



Ru(PPh₃)(OH)-salen complex: a designer catalyst for chemoselective aerobic oxidation of primary alcohols

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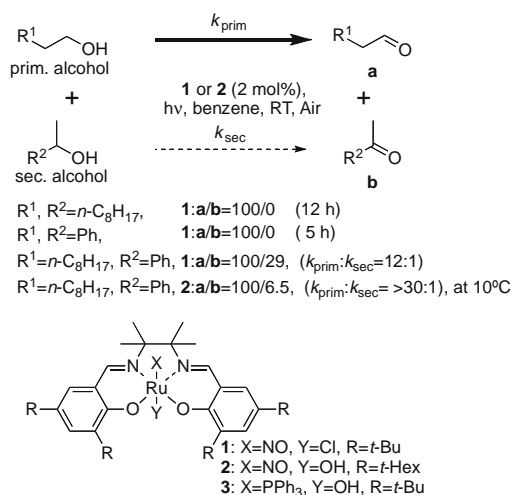
ABSTRACT

Based on the analysis of the mechanism of aerobic oxidation of alcohols using Ru(NO)-salen catalyst, we designed a new complex, Ru(PPh₃)(OH)-salen **3**, which was proved to be an excellent catalyst for chemoselective aerobic oxidation of primary alcohols to the aldehydes in the presence of secondary alcohols under ambient and non-irradiated conditions. Complex **3** was also successfully applied to the oxidation of 1-phenyl-1,*n*-diols to the lactols or the *n*-hydroxy aldehyde. It is of note that selective oxidation of primary alcohols was achieved even in the presence of activated secondary alcohols.

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Aldehydes are useful synthetic intermediates, and the oxidation (dehydrogenation) of primary alcohols is the most conventional method for their synthesis. However, most alcohol substrates are polyols, such as diols and triols, and the chemoselective oxidation of primary alcohols is of tremendous importance for organic synthesis.¹ Although a variety of efficient methods have been developed for this purpose, most of them require a stoichiometric oxidant which generates undesirable waste materials as the coproduct.^{1–5} The ecological sustainability of the dehydrogenation reaction primarily depends on the terminal electron acceptor and the physical properties of the coproduct derived from the acceptor.^{6,7,1c} Among various electron acceptors, molecular oxygen is the most atom efficient, and the accompanying coproduct is water or hydrogen peroxide. In particular, molecular oxygen in air is abundant, safe, and ubiquitous.⁸ Therefore, aerobic oxidations of alcohols using homogeneous⁶ or heterogeneous^{7,1c} transition metal catalysts have been developed, but most of these reactions require the addition of a base, heating, or pressured oxygen. These reactions can be applied generally to the oxidation of both primary and secondary alcohols, but the reports on these reactions generally do not refer to the chemoselectivity between the two oxidations, with the exception of the following. Ishii et al. reported a catalytic version of the Oshima method^{6a} using molecular oxygen as the terminal oxidant.^{6g} Sheldon et al. reported that a CuBr₂/(Bipy)/TEMPO/air system (Bipy=2,2'-bipyridine, TEMPO=2,2,6,6-tetramethylpiperidinyl-1-oxy) catalyzed selective oxidation of primary alcohols in the presence of secondary alcohols under ambient conditions, though oxidation of aliphatic alcohols was slow at these conditions.⁹ Sekar et al. also reported that activated primary alcohols can be selectively oxidized using a CuCl/DABCO/TEMPO/O₂ system (DABCO=1,4-diazabicyclo [2.2.2]octane).¹⁰ On the other

hand, Mizuno and co-workers demonstrated that the Al₂O₃-supported Ru hydroxide-catalyzed oxidation of 4-(1-hydroxy-ethyl)-benzyl alcohol using O₂ at 83 °C gives 4-(1-hydroxyethyl) benzaldehyde with 94% selectivity at >99% conversion, while the intermolecular competitive reaction between the primary and secondary benzylic alcohols proceeded with moderate selectivity.¹¹ Still, the development of an efficient catalyst for chemoselective oxidation between primary and secondary, especially activated secondary, alcohols is a challenging task. Recently, we revealed that Ru(NO)-salen complexes efficiently catalyze aerobic oxidation of alcohols in air under ambient and visible light-irradiated conditions.^{12,13} Among the various Ru(NO)-salen complexes, **1** and **2** efficiently catalyze the selective oxidation of primary alcohols in



Scheme 1.

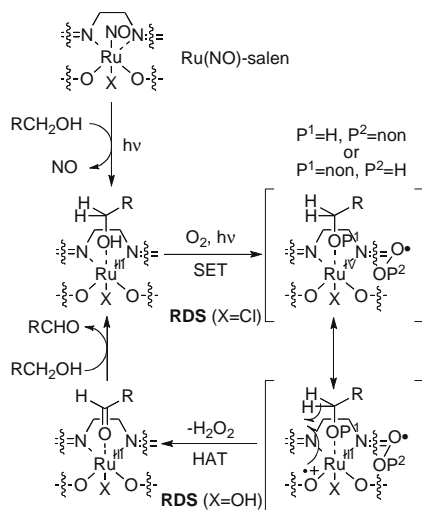
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the presence of secondary alcohols (Scheme 1).¹³ In particular, complex **2** selectively oxidizes aliphatic primary alcohols even in the presence of activated secondary alcohols: for example, the relative oxidation rate between 1-decanol and phenethyl alcohol is >30, while the relative rate in the oxidation using **1** as the catalyst is 12.^{13d} Under these conditions, both aliphatic and activated primary alcohols are oxidized quantitatively to the corresponding aldehydes.¹³ However, the reactions need visible light irradiation, though available light can also be used as the light source. Photo-activation of an asymmetric metal catalyst is a scientifically interesting technique, but irradiation is accompanied by heat evolution, which might make reaction control difficult, especially on a large scale. From a practical point of view, there is still a strong demand for the development of a new catalyst that promotes the chemoselective oxidation of primary alcohols without photo-irradiation or any additive.

The catalytic cycle, including single electron transfer (SET), intramolecular hydrogen atom transfer (HAT), and product/substrate exchange steps, has been proposed for the Ru(NO)-salen-catalyzed aerobic oxidation of alcohols under irradiation, based on the results of the kinetics and kinetic isotope effect studies (Scheme 2).^{12d,13e} It is of note that the rate-determining step (RDS) of this catalytic cycle depends on the nature of the apical ligand (X). For example, the SET step is the RDS when X is an electron-withdrawing Cl group, while the HAT step is RDS when X is a donating OH group. Moreover, the oxidation with the Ru-salen(OH) complex is slower but more chemoselective than that with the Ru-salen(Cl) complex. We speculated that the coordination of a donating ligand reduces the oxidation potential of the Ru(III) ion and the reactivity of the cationic phenol oxygen radical. The oxidation with complex **1** or **2** is commenced by photo-dissociation of the apical NO group and coordination of alcohol.^{12d} We expected that the substitution of the hydroxo ligand on the transition metal ion with an alcohol might occur and, therefore, that the Ru(III)(L)(OH)-salen complex (L = a donating ligand) would be a desired catalyst for the aerobic oxidation of alcohols under non-irradiated conditions. Hence, we investigated the oxidation catalysis of the Ru(PPh₃)(OH)-salen complex **3**.^{14,15} Herein, we communicate the aerobic oxidation of various alcohols using **3** as a catalyst under ambient and non-irradiated conditions (Table 1).

We first examined the oxidation of benzyl alcohol using complex **3** as the catalyst. As expected, the reaction proceeded equally



Scheme 2. Proposed mechanism for Ru(NO)-salen-catalyzed aerobic oxidation of alcohols. The salen ligand is omitted for clarity, except for donor atoms and ethylene carbons.

Table 1

Aerobic oxidation of alcohols in the presence of the Ru(PPh₃)(OH)-salen complex **3** as the catalyst^a

Entry	Mono-ol	Time (h)	Conv. ^b (%)	Yield ^b (%)
1 ^c	Benzyl alcohol	1.5	>99	97
2 ^d	Benzyl alcohol	1.5	>99	97 (93) ^e
3 ^c	1-Decanol	3	98	97
4 ^d	1-Decanol	3	97	97
5 ^c	1-Phenylethanol	4	96	96
6 ^d	1-Phenylethanol	4	93	95
7 ^c	2-Decanol	24	22	20

^a Reaction was run in CDCl₃ (1.0 mL) with substrate (0.5 mmol) and **3** (10 μmol) at room temperature under air.

^b Determined by ¹H NMR analysis (400 MHz) using phenanthrene as an internal standard.

^c The reaction was carried out under light shielding conditions.

^d The reaction was carried out under visible light irradiation.

^e Isolated yield.

well in the dark or under irradiation (entries 1 and 2). The reaction of non-activated primary alcohol, 1-decanol, also proceeded smoothly, irrespective of the reaction conditions (entries 3 and 4). Against our expectation, catalytic activity of **3** was higher than that of **1**, and the reaction of the activated secondary alcohol also proceeded smoothly and gave the ketone in good yields over a slightly extended reaction time (entries 5 and 6). The oxidation of the non-activated secondary alcohol was much slower (entry 7). Over-oxidation of the aldehyde to carboxylic acid was not observed during the oxidation of primary alcohols. Although **3** oxidized both non-activated primary and activated secondary alcohols efficiently, we examined chemoselectivity in the alcohol oxidation using complex **3** under non-irradiated conditions.

Thus, we first examined the relative reaction rate between 1-decanol and 1-phenylethanol in various solvents at room temperature (Table 2, entries 1–4). To our delight, high selectivity [initial reaction ratio (=IRR) > 50] was obtained in the reaction using chloroform as the solvent. Use of other solvents slightly reduced the chemoselectivity. The other competitive oxidation reactions also proceeded with high IRR values greater than 50 under the same conditions (entries 5 and 6). Competitive oxidation between non-activated primary and secondary alcohols or activated primary and secondary alcohols also proceeded with IRR values greater than 50 (entries 7 and 8). This high chemoselectivity may be attributed to the greater ease of the coordination of primary alcohols, compared to that of secondary alcohols.¹⁶

Encouraged by these results, we further examined the oxidation of 1-phenyl-1,*n*-diols (Table 3). The reaction of 1-phenylpropan-1,3-diol was slow. Although 3-hydroxyaldehyde was obtained as the major product at 42% conversion, a complex mixture was produced as the reaction time was extended due to the undesired side reactions (entry 1). On the other hand, oxidation of the other 1,*n*-diols (*n* = 4 and 5) gave the corresponding lactols exclusively, although the formation of small amounts (≤4% yields) of dicarbonyl compounds was detected (entries 2 and 3). The reaction of 1,6-diol also gave the aldehyde with high selectivity (aldehyde/keto-aldehyde = >50) at 38% conversion, and the hydroxy aldehyde was the major product even at the extended reaction time (entries 4 and 5). Formation of a hydroxy ketone was not detected in these reactions (entries 1–5). It is of note that the reaction with the Ru(O=PPh₃)(OH)-salen complex showed modest regioselectivity (entry 6), suggesting that the PPh₃ ligand does not dissociate from the ruthenium ion during the oxidation.

In conclusion, we synthesized the Ru(PPh₃)(OH)-salen complex **3**, based on the analysis of the mechanism of the (ON)Ru(salen)-catalyzed oxidation. This complex was found to be excellent catalyst for the primary selective aerobic oxidation of alcohols to the aldehydes under non-irradiated conditions. Oxidation of 1-phenyl-

Table 2
Primary selective aerobic oxidation of alcohols using complex **3** as the catalyst^a

Entry	Solvent	Alcohols	Yield (%) ^b RCHO/RCOR'	IRR ^c
1	CHCl ₃	1-Decanol/1-phenylethanol	93/8	>50
2 ^d	CH ₂ Cl ₂	1-Decanol/1-phenylethanol	85/9 ^e	50
3 ^d	Hexane	1-Decanol/1-phenylethanol	90/11 ^e	34
4 ^d	AcOEt	1-Decanol/1-phenylethanol	94/12 ^e	30
5 ^d	CHCl ₃	1-Decanol/1-(4-methoxy-phenyl)ethanol	78/5	>50
6 ^d	CHCl ₃	1-Decanol/1-(4-chlorophenyl)ethanol	80/4	>50
7	CHCl ₃	1-Decanol/2-decanol	>99/1	>50
8	CHCl ₃	Benzyl alcohol/1-phenylethanol	99/2	>50

^a Reaction was run in solvent (5.0 mL) with alcohols (0.5 mmol each) and complex **3** (10.0 μmol) at room temperature under air.

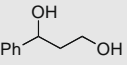
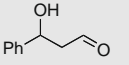
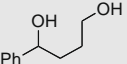
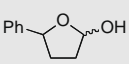
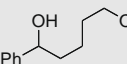
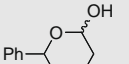
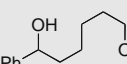
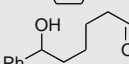
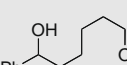
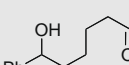
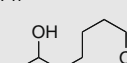
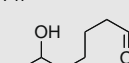
^b Determined by ¹H NMR analysis using phenanthrene as the internal standard.

^c IRR value was calculated based on the yields of aldehydes and ketones at ca. 20% conversion: IRR = (% yield of aldehyde)/(% yield of ketone) × 100.

^d The reaction was run on a 0.1 mmol scale.

^e Determined by GLC analysis using bicyclohexyl as the internal standard.

Table 3
Ru-salen complex **3**-catalyzed intramolecular selective aerobic oxidation of diols^a

Entry	Diols	Product	Time (h)	Conv. ^b (%)	Yield ^b (%)
1			5	42	41
2			5	>99	96 (4) ^c
3			6	99	95 (4) ^c
4			1	38	38 (<0.5) ^c
5			2	78	73 (5) ^c
6 ^{d,e}			6	>99	51 (23) ^c

^a Reaction was run in CDCl₃ (5.0 mL) with 0.5 mmol of substrate and complex **3** (10.0 μmol) at room temperature under air.

^b Determined by ¹H NMR analysis using phenanthrene as the internal standard.

^c Yield of keto-aldehyde.

^d The reaction was run on a 0.1 mmol scale.

^e Using 2 mol% of Ru(O=PPh₃)(OH)-salen complex as a catalyst.

nyl-1,1-diols also proceeded to give the corresponding lactols or *n*-hydroxy aldehyde in good yields.

The typical experimental procedure for the aerobic oxidation of alcohols using **3** as the catalyst is as follows, First, to a 2.0 M solution of Ru(PPh₃)(OH)-salen complex in CHCl₃ (5 mL) was added benzyl alcohol (54.0 mg, 0.5 mmol). The mixture was stirred for 1.5 h under ambient conditions, concentrated by rotary evaporation, and chromatographed on silica gel (hexane/AcOEt = 5:1) to give benzaldehyde (50.8 mg, 93%).

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14. Ru(PPh₃)₂-salen and Ru(PPh₃)(X)-salen complexes [X = Cl, OAc, Cl, ClO₄, NO₃⁻] prepared from Ru(PPh₃)₃Cl₂ have been used as the catalyst for the coupling of carbon dioxide and epoxides, aldehyde olefination, cyclopropanation, and amidation of silyl enol ether: (a) Murray, K. S.; Bergen, A. M.; West, B. O. *Aust. J. Chem.* **1978**, *31*, 203–207; (b) Stephenson, T. A.; Wilkinson, G. *J. Inorg. Nucl. Chem.* **1966**, *28*, 945–956; (c) Jing, H.; Chang, T.; Jin, L.; Wu, M.; Qiu, W. *Catal. Commun.* **2007**, *8*, 1630–1634; (d) Syukri, S.; Sun, W.; Kuehn, P. E. *Tetrahedron Lett.* **2007**, *48*, 1613–1617; (e) Li, G.-Y.; Zhang, J.; Chan, P. W. H.; Xu, Z.-J.; Zhu, N.; Che, C.-M. *Organometallics* **2006**, *25*, 1676–1688; (f) Liang, J.-L.; Yu, X.-Q.; Che, C.-M. *Chem. Commun.* **2002**, 124–125; (g) Pointillart, F.; Bernot, K.; Sorace, L.; Sessoli, R.; Gatteschi, D. *Dalton Trans.* **2007**, 2689–2695.
15. Complex **3** could not be synthesized from Ru(PPh₃)₃Cl₂ according to the reported procedure (Ref. 14); however, it was synthesized from Ru(NO)Cl₃(PPh)₂ with a slight modification of Sessoli's procedure (Ref. 14g): Salen-H₂ (110 mg, 0.2 mmol) and Ru(NO)Cl₃(PPh)₂ (175 mg, 0.26 mmol) were suspended into 20 mL of EtOH. To the suspension was added 0.2 mL of ethyldiisopropylamine. The mixture was heated at reflux. After 24 h, the solvent was removed by rotary evaporation. The resulting residue was chromatographed on silica gel (CH₂Cl₂/EtOH/AcOEt = 20:1:2) to afford Ru(PPh₃)(OH)-salen complex **3** (34.5 mg, 19%).
16. In ¹H NMR analysis, the α- and β-protons of 1-decanol and of 1-phenyletanol appear at 3.65 and 1.57 ppm and at 4.89 and 1.50 ppm, respectively. When complex **3** (1 equiv) was added to the CDCl₃ solution of these alcohols (1 equiv each) under nitrogen atmosphere, all the signals of the alcohols were broadened, and the signals at 3.65 and 1.57 shifted upfield by ca. 0.01 and 0.02 ppm after 3 h and by 0.02 and 0.03 ppm after 7 h. No more shift was observed, even if the measuring time was extended. On the other hand, the signals at 4.89 and 1.50 ppm did not shift. These ¹H NMR data suggest that the coordination of 1-decanol to ruthenium ion is kinetically and thermodynamically more favorable than that of 1-phenyletanol. It should be noted that the aforementioned NMR data depend on the catalyst used. Freshly prepared catalyst was used for this experiment.