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Concise Synthesis of Novel Practical Sulfamide−Amine Alcohols for the Enantioselective Addition of Diethylzinc to Aldehydes

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Novel sulfamide−amine alcohol ligands were designed using a grafting strategy and synthesized from readily available starting materials via a simple, efficient method. The key features of these ligands for the asymmetric addition of diethylzinc to aldehydes included stability, enhanced effectiveness without using $Ti(O^iPr)_4$, suitability for a variety of aldehydes, the ability to operate at room temperature, and selectability to afford either absolute configuration products with enantiomeric excess up to >99%.

Introduction

Great efforts have been devoted to the development of various types of chiral ligands for the asymmetric addition of diorganozinc to aldehydes. Either amino alcohols, amino thiols, disulfides, diselenides, and amines with Zn systems or Ti with diols, phosphoramides, and sulfonamide ligands such as bistriflamide, bissulfonamide, and sulfonamide alcohol could provide high yields and excellent enantioselectivities for the asymmetric addition of diethylzinc to aldehydes. However, Zn with sulfonamide ligand systems were not good catalysts for this reaction.[1−3] To our knowledge, no highly efficient chiral sulfonamide ligand has been reported for the asymmetric addition reaction without the addition of $Ti(O^iPr)_4$.[4] On the other hand, of approximately 600 chiral ligands for the asymmetric addition reactions shown in recent reviews,[1] only a small number of effective ligands were obtained by simple synthetic methods. Furthermore, ligands suitable for the addition reactions of both aromatic and aliphatic or α,β-unsaturated aldehydes are rare. Therefore, stable, easily accessible, operationally simple, and general ligands are still desirable. Recently, many reports showed that a chiral ligand $\mathbf{L_1}$ in combination with another chiral or achiral ligand $\mathbf{L_2}$ as an activator could exhibit enhanced efficiency and enantioselectivity in many asymmetric reactions.[5−10] Herein, using grafting strategy we designed a new type of ligand $\mathbf{L_3}$ by grafting activator $\mathbf{L_2}$ into the chiral ligand $\mathbf{L_1}$, which led to more rigid structures that might better discriminate between the two enantiotopic faces of benzaldehyde within the transition state complex. Thus, an activated catalyst is generated that could accelerate the reaction and afford higher enantiomeric excesses of the carbinol product (Figure 1). Recognizing

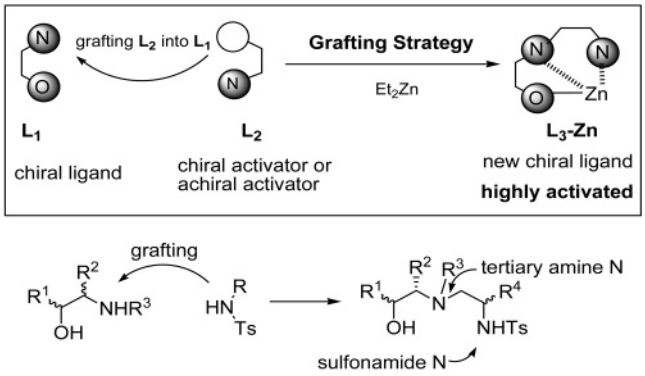

FIGURE 1. Design of novel sulfamide−amine alcohol ligands.

that achiral bissulfonamides are known to increase

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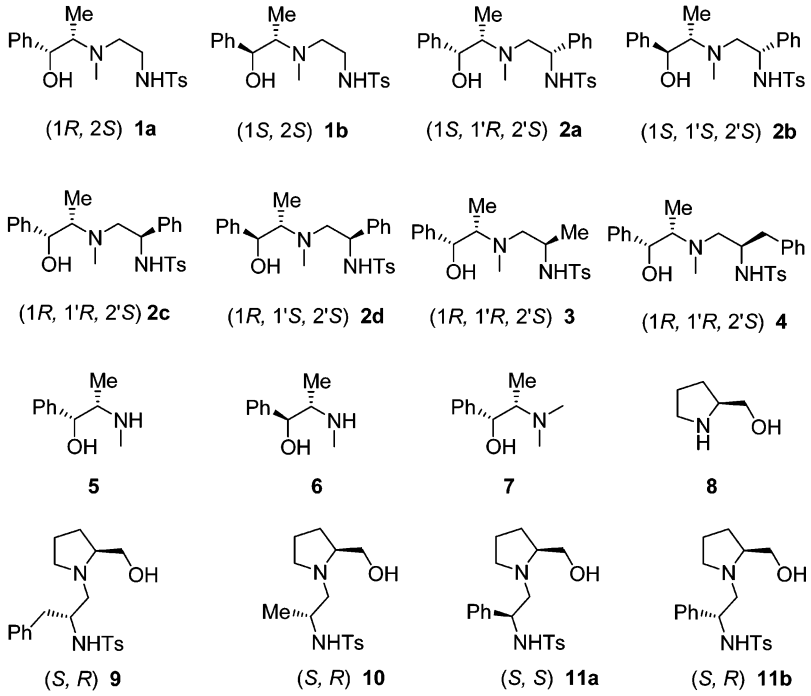
SCHEME 1. Evaluated Ligands

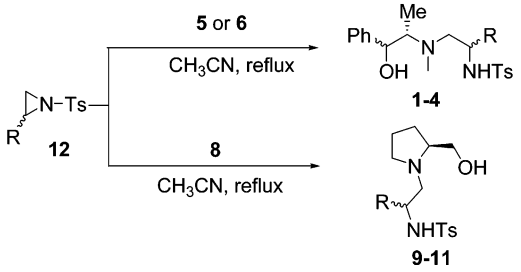


enantioselectivity in the addition of diethylzinc to benzaldehyde,[10] we chose sulfonamide as the activator. Herein, we report a new class of sulfamide−amine alcohol ligands (Scheme 1) obtained by introducing another nitrogen from sulfonamide to a chiral amino alcohol using the grafting strategy for asymmetric addition reactions. The key features of these ligands include (a) ease of preparation and high stability, (b) enhanced effectiveness without using $Ti(O^iPr)_4$, (c) suitability for a variety of aldehydes, (d) the ability to operate at room temperature, and (e) selectability to afford the high ee products with either absolute configurations. Based on the mechanistic consideration of titanium-catalyzed asymmetric additions of organozinc to aldehydes,[11] we expected that the sulfamide−amine alcohol ligands where the oxygen, nitrogen from the tertiary amine, and nitrogen from the sulfonamide could bind zinc in a tridentate fashion would be efficient catalysts for the addition reaction of Et_2Zn to aldehydes without addition of the moisture sensitive $Ti(O^iPr)_4$.

Results and Discussion

Sulfamide−amine alcohol ligands **1**−**4** and **9**−**11** were successfully prepared via reactions between natural chiral resources (−)-ephedrine **5**, (+)-pseudoephedrine **6**, or commercially available L-prolinol **8** and the corresponding aziridines **12**[12] in one step in an atom-economical synthesis (Scheme 2).[13] Pure products were obtained by recrystallization rather than using complex column chromatography. Moreover, these ligands are stable for several months in air.

SCHEME 2. Synthesis of Sulfamide−Amine Alcohols



To investigate the catalytic properties of these ligands, the asymmetric addition of Et_2Zn to benzaldehyde was first carried out in hexane using ligands **1a** and **1b** (Table 1). Poor enantioselectivities were observed with **1a** and **1b** (entries 1 and 2). Therewith, ligands **2a**−**d** were evaluated in this reaction (entries 3−6). Ligand **2c** showed 99% yield and 86% ee (entry 5). Finally, by changing the substituent of the backbone of **2c**, an effective ligand **4** with a benzyl group was obtained and provided the product with 92% ee and 91% yield (entry 8). Obviously, the third suitable sterogenic center was necessary to achieve high enantioselectivities, and the

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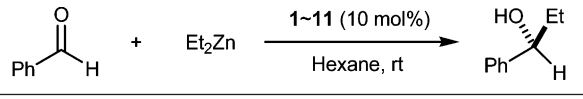
TABLE 1. Addition of Diethylzinc to Benzaldehyde Using Sulfamide−Amine Alcohols[a]



entry	ligand	% isolated yield	% ee[b]
1	**1a**	87	42 (*S*)
2	**1b**	96	28 (*S*)
3	**2a**	99	81 (*S*)
4	**2b**	61	26 (*S*)
5	**2c**	99	86 (*R*)
6	**2d**	99	25 (*S*)
7	**3**	87	84 (*S*)
8	**4**	91	92 (*S*)
9	**5**	86	72 (*R*)
10	**6**	29	35 (*S*)
11	**7**	68	77 (*R*)
12	**8**	32	29 (*R*)
13	**9**	84	66 (*R*)
14	**10**	53	59 (*R*)
15	**11a**	89	87 (*R*)
16	**11b**	86	>99 (*R*)

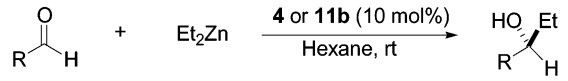
[a] Et_2Zn/aldehyde/ligand = 2.2:1:0.1, hexane, rt, 24 h. [b] The ee values were determined by GC, and the absolute configuration was assigned by comparison to literature values.

stereogenic centers of the ligand derived from (−)-ephedrine and (*R*)-aziridine matched well. To our surprise, ligand **2c** induced (*R*)-enriched product the opposite chirality to other ligands. It was probably related to the conformationally more restricted phenyl group in **2c**.[14] For comparison, the chiral sources **5** and **6** and the chiral aziridines **12** with various substituents were used in the reaction under the same conditions. Expectedly, ligands **5** and **6** afforded poor enantioselectivities, and chiral aziridines gave no enantioselectivity. On the other hand, the literature known (−)-*N*-methylephedrine **7**[15] was also used in the reaction but afforded inferior result to that of ligand **4**. So, it is demonstrated that the suitable and weak coordination of the additional sulfonamide fragment is necessary for further acceleration and stereocontrol in the addition reaction compared to the classic amino alcohols.

To further verify the effectiveness of the weak coordination of the additional sulfonamide, ligands **9**−**11**, derived from inexpensive chiral source L-prolinol **8**[16] by the route shown in Scheme 2, and **8** were next examined. Ligand **8** only provided 32% yield and 29% enantioselectivities (entry 12). Unexpectedly, both **9** with benzyl and **10** with methyl afforded low yields and enantioselectivities (entries 13 and 14). However, by changing the substituent from a benzyl or methyl group to phenyl with *R* configuration, ligand **11b** provided excellent enantioselectivity of >99% (entry 16) with yield and facial selectivity complementary to that afforded by the (−)-ephedrine-derived ligand **4** (entry 8).

With the above-mentioned optimal result, (−)-ephedrine-derived **4** and L-prolinol-derived **11b** were further used in the asymmetric addition of diethylzinc to other aromatic aldehydes (Table 2, entries 1−14). Using **4**, the catalytic diethylzinc addition to the aldehyde possessing an electron-withdrawing group in the *para* position of the aromatic ring proceeded with higher enantioselectivity than that in the *ortho* position of the aromatic ring (entries 1−7). Employing **11b**, high yields and enantioselectivities were observed for various tested aldehydes (entries 9−14). Fortunately, both **4** and **11b** showed excellent optical activity of >99% ee with opposite absolute configuration products for 2-chlorobenzaldehdye and 1-naphthylaldehdye (entries 7, 8, 13, and 14). It is known that in the diethylzinc addition reaction the enantioselectivity is usually much lower with aliphatic and α,β-unsaturated aldehydes than the identical reaction with aromatic aldehydes. Compounds **4** and **11b** were next examined in the addition of Et_2Zn to these more challenging substrates (Table 2, entries 15−22). Apparently, good to excellent reactivity and enantioselectivity were observed with both primary and secondary aliphatic aldehydes. The best results of up to >99% ee were obtained using both **4** and **11b** (entries 17 and 19).

TABLE 2. Addition of Diethylzinc to Various Aromatic, Aliphatic, and α,β-Unsaturated Aldehydes Using 4 and 11b[a]



entry	ligand	R	% isolated yield	% ee[b]
1	**4**	*p*-Cl-Ph	92	89 (*S*)
2	**4**	*p*-Me-Ph	67	85 (*S*)
3	**4**	*p*-F-Ph	91	88 (*S*)
4	**4**	*p*-MeO-Ph	76	87 (*S*)
5	**4**	*p*-Br-Ph	81	88 (*S*)
6	**4**	*o*-MeO-Ph	99	90 (*S*)
7	**4**	*o*-Cl-Ph	74	>99 (*S*)
8	**4**	1-naphthyl	90	>99 (*S*)
9	**11b**	*p*-Cl-Ph	97	94 (*R*)
10	**11b**	*p*-Me-Ph	99	83 (*R*)
11	**11b**	*p*-F-Ph	93	86 (*R*)
12	**11b**	*p*-Br-Ph	98	93 (*R*)
13	**11b**	*o*-Cl-Ph	92	>99 (*R*)
14	**11b**	1-naphthyl	88	>99 (*R*)
15	**4**	*i*-C_4H_9	38	92 (*S*)
16	**4**	$PhCH_2CH_2$	66	75 (*S*)
17	**4**	*c*-C_6H_{11}	51	>99 (*S*)
18	**4**	(*E*)-PhCH=CH	99	54 (*S*)
19	**11b**	*i*-C_4H_9	36	>99 (*R*)
20	**11b**	$PhCH_2CH_2$	50	89 (*R*)
21	**11b**	(*E*)-PhCH=CH	99	81 (*R*)
22	**11b**	*c*-C_6H_{11}	63	46 (*R*)

[a] Et_2Zn/aldehyde/ligand = 2.2:1:0.1, hexane, rt, 24 h [b] The ee values were determined by GC or HPLC, and the absolute configuration was assigned by comparison to literature values.

Possible binding models of Zn with **4** and **11b** are depicted in Figure 2. In the absence of $Ti(O^iPr)_4$, the sulfamide−amine alcohol ligand binds with Zn in a tridentate fashion. Comparing to the inferior results of ligands **5**, **6**, **7**, and **8**, we can reason that the nitrogen atom from the sulfonamide serves as another weakly coordinative site in the cycle because it is a poor electron donor.[17] Thus, this tridentate binding can reduce the number of possible diastereomeric intermediates or

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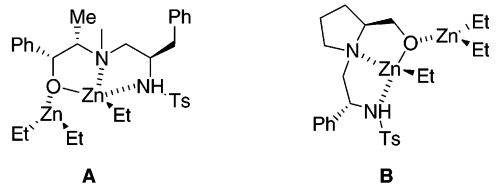

FIGURE 2. Proposed trivalent binding modes of the Zn with **4** and **11b**, respectively.

transition states, strongly increasing the probability of an efficient chirality transfer.[18]

Conclusion

In summary, we have successfully prepared a new class of stable sulfamide−amine alcohol ligands from (−)-ephedrine, (+)-pseuoephedrine, and L-prolinol, which were designed using a grafting strategy, for the enantioselective addition of diethylzinc to a wide range of aldehydes at room temperature. These ligands provide high yields and excellent enantioselectivities for both aromatic and aliphatic or α,β-unsaturated aldehydes in the absence of $Ti(O^iPr)_4$. The products with enantiomeric excess up to >99% and either absolute configuration were obtained by using ligands **4** and **11b**, respectively. The preparation of the ligands and their use in the asymmetric addition of diethylzinc to aldehydes is practical and could be amenable to scale-up.[19] Further work is in progress in this laboratory with the aim of expanding applications of these inexpensive chiral ligands to other enantioselective catalytic processes.

Experimental Section

General Procedure for Preparation of Sulfamide−Amine Alcohols 1−4 and 9−11. (−)-Ephedrine **5** ((+)-pseudoephedrine **6** or L-prolinol **8**) (3.80 mmol) and the corresponding aziridine **12** (3.66 mmol)[12] were dissolved in dry acetonitrile (30 mL), and the mixture was stirred under reflux for 40 h. The solvent was evaporated under reduced pressure. The residue was recrystallized with dichloromethane and petroleum ether and gave the pure ligand.

Characterization of 1a: sticky oil (0.93 g), 70% yield; $[\alpha]^{25}_D$ = −10.85 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.00 (d, *J* = 6.8 Hz, 3H), 1.95 (s, 3H), 2.40 (s, 3H), 2.46 (d, *J* = 15.2 Hz, 2H), 2.70−2.73 (m, 1H), 2.80−2.82 (t, *J* = 5.6 Hz, 2H), 4.58 (d, *J* = 6.8 Hz, 1H), 7.23−7.31 (m, 4H), 7.33−7.37 (m, 2H), 7.55 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 9.3, 21.6, 36.3, 40.2, 53.4, 64.3, 75.7, 126.3, 127.1, 127.9, 128.57, 128.61, 136.9, 143.2, 143.3; HRMS (APCI) calcd for $C_{25}H_{27}N_2O_3S$ (M + H^+) 363.1737, found 363.1718.

Characterization of 1b: white solid; 85% yield; mp 117−118 °C; $[\alpha]^{25}_D$ = +56.37 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.63−0.66 (m, 3H), 2.16 (s, 3H), 2.43−2.48 (m, 4H), 2.53−2.55 (m, 1H), 2.61−2.66 (m, 1H), 3.07−3.09 (s, 2H), 4.17−4.21 (m, 1H), 7.26−7.33 (m, 7H), 7.77−7.80 (m, 2H); ^{13}C NMR ($CDCl_3$)δ 7.8, 21.7, 36.1, 41.1, 52.8, 65.4, 75.0, 127.4, 127.5, 128.1, 128.5, 129.9, 137.1, 141.8, 143.5; HRMS (APCI) calcd for $C_{25}H_{31}N_2O_3S$ (M + H^+) 363.1737, found 363.1744.

Characterization of 2a: white solid (1.12 g); 70% yield; mp 36−38 °C; $[\alpha]^{20}_D$ = −38.21 (*c* 0.62, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.74 (d, *J* = 6.8 Hz, 3H), 1.85 (s, 3H), 2.41 (s, 3H), 2.86−2.91 (m, 1H), 3.04 (t, *J* = 6.8 Hz, 1H), 3.24 (t, *J* = 11.4 Hz, 1H), 3.54−3.57 (m, 1H), 4.52 (d, *J* = 6.8 Hz, 1H), 7.01−7.03 (m, 2H), 7.25−7.27 (m, 5H), 7.32−7.37 (m, 3H), 7.40−7.44 (m, 2H), 7.59 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 12.7, 22.2, 29.5, 43.9, 64.4, 67.8, 77.0, 126.9, 127.7, 128.6, 128.8, 129.0, 129.2, 130.2, 137.4, 137.9, 143.8; HRMS (APCI) calcd for $C_{25}H_{29}N_2O_3S$ (M − H^+) 437.1904, found 437.1887.

Characterization of 2b: white solid; 75% yield (1.20 g); mp 188−189 °C; $[\alpha]^{20}_D$ = +30.23 (*c* 0.63, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.52 (d, *J* = 4.0 Hz, 3H), 2.04 (s, 3H), 2.44 (s, 3H), 2.85−2.89 (m, 1H), 3.16−3.21 (m, 1H), 3.54 (s, 1H), 3.71 (t, *J* = 6 Hz, 1H), 4.23 (d, *J* = 8.0 Hz, 1H), 4.48 (br, 1H), 5.05 (br, 1H), 7.13 (t, *J* = 4.0 Hz, 2H), 7.26−7.35 (m, 10H), 7.72 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 10.8, 22.2, 30.1, 45.4, 64.5, 68.1, 75.8, 127.8, 128.0, 128.5, 129.0, 129.4, 130.4, 137.6, 138.6, 142.5, 144.1; HRMS (APCI) calcd for $C_{25}H_{29}N_2O_3S$ (M − H^+) 437.1904, found 437.1876.

Characterization of 2c: white solid; 78% yield; mp 118−119 °C; $[\alpha]^{25}_D$ = +21.67 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.63 (d, *J* = 6.4 Hz, 3H), 2.13 (s, 3H), 2.42 (s, 3H), 2.88−2.91 (m, 1H), 3.10−3.20 (m, 1H), 3.58 (s, 1H), 4.56−4.57 (d, *J* = 5.2 Hz, 1H), 6.97−6.98 (d, *J* = 3.6 Hz, 2H), 7.23−7.34 (m, 10H), 7.64−7.66 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 10.6, 21.7, 35.3, 44.3, 58.6, 65.8, 76.4, 126.5, 127.3, 127.88, 128.0, 128.3, 128.4, 128.7, 129.7, 137.5, 138.2, 143.1, 143.3; HRMS (APCI) calcd for $C_{25}H_{31}N_2O_3S$ (M + H^+) 439.2050, found 439.2074.

Characterization of 2d: white solid; 60% yield; mp 150−151 °C; $[\alpha]^{25}_D$ = +67.98 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.44 (d, *J* = 6.0 Hz, 3H), 2.17−2.43 (m, 6H), 2.64 (s, 1H), 3.17−3.21 (m, 1H), 3.62 (d, *J* = 45.6 Hz, 2H), 4.22 (d, *J* = 9.2 Hz, 1H), 5.02 (br, 1H), 7.09−7.29 (m, 13H), 7.67 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 8.7, 21.7, 33.1, 45.8, 59.8, 66.6, 74.8, 127.3, 127.4, 127.9, 128.4, 128.5, 129.2, 129.5, 129.9, 137.0, 138.2, 143.1, 143.6; HRMS (APCI) calcd for $C_{25}H_{31}N_2O_3S$ (M + H^+) 439.2050, found 439.2030.

Characterization of 3: white solid; 90% yield; mp 75−76 °C; $[\alpha]^{25}_D$ = −48.15 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.02−1.08 (m, 6H), 1.60 (d, *J* = 6.0 Hz, 3H), 2.21 (d, *J* = 11.6 Hz, 2H), 2.33−2.37 (m, 4H), 2.76−2.85 (m, 2H), 4.52 (d, *J* = 7.2 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.29−7.31 (m, 2H), 7.36 (d, *J* = 4.4 Hz, 7H), 7.38−7.46 (m, 1H), 7.40−7.45 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 9.9, 19.4, 21.6, 34.5, 46.6, 61.7, 65.1, 76.1, 126.4, 127.4, 128.2, 128.9, 129.5, 136.9, 143.2; HRMS (APCI) calcd for $C_{20}H_{29}N_2O_3S$ (M + H^+) 377.1893, found 377.1908.

Characterization of 4: white solid; 80% yield; mp 39−40 °C; $[\alpha]^{25}_D$ = −59.48 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.95 (d, *J* = 6.4 Hz, 3H), 1.60 (s, 3H), 2.28−2.35 (m, 2H), 2.38 (m, 3H), 2.60−2.72 (m, 2H), 3.03−3.07 (t, *J* = 8.2 Hz, 2H), 4.50 (d, *J* = 6.8 Hz, 1H), 7.06 (d, *J* = 6.8 Hz, 2H), 7.17−7.27 (m, 7H), 7.35 (d, *J* = 7.2 Hz, 1H), 7.40−7.45 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 9.9, 21.6, 35.2, 39.8, 52.4, 59.0, 64.8, 75.8, 126.4, 126.5, 127.4, 128.1, 128.5, 128.8, 129.6, 129.6, 136.8, 137.6, 143.2; HRMS (APCI) calcd for $C_{26}H_{33}N_2O_3S$ (M + H^+) 453.2206, found 453.2220.

Characterization of 9: white solid; 97% yield. mp 109−110 °C; $[\alpha]^{26}_D$ = −79.30 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.30−1.44 (m, 1H), 1.53 (d, *J* = 4.0 Hz, 2H), 1.71 (d, *J* = 8.0 Hz, 1H), 1.76−1.87 (m, 1H), 2.29−2.35 (m, 2H), 2.40 (s, 3H), 2.58−2.63 (m, 2H), 2.73 (d, *J* = 4.0 Hz, 1H), 3.06−3.10 (m, 1H), 3.33−3.36 (m, 3H), 3.52−3.56 (m, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.18−7.27 (m, 5H), 7.75 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.6, 23.8, 27.3, 40.6, 54.1, 54.3, 58.0, 63.7, 64.7, 126.5, 127.4, 128.5, 129.6, 137.4, 137.7, 143.2; HRMS (APCI) calcd for $C_{21}H_{29}N_2O_3S$ (M + H^+) 389.1893, found 389.1880.

Characterization of 10: sticky oil; 90% yield; $[\alpha]^{26}_D$ = −67.85 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.14 (d, *J* = 6.4 Hz, 3H), 1.38−1.55 (m, 1H), 1.57−1.61 (m, 2H), 1.77 (d, *J* = 8.8

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(19) For a current state of the art catalyst for the addition of diethylzinc to benzaldehyde with excellent yield and enantiomeric excess on scale, see: Kitamura, M.; Oka, H.; Suga, S.; Noyori, R. *Org. Synth.* **2003**, *79*, 139−145.

Hz, 1H), 1.94 (d, J = 6.4 Hz, 1H), 2.23−2.27 (m, 1H), 2.40 (d, J = 14.4 Hz, 4H), 2.59−2.62 (m, 1H), 2.67 (d, J = 12.4 Hz, 1H), 3.12 (s, 1H), 3.40−3.44 (m, 1H), 3.59−3.63 (m, 1H), 7.29 (d, J = 8.0 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 19.9, 21.6, 23.8, 27.3, 48.8, 54.0, 60.4, 63.7, 64.7, 127.4, 129.6, 137.4, 143.2; HRMS (APCI) calcd for $C_{15}H_{25}N_2O_3S$ ($M + H^+$) 313.1580, found 313.1565.

Characterization of 11a: white solid; 60% yield; mp 94−95 °C; $[\alpha]^{26}_D = -56.51$ (c 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.47−1.64 (m, 4H), 2.21 (d, J = 7.6 Hz, 1H), 2.42 (s, 3H), 2.62 (d, J = 6.0 Hz, 1H), 2.83 (s, 1H), 3.19−3.22 (m, 1H), 3.36−3.48 (m,2H), 3.66−3.70 (m, 1H), 3.89−3.93 (m, 1H), 7.06 (d, J = 7.2 Hz, 2H), 7.29 (d, J = 9.2 Hz, 5H), 7.76 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.7, 23.4, 27.6, 45.0, 46.8, 60.2, 61.8, 63.4, 127.3, 128.1, 128.5, 129.0, 130.0, 135.8, 137.1, 143.5; HRMS (APCI) calcd for $C_{20}H_{27}N_2O_3S$ ($M + H^+$) 375.1737, found 375.1726.

Characterization of 11b: white solid; 65% yield; mp 113−114 °C; $[\alpha]^{25}_D = +1.33$ (c 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.61−1.69 (m, 4H), 2.44 (s, 3H), 2.62 (d, J = 6.8 Hz, 1H), 2.87 (t, J = 8.0 Hz, 2H), 3.03−3.06 (m, 2H), 3.17−3.22 (m, 1H), 3.49−3.54 (m, 1H), 3.63−3.66 (m, 1H), 7.14−7.16 (m, 2H), 7.29 (t, J = 5.2 Hz, 5H), 7.68 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.7, 24.5, 29.1, 45.7, 52.8, 61.5, 64.6, 66.6, 127.3, 128.6, 129.0, 129.9, 137.0, 138.9, 143.6; HRMS (APCI) calcd for $C_{20}H_{27}N_2O_3S$ ($M + H^+$) 375.1737, found 375.1710.

General Procedure for the Addition of Et_2Zn to Aldehydes. Under a dry argon atmosphere, chiral ligand (10 mol %, 0.05 mmol) in dry hexane (4 mL) was cooled to 0 °C, and a solution of Et_2Zn (1.0 M in hexane, 1.1 mmol) was added slowly. After the mixture was stirred for 30 min at 0 °C, freshly distilled aldehyde (0.5 mmol) was added, and the reaction was stirred for 20−24 h at room temperature. The reaction mixture was quenched with 1 M aqueous HCl at 0 °C. The aqueous phase was extracted with ethyl acetate (3 × 5 mL). The combined organic phase was washed with a small amount of brine, dried with anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 12:1) to give the carbinol. The enantiomeric purity of the product was determined by HPLC. The absolute configurations of the products were assigned by comparison to literature values.

Conditions for the Analysis of Chiral Secondary Alcohols. Chiral capillary GC: Chiral cyclodex capillary column β-2, 3, 6-M, 30 m × 0.32 mm. Carrier gas: N_2 (1.67 mL/min). Detector: FID, 250 °C. Injector: 220 °C.

Chiral HPLC: Chiralcel OD-H column; flow rate 1 mL.min^{-1}; 219 nm UV detection.

The racemic alcohol products were obtained by addition of EtMgBr to aldehydes. The conditions of analysis and retention times of the R and S isomers have been reported elsewhere.

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Supporting Information Available: General experimental methods and ^{1}H and ^{13}C NMR and HRMS spectra for characterization compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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