The effects of sulfur substitution in chiral amino thiols on the enantioselective addition of organozinc reagents to aldehydes: a novel method for estimation of free energies of dimerization in monomer–dimer equilibria

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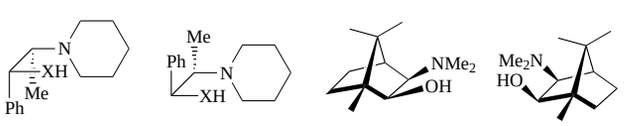
Differences between the thiol ligand 1 and the corresponding alcohol ligand 2 were observed in the catalytic asymmetric alkylation of benzaldehyde with diethylzinc. The thiol ligand 1 was superior for reaction rate, enantioselectivity and asymmetric amplification. The effects of chiral amino thiols are discussed and compared with the results of chiral amino alcohol counterparts. The quantitative and thermodynamic aspects of the monomer–dimer equilibria involved in thiazazincolidine or oxazazincolidine catalysts have also been studied on the basis of colligative properties.

Introduction

Considerable effort has been devoted towards preparation of optically active secondary alcohols through asymmetric addition of alkyl groups to carbonyl carbon, especially with dialkylzinc and aldehydes, in the presence of a catalytic amount of β-amino alcohol.[1] So far, we have developed many chiral cyclic amino thiols which have turned out to be excellent precursors of thiazazincolidine catalysts. The superior catalytic activity of cyclic amino thiols was thought to originate from (*i*) the thiol sulfur is more easily polarizable compared to the oxygen in alcohols, (*ii*) the heterocyclic ring may become a face blocker, (*iii*) the thiol and thiolates have higher affinity towards metals, especially zinc, and (*iv*) the metal thiolates have less tendency to diminish the Lewis acidity of a metal compared to metal alcoholates.[2]

In this study, we wanted to investigate in detail the reasons for the apparent enhancement of catalytic activity and asymmetric amplification by thiol substitution. Specifically, we tried to prove the validity of our initial assumption mentioned above by directly comparing the ligand system **1**, the best among many β-amino thiols we have studied so far,[2,3] with the corresponding β-amino alcohol ligand **2** including the DAIB [3-*exo*-(dimethylamino)isoborneol] **5**, one of the most powerful β-amino alcohol ligands.[4] Since the thiol ligand **1** seemed to show considerable superiority in reaction rate and enantioselectivity over the corresponding alcohol ligand **2** and even **5**, we considered it worthwhile to carry out more physicochemical measurements for this reaction. Extensive studies on the DAIB ligands have already been completed and reported in the literature.



X = S **1** **3**
X = O **2** **4** **5** **6**

Results and discussion

Kinetic studies

One of the important questions we initially posed was how much faster the reaction is in the presence of the thiol ligand relative to the alcohol counterpart. The rate of disappearance of benzaldehyde with 2 equiv. of diethylzinc was determined under typical preparative reaction conditions (0.2 M aldehyde in toluene) in the presence of 5 mol% of four different ligand systems: enantiopure (1*R*,2*S*)-thiol **1**, racemic thiol (**1** and **3**), enantiopure (1*R*,2*S*)-alcohol **2** and racemic alcohol (**2** and **4**). Contrary to the report of Soai,[5] less than 15% of benzaldehyde at 0 °C even after 24 h was converted in the presence of enantiopure (1*R*,2*S*)-alcohol **2**. Therefore, the reactions of the alcoholic ligands had to be monitored at 28 °C instead. The results are summarized in Fig. 1 along with the pseudo-first-order-fittings.

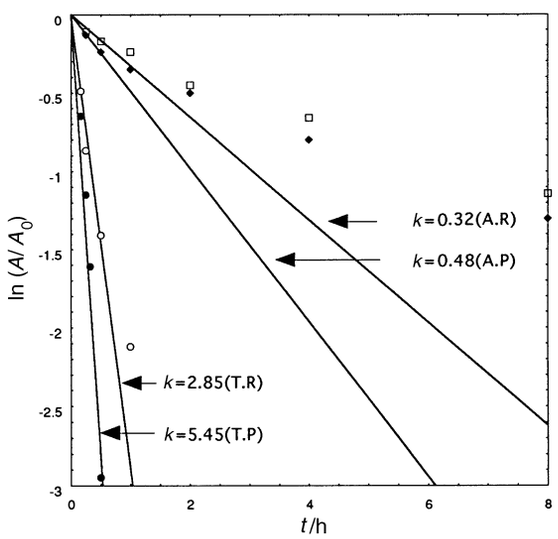


Fig. 1 Rates of disappearance of benzaldehyde in the reaction with diethylzinc in the presence of 5 mol% of ligands [enantiopure (1*R*,2*S*)-thiol (T.P); racemic thiol (T.R); enantiopure (1*R*,2*S*)-alcohol (A.P) and racemic alcohol (A.R)] at 0 °C for thiols and 28 °C for alcohols. The straight lines are the pseudo-first-order fittings.

Two prominent features can be observed here. First, the thiolate catalysed reaction, which showed kinetic behaviour close to first-order, was considerably faster than the corresponding alcoholate system which deviated significantly from first-order kinetics. Secondly, the racemic ligand systems were less reactive than the enantiopure ligands. The difference in initial rates between the thiol and alcohol systems would be far more pronounced when the fact that the thiol reaction was performed at lower temperature is taken into account.

If the monomer form of the complex in equilibrium with the dimeric forms is directly involved in the catalytic reaction, these kinetic observations can be understood as indicating the higher concentration and/or reactivity of the thiol monomer complex compared to the alcohol monomer complex. The decreased rates in racemic mixtures were not so surprising either since it was known that the heterochiral dimers consisting of two enantiomeric monomer complexes are more stable than the homochiral dimers formed from two different enantiomers.[4a] Therefore, the reactions of racemic ligands would be naturally slower since there is less monomer complex to react with. However, the decrease of the initial reaction rates in the racemic mixtures of the amino thiol (approximately 1.9-fold at 0 °C) and of the amino alcohol (approximately 1.5-fold at 28 °C) with respect to the enantiopure systems were much smaller than the DAIB ligand system for which an approximately 13-fold decrease in rate was observed.[4c] This may reflect the fact that the energy difference between the heterochiral and homochiral dimers is not so significant at least for the amino thiol catalysed reactions.

On the other hand, if the dimer forms are somehow responsible for catalytic activity, the slowing down in the racemic mixture indicates higher reactivity, in the subsequent reactions with aldehyde, of the homochiral dimers with respect to the heterochiral dimers, which become more abundant in the racemic mixture. Further discussion on this possibility will be given below in connection with the unusual asymmetric amplification of the thiolate catalysed reaction.

Asymmetric amplification

Since direct comparison of the absolute reaction rates of the amino thiol and alcohol catalysed reactions under typical preparative conditions was not possible, an alternative technique to show that the reaction with the thiol ligand is indeed more rapid had to be devised. Thus, the reaction was carried out in an equimolar mixture of the thiol and its topologically enantiomeric alcohol counterpart. In the presence of 2.5 mol% of the thiol **1** (1*R*,2*S* configuration) and 2.5 mol% of the enantiomeric alcohol **4** (1*S*,2*R* configuration), benzaldehyde was treated with diethylzinc under otherwise identical reaction conditions (toluene, 0 °C, 12 h). If the thiol catalysed reaction is faster than the alcohol pathway, then the product is expected to be predominantly in the *R* configuration. In fact, the ee of (*R*)-1-phenylpropanol was 76.6% as anticipated. If the (1*S*,2*R*)-alcohol **4** is assumed to produce only (*S*)-1-phenylpropanol, the catalyst formed from the thiol **1** is estimated to be approximately eight times more reactive than the alcoholate catalyst resulting from **4** in this mixed ligand system. [In fact, the (1*S*,2*R*)-alcohol ligand gave only 86.4% ee of (*S*)-1-phenylpropanol.] An attempt to confirm the above estimate by varying the composition of the mixed ligands of **1** and **4** was not successful since the product ee was too sensitive to the thiol concentration in the mixture. Nevertheless, it was possible to reach the conclusion that a catalytic system of approximately 3:7 mixture of the (1*R*,2*S*)-thiol **1** and the (1*S*,2*R*)-alcohol **4** would result in a racemic mixture of the alcohol products. Thus, it seems that the thiol **1** is *ca.* 2.3 times more effective than the topologically enantiomeric alcohol **2** in the case of a topologically racemic mixture of ligands. Therefore, asymmetric amplification or enantiomeric nonlinearity[6,7] can clearly arise from this mixed catalytic system.

Although this study was not initially focused on enantiomeric amplification, it became quite clear from these observations that such phenomenon can also appear in chemically homogeneous ligand systems such as (1*R*,2*S*)-thiol–(1*S*,2*R*)-thiol (**1** and **3**) and (1*R*,2*S*)-alcohol–(1*S*,2*R*)-alcohol (**2** and **4**) mixtures. Thus, the product enantiomeric excess *vs.* enantiomeric purity of the ligands was determined for the previously mentioned homogeneous mixtures of thiols and alcohols in addition to the heterogeneous ligand system of (1*R*,2*S*)-thiol–(1*S*,2*R*)-alcohol (**1** and **4**) mixture. The results are summarized in Fig. 2 for all three cases. For the thiol–alcohol mixture, the product ee values were obtained for the full range of the composition. For the homogenenous mixtures of thiols and alcohols, however, there must exist an inherent symmetry in the curve of the product ee with respect to the topological ee of the ligands and thus it is only necessary to determine the product ee values for mixtures with the (1*R*,2*S*)-enantiomer in excess of the (1*S*,2*R*)-enantiomer. Then it was possible to extend the fitted curve over the full range of the composition by using the inherent symmetry.

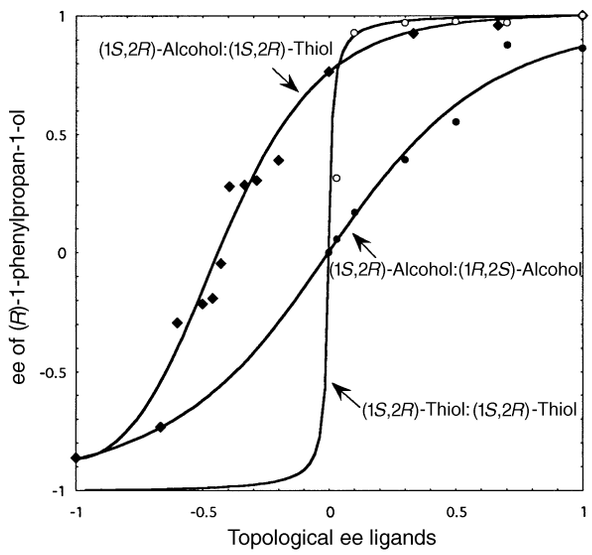


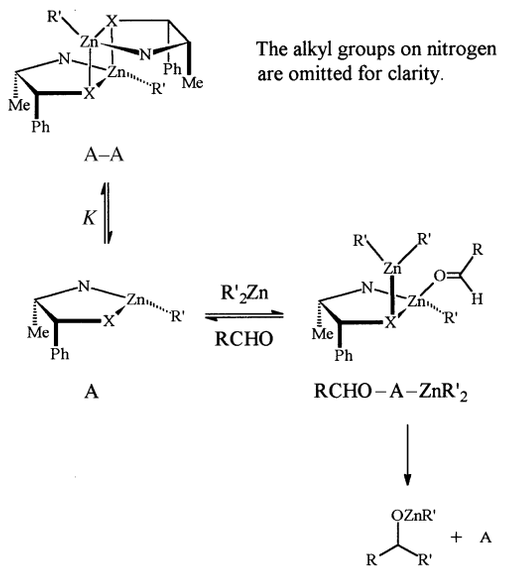
Fig. 2 Enantiomeric excess of (*R*)-phenylpropanol obtained from the reaction of benzaldehyde with diethylzinc with respect to the topological ee of (1*R*,2*S*)-thiols or alcohol of the mixed ligand system. The solid lines are the theoretical curves extended over the full range based on the inherent symmetric nature of the chemically homogeneous mixtures.

Fig. 2 provides many interesting points for these ligand systems. First the amino alcohol catalysed reaction shows mild nonlinearity in the enantioselectivity of the product with respect to the enantiomeric purity of the ligands, a result quite unexpected in view of the already published results on similar systems. Secondly, the heterogeneously mixed ligand system of thiol and alcohol displays an unusual form of nonlinearity. Finally, the thiol ligand system shows an extreme asymmetric amplification, comparable to the DAIB case.[4,6,7] For example, a mere 3% ee of thiol led to 32% ee of the product, whereas 10% ee of the thiol resulted in a surprising 93% ee of the alcohol product.

The mechanism of asymmetric addition of dialkylzinc to aldehyde in the presence of a catalytic amount of β-amino alcohol has been well established.[1] As an attempt to understand the evident asymmetric amplification by β-amino thiols, it was assumed that the same mechanistic pathway was also applicable to β-amino thiols and that no chemical species other than the ones shown in Scheme 1 were present in the equilibrium mixture. Kellogg and co-workers have recently reported the possibility of formation of tetrameric complexes of thiazazincolidine.† In our study, however, there was no indication of the presence of high molecular mass species formed in the reaction mixture at least up to 60 mM (*vide infra*). The reactions were usually carried out at *ca.* 10–15 mM concentration.

†Professor Kellogg and co-workers have reported the mechanistic aspects of the symmetric addition reaction catalysed by analogues of *N*-methylephedrinethiol, in which they claim a tetrameric nature of thiazazincolidine complexes in benzene at unrealistically high concentrations [144 mM as compared to the usual concentration of ligand (*ca.* 10–15 mM) in the reaction] of the complex **8**.

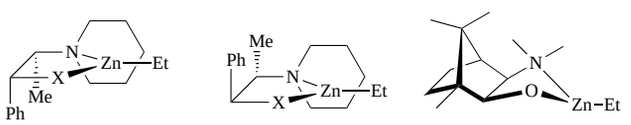
Thus, the monomer complex (thiazazincolidine or oxazazincolidine), **A**, in equilibrium with the corresponding dimer complex, **A**–**A**, is assumed to interact in a stepwise manner with aldehyde and dialkylzinc to give a ternary complex, RCHO–**A**–ZnR'_2, in which the alkyl group R′ is subsequently transferred intramolecularly from zinc to the carbonyl carbon. If this is the mechanistic pathway for asymmetric addition catalysed by thiol and alcohol, various equilibrium constants involved in Scheme 1 can easily be obtained by the method described below.



Scheme 1

Free energy of dimerization of enantiopure and racemic zinc complexes

In order to reach a greater understanding of the enhanced catalytic activity and asymmetric amplification observed from the β-amino thiol and alcohol ligand systems, molecular mass determination of the mixture containing various zinc complexes, **7**–**11**, resulting from the reaction of the thiol and alcohol ligands with diethylzinc, was carried out by the freezing point depression, a method which is not highly accurate but which also provides useful information about the reaction mixture.



X = S **7** **9**
X = O **8** **10** **11**

An approach similar to the one used by Noyori *et al.*[4b] can be utilized to obtain the free energy of dimerization from cryoscopic measurements. We assume that the monomer–dimer equilibria involving the enantiomeric pair of monomer complex (thiazazincolidine or oxazazincolidine), **A** and **A***, shown in eqn. (1) apply.

$$\begin{aligned} \mathbf{A} + \mathbf{A} &\rightleftharpoons \mathbf{A}\text{–}\mathbf{A} \\ \mathbf{A} + \mathbf{A}^* &\rightleftharpoons \mathbf{A}\text{–}\mathbf{A}^* \\ \mathbf{A}^* + \mathbf{A}^* &\rightleftharpoons \mathbf{A}^*\text{–}\mathbf{A}^* \end{aligned} \qquad (1)$$

Let x be the mole fraction of enantiopure monomer, [**A**]/{[**A**] + [**A**–**A**]}, where [**A**] and [**A**–**A**] are the concentrations of enantiopure monomer and dimer complexes, respectively. If we assume that no higher oligomers of zinc complexes are present, then the observed molecular mass, M_o, which is a weighted average of the molar masses of all chemical species present in the mixture, is given by eqn. (2), where M_A is the molar mass of

$$M_o = xM_A + 2(1 - x)M_A \qquad (2)$$

monomer species. In other words, the mole fraction x can be written as eqn. (3), with $\alpha = M_o/M_A$ the degree of dimerization.

$$x = 2 - M_o/M_A = 2 - \alpha \qquad (3)$$

Then, [**A**] and [**A**–**A**] can be expressed in terms of the initial concentration of monomer complex, C = [**A**] + 2[**A**–**A**] by eqns. (4) and (5). Thus, it is possible to express the free energy of

$$[\mathbf{A}] = \frac{Cx}{2 - x} = \frac{C(2 - \alpha)}{\alpha} \qquad (4)$$

$$[\mathbf{A}\text{–}\mathbf{A}] = \frac{C(1 - x)}{2 - x} = \frac{C(\alpha - 1)}{\alpha} \qquad (5)$$

homochiral dimerization by eqn. (6). That is, the free energy of

$$\Delta G = -RT \ln \frac{[\mathbf{A}\text{–}\mathbf{A}]}{[\mathbf{A}]^2} = -RT \ln \frac{\alpha(\alpha - 1)}{C(2 - \alpha)^2} \qquad (6)$$

homochiral dimerization can be calculated directly from the known initial concentration of monomer complex and the degree of dimerization which can be obtained from the average molecular mass determined by the freezing point depression.

A similar argument can be used for the racemic reaction mixture in which **A**, **A***, **A**–**A**, **A**–**A*** and **A***–**A*** are in equilibrium, with [**A**] = [**A***] and [**A**–**A**] = [**A***–**A***]. In this case, the total monomer and dimer concentrations can be written as eqns. (7) and (8). Once again, let us call x the mole fraction of all

$$[\text{Monomer}] = [\mathbf{A}] + [\mathbf{A}^*] = 2[\mathbf{A}] \qquad (7)$$

$$[\text{Dimer}] = [\mathbf{A}\text{–}\mathbf{A}] + [\mathbf{A}^*\text{–}\mathbf{A}^*] + [\mathbf{A}\text{–}\mathbf{A}^*] = 2[\mathbf{A}\text{–}\mathbf{A}] + [\mathbf{A}\text{–}\mathbf{A}^*] \qquad (8)$$

monomer species, **A** and **A***. Then x can be readily expressed in terms of the degree of dimerization, $\alpha = M_o/M_m$, which can be determined from the cryoscopic measurement, eqn. (9). Now

$$x = 2 - M_o/M_A = 2 - \alpha \qquad (9)$$

the concentrations of all chemical species in the racemic reaction mixture can be written in terms of the initial monomer concentration, eqns. (10)–(12), where $K = [\mathbf{A}\text{–}\mathbf{A}]/[\mathbf{A}]^2$ which are

$$[\mathbf{A}] = \frac{[\text{Monomer}]}{2} = \frac{C(2 - \alpha)}{2\alpha} \qquad (10)$$

$$[\mathbf{A}\text{–}\mathbf{A}] = K\frac{C^2(2 - \alpha)^2}{4\alpha^2} \qquad (11)$$

$$[\mathbf{A}\text{–}\mathbf{A}^*] = \frac{C(\alpha - 1)}{\alpha} - K\frac{C^2(2 - \alpha)^2}{2\alpha^2} \qquad (12)$$

obtained from the enantiopure mixture. Eqn. (8) has been used to obtain eqn. (12). The free energy of heterochiral dimerization is now given as eqn. (13).

$$\Delta G = -RT \ln \frac{[\mathbf{A}\text{–}\mathbf{A}^*]}{[\mathbf{A}][\mathbf{A}^*]} = -RT \ln \frac{4\alpha(\alpha - 1) - 2KC(2 - \alpha)^2}{C(2 - \alpha)^2} \qquad (13)$$

In order to obtain thermodynamic data for the dimerization

Table 1 Molecular masses, degrees of dimerization, concentrations and free energy of dimerization for ethylzinc complexes derived from various ligands

Ligands	Initial conc.[a,b]	ΔT/°C	M_w obsd.[c]	α[d]	Mol ratio[e]	[A][a]	[A–A][a]	[A–A*][a]	ΔG[f]
Enantiopure thiol (**1**)	57.9	0.230 ± 0.003	490 ± 5	1.49	51:49	19.9	19.0		−2.05 ± 0.06[g]
Racemic thiol (**1** and **3**)	58.3	0.213 ± 0.002	532 ± 6	1.62	38:62	6.9	2.3	17.6	−3.27 ± 0.09[h]
Enantiopure alcohol (**2**)	61.8	0.125 ± 0.002	601 ± 9	1.92	8:92	2.60	29.6		−4.63 ± 0.46[g]
Racemic alcohol (**2** and **4**)	61.4	0.123 ± 0.001	615 ± 5	1.96	4:96	0.56	2.64	24.9	−6.23 ± 0.76[h]
Enantiopure (−)-DAIB (**5**)	58.9 63[f]	0.163 ± 0.001	535 ± 7 536[i]	1.84 1.84[i]	16:84 16:84[i]				
Racemic DAIB (**5** and **6**)	60.2 34[f]	0.167 ± 0.001	533 ± 4 531[i]	1.83 1.82[i]	17:84 18:82[i]				

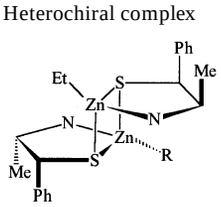
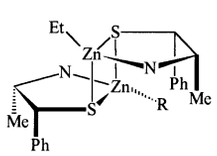
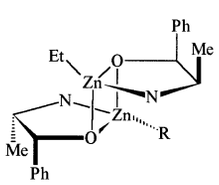
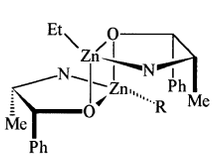
[a] Units: mM. [b] Molecular mass of monomer (329 for **1** and **3**, 313 for **2** and **4** and 291 for **5** and **6**). [c] Determined by freezing point depression. [d] Ratio of molecular masses, $\alpha = M_w^{observed}/M_w^{monomer}$. [e] Molar ratio of monomer and dimer. [f] Data from ref. 4*a*. [g] Free energy of homochiral dimerization (kcal mol^{-1}) which was obtained by eqn. (6) at 278 K (mp of benzene). [h] Free energy of heterochiral dimerization (kcal mol^{-1}) (1 cal = 4.184 J) which was obtained by eqn. (13) at 278 K (mp of benzene). [i] Calculated by using the equations derived in this work.

of β-amino thiol and alcohol derived complexes, we performed freezing point depression measurements for solutions of thiazazincolidine and oxazazincolidine derived from enantiopure and racemic mixtures in benzene. Since the degree of dimerization increases with solute concentration,[4,8] the concentrations of the initial monomer complexes were kept nearly constant for all reaction mixtures. Furthermore, to aid cryogenic measurements, a rather high concentration was used at *ca.* 60 mM which was approximately six times more concentrated than in the usual preparative setup. The free energies of homo- and heterochiral dimerizations of thiol and alcohol ligands were determined using eqns. (6) and (13) together with the degrees of dimerization obtained from the cryogenic measurements, the results of which are given in Table 1. The experimental uncertainties were rather small except for the case of the β-amino alcohol complex for which the equilibrium lies too far to the dimeric species. To demonstrate the utility of the cryogenic method employed in this work, the same experiments were repeated for enantiopure and racemic DAIB complexes, for which independent data have already been reported by Noyori.[4a] The results for the DAIB complexes are also included in Table 1 along with the data calculated from the original reference of Noyori using eqns. (6) and (13). The freezing point depression measurement appears to give reasonably accurate results.

The average molecular mass observed from the enantiopure thiolate complex **7** was 490, indicating that *ca.* 51% of thiolates, an unusually high level compared with other similar systems in Table 1, were present in the monomer form when only the monomer–dimer equilibria were taken into account. Formation of tetrameric complexes appeared highly unlikely since it would require even more monomer in the equilibrium mixture. Among the alcoholate complexes, the DAIB complex **11** is known to show less tendency for dimerization than the complex derived from norephedrine **8**. Thus, if the monomer is responsible for the addition of alkyl group to carbonyl carbon, the higher rate of the thiol catalysed reaction may originate simply from the high concentration of the monomer species. Of course, the possibility of high reactivity of the thiol monomer complex cannot be entirely excluded from these observations.

According to the theory proposed by Noyori, asymmetric amplification arises when the heterochiral complexes are more stable than the homochiral complexes; the heterochiral dimer complex thereby acts as a chiral reservoir. In this mechanism, the remaining monomer, whose ee is amplified due to the chiral

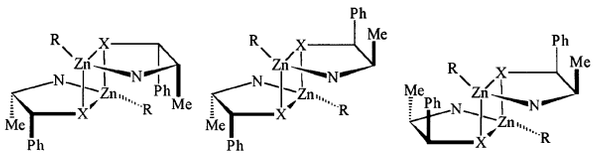
Table 2 Energy differences for various complexes in benzene at 5 °C

Heterochiral complex	Homochiral complex	Energy difference[a]
		1.2 ± 0.1
		1.6 ± 0.8

[a] Energy difference, in kcal mol^{-1}, of homochiral and heterochiral dimer complexes.

reservoir effect of stable heterochiral dimer, is responsible for the positive nonlinearity in asymmetric amplification. If the thiolate catalysed asymmetric amplification follows this mechanism, the heterochiral thiol dimer **14** formed from an enantiomeric pair is expected to be far more stable than the homochiral dimer **12** derived from enantiopure (1*R*,2*S*)-thiol and diethylzinc. Thus, it was anticipated from the strong positive nonlinear effect of the thiolates shown in Fig. 2 that the enantiopure thiol mixture would contain a high level of monomer complexes while the dimer form would be predominant in the racemic thiol mixture.[4] Although our experimental observation shown in Table 1 indicates that the degree of dimerization in the racemic mixture was higher than in the enantiopure mixture, the difference was not large enough to explain the extreme nonlinear behaviour of the thiol-derived catalyst. In other words, the difference in the stabilities of the homo- and hetero-chiral dimers, which was expected to be *ca.* 1.2–1.5 kcal mol^{-1}, as shown in Table 2, were too small to explain the strong asymmetric amplification of the thiol ligand. This observation strongly suggests that the enhanced asymmetric amplification of the thiol catalysed reaction does not simply arise from the above mentioned chiral reservoir effect.

An alternative possibility is that the dimeric form is directly



	(1*R*,2*S*)+ (1*R*,2*S*)	(1*R*,2*S*)+ (1*S*,2*R*)	(1*S*,2*R*)- (1*S*,2*R*)
	A – A	A – A*	A* – A*
X = S	**12**	**14**	**16**
X = O	**13**	**15**	**17**

responsible for the formation of catalytic species. If this is the case, the kinetic data presented here can be regarded as indicating that the thiol dimers are far more reactive than the alcoholic dimers and that the homochiral dimers are more reactive than the heterochiral dimers. Although the stabilities of the homo- and hetero-chiral thiol dimers are not much different, the reactivities and thus the activation energies of the subsequent reactions can be sufficiently different so that the heterochiral thiol dimers act as the kinetic chiral reservoir. Weak asymmetric nonlinearity of the alcohol catalysed reaction may then imply that the reactivities of the homo- and hetero-chiral alcoholic dimers are not much different compared to the thiol dimers. In order for this conclusion involving dimers in the formation of catalytic species to be valid, the rate of dimerization must be much lower than the rate of subsequent steps. Further work to verify this point is currently in progress.

Experimental

General

All reactions involving organometallic reagents were carried out under nitrogen. Solvents were freshly distilled from appropriate reagents. Liquid reagents were transferred by hypodermic syringes. Purifications were performed by radial chromatography (small and medium scale) by using a Harrison Research Chromatotron on plates of 1, 2 or 4 mm thickness made with Merck silica 60 PF_{254} containing gypsum, or by flash chromatography (medium and large scale) on a Tokyo Rikagikai EF-10 with Merck 230–400 mesh silica gel. Mps were determined on a Thomas-Hoover capillary mp apparatus. ^{1}H NMR spectra were obtained on a Varian Gemini 200 (200 MHz) or a Varian Gemini 300 (300 MHz) spectrometer. IR spectra were obtained on a Mattson Galaxy 2000 spectrometer. Mass spectra were taken on a VG Trio 2000 (low resolution) spectrometer with an electron beam energy of 70 eV (EI or CI) and elemental analysis by a Carlo Erba EA 1180 elemental analyser. Optical rotations were obtained on a Rudolph Autopol III digital polarimeter. Optical purity (%ee) was determined by HPLC analyses using chiral columns (Chiralcel, Daicel) and GC analyses using a capillary chiral column (Chiraldex, Advanced Separation Technologies). The amino alcohols and thiols employed in the present study were prepared according to literature procedures.[2–4]

Kinetic experiments

The following conditions are representative. To (1*R*,2*S*)-(−)-1-phenyl-2-piperidinopropane-1-thiol (0.0235 g, 0.10 mmol) in toluene (5.0 ml), diethylzinc (3.64 ml of 1.1 M toluene solution, 4.0 mmol) was added at 32 °C. The mixture was stirred for 15 min. To this solution was added benzaldehyde (2.0 ml, 1.0 M benzaldehyde and dodecane solution in toluene, 2.0 mmol) and the mixture stirred at 32 °C. In all cases the total volume was *ca.* 11 ml. At *ca.* 5–10 min intervals, a portion (*ca.* 0.3 ml) was quickly transferred using a syringe to a vigorously stirred mixture of 1 M hydrochloric acid (2 ml) and methylene chloride (2 ml) at 0 °C. The consumption of benzaldehyde was quantified by GC analysis of the organic layer (Chiraldex B-PH; injection temperature 250 °C; oven temperature 100 °C; detection temperature, 250 °C; split ratio, 118:1; t_R of benzaldehyde, 8.4 min; t_R of dodecane, 6.1 min), and calculated in each case from: ln([**A**]/[**A**]$_0$), where [**A**]$_0$ is the initial concentration of aldehyde and [**A**] is the subsequent concentration.

Table 3 Determination of molecular mass, degree of dimerization, concentrations and free energy of dimerization by freezing-point depression measurements

	ΔT/ °C	M_w	a	[**A**]/M	[**AA**]/M	ΔG/kcal mol^{-1}
1	0.229	492	1.49	0.0196	0.0192	−2.06
2	0.229	492	1.49	0.0196	0.0192	−2.06
3	0.228	494	1.50	0.0192	0.0193	−2.09
4	0.231	487	1.48	0.0203	0.0188	−2.02
5	0.232	485	1.48	0.0206	0.0186	−2.00
6	0.228	494	1.50	0.0192	0.0193	−2.09
7	0.226	498	1.51	0.0186	0.0197	−2.13
8	0.230	490	1.49	0.0199	0.0190	−2.04
9	0.235	480	1.46	0.0216	0.0181	−1.93
10	0.230	490	1.49	0.0199	0.0190	−2.04
Average	0.230	490	1.49	0.0199	0.0190	−2.05
Std. dev.	0.002	5	0.02	0.0008	0.0004	0.06

Asymmetric amplification experiments

The following conditions are representative. To (1*R*,2*S*)-(−)-1-phenyl-2-piperidinopropane-1-thiol (0.0194 g, 0.0824 mmol) and (1*S*,2*R*)-(−)-1-phenyl-2-piperidinopropane-1-thiol (0.0183 g, 0.0777 mmol) in toluene (5.0 ml), diethylzinc (3.64 ml of a 1.1 M toluene solution, 4.0 mmol) was added at 27 °C. The mixture was stirred for 15 min at 27 °C and cooled to 0 °C in an ice bath. To this solution was added dropwise benzaldehyde (0.21 g, 1.98 mmol) in 2.0 ml of toluene and the reaction mixture was stirred for 12 h at 0 °C. The reaction mixture was quenched with 1 M hydrochloric acid. The aqueous layer was extracted with methylene chloride, and combined extracts were dried over sodium sulfate and evaporated. The residue was purified by flash column chromatography to give 1-phenylpropan-1-ol (0.24 g, 88%). The enantiomeric excess was determined by HPLC analysis [Daicel Chiral Ob; eluent, 9:1 hexane–propan-2-ol mixture; flow rate, 0.5 ml min^{-1}; detection, 254 nm; t_R of (*S*)-1-phenylpropan-1-ol, 12.3 min; t_R of *R* isomer, 14.7 min].

Molecular mass determination

Freezing point depression was measured using a standard-type home-made apparatus equipped with a side arm which permitted evacuation of the cell, nitrogen introduction, and flushing of the system with nitrogen while samples were being added. Molecular mass was calculated for each measurement from $\Delta T = K_f M/M_W$, where ΔT is the freezing point depression in degrees, and K_f is the molal depression constant of the solvent, M = mass in gram of solute added to 1000 g of solvent, and M_W is the molecular mass. The K_f value of the apparatus was calculated to be 5.17° mol^{-1} on the basis of the freezing point measurement of the solution made by resolving naphthalene (1.00 g) in benzene (52.44 g). The procedure for molecular mass determination of the complex prepared from an equimolar mixture of (−)-amino thiol and diethylzinc was as follows. The cryoscopic cell described above was evacuated and filled with nitrogen and (−)-amino thiol (0.8592 g, 3.650 mmol) and benzene (55.13 g) were inserted. After diethylzinc (0.37 ml, 3.65 mmol) had been added, the mixture was stirred at 26 °C for 15 min. The benzene solution was degassed by three-way thaw cycles to remove ethane gas generated inside and then the cell was once again filled with nitrogen. The apparatus was immersed into an ice bath and the temperature was measured using a Beckmann thermometer until the solution froze. After warming to room temp., the same procedure was repeated 10

times. Then, M_w, a, the concentrations of the monomer and dimer, and ΔG were calculated individually by using the equations developed in this work for each measurement. The averages of those values together with the standard deviations are summarized in Table 1. In the case of the mixtures of zinc complexes with other compounds such as diethylzinc and benzaldehyde, the species present in excess were assumed to be in independent entities. The data in Table 3 obtained from enantiopure thiazazincolidine complex are representative.

Acknowledgements

This research was supported by the OCRC-KOSEF (for J. K.) and the Korea Research Foundation (J. K. and D. L.).

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Paper 6/06133H
Received 15*th August* 1996
Accepted 17*th October* 1996