Application of chiral 1,3-amino alcohols to asymmetric alkylation and arylation and the substituent effect on chirality control

（光学活性 1,3－アミノアルコールの不斉アルキル化、アリール化反応への応用と置換基によるキラリティーの制御）

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Abstract

This thesis reports the application of novel optically active 1,3-amino alcohols to catalytic asymmetric reactions and the substituent effect on the chirality control.

A series of novel optically active 1,3-amino alcohols have been synthesized from commercially available *cis*-(1*R*,2*S*)-2-benzamidocyclohexanecarboxylic acid, and showed moderate to good enantioselectivities in asymmetric addition of diethylzinc to aromatic aldehydes. Most interestingly, both enantiomers of a given product were obtained using the ligands with the same chirality. The results clearly showed that not only the enantioselectivity but also the stereochemistry of the product was controlled by the *N*-substituents and the substituents on the vicinity carbon to hydroxyl group; (1*R*,2*S*)-2-pyrrolidin-1'-ylcyclohexylmethanol showed the best promoting ability to aromatic aldehydes with (*R*)-selectivity (79.4% ee) in the chiral 1,3-amino alcohols studied. On the other hand (1*R*,2*S*)-2-benzylaminocyclohexyl(diphenyl)methanol showed the opposite (*S*)-selectivity (66.0% ee).

The optically active 1,3-amino alcohols have been also shown to catalyze the asymmetric arylation of aryl aldehydes using boronic acids as the source of transferable aryl groups, with good yields and moderate to high enantioselectivities (up to >99% ee). The results demonstrated that the substituents to the vicinity of hydroxyl group have a crucial effect on chirality control. The substituent effect of 1,3-amino alcohols was confirmed for all the aromatic aldehydes studied. Both enantiomers of a product could be obtained by using the ligands with the same chirality. In addition, a good linear correlation was observed between the enantioselectivity and the electronic propertiy of the substituents on a substrate (The stronger electron-withdrawing substituents on the *para*-position exhibited higher enantiomeric excess, while the stronger electron-donation substituents on the *para*-position showed lower selectivity).

Keywords chirality control, asymmetric alkylation, asymmetric arylation, 1,3-amino alcohols, *cis*-(1*R*,2*S*)-2-benzamidocyclohexanecarboxylic acid, aromatic aldehyde

List of Publications

- **Chirality control by substituents in the asymmetric addition of Et_2Zn to aromatic aldehydes catalyzed by *cis*-(1*R*,2*S*)-2-benzamidocyclohexanecarboxylic acid derived 1,3-amino alcohols**

  Xiang-Bo Wang; Koichi Kodama; Takuji Hirose; Guang-You Zhang

  Chin. J. Chem. **2010**, *28*, 61-68.

- **Chirality control by substituents in the enantioselective arylation of aromatic aldehydes catalyzed by *cis*-(1*R*,2*S*)-2-benzamidocyclohexanecarboxylic acid derived 1,3-amino alcohols**

  Xiang-Bo Wang, Koichi Kodama, Takuji Hirose, Xiao-Feng Yang, Guang-You Zhang

  Tetrahedron:Asymmetry **2010**, *21*, 75-80.

Abstract

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1. Asymmetric synthesis

1.1 Background

Chirality is one of the fundamental and intriguing aspects of life. The essential molecules in living organisms, such as amino acids, sugars, enzymes, peptides, even DNA, the blue-print for our whole body, are all chiral.[1] Although chiral substances are so important and widely distributed in nature, including our bodies, human did not realize them until Louis Pasteur conducted his famous experiments on the resolution of tartaric acids in 1848.[2] Slow progress was made during the next one hundred years. In the past two decades, however, the demands for enantiopure compounds dramatically increased because of not only their excellent performance but also the product liability in many fields, such as agrochemicals and pharmaceuticals.[3] In response to the need, the synthesis and application of various enantiopure compounds have been studied extensively.[4]

Although there are some enantiopure natural compounds which can be used by chemists, such as tartaric acid, abietic acid, cholesterol, they are not enough to satisfy a variety of demands for industry and scientific research. As a result, numerous methods to obtain enantiopure compounds have been developed. Generally, these methods can be categorized into two depending on the methodology: optical resolution and asymmetric synthesis.

Optical resolution was the first method found by chemists to obtain enantiopure compounds. This method involves preparation of the compounds in racemic forms and separation into the isomers.[5] One obvious disadvantage of optical resolution is that only 50% of the racemate can be obtained as a desired enantiomer theoretically. Corresponding to the yield limit of optical resolution, asymmetric synthesis is a good method to obtain enantiopure compounds. Three main approaches are included in “asymmetric synthesis”: chiral pool synthesis, chiral auxiliary method and asymmetric catalysis.

Chiral pool synthesis is attractive for target molecules having the similar chirality to the readily available enantiopure compounds, such as a chiral sugars or amino acids. However, the disadvantage is obvious: this approach requires a stoichiometric amount of a enantiopure starting material, which maybe rather expensive or difficult to isolate

from a natural source. In addition, to achieve the target molecules, long, tortuous synthetic steps may be unavoidable, which means large loss in chemical yield. Another approach, chiral auxiliary method also has to use a stoichiometric amount of enantiopure compound to introduce chirality in a racemic compound. After formation of a new stereocenter, the original auxiliary should be removed. Although high stereoselectivity can be achieved, the cost of chiral auxiliaries and additional synthetic steps still can not be avoided.

Compared to chiral pool synthesis and chiral auxiliary method, asymmetric catalysis is attractive because only small amount of enantiomerically pure substance is used to promote asymmetric reaction and afford a large amount of enantiopure product. Due to the obvious advantages, asymmetric catalysis has been developed extensively.[6] In 2003, a majority of the catalysts developed or studied, at least in the organic literatures, are asymmetric catalysts.[7]

Mostly, three different kinds of chiral catalysts are employed: chiral biocatalyst, chiral organocatalyst and chiral organometallic catalyst.

Asymmetric biocatalysis characterized by the use of isolated enzymes or integral cells profits from reduced processing steps and high selectivity.[8] Environmentally friendly is another speciality which makes biocatalysis attractive. Now, about 10% of the total drugs were synthesized by asymmetric biocatalysis.[9] Some disadvantages also exist. For example, isolated enzymes demand the supplementary addition of cost, and organic solvents are frequently toxic to the integral cells.[8b,9]

Chiral organocatalysts have an advantage than chiral organometallic catalysts: there is no need for metals in the catalytic system, thus making a contribution to green chemistry.[10] However, compared to chiral organocatalysts, chiral organometallic catalysts have more broad application because generally they are more tolerant to heating and various organic solvents. And the metal atoms, which chelated with chiral ligands, are more easy to coordinate to substrates to promote the catalytic reaction. All these chiral catalysts more or less have substrate specificity. As a result, suitable chiral catalysts having high enantioselectivity for a given substrate have to be found in asymmetric catalysis. In other words, all of these methods need to be developed because they are complementary to each other.

Among the asymmetric catalytic reactions, organozinc addition is one of the most important C-C bond formation reactions in organic synthesis.[11] Over the past two decades, organozinc addition, especially the asymmetric addition of dialkylzinc to aldehydes has been attracting much attention as a convenient method for the design of optically active secondary alcohols.[12] In the field of asymmetric addition, chirality inversion is an interesting question but has been discussed little. Generally, in order to obtain both enantiomers of a given product, both enantiomers of a chiral ligand are necessary. Recently it was reported that chirality inversion of the product could be achieved by the substituent effect of chiral ligands with the same framework.[13]

Previously, our group also obtained both enantiomers of a product by using the chiral 1,3-amino phenols with the same (*S*)-configuration in the study of asymmetric diethylzinc addition to aldehydes.[14] The results are very interesting because that it is important for the design of chiral ligands from certain starting materials in hand like natural products. So we continued the study on chirality inversion of a product by using chiral ligands with the same chirality. During our work on chiral 1,3-amino alcohols as ligands for asymmetric alkylation and arylation reactions of aldehydes, we found that some of our new ligands produced opposite chirality in spite of the same configuration of the chiral centers derived from the same framework. The transition state models were established based on the studies of the asymmetric addition of organozinc to aldehydes in the precence of chiral 1,2-amino alcohols by Noyori *et al*,[15] and were correctly predicted the absolute configuration of the products.[16] Later, other researches found the models were also applicable in the cases of 1,3-amino alcohols[17] and 1,4-amino alcohols[18]. Noyori's transition state models were widely used in the asymmetric addition of organozinc to aldehydes to explain the mechanim.[17-19]

1.2 Optically active amino alcohols as chiral ligands

1.2.1 Introduction

In catalytic asymmetric reactions, to achieve maximum chiral multiplication, chemists must create efficient catalysts. The catalysts are often provided with nitrogen or oxygen atoms, which can coordinate to metal atoms such as zinc or copper to form chiral organometallic catalysts. Since the pioneering work of Oguni and Omi for organozinc addition, an impressive number of chiral ligands have been developed. These chiral ligands include: amino alcohols,[20] amino phenols,[21] amides,[22] diamines[23] and diols[24]. In

some systems, the oxygen atoms of the chiral ligands were replaced by sulfur atoms to form amino thiols,[19a,25] sulfonamides.[13a,26] All of them showed high catalytic activity and stereoselectivity.

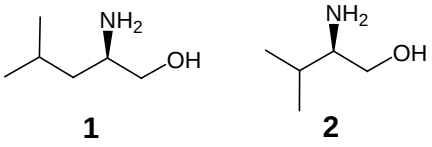
Among these ligands, special attention has been given to chiral amino alcols. They have been widely used in asymmetric synthesis[27] including the asymmetric addition of dialkylzinc to aldehydes,[11b,11c,28] catalytic asymmetric borane reduction of prochiral ketones,[27b,29] asymmetric hydrogen transfer from alcohols to ketones[30] and others.[31]

1.2.2 Application for asymmetric alkylation

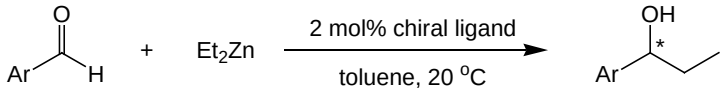
1.2.2.1 Application of 1,2-amino alcohols for asymmetric alkylation

Enantioselective addition of dialkylzinc reagents to aldehydes catalyzed by chiral amino alcohols is one of the most common and effective methods to prepare chiral secondary alcohols.[12]

In 1984, Oguni and Omi prepared chiral 1,2-amino alcohols **1** and **2** by the reduction of α-amino acid and used them as the catalysts for the addition of diethylzinc to benzaldehyde with moderate enantioselectivity (up to 49% ee).[32] Since then, many kinds of chiral 1,2-amino alcohols have been synthesized and applied in the reaction.[11b,11c,33]

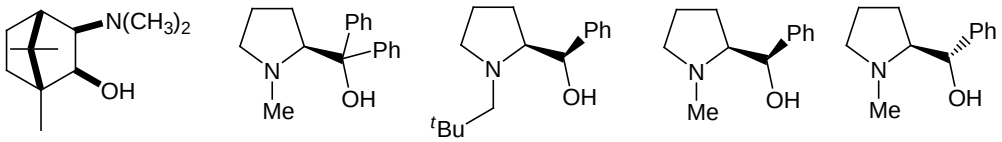


1 **2**



Scheme 1-1

In 1986, Noyori *et al.* reported highly enantioselective addition of organozinc to aromatic aldehydes. They used (-)-3-*exo*-(dimethylamino)isoborneol (DAIB) **3** to catalyze the reaction and obtained (*S*)-1-phenylpropanol in 98% yield with 99% ee.[34] In the case of aliphatic aldehyde (heptanal), moderate enantioselectivity (61% ee) was obtained.

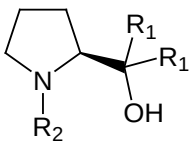


3 **4** **5** **6** **7**

Scheme 1-2

1,2-Amino alcohol derived from proline is useful framework for the design of chiral catalysts. Soai and co-workers synthesized a series of chiral pyrrolidinylmethanols from (*S*)-proline, **4**–**7**.[20a,35] They used 2 mol% of **5** as a chiral catalyst for the addition of diethylzinc to aldehydes and achieved up to 100% ee. In spite of the high yields (90%–100%) in all the cases, the enantioselectivities were found highly dependent on the structure of the chiral catalysts: 97% ee obtained when tertiary alcohol ligand **4** was used as a ligand, 72% ee was obtained when secondary alcohol ligand **6** was used, and 31% ee was obtained when secondary alcohol ligand **7** was used. In addition, the chiral ligands were also effective in the addition of diethylzinc to aliphatic aldehydes (up to 91% ee).[20a,36]

Since then, (*S*)-proline derived 1,2-amino alcohols were extensively used in various asymmetric catalytic reactions. In 1999, Yang *et al.* synthesized **8a**–**d**, and used 10 mol% of them as chiral ligands for the addition of diethylzinc to aldehydes and achieved up to 99.8% ee.[37]



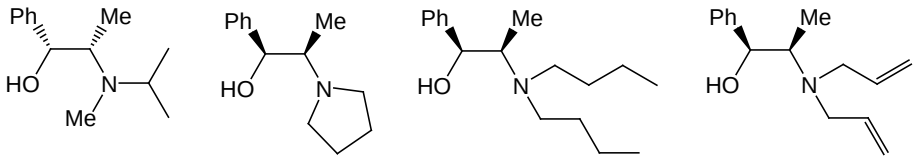
8a: R_1 = Me, R_2 = $PhCH_2$
8b: R_1 = Et, R_2 = $PhCH_2$
8c: R_1 = Ph, R_2 = $PhCH_2$
8d: R_1 = Me, R_2 = H

Scheme 1-3

Ephedrine and norephedrine are two important sources for chiral ligands. In 1987, Chaloner *et al.* found that, in the presence of ephedrine derived **9**, up to 80% ee counld be obtained for the diethylzinc addition to aromatic aldehydes.[38] In the case of aliphatic cyclohexanecarboxaldehyde, although only racemic product was obtained in low yield at that time, they improved the enantiomeric excess to 97% by using excess amount of diethylzinc (Et_2Zn : aldehyde = 4.5 : 1) three years later.[39]

The chiral *N*,*N*-dialkylnorephedrines, **10**–**12** synthesized by Soai *et al.* also showed high enantioselectivities in the dialkylzinc addition to aliphatic aldehydes and aromatic

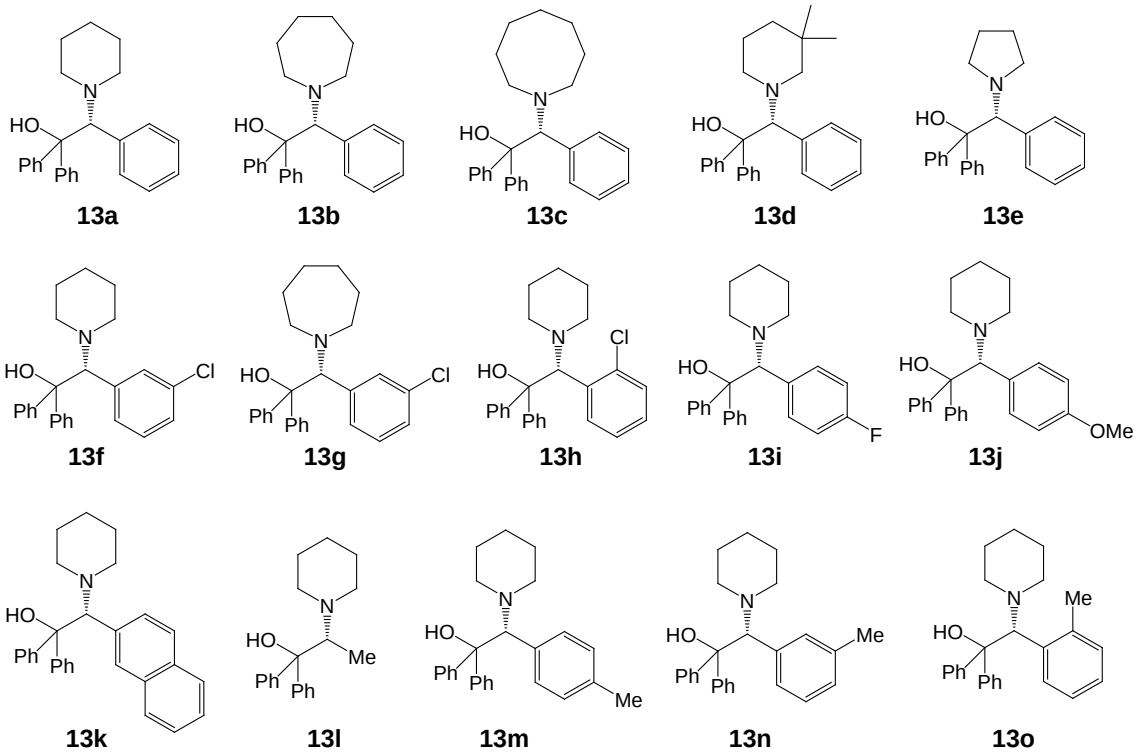
aldehydes (up to 95% ee).[11b,40]



9 **10** **11** **12**

Scheme 1-4

More rigid and bulky pyrrolidinyl or piperidinyl derivatives usually showed higher enantioselectivity in the asymmetric alkylation reactions. The amino alcohols **13a**–**13o** with cyclic tertiary amino groups were synthesized and used as chiral catalysts in the enantioselective addition of diethylzinc to aldehydes by Pericàs *et al.*[41] Among them, **13b** and **13g** showed higher enantioselectivity (up to 98%). Too big (**13c**) or too small (**13e**) *N*-substituents decreased the enantioselectivity.



13a **13b** **13c** **13d** **13e**

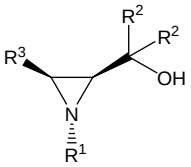
13f **13g** **13h** **13i** **13j**

13k **13l** **13m** **13n** **13o**

Scheme 1-5

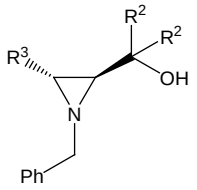
The 1,2-amino alcohols **14**–**16** with a chiral cyclopropane backbone were synthesized

by Tanner and Andersson's team in 1998. They were proved to be very efficient catalysts for the addition of diethylzinc reagents to aldehydes. When **14l** and **15b** were used as chiral catalyst in the asymmetric ethylation, enantioselectivity up to 90% ee was achieved.[42] The research showed that proper steric bulkiness is necessary to give higher enantioselectivity. That is why some ligands (**14c**, **14d**, **14k** & **15b**-**15e**) showed lower enantioselectivity, in spite that they have large substituents on the cyclopropane backbone to provide large steric bulkiness.



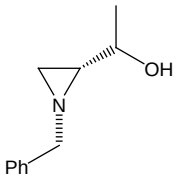
14a-**l**

14a: R^1 = Bn, R^2 = R^3 =H
14b: R^1 = Bn, R^2 = H, R^3 = Me
14c: R^1 = Bn, R^2 = R^3 = Me
14d: R^1 = Bn, R^2 = Ph, R^3 = Me
14e: R^1 = Ph_3C, R^2 = H, R^3 = Me
14f: R^1 = R^2 = H, R^3 = Me
14g: R^1 = R^3 = Me, R^2 = H
14h: R^1 = *n*-Bu, R^2 = H, R^3 = Me
14i: R^1 = *i*-Pr, R^2 = H, R^3 = Me
14j: R^1 = Bn, R^2 = H, R^3 = Ph
14k: R^1 = Bn, R^2 = Me, R^3 = Ph
14l: R^1 = Et, R^2 = H, R^3 = Ph



15a-**f**

15a: R^2 = H, R^3 = Me
15b: R^2 = Et, R^3 = Me
15c: R^2 = *i*-Pr, R^3 = Me
15d: R^2 = *c*-Hex, R^3 = Me
15e: R^2 = Ph, R^3 = Me
15f: R^2 = H, R^3 = Ph



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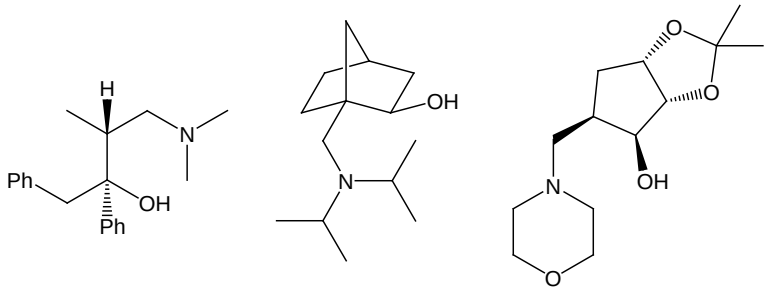
Scheme 1-6

1.2.2.2 Application of 1,3-amino alcohols for asymmetric alkylation

Compared to chiral 1,2-amino alcohol ligands, chiral 1,3-amino alcohol ligands have been studied relatively too less. Only a few examples of the application of chiral 1,3-amino alcohols to asymmetric alkylation have been reported until 2000.[43]

In 1987, Muchow *et al.* reported the first application of 1,3-aminol alcohol **17** in the enantioselective addition of diethylzinc to benzaldehyde. (*R*)-1-phenylpropan-1-ol was obtained in moderate yield and high enantioselectivity (87% ee).[44] In 1988, Oppolzer and Radinov devoleped a novel 1,3-aminol alcohol **18** from camphor-10-sulfonic acid. In the presence of 20 mol% **18**, diethylzinc reacted with benzaldehyde with 82% ee.[45] Cho and Kim found that 1,3-amino alcohol ligands **19** showed high enantioselectivities (up to 96% ee) and good yields for the diethylzinc addition to aromatic aldehydes and aliphatic aldehydes.[46]

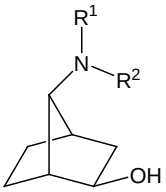


17 **18** **19**

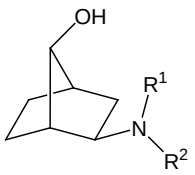
Scheme 1-7

Over the past decade, there has been increased interest in the application of 1,3-amino alcohols as chiral ligands for the enantioselective addition of dialkylzinc to aldehydes.[47]

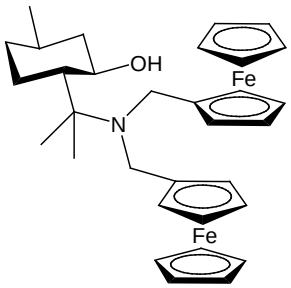
Oliveira and Costa synthesized some 1,3-amino alcohols with a norbornane framework, **20a-c**, and applied them in the enantioselective addition of diethylzinc to benzaldehyde with moderate to high enantioselectivities and yield (up to 99% yield, up to 91% ee).[48] Two years later, Costa *et al*. synthesized the norbornane derivatives **21a-c**, which showed moderate enantioselectivities (up to 78% ee) and good yields (84-98%) for the asymmetric alkylation of benzaldehyde.[49] Molina *et al*. synthesized a chiral ferrocenyl amino alcohol, **22**, which was found to catalyze the enantioselective ethylation of aldehydes to give secondary alcohols with high enantioselectivities (up to 95% ee) and good yields (up to 90%).[47a]



20a: $R^1 = R^2 = Et$
20b: $R^1 = Me$, $R^2 = Et$
20c: $R^1 = R^2 = Me$



21a: $R^1 = R^2 = Et$
21b: $R^1 = R^2 = Me$
21c: $R^1 = R^2 = -(CH_2)_2-$



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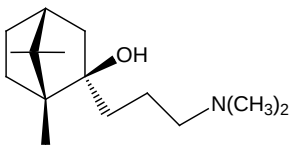
Scheme 1-8

1.2.2.3 Application of 1,4-amino alcohols for asymmetric alkylation

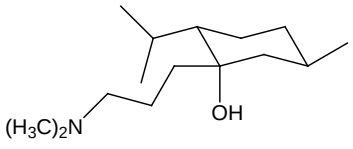
As mentioned above, a wide variety of amino alcohols, mainly 1,2-amino alcohols and occasionally 1,3-amino alcohols, have been reported as effective chiral catalysts for asymmetric alkylation of aldehydes. On the other hand, 1,4-amino alcohols have rarely

been reported.[50]

In 1997, Genov *et al.* made the first effort. They reported that two 1,4-amino alcohols, **23a** and **23b**, acted as ligands for the asymmetric addition of diethylzinc to aromatic aldehydes with up to 89% ee in 99% isolated yield.[44,51]



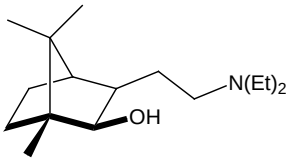
23a



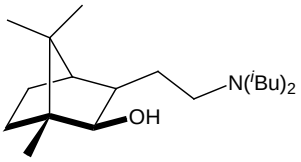
23b

Scheme 1-9

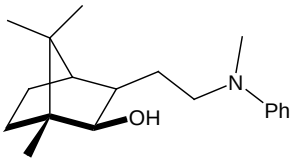
Knollmüller *et al.* synthesized a series of 1,4-amino alcohols **24a**-**24e**, and used them in the enantioselective addition of diethylzinc to benzaldehyde and hexanal. The products, chiral secondary alcohols, were obtained in good chemical yields and up to 87% enantiomeric excess.[52]



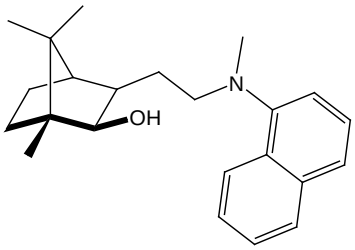
24a



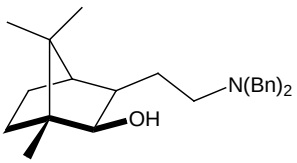
24b



24c



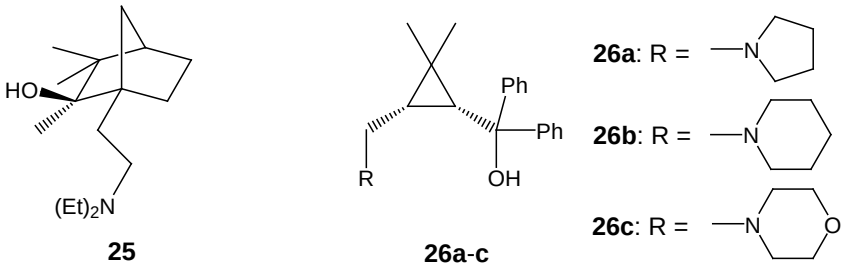
24d



24e

Scheme 1-10

Hanyu *et al.* developed the 1,4-amino alcohols **25**, which improved the enantioselectivity of the asymmetric ethylation of aromatic aldehydes up to 95% ee.[53]



Scheme 1-11

Zhong *et al.* developed a new series of amino alcohols with a chiral cyclopropane backbone, **26a-c**, which showed high enantioselectivities (up to 97% ee) in the addition of diethylzinc to aromatic and aliphatic aldehydes.[54]

1.2.2.4 Chirality inversion in asymmetric alkylation

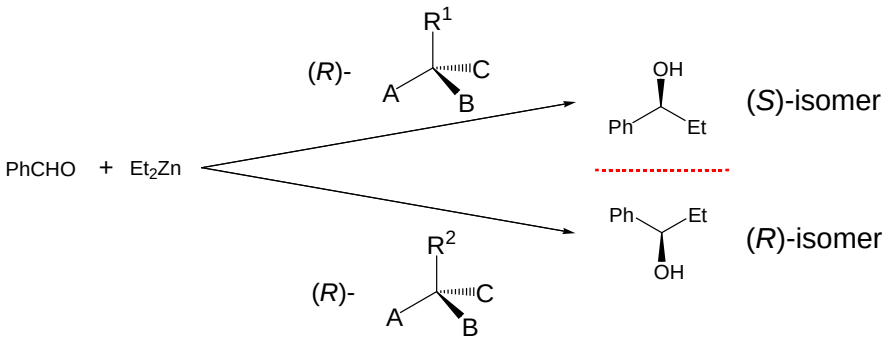
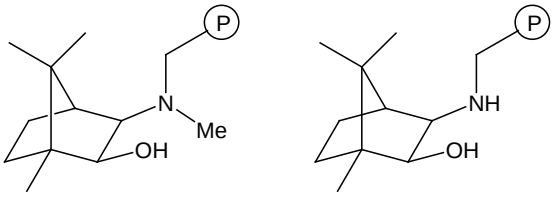


Figure 1-1. Both enantiomers from the ligands with the same chirality.

Chirality inversion caused by the substituent effect of the ligands with the same chirality is an interesting and relatively new topic in asymmetric catalysis (Figure 1-1). It was first observed by Itsuno and Fréchet in 1987. They synthesized the polymer-supported chiral 1,2-amino alcohols including **27a** and **27b** (Scheme 1-12), and used them as chiral ligands in the enantioselctive addition of diethylzinc to benzaldehyde. In the case of **27a** (*S*)-1-phenylpropanol was obtained in 92% ee, however, in the case of **27b** (*R*)-1-phenylpropanol was obtained in 10% ee.[55]

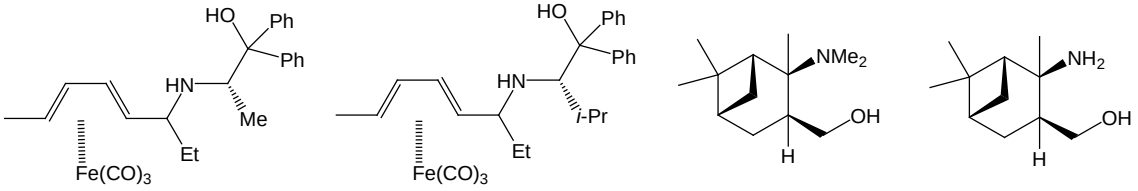
Since then, although the phenomenon has been observed by some other researchers several times, it has been less discussed for a decade.



27a **27b**

Scheme 1-12

In 2001, Okamoto *et al.* obtained both (*R*)- and (*S*)-products in 84% ee and 70% ee, respectively, using their iron tricarbonyl complexes of 1,2-amino alcohols, **28a** and **28b** (Scheme 1-13).[56]



28a **28b** **29a** **29b**

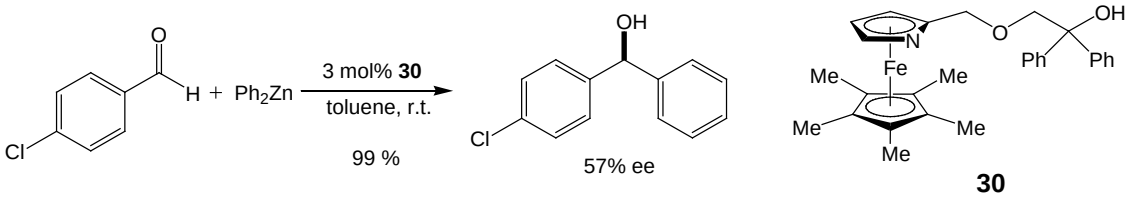
Scheme 1-13

In 2006, Szakonyi *et al.* also obtained both enantiomers of the product in 72% ee and 40% ee, respectively, using their α-pinene derived 1,3-amino alcohols, **29a** and **29b** (Scheme 1-13).[57]

1.2.3 Application for asymmetric arylation

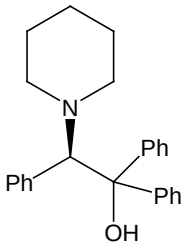
Recently asymmetric arylation towards enantiopure diarylmethanols has become increasingly important, as reflected by the number of publications on this topic during the last 10 years.[58] Chiral amino alcohols have also shown high catalytic ability in the reaction.[59]

In 1997, Fu *et al.* synthesized a chiral ferrocenyl amino alcohol, **30**, and used it to catalyze the diphenylzinc addition to 4-chlorobenzaldehyde. The diarylmethanol was obtained in 99% yield and 57% ee. This is the first attempt of catalytic asymmetric arylation.[58a]



Scheme 1-14

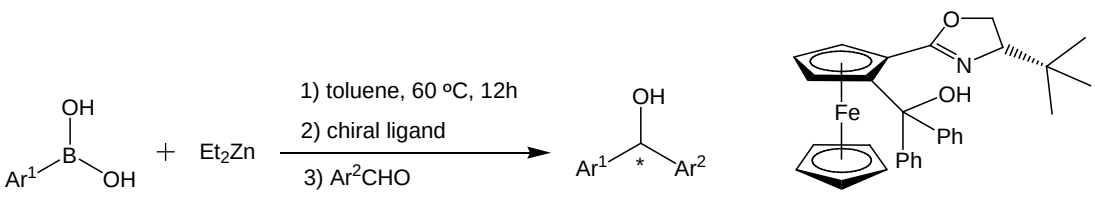
In 2004, Pericàs *et al.* found chiral 1,2-amino alcohol **31** showed high enantioselectivities for the diphenylzinc addition to aromatic aldehydes (up to 98% ee) and aliphatic aldehydes (up to 97% ee).[60]



31

Scheme 1-15

Another approach to the synthesis of diarylmechanol has been recently developed by Bolm *et al.* (Scheme 1-16). They used arylboronic acids as the source of the transferable aryl groups. Compared with the diarylzinc or diaryzinc-diethylzinc system, this new method made the preparation of diarylzinc reagents with various substituents more convenient and inexpensive. In the presence of 10 mol% of **32**, the catalytic asymmetric arylation of aromatic aldehydes was easily performed and yielded a broad range of products with excellent enantioselectivities (up to 98% ee).[58b]



32

Scheme 1-16

The interesting character of Bolm's new approach is that, in the precence of the same

chiral ligand, both enantiomers of a target diarylmethanol can be obtained by interchanging the substituents of the two reactants, arylboronic acids and aldehyde (Table 1-1 & Figure 1-2).

Table 1-1. Asymmetric arylation of aldehydes in the presence of **32**.[58b]

Entry	Chiral ligand (10 mol%)	Ar^1	Ar^2	Yield (%)[b]	ee (%)[c]	Config.[d]
1	**32**	4-ClPh	Ph	89	95	*S*
2	**32**	Ph	4-ClPh	95	92	*R*
3	**32**	4-MePh	Ph	87	89	n.d.
4	**32**	Ph	4-MePh	88	90	n.d.

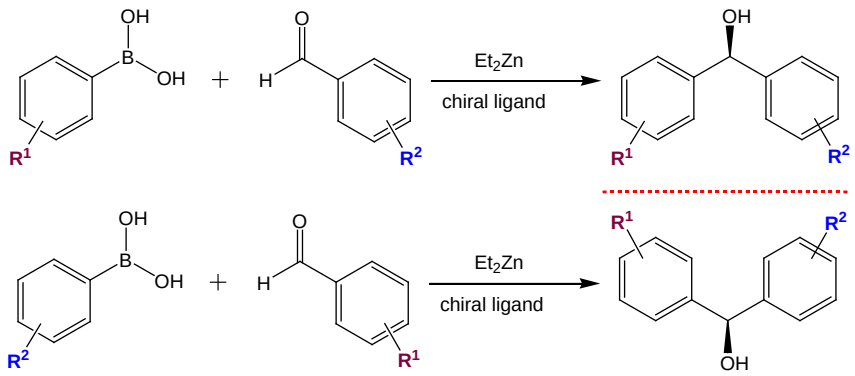
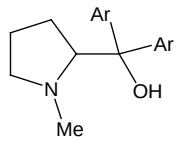
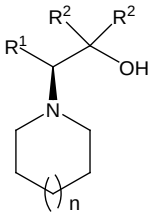


Figure 1-2. Both enantiomers from the same ligand.[58b]

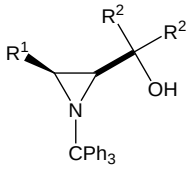
In 2005, (*S*)-proline derived 1,2-amino alcohols **33a-c** were applied in zinc-catalyzed addition of arylboronic acids to aromatic aldehydes by Braga *et al.*[61] The reaction was found to proceed in excellent yields and high enantioselectivities (up to 98% ee). In the same year they synthesized 1,2-amino alcohols **34a-h** and investigated the effects of the catalyst structure to enantioselectivity of asymmetric arylation. Bearing a 5-membered cyclic *N*-substituent, ligand **34f** was identified as the most effective chiral ligand, which made the asymmetric arylation proceed in excellent yields and high enantioselectivities (up to 97% ee).[62] In 2007, they synthesized the aziridine-2-methanols, **35a-c**, derived from serine and used as chiral ligands in the asymmetric aryaltion. They found the reaction is drastically accelerated under microwave irradiation without loss of enantioselectivity (up to 98% ee).[63]



33a: Ph
33b: 4-MePh
33c: 4-ClPh



34a: R^1 = Bn, R^2 = Ph, n=1
34b: R^1 = Bn, R^2 = Et, n=1
34c: R^1 = Bn, R^2 = Me, n=1
34d: R^1 = Bn, R^2 = H, n=1
34e: R^1 = Bn, R^2 = Et, n=1
34f: R^1 = *i*-Pr, R^2 = Et, n=0
34g: R^1 = *s*-Bu, R^2 = Et, n=1
34h: R^1 = *i*-Bu, R^2 = Et, n=1

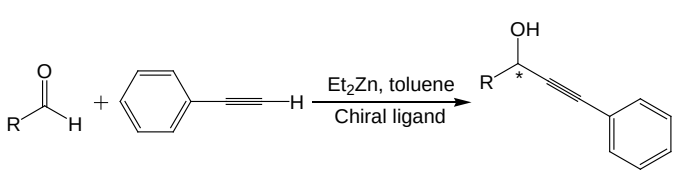


35a: R^1 = H, R^2 = Ph
35b: R^1 = H, R^2 = Et
35c: R^1 = Me, R^2 = Ph

Scheme 1-17

1.2.4 Application for asymmetric alkynylation

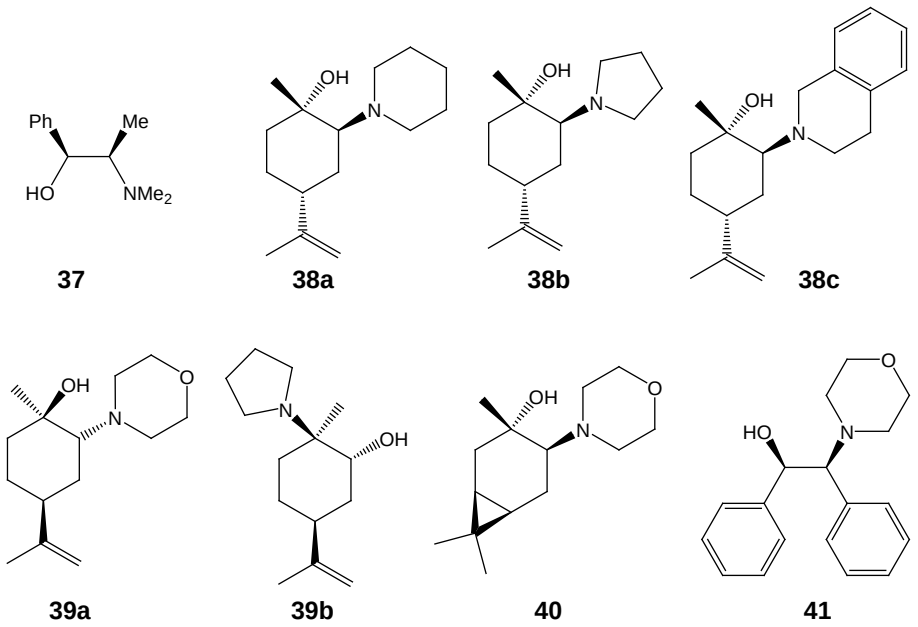
As an effective way to synthesize optically active propargylic alcohols, great progress has been made in the asymmetric alkynylation of aldehydes using chiral amino alcohol ligands.[64] In 1994, Ishizaki and Hoshino used the tridentate amino alcohols **36a-c** to catalyze the enantioselective addition of phenylacetylene to aldehydes with good yields and high enantioselectivities (up to 95% ee for aromatic aldehydes, and up to 91% ee for aliphatic aldehydes).[64a]



36a: Ar = *α*-Naphthyl
36b: Ar = β-Naphthyl
36c: Ar = Ph

Scheme 1-18

Recently Carreira *et al.* developed a new methodology by using $Zn(OTf)_2$ instead of Et_2Zn. It was more efficient and provided higher asymmetric inductions for a wider range of aldehydes and alkynes (up to 99% ee). However, in order to achieve maximum chiral multiplication, they used 0.22~1.2 eq. of (+)-*N*-methylephedrine **37** as a chiral ligand.[65]



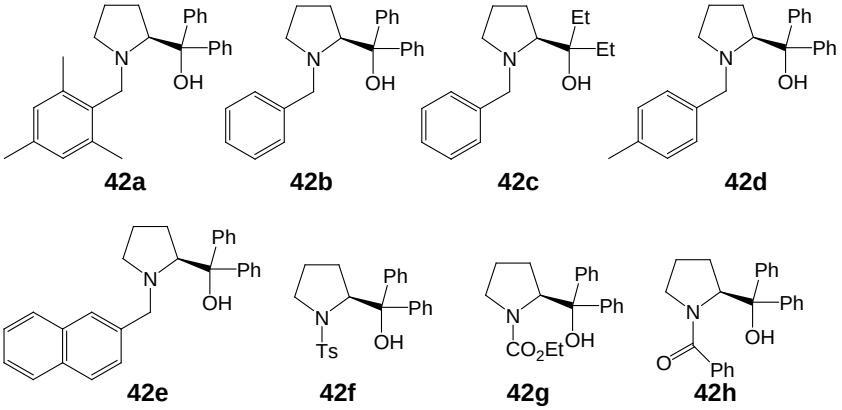
37 **38a** **38b** **38c**

39a **39b** **40** **41**

Scheme 1-19

Singaram *et al.* synthesized a series of terpene derived 1,2-amino alcohols. They used 10 mol% **37**-**41** to catalyze the asymmetric alkynylation reaction using a terminal alkyne and diethylzinc. Chiral propargylic alcohols were obtained in good yields and moderate enantioselectivities (up to 69% ee).[66]

In 2009, Zhang *et al.* reported that a series of (*S*)-proline derived 1,2-amino alcohols, **42a**-**h**, showed moderate to good enantioselectivity in the catalytic asymmetric alkynylation of aldehydes. Most interestingly, although these ligands have the same chirality, configuration change of the products was observed (Fig. 3). Zhang *et al.* mentioned that the presence of another coordinative spite, oxygen atom in C=O, might result in complicated coordination, which led to different configurations of the products.[67]



Scheme 1-20

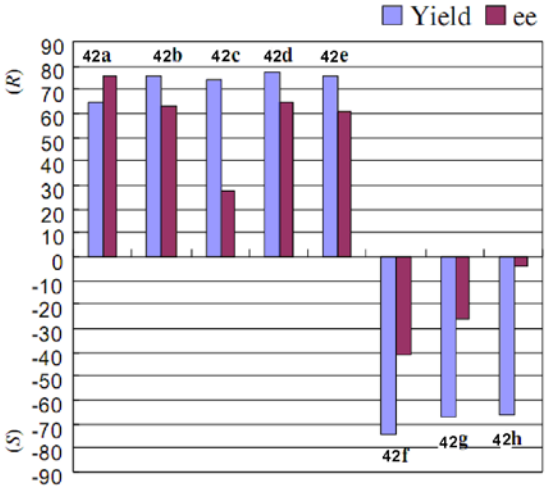


Figure 1-3. Yields and ees of the product catalyzed by **42a-42h.**

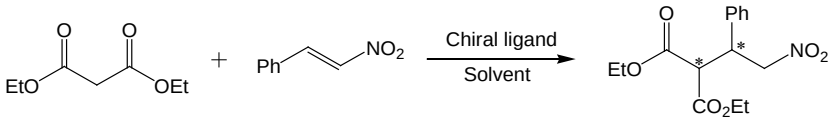
1.2.5 Application for asymmetric Michael addition

Michael addition reaction is one of the most important C–C bond formation reactions in organic synthesis.[68] Great efforts have been made to develop efficient chiral catalysts for the reaction. Although chiral amino acids, especially (*S*)-proline, were frequently used as chirality sourses to synthesize new chiral catalysts, chiral amino alcohols have been less recoganized until recent years.

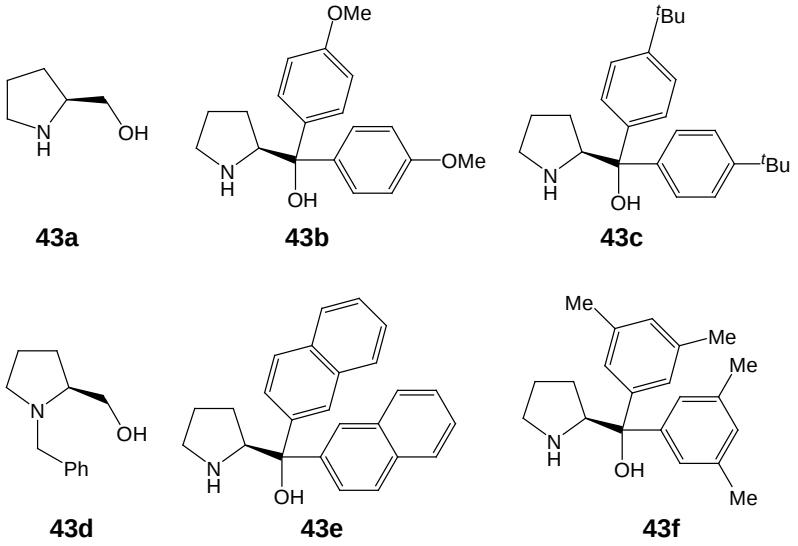
In 2006, Lattanzi used (*S*)-proline derived 1,2-amino alcohols **43a-f** for the enantioselective Michael addition of malonate to nitroolefin (Scheme 1-21), and found **43f** was an efficient bifunctional chiral catalyst, which gave good yields and selectivities up to 56% ee. The 1,2-amino alcohol activated malonate by the secondary

amino group, and its hydroxyl group oriented nitroolefin in close proximity through hydrogen bonding interaction as shown in Figure 1-4.[69]

Zhong *et al.* reported that (*S*)-prolinol, **43a**, catalyzed the asymmetric Michael addition of cyclohexanone to nitroolefins in the presence between benzoic acid to afford Michael adducts with high diastereoselectivity (87:13 – >99:1) and enantioselectivity (82–96% ee).[70]



Scheme 1-21



43a **43b** **43c**

43d **43e** **43f**

Scheme 1-22

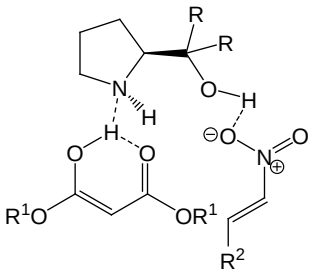
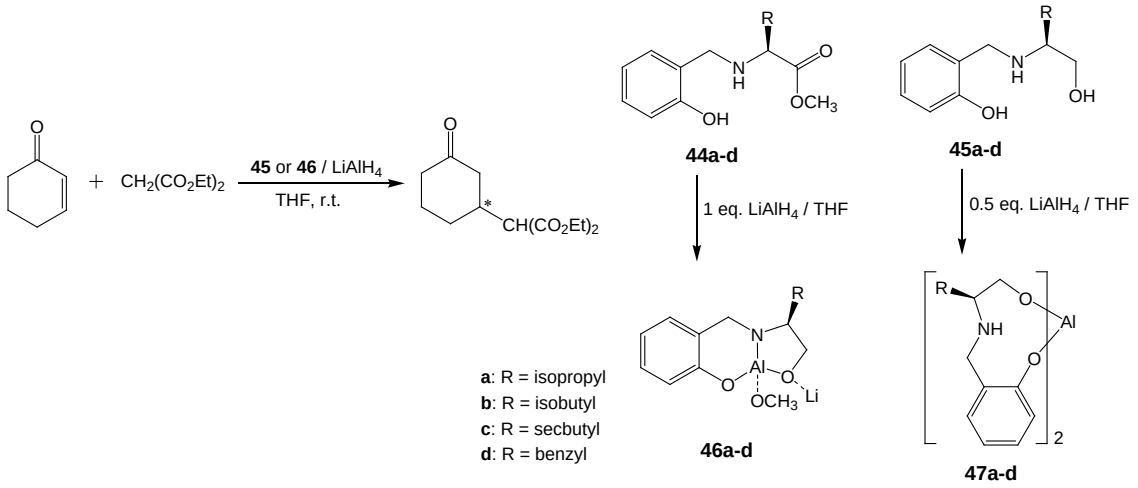


Figure 1-4. Proposed bifunctional model of Michael addition of malonate to nitroolefin catalyzed by **43**.

Narasimhan *et al.* reported that catalysts **44a-d** and **45a-d** showed the opposite enantioselectivity in Michael addition reactions between cyclic enones and malonates resulting in the production of both entiomers of the products in good chemical and optical yields. They discovered that two different types of complexes, **46a-d** and **47a-d** were formed from the ^{27}Al NMR studies. When **46a-d** were used in the asymmetric Michael addition reaction of diethyl malonate to cyclohexane, the (*S*)-product was obtained with moderate enantioselectivity (up to 95% ee). When **47a** was used (*R*)-product was obtained with 60% ee.[71]



Scheme 1-23

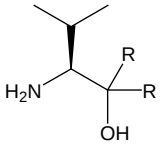
1.2.6 Application for asymmetric aldol reaction

Asymmetric aldol reaction is another fundamental synthetic tool for the construction of C-C bond. However, chiral amino alcohols have not been used as chiral ligands in the reactions until Zhong *et al.* reported the first amino alcohol catalyzed direct asymmetric aldol reaction in 2004.[72] In the presence of 35 mol% (*S*)-prolinol (**43a**), unmodified fluoroacetone reacted with various aldehydes with moderate to high diastereoselectivity (1:4 – >20:1) and enantioselectivity (79–87% ee).

Scheme 1-24

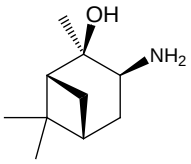
1.2.7 Application for asymmetric reduction reaction

As an important method to synthesize enantiomerically pure secondary alcohols, the asymmetric reduction of prochiral ketones with a reductant, especially borane, in the presence of a chiral ligand has been extensively studied. [29,73]



48a: R = Ph
48b: R = 4-MeO-Ph
48c: R = 4-F-Ph
48d: R = *n*-C_4H_9
48e: R = *n*-$C_{10}H_{21}$
48f: R = *i*-C_4H_9

Scheme 1-25



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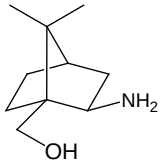

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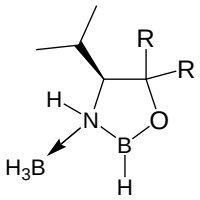
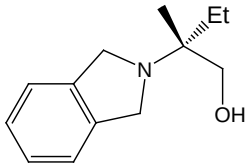


Figure 1-5. Corey's oxazaborolidine.

Corey *et al.* investigated the 1,2-amino alcohol-BH_3·THF system and elucidated the mechanism of asymmetric reduction in 1987.[74] First, borane reacts with amino and hydroxyl groups to form Corey's oxazaborolidine (Figure 1-5), which catalyzes the attack of hydride to ketone substrates. In 1995, Einhorn and Luche used 1,2-amino alcohols, **48a-f**, derived from L-valine as chiral ligands in the asymmetric reductions of ketones. After structural modification, they found **48c** is an efficient chiral ligand, which gave 93% ee and 100% yield for acetophenone, 72% ee and 85% yield for aliphatic cyclohexylmethylketone.[75] Recently, Laschat *et al.* used chiral 1,2-amino alcohol **49**, derived from (-)-α-pinene, to catalyze asymmetric borane reduction of arylketones with good yields and up to 96% ee.[29] Yeung and Yang's team reported that chiral 1,3-amino alcohol **50** showed moderate to high enantioselectivities (up to 91%) and good chemical yields (90-100%) in the asymmetric borane reduction of prochiral ketones.[76] These studies showed that chiral 1,3-amino alcohol-BH_3·THF system worked as effective catalytic system for the asymmetric reduction of a wider range of prochiral ketones.



52

Scheme 1-26

In 1991, on the other hands, Brown *et al.* developed a different system using chirality modified aluminium lithium hydride. They treated $LiAlH_4$ with 2 equivalents of **51**, a readily available chiral 1,2-amino alcohol, then reduced 2-chloro- and 2,4-dimethyl-benzophenones into the corresponding diarylalcohols with up to 100% ee.[77]

1.3 Aim of the thesis

In this thesis we report the synthesis of a series of 1,3-amino alcohools from *cis*-(1*R*,2*S*)-2-benzamidocyclohexanecarboxylic acid and *trans*-(1*R*,2*R*)-2-benzamido-cyclohexanecarboxylic acid and their application to catalatic asymnmetric alkylation and arylation of aldehydes. In addition, we investigate the substituent effect of the 1,3-amino alcohols on chirality control for these reactions. The substituents near chiral center have anticipated effect on chirality inversion. When the number and the size of *N*-substituents or the substituents to the vicinity of hydroxyl group are changed, not only the enantiomeric excess, but also the absolute configuration of the addition product can be changed.

1.4 References

1. (a) Feringa, B. L.; Wynberg, H. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 3418–3438; (b) Thomas, R. *Through the looking-glass, Plus*, Millennium Mathematics Project, University of Cambridge, **2003**, http://plus.maths.org/issue24/features/symmetry/.
2. MacMurry, *J. Organic Chemistry* (6th, Ed.), Thomson Brooks/Cole, **2003**, p. 281–282.
3. (a) Kurihara, N.; Miyamoto, J.; Paulson, G. D.; Zeeh, B.; Skidmore, M. W.; Hollingworth, R. M.; Kuier, H. A. *Pure & Appl. Chem.* **1997**, *69*, 1335–1348; (b) Kodama, S.; Saito, Y.; Chinaka, S.; Yamomoto, A.; Hayakawa, K. *J. Health. Sci.* **2006**, *52*, 489–494.
4. (a) Barker, A. *J. Mol. Catal. A: Chem.* **1997**, *115*, 473–493; (b) Kurihara, N.; Miyamoto, J. *Chirality in Agrochemicals*, **1998**, ISBN: 0-471-98121-4; (c) Williams,

A. *Pesiic. Sci.* **1996**, *46*, 3–9; (d) Francotte, E.; Lindner, W. *Chirality in Drug Research*, **2006**, ISBN: 3-527-31076-2.

5. Kato, Y.; Kitamoto, Y.; Morohashi, N.; Kurama, Y.; Oi, S.; Sakai, K.; Hattori, T. *Tetrahedron Lett*. **2009**, *50*, 1998–2002.
6. (a) William, H. P. *Pure & Appl. Chem.* **1991**, *63*, 1119–1122; (b)Thomas, B. *Current Opinion in Solid State and Materials Science*, **1999**, Vol. 4, Issue 1, p. 85–96; (c) Saluzzo, C.; Halle, R.; Touchard, T.; Fache, F.; Schulz, E.; Lemaire, M. *J. Organomet. Chem*. **2000**, *609*, 30–39; (d) Denmark, S. E.; Fu, J. P. *Chem. Rev*. **2003**, *103*, 2763–2793; (e) Miller, J. J.; Rajaram, S.; Pfaffenroth, C.; Sigman, M. S. *Tetrahedron* **2009**, *65*, 3110–3119.
7. Bolm, C.; Gladysz, J. A. *Chem. Rev*. **2003**, *103*, 2761–2762.
8. (a) Patel, R. N. *Coord. Chem. Rev.* **2008**, *252*, 659–701; (b) Bräutigam, S.; Dennewald, D.; Schürmann, M.; Lutje-Spelberg, J.; Pitner, W.-R.; Weuster-Botz, D. *Enzyme and Microbial Technology,* **2009**, *45*, 310–316.
9. Matsuda, T.; Yamanaka, R.; Nakamura, K. *Tetrahedron: Asymmetry* **2009**, *20*, 513–557.
10. Polshettiwar, V.; Varma, R. S. *Tetrahedron* **2009**, DOI: 10.1016/j.tet.2009.11.015, in press.
11. (a) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833–856; (b) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757–824; (c) Da, C.-s.; Ni, M.; Han, Z.-j.; Yang, F.; Wang, R. *J. Mol. Catal. A: Chem.* **2006**, *245*, 1–7.
12. (a) Ananthi, N.; Balakrishnan, U.; Vinu, A.; Ariga, K.; Velmathi, S. *Tetrahedron: Asymmetry* **2009**, *20*, 1731–1735; (b) Richmond, M. L.; Seto, C. T. *J. Org. Chem.* **2003**, *68*, 7505–7508; (c) Paixao, M. W.; Godoi, M.; Rhoden, C. R. B.; Westermann, B.; Wessjohann, L. A.; Lüdtke, D. S.; Braga, A. L. *J. Mol. Catal. A: Chem.* **2007**, *261*, 120–124.
13. (a) You, J. S.; Shao, M. Y.; Gau, H. M. *Tetrahedron: Asymmetry* **2001**, *12*, 2971–2975; (b) Cicchi, S.; Crea, S.; Goti, A.; Brandi, A. *Tetrahedron: Asymmetry* **1997**, *8*, 293–301.
14. Yang, X.-F.; Wang, Z.-H.; Koshizawa, T.; Yasutake, M.; Zhang, G.-Y.; Hirose, T. *Tetrahedron: Asymmetry* **2007**, *18*, 1257–1263.
15. (a) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc*. **1989**, *111*, 4028–4036; (b) Jessop, P. G.; Brown R. A.; Yamakawa, M.; Xiao, J., Ikariya, T.; Kitamura, M.; Tucker, S. C.; Noyori, R. *J. Supercrit. Fluids* **2002**, *24*, 161–172.
16. (a) Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 6327–6335; (b) Yamakawa, M.; Noyori, R. *Organometal.* **1999**, *18*, 128–133.

17. Panda, M.; Phuan, P.-W.; Kozlowski, M. C. *J. Org. Chem.* **2003**, *68*, 564–571.
18. Scarpi, D.; Occhiato, E. G.; Guarna, A. *Tetrahedron: Asymmetry* **2009**, *20*, 340–350.
19. (a) Gibson, C. L. *Tetrahedron: Asymmetry* **1999**, *10*, 1551–1561; (b) Burguete, M.I.; Escorihuela, J.; Luis, S. V.; Ujaque, G. *Tetrahedron* **2008**, *64*, 9717–9724; (c) Huang, W.-S.; Pu, L. *Tetrahedron Lett.* **2000**, *41*, 145–149.
20. (a) Soai, K.; Ookawa, A.; Ogawa, K. *J. Am. Chem. Soc.*, **1987**, *109*, 7111–7115; (b) Dai, W.-M., Zhu, H.-J.; Hao, X.-J.; *Tetrahedron: Asymmetry* **2000**, *11*, 2315–2337; (c) Rasmussen, T.; Norrby, P.-O. *J. Am. Chem. Soc.* **2001**, *123*, 2464–2465; (d) Parrott II., R. W.; Hitchcock, S. R. *Tetrahedron: Asymmetry* **2008**, *19*, 19–26.
21. (a) Yang, X.-F.; Hirose, T.; Zhang, G.-Y. *Tetrahedron: Asymmetry* **2007**, *18*, 2668–2673; (b) Szatmári, I.; Sillanpää, R.; Fülöp, F. *Tetrahedron: Asymmetry* **2008**, *19*, 612–617.
22. Blay, G.; Fernández, I.; Marco-Aleixandre, A.; Pedro, J. R. *Tetrahedron: Asymmetry* **2005**, *16*, 1207–1213.
23. (a) Asami, M.; Inoue, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1687–1690; (b) Saravanan, P.; Bisai, A.; Baktharaman, S.; Chandrasekhar, M.; Singh, V. K. *Tetrahedron* **2002**, *58*, 4693–4706; (c) Cheng, Y.-Q.; Bian, Z.; Kang, C.-Q.; Guo, H.-Q.; Gao, L.-X. *Tetrahedron: Asymmetry* **2008**, *19*, 1572–1575.
24. (a) Olsson, C.; Friberg, A.; Frejd, T. *Tetrahedron: Asymmetry* **2008**, *19*, 1476–1483; (b) Dean, M. A.; Hitchcock, S. R. *Tetrahedron: Asymmetry* **2008**, *19*, 2563–2567; (c) Gou, S., Judeh, Z. M. A. *Tetrahedron Lett.* **2009**, *50*, 281–283.
25. Andersen, J. C.; Harding, M. *Chem. Commun.* **1998**, 393–394.
26. Grach, G.; Reboul, V.; Metzner, P. *Tetrahedron: Asymmetry* **2008**, *19*, 1744–1750.
27. (a) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835–876; (b) Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1986–2012.
28. L. Pu, *Tetrahedron* **2003**, *59*, 9873–9886.
29. Hobuβ, D.; Baro, A.; Laschat, S.; Frey, W. *Tetrahedron* **2008**, *64*, 1635–1640.
30. Brandt, P.; Roth, P.; Andersson, P. G. *J. Org. Chem.* **2004**, *69*, 4885–4890.
31. (a) Kano, T.; Ueda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 3728–3729; (b) Xu, X.-H.; Qiu, X.-L.; Qing, F.-L. *Tetrahedron* **2008**, *64*, 7353–7361; (c) Biradar, D. B.; Gau, H.-M. *Tetrahedron: Asymmetry* **2008**, *19*, 733–738.
32. Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823–2824.
33. Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49–69.
34. Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071–6072.
35. (a) Soai, K.; Ookawa, A. *J. Chem. Soc., Chem. Commun.* **1986**, 412–413; (b)

Ookawa, A.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1465–1471.
36. Soai, K.; Ookawa, A.; Ogawa, K.; Kaba, T. *J. Chem. Soc., Chem. Commun.* **1987**, 467–468.
37. Yang, X.; Shen, J.; Da, C.; Wang, R.; Choi, M. C. K.; Yang, L.; Wong, K.-Y. *Tetrahedron: Asymmetry* **1999**, *10*, 133–138.
38. Chaloner, P. A.; Perera, S. A. R. *Tetrahedron Lett.* **1987**, *28*, 3013–3014.
39. Chaloner, P. A.; Langadianou, E. *Tetrahedron Lett.* **1990**, *31*, 5185–5188.
40. Soai, K.; Yokoyama, S.; Hayasaka, T.; Ebihara, K. *J. Chem. Soc.* **1988**, *53*, 4149–4151.
41. Rodríguez-Escrich, S.; Reddy, K. S.; Jimeno, C.; Colet, G.; Rodríguez-Escrich, C.; Solá, L.; Vidal-Ferran, A.; Pericàs, M. A. *J. Org. Chem.* **2008**, *73*, 5340–5353.
42. Tanner, D.; Kornø, H. T.; Guijarro, D.; Andersson, P. G. *Tetrahedron* **1998**, *54*, 14213–14232.
43. (a) Hulst, R.; Heres, H.; Fitzpatrick, K.; Peper, N. C. M. W.; Kellogg, R. M. *Tetrahedron: Asymmetry* **1996**, *7*, 2755–2760; (b) Genov, M.; Kostova, K.; Dimitrov, V. *Tetrahedron: Asymmetry* **1997**, *8*, 1869–1876.
44. Muchow, G.; Vannoorenberghe, Y.; Buono, G. *Tetrahedron Lett.* **1987**, *28*, 6163–6167.
45. Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett.* **1988**, *29*, 5645–5648.
46. Cho, B. T.; Kim, N. *Tetrahedron Lett.* **1994**, *35*, 4115–4118.
47. (a) Vilaplana, M. J.; Molina, P.; Arques, A.; Andrés, C.; Pedrosa, R. *Tetrahedron: Asymmetry* **2002**, *13*, 5–8; (b) Panev, S.; Linden, A.; Dimitrov, V. *Tetrahedron: Asymmetry* **2001**, *12*, 1313–1321; (c) Engel, T. C.; Maroto, B.; Martínez, A. G.; Cerero, S. M. *Tetrahedron: Asymmetry* **2008**, *19*, 2003–2006; (d) Olsson, C.; Helgesson, S.; Frejd, T. *Tetrahedron: Asymmetry* **2008**, *19*, 1484–1493.
48. Oliveira, L. F.; Costa, V. E. U. *Tetrahedron: Asymmetry* **2004**, *15*, 2583–2590.
49. Martins, J. E. D.; Mehlecke, C. M.; Gamba, M.; Costa, V. E. U. *Tetrahedron: Asymmetry* **2006**, *17*, 1817–1823.
50. (a) Tanyeli, C.; Sünbül, M. *Tetrahedron: Asymmetry* **2005**, *16*, 2039–2043; (b) Martínez, A. G.; Vilar, E. T.; Fraile, A. G.; Cerero, S. M.; Maroto, B. L. *Tetrahedron: Asymmetry* **2004**, *15*, 753–756; (c) Martínez, A. G.; Vilar, E. T.; Fraile, A. G.; Cerero, S. M.; Maroto, B. L. *Tetrahedron: Asymmetry* **2003**, *14*, 1959–1963.
51. Genov, M. L.; Dimitrov, V.; Ivanova, V. *Tetrahedron: Asymmetry* **1997**, *8*, 3703–3706.
52. Knollmüller, M.; Ferencic, M.; Gartner, P. *Tetrahedron: Asymmetry* **1999**, *10*, 3969–3975.

53. Hanyu, N.; Mino, T.; Sakamoto, M.; Fujita, T. *Tetrahedron Lett.* **2000**, *41*, 4587–4590.
54. Zhong, J.; Guo, H.; Wang, M.; Yin, M.; Wang, M. *Tetrahedron: Asymmetry* **2007**, *18*, 734–741.
55. Itsuno, S.; Fréchet, J. M. J. *J. Org. Chem.* **1987**, *52*, 4140–4142.
56. Okamoto, K.; Kimachi, T.; Ibuka, T.; Takemoto, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 463–467.
57. Szakonyi, Z.; Balázs, Á.; Martinek, T. A.; Fülöp, F. *Tetrahedron: Asymmetry* **2006**, *17*, 199–204.
58. (a) Dosa, P. I.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 444–445; (b) Bolm, C.; Rudolph, J. *J. Am. Chem. Soc.* **2002**, *124*, 14850–14851; (c) Huang,W.-S.; Hu, Q.-S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 7940–7956; (d) Rudolph, J.; Hermanns, N.; Bolm, C. *J. Org. Chem.* **2004**, *69*, 3997–4000; (e) Schmidt, F.; Stemmler, R. T.; Rudolph, J.; Bolm, C. *Chem. Soc. Rev.* **2006**, *35*, 454–470; (f) Yang, X.-F.; Hirose, T.; Zhang, G.-Y. *Tetrahedron: Asymmetry* **2009**, *20*, 415–419.
59. (a) Wu, X.; Liu, X.; Zhao, G. *Tetrahedron: Asymmetry* **2005**, *16*, 2299–2305; (b) Wang, M.-C.; Wang, X.-D.; Ding, X.; Liu, Z.-K. *Tetrahedron* **2008**, *64*, 2559–2564; (c) Rudolph, J.; Lormann, M.; Bolm, C.; Dahmen, S. *Adv. Synth. Catal.* **2005**, *347*, 1362–1368; (d) Liu, X. y.; Wu, X. y.; Chai, Z.; Wu, Y. y.; Zhao, G.; Zhu, S. z. *J. Org. Chem.* **2005**, *70*, 7432–7435; (e) Wang, M.-C.; Zhang, Q.-J.; Zhao, W.-X.; Wang, X.-D.; Ding, X.; Jing, T.-T.; Song, M.-P. *J. Org. Chem.* **2008**, *73*, 168–176.
60. Fontes, M.; Verdaguer, X.; Solà, L.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2004**, *69*, 2532–2543.
61. Braga, A. L.; Lüdtke, D. S.; Schneider, P. H.; Vargas, F.; Schneider, A.; Wessjohann, L. A.; Paixão. *Tetrahedron Lett.* **2005**, *46*, 7827–7830.
62. Braga, A. L.; Lüdtke, D. S.; Vargas, F.; Paixão, M. W. *Chem. Commun.* **2005**, 2512–2514.
63. Braga, A. L.; Paixão, M. W.; Westermann, B.; Schneider, P. H.; Wessjohann, L. A. *J. Org. Chem.* **2008**, *73*, 2879–2882.
64. (a) Ishizaki, M.; Hoshino, O. *Tetrahedron: Asymmetry* **1994**, *5*, 1901–1904; (b) Trost, B. M.; Weiss, A. H.; Wangelin, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 8–9; (c) Frantz, D. E.; Fa ¨ssler, R.; Carreira, E.M. *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807.
65. (a) Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605–2606; (b) Anad, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687–9688.
66. Watts, C. C.; Thoniyot, P.; Hirayama, L. C.; Romano, T.; Singaram, B. *Tetrahedron: Asymmetry* **2005**, *16*, 1829–1835.

67. Xu, Z.; Wu, N.; Ding, Z.; Wang, T.; Mao, J.; Zhang, Y. *Tetrahedron Lett.* **2009**, *50*, 926–929.
68. (a) Permutter, A. *Conjugate Addition Reaction in Organic Synthesis*, Pergamon, Press: Oxford, **1992**; (b) Almaşi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2006**, *7*, 2064–2068; (c) Chen, H.; Wang, Y.; Wei, S.; Sun, J. *Tetrahedron: Asymmetry* **2007**, *18*, 1308–1312.
69. Lattanzi, A. *Tetrahedron: Asymmetry* **2006**, *17*, 837–841.
70. Chua, P. J.; Tan, B.; Zeng, X.; Zhong, g. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3915–3918.
71. Velmathi, S.; Swarnalakshmi, S.; Narasimhan, S. *Tetrahedron: Asymmetry* **2003**, *14*, 113–117.
72. Zhong, G.; Fan, J.; Barbas, III, C. F. *Tetrahedron Lett.* **2004**, *45*, 5681–5684.
73. Brunin, T.; Cabou, J.; Bastin, S.; Brocard, J.; Pélinski, L. *Tetrahedron: Asymmetry* **2002**, *13*, 1241–1243.
74. Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553.
75. Delair, P.; Einhorn, C.; Einhorn, J.; Luche, J. L. *Tetrahedron* **1995**, *51*, 165–172.
76. Li, X.; Yeung, C.-H.; Chan, A. S. C.; Yang, T.-K. *Tetrahedron: Asymmetry* **1999**, *10*, 759–763.
77. (a) Brown, E.; Leze, A.; Touet, J. *Tetrahedron: Asymmetry* **1992**, *3*, 841–844; (b). Brown, E.; Penfornis, A.; Bayma, J.; Touet, J. *Tetrahedron: Asymmetry* **1991**, *2*, 339–342.

2. Asymmetric addition of Et_2Zn to aromatic aldehydes and the substituent effect by the 1,3-amino alcohols derived from *cis*-(1*R*,2*S*)-2- benzamidocyclohexane carboxylic acid.

2.1 Introduction

Since the enantioselective addition of diethylzinc to aldehydes first was reported by Oguni and Omi in 1984,[1] various types of ligands, such as aminothiols,[2] sulfonamides,[3] aminophenols,[4] amides,[5] diamines[6] and diols[7] were synthesized and successfully applied.[8] Therefore, in return, the asymmetric addition of diethylzinc to aldehydes became one of the most common reactions for testing the effectiveness of newly developed chiral ligands.

Among the chiral ligands studied, aminoalcohols are particularly attractive due to their high catalytic activity and excellent enantioselectivity. In the past twenty years, a variety of chiral 1,2-aminoalcohols have been developed and showed excellent enantioselectivity.[9] Whereas, 1,3-aminoalcohols have been studied relatively too less and it is interesting and challenging to examine the chiral controllability.[10] Thus we decided to synthesize some new enantiopure 1,3-aminoalcohols derived from 2-benzamidocyclohexanecarboxylic acid, and studied their catalytic ability in the asymmetric addition of diethylzinc to aromatic aldehydes.

2.2 Synthesis of chiral amino alcohol ligands

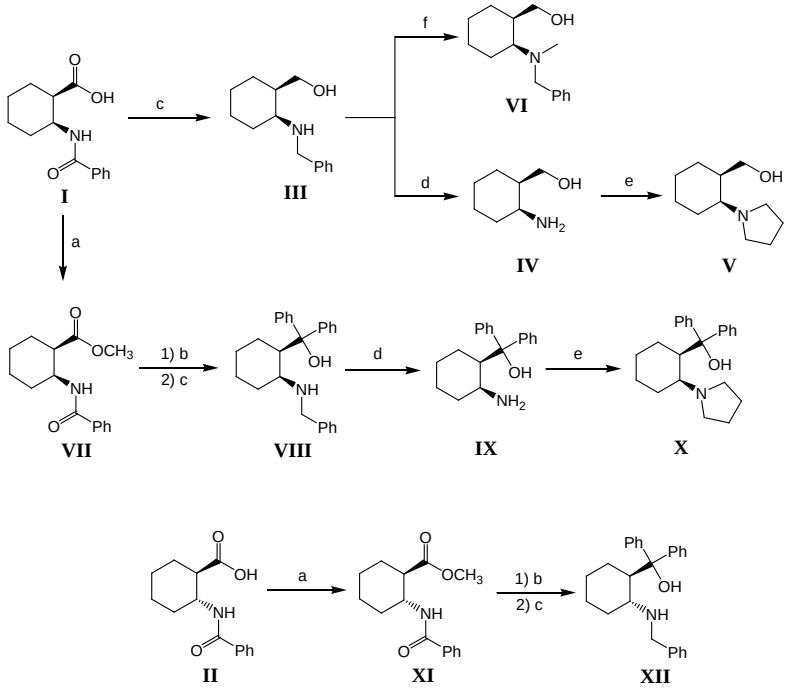
In our synthetic routes, commercially available chiral ligand, *cis*-(1*R*,2*S*)-2-benzamidocyclohexanecarboxylic acid **I** and *trans*-(1*R*,2*R*)-2-benzamidocyclohexanecarboxylic acid **II** were chosen as the starting materials, which can be easily converted into appropriately substituted 1,3-aminoalcohols as follows (Scheme 2-1).

First, *cis*-(1*R*,2*S*)-2-benzamidocyclohexanecarboxylic acid was reduced with $LiAlH_4$ in tetrahydrofuran to give aminoalcohol **III**[11] in good yield. After debenzylation of **3** by catalytic hydrogenolysis under atmospheric pressure of H_2 over 10% Pd/C,[12] primary amine **IV**[13] was obtained in high yield. Cycloalkylation reaction of **IV** with 1,4-dibromobutane afforded **V** in 62.9% yield. In addition, **III** was treated with iodomethane and NaOH in methanol, then reduced with $LiAlH_4$ to give tertiary amine

VI (89.3% yield). Thus, four primary alcohols with different *N*-substituents (**III-VI**) were easily prepared.

In order to introduce bulkiness to the vicinity of hydroxyl group, **I** was quantitatively esterified and subjected to Grignard reaction with PhMgBr, and then to reduction of amide group providing aminoalcohol **VIII** with two phenyl groups in high yield. Debenzylation of **VIII** gave the primary amine **IX** as a white solid (87.5% yield) and cyclic tertiary amine **X** was obtained in 31.2% yield after cycloalkylation of **9**.[14]

On the other hand, **XII**, the *trans*-isomer of **VIII**, was synthesized from **2** following the same procedure applied to **VIII** in 53.5% overall yield.



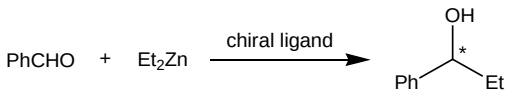
Scheme 2-1. Reagents and conditions: (a) conc. H_2SO_4, MeOH, reflux; (b) 5 equiv. PhMgBr/dry THF, reflux; (c) $LiAlH_4$, dry THF, reflux; (d) 10% Pd/C, H_2, EtOH, 70 ºC; (e) $Br(CH_2)_4Br$, Et_3N, DMF, 60 ºC; (f) i) MeI, NaOH, MeOH, r.t.; ii) $LiAlH_4$, dry THF, reflux.

2.3 Results and discussion

In order to examine the chiral induction abilities of chiral 1,3-aminoalcohols (**III-VI**, **VIII-X**, **XII**), we explored the enantioselective addition reaction of diethylzinc to benzaldehydes in the presence of 10 mol% of these ligands and the results were

summarized in Table 2-1. The structural study has revealed that the enantiomeric excess changed with the number and the size of *N*-substituents; that is, secondary amines (**III** and **VIII**) worked as better ligands than primary amines (**IV** and **IX**), respectively, and **VIII** yielded better chemical yield than tertiary amines (**V** and **VI**). However tertiary amine with a cyclic structure, **V**, showed the best chiral induction ability (71.2% ee) in the ligands studied.

Table 2-1. Enantioselective addition of diethylzinc to benzaldehyde catalyzed by various chiral ligands.[a]



Entry	Ligand	Time (h)	Yield[b] (%)	Ee[c] (%)	Config.[c]
1	**III**	60	11.5	33.0	*S*
2	**IV**	70	13.0	9.8	*S*
3	**V**	40	30.1	71.2	*R*
4	**VI**	40	13.2	58.1	*R*
5	**VIII**	20	68.5	65.5	*S*
6	**IX**	60	46.0	58.9	*S*
7	**X**	18	63.6	27.2	*S*
8	**XII**	30	46.5	7.7	*S*

[a]All reactions were carried out in dry *n*-hexane-toluene (2:3, *V*/*V*) at 0 ºC. Aldehyde/Et_2Zn/chiral ligand = 1/3/0.1; Et_2Zn (1 M solution in *n*-hexane).
[b]Isolated yield.
[c]See the experimental.

On the other hand, increasing the steric bulkiness at the α-position of hydroxyl group also improved the enantioselectivity, that is, when two phenyl groups were introduced to the vicinity of hydroxyl group (**III** vs. **VIII**, **IV** vs. **IX**), the enantiomeric excess increased from 33.0% to 65.5% ee and 9.8% to 58.9% ee (Table 2-1, Entries 1 vs. 5, 2 vs. 6). However, *trans*-derivative **XII** showed the lowest enantioselectivity due to its *trans*-configuration, which will be discussed later.

The most interesting feature of the present system is that both (*R*)- and (*S*)-1-phenyl-1-propanol were provided depending on the substituents in spite of the same chirality of the ligand, (1*R*,2*S*), derived from **I**: primary alcohols with tertiary

amino groups, **V** and **VI**, gave (*R*)-isomer (Table 2-1, Entries 3 and 4) while primary and secondary amines, **II**, **IV**, and **IX**, and tertiary alcohols, **VIII**-**X**, afforded (*S*)-isomer (Table 2-1, Entries 1, 2, and 5–7).

The substituent effect and chirality inversion can be explained by the transition state model proposed by some researchers for 1,3-aminoalcohols,[10b,10g,10h] which also corresponds to that by Noyori *et al.*[15] for 1,2-aminoalcohol (Figures 2-1~2-4). Supposing the *anti*-6/4/4 tricyclic transition state, the cyclohexane ring plays an important role in primary and secondary amine ligands. As an example, *anti*-(*Si*) and *anti*-(*Re*) transition states for the alkylation using **III** are compared in Figure 2-1. In the *anti*-(*Re*) form, large steric repulsion between the cyclohexane ring and the Et group is expected due to the 1,3-diaxial relationship in the six-membered Zn-chelate ring while the *anti*-(*Si*) form avoids such repulsion to afford (*S*)-1-phenyl-1-propanol (33.0% ee, Table 2-1, Entry 1).

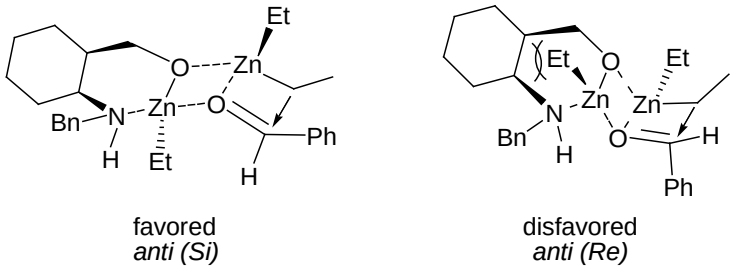


Figure 2-1. Proposed transition states for the alkylation using **III**.

In addition, it was shown that secondary amines, **III** and **VIII**, provided better *ee* values than corresponding primary amines, **IV** and **IX**, (**III** [33.0% ee] vs. **IV** [9.8% ee] and **VIII** [65.5% ee] vs. **IX** [58.9% ee]). The result seems to suggest one *N*-substituent favours the pseudo-equatorial position stabilizing the *anti*-(*Si*) form.

More rigid and bulky cyclic tertiary amine **V**, however, should have much larger steric repulsion with the Et group on Zn in 1,2-relationship of the *anti*-(*Si*) form than that with the cyclohexane ring in 1,3-relationship of the *anti*-(*Re*) (Figure 2-2). As a result, (*R*)-1-phenyl-1-propanol was obtained in a high enantiomeric excess, 71.2% ee (Table 2-1, Entry 3). Similarly another tertiary amine **VI** gave the same stereoselectivity but more flexible structure (benzyl methylamine) seemed to lead to lower enantioselectivity of 58.1% ee (Table 2-1, Entry 4).

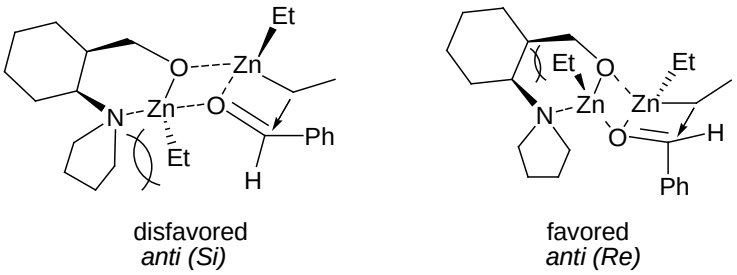


Figure 2-2. Proposed transition states for the alkylation using **V**.

Similar and interesting chirality inversion by *N*-substituent effect has been observed for 1,3-aminoalcohols derived from α-pinene by Szakonyi *et al.*[10i] Their primary and tertiary amines gave 1-phenyl-1-propanol of the same chirality (40 & 62% ee) with those obtained by **IV**, **V**, and **VI** (9.8–71% ee). On the other hand, their secondary amine gave the opposite chirality (13% ee) to that obtained by **III** (33% ee). While the cyclohexyl ring is the common structural feature, the bridging methylene might cause the difference due to its effect on the transition state geometry for the α-pinene derived ligands.[10i]

On the other hand, the bulkiness of the hydroxyl group also affected the stereochemistry of alkylation. When tertiary alcohol **VIII** was used as a chiral ligand, additional repulsion between the Ph group and the Et group on Et_2Zn for alkylation further destabilized the *anti*-(*Re*) form (Figure 2-3). As a result, **VIII** gave higher (*S*)-selectivity (65.5% ee, Table 2-1, Entry 5) than **III** (33.0% ee).

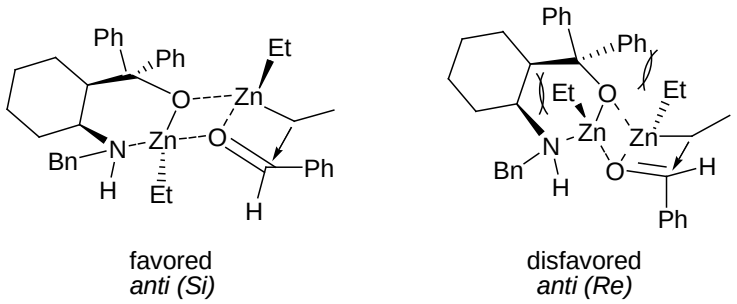


Figure 2-3. Proposed transition states for the alkylation using **VIII**.

Chirality change by the substitution on the α-carbon of hydroxyl group of 1,3-aminoalcohols has been reported by Cicchi *et al.*[10e] In their system, diphenyl methanol and 9-hydroxy fluorene moieties caused opposite chirality in the product. Although similar substitution effect on the α-carbon of hydroxyl group has been also

observed for chiral 1,2-aminoalcohol ligands,[9c] there are only limited systems reported for the chirality inversion by this kind of substituent effect. Considering the diversity of structural modification, chiral 1,3-aminoalcohols would be interesting scaffolds for asymmetric reactions.[4,10e,10f,10i]

In the case of **XII**, the *trans*-(1*R*,2*R*)-configuration allows much less strained transition states than the *cis*-derivatives; that is, the steric repulsion of the substituents on the six-membered chelate ring is largely relieved and the cyclohexane ring has little effect on stereocontrol (Figure 2-4). Consequently, both *anti*-(*Si*) and *anti*-(*Re*) transition states have similar stability showing the least enantioselectivity (7.7% ee, Table 2-1 Entry 8).

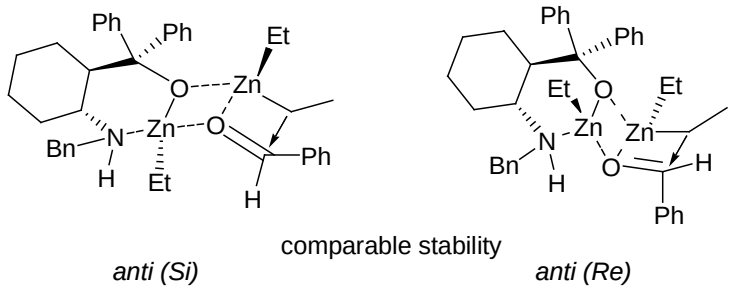


Figure 2-4. Proposed transition states for the alkylation using **XII**.

Enantioselective addition of diethylzinc to various aldehydes

In order to optimize the reaction, the solvent, temperature and ligand loading effects were examined and the results are shown in Table 2-2. Apparently less polar solvents (Entries 1 & 2) gave better chemical yield and enantiomeric excess than polar ethers (Entries 3 & 4), especially in THF (26.8% ee). Many studies have shown that toluene or *n*-hexane-toluene mixture is a proper solvent system to provide higher enantioselectivity[9c-e,9j,9k] so that the ratio of this mixed solvent system was changed in our study as well. Although the ratio of *n*-hexane to toluene had less effect on the chiral control, the yield was observably enhanced when only *n*-hexane was used (Entries 5 vs. 7, 9 vs. 10). At the same time, the effect of the amount of chiral ligand on the enantioselectivity was investigated by the use of **V**. Although the reaction proceeded with 10 mol% ligand loading, the enantioselectivity and the yield were gradually improved by increasing the amount of **V** from 10 to 20 and 30 mol% (Entries 1, 5 & 9).

Table 2-2. Optimization of the reaction conditions.[a]

Entry	**V** (mol%)	Solvent	Time (h)	T (ºC)	Yield[b] (%)	Ee[c] (%)	Config.[c]
1	20	*n*-Hexane	40	0	69.3	71.0	*R*
2	20	CH_2Cl_2	40	0	49.2	51.0	*R*
3	20	Et_2O	40	0	28.0	30.2	*R*
4	20	THF	40	0	19.8	26.8	*R*
5	10	*n*-Hexane	40	0	40.8	63.3	*R*
6	10	H/T[d], 2:3	60	r.t.	26.9	33.5	*R*
7	10	H/T, 2:3	40	0	30.1	71.2	*R*
8	10	H/T, 2:3	25	-18	2.5	-	-
9	30	*n*-Hexane	40	0	72.1	79.4	*R*
10	30	H/T, 2:3	20	0	45.5	76.1	*R*

[a]Aldehyde/Et_2Zn = 1:3; Et_2Zn (1 M solution in *n*-hexane).

[b]Isolated yield.

[c]See the experimental.

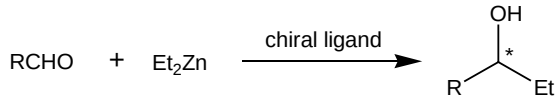
[d]The volume ratio of *n*-hexane to toluene.

When the reaction was carried out at different temperatures, we found a large effect on the conversion and the enantioselectivity. The best result was obtained at 0 ˚C and either lower or higher temperature decreased both the chemical yields and *ee* values (Table 2-2, Entries 6-8). Similar results on the temperature effect were observed by other researchers.[4c,5b,7c,16].

Considering the results shown in Table 2-2, we investigated the ligand effect on the chiral induction in the presence of 20 mol% of **V** and **VIII** for not only various aromatic aldehydes having an electron donating or withdrawing group but also heteroaromatic and aliphatic aldehydes. The results were summarized in Table 2-3. The enantioselectivity observed in Table 2-1 was confirmed for all aromatic aldehydes: **V** gave (*R*)-1-aryl-1-propanol while **VIII** afforded (*S*)-enantiomer in good yields. In addition, little substituent effect was observed for the *meta*- or *para*-substituted benzaldehydes on both chemical yield and enantioselectivity. However, the *ortho*-substituent, especially an *ortho*-bromo substituent, decreased the enantioselectivity. The substituent effect on the substrate needs to be further investigated since the present result is in accordance with the results reported by Yang *et al.*,[4a,4b] Sun *et al.*,[17a] Jaworska *et al.*,[17b] but is opposite to the results reported by Joshi *et al.*[9i]

Among the heteroaromatic aldehydes, a similar result was obtained for furan-2-carboxaldehyde (Entry 8) but lower enantioselectivity was obtained for thiophene-2-carboxaldehyde (Entries 9 and 17). The heteroatom might be the cause as commented by Noyori *et al*.[15a] On the other hand, the present system was not effective for aliphatic aldehydes as complex product mixtures were obtained for three aliphatic aldehydes examined (Entries 10-12). Comparing 1,2-aminoalcohol ligands, a more flexible 6/4/4 tricyclic transition state might be the cause of this limitation. Further control of molecular design is necessary to the present ligand structure.

Table 2-3. Asymmetric addition of diethylzinc to aldehydes in the presence of **V** or **VIII**[a]



Entry	Ligand	Aldehyde	Yield[b] (%)	Ee[c] (%)	Config.[c]
1	**V**	*p*-ClC_6H_4CHO	62.0	65.6	*R*
2	**V**	*p*-MeC_6H_4CHO	56.0	63.6	*R*
3	**V**	*m*-ClC_6H_4CHO	72.5	75.4	*R*
4	**V**	*m*-MeC_6H_4CHO	68.8	75.0	*R*
5	**V**	*o*-BrC_6H_4CHO	58.6	32.6	*R*
6	**V**	*o*-ClC_6H_4CHO	51.1	38.1	*R*
7	**V**	*o*-MeC_6H_4CHO	64.8	53.4	*R*
8	**V**	Furan-2-carboxaldehyde	70.4	52.0	*R*
9	**V**	Thiophene-2-carboxaldehyde	57.1	47.5	*R*
10	**V**	Isobutyraldehyde	trace	–	–
11	**V**	Hexanal	trace	–	–
12	**V**	Cyclohexanecarbaldehyde	trace	–	–
13	**VIII**	*p*-ClC_6H_4CHO	77.3	60.1	*S*
14	**VIII**	*p*-MeC_6H_4CHO	81.0	55.8	*S*
15	**VIII**	*m*-ClC_6H_4CHO	78.3	66.0	*S*
16	**VIII**	*m*-MeC_6H_4CHO	82.5	61.1	*S*
17	**VIII**	Thiophene-2-carboxaldehyde	60.6	27.3	*S*

[a]All reactions were carried out in dry *n*-hexane at 0 ºC for 72 h. Aldehyde/Et_2Zn/chiral ligand = 1/3/0.2; Et_2Zn (1 M solution in *n*-hexane).

[b]Isolated yield.

[c]See the experimental.

2.4 Conclusions

We have synthesized a series of novel optically active 1,3-aminoalcohols from *cis*-(1*R*,2*S*)-2-benzamidocyclohexanecarboxylic acid **I**. The structural characteristics of the chiral ligands were explored in asymmetric diethylzinc addition to various aldehydes. The results demonstrated that the cyclohexane ring, *N*-substituents and the substituents to the vicinity of hydroxyl group have crucial effect on chirality control. Providing the rigid and bulky cyclic tertiary amine **V** showed the best promoting ability to aromatic aldehydes with (*R*)-selectivity (79.4% ee) in the ligands studied in this article. With two phenyl groups to provide the proper steric bulkiness, the tertiary alcohol **VIII** showed the opposite (*S*)-selectivity (66.0% ee). Further studies on chiral control and versatility are currently underway by 1,3-aminoalcohol ligands derived from **I**.

2.5 Experimental

All the asymmetric addition reactions of diethylzinc to aldehydes were carried out under nitrogen in anhydrous solvents. NMR spectra were obtained at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR) on a Bruker DPX400 spectrometer (Molecular Analysis and Life Science Center, Saitama University) using $CDCl_3$ as the solvent. Optical rotations were measured with a JASCO DIP-370 polarimeter. Melting points were obtained using a Mitamura Riken Kogyo MEL-TEMP instrument and uncorrected. IR spectra were recorded on a JASCO FT/IR 400. Enantiomeric excess was determined using a set of JASCO LC 900 series with Chiralcel OB-H or OJ columns (Daicel Chemical Industries, Ltd.). The starting material **I** is commercially available while **II** was prepared according to the literature.[18]

Synthesis of (1*R*,2*S*)-2-benzylaminocyclohexylmethanol III

To a suspension of $LiAlH_4$ (1.2 g, 31.62 mmol) in dry THF (20 mL) was added slowly a solution of **I** (2.49 g, 10.07 mmol) in THF (30 mL). After refluxing for 24 h, the reaction was cautiously quenched with water and the mixture was further treated with 20% NaOH aq. solution. The precipitate was filtered off and washed with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated to dryness. After purification by column chromatography (silica gel, *n*-hexane/ethyl acetate=1/1–0/1, *V*/*V*), **III** was obtained as a white solid (2.01 g, 91.0%). M.p. 68–68.5

ºC, $[\alpha]_{D}^{25}$ –24.0 (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.35–7.14 (m, 5H), 6.25–5.65 (br, 1H), 3.94–3.87 (m, 1H), 3.82 (d, *J*=8.90 Hz, 2H), 3.73–3.71 (m, 1H), 3.00–2.98 (m, 1H), 1.91–1.90 (m, 2H), 1.65–1.36 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 149.7, 128.6, 128.3, 127.2, 66.4, 58.7, 51.7, 39.0, 27.8, 25.9, 23.5, 22.6; IR (KBr) *v*: 3297, 3198, 3065, 3027, 2925, 2844, 1499, 1483, 1462, 1448, 1370, 1348, 1333, 1251, 1228, 1203, 1188, 1143, 1105, 1080, 1065, 1033, 966, 914, 899, 864, 840, 805, 748, 696, 628, 607, 475 cm^{-1}; HRMS (ESI+) calcd for $C_{14}H_{21}NOH^{+}$ 220.1696, found 220.1615.

Synthesis of (1*R*,2*S*)-2-aminocyclohexylmethanol IV

The mixture of **III** (1.80 g, 8.22 mmol) and 10% Pd/C (0.18 g) in ethanol (40 mL) was stirred under hydrogen (1 bar) at 70 ℃ for 24 h. After cooling to room temperature, Pd/C was filtered off and the solvent was removed under reduced pressure to afford **IV** as a white solid (1.06 g, 94.4%), which could be used directly in the next step without further purification. M.p. 60–62 ºC, $[\alpha]_{D}^{19}$ +16.9 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 3.81–3.70 (m, 2H), 3.27–3.25 (m, 1H), 3.21–2.85 (br, 3H), 1.73–1.70 (m, 1H), 1.60–1.44 (m, 7H), 1.36–1.28 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 66.3, 51.0, 41.1, 33.0, 24.6, 24.2, 21.3; IR (KBr) *v*: 3445, 3335, 2934, 2846, 2175, 1630, 1556, 1489, 1464, 1386, 1355, 1335, 1303, 1256, 1217, 1196, 1140, 1105, 1092, 1059, 1047, 1026, 975, 960, 937, 904, 882, 815, 802, 783, 718, 644, 586, 539, 498 cm^{-1}; HRMS (ESI+) calcd for $C_7H_{15}NOH^{+}$ 130.1226, found 130.1278.

Synthesis of (1*R*,2*S*)-2-pyrrolidin-1'-ylcyclohexylmethanol V

Chiral aminoalcohol **IV** (0.49 g, 3.90 mmol), Et_3N (0.79 g, 7.80 mmol) and 1,4-dibromobutane (0.84 g, 3.90 mmol) were dissolved in DMF (5 ml), and stirred at 60 ºC for 36 h. After chloroform (30 ml) was added, the mixture was washed with water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to dryness. The crude product was purified by column chromatography (Al_2O_3, *n*-hexane/ethyl acetate=1/1, *V*/*V*) to afford **5** (0.45g, 62.9%) as a light yellow liquid. $[\alpha]_{D}^{26}$ +21.4 (*c* 0.39, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 4.20–4.10 (m, 1H), 3.48–3.44 (m, 1H), 2.87–2.58 (m, 2H), 2.57–2.39 (m, 2H), 2.38–2.31 (m, 2H), 1.76–1.59 (m, 7H),

1.49–1.46 (m, 1H), 1.38–1.15 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 67.9, 64.0, 52.2, 36.2, 28.1, 25.8, 25.7, 23.0, 20.7; IR (KBr) *v*: 3437, 3393, 3318, 2934, 2856, 2778, 2708, 1654, 1445, 1408, 1126, 1107, 1036, 953, 915, 888 cm^{-1}; HRMS (ESI+) calcd for $C_{11}H_{21}NOH^+$ 184.1696, found 184.1673.

Synthesis of (1*R*,2*S*)-2-[benzyl(methyl)amino]cyclohexylmethanol VI

To a methanol solution (15 mL) of **III** (0.58 g, 2.64 mmol), iodomethane (3.75 g, 26.45 mmol) and NaOH (0.21 mg, 5.29 mmol) were added and the reaction mixture was stirred at room temperature for 48 h. After removal of the solvent, the residue was dissolved in 20 mL of chloroform, washed with water, dried over anhydrous Na_2SO_4, and then concentrated to dryness. Reduction of the white residue with $LiAlH_4$ followed the procedure similar to that for **III** gave **VI** as a colorless liquid (0.55 g, 89.3%). $[\alpha]_D^{19}$ +23.0 (*c* 0.29, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.33–7.25 (m, 5H), 4.33–4.27 (m, 1H), 3.75 (d, *J*=12.58 Hz, 1H), 3.61–3.52 (m, 2H), 2.63–2.56 (m, 2H), 2.15 (s, 3H), 1.97–1.89 (m, 2H), 1.75–1.63 (m, 2H), 1.49–1.44 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 138.4, 129.2, 128.5 127.2, 67.1, 64.1, 59.3, 39.0, 35.4, 28.6, 26.2, 24.6, 20.8; IR (KBr) *v*: 3399, 2930, 2854, 2786, 1495, 1451, 1421, 1375, 1347, 1323, 1253, 1229, 1121, 1069, 1038, 995, 909, 882, 853, 745, 700 cm^{-1}; HRMS (ESI+) calcd for $C_{15}H_{23}NOH^+$ 234.1852, found 234.1352.

Synthesis of methyl (1*R*,2*S*)-2-benzamidocyclohexanecarboxylate VII

To a dry methanol solution (10 mL) of **I** (0.99 g, 4 mmol), was added concentrated H_2SO_4 (32 mg, 0.32 mmol) and the reaction mixture was refluxed for 12 h. After concentration, the residue was dissolved in chloroform (30 ml), washed with water, and dried over anhydrous Na_2SO_4. Removal of the solvent afforded **VII** as a white solid (1.04 g, 99.1%), which could be used directly in the next step. M.p. 80–81.5 ºC, $[\alpha]_D^{26}$ –45.0 (*c* 0.7, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.79–7.79 (m, 2H), 7.51–7.41 (m, 3H), 7.26 (s, 1H), 4.38–4.31 (m, 1H), 3.54 (s, 3H), 2.93–2.91 (m, 1H), 2.20–2.17 (m, 1H), 1.85–1.64 (m, 4H),1.58–1.47 (m, 2H), 1.32–1.21 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 174.9, 166.3, 134.8, 131.3, 128.5, 126.9, 51.8, 48.3, 44.4, 29.4, 27.5, 24.3, 22.5; IR (KBr) *v*: 3321, 3060, 3029, 1727, 1636, 1604 1579, 1534, 1490, 1449, 1396, 1337, 1313, 1277, 1261, 1203, 1132, 1120, 1079, 1028, 1004, 962, 924, 857, 818, 801, 727,

693, 679, 666, 583 cm^{-1}; HRMS (ESI+) calcd for $C_{15}H_{19}NO_3H^+$ 262.1438, found 262.1057.

Synthesis of (1*R*,2*S*)-2-benzylaminocyclohexyl(diphenyl)methanol VIII

A THF (20 mL) solution of **VII** (0.64 g, 16.7 mmol) in a dropping funnel was slowly added to a THF solution of phenyl magnesium bromide (90 mmol) at 0 ºC for 20 min. The reaction mixture was stirred at room temperature for 0.5 h and then heated to reflux for 12 h. After cooling to room temperature, the reaction was quenched with saturated NH_4Cl aq. solution. The mixture was extracted with ether and the organic layer was dried over anhydrous Na_2SO_4. After the solvent was removed, the crude product was obtained as a light yellow solid, which was recrystallized from ethyl acetate to afford a white crystalline solid (0.49 g, 52.3%) for the use in the next step.

To a suspension of $LiAlH_4$ (0.12 g, 3.16 mmol) in dry THF (15 mL) was added slowly a solution of the alcohol in THF (10 mL). After refluxing for 18 h, the reaction was cautiously quenched with water and the mixture was further treated with 20% NaOH aq. solution. The precipitate was filtered off and washed with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. After purification by column chromatography (silica gel, *n*-hexane/ethyl acetate=3/1, *V*/*V*), **VIII** was obtained as a colorless viscous liquid (0.44 g, 93.1%). $[\alpha]_D^{26}$ +85.6 (*c* 2.6, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.54–8.25 (br, 1H), 7.67–7.65 (m, 2H), 7.55–7.52 (m, 2H), 7.34–7.24 (m, 9H), 7.16–7.09 (m, 2H), 3.59 (d, *J*=12.21 Hz, 1H), 3.24 (d, *J*=12.10 Hz, 1H), 3.15–2.94 (m, 1H), 2.48–2.44 (m, 1H), 1.92–1.89 (m, 1H), 1.76–1.68 (m, 1H), 1.67–1.46 (m, 4H), 1.44–1.22 (m, 3H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 149.1, 146.9, 139.3, 128.6, 128.3, 128.2, 128.0, 127.4, 125.9, 125.8, 125.5, 125.2, 80.6, 54.1, 52.0, 47.3, 28.5, 25.8, 21.6, 20.2; IR (KBr) *v*: 3317, 3075, 3060, 3029, 2926, 2852, 1597, 1491, 1468, 1450, 1432, 1381, 1313, 1242, 1210, 1176, 1136, 1067, 1032, 992, 969, 909, 881, 768, 747, 698, 648, 633, 552 cm^{-1}; HRMS (ESI+) calcd for $C_{26}H_{29}NOH^+$ 372.2322, found 372.2896.

Synthesis of (1*R*,2*S*)-2-aminocyclohexyl(diphenyl)methanol IX

The mixture of **VIII** (0.24 g, 0.65 mmol) and 10% Pd/C (24 mg) in ethanol (20 mL) was stirred under hydrogen (1 bar) at 60 ℃ for 24 h. After cooling to room temperature, Pd/C was filtered off and the solvent was removed under reduced pressure. The crude

product was purified by column chromatography (Al_2O_3, *n*-hexane/ethyl acetate=2/1, *V*/*V*) to afford **IX** (0. 16 g, 87.5%). M.p. 228–230 ºC, $[\alpha]_{D}^{25}$ –6.65 (*c* 0.41, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.63–7.61 (m, 2H), 7.53–7.51 (m, 2H), 7.30–7.24 (m, 4H), 7.15–7.09 (m, 2H), 3.91–3.00 (br, 2H), 3.15–3.14 (m, 1H), 2.45–2.40 (m, 1H), 1.80–1.70 (m, 1H), 1.64–1.40 (m, 6H), 1.39–1.19 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 149.0, 147.0, 128.1, 128.0, 125.9, 125.8, 125.7, 125.2, 80.5, 47.2, 46.5, 35.4, 26.1, 20.8, 19.5; IR (KBr) *v*: 3426, 3374, 3313, 3083, 3014, 3013, 2925, 2862, 1598, 1578, 1490, 1459, 1448, 1430, 1387, 1305, 1265, 1246, 1182, 1135, 1063, 1037, 994, 959, 912, 887, 864, 819, 793, 765, 745, 707, 695, 641, 549 cm^{-1}; HRMS (ESI+) calcd for $C_{19}H_{23}NOH^+$ 282.1852, found 282.1457.

Synthesis of (1*R*,2*S*)-2-pyrrolidin-1'-ylcyclohexyl(diphenyl)methanol X

Chiral aminoalcohol **X** was prepared by the procedure similar to that for the preparation of **V** as a white solid (31.2%). M.p. 143–145 ºC, $[\alpha]_{D}^{27}$ +4.4 (*c* 0.34, $CHCl_3$); ^{1}H NMR: (400 MHz, $CDCl_3$) *δ* 9.31–8.65 (br, 1H), 7.66–7.64 (m, 2H), 7.54–7.52 (m, 2H), 7.30–7.23 (m, 4H), 7.14–7.08 (m, 2H), 3.19 (s, 1H), 2.92–2.18 (m, 4H), 1.93–1.83 (m, 2H), 1.69–1.49 (m, 8H), 1.43–1.37 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 149.3, 147.1, 128.1, 128.0, 125.8, 125.7, 125.5, 125.0, 80.6, 63.7, 54.1, 51.9, 48.0, 29.7, 26.4, 24.4, 22.6; IR (KBr) *v*: 3426, 3055, 3032, 2952, 2916, 2840, 1596, 1489, 1460, 1447, 1434, 1399, 1343, 1253, 1179, 1143, 1066, 1032, 994, 908, 855, 768, 752, 707, 666, 638, 555 cm^{-1}; HRMS (ESI+) calcd for $C_{23}H_{29}NOH^+$ 336.2322, found 336.2583.

Synthesis of methyl (1*R*,2*R*)-2-benzamidocyclohexanecarboxylate XI

By the procedure similar to that for the preparation of **VII**, **XI** was quantitatively prepared as a white solid (99.0%) and could be used directly in the next step without further purification. M.p. 151–152.5 ºC, $[\alpha]_{D}^{19}$ –49.2 (*c* 0.5, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.72–7.64 (m, 2H), 7.41–7.33 (m, 3H), 6.11 (s, 1H), 4.12–4.07 (m, 1H), 3.57 (s, 3H), 2.38–2.33 (m, 1H), 2.13–2.11 (m, 1H), 1.93–1.90 (m, 1H), 1.73–1.58 (m, 3H), 1.41–1.37 (m, 1H), 1.23–1.19 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 174.3, 166.8, 134.8, 131.4, 128.5, 126.9, 51.9, 50.7, 49.9, 32.8, 28.4, 24.7, 24.5; IR (KBr) *v*: 3301, 3060, 2948, 2862, 1721, 1637, 1603 1578, 1542, 1491, 1448, 1433, 1372, 1330,

1284, 1248, 1205, 1194, 1179, 1126, 1075, 1049, 1029, 1012, 963, 915, 873, 835, 800, 725, 697, 671, 583 cm^{-1}; HRMS (ESI+) calcd for $C_{15}H_{19}NO_3H^+$ 262.1438, found 262.1081.

Synthesis of (1*R*,2*R*)-2-benzylaminocyclohexyl(diphenyl)methanol XII

Chiral aminoalcohol **XII** was prepared by the procedure similar to that for the preparation of **VIII** as a colorless viscous liquid (54.0%). $[\alpha]_{D}^{19}$ –102.8 (*c* 1.27, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 9.65–10.35 (br, 1H), 7.57–7.49 (m, 2H), 7.42–7.19 (m, 13H), 3.79 (d, *J*=12.4 Hz, 1H), 3.54 (d, *J*=12.4 Hz, 1H), 2.49–2.24 (m, 3H), 1.92–1.62 (m, 3H), 1.35–0.80 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 146.3, 145.1, 139.0, 128.7, 128.2, 128.0, 127.7, 127.5, 127.1, 126.8, 126.5, 82.8, 59.2, 51.4, 51.3, 34.7, 30.0, 26.3, 25.8; IR (KBr) *v*: 3426, 3257, 3086, 3059, 3029, 2932, 2853, 1600, 1581, 1492, 1445, 1356, 1286, 1211, 1140, 1096, 1052, 1032, 1010, 951, 909, 860, 763, 744, 714, 700, 649, 626, 608 cm^{-1}; HRMS (ESI+) calcd for $C_{26}H_{29}NOH^+$ 372.2322, found 372.2673.

General procedure for the asymmetric addition of diethylzinc to aldehydes [4a,,4b]

The chiral 1,3-aminoalcohol (0.03 mmol) was dissolved in *n*-hexane (0.5 mL) at room temperature under nitrogen and diethylzinc (0.9 mmol, 1 M in *n*-hexane) was added to this solution. The mixture was cooled to 0 ºC and stirred for 30 min. Aldehyde (0.3 mmol in 1 ml *n*-hexane) was added to the mixture. After stirring at 0 ºC for 18-72 h, the reaction was quenched with saturated NH_4Cl aq. solution. The mixture was extracted with diethyl ether, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by thin layer chromatography (silica gel, *n*-hexane/ethyl acetate=4/1, *V*/*V*) to give the pure alcohol as a colorless oil. The absolute configuration and the *ee* values were determined by the chiral HPLC analysis[4] and the data are as follows: 1-phenyl-1-propanol; Daicel Chiralcel OB-H, *V*(*n*-hexane)/*V*(2-propanol)=90:10, 0.5 mL/min, 254 nm, t_{R1}=11.9 min (*S*-isomer), t_{R2}=13.5 min (*R*-isomer). 1-(4-Chlorophenyl)-1-propanol; Daicel Chiralcel OJ, *V*(*n*-hexane)/*V*(2-propanol)=97:3, 0.5 mL/min, 254 nm, t_{R1}=32.36 min (*S*-isomer), t_{R2}=35.46 min (*R*-isomer). 1-(4-Tolyl)-1-propanol; Daicel Chiralcel OJ, *V*(*n*-hexane)/*V*(2-propanol)=97:3, 0.5 mL/min, 254 nm, t_{R1}=32.29 min (*S*-isomer), t_{R2}=34.33 min (*R*-isomer). 1-(3-Chlorophenyl)-1-propanol; Daicel Chiralcel OB-H, *V*(*n*-hexane)/*V*(2-propanol)= 90:10, 0.5 mL/min, 254 nm, t_{R1}=12.03 min (*S*-isomer), t_{R2}=13.69 min (*R*-isomer).

1-(3-Tolyl)-1-propanol; Daicel Chiralcel OB-H, *V*(*n*-hexane)/*V*(2-propanol)=95:5, 0.5 mL/min, 254 nm, t_{R1}=12.68 min (*S*-isomer), t_{R2}=14.93 min (*R*-isomer). 1-(2-Bromophenyl)-1-propanol; Daicel Chiralcel OB-H, *V*(*n*-hexane)/*V*(2-propanol)=97:3, 0.5 mL/min, 254 nm, t_{R1}= 16.34 min (*S*-isomer), t_{R2}=17.97 min (*R*-isomer). 1-(2-Chlorophenyl)-1-propanol; Daicel Chiralcel OB-H, *V*(*n*-hexane)/*V*(2-propanol)=98:2, 0.5 mL/min, 254 nm, t_{R1}=18.46 min (*S*-isomer), t_{R2}= 21.00 min (*R*-isomer). 1-(2-Tolyl)-1-propanol; Daicel Chiralcel OB-H, *V*(*n*-hexane)/*V*(2-propanol)=98:2, 0.5 mL/min, 254 nm, t_{R1}=20.92 min (*S*-isomer), t_{R2}=24.41 min (*R*-isomer). 1-(2-Thienyl)-1-propanol; Daicel Chiralcel OD, *V*(*n*-hexane)/*V*(2-propanol)=99.5:0.5, 1.5 mL/min, 230 nm, t_{R1}=24.55 min (*R*-isomer), t_{R2}=27.16 min (*S*-isomer). 1-(2-Furyl)-1-propanol; Daicel Chiralcel OD, *V*(*n*-hexane)/*V*(2-propanol)=99.5:0.5, 1.5 mL/min, 230 nm, t_{R1}=20.17 min (*R*-isomer), t_{R2}=23.55 min (*S*-isomer).

2.6 References

1. Oguni, N.; Omi, T. *Tetrahedron Lett*. **1984**, *25*, 2823–2824.
2. (a) Andersen, J. C.; Harding, M. *Chem. Commun.* **1998**, 393–394; (b) Gibson, C. L. *Tetrahedron: Asymmetry* **1999**, *10*, 1551–1561.
3. (a) You, J. S.; Shao, M. Y.; Gau, H. M. *Tetrahedron: Asymmetry* **2001**, *12*, 2971–2975; (b) Grach, G.; Reboul, V.; Metzner, P. *Tetrahedron: Asymmetry* **2008**, *19*, 1744–1750.
4. (a) Yang, X. F.; Wang, Z. H.; Koshizawa, T.; Yasutake, M.; Zhang, G. Y.; Hirose, T. *Tetrahedron: Asymmetry* **2007**, *18*, 1257–1263; (b) Yang, X. F.; Hirose, T.; Zhang, G. Y. *Tetrahedron: Asymmetry* **2008**, *19*, 1670–1675; (c) Szatmári, I.; Sillanpää, R.; Fülöp, F. *Tetrahedron: Asymmetry* **2008**, *19*, 612–617.
5. (a) Burguete, M.I.; Escorihuela, J.; Luis, S. V.; Ujaque, G. *Tetrahedron* **2008**, *64*, 9717–9724; (b) Blay, G.; Fernández, I.; Marco-Aleixandre, A.; Pedro, J. R. *Tetrahedron: Asymmetry* **2005**, *16*, 1207–1213.
6. (a) Asami, M.; Inoue, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1687–1690; (b) Saravanan, P.; Bisai, A.; Baktharaman, S.; Chandrasekhar, M.; Singh, V. K. *Tetrahedron* **2002**, *58*, 4693–4706; (c) Cheng, Y. Q.; Bian, Z.; Kang, C. Q.; Guo, H. Q.; Gao, L. X.. *Tetrahedron: Asymmetry* **2008**, *19*, 1572–1575.
7. (a) Olsson, C.; Friberg, A.; Frejd, T. *Tetrahedron: Asymmetry* **2008**, *19*, 1476–1483; (b) Dean, M. A.; Hitchcock, S. R. *Asymmetry* **2008**, 19, 2563–2567; (c) Gou, S.; Judeh, Z. M. A. *Tetrahedron Lett*. **2009**, *50*, 281–283.

8. (a) Soai, K.; Niwa, S. *Chem. Rev*. **1992**, *92*, 833–856; (b) Pu, L.; Yu, H. B. *Chem. Rev*. **2001**, *101*, 757–824.
9. (a) Soai, K.; Ookawa, A.; Ogawa, K. *J. Am. Chem. Soc.*, **1987**, *109*, 7111–7115; (b) Paleo, M. R.; Cabeza, I.; Sardina, F. J. *J. Org. Chem*. **2000**, *65*, 2108–2113; (c) Dai, W. M.; Zhu, H. J.; Hao, X. J.; *Tetrahedron: Asymmetry* **2000**, *11*, 2315–2337; (d) Yun, H.; Wu, Y.; Wu, Y.; Ding, K.; Zhou, Y. *Tetrahedron Lett*. **2000**, *41*, 10263–10266; (e) Okamoto, K.; Kimachi, T.; Ibuka, T.; Takemoto, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 463–467; (f) Rasmussen, T.; Norrby, P. O. *J. Am. Chem. Soc*. **2001**, *123*, 2464–2465; (g) Martínez, A. G.; Vilar, E. T.; Fraile, A. G.; de la Moya Cerero, S.; Martínez-Ruiz, P.; Villas, P. C. *Tetrahedron: Asymmetry* **2002**, *13*, 1–4; (h) Bastin, S.; Ginj, M.; Brocard, J.; Pélinski, L.; Novogrocki, G. *Tetrahedron: Asymmetry* **2003**, *14*, 1701–1708; (i) Joshi, S. N.; Malhotra, S. V. *Tetrahedron: Asymmetry* **2003**, *14*, 1763–1766; (j) Rodríguez-Escrich, S.; Reddy, K. S.; Jimeno, C.; Colet, G.; Rodríguez-Escrich, C.; Solá, L.; Vidal-Ferran, A.; Pericàs, M. A. *J. Org. Chem*. **2008**, *73*, 5340–5353; (k) Parrott II., R. W.; Hitchcock, S. R. *Tetrahedron: Asymmetry* **2008**, *19*, 19–26; (l) Xu, C. L.; Wang, M. C.; Hou, X. H.; Liu, H. M.; Wang, D. K. *Chin. J. Chem.* **2005**, *23*, 1443–1448.
10. (a) Muchow, C.; Vannoorenberghe, Y.; Buono, G. *Tetrahedron Lett*. **1987**, *28*, 6163–6167; (b) Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett*. **1988**, *29*, 5645–5648; (c) Cho, B. T.; Kim, N. *Tetrahedron Lett*. **1994**, *35*, 4115–4118; (d) Hulst, R.; Heres, H.; Fitzpatrick, K.; Peper, N. C. M. W.; Kellogg, R. M. *Tetrahedron: Asymmetry* **1996**, *7*, 2755–2760; (e) Cicchi, S.; Crea, S.; Goti, A.; Brandi, A. *Tetrahedron: Asymmetry* **1997**, *8*, 293–301; (f) Genov, M.; Kostova, K.; Dimitrov, V. *Tetrahedron: Asymmetry* **1997**, *8*, 1869–1876; (g) Panda, M.; Phuan, P. W.; Kozlowski, M. C. *J. Org. Chem*. **2003**, *68*, 564–571; (h) de Oliveira, L. F.; Costa, V. E. U. *Tetrahedron: Asymmetry* **2004**, *15*, 2583–2590; (i) Szakonyi, Z.; Balázs, Á.; Martinek, T. A.; Fülöp, F. *Tetrahedron: Asymmetry* **2006**, *17*, 199; (j) Martins, J. E. D.; Mehlecke, C. M.; Gamba, M.; Costa, V. E. U. *Tetrahedron: Asymmetry* **2006**, *17*, 1817–1823.
11. Folöp, F.; Bernáth, G.; Argay, G.; Kálmán, A.; Sohár, P. *Tetrahedron* **1984**, *40*, 2053–2060.
12. Viňa, D.; Santana, L.; Uriarte, E.; Quezada, E.; Valencia, L. *Synthesis*, **2004**, 2517–2523.
13. (a) Wang, X.; Dong, Y.; Sun, J.; Xu, X.; Li, R.; Hu, Y. *J. Org. Chem*. **2005**, *70*, 1897–1900; (b) Bailey, P. D.; Beard, M. A.; Dang, H. P. T.; Phillips, T. R.; Price, R. A.; Whittaker, J. H. *Tetrahedron Lett.* **2008**, *49*, 2150–2153.

14. (a) Ali, H. E. S. *Catal. Commun.* **2007**, *8*, 855–860; (b) Chen, H.; Wang, Y.; Wei, S.; Sun, J. *Tetrahedron: Asymmetry* **2007**, *18*, 1308–1312.
15. (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed.* **1991**, *30*, 49–69; (b) Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc*. **1995**, *117*, 6327–6335; (c) Jessop, P. G.; Brown R. A.; Yamakawa, M.; Xiao, J., Ikariya, T.; Kitamura, M.; Tucker, S. C.; Noyori, R. *J. Supercrit. Fluids* **2002**, *24*, 161–172.
16. Cozzi, P. G.; Papa, A.; Umani-Ronchi, A. *Tetrahedron Lett*. **1996**, *37*, 4613–4616.
17. (a) Sun, J.; Pan, X.; Dai, Z.; Zhu, C. *Tetrahedron: Asymmetry* **2008**, *19*, 2451–2457; (b) Jaworska, M.; Łączkowski, K. Z.; Wełniak, M.; Welke, M.; Wojtczak, A. *Appl. Catal. A: General* **2009**, *357*, 150–158.
18. Nohira, H.; Ehara, K.; Miyashita, A. *Bull. Chem. Soc. Jpn*. **1970**, *43*, 2230–2233.

3. Asymmetric arylation of aromatic aldehydes and the substituent effect by the 1,3-amino alcohols derived from *cis*-(1*R*,2*S*)-2- benzamidocyclohexanecarboxylic acid

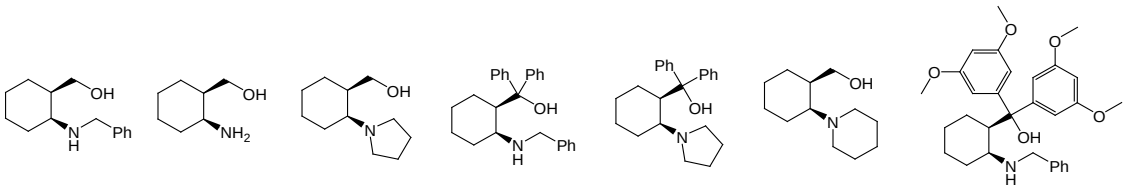
3.1 Introduction

Enantioselective addition of organozinc reagents to aldehydes is one of the most extensively investigated C-C bond formation reactions in the last few decades.[1] A large number of chiral ligands with various structures and reaction features have been developed to meet the demand.[2] Recently, the addition of arylzinc reagents to obtain enantiopure diarylmethanols has gained substantial attention, because they are key structures of pharmaceutically active compounds, such as (*R*)-neobenodine, (*R*)-orphenadrine, and (*S*)-carbinoxamine.[1d-1f,3] In most cases, the desired enantiomer of the product is available from one enantiomer of the ligand. However, it has also recently been reported that chirality inversion of the product can be achieved by a change of substituent with the same framework, that is, with the same ligand chirality.[4] For example, Szakonyi *et al.*[4b] obtained both enantiomers of the product in the asymmetric ethylation of aromatic aldehydes by applying their α-pinene derived 1,3-amino alcohols. However there are as yet no reports on chirality inversion for the asymmetric arylation of aldehydes caused by the substituent effects of chiral ligands. Although both enantiomers of a target diarylmethanol can be obtained by interchanging two reactants, boronic acids and aldehydes, as shown by Bolm *et al.*,[5] it is of interest to determine if a similar chirality inversion is observed by changing the substituents of chiral ligands.

In our previous work on chiral *cis*-(1*R*,2*S*)-2-benzamidocyclohexanecarboxylic acid derived 1,3-amino alcohols as ligands for the catalytic addition of Et_2Zn to arylaldehydes, we found that some ligands with the same configuration of the chiral centers effectively work to induce the opposite chirality in the product.[6] In this study, we investigated the substituent effect of chiral 1,3-amino alcohol ligands to change the chirality of diarylmethanols obtained by the catalytic arylation of arylaldehydes. All optically active 1,3-amino alcohols used in this study were prepared from the same chiral source, *cis*-(1*R*,2*S*)-2-benzamidocyclohexanecarboxylic acid.

3.2 Results and discussion

All of the enantiopure 1,3-amino alcohols in this study were prepared following our previous method.[6]



III **IV** **V** **VIII** **X** **XIII** **XIV**

Figure 3-1. Chiral ligands studied

In order to examine the chiral induction abilities of 1,3-amino alcohols, we chose the aryl transfer reaction to benzaldehyde using 4-chlorophenylboronic acid and diethylzinc as a model reaction. The reaction was conducted in the presence of 20 mol % of 1,3-amino alcohols(**III**–**V**, **VIII**, **X**, **XIII** & **XIV**) and the results are summarized in Table 3-1.

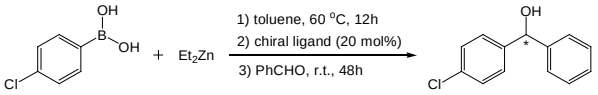
The enantiomeric excess of the obtained diarylmethanol increased with an increase in the number and size of *N*-substituents for primary alcohols **III**–**V**. Primary alcohol **XIII**, which holds larger *N*-substituents, but showed lower enantioselectivity than tertiary amine **V**. With a 5-membered rigid cyclic structure, **V** showed the best chiral induction ability (71.5% ee) than any other ligand studied.

The introduction of two phenyl groups to the vicinity of the hydroxyl group of secondary amine **III** improved both the enantioselectivity (41.7% ee) and the chemical yield (Entries 3 vs. 6). The introduction of two 3,5-dimethoxyphenyl groups further improved the enantioselectivity (53.5% ee) for **XIV**, but decreased the chemical yield dramatically compared with **III** and **VIII** (Entries 3 and 6 vs. 7). This is probably due to increased steric hindrance around the catalytic center. However, in the case of cyclic tertiary amine **X**, the introduction of two phenyl groups largely decreased the enantioselectivity (Entries 1 vs. 5).

In addition, the results summarized in Table 3-1 clearly show the most interesting feature of the present system: both enantiomers of the product were obtained by changing the 1,3-amino alcohol ligands, despite having the same chirality. Primary alcohols **III**–**V** and **XIII** gave (*S*)-isomers, while tertiary alcohols **VIII**, **X** & **XIV** afforded (*R*)-isomers. Previously, we reported that the substituent effect induces opposite chirality in the product of asymmetric ethylation reactions to aldeydes in the

presence of 1,3-amino alcohols **III**–**V**, **X** and **VIII**. Although such phenomena have been observed by several studies, to our knowledge there are still no reports on chirality inversion caused by ligands with the same chirality in the study of asymmetric arylation reactions.

Table 3-1. Asymmetric arylation of benzaldehyde with 4-chlorophenylboronic acid in the presence of 1,3-amino alcohols(**III**–**V**, **VIII**, **X**, **XIII** & **XIV**)[a]



Entry	Chiral ligand	Yield (%)[b]	ee (%)[c]	Config.[d]
1	**V**	80.5	71.5	*S*
2	**XIII**	72.6	51.8	*S*
3	**III**	59.8	16.6	*S*
4	**IV**	29.9	7.3	*S*
5	**X**	75.2	5.4	*R*
6	**VIII**	79.6	41.7	*R*
7	**XIV**	22.9	53.5	*R*

[a]Molar ratio: benzaldehyde/4-$ClC_6H_4B(OH)_2$/Et_2Zn/chiral ligand = 1:2:6:0.2.

[b]Isolated yield.

[c]Determined by HPLC analysis using a chiral column (Chiralpak AD-H; 2-PrOH/*n*-hexane = 10/90; 0.5 mL/min).

[d]Absolute configuration was determined by comparison of the HPLC elution order with the literature data.[7]

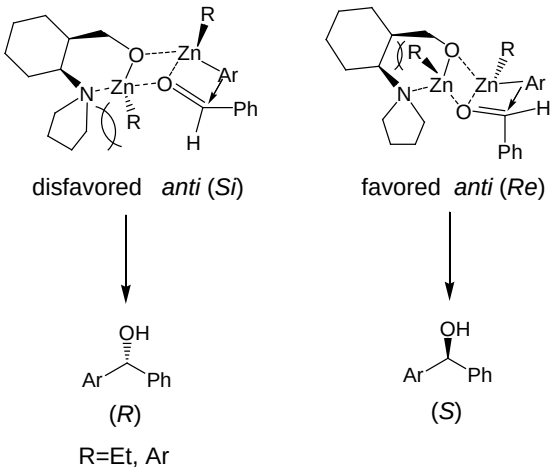


Figure 3-2. Proposed transition states for arylation of benzaldehyde using **V** as a chiral

ligand.

Based on the well-known transition state models proposed by some researchers,[8] the tentative 6/4/4 tricyclo transition states for the asymmetric arylation of aldehydes are shown in Figs. 2, 3 and 4 for **V**, **VIII** and **X**, respectively. In the reaction using **V** as a chiral ligand, the *anti*-(*Re*) transition state, which leads to the formation of the (*S*)-product, is favored over *anti*-(*Si*) because of the steric repulsion difference. In the *anti*-(*Si*) form, large steric repulsion is expected between the R group on Zn atom and the rigid and adjacent bulky cyclic structure of the tertiary amino group in the six-membered Zn-chelate ring, while the *anti*-(*Re*) form has smaller steric repulsion between the cyclohexane ring and the R group on Zn atom in the 1,3-relationship (Fig. 2). The three primary alcohols, **VIII**, **III** and **IV** also showed (*S*)-selectivity but lower enantioselectivity because of the smaller or more flexible *N*-substituents.

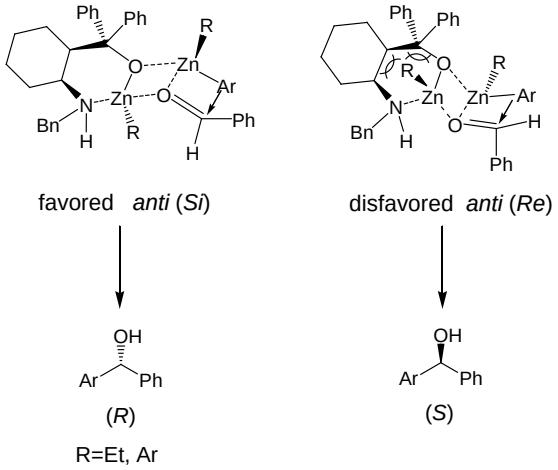


Figure 3-3. Proposed transition states for the arylation of benzaldehyde using **VIII** as a chiral ligand.

Both improved enantioselectivity and the chirality inversion of **VIII** can be similarly explained by the substituent effect in the proposed transition states. It is obvious that the *anti*-(*Re*) form should have much larger steric repulsion with the R group on Zn atom in the 1,3-relationship compared with the transition states of **V**, while the *anti*-(*Si*) form avoids such repulsion to afford the (*R*)-product (Fig. 3).

The additional 1,3-repulsion between the bulky phenyl groups and the R group on Zn atom make the *anti*-(*Re*) form of tertiary alcohol **VIII** less favored than that of primary alcohol **III**. Therefore, the introduction of substituents to the vicinity of the hydroxyl

group can substantially alter the enantioselectivity.

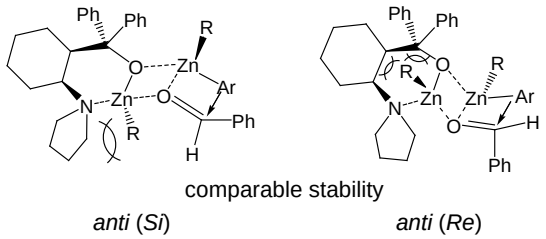
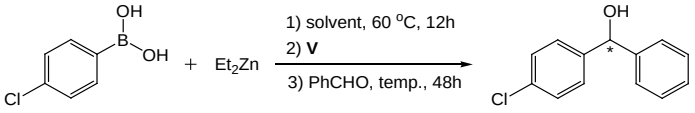


Figure 3-4. Proposed transition states for the arylation of benzaldehyde using **X** as a chiral ligand.

The situation is different, however, for the tertiary amine **X** (Fig. 4); both transition states have comparable steric repulsions. The *anti*-(*Si*) form appears to be slightly favored compared with the *anti*-(*Re*) form, resulting in low enantioselectivity (Entry 5).

Table 3-2. Optimization of the reaction conditions[a]



Entry	Chiral ligand loading (mol %)	Solvent (Toluene / *n*-hexane)	Temp. (°C)	Yield (%)[b]	ee (%)[c]	Config.[d]
1	20	1:0	0	71.3	67.9	*S*
2	20	1:0	r.t.	80.5	71.5	*S*
3	20	1:0	45	85.5	12.8	*S*
4	20	1:1	r.t.	75.9	68.7	*S*
5	20	0:1	r.t.	55.5	59.3	*S*
6	10	1:0	r.t.	73.8	54.9	*S*
7	30	1:0	r.t.	84.6	75.8	*S*
8[e]	20	1:0	r.t.	82.9	71.1	*S*
9[f]	20	1:0	r.t.	37.8	44.3	*S*
10[g]	20	1:0	r.t.	51.8	63.3	*S*

[a]Molar ratio: benzaldehyde/*p*-$ClC_6H_4B(OH)_2$/Et_2Zn = 1:2:6.

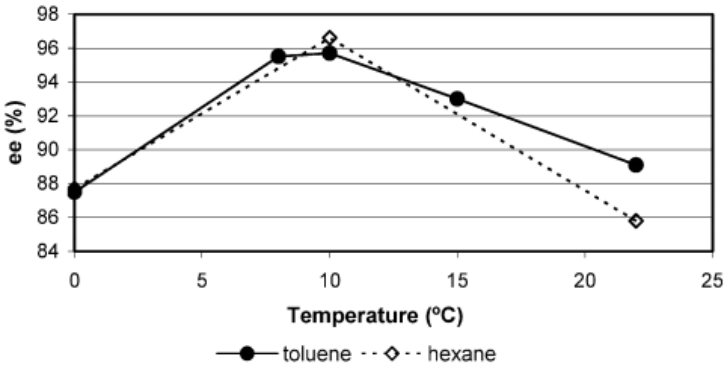
[b]Isolated yield.

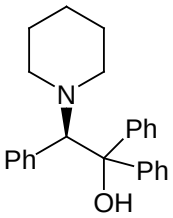
[c]Determined by HPLC analysis using a chiral column (Daicel Chiralpak AD-H; 2-PrOH/hexane = 10/90; 0.5 ml/min).

[d]Absolute configuration was determined by comparison of the HPLC elution order with the literature data.[7,12b]
[e]MPEG (10 mol %): Mw = 2000 g/mol.
[f]Et_3N (10 mol %).
[g]DMAP (10 mol %).

In order to optimize the reaction conditions, tertiary amine **V** was used in the model reaction and the results are summarized in Table 3-2. It was shown that reaction temperature has a large effect on the enantioselectivity, and the best result was obtained at room temperature (71.5% ee; Entry 2). However, only a small effect on conversion was observed (Entries 1–3); therefore, the following reactions were performed at room temperature.

Pericàs *et al.* investigated the relationship between enantioselectivity and temperature at 1 mol% loading of **31**, between 0 °C and 25 °C, for the Ph_2Zn–Et_2Zn addition to 4-tolylaldehyde (Figure 3-5). A maximum enantioselectivity was observed when the reaction was performed around 10 °C in both toluene and hexane. Either raising or lowering the temperature decreased the reaction selectivity.[2e]





31

Figure 3-5. Ee vs temperature in the arylation of 4-tolylaldehyde (**31**, 1 mol%).

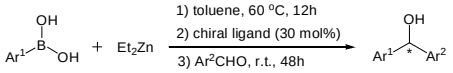
In accordance with reports in the literatures,[3,5-8b,11-17] toluene and *n*-hexane were chosen and the effects on enantioselectivity and conversion were studied (Entries 2, 4 and 5). Toluene afforded a better chemical yield and enantioselectivity than the less polar toluene/*n*-hexane mixture and *n*-hexane, perhaps due to the higher solubility of boronic acid in toluene.

The investigation of ligand loading showed that enantioselectivity and chemical yield

were gradually improved by increasing the amount of **V** (Entries 2, 6 and 7). Ligand loading less than 20 mol % greatly decreased the enantioselectivity of asymmetric arylation reactions (Entries 2 vs. 6).

It has been reported that enantioselectivity is improved by the addition of a catalytic amount of DiMPEG or MPEG.[5,9] However, the addition of MPEG to the present system led to similar enantioselectivity and chemical yield (Entries 2 vs. 8). The addition of Et_3N and DMAP showed that the basic additives could not improve either enantioselectivity or chemical yield (Entries 2, 9 and 10). Possible coordination of the nitrogen atoms of the additives to Zn atoms has a negative effect on the transition states.[10]

Table 3-3. Asymmetric arylation of aldehydes in the presence of **V** and **VIII**[a]



Entry	Chiral ligand	Ar^1	Ar^2	Yield (%)[b]	ee (%)[c]	Config.[d]
1	**V**	4-ClPh	Ph	84.6	75.8	*S*
2	**V**	4-ClPh	4-MePh	78.6	63.5	*S*
3	**V**	4-ClPh	3-MePh	70.9	59.4	-
4	**V**	4-ClPh	2-MePh	60.9	68.5	*R*
5	**V**	4-ClPh	4-MeOPh	78.6	53.2	*S*
6	**V**	4-ClPh	4-BrPh	90.0	>99	*R*
7	**V**	4-ClPh	2-thienyl	56.4	5.2	-
8	**V**	2-MePh	4-MePh	60.3	84.5	*S*
9	**V**	4-MePh	2-MePh	59.0	80.6	*R*
10	**V**	4-MePh	4-MeOPh	38.5	39.3	*R*
11	**V**	4-MePh	4-ClPh	68.8	60.1	*R*
12	**V**	Ph	4-MePh	44.5	49.5	*R*
13	**V**	Ph	4-ClPh	83.5	61.2	*R*
14	**VIII**	Ph	4-ClPh	75.9	46.3	*S*
15	**VIII**	4-ClPh	Ph	74.1	50.2	*R*
16	**VIII**	4-ClPh	4-MePh	78.8	57.2	*R*
17	**VIII**	4-ClPh	4-BrPh	82.7	74.5	*S*
18	**VIII**	4-MePh	4-ClPh	67.6	51.4	*S*
19	**VIII**	4-MePh	4-MeOPh	52.0	34.4	*S*

20	**VIII**	4-MePh	2-MePh	27.6	53.5	*S*

[a]Molar ratio: $Ar^2CHO/Ar^1B(OH)_2/Et_2Zn$/chiral ligand = 1:2:6:0.3.

[b]Isolated yield.

[c]Based on HPLC analysis.

[d]Absolute configuration assigned by comparison of the known elution order with data from reports in the literature.[5,7,8b,11,12b,15,17]

[e]Not determined.

Under optimized conditions, asymmetric arylation reactions of other aromatic aldehydes with arylboronic acids were conducted to further investigate the ligand effect on chiral induction using 30 mol % of **V** and **VIII**. As seen in Table 3-3, all substrates afforded the corresponding diarylmethanols. As is widely known,[5] both enantiomers of the desired products are obtained using the same catalyst by the reverse combination of arylboronic acid and aromatic aldehyde. For example, the reaction of 4-chlorophenylboronic acid with benzaldehyde gave (*S*)-(4-chlorophenyl)-phenylmethanol (75.8% ee, Entry 1), while that of phenylboronic acid and 4-chlorobenzaldehyde gave corresponding (*R*)-isomer (61.2% ee, Entry 13). Unfortunately, the present system was not effective for the heteroaromatic aldehyde (Entry 7), as the enantioselectivity was very low in contrast to the systems by Bolm *et al.*[11] As commented by Noyori *et al.*,[1d] the possible heteroatom coordination to the Zn atom disturbed the transition states of the present ligands.

The substituent effect on chirality inversion (Table 3-1) was reconfirmed for all the other aromatic aldehydes studied; when **V** and **VIII** were used in asymmetric arylation, the opposite enantiomers of each target product were obtained, respectively (e.g., Entries 1 vs. 14, 2 vs. 15, 6 vs. 16, 9-11 vs. 17-19). The use of the substituent effect to switch the product chirality is important for chiral ligand design from certain natural chiral sources.

For the reaction of *p*-substituted benzaldehydes with (4-chlorophenyl)boronic acid, the enantioselectivities decreased in the order of Br > H > Me > OMe for the *para*-substituents of benzaldehyde (Entries 1, 2, 5 and 6). This result suggests that introduction of stronger electron-donating group to benzaldehyde lowers the enantioselectivity. In addition, when comparing the enantioselectivities of the products from *p*-substituted phenylboronic acids and arylaldehydes, (4-chlorophenyl)boronic acid afforded better results than phenylboronic acid and (4-methylphenyl)boronic acid

(e.g., Entries 2 vs. 12, 5 vs. 10). The improved enantioselectivity is attributed to the enhanced reactivity of the arylboronic acid by the electron-withdrawing substituent. In fact, the reaction of (4-chlorophenyl)boronic acid and 4-bromobenzaldehyde afforded excellent chemical yield and selectivity (>99% ee, Entry 6).

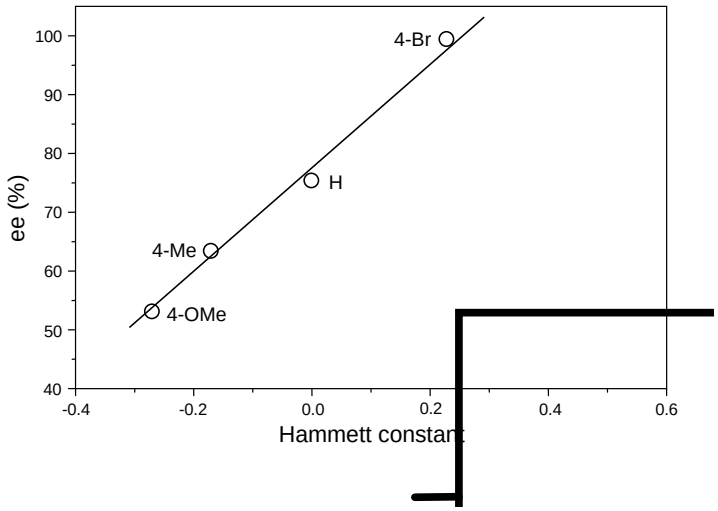


Figure 3-5. The correlation of substituent constants and the asymmetric arylation of *para*-substituted arylaldehydes by 4-chlorophenylboronic acid.

From the slightly higher enantioselectivity observed for the reaction of 2-methylbenzaldehyde (Entry 4) compared with those of 3- and 4-methylbenzaldehydes (Entries 2 and 3), a positional effect of the substituent was suggested for ligand **V**. Considering the *anti*-6/4/4 tricyclo transition states, the *ortho*-substituent will directly lead to an increase in steric repulsion with the alkyl group on Zn atom for the *anti*-(*Si*) form compared with the *anti*-(*Re*) form (Fig. 2). The high enantioselectivity of Entry 9 (80.6% ee) appears to come from the same substituent effect of the *ortho*-methyl group, despite its electron-donating property.

3.3 Conclusions

The enantioselective arylation of aromatic aldehydes was explored in the presence of optically active 1,3-amino alcohols derived from *cis*-(1*R*,2*S*)-2-benzamidocyclohexanecarboxylic acid. The results demonstrated that substituents in the vicinity of the hydroxyl group give a crucial effect on chirality control. Both enantiomers of the product could be obtained using the same chirality ligands with

different substituents. The chirality inversion ability of the substituent effect of 1,3-amino alcohols was confirmed for all aromatic aldehydes studied. The present study will help to design new chiral ligands derived from natural sources, such as amino acids.

3.4 Experimental

All the asymmetric arylation reactions of diethylzinc and arylboronic acid to aldehydes were carried out under nitrogen atmosphere in anhydrous solvents. NMR spectra were recorded at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR) on a Bruker DPX400 spectrometer (Molecular Analysis and Life Science Center, Saitama University) using $CDCl_3$ as solvent. Optical rotations were measured with a JASCO DIP-370 polarimeter. Melting points were obtained using a Mitamura Riken Kogyo MEL-TEMP instrument and uncorrected. IR spectra were recorded on a JASCO FT/IR 400. Enantiomeric excess was determined using a set of JASCO LC 900 series with Chiralpak AD-H, Chiralcel OD, OD-3 or OB-H columns (Daicel Chemical Industries, Ltd.).

(1*R*,2*S*)-2-benzylaminocyclohexylmethanol III

White solid. M.p. 68–68.5 ºC, $[\alpha]_D^{25}$ –24.0 (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35–7.14 (m, 5H), 6.25–5.65 (br, 1H), 3.94–3.87 (m, 1H), 3.82 (d, J = 8.90 Hz, 2H), 3.73–3.71 (m, 1H), 3.00–2.98 (m, 1H), 1.91–1.90 (m, 2H), 1.65–1.36 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.7, 128.6, 128.3, 127.2, 66.4, 58.7, 51.7, 39.0, 27.8, 25.9, 23.5, 22.6; IR (KBr) *v*: 3297, 3198, 3065, 3027, 2925, 2844, 1499, 1483, 1462, 1448, 1370, 1348, 1333, 1203, 1188, 1143, 1105, 1080, 1065, 1033, 966, 914, 899, 864, 840, 805, 748, 696 cm^{-1}; HRMS (ESI+) calcd for $C_{14}H_{22}NO$ 220.1696 ($M+H^+$), found 220.1615.

(1*R*,2*S*)-2-aminocyclohexylmethanol IV

White solid. M.p. 60–62 ºC, $[\alpha]_D^{19}$ +16.9 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.81–3.70 (m, 2H), 3.27–3.25 (m, 1H), 3.21–2.85 (br, 3H), 1.73–1.70 (m, 1H), 1.60–1.44 (m, 7H), 1.36–1.28 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 66.3, 51.0, 41.1, 33.0, 24.6, 24.2, 21.3; IR (KBr) *v*: 3445, 3335, 2934, 2846, 1488, 1386, 1355, 1335, 1303, 1105, 1092, 1059, 1047, 1026 cm^{-1}; HRMS (ESI+) calcd for $C_7H_{16}NO$ ($M+H^+$) 130.1226, found 130.1278.

(1*R*,2*S*)-2-pyrrolidin-1'-ylcyclohexylmethanol V

Light yellow liquid. $[\alpha]_D^{26}$ +21.4 (*c* 0.39, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 4.20–4.10 (m, 1H), 3.48–3.44 (m, 1H), 2.87–2.58 (m, 2H), 2.57–2.39 (m, 2H), 2.38–2.31 (m, 2H), 1.76–1.59 (m, 7H), 1.49–1.46 (m, 1H), 1.38–1.15 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 67.9, 64.0, 52.2, 36.2, 28.1, 25.8, 25.7, 23.0, 20.7; IR (KBr) *v*: 3437, 3393, 3318, 2934, 2856, 2778, 2708, 1654, 1445, 1408, 1126, 1107, 1036, 953, 915, 888 cm^{-1}; HRMS (ESI+) calcd for $C_{11}H_{22}NO$ 184.1696 ($M+H^+$), found 184.1673.

(1*R*,2*S*)-2-benzylaminocyclohexyldiphenylmethanol VIII

Colorless viscous liquid. $[\alpha]_D^{26}$ +85.6 (*c* 2.6, MeOH); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.54–8.25 (br, 1H), 7.67–7.65 (m, 2H), 7.55–7.52 (m, 2H), 7.34–7.24 (m, 9H), 7.16–7.09 (m, 2H), 3.59 (d, *J* = 12.21 Hz, 1H), 3.24 (d, *J* = 12.10 Hz, 1H), 3.15–2.94 (m, 1H), 2.48–2.44 (m, 1H), 1.92–1.89 (m, 1H), 1.76–1.68 (m, 1H), 1.67–1.46 (m, 4H), 1.44–1.22 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.1, 146.9, 139.3, 128.6, 128.3, 128.2, 128.0, 127.4, 125.9, 125.8, 125.5, 125.2, 80.6, 54.1, 52.0, 47.3, 28.5, 25.8, 21.6, 20.2; IR (KBr) *v*: 3317, 3060, 2926, 2852, 1597, 1491, 1468, 1450, 1432, 1381, 1210, 1176, 1136, 1067, 1032, 992, 881, 747, 698 cm^{-1}; HRMS (ESI+) calcd for $C_{26}H_{30}NO$ 372.2322 ($M+H^+$), found 372.2896.

(1*R*,2*S*)-2-pyrrolidin-1'-ylcyclohexyldiphenylmethanol X

White solid. M.p. 143–145 ºC, $[\alpha]_D^{27}$ +4.4 (*c* 0.34, $CHCl_3$); ^1H NMR: ($CDCl_3$, 400 MHz): δ 9.31–8.65 (br, 1H), 7.66–7.64 (m, 2H), 7.54–7.52 (m, 2H), 7.30–7.23 (m, 4H), 7.14–7.08 (m, 2H), 3.19 (s, 1H), 2.92–2.18 (m, 4H), 1.93–1.83 (m, 2H), 1.69–1.49 (m, 8H), 1.43–1.37 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.3, 147.1, 128.1, 128.0, 125.8, 125.7, 125.5, 125.0, 80.6, 63.7, 54.1, 51.9, 48.0, 29.7, 26.4, 24.4, 22.6; IR (KBr) *v*: 3426, 3055, 3032, 2952, 2916, 2840, 1460, 1447, 1434, 1399, 1343, 1253, 1179, 1143, 1066, 1032, 994, 908, 855, 768, 752, 707 cm^{-1}; HRMS (ESI+) calcd for $C_{23}H_{30}NO$ 336.2322 ($M+H^+$), found 336.2583.

(1*R*,2*S*)-2-piperidin-1'-ylcyclohexylmethanol XIII

Light yellow liquid. $[\alpha]_D^{26}$ +16.5 (*c* 0.40, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ

4.22–4.17 (m, 1H), 3.49–3.46 (m, 1H), 2.85–2.40 (br, 1H), 2.50–2.39 (m, 5H), 1.93–1.74 (m, 2H), 1.70–1.15 (m, 13H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 66.8, 63.9, 51.7, 34.9, 28.7, 26.3, 26.2, 24.4, 23.8, 21.0; IR (KBr) *v*: 3334, 3220, 2934, 2862, 2791, 1655, 1638, 1449, 1104, 1077, 1038, 987, 961, 874 cm^{-1}; HRMS (ESI+) calcd for $C_{12}H_{23}NO$ 197.1774 (M^+), found 197.1218.

(1*R*,2*S*)-(2-benzylaminocyclohexyl)bis(3,5-dimethoxyphenyl)methanol XIV

Colorless viscous liquid. $[\alpha]_D^{25}$ +64.7 (*c* 4.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.60–8.32 (br, 1H), 7.51–7.22 (m, 5H), 6.98–6.69 (m, 4H), 6.51–6.23 (m, 2H), 3.76 (s, 12H), 3.62 (d, *J* = 12.24 Hz, 1H), 3.30 (d, *J* = 12.04 Hz, 1H), 3.19–2.99 (m, 1H), 2.48–2.30 (m, 1H), 2.02–1.87 (m, 1H), 1.86–1.28 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.6, 160.4, 151.7, 149.3, 139.2, 128.6, 128.3, 127.4, 104.1, 103.7, 97.8, 80.8, 55.3, 55.2, 54.2, 47.3, 28.5, 25.8, 21.7, 20.2; IR (KBr) *v*: 3437, 3079, 3002, 2934, 2841, 1595, 1509, 1458, 1425, 1335, 1308, 1287, 1204, 1154, 1063, 925, 832, 740, 697 cm^{-1}; HRMS (ESI+) calcd for $C_{30}H_{37}NO_5$ 491.2666 (M^+), found 491.2994

General procedure for the asymmetric addition of diethylzinc to aldehydes

Diethylzinc (0.9 mmol, 1.0 M in *n*-hexane) was added to a solution of arylboronic acid (0.3 mmol) in toluene (1.5 ml) under nitrogen atmosphere. After stirring for 12 h at 60 ºC, the mixture was cooled to room temperature, and chiral ligand (30 mol %, in 0.5 ml toluene) was added. After stirring for additional 30 min, aldehyde (0.15 mmol, in 0.5 ml toluene) was added under nitrogen atmosphere. After stirring for 48 h at room temperature, the reaction was quenched with 1 N HCl aq. The mixture was extracted twice with ethyl acetate. The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4, then filtered and the solvent was removed. After the crude product was purified by silica gel TLC, pure diarylmethanol was obtained. The absolute configuration and the enantiomeric excess were determined by the chiral HPLC analysis.

(*S*)-(4-Chlorophenyl)phenylmethanol[2b,7,12b,6]

White solid. 84.6 % isolated yield. 75.8% ee determined by HPLC analysis (Chiralpak AD-H column, IPA:*n*-hexane = 10:90, 0.5 ml/min, 254 nm). Retention time: *t* = 18.0

min ((*R*)-isomer: *t* = 16.6 min). m.p. 53.5–55.2 °C (69.0% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.26 (m, 9H), 5.81 (s, 1H), 2.26 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.4, 142.1, 133.2, 128.6, 128.5, 128.3, 127.8, 125.9, 75.5.

(*R*)-(4-methylphenyl)phenylmethanol[2b,7,16]

White solid. 44.5 % isolated yield. 49.5% ee determined by HPLC analysis (Chiralcel OB-H column, IPA:*n*-hexane = 10:90, 0.5 ml/min, 254 nm). Retention time: *t* = 29.3 min ((*S*)-isomer: *t* = 44.9 min). m.p. 57.5–59.0 °C (44.9% ee). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42–7.26 (m, 4H), 7.25–7.22 (m, 3H), 7.17–7.12 (m, 2H), 5.83 (s, 1H), 2.33 (s, 3H), 2.17 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.9, 140.9, 137.2, 129.1, 128.4, 127.4, 126.4, 126.4, 76.0, 21.0.

(*S*)-(4-Chlorophenyl)(4'-methylphenyl)methanol[8b]

White solid. 78.6 % isolated yield. 63.5% ee determined by HPLC analysis ((Chiralcel OD and OD-3 columns, IPA:*n*-hexane = 2:98, 1.0 ml/min, 230 nm). Retention time (Chiralcel OD): *t* = 56.7 min ((*R*)-isomer: *t* = 52.2 min). Retention time (Chiralcel OD-3): *t* = 67.9 min ((*R*)-isomer: *t* = 63.9 min). m.p. 64.0–66.0 °C (63.5% ee). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31–7.14 (m, 8H), 5.79 (s, 1H), 2.33 (s, 3H), 2.20 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.3, 140.5, 137.6, 133.1, 129.3, 128.5, 127.7, 126.4, 75.4, 21.0.

(*S*)-(4-Chlorophenyl)(4'-methoxyphenyl)methanol[8b]

White solid. 78.6 % isolated yield. 53.2% ee determined by HPLC analysis (Chiralcel OD and OD-3 columns, IPA:*n*-hexane = 2:98, 0.5 ml/min, 230 nm). Retention time (Chiralcel OD): *t* = 89.3 min ((*R*)-isomer: *t* = 97.7 min). Retention time (Chiralcel OD-3): *t* = 100.0 min ((*R*)-isomer: *t* = 108.6 min). m.p. 65.4–67.0 °C (53.2% ee). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30–7.23 (m, 6H), 6.87–6.85 (m, 2H), 3.79 (d, *J*=5.70 Hz, 3 H), 2.27 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.3, 142.5, 135.8, 133.1, 128.5, 127.9, 127.8, 127.2, 114.0, 113.8, 75.2, 55.3.

(*S*)-(4-Bromophenyl)(4'-chlorophenyl)methanol[7]

White solid. 82.7 % isolated yield. 74.5% ee determined by HPLC analysis (Chiralpak

AD-H column, IPA:*n*-hexane = 1:99, 0.5 ml/min, 230 nm). Retention time: *t* = 183.7 min ((*R*)-isomer: *t* = 179.1 min). m.p. 95.5–97.0 °C (74.5% ee). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46–7.44 (m, 2H), 7.31–7.15 (m, 6H), 5.74 (s, 1H), 2.44 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.4, 141.8, 133.6, 131.7, 131.5, 128.8,128.2, 127.9, 127.7, 121.7, 75.0.

(*S*)-(2-Methylphenyl)(4'-methylphenyl)methanol[7,8b]

Pale yellow oil. 60.3 % isolated yield. 84.5% ee determined by HPLC analysis (Chiralcel OD and OD-3 columns, IPA:*n*-hexane = 2:98, 0.5 ml/min, 254 nm). Retention time (Chiralcel OD): *t* = 41.1 min ((*R*)-isomer: *t* = 36.2 min). Retention time (Chiralcel OD-3): *t* = 55.0 min ((*R*)-isomer: *t* = 48.0 min). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.55–7.53 (m, 1H), 7.25–7.12 (m, 7H), 5.96 (s, 1H), 2.32 (s, 3H), 2.23 (s, 3H), 2.12 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 141.49, 139.87, 137.23, 135.19, 130.41, 129.10, 127.34, 127.02, 126.01, 73.1, 21.0, 19.3.

(*R*)-(4-Chlorophenyl)(2'-methylphenyl)methanol[11,15]

Pale yellow oil. 60.9 % isolated yield. 68.5% ee determined by HPLC analysis (Chiralcel OD column, IPA:*n*-hexane = 1:99, 1.0 ml/min, 254 nm). Retention time: *t* = 48.4 min ((*S*)-isomer: *t* = 54.7 min). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46–7.42 (m, 1H), 7.32–7.13 (m, 7H), 5.97 (s, 1H), 2.24 (s, 3H), 2.16 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 141.4, 141.1, 135.4, 133.3, 130.7, 128.6, 128.4, 127.8, 126.4, 126.3, 72.8, 19.4.

(4-Chlorophenyl)(3'-methylphenyl)methanol

Pale yellow oil. 70.9 % isolated yield. 59.4% ee determined by HPLC analysis (Chiralcel OD column, IPA:*n*-hexane = 1:99, 1.0 ml/min, 230 nm). Retention time: t_{major} = 49.2 min, t_{minor} = 42.9 min. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33–7.21 (m, 5H), 7.15–7.08 (m, 3H), 5.77 (s, 1H), 2.33 (s, 3H), 2.25 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.3, 142,2, 138.3, 133.1, 128.6, 128.5, 127.8, 127.1, 123.5, 75.6, 21.4.

(*R*)-(4-Methoxyphenyl)(4'-methylphenyl)methanol[11]

White solid. 38.5 % isolated yield. 57.1% ee determined by HPLC analysis (Chiralcel OD-H column, IPA:*n*-hexane = 5:95, 0.5 ml/min, 210 nm). Retention time: *t* = 38.4 min

((*S*)-isomer: t = 42.6 min). m.p. 75.2–77.0 °C (57.1% ee). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29–7.24 (m, 4H), 7.15–7.13 (m, 2H), 6.87–6.85 (m, 2H), 5.78 (s, 1H), 3.79 (s, 3H), 2.33 (s, 3H), 2.14 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.5, 138.7, 134.7, 133.9, 126.7, 125.3, 123.9, 111.4, 70.1, 52.8, 18.6.

(4-Chlorophenyl)(2'-thienyl)-methanol[17]

Pale yellow oil. 56.4 % isolated yield. 5.2% ee determined by HPLC analysis (Chiralpak AD-H column, IPA:*n*-hexane = 2:98, 1.0 ml/min, 254 nm). Retention time: t_{major} = 31.8 min, t_{minor} = 36.0 min. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40–7.27 (m, 5H), 6.96–6.89 (m, 2H), 6.05 (s, 1H), 2.40 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.6, 141.5, 133.7, 128.6, 127.6, 126.7, 125.7, 125.0, 71.6.

3.5 References

1. (a) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833–856; (b) Noyori, R.; Kitamura, M. *Angew. Chem. Int. Ed.* **1991**, *30*, 49–69; (c) Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M.; Oguni, N.; Hayashi, M.; Kaneko, T.; Matsuda, Y. *J. Organomet. Chem.* **1990**, *382*, 19–37; (d) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757–824; (e) Walsh, P. J. *Acc. Chem. Res.* **2003**, *36*, 739; (f) Schmidt, F.; Stemmler, R. T.; Rudolph, J.; Bolm, C. *Chem. Soc. Rev.* **2006**, *35*, 454–470; (g) Fontes, M.; Verdaguer, X.; Solà, L.; Pericàs, M. A.; Riera, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 1098–1101; (h) Rolland, J.; Cambeiro, X. C.; Rodriguez-Escrich, C.; Pericàs, M. A. *Beilstein J. Org. Chem.* **2009**, *5*, No. 56, doi:10.3762/bjoc.5.56.
2. (a) Bolm, C.; Hermanns, N.; Hildebrand, J. P.; Muñiz, K. *Angew. Chem. Int. Ed.* **2000**, *39*, 3465–3467; (b) Wu, X.; Liu, X.; Zhao, G. *Tetrahedron: Asymmetry* **2005**, *16*, 2299–2305; (c) Ji, J.-X.; Wu, J.; Au-Yeung, T. T.-L.; Yip, C.-W.; Haynes, R. K.; Chan, A. S. C. *J. Org. Chem.* **2005**, *70*, 1093–1095; (d) Jin, M.-J.; Sarkar, S. M.; Lee, D.-H.; Qiu, H. *Org. Lett.* **2008**, *10*, 1235–1237; (e) Rodríguez-Escrich, S.; Reddy, K. S.; Jimeno, C.; Colet, G.; Rodríguez-Escrich, C.; Solá, L.; Vidal-Ferran, A.; Pericàs, M. A. *J. Org. Chem.* **2008**, *73*, 5340–5353.
3. (a) Harms, A. F.; Nauta, W. T. *J. Med. Pharm. Chem.* **1960**, *2*, 57–77; (b) Sperber, N.; Papa, D.; Schwenk, E.; Sherlock, M. *J. Am. Chem. Soc.* **1949**, *71*, 887–890; (c) Fontes, M.; Verdaguer, X.; Solà, L.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2004**, *69*, 2532–2543.

4. (a) Okamoto, K.; Kimachi, T.; Ibuka, T.; Takemoto, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 463–467; (b) Szakonyi, Z.; Balázs, Á.; Martinek, T. A.; Fülöp, F. *Tetrahedron: Asymmetry* **2006**, *17*, 199–204; (c) You, J.-S.; Shao, M.-Y.; Gau, H.-M. *Tetrahedron: Asymmetry* **2001**, *12*, 2971–2975; (d) Cicchi, S.; Crea, S.; Goti, A.; Brandi, A. *Tetrahedron: Asymmetry* **1997**, *8*, 293–301.
5. (a) Bolm, C.; Rudolph, J. *J. Am. Chem. Soc.* **2002**, *124*, 14850–14851; (b) Rudolph, J.; Hermanns, N.; Bolm, C. *J. Org. Chem.* **2004**, *69*, 3997–4000.
6. Wang, X.; Kodama, K.; Hirose, T.; Zhang, G. *Chin. J. Chem.* **2010**, *28*, 61–68.
7. Yang, X.-F.; Hirose, T.; Zhang, G.-Y. *Tetrahedron: Asymmetry* **2009**, *20*, 415–419.
8. The mechanism study about the asymmetric arylation catalyzed by 1,2-amino alcohols: (a) Liu, C.; Guo, Z.-L.; Weng, J.; Lu, G.; Chan, A. S. C. *Chirality* **2009**, doi: 10.1002/chir.20721, in press; (b) Wang, M.-C.; Wang, X.-D.; Ding, X.; Liu, Z.-K. *Tetrahedron* **2008**, *64*, 2559–2564.

   The mechanism study about the asymmetric ethylation catalyzed by 1,2-amino alcohols: (c) Kiramura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028–4036; (d) Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc*. **1995**, *117*, 6327–6335; (e) Jessop, P. G.; Brown R. A.; Yamakawa, M.; Xiao, J., Ikariya, T.; Kitamura, M.; Tucker, S. C.; Noyori, R. *J. Supercrit. Fluids* **2002**, *24*, 161–172; (f) Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc*. **1987**, *109*, 7111–7115.

   The mechanism study about the asymmetric ethylation catalyzed by 1,3-amino alcohols: (g) Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett*. **1988**, *29*, 5645–5648; (h) Panda, M.; Phuan, P.-W.; Kozlowski, M. C. *J. Org. Chem*. **2003**, *68*, 564–571; (i) Oliveira, L. F.; Costa, V. E. U. *Tetrahedron: Asymmetry* **2004**, *15*, 2583–2590.
9. Rudolph, J.; Loumann, M.; Bolm, C.; Dahmen, S. *Adv. Synth. Catal.* **2005**, *347*, 1361–1368.
10. (a) Asami, M.; Inoue, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1687–1690; (b) Blay, G.; Fernández, I.; Marco-Aleixandre, A.; Pedro, J. R. *Tetrahedron: Asymmetry* **2005**, *16*, 1207–1213.
11. Schmidt, F.; Rudolph, J.; Bolm, C. *Adv. Synth. Catal.* **2007**, *349*, 703–708.
12. (a) Braga, A. L.; Lüdtke, D. S.; Vargas, F.; Paixão, M. W. *Chem. Commun.* **2005**, 2512–2514; (b) Braga, A. L.; Paixão, M. W.; Westermann, B.; Schneider, P. H.; Wessjohann, L. A. *J. Org. Chem.* **2008**, *73*, 2879–2882.
13. Wu, P.-Y.; Wu, H.-L.; Uang, B.-J. *J. Org. Chem.* **2006**, *71*, 833–835.

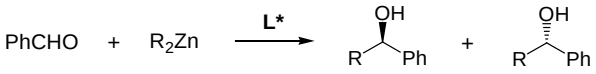
14. Liu, X. Y.; Wu, X. Y.; Wu, Y. Y.; Zhao, G.; Zhu, S. Z. *J. Org. Chem.* **2005**, *70*, 7432–7435.
15. Wang, M.-C.; Zhang, Q.-J.; Zhao, W.-X.; Wang, X.-D.; Ding, X.; Jing, T.-T.; Song, M.-P. *J. Org. Chem.* **2008**, *73*, 168–176.
16. Bolm, C.; Schmidt, F.; Zani, L. *Tetrahedron: Asymmetry* **2005**, *16*, 1367–1476.
17. Liu, X.; Qiu, L.; Hong, L.; Yan, W.; Wang, R. *Tetrahedron: Asymmetry* **2009**, *20*, 616–620.

4. Summary

A series of optically active 1,3-amino alcohols were synthesized and applied as the chiral ligands for the asymmetric alkylation and arylation reactions. Among the optically active 1,3-amino alcohols, (1*R*,2*S*)-2-pyrrolidin-1'-ylcyclohexylmethanol (**V**) showed the best promoting ability to aromatic aldehydes for asymmetric alkylation (up to 72.1 % yeld; up to 79.4 % ee) and arylation (up to 90.0% yeld; up to >99% ee) reactions.

Most interestingly, not only the enantioselectivity but also the stereochemistry of the product was controlled by the *N*-substituents and the substituents on the vicinity carbon to hydroxyl group. The substituent effect on chirality control of 1,3-amino alcohols was confirmed in both of the two organozinc addition reactions: that is, (1*R*,2*S*)-2-pyrrolidin-1'-ylcyclohexylmethanol (**V**) showed the opposite enantioselectivity to that of (1*R*,2*S*)-2-benzylaminocyclohexyl(diphenyl)methanol (**VIII**). The enantioselectivity and the ee values of the products of asymmetric alkylation and arylation reactions are summarized for **III**, **IV**, **V**, **VIII** and **X** in Table 4-1.

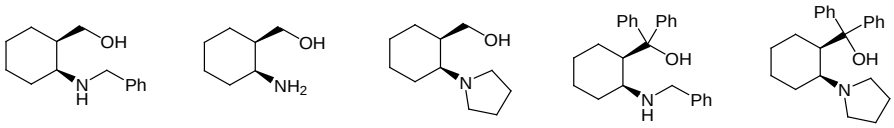
Table 4-1. The ligand effect on enantioselectivity in the asymmetric alkylation and arylation reaction.



R \ L*	**III** (% ee)	**IV** (% ee)	**V** (% ee)	**VIII** (% ee)	**X** (% ee)
Et[a]	33.0/(*S*)	9.8/(*S*)	71.2/(*R*)	65.5/(*S*)	27.2/(*S*)
4-Cl-Ph[b]	16.6/(*S*)	7.3/(*S*)	71.5/(*S*)	41.7/(*R*)	5.4/(*R*)

[a]Molar ratio: PhCHO/Et_2Zn/L* = 1/3/0.1.

[b]Molar ratio: PhCHO/4-$ClC_6H_4B(OH)_2$/ Et_2Zn/L* = 1:2:6:0.2.



III **IV** **V** **VIII** **X**

Figure 4-1. Chiral ligands

The chirality inversion of the product can be explained by employing the well-known *anti*-6/4/4 tricyclic transition state as shown in Figures 4-2 and 4-3.

In the reaction using **V** as a chiral ligand, the *anti*-(*Re*) transition state, which leads to (*Re*)-face attack of the carbonyl carbon, is favored over *anti*-(*Si*) because of the steric repulsion difference. In the *anti*-(*Si*) form, large steric repulsion is expected between the R group on Zn atom in the six-membered ring and the rigid and adjacent bulky cyclic structure of the tertiary amino group, while the *anti*-(*Re*) form has smaller steric repulsion between the cyclohexane ring and the R group on Zn atom in the 1,3-relationship (Fig. 4-2).

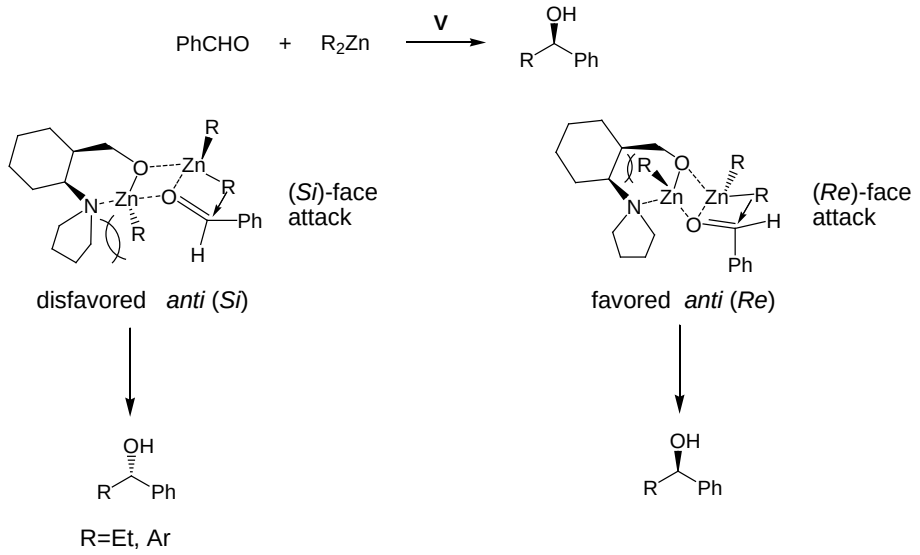


Figure 4-2. Proposed transition states for alkylation or arylation of benzaldehyde using **V** as a chiral ligand.

On the other hand, when **VIII** is used as a chiral ligand, obviously that the *anti*-(*Re*) form has much larger steric repulsion between the cyclohexane ring, the Ph group and the R group on Zn atom in the 1,3-relationship in the six-membered Zn-chelate ring, while the *anti*-(*Si*) form avoids such repulsion to make the (*Si*)-face attack of the carbonyl carbon easier (Fig. 4-3).

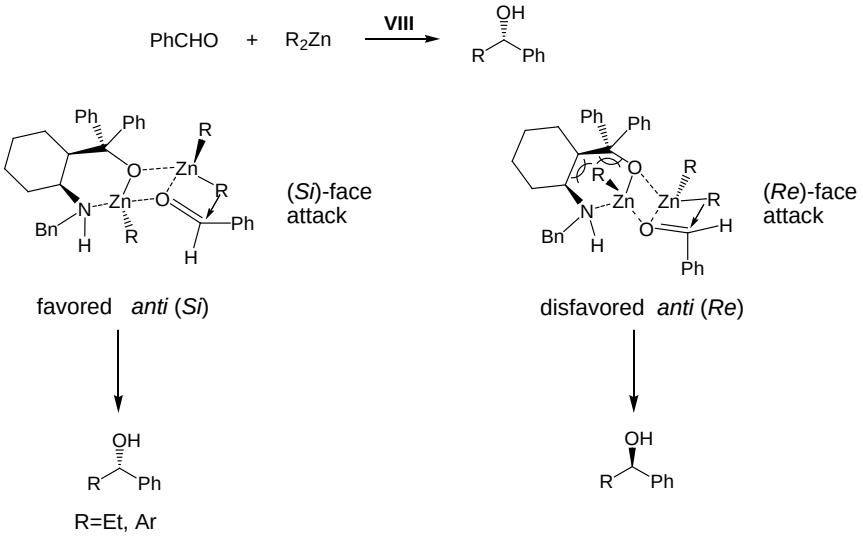


Figure 4-3. Proposed transition states for the alkylation or arylation of benzaldehyde using **VIII** as a chiral ligand.

The ligands **III**, **IV**, and **X** showed low enantioselectivities in the two organozinc addition reactions and the corresponding chirality control in the asymmetric alkylation and alkylation was irregular (Table 4-1). For the ligands **III** and **IV**, the small and flexible substituents can not cause enough steric repulsion deference in the two transition states (*anti*-(*Si*) & *anti*-(*Re*)) to make one of them more favored than another. For the ligands **X**, although it has a rigid bulky cyclic structure of the tertiary amino group and the Ph group, these substituents make the two transition states (*anti*-(*Si*) & *anti*-(*Re*)) have comparable stability and neither of them is greatly favored (Fig. 4-3).

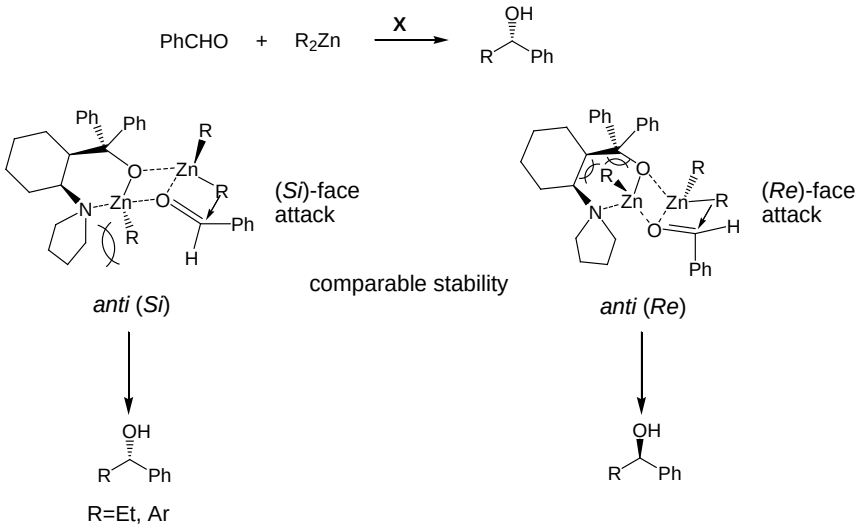


Figure 4-4. Proposed transition states for the alkylation or arylation of benzaldehyde

using **X** as a chiral ligand.

The present research demonstrated that chirality control of the products could be achieved by choosing the proper substituents on the chiral ligands. The results are very interesting because that it is important for the design of chiral ligands from certain starting materials in hand like natural products. When both enantiomers of a chiral ligand are readily available, they can be applied to the asymmetric reactions to give both enantiomers of the product. However, when that is not the case, chemists will find the importance of our research.

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