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Co(II)–salen-catalyzed highly *cis*- and enantioselective cyclopropanation

Tatsuo Niimi, Tatsuya Uchida, Ryo Irie and Tsutomu Katsuki *

Department of Molecular Chemistry, Graduate School of Science, Kyushu University, 33 Hakozaki, Higashi-ku, Fukuoka 812-8581, Japan

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Abstract

The reactions of styrene derivatives and *t*-butyl α-diazoacetate using (*R,R*)-(salen)cobalt(II) complex **6** as a catalyst in the presence of *N*-methylimidazole gave the corresponding cyclopropanecarboxylates with excellent enantio- (>95% ee) and high *cis*-stereoselectivity (98%) as well as good chemical yields.

Keywords: chiral Co(II)–salen complex; asymmetric cyclopropanation; *cis*- and enantioselectivity.

Cycloaddition of oxenoide and its isoelectronic species, nitrenoide and carbenoide, to a π-bond constitutes an important class of olefinic transformations, for example, epoxidation, aziridination and cyclopropanation. Differentiation of the enantiotopic faces of double bonds is the main stereochemical issue in this class of reaction. Different from epoxidation and aziridination, however, another stereochemical issue, *cis–trans* selectivity, is imposed on the cyclopropanation reaction due to the presence of a substituent at the carbenoid carbon. Thus, simultaneous control of these two stereochemical problems is indispensable for achieving highly efficient cyclopropanation.

In 1965, Nozaki et al. first dealt with the stereochemical issue in cyclopropanation by using a chiral copper complex as the catalyst, although stereoselectivity was only modest.[1] This pioneering study was improved by Aratani et al. into a highly enantioselective process by modifying the chiral copper complex.[2] Subsequent to these studies, many excellent metal-catalyzed methodologies have been developed for asymmetric cyclopropanation, but most of them are *trans*-selective.[3] Only a few examples show *cis*-selectivity.[4]

We have recently disclosed that chiral metallosalen complexes (hereafter referred to as M-salen complexes) are excellent catalysts for asymmetric transfer reactions of oxenoide and its isoelectronic species.[5] As a part of this study, we examined asymmetric cyclopropanation using Co–salen complexes as catalysts. Originally, Co–salen-catalyzed asymmetric cyclopropanation was started by using

* Corresponding author. Fax: +81 92 642 2586; e-mail: katsuscc@mbox.nc.kyushu-u.ac.jp (T. Katsuki)

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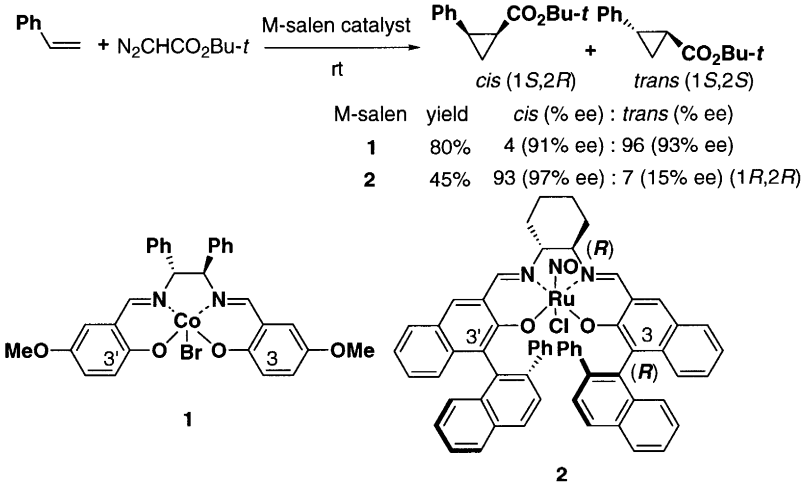
a chiral Co(II)–salen complex as a catalyst but enantioselectivity was low.[6] Later, we found that chiral Co(III)–salen complexes **1** bearing an electron-donating methoxy group at C5 and C5′ and an apical bromo ligand showed high *trans*- and enantioselectivity together with good chemical yields (Scheme 1).[7] It is, however, noteworthy that Co(III)–salen complexes bearing substituents like a methyl or *t*-butyl group at C3 and C3′ showed no catalytic activity. This is probably because olefins approach the intermediary Co(V)-carbenoid species from its C3 and C3′ side and the presence of 3- and 3′-substituents intercepts the olefin's approach from the side. This assumption prompted us to use a chiral Ru–salen complex as the catalyst for asymmetric cyclopropanation for the following reason: the Ru–O_{equat} bond in a Ru–salen complex is ca. 0.2 Å longer than that in Co(III)–salen complexes, and the elongated distance between C3- and C3′-carbons in the Ru–salen complex may allow the olefin's approach from the C3 and C3′ side even if there are substituents at C3 and C3′. As expected, Ru–salen complexes bearing 3,3′-substituents served as the catalyst for cyclopropanation and, among them, (*R*,*R*)-(ON$^+$)(salen)ruthenium(II) complex **2** was for the first time found to show high *cis*- and enantioselectivity in cyclopropanation,[8] but its chemical yield was less than satisfactory due to the undesired reaction of the intermediary Ru–carbenoid and α-diazoacetate to give undesired fumaric and maleic acid esters. To achieve high *cis*- and enantioselectivity and high chemical yields, we again examined Co–salen-catalyzed asymmetric cyclopropanation.

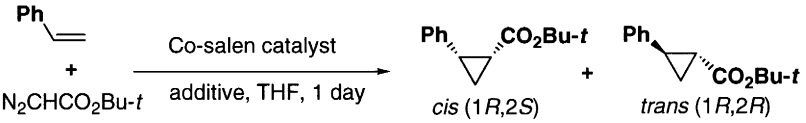


Scheme 1. Highly enantio- and diastereoselective cyclopropanation using metallosalen complexes as catalysts. Co(III)–salen: *trans*-selective; Ru(II)–salen: *cis*-selective

The Co(II)–O_{equat} bond in a Co(II)–salen complex is roughly equal to that in a Co(III)–salen complex. However, the Co(II)–salen complex can adopt various ligand conformations, depending on its ligand substituent or apical ligand.[9] Thus, we expected that a suitably substituted Co(II)–salen complex would show specific catalysis for asymmetric cyclopropanation. To explore this possibility, we prepared five chiral Co(II)–salen complexes (**3**–**7**) and examined the reaction of styrene and *t*-butyl α-diazoacetate (Table 1). Complex **3** which has the same ligand as **1** showed moderate *trans*- and enantioselectivity, although the reaction was slow (entry 1). It is noteworthy that enantiomeric excess of the *cis*-isomer is good (86% ee), although it is a minor product and that the sense of enantioselection by **3** is opposite to that by **1**, suggesting that the conformation of the salen ligand differs in **3** and **1**.[10] To our delight, complexes **4** and **5** bearing substituents at C3 and C3′ were found to catalyze cyclopropanation, although their stereochemistry was moderately *trans*- and enantioselective and the formation of fumaric and maleic acid esters was detected (entries 2 and 3). In these reactions, enantiomeric excesses of minor *cis*-isomers were

also good to high. Encouraged by these results, we next examined the reaction with (*R,R*)-Co(II)–salen complex **6** that has the same ligand as complex **2**. Differing from the reaction with complexes **4** and **5**, the reaction with complex **6** proceeded smoothly with excellent *cis*- and enantioselectivity and only a trace amount of fumaric and maleic acid esters (<1%) was detected (entry 4).

Table 1
Asymmetric cyclopropanation of styrene using Co(II)–salen complexes as catalysts[a)]



Entry	Catalyst	Additive	Yield (%)	*cis*	:	*trans*	*cis* (% ee)	*trans* (% ee)
1	**3**	-	9	19	:	81	86	58
2	**4**	-	39	17	:	83	84	64
3	**5**	-	23	33	:	67	74	20
4	**6**	-	88	92	:	8	96	72
5	**6**	NMI[b)]	89	98	:	2	98	-[c)]
6	**7**	NMI[b)]	18	97	:	3	-99[d)]	-[c)]

a) Styrene (0.48 mmol) and *t*-butyl α-diazoacetate (0.1 mmol) were treated with catalyst (5 mol %, based on α-diazoacetate used) for 24 h at room temperature in THF (1.2 ml) under N_2 atmosphere, 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 comparison of the elution order with the authentic samples. Ratio of *cis*- and *trans*- isomers was determined by ^{1}H NMR analysis (400 MHz). Yield was calculated on the basis of the amount of α-diazoacetate used. Total yield of *cis*- and *trans*-cyclopropanes was determined by ^{1}H NMR analysis (400 MHz) using 1-bromonaphthalene as an internal standard.
b) *N*-Methylimidazole (10 μmol) was added.
c) Enantiomeric excess has not been determined.
d) Absolute configuration is 1*S*,2*R*.

It is noteworthy that the sense of enantioselection by complex **6** was opposite to that by complex **2** bearing the same ligand as **6**, although the reaction conditions were the same. This also suggests that complexes **2** and **6** have different ligand-conformation to each other, but further experimentation is required to draw any conclusion on the ligand-conformation.[10] Quite recently, Yamada et al. reported that the rate and the enantioselectivity of the cyclopropanation using a chiral aldiminato cobalt(II) complex as the catalyst were improved by adding *N*-methylimidazole to the reaction medium.[11] Based on this report, we also performed the reaction in the presence of *N*-methylimidazole and found that both *cis*- and enantioselectivity were further improved up to a ratio of 98:2 and 98% ee (entry 5). We examined the reaction using (*R,S*)-Co(II)–salen complex **7** in the presence of *N*-methylimidazole. The reaction also exhibited excellent *cis*- and enantioselectivity, but the reaction was slow even in the presence of *N*-methylimidazole (entry 6).

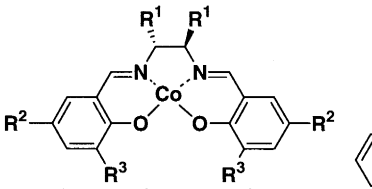
Under the optimized conditions, we examined the cyclopropanation of other substrates (Table 2). All the reactions examined also showed good to excellent *cis*- and enantioselectivity. The chemical yields of the desired cyclopropanes were good, except for the reaction of α-methylstyrene, and only a trace amount of fumaric and maleic acid esters was detected in all the reactions. Although asymmetric configuration of the products has not been determined, the configuration of the major *cis*-isomers was also found to be opposite to the configuration of the corresponding *cis*-isomers obtained with complex **2** by HPLC analyses (vide supra). It is, however, noteworthy that the catalysts **2** and **6** showed the same sense of enantioselection only in the cyclopropanation of α-methylstyrene.

Table 2
Asymmetric cyclopropanation of various olefins using complex **6** as the catalyst[a)]

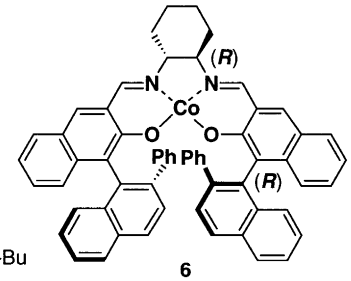
Entry	Substrate	THF (ml)	Yield[b)] (%)	*cis* : *trans*[c)]	% ee[d)] *cis* isomer	% ee[d)] *trans* isomer
1	*p*-chlorostyrene	1.2	85	97: 3	96[e)]	-[f)]
2	*p*-methoxystyrene	0.5	84	97: 3	95[e)]	-[f)]
3	2-vinylnaphthalene	1.2	94	98: 2	97[g)]	-[f)]
4	α-methylstyrene	0.5	39	83:17	99[h)]	99[i)]

a) Olefins (0.5 mmol) and *t*-butyl α-diazoacetate (0.1 mmol) were treated with catalyst **6** (5 mol %, based on α-diazoacetate used) for 24 h in the presence of *N*-methylimidazole (10 μmol) at room temperature in THF.
b) Yield was calculated on the basis of the amount of α-diazoacetate used. 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) Absolute configuration has not been determined.
e) Enantiomeric excess of the product was determined by HPLC analysis using chiral column (DAICEL CHIRALCEL OD-H, hexane).
f) Enantiomeric excess has not been determined.
g) Enantiomeric excess of the product was determined by HPLC analysis using chiral column (DAICEL CHIRALCEL OD-H, hexane/*i*-PrOH = 200/1).
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].

Asymmetric cyclopropanation of styrene with complex **6**:[12] To a THF solution (5 ml) of Co(II)–salen complex **6**[13] (44 mg, 50 μmol) was added a THF solution of *N*-methylimidazole (0.2 ml, 0.5 M, 0.1 mmol) under a nitrogen atmosphere and the mixture was stirred for 2 min. Styrene (550 μl, 4.8 mmol) was added to this solution and the mixture was stirred for another 3 min before being treated with *t*-butyl α-diazoacetate (140 μl, 1.0 mmol). The whole mixture was stirred for 24 h at room temperature and then concentrated in vacuo. The residue was chromatographed on silica gel (hexane:AcOEt=1:0 to 9:1) to give a 98:2 mixture of *cis* and *trans* products in a 89% yield. An aliquot of the mixture was submitted to preparative TLC (silica gel, hexane:*i*-Pr_2O=4:1) to yield the *cis* product which was used for the determination of its enantiomeric excess (98% ee).



3: R^1 = Ph, R^2 = OMe, R^3 = H
4: R^1 = Ph, R^2 = Cl, R^3 = Cl
5: R^1 = -$(CH_2)_4$-, R^2 = *t*-Bu, R^3 = *t*-Bu



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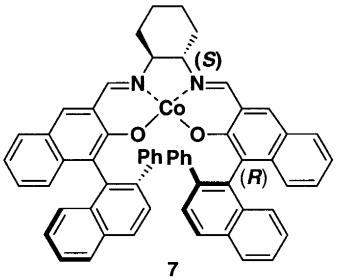

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In conclusion, we were able to disclose that Co(II)– and Co(III)–salen complexes show considerably different asymmetric catalytic activity and, by taking advantage of each cobalt complex, we achieved both *cis*- and *trans*-selective asymmetric cyclopropanations. Further study on the reaction mechanism is now proceeding in our laboratory.

Acknowledgements

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10. The sense and magnitude of enantioselection by metallosalen complexes are dependent on the conformation of their ligands (Ref. 14). The sense of enantioselection by **2** was dependent on the solvent used (Ref. 8b): the complex **2** dissolved in the reaction medium showed the opposite sense of enantioselection to the complex suspended in the reaction medium. The change in the sense of enantioselection from homogeneous to heterogeneous catalysts was attributed to the change of the ligand-conformation caused by the association of the complex. The sense of enantioselection by **6** and **2** in THF that is the solvent of choice for the present reaction is opposite to each other.
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12. A typical experimental procedure was carried out in a 10-fold scale of the experiments described in Tables 1 and 2.
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