Tetrahedron: *Asymmetry* 25 (2014) 289–297

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

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

The synthesis of chiral amino diol tridentate ligands and their enantioselective induction during the addition of diethylzinc to aldehydes

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ARTICLE INFO

Article history:
Received 13 August 2013
Accepted 5 November 2013

ABSTRACT

A series of C_2-symmetric chiral amino diol tridentate ligands **3a–g** were prepared from achiral bulky organolithiums, achiral bulky primary amines, and optically active epichlorohydrin (ECH). The prepared C_2-symmetric chiral amino diol tridentate ligands were capable of inducing enantioselectivity in the model reaction of aromatic and aliphatic aldehydes with diethylzinc with an ee of up to 96%. The enantioselectivity can be modulated by adjusting the steric hindrance of the achiral reagents employed in the synthesis of the chiral ligand. The configuration of the addition product depended on the configuration of the amino diol ligands, which can be simply controlled as desired by using the ECH with the desired configuration during the preparation of the ligand.

1. Introduction

Chiral amino alcohols possess the ability to induce enantioselective reactions and have been used as chiral ligands in many asymmetric reactions, such as asymmetric additions of diethylzinc to aldehydes,[1–6] asymmetric Michael addition reactions,[7–9] asymmetric Diels–Alder reactions,[10,11] and asymmetric hydrogenations of aromatic ketones.[12–15] There are two common methods for preparing a chiral amino alcohol: one is to reduce a natural amino acid,[16–19] while the other is to resolve a racemic amino alcohol.[20–22] With the method that reduces a natural amino acid, the structure of the obtained amino alcohol is restricted by the structure of the amino acid used. With the method that resolves a racemic amino alcohol, an expensive chiral reagent must be employed. In order to diversify the structure of chiral amino alcohols, the reaction of an amine with an optically active epoxide has been used in recent years. Manickam and Sundararajan applied the reaction of optically active styrene oxide with benzylamine to obtain a chiral, C_2-symmetric amino diol tridentate ligand[23] and found that the obtained amino diol possessed the ability to enantioselectively induce Michael addition reactions[24] and Diels–Alder reactions.[25] Grassi et al. prepared (+)-(*S*,*S*,*S*)-triisopropanolamine with 94% ee via the reaction of (*S*)-(+)-1-amino-2-propanol with ammonia[26] while Nugent employed (+)-(*S*,*S*,*S*)-triispropanolamine as a ligand to prepare a chiral Lewis acid to catalyze enantioselective additions of azides to meso epoxides.[27] The problem for preparing chiral amino diol when applying the reaction of an amine with optically active epoxide is the source of the chiral epoxide. There are two methods for preparing optically active epoxides: one is by kinetic resolution of a racemic epoxide[28] while the other is by asymmetric epoxidation of an olefin.[29–33] There is no universal kinetic resolving method and no universal resolving conditions for the resolution of epoxides with various structures. Therefore, the availability of optically active epoxides is limited.

Recently, a method for the kinetic resolution of racemic epichlorohydrin (ECH) has been established. Due to the ease of recovering and recycling the hydrolyzing product, ECH is not lost during the kinetic resolution process. So far, the kinetic resolution of ECH has been industrialized and both (*R*)-ECH and (*S*)-ECH have become very inexpensive (ca. US$ 9 per kilogram).[34] Based on the inexpensive optically active ECH, C_2-symmetric chiral amino diol tridentate ligands were synthesized using optically active ECH as the chiral source and their enantioselective inductivity in the addition of diethylzinc to aldehydes was assessed.

2. Results and discussion

2.1. The design strategy for the synthesis of chiral amino diol tridentate ligands

The reaction of an organometallic reagent R–M with optically active ECH should create an optically active, substituted propylene epoxide **2** (Scheme 1). The reaction of **2** with a primary amine should create chiral amino diol tridentate ligand **3**. The designed synthetic route to the amino diols is shown in Scheme 1.

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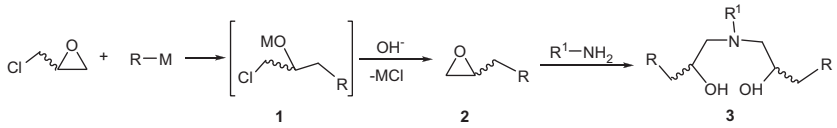
0957-4166/$ - see front matter © 2014 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.tetasy.2013.11.007



Scheme 1. Route for synthesizing chiral amino diol tridentate ligands.

By selecting various R and R^1 groups, the steric hindrance of the chiral amino diol ligand **3** could be adjusted and the enantioselective influence of **3** improved. We assumed that an increase in the bulk of R would be favorable not only to the enhancement of the enantioselectivity of the ligand, but also to the reinforcement of the attack at the CH_2 group of the epoxide ring and to the suppression of attack at the CH of the epoxide ring. Therefore, the bulky organolithium reagents 9-ethyl-9-lithiumfluorene **A**, triphenylmethyl-lithium **B**, and 5-pentyl-5-lithiumdibenzo[*a*,*e*] suberane (**C**) (Fig. 1) were selected as nucleophilic reagents to react with by *n*-BuLi to afford solutions of organolithium **A** and organolithium **B**, respectively.

The preparation of organolithium reagent **C** is described in Scheme 3. 5-Methene dibenzosuberane was reacted with *n*-butyllithium in tetrahydrofuran (THF) to afford a solution of **C**.

A solution of optically active ECH was added dropwise to a solution of the organolithium reagent at −70 °C with stirring. After the addition, the reaction mixture was stirred at −70 °C for 1 h and then stirred at room temperature for 2 h to create the optically active propene oxide **2**. The yield obtained for **2a**, **2b**, and **2c** was

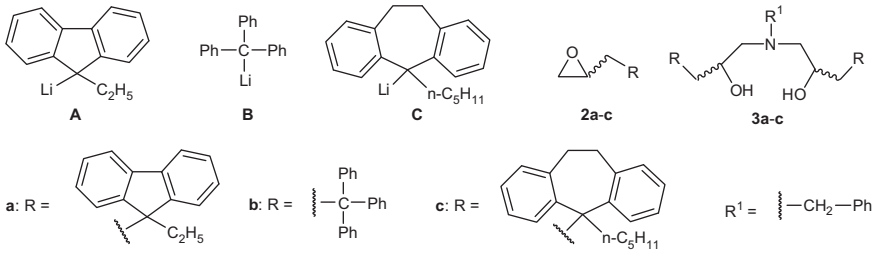


Figure 1. The structures of the organolithium reagent, substituted propylene epoxides **2a**–**c**, and chiral amino diol tridentate ligands **3a**–**c**.

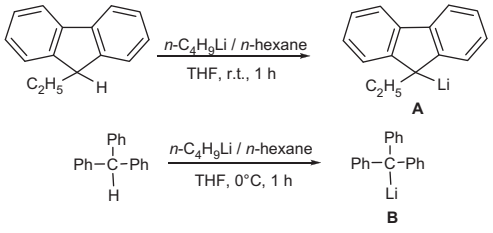
optically active ECH to create optically active, substituted propylene epoxides **2a**–**c**, respectively (Fig. 1). The bulk of the R^1 group should also have an impact on the enantioselectivity of **3**.

With benzylamine in hand, amino diols **3a**–**c** (Fig. 1) were synthesized. The impact of the R group on the enantioselectivity of the amino diol chiral ligand was examined in order to determine which R group gave the amino diol ligand with the best enantioselectivity. Then with the R group established, other amino diols were synthesized and the impact of the R^1 group on the enantioselectivity of the chiral amino diol ligand was examined.

2.2. The synthesis of chiral amino diol ligands 3

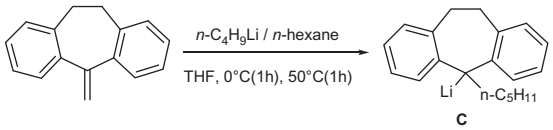
2.2.1. The synthesis of substituted propene oxides 2

The preparation of organolithium reagent **A** and organolithium reagent **B** is described in Scheme 2. 9-Ethylfluorene and triphenyl-



Scheme 2. The preparation of organolithium **A** and **B**.

methane were used, respectively as starting materials. The active hydrogen atom of the starting material molecule was removed



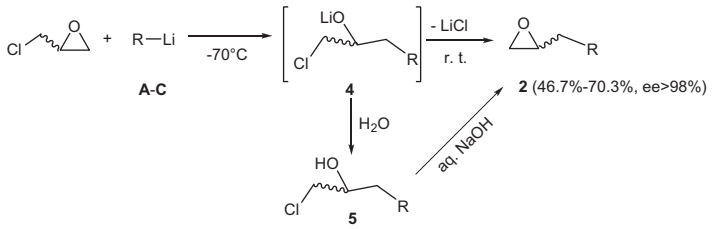
Scheme 3. The preparation of organolithium **C**.

70.3%, 64.8%, and 46.7% respectively. The mechanism of the reaction is shown in Scheme 4.

The nucleophilic reagent R^- attacks the epoxide ring at the less hindered CH_2 to create the ring-opening intermediate **4**. After the temperature is increased to room temperature, the elimination of LiCl from the intermediate **4** takes place to create epoxide **2**. The configuration of the stereogenic carbon atom is retained because it is not involved in the reaction process.

In order to confirm the mechanism, the reaction of organolithium **A** with ECH was quenched with water after the addition of ECH and intermediate **5a** (R = 9-ethylfluoren-9-yl) was obtained in 81.3% yield. When **5a** was stirred in aqueous NaOH at room temperature for two hours, epoxide **2a** was formed.

The ECH addition temperature was chosen to be −70 °C in order to ensure that nucleophilic attack took place entirely at the methene CH_2– of the epoxide ring, rather than at the sterically hindered methine CH–. The yield of **2** was high (>67%) when the ECH addition temperature was below −20 °C. When the addition temperature rose to 0 °C, the yield of **2** decreased dramatically (22%). The structures of **2a**–**c** were determined by ^1H NMR, ^{13}C NMR, and elemental analysis. Analysis by chiral high performance liquid chromatography (HPLC) confirmed that the enantiomeric excess of **2a**–**c** was the same as that of the starting material ECH (98.8% ee). The configuration of **2** was (*S*) when (*S*)-ECH was used as

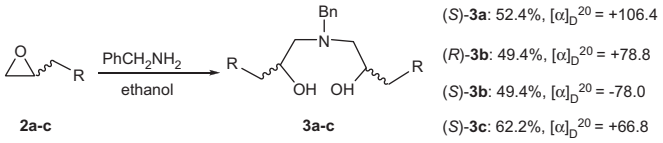


Scheme 4. The formation of optically active propene oxide **2**.

starting material, while the configuration of **2** was (*R*) when (*R*)-ECH was used.

2.2.2. The reaction of the chiral, substituted propene oxides 2 with benzylamine

Benzylamine reacted with chiral epoxides **2a–c** at reflux to create chiral amino diols **3a–c**. In the reaction, the nucleophilic amine attacked the epoxide group at the less sterically hindered methene CH_2 and the configuration of the asymmetric carbon was retained. Compound (*S*)-**3** was obtained when using (*S*)-**2** as a reactant while (*R*)-**3** was obtained when using (*R*)-**2** as a reactant. The reaction is described in Scheme 5.



Scheme 5. The reaction of the chiral epoxide with benzylamine.

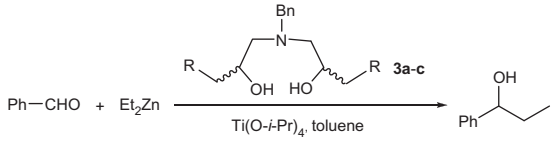
The amino diols obtained were C_2-symmetric. Their structure was confirmed by NMR and elemental analysis. Chiral HPLC analysis confirmed that the ee value of **3** was the same as that of the corresponding **2**. The isolated yields were 49.4–62.2%.

2.3. The enantioselectivity of the chiral, C_2-symmetric amino diol tridentate ligands 3a–c

The enantioselective addition of organozinc reagents to aryl aldehydes in the presence of a catalytic amount of chiral ligand has emerged as an attractive method for the synthesis of optically active secondary alcohols.[35] Recently, C_2-symmetric aziridino diols,[36] chiral epoxy alcohol ligands derived from (+)-camphor and (−)-fenchone,[37] C_2-symmetric chiral 2,2′-bipyridine diol ligands,[38] C_2-symmetrical bis-β-amino alcohols,[39] chiral pyridine ligands,[40] chiral (3*R*,5*R*)-dihydroxypiperidine derivative ligands,[41] chiral hydrazone and imine ligands,[42] and pinane-type tridentate aminodiol ligands[43] have been synthesized and employed as chiral ligands for the enantioselective addition of diethylzincs to aryl aldehydes. However, to the best of our knowledge, there are no C_2-symmetric chiral amino diol tridentate ligands derived from optically active epoxides bearing a bulky group that have been studied except for (1*R*, 5*R*)-3-aza-3-benzyl-1,5-diphenylpentan-1,5-diol which is derived from the (*R*)-styrene oxide.[23–25]

Since the enantioselective addition of diethylzinc to an aldehyde is an attractive reaction for the synthesis of optically active secondary alcohols and is frequently used as a model reaction to assess the enantioselectivity of a chiral catalyst, we selected this addition as a model reaction in order to assess the enantioselectivity of the C_2-symmetric amino diol ligands **3**. The enantioselectivity of **3a–c** for the reaction of diethylzinc with benzaldehyde is listed in Table 1. The absolute configurations of the products were determined by comparing their sign of rotation with that reported in the literature.

Table 1
The enantioselective inductivity of the amino diols **3a–c** for the reaction of diethylzinc with benzaldehyde[a]



Entry	Ligand[b]	Product		
		Yield[c] (%)	Config.[d]	ee[e] (%)
1[f]	(*S*)-**3a**	95	(*S*)-(−)	45
2	(*S*)-**3a**	77	(*S*)-(−)	66
3	(*S*)-**3b**	80	(*S*)-(−)	68
5	(*S*)-**3c**	92	(*S*)-(−)	55
6	(*R*)-**3b**	83	(*R*)-(+)	67

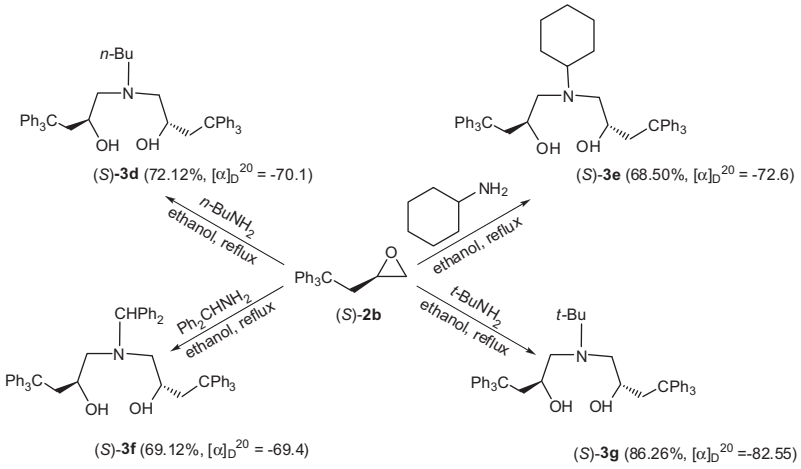
[a] Toluene: 13 mL; PhCHO: 1 mmol; Reaction time: 24 h; Reaction temperature: 0 °C; n(PhCHO)/n(Et_2Zn)/n(Ti(O-*i*-Pr)$_4$)/n(ligand) = 1/3/1.8/0.1.
[b] The letter in the bracket denotes the configuration of the stereogenic carbon atom in the ligand.
[c] The isolated yield.
[d] The absolute configurations of the products were determined by comparing their sign of rotation with that reported in the literature.
[e] The ee of the product was measured by chiral HPLC.
[f] No Ti(O-*i*-Pr)$_4$ was added.

It has been reported that Ti(O-*i*-Pr)$_4$ is capable of increasing the enantioselectivity of the reaction.[44] Our experiment confirmed that the enantioselectivity of the reaction was improved by the addition of Ti(O-*i*-Pr)$_4$ (entry 2 vs entry 1 in Table 1). Therefore, Ti(O-*i*-Pr)$_4$ was added when assessing the enantioselectivity of the C_2-symmetric amino diol.

The data listed in Table 1 shows that the chiral amino diol tridentate ligand **3** derived from optically active ECH possessed the ability to enantioselectively induce the reaction of diethylzinc with benzaldehyde. From Table 1, we can conclude that: (1) (*S*)-**3b** possesses the highest level of enantioselective induction among the three ligands; and (2) changing the configuration of the stereogneic carbon in the ligand inverts the configuration of the product. Therefore, (*S*)-**2b** was used in subsequent work for seeking an amino diol that possesses a high level of enantioselective induction.

2.4. Impact of the steric hindrance of R^1 on the enantioselectivity

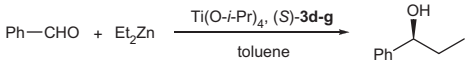
Since the steric hindrance of the R group in the ligand had a significant impact on the enantioselectivity of the chiral amino diol ligand, the steric hindrance of the R^1 group in the ligand should also have an important impact on the enantioselectivity of the ligand. In order to determine which chiral amino diol ligand gave better enantioselectivity, the chiral amino diol ligands (*S*)-**3d–g** were synthesized. The reaction conditions and the yield are shown in Scheme 6. The enantioselectivity of compounds (*S*)-**3d–g** for the addition of diethylzinc to benzaldehyde was examined.



Scheme 6. The synthetic routes of chiral amino diol ligands (*S*)-**3d**–**g**.

The enantioselectivity data of ligands (*S*)-**3d**–**g** are listed in Table 2. Chiral amino diol ligands (*S*)-**3f** and (*S*)-**3g** gave a high level of enantioselective induction even when 5% mol of the chiral ligand was used. The ee of the addition product was 90% and 94% in the presence of ligands (*S*)-**3f** and (*S*)-**3g**, respectively (entries 3 and 4 in Table 2).

Table 2
The enantioselectivity of (*S*)-**3d**–**g** toward the reaction of diethylzinc with a benzaldehyde[a]



Entry	Ligand	Product	
		Yield[b] (%)	ee[c] (%)
1	(*S*)-**3d**	76	80
2	(*S*)-**3e**	72	84
3	(*S*)-**3f**	75	90
4	(*S*)-**3g**	72	94

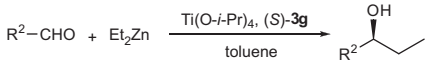
[a] Toluene: 13 mL; PhCHO: 1 mmol; Reaction time: 24 h; Reaction temperature: 0 °C; n(PhCHO)/n(Ti(O-*i*-Pr)$_4$)/Et$_2$Zn/ligand = 1/1.8/3/0.05.
[b] The isolated yield.
[c] The ee of the product was measured by chiral HPLC.

To further investigate the enantioselectivity of ligand (*S*)-**3g**, other aldehydes were employed to replace the benzaldehyde substrate. The results are listed in Table 3. The absolute configurations of the products were determined by comparing their sign of rotation with that reported in the literature except for product 1-(triphenylmethyl)-2-butanol (entry 20). In order to determine the configuration of the product 1-(triphenylmethyl)-2-butanol, (*S*)-1-(triphenylmethyl)-2-butanol was synthesized via the reaction of (*R*)-**2b** with methyllithium, which is shown in Scheme 7.

The reaction shown in Scheme 7 did not involve the asymmetric carbon atom and the configuration of the asymmetric carbon was retained; therefore the reaction of (*R*)-**2b** with methyllithium created (*S*)-1-(triphenylmethyl)-2-butanol. The sign of rotation of the obtained (*S*)-1-(triphenylmethyl)-2-butanol was minus (−) and was the same as that of the product created by the **3g**-induced reaction of 3,3,3-triphenylpropanal with diethylzinc. Thus the configuration of the product created by the **3g**-induced reaction of 3,3,3-triphenylpropanal was assigned as (*S*).

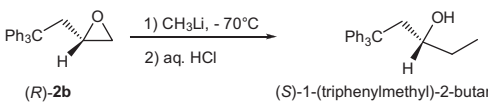
For all of the aldehydes tested, ligand (*S*)-**3g** showed a satisfying level of enantioselective induction. The substituent on the ring of

Table 3
The enantioselectivity of (*S*)-**3g** for the reaction of diethylzinc with different aldehydes[a]



Entry	R^2	(*S*)-**3g** (mol %)	Product	
			Yield[b] (%)	ee[c] (%)
1	Phenyl	5	72	94
2	Phenyl	10	68	96
3[d]	2-Hydroxyphenyl	5	56	82
4[d]	2-Hydroxyphenyl	10	50	86
5	4-Methoxyphenyl	5	84	90
6	4-Methoxyphenyl	10	78	96
7[d]	2-Phenylvinyl	5	68	81
8[d]	2-Phenylvinyl	10	58	86
9[d]	2-Pyridyl	5	70	82
10[d]	2-Pyridyl	10	62	88
11	4-Chlorophenyl	5	65	91
12	2-Naphthyl	5	67	93
13	2-Furyl	5	91	90
14	4-Dimethylaminophenyl	5	85	93
15	2-Methoxyphenyl	5	82	87
16	3-Methoxyphenyl	5	91	93
17	1-Naphthyl	5	81	95
18	4-Methylphenyl	5	84	90
19	3-Phenylpropyl	5	89	91
20	2,2,2-Triphenylethyl	5	76	95[e]
21[d]	Cyclohexyl	5	92	80[f]
22[d]	*n*-Amyl	5	90	78[f]
23[d]	*n*-Octy	5	86	88[f]
24[d]	*n*-Hexyl	5	76	84[f]

[a] Toluene: 13 mL; R^2CHO: 1 mmol; Reaction time: 24 h; Reaction temperature: 0 °C; n(R^2CHO)/n(Ti(O-*i*-Pr)$_4$)/Et$_2$Zn = 1/1.8/3.
[b] The isolated yield.
[c] The ee values of the product were determined by chiral HPLC. The absolute configurations of the products were determined by comparing their sign of rotation with those reported in the literature.
[d] Reaction temperature: −10 °C.
[e] The configuration was determined by comparing the sign of the specific rotation with that of (*S*)-1-(triphenylmethyl)-2-butanol prepared via the reaction of (*S*)-4,4,4-triphenyl-1-butene oxide with MeLi.
[f] The ee value was measured via its benzoate ester.



Scheme 7. The synthetic route to (*S*)-1-(triphenylmethyl)-2-butanol.

the aromatic aldehyde had some impact on the level of the enantioselective induction but the impact was not much. It is noteworthy that (*S*)-**3g** not only gave up to 91% yield and 96% ee value for the aromatic aldehydes tested, but also gave 76–92% yields and 78–95% ee values for all of the aliphatic aldehydes tested (entries 19–24 in Table 3). An enantiomeric excess of 95% was obtained for 3,3,3-triphenylpropanal. So far, many excellent chiral ligands for the enantioselective addition of diethylzinc to aromatic aldehydes have been reported with very high yields and ee values, but most of them are not suitable for aliphatic aldehydes or they have only a limited substrate scope of aliphatic aldehydes.

proposed a penta coordinated Ti transition state for the enantioselective addition induced by C_2-symmetric VERDI disulfonamides.[48]

On the basis of the above mechanistic considerations, we suggest that the asymmetric addition of diethylzinc to an aldehyde induced by a chiral amino diol ligand goes through a hexa-coordinated Ti transition state complex, which contains one chiral amino diol ligand, one ethyl, and one isopropoxy group.

The ^{1}H NMR of the –C***H***–O methyne confirmed our hexa-coordinated Ti transition state suggestion. The –C***H***–O methyne resonance of **3g** is at δ 3.49 ppm (Fig. 2a). The complex (**3g**)$_2$Ti can be readily prepared by removal of isopropanol from a 2:1 mix-

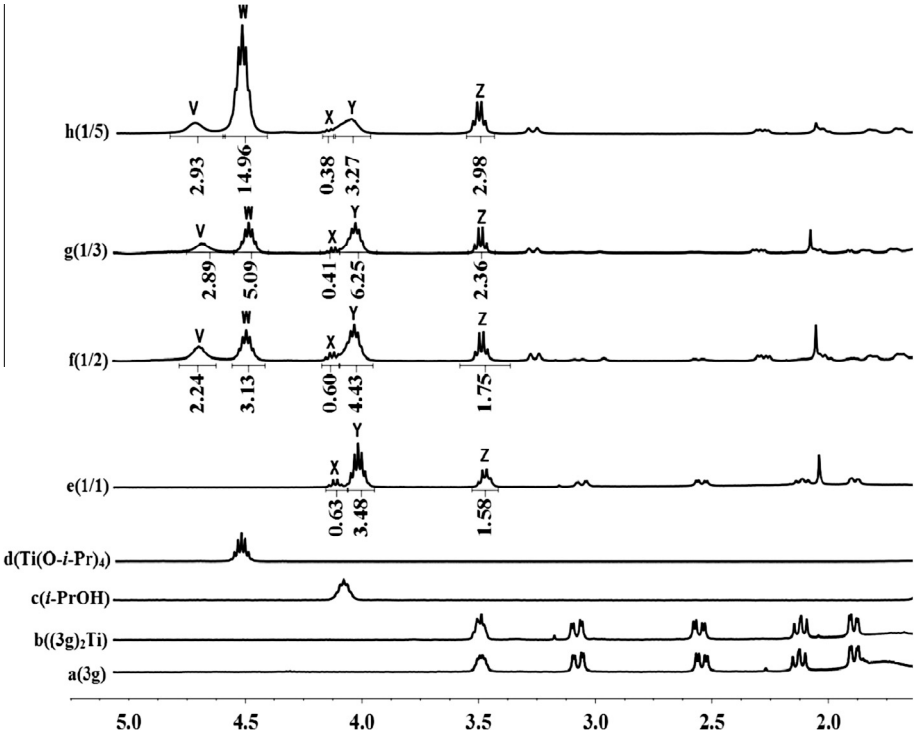


Figure 2. The partial ^{1}H NMR spectra of **3g**, (**3g**)$_2$Ti complex, *i*-PrOH, and titration of **3g** by titanium tetraisopropoxide. (a): **3g**; (b): (**3g**)$_2$Ti complex obtained from evaporating the mixture of 2 mmol of **3g** and 1 mmol of titanium tetraisopropoxide in vacuo. (c): *i*-PrOH; (d): Ti(O-*i*-Pr)$_4$. (e–h): Titration of **3g** by titanium tetraisopropoxide for the ratio 1:1 (e), 1:2 (f), 1:3 (g) and 1:5 (h).

Generally, 5% ligand loading gave a satisfactory level of asymmetric induction. An increase in the ligand loading could enhance the level of asymmetric induction, but the magnitude of enhancement was not much. When the ligand loading was raised to 10 mol %, the magnitude of ee enhancement of the product alcohol was not more than 6%.

2.5. Mechanistic considerations

The exact mechanism for the titanium promoted diethylzinc addition to aldehydes is so far not known for certain and can be different for various types of ligand.[45] Balsells et al. concluded that the active catalytic intermediate could be an ethyl titanium species derived from the transfer of an ethyl group from zinc to titanium.[46] Bauer proposed a hexa-coordinate Ti transition state for the enantioselective addition catalyzed by D-glucosamine derivatives.[45] For the enantioselective additions induced by α-hydroxy carboxylic acids, Tomasz Bauer proposed a penta coordinated Ti transition state with hydrogen bonding between the oxygen of the ligand and the formyl hydrogen of the coordinated aldehyde.[47] Paquette

ture of **3g** and titanium tetraisopropoxide under reduced pressure. The ^{1}H NMR spectrum of the (**3g**)$_2$Ti complex is shown in Figure 2b. The –C***H***–O methyne resonance of the (**3g**)$_2$Ti complex remains almost unchanged (δ 3.47 ppm, Fig. 2b) (possibly due to the N atom participating in the coordination). The *i*-PrOH methyne resonance is at δ 4.04 ppm (Fig. 2c) and the –C***H***–O methyne resonance of Ti(O-*i*-Pr)$_4$ is at 4.43 ppm (Fig. 2d). Figure 2f shows the –C***H***–O methyne resonance of the mixture derived from the titration of **3g** by titanium tetraisopropoxide in a 1:2 ratio. In Figure 2f, **V** belongs to the O***H***, while **W** and **X** belong respectively to the –C***H***–O methyne resonance of Ti(O-*i*-Pr)$_4$ and *i*-PrOH and **Y** and **Z** are the –C***H***–O methyne resonance of complexes formed by the coordination of Ti with other coordinating group such as –NCHO–, –NCHOH–, *i*-PrO–. Figure 2e–h shows respectively the –C***H***–O methyne resonance of the mixture derived from the titration of **3g** by titanium tetraisopropoxide for the 1:1, 1:2, 1:3, and 1:5 ratios. From the numbers of **W**, **Y**, and **Z**, we can calculate the number (**n**) of Ti coordinated by other groups.

The ^{1}H NMR spectrum of a $CDCl_3$ solution of **3g** and titanium tetraisopropoxide (1 equiv) showed a set of resonances derived

from **3g** and free *i*-PrOH without any signals for Ti(O-*i*-Pr)$_4$ (Fig. 2e). Mixing the ligand **3g** with Ti(O-*i*-Pr)$_4$ in a 1:2 ratio gives the **3g**-titanate quantitatively and instantaneously, while ^{1}H NMR analysis indicates that excess tetraisopropyl titanate does not lead to new species such as doubly titanated complex **3g**(Ti)$_2$ (Fig. 2f). When mixed with an excess of up to 4 equiv of Ti(O-*i*-Pr)$_4$, the **3g**-titanate with only one Ti-containing ring, is still formed (Fig. 2g and h).

Table 4 lists the number of coordination groups in the initiate feeds and titration mixtures, the number of Ti, and the number of calculated coordination groups in the titration mixtures.

Table 4 shows that the coordination number (**n**) of the Ti complex in solution in the presence of **3g** is 6. There are six possible steric isomers for the hexa-coordinate Ti transition state complex, which are shown in Figure 3.

Steric isomers **III**, **IV**, **V**, and **VI** can be ignored due to the unfavorable interactions between the benzaldehyde molecule and the ambient group; hence we focused our attention on steric isomers **I** and **II**. The formyl hydrogen can form hydrogen bonds with the oxygen atoms of the amino diol in two possible manners which are depicted in Figure 4.

Isomers **Ia** and **IIa** are unstable due to the high steric energy resulting from the unfavorable interaction between the benzaldehyde and the front Ph_3CCH_2 group. They hardly contribute to the asymmetric addition reaction. Isomers **Ib** and **IIb** have little steric hindrance and control the enantioselective orientation of the reaction. It is obvious that the ethyl group in **Ib** and **IIb** only attacks the *Si* face of the carbonyl group to create the (*S*)-product. However, when the R^1 group in the ligand is not bulky, the situation changes. For example, in the circumstance of using (*S*)-**3d** (R^1 is *n*-butyl) as a ligand, the content of **IIIa** and **VIa** (see Fig. 5) increases and *Re*-attack increases.

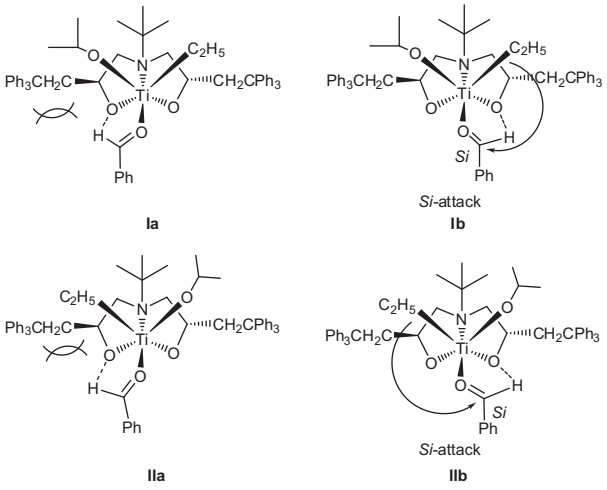


Figure 4. Stereochemical models for the attack of an ethyl group to the carbonyl of the benzaldehyde.

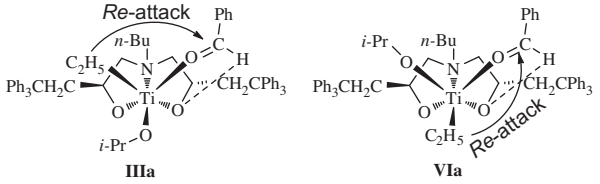


Figure 5. The increase of the *Re*-attack for less bulkiness R^1.

Table 4
^{1}H NMR titration of **3g** in $CDCl_3$ by titanium tetraisopropoxide[a]

Run	Ratio[b]	The number of groups participating in coordination				–C***H***O– in the titration mixture				***n***[d]
		–NCH$_2$C***H***O–	N	Me$_2$C***H***O-Ti	Ti	**W**	**Y**	**Z**	**U**[c]	
1	1:1	2	1	4	1	0	3.48	1.58	1	6.06
2	1:2	2	1	8	2	3.13	4.43	1.75	1.22	6.06
3	1:3	2	1	12	3	5.09	6.25	2.36	1.727	5.98
4	1:5	2	1	20	5	14.96	3.27	2.98	1.26	5.96

[a] Determined by ^{13}H NMR in $CDCl_3$ using TMS as an internal standard.
[b] The initial mole ratio of **3g** to Ti(O-*i*-Pr)$_4$.
[c] The number of Ti coordinated by other coordinating groups, calculated from the formula: (Me$_2$C***H***O–Ti–**W**)÷4.
[d] Coordination number calculated from the formula: (**Y** + **Z**) ÷ **U** + 1 (the number of nitrogen atom.

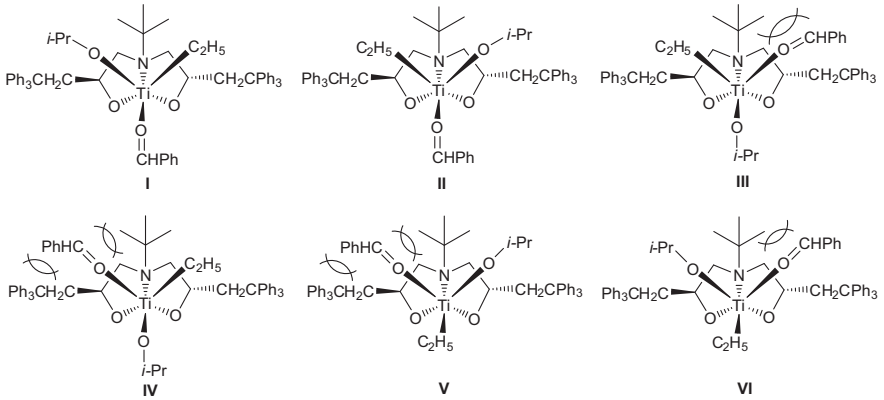


Figure 3. Six steric isomers for the hexa-coordinate Ti complex transition state.

3. Conclusion

The C_2-symmetric chiral amino diol tridentate ligands were synthesized from an achiral bulky organolithium RLi, achiral primary amine R^1NH_2 and optically active ECH, which is inexpensive and commercially available. The chiral amino diol ligands synthesized were employed to induce the enantioselective addition of diethylzinc to aldehydes. The steric hindrance of R and R^1 has a significant impact on the enantioselectivity of the ligands. The ligand (*S*)-**3g**, in which R was triphenylmethyl and R^1 was *tert*-butyl, gave high enantioselectivity. Ligand (*S*)-**3g** not only gave up to 91% yield with 96% ee for the aromatic aldehydes tested, but also gave 76–92% yields and 78–95% ee for all of the aliphatic aldehydes tested.

4. Experimental

4.1. General

^{1}H NMR and ^{13}C NMR spectra were acquired on Bruck Avance 400 at 400 MHz and 100 MHz, respectively using $CDCl_3$ as the solvent and tetramethylsilane as the internal standard. The enantiomeric excess was determined by HPLC analysis performed on Dionex P680 equipped with a UV detector and Chiralcel OD-H (Diacel) chiral column using mixtures of *n*-hexane/isopropanol as the mobile phase in appropriate ratios given in the Experimental; the detecting wavelength was 254 nm; flow (f) is given in mL/min; retention times t_R [for the (*R*)-isomer] and t_S (for the (*S*)-isomer) are given in minutes.

Diethylzinc (1 M in *n*-hexane) and titanium (IV) isopropoxide were purchased from Aladdin Company, Shanghai. THF and diethyl ether were distilled from sodium-benzophenone under argon before use. Optically active epichlorohydrin (ECH) was purchased from Yueyang Branch Company, Shenzhen Yawangkangli Technology Co., Ltd. 9-Ethylfluorene was prepared according to the literature.[49] Other reagents were commercially available and used without special treatment.

4.2. Synthesis of (*S*)-3-(9-ethylfluoren-9-yl) propene oxide (*S*)-2a

A nitrogen-flushed flask equipped with a stirrer was charged with 9.7 g (50 mmol) of 9-ethylfluorene and 40 mL of THF. To the solution of 9-ethylfluorene was added 20 mL of *n*-butyllithium solution in *n*-hexane (2.5 mol/L) at room temperature with stirring. The mixture was stirred at room temperature for 1 h to afford a red solution of 9-ethyl-9-lithiumfluorene **A**. After the temperature of the mixture was cooled to −70 °C, 3.5 g of (*S*)-(+)-ECH was added dropwise. The reaction mixture was then stirred at −70 °C for 1 h after the addition of ECH and then stirred at room temperature for 2 h. Next, THF in the reaction mixture was removed under reduced pressure after which 40 mL of water and 20 mL of diethyl ether were added. The ether layer was separated and the aqueous layer was extracted by diethyl ether. The ether solutions were combined and the combined ether solution was concentrated under reduced pressure. The concentrated residue was recrystallized from methanol to obtain (*S*)-3-(9-ethylfluoren-9-yl) propene oxide (*S*)-**2a** as white crystals. Yield: 70.3%; mp: 74–75 °C; $[\alpha]_D^{20} = +23.1$ (*c* 0.8, THF). ee: 98.8% (*n*-hexane/isopropanol = 98/2, *f* = 1 mL/min, t_S = 11.667 min, t_R = 13.275 min). Elem. Anal. Calcd for $C_{18}H_{18}O$: C, 86.36; H, 7.25. Found: C, 86.30; H, 7.34. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.73 (d, *J* = 5.6 Hz, 2H, Ar-H), 7.44 (d, *J* = 7.2, 1H, Ar-H), 7.29–7.39 (m, 5H, Ar-H), 2.41–2.45 (m, 1H, CH), 2.25–2.28 (m, 2H, CH_2), 1.99–2.12 (m, 4H, CH_2), 0.33 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 149.20, 148.96, 141.12, 140.94, 127.30, 127.26, 127.17, 127.12, 123.29, 123.00, 119.93, 119.90, 54.05, 49.01, 47.21, 42.87, 32.60, 8.02.

4.3. Synthesis of 1-chloro-3-(9-ethylfluoren-9-yl)-2-(*S*)-propanol (*S*)-5a

The reaction described in Section 4.2 was quenched with 40 mL of water after (*S*)-ECH was reacted with 9-ethyl-9-lithiumfluorene at −70 °C for 10 min. Next, 20 mL of diethyl ether was added. The ether layer was separated and the aqueous layer was extracted with diethyl ether. The ether solutions were then combined. Next, the combined ether solution was dried over anhydrous $CaCl_2$ and concentrated under reduced pressure to afford a solid. The solid was recrystallized from ethanol to obtain (*S*)-**5a** as white crystals. Yield: 81.3%; mp: 107–108 °C; $[\alpha]_D^{20} = -19.0$ (*c* 1, THF); Elem. Anal. Calcd for $C_{18}H_{19}ClO$: C, 75.38; H, 6.68. Found: C, 75.44; H, 6.70. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.74 (d, *J* = 3.3 Hz, 2H, Ar-H), 7.45 (d, *J* = 6.6 Hz, 2H, Ar-H), 7.34–7.37 (m, 4H, Ar-H), 3.06–3.11 (m, 2H, CH_2), 2.98–3.02 (m, 1H, CH), 2.37–2.38 (m, 2H, CH_2), 0.26–0.35 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 148.65, 141.06, 140.04, 140.02, 127.57, 127.52, 127.45, 127.24, 123.35, 123.03, 120.23, 120.09, 68.70, 53.80, 50.22, 44.11, 33.83, 7.83.

4.4. Synthesis of (*R*)- or (*S*)-4,4,4-triphenyl-1-butene oxide (*S*)-2b

(*S*)-4,4,4-Triphenyl-1-butene oxide (*S*)-**2b** was prepared with the method used in the preparation of (*S*)-3-(9-ethylfluoren-9-yl) propene oxide (*S*)-**2a** except that triphenylmethane was used instead of 9-ethylfluorene and that butyllithium solution was added at 0 °C instead of at room temperature. (*R*)-ECH was used for synthesizing (*R*)-4,4,4-triphenyl-1-butene oxide. Yield: 64.8%; mp: 100–102 °C; $[\alpha]_D^{20} = -28.0$ (*c* 1, THF) [for the (*S*)-isomer), +28.4 (*c* 1, THF) [for the (*R*)-isomer]; ee: 98.2% (*n*-hexane/isopropanol = 98/2, *f* = 1 mL/min, t_S = 9.547 min, t_R = 10.425 min). Elem. Anal. Calcd for $C_{22}H_{20}O$: C, 87.96; H, 6.71. Found: C, 87.86; H, 7.80. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.21–7.45 (m, 15H, Ar-H), 3.30 (dd, 1H, *J* = 3.5 Hz, *J* = 14.5 Hz, CH_2), 2.90–2.93 (m, 1H, CH), 2.49–2.51 (m, 1H, CH_2), 2.42 (dd, 1H, *J* = 6.8 Hz, *J* = 14.4 Hz, CH_2), 2.14 (m, 1H, CH_2); ^{13}C NMR ($CDCl_3$) δ (ppm): 146.8, 129.0, 127.9, 126.2, 55.8, 50.2, 48.9, 43.7.

4.5. Synthesis of (*S*)-3-(5-pentyl-dibenzo[*a*,*e*]suber-5-yl)propene oxide (*S*)-2c

A nitrogen-flushed flask equipped with a stirrer was charged with 10.3 g (50 mmol) of 5-methenedibenzo[*a*,*e*]suberane and 40 mL of THF. To the solution of 5-methenedibenzo[*a*,*e*]-suberane was added 20 mL of *n*-butyllithium solution in *n*-hexane (2.5 mol/L) at 0 °C. The mixture was then stirred at 0 °C for 1 h and at 50 °C for another 1 h to afford a solution of 5-pentyl-5-lithiumdibenzo[*a*,*e*]suberane **C**. Next, 3.5 g of (*S*)-(+)-ECH was added dropwise at −70 °C. The mixture was then stirred at −70 °C for 1 h after the addition of ECH and then stirred at room temperature for 2 h. Next, 40 mL of water and 20 mL of diethyl ether were added after the THF in the reaction mixture was removed under reduced pressure. The ether layer was separated and aqueous layer was extracted by diethyl ether. The ether solutions were combined. The combined ether solution was dried over anhydrous $CaCl_2$ and concentrated under reduced pressure. The concentrated purified was refined by means of chromatography on silica gel using a mixture of petroleum ether and ethyl acetate (12:1) as eluate to obtain a sticky, oily (*S*)-3-(5-pentyl-dibenzo[*a*,*e*]suber-5-yl)propene oxide (*S*)-**2c**. Yield: 46.7%; $[\alpha]_D^{20} = +82.2$ (*c* 1, THF) ee 98.4% (*n*-hexane/isopropanol = 98/2, *f* = 1 mL/min, t_S = 8.042 min, t_R = 8.642 min). Elem. Anal. Calcd for $C_{23}H_{28}O$: C, 86.20; H, 8.81; N, 2.30. Found: C, 86.28; H, 8.74. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.66 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.55 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.17–7.31 (m, 2H, Ar-H), 7.03–7.14 (m, 4H, Ar-H), 2.80–3.02 (m, 4H, CH_2CH_2), 2.79 (d, *J* = 3.8 Hz, 1H, CH), 2.55–2.57 (m, 1H, CH_2), 2.27–2.32 (m,

2H, CH_2), 2.13–2.27 (m, 1H, CH_2), 1.90–1.95 (m, 1H, CH_2), 1.75–1.77 (m, 1H, CH_2), 0.97–1.08 (m, 4H, CH_2), 0.93–0.96 (m, 2H, CH_2), 0.69–0.72 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 144.58, 143.67, 143.11, 129.66, 126.29, 125.84, 54.12, 51.27, 49.53, 47.44, 38.33, 32.07, 23.70, 22.25, 13.87.

4.6. General procedure for the preparation of chiral amino diol tridentate ligands

A flask equipped with a stirrer was charged with 4 mmol of amine, 8 mmol of substituted propylene epoxide, and 10 mL of ethanol. The mixture was then stirred at 0 °C for 1 h and refluxed for 10 h. Ethanol was then evaporated under reduced pressure. The residue was purified by chromatography on silica gel using a mixture of petroleum ether and ethyl acetate as eluate to obtain amino diol.

4.6.1. Benzyl bis[3-(9-ethylfluoren-9-yl)-2(*S*)-hydroxypropyl] amine (*S*)-3a

Colorless oily liquid; yield: 52.4%; $[\alpha]_D^{20} = +106.4$ (*c* 1, THF); Elem. Anal. Calcd for $C_{43}H_{45}NO_2$: C, 84.79; H, 7.46; N, 2.30. Found: C, 84.32; H, 7.40; N, 2.24. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.69 (t, *J* = 7.1 Hz, 5H, Ar-H), 7.27–7.47 (m, 8H, Ar-H), 7.01–7.27 (m, 8H, Ar-H), 3.00–3.04 (d, *J* = 7.4 Hz, 2H, OH), 2.83–2.86 (dd, *J* = 14.2, 6.1 Hz, 2H, CH), 1.98–2.00 (m, 2H, CH_2), 1.94–1.96 (m, 4H, CH_2), 1.87–1.88 (m, 1H, CH_2), 1.53–1.76 (dd, *J* = 15.0, 7.3 Hz, 1H, CH_2), 1.28–1.43 (m, 2H, CH_2), 1.24–1.26 (t, *J* = 7.1 Hz, 2H, CH_2), 0.66 (t, *J* = 8.8 Hz, 6H, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 149.71, 149.15, 141.09, 140.94, 128.98, 128.12, 127.29, 127.23, 127.12, 127.08, 126.91, 123.62, 123.07, 119.93, 119.87, 65.40, 60.89, 58.41, 53.95, 44.85, 33.58, 7.96.

4.6.2. Benzyl bis(3-triphenylmethyl-2-hydroxypropyl) amine (*S*)-3b

White power; yield: 49.4%; $[\alpha]_D^{20} = +78.8$ (*c* 1, THF) (for the (*R*)-isomer), −78.0 °C (for the (*S*)-isomer) (*c* 1, THF); Elem. Anal. Calcd for $C_{51}H_{49}NO_2$: C, 86.53; H, 6.98; N, 1.98. Found: C, 86.32; H, 6.67; N, 1.76. ^1H NMR ($CDCl_3$) δ (ppm): 7.04–7.52 (m, 35H, Ar-H), 3.61 (dd, *J* = 13.8, 9.3 Hz, 2H, OH), 3.54–3.58 (m, 2H, CH), 2.69–3.01 (m, 2H, CH_2), 2.58–2.63 (dd, *J* = 14.8, 4.2 Hz, 4H, CH_2), 2.31–2.37 (dd, *J* = 14.7, 5.0 Hz, 2H, CH_2), 2.05–2.07 (d, *J* = 9.4 Hz, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ (ppm): 147.23, 147.15, 140.15,129.25, 128.86, 128.38, 128.00, 127.98, 126.96, 126.10, 126.05, 67.57, 56.27, 55.52, 53.35, 46.13.

4.6.3. Benzyl bis[3-(1-pentyldibenzo[*a*,*e*]suber-1-yl)-2(*S*)-hydroxypropyl] amine (*S*)-3c

Colorless oily liquid; Yield: 62.2%; $[\alpha]_D^{20} = +66.8$ (*c* 1, CH_2Cl_2); Elem. Anal. Calcd for $C_{53}H_{65}NO_2$: C, 85.09; H, 8.76; N, 1.87. Found: C, 84.96; H, 8.60; N, 1.82. ^1H NMR ($CDCl_3$) δ (ppm): 7.61 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.30–7.54 (m, 1H, Ar-H), 6.97–7.30 (m, 18H, Ar-H), 3.25 (s, 2H, OH), 3.18 (d, *J* = 13.3 Hz, 2H, CH), 2.95 (m, 8H, CH_2), 2.61–2.66 (m, 2H, CH_2), 2.04 (dd, *J* = 4.0, 10.7 Hz, 2H, CH_2), 1.89–1.91 (m, 2H, CH_2), 1.82–1.85 (m, 2H, CH_2), 1.43 (m, 2H, CH_2), 1.26 (m, 4H, CH_2), 0.95 (d, *J* = 7.25 Hz, 8H, CH_2), 0.86 (s, 4H, CH_2), 0.67–0.70 (t, *J* = 6.6 Hz, 6H, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 144.55, 144.39, 143.91, 143.39, 130.87, 130.19, 129.89, 129.78, 129.70, 129.12, 128.88, 128.16, 126.96, 126.32, 126.25, 125.84, 125.62, 125.52, 66.31, 61.04, 58.62, 54.57, 53.59, 48.32, 38.40, 30.66, 29.71, 23.69, 22.26, 13.89.

4.6.4. *n*-Butyl bis[3-triphenylmethyl-2(*S*)-hydroxypropyl] amine (*S*)-3d

Colorless oily liquid; yield: 72.12%; $[\alpha]_D^{20} = -70.1$ (*c* 1, THF); Elem. Anal. Calcd for $C_{48}H_{51}NO_2$: C, 85.55; H, 7.63; N, 2.08. Found: C, 85.32; H, 7.81; N, 2.02. ^1H NMR ($CDCl_3$) δ (ppm): 7.36 (d, *J* = 7.2 Hz, 10H, Ar-H), 7.28 (d, *J* = 11.3 Hz, 18H, Ar-H), 7.20 (d, *J* = 7.0 Hz, 2H, Ar-H), 3.58 (s, 2H, CH), 3.04 (d, *J* = 14.7 Hz, 1H, CH_2), 2.57 (d, *J* = 14.5 Hz, 1H, CH_2), 2.20–2.41 (m, 4H, CH_2), 1.93 (d, *J* = 11.9 Hz, 4H, CH_2), 1.32 (d, *J* = 19.5 Hz, 4H, CH_2), 0.87 (d, *J* = 6.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 147.24, 129.27, 128.00, 126.08, 67.31, 55.85, 48.86, 46.17, 32.04, 20.27, 13.91.

4.6.5. Cyclohexyl bis[3-triphenylmethyl-2(*S*)-hydroxypropyl] amine (*S*)-3e

Yellowish oily liquid; yield: 68.50%; $[\alpha]_D^{20} = -72.6$ (*c* 1, THF); Elem. Anal. Calcd for $C_{50}H_{53}NO_2$: C, 85.80; H, 7.63; N, 2.00. Found C, 85.55; H, 7.62; N, 1.95. ^1H NMR ($CDCl_3$) δ (ppm): 7.04–7.44 (m, 15H, Ar-H), 3.52 (s, 2H, CH), 3.06 (d, *J* = 14.6 Hz, 1H, CH_2), 2.53 (d, *J* = 14.5 Hz, 1H, CH_2), 1.93–2.26 (m, 8H, CH_2), 1.61 (d, *J* = 11.5 Hz, 2H, CH_2),1.12 (s, 4H, CH_2), 0.99 (d, *J* = 6.4 Hz, 2H, CH_2), 0.88 (d, *J* = 10.6 Hz, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ (ppm): 147.27, 129.29, 127.99, 126.06, 67.76, 56.02, 51.76, 46.90, 33.95, 33.41, 26.06, 24.99.

4.6.6. Diphenylmethyl bis[3-triphenylmethyl-2(*S*)-hydroxypropyl] amine (*S*)-3f

Colorless oily liquid; Yield: 69.12%; $[\alpha]_D^{20} = -69.40$ (*c* 10 mg/mL, THF); Elem. Anal. Calcd for $C_{57}H_{53}NO_2$: C, 87.43; H, 6.69; N, 1.79. Found: C, 88.12; H, 6.07; N, 1.72. ^1H NMR ($CDCl_3$) δ (ppm): ^1H NMR (400 MHz, $CDCl_3$) δ 6.99–7.34 (m, 40H, Ar-H), 4.54 (s, 1H, CH), 3.58 (s, 2H, OH), 2.76 (dd, *J* = 14.9, 4.9 Hz, 2H, CH), 2.52–2.65 (m, 2H, CH_2), 2.20–2.34 (m, 4H, CH_2), 2.02–2.14 (m, 2H, CH_2); ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 147.17, 129.19, 128.46, 127.99, 127.14, 126.10, 68.22, 66.94, 54.45, 46.26.

4.6.7. *tert*-Butyl bis[3-triphenylmethyl-2(*S*)-hydroxypropyl] amine (*S*)-3g

Colorless oily liquid; yield: 86.26%; $[\alpha]_D^{20} = -82.55$ (*c* 1, THF); Elem. Anal. Calcd for $C_{48}H_{51}NO_2$: C, 85.55; H, 7.63; N, 2.08. Found: C, 85.62, H, 7.77; N, 2.10. ^1H NMR ($CDCl_3$) δ (ppm): 7.35–7.37 (m, 9H, Ar-H), 7.25–7.29 (m, 14H, Ar-H), 7.16–7.20 (t, *J* = 16.0 Hz, 7H, Ar-H), 3.48–3.49 (d, *J* = 4.0 Hz, 2H, CH), 3.05–3.09 (dd, *J* = 4.0, 3.6 Hz, 1H, CH_2), 2.53–2.57 (dd, *J* = 4.0, 3.6 Hz, 1H, CH_2), 2.10–2.15 (t, *J* = 20.0 Hz, 4H, CH_2), 1.87–1.91 (dd, *J* = 2.8, 2.2 Hz, 2H, CH_2), 0.93(s, 9H, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 147.29, 129.29, 127.95, 126.03, 68.34, 56.25, 50.31, 48.93, 46.50, 28.96.

4.7. A typical asymmetric addition reaction of diethylzinc with aldehydes induced by chiral amino diol tridentate ligands

A flask flushed with argon was charged with 10 mL of toluene and chiral amino diol tridentate ligand. To the flask was added $Ti(O\text{-}i\text{-}Pr)_4$ under an argon stream. The mixture was then stirred at room temperature for 1 h. Next, 3 mL of the solution of diethylzinc in *n*-hexane was added dropwise and the mixture was stirred for 1 h. 1 mmol of the aldehyde was added at 0 °C and the reaction mixture was stirred at 0 °C for several hours after the addition of aldehyde. The reaction was quenched with hydrochloric acid (1 mol/L). The organic layer was separated and the aqueous layer was extracted with diethyl ether. The organic layer and ether extraction were combined, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The concentrated residue was purified by chromatography on silica gel to obtain the product. The ee of the product was determined by chiral HPLC.

Chromatographic conditions for measuring the ee value of the addition products and the retention time of each enantiomer are listed below.

1-Phenyl-1-propanol: *n*-hexane/isopropanol = 98/2, *f* = 0.8 mL/min, t_R = 10.118 min, t_S = 11.132 min.
1-Phenyl-1-penten-3-ol: *n*-hexane/isopropanol = 90/10, *f* = 0.8 mL/min, t_R = 23.373 min, t_S = 25.920 min.
1-(4′-Methoxyphenyl)-1-propanol: *n*-hexane/isopropanol = 95.5/4.5, *f* = 1 mL/min, t_R = 14.993 min, t_S = 16.118 min.
1-(4′-Chlorophenyl)-1-propanol: *n*-hexane/isopropanol = 99.8/0.2, *f* = 1.2 mL/min, t_R = 6.470 min, t_S = 5.413 min.
1-(2′-Furyl)-1-propanol: *n*-hexane/isopropanol = 98/2, *f* = 0.6 mL/min, t_R = 14.280 min, t_S =16.590 min.
1-(2′-Pyridyl)-1-propanol: *n*-hexane/isopropanol = 97.5/2.5, *f* = 0.7 mL/min, t_R = 11.463 min, t_S = 14.065 min.
1-(2′-Hydroxyphenyl)-1-propanol: *n*-hexane/isopropanol = 95.5/4.5, *f* = 1 mL/min, t_R = 13.520 min, t_S = 11.672 min.
1-(2′-Naphthyl)-1-propanol: *n*-hexane/isopropanol = 97/3, *f* = 0.8 mL/min, t_R = 15.575 min, t_S = 12.498 min.
1-(4′-Dimethylaminophenyl)-1-propanol: *n*-hexane/isopropanol = 99.8/0.2, *f* = 0.8 mL/min, t_R = 13.288 min, t_S = 11.007 min.
1-(Triphenylmethyl)-2-butanol: *n*-hexane, *f* = 0.8 mL/min, t_R = 14.640 min, t_S = 16.638 min.
1-(2′-Methoxyphenyl)-1-propanol: *n*-hexane/isopropanol = 98/2, *f* = 1.2 mL/min, t_R = 13.795 min, t_S = 12.027 min.
1-(3′-Methoxyphenyl)-1-propanol: *n*-hexane/isopropanol = 95/5, *f* = 1.2 mL/min, t_R = 13.577 min, t_S = 11.168 min.
1-(1′-Naphthyl)-1-propanol: *n*-hexane/isopropanol = 90/10, *f* = 1.2 mL/min, t_R = 16.715 min, t_S = 12.823 min.
1-Phenyl-3-pentanol: *n*-hexane/isopropanol = 90/10, *f* = 1 mL/min, t_R = 6.993 min, t_S = 7.635 min.
1-(4′-Methylphenyl)-1-propanol: *n*-hexane/isopropanol = 95/5, *f* = 1.2 mL/min, t_R = 16.715 min, t_S = 12.823 min.
3-Octanol: HPLC (as benzoate): *n*-hexane, *f* = 0.8 mL/min, t_S = 18.341 min, t_R = 20.134 min.
1-Cyclohexyl-1-propanol: HPLC (as benzoate): n-hexane/isopropanol = 99/1, *f* = 0.6 mL/min, t_S = 28.451 min, t_R = 26.734 min.
3-Nonanol: HPLC (as benzoate): *n*-hexane/isopropanol = 99/1, *f* = 1 mL/min, t_S = 12.450 min, t_R = 15.234 min.
3-Undecanol: HPLC (as benzoate): *n*-hexane/isopropanol = 99/1, *f* = 0.5 mL/min, t_S = 10.605 min, t_R = 12.054 min.

4.8. Preparation of (*S*)-1-(triphenylmethyl)-2-butanol

A nitrogen-flushed flask equipped with a stirrer was charged with 0.6 g (2 mmol) of (*S*)-4,4,4-triphenyl-1-butene oxide and 10 mL of THF. To the solution of (*S*)-4,4,4-triphenyl-1-butene oxide was added 2 mL of methyllithium solution in *n*-hexane (1.3 mol/L) at −70 °C with stirring. The mixture was then stirred at room temperature for 1 h. The reaction was then quenched with 1 mL of water. Next, 20 mL of diethyl ether was added. The ether layer was separated and the aqueous layer was extracted with diethyl ether. The ether solutions were then combined. The combined ether solution was dried over anhydrous $CaCl_2$, and concentrated under reduced pressure to afford a liquid. The liquid was purified by chromatography on silica gel using a mixture of petroleum ether and ethyl acetate as eluate to obtain (*S*)-1-(triphenylmethyl)-2-butanol. Yield: 88.2%, $[\alpha]_D^{20} = -33.9$ (*c* 1, THF); ^{1}H NMR ($CDCl_3$) δ (ppm): 7.33–7.35 (d, *J* = 8.0 Hz, 3H, Ar-H), 7.26–7.30 (t, *J* = 2.8 Hz, 9H, Ar-H), 7.18–7.21 (t, *J* = 6.8 Hz, 7.2 Hz, 3H, Ar-H), 3.57 (s, 2H, CH), 2.93–2.97 (d, *J* = 14.8 Hz, 1H, CH_2), 2.64–2.70 (dd, *J* = 8.0, 7.2 Hz, 1H, CH_2), 1.41–1.49 (m, 2H, CH_2), 0.86–0.89 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 147.29, 129.53, 128.05, 126.43, 70.24, 66.05, 42.34, 31.03, 14.02.

Acknowledgement

We are grateful to the National Natural Science Foundation of China (No. 21172186) for generous financial support for our programs.

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