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Aerobic oxidation of primary alcohols in the presence of activated secondary alcohols

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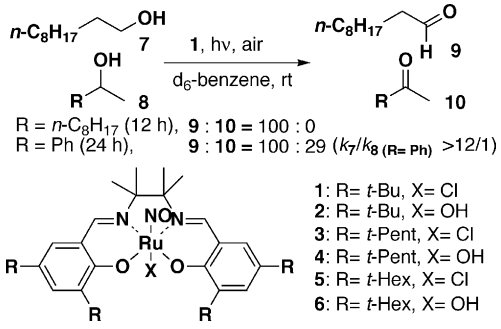
Abstract—Chemoselective aerobic oxidation of primary alcohols in the presence of activated secondary alcohols was effected under irradiation of visible light by using (nitrosyl)Ru(salen) complex **6** that possesses bulky 1-ethyl-1-methylpropyl groups at C3, C3′, C5 and C5′, as catalyst. For example, oxidation of *n*-decanol was >50 times faster than oxidation of 1-phenylethanol at 10 °C.

Oxidation of primary alcohol to aldehyde, especially its selective oxidation in the presence of secondary alcohol, is transformation of tremendous importance in organic synthesis and many methodologies have been reported for this purpose.[1] Although various stoichiometric oxidants have been used for these reactions,[2] use of molecular oxygen, in particular air, is desirable from an ecological and economical points of view.[3] Thus, much effort has been devoted to the development of oxidation using molecular oxygen, and high selectivity, mild reaction conditions, and a wide scope of applications have been achieved by introducing various catalysts.[4] However, most of the reactions need the addition of some mediator[4a–c] or forced reaction conditions[4e,f,n] to promote the desired reaction efficiently. We have recently disclosed that chiral (nitrosyl)Ru(salen) complexes catalyzed various aerobic oxidation of alcohols, kinetic resolution of racemic secondary alcohols,[5] oxidative coupling of 2-naphthol,[6] cyclization of 2,2′-dihydroxystilbene,[7] and desymmetrization of *meso*-diols, under photo-irradiation at room temperature without adding any mediator or base.[8] Furthermore, achiral (nitrosyl)Ru(salen) complex **1** bearing a 1,1,2,2-tetramethylethylenediamine unit has been found to catalyze selective oxidation of primary alcohols in the presence of secondary alcohols (Scheme 1).[9] For example, primary aliphatic and benzylic alcohols were selectively oxidized in the presence of secondary aliphatic and benzylic alcohols, respectively. However, the selectivity was reduced when a mixture of primary aliphatic and activated secondary alcohols was submitted to the reaction conditions: 1-phenylethanol was oxidized at one-twelfth rate of the oxidation of *n*-decanol. In the past year, Sheldon and co-workers reported that a Cu-bipyridine complex, TEMPO and *t*-BuOK system catalyzed selective aerobic oxidation of primary alcohols at room temperature: no oxidation of 1-phenylethanol was observed under this condition, though oxidation of primary aliphatic alcohols was not very fast.[10] This report prompted us to publish our new results.



Scheme 1.

The oxidation using **1** as the catalyst starts with the dissociation of the apical nitrosyl ligand by irradiation of visible light and the ensuing alcohol coordination to the ruthenium ion.[8,9] We assumed that the incoming

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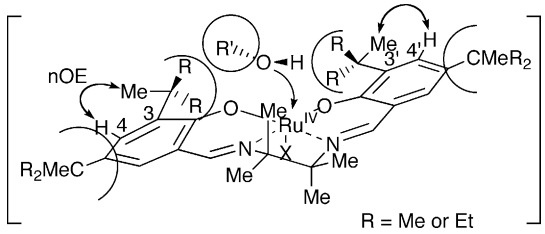


Figure 1.

alcohol would direct its alkyl (**R′**) group away from the pseudo-axial methyl group at the diamine unit and cause steric repulsion with the salen ligand (Fig. 1). Thus, we expected that higher selectivity would be realized, if a Ru(salen) complex bears bulkier substituents on its ligand, and primary aliphatic alcohol would be more selectively oxidized in the presence of an activated secondary alcohol.

Bu and co-workers have recently reported that a 1,1′-dimethylpropyl (*t*-pent) group provides more steric effectiveness than the *t*-butyl group, due to flexibility of the ethyl unit of the *t*-pent group. Indeed, a chiral Mn(salen) complex bearing *t*-pent groups at C3, C3′, C5 and C5′ is a better catalyst for asymmetric epoxidation than the corresponding Mn(salen) complex bearing *t*-butyl groups.[11] On the other hand, the X-ray analysis of a (nitrosyl)Ru(salen) complex bearing *t*-butyl groups has disclosed that one of the three methyl groups of the *t*-butyl groups at C3 and C3′ is located in the plane of the benzene ring and the remaining two methyl groups (R = Me) protrude above and below the plane of the benzene ring (Fig. 1).[12,13] Based on the X-ray analysis, we expected that, if the *t*-butyl groups at C3 and C3′ are replaced with 1-ethyl-1-methylpropyl (*t*-hex) group, the ethyl groups (R = Et) would protrude above and below the basal salen plane and the *t*-hex groups would provide more steric effectiveness.

Thus, we synthesized a series of complexes **1**–**6**[14,15] and examined oxidation of a 1:1 mixture of *n*-decanol (**7**) and activated secondary alcohol, 1-phenylethanol (**8**)

Table 1. Aerobic oxidation of a 1:1 mixture of **7** and **8** using (ON)Ru(salen) complexes **1**–**6** as catalyst[a]

Entry	Catalyst	IRR	Yield of aldehyde **9** (%)	Yield of ketone (%)
1	**1**	15	100	29
2	**2**	18	75	11
3	**3**	>30	77	10
4	**4**	>30	81	9
5	**5**	>30	78	8
6	**6**	>30	60	4
7[b]	**5**	>30	77	4
8[b]	**6**	>30	43	1
9[c]	**6**		100	6.5

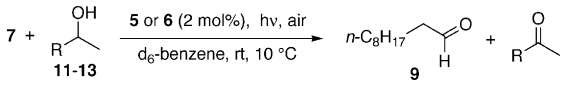
[a] Reactions were carried out for 24 h in C_6D_6 at room temperature under irradiation with a halogen lamp by using 2 mol% of catalyst, unless otherwise mentioned.
[b] The reactions were carried out at 10 °C.
[c] Reaction was carried out for 48 h at 10 °C with 4 mol% of catalyst.

(Table 1 and Scheme 1). Conversion of alcohols and yields of aldehyde and ketone were calculated by ^{1}H NMR (400 MHz) analysis using pentamethylbenzene as the internal standard. Initial reaction ratios (IRRs) of **7** and **8** were calculated from the following equation: IRR = (% yield of **9**)/(% yield of **10**) × 100, at ca. 20% conversion of **7**. No over-oxidation of aldehyde to carboxylic acid was observed. IRRs of the reactions with **1** or **2** as catalyst were 15[16] and 18, respectively (entries 1 and 2). All IRRs of the reactions with **3**–**6** were determined to be >30: because the amounts of the formed ketone **10** were below the measurable limit, the precise IRRs could not be determined (entries 3–6). Thus, the reactions with **3**–**6** were further continued for 24 h. As expected, higher selectivities were observed when complexes **5** and **6** were used as catalysts (entries 5 and 6). However, formation of small but considerable amounts (4–10%) of ketone **10** was detected. In order to improve the selectivity, the reactions were carried out at 10 °C with **5** and **6** as catalyst (entries 7 and 8) and it was found that the reaction with **6** was highly selective (entry 8). Judging from the result at 24 h, the IRR between **7** and **8** in the oxidation with **6** should be greater than 50 (entry 8). When all *n*-decanol was consumed, 6.5% of 1-phenylethanol was oxidized (entry 9). It is also noteworthy that complexes (**2**, **4**, and **6**) bearing an apical hydroxo ligand show somewhat better chemoselectivities than the corresponding complexes bearing a chloro ligand (**1**, **3**, and **5**). To ascertain the conformation of the 3(3′)-*t*-hex groups in complex **6**, we carried out the NOE experiment of **6** in $CDCl_3$. The experiment showed that the *t*-hex groups adopted the expected conformation: strong NOE correlations were observed between 4(4′)-proton and the methyl protons of the 3(3′)-*t*-hex groups and 6(6′)-proton and the methyl protons of the 5(5′)-*t*-hex groups (Fig. 1).

Based on these results, we next examined the oxidation of **7** in the presence of 4-phenyl-3-butyn-2-ol (**11**), 4-cyclohexyl-3-buten-2-ol (**12**), and 4-phenyl-3-buten-2-ol (**13**), respectively, at 10 °C (Table 2) by using **5** or **6** as catalyst (Table 2). Again, the oxidation with **6** as the catalyst showed higher selectivity (entries 1 and 2). High IRR greater than 30 was also observed in the oxidation of the mixture of **7** and **11**. The IRR should also be greater than 50, judging from the result at 24 h (entry 2). However, the IRRs between **7** and allylic alcohols **13** were diminished (entries 4 and 6). The IRR between **7** and **13** was moderate but, exceptionally, the reaction with **5** showed somewhat better IRR than that with **6**, though the reason is unclear (entries 6 and 7).

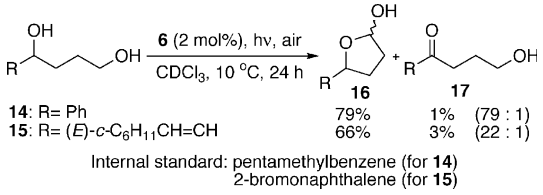
In intermolecular competitive reaction, relative amount of a fast-reacting primary alcohol rapidly decreases as the reaction proceeds and the apparent consumption rate of the primary alcohol becomes slower and the amount of the product from a secondary alcohol relatively increases. Thus, in the present reactions, the yields of ketones increased as the reactions came close to the complete consumption of the primary alcohol (Table 1, entry 9 and Table 2, entries 3 and 5). In contrast, the relative amount of primary and secondary alcohols is kept constant in intramolecular competitive oxidation

Table 2. Aerobic oxidation of **7** in the presence of various alcohols **11**–**13** using complexes **5** or **6** as catalyst[a]



Entry	Substrate (R)	Catalyst	IRR	Yield of aldehyde **9** (%)	Yield of ketone (%)
1[b]	**11**(PhC≡C)	**5**	>30	75	5
2[b]	**11**	**6**	>30	45	1
3[b,c]	**11**	**6**		100	9
4[b]	**12** [(*E*)-(*c*-C_6H_{11})-CH=CH]	**6**	20	42	3
5[b,d]	**12**	**6**		93	16
6[e]	**13** [(*E*)-PhCH=CH]	**5**	12	61	21
7[e]	**13**	**6**	9	45	14

[a] Reactions were carried out for 24 h in C_6D_6 at 10 °C under irradiation with a halogen lamp by using 2 mol% of catalyst.
[b] 2-Bromonaphthalene was used as the internal standard.
[c] Reaction was carried out for 48 h with 4 mol% of catalyst.
[d] Reaction was carried out for 36 h with 4 mol% of catalyst.
[e] Pentamethylbenzene was used as the internal standard.



Scheme 2.

and the product ratio reflects the relative reaction ratio between the alcohols, as long as the product is stable under the reaction conditions. Accordingly, we examined oxidation of 1-phenylbutane-1,4-diol (**14**) and 6-cyclohexyl-5-hexene-1,4-diol (**15**) with complex **6** as the catalyst in $CDCl_3$[17] (Scheme 2) and the ratios of the products (lactol **16** and hydroxy ketone **17**) were found to be 79:1 and 22:1, as expected from the IRRs of the corresponding intermolecular reactions (**7**/**8** and **7**/**12**) (vide supra).

As might be expected, 1-decanol (**7**) was oxidized with perfect selectivity in the presence of 2-decanol by using **6** as catalyst.

Competitive oxidations of primary aliphatic and secondary activated alcohols were examined typically as follows. Primary and secondary alcohols (0.1 mmol each) were weighed into a Schlenk tube (Pyrex) followed by addition of pentamethylbenzene or 2-bromonaphthalene (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. To the solution was added **6** (1.4 mg, 2 μmol), and the mixture was irradiated by using a halogen lamp (150 W) for 24 h at 10 °C with vigorous stirring in air.[18] 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.[19]

In conclusion, we were able to demonstrate that a reasonably modified (ON)Ru(salen) complex bearing an apical hydroxo ligand oxidized primary aliphatic alcohol with good selectivity even in the presence of activated secondary alcohol without addition of a base and/or mediator. Selective oxidation of 1,*n*-diols is very often encountered in syntheses of complex molecules and the present oxidation should provide a useful tool for oxidation of terminal alcohols.

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14. In the course of our study on asymmetric desymmetrization of *meso*-diols using (ON)Ru(salen) complexes as catalysts, we found that the nature of the apical ligands of the complexes affects the selectivity of the reaction (Ref. 8b).
15. 3,5-Di(1-ethyl-1methylpropyl)-2-hydroxybenzaldehyde was prepared from phenol in five steps: (i) treatment of phenol with 3-methyl-2-pentene (1 equiv) in the presence of HY zeolite (30 wt%) at 80 °C (95%), (ii) treatment of the resulting 5-(1-ethyl-1methylpropyl)phenol with 3-methyl-2-pentene (0.35 equiv) in the presence of HY zeolite (30 wt%) at 80 °C (85% based on 3-methyl-2-pentene used), (iii) protection of 3,5-di(1-ethyl-1methylpropyl)-phenol as an MOM ether by treating it with MOMCl and NaH in THF at rt (>99%), (iv) treatment of the resulting MOM ether with *sec*-BuLi in THF at −78 °C followed by *N*,*N*-dimethylformamide at −78 °C ∼ rt (96%), and (v) hydrolysis of the MOM-protected hydroxybenzaldehyde with 2-propanol saturated with HCl at rt (>99%).
16. Although we had reported that the relative reaction ratio between **7** and **8** is >12 (Ref. 9a), the present study revealed that it is 15.
17. Due to low solubility of **14** in benzene-d_6 chloroform-*d* was used as a solvent instead. The IRR of the reactions of **7** and **8** in benzene-d_6 was identical with that in chloroform-*d*. **15** is soluble in benzene-d_6 but its oxidation was also carried out in chloroform-*d*.
18. Irradiation was continued during the reaction. The role of photo-irradiation is twofold: (i) dissociation of the apicalnitrosyl ligand and (ii) acceleration of single electron transfer from Ru(III) species to molecular oxygen. The detailed mechanism of the reaction will be discussed elsewhere.
19. Reaction could be carried out in 5 mmol scale in a round-bottomed flask (100 mL) with three halogen lamps (150 W). The reaction in larger scale needs a more potent light source, because the reaction mixture is colored brownish red due to the presence of Ru complexes.