Tetrahedron: *Asymmetry* 22 (2011) 761–768

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Applications of conformational design: rational design of chiral ligands derived from a common chiral source for highly enantioselective preparations of (*R*)- and (*S*)-enantiomers of secondary alcohols

Min-Can Wang *, Yong-Hui Wang, Gao-Wei Li, Ping-Ping Sun, Jie-Xi Tian, Hui-Jie Lu

Department of Chemistry and Henan Key Laboratory of Chemical Biology and Organic Chemistry, Zhengzhou University, Zhengzhou, Henan 450052, PR China

ARTICLE INFO

Article history:
Received 16 March 2011
Accepted 12 April 2011

ABSTRACT

A pair of diastereomers **7** and **8** were easily synthesized in only two steps from a single common chiral source according to the concept of conformation design. The efficiency of these chiral ligands was evaluated by their application to the asymmetric addition of diethylzinc to aldehydes. This catalytic asymmetric process afforded the a most efficient access to the (*R*)- and (*S*)-enantiomers of a given secondary alcohol with similarly outstanding enantioselectivities and high yields. Our results also showed that the control of the desired conformer's population by conformation design is a new and practical strategy for the rational and precise design of highly enantioselective chiral ligands for metal-catalyzed reactions. The mechanism and possible transition states for the catalytic asymmetric addition have been proposed on the basis of previous studies as well as the crystal structure of the chiral ligands **7** and **8**.

1. Introduction

Asymmetric catalysis is one of the most efficient routes to enantiopure compounds. For this reason, much effort has been devoted to the design of appropriate chiral ligands capable of efficient chirality transfer.[1] From the standpoint of practical applications, ideal chiral ligands have to possess the following advantages: (1) chiral ligands should be accessible from a simple chiral source; (2) the catalytic systems have the generality for a broad range of substrates in a given reaction; (3) the process should provide an approach to both enantiomers of the product with high enantioselectivities (>90% ee), in order to guarantee that the expected isomer can be obtained.

Traditional methods for the efficient preparation of both enantiomers of a chiral compound require the synthesis of both antipodes of the corresponding ligand from natural chiral sources. However, most natural sources, such as amino acids, sugars, and sparteine, are available in only one absolute configuration. The other enantiomer, which is naturally rare, requires resolution or complicated procedures to synthesize.

In order to overcome this limitation, an increasing number of investigators have been exploring the possibility of preparing both antipodes from a single configuration of the chiral elements of the ligand.[2] This can be achieved through a process known as dual or reversible enantioselectivity. Dual asymmetric catalysis can be achieved by structural modification of the chiral ligand,[2f,3] addition of an achiral ligand[4] or additive,[5] changing the metal center in the chiral organometallic complex,[6] or metal/ligand ratio,[7] or the counterion,[8] or the reaction conditions,[9] such as temperature, pressure, or solvent. However, among those different methods for controlling the stereochemistry of the product, only a few examples can give both enantiomers of the desired product with high enantioselectivities (over 90% ee).[2] In addition, it is difficult to establish general relationships between the chiralities of the individual ligand types and the sense of enantiodifferentiation due to the absence of the necessary experimental data. This knowledge is essential for the rational design of chiral catalysts/ligands.

Recently, the preparation of both enantiomers of a chiral compound in excellent ee has been reported by the reverse addition of reactants in the presence of the same chiral ligand, but this method is limited to the arylation of arylaldehydes[10] or arylimines.[11] Therefore, the efficient preparation of both enantiomers of a target molecule still remains a challenge from a single chiral starting material.

In recent years,[12] we have been exploring the use of chiral small-ring heterocycle ligands containing a β-amino alcohol moiety in the catalytic asymmetric addition of organozinc to aldehydes. More recently,[13] we demonstrated, both theoretically and experimentally, that a relationship must exist between the conformational populations of the ground-state ligand and the observed ee values in the asymmetric addition of diethylzinc to benzaldehyde. In addition, this necessary relationship could guide our design of highly enantioselective ligands, or rational improvement of existing ligands. In order to further extend the application of this relationship in the design of novel chiral ligands, we herein report the design a pair of chiral diastereomeric ligands **7** and **8** for the asymmetric preparation of (*R*)- and (*S*)-enantiomers of a given secondary alcohol from

* Corresponding author. Tel./fax: +86 371 67767895.
E-mail address: wangmincan@zzu.edu.cn (M.-C. Wang).

0957-4166/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2011.04.013

a single common chiral source by means of the concept of conformation design. The efficiency of chiral ligands **7** and **8** was evaluated by their application in the asymmetric addition of diethylzinc to aldehydes. The mechanism and possible transition states for the catalytic asymmetric addition have also been proposed based on previous studies as well as the crystal structure of the chiral ligands **7** and **8**.

2. Results and discussion

2.1. Conformation design

Early in 1992,[14a] Hoffmann predicted that the design and synthesis of chiral ligands for metal-catalyzed reactions could be solved by means of conformation design. However, due to the lack of information on a relationship between conformational populations and enantioselectivity, the rational and accurate design (relative to trial and error) of chiral ligands for metal-catalyzed reactions was rarely reported by considering a single conformation and its effect on asymmetric induction. Thus, the most common method for discovering an efficient chiral ligand was screening the numerous structures of chiral compounds. Our previous investigation showed that the enantioselectivity could be enhanced by increasing the amount of the desired conformer.[13] For example, compared with chiral compound **1**, ligands **2**, **3**, **4,** and **5** afforded high ee value in the asymmetric ethylation of benzaldehyde in the presence of 5% catalysts **2**, **3**, **4,** and **5** (Fig. 1), respectively, because of the increase in the population of the desired conformations. The desired conformer population can be controlled by using conformation-determining factors, including intramolecular hydrogen bonds, buttressing groups, *gem*-substituents, and the C_3-symmetry of a quaternary carbon center.[14]

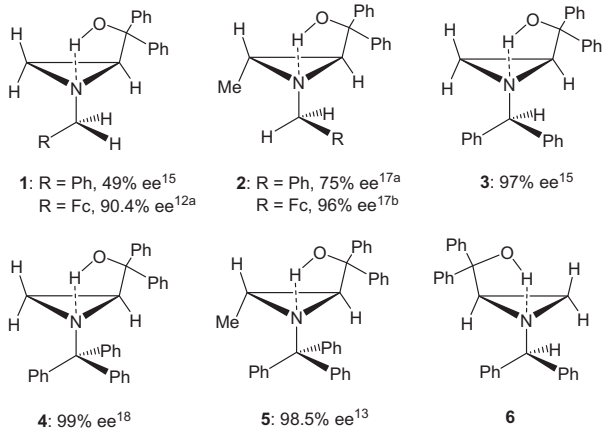
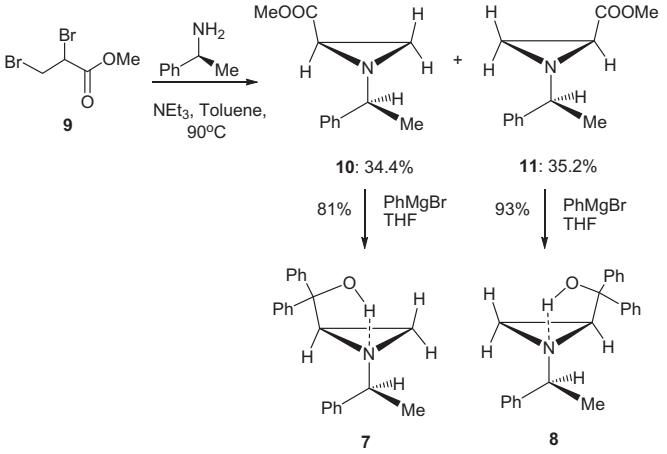


Figure 1. The structures of some chiral aziridine-carbinols.

Chiral ligand **3** bearing an (*S*)-configuration, which gave only the (*S*)-configuration of addition product with 96% ee, was derived from natural L-serine in a multi-step procedure with low yields.[15] In order to obtain the other antipode of the product, the enantiomer **6** with an (*R*)-configuration had to be prepared from unnatural D-serine. Natural L-serine was very expensive compared to unnatural D-serine.[16]

In order to overcome the limitations of enantiomers **3** and **6**, the substitution of one phenyl group of the benzhydryl group with a methyl substituent gave new diastereomeric pairs **7** and **8** (Scheme 1). Conceptually, the replacement of a phenyl group with a methyl substituent is only a small step, but this small structural modification has the following advantages:

(1) Diastereomers **7** and **8** have an additional stereogenic center on the nitrogen atom, which was easily derived in only two steps from commercially available (*S*)-α-methylbenzyl amine and methyl 2,3-dibromopropanoate **9** (Scheme 1).



Scheme 1. Synthesis of chiral compounds **7** and **8**.

(2) Diastereomers **7** (Fig. 2) and **8** (Fig. 4), which were used as chiral ligands for the asymmetric addition diethylzinc to aldehydes, gave the corresponding products with an (*R*)- or (*S*)-configuration, respectively. According to our previous observations,[13,15,17,18] the absolute configuration of the addition products was determined only by the configuration of the aziridine ring because the axial phenyl group on the α-carbon with respect to the five-membered H-bonded ring played a major role in efficiently shielding one face of the chelated zinc atom (a truly chiral catalyst). The substituent on the additional stereogenic center only acted via a cooperative directing effect when it pointed toward the same direction of the axial phenyl group.

(3) The diastereomeric pairs **7** and **8** should show a similar enantioselectivity. Due to the severe geometric anisotropy of the phenyl group, and the effect of the geminal substituent, where the presence of the second substituent, such as a methyl group, hindered the free rotation of the phenyl group, and phenyl group appeared to be slightly smaller than the methyl substituent.[19] In fact, the Van-der Waals radius of the Me is 2.0 Å, while the 'half-thickness' of a benzene ring is ca. 1.7 Å. The 'barrel' formed by a rotating Ph group has a radius of ca. 3.2 Å.[20] In a previous paper, we found that the reaction enantioselectivity depended mainly on the desired conformation populations of the ground-state ligand and the steric hindrance of the directing group.[13] Compared with **6** (Fig. 3), the chiral compound **7** also had three possible conformations due to the exocyclic N–C bond free rotation (Fig. 2, **7a**–**c**). In addition, among the three possible conformations **7a**, **7b**, and **7c**, the conformation **7a** was the most stable due to it avoiding a strong interaction between the aziridine ring unit and phenyl group in **7b** or methyl group in **7c**. In the predominant conformer **7a**, the phenyl group on the nitrogen atom was oriented toward the same direction as the axial phenyl group, which was in agreement with **6a**. Therefore, the preferred conformer **7a** was the desired one. Likewise, the relative position of the methyl group in **7b** was also situated in the same direction as the axial phenyl group. Hence conformation **7b** was also the desired one, which is accordance with **6b**. The slightly bigger Me in **7c** relative to Ph in **6c** led to a stronger interaction between the aziridine ring unit and methyl group, meaning that the conformation populations of **7c** decreased in the equilibrium mixture. Due to the reasons mentioned above, the desired conformation populations (the sum of two desired conformations **7a** and **7b**) and the steric hindrance

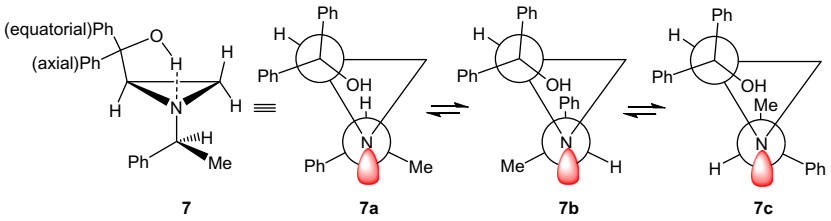


Figure 2. Three conformations about the N–C bond rotation for ligand **7**.

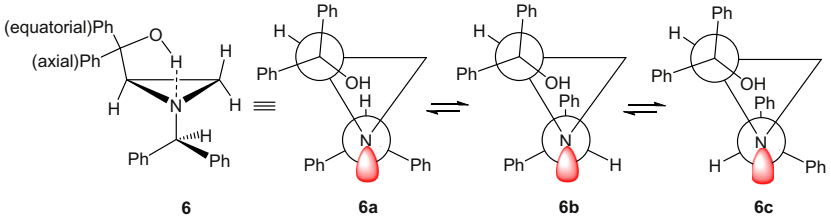


Figure 3. Three conformations about the N–C bond rotation for ligand **6**.

of the directing groups (Me, Ph vs Ph, Ph) in chiral ligand **7** would be increased when compared with **6**. Therefore, the enantioselectivity of the chiral ligands **7** should be better than **6**.

In the same manner, the diastereomer **8** (Fig. 4) was also an outstanding chiral ligand since **8** was similar to **7** in the desired conformation populations (**8a**, **8b** vs **7a**, **7b**) and the steric hindrance of the directing groups (Me, Ph).

2.2. Synthesis of chiral ligands 7 and 8

The diastereomeric pairs **7** and **8** were easily synthesized in a two-step sequence from commercially available (*S*)-α-methylbenzyl amine and methyl 2,3-dibromopropanoate **9** (Scheme 1). At first, methyl 2,3-dibromopropanoate **9** was reacted with enantiomerically pure (*S*)-α-methylbenzyl amine to produce the corresponding mixture of diastereomeric *N*-alkylazetidine esters **10** and **11**. Then the chromatographic separation of the diastereomeric esters by preparative silica gel TLC gave the desired esters **10** (34.4%) and **11** (35.2%),[21] respectively, in enantiomerically pure form. The treatment of the two esters with phenylmagnesiumbromide afforded chiral ligands **7** (81%) and **8** (93%), respectively. Diastereomers **7** and **8** were new compounds. Their absolute configuration was determined by X-ray diffraction (Figs. 5 and 6, respectively);[22] selected structural data in the crystalline state are summarized in Table 1.

2.3. Asymmetric addition of diethylzinc to aldehydes

Since the initial report of Oguni and Omi on the reaction of diethylzinc with benzaldehyde in the presence of a catalytic amount of (*S*)-leucinol with moderate enantioselectivity (49% ee) in 1984,[23] the asymmetric addition of diethylzinc to aldehydes has been studied extensively, and products with excellent enantiomeric excesses have been achieved with all types of substrates.[24] Due to the adequate reactivity of diethylzinc and the sensitivity of the reaction to changes in the ligand structure, the enantioselective reaction of diethylzinc with benzaldehyde has also become a classical test to examine the enantioselectivities of designed chiral ligands. In order to examine the catalytic behavior of the diastereomeric pairs **7** and **8**, the asymmetric addition of diethylzinc to benzaldehyde was investigated in toluene at 0–25 °C in the presence of 5% ligand **7** and **8**, respectively. As expected, the reactions using diastereomers **7** and **8** as catalysts afforded (*R*)- and (*S*)-1-phenylpropanols (Table 2, entries 1 and 2), respectively. Gratifyingly, both diastereomers display nearly the same excellent enantioselectivity (**7**: 98.3% ee, **8**: 98.5% ee). Moreover, they also perform equally well in catalysis. Our results also showed that conformation design is a new and practical strategy for the rational and precise design of highly enantioselective chiral ligands.

In order to examine the generality of diastereomeric pairs **7** and **8**, the asymmetric addition of diethylzinc to a variety of aldehydes was examined in the presence of 5 mol % chiral ligands **7** and **8**, respectively; the results are shown in Table 2. As can be seen from Table 2, in all cases examined, excellent enantioselectivities (91.5–99.5% ee) could be achieved for various aromatic aldehydes, including *ortho*-, *para*-, and *meta*-substituted benzaldehydes (Table 2, entries 3–30), disubstituted benzaldehydes (Table 2, entries 31–34), and α-naphthaldehydes (Table 2, entries 35 and 36). The presence of electron-donating or electron-withdrawing substituents on the benzene ring also furnished the corresponding products with excellent levels (91.5–99.5% ee) of enantioselectivity. Chiral ligands **7** and **8** were also tested with α,β-unsaturated and

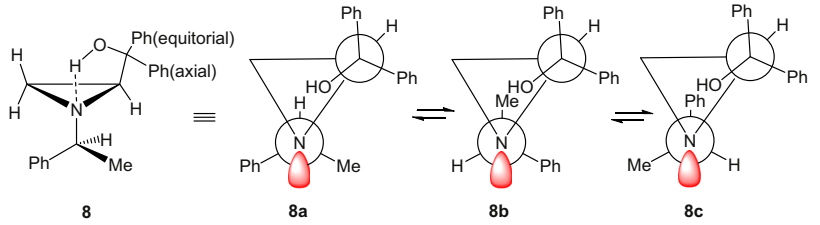


Figure 4. Three conformations about the N–C bond rotation for ligand **8**.

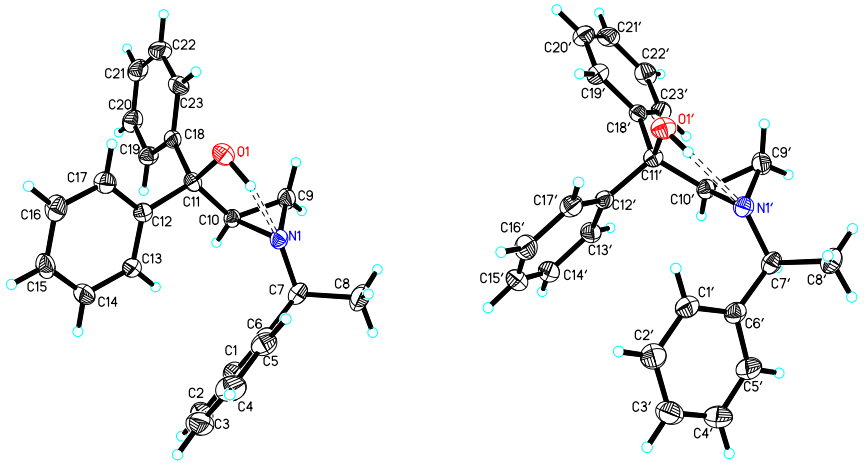


Figure 5. There were two independent conformations **7**, and **7′** present in each asymmetric unit cell of this compound, which had similar structures.

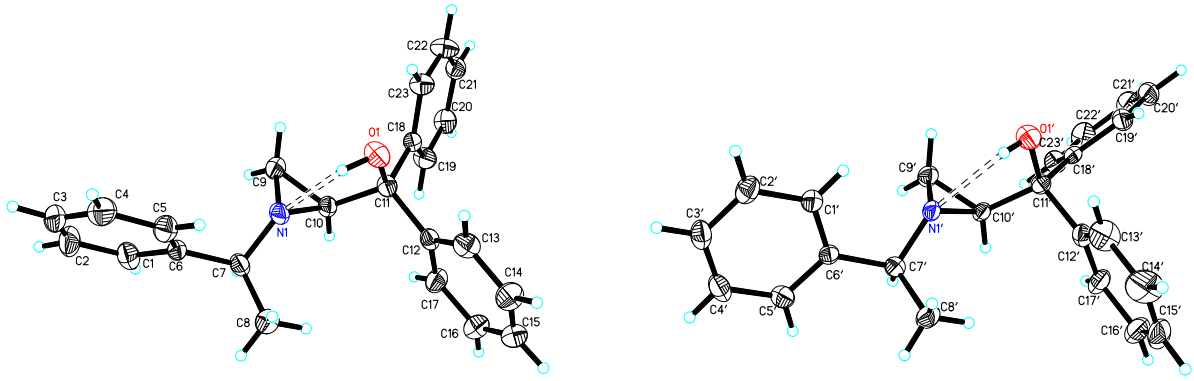


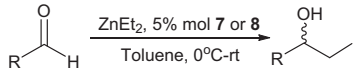
Figure 6. There were two independent conformations **8**, and **8′** present in each asymmetric unit cell of this compound, which had similar structures.

Table 1
Selected bond lengths, bond angles and dihedral angles of **7** and **8**

Entry		7		8	
		7	**7′**	**8**	**8′**
1	Bond lengths				
2	N(1)–C(9)	1.484(5)	1.477(5)	1.479(6)	1.463(7)
3	N(1)–C(10)	1.466(4)	1.461(5)	1.484(5)	1.471(6)
4	C(9)–C(10)	1.481(6)	1.470(6)	1.490(6)	1.490(7)
5	C(10)–C(11)	1.524(5)	1.525(5)	1.533(7)	1.540(7)
6	O(1)–C(11)	1.433(4)	1.433(4)	1.429(6)	1.431(6)
7	N(1)–C(7)	1.471(5)	1.467(5)	1.469(6)	1.462(7)
8	Bond angles				
9	N(1)–C(10)–C(9)	60.5(2)	60.5(3)	59.6(3)	59.2(3
10	C(10)–N(1)–C(9)	60.3(2)	60.0(3)	60.4(3)	61.1(3)
11	C(10)–C(9)–N(1)	59.3(2)	59.4(2)	60.0(3)	59.7(3)
12	C(9)–C(10)–C(11)	119.4(4)	121.6(4)	122.8(4)	121.7(5)
13	N(1)–C(10)–C(11)	114.8(3)	114.3(3)	114.1(4)	114.0(4)
14	C(10)–N(1)–C(7)	116.7(3)	116.6(3)	114.8(4)	118.1(4)
15	C(7)–N(1)–C(9)	114.0(3)	114.1(3)	116.0(4)	116.9(5)
16	Dihedral angles				
17	N(1)–C(10)–C(11)–C(18)	144.4(3)	144.4(3)	−146.7(3)	−139.0(4)
18	N(1)–C(10)–C(11)–C(12)	−92.2(4)	−93.2(4)	91.9(4)	97.6(5)
19	N(1)–C(10)–C(11)–O(1)	27.6(4)	26.5(5)	−28.5(4)	−22.7(6)
20	C(9)–C(10)–C(11)–O(1)	44.7(6)	39.8(5)	39.8(5)	44.7(6)
21	C(10)–N(1)–C(7)–C(6)	−83.2(4)	−87.1(4)	−157.2(4)	−152.2(4)
22	C(10)–N(1)–C(7)–C(8)	152.3(4)	149.8(4)	80.3(5)	84.0(6)

aliphatic aldehydes, respectively. It was found that diastereomers **7** and **8** also showed high enantioselectivities for the addition of diethylzinc to cinnamaldehyde and 3-phenylpropanal (Table 2, entries 37–40). This catalytic process afforded both enantiomers of the corresponding addition product. The chiral ligand **7** always gave (*R*)-configuration products while the chiral ligand **8** gave the (*S*)-configuration. To the best of our knowledge, this is the first example in which a diastereomeric ligand pair from a common chi-

Table 2
Asymmetric addition of diethylzinc to aldehydes catalyzed by **7** and **8**[a], respectively



Entry	R	Ligand	Yield[b] (%)	ee[c] (%)	Configuration[d]
1	C_6H_5	**7**	90	98.3	(*R*)
2		**8**	92	98.5	(*S*)
3	*p*-MeC_6H_4	**7**	93	98.4	(*R*)
4		**8**	98	98.7	(*S*)
5	*m*-MeC_6H_4	**7**	92	93.0	(*R*)
6		**8**	92	97.6	(*S*)
7	*o*-MeC_6H_4	**7**	93	97.5	(*R*)
8		**8**	92	98.7	(*S*)
9	*p*-$MeOC_6H_4$	**7**	92	99.2	(*R*)
10		**8**	98	98.3	(*S*)
11	*m*-$MeOC_6H_4$	**7**	93	99.2	(*R*)
12		**8**	94	99.5	(*S*)
13	*o*-$MeOC_6H_4$	**7**	>99	97.9	(*R*)
14		**8**	99	98.1	(*S*)
15	*m*-$PhOC_6H_4$	**7**	97	97.8	(*R*)
16		**8**	98	98.1	(*S*)
17	*p*-$Me_2NC_6H_4$	**7**	92	97.2	(*R*)
18		**8**	94	97.5	(*S*)
19	*o*-ClC_6H_4	**7**	93	91.5	(*R*)
20		**8**	91	95.9	(*S*)
21	*m*-ClC_6H_4	**7**	93	97.5	(*R*)
22		**8**	89	98.5	(*S*)
23	*p*-ClC_6H_4	**7**	97	97.2	(*R*)
24		**8**	95	98.6	(*S*)
25	*o*-BrC_6H_4	**7**	94	99.4	(*R*)
26		**8**	90	99.1	(*S*)
27	*m*-BrC_6H_4	**7**	99	97.7	(*R*)
28		**8**	97	98.1	(*S*)
29	*p*-BrC_6H_4	**7**	90	98.3	(*R*)
30		**8**	92	98.5	(*S*)
31	3-Br–4-ClC_6H_3	**7**	92	95.3	(*R*)
32		**8**	94	97.9	(*S*)
33	3,4-$OCH_2OC_6H_3$	**7**	96	98.8	(*R*)
34		**8**	94	99.3	(*S*)
35	1-Naph	**7**	99	97.8	(*R*)
36		**8**	>99	99.2	(*S*)
37	3-PhenylCH=CH	**7**	90	86.7	(*R*)
38		**8**	93	84.3	(*S*)
39	3-PhenylCH_2CH_2	**7**	91	91.2	(*R*)
40		**8**	97	84.3	(*S*)

[a] The molar ratio of Et_2Zn:aldehyde was 2:1.
[b] Isolated yields.
[c] Determined by HPLC using chiral columns: Chiralcel OD, OD-H or OB, respectively.
[d] The absolute configuration was assigned by comparison with a known elution order from Chiralcel OD, OD-H or OB columns according to the literature and considering the similarity in the stereochemical reaction pathway.

ral source allowed both enantiomers to be obtained with similar excellent enantioselectivities as well as a broad range of substrates in the asymmetric addition of diethylzinc to aldehydes.

2.4. Mechanism and possible transition state

In principle, a pair of diastereomers usually shows a big difference in enantioselectivity for a given reaction because of the substantial energy barrier between diastereomeric transition states for the formation of the major products. To the best of our knowledge, only one example has been reported in which diastereomeric pairs (*R*,*S*)-**12** and (*S*,*S*)-**13** (Fig. 7) with planar and center chiralities display similar enantioselectivity for (*S*)- and (*R*)-configuration products,[25] but with only a narrow range of substrates with high enantioselectivity (over 90% ee). Diastereomers **7** and **8** showed not only almost equally excellent enantioselectivity with inversion of configurations, but also for a broader range of substrates. Thus, we were required to study the structural features of the catalytically active metal complex and transition state with the aid of reaction mechanism and the determined structural data in the crystalline phase.

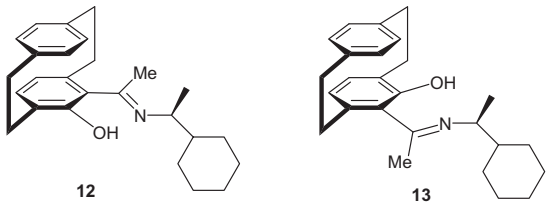
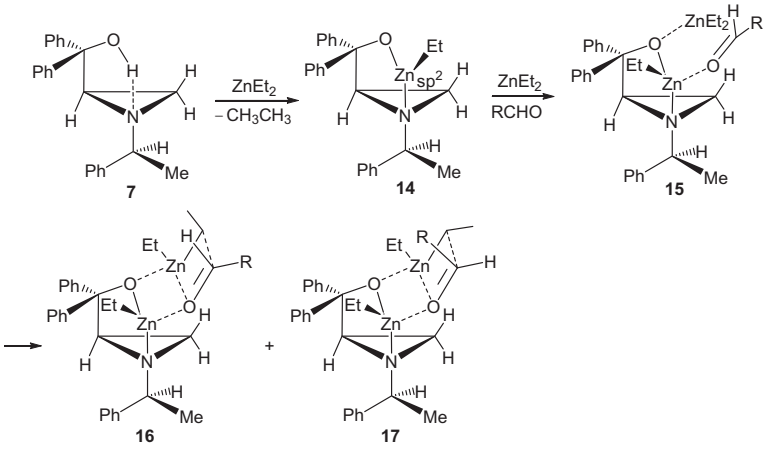


Figure 7. Structures of compounds **12** and **13**.

The X-ray structures of the non-complexed ligands did not provide any direct information about the structures of the catalytically active metal complex and transition state, but the structural data determined in the crystalline state did help with an understanding of the reaction mechanism and the origin of enantioselectivity, especially when the ground-state ligand conformations resembled those of the catalyst. The X-ray structure analysis revealed that an intramolecular hydrogen bond was present in the crystalline state in aziridine alcohols **7** and **8**, which is common feature for aziridino amino alcohol derivatives with a similar backbone. In addition, the presence of an intramolecular hydrogen in solution was further demonstrated in aziridino amino alcohols with the similar skeleton.[26] The reaction of diethylzinc with ligands **7** and **8** first yielded the corresponding zinc aminoalkoxides **14** and **18**, respectively, which act as a bifunctional catalyst.[27] In the case of the zinc complex, the zinc atom should be placed between the oxygen and the nitrogen atoms in a five-membered chelate ring. The calculations showed that the zinc aminoalkoxide had a planar structure Zn although the Zn atom was not fully sp^2-hybridized. Therefore, the replacement of the hydrogen atom in **7** or **8** with a planar structure ethylzinc moiety should not lead to any significant structural distortion, that is, zinc aminoalkoxides **14** and **18** should have nearly the same conformations as the ground-state diastereomers **7** and **8**, respectively. Thus, the structures of free ligands **7** and **8** serve as valuable models for the corresponding zinc complexes, and the structural data determined in the crystalline state provided a basis for mechanistic discussion.

The values of the torsion angles N(1)–C(10)–C(11)–C(18) in **7** and **8** were 144.4(3)° and −139.0(4)° (Table 1, entry 17), respectively, indicating that one phenyl substituent on the α-carbon occupies an equatorial position with respect to the five-membered ring. This arrangement minimizes the steric interaction between the equatorial phenyl group and the aziridine ring moiety. As a result, this non-bonded repulsion, combined with the presence of an intramolecular hydrogen, could lock the conformation of the bulky diphenylhydroxymethyl group. The dihedral angles N(1)–C(10)–C(11)–C(12) in **7** and **8** were −92.2(4)° and 91.9(4)° (Table 1, entry 18), respectively, suggesting that the other phenyl group is located in the axial position. This orientation of the phenyl group plays a vital role in determining the steric origins of the enantioselectivity because it provided high diastereoselectivity in truly chiral catalysts.

The values of the dihedral angles C(10)–N(1)–C(7)–C(6) and N(1)–C(10)–C(11)–C(12) in **7** were −83.2(4)° and −92.2(4)° (Table 1, entries 21 and 17), respectively, indicating that the axial phenyl substituent and the phenyl group on the additional stereogenic carbon atom point in the same direction with respect to the five-membered zinc ring. This spatial disposition of the two phenyl substituents could block more effectively one face of the catalyst **14** derived from **7** (Scheme 2). The values of the torsion angles C(10)–N(1)–C(7)–C(8) and N(1)–C(10)–C(11)–C(12) in **8** were



Scheme 2. Possible transition states.

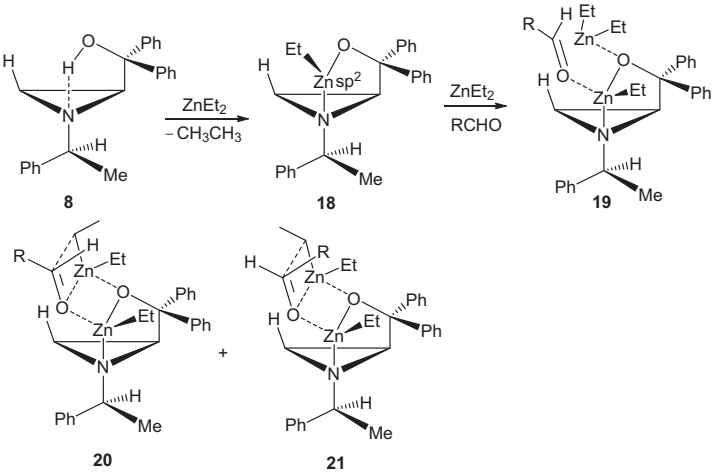
80.3(5)° and 91.9(4)° (Table 1, entries 22 and 18), respectively, suggesting that the axial phenyl substituent and the methyl group on the additional stereogenic carbon atom were located on the *cis* side of the coordinated five-membered ring. This spatial orientation of the axial phenyl and methyl substituents could inhibit cooperatively one face of the catalyst **18** derived from **8** (Scheme 3).

These structural data determined in the crystalline phase showed that the conformation about the bulky diphenylhydroxymethyl group on the aziridine ring was fixed, although the spatial orientation of the methyl or phenyl group on the additional stereogenic center relative to the coordinated five-membered ring was different. One important reason was that (*S*)-*N*-1-phenylethyl group under the arizidine ring was far away from the diphenylhydroxymethyl group above the aziridine ring.

The lone pair of electrons of the oxygen atom of benzaldehyde coordinated with the Lewis acidic Zn atom at the less hindered face of the five-membered ring chelate **14** (Scheme 2), and then the adjacent basic oxygen accepts ethylzinc at Zn to form the product-forming, mixed-ligand complex **15**. The ethyl group transfer from the diethylzinc to the aldehyde both from the *Re*-face and *Si*-face resulted in the *anti*-5/4/4-fused tricyclic transition states **16** and **17**, respectively. The strong steric repulsion between the Et and R groups disfavored the transition state **17**, which gave the (*S*)-configuration as the minor products. In transition state **16**, the non-bonded repulsion between Et and R substituents is absent. As a result, transition state **16** was the favored structure, and afforded an (*R*)-configuration for the major products, which was in agreement with our experimental results. In a similar manner, the structures of transition states **20** and **21** derived from **8** were represented in Scheme 3. The absence of non-bonded interaction between Et and R substituents was observed in transition state **20**, and led to an (*S*)-configuration for the major products, which was in accordance with the experimental results. This explained the inversion of the configuration between both diastereomeric pairs.

Compared with the structures of the transition states **16** for (*R*)-configuration of major products and **20** for (*S*)-configuration of major products, the main difference between **16** and **20** was the different orientation of the reaction active sites relative to the phenyl (or methyl) substituent on the additional stereogenic center. In **16**, the four-membered Zn–O–Zn–O ring and the phenyl group were situated on the opposite side with respective to the five-membered chelate ring, whereas the four-membered Zn–O–Zn–O ring and the phenyl group in **20** were located on the same side.

As can be seen from the structures of the transition states **16** and **20**, the reaction active sites are situated above the arizidine ring. The (*S*)-*N*-1-phenylethyl group under the arizidine ring was far away from the reaction active sites. We inferred that the different spatial orientation of the reaction active sites relative to the phenyl (or methyl) group on the additional stereogenic center did not seem to have an impact on the energy of the transition states **16** and **18**. Because transition state structures of the reaction



Scheme 3. Possible transition states.

active sites above the arizidine ring were enantiomeric relationships, s transition states **16** and **18** should have nearly the same energy, which is responsible for the similar enantioselectivities. Thus, diastereomers **7** and **8** showed almost the equal enantioselectivity in most cases.

In almost all cases, the chiral ligand **8** afforded a slightly better enantioselectivity than **7**. The main reason was that ligand **8** shielded one face of the catalytically active zinc complex more effectively than **7**. For **7** and **8**, conformers **7a** and **8a** were preferred and gave the desired conformations. In **7a**, the directing groups were two phenyl substituents (the axial Ph and the Ph of the additional stereogenic center) pointing in the same direction, while directing groups in **8a** were the phenyl and methyl substituents. Since the steric hindrance effect of the methyl group was more effective than the phenyl substituent (see conformation design), the methyl and phenyl groups could more effectively hinder the approach of the aldehydes and alkynylzinc from this face compared with the two phenyl substituents. As a result, chiral ligand **8** gave a slightly better enantioselectivity than **7**.

3. Conclusion

We have herein described how to rationally and accurately design a pair of diastereomers **7** and **8**, which afforded the most efficient access to (*R*)- and (*S*)-enantiomers of a given secondary alcohol with similar outstanding enantioselectivities and high yields. In addition, compounds **7** and **8** were easily synthesized in only two steps from a single common chiral source. Our results also showed that the conformation design is a new and practical strategy for the rational and precise development of highly enantioselective chiral ligands for metal-catalyzed reactions. The intentional control of the desired conformer populations by means of conformation-determining factors is crucial for designing optimum chiral ligands. Studies are currently underway using the concept of conformational design to develop new and efficient chiral ligands for asymmetric catalysis. Investigations of other applications of these novel diastereomers **7** and **8** is also in progress.

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 Hertz. 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 the aziridine-carbinol

To a Grignard reagent solution prepared from 0.66 mL (6.24 mmol) of bromobenzene in 2 mL of THF and 151.7 mg (6.24 mmol) of magnesium in 5 mL of THF was gradually added 160 mg (0.79 mmol) of compound **10** or **11** dissolved in 2 mL of THF at −20 °C over 30 min. The mixture was then allowed to reach room temperature. After stirring for 12 h, the reaction was quenched with saturated aqueous NH_4Cl (8 mL) at 0 °C. The product was separated and the aqueous phase extracted with Et_2O (3 × 8 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by the preparative TLC with petroleum (60–90 °C)/EtOAc (4:1, v/v) as the developing solvent to give the ligands **7** and **8**, respectively.

4.3. Diphenyl-(l-((1*S*)-phenylethyl)aziridin-(2*R*)-yl)-methanol 7

White solid, yield 81%, $[\alpha]_D^{20} = -50.4$ (*c* 0.660, $CHCl_3$). Mp 91.4–92.0 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 1.41 (d, *J* = 6.8 Hz, 3H), 1.52 (d, *J* = 6.4 Hz, 1H), 2.02 (d, *J* = 3.2 Hz, 1H), 2.48 (dd, *J* = 10, 3.6 Hz, 1H), 2.76 (q, *J* = 6.4 Hz, 1H), 3.82 (br, 1H), 6.88–7.36 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.0, 30.2 (CH_3), 45.5, 69.0, 73.9, 126.0, 126.2, 126.4, 126.9, 127.0, 127.2, 127.6, 128.0, 128.3, 143.5, 145.4, 146.9. IR (KBr pellet): 3356, 3084, 3027, 2969, 2854, 1599, 1491, 1449, 1356, 1170, 1028, 985, 932, 749, 697, 640. MS (ESI): calcd for $C_{23}H_{23}NO$ $(M+H)^+$: 330, found: 329.9. Anal. Calcd for $C_{23}H_{23}NO$: C, 83.85; H, 7.04; N, 4.25. Found: C, 83.75; H, 7.41; N, 4.221.

4.4. Diphenyl-(l-((1*S*)-phenylethyl)aziridin-(2*S*)-yl)-methanol 8

White solid, yield 93%, $[\alpha]_D^{20} = -49.0$ (*c* 0.502, $CHCl_3$). Mp 127.0–127.7 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 0.91 (d, *J* = 6.8 Hz, 3H), 1.60 (d, *J* = 6.4 Hz, 1H), 1.99 (d, *J* = 3.6 Hz, 1H), 2.55 (dd, *J* = 9.6, 3.6 Hz, 1H), 2.77 (q, *J* = 6.4 Hz, 1H), 4.14 (br, 1H), 7.25–7.39 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.5, 30.7, 47.4, 68.1, 73.9, 125.9, 126.7, 126.7, 127.15, 127.22, 128.0, 128.2, 128.4, 144.2, 144.9, 147.9. IR (KBr pellet): 3356, 3084, 3026, 2969, 2828, 1599, 1491, 1448, 1366, 1172, 1032, 991, 932, 748, 697, 642. MS (ESI): calcd for $C_{23}H_{23}NO$ $(M+H)^+$: 330, $(M+Na)^+$: 352, found: 329.9, 351.9. Anal. Calcd for $C_{23}H_{23}NO$: C, 83.85; H, 7.04; N, 4.25. Found: C, 83.68; H, 7.351; N, 4.225.

4.5. Enantioselective addition of diethylzinc to aldehydes

A solution of diethylzinc (1 M in *n*-hexane, 1.1 mL) was added to a solution of a chiral catalyst (0.025 mmol, 8.2 mg, 5 mol %) in dry toluene under a nitrogen atmosphere. The mixture was cooled to 0 °C and stirred for 30 min. A freshly distilled aldehyde (0.5 mmol) was added to the mixture. The resulting mixture was stirred for 10 h at 0–5 °C and then allowed to warm to room temperature, and stirred 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 preparative silica gel TLC plate afforded the corresponding products. The ee was determined by HPLC analyses using a chiral column.

4.6. X-ray crystallographic study[22]

White crystals of **7** (0.20 × 0.18 × 0.17) and **8** (0.20 × 0.18 × 0.16 mm) were selected and mounted on a glass fiber, respectively. Crystallographic data for **7** and **8** were measured on a Rigaku RAXIS-IV imaging plate area detector, respectively. The data were

collected at 291(2) K using graphite-monochromated Mo Kα (λ = 0.71073 Å), 1.07° < θ < 25.00° for **7** and 0.87° < θ < 25.00° for **8**, respectively. The structures were solved by a direct method, and expanded by using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. All calculations were performed using the teXsan crystallographic software package. Crystal data for **7**: triclinic P_1, a = 5.8386(12) Å, α = 92.43(3)°, b = 8.7672(18) Å, β = 91.28(3)°, c = 19.138(4) Å, γ = 106.83(3)°, V = 936.1(3) Å^3; formula unit $C_{23}H_{23}NO$ with Z = 2, D_{calcd} = 1.169 g cm^{-3}, F(0 0 0) = 352, μ(Mo Kα) = 0.071 mm^{-1}. Full-matrix least-squares refinement on F^2 based on 2988 independent reflections (R_{int} = 0.0000) converged with 460 parameters. Final R indices [$I > 2\sigma(I)$]: R_1 = 0.0534, wR_2 = 0.1382; R indices (all data): R_1 = 0.0601, wR_2 = 0.1452; GoF = 1.009. Crystal data for **8**: monoclinic C_2, a = 27.495(6) Å, α = 90.00(0)°, b = 5.92 63(12) Å, β = 113.02(3)°, c = 25.415(5) Å, γ = 90.00(0)°, V = 3811.3 (13) Å^3; formula unit $C_{23}H_{23}NO$ with Z = 8, D_{calcd} = 1.448 g cm^{-3}, F(0 0 0) = 1408, μ(Mo Kα) = 0.069 mm^{-1}. Full-matrix least-squares refinement on F^2 based on 5624 independent reflections (R_{int} = 0.0000) converged with 460 parameters. Final R indices [$I > 2\sigma(I)$]: R_1 = 0.0695, wR_2 = 0.1706; R indices (all data): R_1 = 0.0873, wR_2 = 0.1847; GoF = 1.089.

Acknowledgments

We are grateful to the National Natural Sciences Foundation of China (NNSFC: 20672102 and 20972140), and Henan Outstanding Youth Program (084100410001) for the financial support.

References

1. (a)*Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley: New York, 2000; (b)*Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; (c)*New Frontiers in Asymmetric Catalysis*; Mikami, K., Lautens, M., Eds.; Wiley: New Jersey, 2007.
2. Reviews on the preparation of both enantiomers: (a) Bartók, M. *Chem. Rev.* **2010**, *110*, 1663; (b) Tanaka, T.; Hayashi, M. *Synthesis* **2008**, 3361; (c) Mallat, T.; Orglmeister, E.; Baiker, A. *Chem. Rev.* **2007**, *107*, 4863; (d) Bartók, M. *Curr. Org. Chem.* **2006**, *10*, 1533; (e) Zanoni, G.; Castronovo, F.; Franzini, M.; Vidari, G.; Giannini, E. *Chem. Soc. Rev.* **2003**, *32*, 115; (f) Kim, Y. H. *Acc. Chem. Res.* **2001**, *34*, 955; (g) Sibi, M. P.; Liu, M. *Curr. Org. Chem.* **2001**, *5*, 719.
3. (a) Yan, X. X.; Peng, Q.; Li, Q.; Zhang, K.; Yao, J.; Hou, X. L.; Wu, Y. D. *J. Am. Chem. Soc.* **2008**, *130*, 14362; (b) Wu, W. Q.; Peng, Q.; Dong, D. X.; Hou, X. L.; Wu, Y. D. *J. Am. Chem. Soc.* **2008**, *130*, 9717; (c) Zeng, W.; Chen, G. Y.; Zhou, Y. G.; Li, Y. X. *J. Am. Chem. Soc.* **2007**, *129*, 750; (d) Kobayashi, S.; Horibe, M. *J. Am. Chem. Soc.* **1994**, *116*, 9805; (e) Anderson, J. C.; Cubbon, R. J.; Harling, J. D. *Tetrahedron: Asymmetry* **1999**, *10*, 2829; (f) Hoarau, O.; Aït-Haddou, H.; Daran, J.-C.; Cramailère, D.; Balavoine, G. G. A. *Organometallics* **1999**, *18*, 4718.
4. Kobayashi, S.; Ishitani, H. *J. Am. Chem. Soc.* **1994**, *116*, 4083.
5. (a) Reed, N. N.; Dickerson, T. J.; Boldt, G. E.; Janda, K. D. *J. Org. Chem.* **2005**, *70*, 1728; (b) Desimoni, G.; Faita, G.; Mella, M.; Boiocchi, M. *Eur. J. Org. Chem.* **2005**, 1020; (c) Gothelf, K. V.; Hazell, R. G.; Jøergensen, K. A. *J. Org. Chem.* **1998**, *63*, 5483; (d) Gothelf, K. V.; Hazell, R. G.; Jøergensen, K. A. *J. Org. Chem.* **1996**, *61*, 346; (e) Crosignani, S.; Desimoni, G.; Faita, G.; Filippone, S.; Mortoni, A.; Righetti, P. P.; Zema, M. *Tetrahedron Lett.* **1999**, *40*, 7007; (f) Kawamura, M.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 3213.
6. (a) Goodrich, P.; Hardacle, C.; Paun, C.; Parvulescu, V. I.; Podolean, I. *Adv. Synth. Catal.* **2008**, *350*, 2473; (b) Du, D. M.; Lu, S. F.; Fang, T.; Xu, J. X. *J. Org. Chem.* **2005**, *70*, 3712; (c) Lu, S. F.; Du, D. M.; Zhang, S. W.; Xu, J. *Tetrahedron: Asymmetry* **2004**, *15*, 3433; (d) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559; (e) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett.* **1996**, *37*, 3815.
7. Burguete, M. I.; Collado, M.; Escorihuela, J.; Luis, S. V. *Angew. Chem., Int. Ed.* **2007**, *46*, 9002.
8. Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669.
9. (a) Trost, B. M.; Fettes, A.; Shireman, B. T. *J. Am. Chem. Soc.* **2004**, *126*, 2660; (b) Zhou, J.; Ye, M.-C.; Huang, Z.-Z.; Tang, Y. *J. Org. Chem.* **2004**, *69*, 1309; (c) Perry, M. C.; Cui, X.; Powell, M. T.; Hou, D.-R.; Reibenspies, J. H.; Burgess, K. *J. Am. Chem. Soc.* **2003**, *125*, 113; (d) Sibi, M. P.; Gorikunti, U.; Liu, M. *Tetrahedron* **2002**, *58*, 8357.
10. (a) Schmidt, F.; Rudolph, J.; Bolm, C. *Adv. Synth. Catal.* **2007**, *349*, 703; (b) Wang, M.-C.; Wang, X.-D.; Ding, X.; Liu, Z.-K. *Tetrahedron* **2008**, *64*, 2559.
11. Wang, Z.-Q.; Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 5336.
12. (a) Wang, M.-C.; Wang, D.-K.; Zhu, Y.; Liu, L.-T.; Guo, Y.-F. *Tetrahedron: Asymmetry* **2004**, *15*, 1289; (b) Wang, M.-C.; Liu, L.-T.; Zhang, J.-S.; Shi, Y.-Y.; Wang, D.-K. *Tetrahedron: Asymmetry* **2004**, *15*, 3853; (c) Wang, M.-C.; Hou, X.-H.; Xu, C.-L.; Liu, L.-T.; Li, G.-L.; Wang, D.-K. *Synthesis* **2005**, 3620; (d) Wang, M.-C.; Zhao, W. X.; Wang, X.-D.; Song, M. P. *Synlett* **2006**, 3443; (e) Wang, M.-C.; Zhang, Q.-J.; Zhao, W. X.; Wang, X.-D.; Ding, X. *J. Org. Chem.* **2008**, *73*, 168; (f) Wang, M.-C.; Zhang, Q.-J.; Li, G.-W.; Liu, Z.-K. *Tetrahedron: Asymmetry* **2009**, *20*, 288; (g) Niu, J.-L.; Wang, M.-C.; Lu, L.-J.; Ding, G.-L.; Lu, H.-J.; Chen, Q.-T.; Song, M.-P. *Tetrahedron: Asymmetry* **2009**, *20*, 2616.
13. Wang, M.-C.; Liu, Z.-K.; Li, S.; Ding, X.; Li, Y.; Tang, M.-S. *Tetrahedron: Asymmetry* **2010**, *21*, 486.
14. (a) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1124; (b) Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 2054.
15. Bulman Page, P. C.; Allin, S. M.; Maddocks, S. J.; Elsegood, M. R. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, *36*, 2827.
16. L-Serine is commercially available at 50.32 RMB/g (25 g = 1258 RMB) while the corresponding D-enantiomer is at 6.64 RMB/g (1 kg = 6643 RMB) from Aldrich Chemical Company, 2007–2008.
17. (a) Tanner, D.; Kornø, H. T.; Guijarro, D.; Andersson, P. G. *Tetrahedron* **1998**, *54*, 14213; (b) Wang, M.-C.; Hou, X.-H.; Chi, C.-X.; Tang, M.-S. *Tetrahedron: Asymmetry* **2006**, *17*, 2126.
18. Lawrence, C. F.; Nayak, S. K.; Thijs, L.; Zwanenburg, B. *Synlett* **1999**, 1571.
19. Allinger, N. L.; Tribble, M. T. *Tetrahedron Lett.* **1971**, *12*, 3256.
20. (a) Quinkert, G.; Egert, E.; Griesinger, C. *Aspects of Organic Chemistry: Structure*; Verlag Helvetica Chimica Acta: Basel, 1996; (b) Juaristi, E. *Stereochemistry and Conformational Analysis*; John Wiley & Sons: New York, 1991; (c) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994.
21. Farooq, S.; Swain, W. E., Jr.; Daeppen, R.; Rihs, G. *Tetrahedron: Asymmetry* **1992**, *3*, 51.
22. Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication CCDC-817165 & 817166. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif.
23. Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823.
24. Reviews on enantioselective diethylzinc additions to aldehydes: (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49; (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833; (c) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757; (d) Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 92; (e) Zhu, H.-J.; Jiang, J.-X.; Ren, J.; Yan, Y.-M.; Pittman, C. U. *Curr. Org. Synth.* **2005**, *2*, 547; (f) Hatano, M.; Miyamoto, T.; Ishihara, K. *Curr. Org. Chem.* **2007**, *11*, 127.
25. Lauterwasser, F.; Nieger, M.; Mansikkamki, H.; Nttinen, K.; Bräse, S. *Chem. Eur. J.* **2005**, *11*, 4509.
26. Willems, J. G. H.; Hersmis, M. C.; de Gelder, R.; Smits, J. M. M.; Hamink, J. B.; Dommerholt, F. J.; Thijs, L.; Zwanenburg, B. *J. Chem. Soc., Perkin Trans. 1* **1997**, 963.
27. (a) Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 6327; (b) Yamakawa, M.; Noyori, R. *Organometallics* **1999**, *18*, 128.