



# Chemoselective aerobic oxidation of primary alcohols catalyzed by a ruthenium complex

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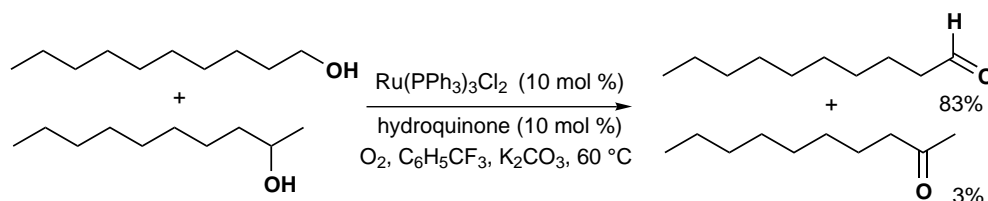
**Abstract**—In the presence of secondary alcohols, primary alcohols are selectively oxidized to aldehydes under aerobic conditions by using a (nitrosyl)Ru(salen) complex as catalyst. © 2001 Elsevier Science Ltd. All rights reserved.

Oxidation of primary alcohols to aldehydes is transformation of tremendous importance in organic synthesis<sup>1</sup> and many transition metal compounds have been used for this purpose. Ruthenium compounds are intensively studied transition metal compounds and many methodologies have been developed with them.<sup>2</sup> However, stoichiometric chemical oxidants were needed in most cases. Use of air or molecular oxygen as the terminal oxidant is desirable from economical and environmental points of view. Recently, several aerobic oxidations of alcohols have been reported.<sup>3,4</sup> However, most of them oxidize not only primary alcohols but also secondary alcohols.<sup>5</sup> Oshima et al. reported that primary alcohols are selectively oxidized to aldehydes in the presence of secondary alcohols by using stoichiometric Ru(PPh<sub>3</sub>)<sub>3</sub>Cl<sub>2</sub> or a Ru(PPh<sub>3</sub>)<sub>3</sub>Cl<sub>2</sub> and TMSOOTMS system.<sup>2c,e</sup> Ishii et al. successfully achieved aerobic oxidation using Ru(PPh<sub>3</sub>)<sub>3</sub>Cl<sub>2</sub> as the catalyst in the presence of hydroquinone without diminishing chemoselectivity (Scheme 1).<sup>6</sup> Hydroquinone has been considered to be oxidized in situ to benzoquinone, which participates in the oxidative recycling of the ruthenium species.

We recently found that (nitrosyl)Ru(salen) **1**-catalyzed

aerobic oxidation of racemic secondary alcohols under photo-irradiation with good enantiomer-differentiation (Scheme 2).<sup>7</sup> Since the ruthenium ion is directly oxidized by oxygen through single electron-transfer, a mediator such as hydroquinone is not necessary for this reaction. To take advantage of this reaction, we examined (nitrosyl)Ru(salen)-catalyzed oxidation of primary alcohols.

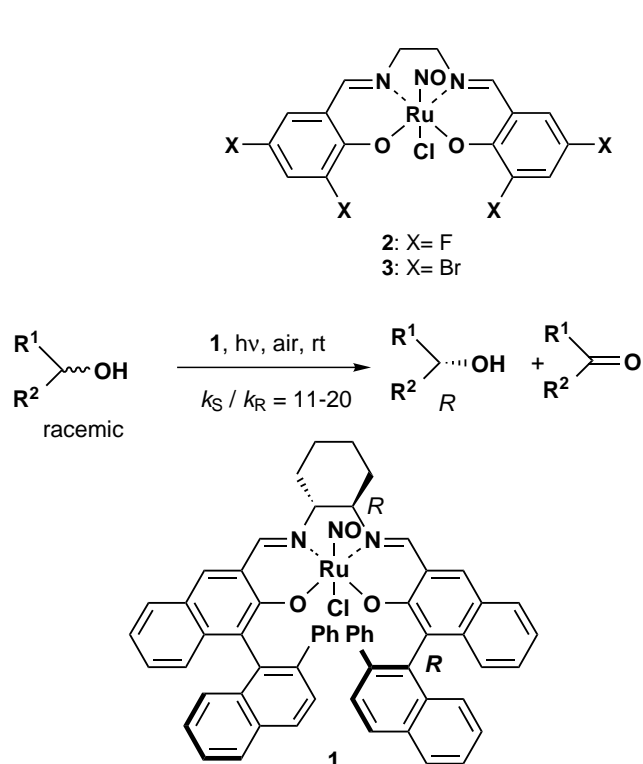
We first synthesized (nitrosyl)Ru(salen) **2** and **3** bearing electron-withdrawing groups, expecting enhancement of catalytic activity and catalyst stability by introducing such groups. Contrary to our expectation, however, complexes **2** and **3** showed poor catalytic activity. The poor catalytic activity was partly attributed to the fact that the single electron transfer is retarded by introduction of the electron-withdrawing group. Accordingly, we next synthesized poly-alkylated (nitrosyl)Ru(salen) **4**. It has been reported that a five-membered chelate ring formed by the ruthenium ion and the ethylenediamine unit in cationic (nitrosyl)Ru(salen) adopts a half-chair conformation.<sup>8</sup> Therefore, we expected that two of the four methyl groups at the ethylenediamine unit in **4** occupy pseudo-axial position.



**Scheme 1.**

**Keywords:** Ru(salen); oxidation; oxygen; primary alcohol; aldehyde; photo-irradiation.

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Scheme 2.

On the other hand, the above-described (ON)Ru(salen)-catalyzed oxidation of secondary alcohols is considered to follow the sequence: (i) dissociation of the nitrosyl group by photo-irradiation, (ii) oxidation of the resulting Ru(III) complex **5** via single electron transfer, (iii) coordination of alcohol to the Ru(IV) species and (iv) oxidation of alcohol to ketone via hydrogen atom and proton abstraction, regenerating complex **5** (Scheme 3).<sup>7,9</sup> We considered that the alcohols approaching the Ru(IV) species derived from complex **4** should suffer 1,3-diaxial repulsion (Fig. 1) and that primary alcohols should coordinate to the ruthenium(IV) ion in preference to secondary alcohols and be selectively oxidized.

Based on this analysis, we studied the relative aerobic oxidation rate between primary and secondary alcohols by using complex **4** as the catalyst under photo-irradiation (Scheme 4). As expected, primary alcohols were selectively oxidized at room temperature under the conditions. No oxidation of secondary alcohols was observed in the competitive reactions of 1-/2-decanols

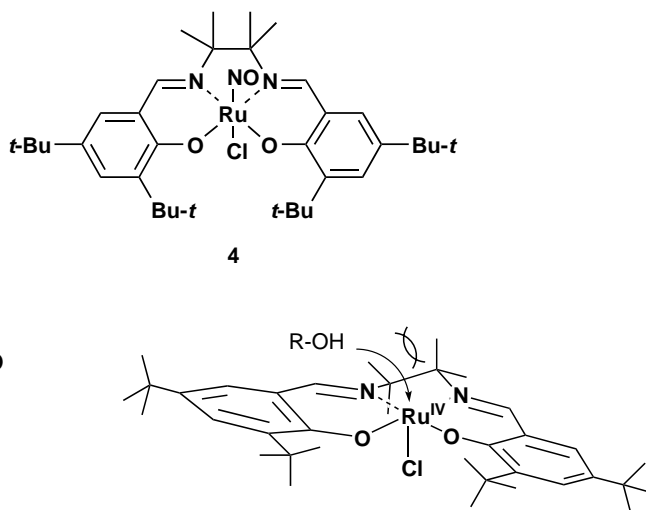


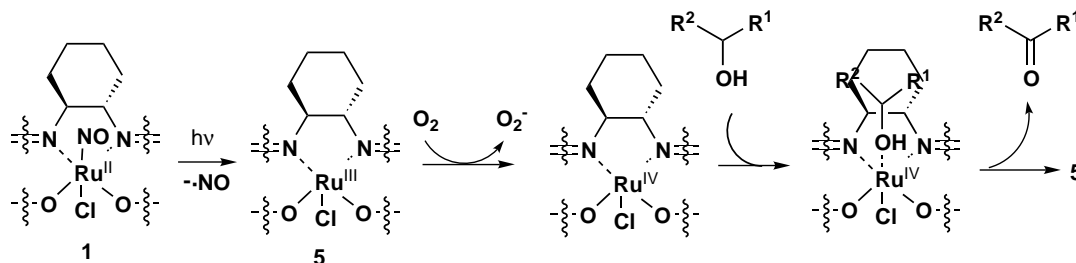
Figure 1.

and benzyl/phenethyl alcohols. Even in the presence of secondary benzylic alcohol, non-activated primary alcohol was oxidized much faster (relative rate >12), though the amount of ketone was gradually increased as the reaction time was prolonged.

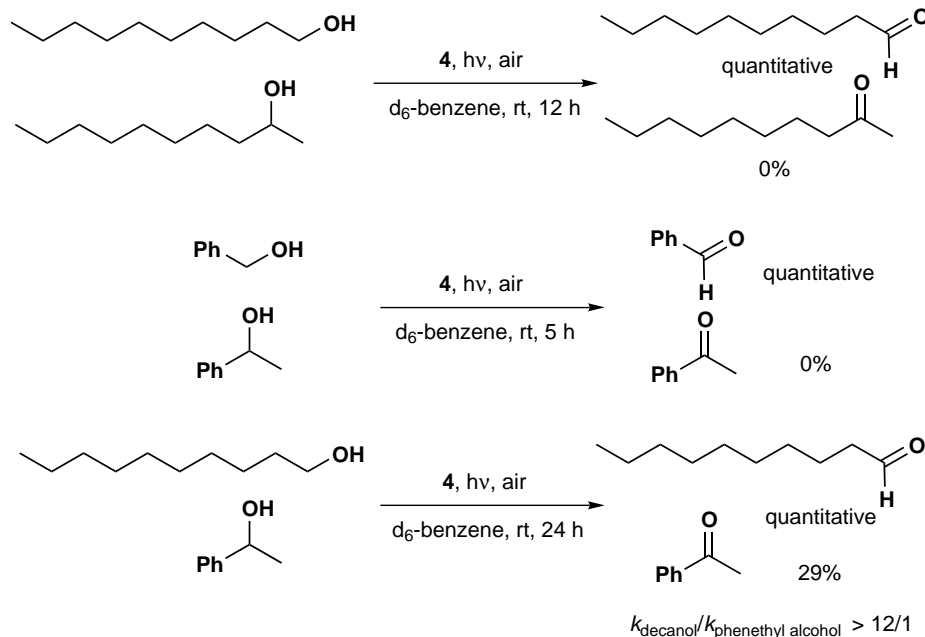
Functionalized primary alcohols were also oxidized in quantitative yields under the present reaction conditions except for *p*-cyanobenzyl alcohol (Scheme 5). The cyano group of the latter compound was considered to strongly coordinate to the ruthenium ion of the catalyst, poisoning the catalytic activity.

It is noteworthy that the resulting aldehyde was not oxidized to the corresponding carboxylic acids, though aldehydes served as co-reductants under Mukaiyama aerobic oxidations.<sup>10</sup>

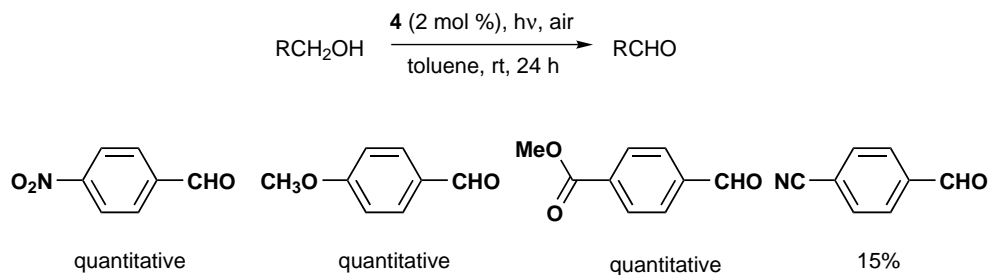
Typical experimental procedure was exemplified by the oxidation of *p*-nitrobenzyl alcohol. *p*-Nitrobenzyl alcohol (15.3 mg, 0.1 mmol) and **4** (1.4 mg, 2  $\mu$ mol) were weighed into a round-bottomed flask (Pyrex) and dissolved in toluene (1 mL). The mixture was irradiated with a halogen lamp (15 V, 150 W) through an infrared filter at room temperature for 24 h.<sup>11</sup> The reaction mixture was directly deposited on a silica gel column and eluted with a 9:1 mixture of hexane and ethyl acetate to give *p*-nitrobenzaldehyde (15.1 mg) in quantitative yield.



Scheme 3.



Scheme 4.



Scheme 5.

Competitive oxidations of primary and secondary alcohols were examined typically as follows. Primary and secondary alcohols (0.1 mmol) were weighed into a round-bottomed flask (Pyrex) followed by addition of pentamethylbenzene (0.1 mmol) as an internal standard and  $d_6$ -benzene (1 mL). An aliquot was taken out of the flask and submitted to  $^1\text{H}$  NMR (400 MHz) analysis to adjust the molar ratio of the components. To the solution was added **4** (1.4 mg, 2  $\mu\text{mol}$ ) and the mixture was irradiated for the specified period as shown in Scheme 4 under the same conditions as described above. The reaction mixture was analyzed by GC and  $^1\text{H}$  NMR to calculate the ratio of unreacted alcohols, aldehyde, and ketone. In all the reactions, the mass balances were excellent and no carboxylic acid was detected.

In conclusion, we were able to demonstrate that a reasonably designed (ON)Ru(salen) complex oxidized primary alcohols selectively in the presence of secondary alcohols. Further study is under way in our laboratory.

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11. The dissociated NO radical is considered to be oxidized to NO<sub>2</sub> under the conditions. Therefore, irradiation with a halogen lamp should be required only at the initial stage of the reaction, though irradiation was continued throughout the oxidation described in the text. Indeed, the reaction irradiated for only 2 h gave the same result as that described in the text.