Catalysis of a hydroxyapatite-bound Ru complex: efficient heterogeneous oxidation of primary amines to nitriles in the presence of molecular oxygen

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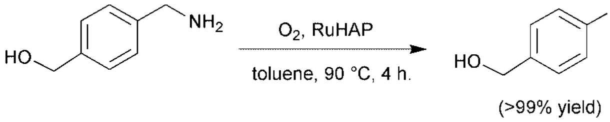
A hydroxyapatite-bound Ru complex could efficiently catalyze the aerobic oxidation of various *primary* amines to nitriles which were further hydrated to amides in the presence of water.

Nitriles are versatile synthetic intermediates which are generally prepared by nucleophilic displacement of halides with cyanide ions, ammoxidation, and the Sandmeyer reaction. These conventional methods often require hazardous reagents and severe reaction conditions. Direct synthesis of nitriles from *primary* amines by the oxidative dehydrogenation is one powerful candidate for a clean synthesis. Many stoichiometric reagents in the above dehydrogenation have, however, been used,[1] which often result in the production of a vast amount of environmental waste.[2] Catalytic methods using molecular oxygen as an oxidant[3] are more desirable from the consideration of 'green and sustainable chemistry'.[2]

We have recently 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.[4] During the course of these studies, we have also found and herein wish to report 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.*

A calcium hydroxyapatite**,** $Ca_{10}(PO_4)_6(OH)_2$, was synthesized according to the literature procedure.[5] 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 g^{-1}). The surface structure of the present RuHAP was determined by X-ray absorption fine structure.[4] A typical RuHAP-catalyzed amine oxidation is as follows. Into a reaction vessel with a reflux condenser were successively placed the RuHAP (0.2 g, Ru^{3+}: 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).

Oxidation of various *primary* amines is 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*-$[Ru^{VI}(tmp)(O_2)]$[3a] (H_2tmp = 5,10,15,20-tetramesitylporphyrin) and $RuCl_2(PPh_3)_3$[3c] using molecular oxygen. When an equimolar mixture of *n*-octylamine and octan-1-ol was used as substrate, the oxidation of *n*-octylamine occurred exclusively to afford *n*-octanenitrile in 91% yield for 12 h without any oxidation products derived from octan-1-ol.‡ Also, an intramolecular competitive oxidation of 4-(aminomethyl)benzyl alcohol afforded chemoselectively 4-cyanobenzyl alcohol in a quantitative yield [eqn. (1)] because the amino function coordinates more strongly to a Ru center than the hydroxy one.

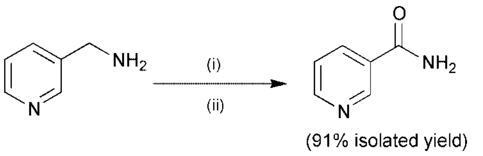


(1)

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). In a *secondary* amine of dibenzylamine, *N*-benzylidenebenzylamine could be obtained in 91% yield (entry 16). 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. 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. This catalyst could be reused with retention of its high catalytic activity and selectivity for the oxidation (entry 3).

Interestingly, when water was used as a solvent instead of toluene under N_2 atmosphere, 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 formation of carboxylic acids, respectively, as shown in Table 2. This hydration system using RuHAP has advantages over other reported methods because of its simple and clean operation under neutral conditions and its high reactivity for both aliphatic and aromatic nitriles.[6] 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 1).

We here propose a possible mechanism for this amine oxidation. Initially, a ligand exchange between an amine and a surface Cl moiety of the RuHAP[4] gives a Ru–$NHCH_2R$ species, followed by elimination to produce a Ru–H species and an



Scheme 1 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.

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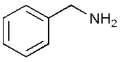
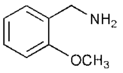
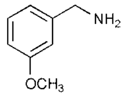
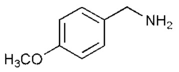
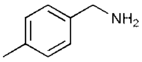
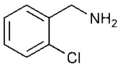
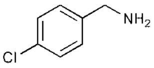
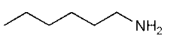
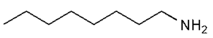
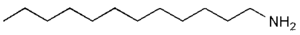
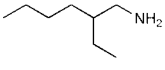
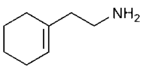
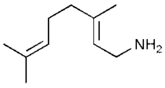
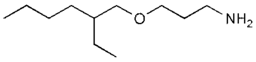
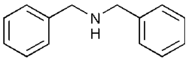
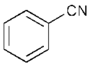
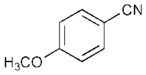
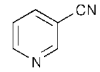
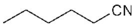
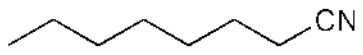
Table 1 Oxidation of various amines using RuHAP in the presence of O_2[a]

Entry	Substrate	Conversion[b](%)	Yield of nitrile[b] (%)
1		100	90[c]
2		100	96
3[d]		100	97
4		92	90
5		100	97
6		100	96
7		100	>99
8		95	95
9		100	91
10[e]		100	>99
11[e]		100	98
12[e]		100	>99
13[e]		100	>99
14		100	81
15[e]		100	94
16[e,f]		98	91[g]

[a] Amine (1 mmol), RuHAP (0.1 g), toluene (10 mL), O_2 atmosphere, 110 °C, 12 h. [b] Determined by GC using biphenyl as an internal standard. [c] *N*-Benzylidenebenzylamine was also formed (10% yield). [d] Recycling experiment. Same conditions except that the recovered RuHAP catalyst was used. [e] 24 h. [f] *p*-Xylene (10 mL) was used as a solvent instead of toluene, 130 °C. [g] Yield of *N*-benzylidenebenzylamine.

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* a similar path to that described above. 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,[6b] subsequently undergoes a ligand exchange with water to give the amide accompanied by the Ru–OH species.

Table 2 Hydration of various nitriles using RuHAP in the presence of H_2O[a]

Entry	Substrate	Conversion[b](%)	Yield of amide[b] (%)
1		100	>99
2		100	96
3		100	97
4		100	98
5		100	97

[a] Nitrile (1 mmol), RuHAP (0.1 g), water (3 mL) , N_2 atmosphere, 150 °C, 24 h. [b] Determined by GC using biphenyl as an internal standard.

In conclusion, the RuHAP efficiently catalyzed the oxidation of many *primary* amines using molecular oxygen, and could be further extended for the nitrile hydration. 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. We have continuously designed hydroxyapatite catalysts containing various other transition metal complexes for developing many functional transformations in organic synthesis.

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Notes and references

† In the oxidation of *para*-substituted benzylamines, the Hammett plot showed a negative ρ value, -0.137, which is close to that with a monomeric $RuCl_2(PPh_3)_3$, $\rho = -0.118$.

‡ Octan-1-ol alone was smoothly oxidized to afford 1-octanoic acid in 82% yield within 6 h under the same reaction conditions as in Table 1: See ref. 4.

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