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An experimental and theoretical study on free ligand conformational preferences and enantioselectivity relationship for the asymmetric addition of diethylzinc to benzaldehyde

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ABSTRACT

An experimental and theoretical study on free ligand conformational preferences and enantioselectivity relationship has been described for the asymmetric addition of diethylzinc to benzaldehyde. The results show that a correlation must exist between the ground-state ligand conformational populations and the observed ee values in this reaction. As the populations of the free ligand conformation (the desired conformation) in favor of the improvement of the reaction enantioselectivity increase, so does the reaction enantioselectivity. However, the desired conformation must not be the preferred one of the ground-state ligand. This conformation-enantioselectivity relationship is well explained based on a zinc amino-alkoxide (a true asymmetric catalyst). The final synthesis and assessment of the new chiral catalyst in the asymmetric addition of Et_2Zn to benzaldehyde revealed that this necessary relationship guided our design of highly enantioselective ligands or rational improvement of existing ligands by means of knowledge of conformational analysis.

1. Introduction

Over the last three decades, many of the most general and efficient methods for the synthesis of enantiomerically enriched compounds have depended on chiral metal catalysts. Much effort has been devoted to the design of appropriate chiral ligands capable of efficient chirality transfer,[1] since the chiral ligands are responsible not only for the activation of the metal atom where the catalytic activity of the reaction resides but also for the generation of a chiral environment around the metal atom, which controls the enantioselectivity of the reaction. One important question is how one goes about identifying an optimal chial ligand? The most common method for discovering an efficient chiral catalyst seems to be one of the trial and error, wherein, a reasonable lead catalyst is first found. Then, based on intuition or chemical knowledge about mechanistic studies of the reaction being catalyzed, numerous catalyst structures are prepared by placing different substituents on the substructure of the initial lead catalyst. Finally, catalyst candidates are screened in terms of the evaluation of activity and selectivity, and an optimal catalyst is identified after months or years. Therefore, the process of finding an effective chiral catalyst has occupied the time of many investigators over the last three decades.

Combinatorial approaches in association with high throughput screening have already been put forth to accelerate and increase the efficiency of the research process,[2] however, they do not provide with regard to the origin of enantioselectivities. This knowledge, however, is essential for the rational design of a chiral catalyst.

Computational chemistry methods have been extensively used to rationalize the origin of the observed enantioselectivity based on transition structure calculations.[3] However, only a very few examples have been reported that have attempted to predict the stereochemical results of reactions,[4] with even fewer uses with regard to the design of new chiral catalysts.[5] The main reason for the lack of progress may be (1) a detailed knowledge of the reaction mechanism is required; (2) accurate parameters are lacking for metal complexes, which are necessary to model metal-catalyzed reactions; and (3) many variables must be assessed, which requires extensive time, effort, and resources.

Therefore, it is highly desirable to develop simple, practical, and efficient approaches for finding a highly enantioselective chiral catalyst. Herein, we initially describe our observations: the necessary relationship which exists between the free ligand conformational populations and enantioselectivity in the asymmetric addition of diethylzinc to benzaldehyde. Subsequent theoretical computation supports our observation. The final synthesis and evaluation of a new chiral ligand in the asymmetric addition of organozinc to aldehydes reveal further that this necessary relationship can guide our design of highly enantioselective ligands, or rational improvement of existing ligands with only the knowledge of conformational analysis.

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We have selected this catalytic system to study because a considerable number of catalysts have been designed and evaluated for their ability to induce asymmetry,[6] but more importantly because a relationship between the free ligand conformational populations and enantioselectivity has already been noted by Zhu et al.[7] In their work, due to the flexibility of the backbone of a chiral ligand, numerous conformers, resulting in a flip of a five- or six-membered ring, pyramidal inversion at nitrogen, and rotation about the exocyclic bonds might exist at ambient room temperature. All the likely minimum energy conformations (72 total possibilities) at the HF/3-21G level were initially examined in order to find the most stable *cis*- and *trans*-conformations. As a result of these complexities, what they discovered was that the observed ee values, in most cases, were only related to the populations of the *cis*- versus *trans*-free ligand conformations formed by pyramidal inversion at nitrogen, which led to a reversal of the absolute configuration of the stereogenic nitrogen. To the best of our knowledge, there have been no reports on the effect of ground-state ligand conformational equilibria on the observed enantioselectivity.

2. Results and discussion

In recent years,[8] we have been exploring the use of chiral ferrocene-based small-ring heterocycle ligands containing a β-amino alcohol moiety in the catalytic asymmetric addition of organozinc to aldehydes. In our previous work,[8a,c] we reported the synthesis of chiral ferrocenyl aziridino alcohol ligands **1** and **2** (Fig. 1) and their applications in the enantioselective addition of diethylzinc to benzaldehyde. The introduction of a methyl group on aziridine ring, with the C-3 methyl group anti to the C-2 bulky diphenylhydroxymethyl group, led to a further improvement in the enantioselectivity from 92.6% to 96.0% ee. On the basis of our analysis of the reaction pathway and the proposed possible transition states,[8c] the methyl group situated far away from the reaction active sites did not seem to have an impact on the reaction enantioselectivity. Why does the introduction of the methyl substituent result in an increase in enantioselectivity? Further insight into these chiral ligands revealed that the introduction of a methyl group on the aziridine ring resulted in the differences in relative free conformational populations of **1** and **2**, that is, the introduction of a methyl group did not affect the flexibility of the framework, yet it led to the equilibrium redistributions of the conformational isomers. This observation suggested that a relationship must exist between the free ligand conformational populations and the observed ee values in the asymmetric addition of diethylzinc to benzaldehyde.

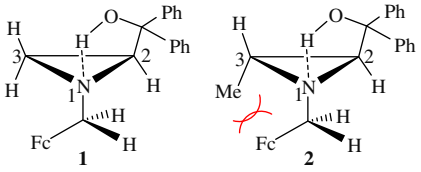


Figure 1. The structures of chiral ligands **1** and **2**.

For the sake of better understanding, the structural features of aziridino amino alcohol compounds are first described as follows. In (2*S*)-1-(ferrocenylmethyl)aziridin-2-yl(diphenyl)methanol **1** (Fig. 1),[8a] the aziridine ring has completely planar-ring structure, and thereby free of ring flip conformation. Due to the formation of the intramolecular hydrogen bond (in a five-membered ring structure, Fig. 1) as well as the strong repulsive interaction between the bulky ferrocenyl group on the nitrogen atom of the aziridine ring and the bulky diphenylhydroxymethyl group on the three-membered ring, nitrogen pyramidal inversion is effectively blocked. As a result, the nitrogen atom on the aziridine ring also becomes a stereocenter. The crystal structure of compound **1** revealed that the value of the torsion angle N(1)–C(13)–C(14)–C(15) in **1** is 90.0(3)° (Fig. 2),[8a] suggesting that one phenyl substituent on the α-carbon occupies an axial position with regard to the five-membered ring, which we called the axial phenyl group. The values of the torsion angles N(1)–C(13)–C(14)–C(21) and C(12)–C(13)–C(14)–C(21) in **1** are −147.6(3)° and −78.7(4)°, respectively, indicating that the other phenyl group is located in the equatorial position, which we called the equatorial phenyl group, where this arrangement minimizes the steric interaction between the equatorial phenyl group and the aziridine ring moiety. As a result of the aforementioned reasons a fixed conformation about the bulky diphenylhydroxymethyl group results in the aziridine ring at the C-2 position. Such structural features are common for those aziridino amino alcohol derivatives which bear two bulky phenyl

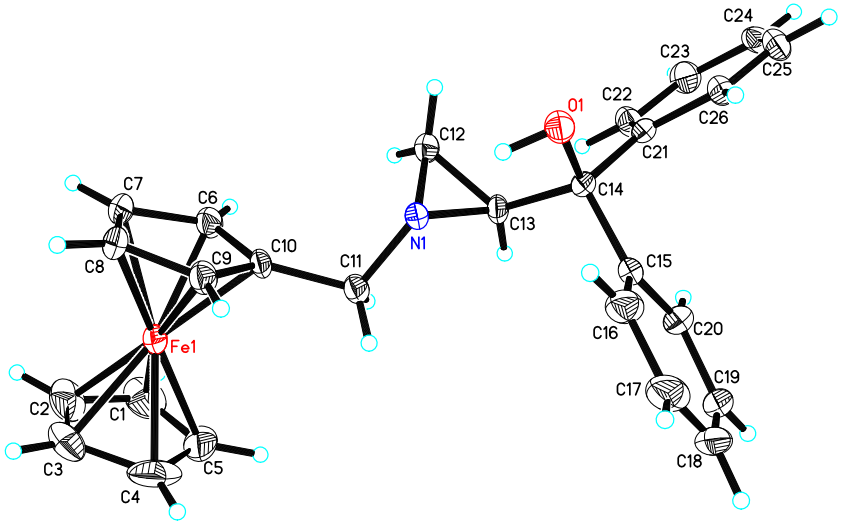


Figure 2. Perspective view of compound **1**. Selected bond distances (Å), angles (°), and torsion angles (°) are N(1)–C(13), 1.458(4); N(1)–C(12), 1.460(4); C(12)–C(13), 1.454(4); C(13)–C(14), 1.537(5); O(1)–C(14), 1.423(4); O(1)–H(1), 0.89(5); O(1)–N(1), 2.678(5); N(1)–H(1), 1.977(5). C(13)–N(1)–C(12), 59.8(2); C(13)–C(12)–N(1), 60.1(2); C(12)–C(13)–N(1), 60.1(2); N(1)–C(13)–C(14), 114.5(3); C(14)–O(1)–H(1), 97(3); N(1)–H(1)–O(1), 134. N(1)–C(13)–C(14)–C(15), 90.0(3); N(1)–C(13)–C(14)–C(21), −147.6(3); C(12)–C(13)–C(14)–C(21), −78.7(4); C(13)–N(1)–C(11)–C(10), −147.4(3); C(12)–N(1)–C(11)–C(10), −80.6(4); N(1)–C(13)–C(14)–O(1), −30.1(4).

groups at the α-position.[8a,9] The value of the torsion angle C(13)–N(1)–C(11)–C(10) in **1** is −147.4(3)°, suggesting that a nonbonded interaction exists between the bulky ferrocenyl group and the axial phenyl substituent on α-carbon because of the ferrocenyl cylindrical shape.

Due to the aforementioned reasons, the chiral compound **1** has three possible conformations about the exocyclic N–C bond-free rotation (**1a**–**c**, Fig. 3). In conformation **1c**, the ferrocenyl group lies under the aziridine ring, while in conformations **1a** and **1b**, a hydrogen atom lies under the aziridine ring. Because of the nonbonded repulsion between the bulky ferrocenyl group and the aziridine ring unit in **1c**, and the interaction between the bulky ferrocenyl group and the axial phenyl substituent on α-carbon in **1b**, conformation **1a** is more stable than conformations **1b** and **1c**. Thus, in the equilibrium mixture, conformer **1a** is the predominant one, which is in agreement with the X-ray crystal structure of the ligand **1**.

When a hydrogen atom of the aziridine ring at the 3-position, which is positioned *anti* to the diphenylhydroxymethyl group, is replaced by a methyl group to yield derivative **2**, there are three possible conformations **2a**–**2c** (Fig. 4). Conformation **2b** is the most stable due to minimizing the steric interaction between the bulky ferrocenyl group and the methyl group. Therefore, the conformational isomer **2b** is the predominant one in the equilibrium mixture.

To further examine the equilibrium distributions of the conformational isomers, the relative energies of the conformers of **1** and **2** were calculated using GAUSSIAN 03 program.[10] All geometries were optimized at the HF level using the 6-31G basis set for C, H, N, and O, LanL2DZ basis set for Fe. The single-point energy was determined at B3LYP/6-31+g (d,p). The calculated results are summarized in Table 1 (entries 1–6). As seen from Table 1, the order of relative energies for conformers of the ligands **1** and **2** is **1a** < **1b** < **1c** (relative conformational populations of **1a**/**1b**/**1c** = 50.0:27.5:22.5) and **2b** < **2a** < **2c** (**2a**/**2b**/**2c** = >99.9:0:0), respectively. The calculated results were in agreement with conformational analysis. The reliability of an ab initio approach to examine the relative stability of conformers had previously been

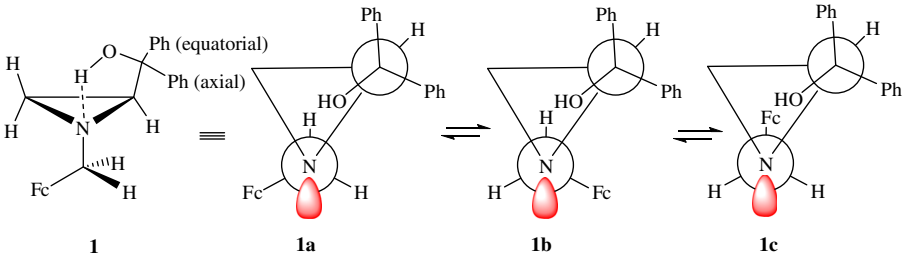


Figure 3. Three conformations about the N–C bond rotation for ligand **1**.

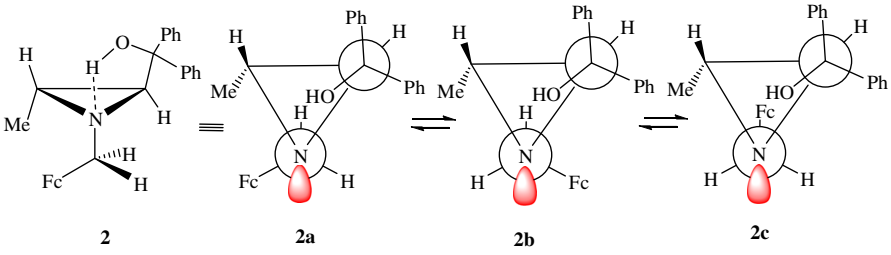
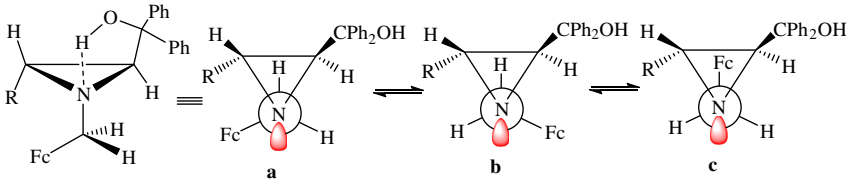


Figure 4. Three conformations about the N–C bond rotation for ligand **2**.

Table 1
The relationship between the free ligand conformational equilibria and the observed enantioselectivity in the addition of diethylzinc to benzaldehyde



Entry	Ligands	R	Comf	E (Hartree)	E_{rel}[a] (kJ/mol)	Ratio[b] (%)	ee
1	**1**	H	**1a**	−1259.21374	0.0	50.0	92.7
2		H	**1b**	−1259.21319	1.5	27.5	
3		H	**1c**	−1259.21296	2.0	22.5	
4	**2**	Me	**2a**	−1298.52079	27.3	0.0	96.0
5		Me	**2b**	−1298.53118	0.0	>99.9	
6		Me	**2c**	−1298.51769	35.4	0.0	

[a] Relative to the lowest energy conformation (shown as zero kJ/mol).
[b] Conformational population is obtained from a Boltzmann distribution of relative energies at 298 K.

acknowledged.[11] In addition, solvent calculations using the IPCM model for the conformers qualitatively agree with the gas-phase ab initio results.[11d]

A comparison of the enantioselectivity (96.0% ee) induced by **2** with that (92.6% ee) by **1** shows that the introduction of a methyl group that is positioned *anti* to the diphenylhydroxymethyl group leads to an improvement in the enantioselectivity when used as the catalyst in the addition of diethylzinc to benzaldehyde. The enantioselective differences afforded by **1** and **2** could be attributed to the difference of the relative free conformational populations in **1** and **2**. Compared with the relative ground-state conformational populations (**1b**/**1a** ratios as 0.55) in **1**, the substantial increase in free conformational populations (>99.9%) of **2b** resulted in an improvement in the enantioselectivity, that is, the observed enantioselectivity increases when increasing the amount of the conformation isomer **2b**. Therefore, the structure of the conformation **2b**, where the relative position of the bulky ferrocenyl group is oriented toward the same direction of the axial phenyl group, as in **2b**, favored the enhancement of the reaction enantioselectivity. For the sake of convenience, the conformation in favor of the relative improvement of the reaction enantioselectivity is called the desired conformation. These analyses and results suggest that a relationship must exist between the free ligand conformational populations and the observed ee values in the asymmetric addition of diethylzinc to benzaldehyde. In addition, the preferred conformation of the free ligand must not be the desired conformation.

This conformation-enantioselectivity relationship is understandable. Noyori et al. have studied the mechanism of this reaction extensively, both theoretically and experimentally.[12] The true asymmetric catalyst is believed to be a zinc amino-alkoxide (a planar Zn structure, Fig. 5). Compared with free ligands, the replacement of the chelated proton with an ethylzinc moiety should not lead to any significant structural distortion because ligand ground-state conformation resembles that in the complex. Theoretical computation also demonstrated that stable five-membered Zn-chelate ring conformations resembled those of the free ligand for aziridino alcohol analogue.[13] Therefore, the chiral catalyst, generated by the reaction of the conformationally flexible ligands **1** and **2** with diethylzinc, has also three possible conformations about the corresponding N–C bond-free rotation (**a**–**c**, Fig. 5). In conformation **b**, the ferrocenyl group and the axial phenyl group on the diphenylhydroxymethyl group point toward the same direction with respect to the five-membered coordination ring. As a result, the ferrocenyl and phenyl groups in **b**, due to the cooperatively directing effect of the two substituents, can block more effectively the approach of benzaldehyde and diethylzinc from this face, when compared with the hydrogen atom and phenyl substituents in **a** and **c**. That is, the conformer **b** of the chiral catalysts efficiently distinguishes between the face of the five-membered Zn-chelate ring, which resulted in the improvement of the enantioselectivity. Therefore, the enantioselectivity will be enhanced when the amount of the desired conformer **b** increases.

The next question one might ask is does the same conformation-enantioselectivity relationship exist between the free ligand conformational populations and the ee values obtained in the asymmetric addition of diethylzinc to benzaldehyde when the ferrocenylmethyl group on the nitrogen atom of aziridine-based skeleton was replaced by other substituents? This question is very important because if the necessary correlation exists, one can envision a number of different procedures to design the preferred conformation that will increase the reaction enantioselectivity by intentionally modifying a conformationally flexible ligand's structure, which is called the conformational design of flexible molecules.[14]

In previous literature,[9b,15] chiral ligands **3**–**6** with the same backbone as **1** and **2** were reported which were used in the asymmetric addition of diethylzinc to benzaldehyde with large differences in ee values. However, these big differences in ee values have to date not been rationalized. Inspection of such structures revealed that the observed enantioselectivity also correlated with the equilibrium distributions of ground-state conformers.

For chiral ligand **3** (Fig. 6),[15a] which replaces the ferrocenyl group in **1** with a phenyl substituent, the relative energy order of conformational isomers for the ligand **3** was **3a** < **3b** < **3c** (relative populations: **3a**/**3b**/**3c** = 66.8:21.4:11.8, Table 2, entries 1–3). This shows that conformer **3a** is the preferred one, which is in agreement with the case of the chiral ligand **1**. However, the chiral ligand **3** only gave 49.0% ee, whereas the chiral ligand **1** afforded up to 92.7% ee. This big difference (92.7% vs 49.0%) in enantioselectivity is due to the steric effect of the bulky ferrocenyl group compared with the phenyl substituent, even though the ferrocenyl group in conformer **1a** can also exert steric hindrance because of its cylindrical shape (relative to the planar phenyl group). These results indicate that the observed enantioselectivity was related to not only the amount of the desired conformation but also the size of the substituent steric hindrance.

The replacement of the hydrogen atom of **3** at the 3-position below the aziridine ring with a methyl group afforded chiral ligand **4** (Fig. 7).[15a] For ligand **4**, the energy ordering with the **4a** < **4b** < **4c** sequence (relative populations: **4a**/**4b**/**4c** = 72.2:27.4:0.3, Table 2, entries 4–6) was the same as that of **3**. However, the relative conformational populations (**4b**/**4a** ratios as 0.38) in **4** were higher than those (**3b**/**3a** ratios as 0.32) in **3**. The larger populations of the desired conformation **4b** relative to **3b** are responsible for the higher

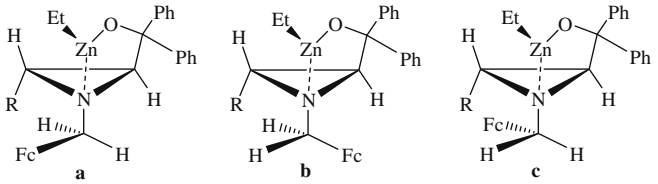


Figure 5. The conformers of the true asymmetric catalyst.

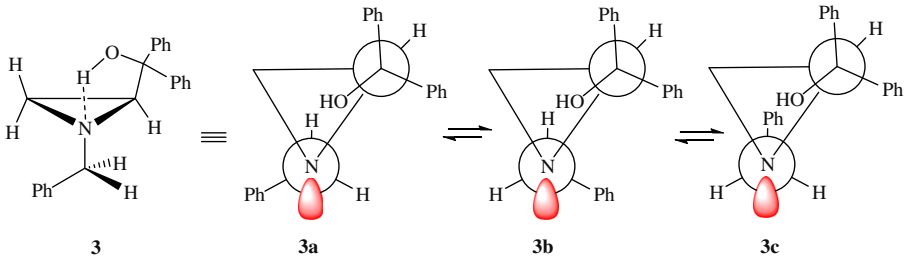
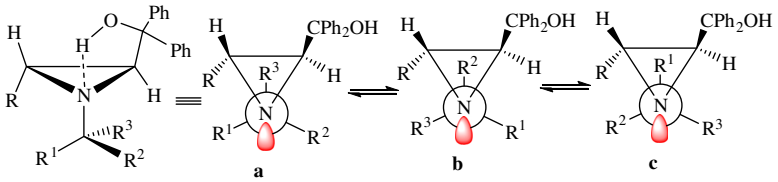


Figure 6. Three conformations about the N–C bond rotation for ligand **3**.

Table 2
The relationship between the free ligand conformational equilibria and the observed enantioselectivity in the addition of diethylzinc to benzaldehyde



Entry	Ligands	R	Comf	E (Hartree)	E_{rel}[a] (kJ/mol)	Ratio[b] (%)	ee
1	**3** (R_1 = Ph, R_2 = R_3 = H)	H	**3a**	−980.97938	0.0	66.8	49.0[15a]
2		H	**3b**	−980.97832	2.8	21.4	
3		H	**3c**	−980.97773	4.3	11.8	
4	**4** (R_1 = Ph, R_2 = R_3 = H)	Me	**4a**	−1020.29807	0.0	72.2	75.0[15a]
5		Me	**4b**	−1020.29716	2.4	27.4	
6		Me	**4c**	−1020.29319	12.8	0.30	
7	**5** (R_1 = R_2 = Ph, R_3 = H)	H	**5a**	−1212.04074	0.0	84.5	96.0[9b]
8		H	**5b**	−1212.03674	10.5	1.20	
9		H	**5c**	−1212.03907	4.4	14.3	
10	**6** (R_1 = R_2 = R_3 = Ph)	H	**6**			100	99.0[15b]

[a] Relative to the lowest energy conformation (shown as zero kJ/mol).
[b] Conformational population is obtained from a Boltzmann distribution of relative energies at 298 K.

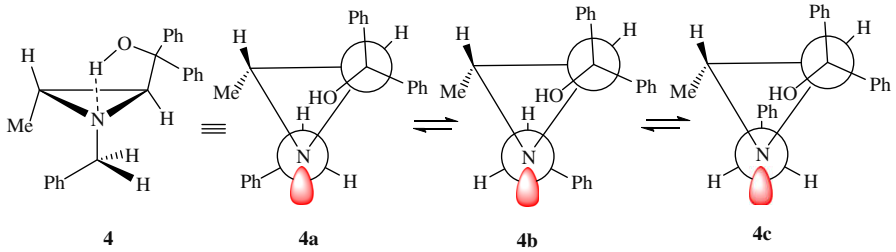


Figure 7. Three conformations about the N–C bond rotation for ligand **4**.

enantioselectivity (75% ee) for **4** than that (49% ee) for **3**. This result shows that the introduction of methyl group did not affect the flexibility of the backbone, yet it resulted in the equilibrium redistributions of the conformational isomers. Consequently, the increase in the population of the desired conformation **4b** led to an improvement in reaction enantioselectivity.

Ligand **5** (Fig. 8),[9b] which contains a *gem*-diphenyl group on the nitrogen atom of the three-membered ring adopted a preferred conformation **5a** in order to avoid strong interaction between the aziridine ring unit and phenyl group in **5b** and **5c**, respectively. The crystal structure of **5** also clearly illustrated this arrangement.[9b] The theoretical calculations showed that the preferred conformation **5a** constituted of about 84.5% of the equilibrium mixture (Table 2, entry 7). Unlike ligands **3** and **4** which contain only one desired conformation **3b**, or **4b**, respectively, ligand **5** with a benzhydryl group had two desired conformations **5a** and **5b** (i.e., 85.7% populations for the sum of two desired conformations **5a** and **5b**) because conformations **5a** and **5b**, respectively, had a phenyl substituent that was oriented in the same direction as the axial phenyl group, as in **5a** and **5b**. Therefore, both **5a** and **5b** favored the improvement of the reaction enantioselectivity. As a result, the chiral ligand **5** gave enantioselectivities of up to 96% ee.

Ligand **6** (Fig. 9)[15b] has only a single conformation because a Ph_3C substituent on the nitrogen atom displays the expected C_3-symmetry in its substituent conformational preference, that is, due to the presence of a quaternary center that is usually used to control the conformation,[15] there is always one phenyl group pointing toward the same direction of the axial phenyl group on the diphenylhydroxymethyl group with respect to the five-membered ring, as indicated in **6**. Therefore, ligand **6** with one single

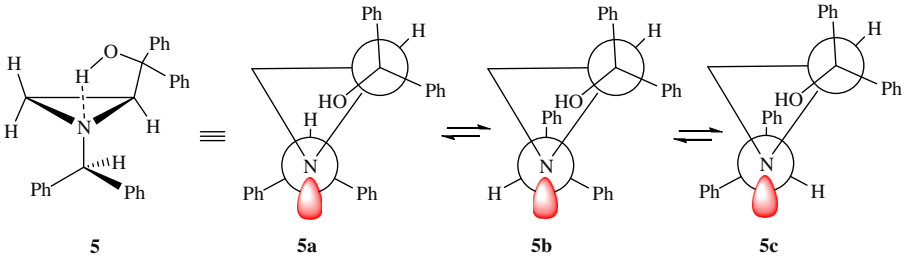


Figure 8. Three conformations about the N–C bond rotation for ligand **5**.

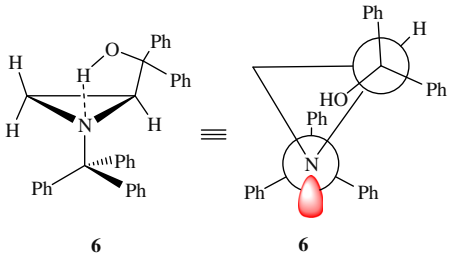


Figure 9. Conformation about the N–C bond rotation for ligand **6**.

conformation (i.e., 100% desired conformation) gave the best asymmetric induction of up to 99% ee.

Based on the aforementioned relationship between the free ligand conformational populations and the observed ee values, new compound **9** (Fig. 10) with only one single conformation should also be the same outstanding chiral ligand as **6** because the introduction of the methyl group, compared with the ligand **6**, cannot alter the equilibrium redistributions of the conformational isomers.

To further verify this prediction, the new chiral ligand **9** was synthesized in enantiopure form from starting material *allo*-L-threonine using the protocol outlined in Scheme 1.[9a,16]

With chiral ligand **9** in hand, the asymmetric addition of diethylzinc to benzaldehyde was examined in toluene in 0–5 °C in the presence of 5% ligand **9**. As expected, ligand **9** with a single conformation gave the desired product with outstanding enantioselectivities of up to 98.5% ee (Scheme 2). For the sake of comparing the asymmetric induction efficiency of **6** and **9**, the chiral ligand **6** was also tested under the same conditions as **9**, and the ligand **6** afforded 98.7% ee. From these results, the ligand **9** did not result in a change in the enantioselectivity (relative to **6**) because there was no change in the equilibrium distributions of the conformational isomers even when a methyl group was introduced on the aziridine ring. However, looking at **2** versus **1** and **4** versus **3**, the introduction of a methyl group led to a substantial increase in the reaction enantioselectivity because the introduction of a methyl group resulted in the equilibrium redistributions of the conformational isomers.

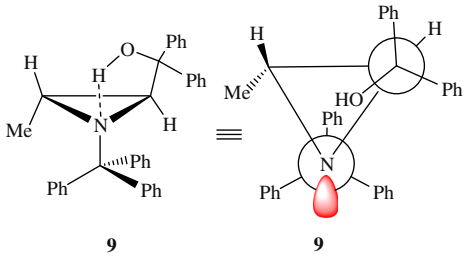
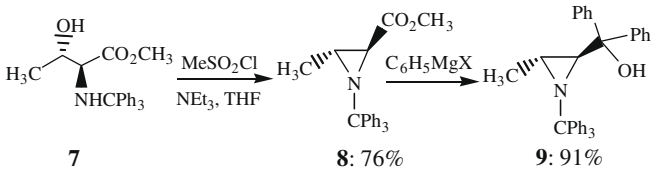
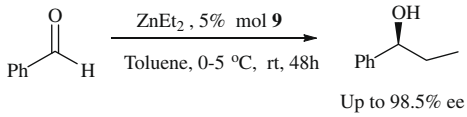


Figure 10. Conformation about the N–C bond rotation for ligand **9**.



Scheme 1. Synthesis of chiral ligand **9**.



Scheme 2. Addition of diethylzinc to benzaldehyde.

3. Conclusion

In conclusion, we have shown that a relationship must exist between the free ligand conformational populations and the observed ee values in the asymmetric addition of diethylzinc to benzaldehyde. The increase in populations of the desired free ligand conformations led to an enhancement of the reaction enantioselectivity. Based on this necessary correlation between free ligand conformational populations and the observed ee values, it is an alternative simple and practical method that the concept of conformational design is used to develop efficient chiral ligands in catalytic asymmetric reactions by means of knowledge of conformational analysis. Studies are currently underway using the concept of conformational design to synthesize new and efficient chiral ligands for asymmetric catalysis.

4. Experimental

4.1. General

Unless otherwise noted, all reactions were carried out under argon or nitrogen using standard Schlenk and vacuum line techniques. Toluene was freshly distilled over calcium hydride prior to use. Other reagents were obtained from commercial sources and used as received without further purification. Melting points were determined using YRT-3 melting point apparatus and are uncorrected. Optical rotations were measured with Perkin–Elmer, model 341 Polarimeter at 20 °C in $CHCl_3$. The enantiomeric purity was determined by HPLC using a chiral column with hexane/propan-2-ol (ratio as indicated) as the eluent. The chromatographic system consisted of a JASCO model PU-1580 intelligent HPLC pump and a JASCO model UV-1575 intelligent UV–vis detector (254 nm). The injection loop had a 20 μL capacity. The column used was a Chiralcel OD (250 × 4.6 mm) from Daicel Chemical Ind., Ltd (Japan). The column was operated at ambient temperature. NMR spectra (^1H and ^{13}C) were performed on a Bruker DPX 400 (400 MHz) spectrometer using solutions in $CDCl_3$ (referenced internally to Me_4Si); *J* values are given in Hz. TLC was performed on dry silica gel plates developed with hexane/ethyl acetate. Mass spectra were obtained using a Bruker esquire-3000 instrument with an electrospray ionization source (ESIMS). All the ESIMS spectra were performed using MeOH as the solvent. Methanol was dried with $Mg(OCH_3)_2$.

4.2. Synthesis of chiral compound 8

To a stirred suspension of *allo*-L-threonine methyl ester hydrochloride (2.5 g, 15 mmol) in dichloromethane (20 mL), triethylamine (4.2 mL, 30 mmol) was added dropwise at 0 °C, and then trityl chloride (4.18 g, 15 mmol) dissolved in chloroform was added dropwise. After stirring for 72 h at 0 °C, the mixture was washed with 10% aqueous citric acid solution (3 × 10 mL) and water (3 × 10 mL). After the combined organic extracts were dried over Na_2SO_4, the solvent was removed in vacuo. The residue was purified by recrystallization (ethyl acetate/petroleum) to afford the product **7** as a yellowish solid (4.7 g, 84%), mp145–147 °C. $[\alpha]_D^{20} = +17.1$ (*c* 1.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.11 (d, *J* = 6.8 Hz, 3H, *CH*$_3$), 2.40 (br, 1H), 3.01 (d, *J* = 9.6 Hz, 1H, *CH*–CO_2),

3.23 (s, 3H, OCH_3), 3.38–3.41 (m, 1H, CH_3CH), 3.99 (br, 1H), 7.17–7.28 (m, 9H, PhH), 7.49–7.51 (m, 6H, PhH). ^{13}C NMR: (100 MHz, $CDCl_3$) δ 19.5, 51.5, 61.1, 69.9, 70.9, 126.5, 127.8, 128.8, 145.6, 173.1. IR (KBr): 3512, 3361, 3068, 3050, 2970, 2936, 1713, 1595, 1490, 1444, 1429, 1266, 1223, 1090, 1050, 1090, 778, 751, 705. MS (ESI): m/z (M + Na) $^+$ calcd for $C_{24}H_{25}NO_3$: 389.5; found: 398.6.

To a stirred solution of trityl *allo*-L-threonine methyl ester **7** (1.3 g, 3.47 mmol) in tetrahydrofuran (9.8 mL), triethylamine (6.9 mL, 50 mmol) was added dropwise at 0 °C. Methanesulfonyl chloride (0.4 mL, 5.2 mmol) was added dropwise. After stirring for 30 min at room temperature, the solution was refluxed for another 48 h. The solvent was removed in vacuo to leave a residue which was taken up in ethyl acetate (8 mL) and washed with 10% aqueous citric acid solution (3 × 5 mL) followed by saturated aqueous sodium bicarbonate solution (2 × 5 mL). After the combined organic extracts were dried over Na_2SO_4, the solvent was removed in vacuo. The residue was purified on a preparative silica gel TLC plate (petroleum/EtOAc = 20:1) and afforded compound **8** (0.94 g) in 76% yield, mp 140–142.5 °C, (lit.[17] mp 141–143 °C). $[\alpha]_D^{20} = +11.3$ (c 1.38, $CHCl_3$), {lit.[17] $[\alpha]_D^{20} = +10$ (c 1.0, $CHCl_3$)}. $[\alpha]_D^{20} = +11.3$ (c 1.38, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.60 (d, J = 6.4 Hz, 3H, CH_3), 2.35 (d, J = 2.4 Hz, 1H, CH–CO_2), 2.96–3.01 (m, 1H, CH_3CH), 3.70 (s, 3H, OCH_3), 7.19–7.30 (m, 9H, PhH), 7.49–7.51 (m, 6H, PhH). IR (KBr): 3060, 3021, 2952, 1748, 1596, 1489, 1445, 1274, 1199, 1178, 1065, 1032, 755, 706. MS (ESI): m/z (M+Na) $^+$ calcd for $C_{24}H_{23}NO_2$: 380.4; found: 379.9.

4.3. Synthesis of chiral compound 9

A Grignard reagent was prepared in the usual way from 146 mg (6 mmol) of magnesium and bromobenzene 6 mmol in THF (5 mL). The solution was cooled to −20 °C before the addition of a solution of **8** (515 mg, 1.5 mmol) in THF (2 mL). The mixture was allowed to reach the room temperature. After stirring for 24 h, the reaction was quenched with saturated aqueous NH_4Cl (10 mL) at 0 °C. The phases were separated and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic phases were washed with brine (15 mL), dried over Na_2SO_4, and after filtration the solvent was removed under reduced pressure. The resulting residue was purified by the preparative TLC with petroleum/EtOAc (20:1) as developing solvent to give **9** (665 mg, 91%), mp 164.5–165.9 °C. $[\alpha]_D^{20} = +44.2$ (c 1.01, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.77 (d, J = 6.4 Hz, 3H, CH_3), 2.46 (d, J = 3.2 Hz, 1H, CH_3CHCH), 2.65–2.71 (m, 1H, CH_3CH), 3.74 (s, 1H, OH), 6.98–7.31 (m, 25H, PhH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.54, 37.41, 50.02, 72.53, 74.26, 125.94, 126.15, 126.58, 126.96, 127.40, 127.47, 127.93, 128.05, 129.86, 145.60, 147.18. IR (KBr): 3368, 3084, 3055, 3021, 2956, 2928, 1595, 1489, 1446, 1369, 1334, 1182, 1151, 1069, 1033, 745, 7012. MS (ESI): m/z (M+H)$^+$ calcd for $C_{35}H_{31}NO$: 482.6; found: 482.5. Anal. Calcd for $C_{35}H_{31}NO$ requires: C, 87.28; H, 6.49; N, 2.91. Found: C, 87.32; H, 6.47; N, 2.97.

4.4. General procedure for the asymmetric addition of diethylzinc arylaldehydes

A solution of diethylzinc (1 M in n-hexane, 1.1 mL) was added to a solution of a chiral catalyst **9** (0.025 mmol, 5 mol %) in dry toluene under a nitrogen atmosphere. The mixture was cooled to 0 °C and stirred for 30 min. Freshly distilled benzaldehyde (0.05 mL, 0.5 mmol) was added to the mixture. The resulting mixture was stirred for 10 h in 0–5 °C and was allowed to warm to room temperature, and kept stirring for another 38 h at the same temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl (4 mL). The mixture was extracted with Et_2O (3 × 8 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. Purification of the residue by the preparative silica gel TLC plate (hexane/EtOAc = 4:1) afforded the (*S*)-1-phenyl-1-propanol. The ee was determined by HPLC analyses using a chiral column (a Chiralcel OD). Hexane/*i*-PrOH = 100:2, 1 mL/min, t_R = 13.2 min, t_S = 16.2 min.

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