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Chiral Ligands Derived from *Abrine* 8. An Experimental and Theoretical Study of Free Ligand Conformational Preferences and the Addition of Diethylzinc to Benzaldehyde

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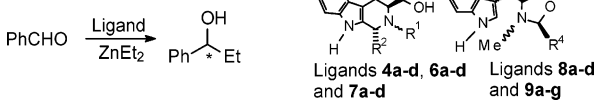
Received February 11, 2004



Three structurally similar series of 1,2,3,4-tetrahydro-β-carboline ligands, **4a**−**d**, **6a**−**d** and **7a**−**d**, and two series of chiral oxazolidines, **8a**−**d** and **9a**−**g**, were synthesized and used as chiral catalysts in the addition of diethylzinc to benzaldehyde. The enantioselectivities of the resulting 1-phenyl-1-propanol were obtained in each case, and these ee values were, in most cases, related to the conformational populations of the free ligand as expressed by the calculated differences in the energies of the ligand conformations formed by inversion at nitrogen. This suggested the possible existence of a linear free energy relationship. The effect on enantioselectivity of the carbon chain length of the R group located (1) on the C-3 substituent of **4a**−**d**, **6a**−**d**, and **7a**−**d** or (2) at C-5 in **8a**−**d** and **9a**−**g** was studied in detail. On the basis of the correlations observed and the ligands' structural characterization, a structure was proposed for the transition state during ethyl group transfer when using ligands **8a**−**d**. Furthermore, the change in enantioselectivity was successfully predicted when diastereomeric ligands **11** and **12** were compared in this chiral addition.

Introduction

Chiral β-amino alcohols were shown to promote the enantioselective addition of diethylzinc to aldehydes[1] about 20 years ago. A representative chiral ligand having a high enantioselectivity in early dimethylzinc additions was (−)-3-exo-dimethylaminoisoboroenol [(−)-DAIB], reported by Noyori and co-workers.[1c] Its mechanism for catalyzing the organozinc addition was also well studied.[1d] Many chiral ligands were subsequently synthesized and employed in additions of dialkylzinc to aldehydes.[2] Many chiral ligands, such as ephedrine-based amino alcohol,[1f] derivatives from Betti's base,[2d] chiral aziridino alcohols,[2e] the dimer of bicyclic amino alcohol,[2f] the analogues derived from (*S*)-leucine,[2g] the modified DAIB catalysts,[2h] C_2-symmetric pyridine-based dimeric amino alcohols,[2i] ferrocene-based ligands,[2j] Ag^+-complexes,[2m] and so on, induced high enantioselectivity in the dialkylzinc additions.[2n−p] Dialkylzinc additions have also been extended to ketones[3] and imines[4] in the presence of chiral ligands. Enantiose-

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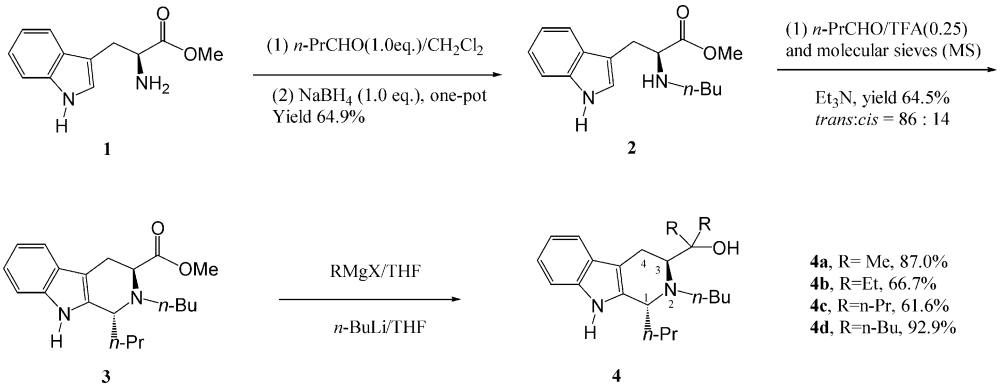
10.1021/jo049754c CCC: $30.25
Published on Web 11/26/2004

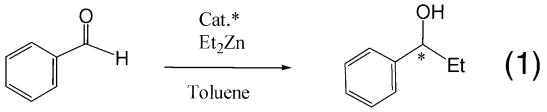
SCHEME 1



lective reductions have also been investigated.[5] Chirality amplification (observed in similar additions using other chiral ligands and termed nonlinear effects[6]), as well as self-catalysis,[7] have been observed in the similar additions of dialkylzinc to aldehydes. The syntheses of new types of chiral ligands and their behavior in enantioselective syntheses continue to be important research aims.

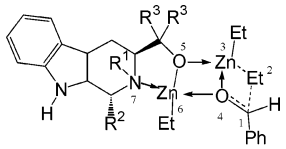
Calculations have been used to predict the transition state (TS) structures for dialkylzinc addition to aldehydes.[8] Very recently, Kozlowski et al. reported that catalysts giving low, moderate, and high ee values in the addition of diethylzinc to benzaldehyde could easily be distinguished using a QSSR approach based on quantum mechanical models (PM3).[8c] However, studies of how free ligand conformational equilibria might effect the observed enantioselectivity in this addition reaction have not been reported.

Previously, we have reported the ee values of 1-phenyl-1-propanol produced in additions of diethylzinc to benzaldehyde (eq 1) using chiral 5-*p*-tolyl- or 5-*o*-tolyl-1,3-oxazolidine ligands, where the substituents at C-2 were Me, Et, *n*-Pr, *n*-Bu, and *n*-amyl,[9] respectively. The highest ee value was achieved when *n*-Pr was the C-2 substituent in both series of oxazolidine ligands. Furthermore, differences in ee values for diethylzinc/benzaldehyde additions have been observed[9c] using chiral amino alcohol ligands, substituted on N with various linear aliphatic substituents (methyl, ethyl, *n*-propyl, and *n*-butyl).



Herein, we report the synthesis and use of five series of chiral ligands (Schemes 1 and 2) for the enantioselective addition of diethylzinc to benzaldehyde (eq 1) at ambient temperature.

These ligands include three series of chiral 1,2,3,4-tetrahydro-β-carboline ligands, **4a**−**d**, **6a**−**d**, and **7a**−**d**, where the C-1 ring substituent is *n*-propyl, 2-methylpropyl, and phenyl, respectively, and the R groups at the C-3 alcohol substituent for each series are (**a**) methyl, (**b**) ethyl, (**c**) *n*-propyl, and (**d**) *n*-butyl. In addition, two series of chiral 2,5,5-alkyl-substituted 4-(3-indolymethyl)-1,3-oxazolidine ligands, **8a**−**d** and **9a**−**g**, were employed. In oxazolidine series **8**, the ring substituent at C-2 was isopropyl and the C-5 substituents were (**a**) methyl, (**b**) ethyl, (**c**) *n*-propyl, and (**d**) *n*-butyl, respectively. In the oxazolidine ligand series **9**, two ethyl groups were located at C-5 and the C-2 substituents were (**a**) methyl, (**b**)ethyl, (**c**) *n*-propyl, (**d**) *n*-butyl, (**e**) *n*-amyl, (**f**) 2-methylpropyl, and (**g**) 2,2-dimethylpropyl, respectively. We found that the ee values observed in the diethylzinc additions varied using ligands **4a**−**d**, **6a**−**d**, and **7a**−**d** as the R groups on the C-3 alcohol substituent changed from methyl to ethyl to *n*-propyl and to *n*-butyl. The TS structure **10**, containing two zinc atoms, was invoked in accord with previous studies. A regular alternation in the ee values was also observed upon systematically changing the C-5 groups in ligands **8a**−**d** and the C-2 substituent in ligands **9a**−**g** from Me → Et → *n*-Pr → *n*-Bu → *n*-amyl. When all of these results are combined with our previous reports,[9] it appears that varying the substituent's carbon chain length gives variations of the ee values that depend on the number of carbons present in the linear alkyl substituents (e.g., an "odd−even" alternating effect).



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The effect that the different free ligand conformational populations might have on the enantioselectivity was

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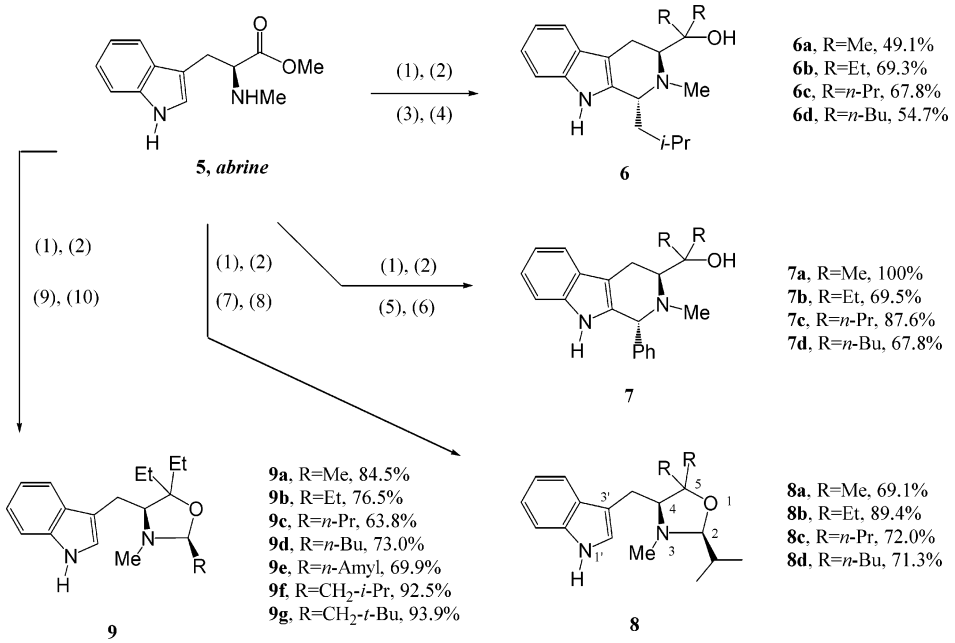
SCHEME 2[a]



[a] Conditions: (1) $SOCl_2$/MeOH (−5 to 0 °C, then to room temperature), (2) H_2O/Na_2CO_3 (room temperature), (3) Me_2CHCH_2CHO (1.02 equiv)/MS, CH_2Cl_2/TFA (0.25 equiv), (room temperature), (4) RMgX and *n*-BuLi (ice water bath), (5) PhCHO (1.02 equiv)/MS, CH_2Cl_2/TFA (0.25 equiv), (room temperature), (6) RMgX and *n*-BuLi (ice water bath), (7) RMgX and *n*-BuLi (ice water bath), (8) Me_2CHCHO/MS (room temperature), (9) EtMgCl/THF (ice water bath), (10) RCHO/CH_2Cl_2, MS (room temperature).

probed. The differences in enantioselectivity induced by these series of tetrahydro-*β*-carboline and indolylmethyl-substituted oxazolidine ligands were evaluated, and the differences in enantioselectivity were approximately predicted in this paper. Some correlation between the energy differences of the cis versus trans free ligand conformations ($\Delta E_{(trans-cis)}$) and the observed ee values was found using ligands **4a**−**d**, **6a**−**d**, and **7a**−**d** in additions of Et_2Zn to benzaldehyde. A possible TS structure for the reaction of diethylzinc with benzaldehyde in the presence of ligands **8a**−**d** was proposed. Finally, the 1-neopenyl-1,2,3,4-tetrahydro-*β*-carboline analogues of **6a** were prepared (**11** and **12**), and their experimental ee values when used in eq 1 were compared to predictions.

Discussion and Results

Soai et al.[1d,10] have shown that the use of a chiral amino alcohol ligand, which has two *n*-Bu groups on nitrogen, led to good enantioselectivity in the additions of diethylzinc to benzaldehyde. On the basis of this insight, we first synthesized chiral 1,2,3,4-tetra-*β*-carbolines **4a**−**d** (Scheme 1) and **6a**−**d** (Scheme 2) where the R^3 groups on the C-3 alcohol substituent were varied (methyl, ethyl, *n*-propyl, and *n*-butyl substituents were used). Ligands **4a**−**d** are derived from L-trypotophan methyl ester, **1**, and ligands **6a**−**d** are based on the indole alkaloid *abrine*, **5**, from the seeds of *abrus precatorius*, native to Yunnan province, China.

Condensation of **1** with *n*-butanal, using 4 Å molecular sieves to remove water, formed the corresponding imine, which was reduced with $NaBH_4$ to **2** (Scheme 1). The Pictet−Spengler condensation of **2** with *n*-propanal generated **3**. Treatment of **3** with alkyl Grignards or *n*-BuLi gave the ligand series **4a**−**d**. The alkaloid, *abrine*, was used to prepare chiral ligands **6a**−**d**, **7a**−**d**, **8a**−**d**, and **9a**−**g** (Scheme 2) and **11** and **12**. Seeds of *abrus precatorius* were extracted with ethanol, and *abrine* was isolated from this extract. Treatment of **5** with $SOCl_2$/CH_3OH followed by aqueous Na_2CO_3 and then 3-methylbutanal produced the tetrahydro-*β*-carboline structure with the C-3 methyl ester substituent. This was converted to **6a**−**d** by treatment with alkyl Grignard reagents or *n*-BuLi. The conversion of **5** to **7a**−**d** was performed in a similar fashion using benzaldehyde in place of 3-methybutanal. Conversion of **5** to **8a**−**d** and **9a**−**g** was achieved using $SOCl_2/CH_3OH$ followed by aqueous Na_2CO_3 and then treatment with either alkyl Grignard reagents or *n*-BuLi and finally condensation with the appropriate aldehydes.

It was expected that the ligands **4a**−**d**, in which the N-2 substituent, R^1, was *n*-Bu (as opposed to methyl found in **6a**−**d**), would have higher enantioselectivities than those exhibited by **6a**−**d**. However, these expected higher enantioselectivities did not appear in diethylzinc additions using this series of ligands. In fact, all the ee values induced by **4a**−**d** were lower than those induced by **6a**−**d** (Table 1). Furthermore, when plots were made of the ee values versus the length of the carbon chain (LCC) of the R^3 group on the C-3 alcohol substituent, the curve for **4a**−**d** appeared as almost the mirror image of the curve for the **6a**−**d** series (Figure 1).

The TS structure in the addition of diethylzinc to benzaldehyde using *β*-amino alcohol ligands has been well studied.[1d,2] It contains a 5/4/4 three-ring system where 2 equiv of Et_2Zn have reacted, giving two Zn atoms and two oxygen atoms in the four-membered ring (**10**). If the activation energies[8] could be calculated for forma-

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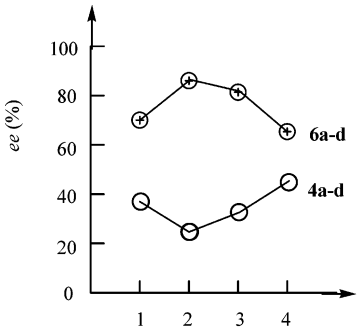


FIGURE 1. Change in ee values with the length of R on the C-3 substituent of ligands **4a**−**d** and **6a**−**d** during diethylzinc additions to benzaldehyde: ee values of ligand **4a**−**d**, ○; ee values of ligand **6a**−**d**, ⊕.

TABLE 1. Enantioselectivities Obtained Using Ligands 4a−d, 6a−d, and 7a−d in the Addition of Diethylzinc to Benzaldehyde: Effect of Chain Length of the R Group on the C-3 Substituent

entry[a]	R at C-3	chiral ligand	yield[b] (%)	ee[c] (%)	ee[d] (optical %)	product configuration[d]
1	Me	**4a**	72	35.0	37.8	*R*
2	Et	**4b**	89	23.5	23.9	*R*
3	*n*-Pr	**4c**	69	31.5	33.7	*R*
4	*n*-Bu	**4d**	74	42.3	43.1	*R*
5	Me	**6a**	95	71.6	70.6	*R*
6	Et	**6b**	88	85.2	85.7	*R*
7	*n*-Pr	**6c**	98	81.9	82.4	*R*
8	*n*-Bu	**6d**	96	65.2	64.8	*R*
9	Me	**7a**	100	58.5	56.2	*R*
10	Et	**7b**	71	55.7	54.6	*R*
11	*n*-Pr	**7c**	97	45.2	44.3	*R*
12	*n*-Bu	**7d**	93	43.9	43.5	*R*

[a] Reactions 1−8 were carried out at 22 °C for 46−48 h, while reactions 9−12 were performed at 20 °C for 46−48 h. [b] Isolated yield. [c] Determined with a chiral OD HPLC column using hexane/2-propanol (95:5%) as the eluent at the flow rate of 1.0 mL/min, detected by UV at 254 nm. [d] Reported specific rotation of the (*R*)-enantiomer, $[\alpha]_D$ +45.6° ($CHCl_3$)[8b], was used for calculation of optical rotation excess and determination of the configuration.

tion of the *R* and *S* enantiomers, then the differences between these activation energies would permit one to explain and predict the observed ee values. However, there are seven stereogenic centers in TS **10**, and the chiral 1,2,3,4-tetrahydro-*β*-carboline ligands have a total of $2^7 = 128$ stereoisomers for consideration in the TS calculations. Even if three stereogenic centers are ignored (stereogenic centers 1, 4, and 5 in structure **10**), $2^4 = 16$ **TS** stereoisomers would need to be evaluated for each substituent variation. If one used HF/6-31G** level ab initio calculations to compute the TS activation energy, the smallest number of basis functions is 862 for the smallest ligand **7a** in the series used in this manuscript. Selecting ligands **4a**−**d**, **6a**−**d**, **7a**−**d**, and **8a**−**d** for TS activation energy calculations requires that at least 1024 (=16 × 4 × 16) TS structures would need to be investigated, making this approach very difficult.

Due to these difficulties, evaluation of the TS and activation energies by calculations was not attempted. Instead, the energy differences between the most stable individual cis and trans conformation of ligands **4a**−**d**, **6a**−**d**, and **7a**−**d** were calculated at the HF/6-31G** level, and these energy differences ($\Delta E_{(cis-trans)}$) are listed

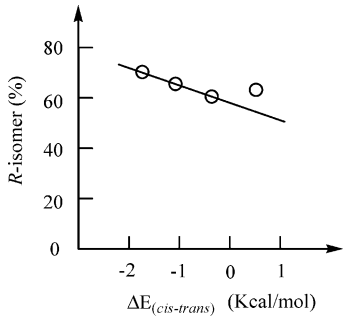


FIGURE 2. Relationship between % (*R*)-isomer values and $\Delta E_{(cis-trans)}$ values in the diethylzinc additions to benzaldehyde using ligands **4a**−**d**.

TABLE 2. Calculated Energy Differences ($\Delta E_{(cis-trans)}$) between trans and cis Conformations of Ligands 4a−d, 6a−d, and 7a−d at the HF/6-31g Level**

entry	ligand (R)	calculated $\Delta E_{(cis-trans)}$[a] HF/6-31G** (kcal/mol)	(*R*)-isomer produced (%)
1	**4a** (Me)	−1.02	67.5
2	**4b** (Et)	−0.37	61.5
3	**4c** (*n*-Pr)	0.43	65.8
4	**4d** (*n*-Bu)	−1.72	71.2
5	**6a** (Me)	0.57	85.8
6	**6b** (Et)	2.46	92.6
7	**6c** (*n*-Pr)	−0.35	90.9
8	**6d** (*n*-Bu)	−0.51	82.9
9	**7a** (Me)	−4.27	79.2
10	**7b** (Et)	−1.44	77.9
11	**7c** (*n*-Pr)	−1.89	72.6
12	**7d** (*n*-Bu)	+3.98	72.0

[a] Positive values of ΔE means that the trans conformation is more stable than the cis conformation.

in Table 2. The most stable cis and trans conformations were initially found by examining all the likely minimum energy conformations (72 total possibilities) at the HF/3-21G level. Then, the most stable cis and trans conformation geometry for each was optimized at the HF/6-31G** level for all 12 ligands (**4a**−**d**, **6a**−**d**, and **7a**−**d**). Searches were made from a variety of starting geometries to ensure that the global minimum energy structure was found in each case at the HF/6-31G** level. Plots of the % (*R*)-enantiomer, obtained using these ligands in Et_2Zn additions to benzaldehyde, were made versus the calculated $\Delta E_{(cis-trans)}$ values. We define ΔE values as (+) when the trans conformer is more stable than the cis conformer. These plots are shown in Figures 2, 3, and 4 for **4a**−**d**, **6a**−**d**, and **7a**−**d**.

In all three ligand series, the ee values dropped with an increase in the magnitude of ΔE. This suggested a relationship might exist between the free ligand conformational populations and the ultimately induced ee values obtained in the Et_2Zn additions. Therefore, two additional series of chiral ligands, the 2,5,5-alkyl-substituted 4-(3-indolylmethyl)-1,3-oxazolidines, **8a**−**d** and **9a**−**f**, were synthesized and employed in Et_2Zn additions to benzaldehyde (Table 3). The ee values, yields, and configuration induced by ligands **9a**−**f** varied only from 12.1 to 3.6%. Therefore, no attempt was made to examine the conformational energy differences in this series of ligands with the very small variation in ee values. However, the calculated ΔE values for ligands **8a**−**d** again showed a general correlation with the

TABLE 3. Ee Values in Diethylzinc Additions to Benzaldehyde in the Presence of Ligands 8a–d and 9a–g

entry[a]	ligand (R)	yield[c] (%)	ee[d] (%)	(*R*)-isomer[f] (%)	ee[e] (optical %)	configuration[e]
1	**8a** (Me)	48	3.4	51.7	3.9	*R*
2	**8b** (Et)	74	61.8	80.9	62.0	*R*
3	**8c** (*n*-Pr)	45	1.2	50.6	0.0	*R*
4	**8d** (*n*-Bu)	62	28.8	64.4	28.0	*R*
5	**9a** (Me)	40	4.2	52.1	4.5	*R*
6	**9b** (Et)	51	12.1	56.1	12.2	*R*
7	**9c** (*n*-Pr)	58	9.9	55.0	10.5	*R*
8	**9d** (*n*-Bu)	45	8.5	54.2	8.9	*R*
9	**9e** (*n*-Amyl)	39	3.6	51.8	3.1	*R*
10	**9f** (CH_2-*i*-Pr)	49	6.0	53.0	6.4	*R*
11	**9g** (CH_2-*t*-Bu)	43	7.6	53.8	8.2	*R*

[a] Reactions were carried out at an average of 20 °C for 46–48 h. [b] Terms *cis* 2 and trans 2 refer to the conformations shown in Figure 6. [c] Isolated yield. [d] Determined with a chiral OD HPLC column using hexane/2-propanol (95:5%) as the eluent at the flow rate of 1.0 mL/min, detected by UV 254 nm. [e] Reported specific rotation of the (*R*)-enantiomer, $[\alpha]_D$ +45.6° ($CHCl_3$),[8b] was used for the calculation of optical rotation excess and determination of the configuration. [f] Based on the HPLC ee values.

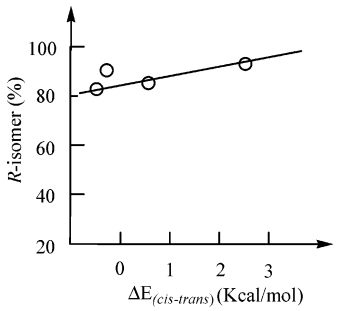


FIGURE 3. Relationship between % (*R*)-isomer values and $\Delta E_{(cis-trans)}$ values in the diethylzinc additions to benzaldehyde using ligands **6a–d**.

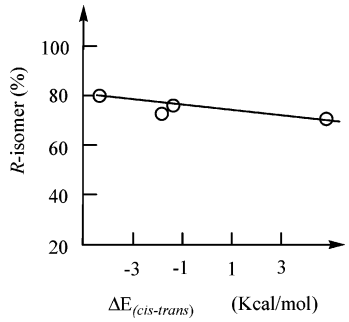


FIGURE 4. Relationship between % (*R*)-isomer values and $\Delta E_{(cis-trans)}$ values in the diethylzinc additions to benzaldehyde using ligands **7a–d**.

enantioselectivity, as illustrated in plots of the % (*R*)-enantiomer obtained versus ΔE (Figure 5). Thus, in four series of ligands (**4**, **6**, **7**, and **8**), the ee values induced in Et_2Zn additions seem to generally correlate with free ligand conformational preferences.

Ligands **8a–d** and **9a–g** have several possible conformations and contain no free hydroxyl groups. Calculations at the HF/6-31G** level showed that eight stable (minimum energy) conformations exist for each of ligands **8a–d**. These eight conformations are shown in Figure 6 and are labeled *trans* 1–4 and *cis* 1–4, respectively. Their relative energies are listed in Table 4. The ee values induced by **8a–d** and **9a–g** are summarized in Table 3. Also, plots of ee versus ΔE values are shown in Figures 4 and 5 for ligands **7a–d** and **8a–d**, respectively.

Since there are eight possible conformations for ligands **8a–d**, more than one might contribute strongly in similar

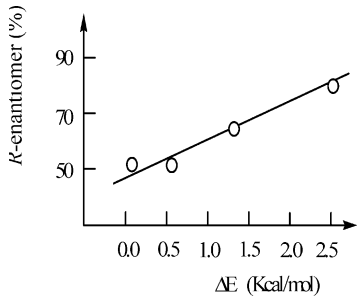


FIGURE 5. Relationship between % (*R*)-enantiomer formed and weighted average of ΔE values of *trans* 2 and *trans* 3 in the diethylzinc additions to benzaldehyde using ligands **8a–d**.

transition states. However, there are only two conformations, *trans 2* and *trans 3*, that form stable TS structures (see the discussion of the TS structure below). Therefore, major contributions to the observed ee values are derived from these two conformations. The energy differences between the *trans 2* and *trans 3* conformations are 2.0, 0.5, 0.5, and −1.3 kcal/mol for **8a**, **8b**, **8c**, and **8d**, respectively, where the *trans 2* conformation is more stable than *trans 3* in every case except **8d**. The energies of the cis conformations are considerably higher (see Table 4). From the *trans 2* versus *trans 3* energy differences, one can approximate the *trans 2*/*trans 3* ratios as 96/4, 70/30, 70/30, and 10/90 for **8a**, **8b**, **8c**, and **8d**, respectively. Using these relative conformational populations, one can compute the weight-averaged ΔE values shown in the last column of Table 4. These values are used in Figure 5.

The reason that only the *trans 2* and *trans 3* conformations of ligands **8a–d** contribute to product formation is illustrated in Figure 7. The *N*-methyl group in chiral oxazolines **8a–d** is either trans or cis to the C-2 isopropyl group. The indole ring nitrogen also can be oriented either toward the front (e.g., *trans* 3) or toward the rear (e.g., *trans* 2). We argue that the isopropyl group's predominant conformations should resemble that in Figure 7a, which is the same conformation as *trans* 2 and *trans* 3 in Figure 6. The two methyl groups of the isopropyl substituent are down, and the proton is up. This decreases the repulsion between the *N*-methyl and 2-isopropyl groups. Thus, these two methyl groups would point toward the PhCHO group in the proposed TS structure shown in Figure 7b. In the structure in Figure

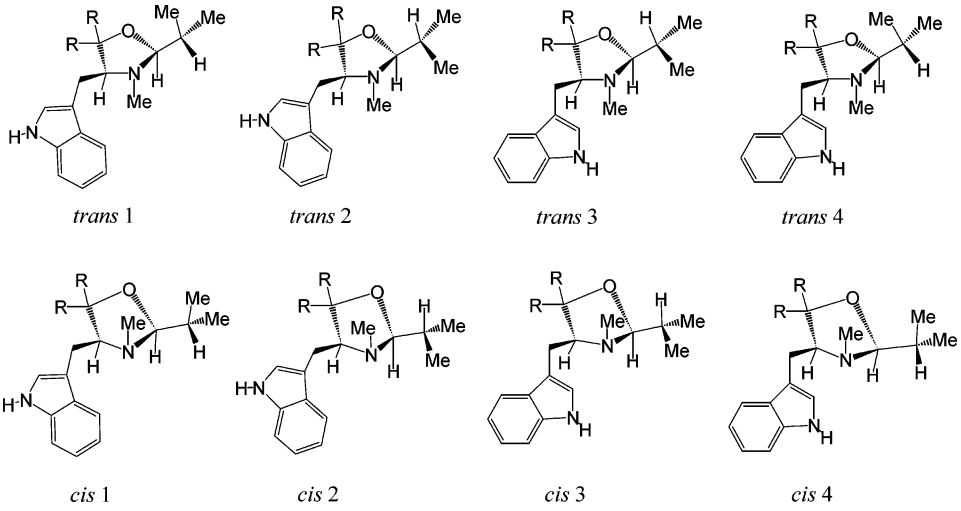


FIGURE 6. Eight minimum energy conformations considered for ligands **8a**−**d**.

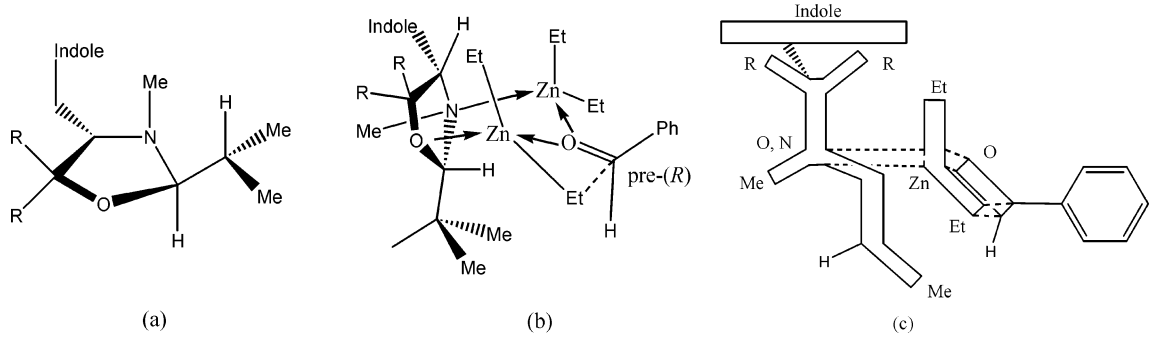


FIGURE 7. (a) Conformation of the isopropyl group at C-2 in ligands **8a**−**d** in the TS for Et_2Zn addition. (b) Proposed TS structure for ligands **8a**−**d**. (c) Space match plot for the TS structure.

TABLE 4. Calculated Δ*E* Values of the Different Conformations of Ligands 8a−d[a]

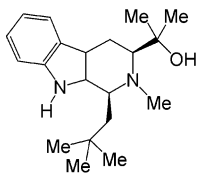
	Δ*E* (kcal/mol) calculated at the HF/6-31G** level								
R	*cis* 1	*cis* 2	*cis* 3	*cis* 4	*trans* 1	*trans* 2	*trans* 3	*trans* 4	(*trans 2* + *trans 3*) weighted average[b]
8a (Me)	6.7	4.0	17.4	5.0	2.0	0.0	2.0	0.0	0.08
8b (Et)	3.8	6.4	18.0	4.3	1.9	2.4	2.8	0.0	2.57
8c (*n*-Pr)	5.2	8.2	18.1	2.3	0.0	0.4	0.9	0.6	0.55
8d (*n*-Bu)	5.5	8.6	19.0	3.5	0.0	2.5	1.2	0.9	1.33

[a] Energies are given relative to the lowest energy conformation (shown as zero kcal/mol). [b] Fraction of each conformer was multiplied by its respective Δ*E*, and the sum of these two quantities is shown.

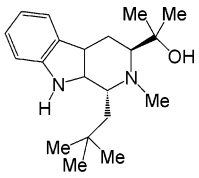
7b, the 2-isopropyl and *N*-CH_3 groups are cis, allowing the nitrogen to bind to zinc. If this conformation is maintained in the TS for ethyl group transfer to the carbonyl carbon, then the aldehyde hydrogen atom will lie between the two isopropyl methyl groups. The big indole group will then serve as a "wall" in the TS as illustrated in Figure 7c. Thus, *trans* 2 and *trans* 3 (Figure 6) conformations approach and bind to zinc, requiring the *N*-methyl group to become cis to the 2-isopropyl and 4-indole functions as shown in Figure 7c. This explanation best fits all the available data for the use of ligands **8a**−**d** in Et_2Zn additions to benzaldehyde. When the 2-isopropyl function of **8a**−**d** was replaced with linear alkyl groups (as in **9a**−**d**), the enantioselectivity of the ligands **9a**−**d** decreased. The stabilization of the benzaldehyde orientation within the TS, by the two methyls of the isopropyl function flanking the aldehyde hydrogen, is lost where ligands **8a**−**d** are replaced by any ligand in the **9a**−**d** series. This is in accord with the experimental results. Ligands **9a**−**d** induce low ee values (Table 3, entries 5−11). Thus, the isopropyl group acts like a "hand" to hold the hydrogen atom of benzaldehyde during the formation of TS.

The enantioselectivity induced by ligands **4a**−**d**, **6a**−**d**, and **7a**−**d** were described above. Searches were made from a variety of starting geometries to ensure that the global minimum energy structure was found in each case at the HF/6-31G** level. In this series, the substituents at the C-1 position were varied from *n*-propyl to 2-methylpropyl and phenyl, respectively. Ligand series **6** and **7** both have an *N*-methyl substituent. If the presence of an *N*-methyl substituent is maintained, what would be the effect of using a more sterically demanding substituent at C-1? To test this question, ligands **11** and **12** were synthesized for direct comparison to **6a** and **7a**. The bulky 2,2-dimethylpropyl substituent was installed at C-1. In

TABLE 5. ee Values Achieved in the Addition of Diethylzinc to Benzaldehyde Using Ligands 11 and 12 and the Differences of the Heats of Formation between trans and cis Conformations in Ligands 11 and 12



11



12

			experimental results			
entry[a]	ligand	calculated ΔE HF/6-31G** (kcal/mol)	yield[b] (%)	ee[c] (%)	ee[d] (optical %)	configuration[d]
1	**11**	−1.2	100	80.6	80.9	*R*
2	**12**	3.4	86	40.0	38.6	*R*

[a] Reactions were carried out at 20 °C for 46−48 h. [b] Isolated yield. [c] Determined with a chiral OD HPLC column using hexane/2-propanol (95:5%) at the flow rate of 1.0 mL/min, detected by UV 254 nm. [d] Reported specific rotation of the (*R*)-enantiomer, $[\alpha]_D$ +45.6° ($CHCl_3$),[8b] was used for calculation of optical rotation excess and determination of the configuration.

11, this was placed cis to the C-3 branched alcohol substituent, whereas in **12**, these substituents were trans. Then, HF/6-31G** calculations were carried out to obtain the conformational energy differences, $\Delta E_{(cis-trans)}$ (*N*-methyl vs C-3 substituent) for both **11** and **12** (Table 5). These ΔE values differed sharply (−1.2 kcal/mol for **11** and 3.4 kcal/mol for **12**). The trans conformation of **11** is less stable, while the cis conformation of **12** prevails. Thus, in accord with the previous observations with **6a**−**d** and **7a**−**d**, one would predict a higher ee value when using **11** (vs **12**) in Et_2Zn additions to benzaldehyde. This prediction agrees well with the experimental ee values (Table 5) of 80−81% for **11** versus 38−40% for **12**.

Conclusions

The chiral ligands studied here exert their enantioselective influence in the transition state for ethyl group transfer to the carbonyl carbon. A single ligand conformation, when captured in the bis-zinc complex, **10**, can exert its preference for forming the (*R*)- versus (*S*)-1-phenylpropanol based on the value of $\Delta G^{\ddagger}$ (for *R* versus *S*). The transition state complex is formed in a series of at least three prior individual reaction steps. The free ligand must first complex Et_2Zn. A second Et_2Zn molecule must then combine with this complex, followed by coordination of benzaldehyde. Then, ethyl transfer may occur. Thus, it takes several reaction steps before a free ligand molecule in solution is incorporated into the transition state complex. Therefore, there is no necessary relationship between the conformational populations of the free ligand and the transition state species. Any correlation that might be found would seem rather unexpected. However, ligand families **4**, **5**, **7**, and **8** do exhibit a general trend between enantioselectivity and conformation populations as represented in the ΔE versus % (*R*)-enantiomer plots.

Where several ligand conformations exist, the initial complexation with zinc should produce more than one intermediate zinc complex. If no equilibration back to the free ligand from the zinc complex occurred, the conformation coordinated to zinc would proceed to the next step and ultimately to complex **10** as long as no other processes interrupted this sequence. If zinc reacts with each free ligand conformation in direct proportion to its conformational population and also no conformational equilibria occur at any stage after this initial complexation on though formation of the transition states for ethyl group transfer, then it is possible that the original conformational populations would be related to the observed enantioselectivities. If $\Delta E_{(cis-trans)}$ is large, then one free ligand conformation dominates. That conformation would then dominate in all complexes up through the formation of **10** since no reverse reactions occur. Furthermore, that conformation would dominate in the enantioselective step. However, if two conformations were present in significant amounts in the free ligand (hence, in the enantioselective transition states), their impacts on enantioselectivity could compete and both would contribute to the overall enantioselectivity in a given series. We suggest that ligand complexation to zinc is not reversible and that the ligand conformations in transition state complex **10** mirror the populations of the free ligand in solution. This hypothesis would permit correlations between $\Delta E_{(cis-trans)}$ and enantioselectivity in a given series of ligands.

Acknowledgment. This work was supported by the "Hundred Talents Program" Fund from the Chinese Academy of Sciences, Department of Chemistry of Mississippi State University, National Science Foundation (NSF) Grant EPS0132618, and NSCF#20242012, the Science and Technology Committee of Yunnan Province of China, to H. J. Zhu and by the financial assistance by Rohm and Haas Corporation and Ferro Corporation to C. U. Pittman, Jr.

Supporting Information Available: All experimental procedures, synthesis, and characterization of new compounds (IR, ^1H NMR, ^{13}C NMR, elemental analysis, optical rotation, some DEPT spectra, HRMS, and melting point). This material is available free of charge via the Internet at http://pubs.acs.org.

JO049754C