Ru-Salen Catalyzed Asymmetric Epoxidation: Photoactivation of Catalytic Activity

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Abstract: (ON^+)(Salen)ruthenium(II) complex **1** was found to be an efficient catalyst for the epoxidation of conjugated olefins under sunlight coming through windows or incandescent light. The most suitable terminal oxidant was 2,6-dichloropyridine *N*-oxide **2**. All the examined conjugated olefins showed high enantioselectivity greater than 80% ee, irrespective of their substitution pattern.

Key words: asymmetric epoxidation, (ON^+)(salen)ruthenium(II) complexes, conjugated olefins, Ru-salen complex, photoactivation

Chiral metallosalen complexes (hereafter referred to as M-salen complexes) show versatile asymmetric catalysis for a wide range of chemical transformations, especially for oxene, nitrene, carbene transfer reactions.[1)] Thus far, chiral Mn-salen complexes have been recognized as the best catalyst for asymmetric epoxidation of conjugated olefins. However, good substrates for this reaction are mostly limited to conjugated *cis*-di-, tri- and some tetra-substituted olefins.[2)] Epoxidation of conjugated monosubstituted olefins such as styrene requires low reaction temperature as low as -78 °C.[3)] Recently chiral dioxiranes have been found to be excellent oxidants for enantioselective oxidation of *trans*-di and tri-substituted olefins.[4)] Still, there is no general methodology for enantioselective epoxidation. In the course of our study on the catalysis of chiral M-salen complexes, we found that the stereochemistry of M-salen- catalyzed epoxidation is affected by the metal ion, chiral ligand, and solvent used.[5)] On the other hand, Ru complexes are well known to serve as catalysts for oxidation[6)] and some chiral Ru-complexes such as Ru-porphyrin,[7)] Ru-Schiff base complex,[8)] desymmetric Ru-Schiff base complex,[9)] and Ru-bisamide complex,[10)] have already been used for asymmetric epoxidation. Although enantioselectivity so far obtained with these complexes are moderate, some interesting phenomena have been observed: i) epoxidation of *p*-nitrostyrene with Ru-Schiff base complex shows good enantioselectivity of 80% ee, though epoxidation of styrene is moderate (58% ee).[8,11)] ii) Differing from M-salen and M-porphyrin catalyzed epoxidations, *trans*-β-methylstyrene shows better enantioselectivity than *cis*-β-methylstyrene in the epoxidation using Ru-bisamide complex (62 and 25% ee, respectively).[10)] These results suggest that the scope of metal-catalyzed asymmetric epoxidation could be further expanded by taking the advantage of ruthenium chemistry.

We have revealed that the salen ligands bearing chiral binaphthyl unit as a chiral element are excellent chiral auxiliaries for Mn-catalyzed asymmetric oxidations. In order to expand ruthenium chemistry, we synthesized (ON^+)(salen)ruthenium(II) complex [(ON)Ru-salen complex] **1** and examined asymmetric epoxidation of 6-acetamido-2,2-dimethyl-7-nitrochromene as a substrate in the presence of various oxidants (Table 1). Although the chemical yields of the epoxide **3** were poor, all the reactions proceeded with good to high enantioselectivity. However, enantioselectivity of the reaction decreased as the reaction time was elongated (entries 2 and 3). This suggested that (ON)Ru-salen complex **1** was decomposed during the reaction and the generated Ru-species catalyzed epoxidation with the lower enantioselectivity.[12)]

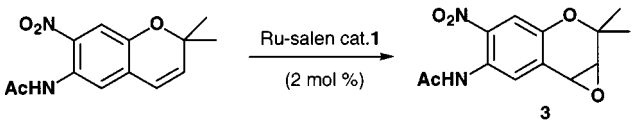

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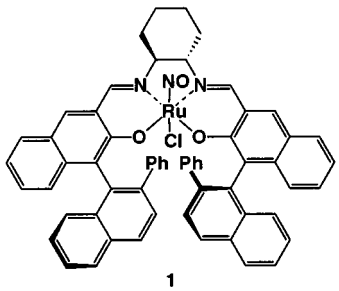
Table 1 Asymmetric epoxidation of 6-acetamido-2,2-dimethyl-7-nitrochromene using **1** as a catalyst.

entry	oxidant	time (h)	yield (%)	% ee[a)]
1	PhIO[b)]	2	1.9	85
2	$NaIO_4$[c)]	24	2.9	82
3	"	115	6.5	74
4	Oxone[c)]	24	4	93
5	NaOCl[c)]	24	4	76

a) Determined by HPLC analysis using optically active column (DAICEL CHIRALCEL OJ, hexane/2-propanol= 1/1)
b) Reactions were carried out at 4 °C in CH_2Cl_2.
c) Reactions were carried out at 4 °C in CH_2Cl_2-H_2O.



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On the other hand, Hirobe et al. have reported that 2,6-dichloropyridine *N*-oxide **2** is an excellent terminal oxidant for Ru-porphyrin-catalyzed epoxidation.[13)] Therefore, we examined the epoxidation of dihydronaphthalene[14)] in ether using *N*-oxide **2** as the oxidant and found that the chemical yield of the epoxide was

considerably improved (Table 2). However, the enantioselectivity again decreased with the formation of ketone **4** which was the rearrangement product of the epoxide, as the reaction proceeded. Decrease of enantioselectivity was considered to be attributable to the decomposition of (ON)Ru-salen complex **1** and to the enantiomer-differentiating rearrangement.[15] This suggested that the Ru-species generated in the reaction or (ON)Ru-salen complex **1** itself served as a Lewis acid catalyst (*c.f.*, entries 2 and 3).[15]

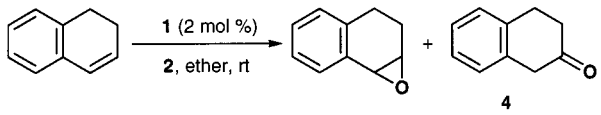

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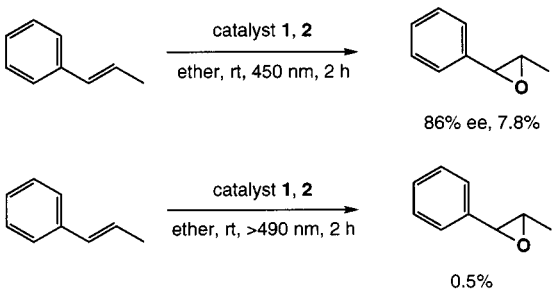
Table 2 Asymmetric epoxidation of dihydronaphthalene using **1** as a catalyst and 2,6-dichloropyridine *N*-oxide as a terminal oxidant.

entry	time (h)	yield (%)[a]	% ee[b]
1	2	19 (1)	87.2
2	6	57 (8)	84.2
3	15	58 (30)	77.5
4	"	3.3 (0.1)[c]	84.1

a) The number in the parentheses is the yield of ketone.
b) Determined by HPLC analysis using optically active column (DAICEL CHIRALCEL OB-H, hexane/2-propanol= 50/1)
c) Reaction was performed in the dark.

Furthermore, the present reaction was found to be accelerated by exposition to sunlight. The reaction in the dark was slow and showed slightly lower enantioselectivity (entry 4). The light around 450 nm accelerated the reaction most effectively (Scheme 1). This suggests that the electron-transfer from ruthenium ion to a ligand and the subsequent ligand dissociation is responsible for this photo-acceleration.[16] Exposure of the reaction medium to UV-light provided the complex products.



Scheme 1

We next examined the effect of solvent using dihydronaphthalene as a substrate under incandescent light (100V, 60W). The reaction proceeded smoothly in a less polar solvent such as benzene or ether. Although complex **1** and *N*-oxide **2** are soluble to benzene, their solubility to ether is small and the reaction in ether was carried out under the suspended conditions. Despite this, the reactions in ether proceeded smoothly. With respect to enantioselectivity and chemical yield, benzene and ether were considered to be the solvents of choice. In particular, benzene was a good solvent for the reaction yielding an acid-sensitive epoxide such as 1,2-epoxy-3,4-dihydro-naphthalene (*vide infra*). The reaction in a polar solvent such as acetone or ethyl acetate which more solubilized the catalyst was very slow.

The epoxidations of various olefins under the optimized conditions are summarized in Table 3. As we expected, epoxidation of *cis*-disubstituted olefins proceeded with high enantioselectivity. The sense of asymmetric induction by **1** was the same as that by Mn-salen complex bearing the same salen ligand as **1**. Although the reactions in ether generally showed slightly better enantioselectivity, higher chemical yields were attained in benzene. This is probably because the decomposition of epoxides was slower in benzene than in ether (*c.f.*, Table 2, entry 3 and Table 3, entry 5). No formation of ketone was observed in the epoxidation of other olefins, except for styrene: Formation of only a trace amount of the aldehyde is detected by TLC analysis in the reaction of styrene. Despite this, enantioselectivity of the reactions gradually decreased especially in the ether, suggesting the slow decomposition of the catalyst under the reaction conditions (entries 6 and 7). The decomposition of the catalyst seemed to be suppressed by use of benzene as a solvent (entries 8 and 9).[17,18] The unexpected good results were, however, observed when we examined the epoxidation of *trans*-di- and mono-substituted olefins which are poor substrates for Mn-salen-catalyzed epoxidation (entries 8, 11, and 13). It is also noteworthy that epoxidations of *trans*- and *cis*-β-methylstyrenes proceeded to exclusively give *trans*- and *cis*-epoxides respectively, though the formation of a trace amount (<0.5%) of the isomerized *cis*- and *trans*-epoxides was detected by GLC analysis (entries 6-9 and 10). Epoxidation of *trans*-stilbene also gave the corresponding *trans*-epoxide exclusively (entry 11).

Preparation of the complex **1** and the typical experimental procedure for the epoxidation using it as a catalyst are described below. The equipments made with Pyrex glass were used through these reactions.

Preparation of Ru-salen complex **1**:[19] NaH (60% dispersion in mineral oil, 44 mg, 1.1 mmol) was weighed into a flask and washed with dry hexane (3 x 1.0 ml). DMF (5 ml) was added to the flask with stirring, followed by salen-H_2 (413.5 mg, 0.50 mmol). Hydrogen evolved and the mixture turned to a clear red solution. After 30 min, a solution of $Ru(NO)Cl_3 \cdot H_2O$ (191.6 mg, 0.75 mmol) in DMF (5 ml) was added. The mixture was stirred at 110 °C for 48 h. The resulting opaque red-brown mixture was concentrated under high vacuum. The residue was dissolved in CH_2Cl_2 and washed with H_2O. The CH_2Cl_2 layer was dried over Na_2SO_4, then evaporated to dryness. The residue was recrystallized from CH_2Cl_2/CH_3CN to give **1** [Ru(salen)(NO)(Cl)] as red-brown crystals (160 mg, 32%).

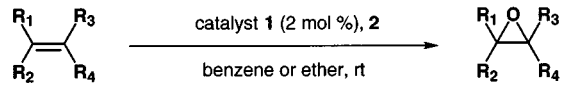
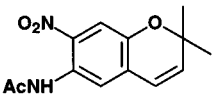
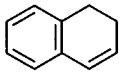
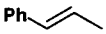
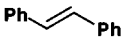


Table 3 Asymmetric epoxidation of conjugated olefins using **1** as a catalyst.

entry	substrate	time (h)	yield (%)	% ee	confign
1[a]		5	54	98[c]	3*S*,4*S*
2[b]	"	20	59	97[c]	3*S*,4*S*
3[a]		6	57 (8)[d]	84[e]	1*S*,2*R*
4[b]	"	2	51 (5)[d]	87[e]	1*S*,2*R*
5[b]	"	6	70 (23)[d]	81[e]	1*S*,2*R*
6[a]		2	26	86[f]	1*S*,2*S*
7[a]	"	32	64	75[f]	1*S*,2*S*
8[b]	"	6	28	82[f]	1*S*,2*S*
9[b]	"	20	75	80[f]	1*S*,2*S*
10[b]		30	60	89[f]	1*S*,2*R*
11[b]		72	52	87[g]	1*R*,2*R*
12[a]		2	11	87[h]	*S*
13[b]	"	12	34 (<1)[d]	79[h]	*S*

a) The reaction was carried out in ether under incandescent light.
b) The reaction was carried out in benzene under incandescent light.
c) Determined by HPLC analysis using optically active column (DAICEL CHIRALCEL OJ, hexane/2-propanol= 1/1).
d) The number in parentheses is the yield of the corresponding ketone or aldehyde.
e) Determined by HPLC analysis using optically active column (DAICEL CHIRALCEL OB-H, hexane/2-propanol= 50/1)
f) Determined by GLC analysis using optically active column (SUPELCO β-DEX™ 225 fused silica capillary column, 30 m x 0.25 mm ID, 0.25 μm film: 90 °C)
g) Determined by HPLC analysis using optically active column (DAICEL CHIRALCEL OJ, hexane/2-propanol= 9/1)
h) Determined by HPLC analysis using optically active column (DAICEL CHIRALCEL OD-H, hexane/2-propanol= 1000/1)

Epoxidation of 6-acetamido-2,2-dimethyl-7-nitrochromene: (ON)Ru-salen complex **1** (2.0 mg, 2 mol%) was added to a solution of the substrate (26.2 mg, 0.1 mmol) in benzene (1.0 ml). To the solution was added 2,6-dichloropyridine *N*-oxide (16.4 mg, 0.1 mmol) and the whole mixture was stirred for 20 h at room temperature under incandescent light (100V, 60W). The mixture was directly submitted to column chromatography (SiO_2, hexane/AcOEt = 8/2 to 7/3) to give the corresponding epoxide (16.5 mg, 59%). The enantiomeric excess of the epoxide was determined by HPLC analysis using optically active column (DAICEL CHIRALCEL OJ, hexane/2-propanol = 1/1).

In conclusion, we were able to find a general methodology for the epoxidation of conjugated olefins. Further study is now proceeding in our laboratory.

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(11) Unfortunately, the correct reaction temperature of this reaction was not given.
(12) The rearrangement of the epoxide giving a ketone was not detected in this reaction.
(13) Higuchi, T.; Ohtake, H.; Hirobe, M. *Tetrahedron Lett.* **1989**, *30*, 6545-6548.
(14) We changed the substrate from 6-acetamido-2,2-dimethyl-7-nitrochromene to dihydronaphthalene which provides the more Lewis acid-sensitive epoxide, to clarify the effect of the Lewis acidity of Ru-complexes to the reaction.
(15) See the succeeding communication.
(16) It has been reported that flash photolysis of Ru(TPP)(NO)Cl presumably generates a transient species, Ru(TPP)Cl: Lorkovic, I. M.; Miranda, K. M.; Lee, B.; Bernhard, S.; Schoonover, J. R.; Ford, P. C. *J. Am. Chem. Soc.* **1998**, *120*, 11674-11683. However, we can not remove the possibility that the chloro ligand in **1** dissociates under the present reaction conditions from the result obtained in the asymmetric cyclopropanation described in the succeeding communication.
(17) This is probably due to that benzene absorbs unnecessary UV light.
(18) Absorption maximums in UV-vis spectrum of **1** in benzene (2.0×10^{-4} M): λ_{max} = 456 nm (ε 5.5×10^3); λ_{max} = 535 nm (ε 2.7×10^3). The broad signal at 535 nm became gradually weak with the exposure of complex **1** under the reaction conditions to incandescent light. This probably suggests that the decomposition of complex **1** was brought about on irradiation.
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