Chiral (ON)Ru-Salen Catalyzed Cyclopropanation: High *Cis*- and Enantioselectivity

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Abstract: (*R*,*R*)-(ON^+)(Salen)ruthenium(II) complex **2** was found to be an effective catalyst for *cis*-selective asymmetric cyclopropanation (up to 89% ee) which was performed under sunlight coming through a window or incandescent light. Furthermore, (*R*,*R*)-(ON^+)(hydroxo)-(salen)ruthenium(II) complex **5** was also found to show good *cis*- and enantio-selectivities (up to 92% ee) in the reaction in the dark.

Key words: (ON^+)(salen)ruthenium(II) complex, photo-activation, cyclopropanation, *cis*-selectivity

We disclosed the unusual asymmetric catalysis of (*R*,*S*)-(ON^+)(salen)ruthenium(II) complex [(*R*,*S*)-(ON)Ru-salen complex] **1** under sunlight or incandescent light.[1)] With this complex as a catalyst, high enantioselectivity has been achieved in asymmetric epoxidation and hetero Diels-Alder reaction and also in kinetic resolution of racemic epoxides. On the other hand, we had found that chiral metallosalen complexes [(salen)manganese(III) or (salen)-cobalt(III) complexes) serve as catalysts not only for oxene transfer (oxo transfer) reaction but also for carbene transfer reaction.[2)] Thus it was expected that chiral (salen)ruthenium complex would also serve as a catalyst for enantioselective cyclopropanation. Although there have been many metal-catalyzed asymmetric cyclopropanation reactions[3)] including ruthenium complexes[4)] such as Ru-Pybox and Ru-porphyrin reported, most of these metal-catalyzed reactions show moderate to high *trans*-selectivity and few *cis*-selective cyclo-propanations are known.[5)]

Chiral (5,5'-methoxysalen)cobalt(III) complex bearing no substituent at C3(C3') is an excellent catalyst for asymmetric cyclopropanation and shows high enantio- and *trans*-selectivity, while (salen)cobalt(III) complexes bearing substituents at C3(C3') show no catalytic activity.[6)] However, it has been well known that, in the asymmetric epoxidation using (salen)manganese(III) complexes as catalysts, the chirality in C3(C3')-substituents strongly affects asymmetric induction by the complexes. Therefore it was expected that the stereochemistry of metallosalen-catalyzed asymmetric cyclopropanation could be modified by introducing chiral substituents at C3(C3')-carbons. Although the presence of C3(C3')-substituents in (salen)cobalt(III) complexes ruins their catalytic activity, we considered that metallosalen complexes having longer metal-$oxygen_{(eq)}$ bond would allow the presence of C3(C3')-substituents.[7)] Therefore, we examined asymmetric cyclopropanation using (ON)Ru-salen complexes as catalysts.

We first examined the reaction of styrene and *t*-butyl α-diazoacetate in the presence of **1**. The reaction proceeded slowly to give cyclopropanation products but the stereochemistry observed was not reproducible. However, in accord with the other reactions using **1** as the catalyst, the present reaction was also accelerated when the reaction was carried out under incandescent light and showed the reproducible stereochemistry,[1)] though selectivity was poor (Table 1, entry 1). Being encouraged with this result, we examined cyclopropanation using (*R*,*R*)-(ON)Ru-salen complex **2** and complexes **3** and **4** as catalysts also under incandescent light. To be surprised, complex **2** showed high *cis*-selectivity as well as good enantioselectivity (entry 2). In contrast to this, complexes **3** and **4** showed usual *trans*-selectivity, though enantioselectivities were moderate (entries 3 and 4). The stereoselectivities observed in these reactions are probably the minimum ones, because the uncatalyzed cyclopropanation occurred under the present reaction conditions (entry 5). The reaction in the dark was very slow and *cis*-*trans* selectivity was poor (entry 6). Although the mechanism of asymmetric induction by (ON)Ru-salen complexes is unclear at present, it is worth mentioning that the axial chirality in the ligand plays a very important role in determining the sense of asymmetric induction (*cf.*, entries 1 and 2).[8)] We next examined the reactions in benzene or in dichloromethane. Although chemical yield was decreased, both enantio- and *cis*-selectivities were further increased (up to 89% ee) (entries 7 and 8).

The complex **2** was purified by silica gel column chromatography upon its synthesis. However, it was found that a new Ru-species was generated during this procedure (*vide infra*). The new species was isolated and identified as (hydroxo)Ru-salen complex **5** by measurement of FABMS (*m*-nitrobenzyl alcohol): m/z 973(M^+), 956(M^+-OH). We were intrigued by the catalysis of complex **5**. Thus, we examined the reaction of styrene and *t*-butyl α-diazoacetate in the presence of **5** (Table 2). The reaction proceeded even in the dark and showed high *cis*- (89:11) and enantioselectivities (92% ee). On the other hand, the reaction under incandescent light showed a similar level of *cis*- and enantio-selectivities to those observed with the complex **2** under incandescent light (*cf.*, Table 1, entry 2 and Table 2, entry 2). Effect of light observed in the above and this re-

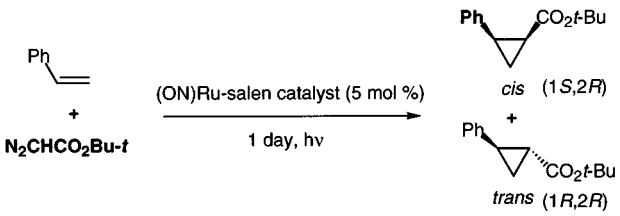


Table 1 Asymmetric cyclopropanation of styrene using (ON)Ru-salen complexes as catalysts[a)]

entry	catalyst	solvent	yield[b)] (%)	*cis* : *trans*	*cis* % ee	*trans* % ee
1	**1**	-	12	37 : 63	12	51
2	**2**	-	53	80 : 20	81	51
3	**3**	-	45	11 : 89	58	-23[c)]
4	**4**	-	10	18 : 82	31	35
5	-	-	11	44 : 56	0	0
6[d)]	**2**	-	6	44 : 56	71	78
7[e)]	**2**	benzene	16	83 : 17	89	57
8[e)]	**2**	CH_2Cl_2	21	84 : 16	89	79

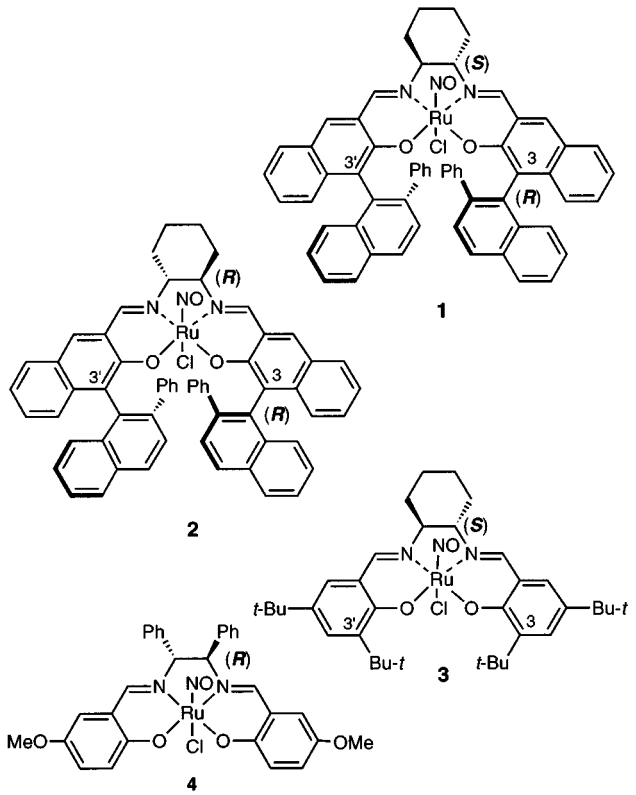
a) Reaction was carried out in styrene at room temperature under incandescent light, unless otherwise mentioned. Enantiomeric excess of the product was determined by HPLC analysis using chiral column (DAICEL CHIRALCEL OD-H, hexane). Configuration was determined by the comparison of the elution order with the authentic samples.

b) Yield was calculated on the amount of α-diazoacetate used by ^{1}H NMR analysis (see the typical experimental procedure).

c) The configuration of the product is 1*S*,2*S*.

d) Reaction was carried out in the dark.

e) Styrene (0.3 mmol, 3 equivalents to α-diazoacetate) was dissolved in the solvent (0.35 ml) described in the Table and used for the reaction.



actions is considered to be attributable to a ligand dissociation induced by irradiation.[9)]

Table 2 Asymmetric cyclopropanation of styrene using (ON)Ru-salen complex **5** as the catalyst[a)]

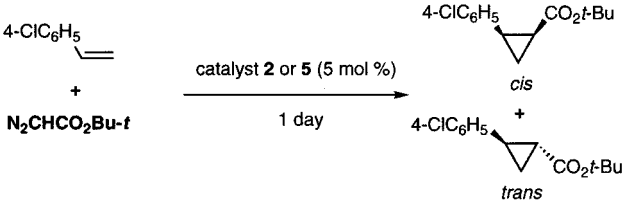
entry	yield (%)	*cis* : *trans*	*cis* (% ee)	*trans* (% ee)
1	62[b)]	89 : 11	92	37
2	45[c)]	78 : 22	81	54

a) Reaction was carried out in styrene using **5** (5 mol %) at room temperature for 1 day. For the determination of enantiomeric excess of the product and the configurations of the product, see the footnote of Table 1.

b) Isolated yield. The reaction was carried out in the dark.

c) Yield was calculated by ^{1}H NMR analysis. The reaction was carried out under incandesent light.

We also examined the cyclopropanation of *p*-chlorostyrene using **2** and **5** as catalysts under the irradiated and unirradiated conditions, respectively (Scheme 1). Again the reaction with **2** showed good *cis*- and enantio-selectivities,[10)] while the reaction with **5** exhibited diminished *cis*- and enantio-selectivities to some extent.



(under incandescent light)
2: 47%, *cis* : *trans* = 82 : 18, *cis* (80% ee), *trans* (50% ee)
(in the dark)
5: 32%, *cis* : *trans* = 77 : 23, *cis* (72% ee), *trans* (34% ee)

Scheme 1

Preparation of complexes **2** and **5** and the typical procedure of ruthenium-catalyzed cyclopropanation were described below. All the reactions except for the synthesis of complex **5** were carried out under nitrogen atmosphere.

Preparation of complex 2: (NO)$RuCl_3.H_2O$ (383.2 mg, 1.5 mmol) was dissolved in dry *N*,*N*-dimethylformamide (DMF) (10 ml) and the solvent was removed azeotropically at 110 °C. The resulting anhydrous (NO)$RuCl_3$ was redissolved in dry DMF (10 ml).

NaH (60% dispersion in mineral oil, 80 mg, 2.2 mmol) was weighed into a flask and washed with dry hexane (3 x 1.0 ml). Dry DMF (10 ml) and subsequently $salenH_2$ (827 mg, 1.0 mmol) were added to the flask and stirred for 1 h. To this mixture, was added the above DMF solution of (NO)$RuCl_3$. The whole mixture was stirred at 110 °C for 48 h. The solvent was removed under vacuum and the residue was quickly chromatographed on silica gel column (CH_2Cl_2/acetone = 50/1) to give the (ON)Ru-salen complex **2** as red-brown crystals (593 mg, 60%).

Preparation of complex 5: Ru-salen complex **2** (115.2 mg, 0.12 mmol) was dissolved in $CHCl_3$. To the solution was

added silica gel (3 g) and the mixture was stirred for 1 day. The suspension was filtered and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel column (CH_2Cl_2/acetone/MeOH = 50/1/1) to give (ON)Ru-salen complex **5** as red crystals (53.6 mg, 47%).

*Asymmetric cyclopropanation of styrene with complex **2***: To a suspension of complex **2** (5.0 mg, 5.0 μmol) in styrene (0.35 ml) was added *t*-butyl α-diazoacetate (14 μl, 0.1 mmol) and the suspension was stirred at room temperature for 1 day under incandescent light (100V, 60W). The suspension was directly subjected to a short silica gel column eluting with hexane/diisopropyl ether (4/1) to remove styrene and the catalyst. The eluate including *cis*- and *trans*-products, di-*t*-butyl fumarate and di-*t*-butyl maleate was concentrated and diluted with $CDCl_3$ (0.7 ml). 1-Bromonaphthalene (4 μl) was added to the $CDCl_3$ solution as an internal standard and analyzed by ^1H NMR analysis (270 MHz) to determine the chemical yield of *cis*- and *trans*-products and *cis*-*trans* ratio. An aliquot of the eluate was concentrated and submitted to preparative TLC to yield the *cis*- and *trans*-products which were used for the determination of their enantiomeric excesses.

*Asymmetric cyclopropanation of styrene with complex **5***: To a solution of complex **5** (18.5 mg, 7.6 μmol) in styrene (1.33 ml) was added *t*-butyl α-diazoacetate (53 μl, 0.38 mmol) and the solution was stirred at room temperature for 1 day in the dark. The mixture was directly submitted to column chromatography (silica gel, hexane/diisopropyl ether = 30/1) to give the *cis*- (45.6 mg, 55%) and *trans*-products (6.0 mg, 7.2%).

In conclusion, we were able to achieve the first highly *cis*- and enantioselective cyclopropanation by using (*R*,*R*)-(ON)Ru-salen complex. Further study is now proceeding in our laboratory.

Acknowledgement

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References and Notes

(1) The preceding communications.
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(5) a) Maxwell, J. L.; O'Malley, S.; Brown, K. C.; Kodadek. T. *Organometallics* **1992**, *11*, 645-652. b) It has reported that cyclopropanation using a cyclopentadienyl iron complex as the catalyst shows high *cis*-selectivity, though in a non-enantioselective manner: Seitz, W. J.; Saha, A. K.; Hossain, M. M. *Organometallics* **1993**, *12*, 2604-2608.
(6) a) Fukuda, T.; Katsuki, T. *Synlett* **1995**, 825-826. b) Fukuda, T.; Katsuki, T. *Tetrahedron* **1997**, *53*, 7201-7208.
(7) In (salen)cobalt(III) complexes, the lengths of Co-equatorial oxygen atom are in the range of 1.84-1.91 Å. (ON)Ru-salen complex **1** has a longer Ru-oxygen bond: see the following communication.
(8) In accord with this observation, the complex bearing the chirality only at the binaphthyl part and ethylenediamine as the diamine unit also showed good *cis*-*trans* selectivity (79:21) and high enantioselectivity (91% ee, *cis*-isomer; 0% ee, *trans*-isomer). However, due to its very poor solubility to organic solvent, the yield of the cyclopropanation products was low (<5%).
In connection to this problem, it is noteworthy that the reactions of styrene and diazoacetate in the presence of chiral Cu, Co, and Rh complexes give *trans* and *cis* products, the configurations at C1 of which are the same (reference 3), while the present reaction provided the *trans* and *cis* products isomeric at C1. The reason for this unusual selectivity is unclear at present.
(9) 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 and hydroxo ligands in **2** and **5** dissociate, respectively, under the present reaction conditions to give the same transient species.
(10) Absolute configuration of the products has not been determined.

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