Highly *cis*- and Enantioface-Selective Cyclpropanation Using (*R*,*R*)-Ru-Salen Complex: Solubility Dependent Enantioface Selection

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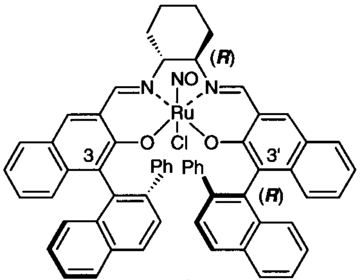
Abstract: The reaction of styrene and *t*-butyl α-diazoacetate in the presence of (*R*,*R*)-(ON$^+$)(salen)ruthenium(II) complex **1** under the irradiation of incandescent light in THF gave the corresponding (1*S*,2*R*)-cyclopropanecarboxylate with high stereoselectivity of 99% ee (*cis* : *trans* = 96 : 4), while the same reaction in hexane gave the enantiomeric (1*R*,2*S*)-cyclopropanecarboxylate preferentially (83% ee, *cis* : *trans* = 68 : 32).

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



1

Compound **1**

Optically active metallosalen complexes have been well-recognized as excellent catalysts for enantioselective transfer reactions of oxene and its isoelectronic species such as nitrene and carbene.[1] We have recently reported that (*R*,*R*)-(ON$^+$)(salen)ruthenium(II) [(*R*,*R*)-Ru-salen] complex **1** catalyzed the unprecedented high *cis*- and enantioselective cyclopropanation of styrene (89% ee, *cis* : *trans* = 84 : 16) when the reaction was carried out under the irradiation of incandescent light.[2] However, these irradiated conditions caused undesired decomposition of α-diazoacetate and brought about non-catalyzed cyclopropanation which is non-stereoselective and diminishes the enantiomeric excess of the desired cyclopropane product.[2] To overcome this side reaction and to improve the stereoselectivity of the reaction, we examined the relationship between wavelength of the irradiated light and stereoselectivity. On the other hand, we recently found that the ligands of the metallosalen complexes are highly flexible and their conformation is affected even by a weak bond interaction such as CH-π or OH-π interaction.[3] Therefore, we expected that the association state (monomeric or aggregated) of the catalyst would have influence on the conformation of the salen ligand and, in turn, the enantioface selection by the metallosalen complex. Thus we also examined the effect of solvent on the stereoselectivity of the Ru-salen catalyzed cyclopropanation in order to know whether the monomeric and aggregated catalysts behave in a different way.[4,5]

We first examined the effect of wavelength on the stereoselectivity of the reaction in THF (Table 1). The light of wavelength >500 nm did not efficiently activate the catalyst and the reaction irradiated by the light of such wavelength was slow (entry 3). Thus the reaction competed with the reaction catalyzed by non-activated catalyst and showed moderate selectivity (*c.f.* entries 3 and 5). Non-irradiated catalyst also slowly catalyzed cyclopropanation with moderate enantioselectivity but poor *cis*-*trans* selectivity (entry 5). The reaction under irradiation of the light of ~440 nm showed excellent *cis*- and enantioselectivity (entry 2). The reaction irradiated by the light of ~390 nm showed the diminished selectivity, probably because decomposition of α-diazoacetate was caused by the irradiation (entry 1). Furthermore the reaction irradiated by the incandescent light of wavelength mostly >400 nm was found to show an excellent level of stereoselectivity similar to the reaction irradiated by the light of ~440 nm. Therefore, with an incandescent lamp (National/Panasonic LW100v57w) as a light source, we next examined the effect of solvent.

We examined the reaction in three different kinds of solvents: i) solvents of high dissolving power such as THF, dimethoxyethane (DME), ethyl acetate, and dichloromethane; ii) solvents of high dissolving power and high coordinating ability such as acetonitrile and pyridine; iii) solvents of poor dissolving power such as hexane, heptane, and diisopropyl ether (Table 2). Catalyst **1** was dissolved in the first class of solvents and the reactions in these solvents all showed high enantio- and *cis*-selectivity to give the (1*S*,2*R*)-isomer preferentially, though ethereal solvents gave slightly better results (entries 1-4). On the other hand, no reaction occurred in the second class of solvents, though **1** was dissolved in these solvents (entries 5 and 6). These results agreed with the proposed mechanism on metal-catalyzed diazo decomposition, in which the diazo compound is coordinated to the metal ion and generates a metal-carbene complex.[4a] A coordinating solvent should disturb the coordination of α-diazoacetate to ruthenium ion. Complex **1** was insoluble to the third class of solvents and the reaction was carried out with suspended **1** in the solvents. These reactions also showed moderate *cis*- and good enantio-selectivity (entries 7-9). However,

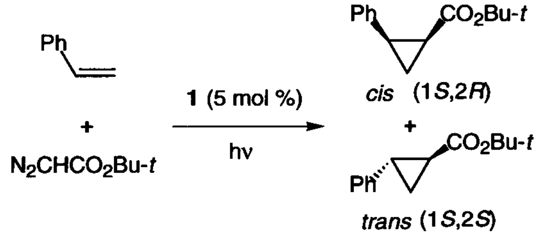


Table 1 Effect of wavelength$^{a)}$

entry	wavelength (nm)	yield$^{b)}$ (%)	*cis* : *trans*$^{c)}$	% ee$^{d)}$	
				cis	*trans*
1	~390	11	91 : 9	91	-$^{e)}$
2	~440	16	97 : 3	97	5
3	>500	3	71 : 29	79	-59$^{f)}$
4	IL$^{g)}$	18	96 : 4	99	9
5	-$^{h)}$	6	44 : 56	71	-78$^{f)}$

a) Reaction was carried out in the presence of the catalyst **1** (5 mol %, based on α-diazoacetate used) at room temperature for 24 h in THF-styrene (10/1=v/v) under irradiation of light of the described wavelength, unless otherwise mentioned. Styrene and α-diazoacetate were distilled before use. Use of non-freshly distilled styrene and α-diazoacetate may decay stereoselectivity of the reaction.

b) Yield was calculated on the basis of the amount of α-diazoacetate. Total yield of *cis*- and *trans*-cyclopropanes was determined by ^{1}H NMR analysis (400 MHz) using 1-bromonaphthalene as an internal standard.

c) Ratio of *cis*- and *trans*-isomers was determined by ^{1}H NMR analysis (400 MHz).

d) 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.

e) Not determined.

f) Configuration of the product is 1*R*,2*R*.

g) IL= incandescent light

h) Reaction was carried out in the dark.

Table 2 Effect of solvent$^{a)}$

entry	solvent	yield$^{b)}$ (%)	*cis* : *trans*$^{c)}$	% ee$^{d)}$	
				cis	*trans*
1	THF	18	96 : 4	99$^{e)}$	9$^{f)}$
2	DME	16	96 : 4	98$^{e)}$	-10$^{g)}$
3	AcOEt	17	92 : 8	96$^{e)}$	-51$^{g)}$
4	CH_2Cl_2	21	86 : 14	92$^{e)}$	-79$^{g)}$
5	CH_3CN	N.R.$^{h)}$	-	-	-
6	pyridine	N.R.	-	-	-
7	hexane	10	68 : 32	-83$^{i)}$	-50$^{g)}$
8	heptane	14	74 : 26	-71$^{i)}$	-72$^{g)}$
9	*i*-Pr_2O	5	67 : 33	-81$^{i)}$	-48$^{g)}$

a) Reaction was carried out in the presence of the catalyst **1** (5 mol %, based on α-diazoacetate used) at room temperature for 24 h in a mixture of solvent and styrene (10/1=v/v) under irradiation of incandescent light. Styrene and α-diazoacetate were distilled before use.

b) Yield was calculated on the basis of the amount of α-diazoacetate. Total yield of *cis*- and *trans*-cyclopropanes was determined by ^{1}H NMR analysis (400 MHz) using 1-bromonaphthalene as an internal standard.

c) The ratio of *cis*- and *trans*-isomers was determined by ^{1}H NMR analysis (400 MHz).

d) 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.

e) Configuration of the product is 1*S*,2*R*.

f) Configuration of the product is 1*S*,2*S*.

g) Configuration of the product is 1*R*,2*R*.

h) N.R.: No reaction occurred.

i) Configuration of the product is 1*R*,2*S*.

the sense of enantioselection in the formation of the major *cis*-isomer is opposite to that observed in the reactions in the first class of solvents (*c.f.* entries 1-4 and 7-8). The reversal of enantioselection does not seem to relate to the functionality of solvents or to their polarity. The following explanation seems to be the most rational at this moment. Complex **1** is dissolved completely in the first class of solvents and gives a monomeric activated species which decomposes α-diazoacetate, upon irradiation, while **1** is not dissolved in the third class of solvents and the activation should occur on the surface of the insoluble solid **1**.[6] It is reasonable to consider that these monomeric and aggregated active species may have different ligand-conformation which is correlated with the sense of asymmetric induction, since salen ligands are highly pliable.[3] The reaction in styrene without solvent showed *cis*- and enantio-selectivity of *cis* : *trans* = 84 : 16 and 89% ee, respectively.[2] As discussed in the beginning of this paper, we had attributed this unsatisfactory result to the intervention of non-catalyzed reaction.[7] However, as the solubility of complex **1** to styrene is not very high, it was not completely dissolved in the reaction medium. Therefore, we can not exclude the possibility that both monomeric and aggregated catalysts **1** catalyzed cyclopropanation competitively and caused some diminishment of enantioselectivity in this reaction.

The reaction between the intermediary Ru-carbenoid and styrene was considered to be slow, since a considerable amount of the mixture of fumaric and maleic acid esters was formed during the reaction.[8] Therefore, improvement of the yield of cyclopropanecarboxylate was expected to be attained by the enhancement of substrate-concentration. Thus, we tried to reduce the amount of THF which was the best solvent for the present reaction in terms of stereoselectivity (Table 3). As expected, chemical yield increased to a considerable extent as the ratio of THF was reduced but stereoselectivity was slightly decreased (entries 1,2).[9] We also examined the cyclopropanation of other olefins with high substrate-concentration and could achieve excellent enantioselectivity (>95% ee) as well as high *cis*-selectivity (entries 3-8). Again, reduction of THF content increases the chemical yields of the desired products (entries 4,5 and 6-8).

Although the experiments described in Tables 1, 2, and 3 were carried out on 0.1 mmol scale about *t*-butyl α-diazoacetate, the following experiment was carried out on 1 mmol scale. Large-scale experiment showed a slightly diminished enantioselectivity (94% ee).

*Asymmetric cyclopropanation of styrene with complex **1***: To a THF solution (2.4 ml) of complex **1** (49 mg, 50 μmol) and styrene (1.2 ml) was added *t*-butyl α-diazoacetate

Table 3 Asymmetric cyclopropanation of various olefins[a)]

entry	substrate	THF-substrate (v/v)	time (h)	yield[b)] (%)	*cis* : *trans*[c)]	% ee *cis* (confign)	% ee *trans* (confign)
1	styrene	2 : 1	48	36	93 : 7	98[d)] (1*S*,2*R*)[e)]	2[d)] (1*R*,2*R*)[e)]
2	"	1 : 1	48	45	93 : 7	97[d)] (1*S*,2*R*)[e)]	-[f)]
3	*p*-chlorostyrene	2 : 1	48	44	93 : 7	95[d,g)]	-[f)]
4	*p*-methoxystyrene	2 : 1	48	62	94 : 6	96[d,g)]	5[d,g)]
5	"	1 : 1	48	80	94 : 6	97[d,g)]	17[d,g)]
6	α-methylstyrene	10 : 1	24	38	83 : 17	97[g,h)]	23[g,i)]
7	"	2 : 1	48	74	81 : 19	97[g,h)]	-[f)]
8	"	1 : 1	48	77	80 : 20	96[g,h)]	-[f)]

a) Reaction was carried out in the presence of the catalyst **1** (5 mol %, based on α-diazoacetate used) at room temperature in a mixture of THF and substrate under irradiation of incandescent light.

b) Yield was calculated on the basis of the amount of α-diazoacetate. Total yield of *cis*- and *trans*-cyclopropanes was determined by ^{1}H NMR analysis (400 MHz) using 1-bromonaphthalene as an internal standard.

c) Ratio of *cis*- and *trans*- isomers was determined by ^{1}H NMR analysis (400 MHz).

d) Enantiomeric excess of the product was determined by HPLC analysis using chiral column (DAICEL CHIRALCEL OD-H, hexane).

e) Configuration was determined by the comparison of the elution order with the authentic samples.

f) Enantiomeric excess has not been determined.

g) Abosolute configuration has not been determined.

h) Enantiomeric excess of the product was determined by HPLC analysis using chiral column (DAICEL CHIRALCEL OJ, hexane).

i) Enantiomeric excess of the product was determined by HPLC analysis using chiral column (DAICEL CHIRALCEL OD-H(x 2), hexane).

(0.14 ml, 1 mmol) and the mixture was stirred at room temperature for 2 days under the incandescent light (100V, 57W) and nitrogen. The mixture was concentrated *in vacuo* and passed through a short silica gel column (hexane/diisopropyl ether=1/0 to 4/1) to remove styrene and the catalyst. The fraction including *cis*- and *trans*-products, di-*t*-butyl fumarate and di-*t*-butyl maleate was concentrated and an aliquot of the sample was diluted with $CDCl_3$ (0.7 ml). *Cis-trans* ratio was determined to be 97 : 3 by ^{1}H NMR analysis (400 MHz). Then all the samples were combined and submitted to silica gel chromatography (hexane/diisopropyl ether=30/1) to yield the *cis*- (76.3 mg, 35%) and *trans*-products (2.1 mg, 1%). Enantiomeric excesses of the *cis*- and *trans*-products were determined by HPLC analysis to be 94 and 10% ee's, respectively.

In conclusion, we were able to demonstrate that stereoselection by the catalyst of high pliability is dependent on the association state (monomeric or aggregated) which in turn depends on the solubility of the catalyst to solvent. Taking this fact into consideration, high *cis*- and enantioselective cyclopropanation was realized. Further study is now proceeding in our laboratory.

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References and Notes

(1) a) Katsuki, T. *J. Mol. Cat. A: Chem.* **1996**, *113*, 87-107. b) Ito, Y. N.; Katsuki, T. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 603-619.

(2) Uchida, T.; Irie, R.; Katsuki, T. *Synlett* **1999**, 1163-1165.

(3) Punniyamurthy, T.; Irie, R.; Katsuki, T.; Akita, M.; Moro-oka, Y. *Synlett*, **1999**, 1049-1052.

(4) For the review of metal-catalyzed asymmetric cyclopropanation, see: a) Doyle, M. P.; McKervey, M. A.; Ye, T. "Modern Catalytic Methods for Organic Synthesis with diazo Compounds," John Wiley & Sons (New York), 1998. b) Doyle, M. P.; Protopopova, M. N. *Tetrahedron* **1998**, *54*, 7919-7946. c) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263-309.

(5) For ruthenium-catalyzed asymmetric cyclopropanation, see: a) Nishiyama, H.; Itoh, Y.; Matsumoto, H.; Park, S.-B.; Itoh, K. *J. Am. Chem. Soc.* **1994**, *116*, 2223-2224. b) Nishiyama, H.; Itoh, Y.; Sugawara, Y.; Matsumoto, H.; Aoki, K.; Itoh, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1247-1262. c) Frauenkron, M.; Berkessel, A. *Tetrahedron Lett.* **1997**, *38*, 7175-7176. d) Lo, W.-C.; Che, C.-M.; Cheng, K.-F.; Mak, T. C. W. *Chem. Commun.* **1997**, 1205-1206. e) Song, J.-H.; Cho, D.-J.; Kim, Y.-H.; Kim, T.-J. *Inorg. Chem.* **1999**, *38*, 893-896.

(6) Catalyst has been considered to be activated by dissociation of the apical ligand which is promoted by irradiation (reference 2 and reference 10).

(7) We observed that non-catalyzed reaction actually occurred in the absence of the catalyst **1** (reference 2).

(8) The yield of a mixture of maleic and fumaric acid esters was 32%, when the reaction was performed in THF-styrene (10/1).

(9) The reaction with ethyl α-diazoacetate in the presence of the catalyst **1** (5 mol %, based on α-diazoacetate used) at room temperature in a mixture of THF and styrene (2/1) under irradiation of incandescent light also proceeded with high *cis*- and enantio-selectivity [*cis* : *trans* = 93 : 7, 95% ee (*cis*-isomer)].

(10) 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.

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