Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 46 (2005) 6049–6052

Tetrahedron Letters

A reasonable explanation for the mechanism of photo-promoted chemoselective aerobic oxidation of alcohols using (ON)Ru(salen) complex as catalyst

Hiromichi Egami, Satoaki Onitsuka and Tsutomu Katsuki*

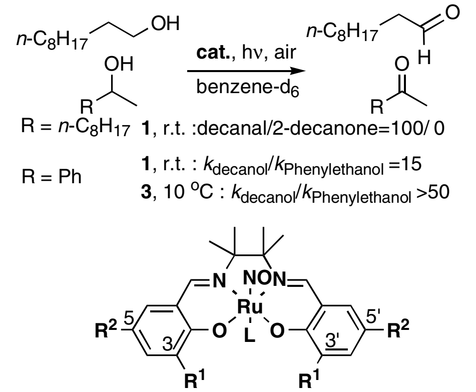
Department of Chemistry, Faculty of Science, Graduate School, Kyushu University 33, CREST, Japan Science and Technology Agency (JST), 6-10-1 Hakozaki, Higashi-ku, Fukuoka 812-8581, Japan

Received 7 June 2005; revised 1 July 2005; accepted 4 July 2005
Available online 18 July 2005

Abstract—The mechanism of aerobic oxidation of alcohols using (ON)Ru(salen) complex as catalyst under photo-irradiation was examined through studies of kinetics of the oxidation, kinetic isotope effect in the oxidation, and effect of the ligand structure on the chemoselectivity of the oxidation of primary and secondary alcohols. It was demonstrated that the aerobic oxidation includes an intramolecular hydrogen atom transfer process that is attributed to realization of efficient differentiation of primary and secondary alcohols in the oxidation.

© 2005 Elsevier Ltd. All rights reserved.

Oxidation of primary alcohols to aldehyde, especially in the presence of secondary alcohols, is an important topic in organic synthesis and many methodologies have been developed.[1,2] Of the various methods, aerobic oxidation or oxidation using molecular oxygen as the stoichiometric oxidant has attracted the attention of chemists due to its high atom efficiency and ecological benignity.[3,4] Some of the reported aerobic oxidations show high chemoselectivity, but the addition of some mediator[4a–c,p] or forced conditions[4e,f,n] are required for such reactions. We have recently found that (ON)Ru(salen) complexes catalyze aerobic oxidation at room temperature under irradiation of visible light in the absence of any additive.[3e] In the course of the study on this aerobic oxidation, (ON)Ru(salen) complex **1** that bears the 1,1,2,2-tetramethylethylene-diamine unit was found to catalyze selective aerobic oxidation of primary alcohols in the presence of secondary alcohols (Scheme 1).[5] Complex **1** had been designed on the assumption that two of the four methyl groups should adopt pseudo-axial orientation and the alkyl part of the incoming alcohols would be directed away from the axial methyl group and a bulkier alkyl part should cause stronger steric interaction with the C3- or C3′-*tert*-butyl group: oxidation of secondary alcohols is slower than that of primary alcohols. Along this line, we further designed (ON)Ru(salen) complexes (**2** and **3**) bearing a 1-ethyl-1-methylpropyl group at C3, C3′, C5, and C5′, in which C3- and C3′-substituents were expected to adopt a C–Me in-plane conformation and the two ethyl groups protrude above and below the basal salen plane, increasing steric



1: R^1=R^2= *tert*-Bu, L = Cl

2: R^1=R^2= 1-ethyl-1-methylpropyl, L = Cl

3: R^1=R^2= 1-ethyl-1-methylpropyl, L = OH

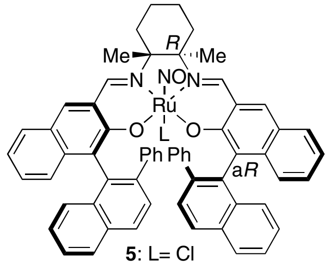
4: R^1=R^2= *tert*-Bu, L = OH

Scheme 1.

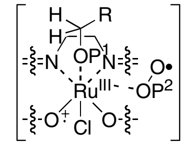
Keywords: (ON)Ru(salen) complex; Aerobic oxidation; Intramolecular hydrogen atom transfer.

* Corresponding author. Fax: +81 92 642 2607; e-mail: katsuscc@mbox.nc.kyushu-u.ac.jp

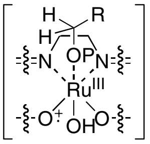
0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.07.005



5: L= Cl
6: L= OH



A: P^1= H, P^2= non or
P^1= non, P^2= H



B: P = H
P = non

Figure 1.

Table 1. Kinetic isotope effect for (ON)Ru(salen)-catalyzed oxidation of alcohols[a]

Entry	Substrate (R)	Catalyst	KIE (k_H/k_D)[b]
1	$Ph(CH_2)_2CHDOH$	**1**	9.8 ± 0.3
2	$Ph(CH_2)_2CHDOH$	**4**	7.9 ± 0.4
3	$Ph(CH_2)_3OH/Ph(CH_2)_2CD_2OH$	**1**	8.8 ± 0.4
4	$Ph(CH_2)_3OH/Ph(CH_2)_2CD_2OH$	**4**	5.05 ± 0.06
5[c]	$Ph(CH_2)_3OH/Ph(CH_2)_2CD_2OH$	**1**	1.5 ± 0.2
6[c]	$Ph(CH_2)_3OH/Ph(CH_2)_2CD_2OH$	**4**	2.6 ± 0.3

[a] Reactions were carried out for 24 h in C_6D_6 at room temperature under irradiation with a halogen lamp using 2 mol % of catalyst. 2-Bromonaphthalene was used as the internal standard.

[b] Average of four runs.

[c] Independent measurement was examined under the same condition.

effectiveness of the C3- and C3′-groups remarkably.[6] As expected, primary alcohols were selectively oxidized even in the presence of activated secondary alcohols such as 1-phenylethanol, especially when complex **3** bearing an apical hydroxo ligand was used as catalyst.

On the other hand, our recent study on the mechanism of aerobic oxidation of mono-ols using (ON)Ru(salen) complexes (**5** and **6**) as catalyst disclosed that hydrogen atom transfer (HAT) from their α-carbons occurs in an intramolecular way via oxygen radical intermediates (**A** and **B**), respectively (Fig. 1, vide infra).[7c] In contrast to the above assumption, this mechanistic study means that the alkyl part of the mono-ol is forced to come close to the C3- and C3′-substituent sites at the event of hydrogen atom transfer not by the steric but by the mechanistic reason. However, the oxygen radicals in **A** and **B** are stabilized by the resonance with the naphthalene ring, but complexes **1** and **3** possess a benzene ring in place of the naphthalene ring. Thus, we examined if the proposed mechanism for the oxidation using **5** or **6** can be applied to the oxidation using usual (ON)Ru(salen) complexes such as **1**. We then examined the kinetics and kinetic isotopic effect in the oxidation using **1** and **4** as catalyst.

The kinetics of the oxidation using complexes **1** and **4** as catalyst were determined by using 1-decanol as the test material: the rate law for the oxidation with **1** was rate = k[1-decanol][**1**][O_2]$^{0.1}$, while the rate law for the oxidation with **4** was rate = k[**4**].[8] The observed kinetics with **1** and **4** were similar to those for the oxidation with **5** and **6** (rate = k[alcohol][**5**][O_2] and rate = k[**6**][O_2]$^{0.42}$), respectively, except that the influence of the oxygen pressure to the rate was markedly reduced: the ligand exchange exclusively contributed to the rate-determining step (RDS) for the oxidation with **1**, while HAT was the RDS for the oxidation with **4**. We also examined kinetic isotopic effect (KIE) for the oxidation using complexes **1** and **4** under three different conditions (intra- and intermolecular competitive conditions and independent measurement conditions) and the observed H/D relative reaction rates (k_H/k_D) are summarized in Table 1. The two k_H/k_D values obtained under competitive conditions directly reflect KIE for HAT but the value obtained by the third method depends not only on the KIE in RDS but also on the reaction coordinate of the oxidation: if the HAT is not the RDS of the oxidation, the k_H/k_D value measured by the third method should be small.[7c] The k_H/k_D values reported for HAT from α-methylene of metal alkoxide in oxidation with galactose oxidase or its model compounds, a Cu(II)-Schiff base catalyst, and a Cu(I)-TEMPO system, range from 3 to 7.[9,10] The k_H/k_D values measured under intra- and intermolecular competitive conditions with **1** and **4** were 9.8, 7.9, 8.8, and 5.05, respectively, and these values indicated that the hydrogen atom was abstracted from the α-methylene carbon and the oxygen radical was generated on the phenol oxygen atom (entries 1–4).[7c] Intermolecular KIEs determined by independent measurement were found to be 1.5 and 2.6 for the oxidation with **1** and **4**, respectively (entries 5 and 6). These results support the above-described kinetics: HAT is not RDS for the oxidation with **1**, while HAT is RDS for the oxidation with **4**. However, if only HAT step contributes to the TS of the oxidation, the intermolecular KIE value does not depend on its measurement method. Indeed, the intermolecular KIEs observed for the oxidation of $Ph(CH_2)_3OH/Ph(CH_2)_2CD_2OH$ using **6** as catalyst under competitive and independent measurements are similar values [3.42 and 2.51 (KIE_{compet}/KIE_{indep} = 1.36), respectively].[7c] On the other hand, the KIE_{compet}/KIE_{indep} value observed for the oxidation using **4** was 1.94 (cf. entries 4 and 6).[11] This indicated that the KIEs for the latter oxidation might depend on measurement method, though the kinetics and the kinetic isotope effect of the oxidation unambiguously demonstrated that the HAT was the RDS of the oxidation. These paradoxical phenomena may be explained if the product serves as a week catalytic poison. Thus, we examined the oxidation of $Ph(CH_2)_3OH$ by using **4** or **6** as catalyst in the absence or the presence of an equimolar amount of $Ph(CH_2)_2CHO$. Indeed, the oxidation rate of the alcohol in the absence of the aldehyde was 2.3 times faster than that in the presence of the aldehyde, when the catalyst was **4**. On the other hand, the oxidation rate of the alcohol did little depend on the presence or absence of the aldehyde, when **6** was used as catalyst. Since the selectivity of the oxidation using **4** or **6** is high

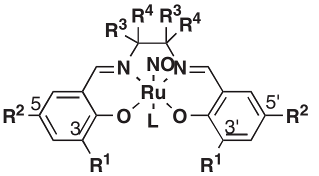
Table 2. IRR between 1-decanol and 1-phenylethanol observed with complexes (**1**, **4**, and **8**–**13**)[a]

Entry	Catalyst	IRR (1-decanol/1-phenylethanol)
1	**1**	15
2	**4**	18
3	**8**	9
4	**9**	14
5	**10**	6
6	**11**	5.5
7	**12**	4
8	**13**	13.5

[a] Reactions were carried out for 24 h in C_6D_6 at room temperature under irradiation with a halogen lamp by using 2 mol % of catalyst, unless otherwise mentioned. Pentamethylbenzene was used as the internal standard.

and formation of a product other than the aldehyde is unlikely, these results support the assumption that the aldehyde produced could be a week catalytic poison for catalyst **4**. However, it is unclear why the aldehyde coordinates with complexes **4** and **6** differently.

We further examined the oxidation of 1-decanol in the presence of 1-phenylethanol using several (ON)Ru-(salen) complexes (**1**, **4**, and **8**–**13**) (Table 2). Initial reaction ratios (IRRs) between 1-decanol and 1-phenylethanol were calculated from the following equation: IRR = (% yield of decanal)/(% yield of acetophenone), at ca. 20% conversion of 1-decanol. The IRRs of the oxidation with **8** or **9**, which has no pseudo-axial methyl group at the diamine unit were 9 and 14, respectively (entries 3 and 4). On the other hand, the IRRs of the oxidation with **10** or **11**, which has no substituent at C3, C3′ of the salen ligand were 6 and 5.5, respectively (entries 5 and 6). These results suggested that the IRR is primarily determined by steric repulsion between the alkyl part of alcohols and the ligand substituents, mainly the substituents at C3 and C3′ (cf., entries 3, 5, 7, and 8) and the orientation of the alkyl part is not dictated by the steric factor but is due to mechanistic reason (Fig. 2). This agreed with the above discussions. However, the presence of the pseudo-axial methyl group increased the IRR to some extent, probably because coordination of a bulkier alcohol becomes disfavored by the presence of the axial methyl group (cf. entries 1–4). It is noteworthy that the effect of the pseudo-axial methyl group was influenced by the location of RDS (cf., entries 3 and 4, and entries 5 and 6).



8: $R^1=R^2=$ *tert*-Bu, $R^3=-(CH_2)_4-$, $R^4=$ H, L = Cl

9: $R^1=R^2=$ *tert*-Bu, $R^3=-(CH_2)_4-$, $R^4=$ H, L = OH

10: $R^1=$ H, $R^2=$ *tert*-Bu, $R^3=R^4=$ Me, L = Cl

11: $R^1=$ H, $R^2=$ *tert*-Bu, $R^3=R^4=$ Me, L = OH

12: $R^1=$ H, $R^2=$ H, $R^3=R^4=$ Me, L = Cl

13: $R^1=$ *tert*-Bu, $R^2=$ H, $R^3=R^4=$ Me, L = Cl

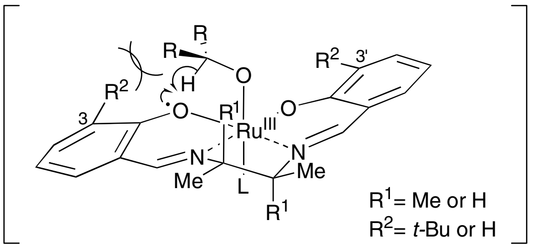
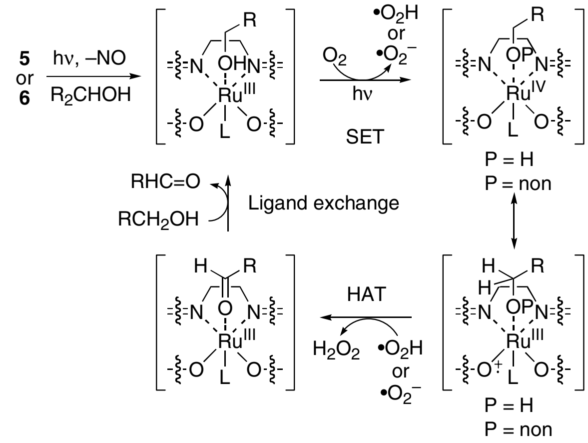


Figure 2.



Scheme 2.

Our previous study on the mechanism of aerobic oxidation of alcohols and oxidative desymmetrization of *meso*-diols using complexes (**5** and **6**) has disclosed that the catalytic cycles of these oxidations include SET, HAT, and ligand exchange steps (Scheme 2). The present study supported that the oxidation of alcohols using **1** and **4** as catalyst also proceeds through the same catalytic cycle (Fig. 2), though the influence of the oxygen pressure to the rate was markedly reduced. Therefore, high chemoselectivity observed in the oxidation using complexes **1**–**4** is mainly attributed to steric repulsion caused by the intramolecular HAT step; however, the effect of the axial substituent on chemoselectivity can not be completely ruled out, especially when ligand exchange step is the RDS for oxidation (vide supra).

General procedure for the determination of IRR: primary and secondary alcohols (0.1 mmol, each) were weighed into a Schlenk tube (Pyrex) followed by addition of pentamethylbenzene (0.1 mmol) as an internal standard and benzene-d_6 (1 mL). An aliquot was taken out of the tube and submitted to ^{1}H NMR (400 MHz) analysis to adjust the molar ratio of the components. Ru complex (2 μmol) was added to the solution and the mixture was vigorously stirred with irradiation using a halogen lamp (150 W) in air. The reaction mixture was traced by ^{1}H NMR analysis to calculate the ratio of unreacted alcohols, aldehyde, and ketone. In all the reactions, the mass balances were excellent and no formation of carboxylic acid was detected.

In conclusion, based on the present study, we propose a new mechanism for photo-promoted chemoselective oxidation of alcohols using (ON)Ru(salen) complexes **1** and **4** as catalyst, in which the intramolecular HAT step is responsible for chemoselection by the catalysts. Kinetics and kinetic isotope effects observed in the oxidations with complexes (**1** and **4**) and with complexes (**5** and **6**) were found to be similar, though the influence of the oxygen pressure to the rate was markedly reduced in the oxidation using **1** or **4**, as compared with the oxidation using **5** or **6**. The reason for the reduced influence of the oxygen pressure is unclear.

References and notes

1. (a) Ley, S. V.; Madin, A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Ley, S. V., Eds.; Pergamon Press: Oxford, 1991; Vol. 7, pp 251–289; (b) Lee, T. V. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Ley, S. V., Eds.; Pergamon Press: Oxford, 1991; Vol. 7, pp 291–303; (c) Procter, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Ley, S. V., Eds.; Pergamon Press: Oxford, 1991; Vol. 7, pp 305–327.
2. For non-aerobic highly chemoselective oxidation of primary alcohols, (a) Tomioka, H.; Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1605–1608; (b) Saint-Arnan, E.; Menage, S.; Pierre, J.-L.; Defrancq, E.; Gellon, G. *New J. Chem.* **1998**, 393; (c) Luca, L. D.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 3041; (d) Matsuo, J.; Iida, D.; Yamanaka, H.; Mukaiyama, T. *Tetrahedron* **2003**, *59*, 6739.
3. (a) Sheldon, R. A.; Arends, I. W. C. E. In *Advances in Catalytic Activation of Dioxygen by Metal Complexes*; Simandi, L. I., Ed.; Kluwer Academic: Dordrecht, 2003, p 123; (b) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750–6755; (c) Markó, I.-E.; Giles, P.-R.; Tsukazaki, M.; Brown, S.-M.; Urch, C.-J. *Science* **1996**, *274*, 2044–2046; (d) Stolz, B. M. *Chem. Lett.* **2004**, *33*, 362–367; (e) Irie, R.; Katsuki, T. *Chem. Rec.* **2004**, *4*, 96–109.
4. (a) Hanyu, A.; Takezawa, E.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **1998**, *39*, 5557–5560; (b) Semmelhack, M. F.; Schmid, C. R.; Cortes, D. A.; Chou, C. S. *J. Am. Chem. Soc.* **1984**, *106*, 3374–3376; (c) Gamez, P.; Arends, I. W. C. E.; Reedijk, J.; Sheldon, R. A. *Chem. Commun.* **2003**, 2414–2425; (d) Choi, K.-M.; Akita, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *New J. Chem.* **2003**, *27*, 324–328; (e) Hasan, M.; Musawir, M.; Davey, P. N.; Kozhevnikov, I. V. *J. Mol. Catal. A* **2002**, *180*, 77–84; (f) Lorber, C. Y.; Smidt, S. P.; Osborn, J. A. *Eur. J. Inorg. Chem.* **2000**, 655–658; (g) Ebitani, K.; Fujie, Y.; Kaneda, K. *Langmuir* **1999**, *15*, 3557–3562; (h) Hinzen, B.; Lenz, R.; Ley, S. V. *Synthesis* **1998**, 977–979; (i) Kaneda, K.; Fujie, Y.; Ebitani, K. *Tetrahedron Lett.* **1997**, *38*, 9023–9026; (j) Liu, X.; Qiu, A.; Sawyer, D. T. *J. Am. Chem. Soc.* **1993**, *115*, 3239–3243; (k) Bilgrien, C.; Davis, S.; Drago, R. J. *Am. Chem. Soc.* **1997**, *109*, 3786–3787; (l) Musawir, M.; Davey, P. N.; Kelly, G.; Kozhevnikov, I. V. *Chem. Commun.* **2003**, 1414–1415; (m) Matsumoto, M.; Ito, S. *J. Chem. Soc., Chem. Commun.* **1981**, 907–908; (n) Matsumoto, M.; Watanabe, N. *J. Org. Chem.* **1984**, *49*, 3436–3437; (o) Uozumi, Y.; Nakano, R. *Angew. Chem., Int. Ed.* **2003**, *42*, 194–197; (p) Gamez, P.; Arends, I. W. C. E.; Reedijk, J.; Sheldon, R. A. *Chem. Commun.* **2003**, 2414–2415.
5. (a) Miyata, A.; Murakami, M.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* **2001**, *42*, 7067–7070; (b) Miyata, A.; Furukawa, M.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* **2002**, *43*, 3481–3484.
6. (a) Egami, H.; Shimizu, H.; Katsuki, T. *Tetrahedron Lett.* **2005**, *46*, 783–786; (b) Gaquere, A.; Liang, S.; Hus, F.-L.; Bu, X. R. *Tetrahedron: Asymmetry* **2002**, *13*, 2089–2093.
7. (a) Shimizu, H.; Nakata, K.; Katsuki, T. *Chem. Lett.* **2002**, 1080–1081; (b) Shimizu, H.; Katsuki, T. *Chem. Lett.* **2003**, *32*, 480–481; (c) Shimizu, H.; Onitsuka, S.; Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2005**, *127*, 5396–5413.
8. For determination of the rate raws, see Ref. 7c: irradiation of a (nitrosyl)Ru(salen) complex in air gives the corresponding nitrosyl-free Ru(salen) complexes at the early stage of the oxidation under the conditions.
9. (a) Minasian, S. G.; Whittaker, M. M.; Whittaker, J. W. *Biochemistry* **2004**, *43*, 13683–13693; (b) Pratt, R. C.; Stack, T. D. P. *J. Am. Chem. Soc.* **2003**, *125*, 8716–8717; (c) Whittaker, M. M.; Whittaker, J. W. *Biochemistry* **2001**, *40*, 7140–7148; (d) Wang, Y.; DuBois, J. L.; Hedman, B.; Hodgson, K. O.; Stack, T. D. P. *Science* **1998**, *279*, 537–540; (e) Dijksman, A.; Arends, I. W. C. E.; Sheldon, R. A. *Org. Biomol. Chem.* **2003**, *1*, 3232–3237.
10. A similar mechanism including intramolecular hydrogen atom transfer has been proposed for Cu(II)-Schiff base-catalyzed aerobic oxidation of alcohols (Ref. 9d).
11. A reviewer of this manuscript pointed out that the present $\text{KIE}_{\text{compet}}/\text{KIE}_{\text{indep}}$ value may be too large, if only HAT contributes to the TS of the oxidation. This comment led us to an idea that the product might behave as a catalytic poison. The authors are grateful to him for this comment.