. (b) Zhu, Z.; Espenson, J. H. *J. Am. Chem. Soc.* **1997**, *119*, 3507. (c) Kündig, E.P.; Saudan, C. M.; Alenzra, V.; Viton, F; Bernardinelli, G. *Angew. Chem. Int. Ed.* **2001**, *40*, 4481.

[10] (a) Mikami, K.; Terada, M.; Motoyama, Y.; Nakai, Y. *Tetrahedron: Asymm.* **1991**, *32*, 6289. (b) Corey, E. J.; Matsumura, Y. *Tetrahedron Lett.* **1991**, *32*, 6289. (c) Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M., Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340.

[11] Pigant, K.; Vallotto, J.; Pinna, F.; Strukul, G. *Organometallics* **2000**, *19*, 5160.

[12] (a) Murahashi, S.-I.; Takaya, H. *Acc. Chem. Res.* **2000**, *33*, 225. (b) Murahashi, S.-I.; Naota, T. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1805.

[13] (a) Murahashi, S.-I.; Hirano, T.; Yano, T. *J. Am. Chem. Soc.* **1978**, *100*, 348. (b) Murahashi, S.-I.; Watanabe, T. *J. Am. Chem. Soc.* **1979**, *101*, 7429. (c) Murahashi, S.-I.; Yoshimura, N.; Tsumiyama, T.; Kojima, T.; *J. Am. Chem. Soc.* **1983**, *105*, 5005.

[14] (a) Naota, T.; Taki, H.; Mizuno, M.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1989**, *111*, 5945. (b) Murahashi, S.-I.; Naota, T.; Taki, H.; Mizuno, M.; Takaya, H.; Komiya, S.; Mizuho, Y.; Oyasato, N.; Hiraoka, M.; Hirano, M.; Fukuoka, A. *J. Am. Chem. Soc.* **1995**, *117*, 12436. (c) Gomez-Bengoa, E.; Cuerava, J. M.; Mateo, C.; Echavarren, A. M. *J. Am. Chem. Soc.* **1996**, *118*, 8553. (d) Naota, T.; Tanna, A.; Murahashi, S.-I. **2000**, *122*, 2961. (e) Naota, T.; Tanna, A.; Kamuro, S.; Murahashi, S.-I. **2002**, *124*, 6842.

[15] (a) Rechavi, D.; Lemaire, M. *J. Mol. Cat. A: Chemical* **2002**, *182-183*, 239. (b) Rechavi, D.; Lemaire, M. *Org. Lett.* **2001**, *3*, 2493. (c) Gerstberger, G.; Palm, C.; Anwander, R. *Chem. Eur. J.* **1999**, *5*, 997. (d) Anwander, R.; Görlitzer, H. W.; Gerstberger, G.; Palm, C.; Runte, O.; Spiegler, M.; *J. Chem. Soc., Dalton Trans.* **1999**, 3611.

[16] (a) Yamaguchi, K.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2000**, *122*, 7144. (b) Mori, K.; Yamaguchi, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Chem. Commun.* **2001**, 461. (c) Mori, K.; Tano, M.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *New. J. Chem.* **2002**, *26*, 1536. (d) Mori, K.; Yamaguchi, K.; Hara, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2002**, *124*, 11572.

[17] (a) Elliott, J. C. *Structure and Chemistry of the Apatites and Other Calcium Orthophosphates*; Elsevier: Amsterdam, 1994. (b) Sugiyama, S.; Minami, T.; Hayashi, H.; Tanaka, M.; Shigemoto, N.; Moffat, J. B. *J. Chem. Soc., Faraday Trans.* **1996**, *92*, 293.

[18] (a) Kobayashi, S.; Manabe, K. *Acc. Chem. Res.* **2002**, *35*, 209. (b) Manabe, K.; Kobayashi, S. *Chem. Eur. J.* **2002**, *8*, 4095.

[19] For leading references of transition metal complex-catalyzed aldol reaction of nitriles, see: (a) Lin, Y; Zhu, X; Xiang, M. *J. Organomet. Chem.* **1993**, *448*, 215. (b) Hirano, M.; Ito, Y.; Hirai, M.; Fukuoka, A.; Komiya, S. *Chem. Lett.* **1993**, 2057. (c) Nemoto, H.; Kubota, Y.; Yamamoto, Y., *J. Chem. Soc., Chem. Commun.* **1994**, 1665. (d) Hirano, M.; Takenaka, A.; Mizuho, Y.; Hiraoka, M.; Komiya, S. *J. Chem. Soc., Dalton Trans.* **1999**, 3209. (e) Takaya, H.; Murahashi, S.-I. *Synlett.* **2001**, SI, 991. (f) Mizuho, Y.; Kasuga, N.; Komiya, S. *Chem. Lett.* **1991**, 2127. (f) Alevarez, S. G.; Hasegawa, S.; Hirano, M.; Komiya, S. *Tetrahedron Lett.* **1998**, *39*, 5209.

[20] (a) Nesper, R.; Pregosin, P. S.; Püntener, K.; Wörle, M. *Helv. Chim. Acta* **1993**, *76*, 2239. (b) Stark, M. A.; Richards, C. J. *Tetrahedron Lett.* **1997**, *38*, 5881. (c) Fossey, J. S.; Richards, C. *Organometallics* **2002**, *21*, 5259. (d) Gimenes, R.; Swager, T. M. *J. Mol. Cat. A: Chemical* **2001**, *166*, 265. (e) Schlenk, C.; Kleiji, A. W.; Frey, H.; van Koten, G. *Angew. Chem. Int. Ed.* **2000**, *439*, 3445. (f) Meijer, M. D.; Ronde, N.; Vogt, D.; van Klink, G. P. M.; van Koten, G. *Organometallics* **2001**, *20*, 3993.

[21] (a) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Chem. Soc., Chem. Commun.* **1986**, *108*, 1090. (b) Ito, Y.; Sawamura, M.; Hayashi, T. *Tetrahedron* **1987**, *28*, 6215. (c) Ito, Y.; Sawamura, M.; Sirakawa, E.; Hayashizaki, E.; Hayashi, T. *Tetrahedron* **1988**, *29*, 235. (d) Ito, Y.; Sawamura,

M.; Kobayashi, M.; Hayashi, T. *Tetrahedron* **1987**, *28*, 239. (e) Hayashi, T; Sawamura, M.; Ito, Y.; *Tetrahedron* **1992**, *48*, 1999.

[22] (a) Joris, S. J.; Amberg, C. H.; *J. Phys. Chem.* **1971**, *75*, 3172. (b) Elliott, J. C. *Structure and Chemistry of the Apatites and Other Calcium Orthophosphates:* Elsevier, Amsterdam, **1994**. (c) Zahouily, M.; Abrouki, Y.; Rayadh, A.; *Tetrahedron Lett.* **2002**, *43*, 7729.

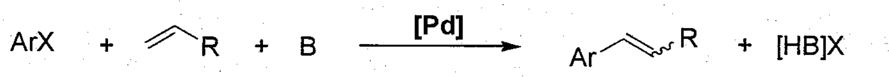
Chapter IV

Hydroxyapatite-Bound Palladium Complex as Highly Efficient Heterogeneous Catalyst for Mizoroki-Heck and Suzuki-Miyaura Coupling Reactions

1. Introduction

Palladium is one of the most versatile and efficient catalyst metals in organic syntheses because of its unique catalytic performance for a wide-range of functional group transformations [1], most notably Wacker process, and for carbon-carbon bond formations such as Mizoroki-Heck coupling reaction, Fujiwara coupling, and hydroarylation reactions [2]. In modern palladium chemistry, various forms of Pd reagents such as simple Pd salts like $PdCl_2$ and $Pd(OAc)_2$, mononuclear organopalladium complexes, molecular clusters, and colloidal particles have been explored as catalysts [1]. Generally, the precise architectures of Pd structures play a crucial role in designing highly functionalized Pd catalyst systems responsible for the target of organic transformations. In particular, transition metal complexes, in which both steric and electronic properties can be tuned up by varying the active metal center and/or organic ligands, have been developed to greatly contribute toward making the arsenal of powerful synthetic methods. The use of homogeneous metal catalysts on an industrial scale, however, is complicated by practical problems, such as difficulties associated with corrosion, plating out on the reaction wall, and catalyst or ligand recovery from the reaction mixture. Much attention has accordingly been directed toward the heterogenization of metal complexes to create stable and well-defined active centers on solid surfaces [3]. These attempts have also led to the development of unique catalytic functions, including active site isolation, cooperative catalysis by several sites, and steric control of a reaction intermediate [4]. The remarkable progress in the development of these hybrid catalysts has resulted in an exciting field of research in novel methodologies for catalyst design and new organic reactions.

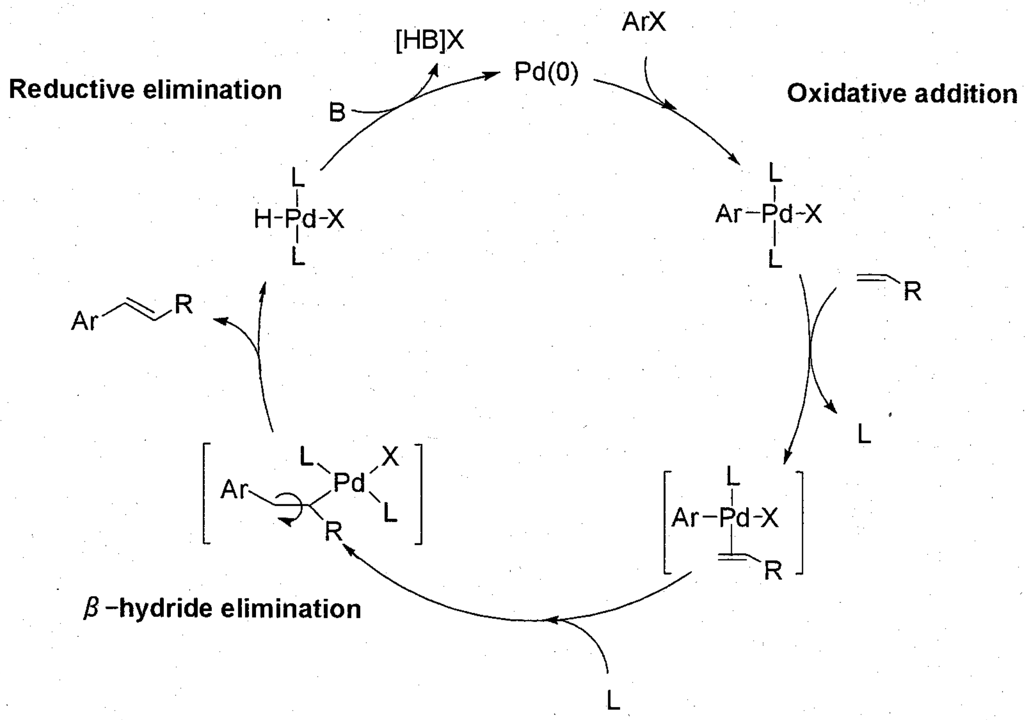
Palladium-catalyzed Mizoroki-Heck reaction and cross coupling reactions between aryl halide and nucleophiles have received considerable attention due to an enormous synthetic potential to form new carbon-carbon bonds (eqs 1 and 2) [5]. In both cases, the first step of the catalytic cycle is an addition of the aryl halide to the usually supposed 14-electron complex Pd^0L_2 (L=monodentate phosphine ligand) to afford a σ-arylpalladium(II) complex, *trans*-ArPdXL$_2$. The second step is a nuclephilic attack on *trans*-ArPdXL$_2$, either a *syn*-addition (Mizoroki-Heck reaction) or transmetalation (cross coupling reactions). The final product is generated by β-hydride elimination (Mizoroki-Heck reaction) or reductive elimination (cross coupling reactions), as respectively shown in Scheme 1 and 2. In spite of their synthetic advantages, commercial application has been limited due to the low turnover numbers and relatively short catalyst lifetime [6]. Thus, current research focuses on developing effective Pd catalysts for highly active, stable and substrate tolerance.



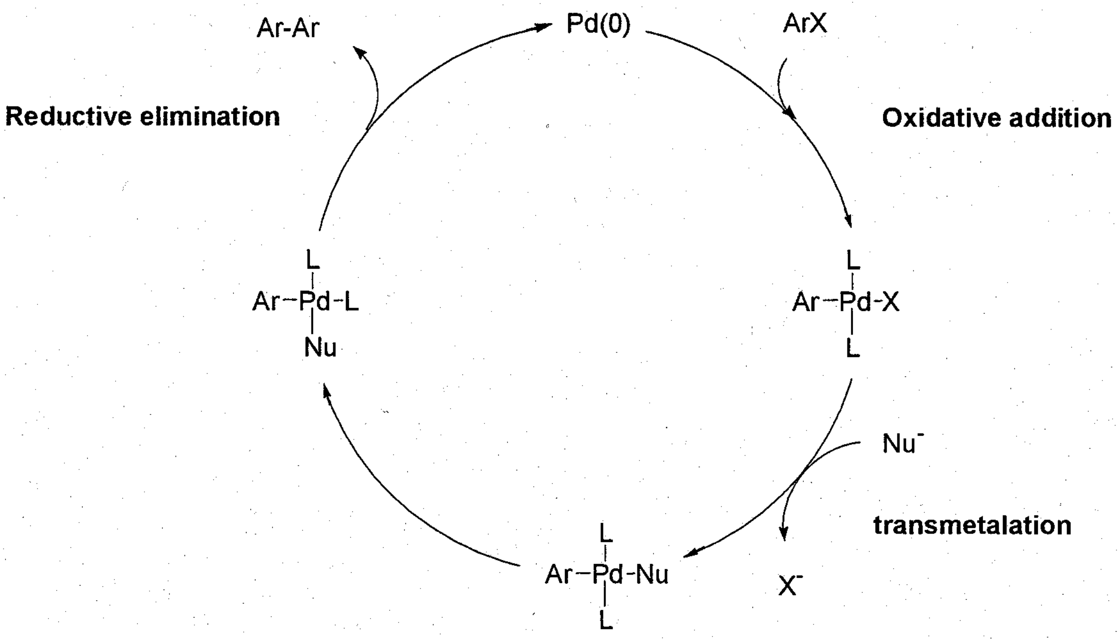
(1)

$$\mathrm{ArX} + \mathrm{mNu} \xrightarrow{[\mathrm{Pd}]} \mathrm{ArNu} + \mathrm{mX} \qquad (2)$$

X= I, Br, Cl, etc. B= Base



Scheme 1. Mechanism of MIzoroki-Heck reaction

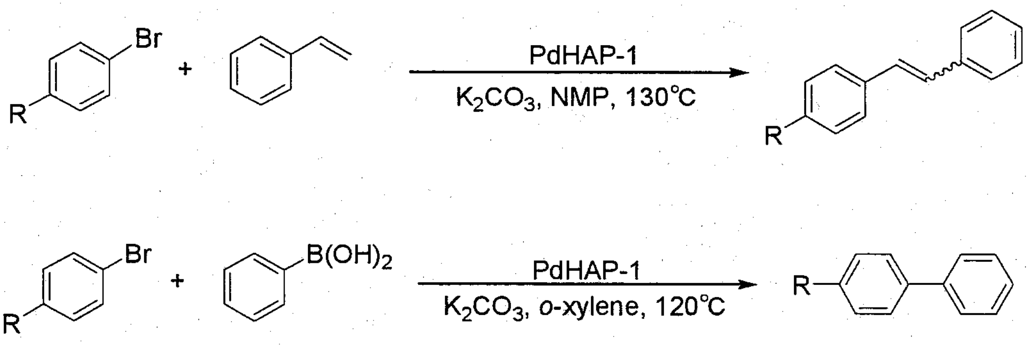


Scheme 2. Mechanism of cross-coupling reaction

The problems discussed above could be principally minimized by heterogeneously-catalyzed reaction. In general, the most outstanding advantages of heterogeneous catalytic system are their ease of recovery and reusability [7]. On the other hand, deactivation due to undesired irreversible agglomeration of Pd metal and dissolution of active species are encountered under the drastic reaction conditions. Only a few reports exist on the synthesis of heterogeneous palladium catalysts, e.g., palladium-loaded porous glass [8], zeolite(NaY-type)-entrapped Pd complex [9], or Pd-grafted MCM-41 [10]. Examples of some systems have been used with varying degrees of success, however, the demand for novel heterogeneous systems is still extremely high.

In Chapter II, the author demonstrated that monomeric Ru cation species could be uniformly introduced into the apatite framework via their high cation-exchange ability [11]. This Ru-exchanged hydroxyapatite exhibits excellent catalytic performances, attributed to the stable monomeric Ru phosphate complex structure on the solid surface. The chemical composition of hydroxyapatites can be also modified from the stoichiometric form, $Ca_{10}(PO_4)_6(OH)_2$ (Ca/P = 1.67), to the nonstoichiometric Ca-deficient form without significant changes in the crystallographic structure. Nonstoichiometric hydroxyapatites have the formula $Ca_{10-Z}(HPO_4)_Z(PO_4)_{6-Z}(OH)_{2-Z}$ ($0 < Z \leq 1$, $1.5 \leq Ca/P < 1.67$), in which the charge deficiency due to the lack of Ca^{2+} in the lattice is compensated by both H^+ introduction and OH^- removal [12].

In this Chapter, the author presents two new classes of hydroxyapatite-bound Pd complexes, designed with both stoichiometric and Ca-deficient hydroxyapatites, and its evaluation as heterogeneous catalysts for Mizoroki-Heck and Suzuki-Miyaura coupling reactions. The author also mentions their unique catalytic performances for the cross coupling reactions on the basis of the characterization of the active palladium species using physicochemical methods.



2. Experimental

2-1. General

^1H- and ^{13}C-NMR spectra were obtained on JEOL GSX-270 or JNM-AL400 spectrometers at 270 or 400 MHz in $CDCl_3$ with TMS as an internal standard. Infrared spectra were measured with a JASCO FTIR-410. Elemental analysis was carried out by Perkin Elmer 2400CHN. Analytical GLC was performed by Shimadzu GC-8A PF with flame ionization detector equipped with KOCL 3000T, Silicon SE-30, and OV-17 columns. Powder X-ray diffraction patterns were recorded using Philips X'Pert -MPD with Cu Kα radiation. XPS were recorded on Shimadzu ESCA-KM using MgKα radiation. X-ray absorption spectra were recorded using a fluorescence-yield collection technique at the beam line 01B1 station with attached Si (311) monochromator at SPring-8, JASRI, Harima, Japan (prop. No. 2001A0563-UX-np). Fluorescence-yield was collected at room temperature using the 19-element solid-state detector. Details of data analysis are referred to the reported procedure [13].

$(NH_4)_2HPO_4$ and $Ca(NO_3)_2 \cdot 4H_2O$ were purchased from Wako Pure Chemical as a special grade. $PdCl_2$ was obtained from N. E. Chemcat. Substrate and solvents were purchased from Wako Pure Chemical, Tokyo Kasei, and Aldrich, and purified by the standard procedures prior to use. All of products are well known compounds. Their identities were confirmed by comparison with infrared spectra, elemental analyses, and NMR spectra.

2-2. Synthesis of Hydroxyapatite-Bound Palladium Complexes

Hydroxyapatites were synthesized from $Ca(NO_3)_2 \cdot 4H_2O$ and $(NH_4)_2HPO_4$ by the precipitation method [14]. Selecting appropriate Ca/P molar ratios gave the stoichiometric hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$ ($Z = 0$, HAP-0) and the nonstoichiometric Ca-deficient hydroxyapatite $Ca_9(HPO_4)(PO_4)_5(OH)$ ($Z = 1$, HAP-1), respectively. The treatment of the HAP-0 with an acetone solution of $PdCl_2(PhCN)_2$ yielded the hydroxyapatite-bound Pd complex, PdHAP-0 (Pd content: 0.02 $mmol \cdot g^{-1}$) as a pale yellow powder. The PdHAP-1 (Pd content: 0.015 $mmol \cdot g^{-1}$) was obtained using the HAP-1 as a white powder by the same method.

2-3. A Typical Example of the Heck Coupling Reaction

PdHAP-1 (0.05 g, Pd: 0.75 μmol) and K_2CO_3 (6.2 g, 45 mmol) were placed into a reaction vessel with a reflux condenser. Under Ar atmosphere, *N*-methylpyrrolidone (NMP) (50 mL), bromobenzene (5.9 g, 37.5 mmol), and styrene (4.7 g, 45 mmol) were added, and then the resulting mixture was stirred at 130 °C. The progress of reaction was monitored by GC analysis. After 24 h, 94% yield of stilbene ($E : Z = 15 : 1$) was obtained. For recycling experiments, fresh reaction using bromobenzene (2 mmol), styrene (2.4 mmol), K_2CO_3 (2.4

mmol), NMP (5 mL), and PdHAP-1 (0.1 g, Pd: 1.5 μmol) was carried out at 130 °C under Ar atmosphere. After 4 h, the reaction mixture was centrifuged and the liquid phase was decanted. The residual solid catalyst was again added to the substrate and reacted under identical conditions. The first, the second, and the third runs gave stilbene in over 92% GC yields.

2-4. A Typical Example of the Suzuki Coupling Reaction

PdHAP-1 (0.05 g, Pd: 0.75 μmol), K_2CO_3 (6.2 g, 45 mmol), and phenylboronic acid (5.5 g, 45 mmol) were placed into a reaction vessel with a reflux condenser. Under Ar atmosphere, *o*-xylene (50 mL) and 4-bromoanisole (7.0 g, 37.5 mmol) were added, and the resulting mixture was stirred at 120 °C. The progress of reaction was monitored by GC analysis. After 6 h, 91 % yield of 4-methoxybiphenyl was obtained.

3. Results and Discussion

3-1. Characterization of Hydroxyapatite-Bound Palladium Complexes

XRD peaks for the PdHAPs were similar to that of the parent hydroxyapatites. The presence of chlorine in the PdHAP-0 was confirmed by XPS and EDX; the atomic ratio of Pd to Cl was 1:2, and no chlorine was detected in the PdHAP-1. No signals assignable to the ν(CN) bond could be observed by IR spectroscopy, showing that the PhCN ligand of Pd precursor are not involved in the immobilized Pd species. ICP analysis revealed that no Ca^{2+} was present in the filtrate after palladium loading. Therefore, isomorphic substitution of Ca for Pd did not occurred in the above preparation sequence using organic solvent, which is in sharp contrast to Ru-hydroxyapatite prepared previously based on the cation-exchange method in aqueous media [11]. The Pd K-edge XANES spectra of both PdHAPs differed from that of Pd metal but were similar to that of Pd oxide, which reveals that all Pd species are in the 2+ oxidation state (Figure 1a, A and B). In the Fourier transform (FT) of k^3-weighted EXAFS data for the PdHAPs, the absence of peaks around 2.5 Å shows that there are no Pd-Pd bonds (Figure. 1b, A and B). The inverse FT of the peaks around 1-2 Å for the

PdHAP-0 was well fitted using Pd-Cl and Pd-O shells (Table 1A), whereas the best fit for the PdHAP-1 was achieved using only a Pd-O shell (Table 1B). The interatomic distances from Pd to the Cl and to the nearest O atoms are consistent with the values for the Pd-Cl bond of $PdCl_2$ and the Pd-O bond of Pd oxide. The second neighboring Pd-O bonds are assigned to the weak interaction between Pd and PO_4^{3-} ions of hydroxyapatite. On the basis of these results, we can propose the most reasonable surface structure for the PdHAPs, as illustrated in Figure 2. A monomeric $PdCl_2$ species is grafted by chemisorption on the P=O groups of the HAP-0 surface (Figure. 2**A**), whereas a monomeric Pd^{II} phosphate complex surrounded by four oxygen atoms is formed in a Ca-deficient site of the HAP-1 (Figure. 2**B**). Accordingly, two unique monomeric Pd species with intrinsically different surroundings can be created on a solid surface through precise control of the Ca/P ratios of the parent hydroxyapatites.

Table 1. Results of Curve-fitting Analyses for PdHAP Catalysts[a]

Sample	Shell	C.N.[b]	R (Å) [c]	$\Delta\sigma$ (Å^2) [d]
PdHAP-0 (**A**)	Pd-Cl	2.0	2.36	0.0087
	Pd-O(1)	2.1	2.01	0.0006
	Pd-O(2)	3.0	2.37	0.0199
PdHAP-1 (**B**)	Pd-O(1)	4.2	2.01	0.0031
	Pd-O(2)	3.0	2.34	0.0342
used PdHAP-0 (**C**)	Pd-Pd	6.9	2.79	0.0018
used PdHAP-1 (**D**)	Pd-O(1)	4.2	1.98	0.0023
	Pd-O(2)	3.0	2.23	0.0325

[a] The region of 0.9-2.2 Å in Figure 1**A**, 0.9-2.0 Å in Figure 1**B**, 1.95-3.0 Å in Figure 1**C**, 0.8-1.85 Å in Figure 1**D** were inversely Fourier transformed. [b] $\Delta\sigma$ is the difference between Debye-Waller factor of PdHAP and that of the reference sample.

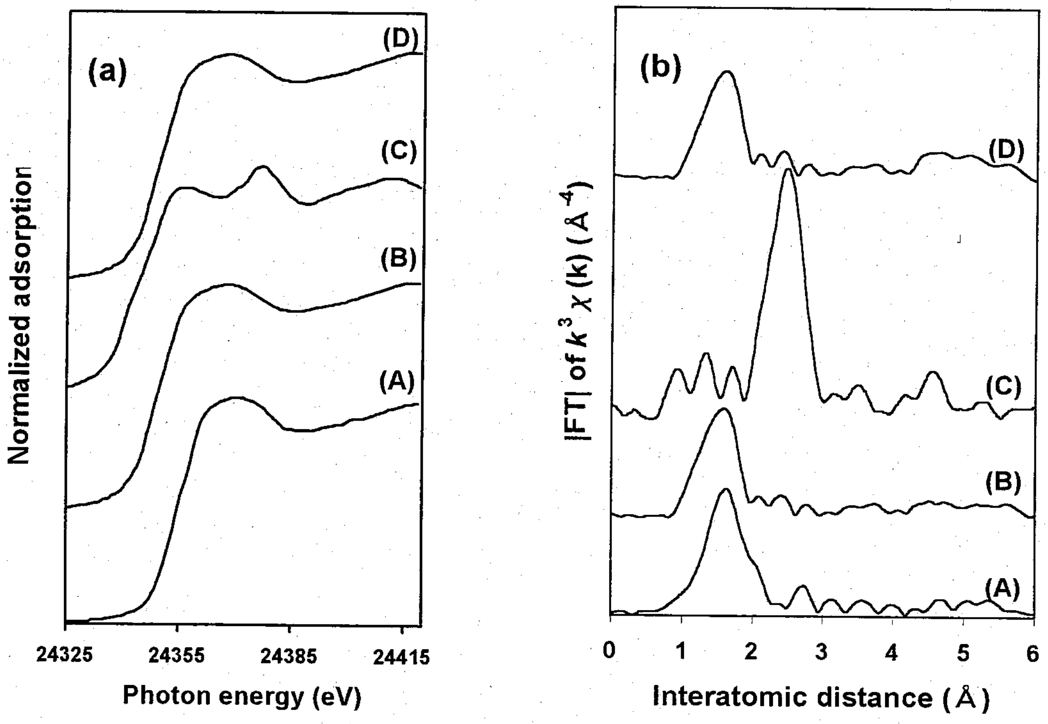


Figure 1. (a) Normalized Pd Pd K-edge XANES spectra of Fourier-transforms of k^3-weighted Pd K-edge EXAFS experimental data for (**A**) PdHAP-0, (**B**) PdHAP-1, (**C**) recovered PdHAP-0, (**D**) recovered PdHAP-1 for the Heck reaction of bromobenezene with styrene. (b) Inverse Fourier-transforms of k^3-weighted Pd K-edge EXAFS experimental data for (**A**) PdHAP-0, (**B**) PdHAP-1, (**C**) recovered PdHAP-0, (**D**) recovered PdHAP-1 for the Heck reaction of bromobenezene with styrene. Reactions were conducted with bromobenzene (2 mmol), styrene (2,4 mmol), K_2CO_3 (2,4 mmol), NMP (5 ml), 130 °C, Ar atmosphere.

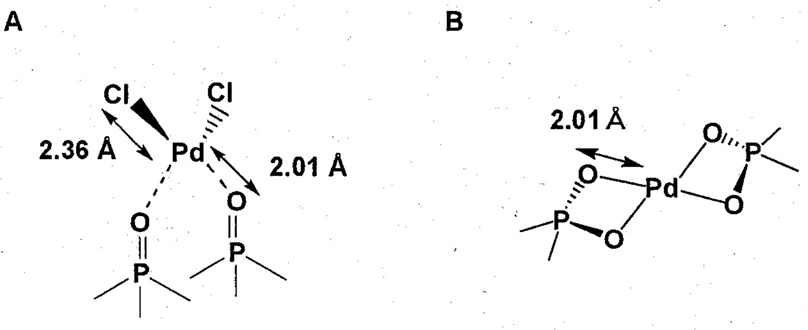


Figure 2. Proposed surface structures around Pd^{II} of PdHAP-0 (A) and PdHAP-1 (B). The nearest oxygen and chlorine atoms around the Pd^{II} are shown.

3-2. Comparison of Catalytic Activities of Hydroxyapatite-Bound Palladium Complexes for Mizoroki-Heck Reaction

To explore potential catalytic activity of these PdHAPs, the Mizoroki-Heck reaction of bromobenzene with styrene was carried out using various Pd catalysts. The results are shown in Figure 3 and Table 2. The PdHAP-1 displayed the highest catalytic activity to give stilbene in 97 % yield for 3 h (entry 1). In contrast, the PdHAP-0 was less effective under the identical conditions with a concomitant color change from yellow to light gray (entry 2). In the case of conventional palladium catalysts, *e.g.* Pd/Caron, Pd/Al_2O_3, and Pd/SiO_2, full conversion was not achieved and the yield of stilbene were 24, 7, and 11 %, respectively

Table 2. Heck Reaction of Bromobenzene with Styrene using Various Pd Catalysts[a]

entry	catalyst	Pd (mol %) [b]	time (h)	convn. (%)	yield (%) [c]
1	PdHAP-1	0.075	3	>99	97
2	PdHAP-0	0.075	12	80	79
3	Pd/C (0.5 wt%)	0.15	12	27	24
4	Pd/Al_2O_3 (0.5 wt%)	0.15	12	10	7
5	Pd/SiO_2 (0.5 wt%)	0.15	12	16	11
6	$PdCl_2(PhCN)_2$	0.5	12	86	85

[a] Reaction conditions: Bromobenzene (2 mmol), styrene (2,4 mmol), K_2CO_3 (2,4 mmol), NMP (5 ml), 130 °C, Ar atmosphere. [b] Related to Bromobenzene. [c] Yield = (mol of coupling product (E+Z)) / (mol of Bromobenzene).

(entries 3-5). The use of homogeneous Pd precursor of $PdCl_2(PhCN)_2$ led to the significant decrease of catalytic activity, accompanied with the formation of Pd black (entry 6).

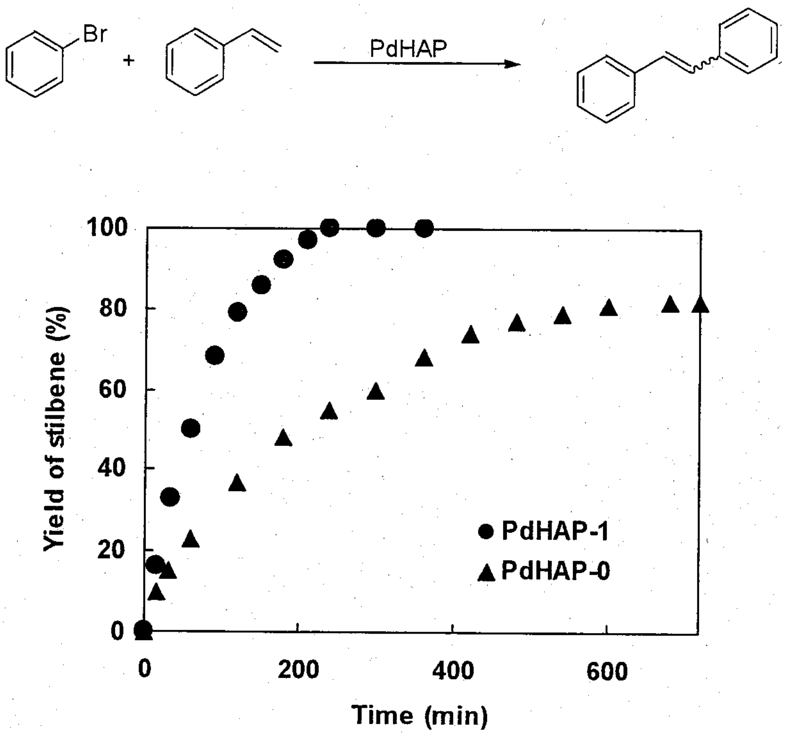


Figure 3. Time profile for the Heck reaction of bromobenzene with styrene catalyzed by PdHAP. Reaction conditions: PdHAP (0.05 g, 0.075 mol%) bromobenzene (2 mmol), styrene (2,4 mmol), K_2CO_3 (2,4 mmol), NMP (5 ml), 130 °C, Ar atmosphere.

In order to gain insight into structure-activity relationship for the Mizoroki-Heck reaction, the recovered PdHAP catalysts were characterized by means of XAFS and TEM analysis. Figure 1C shows the FT of k^3-weighted EXAFS for the isolated PdHAP-0 after the Heck reaction of bromobenzene with styrene, which exhibited a single peak at approximately 2.5 Å due to the Pd-Pd bond with a coordination number of 6.9. TEM analysis of the recovered PdHAP-0 also revealed the presence of Pd nanoparticles with diameter of *ca.* 50 Å. These results suggest that monomeric Pd^{II} species on hydroxyapatite surface are reduced to Pd^0 and subsequently transformed into Pd nanoparticles throughout the reaction. On the contrary, an original monomeric Pd^{II} structure of the PdHAP-1 was retained even after the reaction; none of structural change around the Pd^{II} center and Pd particle formation was confirmed by EXAFS (Figure. 1D) and TEM analyses. The Ca-deficient hydroxyapatite serves as a suitable macroligand for the catalytically active center, which provide structurally robust phosphate complex on solid surface. It can be concluded that the high catalytic activity of the PdHAP-1, as compared to the PdHAP-0 and other conventional palladium catalysts, is ascribed to the exceptional stability of the monomeric Pd^{II} species under the reaction conditions.

3-4. Mizoroki-Heck and Suzuki-Miyaura Reactions Catalyzed by Hydroxyapatite-Bound Palladium Complex

A preliminary screening of the optimal reaction conditions for the Mizoroki-Heck reaction of bromobenzene with styrene was carried out, as summarized in Table 3. With respect to the solvent, NMP was most effective among examined, and DMSO and *o*-xylene gave poor results. The choice of base also has a significant influence on the efficiency of the

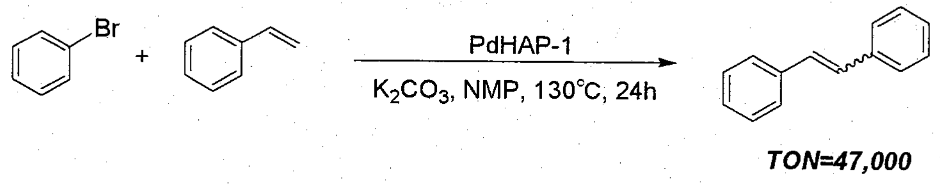
Table 3. Effects of Solvent and Base on PdHAP-1-Catalyzed Heck Reaction[a]

entry	solvent	base	convn. (%)	yield (%)[b]
1	NMP	K_2CO_3	77	75
2	DMF	K_2CO_3	31	30
3	DMA	K_2CO_3	20	12
4	DMSO	K_2CO_3	0	0
5	*p*-xylene	K_2CO_3	0	0
6	NMP	KOAc	41	34
7	NMP	Na_2CO_3	21	18
8	NMP	NaOAc	8	3
9	NMP	$N(Et)_3$	3	3
10	NMP	$N(Bu)_3$	3	1

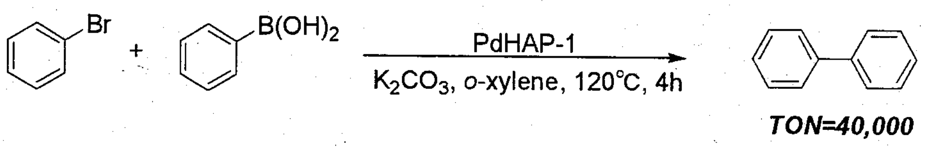
[a] Reaction conditions: bromobenzene (2 mmol), styrene (2.4 mmol), base (2.4 mmol), solvent (5 ml), PdHAP (0.1g, 0.075 mol % Pd with respect to bromobenzene), 2 h, 130℃, Ar atmosphere. [b] Yield = (mol of coupling product(E+Z)) / (mol of reactant)

reaction; K_2CO_3 was the base of choice, whereas organic base such as NEt_3 and $N(n\text{-Bu})_3$ gave no yield.

The results of the cross coupling reactions catalyzed by the PdHAP-1 under optimal conditions are summarized in Table 4. It was found that the PdHAP-1 acts as an outstanding catalyst for the Mizoroki-Heck reaction. For example, the TON based on Pd reached 47,000 for 24 h in the case of bromobenzene with styrene (entry 1, eq. 3). The reaction proceeded efficiently without the significant influence of the substituents, giving the corresponding coupling products in excellent yields. To the best of my knowledge, the PdHAP-1 is the most active heterogeneous catalyst for the Heck reaction of bromoarenes among the reported so far. Unfortunately, electron-donating groups at *ortho* position retarded the reaction, presumably because of the steric hindrance on solid surface. Moreover, the PdHAP-1 was applicable to the Suzuki-Miyaura coupling reactions with a TON approaching 40,000 for 4 h in the reaction of bromobenzene with phenylboronic acid (entry 7, eq. 4) [15]. With respect to the solvent, o-xylene was superior to polar solvent such as DMF, NMP in the Suzuki coupling reaction.



(3)



(4)

A crucial question then becomes whether the coupling reactions occur on the solid surface or with dissolved palladium species [16]. In the Heck reaction of bromobenzene with styrene, the catalyst was removed after 50% conversion under Ar atmosphere, followed by addition of K_2CO_3 to the filtrate and further reaction at 130 °C for 6 h. The Heck reaction hardly occurred after catalyst removal. No Pd leaching in the filtrate was detected by ICP analysis. In a separate experiment, the used PdHAP-1 catalyst was found to be recyclable with

Table 4. Heck and Suzuki Coupling Reactions Catalyzed by PdHAP-1[a]

entry	aryl halide	acceptor	time (h)	yield (%)[b]	TON (-)
1	bromobenzene	styrene	24	94	47000
2	4-bromoacetophenone	styrene	20	96	48000
3	4-bromoanisole	styrene	24	90	45000
4	bromobenzene	*n*-buthyl acrylate	20	91	45500
5	4-bromoacetophenone	*n*-buthyl acrylate	20	98	49000
6	4-bromoanisole	*n*-buthyl acrylate	24	94	47000
7[c]	bromobenzene	phenylboronic acid	4	80	40000
8[c]	4-bromoacetophenone	phenylboronic acid	4	94	47000
9[c]	4-bromoanisole	phenylboronic acid	6	91	45500

[a] Reaction conditions: aryl bromide (37.5 mmol), acceptor (45 mmol), PdHAP-1 (0.05 g, 2 × 10^{-3} mol % of Pd based on aryl bromide), K_2CO_3 (45 mmol), NMP (50 mL), 130 °C, Ar atmosphere. [b] Yields were determined by GC analysis based on aryl halide using an internal standard technique. [c] *o*-Xylene (50 mL) was used as solvent. 120 °C.

retention of its high catalytic activity. Therefore, it can be said that this Mizoroki-Heck reaction undergoes heterogeneously on the PdHAP-1 surface.

3-5. Mechanistic Investigation

A new class of Pd^{II} complexes having Pd-carbon σ bonds, such as palladacycle complexes [17], PCP pincer-type complexes [18] and cyclometallated imine complexes [19], have recently been demonstrated to show high activities for the Mizoroki-Heck reaction. It is suggested that the Mizoroki-Heck reaction catalyzed by these Pd complexes proceed *via* the Pd^{II}/Pd^{IV} rather than the traditional Pd^{0}/Pd^{II} cycle because of their thermal stability. The PdHAP-1 catalyst also exhibited an exceptionally high stability under this reaction; the EXAFS spectra of the recovered catalyst showed the Pd exist as a monomeric cation species even after the reaction. The above result indicate that the involvement of a Pd(0) as the active species seems unlikely. Therefore, the comparisons of catalytic behavior in the Mizoroki-Heck reaction were performed. In the present PdHAP-1 catalytic system, the competitive Heck reactions in an equimolar mixture of *p*-substituted iodobenzenes using styrene gave a Hammett ρ value of 1.09, which differs from 2.00 with $Pd(PPh_3)_4$ [20], but is similar to 1.39 with the Pd^{II} PCP-type complex [18]. In a competitive reaction between *n*-butylacrylate and styrene with iodobenzene, the PdHAP-1 and the palladacycle gave relatively high product ratios between *n*-butylcinnamate and stilbene, of 9.6 and 7.3, respectively. These values significantly exceeded 4.1 observed with $Pd(PPh_3)_4$. The above phenomena associated with the extremely robust monomeric Pd^{II} structure of the PdHAP-1 strongly support that this Heck reaction does not proceed *via* the traditional Pd^{0}/Pd^{II} cycle. Furthermore, it is thought that the rate-determining step in Heck reaction catalyzed by the PdHAP-1 is not the oxidative addition, but rather than the insertion of the olefin into the arylpalladium intermediate. This assumption is also supported by the kinetic studies for the reaction of bromobenzene with styrene; the reaction rate is zero order in aryl bromide and first order in olefin. These unusual Pd performances are attributed to a phosphate ligand on the hydroxyapatite surface, which effectively serves as a powerful alternative to organic ligands.

3-6. Suzuki-Miyaura Coupling Reactions of Chloroarens Catalyzed by Hydroxyapatite-Bound Palladium Complex

The use of more readily available aryl chlorides in the palladium-catalyzed cross coupling reactions is a challenging task for industrial application [21]. The low activity of aryl chlorides is attributed to the strong dissociation energy of the C-Cl bond (bond dissociation energies for Ph-X: Cl: 96 kcal•mol^{-1}; Br: 81 kcal•mol^{-1}; I: 65 kcal•mol^{-1}), which leads to reluctance of oxidative addition to Pd centers [22]. As mentioned above, the PdHAP-1 has

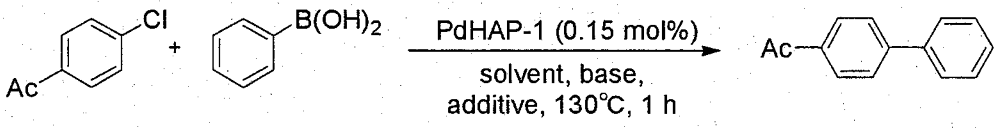


Table 5. A Screening of the Optimal Reaction Conditions for Suzuki Coupling Reaction Catalyzed by PdHAP-1[a]

entry	solvent	base	additive	yield (%) [b]
1	DMF/H_2O (50:1)	K_3PO_4	TBAB	92
2	DMF/H_2O (50:1)	K_3PO_4	—	34
3	DMF	K_3PO_4	TBAB	60
4	DMF/H_2O (50:1)	K_3PO_4	TBAI	90
5	DMF/H_2O (50:1)	K_3PO_4	TBACl	trace
6	DMF/H_2O (50:1)	K_3PO_4	SDS	29
7	DMF/H_2O (50:1)	K_3PO_4	Span 80	29
8	*o*-xylene/H_2O (50:1)	K_3PO_4	TBAB	trace
9	NMPH_2O (50:1)	K_3PO_4	TBAB	90
10	DMF/H_2O (50:1)	Li_3PO_4	TBAB	trace
11	DMF/H_2O (50:1)	K_2CO_3	TBAB	82
12	DMF/H_2O (50:1)	KOH	TBAB	67
13	DMF/H_2O (50:1)	KO*t*Bu	TBAB	63
14	DMF/H_2O (50:1)	NEt_3	TBAB	15

[a] Reaction conditions: 4-chloroacetophenone (1 mmol), phenyl boronic acid (1.5 mmol), PdHAP-1 (0.15 mol % of Pd based on aryl chloride), solvent (5 ml), H_2O (0.1 ml), base (2 mmol), additive (0.1 mmol), 130 ℃, Ar atmosphere.

[b] Determined by GC analysis based on aryl halide using an internal standard technique.

proved to be an efficient heterogeneous catalyst for the Suzuki-Miyaura coupling reaction of aryl bromides. However, the reaction of aryl chlorides hardly occurred under the standard conditions employed for the aryl bromide (*o*-xylene, K_2CO_3, 120 °C). Therefore, a preliminary screening of optimal reaction conditions for this coupling reaction of *p*-chloroacetophenone with phenyl boronic acid was carried out as the test reaction.

As shown in Table 5, the catalytic activity of the PdHAP-1 was significantly improved in the presence of TBAB ($Bu_4N^+Br^-$: 10 mol %) and small amount of water (volumetric ratio: DMF/H_2O=50/1), affording the corresponding *p*-acethylbiphenyl in 92 % yield (entry 1). Addition of TBAI ($Bu_4N^+I^-$) led to similar result (entry 4), but TBAC ($Bu_4N^+Cl^-$) gave lower yield (entry 5). The use of anionic (SDS) and nonionic surfactants (Span 80) did not influence the reaction rate (entries 6 and 7). Among the solvent examined, DMF and NMP gave satisfactory yields (entry 9), while non-polar solvent like *o*-xylene, which was the best solvent for the aryl bromide, failed to promote the reaction (entry 8). With respect to the bases, K_3PO_4 and K_2CO_3 were the bases of choice. Other bases such as KOH, K*t*OBu, and NEt_3 were substantially less effective, and the use of Li_3PO_4 gave no product (entries 11-14). These optimal conditions are generally applicable to the Suzuki coupling reaction of aryl chloride bearing electron-withdrawing substituents and gave excellent yields of cross-coupled products, as summarized in Table 6. The PdHAP-1 exhibited the highest catalytic activity, as compared with that of other conventional heterogeneous catalysts, e.g. Pd/Carbon, Pd/Al_2O_3, and Pd/SiO_2, under identical conditions (entries 1-4). In the case of chlorobenzene, however, moderate yield of biphenyl was obtained (entry 8).

The TEM image of the isolated PdHAP-1 catalyst after the Suzuki-Miyaura coupling reaction of *p*-chloroacetophenone with phenyl boronic acid showed the presence of Pd nanoparticles with diameter of *ca.* 50 Å. It can be said that the monomeric Pd^{II} species of the PdHAP-1 surface, which was extremely stable under the reaction conditions of aryl bromide, were transformed into Pd nanoparticles throughout the reaction of aryl chloride. It has been known that chemical and electrochemical reduction of transition metal salts in the presence of ammonium salts leads to $R_4N^+X^-$ stabilized colloids [23]. A recent study points to the involvement of intermediary colloidal Pd nanoparticles generated under thermolytic conditions for the Heck reaction [24]. Hence, it is likely that under PdHAP-1 reaction conditions, Bu_4N^+Br-stabilized Pd^0 nanoparticles are formed *in situ* and then function as catalysts. Furthermore, the enhancement of catalytic activity of the PdHAP-1 by the addition of TBAB may be ascribed to the formation of anionic $[Br\text{-}Pd^0\text{-}L]^-$ (L=ligand or neighboring Pd) species on the surface of Pd particles, which facilitate oxidative addition and reductive elimination during the Pd^0/Pd^{II} catalytic cycle [25].

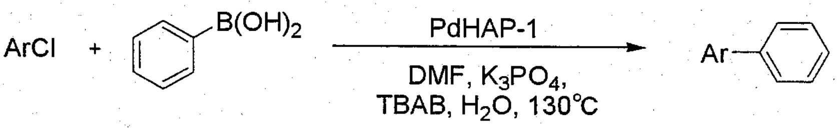
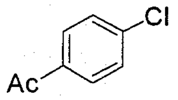
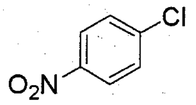
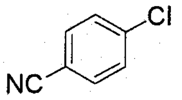
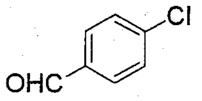
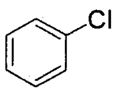


Table 6. Suzuki Coupling Reaction Catalyzed by PdHAP-1[a]

entry	catalyst	aryl chloride	time (h)	yield (%) [b]
1	PdHAP-1		1	92
2	Pd/Carbon		1	48
3	Pd/Al_2O_3		1	trace
4	Pd/SiO_2		1	trace
5	PdHAP-1		1	>99
6[c]	PdHAP-1		1	>99
7[d]	PdHAP-1		2	70
8[d]	PdHAP-1		5	30

[a] Reaction conditions: aryl chloride (1 mmol), phenyl boronic acid (1.5 mmol), PdHAP-1 (0.15 mol % of Pd based on aryl chloride), DMF (5 ml), H_2O (0.1 ml), K_3PO_4 (2 mmol), TBAB (0.1 mmol), 130 °C, Ar atmosphere.

[b] Determined by GC analysis based on aryl halide using an internal standard technique. [c] Without H_2O. [d] PdHAP-1 (0.3 mol % of Pd)

4. Conclusions

The author demonstrated a novel approach to catalyst design using hydroxyapatites and realized excellent catalytic performances. Accurate control of the Ca/P ratios of hydroxyapatites afforded two different Pd species on their surfaces. Using the stoichiometric hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$, monomeric $PdCl_2$ species could be grafted on its surface (PdHAP-0). The PdHAP-0 gave a poor TON in the Mizoroki-Heck reaction of bromobenzene with styrene, accompanied with the formation of Pd particles. Another monomeric Pd^{II} phosphate complex could be generated in a Ca-deficient site of the nonstoichiometric hydroxyapatite, $Ca_9(HPO_4)(PO_4)_5(OH)$, affording a catalyst with monomeric Pd^{II} structure and high activity for the Mizoroki-Heck reaction. Moreover, the PdHAP-1 catalyst was also applicable to the Suzuki-Miyaura coupling reaction of chloroarens bearing electron-withdrawing substituents in the presence of TBAB and a small amount of water. No Pd leaching was observed for the above reactions, and then the catalysts were recyclable. The PdHAP-1 catalytic system is therefore highly suitable for large-scale operations, meeting the increasing demands for environmentally-friendly chemical processes.

References

[1] (a) Heck, R. F. *Palladium Reagents in Organic Syntheses*, Academic Press: London, 1985; (b) Tsuji, J. *Palladium Reagents and Catalysts*, Wiley: Chichester, 1995. (c) Trost, B. M. *Angew. Chem. Int. Ed.* **1995**, *34*, 259. (d) *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann, W. A., Eds., VCH: Weinheim, 1996. (e) Beller, M.; Riermeir, T. H. In *Transition Metals for Organic Syntheses*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1996.

[2] (a) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (b) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y.; *Science* **2000**, *287*, 1992.

[3] (a) Gates, B. C. *Chem. Rev.* **1995**, *95*, 511. (b) Basset, J.-M.; Lefebre, F.; Santini, C. *Coord. Chem. Rev.* **1998**, *178-180*, 1703. (c) Iwasawa, Y. *Prep. Solid Catal.* **1999**, 427.

[4] Bergbreiter, D. E. *Med. Res. Rev.* **1999**, *19*, 439.

[5] (a) Negishi. E.-I.; Liu, F. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998. (b) Yang, B. H.; Buchwald, S. L.; *J. Organomet. Chem.* **1999**, *576*, 125. (c) Sturmer, R. *Angew. Chem. Int. Ed.* **1999**, *38*, 3307. (d) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (e) Hartwing, J. F. *Angew. Chem. Int. Ed.* **1998**, *37*, 2046.

[6] Beller, M.; Riermeier, T. H. *Tetrahedron Lett.* **1996**, *37*, 6537.

[7] Wijngaarden, R. J.; Kronberg, A.; Westerterp, K. R. *Industrial Catalysis*; Wiley-VCH: Weinheim, 1997.

[8] (a) Jintong, L, Albert, W.-H.; Christopher, R. S. *Chem. Commun.* **1997**, 1275.

[9] (a) Jayasree, S.; Seayad, A.; Laurent, R.D.; Henrike, H.; Klaus, K. *J. Am. Chem. Soc.* **2001**, *123*, 5990.

[10] (a) Christian, P. M.; David, W. W.; Jackie, Y. Y. *J. Am. Chem. Soc.* **1998**, *120*, 12289. (b) Christian, P. M.; Jackie, Y. Y. *Chem. Commun.* **1997**, 2215.

[11] (a) Yamaguchi, K.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2000**, *122*, 7144. (b) Mori, K.; Yamaguchi, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Chem.*

Commun. **2001**, 461. (c) Mori, K.; Tano, M.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *New. J. Chem.* **2002**, *26*, 1536.

[12] Elliott, J. C. *Structure and Chemistry of the Apatites and Other Calcium Orthophosphates* Elsevier, Amsterdam, **1994**.

[13] Sugiyama, S.; Minami, T.; Hayashi, H.; Tanaka, M.; Shigemoto, N.; Moffat, J. B. *J. Chem. Soc., Faraday Trans.* **1996**, *92*, 293.

[14] Tanaka, T.; Yamashita, H.; Tsuchitani, R.; Funabiki, T.; Yoshida, S. *J. Chem. Soc., Faraday Trans.* **1988,** *84*, 2987.

[15] For recent reports of heterogeneous Pd-catalyzed Suzuki reactions, see: (a) Mubofu, E. B.; Clark, J. H.; Macquarrie, D. J. *Green Chem.* **2001**, *3*, 23. (b) LeBlomd, C. R.; Andrews, A. T.; Sun, Y.; Sawa, Jr. J. R. *Organic Lett.* **2001**, *3*, 1555. (c) Zhang, T. Y.; Allen, M. J. *Tetrahedron Lett.* **1999**, *40*, 5813. (d) Parrish, C. A.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 3820. (e) Shimizu, K.-I, Kan-no, T.; Kodama, T.; Hagiwara, H.; Kitayama, Y. *Tetrahedron Lett.* **2002**, *43*, 5653. (f) Bulut. H.; Artok, L.; Yilmaz, S. *Tetrahedron Lett.* **2003**, *44*, 289. (g) Yamada, Y. M. A.; Takeda, K.; Takahashi, H.; Ikegami, S. *Organic Lett.* **2002**, *4*, 3371. (h) Kim, S,-W.; Kim, M.; Lee, W. H., Hyeon, T. *J. Am. Chem. Soc.* **2002**, *124*, 7642.

[16] There is controversy whether the Heck reaction using solid Pd catalysts occurred on their surface or not, see: (a) Zhao, F.; Murakami, K.; Shirai, M.; Arai, M. *J. Catal.* **2000**, *194*, 479. (b) Davies, I. W.; Matty, L.; Hughes, D. L.; Reider, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 10139.

[17] (a) Herrmann, W. A.; Brossmer, C.; Öfele, K.; Reisinger, C.-P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem. Int. Ed.* **1995**, *34*, 1844. (b) Shaw, B. L.; Perera, S. D.; Staley, E. A. *Chem. Commun.* **1998**, 1361.

[18] Ohff, M.; Ohff, A.; van der Boom, M. E.; Milstein, D. *J. Am. Chem. Soc.* **1997**, *119*, 11687.

[19] Herrmann, W. A.; Elison, M.; Ficher, C.; Köcher, C.; Artus, G. R. J. *Angew. Chem. Int. Ed.* **1995**, *34*, 2371.

[20] Fauvarque J.-F.; Pflüger, F. *J. Organomet. Chem.* **1981**, *208*, 419.

[21] Litteke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 4177.

[22] (a) Grushin, V. V.; Alper, H. In *Activation of Unreactive Bonds and Organic Synthesis*, Murai, S. Eds., Springer, Berline, 1999. (b) Grushin, V. V.; Alper, H. *Chem. Rev.*, **1994**, *94*, 1047.

[23] (a) Toshima, N.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 400. (b) Reetz, M. T.; Quaiser, S. A. *Angew. Chem. Int. Ed.* **1995**, *34*, 2240. (c) Reetz, M. T.; Helbig, W.; Quaiser, S. A.; Stimming, U.; Breuer, N.; Vogel, R. *Science* **1995**, *267*, 367.

[24] Reetz, M. T.; Westermann, E. *Angew. Chem. Int. Ed.* **2000**, *39*, 165.

[25] (a) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314. (b) Crip. G. T. *Chem. Soc. Rev.* **1998**, *27*, 427.

General Conclusions

This thesis deals with the study on the catalyst design of high-performance hydroxyapatite-bound ruthenium and palladium complex catalysts for various types of selective oxidation using molecular oxygen and carbon-carbon bond-forming reactions. The hydroxyapatite-bound transition metal complex catalysts for the above organic reactions could be developed based on the promising ability of the hydroxyapatite as a macroligand for catalytically active centers.

Chapter I surveys the methodologies for the preparation of the hybrid-catalysts that combine the advantages of both homogeneous and heterogeneous catalysis. The author emphasized the importance of the sophisticated catalyst design at atomic and molecular levels, which makes a pivotal contribution to developing environmentally-acceptable organic syntheses.

In Chapter II, the author described the hydroxyapatite-bound Ru complex (RuHAP), which was synthesized based on cation-exchange ability of hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$, by treatment with an aqueous $RuCl_3$ solution. Characterizations using physicochemical methods have proved that the equimolar substitution of Ru^{3+} for Ca^{2+} occurred on the surface of hydroxyapatite, which afforded a monomeric Ru^{3+} species surrounded by oxygen and chlorine atoms. This RuHAP acted as an effective heterogeneous catalyst for the oxidation of various alcohols using molecular oxygen to give corresponding carbonyl compounds in excellent yields. In the case of homogeneous $RuCl_2(PPh_3)_3$ complex, the catalytic cycle was not completed without hydroquinone or 2,2',6,6'-tetramethylpiperidine *N*-oxyl, whereas our RuHAP catalyst does not need any additives for the above aerobic oxidation. Moreover, this RuHAP catalyst was applicable to the oxidations of amines and silanes in the presence of molecular oxygen, giving the corresponding nitriles and silanols in high yields, respectively.

In Chapter III, the novel synthesis and unique catalytic performances of the hydroxyapatite-bound cationic Ru complexes were described. Treatment of the neutral RuHAP with an aqueous solution of AgX (X=SbF_6^-, OTf $^-$) readily afforded cationic Ru species having potentially vacant coordination sites. Such cationic RuHAPs acted as heterogeneous Lewis acid catalysts, which could effectively promote the Diels-Alder and aldol reactions under mild and neutral reaction conditions. Notably, in the reaction of nitriles with α, β-unsaturated carbonyl compounds, 1,2-addition exclusively occurred by the cationic RuHAP in contrast to the homogeneous Ru complex, $RuH_2(PPh_3)_4$, which prefers 1,4-addition. IR and FT-EXAFS analyses for the reaction intermediate suggested that the cationic RuHAP-(II)-catalyzed aldol reaction using nitriles involves cooperative catalysis between the cationic Ru species and the basic phosphate ligand on the HAP surface; the former activates the nitrile as a Lewis acid, while the latter phosphate abstracts an acidic α-proton of the nitrile to generate enolate species as a reaction intermediate.

In Chapter IV, the author represented a novel approach to catalyst design using hydroxyapatites based on the nomstoichiometry of the HAP. Treatment of Ca-deficient hydroxyapatite, $Ca_9(HPO_4)(PO_4)_5(OH)$, with $PdCl_2(PhCN)_2$ provided a highly efficient catalyst (PdHAP-1) for the Mizoroki-Heck and Suzuki-Miyaura coupling reactions. It is notable that the original monomeric Pd^{II} structure of the PdHAP-1 was retained even after the Heck reaction; none of structural change around the Pd^{II} center and Pd particle formation was confirmed by EXAFS and TEM analyses. Furthermore, the catalytic performances of the PdHAP-1 was different from that of the $Pd(PPh_3)_4$, but was similar to those of the Pd^{II} PCP-type complex and the palladacycle. These phenomena associated with the extremely robust monomeric Pd^{II} structure of the PdHAP-1 strongly supported that this Heck reaction does not proceed *via* the traditional Pd^0/Pd^{II} cycle mechanism.

The present thesis described catalysts design of the hydroxyapatite-bound transition metal complex catalysts based on the unique properties, and their prominent catalyses for various types of organic syntheses. The hydroxyapatite catalysts could be easily separated from the reaction mixture without metal leaching and reused with retention of their high catalytic performance for the above reactions. The author hopes that this design strategy for hydroxyapatite-bound transition metal catalysts can be further applied to a wide range of functional group transformations including asymmetric reactions, aiming at "green" organic synthesis.

Finally, the author points out the further extended developments for the synthesis of highly functionalized hydroxyapatite catalysts as follows.

- The immobilization of metal ions on inorganic matrices has opened many tracks to more practical organic synthetic processes. As stated in the present thesis, various kinds of transition metal cations can be readily accommodated into the hydroxyapatite framework based on their large cation exchange ability. Another notable feature of the hydroxyapatites is anion exchange ability. The author has found that transition metal anions such as RuO_4^- and OsO_4^{2-} were substituted for PO_4^{3-} on the surface of hydroxyapatite as the catalytically active center. It is expected that such catalysts would have high potential abilities for aerobic alcohol oxidation and oxidative cleavage reaction of olefins using H_2O_2 as an oxidant.

- The immobilization of biological catalysts e. g., enzymes, catalytic antibodies, and whole cells in robust matrices to enhance their life time as well as their recovery and repeated use have been the focus of attention for several years. Hydroxyapatites, the main components of bones and teeth, have high potentiality for the function as a promising support of heterogeneous biocatalysts because of their strong affinity toward biological molecules. The author expects that a fusion of organic chemistry and biochemistry through hydroxyapatite open up the new field on chemistry and chemical engineering.

List of Publications

[1] Kazuya Yamaguchi, Kohsuke Mori, Tomoo Mizugaki, Kohki Ebitani, and Kiyotomi Kaneda, "Creation of a Monomeric Ru Species on the Surface of Hydroxyapatite as an Efficient Heterogeneous Catalyst for Aerobic Alcohol Oxidation",

Journal of the American Chemical Society, **2000**, *122*, 7144-7145.

[2] Kohsuke Mori, Kazuya Yamaguchi, Tomoo Mizugaki, Kohki Ebitani, and Kiyotomi Kaneda, "Catalysis of a Hydroxyapatite-bound Ru Complex: Efficient Heterogeneous Oxidation of Primary Amines to Nitriles in the Presence of Molecular Oxygen",

Chemical Communications, **2001**, 461-462.

[3] Kohsuke Mori, Makoto Tano, Tomoo Mizugaki, Kohki Ebitani, and Kiyotomi Kaneda, "Highly Efficient Heterogeneous Oxidation of Organosilane to Silanols Catalyzed by a Hydroxyapatite-bound Ru Complex in the Presence of Water and Molecular Oxygen",

New Journal of Chemistry, **2002**, *26*, 1536-1538.

[4] Kohsuke Mori, Kazuya Yamaguchi, Takayoshi Hara, Tomoo Mizugaki, Kohki Ebitani, and Kiyotomi Kaneda,
"Controlled Synthesis of Hydroxyapatite-Supported Palladium Complexes as Highly Efficient Heterogeneous Catalysts",

Journal of the American Chemical Society, **2002**, *124*, 11572-11573.

[5] Kohsuke Mori, Takayoshi Hara, Tomoo Mizugaki, Kohki Ebitani, and Kiyotomi Kaneda "Hydroxyapatite-Bound Cationic Ruthenium Complexes as Novel Heterogeneous Lewis Acid Catalysts for Diels-Alder and Aldol Reactions",

Journal of the American Chemical Society, **2003**, in press.

【Related Works】

[6] Kazuya Yamaguchi, Kohsuke Mori, Tomoo Mizugaki, Kohki Ebitani, and Kiyotomi Kaneda, "Epoxidation of α, β-Unsaturated Ketones Using Hydrogen Peroxide in the Presence of Basic Hydrotalcite Catalysts",

The Journal of Organic Chemistry, **2000**, *65*, 6897-6903.

[7] Kiyotomi Kaneda, Kazuya Yamaguchi, Kohsuke Mori, Tomoo Mizugaki, Kohki Ebitani, "Catalyst Design of Hydrotalcite Compounds for Efficient Oxidations",

Catalysis Surveys from Japan, **2000**, *4*, 31-38.

[8] Kiyotomi Kaneda, Kazuya Yamaguchi, Kohsuke Mori, Tomoo Mizugaki, Kohki Ebitani, "Design of High Performance Hydrotalcite Catalysts in Efficient Monoxygeneation Type Reactions using Hydrogen Peroxide",

Recent Research Development Organic Chemistry, **2002**, *6*, 281-295.

[9] Makoto Murata, Takayoshi Hara, Kohsuke Mori, Masahiko Ooe, Tomoo Mizugaki, Kohki Ebitani, and Kiyotomi Kaneda,
"Efficient Deprotection of *N*-benzyloxycarbonyl Group from Amino Acids by Hydroxyapatite-Bound Palladium Catalyst in the Presence of Molecular Hydrogen"

Tetrahedron Letters, **2003**, *44*, 4981-4984.

[10] Takayoshi Hara, Kohsuke Mori, Tomoo Mizugaki, Kohki Ebitani, and Kiyotomi Kaneda, "Highly Efficient Dehydrogeneation of Indolines to Indoles using Hydroxyapatite-Bound Palladium Complex Catalyst",

Tetrahedron Letters, **2003**, *44*, 6207-6210.

Acknowledgement

The author wishes to express his deepest gratitude to Professor Kiyotomi Kaneda for the instructive guidance and encouragement throughout the present work. Hearty thanks are made to Professor Kazushi Mashima (Department of Chemistry, Graduate School of Engineering Science, Osaka University), Professor Toshikazu Hirao (Department of Materials Chemistry, Graduate School of Engineering, Osaka University), and Professor Takayuki Hirai (Research Center for Solar Energy Chemistry, Osaka University), who acted as examiner of this dissertation of their helpful and useful suggestion.

The author deeply thanks Assistant Professor Kohki Ebitani (Department of Chemical Science and Engineering, Graduate School of Engineering Science, Osaka University) for numerous valuable comments. The author is also grateful to Dr. Tomoo Mizugaki (Department of Chemical Science and Engineering, Graduate School of Engineering Science, Osaka University) for numerous discussion and encouragement. He would like to thank Dr. Kazuya Yamaguchi (Department of Applied Chemistry, School of Engineering, The University of Tokyo) for the helpful advice and suggestion.

The author is grateful to Assistant Professor Tetsuya Shishido (Department of Chemistry, Tokyo Gakugei University), Dr. Hisao Yoshida (Department of Applied Chemistry, School of Engineering, Nagoya University). Dr. Takashi Yamamoto (Chemical Resources Laboratory, Tokyo Institute Technology), and Dr. Tomoya Uruga (JASRI) for XAFS measurements, Dr. Tomoki Akita (Special Division for Green Life Technology, National Institute of Advanced Industrial Science and Technology) for TEM measurements.

Thanks must be made to Mr. Masahiko Ooe, Mr. Tomonori Kawabata, Mr. Makoto Murata, Mr. Atsushi Sugimoto, Mr. Takayoshi Hara, Mr. Makoto Tano, and Mr. Michitaka, Oshiba for their collaboration and lively discussion; without their devoted supports, completion of this work would not have been possible. He is indebted to all the students studied together with him at this laboratory led by Professor Kiyotomi Kaneda. The author also wishes to thank his parents Shinsuke Mori and Miyoko Mori for their continuous supports.

This study was supported financially by the Research Fellowship of the Japan Society for the Promotion of Science for Young Scientists.

Kohsuke MORI
September, 2003