Synthesis of Novel 1,4-Bissulfonamide Ligands for Enantioselective Addition of Diethylzinc to Aldehydes

Yang, Minghua*[,a,b](杨明华) Sun, Jiangtao[b](孙江涛) Zhu, Chengjian*[,b](朱成建)

[a] *Department of Chemistry, Lishui University, Lishui, Zhejiang 323000, China*
[b] *School of Chemistry and Chemical Engineering, State Key Laboratory of Coordination Chemistry, Nanjing University, Nanjing, Jiangsu 210093, China*

Several novel chiral sulfonamide ligands based on (1*R*,2*S*,4*R*,5*S*)-1,4-diamino-2,5-dimethylcyclohexane skeleton have been synthesized and their application in the enantioselective addition of diethylzinc to aldehydes was investigated in the presence of $Ti(O^iPr)_4$. The effect of ligands, temperature and the loading amount of ligands was studied. Under optimized conditions, enantioselective addition of diethylzinc with various aryl aldehydes and aliphatic aldehydes proceeded smoothly and afforded chiral secondary alcohols in up to 88% *ee*.

Keywords asymmetric catalysis, chiral sulfonamide, diethylzinc, aldehyde

Introduction

Optically active alcohols are important components of many naturally occurring compounds, biologically active compounds, and materials such as liquid crystals. Enantioselective addition of organometallic reagents to aldehydes or ketones affords optically active alcohols, which became one of the most important and fundamental asymmetric reactions.[1] Over past several decades, various types of catalyst, such as amino alcohols, amino thiols, amines, diols and sulfonamides, have been developed as chiral auxiliaries for the catalytic enantioselective alkylation or arylation of aldehydes or ketones.[1,2] Since sulfonamides as ligands in the asymmetric addition of dialkyl zinc to aldehydes were investigated for the first time by Yoshioka *et al.*,[3] many chiral sulfonamide ligands were preprared.[4] Among these ligands, several typical sulfonamide ligands derived from 1,2-cyclohexanediamine were synthesized by Kobayashi group,[5a] Walsh group[5b-5f] and Yus group[5g] (Figure 1) and also applied to the enantioselective addition reaction of organozinc reagents to aldehydes or ketones with good results. We also found that those ligands derived from xylyenediamine[6a] and containing two isoborneol fragments connected with the aliphatic diamine[6b] (Figure 1), were applied to the similar reaction and afforded the products only in low to moderate *ee*s. These results indicated that the cyclohexane backbone may be a crucial component for this type of ligands. Among the game of modification ligands, comparatively little attention has been paid to significantly modifying the diamine backbone, although a few chiral 1,4-diamines were also prepared.[7] We anticipated that this parameter might play an important role in further improving the catalytic properties, and thus, we designed a novel chiral cyclohexanediamine, 1,4-diamino-2,5-dimethylcyclohexane[8] that exhibits a larger nitrogen-atom separation. We report herein the synthesis of some chiral sulfonamides derived from the novel 1,4-diamino-2,5-dimethylcyclohexane and their application in the enantioselective addition of diethylzinc to aldehydes.

Results and discussion

As outlined in Scheme 1, the synthesis of ligands **5**—**8** started with the conversion of 1,4-dimethyl benzene into 1,4-dimethylcyclohexandiene by a modified Birch reduction. Treatment of 1,4-dimethylcyclohexandiene with excess enantiopure monoisopinocampheyl-borane ($IpcBH_2$)[9] followed by oxidation with basic hydrogen peroxide, provided the enantiopure diol, (1*S*,2*S*,4*S*,5*S*)-**2**.[10] Substitution of **2** with diphenylphosphoryl azide under Mitsunobu reaction[11] in the presence of triphenylphosphine and diethyl azodicarboxylate in THF obtained the diazide (1*R*,2*S*,4*R*,5*S*)-**3** in 85% yield. Diazide **3** was then reduced with $LiAlH_4$ to give 1,4-diamine followed by treatment with dry hydrogen chloride, and obtained the salt of (1*R*,2*S*,4*R*,5*S*)-**4** with hydrochloride for easy purification and high stability. Exposure of (1*R*,2*S*,4*R*,5*S*)-**4** with commercially available (1*S*)-(+)-camphorsulfonyl chloride in the presence of triethylamine formed sulfonamide **5**. In a similar manner, sulfonamides **6**, **7** and **8** were also easily

* E-mail: mhyang@lsu.edu.cn; Tel.: 0086-0578-2271087
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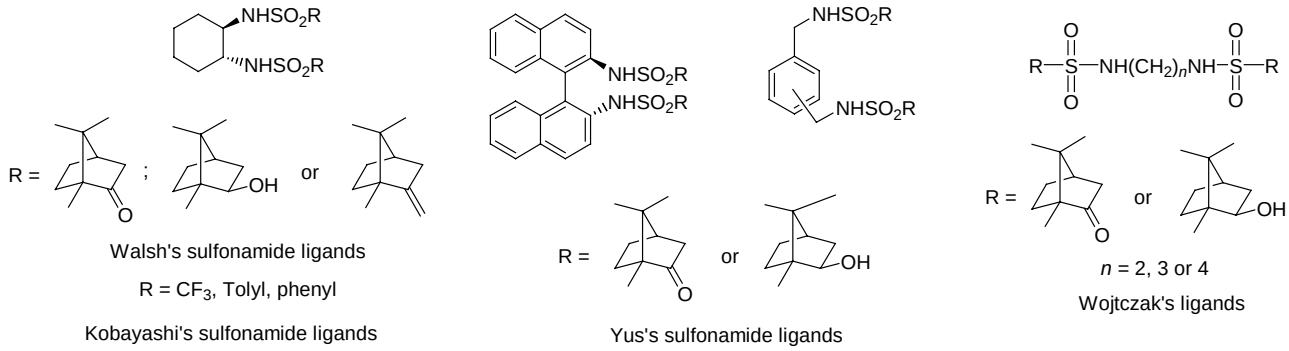
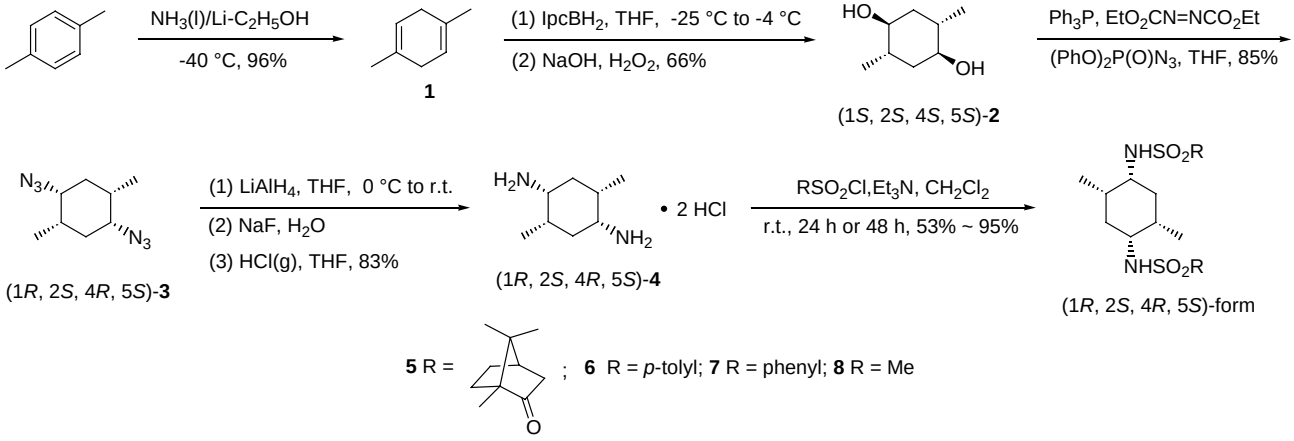
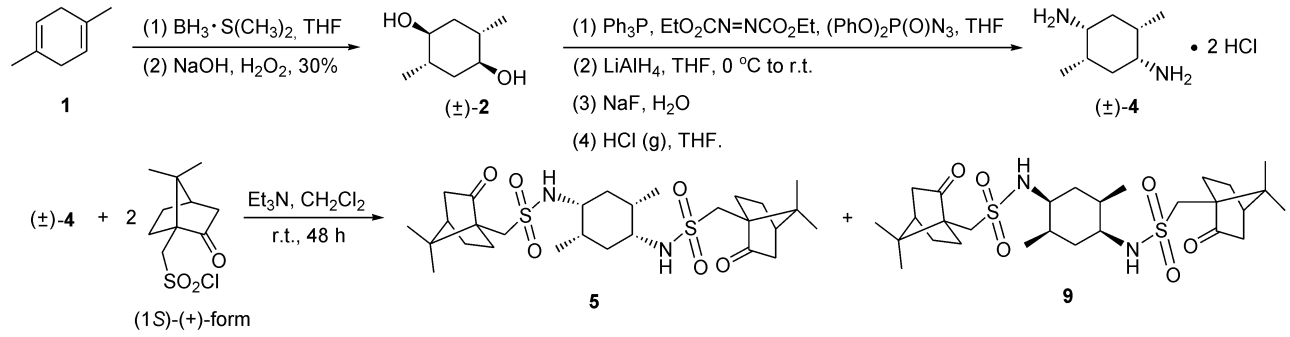


Figure 1 Some typical sulfonamide ligands.

Scheme 1 Synthesis of ligands **5**—**8**



Scheme 2 Synthesis of ligand **9**



prepared by the reaction of the chiral diamine with *p*-tolylsulfonyl chloride, phenylsulfonyl chloride or methylsulfonyl chloride in yields of 53%—95%, respectively.

As shown in Scheme 2, (±)-**2** and (±)-**4** were also prepared in a similar manner above mentioned. (±)-**4** was treated with (1*S*)-(+)-camphorsulfonyl chloride in the presence of triethylamine at room temperature and formed two diastereomers **5** and **9** in the yield of 47% and 23%, respectively, after separating by flash chromatography.

Then those ligands were initially tested in the enantioselective addition of diethylzinc to benzaldehyde in the presence of 1.2 equivalent $Ti(O^iPr)_4$. As shown in Table 1, 1-phenyl-1-propanol was obtained in 76%—93% yields for 10 h at room temperature. Ligand **9** gave inferior selectivity and inverse configuration compared with the ligand **5**. Maybe the bulky sterically hindered camphorsulfonyl group is not good for this addition. Ligand **5**, which contains camphorsulfonyl group, gave 69% *ee*, but the simple ligand **6** can gave 77% *ee*. The *ee* values and yields were also affected by the reaction temperature. Enantioselectivity of 1-phenyl-1-propanol slightly increased by lowering the reaction temperature to −25 ℃ (Table 1, Entry 8) but both the *ee* and yield decreased by further lowering the reaction temperature

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to −50 ℃ (Table 1, Entry 9). When increasing the amount of ligand to 10 mmol%, both the yield and *ee* increased (Table 1, Entry 3 vs. 6); and while 15 mmol% ligand was used, the yield and *ee* changed slightly (Table 1, Entry 6 vs. 7). Based on these results, we examined the enantioslective addition of diethylzinc to various aldehydes at −25 ℃ in the presence of 10 mmo% ligand **6**. The results are shown in Table 2.

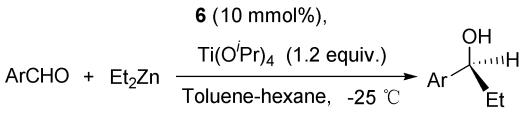
Table 1 Results of enantioselective addition of diethylzinc to benzaldehyde using the sulfonamides **5**—**9** as ligands[a]

Entry	Ligand	Time/h	Yield[b]/%	*ee*[c]/%	Configuration[d]
1	**5**	10	88	69	*S*
2	**9**	10	76	39	*R*
3	**6**	10	89	77	*S*
4	**7**	10	93	68	*S*
5	**8**	10	88	60	*S*
6	**6**	10	93	80[e]	*S*
7	**6**	10	94	79[f]	*S*
8	**6**	18	92	82[g]	*S*
9	**6**	18	71	80[h]	*S*

[a] Reaction conditions: benzaldehyde (1.0 mmol), Et_2Zn (1.2 mmol), $Ti(O^iPr)_4$ (1.2 mmol), ligands (0.05 mmol), in toluene-hexane, r.t. [b] Isolated yields. [c] Determined by HPLC analysis with chiral OD-H column. [d] The absolute configurations were assigned based on the specific rotation in comparison with literature.[12] [e] 10 mmol% ligand was used. [f] 15 mmol% ligand was used. [g] At −25 ℃. [h] At −50 ℃.

From Table 2, it can be found that all reactions proceeded smoothly under optimized conditions to afford the desired (*S*)-alcohols with moderate to high *ee*. Enantiomeric excess of the products were sensitive to both the position and electronic property of substituent. In general, for a certain substituent (*e.g.* a methoxyl, chloro or nitro group), the *para* substituent can provide products with higher *ee* than that from the *meta* or *ortho* substituent. For example, when the *p*-chlorobenzaldehyde was used, the alcohol (*S*)-1-(4-chlorophenyl)-1-propanol was afforded in 85% *ee*, but product was obtained in 79% *ee* when *o*-chlorobenzaldehyde was used (Table 2, Entries 4 and 5). For the *para*-substituted benzaldehyde, an electron-withdrawing substituent (*e.g.* a nitro or chrolo group) was found to increase the enantioselectivity while electron-donating substituents, such as methoxy and methyl group were found to give negative results (Table 2, Entries 2, 4, 7, 9). When the electron-withdrawing substituent, nitro group was located the *para*-position of benzaldehyde, the highest eantioselectivity was obtained. When aliphatic aldehydes, such as cyclohexylaldehyde and *n*-butylaldehyde, were introduced the reaction and aliphatic secondary alcohols were obtained with low reactivity and enantioselectivity (Table 2, Entries 11 and 12).

Table 2 Enantioselective addition of diethylzinc to different aromatic aldehydes[a]



Entry	Ar	Time/h	Yield[b]/%	*ee*[c]/%	Configuration[d]
1	Ph	18	92	82	*S*
2	*p*-$MeOC_6H_4$	24	85	78	*S*
3	*o*-$MeOC_6H_4$	24	81	61	*S*
4	*p*-ClC_6H_4	24	95	85	*S*
5	*o*-ClC_6H_4	24	96	79	*S*
6	(*E*)-PhCH=CH	24	95	52	*S*
7	*p*-$NO_2C_6H_4$	24	83	88	*S*
8	*m*-$NO_2C_6H_4$	24	85	73	*S*
9	*p*-$CH_3C_6H_4$	24	92	79	*S*
10	*m*-FC_6H_4	24	94	83	*S*
11	*c*-Hexyl	24	56	43	*S*
12	*n*-Bu	24	83	52	*S*

[a] Reaction conditions: aldehydes (1.0 mmol), Et_2Zn (1.2 mmol), $Ti(O^iPr)_4$ (1.2 mmol), ligand **6** (0.10 mmol), in toluene-hexane, at −25 ℃. [b] Isolated yields. [c] Determined by HPLC analysis with Chiral OD-H or OB-H column. [d] The absolute configurations were assigned based on the specific rotation in comparison with literature.[12-17]

Conclusion

In conclusion, several chiral sulfonamides based on novel racemic 4-diamino-2,5-dimethylcyclohexane or chiral (1*R*,2*S*,4*R*,5*S*)-1,4-diamino-2,5-dimethylcyclohexane were synthesized, and the catalytic activity for enantioselective addition of diethylzinc to aldehydes was investigated. The high enantioselectivities and yields have been obtained for simple ligand **6**. This research also afforded an alternative method to obtain chiral secondary alcohols. Further studies are in progress in our laboratory in order to expand the application of these chiral ligands to other catalytic asymmetric reactions.

Experimental

NMR data were recorded on a Bruker Advance (300 MHz) spectrometer with chemical shifts referenced to $SiMe_4$ as the internal standard. Electrospray ionization mass spectra were recorded on Finnigan LCQ electrospray mass spectrometer. Optical rotations were recorded on a PerkinElmer 241 polarimeter. The *ee* values were determined by a PerkinElmer 200 HPLC on a Daicel chiral OD-H or OB-H column with UV detection at 254 nm. Elemental analyses were carried out on a PerkinElmer 240 C elemental analyzer. Toluene, hexane and THF were distilled from sodium/benzophenone before

use. Benzaldehyde and other substituted benzaldehydes, BH_3•$S(CH_3)_2$, (1*R*)-(+)-*α*-pinene, azodicarboxylate, diphenylphosphoryl azide Et_2Zn (1.0 mol/L solution in hexane) and (1*S*)-(+)-10-camphorsulfonyl chloride were purchased from Acros and used without further purification. Unless otherwise specified, reactions were performed under a nitrogen atmosphere.

Preparation of 1,4-dimethylcyclohexan-1,4-diene (1)

Liquid ammonia (300 mL) and *p*-xylene (43.0 g, 40.6 mmol) were added to a two-liter three-neck flask equipped with mechanism stirrer. Lithium wire (15 g, 2.16 mol) and anhydrous ethanol (150 mL) were added intermittently at −40 ℃. Water (400 mL) was added slowly to the mixture. Two hours later, diethyl ether (400 mL) was added and the aqueous phase was extracted with diethyl ether (400 mL×3). The combined organic phase was dried over sodium sulfate and the solvent was removed via vacuum. The colorless liquid was obtained in the yield of 96%. The purity of product is over 98% determined by ^{1}H NMR and the product was directly used for next step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 5.43 (s, 2H), 2.59 (s, 4H), 1.69 (s, 6H).

Preparation of (1*S*,2*S*,4*S*,5*S*)-2,5-dimethylcyclohexane-1,4-diol (2)

1,4-Dimethylcyclohexan-1,4-diene (98%, 5.2 g, 47.0 mmol) was added to the solution of $IpcBH_2$ (0.8 mol/L in THF, 154 mL, 123 mmol, derived from (*R*)-(+)-*α*-pinene) at −25 ℃. The mixture was stirred for 0.5 h and then left at −25 ℃ without stirring for a week followed by treatment with methanol (8.6 mL, 212 mmol) at −25 ℃. The resulting organoboranes were oxidized with hydrogen peroxide (30% in water, 35 mL, 339 mmol) in the presence of NaOH (80 mL, 4 mol/L, 320 mmol) at 0 ℃. The mixture was heated to 50 ℃ and then potassium carbonate (5 g) was added. The aqueous layer was extracted with ether (80 mL×3) and the combined organic phase was dried over sodium carbonate and removed solvent via vacuum. After purified by flash chromatograph (silica gel, petroleum ether-ethyl acetate, 1∶2, *V*∶*V*), white solid (4.5 g) was obtained in 66% yield. $[\alpha]_D^{25}$ +32.7 (*c* 1.0, CH_2Cl_2), >97% *ee* (calculating according to the optical rotation gave by literature[10]). m.p. 120—121 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 3.51—3.57 (m, 2H), 1.87—1.93 (m, 2H), 1.68—1.78 (m, 4H), 1.53—1.59 (m, 2H), 1.01 (d, *J*=6.9 Hz, 6H); IR (KBr) *v*: 3314 cm^{-1}; MS (EI) *m/z* (%): 144.1 (M^+, 4), 126.0 (4), 111.1 (10), 72 (100). Anal. calcd for $C_8H_{16}O_2$: C 66.63, H 11.18; found C 66.34, H 11.22.

Preparation of racemic 1,4-dihydroxy-2,5-dimethylcyclohexane (±)-2

Under nitrogen, BH_3•$S(CH_3)_2$ (199.5 mmol) was added slowly to the THF solution of 1,4-dimethylcyclohexan-1,4-diene (98%, 14.7 g, 133 mmol in 500 mL THF) at 0 ℃. The resulting mixture was stirred at room temperature for 12 h and was then heated to reflux for 4 h. After the mixture was cooled to room temperature, methanol (20 mL, 500 mmol) was added slowly. The resulting organoboranes were cooled to 0 ℃ and oxidized by addition of NaOH (5 mol/L, 70 mL, 350 mmol), followed by slow addition of hydrogen peroxide (30 wt% in water, 46 mL, 450 mmol). The mixture was heated to 50 ℃ for 3 h and then potassium carbonate (5 g) was added. The aqueous layer was extracted with ether (150 mL×3) and the combined organic phase was dried over sodium carbonate and removed solvent via vacuum. After purified by flash chromatograph (silica gel, petroleum ether-ethyl acetate, 1∶2, *V*∶*V*), white solid (5.7 g) was obtained in 30% yield. m.p. 120—121 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 3.52—3.57 (m, 2H), 1.88—1.90 (m, 2H), 1.71—1.77 (m, 2H), 1.53—1.61 (m, 4H), 1.01 (d, *J*=6.9 Hz, 6H); IR (KBr) *v*: 3314 cm^{-1}; MS (EI) *m/z* (%): 144 (M^+, 6).

Synthesis of (1*R*,2*S*,4*R*,5*S*)-1,4-diazido-2,5-dimethylcyclohexane (3)

Ph_3P (9.3 g, 35.2 mmol) and (1*S*,2*S*,4*S*,5*S*)-2,5-dimethylcyclohexane-1,4-diol (2.3 g, 16 mmol) were dissolved in 200 mL THF and then diethyl azodicarboxylate (6.15 g, 35.2 mmol) and diphenylphosphoryl azide (9.69 g, 35.2 mmol) were added at 0 ℃. The resulting clear orange solution was stirred for 12 h at room temperature. Solvent was removed via vacuum and 1,4-diazido-2,5-dimethylcyclohexane was obtained after purification by flash chromatography (silica gel, petroleum ether-ethyl acetate, 5∶1, *V*∶*V*) as yellow oil in 85% yield (2.64 g). $[\alpha]_D^{25}$ −44.6 (*c* 0.20, THF); ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 3.62 (m, 2H), 1.95 (m, 2H), 1.83 (ddd, *J*=13.5, 7.5, 4.2 Hz, 2H), 1.64 (ddd, *J*=13.5, 7.5, 4.3 Hz, 2H), 1.11 (d, *J*=7.0 Hz, 6H); IR (KBr) *v*: 2969, 2934, 2882, 2098, 15138, 1381, 1352, 1255 cm^{-1}; MS (EI) *m/z* (%): 194.0 (M^+, 1), 166 (1), 141 (1), 109 (7), 81 (20), 42 (100). Anal. calcd for $C_8H_{14}N_6$: C 49.47, H 7.26, N 43.27; found C 49.32, H 7.23, N 43.41.

Synthesis of (1*R*,2*S*,4*R*,5*S*)-1,4-diamino-2,5-dimethylcyclohexane (4)

Under nitrogen atmosphere, 2.5 g (65.7 mmol) $LiAlH_4$ and 2.0 g (10.3 mmol) (1*R*,2*S*,4*R*,5*S*)-**3** were added to 90 mL THF at 0 ℃ and the resulting mixture was stirred for 24 h at room temperature before quenching with 11.0 g (263.16 mmol) NaF and 3.0 mL H_2O. After 80 mL THF added, the mixture was continued to stir for 2 h and then filtered. The dry gaseous of hydrochloride was bubbled into the resulting solution. After filtering, white precipitate, the slat of 1,4-diamino-2,5-dimethylcyclohexane **4** with hydrochloride was obtained in 83% yield (1.84 g). $[\alpha]_D^{25}$ +3.3 (*c* 0.50, H_2O); m.p. > 200 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 3.40—3.45 (m, 2H), 2.13—2.18 (m, 2H), 1.75—1.88 (m, 4H), 1.00 (d, *J*=7.3 Hz, 6H); IR (KBr) *v*: 3456, 3022, 2895, 1653, 1559, 1465, 1455, 1399 cm^{-1}; MS

(EI) *m/z* (%): 142.1 (M^+−HCl, 2), 125.1 (7), 110.1 (6), 83.1 (6), 72.0 (100). Anal. calcd for $C_8H_{20}N_2Cl_2$: C 44.66, H 9.37, N 13.02; found C 44.93, H 9.30, N 13.25.

General procedure for synthesis of ligands 5—8

Under nitrogen atmosphere, the salt of (1*R*,2*S*,4*R*,5*S*)-**4** with hydrochloride (430 mg, 2 mmol) was dissolved in the saturated solution of KOH, and then extracted with CH_2Cl_2 (10 mL×3). The organic phase was dried over anhydrous Na_2SO_4 and gave the solution of diamine (1*R*,2*S*,4*R*,5*S*)-**4** in CH_2Cl_2. Sulfonyl chloride (4 mmol in 20 mL CH_2Cl_2) was added slowly to the solution of diamine (1*R*,2*S*,4*R*,5*S*)-**4** and triethylamine (0.56 mL, 2.7 g, 4 mmol) in 30 mL CH_2Cl_2 at 0 ℃. The mixture was stirred at room temperature for 48 h and then HCl (20 mL, 1 mol/L, 20 mmol) was added. The organic phase was dried over anhydrous Na_2SO_4 and the solvent was removed via vacuum. The product was purified by flash chromatography.

(1*R*,2*S*,4*R*,5*S*)-2,5-Dimethyl-1,4-*N*,*N*′-biscamphorsulfonamino-2,5-dimethylcyclohexane (5) White solid, 53% yield (0.60 g); $[\alpha]_D^{25}$ +9.9 (*c* 0.80, THF); m.p. 169—171 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 5.30 (d, *J*=7.6 Hz, 2H), 3.60—3.62 (m, 2H), 3.00—3.40 (m, 4H), 1.90—2.44 (m, 12H), 1.70—1.73 (m, 4H), 1.38—1.52 (m, 4H), 1.12 (d, *J*=7.2 Hz, 6H), 0.92 (s, 6H), 1.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 17.0, 20.0, 20.3, 27.0, 27.4, 34.1, 34.4, 43.2, 43.3, 49.0, 52.3, 54.1, 59.7, 217.0; IR (KBr) *v*: 3306, 2958, 1736, 1429, 1324, 1132, 1049 cm^{-1}; MS (ESI) *m/z*: 571 (M^++1). Anal. calcd for $C_{28}H_{46}N_2O_6S_2$: C 58.92, H 8.12, N 4.91; found C 58.67, H 8.19, N 4.74.

(1*R*,2*S*,4*R*,5*S*)-1,4-*N*,*N*-Bis(*p*-methylphenylsulfonamino)-2,5-dimethylcyclohexane (6) White solid, 92% yield (0.83 g); $[\alpha]_D^{25}$ −22.7 (*c* 3.16, THF); m.p. 195—197 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 7.93—7.96 (d, *J*=8.3 Hz, 4H), 7.29—7.31 (d, *J*=8.3 Hz, 4H), 4.85 (s, br, 2H), 3.22—3.28 (m, 2H), 2.43 (s, 6H), 1.74—1.86 (m, 2H), 1.40—1.42 (m, 4H), 0.82 (d, *J*=6.7 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 16.5, 21.9, 33.3, 33.8, 53.7, 127.8, 129.1, 138.3, 143.7; IR (KBr) *v*: 3362, 3264, 3064, 2964, 1598, 1431, 1345, 1263, 1161, 1093, 1055, 971 cm^{-1}; MS (ESI) *m/z*: 451 (M^++1). Anal. calcd for $C_{22}H_{30}N_2O_4S_2$: C 58.64, H 6.71, N 6.22; found C 58.90, H 6.44, N 6.54.

(1*R*,2*S*,4*R*,5*S*)-1,4-*N*,*N*′-Bisphenylsulfonamino-2,5-dimethylcyclohexane (7) White solid, 95% yield (0.80 g); $[\alpha]_D^{25}$ −17.8 (*c* 3.14, THF). m.p.>210 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 7.84—7.87 (m, 4H), 7.53—7.58 (m, 6H), 4.54 (s, 2H), 3.23—3.28 (m, 2H), 1.45—1.87 (m, 6H), 0.81—0.83 (d, *J*=7.0 Hz, 6H); ^{13}C NMR (DMSO-d_6, 75 MHz) *δ*: 16.4, 31.3, 33.7, 54.1, 127.3, 129.8, 132.9, 142.4; IR (KBr) *v*: 3358, 3260, 3061, 3059, 2963, 2888, 1452, 1330, 1262, 1162, 1093, 949 cm^{-1}; MS (ESI) *m/z*: 423 (M^++1). Anal. calcd for $C_{20}H_{26}N_2O_4S_2$: C 56.85, H 6.20, N 6.63; found C 56.70, H 6.27, N 6.32.

(1*R*,2*S*,4*R*,5*S*)-1,4-*N*,*N*′-Bismethylsulfonamino-2,5-dimethylcyclohexane (8) White solid, 71% yield (0.42 g); $[\alpha]_D^{25}$ −12.8 (*c* 0.35, THF), m.p.>210 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 4.31 (s, br, 2H), 3.55 (s, 2H), 2.99 (s, 6H), 2.27—2.29 (m, 2H), 172—1.75 (m, 4H), 1.10 (d, *J*=6.4 Hz, 6H); ^{13}C NMR (DMSO-d_6, 75 MHz) *δ*: 16.8, 31.3, 33.9, 34.7, 54.0; IR (KBr) *v*: 3289, 3252, 2966, 2905, 1473, 1411, 1313, 1262, 1160, 1100, 982 cm^{-1}; MS (ESI) *m/z*: 299 (M^++1). Anal. calcd for $C_{10}H_{22}N_2O_4S_2$: C 40.25, H7.43, N 9.39; found C 40.53, H 7.56, N 9.51.

Synthesis of ligand 9

Under nitrogen atmosphere, dihydrochloride salt of (±)-**4** (430 mg, 2 mmol) was dissolved with 2 mL saturated solution of KOH, and then extracted with CH_2Cl_2 (10 mL×3). The organic phase was dried over anhydrous Na_2SO_4 and gave the solution of diamine (±)-**4** in CH_2Cl_2. (1*S*)-(+)-Camphorsulfonyl chloride (1.0 g, 4 mmol in 20 mL CH_2Cl_2) was added slowly to the solution of diamine (±)-**4** and triethylamine (0.56 mL, 2.7 g, 4 mmol) in 30 mL CH_2Cl_2 at 0 ℃. The mixture was stirred at room temperature for 48 h and then HCl (20 mL, 1 mol/L, 20 mmol) was added. The organic phase was dried over anhydrous Na_2SO_4 and the solvent was removed. The product was purified by flash chromatography. Two white solid, enantiomerically pure sulfonamides **5** and **9** were obtained in the yield of 23% and 47% respectively.

(1*S*,2*R*,4*S*,5*R*)-2,5-Dimethyl-1,4-*N*,*N*′-biscamphorsulfonamino-2,5-dimethylcyclohexane (9) 0.53 g, $[\alpha]_D^{25}$ +18.3 (*c* 1.24, THF); m.p. 134—136 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 5.20 (s, 2H), 3.18—3.21 (m, 2H), 2.90—3.40 (m, 4H), 1.90—2.50 (m, 12H), 1.35—1.70 (m, 8H), 1.16 (d, *J*=7.0 Hz, 6H), 0.91 (s, 6H), 1.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 15.9, 20.3, 20.4, 27.0, 27.4, 30.1, 39.1, 42.7, 43.0, 43.2, 49.2, 49.7, 59.6, 217.4; IR (KBr) *v*: 3293, 2964, 1743, 1535, 1454, 1416, 1392, 1127, 1261, 1095 cm^{-1}; MS (ESI) *m/z*: 571 (M^++1). Anal. calcd for $C_{28}H_{46}N_2O_6S_2$: C 58.92, H 8.12, N 4.91; found C 58.73, H 8.05, N 4.86.

General procedure for enantioselective addition of dialkylzinc to aldehydes in the presence of titanium isopropoxide

Diethylzinc (1.2 mmol, 0.88 mmol/mL in *n*-hexane) was dropped slowly to the toluene solution of the chiral sulfonamide **6** (0.1 mmol) under the nitrogen. The solution was stirred for 20 min at room temperature. After the flask was cooled to −78 ℃, a solution of titanium tetraisopropoxide (1.2 mmol, 1.0 mol/L in hexane) was added slowly by a syringe. After 30 min, the aldehyde (1.0 mmol) was dropwise added and the resulting mixture was kept under smooth stirring for 24 h at −25 ℃, after which the reaction was quenched by the addition of 2 mol/L HCl and then extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 and removed the solvent. After purification by preparative silica gel

TLC, corresponding products were obtained. All compounds were already characterized by comparison of their spectroscopic data with literatures.[12-17]

(*S*)-1-(4-Methoxyphenyl)-1-propanol (11b)[13] 78% *ee* by HPLC analysis using Chiral OD-H column eluted with *V*(*n*-hexane) ∶ *V*(2-propanol)=97 ∶ 3 at 0.5 mL/min, t_R=19.3 min for (*R*) and t_R=24.6 min for (*S*).

^{1}H NMR ($CDCl_3$) δ: 7.11 (t, *J*=8.5 Hz, 4H), 4.46—4.51 (m, 1H), 3.81 (s, 3H), 2.15 (s, 1H), 1.60—1.79 (m, 2H), 0.89 (t, *J*=7.4 Hz, 3H).

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