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Synthesis of new Schiff base-camphorsulfonyl amide ligands and in situ screening in the asymmetric additions of organozinc reagents to aldehydes

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ABSTRACT

We have designed and synthesized a new library of highly modular Schiff base-camphorsulfonyl amide ligands from readily available starting materials. These ligands have been used in the asymmetric addition of diethyl zinc to aldehydes in good yields (up to 91%) and high enantioselectivities (up to 93%). Moreover, when the ligands were used in the asymmetric addition of phenylacetylene to aldehydes, good yields and moderate to high ee values (up to 90%) were obtained. The introduction of the camphorsulfonyl moiety into the ligands is highly critical for the selectivities of the reactions.

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1. Introduction

To obtain enantiomerically pure organic compounds, asymmetric catalysis is one of the most important methods. A successful asymmetric reaction is highly depended on the choice of a suitable chiral ligand. However, there is no general ligand that is good for every reaction and every substrate.[1] Therefore, exploring new efficient ligands is always one of the key interests of synthetic

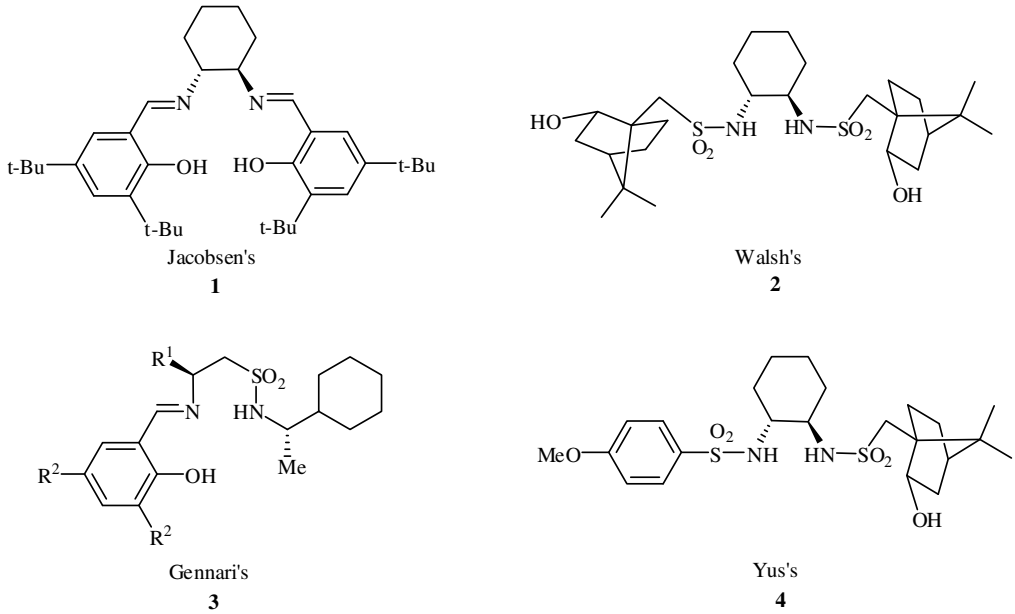

Figure 1.

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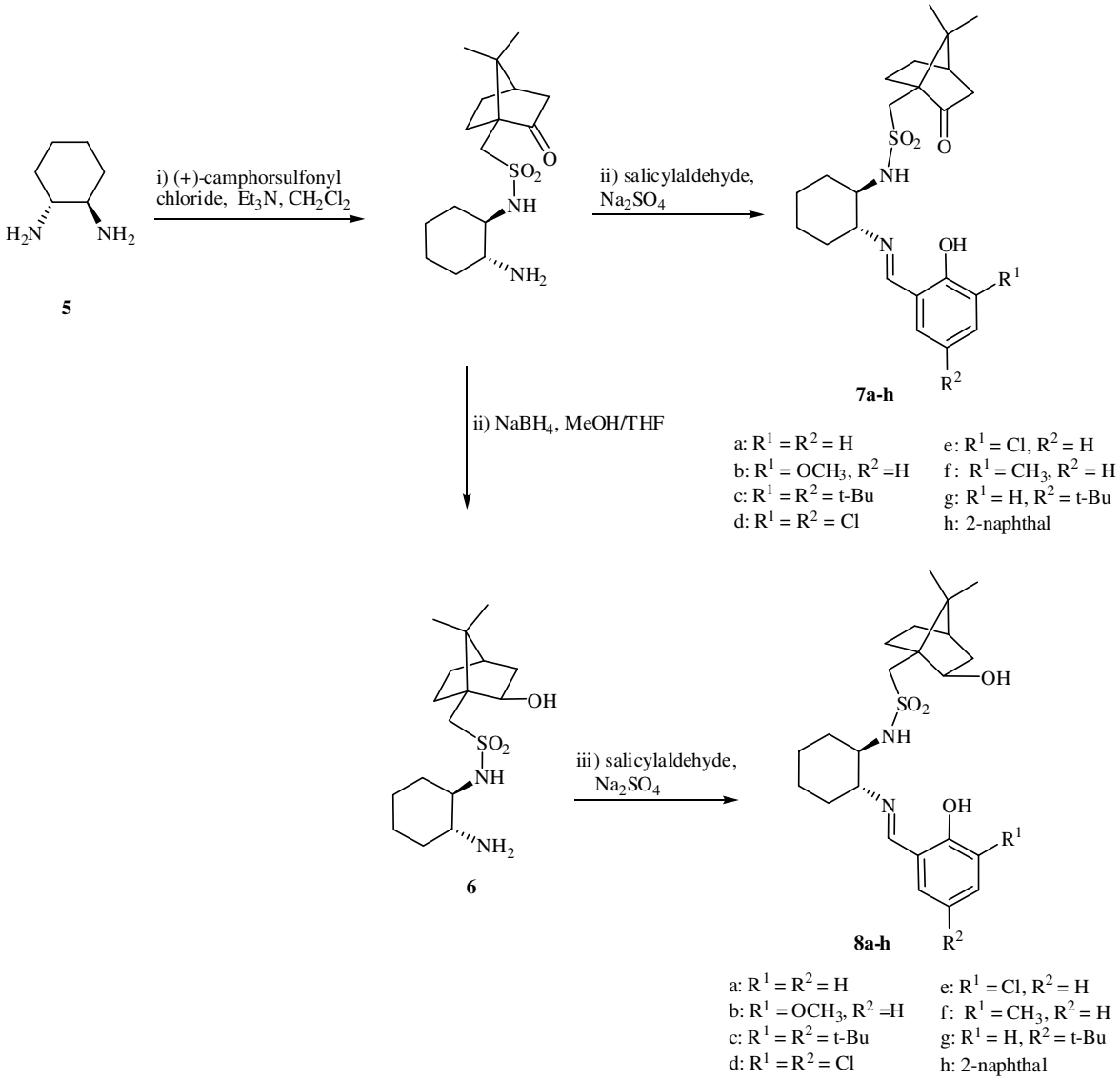
chemists. However, the synthetic procedures toward chiral ligands are often lengthy and tedious. Moreover, expensive chiral starting materials are often required. An efficient and flexible synthetic strategy for a much simpler ligand structure from the readily available starting materials is strongly desired (Fig. 1).

Chiral Salen ligand **1** has been successfully used in various asymmetric reactions with excellent results.[2] Yus and Walsh independently reported their applications of ligand **2** bearing a camphor and cyclohexane backbone in various reactions with good results.[3] Recently, Gennari reported their discoveries of new efficient ligands **3** for several reactions by the screening of a parallel library.[4] More recently, Yus reported the utilizations of ligands **4** in a series of asymmetric reactions.[5] The excellent performances of these types of ligands are due to the fact that these multidentate donors favor the formation of organometallic complexes, which possess well-organized spatial arrangements to give rise to good asymmetric induction in the catalytic process.[6] Moreover, different chiral moieties of the ligand may play different roles in the catalytic cycle, which results in a cooperation effect by activating the substrate, the nucleophile or the electrophile. Herein, we report a rapid synthesis of a new library of ligands with three different moieties, and the applications of this library in the asymmetric addition of organozinc reagents to aldehydes.[7,8]

2. Results and discussion

The synthesis of a new library of Schiff base-camphorsulfonylamide ligands is straightforward (Scheme 1). They were synthesized very efficiently in two or three steps from commercially available chiral 1,2-cyclohexanediamine and chiral camphorsulfonyl chloride. Firstly, treatment of chiral diamine (*R,R*)-**5** with 1 equiv of chiral (1*S*)-(+)-10-camphorsulfonyl chloride furnished the single-substituted sulfonylamide. The reduction with sodium borohydride under standard conditions produced a mixture of two possible diastereomeric alcohols, the major *exo*-**6** and the minor *endo*-**6** (in a ratio of 6:1). The crude products were recrystallized from acetone/*n*-hexane to afford the desired *exo*-**6** as a white solid. Alternatively, the mixture of the two diastereomers can be used directly for the next condensation reaction, and the Schiff base-camphorsulfonylamide was obtained as a mixture of two diastereomers. The minor one can be easily removed by a simple recrystallization from a mixed solvent of acetone and *n*-hexane.

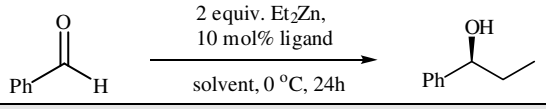


Scheme 1. Synthesis of chiral ligands.

Then, the pure target chiral ligands were obtained as yellow needles in a yield of 62–75% from (*R*,*R*)-**5**. Next, these ligands had been tested in the asymmetric addition of organozinc reagents to aldehydes.

Table 1 shows the results of the additions of diethyl zinc to benzaldehyde in the presence of Schiff base-camphorsulfonylamide ligands **7a**–**h** and **8a**–**h**. The reactions were carried out with 2 equiv of Et_2Zn and 10 mol % of ligand in hexane at 0 °C for 24 h. Over this period, the benzaldehyde was completely consumed, and the ee values of the 1-phenyl-1-propranol were determined by chiral HPLC in a range from 16% to 90%.

Table 1
Asymmetric addition of $ZnEt_2$ to benzaldehyde in the presence of Schiff base-camphorsulfonylamide ligands[a]



Entry	Ligand	Solvent	Yield[b] (%)	ee[c] (%)
1	**7a**	Hexane	62	42
2	**7b**	Hexane	55	46
3	**7c**	Hexane	47	57
4	**7d**	Hexane	64	35
5	**7e**	Hexane	46	54
6	**7f**	Hexane	62	36
7	**7g**	Hexane	66	49
8	**7h**	Hexane	51	61
9	**8a**	Hexane	88	90
10	**8b**	Hexane	80	33
11	**8c**	Hexane	87	85
12	**8d**	Hexane	92	47
13	**8e**	Hexane	91	62
14	**8f**	Hexane	68	45
15	**8g**	Hexane	81	64
16	**8h**	Hexane	82	71
17	**8a**	Toluene	86	70
18	**8a**	CH_2Cl_2	75	65
19	**8a**	THF	56	43
20	**9**	Hexane	52	22
21	**10**	Hexane	76	<10

[a] Unless otherwise noted, all reactions were carried out at 0 °C for 24 h. Molar ratio: Et_2Zn/aldehyde/ligand = 2:1:0.1.
[b] The yields of isolated products.
[c] Determined by HPLC with a Daicel Chiralcel OD column.

The results from Table 1 also indicate that the catalytic performance of the ligands is highly affected by the sulfonylamide moiety and the Schiff base part. In general, ligands **8a–h**, which bear a hydroxy group of the camphor backbone, gave better asymmetric induction than those with the carbonyl group **7a–h** (entries 9–16 vs entries 1–8). Namely, to obtain high enantioselectivity and good reactivity in this reaction, the hydroxy group of the camphor moiety is necessary. The different substituent at the aromatic ring of the Schiff base moiety also affected both the reactivity and the selectivity. The *ortho*- and *para*-substituted ligands gave lower enantioselectivities than **8a**. The ligands with an electron-donating group at the phenyl ring displayed better asymmetric induction than those bearing electron-withdrawing substitutes (entries 11 and 15 vs entries 12 and 13, Table 1). In particular, the best enantioselectivity was obtained when ligand **8a** was employed. In addition, all of the products were obtained with (*S*)-configuration.

To determine whether there were cooperative effects between the chiral 1,2-cyclohexanediamine and the chiral camphor moiety, ligand **9**[3l] bearing an achiral tolyl sulfonylamide group and ligand **10** bearing (*S*,*S*)-1,2-cyclohexanediamine moiety had been prepared and investigated in this reaction. However, they both afforded poor reactivities and selectivities (Table 1, entries 20 and 21). Changing the (*R*,*R*)-diamine to the (*S*,*S*)-diamine furnished the product in the same configuration but a sharply decreased selectivity (Table 1, entry 9 vs entry 21). Although the substituents on the phenyl ring of the salicyl part would significantly affect the stereoselectivity, for un-substituted ligand, the stereoselectivity was exclusively governed by the camphor portion. On the other hand, for the matched cases, both the chirality of cyclohexanediamine and camphor will be responsible for the high enantioselectivity. For the mis-matched cases, the selectivity dropped sharply, which may be due to the competitive effects between the two chiral factors.

The results in Table 1 also showed that the efficiency of the catalytic process strongly depended on the nature of the solvent. Among all the four solvents investigated, hexane proved to be the best choice in terms of reactivity and selectivity. Toluene or CH_2Cl_2 gave good yields but moderate selectivities, while THF gave both low yields and poor selectivities (Fig. 2).

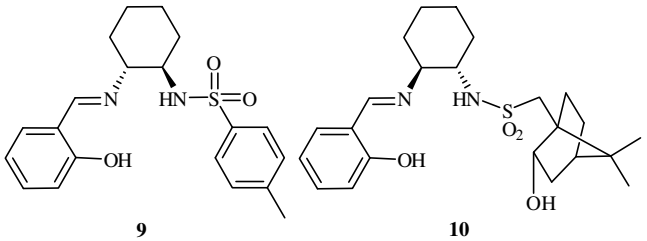
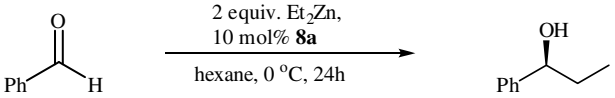


Figure 2.

Under the optimized conditions, we examined the utility of ligand **8a** for the alkylation of a variety of aromatic and aliphatic aldehydes. The results are summarized in Table 2. In all of the reactions, the aldehydes were completely consumed after 24 h. In general, the *para*- or *ortho*-substituted aromatic aldehydes with an electron-withdrawing group furnished the products with a slight higher ee values than those bearing electron-donating group (entries 4–6 vs entries 2 and 3). In particular, 4-chloro benzaldehyde gave the chiral alcohol in high yield (91%) and the highest ee value (93%) (entry 4). And the aliphatic aldehydes gave both moderate chemical yields and enantioselectivities (entries 9 and 10).

Table 2
Asymmetric addition of $ZnEt_2$ to aldehydes in the presence of ligand **8a**[a]

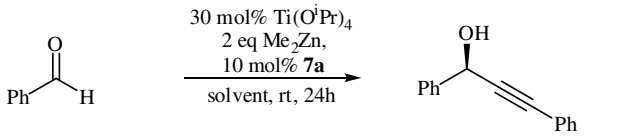


Entry	Aldehyde	Yield[b] (%)	ee[c] (%)
1	Ph	88	90
2	*p*-$CH_3OC_6H_5$	84	88
3	*o*-$CH_3OC_6H_5$	82	82
4	*p*-ClC_6H_5	91	93
5	*o*-ClC_6H_5	84	89
6	*p*-BrC_6H_5	89	90
7	1-Naphthyl	78	65
8	2-Naphthyl	91	79
9	*i*-Bu	76	76
10	Cyclohexyl	82	82

[a] Unless otherwise noted, all reactions were carried out in hexane at 0 °C for 24 h. Molar ratio: Et_2Zn/aldehyde/ligand = 2:1:0.1.
[b] The yields of isolated products.
[c] Determined by HPLC with a Daicel Chiralcel OD column.

Furthermore, ligands **7a–h** and **8a–h** were investigated in the enantioselective addition of phenylacetylene to benzaldehyde. This catalytic reaction was a two-step procedure. Firstly, deprotonation of phenylacetylene with dimethylzinc yielded the corresponding alkynyl zinc reagent. Secondly, the alkynyl zinc reagent reacted with aldehyde in the presence of substoichiometric amounts of chiral ligand and $Ti(O^iPr)_4$. The results are summarized in Table

Table 3
Asymmetric addition of phenylacetylene to benzaldehyde in the presence of different chiral ligands[a]

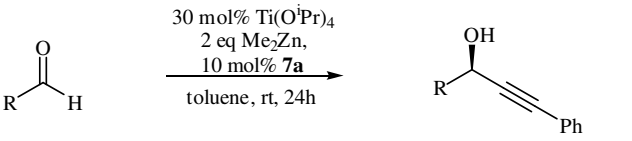


Entry	Ligand	Solvent	Yield[b] (%)	ee[c] (%)
1	**7a**	Toluene	84	86
2	**8a**	Toluene	83	65
3	**9**	Toluene	66	12
4	**10**	Toluene	58	18
5	**7a**	Hexane	57	32
6	**7a**	CH_2Cl_2	77	56
7	**7a**	THF	92	15
8	**7b**	Toluene	83	81
9	**7c**	Toluene	35	32
10	**7d**	Toluene	92	44
11	**7e**	Toluene	78	26
12	**7f**	Toluene	67	55
13	**7g**	Toluene	43	29
14	**7h**	Toluene	27	36
15[d]	**7a**	Toluene	85	89
16[e]	**7a**	Toluene	80	78
17[f]	**7a**	Toluene	76	72

[a] Unless otherwise noted, all reactions were carried out at room temperature for 24 h. Molar ratio: phenylacetylene/Me_2Zn/aldehyde/Ti(O^iPr)$_4$/ligand = 2:2:1:0.3:0.1.
[b] The yields of isolated products.
[c] Determined by HPLC with a Daicel Chiralcel OD column.
[d] Phenylacetylene/Me_2Zn/aldehyde/Ti(O^iPr)$_4$/ligand = 2:2:1:0.3:0.15.
[e] Phenylacetylene/Me_2Zn/aldehyde/Ti(O^iPr)$_4$/ligand = 2:2:1:0.3:0.05.
[f] This reaction was performed at 0 °C.

3. The best enantioselectivity was obtained when **7a** was chosen as the ligand. By comparing the reactivity and selectivity of **7a** and **8a**, we chose **7a–h** for further investigation. From the summarized results, we can see that the substituted salicyl part had a large influence on the reactivity and selectivity. The *para*- or *ortho*-substituted ligands furnished chiral alcohols with lower enantioselectivity than **7a**. However, there were no regular rules for the reactivity. Ligands **9** and **10** also gave both low reactivities and poor selectivities.

Table 4
Asymmetric addition of phenylacetylene to aldehydes in the presence of ligand **7a**[a]



Entry	Aldehyde	Yield[b] (%)	ee[c] (%)
1	Ph	84	86
2	*p*-ClC_6H_4	82	84
3	*o*-ClC_6H_4	78	81
4	*o*-$MeOC_6H_4$	91	72
5	*p*-$MeOC_6H_4$	76	73
6	*p*-BrC_6H_4	83	85
7	Piperonyl	54	78
8	*n*-Bu	73	82
9	*i*-Bu	74	68
10[d]	Ph	85	89
11[d]	*p*-ClC_6H_4	80	87
12[d]	*p*-BrC_6H_4	82	90

[a] Unless otherwise noted, all reactions were carried out in toluene at room temperature for 24 h. Molar ratio: phenylacetylene/Me_2Zn/aldehyde/Ti(O^iPr)$_4$/ligand = 2:2:1:0.3:0.1.
[b] The yields of isolated products.
[c] Determined by HPLC with a Daicel Chiralcel OD column. Absolute configuration of the products was (*S*) by comparison of specific rotation reported in the literature.
[d] Phenylacetylene/Me_2Zn/aldehyde/Ti(O^iPr)$_4$/ligand = 2:2:1:0.3:0.15.

We also investigated the effect of the solvent in this reaction. Among all the four solvents, toluene gave both good reactivity and selectivity. THF displayed the best reactivity but poor selectivity (entry 7). Hexane gave both poor reactivity and selectivity (entry 5). Also, CH_2Cl_2 afforded the product with moderate yield but poor selectivity (entry 6). Increasing the catalyst loading (15 mol % of **7a**) gave a slightly higher enantioselectivity (89% ee) but similar yield (entry 15). A lower catalyst loading gave a decrease in yield and poor selectivity (entry 16). Moreover, when the reaction was carried out at 0 °C, moderate yields and moderate ee values were observed (entry 17).

Under the aforementioned reaction conditions, we used **7a** in the asymmetric addition of phenylacetylene to a number of aldehydes. The results are summarized in Table 4. Moderate to high chemical yields were obtained for all of the substrates. The aromatic aldehydes bearing an electron-withdrawing group at the *para*-position gave products with higher enantioselectivity than those with electron-donating group (entries 2–7). The aliphatic aldehydes gave moderate chemical yields and moderate to high enantioselectivities (entries 8 and 9). Increasing the ligand loading to 15 mol % gave slightly higher ee values (entries 10–12).

3. Conclusions

In conclusion, we have prepared a new library of highly modular Schiff base-camphorsulfonyl amide ligands, and have applied them to the enantioselective addition of organozinc reagents to aldehydes, in which high yields and moderate to high enantioselectivities were obtained. This ligand library is very easily prepared and only one simple recrystallization in the purification procedure is needed. The results also showed that the cooperative effects of the chiral 1,2-cyclohexanediamine and the chiral camphor moiety are involved in our catalytic system. The matched chirality of the two chiral parts of the ligand is essential for the high enantioselectivity.

4. Experimental

4.1. General information

Elemental analyses were carried out on a Perkin–Elmer 240 C elemental analyzer. ^1H NMR data were recorded on a Bruker AMX-300 spectra with chemical shifts referenced to $SiMe_4$ as internal standard. Electrospray ionization mass spectrums were recorded on Finnigan LCQ Electrospray Mass Spectrometer. Optical rotations were recorded on a Perkin–Elmer 241 Polarimeter. Ee values were determined by a Perkin–Elmer 200 HPLC on a chiral Chiralcel OD column with UV detection at 254 nm. All reagents were obtained from commercial suppliers, and were used without further purification unless otherwise stated. Toluene, hexane, and THF were distilled from sodium/benzophenone. CH_2Cl_2 were distilled from CaH_2. All reactions were carried out under an argon atmosphere. All catalytic reactions were carried out in a Schlenk tube.

4.2. Synthesis of chiral ligands

4.2.1. Synthesis of intermediate 6

To a solution of (*R,R*)-1,2-diaminecyclohexane (1.7 g, 15 mmol) in CH_2Cl_2 (40 mL) at 0 °C, was added dropwise (+)-camphor sulfonyl chloride (2.0 g, 8 mmol) in CH_2Cl_2 (40 mL) over 60 min. After the addition was completed, the mixture was allowed to warm to room temperature. After being stirred overnight, the mixture was washed with water. The organic phase was separated and dried over anhydrous sodium sulfate. Then, the solvents were then

removed under reduced pressure. The following recrystallization from acetone and *n*-hexane gave the single-substituted camphorsulfonyl amine (4.48 g, 91% yield) as a white solid. Mp 136–138 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.42–3.37 (d, J = 15 Hz, 1H), 3.07–3.02 (d, J = 15 Hz, 1H), 3.42–1.18 (m, 8H), 1.04 (s, 3H), 0.92 (s, 3H) ppm; ESI (MS) m/z: 328.3 (M^+); Anal. Calcd for $C_{16}H_{28}N_2O_3S$: C, 58.50; H, 8.59; N, 8.53. Found: C, 58.62; H, 8.48; N, 8.41.

In a 250 mL-three-necked flask equipped with a reflux condenser, the single-substituted camphorsulfonyl amine (4.3 g, 13.1 mmol) was dissolved in a mixed solvent (200 mL, MeOH/THF = 1:1). Next, $NaBH_4$ (1.89 g, 50 mmol) was added slowly. The mixture was stirred for another 4 h. The reaction mixture was quenched with saturated aqueous ammonium chloride, and the solid was filtered. The filtrate was extracted with CH_2Cl_2 (3×50 mL). The organic phase was washed with water and was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The crude product was recrystallized from acetone and *n*-hexane to give *exo*-**6** (3.36 g, 78% yield) as a white solid. Mp 64–67 °C; $[\alpha]_D^{26} = -24.6$ (c 0.1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.57–3.53 (d, J = 13.5 Hz, 1H), 3.20–3.10 (m, 2H), 2.86–2.82 (d, J = 13.5 Hz, 2H), 2.07 (m, 2H), 1.66 (m, 6H), 1.45–1.26 (m, 6H), 1.0 (s, 3H), 0.85 (m, 1H), 0.77 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 75.7, 62.4, 57.8, 53.5, 51.2, 48.3, 45.1, 39.4, 34.9, 34.1, 31.8, 28.2, 25.5, 24.6, 20.3, 19.7 ppm; ESI (MS) m/z: 330.1 (M^+); Anal. Calcd for $C_{16}H_{30}N_2O_3S$: C, 58.15; H, 9.15; N, 8.48. Found: C, 58.32; H, 9.31; N, 8.56.

4.2.2. General procedure for synthesis of ligands 7a–h, 8a–h

To a solution of single-substituted sulfonyl amide (0.5 mmol) in 20 mL CH_2Cl_2 was added the aldehyde (0.5 mmol) at room temperature. After being stirred overnight, the solid was filtered, and the reaction mixture was washed with CH_2Cl_2. The filtrate was evaporated under reduced pressure to give a crude yellow solid. Purification of the crude solid by recrystallization from acetone and *n*-hexane gave the ligand as a yellow solid in 75–93% yield.

4.2.2.1. Compound 7a. Yellow solid, mp 150–152 °C. $[\alpha]_D^{26} = -59.0$ (c 0.1, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.1 (s, 1H), 8.36 (s, 1H), 7.33–7.28 (m, 2H), 6.95–6.86 (m, 2H), 4.79–4.76 (d, J = 15 Hz, 1H), 3.57 (m, 1H), 3.42–3.37 (d, J = 15 Hz, 1H), 3.08 (m, 1H), 2.80–2.75 (d, J = 15 Hz, 1H), 2.30–1.47 (m, 15H), 0.9 (s, 3H), 0.76 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 216.5, 165.5, 161.4, 132.8, 131.9, 119.0, 117.5, 72.9, 59.1, 57.4, 51.6, 48.9, 43.0, 33.7, 27.2, 26.7, 26.0, 24.7, 24.0, 20.0, 19.7 ppm; ESI (MS) m/z: 432.1 (M^+); Anal. Calcd for $C_{23}H_{32}N_2O_4S$: C, 63.86; H, 7.46; N, 6.48. Found: C, 63.97; H, 7.61; N, 6.62.

4.2.2.2. Compound 7b. Yellow solid, mp 178–182 °C. $[\alpha]_D^{26} = -66.0$ (c 0.1, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.13 (s, 1H), 9.92 (s, 1H), 7.20–7.18 (d, J = 7.8 Hz, 1H), 7.14–7.11 (d, J = 7.8 Hz, 1H), 7.0–6.95 (m, 1H), 4.33–4.28 (d, J = 15 Hz, 1H), 3.92 (s, 3H), 3.76–3.71 (d, J = 15 Hz, 1H), 2.45 (m, 3H), 2.17–2.02 (m, 10H), 1.77 (m, 1H), 1.49 (m, 2H), 1.18 (s, 1H), 1.14 (s, 3H), 1.06 (s, 1H), 0.92 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 213.2, 197.1, 151.9, 148.6, 124.9, 121.1, 120.0, 118.2, 64.6, 60.1, 56.6, 49.1, 48.6, 45.6, 43.1, 42.7, 27.2, 26.1, 25.7, 22.0, 21.4, 20.1, 20.0 ppm; ESI (MS) m/z: 462.1 (M^+); Anal. Calcd for $C_{24}H_{34}N_2O_5S$: C, 62.31; H, 7.41; N, 6.06. Found: C, 62.48; H, 7.57; N, 6.16.

4.2.2.3. Compound 7c. Yellow solid, mp 215–217 °C. $[\alpha]_D^{26} = -44.8$ (c 0.1, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.39 (s, 1H), 8.35 (s, 1H), 7.38 (s, 1H), 7.10 (s, 1H), 4.95 (s, 1H), 3.59 (m, 1H), 3.42–3.37 (d, J = 15 Hz, 1H), 3.08 (m, 1H), 2.82–2.77 (d, J = 15 Hz, 1H), 2.20–1.59 (m, 14H), 1.43 (s, 9H), 1.31 (s, 9H), 1.06 (s, 1H), 0.9 (s, 3H), 0.72 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 216.5, 166.6, 158.4, 140.5, 137.1, 127.5, 126.5, 118.0, 72.7, 59.0, 57.3, 51.3, 48.8, 42.9, 35.4, 34.5, 33.8, 33.65, 31.9, 29.8, 27.2, 25.8, 24.6, 24.0, 20.1, 19.8 ppm; ESI (MS) m/z: 544.1 (M^+); Anal. Calcd for $C_{31}H_{48}N_2O_4S$: C, 68.34; H, 8.88; N, 5.14. Found: C, 68.51; H, 8.76; N, 5.27.

4.2.2.4. Compound 7d. Yellow solid, mp 202–204 °C. $[\alpha]_D^{26} = -60.2$ (c 0.1, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.16 (s, 1H), 8.25 (s, 1H), 7.30 (m, 1H), 7.14 (m, 1H), 5.08 (m, 1H), 3.51 (m, 1H), 3.26–3.21 (d, J = 15 Hz, 1H), 3.03 (m, 1H), 2.76–2.72 (d, J = 15 Hz, 1H), 2.20–1.19 (m, 15H), 0.90 (s, 3H), 0.74 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 217.1, 164.9, 160.7, 132.4, 131.2, 124.3, 120.1, 119.3, 73.0, 59.5, 58.1, 52.3, 48.3, 43.3, 34.9, 27.5, 26.6, 25.1, 24.1, 20.2, 19.5 ppm; ESI (MS) m/z: 500.6 (M^+); Anal. Calcd for $C_{23}H_{30}Cl_2N_2O_4S$: C, 55.09; H, 6.03; N, 5.59. Found: C, 55.13; H, 55.16; N, 5.57.

4.2.2.5. Compound 7e. Yellow solid, mp 187–189 °C. $[\alpha]_D^{26} = -71.4$ (c 0.2, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.10 (s, 1H), 8.23 (s, 1H), 7.21–7.13 (m, 2H), 6.81 (m, 1H), 5.10 (m, 1H), 3.50 (m, 1H), 3.29–3.24 (d, J = 15 Hz, 1H), 3.0 (m, 1H), 2.74–2.69 (d, J = 15 Hz, 1H), 2.20–1.19 (m, 15H), 0.84 (s, 3H), 0.70 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 216.5, 164.5, 160.0, 132.5, 131.0, 123.5, 119.8, 119.0, 72.8, 59.2, 57.5, 51.9, 48.8, 43.0, 33.7, 27.2, 26.3, 24.8, 24.0, 20.0, 19.7 ppm; ESI (MS) m/z: 466.4 (M^+); Anal. Calcd for $C_{23}H_{31}ClN_2O_4S$: C, 59.15; H, 6.69; N, 6.00. Found: C, 59.23; H, 6.65; N, 6.04.

4.2.2.6. Compound 7f. Yellow solid, mp 172–174 °C. $[\alpha]_D^{26} = -64.3$ (c 0.1, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.27 (s, 1H), 8.26 (s, 1H), 7.10–7.04 (m, 2H), 6.76–6.69 (m, 1H), 4.88 (m, 1H), 3.50 (m, 1H), 3.34–3.29 (d, J = 15 Hz, 1H), 2.99 (m, 1H), 2.68–2.63 (d, J = 15 Hz, 1H), 2.20–2.18 (m, 2H), 2.15 (s, 3H), 1.91–1.14 (m, 12H), 0.80 (s, 3H), 0.65 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 216.1, 165.8, 159.6, 133.8, 129.6, 126.3, 118.6, 72.6, 58.9, 57.5, 51.3, 48.8, 43.0, 33.8, 27.2, 25.9, 24.7, 24.0, 20.0, 19.7, 15.8 ppm; ESI (MS) m/z: 446.0 (M^+); Anal. Calcd for $C_{24}H_{34}N_2O_4S$: C, 64.54; H, 7.67; N, 6.27. Found: C, 64.68; H, 7.77; N, 6.26.

4.2.2.7. Compound 7g. Yellow solid, mp 163–166 °C. $[\alpha]_D^{26} = -78.4$ (c 0.2, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.54 (s, 1H), 8.27 (s, 1H), 7.24–7.22 (d, J = 6 Hz, 1H), 7.06–7.04 (d, J = 6 Hz, 1H), 6.75–6.69 (m, 1H), 4.98 (m, 1H), 3.50 (m, 1H), 3.32–3.27 (d, J = 15 Hz, 1H), 3.0 (m, 1H), 2.74–2.69 (d, J = 15 Hz, 1H), 2.10–1.53 (m, 11H), 1.38 (s, 9H), 1.01 (m, 1H), 0.83 (s, 3H), 0.65 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 216.4, 116.4, 160.7, 137.7, 130.3, 129.9, 118.9, 118.3, 72.6, 59.0, 57.3, 51.4, 48.8, 43.0, 35.2, 33.8, 29.8, 27.2, 25.9, 24.7, 24.0, 20.1, 19.7 ppm; ESI (MS) m/z: 487.8 (M^+); Anal. Calcd for $C_{27}H_{40}N_2O_4S$: C, 66.36; H, 8.25; N, 5.73. Found: C, 66.48; H, 8.34; N, 5.89.

4.2.2.8. Compound 7h. Yellow solid, mp 145–147 °C. $[\alpha]_D^{26} = -28.5$ (c 0.1, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 14.65 (s, 1H), 8.94 (s, 1H), 7.99–7.96 (d, J = 8.4 Hz, 1H), 7.68–7.62 (m, 2H), 7.48–7.43 (m, 1H), 7.26–7.24 (m, 1H), 6.99–6.96 (d, J = 9 Hz, 1H), 5.66–5.64 (d, J = 5.5 Hz, 1H), 5.54–5.51 (d, J = 7.8 Hz, 1H), 3.54–3.49 (m, 2H), 3.39–3.34 (m, 2H), 2.83–1.54 (m, 9H), 1.12 (m, 1H), 1.04 (s, 2H), 0.9 (s, 2H), 0.84 (s, 3H), 0.69 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 216.8, 173.6, 159.0, 136.9, 133.9, 129.4, 128.3, 126.8, 124.1, 123.2, 118.9, 107.4, 67.5, 59.1, 57.5, 51.6, 48.8, 43.0, 33.6, 32.9, 31.3, 27.2, 26.1, 24.5, 24.0, 19.9 ppm; ESI (MS) m/z: 482.0 (M^+); Anal. Calcd for $C_{27}H_{34}N_2O_4S$: C, 67.19; H, 7.10; N, 5.80. Found: C, 67.31; H, 7.23; N, 5.95.

4.2.2.9. Compound 8a. Yellow solid, mp 86–90 °C. $[\alpha]_D^{26} = -61.5$ (c 0.1, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.10 (s, 1H), 8.38 (s, 1H), 7.32–7.26 (m, 2H), 6.94–6.85 (m, 2H), 4.91–4.98 (d,

J = 8.1 Hz, 1H), 3.97 (m, 1H), 3.48 (m, 2H), 3.39–3.34 (d, J = 13.8 Hz, 1H), 3.0 (m, 1H), 2.45–2.41 (d, J = 13.8 Hz, 1H), 2.32–2.28 (m, 1H), 1.93–1.20 (m, 14H), 0.99 (s, 3H), 0.32 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.1, 161.2, 133.0, 132.0, 119.2, 118.7, 117.7, 76.8, 73.1, 58.5, 53.7, 50.7, 49.0, 44.8, 39.2, 35.3, 34.3, 31.3, 27.7, 25.2, 24.3, 20.0, 19.6 ppm; ESI (MS) m/z: 433.8 (M^+); Anal. Calcd for $C_{23}H_{34}N_2O_4S$: C, 63.56; H, 7.89; N, 6.45. Found: C, 63.63; H, 7.94; N, 6.51.

4.2.2.10. Compound 8b. Yellow solid, mp 89–92 °C. $[\alpha]_D^{26}$ = −42.2 (c 0.1, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.20 (s, 1H), 8.29 (s, 1H), 6.85–6.71 (m, 4H), 5.30 (s, 1H), 4.67 (m, 1H), 3.82 (s, 3H), 3.41–2.86 (m, 4H), 2.10–1.27 (m, 14H), 0.99 (s, 3H), 0.28 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 152.6, 141.2, 135.1, 128.5, 127.1, 117.2, 74.1, 72.2, 57.5, 56.7, 54.2, 50.1, 49.2, 44.8, 39.7, 35.6, 35.4, 33.8, 32.1, 31.6, 29.8, 28.1, 25.6, 24.5, 19.8, 19.6 ppm; ESI (MS) m/z: 464.1 (M^+); Anal. Calcd for $C_{24}H_{36}N_2O_5S$: C, 62.04; H, 7.81; N, 6.03. Found: C, 62.21; H, 7.95; N, 6.17.

4.2.2.11. Compound 8c. Yellow solid, mp 103–105 °C. $[\alpha]_D^{26}$ = −49.0 (c 0.1, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.40 (s, 1H), 7.38 (s, 1H), 7.08 (s, 2H), 4.89–4.87 (d, J = 8.2 Hz, 1H), 3.98 (m, 1H), 3.37–3.33 (d, J = 13.8 Hz, 1H), 3.25 (m, 1H), 3.0 (m, 1H), 2.57–2.53 (d, J = 13.8 Hz, 1H), 2.34 (s, 1H), 2.17 (s, 4H), 2.07 (s, 1H), 2.05–1.50 (m, 9H), 1.42 (s, 9H), 1.29 (s, 9H), 0.96 (m, 1H), 0.85 (s, 3H), 0.35 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.3, 158.3, 140.8, 137.2, 127.9, 126.3, 117.9, 76.7, 72.7, 58.5, 53.8, 50.6, 48.8, 44.6, 39.2, 35.4, 35.1, 34.5, 31.9, 31.1, 30.0, 27.7, 25.2, 24.3, 20.4, 20.1 ppm; ESI (MS) m/z: 546.2 (M^+); Anal. Calcd for $C_{31}H_{50}N_2O_4S$: C, 68.09; H, 9.22; N, 5.12. Found: C, 68.25; H, 9.42; N, 5.24.

4.2.2.12. Compound 8d. Yellow solid, mp 130–132 °C. $[\alpha]_D^{26}$ = −62.3 (c 0.2, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 14.06 (s, 1H), 8.23 (s, 1H), 7.32 (s, 1H), 7.12 (s, 1H), 5.06–5.0 (m, 1H), 3.87–3.88 (m, 1H), 3.41 (m, 2H), 3.31–3.26 (d, J = 13.6 Hz, 1H), 2.98 (m, 1H), 2.39–2.34 (d, J = 13.6 Hz, 1H), 1.87–1.10 (m, 15H), 0.96 (s, 3H), 0.37 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.6, 157.1, 132.9, 129.7, 123.6, 123.2, 119.5, 76.8, 72.0, 58.4, 53.8, 50.8, 49.0, 44.7, 39.3, 35.0, 34.0, 31.2, 27.7, 25.0, 24.1, 20.1, 19.8 ppm; ESI (MS) m/z: 502.3 (M^+); Anal. Calcd for $C_{23}H_{32}Cl_2N_2O_4S$: C, 54.87; H, 6.41; N, 5.56. Found: C, 58.86; H, 6.44; N, 5.58.

4.2.2.13. Compound 8e. Yellow solid, mp 95–98 °C. $[\alpha]_D^{26}$ = −45.9 (c 0.2, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 13. 02 (s, 1H), 8.24 (s, 1H), 7.18–7.14 (m, 2H), 6.80–6.77 (d, J = 9 Hz, 1H), 4.95 (m, 1H), 3.88 (m, 1H), 3.40 (m, 1H), 3.30–3.26 (d, J = 13.6 Hz, 1H), 2.92 (m, 1H), 2.36–2.32 (d, J = 13.6 Hz, 1H), 2.22–2.20 (m, 1H), 1.80–1.14 (m, 14H), 0.91 (s, 3H), 0.32 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.1, 159.9, 132.8, 131.1, 123.8, 119.6, 119.2, 76.8, 72.9, 58.5, 53.8, 50.8, 49.0, 44.8, 39.2, 35.3, 34.3, 31.3, 27.7, 25.1, 24.2, 20.1, 19.7, 18.7 ppm; ESI (MS) m/z: 468.3 (M^+); Anal. Calcd for $C_{23}H_{33}ClN_2O_4S$: C, 58.90; H, 7.09; N, 5.97. Found: C, 58.86; H, 7.13; N, 6.01.

4.2.2.14. Compound 8f. Yellow solid, mp 97–99 °C. $[\alpha]_D^{26}$ = −64.3 (c 0.2, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.21 (s, 1H), 8.28 (s, 1H), 7.10–7.03 (m, 2H), 6.71–6.67 (m, 1H), 4.97–4.92 (m, 1H), 3.87 (m, 1H), 3.32–3.24 (m, 3H), 2.89 (m, 1H), 2.36–2.31 (d, J = 13.6 Hz, 1H), 2.23–2.20 (m, 1H), 2.15 (s, 3H), 1.84–1.12 (m, 14H), 0.91 (s, 3H), 0.23 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.4, 159.5, 134.1, 129.7, 126.5, 118.8, 118.0, 76.8, 72.9, 58.6, 53.6, 50.7, 48.9, 44.7, 39.2, 35.4, 34.5, 31.3, 27.7, 25.2, 24.3, 19.9, 19.7, 15.8 ppm; ESI (MS) m/z: 448.1 (M^+); Anal. Calcd for $C_{24}H_{36}N_2O_4S$: C, 64.25; H, 8.09; N, 6.24. Found: C, 64.28; H, 8.12; N, 6.21.

4.2.2.15. Compound 8g. Yellow solid, mp 95–97 °C. $[\alpha]_D^{26}$ = −78.2 (c 0.2, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.36 (s, 1H), 8.31 (s, 1H), 7.26–7.24 (d, J = 7.8 Hz, 1H), 7.07–7.04 (d, J = 9 Hz, 1H), 6.77–6.72 (m, 1H), 4.62 (m, 1H), 3.91 (m, 1H), 3.40–3.32 (m, 1H), 3.33–3.28 (d, J = 13.2 Hz, 1H), 3.18 (m, 1H), 2.92 (m, 1H), 2.51–2.46 (d, J = 13.2 Hz, 1H), 2.29–2.27 (m, 1H), 1.98 (s, 1H), 1.87–1.38 (m, 10H), 1.34 (s, 9H), 1.23–1.17 (m, 2H), 0.82 (s, 3H), 0.33 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.0, 160.6, 137.9, 130.3, 118.8, 118.6, 76.7, 72.8, 58.5, 53.8, 50.7, 48.9, 44.7, 39.2, 34.9, 34.4, 31.2, 29.9, 27.7, 24.3, 20.3, 20.3, 20.1 ppm; ESI (MS) m/z: 490.4 (M^+); Anal. Calcd for $C_{27}H_{42}N_2O_4S$: C, 66.09; H, 8.63; N, 5.71. Found: C, 66.12; H, 8.67; N, 5.68.

4.2.2.16. Compound 8h. Yellow solid, mp 116–118 °C. $[\alpha]_D^{26}$ = −25.4 (c 0.1, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 14.72 (s, 1H), 9.0 (s, 1H), 8.0 (m, 1H), 7.74–7.66 (m, 3H), 7.48–7.46 (m, 1H), 7.32–7.28 (m, 1H), 7.02–6.99 (m, 1H), 5.28 (s, 1H), 3.85 (m, 1H), 3.50–3.22 (m, 4H), 1.85–1.31 (m, 13H), 0.93 (s, 3H), 0.68 (s, 1H), 0.34 (s, 1H), 0.28 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 160.0, 136.5, 133.5, 129.6, 128.4, 127.4, 123.5, 122.9, 119.0, 107.7, 76.6, 69.5, 58.7, 53.8, 50.7, 48.9, 44.7, 39.1, 35.4, 33.9, 31.0, 27.5, 24.5, 20.0, 19.7 ppm; ESI (MS) m/z: 484.2 (M^+); Anal. Calcd for $C_{27}H_{36}N_2O_4S$: C, 66.91; H, 7.49; N, 5.78. Found: C 66.91; H, 7.49; N, 5.78.

4.2.2.17. Compound 10. Yellow solid, mp 53–55 °C. $[\alpha]_D^{26}$ = −20.2 (c 0.1, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.13 (s, 1H), 8.42 (s, 1H), 7.36–7.30 (m, 2H), 7.04–6.95 (m, 2H), 5.01–4.96 (d, J = 7.9 Hz, 1H), 4.02 (m, 1H), 3.51 (m, 2H), 3.43–3.38 (d, J = 13.6 Hz, 1H), 3.11 (m, 1H), 2.52–2.46 (d, J = 13.6 Hz, 1H), 2.28–2.26 (m, 1H), 1.90–1.22 (m, 14H), 1.02 (s, 3H), 0.36 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.2, 161.4, 133.3, 132.2, 119.6, 118.2, 117.3, 76.6, 73.3, 58.9, 54.2, 50.2, 48.3, 43.2, 38.7, 35.6, 34.7, 32.4, 28.2, 26.3, 25.7, 20.4, 19.4 ppm; ESI (MS) m/z: 433.8 (M^+); Anal. Calcd for $C_{23}H_{34}N_2O_4S$: C, 63.56; H, 7.89; N, 6.45. Found: C, 63.63; H, 7.94; N, 6.51.

4.2.3. General procedure for the catalytic asymmetric addition of diethylzinc to aldehydes

Under a dry argon atmosphere, a chiral ligand (10 mol %) in dry n-hexane (2 mL) was cooled to 0 °C, and a solution of $ZnEt_2$ (1.0 M in hexanes, 3 mmol) was added slowly into the mixture. After being stirred for an additional 1 h, freshly distilled aldehyde (1 mmol) was added by a syringe. The resulting mixture was stirred at 0 °C for another 24 h. Next, the reaction mixture was quenched with 2 M aqueous HCl. The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic phase was dried over anhydrous sodium sulfate. Then, the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 6:1) to give the product. The enantiomeric excess of the product was determined by HPLC using a Daicel Chiralcel OD column. The absolute configurations of the products were assigned by comparison to the literature values.

4.2.4. General procedure for the catalytic asymmetric addition of phenylacetylene to aldehydes

Under a dry argon atmosphere, to a solution of chiral ligand (10%, 0.1 mmol) in dry toluene (1 mL) was added $Ti(O^iPr)_4$ (0.3 mmol) at room temperature. Then, the above mixture was introduced by a syringe into the system in which phenylacetylene (2 mmol) and $ZnMe_2$ (2 mmol) were premixed and stirred for 1 h at room temperature. Then, the mixture was stirred for another 30 min, and aldehyde (1 mmol) was added. After being stirred for 24 h at the same temperature, the reaction mixture was quenched with saturated aqueous ammonium chloride. The mixture was

then extracted with diethyl ether (10 mL × 3). The organic phase was washed with brine and was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give the crude product. Purification of the residue by column chromatography furnished the pure chiral alcohol. The enantiomeric excess was determined by HPLC analysis using a Chiralcel column. The configuration was assigned by comparison with the sign of the specific rotation of the known compounds.

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