10. Ramamurthy, V.; Sanderson, D. R.; Eaton, D. F. *J. Phys. Chem.* **1993**, *97*, 13380.
11. Kang, W.-K.; Cho, S.-J.; Lee, M.; Kim, D.-H.; Ryoo, R.; Jung, K.-H.; Jang, D.-J. *Bull. Korean Chem. Soc.* **1992**, *13*, 140.
12. Hong, S. B.; Shin, E. W.; Moon, S. H.; Pyun, C.-H.; Kim, C.-H.; Uh, Y. S. *J. Phys. Chem.* **1995**, *99*, 12274.
13. Baker, M. D.; Olken, M. M.; Ozin, G. A. *J. Am. Chem. Soc.* **1988**, *110*, 5709.
14. Bada, T.; Hikita, S.; Ono, Y.; Yoshida, T.; Tanaka, T.; Yoshida, S. *J. Mol. Cat. A: Chem.* **1995**, *98*, 49.
15. Yamase, T.; Kobayashi, T.; Sugeta, M.; Naruke, H. *J. Phys. Chem. A* **1997**, *101*, 5046.
16. Gfeller, N.; Calzaferri, G. *J. Phys. Chem. B* **1997**, *101*, 1396.
17. Wolbers, M. P. O.; van Veggle, F. C. J. M.; Snellink-Ruël, B. H. M.; Hofstraat, J. W.; Geurts, F. A. J.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1997**, *119*, 138.
18. Mirochnik, A. G.; Petrochenkova, N. V.; Karasev, V. E. *Russian Chem. Bull.* **1996**, *45*, 1356.
19. Prodi, L.; Maestri, M.; Ziessel, R.; Balzani, V. *Inorg. Chem.* **1991**, *30*, 3798.
20. Fujita, K.; Tanaka, K.; Hirao, K.; Soga, N. *J. Appl. Phys.* **1997**, *81*, 924.
21. Pucker, G.; Catterer, K.; Fritzer, H. P.; Bettinelli, M.; Ferrari, M. *Phys. Rev. B* **1996**, *53*, 6225.
22. Tanaka, T.; Yoshida, T.; Yoshida, S.; Baba, T.; Ono, Y. *Physica B* **1995**, *208&209*, 687.
23. Rizk, M.; El-Shabrawy, Y.; Zakhari, N. A.; Toubar, S. S.; Carreira, L. A. *Spectrosc. Lett.* **1995**, *28*, 1235.
24. Reuben, J. *Handbook on the Physics and Chemistry of Rare Earths*; North-Holland Publishing Company: 1979; p 515.
25. Jameson, D. M.; Weber, G. *J. Phys. Chem.* **1981**, *85*, 953.
26. Gratton, E.; Limkeman, M. *Biophys. J.* **1983**, *44*, 315.
27. Lakowicz, J. R.; Laczko, G.; Gryczynski, I.; Cherek, H. *J. Biol. Chem.* **1986**, *261*, 2240.
28. Weber, G. *J. Phys. Chem.* **1981**, *85*, 949.
29. Bunzli, J.-C. G.; Choppin, G. R. *Lanthanide Probes in Life, Chemical and Earth Sciences*; Elsevier Science: Amsterdam, The Netherlands, 1989; p 219.
30. Bergaya, F.; van Damme, H. *J. Chem. Soc., Faraday Trans.* **1983**, *79*, 505.
31. Oomen, E. W. J. L.; van Dongen, A. M. A. *J. Non-Cryst. Sol.* **1989**, *111*, 205.
32. Carlos, L. D.; Videira, A. L. L. *Phys. Rev. B* **1994**, *49*, 11721.
33. Richardson, F. S. *Chem. Rev.* **1982**, *82*, 541.
34. Levy, D.; Reisfeld, R.; Avnir, D. *Chem. Phys. Lett.* **1984**, *109*, 593.
35. Horrocks, Jr., W. DeW.; Subnick, D. R. *Acc. Chem. Res.* **1981**, *14*, 384.
36. Haas, Y.; Stein, G. *J. Phys. Chem.* **1972**, *76*, 1093.
37. Horrocks, Jr., W. DeW.; Subnick, D. R. *J. Am. Chem. Soc.* **1979**, *101-2*, 334.
38. Iton, L. E. *J. Phys. Chem.* **1977**, *81*, 435.
39. Breck, D. W. *Zeolite Molecular Sieves: Structure, Chemistry, and Use*; John Wiley & Sons: U.S.A., 1974; p 100.

The Interaction of Chiral Amino Thiols with Organozinc Reagents and Aldehydes: A Mechanism of Amino Thiol-Catalyzed Addition of Organozinc Reagents to Aldehydes

Jahyo Kang*, Jin Bum Kim, Jeeyoung Kim, and Duckhwan Lee*

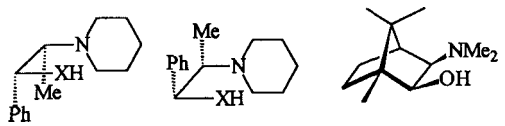
Department of Chemistry, Sogang University, Seoul 121-742, Korea
Received February 4, 1998

Details of various equilibria involved in the reactions of oxaza- and thiazazincolidine catalysts, generated from either β-amino alcohol or β-amino thiol, with aldehyde were studied by colligative measurements. The results indicated that the coordination of diethylzinc prior to the coordination of aldehyde is essential for high enantioselectivity of the thiol catalyzed reaction. The probable origin of asymmetric nonlinearity is also presented.

Introduction

The β-amino alcohol catalyzed addition of dialkylzinc reagents to aldehydes is quite general for preparation of optically active secondary alcohols, for which extensive mechanistic studies have been carried out by many groups.[1,2] We have also developed chiral cyclic amino *thiols*, especially piperidine compound **1** derived from commercially available enantiopure norephedrine, which have turned out to be an excellent ligand for thiazazincolidine catalyst. The thiol ligands were expected to be highly effective due to the fact 1) the sulfur in thiol is more easily polarizable compared to the oxygen in alcohol, 2) the heterocyclic ring may become a face blocker, 3) the thiol and thiolates have higher affinity toward metals, especially zinc, and 4) the metal thiolates have less tendency of diminishing the Lewis

acidity of metal compared to the alcohlates.[3] Recently, we have found several favorable effects of the β-amino thiol including the faster reaction rate, higher enantioselectivity, and higher degree of asymmetric amplification comparing with β-amino alcohol **2**. Unlike the conventional explanations,[1,2] we have found that *the stability difference between the homo- and hetero-chiral dimers may not be the sole reason for high asymmetric nonlinearity of the thiol catalyzed alkylation of aldehyde.*[4]



X = S	1	3	
X = O	2	4	5

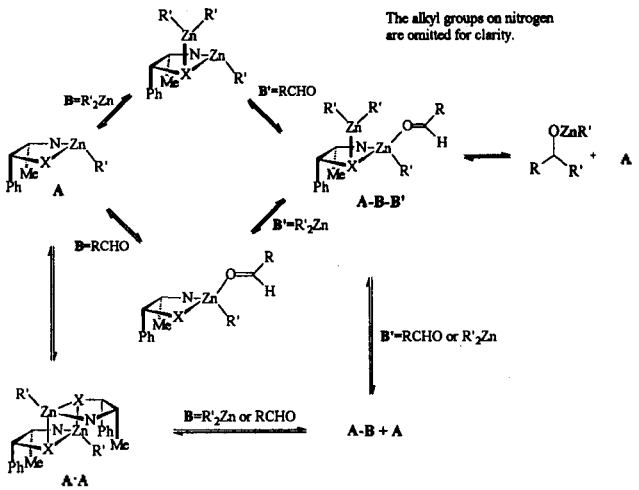
In this paper, we investigated in more detailed manner whether or not our initial presumptions on β-amino thiol ligands mentioned above are indeed applicable for ligand system **1**, the best among many β-amino thiols we have prepared and studied so far.[3,4] The possible reaction mechanism will be proposed from our analysis. We also look for the factors affecting strong asymmetric nonlinearity of the thiol catalyzed reaction. The freezing point depression measurement turned out to provide useful information for our study.

Results and Discussion

Prior Knowledge. The mechanistic pathway of asymmetric addition of dialkylzinc to aldehyde in the presence of catalytic amount of β-amino thiol is supposed to be almost identical to the case of β-amino alcohol for which the reaction mechanism has been well established.[1] The reaction is the first order with respect to the catalyst. Thus, upon reaction with dialkylzinc, β-amino alcohol or thiol is converted to a five-membered ring complex **A**, which then undergoes dimerization to form a dimer **A-A** (Scheme 1). Although there were reports suggesting the possible formation of tetrameric complexes of thiazazincolidine derived from analogous N-methylephedrine,[2a] we were unable to find any indication of high molecular mass species formed in the reaction mixture at least up to 60 mM.[4]

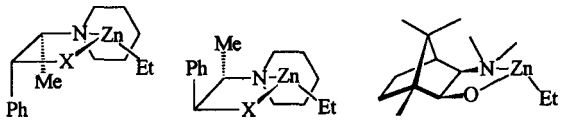
We can now consider two possible reaction pathways for the thiol catalyzed reaction. In the mechanism depicted in the upper part of Scheme 1, the five-membered ring complex **A** is a Lewis acid. But it can also act as a Lewis base to which an organometallic reagent and aldehyde can coordinate in a stepwise manner. Thus, **A** forms a binary complex with **B** (B=dialkylzinc or aldehyde) first and then the complex **A-B** interacts with aldehyde or dialkylzinc resulting in a ternary complex **A-B-B'** in which the intermolecular transfer of the R' group from zinc to the carbonyl carbon takes place.

Alternatively, as indicated in the lower part of Scheme 1, the dimer complex **A-A** itself can interact directly with dialkylzinc or aldehyde to form a binary complex **A-B** which then undergoes the same reaction path as the above mentioned mechanism to the final product.



Scheme 1.

Reaction Free Energies from Enantiopure Mixture. It was proved that the cryogenic measurement is quite useful for studying the equilibria involved in the β-amino alcohol or thiol catalyzed alkylation of benzaldehyde in the presence of diethylzinc. In our previous study,[4] the same experimental technique was successfully applied for determining the free energies of formation of homo- and heterochiral dimerizations of zinc complexes. In this study, the same technique was employed to obtain much more detailed information for an *equimolar* mixture of the complex **A** with dialkylzinc or aldehyde. In this analysis, it was assumed that no addition reaction of dialkylzinc took place in the mixture containing the complexes, **6** through **10**, and aldehyde.



X = S	6	8	
X = O	7	9	10

Let us consider here *equimolar* mixture of *enantiopure* complex **A** with dialkylzinc or aldehyde which is denoted by **B**. If the initial concentration of **A** is c, then

$$[\mathbf{A}] + [\mathbf{A\text{-}B}] + 2[\mathbf{A\text{-}A}] = c \tag{1}$$

For equimolar mixture, the initial concentration of **B** also becomes c and thus

$$[\mathbf{B}] + [\mathbf{A\text{-}B}] = c. \tag{2}$$

Since $K=[\mathbf{A\text{-}A}]/[\mathbf{A}]^2$ at equilibrium, one can readily find the following relations.

$$[\mathbf{A}] = \sqrt{\frac{[\mathbf{A\text{-}A}]}{K}} \tag{3}$$

$$[\mathbf{B}] = [\mathbf{A}] + 2[\mathbf{A\text{-}A}] = \sqrt{\frac{[\mathbf{A\text{-}A}]}{K}} + 2[\mathbf{A\text{-}A}] \tag{4}$$

$$[\mathbf{A\text{-}B}] = c - [\mathbf{B}]. \tag{5}$$

On the other hand, the molar mass M_o obtained from the

freezing point depression measurement is the weighted average of the molar masses of solute species present in the mixture. Therefore,

$$M_o = \frac{M_A[\mathbf{A}]+M_B[\mathbf{B}]+M_{AB}[\mathbf{A\text{-}B}]+M_{AA}[\mathbf{A\text{-}A}]}{[\mathbf{A}]+[\mathbf{B}]+[\mathbf{A\text{-}B}]+[\mathbf{A\text{-}A}]} \quad (6)$$

where M_A, M_B, M_{AB}, and M_{AA} are the molar masses of the chemical species, **A**, **B**, **A-B**, and **A-A**, respectively. By using Eqs. (3), (4), and (5) and recognizing the relations, $M_{AB}=M_A+M_B$ and $M_{AA}=2M_A$, one can rearrange Eq. (6) into the following form,

$$\sqrt{K}\ M_o[\mathbf{A\text{-}A}]+M_o\sqrt{[\mathbf{A\text{-}A}]}-(M_{AB}-M_o)c\sqrt{K}=0 \quad (7)$$

which can be further reduced to the following expression for [**A-A**],

$$[\mathbf{A\text{-}A}]^{1/2}=\frac{-M_o+\sqrt{M_o^2+4KM_o(M_{AB}-M_o)c}}{2\sqrt{K}\ M_o}. \quad (8)$$

The equilibrium constant for homochiral dimerization, K, can also be determined by cryogenic measurement described in our previous study.[4] The concentrations of **A**, **B**, and **A-B** can be easily calculated from the concentration of **A-A** by using Eqs. (3), (4), and (5). The concentrations obtained in this fashion can be used to calculate the change of free energy for the following reaction,

$$\mathbf{A\text{-}A} + \mathbf{B} \rightarrow \mathbf{A\text{-}B} + \mathbf{A}$$

from the relation

$$\Delta G = -RT\ \ln\frac{[\mathbf{A\text{-}B}][\mathbf{A}]}{[\mathbf{A\text{-}A}][\mathbf{B}]}. \quad (9)$$

Reaction Free Energies from Racemic Mixture. The same treatment can be applied to an *equimolar* mixture of the *racemic complex* **A** with dialkylzinc or aldehyde which is again denoted by **B**.

For racemic mixture, [**A**]=[**A***], [**A-A**]=[**A***-**A***], and [**A-B**]=[**A***-**B**]. And if the initial total concentration of the complex, **A** and **A***, is c, then

$$2[\mathbf{A}]+2[\mathbf{A\text{-}B}]+4[\mathbf{A\text{-}A}]+2[\mathbf{A\text{-}A^*}]=c \quad (10)$$

For equimolar mixture, the initial concentration of **B** is also c and thus

$$[\mathbf{B}]+2[\mathbf{A\text{-}B}]=c \quad (11)$$

The equilibrium constants for homochiral dimerizaiton, $K=[\mathbf{A\text{-}A}]/[\mathbf{A}]^2=[\mathbf{A^*\text{-}A^*}]/[\mathbf{A^*}]^2$, and for heterochiral dimerization, $K'=[\mathbf{A\text{-}A^*}]/[\mathbf{A}][\mathbf{A^*}]$, can be used to express the dimer concentrations in terms of the monomer concentration.

From Eqs. (10) and (11), the following expressions for [**B**] and [**A-B**] can be easily obtained,

$$[\mathbf{B}]=2[\mathbf{A}]+4[\mathbf{A\text{-}A}]+2[\mathbf{A\text{-}A^*}] \quad (12)$$

$$[\mathbf{A\text{-}B}]=\frac{c-2[\mathbf{A}]-4[\mathbf{A\text{-}A}]-2[\mathbf{A\text{-}A^*}]}{2}. \quad (13)$$

Now, the observed molar mass can be written as following,

$$M_o=\frac{M_B[\mathbf{A}]+2M_A[\mathbf{A}]+2M_{AB}[\mathbf{A\text{-}B}]+2M_{AA}[\mathbf{A\text{-}A}]+M_{AA}[\mathbf{A\text{-}A^*}]}{[\mathbf{B}]+2[\mathbf{A}]+2[\mathbf{A\text{-}B}]+2[\mathbf{A\text{-}A}]+[\mathbf{A\text{-}A^*}]} \quad (14)$$

which can be simplified further by recognizing $M_{AB}=M_A+M_B$ and $M_{AA}=2M_A$. The resulting expression can be rearranged, by using Eqs. (10), (11), (12), and (13) as well as the equilibrium constants for monomer-dimer equilibria, into the following form,

$$M_o(2K+K')[\mathbf{A}]^2+2M_o[\mathbf{A}]+c(M_o-M_{AB})=0. \quad (15)$$

For [**A**]=[**A***], Eq. (15) can be solved analytically,

$$[\mathbf{A}]=\frac{-M_o+\sqrt{M_o^2-M_o(2K+K')c(M_o-M_{AB})}}{M_o(2K+K')} \quad (16)$$

The equilibrium constants, K and K', obtained from our previous study[4] can be used to find the monomer concentration, from which the concentrations of all chemical species present in the mixture including [**B**], [**A-A**], [**A-A***], and [**A-B**], can also be easily calculated. These values can be later used when calculating the free energy change accompanying the following reaction,

$$2\mathbf{A\text{-}A^*} + 2\mathbf{B} \rightarrow \mathbf{A\text{-}B} + \mathbf{A^*\text{-}B} + \mathbf{A} + \mathbf{A^*}$$

which is given as

$$\Delta G = -RT\ \ln\frac{[\mathbf{A\text{-}B}][\mathbf{A^*\text{-}B}][\mathbf{A}][\mathbf{A^*}]}{[\mathbf{A^*\text{-}A}]^2[\mathbf{B}]^2}=-2RT\ \ln\frac{[\mathbf{A\text{-}B}][\mathbf{A}]}{[\mathbf{A^*\text{-}A}][\mathbf{B}]} \quad (28)$$

In getting the final expression, the racemic nature of the mixture, [**A**]=[**A***] and [**A-B**]=[**A***-**B**], has been taken into account.

Experimental Results. The method described above was applied to the systems containing equimolar mixtures of **A** and **B**, **A** being thiazazincolidine (enantiopure and racemic), oxazazincolidine (enantiopure and racemic), or enantiopure DAIB (3-exo-(dimethylamino)-isoborneol) complex, and **B** being either Et_2Zn or benzaldehyde in benzene, in which the initial concentration of complex **A** was kept nearly constant (*ca.* 60 mM). It is noted here that the concentration chosen for the convenience of measurements was nearly 6 times higher than the usual preparative concentration (10-15 mM) and might well give more dimeric species than the usual condition since the degree of dimerization increases with the concentrations of solutes.[2] Nevertheless, the presence of oligomer other than dimeric species was hardly noticed in our current study.[4]

In the equations for various equilibrium concentrations derived above, M_{AB} is the known molar mass of the adduct **A-B**, K and K' are the equilibrium constants for homo- and heterochiral dimer formations, respectively, and c is the initial total concentration of the complex **A**. The average molar mass, M_o, was determined in this study by measuring the depression of the freezing point of the equilibrium reaction mixture. It was assumed that excess amounts of chemical species present in the mixture were present as independent entities. Now, from these information along with the expressions derived above, it was possible to determine the free energy changes for the enantiopure and racemic reaction mixtures. The results are summarized in Table 1. It is apparent here that the experimental and calculated results are reliable except for a few cases where the concentrations of the adduct, **A-B**, were too small to achieve reasonable experimental determination.

Aldehyde or Dialkylzinc, Which One is the First

Table 1. Equilibrium Concentrations and Free Energy Change

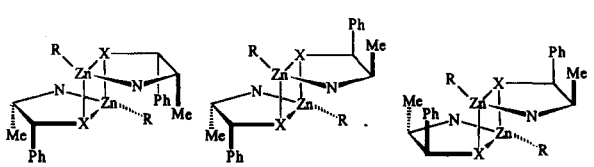
Complex (A)	Edduct (B)	c^a (mM)	M_o^b	[A]^c (mM)	[A-A]^d (mM)	[A-A*] (mM)	[B]^e (mM)	[A-B]^f (mM)	ΔG^g (kcal/mol)
	none	57.9	490±5	19.9±0.8	19.0±0.4				
6^h	Et_2Zn^k	57.5	403±2	5.5±0.2	1.5±0.1		8.5±0.5	49.0±0.5	−1.62±0.06
	PhCHO^l	60.1	262±1	20.1±0.1	19.6±0.2		59.3±0.6	0.8±0.6	2.41±0.47
	none	58.3	532±6	6.9±0.4	2.3±0.3	17.6±0.9			
6 and **8**^{h}	Et_2Zn^k	60.7	422±7	1.6±0.3	0.12±0.05	0.9±0.3	5.5±1.5	27.6±0.7	−1.16±0.30
	PhCHO^l	55.1	270±4	6.6±0.2	2.1±0.1	16.2±0.8	54.1±2.5		
	none	61.8	601±9	2.60±1.0	29.6±0.5				
7^i	Et_2Zn^m	60.0	288±1	2.52±0.02	28.3±0.3		59.1±0.7	0.9±0.7	3.68±0.56
	PhCHO^n	59.0	311±2	2.03±0.02	18.4±0.4		38.8±0.8	20.2±0.8	1.50±0.04
	none	61.4	615±5	0.6±0.3	2.6±2.2	24.9±4.6			
7 and **9**^{j}	Et_2Zn^m	59.0	291±5	0.57±0.01	1.4±0.1	25.4±1.3	57.6±2.8	0.8±0.9	4.53±0.61
	PhCHO^n	58.8	294±5	0.50±0.01	1.1±0.1	19.8±1.1	44.9±2.6	7.0±1.3	2.92±0.15
10^i	Et_2Zn^o	59.9	370±2	2.18±0.05	4.9±0.2		12.0±0.5	47.9±0.5	-0.30±0.04
	PhCHO^p	59.7	260±1	5.07±0.03	26.5±0.3		58.0±0.7	1.7±0.7	2.76±0.25

^{a} Initial concentrations of each of the complex ([A]$_o$) and the edduct ([B]$_o$). ^{b} Molar mass determined by freezing point depression. ^{c} Concentration of monomer complex. ^{d} Concentration of dimer complex. ^{e} Concentration of Et_2Zn or of PhCHO. ^{f} Concentration of adduct, **A-B**, *i.e.* **A-B**(Et_2Zn) or **A-B**(PhCHO). ^{g} Free energy change of rupture of dimer complex to form **A-B** upon addition of **B**. ^{h} Equilibrium constant for monomer-dimer equilibrium, K=48.0, K'=370. ^{i} Equilibrium constant for monomer-dimer equilibrium, $K=4.38\times10^3$, $K'=7.88\times10^4$. ^{j} Equilibrium constant for monomer-dimer equilibrium, $K=1.01\times10^3$, $K'=1.40\times10^3$. ^{k} Molar mass of adduct, **A-B**, is 452. ^{l} Molar mass of adduct, **A-B**, is 435. ^{m} Molar mass of adduct, **A-B**, is 436. ^{n} Molar mass of adduct, **A-B**, is 419. ^{o} Molar mass of adduct, **A-B**, is 414. ^{p} Molar mass of adduct, **A-B**, is 397.

to Coordinate?. There would be no difference in the coordination rate of **B** to **A** or **A***. Therefore, if the various equilibria shown in Scheme 1 is indeed operative, the major differences in reaction rate, enantioselectivity, asymmetric nonlinearity, *etc.* between the enantiomerically pure and impure (even racemic) catalyst must originate from the different degree of coordination of **B** to a dimer complex **A-A** (or **A-A***) to form a binary complex **A-B** (or **A*-B**) and a monomer **A** (or **A***). It is apparent from Table 1 that the reaction of the thiazazincolidine catalyst with dialkylzinc is spontaneous unlike the simultaneous rupture of the dimer complex and coordination of aldehyde.

The enantiopure thiazazincolidine complex **6** was present as a 51 : 49 mixture of monomer and dimer before the addition of diethylzinc. However, almost all (85%) of the complex was converted to the diethylzinc adduct **A-B** upon addition of equimolar diethylzinc. Therefore, the concentration of **A-B**(PhCHO) species in the real reaction mixture would become almost negligible.

On the contrary, the oxazazincolidine complex **7** appeared to coordinate preferentially to aldehyde even though simultaneous rupture of the coordination between dimer complex and aldehyde was thermodynamically unfavorable. Therefore, only a third of the oxazazincolidine dimer **12**, which was present predominantly over the monomer complex **7** (8 : 92), broke up to **A-B**(PhCHO) species upon addition of aldehydes. This result should be compared with the fact that the DAIB complex binds preferentially to dialkylzinc even though the ligands for complexes **7** and **10** are β-amino alcohols. The difference can be attributed mostly to the fact that the free energies of dimerization for the enantiopure amino alcohols **7** (−4.6 kcal/mol) and **10**



	A-A	A-A*	A*-A*
X = S	11	13	15
X = O	12	14	16

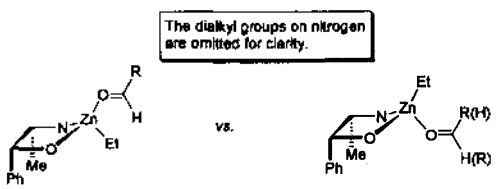
(−3.8 kcal/mol) are more negative than the free energy change for the enantiopure amino thiol **6** (−2.1 kcal/mol).[4] The free energies of coordination of benzaldehyde to the complex **7**, **10**, and **6** were not much different; 1.5 kcal/mol, 2.8 kcal/mol, and 2.4 kcal/mol, respectively. (The dialkyl groups on nitrogen are omitted for clarity in the following structures.)

Based on both functional (thiol *vs.* alcohol) and geometrical (or steric) factors, we may conclude tentatively that the *high affinity toward dialkylzinc reagents must be crucial for high catalytic activity in alkylation of aldehyde.* This conclusion appears to be consistent with our initial assumption regarding the higher affinity of thiolate toward metals, especially for zinc in thiazazincolidine **6** compared with oxazazincolidine **7**.

On the other hand, the oxazazincolidine monomer **7**, derived from norephedrine, seems to coordinate to aldehyde prior to dialkylzinc although the extent of coordination is rather small. At first we expected, solely from the pK_a arguments on thiol and alcohol, that the thiazazincolidine **6** may show stronger Lewis acidity than the

oxazazincolidine **7**. However, our estimates of equilibrium constants indicates the opposite. That is, the Lewis acidity of oxazazincolidine monomer **7** is larger than the corresponding thiol analog **6**.

The observations presented so far seem to be sufficient for explaining the higher enantioselectivity of the amino thiol-catalyzed reactions. In the thiol-catalyzed reaction, the dialkylzinc would coordinate to the thiazazincolidine **6** in a diastereoselective anti fashion to the phenyl group to form the complex **A-B**(R'_2Zn). Therefore, the sulfur atom in **6** acquires chiral property to the same extent. On the contrary, for oxazazincolidine **7**, aldehyde coordinates first to the zinc atom which is located far away from any chiral center. This leads to formation of the unwanted syn diastereomer com-



17 **18**

plex **18**, instead of **17**, which may eventually furnish enantiomeric alcohol.

Asymmetric Nonlinearity. It has been generally thought that the asymmetric amplification arises from the stability of the heterochiral complexes with respect to the homochiral complexes.[1,2] In other words, the relative excess of the major enantiomer becomes amplified in comparison with the minor enantiomer when the more stable heterochiral dimer complexes become predominant.[5]

However, according to our previous study, the energy differences between the homochiral and heterochiral complex pairs turned out to be about the same for the alcoholates and the thiolates, indicating that the chiral reservoir effect may not be much different for the two catalytic reactions.[4] Thus, the simple chiral reservoir effect may not be sufficient for explaining the much greater positive nonlinearity observed from the thiol catalyzed reaction compared to the alcohol catalyzed reaction.

As mentioned before, the dimer structures undergo spontaneous rupture upon reacting with diethylzinc and are converted to the binary complexes. As shown in Table 1, the extent of such conversion was 85% for enantiopure thiazazincolidine **6**, 45% for racemic thiazazincolidine, and 80% for enantiopure DAIB complex **10**. However, the conversion of the alcoholates to the binary complex with aldehyde was much lower: 34% for enantiopure oxazazincolidine **7** and 12% for racemic oxazazincolidine. The ee's of the resulting product from the alcoholates were below 86% with benzaldehyde, while the ee's from the thiolates went up close to 100%.[4] Thus, the difference in the extent of binary complex formation seems to be related to the experimentally observed asymmetric nonlinear behaviors of the thiolates and the alcoholates. It was however impossible for us to quantify further due to our relatively crude nature of our measurements. It was also not possible to determine the second equilibrium constants for formation of the ternary complex, **A-B-B'**, due to fast internal delivery of an alkyl group to the coordinated carbonyl carbon within the ternary adduct.

Model Calculation. We also tried to analyze the experimental enantiomeric amplification data by using the model proposed by Guillaneus, Zhao, Samuel, Rainford and Kagan.[5] This model assumed a fast equilibrium between the dimeric species and an irreversible pseudo-first order steps leading to the final product. In addition, the rate of final product formation was assumed to be independent of the concentrations of other substrates. In this model, hetero- and homochiral dimeric species are responsible for the racemic and enantiomeric products, respectively. Then, the ee of the product, $EE_{product}$, is expressed as

$$EE_{product} = EE_0\, EE_{catalyst}\, \frac{1+\beta}{1+g\beta} \tag{18}$$

EE_0 is the enantiomeric excess of the product, (R)-1-phenylpropan-1-ol, when using an enantiopure chiral lingand. Here, $EE_{catalyst}$ is the enantiomeric excess of the catalytic thiolate or alcoholate complexes. And, β and g are respectively the relative amount and reactivity of the homo- and heterochiral dimers. The expression for β is given by

$$\beta = \frac{-P\,EE_{catalyst}^2 + \sqrt{-4P\,EE_{catalyst}^2 + P(4+P\,EE_{catalyst}^2)}}{4+P\,EE_{catalyst}^2} \tag{19}$$

where the parameter P is defined as [**13** or **14**]^2/[**11** or **12**][**15** or **16**] which is reduced to the equilibrium constant when the distribution of the complexes becomes close to the thermodynamic equilibrium. Figure 1 shows the best fits of this model to experimental data with three adjustable parameters, EE_0, g and P.

The model can be readily extended to the case where mixture of thiolates and alcoholates are used. With the same assumptions, the enantiomeric excess of the product is now expressed as following,

$$EE_{product} = \frac{EE_1 g_2 Q_1 - g_1 g_3 EE_2 Q_2}{Q_1 + g_1 g_3 Q_2} \tag{20}$$

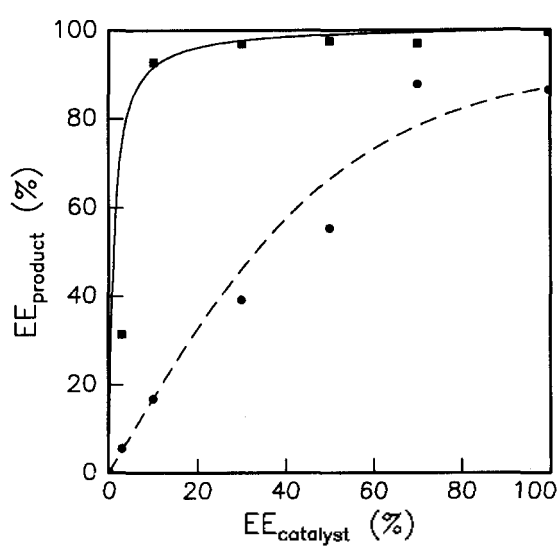


Figure 1. Model calculation for enantiomeric amplifications of the thiol and alcohol catalyzed reactions. The solid squares and circles are the experimental points for thiolates and alcoholates, respectively. EE_0=1.0, g=0.01, and P=10^5 are used for thiolates (solid line), and EE_0=0.87, g=0.20, and P=10 for alcoholates (dashed line) are used.

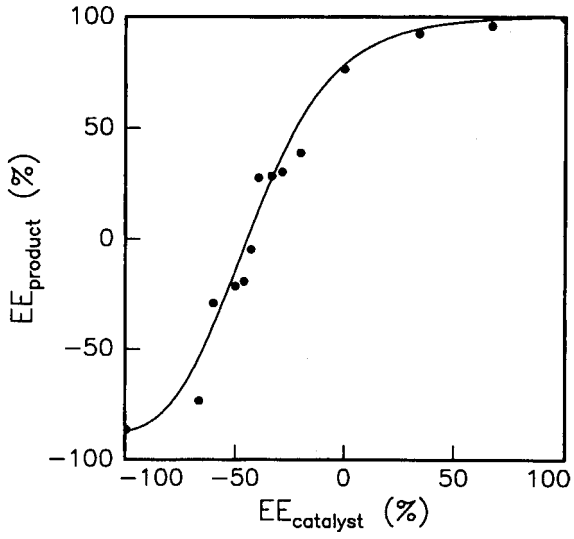


Figure 2. Model calculation for enantiomeric amplification of the thiol-alcohol catalyzed reaction. The solid circles are the experimental points. In this figure, EE_1=1.00, EE_2=0.87, g_1=0.01, g_2=0.20, g_3=2.00, and P=10 are used.

where

$$Q_1 = 1 + EE_{catalyst} + (g_1 + EE_{catalyst})\,\beta \quad (21)$$

$$Q_2 = 1 - EE_{catalyst} + (g_2 - EE_{catalyst})\,\beta \quad (22)$$

and g_1 (g_2) is the relative reactivity of the homo- and heterochiral thiolates (alcoholates), and g_3 is the relative reactivity of the heterochiral thiol and alcohol derived ligands. The expression for β in Eq. (19) is still valid in the mixed case. EE_1 and EE_2 are the ee of the products formed from enantiopure thiol and alcohol derived ligands. Figure 2 shows the best fit using the modified model for the mixed case.

The model seems to be quite successful in all cases studied in this work. From the parameters obtained, it was possible to draw a few interesting conclusions on the differences between the thiolates and alcoholates. First of all, alcoholates tend to lose enantiomeric purity more easily than thiolates. This may be related to the above mentioned observation that the thiolates coordinate first to the dialkylzinc while the alcoholates are attacked by the aldehyde fisrt. Secondly, the heterochiral thiolate dimers are far more abundant than the homochiral dimers in the reaction mixture, not consistent with the data in Table 1 which were obtained from the equilibrium mixtures. This implies that the interconversion between the hetero- and homochiral thiolate dimers is not fast enough compared to the subsequent reaction of dimeric species with dialkylzinc. The high sensitivity of the equilibirum dimeric compositions of thiolates upon the presence of other substrates which can be seen in Table 1 may also be related to this result. On the other hand, the relative amounts of hetero- and homochiral dimers of alcoholates seem to agree quite well with Table 1. And, the equilibrium dimeric compositions of alcoholates do not change radically in the presence of other substrates, even in the presence of aldehyde. Finally, the thiolates are more reactive than the alcoholates, and the heterochiral thiolate dimers are far less reactive than the homochiral alcoholate dimers.

Conclusion. From these observations, the following considerations must be taken into account in the future design of asymmetric catalyst: 1) The affinity of ligating atom for dialkylzinc must be large enough to accommodate dialkylzinc preferentially. It is noted that the Lewis basicity can be enhanced by geometrical (or steric) factors as evidenced by the example of DAIB. In this regards, the strategy for enhancing Lewis acidity at the cost of Lewis basicity appears not to be a good idea since it would lead to premature coordination of aldehyde to wrong face of the catalyst. 2) The high Lewis acidity of the central metal does not seem to be so essential to say the least. 3) The structure should be able to inhibit formation of the *syn* diastereomer complex such as **18** somehow, for example by steric crowding. 4) The steric crowding around the nitrogen in the β-amino thiol (or alcohol) is beneficial since the stability of dimer formation can be weakened and thus the formation of the binary complex **A-B** with dialkylzinc can be enhanced.

Table 2. Determination of Molar Mass, Concentrations, and Reaction Free Energies by Freezing Point Depression Measurements

Run	ΔT (degree)	MW	[A] (mM)	[A-A] (mM)	[B] (mM)	[A-B] (mM)	ΔG^a (kcal/mol)	ΔG^b (kcal/mol)
1	0.433	401	5.73	1.59	8.91	48.6	−3.61	−1.57
2	0.433	401	5.73	1.59	8.91	48.6	−3.61	−1.57
3	0.432	402	5.63	1.54	8.71	48.8	−3.63	−1.59
4	0.431	403	5.54	1.49	8.51	49.0	−3.66	−1.61
5	0.428	406	5.24	1.33	7.91	49.6	−3.73	−1.69
6	0.428	406	5.24	1.33	7.91	49.6	−3.73	−1.69
7	0.432	402	5.63	1.54	8.71	48.8	−3.63	−1.59
8	0.432	402	5.63	1.54	8.71	48.8	−3.63	−1.59
9	0.427	407	5.14	1.28	7.71	49.8	−3.76	−1.71
10	0.433	401	5.73	1.59	8.91	48.6	−3.61	−1.57
Average	0.431	403	5.52	1.48	8.49	49.0	−3.66	−1.62
Std. Dev.	0.002	2	0.23	0.12	0.47	0.47	0.06	0.06

[a] Free energy change of reaction between **A** and **B**. [b] Free energy change of rupture of dimer complex to form **A-B** upon addition of **B**.

Experimental

General. All reactions involving organometallic reagents were carried out under an inert atmosphere of nitrogen. Solvents were freshly distilled from appropriate reagents. The experimental details of purifications and analysis can be found in our previous paper.[4]

Molar Mass Determination. The determination of molar mass was carried out with a standard-type homemade freezing point depression apparatus equipped with a side arm which permitted evacuation of the cell, nitrogen introduction and flushing the system with nitrogen while samples were being added. Molar mass was calculated in each case from: $\Delta T=K_f w/MW$, where ΔT=depression (degrees), K_f =molal depression of the solvent, w=weight in g of solute in 1000 g of solvent, and MW=molecular weight. K_f value of this apparatus was calculated to be 5.17 on the basis of the depression of a benzene (52.44 g) solution of naphthalene (1.00 g). The procedure for molecular weight determination of the complex prepared from an equimolar mixture of (−)-amino thiol and diethylzinc is as follow: The cryoscopy cell described above was evacuated and filled with nitrogen and (−)-amino thiol (0.8300 g, 3.526 mmol) and benzene (55.60 g) were placed there. After addition of diethylzinc (0.72 mL, 7.052 mmol), and the mixture was stirred at 26.0C for 15 min.

The benzene solution was degassed by three freeze-thaw cycles to remove the generated ethane gas and the cell was again filled with nitrogen. The apparatus was immersed into an ice bath, and the temperature was measured by a Beckmann thermometer until the solution froze. After warming up to room temperature, the same procedure was repeated ten times. Subsequently, using the equations developed in this work, the values of MW, α, the concentrations (of monomer and dimer) and ΔG were calculated individually from these ΔT values out of 10 experiments. And finally averages of these values and standard deviations were determined. In the determination of molar mass of mixtures of the zinc complexes with other compounds such as diethylzinc or benzaldehyde, excess amounts present in the mixture were assumed to exist as independent entities. The data given in Table 2 which were obtained from enantiopure thiazazincolidine complex with diethylzinc are representative.

Acknowledgment. This research is supported by OCRC-KOSEF (for JK) and Korea Research Foundation (for JK and DL).

References

1. (a) For reviews on catalytic addition of organozinc reagents to carbonyl compounds, see Noyori, R.; Kitamura, M. *Angew. Chem. Int. Ed.* **1991**, *30*, 49 and Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833. (b) Oguni, N.; Matsuda, Y.; Kaneko, T. *J. Am. Chem. Soc.* **1988**, *110*, 7877. (c) Hones, G. B.; Heaton, S. B. *Tetrahedron: Asymmetry* **1993**, *4*, 649. (d) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071. (e) Soai, K.; Okawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111.
2. (a) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028. (b) Kitamura, M.; Suga, S.; Niwa, M.; Noyori, R.; Zhai, Z.-X.; Suga, H. *J. Phys. Chem.* **1994**, *98*, 12776. (c) Kitamura, M.; Suga, S.; Niwa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 4832. (d) Fitzpatrick, K.; Hulst, R.; Kellogg, R. M. *Tetrahedron: Asymmetry* **1995**, *6*, 1861.
3. (a) Kang, J.; Lee, J. W.; Kim, J. I. *J. Chem. Soc., Chem. Commun.* **1994**, 2009. (b) Kang, J.; Kim, D. S.; Kim, J. I. *Synlett* **1994**, 842.
4. Kang, J.; Kim, J. B.; Kim, J. W.; Lee, D. *J. Chem. Soc., Perkin 2* **1997**, 189.
5. Guillaneus, D.; Zhao, S. H.; Samuel, O.; Rainford, D.; Kagan, H. B. *J. Am. Chem. Soc.* **1994**, *116*, 9430 and references cited therein.