Aerobic Ruthenium-Catalyzed Oxidative Transformation of Secondary Amines to Imines

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This work is dedicated to the memory of Professor Yoshihiko Ito.

Abstract: Aerobic, catalytic oxidation of secondary amines is performed efficiently in the presence of a diruthenium complex catalyst $Ru_2(OAc)_4Cl$ to give the corresponding imines. The catalytic system is characterized by its high selectivity, activity, and operational simplicity.
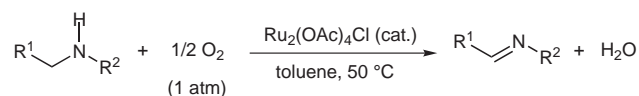
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Metal-catalyzed oxidation of secondary amines is one of the most important functional transformations in organic synthesis, because the oxidation products such as imines and nitrones are highly useful intermediates for synthesis of biologically active nitrogen compounds.[1,2] In 1985, we reported the first catalytic and general method for oxidative transformation of secondary amines to the corresponding imines using $RuCl_2(PPh_3)_3$ catalyst and *t*-BuOOH.[3] After this finding, many methods for metal-catalyzed oxidations of secondary amines with oxidants such as $RuCl_2(PPh_3)_3$/PhIO,[4] Pr_4NRuO_4/*N*-methyl morpholine *N*-oxide,[5] [{$Ph_4(\eta^4$-$C_4CO)$}$Ru(CO)_3$]/Co(salen)/MnO_2,[6] $NiSO_4$/$K_2S_2O_8$,[7] and $Rh_2(cap)_4$/*t*-BuOOH[8] were reported.

Recently, aerobic oxidation is recognized to be very important in view of green chemistry.[9] Many methods for metal-catalyzed aerobic oxidative transformation of primary amines to the corresponding nitriles have been explored;[10–17] however, the methods for catalytic aerobic oxidative transformation of secondary amines to the corresponding imines are limited to a few systems, which include Ru/Co/benzoquinone-based coupled redox system,[18] heterogeneous Ru/Al_2O_3 catalyst,[15] and CuCl catalyst in the presence of MS 3 Å.[17] The difficulty of the aerobic oxidation of secondary amines is due to the unstableness of the product imines under the oxidation conditions and easy hydrolysis to carbonyl compounds.

We wish to report diruthenium complex catalyzed aerobic oxidative transformation of secondary amines to imines,[19] which are highly useful intermediates for synthesis of biologically important nitrogen compounds.[20] We found that dinuclear ruthenium complex, $Ru_2(OAc)_4Cl$[21] is an

excellent catalyst for the oxidative transformation of secondary amines to imines using molecular oxygen (1 atm, balloon) under mild conditions (50 °C, Equation 1).[19]

Equation 1

First of all, we examined the catalytic activity of various ruthenium complexes for the aerobic oxidation of 1,2,3,4-tetrahydroisoquinoline (**1**, Table 1). The oxidation of **1** was carried out under molecular oxygen (1 atm, balloon) in the presence of a catalytic amount of a ruthenium complex (2 mol%) in toluene at 50 °C. The conversions of **1** and the yields of 3,4-dihydroisoquinoline (**2**) and isoquinoline (**3**) were determined by GLC analyses. It is noteworthy that only dinuclear ruthenium complex, $Ru_2(OAc)_4Cl$, was found to be effective among the ruthenium catalysts

Table 1 Catalytic Activity of Various Ruthenium Complexes for the Oxidation of 1,2,3,4-Tetrahydroisoquinoline with Molecular Oxygen[a]

Entry	Catalyst	Conv. (%)[b]	Yield (%)[b]	
			2	**3**
1	$Ru_2(OAc)_4Cl$	98	77	6
2	$RuCl_3$	18	10	1
3	RuO_2	15	14	1
4	$RuCl_2(PPh_3)_3$	6	5	1
5	$Ru(bpy)_2Cl_2$	2	2	Trace
6	$Ru(bpy)_3Cl_2$	4	3	Trace
7	$Ru(TPP)(CO)$	5	4	Trace

[a] Reaction conditions: $Ru_2(OAc)_4Cl$ (0.015 mmol), 1,2,3,4-tetrahydroisoquinoline (0.75 mmol), toluene (1 mL), O_2 (1 atm), 50 °C.
[b] Determined by GLC analysis using an internal standard.

examined (entry 1). RuCl$_3$ and RuO$_2$ showed moderate catalytic activity (entries 2 and 3), while Ru(bpy)$_2$Cl$_2$, Ru(bpy)$_3$Cl$_2$, Ru(TPP)(CO) (TPPH$_2$ = tetraphenylporphyrin) showed almost no catalytic activity under these conditions (entries 4–7).

Typical procedure for the oxidation of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**4**) is as follows. In a flask were placed amine **4** (0.75 mmol) and Ru$_2$(OAc)$_4$Cl (0.030 mmol). After the flask was flushed with molecular oxygen, toluene (1 mL) was added, and the mixture was stirred under oxygen atmosphere (1 atm) at 50 °C for 12 hours. Removal of the solvent followed by column chro-

matography on Al$_2$O$_3$ (eluent: hexane–EtOAc = 2:1 to 1:1) gave 6,7-dimethoxy-3,4-dihydroisoquinoline (**5**) and 6,7-dimethoxyisoquinoline in 80% and 4% yields, respectively.

The representative results of the ruthenium-catalyzed oxidative transformation of secondary amines are summarized in Table 2. The Ru$_2$(OAc)$_4$Cl-catalyzed oxidation of 1,2,3,4-tetrahydroisoquinolines **1** and **4** gave efficiently the corresponding imines **2** and **5**, which are important precursors for synthesis of isoquinoline alkaloids (entries 1 and 2). 1,2,3,4-Tetrahydroquinoline (**6**) was converted into the imine, which subsequently underwent dehydro-

Table 2 Ruthenium-Catalyzed Oxidation of Various Amines with Molecular Oxygen[a]

Entry	Substrate	Product	Time (h)	Conv. (%)[b]	Yield (%)[b]
1	**1**	**2**	3	100	77[f]
2	**4**	**5**	12	100	80[g,h]
3[c]	**6**	**7**	72	86	55
4	**8**	**9**	1	100	83
5	**10**	**11**	48	100	79
6[d]	**12**	**13**	18	97	72[i]
7[e]	**14**	**15**	48	38	27
8	**16**	**17**	7	100	66

[a] Reaction conditions: Ru$_2$(OAc)$_4$Cl (0.03 mmol), amine (0.75 mmol), toluene (1 mL), O$_2$ (1 atm), 50 °C.
[b] Determined by GLC analysis using an internal standard.
[c] Reaction was carried out at 80 °C.
[d] Reaction was carried out with oxygen bubbling.
[e] In the presence of nitrogen ligands **1** (0.06 mmol).
[f] Quinoline **3** was also formed in 6% yield.
[g] Isolated yield.
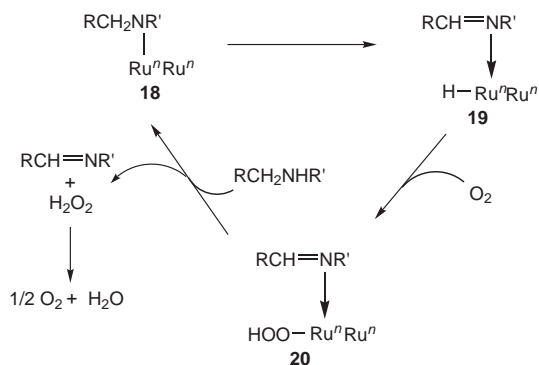[h] 6,7-Dimethoxyquinoline was also formed in 4% yield.
[i] Benzaldehyde was also formed in 17% yield.

genation under the reaction conditions to give quinoline **7** (entry 3). The treatment of indolines gave the corresponding indoles in good yields (entries 4 and 5). Linear secondary amines such as dibenzylamine (**12**) were also converted into the corresponding imine **13** (entry 6). The bulky secondary amine *N*-phenylbenzylamine (**14**) is not reactive under the reaction conditions (entry 7). However, addition of a catalytic amount of external ligands such as **1** and **2** improved the catalytic efficiency dramatically. For example, the $Ru_2(OAc)_4Cl$-catalyzed oxidation of **14** gave a trace amount of imine **15**; however, **15** was obtained in 27% yield in the presence of a catalytic amount of **1**, indicating that coordination of nitrogen ligands to the ruthenium species is important for the oxidation. The green complex formed from a 1:2 mixture of $Ru_2(OAc)_4Cl$ and **1** is soluble in toluene, while $Ru_2(OAc)_4Cl$ alone is insoluble in toluene.

It is noteworthy that the ruthenium complex formed in situ upon treatment of $Ru_2(OAc)_4Cl$ with amine **1** was also found to be highly effective for the oxidation of alcohols. Thus, the aerobic oxidation of benzyl alcohol in the presence of a catalytic amount of $Ru_2(OAc)_4Cl$ and **1** (1:2) gives benzaldehyde in 97% yield, while $Ru_2(OAc)_4Cl$ alone shows no catalytic activity (<1%). The addition of inorganic bases such as K_2CO_3 and NaOAc showed negative effect, indicating that the amine **1** plays an important role as a ligand to the ruthenium rather than a base for deprotonation. The oxidation of primary amine **16** gives the corresponding nitrile **17** in a highly efficient manner (entry 8).

The oxidation of secondary amines can be rationalized by assuming the mechanism shown in Scheme 1. The diruthenium(II,III) core of $Ru_2(OAc)_4Cl$ is tentatively represented as Rn^nRu^n, because the oxidation states of the rutheniums may be electrically symmetric during the reaction.

Initially, secondary amines (RCH_2NHR') coordinate to $Ru_2(OAc)_4Cl$ to give **18** by ligand-exchange reaction. β-Hydride elimination from **18** would give imine–ruthenium hydride species **19**. Insertion of molecular oxygen to the ruthenium hydride species **19** would afford a ruthenium hydroperoxide **20**. Such oxidation of a metal hydride M–H species with molecular oxygen to give M–OOH spe-
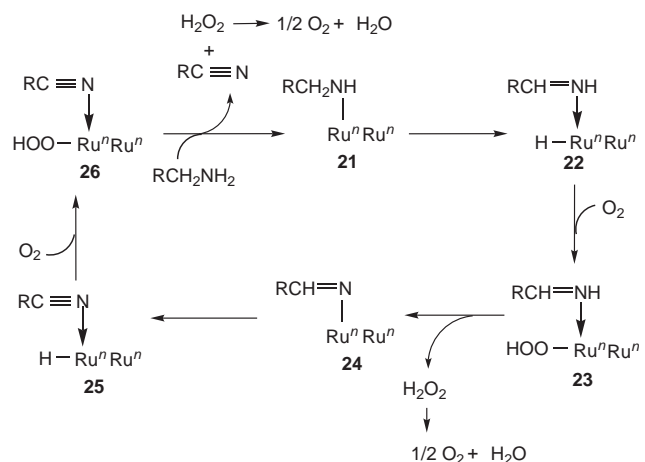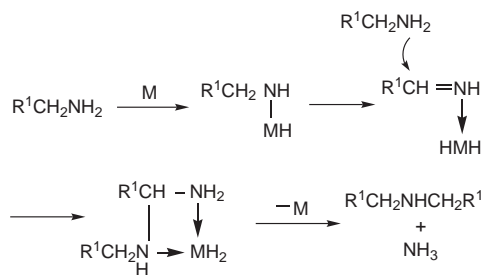
cies was demonstrated for the first time in the asymmetric oxypalladation of allylphenols,[22] and later palladium-catalyzed aerobic oxidation of alcohols,[23] and ruthenium-catalyzed oxidative transformation of primary amines to nitriles.[15] The reaction of **20** with secondary amines would give the product imine, hydrogen peroxide, and recovered the intermediate **18** to complete the catalytic cycle. Control experiments confirmed that hydrogen peroxide thus formed undergoes fast decomposition to give molecular oxygen and water under the reaction conditions; however, hydrogen peroxide does not work as an oxidant for oxidation of amines.[24] The result of the oxygen-uptake measurement also supports this mechanism. One equivalent of molecular oxygen is consumed for the oxidation of two equivalents of **1** under the standard reaction conditions. In this scheme, we describe that the reaction takes place on one ruthenium atom for simplicity; however, it is likely the reaction uses both of the ruthenium atoms. High catalytic activity at low temperature is due to the synergic effect of dinuclear structure of the ruthenium catalyst.

When substrates are primary amines (R′ = H), the reaction proceeds by two-step oxidation via imine intermediate as shown in Scheme 2. The intermediate **22**, which is formed by β-hydride elimination of **21**, undergoes reaction with molecular oxygen to give Ru–OOH species **23**. The intramolecular proton transfer from **23** would give **24** and hydrogen peroxide. Further β-hydride elimination of **24** would give ruthenium hydride species **25**. Insertion of molecular oxygen to the metal hydride of **25** would give **26**, and subsequent reaction with primary amine would give the nitrile, hydrogen peroxide, and recovered **21** to complete the catalytic cycle.

It is noteworthy that the oxidation of primary amines gives the corresponding nitriles rather than the dimeric products in the present system. This is in contrast to the transition-metal-catalyzed alkyl group exchange reaction, giving the dimerization products via addition of an amine to the imine complex as shown in Scheme 3.[25]

Scheme 1

Scheme 2

$$R^1CH_2NH_2 \xrightarrow{\text{M}} R^1CH_2\overset{\overset{\displaystyle NH}{|}}{\underset{\underset{\displaystyle MH}{|}}{}} \longrightarrow R^1CH=NH \xleftarrow{R^1CH_2NH_2}$$

$$\text{HMH}$$

$$\longrightarrow \quad \overset{\displaystyle R^1CH-NH_2}{\underset{\displaystyle R^1CH_2N\overset{}{\underset{\displaystyle H}{}}\rightarrow MH_2}{|}} \xrightarrow{-M} R^1CH_2NHCH_2R^1 + NH_3$$

Scheme 3

Work is in progress to determine the structure of the reactive ruthenium species and to apply this new catalytic system to the other reactions.

Acknowledgment

References

(1) Murahashi, S.-I. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2443.

(2) (a) Murahashi, S.-I.; Komiya, N. *Biomimetic Oxidations Catalyzed by Transition Metal Complexes*; Munier, B., Ed.; Imperial College Press: London, **2000**, 563–611. (b) Murahashi, S.-I.; Imada, Y. *Transition Metals for Organic Synthesis*, 2nd ed., Vol 2; Wiley-VCH: Weinheim, **2004**, 497–507.

(3) Murahashi, S.-I.; Naota, T.; Taki, H. *J. Chem. Soc., Chem. Commun.* **1985**, 613.

(4) (a) Müller, P.; Gilabert, D. M. *Tetrahedron* **1988**, *44*, 7171. (b) Porta, F.; Crotti, C.; Cenini, S.; Palmisano, G. *J. Mol. Catal.* **1989**, *50*, 333.

(5) Goti, A.; Romani, M. *Tetrahedron Lett.* **1994**, *35*, 6567.

(6) Éll, A. H.; Samec, J. S. M.; Brasse, C.; Bäckvall, J.-E. *Chem. Commun.* **2002**, 1144.

(7) Yamazaki, S. *Chem. Lett.* **1992**, 823.

(8) Choi, H.; Doyle, M. P. *Chem. Commun.* **2007**, 745.

(9) (a) Anastas, P.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, **1998**. (b) Punniyamurthy, T.; Velusamy, S.; Iqbal, J. *Chem. Rev.* **2005**, *105*, 2329. (c) Hill, C. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 402. (d) Stahl, S. S. *Angew. Chem. Int. Ed.* **2004**, *43*, 3400. (e) Stahl, S. S. *Science* **2005**, *309*, 1824. (f) Thomas, J. M.; Raja, R. *Catal. Today* **2006**, *117*, 22.

(10) Tang, R.; Diamond, S. E.; Neary, N.; Mares, F. *J. Chem. Soc., Chem. Commun.* **1978**, 562.

(11) Schröder, M.; Griffith, W. P. *J. Chem. Soc., Chem. Commun.* **1979**, 58.

(12) Bailey, A. J.; James, B. R. *Chem. Commun.* **1996**, 2343.

(13) (a) Griffith, W. P.; Reddy, B.; Shoair, A. G. F.; Suriaatmaja, M.; White, A. J. P.; Williams, D. J. *J. Chem. Soc., Dalton Trans.* **1998**, 2819. (b) Griffith, W. P.; Suriaatmaja, M. *Can. J. Chem.* **2001**, *79*, 598.

(14) Mori, K.; Yamaguchi, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Chem. Commun.* **2001**, 461.

(15) Yamaguchi, K.; Mizuno, N. *Angew. Chem. Int. Ed.* **2003**, *42*, 1480.

(16) Gao, S.; Herzig, D.; Wang, B. *Synthesis* **2001**, 544.

(17) Maeda, Y.; Nishimura, T.; Uemura, S. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2399.

(18) Samec, J. S. M.; Éll, A. H.; Bäckvall, J.-E. *Chem. Eur. J.* **2005**, *11*, 2327.

(19) (a) Murahashi, S.-I.; Komiya, N.; Okano, Y.; Sato, H. *The 79th Annual Meeting of Chemical Society of Japan*; Kobe: Japan, **2001**, Abstr. 1H306. (b) Murahashi, S.-I.; Komiya, N.; Okano, Y. JP 2002265430, **2002**.

(20) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407.

(21) Ru$_2$(OAc)$_4$Cl was prepared from RuCl$_3$ with AcOH, Ac$_2$O, and LiCl according to the literature procedure. See: Mitchell, R. W.; Spencer, A.; Wilkinson, G. *J. Chem. Soc., Dalton Trans.* **1973**, 846.

(22) (a) Hosokawa, T.; Uno, T.; Inui, S.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1981**, *103*, 2318. (b) Hosokawa, T.; Murahashi, S.-I. *Acc. Chem. Res.* **1990**, *23*, 49.

(23) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6760.

(24) Murahashi, S.-I.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc.* **2003**, *125*, 15312.

(25) Murahashi, S.-I.; Yoshimura, N.; Tsumiyama, T.; Kojima, T. *J. Am. Chem. Soc.* **1983**, *105*, 5002.