ENANTIOSELECTIVE REACTIONS THROUGH CHIRAL METAL-CARBENE INTERMEDIATES

Akira Nakamura

Department of Chemistry, Faculty of Engineering Science, and Department of
Polymer Science, Faculty of Science, Osaka University, Toyonaka, Osaka, 560 JAPAN.
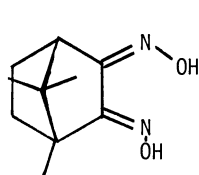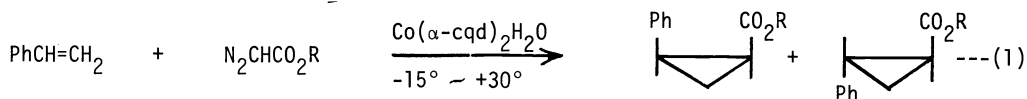
Abstract - Olefin cyclopropanation with prochiral diazoalkanes, e.g.
N_2CHCO_2R, has been found to proceed with high degree of enantioselection
(max. 88% e.e.) by catalysis of novel cobalt(II) chelates prepared from
natural camphor or β-pinene; viz. bis(camphorquinonedioximato) or
bis(nopinoquinonedioximato)cobalt(II). A mechanism involving enantioface
selective olefin attack upon transient chiral cobalt-carbene complexes
formed from prochiral diazoalkanes was proposed. Chirality at the Co(II)
seems to be an important factor in determining the chirality of the
prevailing cyclopropane enantiomeric product.
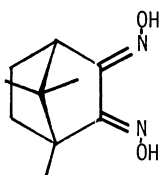
INTRODUCTION

Transition metal-carbene complexes has recently been shown (Ref. 1) to be involved in some
important catalytic reactions such as a) decomposition of diazoalkanes, b) olefin metathesis,
and c) skeletal isomerization of strained ring compounds. Since many different transition
metal compounds have been found to homogeneously catalyze the cyclopropanation with
diazoalkanes we are interested in enantioselective synthesis of chiral cyclopropanes by
using various optically active ligands to modify the catalytically active metal complexes.
In principle, the cyclopropanation with prochiral diazoalkanes and prochiral olefins should
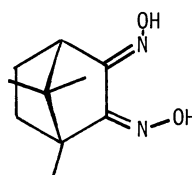give four cyclopropane stereoisomers.
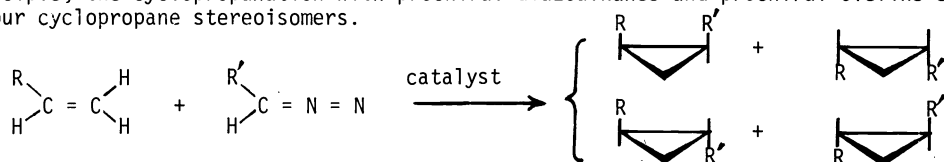
Suitable choice of the catalyst should give one enantiomer in large excess. Nozaki et al.
and Moser have already reported enantiomer formation of ethyl trans-2-phenylcyclopropane-
carboxylate in 6 and 3% excess by the reaction of styrene with ethyl diazoacetate in the
presence of copper complexes containing chiral Schiff base or phosphite (Ref. 2). These
studies thus established the intermediacy of Cu-carbene complexes as an important
intermediate but the efficiency of the enantioselection was not enough for the preparative
purposes. After examination of a number of chiral metal complexes as possible candidates,
air-sensitive Co(II) complexes of camphorquinonedioximes(cqd H) isomers(I - Ⅲ) prepared
from natural d-camphor were found very active as catalysts for cyclopropanation with
diazoacetates (Ref. 3).

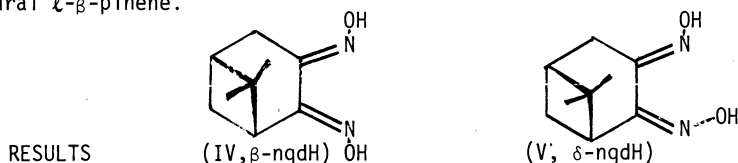$$PhCH=CH_2 \quad + \quad N_2CHCO_2R \quad \xrightarrow[-15° \sim +30°]{Co(\alpha\text{-}cqd)_2H_2O} \quad \text{[Ph, } CO_2R\text{]} \quad + \quad \text{[} CO_2R\text{, Ph]} \quad \text{---(1)}$$

(I, α-cqdH)   (II, β-cqdH)   (Ⅲ, δ-cqdH)

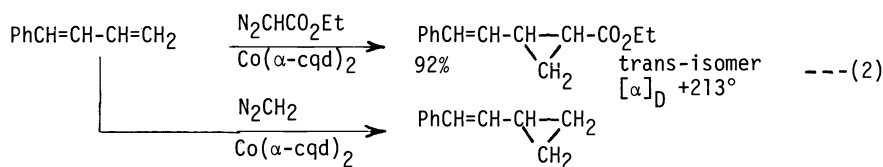Similar chiral dioximes ((+)-nopinoquinonedioxime isomers, nqdH, IV and V) were prepared from natural ℓ-β-pinene.

RESULTS   (IV,β-nqdH)   (V, δ-nqdH)

The cyclopropanation with Co(α-cqd)$_2 \cdot$H$_2$O as catalyst, gave very good yield (80~95%) of a mixture of cis- and trans-2-phenylcyclopropanecarboxylates with unusually high enantiomer excess (see eq.1). The optical yield of the trans-isomer reached up to 88% starting with neo-pentyl diazoacetate. The Co(α-cqd)$_2$-catalysis is also substrate selective on both sides of olefin and diazoalkane. Terminal olefinic double bonds with aryl, vinyl, or CO$_2$R groups in conjugation have been cyclopropanated in the presence of a large amount of internal olefins. Diazo compounds of the type, N$_2$CHR(R = CO$_2$R, COR)   , give good optical yields in the reaction with styrene. Typical examples of the results are listed in Table 1.
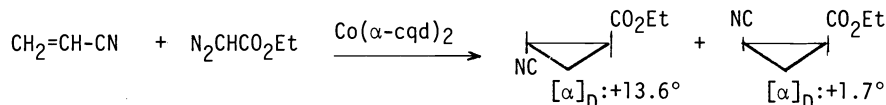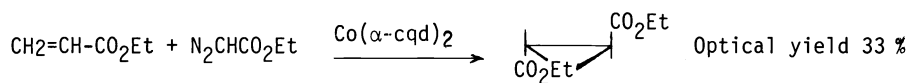
TABLE 1.   Asymmetric Cyclopropanation of Various Olefins with Ethyl
           Diazoacetate by Co(α-cqd)$_2$-Catalysis.

Olefin Substrate	Catalyst mol %	Yield %	Product	Configuration	Optical Yield % ([α]$_D$)
PhCH=CH$_2$	3.0	92	Ph CO$_2$Et	(1S, 2R)	67
			CO$_2$Et / Ph	(1S, 2S)	75
Ph$_2$C=CH$_2$	2.5	95	Ph CO$_2$Et / Ph	(1S)	70
Ph C=CH$_2$ / MeO$_2$C	2.1	92	CO$_2$Me CO$_2$Et / Ph	(1R, 2S)	37
			Ph CO$_2$Et / CO$_2$Me	(1S, 2S)	71

The substrate selectivity for olefins indicates that the catalysis may also be regioselective in cyclopropanation of conjugated dienes. Thus, regioselective cyclopropanation at the terminal double bond was found(eq.2).

PhCH=CH-CH=CH$_2$ $\xrightarrow[\text{Co($\alpha$-cqd)}_2]{\text{N}_2\text{CHCO}_2\text{Et}}$ PhCH=CH-CH—CH-CO$_2$Et 92%   CH$_2$ trans-isomer   [α]$_D$ +213°   ---(2)

$\xrightarrow[\text{Co($\alpha$-cqd)}_2]{\text{N}_2\text{CH}_2}$ PhCH=CH-CH—CH$_2$ CH$_2$

The high catalytic activity of Co(α-cqd)$_2$ catalyst has made cyclopropanation of activated olefins possible. Thus, any previous attempt to cyclopropanate methyl acrylate with ethyl diazoacetate has led to the formation of pyrazolines via 1,3-dipolar addition. In the presence of Co(α-cqd)$_2$ the same reaction yielded the expected cyclopropane in an enantiomeric excess at 22° (Ref. 4).

CH2=CH-CO$_2$Et + N$_2$CHCO$_2$Et $\xrightarrow{\text{Co($\alpha$-cqd)}_2}$ CO$_2$Et / CO$_2$Et   Optical yield 33 %

CH$_2$=CH-CN + N$_2$CHCO$_2$Et $\xrightarrow{\text{Co($\alpha$-cqd)}_2}$ CO$_2$Et / NC [α]$_D$:+13.6°   +   NC   CO$_2$Et [α]$_D$:+1.7°

It is one of the important characteristics of Co(α-cqd)$_2$catalyst that olefins having electronegative substituents are catalytically cyclopropanated by direct reaction with diazo compounds. Conventional copper-catalysis is inert to these olefins.
The variation of the bulkiness at the ester alkyl group of diazoacetate was examined to find the best optical yield of 88% in the case of the most bulky neo-pentyl group. This trend indicates the importance of steric effect of the diazo side in the enantioselective step.

TABLE 2.   Effect of Bulkiness at the Ester group(CO_2R) of Alkyl Diazoacetate
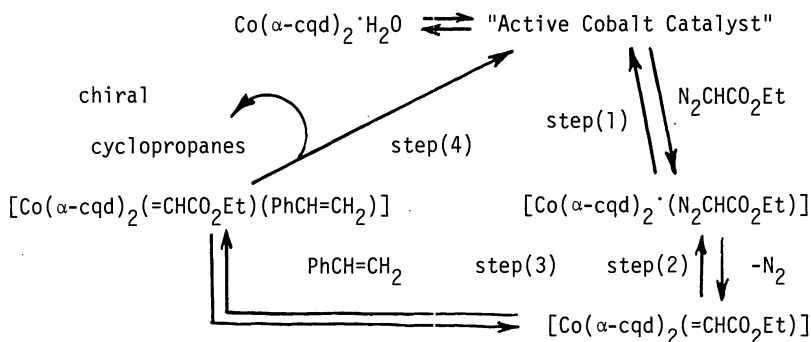in the Co(α-cqd)$_2$-catalysis(eq.1).

	R	Me	Et	i-Pr	i-Bu	cyclo -Hex	neo -Pent
Cyclopro- panation product	Optical Yield % (trans isomer)	61	75	84	80	78	88
	trans/cis ratio	0.69	0.85	1.15	0.92	1.46	2.34

It is important to point out the all the prevailing enantiomers obtained by Co(α-cqd)$_2$ -catalysis have (S)-configuration at the ring carbon derived from the carbenoid moiety (cf.Table 1). Strong enantioselecting control at the carbenoid reactant exsits in this catalysis.

Reaction Paths

Kinetics of the present catalysis in neat styrene revealed a clean 1-st order dependence of the rate upon the concentration of diazoacetates until ca. 80% reaction. No induction period was observed. Dilution of neat styrene with toluene or ethyl acetate below 1 mol/ℓ deactivates the catalysis completely even when utmost care was excercised to remove strongly poisonous oxygen. At the olefin concentration range of 2 - 8 mol/ℓ, practically no dependence of the rate upon the olefin concentration was found. These kinetic results indicates that the rate-determining step exists at the bimolecular reaction of the catalyst with diazoacetate. The following catalytic cycle is proposed on the basis of kinetics as well as other relevant observations(Ref. 5).

Scheme 1

$$\text{Co}(\alpha\text{-cqd})_2 \cdot H_2O \rightleftharpoons \text{"Active Cobalt Catalyst"}$$

chiral
cyclopropanes

step(4)   step(1) N_2CHCO_2Et

[Co(α-cqd)$_2$(=CHCO$_2$Et)(PhCH=CH$_2$)]   [Co(α-cqd)$_2 \cdot$(N$_2$CHCO$_2$Et)]

PhCH=CH$_2$ step(3)   step(2)   -N$_2$

[Co(α-cqd)$_2$(=CHCO$_2$Et)]

Mechanism of Enantioselection

When formation of one enantiomeric product in excess from two achiral reactants is achieved by the chiral influence of a catalyst, simplest mechanism of enantioselection involves rate-determining diastereomeric transition states of different energy. The free energy difference ($\Delta\Delta G$) between these transition states is related to the enantiomer ratio ((R)/(S) value) of the products by the following equation: $\Delta\Delta G_{S-R}^{\ddagger} = -RT \ell n((R)/(S))$
The temperature dependence of the present reaction gave the G_{S-R} values listed in Table 3. The energetic values increase with an increase in the bulkiness of the ester alkyl group.

TABLE 3.   Energetics of the Enantioselection in the Cyclopropanation of Styrene with Various Diazoacetates.[a]

Diazoacetate	$\Delta\Delta G_{S-R}^{\ddagger}$(at 25°) Kcal/mol	$\Delta\Delta H_{S-R}^{\ddagger}$ Kcal/mol	$\Delta\Delta S_{S-R}^{\ddagger}$ e.u.
N$_2$CHCO$_2$Me	0.91	3.1	7.4

N_2CHCO_2Et	1.2	3.8	8.8
$N_2CHCO_2\underline{i}\text{-}Pr$	1.4	5.4	13.3

a. Parameters are obtained for trans-2-phenylcyclopropancarboxylic acid
formed at 25-100°.

In the present reaction, enantioface selection is possible at a) rate-determining reaction
of prochiral diazo compounds by the chiral catalyst and at b) reaction of prochiral
Co-carbene moiety with olefin. Further insight into the enantioselection mechanism
requires detailed knowledge of the inorganic chemistry of the chiral Co(II) complexes.
In order to better understand the stereochemical environment of the chiral Co(II)
catalysts, we have prepared a number of Group 8 metal complexes of isomeric cqd and nqd
ligands. Study of the spectroscopic and magnetic properties of these new chiral
complexes has lead to the assignment of distorted 5-coordinate structure for the Co(II)
derivatives as shown below. The apical aqua ligand will be replaced first with diazo
alkane and then with the carbene ligand (cf. Scheme 1). Since no geometrical isomeriza-
tion of the isomeric dioximato ligand is caused by the metal ions, the structure of
$Co(\alpha\text{-}cqd)_2 \cdot H_2O$ involves two α-cqd ligands each as an N,O-chelate and the molecule is
associated by two hydrogen bonds. Then the probable structure of the carbene intermediate
is composed of two different conformers with respect to rotation around the metal-carbene
bond.

$[Co(\alpha\text{-}cqd)_2 \cdot H_2O]$
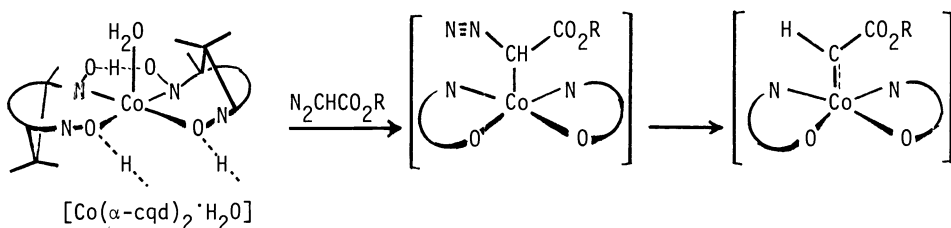
Since there will be only a little energy barrier imposed by the metal-carbene multiple
bonding, the interconversion (I ⇌ II) prior to the attack of olefins would make the
enantioface selection at the diazo side meaningless. The conformer I will predominate
because more space is available to accommodate the ester group. Then the olefin attack
on the enantiofaces of the prochiral Co-carbene moiety will be controlled by the
difference in effective bulkiness between the two cqd ligands flanking the reacting
center. Consideration of the steric crowding of the ligand indicates that an attack on I at
the left-side(viewed from the front) or on the si-face(Ref.5) is favored. Then the
cyclopropane, resulted through the ring contraction step(with retention of the stereo-
chemistry see Scheme 1), should have (1S)-configuration. Actually, prevalence of (1S)
-enantiomer has been experimentally confirmed in more than ten different combinations of
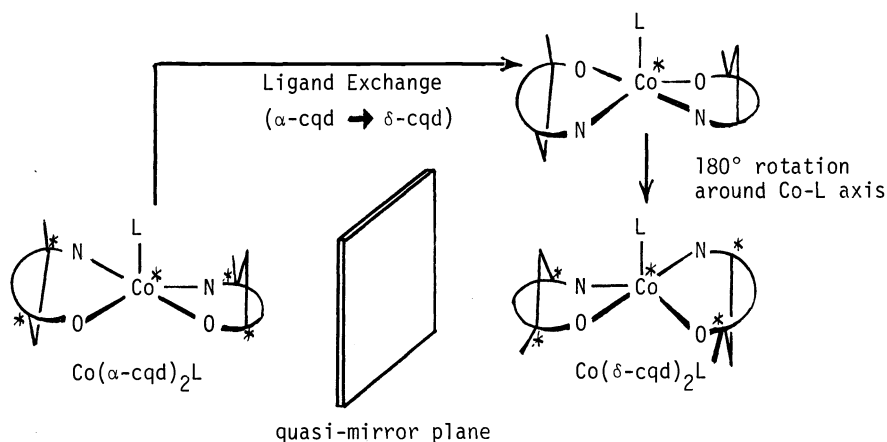olefins and diazoalkanes.
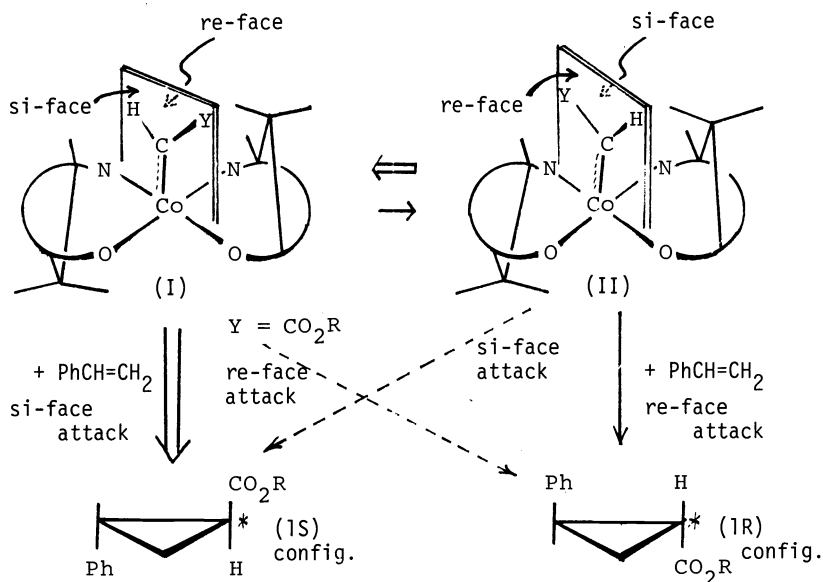
Since this mechanism seems to be oversimplified, we have examined the stereochemistry around the metal by changing the chiral dioximato ligands(II V) and investigated the catalysis.

Distortion of Cobalt-Carbene Reactive Intermediates and Chirality at Cobalt.

Consideration of high π-acidity of the carbene ligand, $:CHCO_2R$, the 5-coordinated cobalt -carbene complex must be distorted from regular square pyramidal(sqpy)structure. C_{2v}-distortion of the sqpy structure by the apical carbene is predicted by application of the theory of R. Hoffmann et al(Ref.6). The distortion of $[Co(\alpha-cqd)_2(CHCO_2R)]$ produces another chiral center at the reactive Co(II) as shown below(note a).

diastereomer(A)   diastereomer(B)
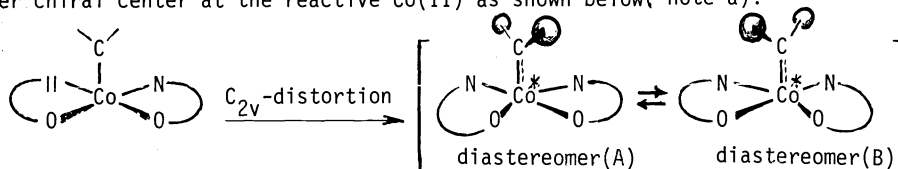
Interestingly, the conformational change at the carbene ligand(partial rotation at the cobalt-carbene bond) is accompanied by inversion of chirality at Co(II). This inversion is clearly a result of well-known non-rigidity of 5-coordinated metal complexes. Relative population of these two diastereomers would be influenced by the carbon chirality at the cqd ligand. Selective si-face attack on the prochiral cobalt-carbene moiety of the diastereomer(A) seems to be favored as judged from the steric hindrance in the olefin attack. If this enantioselection mechanism is correct, enantiomer preference of $Co(\delta-cqd)_2H_2O$ catalyst can be predicted as described in the followings. Firstly, the hypothetical ligand exchange of α-cqd in $Co(\alpha-cqd)_2$ with δ-cqd is considered while the bond angles around the metal are retained(see below).

Ligand Exchange
(α-cqd → δ-cqd)

180° rotation
around Co-L axis

$Co(\alpha-cqd)_2L$ $Co(\delta-cqd)_2L$

quasi-mirror plane

The exchange gives "pseudo-enantiomeric complex" which has the same carbon chirality but the opposite metal chirality. Secondly, the steric hidrance for olefin attack is taken into account. Then the $Co(\delta-cqd)_2$ catalysis(eq.1)is expected to give the (1R)-cyclopropane enantiomer in excess. Purification of δ-cqdH required tedius steps and optically pure sample was obtained after a considerable effort. The cobalt complex, $Co(\delta-cqd)_2 \cdot H_2O$, was found to be an effective enantioselective catalyst for production of (1R)-cyclo-propanecarboxylates in large excess(see Table 4). By contrast, the use of N,N-chelated complexes, $Co(\beta-cqd)_2H_2O$ or $Co(\beta-nqd)_2H_2O$ as catalysts gave low optical yields of the products. This poor efficiency may be related to the absence of metal chirality even at the C_{2v}-distorted states. The proposed enantioselection mechanism also seems to be supported by examination of catalysis of $Co(\delta-nqd)_2$ prepared from natural β-pinene. Upon consideration of the carbon chirality of the nqd ligand, one can predict the chirality of prevailing enantiomer in the $Co(\delta-nqd)_2$-catalyzed cyclopropanation product to be (1R). Actually, the reaction was found to yield (1R)-cyclopropanecarboxylates in excess as shown in Table 4.

Note a. The asterisk indicates presence of chirality center at the atom.

TABLE 4. Asymmetric Cyclopropanation(eq.1.) by Various Cobalt(II)
         Chiral Chelate Catalysts

| Catalyst | Cyclopropanation Products(PhCH—CHCO$_2$Et)CH$_2$ | | | | | |
| | cis-isomer | | | trans-isomer | | |
	$[\alpha]_D$	Config.	Optical Yield (%)	$[\alpha]_D$	Config.	Optical Yield (%)
Co(α-cqd)$_2$·H$_2$O	+12°	(1S,2R)	66	+236°	(1S,2S)	75
Co(δ-cqd)$_2$·H$_2$O	-11°	(1R,2S)	63	-202°	(1R,2R)	64
Co(δ-nqd)$_2$·H$_2$O	- 3.7°	(1R,2S)	21	-237°	(1R,2R)	74
Co(β-cqd)$_2$·H$_2$O	- 5.6°	(1R,2S)	31	+ 29°	(1S,2S)	9
Co(β-nqd)$_2$·H$_2$O	+ 0.6°	(1S,2R)	4	- 0.6°	(1R,2R)	0.2

CONCLUDING REMARKS

In summary, a novel highly enantioselective cyclopropanation is thus achieved by an effective
steric control of the reactions of cobalt-carbene species. Presence of a new N,O-chelated
vicinal dioximato structure coupled with bulky strained bicyclic chiral carbon skeletons is
a remarkable feature of the catalyst. In addition to the unique enantioselection mechanism,
this catalysis has practical utility; a) ready availability of the chiral dioximato ligands,
b) low price of the metal, and c) good chemical yield and regioselectivity in the cyclopro-
panation.
The β-isomers of the chiral dioximato ligands(i.e. β-cqd or β-nqd) act as N,N-chelates to
various metals. Some of them serve as interesting inorganic models of cobalamin or heme.
The chirality and bulkiness of the β-cqd ligands introduces unique features to the metal
complexes and the chemical results of these features will be explored in future.
Our preliminary experiment shows that Co(β-nqd)$_2$·H$_2$O and Fe(β-nqd)$_2$py$_2$ add dioxygen at
atmospheric pressure giving 2:1 complexes. Co(β-nqd)$_2$·H$_2$O is a hydrogenation catalyst for
PhCOCOPh. Benzoin was obtained in 2% enantiomeric excess. In addition to the inorganic
potentiality of cqd or nqd ligands, the corresponding di-imine derivatives of camphor or
nopinone, e.g. camphorquinodi(phenylimine) (abbreviated as cdi), are also utilized as N,N-
chelate ligands. A rhodium complex, RhCl(cdi)(1,5-cod), was prepared and found to decompose
diazoalkanes catalytically.
Future aspects of the present investigations may be effective stereochemical controls of
many reactions mediated by reactive metal-carbene intermediates, e.g. olefin metathesis and
skeletal isomerization of organic rings.

REFERENCES

1. a) W. Kirmse, "Carbene Chemistry", Vol. 1, Academic Press, New York and London(1971).
   b) K.C. Bishop,III, Chem. Rev., 76, 461-486 (1976).
   c) N. Calderon, E.A. Ofstead, and W.A. Judy, Angew. Chem. Int. Ed., 15, 401-409(1976).
2. H. Nozaki, H. Takaya, S. Moriuti, and R. Noyori, Tetrahedron,24, 3655-3669(1968);
   W.R. Moser, J. Am. Chem. Soc., 91, 1135-1140; 1141-1146(1969). A recent improvement, see
   T. Aratani, Y. Yoneyoshi, and T. Nagase, Tetrahedron Lett.,1975, 1707-1710.
3. Preliminary note: Y. Tatsuno, A. Konishi, A. Nakamura, and S. Otsuka, Chem. Comm., 1974,
   588-589. Structures and nomenclature of the dioximes, see, A. Daniel and A.A. Pavia,
   Tetrahedron Lett.,1967, 1145-1148.
4. See also, Ph.G. Moniottes, A.J. Hubert, and Ph. Teyssie, J. Organometal. Chem., 88,
   115-120(1975).
5. See rules for the designation of enantiofaces; K. Mislow and M. Raban, in "Topics in
   Stereochemistry", eds., N.L. Allinger and E.L. Eliel, Vol. 1, p.1, Intersci.,
   New York(1967).
6. M. Elian and R. Hoffmann, Inorg, Chem., 14, 1058-1076(1975).