Hydroxyapatite-Bound Cationic Ruthenium Complexes as Novel Heterogeneous Lewis Acid Catalysts for Diels–Alder and Aldol Reactions

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The design of promising Lewis acid catalysts has attracted considerable interest in organic synthesis because of their unique catalytic performances across a diverse array of carbon–carbon bond-forming reactions.[1] Despite the advantages of homogeneous metal complex catalysts,[2] 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 been directed toward the anchoring of efficient soluble systems on insoluble matrixes. These hybrid-catalysts, however, have been inadequate due to (i) inferior activities, as compared to homogeneous analogues, (ii) tedious multistep preparations, and (iii) leaching of active components.

Our alternative strategy for the design of the hybrid-catalysts focuses on the utilization of hydroxyapatites (HAP), having a promising ability as a macroligand for catalytically active centers.[3] Recently, by using the cation-exchange method, we have successfully created a stable monomeric Ru phosphate complex on the surface of the hydroxyapatite (RuHAP) as a versatile catalyst with superior activity for the selective oxidation reactions and possessing high reusability.[3a–c] Herein, we present a new type of hydroxyapatite-bound cationic Ru complex with potentially vacant coordination sites that are generated 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.

Treatment of a hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$, with an aqueous $RuCl_3 \cdot nH_2O$ solution at room temperature yielded the RuHAP (Ru content: 0.97 mmol g^{-1}). Characterizations by means of elemental analysis, XPS, EDX, and Ru–K edge XAFS demonstrated the occurrence of an equimolar substitution of Ru^{3+} for Ca^{2+} to generate a monomeric Ru^{3+} species surrounded by four oxygen atoms and one chlorine atom (Figure 1A).[3a] The cationic RuHAP-(**I**) and -(**II**) were prepared by treatment of the RuHAP, at room temperature under argon atmosphere, with an 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.[4] 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.[4] In the Fourier transform (FT) of k^3-weighted Ru K-edge EXAFS, there were no peaks around 3.5 Å due to the presence of contiguous Ru sites. 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.[5] Consequently, a well-defined cationic Ru phosphate complex can be created on the hydroxyapatite surface, as illustrated in Figure 1B.

As can be seen from Table 1, 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
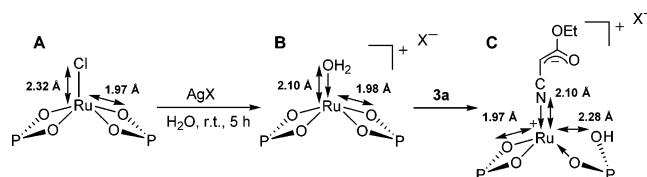

Figure 1. Proposed structures of (A) RuHAP, (B) cationic RuHAP-(**I**) and -(**II**) (**I**, X = SbF$_6$; **II**, X = OTf), and (C) Ru-enolate intermediate (X = OTf).
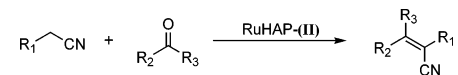
Table 1. RuHAP-(**I**)-Catalyzed Diels–Alder Reaction^a

	1a n=1 1b n=2	1c	2a R=Me 2b R=OMe	2c	2d	2e

entry	diene	dienophile	time (h)	yield (%)^b	endo/exo^c
1	**1a**	**2a**	4	92	90/10
2^d	**1a**	**2a**	4	82	91/9
3	**1a**	**2b**	5	92	91/9
4	**1a**	**2c**	4	91	100/0
5	**1b**	**2d**	6	89	100/0
6	**1c**	**2d**	6	83	
7	**1c**	**2e**	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 ^{1}H NMR. ^{d} Cationic RuHAP-(**II**).

room temperature. For example, reaction between cyclopentadiene **1a** and methyl vinyl ketone **2a** proceeded smoothly to afford 5-acetyl-2-norbornene in 92% yield with a favorable endo:exo selectivity (entry 1). In marked contrast to the homogeneous [Ru^{III}(salen)(NO)H$_2$O]$^+$SbF$_6^-$ complex, the RuHAP-(**I**) was applicable to a less reactive dienophile of methyl acrylate **2b** (entry 3).[6a] It is generally known that product inhibition is a crucial drawback in traditional Al-, Ti-, or B-based Lewis acid catalysis. When the above reaction of **1a** with **2b** was completed, two substrates were added, and a new mixture was allowed to further react. The subsequent three reactions gave the corresponding cycloadduct in over 92% yields at essentially the same rates, showing that the present catalyst can keep its inherent activity during the successive reactions.

From practical and environmental considerations, the development of water-tolerant Lewis acid catalysts is particularly attractive.[7] 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.[8] Representative results are summarized in Table 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

Table 2. RuHAP-(**II**)-Catalyzed Aldol Reaction Using Nitriles[a]

	donor	acceptor			
entry	R₁ =	R₂ =	R₃ =	time (h)	yield (%)[b]
1	CO₂Et (**3a**)	Ph	H (**4a**)	4	>99
2[c]	CO₂Et (**3a**)	Ph	H (**4a**)	4	78
3	CONH₂ (**3b**)	Ph	H (**4a**)	4	98
4[d]	CO₂Et (**3a**)	PhCH=CH	H (**4b**)	8	95
5[d]	CO₂Et (**3a**)	n-C₃H₇	H (**4c**)	3	95
6[d]	CO₂Et (**3a**)	3-cyclohexene	H (**4d**)	5	92
7[e]	CN (**3c**)	Ph	Me (**4e**)	6	82
8[e]	CN (**3c**)	−C₅H₁₀− (**4f**)		3	>99
9[e]	CN (**3c**)	−C₄H₈− (**4g**)		5	91

[a] Reaction conditions: nitrile (1.0 mmol), carbonyl compound (1.2 mmol), cationic RuHAP-(**II**) (0.05 g, Ru: 0.05 mmol), H₂O (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.

Scheme 1
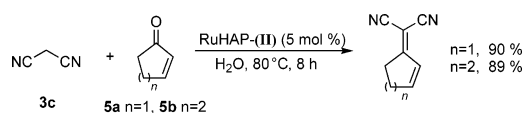
Scheme 2
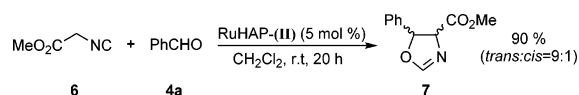
are similar to that of ethylcyanoacetate **3a**, did not yield aldol products under the above conditions. It is notable that treatment of α,β-unsaturated carbonyl compounds **5a**−**b** with **3c** gave the 1,2-addition products in high yields, as shown in Scheme 1; attack of an enolate species on the carbonyl function exclusively occurred without the 1,4-addition. This phenomenon is quite distinct from that of the Ru^{II}H₂(PPh₃)₄-catalyzed reaction, whose products are predominantly a result of the 1,4-addition.[8d] 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 species, which allows a favorable interaction with the carbonyl groups to enhance the 1,2-addition. Furthermore, the present catalytic system is highly suitable for large-scale operations. A 100 mmol scale reaction of **3a** with **4a** 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 **3a** with **4a**.

For the aldol reaction of methyl isocyanoacetate **6** with **4a**, the cationic RuHAP-(**II**) gave the corresponding oxazoline **7** in 90% yield without any additives (Scheme 2), whereas the [Ru(salen)-(NO)H₂O]⁺SbF₆⁻ complex required a Hunig's base (i-Pr₂NEt) to complete the catalytic cycle.[9] The IR spectrum of the cationic RuHAP-(**II**), upon treatment with **3b**, showed a shift of the ν(CN) band toward 2093 cm⁻¹ in comparison with the free cyano group at 2260 cm⁻¹, along with a new peak at 870 cm⁻¹ assigned to the P−OH group of a HPO₄²⁻ ion on the hydroxyapatite surface.[5,10] 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.[5] These results are in agreement

with the formation of a Ru-enolate species surrounded by three oxygens, as shown in Figure 1C. It is reasonable to suggest that the cationic RuHAP-(**II**)-catalyzed aldol reaction using nitriles involves the Ru-enolate intermediate, which is generated through 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 an 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 **7** (trans:cis = 9:1), as compared to those of other homogeneous systems,[9,11] and the effective suppression of product inhibition in the Diels−Alder reaction can be attributed to the steric hindrance imposed by solid surface.

In summary, the design of novel Lewis acid catalysts and their effectiveness for useful carbon−carbon bond-forming reactions were demonstrated. No Ru leaching in the reaction media was observed, and then the catalyst was recyclable. Our protocol based on hydroxyapatites as a macroligand represents an opportunity for the nanoscale design of functionalized catalysts, and further extension to asymmetric catalysis remains to be explored.

Supporting Information Available: Experimental procedures, XAFS analysis, and IR measurements (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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.

(2) (a) Bosnich, B. *Aldrichimica Acta* **1998**, *31*, 76. (b) Murahashi, S.-I.; Takaya, H. *Acc. Chem. Res*. **2000**, *33*, 225.

(3) (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.

(4) For XPS and XAFS analyses, sodium salts such as NaSbF₆ and NaOTf were used instead of silver salts to avoid an interference of insoluble AgCl.

(5) See Supporting Information.

(6) For some recent reports on Lewis acid-catalyzed Diels−Alder reaction, see: (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) Pigant, K.; Vallotto, J.; Pinna, F.; Strukul, G. *Organometallics* **2000**, *19*, 5160. (d) Kündig, E. P.; Saudan, C. M.; Alenzra, V.; Viton, F.; Bernardinelli, G. *Angew. Chem., Int. Ed*. **2001**, *40*, 4481.

(7) For example, see: Kobayashi, S.; Manabe, K. *Acc. Chem. Res*. **2002**, *35*, 209.

(8) 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) 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.

(9) It is said that the base abstracts a proton of isonitriles coordinating to the metals, see: (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.

(10) (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.

(11) Steric repulsion between the phenyl groups of **4a** and the isocyano moiety bound to the Ru phosphate complex in synclinal configuration severely limits the formation of cis-isomer.

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