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단 신

펩타이드-코발트(III) 결합체에 의한 올레핀 에폭사이드화 반응

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Olefin Epoxidation Catalysis by Peptidic Co(III) Complexes

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Epoxides are the valuable intermediate in organic synthesis and thus the development of efficient catalysts for olefin epoxidation is a highly demanding research area to organic chemists.[1] Recently, Co(III)[2] and Ni(II)[3] complexes with peptidic ligands were reported to catalyze olefin epoxidation. Also, peptidic Fe(II) and Fe(III)[4] complexes with the antitumor antibiotic bleomycin and its synthetic analoges were found to catalyze the epoxidation of olefin effectively.[5] Here, to develope novel catalysts for olefin epoxidation and expand the scope of alkene epoxidation catalysis, epoxidation of styrene derivatives catalyzed by novel peptidic Co(III) complexes **1-3** are described.

In recent studies on olefin epoxidation reactions, the planar metal-oxo complex such as Mn(V)=O and Fe(V)=O has been proposed as an active species. Thus a promising approach to olefin epoxidation catalysts is to produce novel metal-oxo complex, often as reactive intermediates, and study their usefulness in olefin epoxidation reactions. Certain Co(III) complexes have been known to have the planar structures and produce Co(V)-oxo intermediates upon reaction with PhIO.[6] Thus Co (III) complexes **1-3** would be likely candidates for study on olefin epoxidation catalysis. Furthermore, these Co (III) complexes **1-3** have the well defined chirality derived from optically active peptidic ligands. It is reasoned that chiral centers of the ligands held close to the cobalt reaction center might assist chiral recognition of substrates such as simple olefins. Thus Co(III) complexes **1-3** might act novel asymmetric epoxidation catalysts for simple unfunctionalized olefins.[7]

The chiral planar Co(III) complexes (**1-3**) were prepared by following procedures as shown in *Scheme* 1. Synthesis began with the preparation of peptidic ligands. DIC-promoted amide formation reaction between (1*R*, 2*R*)-1,2-diphenylethylene diamine and N-Boc-(*R*)-phenylglycine provided bis-(*R*)-phenylglycine adducts. TFA deprotection of Boc protection groups, and the subsequent tosylation reaction afforded ligand for **1**. Macrocyclization between bis-(*R*)-phenylglycine adducts diTFA salts and dimethyl malonyl dichloride in the high dilution condition provided macrocyclic ligand for **3**. Interestingly, the similar macrocyclization with bis-(*S*)-phenyl-

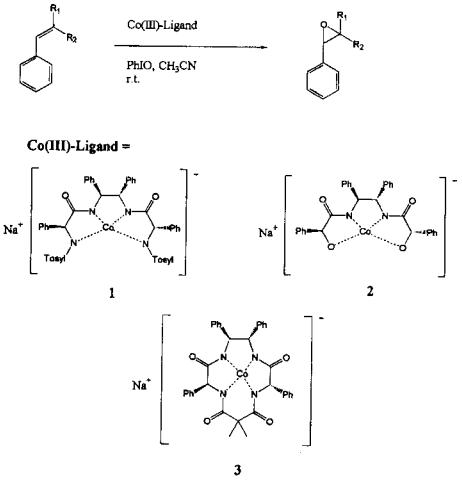
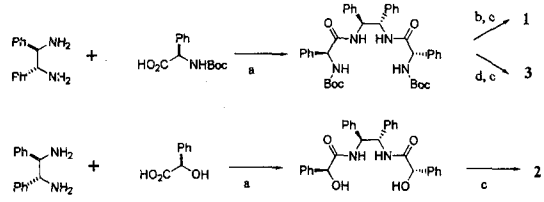


Fig. 1. Co(III)-peptidic ligand complexes(**1-3**) catalyzed olefin epoxidation.



Scheme 1. Synthesis of Co(III) complexes (**1-3**); (a) DIC, HOBT. (b) TFA, then TsCl, Et_3N. (c) $Co(OAc)_2$, NaOH. (d) TFA, then slow addition with dimethyl malonyl dichloride to iPr_2NEt in THF.

glycine adducts diTFA salts provided only the polymeric products. This observation indicate that the stereochemical and conformational property of the linear precursor have the markable effect in macrocyclization. DIC-promoted amide coupling reaction between (1*R*, 2*R*)-1,2-diphenylethylene diamine and (*R*)-mandelic acid provided ligand for **2**. Co(III) complexes (**1-3**) were prepared by heating methanol solution of $Co(OAc)_2$ and the corresponding ligand in the presence of excess NaOH.[8] The products, Co(III) complexes **1**, **2** and **3** are air-stable, moisture-insensitive, and soluble in various organic solvents including dichloromethane, chloroform, acetone, and dimethyl sulfoxide.

A typical procedure for the synthesis of epoxide is the following; To a CH_3CN solution (10 ml) of styrene derivatives (1 mmol) and iodosylbenzene (600 mmol) was added a solid cobalt(III) complexes (15 mmol). The mixture was stirred for 24 hr at 0 °C. Organic materials were extracted with dichloromethane, and dried over $MgSO_4$. After passing through a short silica gel pad, a portion of solution was injected into GC to check the yields except (*E*)-stilbene oxide. In the case of (*E*)-stilbene epoxidation, (*E*)-stilbene oxide was purified by column chromatography using silica gel and the yield was determined.

To optimize the reaction conditions, effect of different reaction solvents and oxidants on the chemical yields were studied. However, different solvents including acetone, methylene chloride, methanol and dimethoxymethane, and different oxidants such as NaOCl, tBuOOH and H_2O_2 provide the lower chemical yields.

Several epoxides were prepared under the same conditions in a typical procedure. The results are summarized in *Table* 1.

Table 1. The Co(III) complexes catalyzed olefin epoxidation

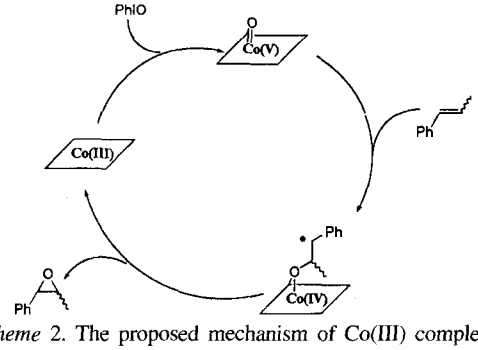
Entry	Olefin	Catalysts	Yield (%)[a]
1	PhCH=CH_2	1	33.6
2	(*Z*)-PhCH=CHMe	1	64.0(45:55)[b]
3	(*E*)-PhCH=CHMe	1	60.0
4	(*E*)-PhCH=CHPh	1	42.2
5	PhCH=CH_2	2	41.0
6	(*Z*)-PhCH=CHMe	2	36.0(40:60)[b]
7	(*E*)-PhCH=CHMe	2	59.0
8	(*E*)-PhCH=CHPh	2	46.7
9	PhCH=CH_2	3	68.1
10	(*Z*)-PhCH=CHMe	3	50.0(50:50)[b]
11	(*E*)-PhCH=CHMe	3	73.0
12	(*E*)-PhCH=CHPh	3	50.0

a; yields are based on PhIO, b; cis epoxide:trans epoxide.

The results in *Table* 1 clearly demonstrate that peptidic Co(III) complexes catalyze the epoxidation of styrene derivatives. Particularly, Co(III) complex **3** catalyze the epoxidation of styrene derivatives to provide the corresponding epoxide with the 50-70% yields.Also, in the case of (*Z*)-methylstyrene, cis-trans isomerizationwere observed.For example, these Co(III) complexes catalyzed (*Z*)-methylstyrene epoxidation provide trans epoxide with about 50% yields. Although such observation make these reactions undesirable for applications in synthesis, this is valuable in mechanistic studies because of the number of clues provided for elucidation of the reaction pathway.

To account the peptidic Co(III) complexes catalyzed epoxidation of olefin, the following reaction mechanism is proposed.

The catalytic yields of the epoxides imply the existence of Co(V)-oxo intermediate as the reactive species.



Scheme 2. The proposed mechanism of Co(III) complexes catalyzed epoxidaton of olefin.[3]

This Co(V)-oxo species derived by oxygen atom transfer from the iodosobenzene to square planar Co(III) complexes are isoelectronic with five-coordinate iron(V)-oxo and manganase(V)-oxo complexes, which are accepted as the possible intermediate in the other metal oxo complexes catalyzed reactions.[9] The formation of both cis and trans epoxides from cis olefin in Co(III) complexs catalyzed reactions strongly suggests the existence of the radical-type Co(IV) species as the discrete reaction intermediate. In this stepwise reaction mechanism, the discrete radical intermediate undergoes competitive collapse to cis epoxide and rotation/collapse to trans epoxide.[10] To test a possibility that these peptidic Co(III) complexes assisted-epoxidation might be the novel asymmetric epoxidation catalysis for simple unfunctionalized olefins, enantioselectivities of the resulting epoxides were investigated using chiral gas chromatography. Until now, enantiomeric excess of styrene-derived epoxides are less than 10% ee. Presumably, in the radical intermediate-like transition state, there is a relatively loose interactions between catalysts and substrates, and thus the free-energy difference between the diastereomeric intermediates leading to asymmetric discrimination is not large enough.

In conclusion, although these catalytic processes are undesirable for applications in synthesis, novel peptidic Co(III) complexes are found to catalyze epoxidation of styrene derivatives. Based on the proposed mechanism, studies on the efficient olefin epoxidation catalysis are in progress in this laboratory.

EXPERIMENTAL SECTION

Synthesis of Ligand of 1. To a solution of 0.2 g of (1*R*, 2*R*)-1,2-diphenylethylene diamine (0.94 mmol), 0.51 g of N-Boc-(*R*)-phenylglycine (2.20 mmol) and 0.1 g of HOBT (1.0 mmol)in 20 ml of THF and methylene chloride (V/V=1/1) were added 0.4 ml of DIC (2.65 mmol) at 0 °C. After stirring for 12 hr at room temperature, all volatiles were removed at reduced pressure. The residue was purified by flash chromatography on silica gel using 5% MeOH in methylene chloride to give bi-Boc, bis-phenylglycine adduct as an amorphous white solid (0.5 g, 78 %): ^{1}H NMR (DMSO-d_6)1.36 (s, 18H), 5.16 (d, 2H, J=8.5 Hz), 5.41 (d, 2H, J=8.0 Hz), 6.94 (d, 4H, J=7.0 Hz), 7.17 (t, 6H, J=7.0 Hz), 7.23 (d, 2H, J=4.5 Hz), 7.36 (d, 2H, J=9.0 Hz), 8.57 (d, 2H, J=8.0 Hz).

To a solution of 0.4 g of di-Boc, bis-phenylglycine adduct (0.59 mmol) in 10 ml of methylene chloride was added 3 ml of TFA. After stirring for 2 h at r.t., all volatiles were removed at reduced pressure. The crude bis-phenylglycine adduct diTFA salts were used the next reaction without further purifications.

To a solution of 0.4 g of bis-phenylglycine adduct diTFA salts (0.56 mmol) in 10 ml of THF was added 0.31 ml of triethylamine (2.24 mmol) and 0.21 g of tosylchloride (1.14 mmol). After stirring for 12 hr at room temperature, all volatiles were removed at reduced pressure. The residue was purified by flash chromatography on silica gel using ethyl acetate: hexane=1:1 to give ligand of **1** as an amorphous white solid (0.39 g, 87 %): ^{1}H NMR ($CDCl_3$)2.35 (s, 6H), 4.82 (d, 2H, J=6.5 Hz), 5.05 (d, 2H, J=5.0 Hz), 6.07 (d, 2H, J=6.0 Hz), 6.76 (d, 4H, J=1.0 Hz), 6.96 (d, 4H, J=1.5 Hz), 7.08 (t, 4H, J=1.5 Hz), 7.13 (d, 4H, J=1.5 Hz), 7.24 (t, 4H, J=1.5 Hz), 7.28 (t, 4H, J=1.0 Hz), 7.41 (d, 4H, J=1.0 Hz), 7.53 (d, 4H, J=5.0 Hz); IR (KBr) 3342, 1664, 1599, 1530, 1455, 1329, 1158 cm^{-1}.

Synthesis of Ligand of 2. To a solution of 0.12 g of (1*R*, 2*R*)-1,2-diphenylethylene diamine (0.56 mmol) and 0.2 g of (*R*)-mandelic acid (1.3 mmol) in 30 ml of THF were added 0.3 ml of DIC (1.95 mmol) and 0.21 g of HOBT (1.56 mmol) at 0 °C. After stirring for 24 hr at room temperature, all volatiles were removed at reduced pressure. The residue was purified by flash chromatography on silica gel usingethyl acetate: hexane=1:1 to give ligand of **2** as an amorphous white solid (0.19 g, 70 %): ^{1}H NMR ($CDCl_3$)3.71 (m, 2H), 4.89 (s, 2H), 7.00 (d, 4H, J=7.5 Hz), 7.05 (d, 4H, J=1.5 Hz), 7.13 (t, 4H, J=7.5 Hz), 7.18 (t, 4H, J=7.5 Hz), 7.22 (d, 4H, J=8.0 Hz), 7.60 (d, 2H, J=1.5 Hz); IR (KBr) 3342, 1624, 1572, 1546, 1383, 1247, 1169, 1051 cm^{-1}.

Synthesis of Ligand of 3. To a solution of 0.68 g of bis-phenylglycine adduct diTFA salts (1.0 mmol) and 0.15 ml of diisopropylethylamine (10.0 mmol) in 500 ml of THF was added 0.132 ml of dimethylmalonyl dichloride (1.0 mmol) at room temperature. After stirring for 48 hr at room temperature, all volatiles were removed at reduced pressure. The residue was purified by flash chromatography on silica gel using 5% MeOH in meth-

ylene chloride to give ligand of **2** as an amorphous white solid (0.32 g, 55%): ^{1}H NMR ($CDCl_3$)1.64 (s, 6H), 5.14 (d, 2H, J=5.0 Hz), 5.35 (d, 2H, J=5.5 Hz), 6.88 (d, 2H, J=5.5 Hz), 7.05 (d, 2H, J=5.5 Hz), 7.20 (m, 20H); IR (KBr) 3343, 1665, 1523, 1495 cm^{-1}.

General Method for Synthesis of Co(III) Complexes.[11] To a solution of 0.15 g of cobalt acatate (0.6 mmol) and the ligand (0.5 mmol) in ethanol was added 0.023 g of NaOH (0.5 mmol) under air.After stirring for 24 hr at room temperature, all volatiles were removed at reduced pressure. The residue was purified by flash chromatography on silica gel using 5% MeOH in methylene chloride to give Co(III) complexe as an amorphous dark green solid (45-55%).

1: IR (KBr) 2340, 1679, 1655, 1628, 1563, 1339, 1156 cm^{-1}; Anal. Calcd for $C_{44}H_{38}CoN_4NaO_6S_2$: C, 61.11; H, 4.43; N, 6.48. Found: C, 61.01; H, 4.25; N, 6.85.

2: IR (KBr) 1682, 1653, 1625, 1539, 1392, 1168 cm^{-1}; Anal. Calcd for $C_{30}H_{24}CoN_2NaO_4$: C, 64.52; H, 4.33; N, 4.12. Found: 64.32; H, 4.12; N, 4.54.

3: IR (KBr) 2364, 1640, 1390, 1343 cm^{-1}; Anal. Calcd for $C_{35}H_{30}CoN_4NaO_4$: C, 64.42; H, 4.63; N, 8.59. Found: C, 64.21; H, 4.34; N, 8.98.

Determination of Yields and Enantioselectivities of Epoxide.[12] Gas chromatographic analysis of products of styrene and methylstyrene epoxidations were performed on a Domam System 6200 gas chromatograph with a PEG-5 capillary Column (3 m, 0.25 mm diameter) and J & W γ-cyclodextrin Trifluoroacetyl capillary column (3 m; 0.25 mm diameter) using Hellium as carrier gas. In optimal condition, retention times for enantiomers of epoxides are following; 17.60 min and 18.70 min for styrene oxide, 27.0 min and 28.20 min for (*E*)-methylstyrene oxide, and 32.13 min and 34.15 min for (*Z*)-methylstyrene oxide (flow rate=0.8 ml/min, split ratio=1:100, oven temperature=120 °C).In the case of (*E*)-stilbene epoxidation, (*E*)-stilbene oxide was purified by column chromatography using silica gel and the yield was determined, and then enantioselctivities were measured by NMR spectroscopy using chiral shifting reagent such as (+)-Eu(hfc). Although the complete resolution of enantiomers could not be obtained in NMR, the partially resolved NMR data suggested that enantimeric excess of (*E*)-stilbene oxide from the above reactions was less than 10%. In optimal codition (in the presence of 1 eq. of (+)-Eu(hfc) in 1 mM solution of (*E*)-stilbene oxide in $CDCl_3$ at 25 °C), the partially resolved chemical shifts of peaks (bs) arising from benzylic protons of (*E*)-stilbene oxide are 5.10 and 5.15 ppm.

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