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Catalytic asymmetric and chemoselective aerobic oxidation: kinetic resolution of *sec*-alcohols

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Abstract

Optically active (nitroso)(salen)ruthenium(II) chloride (**2**) was found to be an efficient catalyst for aerobic oxidation of racemic secondary alcohols under irradiation with a halogen or fluorescent lamp, which proceeded with good enantiomer-differentiation ($k_{\text{rel}} = 11\text{--}20$). Furthermore, no epoxidation was observed in the oxidation of racemic 4-phenyl-3-buten-2-ol. © 2000 Elsevier Science Ltd. All rights reserved.

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Oxidation is a fundamental organic reaction and is widely used for organic synthesis, especially for functionalization of organic molecules. Today, various kinds of oxidation such as hydroxylation, epoxidation, and dihydroxylation can be performed in a highly enantioselective manner by using a catalytic amount of an optically active transition metal complex as the catalyst in the presence of a stoichiometric terminal oxidant.¹ Although a variety of oxidants have been used as stoichiometric ones, molecular oxygen is the most suitable in terms of atom economics as well as being environmentally friendly. Thus, aerobic oxidation or oxidation with molecular oxygen has been extensively studied for many years.^{1a}

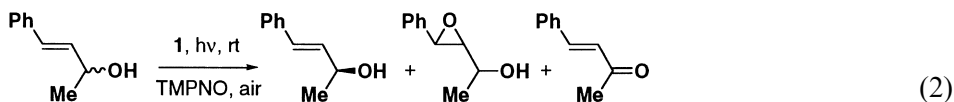
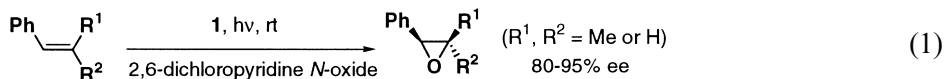
Although many strategies have been developed for oxidation with molecular oxygen as stoichiometric oxidant, methodology for transition metal-mediated asymmetric aerobic oxidation is still limited in number.

Mukaiyama et al. reported the first asymmetric epoxidation using an optically active (salen)-manganese(III) or (aldiminato)manganese(III) complex as the catalyst in the presence of molecular oxygen and a reductant such as pivalaldehyde.² Bolm et al. applied this methodology to asymmetric Baeyer–Villiger reaction by using an optically active copper Schiff–base complex as the catalyst and achieved good enantioselectivity.³ On the other hand, Groves et al. reported that a (dioxo)-ruthenium–porphyrin complex catalyzed aerobic epoxidation in the absence of a co-reductant.⁴ An asymmetric version of this reaction has been reported by Che et al., but the turnover number

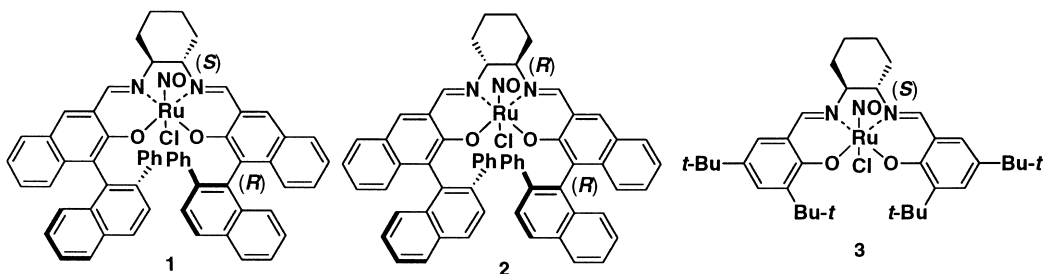
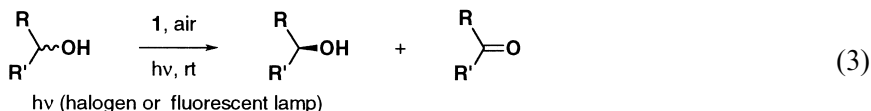
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of the reaction is moderate (< 20 times at maximum).⁵ Wacker oxidation was also carried out in an enantioselective manner with chiral palladium complexes as catalyst.⁶ Oxidation of 2-naphthol derivatives with a chiral copper complex as the catalyst under oxygen atmosphere was reported by Hashimoto et al. to give the corresponding binol derivatives with good enantioselectivity.⁷ More recently, Beller et al. and Krief et al. independently reported Sharpless asymmetric dihydroxylation with molecular oxygen in the absence^{8a} or presence of benzyl phenyl selenide, in which molecular oxygen oxidized selenide to selenoxide that, in turn, oxidized Os(VI) to Os(VIII) species.^{8b}

We recently disclosed that optically active (*R,S*)-(nitroso)(salen)ruthenium(II) complex **1** serves as a potent catalyst for enantioselective epoxidation in the presence of 2,6-dichloropyridine *N*-oxide under irradiation of incandescent light in dry air (Scheme 1, Eq. (1)).⁹ With this result in hand, we next examined epoxidation of 4-phenyl-3-buten-2-ol under the same conditions except for using tetramethylpyrazine *N,N'*-dioxide¹⁰ (TMPNO, 50 mol%) which is also a good stoichiometric oxidant for epoxidation (Eq. (2)). The reaction was slow but, unexpectedly, OH-oxidation was found to occur in preference to epoxidation (OH-oxidation:epoxidation = ca. 3:1, Eq. (2)).^{11,12} Furthermore, the reaction under irradiation with a halogen lamp gave ketone exclusively with modest differentiation of the enantiomers of the alcohol (k_{rel} (k_R/k_S) = 2.3, Eq. (2)) but, surprisingly, the conversion (67%) of the alcohol was found to exceed the amount of the consumed *N,N'*-dioxide [53.9%: formation of pyrazine *N*-oxide (42.7%) and pyrazine (5.6%)]. This suggested that molecular oxygen partly served as a stoichiometric oxidant. Thus, we examined aerobic oxidation of secondary alcohols (Eq. (3)).



hv (incandescent lamp): conversion of alcohol (48%); epoxide (11%), ketone (29%)
 hv (halogen lamp): conversion of alcohol (67%); epoxide (<1%), ketone (62%)



Scheme 1.

The aerobic oxidation of racemic 4-phenyl-3-buten-2-ol was first carried out in the presence of complex **1** in benzene under irradiation with a halogen lamp as an illuminant (Table 1, entry 1).¹³ The reaction proceeded chemoselectively to give the corresponding ketone and no epoxidation was observed. However, the relative reaction rate was only modest ($k_{\text{rel}} = 3$). We also examined the same reaction with a fluorescent or incandescent lamp as the illuminant. The reaction with fluorescent lamp gave the same result as that with a halogen lamp, while the reaction with an incandescent lamp was sluggish. Therefore, the following reactions were carried out with a fluorescent lamp. The oxidation of racemic 4-phenyl-3-buten-2-ol was next carried out by using complex **2** as the catalyst instead of **1**, and considerably improved k_{rel} was observed (entry 2). The reaction with complex **3** bearing a Jacobsen-type chiral salen ligand was slow and less selective ($k_{\text{rel}} = 1.3$) (entry 4). To optimize the reaction, we examined the effect of the solvent on k_{rel} with complex **2** as the catalyst and 4-phenyl-3-buten-2-ol as a test material. Although the solvent effect was small, aromatic solvents like benzene, toluene, or chlorobenzene generally gave better results than other solvents such as THF and ethyl acetate. Kinetic resolution of 4-phenyl-3-buten-2-ol was best effected in chlorobenzene (entry 3). Substrates for the present reaction are not limited to allylic alcohols. Benzylic alcohol, propargylic alcohol and dialkyl carbinol were also oxidized and resolved efficiently, though the reaction of dialkyl carbinol was a little slower than those of other activated alcohols (entries 4, 5, and 6). The best solvent varied with substrates, and efficiency of kinetic resolution also varied with substrates. Under the optimized conditions, relative reaction rates ranged from 11 to 20 (Fig. 1). Although the reactions were quenched at some point when conversion exceeded 55%, they were all still proceeding at those points. These results indicate that turnover numbers of the reactions are at least > 27.5 .

Table 1
Catalytic asymmetric aerobic oxidation of racemic secondary alcohols^a

Entry	Substrate	Catalyst	Solvent	conversion (%) ^b	% ee	Confign ^c	k_{rel}
1 ^d	4-phenyl-3-buten-2-ol	1	benzene	71.8	61.8 ^e	<i>S</i>	3
2		2	benzene	76.1	97.2 ^e	<i>R</i>	8
3		2	chlorobenzene	60.7 (60.7)	90.6 ^e	<i>R</i>	11
4		3	benzene	59.9	11.0 ^e	<i>S</i>	1.3
5	phenethyl alcohol	2	chlorobenzene	64.7 (64.4)	94.9 ^f	<i>R</i> ^g	11
6	4-phenyl-3-butyn-2-ol	2	chlorobenzene	65.3 (64.6)	>99.5 ^e	<i>R</i>	20
7	1-phenylpropan-2-ol	2	toluene	57.8 (50.9)	82.1 ^h	<i>R</i>	11

- a) Reaction was carried out in benzene in the presence of **2** (2 mol%) in air with a fluorescent lamp, unless otherwise mentioned.
- b) The number in parentheses is the yield of ketone. Conversion of racemic alcohol and yield of ketone were determined by GLC analysis.
- c) Configuration was determined by the measurement of specific rotation, unless otherwise mentioned (reference 14).
- d) Reaction was carried out with a halogen lamp.
- e) Determined by HPLC analysis using optically active column (DAICEL CHIRALCEL OD-H, hexane/2-propanol = 15/1).
- f) Determined by HPLC analysis using optically active column (DAICEL CHIRALCEL OB-H, hexane/2-propanol = 15/1).
- g) Configuration was determined by the comparison of the elution order with the authentic sample.
- h) Determined by HPLC analysis using optically active column (DAICEL CHIRALCEL OD-H, hexane/2-propanol = 100/1).

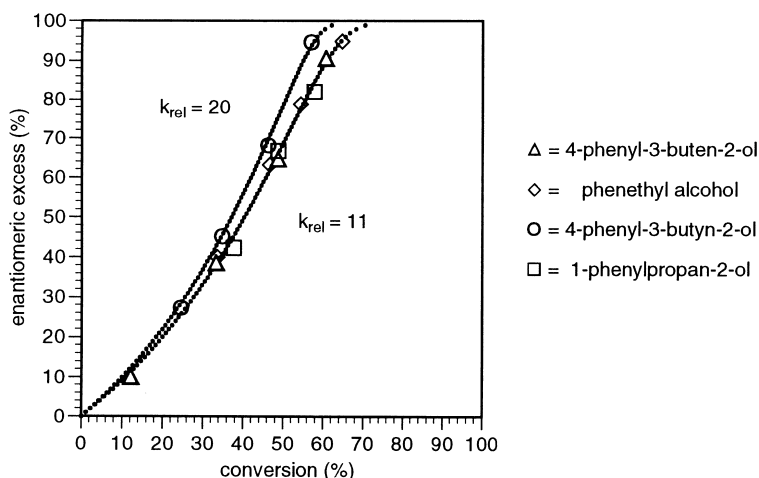


Figure 1.

Although the reaction mechanism is unclear at present, it is noteworthy that 1-phenyl-2,2-dimethylpropan-1-ol bearing a bulky *t*-butyl group next to the carbinol carbon was not oxidized under the present conditions. This suggests that coordination of a hydroxyl group is essential for the oxidation and it occurs in the coordination sphere of the ruthenium ion. In accord with this, the reactions in polar solvents are very slow: the reaction in THF or acetone was sluggish and no reaction occurred in acetonitrile. The configuration of all the unreacted alcohols in the reactions with complex **2** was *R* (Table 1), indicating that the sterically small acetylenic group behaved as though they were larger than the methyl group. This suggests that stereochemistry of the present oxidation is controlled not only by a steric factor but also by another factor such as π - π antibonding interaction which also participates in stereocontrol of the Mn-salen catalyzed epoxidation of conjugated olefins.^{15,16} Furthermore, the oxo-ruthenium species which is considered to be the active species in Ru-salen catalyzed epoxidation under irradiation of incandescent light,⁹ does not seem to participate in the present reaction, because OH-oxidation and epoxidation compete under such conditions as described above but only OH-oxidation proceeds under the present conditions. In connection with this issue, it is also noteworthy that tetramethylpyrazine *N,N'*-dioxide is slowly decomposed under irradiation with a halogen lamp ($t_{1/2}$ = 18 h). This partly explains why OH-oxidation prevails upon irradiation with a halogen lamp, but the desired OH-oxidation itself is accelerated under irradiation with a fluorescent or halogen lamp.¹⁷

Typical experimental procedure is exemplified with kinetic resolution of racemic 4-phenyl-3-butyn-2-ol: To a solution of racemic 4-phenyl-3-butyn-2-ol (14.6 mg, 0.10 mmol) in chlorobenzene (1.0 ml) was added bicyclohexyl (16.6 mg, 0.10 mmol) as an internal standard for GLC analysis. An aliquot (50 μ l) of this solution was taken out of the flask as a zero point and passed through a pad of silica gel which was washed out with a small amount of hexane:ethyl acetate (8:2). The eluate was submitted to GLC analysis.

To the remnant solution was added complex (**2**, 2.0 mg, 2.0 μ mol) and the mixture was stirred in air for 17 h at room temperature under irradiation of fluorescent light (100 V, 25 W). To remove the complex, the mixture was filtered through a pad of silica gel which was washed with hexane:ethyl acetate (8:2). The filtrate was submitted to GLC analysis to determine conversion of the alcohol to be 65.3%, then concentrated and chromatographed on silica gel (hexane:ethyl

acetate = 8:2). The fractions containing the alcohol were collected and an aliquot of the solution was submitted to HPLC analysis using optically active column (Daicel Chiralcel OD-H, hexane: 2-propanol = 15:1) to determine the enantiomeric excess of the unreacted alcohol to be > 99.5% ee. The remaining solution was concentrated to isolate the unreacted alcohol in 30% yield.

In conclusion, we were able to disclose that aerobic enantiomer-differentiating oxidation of racemic secondary alcohols was efficiently promoted by using (*R,R*)-(nitroso)Ru–salen complex **2** as the catalyst under irradiation of fluorescent light. Further study on the reaction mechanism is now proceeding in our laboratory.

Acknowledgements

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