# CHAPTER III

LITERATURE REVIEWS

3.1 Inclusion

Since their discovery, cyclodextrin have served as novel host compounds and catalysts. The effects of cyclodextrin on the reactions are devided mainly into two types. The first is effect on covalent bonds, this effect has been studied as the enzyme model. The second effect, the hydrophobic cavity of cyclodextrin gives the reactant access to a new reaction environment, which the reactivity such as rate or selectivity changes. In these cases, the role of the cyclodextrin is not always defined as catalyst.[18]

In 1977, Bender et al.[19] showed that *m-tert*-butylphenyl acetate bound into the cyclodextrin cavity could acylate the hydroxyl groups on the cyclodextrin rim with some geometric preference as shown in Scheme 3.1.
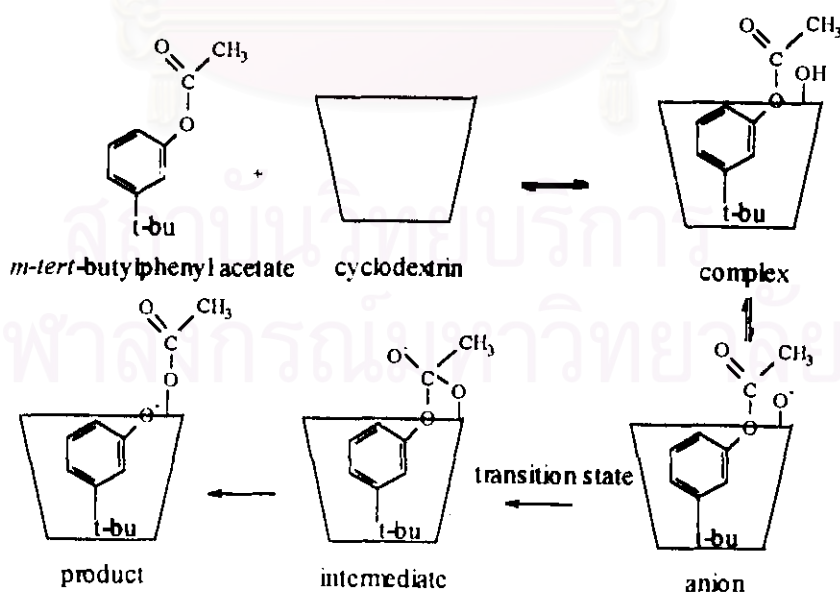
Scheme 3.1 Substrate binding into the cavity of the cyclodextrin

In 1983, Breslow et al.[20] showed a series of p-nitrophenyl ferroceneacrylate esters (e.g. Figure 3.1) bound well into the cavity, and acylated a β-cyclodextrin hydroxyl group with as much as a 5,900,000-fold acceleration relative to substrate hydrolysis under the same condition.
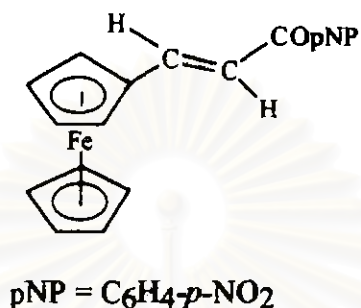

$pNP = C_6H_4\text{-}p\text{-}NO_2$

Figure 3.1   p-Nitrophenyl ferroceneacrylate ester

In 1988, Harada et al.[21] prepared inclusion compounds of ferrocene and its derivatives with cyclodextrins by mixing an alcohol solution of ferrocene or derivative with an aqueous or alcohol solution of cyclodextrin. The better method is adding fine crystals of ferrocene or derivative directly to an aqueous solution of cyclodextrin at 60 °C.

β- and γ-Cyclodextrin formed 1:1 stoichiometric inclusion compounds while α-cyclodextrin formed 2:1. The proposed structures shown in Figure 3.2 were concluded from induced circular dichroism (i.c.d.) spectra.
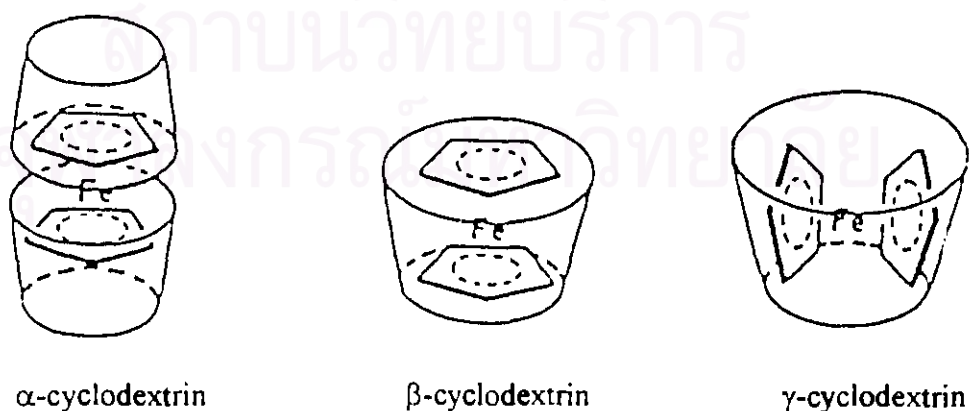

α-cyclodextrin   β-cyclodextrin   γ-cyclodextrin

Figure 3.2   Proposed structures for ferrocene-α, -β and γ-cyclodextrin inclusion compounds

Molecular models of the cyclodextrins and ferrocene indicate that a ferrocene molecule could fit well into a β-cyclodextrin cavity by axial inclusion, while γ-cyclodextrin cavity is large enough to accommodate a ferrocene molecule equatorially. A consideration of the molecular dimensions of α-cyclodextrin and ferrocene implies that the ferrocene molecule is too large to be completely included in a single cavity of this cyclodextrin, which can accommodate only one cyclopentadienyl ring, but appears to fit well into the cavity formed by two such molecules.

Inclusion compounds of ferrocene with α- and β-cyclodextrins are so stable that they can be recrystallized from water to give yellow crystals. The complexes of ferrocene with α-and β-cyclodextrins are thermally stable and do not liberate ferrocene on heating at 100 °C in *vacuo*. Thermogravimetic analyses showed that these complexes are stable up to 200 °C and decompose around the melting point of the cyclodextrin as shown in Figure 3.3
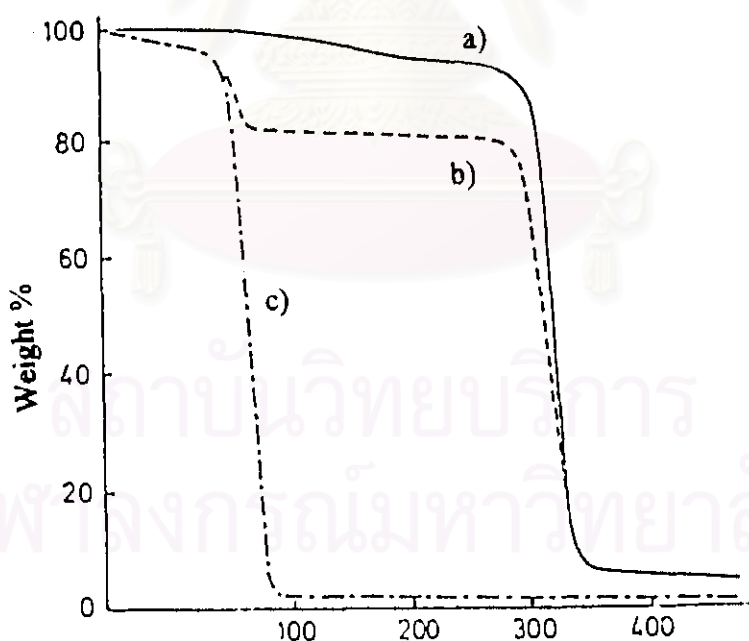

Figure 3.3 Thermogravimetric analysis of

a) β-cyclodextrin-ferrocene inclusion compound

b) mixture of the β-cyclodextrin and ferrocene

c) ferrocene

The inclusion compounds were characterized by ^{1}H NMR, IR, UV, and circular dichroism spectroscopies. A large positive induced Cotton effect was observed in the case of β-cyclodextrin-ferrocene, while the γ-cyclodextrin-ferrocne showed a negative spectrum as shown in Figure 3.4.
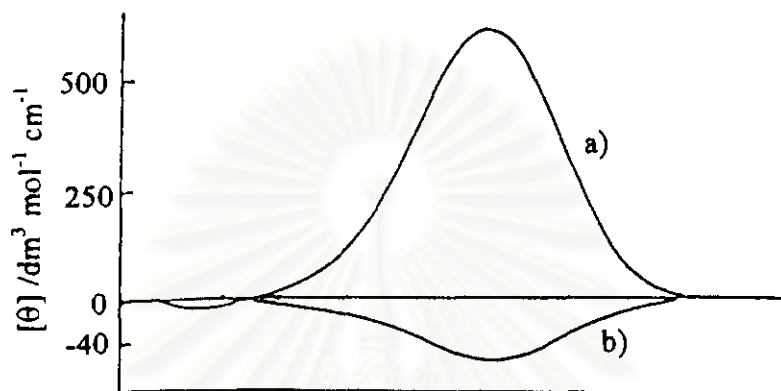

Figure 3.4 Absorption spectra of

    a) β-cyclodextrin-ferrocene

    b) γ-cyclodextrin-ferrocene

In 1989, Kawajiri et al.[22] reported the reduction of ferrocenylketones using the aqueous suspension of β-cyclodextrin inclusion compound with sodium borohydride, gave fairy enantioselectivity of optically active alcohol (Scheme 3.2). They found that strong asymmetric induction may be attributed to the steric requirement in the inclusion compound formation and sodium borohydride may attack from the opposite direction of the host molecule.
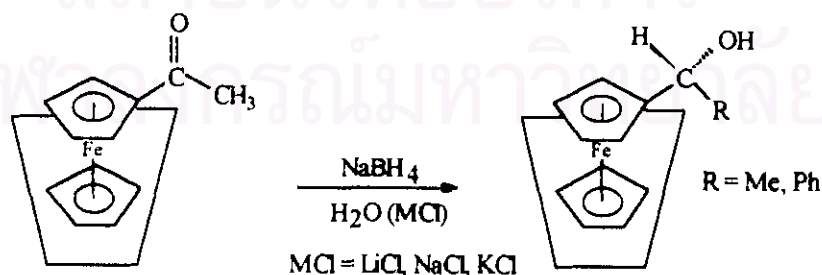
Scheme 3.2 Reduction of β-cyclodextrin-ferrocenylketones

In 1991, Harada et al.[23] reported an X-ray analysis of the α-cyclodextrin-ferrocene inclusion compound. Ferrocene molecule sitting in the hydrophobic cavity of dimer formed by two α-cyclodextrin molecules joined in a head-to-head fashion via hydrogen bonding. The ferrocene sits at an angle of 42° to the sixfold axis of the cyclodextrins, which have a mutual lateral shift of ca.130 pm (Figure 3.5). By this means maximum van der Waals's stabilization is achieved. The cyclopentadienyl moieties are mutually rotated by ca. 30° from the eclipsed conformation.
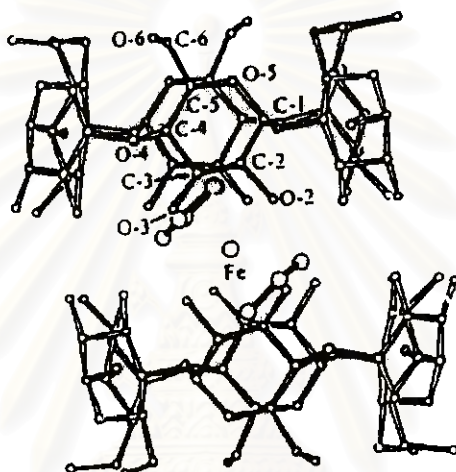

Figure 3. 5 A view based on X-ray crystallographic data of the α-cyclodextrin ferrocene (2:1) inclusion compound, along a local two fold axis through the iron atom.

In 1996 Li Yue-Ming et al.[24] studied aldol condensation of acetylferrocene with benzaldehyde *via* the formation of the β-cyclodextrin inclusion compound (Scheme 3.3). The study revealed that the definite asymmetry-inducing ability of β-cyclodextrin gave optical yields of the products in the range 6.0-30.4 %.
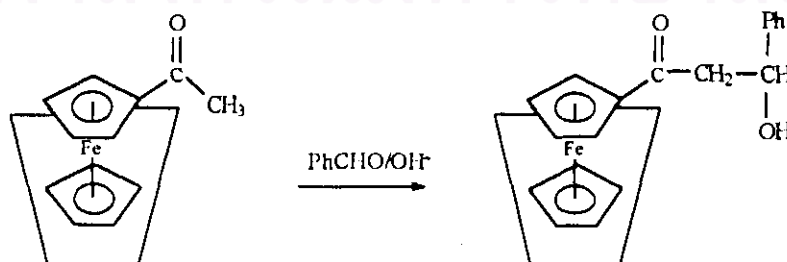

Scheme 3.3 Asymmetric aldol condensation of acetylferrocene with benzaldehyde
via the formation of the β-cyclodextrin inclusion compound

3.2 Asymmetric Alkylation

Asymmetric alkylation of dialkylzincs (R_2Zn) to aldehydes catalyzed by chiral β-amino alcohols is a convenient method for the preparation of optically active secondary alcohols.

In 1986, Noyori et al.[25] demonstrated that (-)-3-*exo*-(dimethylamino)iso borneol [(-)-DAIB] is a remarkably efficient catalyst for the asymmetric alkylation of diethylzinc to aldehydes, in the presence of 2 % of [(-)-DAIB]. The reaction of benzaldehyde and diethylzinc proceeds smoothly, after aqueous workup, gives (S)-1-phenyl-1-propanol (Scheme 3.4) in 98 % e.e. and in 97 % yield along with a small amount of benzyl alcohol.
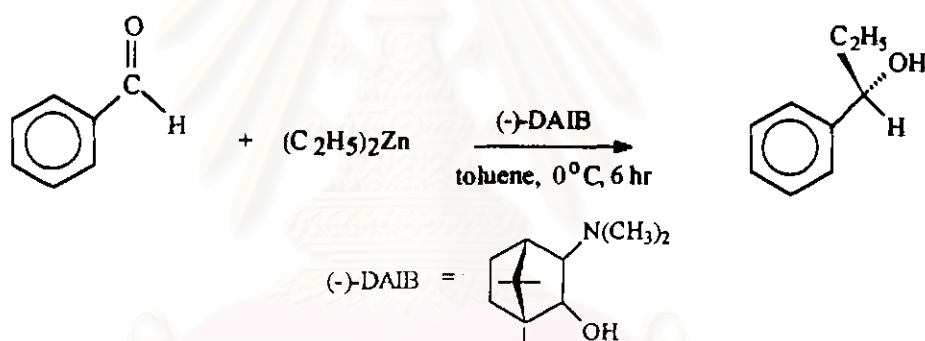
Scheme 3.4 Alkylation of diethylzinc with (-)-DAIB catalyst

In 1989, Tanaka et al.[26] reported that N-alkyl derivative of *endo*-3-amino-*endo*-2-hydroxybornane in Figure 3.6(a) prepared from D-camphor catalyzed the alkylation of diethylzinc to benzaldehyde to afford (R)-1-phenyl-1-propanol with 92 % e.e. On the other hand, *exo*-3-amino-*exo*-2-hydroxybornane in Figure 3.6(b) afforded (S)-1-phenyl-1- propanol with 88 %
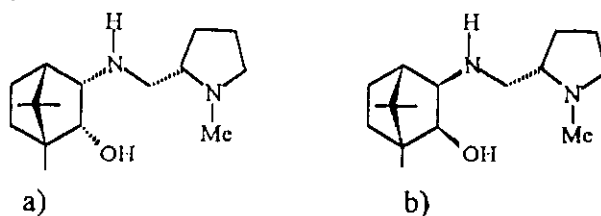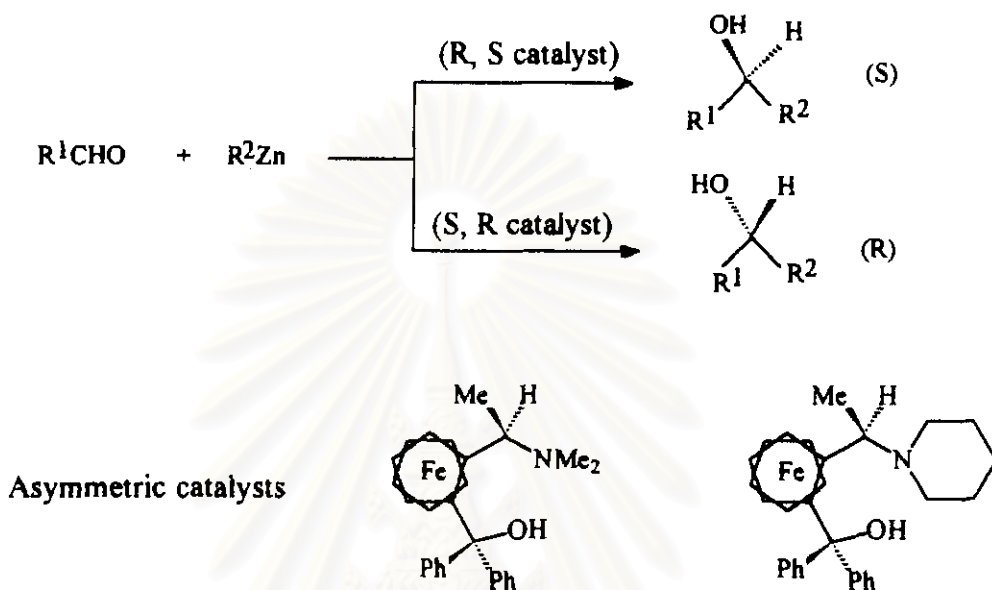

a)   b)

Figure 3.6 β-Secondary amino alcohol catalysts

    a) *endo*-3-amino-*endo*-2-hydroxybornane

    b) *exo*-3-amino-*exo*-2-hydroxybornane

In 1991, Watanabe et al.[27] used chiral 1, 2-disubstituted ferrocenylamino-
alcohols as catalysts to afford optically active alcohol with 99 % e.e. as shown in
Scheme 3.5

Scheme 3.5 Asymmetric alkylation of aldehyde with 1, 2-disubstituted ferrocenyl
aminoalcohol catalysts.

A proposed mechanism for the enantioselective alkylation of diethylzinc to an
aldehyde is shown in Figure 3.7. The Zn atom of the seven membered ring coordinated
to the substrate, a second diethylzinc bound to the ring to give a chair-like, six-
membered transition state resulting in minimum steric repulsion. This geometry should
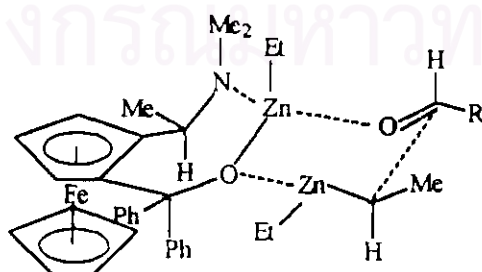highly favor an attack of the ethyl group to the si-side of the aldehyde.

Figure 3.7 Proposed mechanism for the enantioselective alkylation of diethylzinc to
aldehyde

In 1995, Fukuzawa et al.[28] demonstrated that new chiral ferrocenylselenium-based enantioselective catalysts for ethylation of aldehyde with diethylzinc. Reaction of benzaldehyde with diethylzinc in toluene and 5 mol % of catalysts at room temperature for 15 hr gave 1-phenyl-1-propanol in good yields with up to 94 % e.e. (Scheme 3.6)

$$RCHO \ + \ (CH_3CH_3)_2Zn \xrightarrow[\text{toluene}]{\text{catalyst}}$$
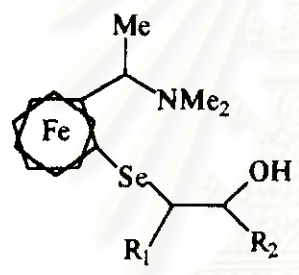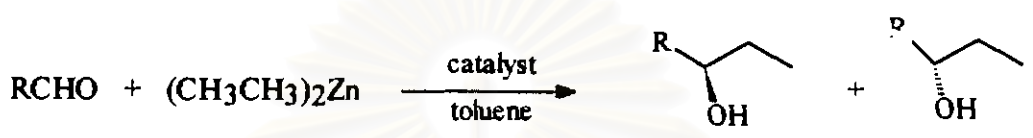
1a; R_1 = H, R_2 = Ph
1b; R_1 = H, R_2 = Me
1c; R_1 = H, R_2 = But
1d; R_1 = Ph, R_2 = Ph
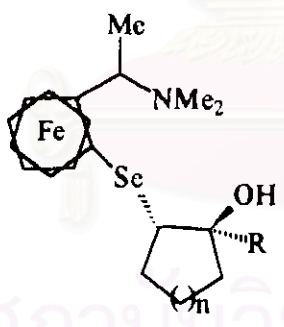
2a; n = 1, R = H
2b; n = 2, R = H
2c; n = 2, R = Me
2d; n = 2, R = Ph
2e; n = 4, R = H

Scheme 3.6 Ethylation of aldehyde with ferrocenylselenium-based enantioselective catalysts