光学活性なサレン-コバルト錯体を用いた触媒的不斉カルベン移動反応に関する研究

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Study on Catalytic and Asymmetric Carbene Transfer Reactions
Using Chiral (Salen)cobalt(III) Complexes
Study on Catalytic and Asymmetric Carbene Transfer Reactions Using Chiral (Salen)cobalt(III) Complexes

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Contents

Chapter 1 Introduction 1

Chapter 2 Study on Enantioselective Cyclopropanation Using Co(III)-Salen Complex as a Catalyst 15
  2-1 Previous Examples of Asymmetric Cyclopropanation 16
  2-2 Preparation of Co(II)- and Co(III)-Salen Complexes 19
  2-3 Asymmetric Cyclopropanation of Styrene Derivatives Using Co(III)-Salen Complexes 20
  2-4 Asymmetric Induction Mechanism of Co(III)-Salen Catalyzed Cyclopropanation 24

Chapter 3 Study on Catalytic and Asymmetric [2,3]Sigmatropic Rearrangement 26
  3-1 Previous Examples of Carbenoid-Mediated Asymmetric [2,3]Sigmatropic Rearrangement 27
  3-2 Asymmetric [2,3]Sigmatropic Rearrangement of Chiral S-Ylides Derived from Allyl Aryl Sulfides Using Co(III)-Salen Complexes as Catalysts 32
  3-3 Determination of Absolute Configuration of Major anti-Isomer Obtained by Reaction of Cinnamyl Phenyl Sulfide 36
  3-4 Discussion on Stereochemistry of [2,3]Sigmatropic Rearrangement of S-Ylide 38

Chapter 4 Conclusion 41

Chapter 5 Experimental 43

References and Notes 57
Chapter 1

Introduction
Carbene is a neutral active species reacting with C=C and C-H bonds with the formation of new carbon-carbon bond(s). Thus, the stereocontrolled carbene reactions are expected to be useful tools for stereoselective construction of organic compounds. However, carbene itself is so reactive that its reaction is difficult to be controlled. On the other hand, carbene makes complexes with various metal ions. These complexes are called carbenoids (or metal carbenoids). Although carbenoids show reactivity similar to carbene, their reactivities vary with the nature of the metal ion and its ligand. That is, the reactivity of carbenoid can be regulated by the appropriate choice of metal ion or of its ligand. Furthermore, metal carbenoids can be readily prepared \textit{in situ} by the decomposition of diazo compounds in the presence of transition metal ions such as Cu(I), Cu(II), Co(II), Co(III), Ru(II), Rh(II), Rh(III), etc. For these reasons, the chemistry of carbenoid has attracted the attention of synthetic chemists. In this chapter, we briefly outline carbenoid and the related chemistries.

Olefins react with diazo compounds in the presence of transition metal complex to give the corresponding cyclopropanes. In this reaction, diazo compound 1 first coordinates with Lewis acidic transition metal complex L_nM to give complex 2, which undergoes elimination of N_2 affording carbenoid 3. Carbenoid 3 transfers carbene to olefins to give cyclopropanes 4.

![Scheme 1](image-url)
regenerating the catalyst $L_nM$ (Scheme 1). If the ligand $L$ of the metal complex is chiral, cyclopropanation occurs in an asymmetric coordination sphere.

In 1966, Nozaki et al. reported the first catalytic and enantioselective carbene transfer reactions, asymmetric cyclopropanation and enantiomer-differentiating carbon-oxygen bond insertion reaction by using chiral copper(II)-Schiff base complex 5 as a catalyst (Scheme 2). This is the dawn of metal-catalyzed asymmetric carbenoid chemistry, though enantioselectivity of the reactions was low.

In asymmetric cyclopropanation, there are two stereochemical problems, enantiofacial selection of prochiral olefins and trans-cis selectivity. These problems must be solved for asymmetric cyclopropanation to be practical and much effort has been directed toward this goal.

Following the Nozaki's pioneering investigation, Aratani et al. have performed extensive study on asymmetric cyclopropanation using copper(II)-Schiff base complex as a catalyst and attained the practical level of asymmetric cyclopropanation with the improved copper(II)-Schiff base catalyst 6 (Scheme 3). For example, cyclopropanation of 2,5-dimethylhexa-2,4-diene with catalyst 6 provides the corresponding cyclopropanecarboxylic acid ester of 94% ee, that serves as
the acid component of pyrethroids (Scheme 3). In parallel with Aratani’s study, cobalt(II)-bis(α-
camphorquinonedioximato) complex 7 has been found to be an efficient catalyst for
enantioselective cyclopropanation by Nakamura and Otsuka et al.\textsuperscript{4}) This catalyst also shows good
enantioselectivity of up to 88\% ee (Scheme 4).

\[
\begin{align*}
\text{N}_{2}\text{CHCO}_{2}\text{R} & \quad \xrightarrow{6} \quad \text{CO}_{2}\text{R} \quad \xrightarrow{6} \quad \text{R} = \text{I-menthyl} \\
\text{CO}_{2}\text{R} & \quad \xrightarrow{6} \quad \text{CO}_{2}\text{R} \\
\end{align*}
\]

\(94\% \text{ ee} \quad (93:7) \quad 46\% \text{ ee}\)

\[
\text{R} = \text{5-tert-butyl-2-octyloxyphenyl}
\]

Scheme 3

\[
\begin{align*}
\text{Ph} & \quad \xrightarrow{7} \quad \text{CO}_{2}\text{R} \\
\text{R} = \text{neopentyl} \\
\end{align*}
\]

\(88\% \text{ ee} \quad 81\% \text{ ee}\)

Furthermone, high enantioselectivity greater than 95\% ee has been realized by introduction of
copper complexes bearing new type of chiral bidentate nitrogen ligand(s), which are possessed of
\(C_2\)-symmetry, such as Cu(II)-semicorrin 8\textsuperscript{5a,b)} Cu(I)-azasemicorrin 9\textsuperscript{5d)} Cu(II)-bis(oxazoline)
10\textsuperscript{6a)} and Cu(I)-bis(oxazoline) 11.\textsuperscript{7)} Among these catalysts, complexes 8 and 10 are copper(II)
species and are reduced in situ to the corresponding copper(I) species prior to the reaction by treatment with a diazo ester or phenylhydrazine (Scheme 5).

\[
\text{Ph} + \text{N}_2\text{CHCO}_2\text{R} \xrightarrow{\text{catalyst}} \begin{array}{c}
\text{trans} \\
\text{cis}
\end{array}
\]

<table>
<thead>
<tr>
<th>No.</th>
<th>R</th>
<th>ee (1S,2S)</th>
<th>ee (1S,2R)</th>
<th>ee (1R,2S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>d-menthyl</td>
<td>97%</td>
<td>95%</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>d-menthyl</td>
<td>98%</td>
<td>99%</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>l-menthyl</td>
<td>98%</td>
<td></td>
<td>96%</td>
</tr>
<tr>
<td>11</td>
<td>t-Bu, CN</td>
<td>96%</td>
<td></td>
<td>93%</td>
</tr>
</tbody>
</table>

\[\text{Scheme 5}\]

Doyle et al. have reported asymmetric cyclopropanation using dirhodium(II)-tetrakis(carboxamidates) complex 12 as a catalyst. This catalyst reveals a high level of enantiocontrol in intramolecular cyclopropanation, while moderate enantioselectivity is observed in intermolecular cyclopropanation (Scheme 6).\(^8\) Another rhodium catalyst, rhodium(III)-porphyrin complex 13 bearing 1-(1-pyrenyl)-2-naphthyl group as a chiral moiety has been introduced by Kodadek et al. It is noteworthy that this reaction shows high cis-selectivity different from the many other cyclopropanations, though its enantioselectivity is only modest (Scheme 7).\(^9\)
Katsuki and Ito have developed a series of copper(I) complexes bearing $C_2$-symmetric bipyridine ligand such as 14 and 15 (Scheme 8). The complexes that have structures similar to semicorrin and bis(oxazoline) complexes show excellent enantioselectivity in cyclopropanation.\textsuperscript{10)
Furthermore, the complex 15 promotes enantiospecific ring expansion of oxetanes that provides an efficient method for enantioselective synthesis of tetrahydrofurans.\textsuperscript{10c)}

\[
\text{Ph} + \text{N}_2\text{CHCO}_2\text{Bu-t} \rightarrow 14 \rightarrow \text{Ph} + \text{PhCO}_2\text{Bu-t}
\]

\[
\text{Ph}_2\text{O} + \text{N}_2\text{CHCO}_2\text{Bu-t} \rightarrow 15 \rightarrow \text{Ph}_2\text{O} + \text{Ph}_2\text{CO}_2\text{Bu-t}
\]

\[
\text{Nishiyama et al. have reported that chiral ruthenium(II)-bis(2-oxazolin-2-yl)pyridine complex 16 catalyzes asymmetric cyclopropanation with high enantioselectivity as well as remarkable trans-selectivity (Scheme 9). This is the first example which overcomes the two stereochemical problems (enantioface selectivity and trans-cis selectivity) imposed by cyclopropanation.}^{11)}
\]

\[
\text{Ph} + \text{N}_2\text{CHCO}_2\text{R} \rightarrow 16 \rightarrow \text{Ph} + \text{PhCO}_2\text{R}
\]

\[
\text{Scheme 8}
\]

\[
\text{Scheme 9}
\]
Quite recently, ruthenium(II)-porphyrin complex 17 was found to be an effective catalyst for asymmetric cyclopropanation of styrene by two groups independently (Scheme 10).\textsuperscript{12,13} Like ruthenium catalyst 16, this catalyst also showed excellent \textit{trans}-selectivity with high enantioselectivity of \textit{trans}-isomer, though enantioselectivity of \textit{cis}-isomer was low. Furthermore over 1000 catalyst turnover was achieved. Unfortunately, however, the reported absolute configuration of the \textit{trans}-product is not consistent with each other, though they used the same complex as the catalyst.

\begin{center}
\begin{tikzpicture}
\node at (-2,0) {\textbf{Scheme 10}};
\end{tikzpicture}
\end{center}

In the preceding paragraphs, we discussed about carbene and carbenoid chemistries. Carbene has the same electronic structure as oxene and nitrene and, therefore, it is expected that carbene transfer can be catalyzed by the complex which catalyzes oxene and/or nitrene transfer reaction (Scheme 11).

Several types of enzymes and catalysts catalyze highly enantioselective oxene and nitrene transfer reactions. In biological oxidations, oxidizing enzymes such as cytochrome P-450 which
carries ironporphyrin complex as a reacting site, catalyze oxygen (oxene) transfer reaction such as epoxidation and C-H hydroxylation in a highly enantioselective manner. Many optically active synthetic metalloporphyrins have been synthesized as model compounds for the active site of cytochrome P-450 and used as catalysts for epoxidation of simple olefins. Epoxidation of mono-substituted and cis-disubstituted olefins with these porphyrin complexes generally shows moderate to good level of enantioselectivity. One example of asymmetric epoxidation using a chiral metalloporphyrin catalyst is depicted in Scheme 12.
On the other hand, Kochi et al. have reported that (salen)chromium(III) and (salen)manganese(III) complexes, the structures of which are similar to that of porphyrin complex, are effective catalysts for the epoxidation of simple conjugated olefins, when iodosylbenzene is used as a terminal oxidant. These epoxidations also proceed through metallooxenyenoid species. Following this study, asymmetric epoxidation using optically active Mn(III)-salen complexes, 19 and 20 as catalysts was reported independently by Katsuki's and Jacobsen's groups. Excellent enantioselectivity has been achieved in the epoxidation of conjugated cis-disubstituted and trisubstituted olefins especially when the complex 19 is used as the catalyst (Scheme 13).

The high enantioselectivity observed in Mn(III)-salen catalyzed asymmetric epoxidation is partly attributed to those stereogenic carbons (C1" and C2" and/or C8 and C8' carbons) in Mn(III)-salen complexes locate closer to the metal center than those in chiral porphyrin complexes (Fig. 1).

Asymmetric nitrene transfer reaction such as aziridination has also been investigated by using (salen)manganese(III) complexes. Burrows et al. first examined asymmetric aziridination with chiral Mn(III)-salen complex 21 as a catalyst and \( N-(p\text{-tolylenesulfonyl})\text{imino} \)phenyliodinane...
Phi=NTs as a nitrene source. However, no asymmetric induction was observed in the aziridination of styrene, while the epoxidation of the same substrate with 21 showed modest enantioselectivity (Scheme 14).18)

Recently, Katsuki et al. have reported that Mn(III)-salen complexes 22 and 23 bearing bulky chiral substituents at C3 and C3’ carbons are effective catalysts for asymmetric aziridination of styrene.19) In particular, newly designed Mn(III)-salen catalyst 23 which is possessed of 2-biphenyl
groups at C3 and C3' carbons, showed high level of enantioselectivity (94% ee) in the presence of 4-phenylpyridine N-oxide (Scheme 15).^{19b}

![Scheme 15](image)

Judging from the above metallosalen-catalyzed asymmetric oxene and nitrene transfer reactions, chiral metallosalen complexes are also expected to serve as catalysts for enantioselective carbene transfer reaction with high efficiency (Scheme 16), nevertheless there has been no report on asymmetric cyclopropanation using chiral metallosalen complex as a catalyst except for one example: Nakamura and Otsuka \textit{et al.} have reported asymmetric cyclopropanation of styrene using optically active Co(II)-salen complex \(^{24}\) as a catalyst, though enantioselectivity of the reaction is low (< 5% ee) (Scheme 17).^{4a}

However, in the study of Mn-salen catalyzed epoxidation, it has been observed that the axial ligand gives strong influence on asymmetric induction by (salen)manganese complex.\(^{16}\) This suggested the author that the use of chiral Co(III)-salen complex bearing an axial ligand instead of Co(II)-salen complex may improve the asymmetric induction in carbene transfer reaction. In order to explore this possibility, the author investigated the Co(III)-salen catalyzed carbene transfer reaction.
In this thesis, the author discusses about catalytic asymmetric cyclopropanation reaction and [2,3]sigmatropic rearrangement reaction using chiral Co(III)-salen complexes as catalysts (Fig. 2).

\[ \text{R} \quad \text{R} \quad \text{X} \]
\[ \text{\rotatebox{90}{N}} \quad \text{\rotatebox{90}{N}} \quad \text{\rotatebox{90}{M}} \]
\[ \text{\rotatebox{90}{O}} \quad \text{\rotatebox{90}{O}} \quad \text{\rotatebox{90}{O}} \]

\( \text{X}=\text{O}, \text{oxenoid species} \)
\( \text{X}=\text{NR}^\prime, \text{nitrenoid species} \)
\( \text{X}=\text{CHR}^\prime, \text{carbenoid species} \)

Scheme 16

\[ \text{Ph} + \text{N}_2\text{CHCO}_2\text{Et} \xrightarrow{24} \text{Ph}^\text{CO}_2\text{Et} + \text{Ph}^\text{CO}_2\text{Et} \]

\( \leq 5\% \text{ ee} \)

Scheme 17
Fig. 2
Chapter 2

Study on Enantioselective Cyclopropanation Using Co(III)-Salen Complex as a Catalyst
2-1. Previous Examples of Asymmetric Cyclopropanation

Many transition metal complexes are known to catalyze decomposition of α-diazo esters and the resulting carbenoid species undergo methylene transfer reaction to olefins, giving the corresponding cyclopropane adducts without difficulty (Scheme 18).

\[ \text{transition metal catalyst} \quad \text{cis} \]

Scheme 18

Cyclopropane structures have been widely seen as subunits of various natural products, therefore, control of the stereochemistry (enantioselectivity and trans-cis selectivity) in cyclopropane formation is one of the most important subjects in organic synthesis and many methodologies have so far been developed for this purpose. Especially, chiral transition metal complex-catalyzed asymmetric cyclopropanation has been intensively investigated since Nozaki's pioneering work in 1966 (Chapter 1, Scheme 2).

In consequence, high enantioselectivity has been realized by using Cu(II)-Schiff base, Co(II)-bis(dioxime), Cu(II)-semicorrin, Cu(I)-azasemcorrin, Cu(II)-bis(oxazoline), Cu(I)-bis(oxazoline), Rh₂(5S-MEPY)₄, Cu(I)-bipyridine, Ru(II)-pybox, and Ru(II)-porphyrin complexes as catalysts, as discussed in the preceding chapter.

Catalytic asymmetric cyclopropanation of styrene with α-diazo ester derivatives in the presence of these complexes are summarized in Table 1. Most of the reactions show good to excellent enantioselectivity. However, they exhibit moderate trans-cis selectivity, except for the reactions with Ru(II)-complexes 16 and 17 which show high enantioselectivity as well as high trans-cis selectivity.
Table 1. Asymmetric cyclopropanation of styrene using various catalysts.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>R</th>
<th>Yield</th>
<th>trans:cis</th>
<th>trans(% ee)</th>
<th>cis(% ee)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>l-menthyl</td>
<td></td>
<td>82:18</td>
<td>81(1R,2R)</td>
<td>78(1R,2S)</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>Et</td>
<td>80</td>
<td>49:51</td>
<td>76(1S,2S)</td>
<td>72(1S,2R)</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>Et</td>
<td>65</td>
<td>73:27</td>
<td>92(1S,2S)</td>
<td>79(1S,2R)</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>t-Bu</td>
<td>60</td>
<td>84:16</td>
<td>93(1S,2S)</td>
<td>92(1S,2R)</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>d-menthyl</td>
<td>70</td>
<td>82:18</td>
<td>97(1S,2S)</td>
<td>95(1S,2R)</td>
</tr>
<tr>
<td>6</td>
<td>9</td>
<td>Et</td>
<td>45</td>
<td>77:23</td>
<td>95(1S,2S)</td>
<td>90(1S,2R)</td>
</tr>
<tr>
<td>7</td>
<td>9</td>
<td>t-Bu</td>
<td>75</td>
<td>81:19</td>
<td>94(1S,2S)</td>
<td>95(1S,2R)</td>
</tr>
<tr>
<td>8</td>
<td>9</td>
<td>d-menthyl</td>
<td>75</td>
<td>84:16</td>
<td>98(1S,2S)</td>
<td>99(1S,2R)</td>
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<tr>
<td>9</td>
<td>10</td>
<td>Et</td>
<td>80</td>
<td>75:25</td>
<td>90(1R,2R)</td>
<td>77(1R,2S)</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>t-Bu</td>
<td>73</td>
<td>80:20</td>
<td>94(1R,2R)</td>
<td>89(1R,2S)</td>
</tr>
<tr>
<td>11</td>
<td>10</td>
<td>l-menthyl</td>
<td>72</td>
<td>86:14</td>
<td>98(1R,2R)</td>
<td>96(1R,2S)</td>
</tr>
<tr>
<td>12</td>
<td>11</td>
<td>Et</td>
<td>77</td>
<td>73:27</td>
<td>99(1R,2R)</td>
<td>97(1R,2S)</td>
</tr>
<tr>
<td>13</td>
<td>11</td>
<td>t-Bu</td>
<td>75</td>
<td>81:19</td>
<td>96(1R,2R)</td>
<td>93(1R,2S)</td>
</tr>
<tr>
<td>14</td>
<td>12</td>
<td>Et</td>
<td>59</td>
<td>56:44</td>
<td>58(1S,2S)</td>
<td>33(1S,2R)</td>
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<tr>
<td>15</td>
<td>12</td>
<td>t-Bu</td>
<td>55</td>
<td>60:40</td>
<td>57(1S,2S)</td>
<td>73(1S,2R)</td>
</tr>
<tr>
<td>16</td>
<td>12</td>
<td>d-menthyl</td>
<td>69</td>
<td>67:33</td>
<td>48(1S,2S)</td>
<td>86(1S,2R)</td>
</tr>
<tr>
<td>17</td>
<td>14</td>
<td>t-Bu</td>
<td>75</td>
<td>86:14</td>
<td>92(1S,2S)</td>
<td>98(1S,2R)</td>
</tr>
<tr>
<td>18</td>
<td>16</td>
<td>Et</td>
<td>73</td>
<td>91:9</td>
<td>89(1R,2R)</td>
<td>79(1R,2S)</td>
</tr>
<tr>
<td>19</td>
<td>16</td>
<td>t-Bu</td>
<td>65</td>
<td>97:3</td>
<td>94(1R,2R)</td>
<td>87(1R,2S)</td>
</tr>
<tr>
<td>20</td>
<td>16</td>
<td>l-menthyl</td>
<td>83</td>
<td>97:3</td>
<td>96(1R,2R)</td>
<td>80(1R,2S)</td>
</tr>
<tr>
<td>21c</td>
<td>17</td>
<td>Et</td>
<td>quant.</td>
<td>96:4</td>
<td>91(1S,2S)</td>
<td>4b)</td>
</tr>
<tr>
<td>22c</td>
<td>17</td>
<td>Et</td>
<td>63</td>
<td>95:5</td>
<td>91(1R,2R)</td>
<td>27(1R,2S)</td>
</tr>
</tbody>
</table>

a) Reported by Che and Cheng's group (ref. 12).
b) Absolute configuration was not determined.
c) Reported by Berkessel's group (ref. 13).
On the other hand, optically active metallosalen complexes are expected to be efficient catalysts for asymmetric carbene transfer reaction in analogy with highly enantioselective oxene\textsuperscript{16)} and nitrene\textsuperscript{19b)} transfer reactions catalyzed by optically active (salen)manganese(III) complexes. However, study of metallosalen-catalyzed asymmetric cyclopropanation had been very limited. Nakamura and Otsuka \textit{et al.} reported asymmetric cyclopropanation using optically active (salen)cobalt(II) complex 24 as a catalyst but its enantioselectivity was low (Chapter 1, Scheme 17).\textsuperscript{4a)}

During the study on asymmetric epoxidation and aziridination using optically active cationic (salen)manganese(III) complex, the axial ligand (fifth ligand) of the complexes was found to play an important role in inducing asymmetry. For example, enantioselectivity of epoxidation using (salen)manganese(III) complex is improved by adding a donor ligand such as 4-phenylpyridine N-oxide.\textsuperscript{22)} By analogy, the author expected that chiral (salen)cobalt(III) complex bearing an axial ligand such as iodine or bromine would be a better catalyst for asymmetric cyclopropanation (Fig. 3) than the corresponding (salen)cobalt(II) complex. Thus, the author examined the Co(III)-salen catalyzed asymmetric cyclopropanation.

\begin{center}
\includegraphics[width=0.8\textwidth]{Fig3.png}
\end{center}

\textit{Fig. 3}
2-2. Preparation of Co(II)- and Co(III)-Salen Complexes

Co(II)-salen complexes 25-30 were synthesized from Co(OAc)$_2$ and the corresponding salen ligands, which were in turn prepared from (1$R$,2$R$)-1,2-diphenylethlenediamine and the corresponding salicylaldehydes, in ethanol under nitrogen atmosphere.$^{23}$ Complexes 25-30 thus obtained were in situ oxidized by treatment with $X_2$ (iodine or bromine) in dichloromethane into the corresponding Co(III)-salen complexes 25-X-30-X which were used for asymmetric cyclopropanation without further purification (Scheme 19)$^{24}$.
2-3. Asymmetric Cyclopropanation of Styrene Derivatives Using Co(III)-Salen Complexes

Cyclopropanation of styrene was examined by using these Co(III)-salen complexes as catalysts and tert-butyl diazoacetate as a carbene source in dichloromethane. Since Mn(III)-salen complexes bearing bulky and/or chiral substituents at C3- and C3'-carbons have been known to be efficient catalysts for asymmetric epoxidation (Chapter 1, Scheme 13), the author first examined asymmetric cyclopropanation using Co(III)-salen complexes (26-I, 26-Br, 29-I, or 29-Br) as catalysts. Contrary to his expectation, these complexes showed no or very poor catalytic activity (Table 2, entries 3, 4, 9, and 10). Complexes 25-I, 27-I, and 28-I which had no C3 and C3' substituent, however, was found to catalyze the desired reaction with moderate enantioselectivity (64-75% ee) and high trans-cis selectivity (Table 2, entries 1, 5, and 7). Introduction of sterically bulky tert-butyl group at 4(4')- or 5(5')-carbons only slightly improves the enantioselectivity (entries 5 and 7). Therefore, the author tried to improve asymmetry-inducing ability of the catalyst by changing the electronic nature of the ligand. The author first examined the trans-ligand effect on enantioselectivity. The axial iodide ligand is trans to carbenoid ligand. It is expected that coordination of the axial ligand of weaker trans-effect strengthens the metal-carbenoid bond, that is, reactivity of the metal carbenoid is decreased by the coordination of such an axial ligand. Since the trans-effect of bromide ligand is weaker than that of iodide ligand, we next examined the reaction using the bromide complexes as catalysts. As expected, the complexes 25-Br, 27-Br, and 28-Br showed better enantioselectivity than the corresponding iodides 25-I, 27-I, and 28-I, respectively (Table 2, entries 2, 6, and 8). However, further improvement is needed for practical use.

To improve enantioselectivity, the author also examined the effect of electronic nature of the substituent of the salen ligand. Fujita et al. had reported that chiral (salen)vanadium complex 34 bearing electron-donating methoxy group at C3- and C3'-carbons showed better asymmetric induction in the oxidation of thioanisole than the (salen)vanadium complexes 32 and 33 (Scheme 20). A similar phenomenon was also observed in Mn(III)-salen catalyzed asymmetric oxidation of sulfides (Scheme 21).
Table 2. Asymmetric cyclopropanation of styrene using Co(III)-salen complex as a catalyst.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield (%)</th>
<th>trans:cis&lt;sup&gt;a&lt;/sup&gt;</th>
<th>% ee&lt;sup&gt;b&lt;/sup&gt;(trans)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>% ee&lt;sup&gt;d&lt;/sup&gt;(cis)&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25-I</td>
<td>79</td>
<td>95:5</td>
<td>64(1S,2S)</td>
<td>51(1S,2R)</td>
</tr>
<tr>
<td>2</td>
<td>25-Br</td>
<td>83</td>
<td>95:5</td>
<td>66(1S,2S)</td>
<td>82(1S,2R)</td>
</tr>
<tr>
<td>3</td>
<td>26-I</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>26-Br</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>27-I</td>
<td>76</td>
<td>98:2</td>
<td>73(1S,2S)</td>
<td>-&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>27-Br</td>
<td>85</td>
<td>96:4</td>
<td>89(1S,2S)</td>
<td>93(1S,2R)</td>
</tr>
<tr>
<td>7</td>
<td>28-I</td>
<td>76</td>
<td>95:5</td>
<td>75(1S,2S)</td>
<td>-&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>28-Br</td>
<td>55</td>
<td>94:6</td>
<td>83(1S,2S)</td>
<td>42(1S,2R)</td>
</tr>
<tr>
<td>9</td>
<td>29-I</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>29-Br</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>30-Br</td>
<td>80</td>
<td>96:4</td>
<td>93(1S,2S)</td>
<td>91(1S,2R)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by <sup>1</sup>H NMR analysis (270 MHz).
<sup>b</sup> Determined by HPLC analysis using optically active column (DAICEL CHIRALCEL OJ; hexane/i-PrOH = 9/1), after the ester was reduced to the corresponding alcohol by LiAlH<sub>4</sub>.
<sup>c</sup> Determined by the comparison of HPLC elution order of the enantiomers of trans-2-(phenylcyclopropyl)methanol after LiAlH<sub>4</sub>-reduction, with the authentic samples prepared according to the reported procedure (ref. 10).
<sup>d</sup> Determined by GC analysis (SUPELCO B-DEX 120 fused silica capillary column, 30 m x 0.25 mm ID, 0.25 μm film, col. temp.: 110 °C), after the tert-butyl ester was converted into the corresponding methyl ester by the sequence: i) TFA deprotection and ii) CH<sub>2</sub>N<sub>2</sub> methylation.
<sup>e</sup> Determined by the comparison of GC elution order of the enantiomers of methyl cis-2-(phenylcyclopropyl)carboxylate derived from the obtained cis-isomer by hydrolysis and the subsequent CH<sub>2</sub>N<sub>2</sub> treatment, with the authentic sample prepared according to the reported procedure (ref. 10).
<sup>f</sup> The formation of only a trace amount of the product was detected by TLC analysis.
<sup>g</sup> Not determined.
Therefore, the author next examined cyclopropanation using complex 30-Br bearing methoxy group at C5- and C5'-carbons. Enantioselectivity could be improved as high as 93% ee, without decaying high trans-cis selectivity (entry 11). With this catalyst, asymmetric cyclopropanation of other styrene derivatives was also examined. They also showed high enantioselectivity as well.
as high trans-selectivity (Table 3). However, the reaction of disubstituted olefins such as indene was sluggish.

Cyclopropanation of 4-chlorostyrene bearing electron withdrawing group showed higher enantioselectivity than that of styrene. This indicates that the intermediate Co-salen carbene species is possessed of electrophilic character.

![Chemical reaction diagram]

Table 3. Asymmetric cyclopropanation of styrene derivatives using complex 30-Br as a catalyst.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Yield (%)</th>
<th>trans:cis&lt;sup&gt;a&lt;/sup&gt;</th>
<th>% ee(trans)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-naphthyl</td>
<td>87</td>
<td>95:5</td>
<td>92&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>4-ClC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>86</td>
<td>97:3</td>
<td>96&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

a) Determined by <sup>1</sup>H NMR analysis (270 MHz).
b) Absolute configuration has not been determined.
c) Determined by HPLC analysis using optically active column (DAICEL CHIRALCEL OB-H; hexane/i-PrOH = 50/1).
d) Determined by HPLC analysis using optically active column (DAICEL CHIRALCEL OD; hexane/i-PrOH = 100/1), after the ester was converted into the acetate by the sequence: i) LiAlH<sub>4</sub> reduction and ii) acetylation.
2-4. Asymmetric Induction Mechanism of Co(III)-Salen Catalyzed Cyclopropanation

In a series of the mechanistic investigations on Mn(III)-salen catalyzed epoxidation, it has been proposed that the ligands of the intermediary oxene Mn(V)-salen complexes have non-planar structures and that non-planarity of the salen ligand played very important role in asymmetric induction by Mn-salen catalyst. In present reaction, however, the carbenoid carbon of Co(V)-salen carbenoid species also had a non-planar structure, as shown in Fig. 4, which was drawn by calculation using TRIPOS-SYBYL on an IRIS Indigo 2. Differing from the oxygen atom of oxene Mn(V)-salen species, however, the carbenoid carbon of Co(V)-salen species carries a bulky tert-butoxycarbonyl group on it and it is considered to protrude over the downward benzene ring (A). In Mn(III)-salen catalyzed epoxidation, olefins have been proposed to approach metal oxene bond from it side passing over the downward benzene ring. In the present reaction, however, this pathway is blocked by the presence of the carbenoid ester group. Thus styrene is forced to approach the carbenoid carbon from the front side (Fig. 4), directing its phenyl group away from the ester group to give (1S,2S)-isomer in preferential. This assumption is well compatible with the observation that the Co(III)-salen complexes bearing C3(3')-substituents show no or very poor catalytic activity. C3(3')-Substituents probably interfere with the incoming olefins. Effect of axial ligand and the substituent of salen ligand on enantioselectivity may be explained as follows. Introduction of axial bromide ligand and 5(5')-methoxy groups decreases the reactivity of carbenoid species and the reaction of the less reactive carbenoid species with olefins proceeds via a more product-like transition state, resulting in more specific non-bonded interactions between the complex and the incoming olefin and, as a result, higher stereoselectivity.
The frontside and top views of carbene Co(V)-salen complex derived from the corresponding Co(II)-complex (30-Br)

Fig. 4
Chapter 3

Study on Catalytic and Asymmetric [2,3]Sigmatropic Rearrangement
3-1. Previous Examples of Carbenoid-Mediated Asymmetric [2,3]Sigmatropic Rearrangement

Carbon-carbon bond formation reaction accompanied with generation of two vicinal asymmetric carbons is of high synthetic use as a tool for the construction of carbon skeleton. This type of reactions such as aldol condensation, [3,3] and [2,3]sigmatropic rearrangement, and Diels-Alder reactions are now widely used in organic synthesis, and most of these reactions can be carried out in a catalytic and enantioselective manner. However, examples of catalytic and enantioselective [2,3]sigmatropic rearrangement are still rare and their stereoselectivity is not satisfactory. This is probably due to difficulty in generation of carbanion \( \alpha \) to heteroatom in a catalytic manner.

On the other hand, it is known that carbene reacts with a heteroatom such as oxygen and sulfur atoms and to produce the corresponding ylides. Thus, treatment of a substrate such as allyl ethers or allyl sulfides with carbene or carbenoid species is expected to give the corresponding ylides which can undergo [2,3]sigmatropic rearrangement (Scheme 22). As a matter of course, stereochemistry of this reaction is dependent upon enantioselectivity in the ylide formation step and diastereoselectivity in the rearrangement step (Scheme 23).

Several years ago, Doyle et al. reported that the reaction of allyl ether and diazoacetate in the presence of \( \text{Rh}_2(\text{OAc})_4 \) proceeded with moderate to good diastereoselectivity (79:21-97:3), giving the corresponding [2,3]sigmatropic rearrangement products by way of the intermediary oxonium.
ylide formation step

R₁\rightarrow R₂\rightarrow R₃ \quad + \quad L_nM=CHCO₂R \quad \rightarrow \quad R₁\rightarrow R₂\rightarrow R₃ \quad CO₂R

rearrangement step

\[ \text{OMe} + \quad \text{OMe} \quad \text{P} \quad \cdot \quad \cdot \quad \cdot \quad \cdot \quad \cdot \quad \cdot \quad \cdot \quad \cdot \quad \cdot \quad \cdot \quad \text{Ph} \quad \text{CO₂Et} \quad \text{R₁} \quad \rightarrow \quad R₁\rightarrow R₂\rightarrow R₃ \quad CO₂R \]

(83:17)

In 1995, Uemura et al. first reported the catalytic asymmetric [2,3]sigmatropic rearrangement of allylic charcogen-ylides that were prepared by treatment of allylic sulfides or selenides with
diazoacetate in the presence of Cu(I)-bis(oxazoline) complex (CuOTf-39) or Rh$_2$(5S-MEPY)$_4$ complex 12, respectively, which were efficient catalysts for asymmetric cyclopropanation reaction (Scheme 25).\cite{6,8} These reactions, however, proceeded with only moderate enantioselectivity (up to 41% ee).\cite{33}

![Scheme 25](image)

After we communicated our results on catalytic asymmetric [2,3]sigmatropic rearrangement,\cite{34} Doyle et al. reported that Rh$_2$(4S-MEOX)$_4$ complex 40 was an effective catalyst for asymmetric [2,3]sigmatropic rearrangement via oxonium ylide, which was prepared from corresponding trans-cinnamyl methyl ether and ethyl diazoacetate (Scheme 26).\cite{21b} According to their literature, enantioselectivity greater than 90% was attained in both anti- and syn-products. To be interested, the sense of diastereoselection in this reaction is opposite to that of the reaction using Rh$_2$(OAc)$_4$ as a catalyst.\cite{32}

On the other hand, Katsuki et al. have reported that the well-designed Mn(III)-salen complexes bearing bulky groups at C3- and C3'-carbons are efficient catalysts for asymmetric epoxidation of conjugated olefins (Chapter 1, Scheme 13)\cite{16} and asymmetric oxidation of alkyl aryl sulfides (Scheme 27)\cite{26c} in the course of their study on the metallosalen complexes.
As discussed in the preceding chapter, the author found that (salen)cobalt(III) complexes were efficient catalysts for asymmetric cyclopropanation of styrene derivatives (up to 96% ee) (see Chapter 2, Table 2 and 3). In analogy with (salen)manganese(III) complexes which are efficient catalysts for asymmetric oxidations (epoxidation and oxidation of sulfide), (salen)cobalt(III)
complexes are also considered to be efficient catalysts not only for cyclopropanation but also for S-ylide formation. Thus, the author examined the reaction of allylic sulfides and diazoacetate in the presence of chiral Co(III)-salen complex.

In order to explore the above possibility, the author first examined the reaction of trans-cinnamyl phenyl sulfide 42 and tert-butyl α-diazoacetate using various Co(III)-salen complexes as catalysts in dichloromethane (Table 4). Since Katsuki et al. had found that Mn(III)-salen catalyzed asymmetric epoxidation and oxidation of sulfides have common features in many respects, the author also expected that Co(III)-salen catalyzed asymmetric cyclopropanation and S-ylide formation would also show similar features. Mn(III)-salen catalysts bearing no substituents at C3- and C3'-carbons generally show poor asymmetric induction in epoxidation of olefins and oxidation of sulfides, while Co(III)-salen catalysts bearing substituents at C3- and C3'-carbon show no catalytic activity for cyclopropanation reaction. In accord with the latter case, Co(III)-salen complexes 26-I and 29-I bearing bulky tert-butyl groups at 3- and 3'-carbons did not catalyze asymmetric [2,3]sigmatropic rearrangement reaction of 42 via the corresponding S-ylide (Table 4, entries 2 and 5). In contrast to this, complexes 25-I, 27-I, and 28-I which had no C3- and C3'-substituent catalyzed the desired reaction with moderate enantioselectivity (42-48% ee) and with similar level of anti-syn selectivity (83:17-85:15) (Table 4, entries 1, 3, and 4). The reaction with complex 30-I bearing electron-donating methoxy group at C5- and C5'-carbons showed a slightly improved enantioselectivity, but complex 44-I bearing electron-donating acetonide groups showed a slightly diminished enantioselectivity (entries 6 and 7). Further improvement of enantioselectivity up to 64% ee was observed, when complex 30-Br was used as a catalyst (entry 8). This was probably attributed to the poorer trans-effect of axial bromide ligand as compared with iodide ligand. However, no improvement in diastereoselectivity was observed (entry 8). These results strongly suggested that S-ylide formation was performed in the coordination sphere of a chiral Co-salen complex but the rearrangement of the resulting S-ylide proceeded out of the coordination sphere, that is, the resulting S-ylide was not combined any more to the catalyst. This means that the diastereoselectivity in [2,3]sigmatropic rearrangement step does not depend on the catalysts used.
Table 4. Co(III)-salen catalyzed asymmetric [2,3]sigmatropic rearrangement using trans-cinnamyl phenyl sulfide as a substrate.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield (%)</th>
<th>anti : syn</th>
<th>% ee&lt;br&gt;(&lt;sup&gt;b,c&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25-1</td>
<td>31</td>
<td>85:15</td>
<td>48</td>
</tr>
<tr>
<td>2</td>
<td>26-1</td>
<td>.&lt;sup&gt;d&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>27-1</td>
<td>53</td>
<td>83:17</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
<td>28-1</td>
<td>74</td>
<td>83:17</td>
<td>47</td>
</tr>
<tr>
<td>5</td>
<td>29-1</td>
<td>.&lt;sup&gt;d&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>30-1</td>
<td>64</td>
<td>82:18</td>
<td>50</td>
</tr>
<tr>
<td>7</td>
<td>44-1</td>
<td>77</td>
<td>84:16</td>
<td>47</td>
</tr>
<tr>
<td>8</td>
<td>30-Br</td>
<td>81</td>
<td>85:15&lt;sup&gt;e&lt;/sup&gt;</td>
<td>64</td>
</tr>
</tbody>
</table>

a) Determined by <sup>1</sup>H NMR analysis (270 MHz).

b) The enantiomeric excess of the anti-isomer.

c) Determined by HPLC analysis using DAICEL CHIRALPAK AD (hexane/i-PrOH = 100/1).

d) The formation of only a trace amount of the product was detected by TLC analysis.

e) The enantiomeric excess of syn-isomer was determined to be 64% by HPLC analysis using DAICEL CHIRALPAK AD (hexane/i-PrOH = 100/1).

The reaction of trans-cinnamyl 2-methoxyphenyl sulfide 45 and tert-butyl α-diazoacetate also showed a good diastereoselectivity and moderate enantioselectivity, when complex 30-Br was used as a catalyst (Table 5, entry 1). The author also examined the reaction using cis-cinnamyl phenyl
sulfide 47 as a substrate and 30-Br as a catalyst. The reaction proceeded with good anti-selectivity, though enantioselectivity was diminished to some extent (entry 2).  

\[ \text{Ar-S-R} \quad \xrightarrow{30-Br} \quad \text{Ph-SAr} \quad \text{N}_2\text{CHCO}_2\text{Bu-t} \]

45: R= trans-cinnamyl, Ar= 2-methoxyphenyl
47: R= cis-cinnamyl, Ar= phenyl

Table 5. Co(III)-salen complex 30-Br catalyzed asymmetric [2,3]sigmatropic rearrangement of other substrates.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
<th>anti : syn</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45</td>
<td>46</td>
<td>75</td>
<td>83:17</td>
<td>60c</td>
</tr>
<tr>
<td>2</td>
<td>47</td>
<td>43</td>
<td>87</td>
<td>87:13</td>
<td>51c,d</td>
</tr>
</tbody>
</table>

a) Determined by $^1$H NMR analysis (270 MHz) unless otherwise noted.
b) The enantiomeric excess of the anti-isomer.
c) Determined by HPLC analysis using DAICEL CHIRALPAK AD (hexane/i-PrOH = 100/1).
d) Configuration of anti-isomer was (2R,3S).

The above conjecture that S-ylides are not bound to the Co-salen catalyst, indicated that the diastereoselectivity of the reaction could not be improved by the modification of the catalyst. However, the use of chiral diazoacetate was expected to improve diastereoselectivity by double diastereodifferentiation, stereoselection by the catalyst and by the chiral substrate. Both the enantioselectivity in S-ylide formation and anti-syn ratio of the product were improved to 74% ee and to 93:7, respectively, when (-)-menthyl $\alpha$-diazoacetate was used. This means that the sense of asymmetric induction by the (-)-menthyl moiety matches that by 30-Br (Scheme 28).

To clarify the scope of the reaction, the author further examined the reactions of prenyl phenyl sulfide 49, geranyl phenyl sulfide 51 and neryl phenyl sulfide 53, under the same reaction conditions (Scheme 29). The reaction of prenyl phenyl sulfide 49 and (-)-menthyl diazoacetate in the presence of catalyst 30-Br proceeded with good stereoselectivity of 74% de. As suggested from the previous result that the sense of asymmetric induction by catalyst 30-Br matched that by (-)-
menthyl moiety (vide supra), the same reaction in the presence of 54-Br which was the enantiomer of 30-Br, showed poor selectivity (8% de). The reaction of geranyl phenyl sulfide 51 proceeded with good enantio- and anti-stereoselectivity.36) The reaction of neryl phenyl sulfide 53 showed opposite syn-selectivity reflecting the geometry of the allyl moiety.
3-3. Determination of Absolute Configuration of Major anti-Isomer Obtained by Reaction of Cinnamyl Phenyl Sulfide

Configuration of the major anti-isomer obtained by the reaction of cinnamyl phenyl sulfide was determined to be $2R,3S$ by chemical correlation and chiroptical comparison as follows (Schemes 30 and 31): tert-Butyl 3-phenyl-2-phenylthio-4-pentenoate 43 was converted into alcohol 55 by LiAlH$_4$ reduction. Successive treatment of 55 with trimethylxonium tetrafluoroborate and with aqueous solution of NaOH gave epoxide 56.$^{37}$ Reduction of epoxide 56 with LiBEt$_3$H afforded alcohol 57, which was successively treated with 9-BBN and with H$_2$O$_2$ to give diol 58. Treatment of diol 58 with $p$-toluenesulfonyl chloride and triethylamine in the presence of 4-dimethylaminopyridine (DMAP) gave a mixture of tosylate 59 and ($2R,3S$)-2-methyl-3-phenyltetrahydrofuran 60. Treatment of 59 with n-BuLi also gave 60 (Scheme 30).

On the other hand, tert-butyl ($2R,3R$)-3-phenyltetrahydrofurancarboxylate 61 which has been prepared according to the reported procedure,$^{10c}$ was converted into the enantiomer of 60. LiAlH$_4$
reduction of 61 afforded alcohol 62. Treatment of 62 with trifluoromethanesulfonic anhydride and pyridine gave 63. Reduction of 63 with LiBEt3H gave stereochemically defined ent-60 (Scheme 31). Comparison of the specific rotations of 60 and ent-60 demonstrated that the starting 43 had the configuration of 2R,3S.

\[
\begin{align*}
\text{Ph} & \quad \text{LiAlH}_4 & \quad \text{Ph} \\
\text{CO}_2 \text{Bu-t} & \quad \text{OH} & \quad \text{Ph}
\end{align*}
\]

\[
\begin{align*}
61 & \quad \text{LiBEt}_3\text{H} & \quad \text{ent-60} \\
62 & \quad \text{Tf}_2\text{O}, \text{Py} & \quad 63
\end{align*}
\]

\[\{\alpha\}_D^{25} -56.7^\circ (c \ 0.75, \ \text{CHCl}_3)\]

Scheme 31
3-4. Discussion on Stereochemistry of [2,3]Sigmatropic Rearrangement of S-Ylide

To understand the stereochemical course of the [2,3]sigmatropic rearrangement of S-ylide, heat of formation ($\Delta H$) of the diastereomeric transition structures of the reaction of the S-ylide derived from trans- and cis-cinnamyl phenyl sulfides was evaluated by semi-empirical molecular orbital method (Scheme 32). Calculation suggests that the reaction starting from (R)-trans-S-ylide proceeds through transition state TA, which possesses the lowest $\Delta H$ among the transition states TA, TB, TC and TD, to give (2R,3S)-anti-product preferentially, in accord with the experimental result described in the preceding section. On the other hand, in the reaction of cis-cinnamyl phenyl sulfide, both transition states CB and CC suffers from unfavorable gauche interaction between the phenyl group on the allyl moiety and the ester group. Transition state CD suffers from eclipsed interaction between the phenyl group on the S atom and the ester group. Thus, the reaction proceeds through transition state CA, showing anti-selectivity. This is also in accord with the experimental result (Table 5, entry 2). These calculations support our proposal that both the reactions of trans- and cis-cinnamyl phenyl sulfides and $\alpha$-diazo ester in the presence of complex 30-Br give the (R)-S-ylides preferentially (vide infra).

In previous chapter, the author mentioned that the stereochemistry of the Co(III)-salen catalyzed cyclopropanation can be readily explained by assuming that the basal salen ligand of the intermediary Co(V)-salen carbenoid species has a non-planar structure and that olefins approach Co(V)-salen species from its sterically less congested front side, orientating their bulky substituent away from the bulky tert-butoxycarbonyl group (Chapter 2, Fig. 4). The fact that Co(III)-salen complexes bearing substituents at C3- and C3'-carbons does not show any catalytic activity for asymmetric cyclopropanation supports this assumption. In the present reaction, Co(III)-complexes bearing tert-butyl group at C3- and C3'-carbons also showed no or very poor catalytic activity (Table 4, entries 2 and 5). This also strongly supports that sulfides approach Co(V)-salen carbenoid species from its front side, directing their phenyl group away from the carbenoid ester group (Fig. 5). Thus, the reaction of trans- and cis-cinnamyl phenyl sulfides in the presence of complex 30-Br gives the corresponding (R)-S-ylides in preferential, which undergo the rearrangement via transition states TA and CA, respectively, to give the products of (2R,3S)-configuration (Scheme 32).
(R)-trans-S-ylide

\[ \text{Ph} \begin{array}{c} \text{H} \\ \text{E} \end{array} \text{S} \begin{array}{c} \text{Ph} \\ \text{E} \end{array} \text{Ph} \]

\[ \Delta H \text{ kcal mol}^{-1} = 19.8 \]

\[ \Delta \Delta H \text{ kcal mol}^{-1} = 0 \]

\[ \text{TA} \]

\[ \text{H} \begin{array}{c} \text{Ph} \\ \text{E} \end{array} \text{S} \begin{array}{c} \text{Ph} \\ \text{E} \end{array} \text{Ph} \]

\[ \Delta H \text{ kcal mol}^{-1} = 24.5 \]

\[ \Delta \Delta H \text{ kcal mol}^{-1} = 4.7 \]

\[ \text{TB} \]

\[ \text{Ph} \begin{array}{c} \text{H} \\ \text{E} \end{array} \text{S} \begin{array}{c} \text{Ph} \\ \text{E} \end{array} \text{Ph} \]

\[ \Delta H \text{ kcal mol}^{-1} = 23.8 \]

\[ \Delta \Delta H \text{ kcal mol}^{-1} = 4.0 \]

\[ \text{TC} \]

\[ \text{Ph} \begin{array}{c} \text{H} \\ \text{E} \end{array} \text{S} \begin{array}{c} \text{Ph} \\ \text{E} \end{array} \text{Ph} \]

\[ \Delta H \text{ kcal mol}^{-1} = 22.1 \]

\[ \Delta \Delta H \text{ kcal mol}^{-1} = 2.3 \]

\[ \text{TD} \]

\[ \text{Ph} \begin{array}{c} \text{H} \\ \text{E} \end{array} \text{S} \begin{array}{c} \text{Ph} \\ \text{E} \end{array} \text{Ph} \]

\[ \text{Ph} \begin{array}{c} \text{H} \\ \text{E} \end{array} \text{S} \begin{array}{c} \text{Ph} \\ \text{E} \end{array} \text{Ph} \]

\[ \Delta H \text{ kcal mol}^{-1} = 28.0 \]

\[ \Delta \Delta H \text{ kcal mol}^{-1} = 4.4 \]

\[ \text{CA} \]

\[ \text{Ph} \begin{array}{c} \text{H} \\ \text{E} \end{array} \text{S} \begin{array}{c} \text{Ph} \\ \text{E} \end{array} \text{Ph} \]

\[ \Delta H \text{ kcal mol}^{-1} = 28.3 \]

\[ \Delta \Delta H \text{ kcal mol}^{-1} = 4.7 \]

\[ \text{CB} \]

\[ \text{Ph} \begin{array}{c} \text{H} \\ \text{E} \end{array} \text{S} \begin{array}{c} \text{Ph} \\ \text{E} \end{array} \text{Ph} \]

\[ \text{Ph} \begin{array}{c} \text{H} \\ \text{E} \end{array} \text{S} \begin{array}{c} \text{Ph} \\ \text{E} \end{array} \text{Ph} \]

\[ \Delta H \text{ kcal mol}^{-1} = 25.1 \]

\[ \Delta \Delta H \text{ kcal mol}^{-1} = 1.5 \]

\[ \text{CD} \]

\[ \text{Ph} \begin{array}{c} \text{H} \\ \text{E} \end{array} \text{S} \begin{array}{c} \text{Ph} \\ \text{E} \end{array} \text{Ph} \]

\[ (R)-cis-S-ylide \]

\[ \text{E} \equiv \text{CO}_2\text{Bu}-t \]

Scheme 32

calculated by MOPAC Ver. 6 (MNDO-PM3)
The frontside and top views of carbene Co(V)-salen complex derived from the corresponding Co(III)-complex (30-Br)

Fig. 5
Chapter 4

Conclusion
Through the present study, the author was able to demonstrate that a well-designed chiral Co(III)-salen complex such as 30-Br catalyzes carbene transfer reactions such as cyclopropanation of styrene derivatives and S-ylide formation in an enantioselective manner. He also found that electronic natures of the substituent of salen ligand and axial ligand exert a strong influence on the stereoregulation by the Co(III)-complex. The electronically well-adjusted 30-Br showed excellent enantioselectivity and trans-cis selectivity in cyclopropanation. Finally, based on the present results, he proposed the mechanism of asymmetric induction by the Co(III)-complex, which might lead to the design of a new Co-salen complex.
Chapter 5

Experimental
NMR spectra were recorded at 270 MHz on a JEOL EX-270 instrument or at 400 MHz on a JEOL GX-400 instrument. All signals were expressed as ppm down field from tetramethylsilane used as an internal standard (δ-value in CDCl₃). IR spectra were obtained with a SHIMADZU FTIR-8600 instrument. Optical rotation was measured with a JASCO DIP-360 automatic digital polarimeter. High resolution mass spectra were recorded on a JEOL JMS-SX/SX 102A instrument. Column chromatography was conducted on Silica Gel BW-820MH, 70-200 mesh ASTM, available from FUJI SILYSIA CHEMICAL LTD. Preparative thin layer chromatography was performed on 0.5 mm x 20 cm x 20 cm E. Merck silica gel plate (60 F-254). Solvents were dried and distilled shortly before use. Reactions were carried out under an atmosphere of nitrogen if necessary. HPLC analysis of enantiomeric excess was carried out using Hitachi L-4000 equipped with an appropriate optically active column, as described in the footnote of Tables. GC analysis of enantiomeric excess was carried out using GASUKURO KOGYO GC-380 with SUPELCO B-DEX 120 fused silica capillary column, as described in the footnote of Table 2. trans-Cinnamyl phenyl sulfide 42 was prepared according to the literature procedure.40)

**General procedure for Co(II)-salen complex: Co(II)-salen complex 30**

(1R,2R)-1,2-Diphenylethlenediamine (102 mg, 0.48 mmol) was added to a solution of 2-hydroxy-5-methoxybenzaldehyde41) (145 mg, 0.96 mmol) in ethanol (2 ml) and stirred overnight at room temperature. The mixture was concentrated in vacuo and to this residue were added deaerated ethanol (8 ml) and a freshly prepared ethanol solution (960 μl) of Co(OAc)₂42) (0.5 mol dm⁻³, 0.48 mmol) under nitrogen atmosphere. The mixture was refluxed for 9 h, and then allowed to cool to room temperature. The resulting brown precipitate was separated from the solution by filtration, washed with deaerated ethanol under nitrogen atmosphere, and dried under vacuum to give 30 (198 mg, 77%). 30; IR (KBr): 3028, 3001, 2943, 2905, 2833, 1595, 1533, 1462, 1421, 1362, 1302, 1256, 1219, 1167, 1030, 824, 698 cm⁻¹. Calcd. for C₃₀H₂₆N₂O₄Co: C, 67.04; H, 4.88; N, 5.21%. Found: C, 66.98; H, 4.90; N, 5.20%.

**Co(II)-salen complex 25**
Co(II)-salen complex 25 was synthesized from salicylaldehyde and (1R,2R)-1,2-diphenylethlenediamine in the same procedure as described for the synthesis of 30. 25 (82%); IR (KBr): 3057, 1603, 1533, 1497, 1348, 1317, 1205, 1148, 908, 849, 752, 702, 532, 467 cm\(^{-1}\). Calcd. for C\(_{28}\)H\(_{22}\)N\(_2\)O\(_2\)Co: C, 70.44; H, 4.64; N, 5.87%. Found: C, 70.56; H, 4.63; N, 5.70%.

Co(II)-salen complex 26

Co(II)-salen complex 26 was synthesized from 2-hydroxy-3-tert-butylbenzaldehyde\(^{43}\) and (1R,2R)-1,2-diphenylethlenediamine in the same procedure as described for the synthesis of 30. 26 (73%); IR (KBr): 2947, 2905, 2866, 1591, 1531, 1491, 1484, 1416, 1400, 1387, 1337, 1312, 1234, 1200, 1146, 1084, 1065, 868, 760, 698, 513 cm\(^{-1}\). Calcd. for C\(_{36}\)H\(_{35}\)N\(_2\)O\(_2\)Co: C, 73.33; H, 6.50; N, 4.75%. Found: C, 73.22; H, 6.47; N, 4.71%.

Co(II)-salen complex 27

Co(II)-salen complex 27 was synthesized from 2-hydroxy-4-tert-butylbenzaldehyde\(^{43}\) and (1R,2R)-1,2-diphenylethlenediamine in the same procedure as described for the synthesis of 30. 27 (82%); IR (KBr): 2955, 2901, 2866, 1609, 1520, 1456, 1412, 1379, 1302, 1225, 1200, 1090, 1020, 962, 868, 789, 766, 700, 669 cm\(^{-1}\). Calcd. for C\(_{36}\)H\(_{35}\)N\(_2\)O\(_2\)Co: C, 73.33; H, 6.50; N, 4.75%. Found: C, 73.42; H, 6.59; N, 4.77%.

Co(II)-salen complex 28

Co(II)-salen complex 28 was synthesized from 2-hydroxy-5-tert-butylbenzaldehyde\(^{43}\) and (1R,2R)-1,2-diphenylethlenediamine in the same procedure as described for the synthesis of 30. 28 (78%); IR (KBr): 3061, 2953, 2901, 2866, 1614, 1591, 1526, 1474, 1454, 1417, 1377, 1362, 1317, 1256, 1219, 1188, 1146, 831, 698, 561 cm\(^{-1}\). Calcd. for C\(_{36}\)H\(_{35}\)N\(_2\)O\(_2\)Co: C, 73.33; H, 6.50; N, 4.75%. Found: C, 73.17; H, 6.57; N, 4.50%.
Co(II)-salen complex 29 was synthesized from 2-hydroxy-3,5-di-tert-butylbenzaldehyde and (1R,2R)-1,2-diphenylethanediamine in the same procedure as described for the synthesis of 30. 29 (80%); IR (KBr): 2957, 2903, 2866, 1612, 1589, 1526, 1454, 1429, 1387, 1358, 1319, 1252, 1202, 1178, 787, 698 cm⁻¹. Calcd. for C₄₄H₄₄N₂O₂Co: C, 75.30; H, 7.76; N, 3.99%. Found: C, 75.32; H, 7.75; N, 4.00%.

General procedure for asymmetric cyclopropanation using Co(III)-salen complex 30-Br as a catalyst

To a dichloromethane solution (0.5 ml) of Co(II)-salen catalyst 30 (2.3 mg, 4.2 µmol) was added a dichloromethane solution of Br₂ (17 µl, 0.12 mol dm⁻³, 2.1 µmol) and the mixture was stirred for 1 h at room temperature. To this solution was added styrene (49 µl, 0.42 mmol) and the whole mixture was stirred for another 10 min. tert-Butyl diazoacetate (11.9 µl, 85 µmol) was added to this mixture at room temperature, stirred for 24 h, and then concentrated in vacuo. The residue was passed through a short silica gel column (hexane-AcOEt = 1:0 to 9:1) to give a 96:4 mixture of tert-butyl trans- and cis-2-phenylcyclopropane-1-carboxylates 31 (14.9 mg, 80%). The % ee and configuration of trans- and cis- isomers were determined as described in the footnote of Table 2. Further purification by preparative TLC (silica gel, hexane-(i-Pr)₂O = 4:1) gave tert-butyl trans-2-phenylcyclopropane-1-carboxylate 31t as a single isomer.

**tert-Butyl trans-2-phenylcyclopropane-1-carboxylate 31t**

31t (93% ee); [α]D³⁰ +253.3° (c 0.73, CHCl₃). IR (KBr): 2980, 2934, 1720, 1607, 1458, 1402, 1367, 1342, 1288, 1258, 1209, 1153, 1078, 1045, 1024, 937, 843, 781, 758, 743, 696, 525 cm⁻¹. ¹H NMR (270 MHz): δ 7.31-7.07 (m, 5H), 2.43 (ddd, J= 4.2, 6.4 and 9.2 Hz, 1H), 1.83 (ddd, J= 4.2, 5.2 and 8.4 Hz, 1H), 1.53 (ddd, J= 4.4, 5.2 and 9.2 Hz, 1H), 1.47 (s, 9H), 1.23 (ddd, J= 4.4, 6.4 and 8.4 Hz, 1H). HRFABMS m/z. Calcd. for C₁₄H₁₉O₂ (M⁺+H): 219.1385. Found 219.1385.

**tert-Butyl trans-2-(2-naphthyl)cyclopropane-1-carboxylate 37t**

37t (92% ee); [α]D³⁰ +211.8° (c 0.56, CHCl₃). IR (KBr): 2980, 2932, 1717, 1508, 1450, 1404, 1389, 1367, 1310, 1252, 1207, 1146, 1045, 964, 935, 901, 868, 845, 820, 748, 484 cm⁻¹. ¹H NMR
(270 MHz): δ 7.80-7.74 (br t, 3H), 7.56 (br s, 1H), 7.49-7.38 (m, 2H), 7.19 (dd, J= 1.7 and 8.5 Hz, 1H), 2.61 (ddd, J= 4.2, 6.4 and 9.2 Hz, 1H), 1.94 (ddd, J= 4.2, 5.3 and 8.4 Hz, 1H), 1.60 (ddd, J= 4.5, 5.3 and 9.2 Hz, 1H), 1.48 (s, 9H), 1.35 (ddd, J= 4.5, 6.4 and 8.4 Hz, 1H). HRFABMS m/z.
Calcd. for C_{18}H_{20}O_{2} (M+): 268.1463. Found 268.1463.

**tert-Butyl trans-2-(4-chlorophenyl)cyclopropane-1-carboxylate 38t**

38t (96% ee); [α]_{D}^{21} +232.8° (c 1.08, CHCl_{3}). IR (KBr): 3003, 2984, 2939, 1717, 1497, 1447, 1396, 1367, 1335, 1302, 1277, 1250, 1219, 1151, 1099, 1047, 1011, 943, 930, 847, 818, 748, 525, 473 cm⁻¹. ¹H NMR (270 MHz): δ 7.23 (d, J= 8.4 Hz, 2H), 7.01 (d, J= 8.4 Hz, 2H), 2.41 (ddd, J= 4.2, 6.3 and 9.2 Hz, 1H), 1.79 (ddd, J= 4.2, 5.3 and 8.4 Hz, 1H), 1.53 (ddd, J= 4.5, 5.3 and 9.2 Hz, 1H), 1.47 (s, 9H), 1.19 (ddd, J= 4.5, 6.3 and 8.4 Hz, 1H). HRFABMS m/z. Calcd. for C_{14}H_{15}O_{2}Cl (M+H): 253.0995. Found 253.0995.

**trans-Cinnamyl 2-methoxyphenyl sulfide 45**

trans-Cinnamyl 2-methoxyphenyl sulfide 45 was synthesized from trans-cinnamyl alcohol and 2-methoxybenzenethiol in the same procedure as described for the synthesis of trans-cinnamyl phenyl sulfide except for purification. Crude 45 was purified successively by column chromatography (SiO₂, hexane-AcOEt = 9:1) and recrystallization (Hexane-CH₂Cl₂) to give pure 45 as colorless crystals in 75% yield. 45; IR (KBr): 2997, 2937, 2837, 1574, 1475, 1450, 1435, 1304, 1277, 1240, 1182, 1132, 1072, 1042, 1020, 989, 972, 914, 845, 789, 750, 714, 683 cm⁻¹. ¹H NMR (270 MHz): δ 7.36-7.17 (m, 7H), 6.93-6.84 (m, 2H), 6.43 (br d, J= 15.7 Hz, 1H), 6.25 (dt, J= 7.0 and 15.7 Hz, 1H), 3.89 (s, 3H), 3.71 (dd, J= 1.0 and 7.0 Hz, 2H). HREIMS m/z. Calcd. for C_{16}H_{16}OS (M⁺): 256.0922. Found: 256.0922. Calcd. for C_{16}H_{16}OS: C, 74.96; H, 6.29%. Found: C, 74.66; H, 6.45%.

**cis-Cinnamyl phenyl sulfide 47**

To a solution of ethanol (21.2 ml) and aqueous 2N NaOHaq (1.13 ml) was added NaBH₄ (883 mg, 23.3 mmol) at room temperature. After being stirred for 10 min, the mixture was filtered
through a pad of Celite. A portion (12.0 ml) of the filtrate was added dropwise to a suspension of Ni(OAc)$_2$•4H$_2$O (2.39 g, 9.60 mmol) in ethanol (226 ml) with vigorous stirring under hydrogen. To this mixture were added ethylenediamine (1.92 ml, 28.7 mmol) and 1-phenyl-1-propyn-3-ol (5.08 g, 38.4 mmol) in ethanol (102 ml). After being stirred for 4 h, the mixture was diluted with water and extracted with AcOEt. The extract was dried over Na$_2$SO$_4$ and concentrated. Silica gel chromatography of the residue (hexane-AcOEt = 8:2) gave pure cis-cinnamyl alcohol (4.63 g, 90%) as an oil.$^{45}$ cis-Cinnamyl alcohol; IR (neat): 3331, 3103, 3082, 3057, 3022, 2928, 2866, 1601, 1576, 1495, 1447, 1339, 1317, 1248, 1217, 1182, 1078, 1018, 947, 916, 800, 773, 700 cm$^{-1}$. $^1$H NMR (270 MHz): $\delta$ 7.38-7.19 (m, 5H), 6.57 (br d, $J$ = 11.7 Hz, 1H), 5.87 (dt, $J$ = 6.4 and 11.7 Hz, 1H), 4.43 (dd, $J$ = 1.6 and 6.4 Hz, 2H), 1.69 (s, 1H). HREIMS m/z. Calcd. for C$_9$H$_{10}$O (M$^+$): 134.0732. Found: 134.0732. Calcd. for C$_9$H$_{10}$O: C, 80.56; H, 7.51%. Found: C, 80.50; H, 7.60%.

Butyllithium (21.6 ml, 1.60 mol dm$^{-3}$ in hexane) was added to the solution of the above cis-cinnamyl alcohol (4.41 g, 32.9 mmol) in ether (33 ml) over 20 min at -78 °C. The mixture was gradually raised to room temperature and diluted with N,N-dimethylformamide (20 ml).

On the other hand, butyllithium (24.7 ml, 1.60 mol dm$^{-3}$ in hexane) was added to a solution of thiophenol (4.05 ml, 39.4 mmol) in ether (24.7 ml) at -78 °C. The mixture was gradually raised to room temperature and then diluted with N,N-dimethylformamide (20 ml).

The previously synthesized solution of lithium cis-cinnamyl alkoxide was added to a solution of methanesulfonyl chloride (2.80 ml, 36.2 mmol) in N,N-dimethylformamide (20 ml) and ether (21.6 ml) at 0 °C over 1 h and stirred for 30 min. To the mixture, was added the solution of lithium thiophenoxide prepared above and the whole mixture was gradually raised to room temperature. After being stirred overnight, the mixture was quenched with 2N NaOHaq (100 ml) and extracted with ether. The extract was washed successively with 2N NaOHaq, water and brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by column chromatography (SiO$_2$, hexane-AcOEt = 1:0 to 8:2) to give 47 (4.22 g, 57%) as a colorless oil. 47; IR (neat): 3076, 3057, 3020, 2924, 1583, 1479, 1439, 1223, 1090, 1072, 1026, 964, 918, 895, 810, 772, 739, 691 cm$^{-1}$. $^1$H NMR (270 MHz): $\delta$ 7.36-7.12 (m, 10H), 6.57 (br d, $J$ = 11.4 Hz, 1H), 5.79 (dt, $J$ = 7.8 and 11.4 Hz, 1H), 3.80 (dd, $J$ = 1.3, 7.8 Hz, 2H). HREIMS m/z. Calcd. for C$_{15}$H$_{14}$S (M$^+$): 226.0816. Found: 226.0816.
Prenyl phenyl sulfide 49

Prenyl phenyl sulfide 49 was synthesized from 3-methyl-2-buten-1-ol and thiophenol in the same procedure as described for the synthesis of 42 except for purification. Crude 49 was further purified by distillation (100 °C, 1 mmHg) after column chromatography (SiO2, hexane) to give pure 49 (57%) as a colorless oil. 49; IR (neat): 3057, 2968, 2930, 2912, 1583, 1479, 1439, 1375, 1217, 1088, 1061, 1026, 843, 739, 691 cm⁻¹. ¹H NMR (270 MHz): δ 7.36-7.14 (m, 5H), 5.33-5.27 (m, 1H), 3.54 (br d, J= 7.7 Hz, 2H), 1.71 (s, 3H), 1.58 (s, 3H). HREIMS m/z. Calcd. for C₁₁H₁₄S (M⁺): 178.0816. Found: 178.0816. Calcd. for C₁₁H₁₄S: C, 74.10; H, 7.91%. Found: C, 74.12; H, 7.95%.

Geranyl phenyl sulfide 51

60% NaH in oil (524 mg, 13.1 mmol) was washed with THF and suspended in THF (40 ml). To the suspension, was added thiophenol at 0 °C and stirred for 1 h. To this solution, was added geranyl bromide (2.0 ml, 10.1 mmol) at the same temperature and whole mixture was gradually warmed to room temperature. The mixture was stirred overnight at room temperature and quenched with 2N NaOHaq (40 ml). The mixture was extracted with ether, washed successively with 2N NaOHaq, water and brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (SiO2, hexane-AcOEt = 1:0 to 9:1) to give 51 (2.46 g, 99%) as a colorless oil. 51; IR (neat): 3057, 2966, 2924, 2855, 1583, 1479, 1439, 1375, 1227, 1107, 1026, 737, 691 cm⁻¹. ¹H NMR (270 MHz): δ 7.36-7.14 (m, 5H), 5.34-5.27 (m, 1H), 5.09-5.03 (m, 1H), 3.55 (d, J= 7.7 Hz, 2H), 2.08-1.96 (m, 4H), 1.67 (s, 3H), 1.58 (d, J= 3.0 Hz, 3H), 1.57 (d, J= 0.5 Hz, 3H). ¹³C NMR: δ 139.9, 136.7, 131.6, 129.8, 128.6, 125.9, 123.9, 119.2, 39.5, 32.1, 26.4, 25.6, 17.6, 16.0. HREIMS m/z. Calcd. for C₁₆H₂₂S (M⁺): 246.1442. Found: 246.1442. Calcd. for C₁₆H₂₂S: C, 77.99; H, 9.00%. Found: C, 78.19; H, 9.02%.

Neryl phenyl sulfide 53

Neryl phenyl sulfide 53 was synthesized from nerol and thiophenol in the same procedure as described for the synthesis of 47 except for purification. 53 was purified successively by column chromatography (SiO2, hexane-AcOEt = 9:1) to give 53 as a colorless oil. 53 (75%); IR (neat):
3058, 2966, 2856, 1583, 1479, 1439, 1375, 1221, 1090, 1026, 837, 737, 691 cm\(^{-1}\). \(^1\)H NMR (270 MHz): \(\delta\) 7.36-7.13 (m, 5H), 5.35-5.29 (m, 1H), 5.13-5.07 (m, 1H), 3.55 (dd, \(J= 0.9\) and 7.8 Hz, 2H), 2.04 (br d, \(J= 3.1\) Hz, 4H), 1.72 (d, \(J= 1.2\) Hz, 3H), 1.68 (s, 3H), 1.60 (s, 3H). \(^{13}\)C NMR: \(\delta\) 139.9, 137.0, 131.9, 129.3, 128.7, 125.8, 123.8, 119.8, 31.9, 31.8, 26.5, 25.6, 23.3, 17.6.

HREIMS m/z. Calcd. for C\(_{16}\)H\(_{22}\)S (M\(^+\)) : 246.1442. Found 246.1442. Calcd. for C\(_{16}\)H\(_{22}\)S: C, 77.99\%; H, 9.00\%. Found: C, 78.21; H, 9.04\%.

**General procedure for asymmetric [2,3]sigmatropic rearrangement using Co(III)-salen complex as a catalyst**

Representative procedure is exemplified with the reaction of trans-cinnamyl phenyl sulfide with tert-butyl diazoacetate in the presence of complex 30-Br: Co(II)-salen complex 30 (13.4 mg, 0.25 \(\mu\)mol) was dissolved in dichloromethane (3 ml) and treated with a solution of bromine in dichloromethane (0.12 mol dm\(^{-3}\), 102 \(\mu\)l, 12 \(\mu\)mol) at room temperature for 1 h. A solution of trans-cinnamyl phenyl sulfide (113 mg, 0.50 mmol) in dichloromethane (3 ml) was loaded and the mixture was stirred for another 10 min. tert-Butyl diazoacetate (70 \(\mu\)l, 0.50 mmol) was added to this mixture and stirred for 24 h at room temperature. The reaction mixture was concentrated in vacuo and the residue was chromatographed on silica gel (hexane-AcOEt = 8:1) to give a mixture of tert-butyl anti- and syn-3-phenyl-2-phenylthio-4-pentenoates as crystallines (138 mg, 81\%). The anti-syn ratio was determined to be 85:15 by \(^1\)H NMR analysis. 43 (a mixture of anti- and syn-isomers); \(^1\)H NMR (270 MHz): \(\delta\) 7.49 (dd, \(J= 1.7\) and 8.0 Hz, 1H), 7.36-7.15 (m, 6H), 6.90-6.78 (m, 2H), 6.22-5.98 (m, 1H), 5.24-5.15 (m, 2H), 4.25-4.16 (m, 1H), 3.92-3.85 (m, 3H), 3.77-3.70 (m, 1H), 1.23 (s, 1.35H), 0.94 (s, 7.65H). Calcd. for C\(_{21}\)H\(_{24}\)O\(_2\)S: C, 74.08; H, 7.10\%. Found: C, 74.10; H, 7.17\%. The % ees of the products were determined to be 64\% ee by HPLC analysis as described in the footnote to Table 4. The crystalline mixture was recrystallized twice from hexane at 0 °C to afford the enantiomerically pure anti isomer (6.3 mg, 3.7\%). M.p. 79.5-80.5 °C. \([\alpha]_D^{25}\) +147° (c 0.244, CHCl\(_3\)). \(^1\)H NMR (400 MHz): \(\delta\) 7.52 (dd, \(J= 1.6\) and 7.8 Hz, 2H), 7.32-7.17 (m, 8H), 6.12 (ddd, \(J= 8.3, 9.3, \) and 17.1 Hz, 1H), 5.18 (d, \(J= 9.3\) Hz, 1H), 5.15 (d, \(J= 17.1\) Hz, 1H), 3.93 (d, \(J= 11.7\) Hz, 1H), 3.68 (dd, \(J= 8.3\) and 11.7 Hz, 1H), 1.02 (s, 9H). IR (KBr): 3422, 3080, 3059, 3028, 3005, 2978, 2928, 1598, 1884, 1720, 1641, 1601, 1582, 1493, 1475, 1454, 1441, 1420, 1391, 1367, 1026, 837, 737, 691 cm\(^{-1}\). \(^{13}\)C NMR: \(\delta\) 139.9, 137.0, 131.9, 129.3, 128.7, 125.8, 123.8, 119.8, 31.9, 31.8, 26.5, 25.6, 23.3, 17.6.
1350, 1339, 1286, 1256, 1200, 1151, 1090, 1070, 1028, 995, 910, 862, 841, 772, 748, 727, 700, 669 cm\(^{-1}\). HREIMS m/z. Calcd. for C\(_{21}\)H\(_{24}\)O\(_2\)S (M\(^{+}\)): 340.1497. Found 340.1497.

tert-Butyl 2-(2-methoxyphenylthio)-3-phenyl-4-pentenoate 46 (as a mixture of anti- and syn-isomers)

\(^1\)H NMR (270 MHz): \(\delta\) 7.49 (dd, \(J= 1.7\) and 8.0 Hz, 1H), 7.36-7.15 (m, 8H), 6.22-5.98 (m, 1H), 5.24-5.15 (m, 2H), 4.25-4.16 (m, 1H), 3.92 (s, 2.59H), 3.85 (s, 0.41H), 3.77-3.70 (m, 1H), 1.23 (s, 1.53H), 1.02 (s, 7.47H). The anti-syn ratio was determined to be 83:17 by comparison of peak areas of the signals of tert-butyl groups in a pair of diastereomers (\(\delta\) 1.23 and 1.02). Calcd. for C\(_{22}\)H\(_{26}\)O\(_3\)S: C, 71.32; H, 7.07%. Found: C, 71.17; H, 7.00%.

(-)-Menthyl 3-phenyl-2-phenylthio-4-pentenoate 48 (as a mixture of two anti- and two syn-isomers)

\(^1\)H NMR (400 MHz): \(\delta\) 7.54-7.50 (m, 2H), 7.32-7.17 (m, 8H), 6.19-6.00 (m, 1H), 5.20-5.06 (m, 2H), 4.37-4.31 (m, 1H), 4.06 (d, \(J= 11.5\) Hz, 0.121H), 4.04 (d, \(J= 11.5\) Hz, 0.819H), 4.03 (d, \(J= 11.5\) Hz, 0.042H), 4.02 (d, \(J= 11.0\) Hz, 0.018H), 3.81-3.71 (m, 1H), 1.70-0.29 (m, 18H). Calcd. for C\(_{27}\)H\(_{34}\)O\(_2\)S: C, 76.73; H, 8.11%. Found: C, 76.53; H, 8.26%. The anti-syn ratio was determined after 48 was converted into acetate 64 by the sequence: i) treatment of 48 with LiAlH\(_4\) and ii) acetylation of resulting alcohol with Ac\(_2\)O in the presence of DMAP and Et\(_3\)N. 48; \(^1\)H NMR (400 MHz): \(\delta\) 7.36-7.18 (m, 10H), 6.25-6.16 (m, 1H), 5.25-5.14 (m, 2H), 4.23-4.05 (m, 2H), 3.72-3.60 (m, 2H), 3.81-3.71 (m, 1H), 1.98 (s, 0.22H), 1.94 (s, 2.78H). Evaluation of integrals of methyl signals (\(\delta\) 1.94 and 1.98) in acetyl groups indicated diastereomer ratio to be 93:7.

\[\text{SPh} \quad \text{OAc} \]
\[\text{Ph} \quad 64\]

(-)-Menthyl 3,3-dimethyl-2-phenylthio-4-pentenoate 50 (as a mixture of two diastereomers)
1H NMR (400 MHz): δ 7.46-7.42 (m, 2H), 7.29-7.20 (m, 3H), 6.08-5.99 (m, 1H), 5.13-5.05 (m, 2H), 4.64-4.57 (m, 1H), 3.62 (s, 0.13H), 3.58 (s, 0.87H), 2.04-0.56 (m, 24H). The diastereomer excess was determined to be 74% de by comparison of peak areas of the signals of C2-protons in a pair of diastereomers (δ 3.62 and 3.58) 50 (diastereomer mixture); [α]$_D^2$ +24.8° (c 1.97, CHCl$_3$).

HREIMS m/z. Calcd. for C$_{16}$H$_{22}$S (M+): 374.2280. Found 374.2280.

(-)-Menthyl 3-methyl-3-(4-methyl-3-pentenyl)-2-phenylthio-4-pentenoate 52 (obtained from sulfide 51 as a mixture of two anti- and two syn-isomers)

1H NMR (400 MHz): δ 7.45-7.42 (m, 2H), 7.28-7.20 (m, 3H), 6.02-5.83 (m, 1H), 5.21-5.05 (m, 3H), 4.68-4.57 (m, 1H), 3.70 (s, 0.121H), 3.66 (s, 0.024H), 3.64 (s, 0.737H), 3.61 (s, 0.118H), 1.92-0.55 (m, 31H). Calcd. for C$_{23}$H$_{42}$O$_2$S: C, 75.97; H, 9.56%. Found: C, 75.93; H, 9.55%. The anti-syn ratio was determined to be 83:17 by the comparison of peak areas of the signals of C2-protons in pairs of diastereomers. The signals at δ 3.70 and 3.64 was assigned to anti-isomers and the signals at δ 3.66 and 3.61 to syn-isomers by the comparison of 1H NMR data with those of 52 synthesized from neryl phenyl sulfide 53.

5-Hydroxy-3-phenyl-4-phenylthio-1-pentene 55

To a solution of 43 (547 mg, 1.6 mmol, a 85:15 mixture of anti- and syn-isomers) in THF (16 ml) was added LiAlH$_4$ (122 mg, 3.2 mmol) at 0 °C. The mixture was stirred for 30 min and quenched with saturated aqueous KF (380 µl). The suspension was filtered through a pad of Celite and washed with AcOEt. The filtrate was dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by column chromatography (SiO$_2$, hexane-AcOEt = 8:2) to give 55 (429 mg, 99%) as a colorless oil. 55 (a 85:15 mixture of anti- and syn-isomers); 1H NMR (270 MHz): δ 7.45-7.17 (m, 10H), 6.30-6.00 (m, 1H), 5.25-5.05 (m, 2H), 3.65-3.30 (m, 4H), 2.00-1.55 (br s, 1H).

4,5-Epoxy-3-phenyl-1-pentene 56

Trimethyloxonium tetrafluoroborate (416 mg, 2.8 mmol) was added over 30 min to a stirred solution of 55 (246 mg, 0.91 mmol, a 85:15 mixture of anti- and syn-isomers) in dry
dichloromethane (8.9 ml) at room temperature and the mixture was stirred for another 30 min. To this solution was added 10% NaOHaq (12 ml). Stirring was further continued for 4 h and the reaction mixture was neutralized with saturated NH₄Cl (100 ml). The mixture was extracted with dichloromethane, dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography (hexane-AcOEt = 9:1 to 1:1) to give 56 (109 mg, 75%) as a colorless oil.³⁷ 56 (a 85:15 mixture of syn- and anti-isomers); ¹H NMR (270 MHz): δ 7.27-6.89 (m, 5H), 6.02-5.76 (m, 1H), 5.19-4.93 (m, 2H), 3.12-2.88 (m, 2H), 2.35-2.16 (m, 1H).

3-Phenyl-1-penten-4-ol 57

To a solution of 56 (93 mg, 0.58 mmol) in THF (10 ml) was added LiBEt₃H (870 μl, 1.0 mol dm⁻³ in THF) at 0 °C and stirred for 1.5 h. To this mixture were added saturated aqueous NaHCO₃ and 30% H₂O₂. After vigorous stirring for 30 min, the mixture was diluted with water and extracted with ether. The extract was dried over MgSO₄ and concentrated. The residue was purified by column chromatography (SiO₂, hexane-AcOEt = 8:2) gave alcohol 57 (67 mg, 71%) as a colorless oil. 57 (a 85:15 mixture of syn- and anti-isomers); ¹H NMR (270 MHz): δ 7.38-7.18 (m, 5H), 6.19-5.97 (m, 1H), 5.26-5.10 (m, 1H), 4.13-3.95 (m, 1H), 3.27-3.14 (m, 1H), 1.54 (br s, 1H), 1.24 (d, J= 6.3 Hz, 2.55H), 1.07 (d, J= 6.3 Hz, 2.55H).

3-Phenylpentan-1,4-diol 58

To a solution of 57 (59 mg, 0.37 mmol) in THF (10 ml) was added 9-BBN (1.6 ml, 0.5 mol dm⁻³ in THF) at 0 °C and the mixture was allowed to gradually warm to room temperature. After being stirred for 4 h, 6N NaOHaq and 30% H₂O₂ were added to this mixture and stirred vigorously for 30 min. The mixture was diluted with water and extracted with ether. The extract was dried over MgSO₄ and concentrated. The residue was purified by column chromatography (SiO₂, hexane-AcOEt = 8:2) to give alcohol 58 (58 mg, 87%) as a colorless oil. 58 (a 85:15 mixture of syn- and anti-isomers); ¹H NMR (270 MHz): δ 7.37-7.23 (m, 5H), 3.98 (quintet, J= 6.3 Hz, 1H), 3.60 (ddd, J= 5.0, 6.3 and 10.6 Hz, 1H), 3.47 (ddt, J= 6.0, 8.3 and 10.6 Hz, 1H), 2.75 (dt, J= 5.3 and 10.6 Hz, 1H), 2.13-1.86 (m, 2H), 1.54 (br s, 2H), 1.19 (d, J= 6.3 Hz, 3H).
3-Phenyl-5-(p-toluenesulfoxyloxy)-pentan-2-ol 59

p-Toluenesulfonyl chloride (61 mg, 0.32 mmol) was added to a solution of DMAP (3.9 mg, 0.032 mmol), triethylamine (49 µl, 0.35 mmol), and alcohol 58 (58 mg, 0.32 mmol) in dichloromethane (3.2 ml) at 0 °C and gradually warmed to room temperature. The mixture was stirred overnight and directly subjected to silica gel chromatography (hexane-AcOEt = 9:1 to 0:1) to give 59 (29 mg, 27%) and 60 (22 mg, 43%) as colorless oils, respectively. 59 (a 76:24 mixture of syn- and anti-isomers); 1H NMR (270 MHz): δ 7.78-7.67 (m, 2H), 7.34-7.04 (m, 7H), 4.28-3.68 (m, 4H), 2.70-1.91 (m, 5H), 1.12 (d, J= 6.3 Hz, 2.26H), 0.84 (d, J= 6.3 Hz, 0.7347H).

(2R,3S)-2-Methyl-3-phenyltetrahydrofuran 60

Butyllithium (54 µl, 1.60 mol dm\(^{-3}\) in hexane) was added to a solution of tosylate 59 (29 mg, 0.086 mmol) in THF (8.6 ml) at 0 °C and gradually raised to room temperature. After being stirred for 4 h at the temperature, the mixture was quenched with water and extracted with ether. The extract was dried over MgSO\(_4\) and concentrated. The residue was purified successively by column chromatography (SiO\(_2\), hexane-AcOEt = 8:2) to give 60 (9.4 mg, 67%) as a colorless oil. The anti-59 was found to remain unreacted. 60 (a single isomer); \([\alpha]_D^{22} +48.7^\circ\) (c 1.23, CHCl\(_3\)). 1H NMR (270 MHz): δ 7.33-7.15 (m, 5H), 4.21-4.11 (m, 2H), 3.87 (dd, J\(_1\)= 8.4 and J\(_2\)= 16.2 Hz, 1H), 3.34 (dt, J\(_1\)= 6.1, 8.1 Hz, 1H), 2.46-2.33 (m, 1H), 2.24-2.11 (m, 1H), 0.84 (d, J= 6.4 Hz, 3H). HREIMS m/z. Calcd. for C\(_{11}\)H\(_{14}\)O (M\(^+\)): 162.1045. Found 162.1045.

(2R,3R)-2-Hydroxymethyl-3-phenyltetrahydrofuran 62

To a solution of 61 (30 mg, 0.12 mmol) in THF (2.0 ml) was added LiAlH\(_4\) (14 mg, 0.36 mmol) at 0 °C. and gradually raised to room temperature. The mixture was stirred overnight and quenched with 1N HClaq. The mixture was extracted with AcOEt, dried over MgSO\(_4\), and concentrated in vacuo. The residue was purified by column chromatography (SiO\(_2\), hexane-AcOEt = 6:4) to give 62 (17 mg 77%) as a colorless oil. 62; 1H NMR (270 MHz): δ 7.34-7.20 (m, 5H), 4.27-4.15 (m, 2H), 3.94 (q, J= 8.3 Hz, 1H), 3.52 (q, J= 7.6 Hz, 1H), 3.23 (br d, J= 6.3 Hz, 1H), 2.42-2.19 (m, 2H), 1.80 (br s, 1H).
(2R,3R)-2-Trifluoromethanesulfonyloxymethyl-3-phenyltetrahydrofuran 63

A solution of trifluoromethanesulfonic anhydride (23 μl, 0.14 mmol) in dichloromethane (1.0 ml) was added to a solution of pyridine (22 μl, 0.27 mmol) and alcohol 62 (16 mg, 0.091 mmol) in dichloromethane (1.0 ml) at 0 °C and stirred for 1 h. The mixture was directly subjected to column chromatography (SiO₂, hexane-AcOEt = 9:1) to give 63 (22 mg, 78%) as a colorless oil. 63; ¹H NMR (270 MHz): δ 7.41-7.18 (m, 5H), 4.42-4.26 (m, 2H), 4.17-4.04 (m, 2H), 3.98 (q, J= 8.3 Hz, 1H), 3.61 (q, J= 7.6 Hz, 1H), 2.48-2.21 (m, 2H).

(2S,3R)-2-Methyl-3-phenyltetrahydrofuran ent-60

To a solution of 63 (22 mg, 0.070 mmol) in THF (2.0 ml) was added LiBEt₃H (105 μl, 1.0 mol dm⁻³ in THF) at 0 °C and gradually raised to room temperature. After being stirred for 2 h, 2N NaOHaq and 30% H₂O₂ were added to this mixture and stirred vigorously for 30 min. The mixture was diluted with water and extracted with ether. The extract was dried over MgSO₄ and concentrated. The residue was purified by column chromatography (SiO₂, hexane-AcOEt = 9:1) to give alcohol ent-60 (9.2 mg, 81%) as a colorless oil. ent-60; [α]D²⁺ -56.7° (c 0.75, CHCl₃).
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References and Notes


27) Asymmetric cyclopropanation of styrene and tert-butyl diazoacetate in the presence of complex 44-Br was examined at room temperature and afforded a 96:4 mixture of tert-butyl trans- and cis- 2-phenylcyclopropane-1-carboxylate in 84%. The enantiomeric excess of the trans-isomer was 89%, which was inferior to that observed with complex 30-Br.


35) It has been reported that both the [2,3]Wittig rearrangement of (E)- and (Z)-(2-alkenyloxy)acetic acid esters showed syn-selectivity (ref. 30a).

36) Configuration of the major diastereomer was tentatively assigned to be *anti* by the mechanical analogy with [2,3]sigmatropic rearrangement of the S-ylide derived from cinnamyl phenyl sulfide.


38) These transition structures were searched and optimized by MOPAC Ver. 6.0 using MNDO-PM3 hamiltonian. Each transition structure is found to have only one imaginary frequency.


41) The aldehyde was purchased from nacalai tesque and used after distillation.

42) Co(OAc)$_2$ was prepared from Co(OAc)$_2$•4H$_2$O by heating at 70 °C under vacuum for 2 h.


44) Configuration of the major isomer of tert-butyl 2-(2-naphthyl)cyclopropane-1-carboxylate and of tert-butyl 2-(4-chlorophenyl)cyclopropane-1-carboxylates was tentatively assigned to be *trans* by the comparison of their $^1$H NMR spectroscopic data with those of tert-butyl *trans*- and *cis*-2-phenylcyclopropane-1-carboxylates (reference 5b).
