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Syntheses of Novel Chiral Sulfinamido Ligands and Their Applications in Diethylzinc Additions to Aldehydes†

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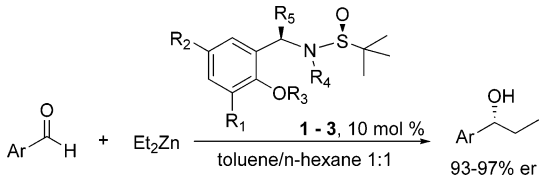

A novel class of sulfinamido alcohol ligands **1**−**6** was synthesized from (*S*)-*tert*-butanesulfinamide. These ligands showed excellent catalytic activities and enantiomeric selectivities in asymmetric additions of diethylzinc to aromatic aldehydes.

Introduction

Over the last two decades, the asymmetric addition of dialkylzinc to aldehyde has been well developed since the initial report of Oguni.[1] Most of the ligands are based upon chiral amino alcohols, amino thiols, amino disulfides, amino diselenides, diamines, or diols.[2] Ligands possessing carbon atomic chirality or axial chirality with two coordinating heteroatoms feature the most common frameworks for the successful chiral ligands. However, chiral ligands with a stereogenic heteroatom that can effectively catalyze the diethylzinc addition with high levels of enantioselectivity are scarcely reported.[3] Therefore, research on asymmetric addition of diethylzinc to aldehydes catalyzed by chiral ligands with a stereogenic heteroatom remains an interesting topic in asymmetric synthesis.

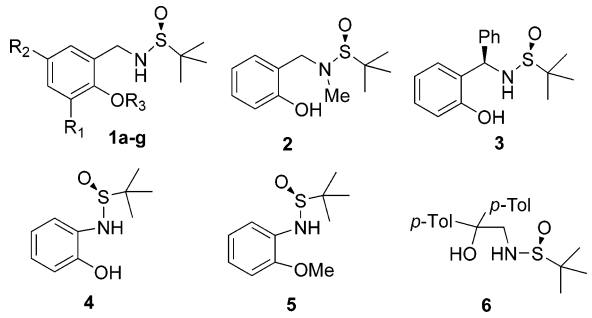

FIGURE 1. Structures of sulfinamido ligands **1**−**6**.

Chiral *tert*-butanesulfinamide (TBSA)[4] has been extensively used as a chiral auxiliary in recent years,[5] but few studies have focused on the applications of its derivatives as chiral catalysts.[6] To extend our studies on TBSA chemistry,[7] herein we report on the synthesis of a novel class of sulfinamido alcohol ligands

† Dedicated to Prof. Yaozhong Jiang on the occasion of his 70th birthday.

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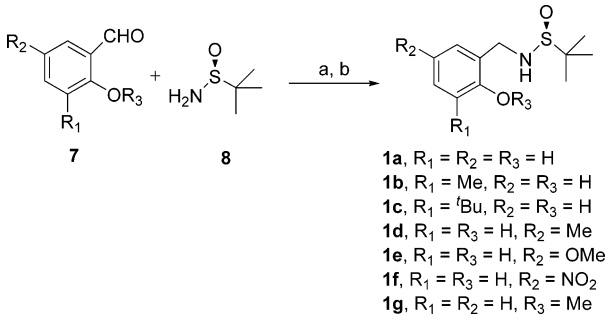
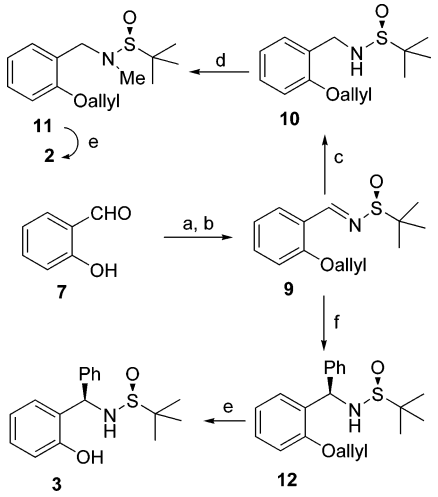
SCHEME 1[a]



[a] Reagents and conditions: (a) $KHSO_4$, toluene, 45 °C; (b) $NaBH_4$, two steps, 70−92% overall yields.

SCHEME 2[a]



[a] Reagents and conditions: (a) allyl bromide, K_2CO_3; (b) **8**, $KHSO_4$, two steps, 93% overall yield; (c) $NaBH_4$, 95% yield; (d) KH, MeI, 95% yield; (e) $Pd(PPh_3)_4$, $NaBH_4$, 90% yield; (f) PhMgBr, CH_2Cl_2, −48 °C, 92% yield, 98% dr; (g) $Pd(PPh_3)_4$, $NaBH_4$, 95% yield.

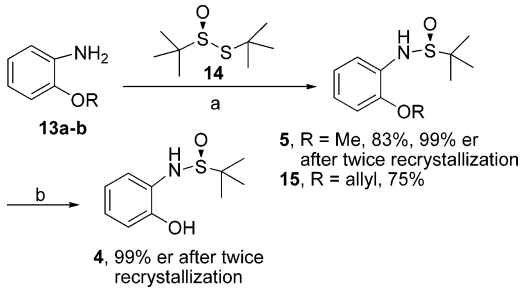
1−**6** incorporating a (*S*)-TBSA moiety and their applications in asymmetric additions of diethylzinc to aldehydes.

Results and Discussion

Syntheses of Ligands 1−**6**. Our efforts to prepare ligands **1**−**6** incorporating a (*S*)-TBSA moiety began with the syntheses of ligands **1a**−**g**.[8] Ligands **1a**−**g** were readily prepared by a two-step reaction in 70−92% yield from corresponding aldehydes **7** and (*S*)-TBSA **8** (Figure 1). Condensation of **7** with **8** was performed without racemization using our previous protocol for sulfimine formation.[7c] Reduction of the resulting sulfimine with $NaBH_4$[9] afforded ligands **1a**−**g** (Scheme 1).

Ligand **2** with a methyl substituent on nitrogen and ligand **3** with a phenyl substituent on the tertiary carbon were both prepared from *O*-allyl protected (*S*)-sulfimine **9** by using the procedure presented in Scheme 2. After reduction of the C═N double bond in **9** with $NaBH_4$, the resulting compound **10** was treated with MeI in the presence of 2 equiv of KH in THF at −20 °C to afford compound **11** in 95% yield. Deprotection of the allyl group with $NaBH_4$ catalyzed by 2 mol % of $Pd(PPh_3)_4$[10] provided ligand **2** in 90% yield and >99% er. However, methylation of **10** resulted in about 1.5% racemization of compound **11** with a diminished er of 97% when NaH was employed as base rather than KH. Similar racemization was also observed in the acylation of TBSA **8** with NaH as base.[11] The addition of PhMgBr to sulfimine **9** in CH_2Cl_2 at −48 °C provided compound **12** in 92% yield and 99:1 dr.[12] Deprotection of the allyl group in **12** with $Pd(PPh_3)_4$ and $NaBH_4$ gave ligand (S_S,*R*)-**3** in 95% yield. The absolute configuration of the major isomer was secured by the X-ray crystallographic analysis of **3**.[13]

SCHEME 3[a]



[a] Reagents and conditions: (a) $LiNH_2$ in liquid NH_3; (b) $Pd(PPh_3)_4$, $NaBH_4$, THF, 90% yield, 90% er, 99% er after twice recrystallization.

Ligand **4** was prepared from *O*-protected 2-aminophenol **13**[14] and enantiomeric rich (S_S)-thiosulfinate **14**[4c,e] (Scheme 3). Ammonolysis of (S_S)-**14** (93% er) with the lithium salts of **13a** (R = Me) and **13b** (R = allyl), generated in situ by the reaction of **13** with $LiNH_2$ in liquid ammonia, afforded (S_S)-**5** in 83% (90% er) and (S_S)-**15** in 75% yields, respectively. After twice recrystallization from a mixture of petroleum and ethyl acetate (10:1), an enantiopure sample of **5** was obtained. The efforts to remove the *O*-methyl group in **5** were unsuccessful with use of the common demethylation reagents such as BF_3, $AlCl_3$, and Me_3SiI. In all cases, a dark-colored mixture was obtained probably because the TBSA moiety in **5** is highly sensitive to Lewis acids and the phenol group tends to be easily oxidized in the system. Fortunately, deallylation of **15** was successful with $Pd(PPh_3)_4$ and $NaBH_4$, which generated **4** in 90% yield and 90% er. The enantiomeric purity of **4** was greatly enhanced to 99.4% after twice recrystallization from a degassed mixture of hexane and ethyl ether (4:1). Notably, when exposed to air at room temperature, ligand **4** is prone to be oxidized. Therefore, storage of **4** in an inert atmosphere at −30 °C is strongly recommended.

Ligand **6** was prepared from methyl dimethoxyacetate **16** by a four-step reaction shown in Scheme 4. Grignard addition of

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(13) A colorless crystal of **3** ($C_{17}H_{21}N_1O_2S_1$, mp 215−216 °C) for X-ray analysis was obtained by recrystallization from MeOH. The crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, CCDC 620263, and are also available in the Supporting Information (the ORTEP/X-ray figure of **3** is shown in the Supporting Information).

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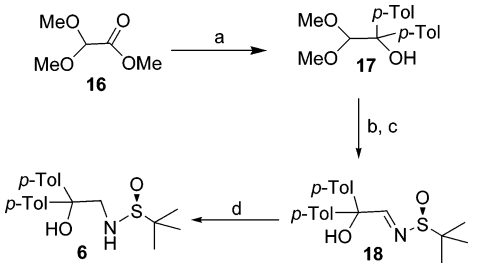
SCHEME 4[a]



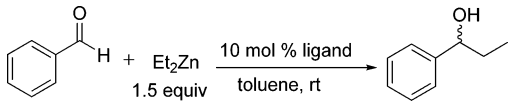
[a] Reagents and conditions: (a) *p*-TolMgBr, 83% yield; (b) I_2, acetone; (c) **8**, $KHSO_4$, toluene, 87% yield; (d) $NaBH_4$, 92% yield.

p-tolMgBr to **16** provided alcohol **17** in 83% yield. Hydrolysis of **17** with I_2 in acetone[15] was followed by condensation with (*S*)-**8** to give sulfimine **18** in 87% yield. Reduction of **18** provided ligand **6** in 92% yield.

Ligand Screening. Ligands **1**−**6** were roughly divided into two types, namely the α-sulfinamido alcohol ligands and the *β*-sulfinamido alcohol ligands. We sought to compare the coordinating abilities of the two types as well as the catalytic performance of the corresponding zinc complexes formed from the ligands. The ligands were evaluated for their catalytic activities in the asymmetric addition of diethylzinc to benzaldehyde. Unless otherwise stated, all the reactions were carried out in toluene with 10 mol % of individual ligand, using 1.5 equiv of diethylzinc at room temperature. The results are shown in Table 1. The initial experiment provided a promising result that the addition reaction catalyzed by ligand **1a** proceeded smoothly to afford (*R*)-1-phenyl-1-propanol in 89% yield and 94% er (Table 1, entry 1). The enantioselectivity of the reaction was unambiguously induced by the stereogenic heteroatom of sulfur in **1a**. The results of the reactions with ligands **1a**−**f** demonstrated the steric and electronic effects of a variety of comparable substituents at the ortho and para positions of the hydroxy group. Increasing the substituent size at the adjacent position from the smallest hydrogen (**1a**) to the bulky *tert*-butyl group (**1c**) resulted in decreased yield and enantiomeric excess (Table 1, entries 1−3). Ligand **1d** with a methyl group at the para position showed the same catalytic activity as ligand **1a**. Replacement of the hydrogen (**1a**) with an electron-donating group (**1e**) or an electron-withdrawing group (**1f**) at the para position resulted in critically diminished catalytic activity (Table 1, entries 5 and 6). Methylation of the hydroxy group (ligand **1g**) provided the product in a low yield (47%) with an inverse configuration (Table 1, entry 7).

It was reported that α-amino alcohol ligands with tertiary amine generally provided better enantioselectivities than the ligands with secondary amine in the additions of dialkylzinc to aldehydes.[16] In contrast to these observations, the addition reaction catalyzed by ligand **2** with a tertiary sulfinamido functionality gave racemic 1-phenylpropanol in 36% yield (Table 1, entry 8). Addition reaction catalyzed by ligand **3** also provided a low yield and poor enantioselectivity (Table 1, entry 9). Although ligand **3** has the same structural motif as ligand **1a**, the disappointing result indicated that the crowded phenyl substituent between the sulfinamido group and the hydroxy group might have shielded the coordination of aldehyde to the catalytically active zinc complex.

TABLE 1. Screening of Ligands 1−6 in Asymmertic Addition of Diethylzinc to Benzaldehyde



entry	L*	R_1	R_2	R_3	time (h)	yield (%)	er %[a] (config)
1	**1a**	H	H	H	18	89	94 (*R*)
2	**1b**	Me	H	H	18	90	94 (*R*)
3	**1c**	^{t}Bu	H	H	18	67	79 (*R*)
4	**1d**	H	Me	H	18	87	94 (*R*)
5	**1e**	H	OMe	H	24	15	78 (*R*)
6	**1f**	H	NO_2	H	18	66	84 (*R*)
7	**1g**	H	H	Me	13	47	33 (*S*)[b]
8	**2**				24	36	0
9	**3**				24	40	17 (*R*)
10	**4**				16	70	40 (*R*)
11	**5**				18	78	0
12	**6**				18	80	75 (*R*)
13	**1a**	H	H	H	18	93	96 (*R*)[c]
14	**1a**	H	H	H	24	89	94 (*R*)[d]
15	**1a**	H	H	H	18	95	96 (*R*)[e]
16	**1a**	H	H	H	18	58	96 (*R*)[f]

[a] Determined by chiral stationary phase HPLC, Chiralcel OD. [b] The inverse (*R*)-configuration (32% er) and similar yield (52%) of adduct were observed when the enantiomer of **1g** with the opposite (*R*)-TBSA moiety was employed. [c] Toluene/hexane 1:1, 10% mol of **1a**. [d] Toluene/hexane 1:1, 5% mol of **1a**. [e] Toluene/hexane 1:1, 20% mol of **1a**. [f] Toluene/hexane 1:1, 10% mol of **1a**, at 0 °C.

The α-sulfinamido alcohol ligands **4** and **6** showed inferior catalytic activity to ligand **1a** of the *β*-sulfinamido alcohol type. The former achieved but moderate yields and enantiomeric excess (Table 1, entries 10 and 12). Surprisingly, the addition reaction catalyzed by ligand **5** with a methoxy group on the phenyl ring provided a racemic product (Table 1, entry 11).

According to the above results, ligand **1a** was the best catalyst among those tested. We subsequently found that the use of a mixture solvent of toluene and *n*-hexane (1:1) slightly increased the yield and er (93% yield, 96% er) relative to the use of toluene alone (89% yield, 94% er) for benzaldehyde addition (Table 1, entries 1 and 13). Further changes in the loading amount of **1a**, by either increasing or decreasing it (20 and 5 mol %), had little effect on the yield and er (Table 1, entries 14 and 15). Lowering the reaction temperature from 25 to 0 °C failed to bring up the er value and cut down the yield by 35% (Table 1, entry 16).

Asymmetric Additions of Diethylzinc to Aldehydes. The performance of ligand **1a** was examined in the asymmetric additions of diethylzinc to a variety of aldehydes under the optimal condition (10 mol % of **1a** in a mixture of toluene and *n*-hexane (1:1) and 1.5 equiv of Et_2Zn at room temperature). The results are shown in Table 2. Similar to the results for benzaldehyde, all the additions to aromatic aldehydes provided the corresponding *R*-configuration alcohols as the major isomer with excellent enantioselectivities (93−97% er) and in moderate to high yields (Table 2, entries 1−6). Under the same condition, the additions of diethylzinc to phenylpropionaldehyde and *trans*-cinnamaldehyde afforded the (*R*)-configuration alcohols in moderate yields and enantioselectivities (Table 2, entries 7 and 8).

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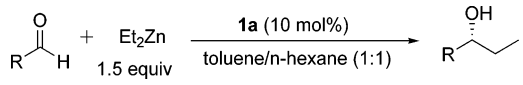
TABLE 2. Asymmertic Additions of Diethylzinc to Aldehydes Catalyzed by 1a[a]



entry	aldehydes	time (h)	yield[b] (%)	er %[c] (config)
1	C_6H_5CHO	18	93	96 (*R*)
2	*p*-ClC_6H_4CHO	20	90	96 (*R*)
3	*p*-$CH_3OC_6H_4CHO$	24	77	94 (*R*)
4	*p*-$(CH_3)_2NC_6H_4CHO$	24	58	97 (*R*)
5	3-furaldehyde	15	71	93 (*R*)
6	2-thiophenealdehyde	20	78	94 (*R*)
7	$PhCH_2CH_2CHO$	24	70	70 (*R*)
8	*trans*-PhCH=CHCHO	15	82	54 (*R*)

[a] Unless otherwise noted, reactions were carried out in the presence of 10 mol % of ligand, 1.5 equiv of Et_2Zn at rt. [b] Isolated yield. [c] Determined by chiral stationary phase HPLC, Chiralcel OD.

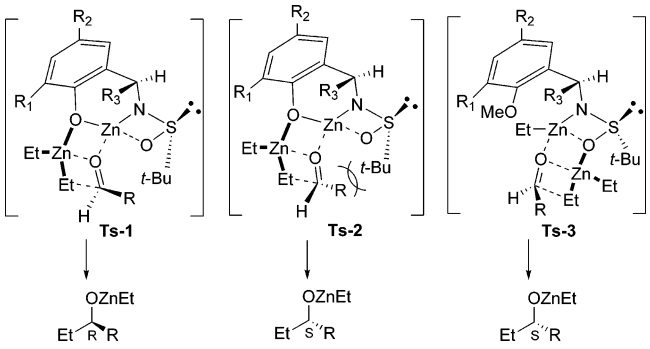


FIGURE 2. Proposed transition states.

Mechanistic Considerations. On the basis of the stereochemical outcome of the adducts and the structure−activity relationship of ligands **1**−**3** revealed in the addition of diethylzinc to benzaldehyde, the canonical *anti* transition states[17] are proposed in Figure 2. Accordingly, both the nitrogen atom and the oxygen atom of the sulfinamido group, along with the oxygen atom of hydroxy group, participate in the coordination with zinc to form *O*,*N*,*O*-chelating six/four bicyclic transition states **Ts-1** and **Ts-2** as the catalytically active species. **Ts-1** is the dynamically favorable transition state except for the case that the bulky R_3 group (ligand **3**, R_3 = Ph) faces upward to have an interaction with the R group and to shield the coordination of aldehyde to zinc. The transfer of the ethyl group from diethylzinc to the *Re*-face of aldehyde in **Ts-1** results in the formation of *R*-configuration alcohol. The unfavorable transition state **Ts-2** is responsible for the formation of *S*-configuration alcohol, in which a strongly steric interaction of the *tert*-butyl group with R takes place. Methylation of either the hydroxy group or the sulfinamido group undoubtedly precludes the formation of transition states **Ts-1** and **Ts-2**. When the hydroxyl group on the phenyl ring is replaced with a methoxy group (ligand **1g**), the addition reaction may proceed with a different transition state **Ts-3**, in which only the nitrogen atom and oxygen atom of the sulfinamido moiety participate in the coordination with zinc (Figure 2). In this way, the transfer of ethyl to the *Si*-face affords *S*-configuration alcohol. Methylation of the sulfonamide (ligand **2**) totally rules out the possible formation of a chelating zinc complex. Therefore, the diethylzinc addition to benzaldehyde catalyzed by ligand **2** affords a racemic product. The proposed transition states may well explain our experimental observations that the substituents on the phenyl ring and the sulfinamide have considerable effects on the catalytic activities of ligands **1**−**3** and the configuration of the resulting adducts.

Conclusion

In summary, a novel class of sulfinamido alcohol ligands possessing the stereogenic heteroatom rather than the carbon atomic chirality was synthesized from commercially available (*S*)-*tert*-butanesulfinamide. These ligands were evaluated in the asymmetric additions of diethylzinc to aldehydes and showed excellent enantiomerically catalytic activities for aromatic aldehydes. Further efforts will be focused on the applications of these ligands toward different asymmetric reactions and the exploration of new ligands based on chiral *tert*-butanesulfinamide.

Experimental Section

Synthesis of Ligand (*S*)-1 (a representative procedure for ligand 1a). To a stirred solution of **8** (121 mg, 1.0 mmol) in dry toluene (5 mL) at 45 °C was added anhydrous $KHSO_4$ (272 mg, 2.0 mmol) and salicylaldehyde **7** (213 μL, 2.0 mmol). After 24 h, The reaction mixture was filtered and concentrated in vacuum to afford sulfimine as a white solid. The solid was dissolved in THF (10 mL), and $NaBH_4$ (38 mg, 1.0 mmol) was added at 0 °C. Once the addition was complete, the mixture became yellow and was stirred for additional 2 h at 0 °C. The solution turned colorless before saturated aqueous NH_4Cl was added to quench the reaction. The resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. (*S*)-**1a** (198 mg, 87% yield for two steps) was obtained as a white solid after purification by column chromatography (1:2 ethyl acetate/hexanes). The enantiomeric excess was determined to be >99.9% by HPLC analysis on a Diacel Chiralcel OD column (95:5 hexanes/IPA, 1.0 mL/min; 227 nm; (*R*)-**1a**, t_R = 14.2 min, (*S*)-**1a**, t_R = 16.0 min). A needle crystal of **1a** was obtained by recrystallization from a mixture solvent of ethyl acetate and hexanes (1:4): mp 116−117 °C; $[\alpha]^{20}_D$ +48.3 (*c* 1.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.20−7.12 (m, 2H), 6.88−6.81 (m, 2H), 4.30 (d, J = 5.6 Hz, 2H), 3.91 (t, J = 5.6 Hz, 1H), 1.26 (s, 9H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.5 (3C), 46.9, 56.1, 115.9, 119.3, 124.2, 129.2, 129.4, 155.5 ppm; IR (KBr) 3267, 3178, 1458, 1245, 1035, 757 cm^{-1}; HRMS-ESI calcd for $C_{11}H_{17}NNaO_2S$ $(M + Na)^+$ 250.0872, found 250.0866.

Ligand (*S*)-1b. (*S*)-**1b** was purified by column chromatography (1:2 ethyl acetate/ hexanes) as a white powder (89% yield). The enantiomeric excess was determined to be >99.9% by HPLC analysis on a Diacel Chiralcel OD column (95:5 hexanes/IPA, 1.0 mL/min; 227 nm; (*R*)-**1b**, t_R = 11.3 min, (*S*)-**1b**, t_R = 8.7 min). Mp 74−75 °C; $[\alpha]^{20}_D$ +54.0 (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.12 (d, J = 7.2 Hz, 1H), 6.97 (dd, J = 7.6, 1.2 Hz, 1H), 6.77 (t, J = 7.6 Hz, 1H), 4.38 (dd, J = 13.2, 7.2 Hz, 1H), 4.35 (dd, J = 13.2, 4.0 Hz, 1H), 3.59 (dd, J = 7.2, 4.0 Hz, 1H), 2.24 (s, 3H), 1.26 (s, 9H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.0, 22.6 (3C), 46.9, 56.1, 119.7, 123.4, 126.0, 127.5, 131.0, 153.7 ppm; IR (KBr) 3302, 2960, 1473, 1210, 1052, 752 cm^{-1}; HRMS-ESI calcd for $C_{12}H_{19}NNaO_2S$ $(M + Na)^+$ 264.1029, found 264.1018.

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Ligand (*S*)-1c. (*S*)-**1c** was purified by flash chromatography (1:4 ethyl acetate/hexanes) as a colorless liquid (87% yield). The enantiomeric excess was determined to be >99.9% by HPLC analysis on a Diacel Chiralcel OD column (95:5 hexanes/IPA, 1.0 mL/min; 227 nm; (*R*)-**1c**, t_R = 9.6 min, (*S*)-**1c**, t_R = 6.1 min). $[\alpha]^{20}_D$ +34.8 (*c* 0.54, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.27 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.01 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.81 (t, *J* = 7.6 Hz, 1H), 4.39 (dd, *J* = 13.2, 7.2 Hz, 1H), 4.28 (dd, *J* = 13.2, 3.6 Hz, 1H), 3.59 (dd, *J* = 7.2, 3.6 Hz, 1H), 1.40 (s, 9H), 1.27 (s, 9H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.6 (3C), 29.6 (3C), 34.8, 45.9, 56.1, 119.6, 123.4, 127.3, 128.0, 136.0, 154.6 ppm; IR (KBr) 3485, 3140, 1440, 1229, 1027, 750 cm^{-1}; HRMS-ESI calcd for $C_{15}H_{25}NNaO_2S$ $(M + Na)^+$ 306.1498, found 306.1488.

Ligand (*S*)-1d. (*S*)-**1d** was purified by flash chromatography (1:2 ethyl acetate/ hexanes) as a white solid (90% yield). The enantiomeric excess was determined to be >99.9% by HPLC analysis on a Diacel Chiralcel AS column (90:10 hexanes/IPA, 1.2 mL/min; 227 nm; (*R*)-**1d**, t_R = 30.4 min, (*S*)-**1d**, t_R = 24.0 min). Mp 136−137 °C; $[\alpha]^{20}_D$ +53.5 (*c* 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.02 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.93 (d, *J* = 2.4 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 4.30 (dd, *J* = 13.6, 6.8 Hz, 1H), 4.24 (dd, *J* = 13.6, 4.4 Hz, 1H), 3.67 (t, *J* = 4.8 Hz, 1H), 2.26 (s, 3H), 1.26 (s, 9H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.3, 22.6 (3C), 47.0, 56.1, 115.9, 123.6, 126.5, 129.6, 130.1, 153.3 ppm; IR (KBr) 3261, 3160, 1512, 1268, 1027, 818 cm^{-1}; HRMS-ESI calcd for $C_{12}H_{19}NNaO_2S$ $(M + Na)^+$ 264.1029, found 264.1025.

Ligand (*S*)-1e. (*S*)-**1e** was purified by flash chromatography (1:2 ethyl acetate/hexanes) as a white solid (89% yield). The enantiomeric excess was determined to be >99.9% by HPLC analysis on a Diacel Chiralcel AS column (85:15 hexanes/IPA, 1.2 mL/min; 227 nm; (*R*)-**1e**, t_R = 27.2 min, (*S*)-**1e**, t_R = 20.1 min). Mp 145−146 °C; $[\alpha]^{20}_D$ +70.6 (*c* 0.96, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1H), 6.82 (d, *J* = 8.8 Hz, 1H), 6.75 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.69 (d, *J* = 2.8 Hz, 1H), 4.26 (d, *J* = 5.6 Hz, 2H), 3.83 (t, *J* = 5.6 Hz, 1H), 3.74 (s, 3H), 1.25 (s, 9H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.6 (3C), 46.7, 55.6, 56.1, 114.2, 115.1, 117.1, 124.6, 149.3, 152.7 ppm; IR (KBr) 3249, 3164, 1512, 1223, 1021, 823 cm^{-1}; HRMS-ESI calcd for $C_{12}H_{19}NNaO_3S$ $(M + Na)^+$ 280.0978, found 280.0971.

Ligand (*S*)-1f. (*S*)-**1f** was purified by recrystallization from the mixture solvent (1:1 ethyl acetate/hexanes) to afford a yellow solid (70% yield for two steps). The enantiomeric excess was determined to be >99.9% by HPLC analysis on a Diacel Chiralcel AS column (85:15 hexanes/IPA, 1.2 mL/min; 227 nm; (*R*)-**1f**, t_R = 34.8 min, (*S*)-**1f**, t_R = 21.8 min). Mp 146−147 °C; $[\alpha]^{20}_D$ +48.4 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.5 (s, 1H), 8.10 (d, *J* = 2.8 Hz, 1H), 7.95 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.75 (d, *J* = 8.8 Hz, 1H), 4.40−4.34 (m, 1H), 4.29−4.22 (m, 2H), 1.29 (s, 9H) ppm; ^{13}C NMR (50 MHz, DMSO-d_6) δ 22.6 (3C), 42.5, 55.6, 115.2, 124.6, 124.6, 127.7, 139.6, 161.4 ppm; IR (KBr) 3183, 3108, 1597, 1503, 1342, 1292, 1030, 799 cm^{-1}; HRMS-ESI calcd for $C_{11}H_{16}N_2NaO_4S$ $(M + Na)^+$ 295.0723, found 295.0717.

Ligand (*S*)-1g. (*S*)-**1g** was purified by flash chromatography (1:4 ethyl acetate/hexanes) as a colorless liquid. The enantiomeric excess was determined to be >99.9% by HPLC analysis on a Diacel Chiralcel OD column (95:5 hexanes/IPA, 1.0 mL/min; 227 nm; (*R*)-**1g**, t_R = 14.4 min, (*S*)-**1g**, t_R = 17.4 min). $[\alpha]^{20}_D$ +20.4 (*c* 0.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.25 (m, 2H), 6.93 (t, *J* = 7.2 Hz, 1H), 6.87 (t, *J* = 4.0 Hz, 1H), 4.42 (dd, *J* = 14.0, 5.2 Hz, 1H), 4.16 (dd, *J* = 14.0, 8.0 Hz, 1H), 3.84 (s, 3H), 3.69 (t, *J* = 5.2 Hz, 1H), 1.20 (s, 9H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.5 (3C), 45.4, 55.2, 55.7, 110.3, 120.5, 127.0, 128.8, 129.3, 157.3 ppm; IR (KBr) 3249, 1526, 1215, 1037, 758 cm^{-1}; HRMS-ESI calcd for $C_{12}H_{19}NNaO_2S$ 264.1029, found 264.1028.

Synthesis of Ligand (*S*)-2. To a solution of salicylaldehyde **7** (1.20 g, 10 mmol) in dry acetone (20 mL) was added allyl bromide (1.3 mL, 15 mmol) and anhydrous potassium carbonate (4.20 g, 30 mmol). After stirring for 2 h at rt, the resulting mixture was concentrated in vacuum. The residue was diluted with ethyl acetate (10 mL), filtered, and concentrated to afford the crude *O*-allyl salicylaldehyde, which was then condensed directly with 0.61 g (5 mmol) of (*S*)-TBSA to afford 1.33 g of sulfimine **9** in 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.01 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.46 (td, *J* = 7.2, 1.6 Hz, 1H), 7.03 (t, *J* = 7.6 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.13−6.03 (m, 1H), 5.47−5.42 (m, 1H), 5.34−5.31 (m, 1H), 4.67−4.65 (m, 2H), 1.29 (s, 9H) ppm.

Crude compound **10** obtained by reducing sulfimine **9** (530 mg, 2.0 mmol) dissolved in THF (20 mL). KH (35% in oil, 450 mg, 4.0 mmol) was added slowly at −20 °C. After being stirred for 20 min, MeI (187 μL, 3.0 mmol) was added. The mixture was stirred for an additional 4 h at −20 °C and quenched with saturated aqueous NH_4Cl. Following the extraction with ethyl acetate (3 × 15 mL), the combined organic layers were dried (Na_2SO_4), concentrated, and purified by flash chromatography (1:8 ethyl acetate/hexanes) to give 506 mg (90% yield for two steps) of **11** as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 7.2 Hz, 1H), 7.23 (t, *J* = 8.0 Hz, 1H), 6.94 (t, *J* = 7.2 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.10−6.00 (m, 1H), 5.33 (dd, *J* = 43.2, 28.0 Hz, 2H), 4.54 (d, *J* = 4.4 Hz, 2H), 4.29 (dd, *J* = 43.2, 28.0 Hz, 2H), 2.63 (s, 3H), 1.19 (s, 9H) ppm.

Compound **11** (470 mg, 1.70 mmol) and $Pd(PPh_3)_4$ (42 mg, 0.03 mmol) were dissolved in 10 mL of dry THF at 0 °C. After the mixture was stirred for 5 min at 0 °C, $NaBH_4$ (95 mg, 2.50 mmol) was slowly added. The stirring was continued for an additional 2 h at room temperature and the reaction was quenched with saturated aqueous NH_4Cl at 0 °C. Following the extraction with CH_2Cl_2 (3 × 10 mL), the combined organic layers were dried (Na_2SO_4), concentrated, and purified by flash chromatography (1:10 ethyl acetate/hexanes) to afford 367 mg (90% yield) of ligand (*S*)-**2** as a light yellow liquid. The enantiomeric excess was determined to be >99.9% by HPLC analysis on a Diacel Chiralcel OD column (98:2 hexanes/IPA, 0.5 mL/min; 227 nm; (*R*)-**2**, t_R = 38.9 min, (*S*)-**2**, t_R = 41.1 min). $[\alpha]^{20}_D$ +102.2 (*c* 0.96, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.22 (td, *J* = 8.0, 1.6 Hz, 1H), 7.04 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 6.80 (td, *J* = 7.6, 1.2 Hz, 1H), 4.86 (d, *J* = 14.0 Hz, 1H), 3.67 (d, *J* = 14.0 Hz, 1H), 2.70 (s, 3H), 1.26 (s, 9H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.3 (3C), 36.2, 46.2, 59.6, 117.6, 119.1, 120.4, 130.4, 143.3, 156.1 ppm; IR (KBr) 3192, 1457, 1037, 912, 755 cm^{-1}; HRMS-ESI calcd for $C_{12}H_{19}NNaO_2S$ $(M + Na)^+$ 264.1029, found 264.1027.

Synthesis of Ligand (S_S,*R*)-3. To a solution of **9** (3.00 g, 11.3 mmol) in 50 mL of dry CH_2Cl_2 was added phenylmagnesium bromide (19 mL, 1.2 M in THF, 22.8 mmol) at −48 °C. After being stirred for 5 h at −48 °C, the reaction was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuum. The dr value (99:1) of the crude product was determined by ^{1}H NMR spectrum. The major isomer **12** as a white solid (92% yield) was obtained by flash chromatography (1:5 ethyl acetate/hexanes). Mp 67−68 °C; $[\alpha]^{20}_D$ +70.0 (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.29 (t, *J* = 7.2 Hz, 2H), 7.24−7.20 (m, 1H), 6.97 (t, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.02 (d, *J* = 4.4 Hz, 1H), 5.95−5.88 (m, 1H), 5.29−5.19 (m, 2H), 4.47−4.46 (m, 2H), 3.88 (d, *J* = 3.6 Hz, 1H), 1.12 (s, 9H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.5 (3C), 55.6, 57.1, 68.8, 112.1, 117.3, 120.6, 127.2, 127.3 (2C), 128.0, 128.1, 128.3 (2C), 128.4, 130.2, 142.4, 155.7 ppm.

Similar to the synthesis of ligand **2**, the *O*-allyl protecting group in **12** was also removed with $NaBH_4$ catalyzed by $Pd(PPh_3)_4$ to give crude **3**, which was purified by flash chromatography (1:5 acetone/hexanes) to afford pure (S_S,*R*)-**3** in 95% yield as a white solid. A colorless crystal of **3** was obtained by recrystallization from MeOH. Mp 215−216 °C; $[\alpha]^{20}_D$ +46.7 (*c* 0.24, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.39 (d, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 7.2 Hz, 1H), 7.18 (d, *J* = 7.2 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.81 (t,

J = 7.6 Hz, 1H), 5.90 (d, J = 4.0 Hz, 1H), 4.05 (d, J = 4.0 Hz, 1H), 1.24 (s, 9H) ppm; ^{13}C NMR (50 MHz, DMSO-d_6) δ 22.6 (3C), 55.6, 56.8, 115.3, 119.1, 126.6, 127.6 (2C), 128.0, 128.2 (2C), 128.5, 129.3, 143.6, 154.2 ppm; IR (KBr) 3176, 1456, 1356, 1265, 1032, 754 cm^{-1}; HRMS-ESI calcd for $C_{17}H_{21}NNaO_2S$ $(M + Na)^+$ 326.1185, found 326.1185.

Synthesis of Ligand (*S*)-4. To a solution of ammonia (20 mL) was added a catalytic crystal of $Fe(NO_3)_3$ at −78 °C, and the solution became yellow immediately. Lithium bars (0.172 g, 24.0 mmol) were added. The resulting blue solution was slowly warmed to −40 °C until it turned gray. The resulting $LiNH_2$ mixture was chilled to −78 °C, and 2-allyloxyphenylamine **13b** (3.870 g, 26.0 mmol) was added slowly. After being stirred for 3 h, a solution of (S_S)-thiosulfinate **14** (1.540 g, 8.0 mmol, 92% er) in 4 mL of dry THF was added slowly to the light pink lithium anilide solution. The mixture was stirred for 5 h at −78 °C, and then NH_4Cl crystals were carefully added. The volatile material was removed by warming the solution slowly. After the residue was diluted with ethyl acetate (80 mL) and water (40 mL), the resulting mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and purified by flash chromatography (1:10 ethyl acetate/hexanes) to afford 1.520 g of (*S*)-**15** (75% yield) as a pink liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22−7.20 (m, 1H), 6.95−6.92 (m, 2H), 6.89−6.86 (m, 1H), 6.11−6.02 (m, 1H), 6.10 (s, 1H), 5.44−5.30 (m, 2H), 4.60−4.58 (m, 2H), 1.35 (s, 9H) ppm.

The *O*-allyl protecting group in **15** (1.260 g, 5.0 mmol) was removed by $NaBH_4$ (0.285 g, 7.5 mmol) in the presence of Pd-$(PPh_3)_4$ (0.125 g, 0.1 mmol) in THF. The crude product was purified by chromatography (1:2 ethyl acetate/hexanes) to afford 0.960 g (90% yield) of ligand (*S*)-**4** as a yellow solid with 90% er. After twice recrystallization from degassed ethyl ether/hexanes (1:4), (*S*)-**4** was obtained with 99.4% er (HPLC, Diacel Chiralcel OD column 90:10 hexanes/IPA, 1 mL/min; 227 nm; (*R*)-**4**, t_R = 12.8 min, (*S*)-**4**, t_R = 16.3 min). Mp 132−134 °C; $[\alpha]^{20}_D$ +48.2 (*c* 0.38, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.02 (dd, J = 7.2, 2.0 Hz, 1H), 6.78−6.66 (m, 3H), 5.89 (s, 1H), 1.37 (s, 9H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.5 (3C), 56.5, 116.2, 119.6, 120.2, 124.6, 129.1, 146.1 ppm; IR (KBr) 3084, 1545, 1454, 1284, 1038, 767 cm^{-1}; HRMS-ESI calcd for $C_{10}H_{15}NNaO_2S$ $(M + Na)^+$ 236.0721, found 236.0726.

Synthesis of Ligand (*S*)-5. By using the same procedure as the preparation of compound **15**, ligand **5** was prepared from *o*-anisidine **13a** in 83% yield and with 90% er as a brown solid. After twice recrystallization from a mixture of petroleum and ethyl acetate (10:1), (*S*)-**5** was obtained with 99% er (HPLC, Diacel Chiralcel OD column 90:10 hexanes /IPA, 1.0 mL/min; 227 nm; (*R*)-**5**, t_R = 8.5 min, (*S*)-**5**, t_R = 11.2 min). Mp 112−113 °C; $[\alpha]^{20}_D$ +35.6 (*c* 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (dd, J = 7.6, 1.6 Hz, 1H), 6.98−6.88 (m, 1H), 6.85 (dd, J = 7.6, 1.6 Hz, 1H), 3.85 (s, 3H), 1.28 (s, 9H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.3 (3C), 55.7, 56.4, 110.7, 116.5, 121.1, 122.5, 131.6, 146.5 ppm; IR (KBr) 2959, 1500, 1459, 1248, 1082, 744 cm^{-1}; HRMS-ESI calcd for $C_{11}H_{17}NNaO_2S$ $(M + Na)^+$ 250.0872, found 250.0862.

Synthesis of Ligand (*S*)-6. Under N_2, to a solution of methyl dimethoxyacetate **16** (0.686 g, 5.1 mmol) in THF (14 mL) was added *p*-tolylmagnesium bromide (14 mL, 21.0 mmol, 1.5 M in THF) at 0 °C. The solution was stirred at 25 °C for 36 h and quenched with saturated aqueous NH_4Cl at 0 °C. The resulting mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuum. The residue was purified by chromatography (1:15 ethyl acetate/hexanes) to give 1.216 g (83% yield) of **17** as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.09 (m, 8H), 4.72 (s, 1H), 3.73 (s, 6H), 2.31 (s, 6H) ppm.

A mixture of **17** (572 mg, 2.0 mm) and a catalytic amount of I_2 (51 mg, 0.2 mmol) in acetone (10 mL) was stirred for 5 min to afford crude aldehyde for the next step. After the aldehyde was condensed with (*S*)-TBSA (121 mg, 1.0 mmol), sulfimine (*S*)-**18** (298 mg) was obtained as a white solid in 87% yield (for two steps). To a THF (10 mL) solution of **18** (343 mg, 1.0 mmol) was added $NaBH_4$ (19 mg, 0.5 mmol) at 0 °C. After being stirred for 2 h at 0 °C, the reaction was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuum. The residue was purified by recrystallization from a mixture of ethyl acetate and hexanes (1:3) to give 317 mg (92% yield) of ligand **6** as a white solid. The enantiomeric excess of **6** was determined to be >99.9% by HPLC analysis on a Diacel Chiralcel AS column (90:10 hexanes/IPA, 1.0 mL/min; 227 nm; (*R*)-**6**, t_R = 20.4 min, (*S*)-**6**, t_R = 9.5 min). Mp 160−161 °C; $[\alpha]^{20}_D$ +59.8 (*c* 0.99, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.28 (m, 4H), 7.16−7.10 (m, 4H), 4.45 (s, 1H), 3.96 (dd, J = 14.0, 5.2 Hz, 1H), 3.84 (dd, J = 14.0, 8.0 Hz, 1H), 3.46 (dd, J = 8.0, 5.2 Hz, 1H), 2.32 (s, 3H), 2.30 (s, 3H), 1.11 (s, 9H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.6, 22.5 (3C), 55.9, 56.4, 77.2, 125.9 (2C), 126.2 (2C), 128.9 (2C), 129.0 (2C), 136.6, 136.7, 141.2, 141.6 ppm; IR (KBr) 3471, 3187, 1510, 1047, 824 cm^{-1}; HRMS-ESI calcd for $C_{20}H_{27}NNaO_2S$ $(M + Na)^+$ 368.1655, found 368.1668.

Asymmetric Addition of Diethylzinc to Benzaldehyde Catalyzed by Ligand 1a (a representative procedure). To a solution of **1a** (11 mg, 0.05 mmol) in dry hexanes/toluene (1 mL/0.5 mL) was added diethylzinc (1.5 M in toluene, 0.5 mL, 0.75 mmol) at room temperature under N_2. The resulting mixture was stirred for 30 min and benzaldehyde (53 mg, 0.50 mmol) was added. After being stirred for an additional 18 h, the reaction was quenched with saturated aqueous NH_4Cl at 0 °C and the resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuum. The residue was purified by chromatography (1:15 ethyl acetate/hexanes) to afford 63 mg (93% yield) of (*R*)-1-phenyl-1-propanol (96% er).

The absolute configuration of adducts in Table 2 was determined by rotation and the enantiomeric excess was determined by chiral stationary phase HPLC analysis (Chiralcel OD column).[18]

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Supporting Information Available: Chiral HPLC analysis of ligands, data of ^{1}H and ^{13}C NMR spectra of new compounds, er determination of adducts, and X-ray crystallographic data for **3** as a CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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