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Modular amino acids and β-amino alcohol-based chiral ligands for enantioselective addition of diethylzinc to aromatic aldehydes

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Enantioselective addition of diethylzinc to a series of aromatic aldehydes was developed using a modular amino acids and β-amino alcohol-based chiral ligand (2*R*)-*N*-[(1*R*,2*S*)-1-hydroxy-1-phenylpropan-2-yl]-3-phenyl-2-(tosylamino) propanamide (1f) without using titanium complex. The catalytic system employing 15 mol% of 1f was found to promote the addition of diethylzinc ($ZnEt_2$) to a wide range of aromatic aldehydes with electron-donating and electron-withdrawing substituents, giving up to 97% ee of the corresponding secondary alcohol under mild conditions.

Keywords: addition reaction; aldehyde; β-amino alcohol; diethylzinc; norephedrine

Introduction

Synthesis of a chiral secondary alcohol by enantioselective addition of diorganozinc to an aldehyde is one of the most successful areas in the field of asymmetric C–C bond formation reactions.[1] Therefore, a remarkable number of chiral ligands such as diols,[2] diamines,[3] aminothiols,[4] aminodisulfides,[5] amino alcohols[6] diphosphoryldiols,[7] phosphoramides[8] and aminodiselenides[9] have been developed for the enantioselective addition of diethylzinc to aldehydes. Despite the achievements made in this field of the addition of aldehydes, it has not yet reached the level of practicability that is required for a synthetically useful catalytic system. Thus, it is still necessary to develop new types of catalytic system and probe how the chiral catalysts work for the addition of diethylzinc to aldehyde. On the other hand, β-amino alcohols and natural amino acid and their derivatives have been used in many asymmetric reactions, and good to excellent results have been obtained by many research groups.[6,10] Based on these works, we continued to search for a new highly efficient catalyst system using β-amino alcohols and natural amino acid derivatives to achieve structural diversity. In this report, we prepared sulfonamide alcohols (see Fig. 1) from natural amino acid and β-amino alcohols used them as ligands for the enantioselective addition of diethylzinc to aromatic aldehydes.

Results and Discussion

Catalyst System Screening

Initially, we investigated the addition reaction of diethylzinc (Et_2Zn) to benzaldehyde (**2a**) in the presence of 15 mol% chiral ligand (**1a–h**) combined with 15 mol% Ti(*i*-OPr)$_4$ (1 : 1 ratio) in dry toluene at 0 °C under nitrogen atmosphere (Table 1, entries 1–8). The results in Table 1 show that these titanium complexes (IV) could promote the reactions with good to excellent yields. The **1g**–Ti(IV) complex gave the highest enantioselective excess (58% ee) with 88% yield (Table 1, entry 7); other titanium complexes (IV) gave very low ee values (Table 1, entries 1–6, 8). We then thought of changing the pK_a value by adjusting the Lewis acid (centre metal) of the catalyst system for the addition reaction according to the bifunctional concept, aiming to improve the enantioselective. Therefore, we investigated the serial chiral ligands **1a–h** without Ti(*i*-OPr)$_4$ under same conditions (Table 1, entries 9–15). It was found that a significant improvement was achieved when 15 mol% **1f** without Ti(*i*-OPr)$_4$ was employed in the enantioselective addition of diethylzinc to benzaldehyde with 83% ee and 69% yield (Table 1, entry 14). Other catalyst systems could also improve the ee's, although the yields were decreased dramatically (Table 1, entries 9–13, 15). The **1g** only gave 30% ee with 43% yield (Table 1, entry 13), although the corresponding complex of **1g**–Ti(*i*-OPr)$_4$ could gave the highest ee under the same conditions (Table 1, entry 7). Ligand **1h**, which has a different configuration from **1g**, gave the corresponding product with *R* configuration (Table 1, entries 7 and 16).

Next, we investigated the effect of different solvents (toluene, CH_2Cl_2, THF, Et_2O and hexane) using the **1f** catalyst system (Table 2, entries 1–5). It was found that THF gave very low yield with 26% ee (Table 2, entry 2). Et_2O gave 20% yield and 21% ee (Table 2,

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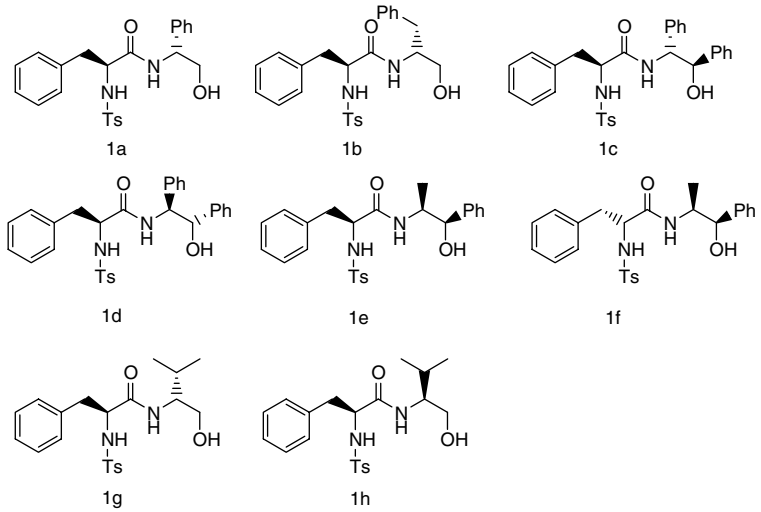
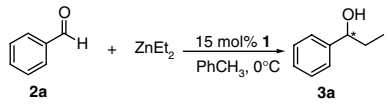


Figure 1. The structures of the chiral ligands for the addition of diethylzinc to aldehydes.

Table 1. Screening of the ligands **1a–h** for the enantioselective addition of diethylzinc to benzaldehyde



Entry[a]	Ligand	Ti(*i*-OPr)$_4$ (mol%)	Time (h)	Yield (%)[b]	Ee (%)[c]
1	**1a**	15	24	95	11(*S*)
2	**1b**	15	24	95	12(*S*)
3	**1c**	15	24	86	8(*S*)
4	**1d**	15	20	96	21(*S*)
5	**1e**	15	24	93	11(*S*)
6	**1f**	15	24	93	27(*S*)
7	**1g**	15	24	88	58(*S*)
8	**1h**	15	24	87	15(*R*)
9	**1a**	0	24	35	54(*S*)
10	**1b**	0	24	65	53(*S*)
11	**1c**	0	24	30	26(*S*)
12	**1d**	0	24	38	20(*S*)
13	**1e**	0	24	51	54(*S*)
14	**1f**	0	24	69	83(*S*)
15	**1g**	0	24	43	30(*S*)
16	**1h**	0	24	51	24(*R*)

[a] Conditions: concentration of **2a**, 0.25 M in $PhCH_3$; Et_2Zn, 1.5 equiv. in hexane solution.
[b] Isolated yields.
[c] The ee was determined by chiral GC G-TA column, and the (*S*- or *R*)-configuration was confirmed by comparison with the reported configuration.[2a,7b,11,12]

Table 2. Screening of the solvent enantioselective addition of diethylzinc to benzaldehyde

Entry	Solvent	Temperature (°C)	Time (h)	Yield (%)	Ee (%)
1	$PhCH_3$	0	24	69	83(*S*)
2	THF	0	24	trace	26(*S*)
3	Et_2O	0	24	20	21(*S*)
4	CH_2Cl_2	0	24	25	60(*S*)
5	Hex	0	24	71	80(*S*)

[a] Conditions: concentration of **2a**, 0.25 M in $PhCH_3$; Et_2Zn: 1.5 equiv. in hexane solution; **1f**: 15 mol%.
[b] Isolated yields.
[c] The ee was determined by chiral GC G-TA column, and the (*S*)-configuration was confirmed by comparison with the reported configuration.[2a,7b,11,12]

entry 3). CH_2Cl_2 gave 60% ee values with 25% yield (Table 2, entry 4). Hexane gave similar results to toluene ($PhCH_3$) under same conditions (Table 2, entry 5 vs entry 1).The highest ee of 83% was obtained in toluene (Table 2, entry 1).

The optimum loadings of **1f** and Et_2Zn, temperature and concentration of **2a** were also investigated under the best conditions (Table 3, entries 1–9). It was found that the best loading was 15 mol% **1f** (Table 3, entry 1). In these loadings (20 and 10 mol%), there were significant drops: ee channged from 83 to 72 and 71%, respectively (Table 3, entries 8 and 9). A possible reason may be that the 15 mol% loading of **1f** could form more active catalytic species than 10 or 20 mol% loading. Better enantioselectivity could not be obtained when lowering or increasing the concentration of **2a** (Table 3, entries 2 and 3). Changing the reaction temperature and loadings of Et_2Zn also could not improve the enantioselectivity (Table 3, entries 4–7). The optimal catalyst system and reaction conditions were 15 mol% **1f**, 1.5 equiv. Et_2Zn and 0.25 M **2a** in $PhCH_3$ at 0 °C.

Substrate Generality

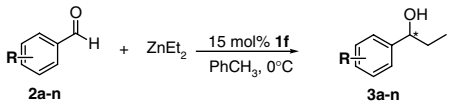
To study the generality of the **1f** catalyst system for the enantioselective addition of diethylzinc to various aldehydes, a number of aromatic aldehydes having electron-donating, electron-withdrawing groups, *α*- and *β*-naphthaldehydes and (*E*)-cinnamaldehyde were examined under the optimized conditions reported in Table 3. In comparison to the results obtained with **2a**, the poor electron-donating substituents, methyl group, led to a decrease in the ee of the products **3b** and **c** (Table 4, entries 2 and 3 vs entry 1). In the case of stronger electrondonating substituents, X = MeO group, lower yields but comparable ee of **3b** (Table 4,

Table 3. Optimization of the catalytic system for the enantioselective addition of diethylzinc to benzaldehyde catalyzed by **1f**

Entry[a]	**1f** (mol%)	Concentration of **2a**	Et_2Zn (equiv.)	Temperature (°C)	Time (h)	Yield (%)[b]	Ee (%)[c]
1	15	0.25	1.5	0	24	69	83
2	15	0.5	1.5	0	10	87	62
3	15	0.1	1.5	0	40	46	80
4	15	0.25	1.8	0	24	71	81
5	15	0.25	1.0	0	40	51	77
6	15	0.25	1.5	−20	48	41	69
7	15	0.25	1.5	20	10	88	54
8	10	0.25	1.5	0	24	59	71
9	20	0.25	1.5	0	10	86	72

[a] Conditions: solvent, $PhCH_3$; Et_2Zn, hexane solution.
[b] Isolated yields.
[c] The ee was determined by chiral GC G-TA column, and the (*S*)-configuration was confirmed by comparison with the reported configuration.[2a,7b,11,12]

Table 4. Enantioselective addition of diethylzinc to various aromatic aldehydes catalyzed by **1f**



2a-n **3a-n**

Entry	Aldehyde	Time (h)	Yield (%)	Ee (%)[c]
1	Benzaldehyde (**2a**)	24	69	83(*S*)
2	4-Methyl-benzaldehyde (**2b**)	40	55	61(*S*)
3	2-Methyl-benzaldehyde (**2c**)	40	51	54(*S*)
4	4-Methoxy-benzaldehyde (**2d**)	40	42	64(*S*)
5	3-Methoxy-benzaldehyde (**2e**)	40	38	52(*S*)[d]
6	4-Fluoro-benzaldehyde (**2f**)	24	74	73(*S*)
7	4-Chloro-benzaldehyde (**2g**)	24	70	81(*S*)
8	2-Chloro-benzaldehyde (**2h**)	24	65	71(*S*)
9	4-Bromobenzaldehyde (**2i**)	24	81	84(*S*)
10	4-Iodobenzaldehyde (**2j**)	24	84	82(*S*)
11	4-(Trifluoromethyl)benzaldehyde (**2k**)	24	69	67(*S*)[e]
12	(*E*)-Cinnamaldehyde (**2l**)	40	51	59(*S*)[d]
13	Naphthalene-2-carbaldehyde (**2m**)	24	75	97(*S*)[d]
14	Naphthalene-1-carbaldehyde (**2n**)	24	81	80(*S*)[d]

[a] Conditions: solvent, $PhCH_3$; 0 °C; concentration of **2**, 0.25 M; Et_2Zn, in hexane solution.
[b] Isolated yields.
[c] The ee was determined by chiral GC G-TA column, and the (*S*)-configuration was confirmed by comparison with the reported configuration.[2a,7b,11,12]
[d] The ee was determined using a Chiral OD-H or OD column.[2a,7b,11,12]
[e] The ee was determined using a Chiral OJ-H column.[2a,7b,11,12]

entries 4 and 5 vs entry 2) were observed. Electron-withdrawing groups (F, Cl, Br, I and CF_3, Table 4, entries 6–11) showed variation in the yields, but no major differences in the ees of **3f–j** except for the strongly electron-withdrawing CF_3 group, which led to a lower 67% ee for product **3k** (Table 4, entry 11). (*E*)-cinnamaldehyde only gave 51% yield with 59% ee (Table 4, entry 12). Reaction of *α*- and *β*-naphthaldehydes **2j** and **2k**, resulted in up to 97 and 80% ee, respectively (Table 4, entries 13 and 14). In general, moderately to very good yields and enantioselectivities of the secondary alcohols **3a–n** were obtained (Table 4). These results revealed that the **1f** catalyst system was effective for the1,2-addition of diethylzinc to various aromatic aldehydes.

Catalytic Cycle and Transition States Considerations

Based on previous works in the field of the enantioselective addition diethylzinc to aldehydes,[1–10] the Zn (II) complex might play a bifunctional role in this reaction.[7b] As shown in Fig. **2**, the expected active species **I** could be generated in addition to Et_2Zn from the solution of **1f**; herein, the TsNH group has stronger coordination ability than CONH group,[13] which might attributed to the different pK_a value. When the benzaldehyde (**2a**) was added to the mixture, the metal moiety (Zn) of complex **I** might act as a Lewis acid to activate the benzaldehyde (**2a**), and engender the species **II**. Then the product **3a** could be obtained by working up with aqua acid (HCl) and accomplishing one catalytic cycle. At the same time, a possible asymmetric transition state 5 and 6 (Fig. 3) was proposed according to the observed absolute configuration of **3a** and Noyori's method.[6b,14] Because of the 1,3-repulsion between Ph- and Zn-linked Et, the bulkier phenyl group would take the energetically favorable equatorial position to form transition state 6. Thus, the transfer of the ethyl group occurs predominantly from the *Re*-face of benzaldehyde to furnish the observed (*S*)-1-phenyl-1-propanol.

Conclusion

In summary, the modular amino acids and *β*-amino alcohols (norephedrine)-based chiral ligand **1f**, readily prepared in several steps from commercially available starting materials, showed excellent catalytic activities and very good enantioselectivities (up to 97% ee) in the asymmetric additions of diethylzinc to various aldehydes. Further investigation on the applications of these ligands for other asymmetric reactions is ongoing.

Experimental Section

General Remarks

All reactions were conducted in oven-dried glassware under inert atmosphere of nitrogen with anhydrous solvents unless otherwise stated. The solvents were purified and dried according to standard procedures. Analytical thin-layer chromatography (TLC) was performed on alumina- or glass-backed silica plates (F254, 250 micron thickness) and visualized with UV light. Flash column chromatography was carried out on silica gel 60 (250–400 mesh) under air pressure. Enantiomeric ratios of the products were determined using chiral GC and HPLC techniques. Specific rotations were determined as $[\alpha]^{22}_D$ (c = 0.5 g/ml in CH_2Cl_2). Melting points are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) chemical shifts in $CDCl_3$ are quoted as as δ values relative to TMS (δ = 0.00) and $CDCl_3$ (δ = 77.0), respectively, in ppm and coupling constants in Hz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High-resolution mass spectra (HRMS) were obtained using positive electrospray ionization (*m/z* values are given).

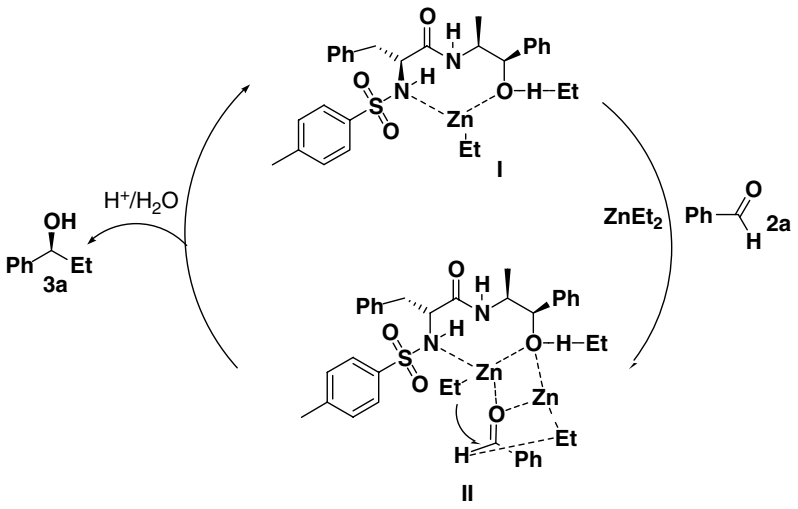


Figure 2. The proposed catalytic cycle.

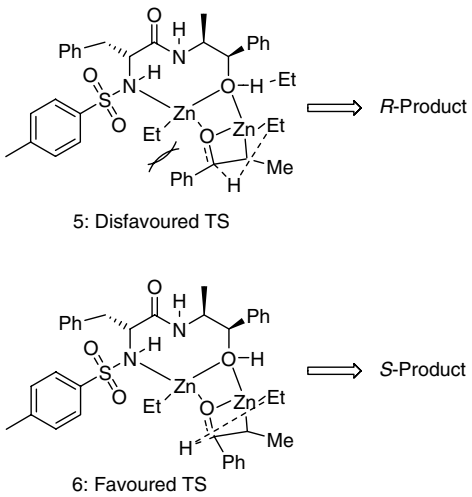


Figure 3. The proposed transition states (TS).

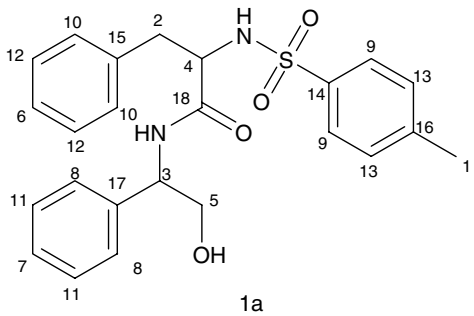
Materials

L-Phenylalanine, diethylzinc (Et_2Zn), PCl_5, Ti(*i*-OPr)$_4$, all aldehydes and all β-amino alcohols were commercially available, and used without further purification, unless otherwise noted. 3-Phenyl-2-(toluene-4-sulfonylamino)-propionyl chloride (**4a**) was synthesized according to the literature.[15]

General Procedure for the Synthesis of Ligands 1a–h

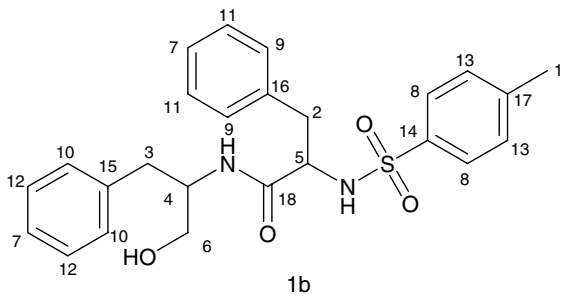
3-Phenyl-2-(toluene-4-sulfonylamino)-propionyl chloride (405 mg, 1.2 mmol) was added to a solution of amino alcohols (1.0 mmol) and Et_3N (0.21 ml, 1.5 mmol) in CH_2Cl_2 (10 ml) at 22 °C. After stirring for 2 h (TLC), the reaction mixture was diluted with CH_2Cl_2 (50 ml), washed with aqueous HCl (1.0 M, 2 × 20 ml), aqueous K_2CO_3 or $NaHCO_3$ (1.0 M, 2 × 20 ml) and then with brine (2 × 20 ml). The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness on a rotary evaporator. The crude products were purified using column chromatography on silica gel (EA-Hexane) and recrystallized from a mixture of EA : hexane (10 : 1, v/v). The corresponding products were obtained as white solids in 80–89% yield (Scheme 1).

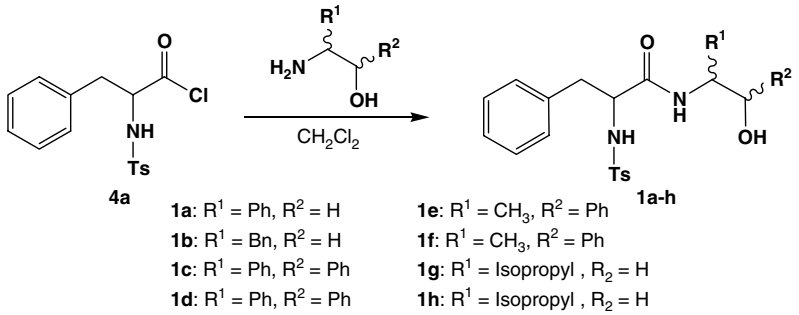
*(2S)-N-[(R)-2-hydroxy-1-phenylethyl]-3-phenyl-2-(tosylamino)propanamide (**1a**)*



White solid in 85% yield. $[\alpha]_D^{22}$ −58.88 (0.5 M, CH_2Cl_2), m.p.178–180 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.40(s, 3H, ArCH_3), 2.94 (d, J = 6.9 Hz, 2H, PhCH_2-), 3.69–3.75 (m, 2H, -CHCH_2OH), 3.98 (br, 1H, -CH_2OH), 4.95 (d, J = 7.5 Hz, 1H, -CHNHTs), 5.50 (d, J = 7.5 Hz,1H, -CHNHCO-), 6.92–6.96 (m, 2H, ArH), 7.01–7.19 (m, 8H, ArH), 7.23–7.32 (m, 4H, ArH), 7.53 (d, J = 8.1 Hz, 2H, NH). ^{13} C NMR (75 MHz, $CDCl_3$) δ (ppm) 170.8 (C18), 143.6(C17), 138.2(C16), 138.9(C15), 135.5(C14), 129.3(C13), 128.6(C12), 128.4(C11), 127.7(C10), 127.2(C9), 127.1(C8), 126.9(C7), 126.0(C6), 65.9(C5), 58.1(C4), 56.8 (C3), 38.4(C2), 21.6(C1). HRMS(ESI): calcd for (M^+ + 1) $C_{24}H_{27}N_2O_4S$: 439.5472; found: 439.5486. Anal. calcd for $C_{24}H_{26}N_2O_4S$: C, 65.73%; found: 65.84%; H, 5.98%; found: 6.09%; N, 6.39%; found: 6.48.

*(2S)-N-[(R)-1-hydroxy-3-phenylpropan-2-yl]-3-phenyl-2-(tosylamino)propanamide (**1b**)*

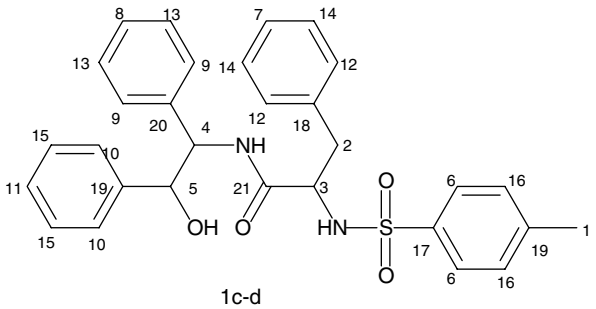




Scheme 1. The synthesis of chiral ligands **1a–h**.

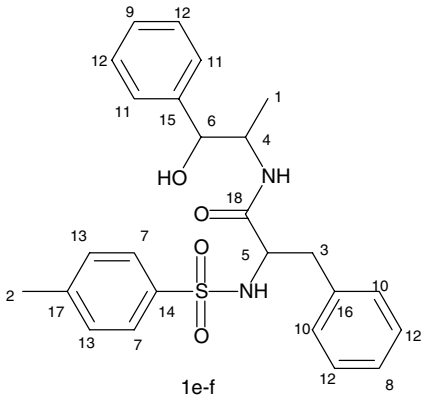
White solid in 87% yield. $[\alpha]_D^{22}$ −16.0 (0.5 M, CH_2Cl_2), m.p.128–130 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.39(s, 3H, ArCH_3), 2.72–2.74 (m, 2H, PhCH_2-), 2.83–2.86[m, 2H, PhCH_2CH(TsNH)CONH-], 3.45–3.51 (m, 2H, -CH_2OH), 3.89–3.92 [m, 1H, PhCH_2CH(TsNH)CONH], 4.10 (br, 1H, -CH_2OH), 5.53 [d, J = 7.5 Hz, 1H, PhCH_2CH(CH_2OH)NHCO-], 6.67(d, J = 8.1 Hz, 2H, Ar*H*), 6.89–6.92 (m, 2H, Ar*H*), 7.10–7.30 (m, 10H, Ar*H*), 7.55 (d, J = 8.4 Hz, 2H, N*H*).[13] C NMR (75 MHz, $CDCl_3$) δ (ppm) 170.8(C18), 143.8(C17), 137.4 (C16), 136.1(C15), 135.5(C14), 129.8 (C13), 129.3 (C12), 128.8 (C11), 128.4(C10), 127.8 (C9),127.1 (C8), 126.6(C8), 126.0 (C7), 63.3(C6), 58.1(C5), 53.1(C4), 38.4(C3), 36.7(C2), 21.5(C1). HRMS(ESI): calcd for (M^+ + 1) $C_{25}H_{29}N_2O_4S$: 453.5738; found: 453.5750. Anal. calcd for $C_{25}H_{28}N_2O_4S$: C, 66.35%; found: 66.47%; H, 6.24%; found: 6.37%; N, 6.19%; found: 6.27%.

*(2S)-*N*-[(1R,2R)-2-hydroxy-1,2-diphenylethyl]-3-phenyl-2-(tosylamino)propanamide (**1c**); (2S)-*N*-[(1S,2S)-2-hydroxy-1,2-diphenylethyl]-3-phenyl-2-(tosylamino)propanamide (**1d**)*



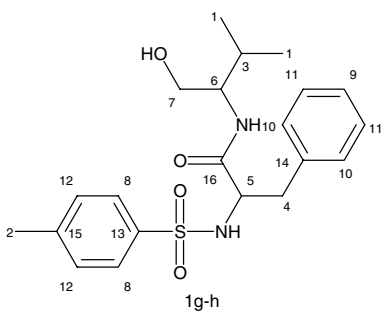
1c was a white solid in 81% yield. $[\alpha]_D^{22}$ −64.56 (0.5 M, CH_2Cl_2), m.p.149–151 °C. **1d** was a white solid in 80% yield. $[\alpha]_D^{22}$ −27.56 (0.5 M, CH_2Cl_2), m.p. 84–86 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.39 (s, 3H, TsCH_3), 2.65–2.73 [m, 2H, PhCH_2CH(NHCO)NHSO$_2$-], 3.81–3.92 (m, 1H, TsNHC*H*-), 3.85 (br, 1H, -CHO*H*), 4.92–5.01 [dd, J_1 = 13.8 Hz, J_2 = 6.9 Hz, 1H, PhC*H*(NHCO)CH-], 5.20–5.28 (m, 1H, -*CH*OH), 6.86–6.99 (m, 6H, Ar*H*), 7.01–7.25(m, 13H, Ar*H*), 7.48(d, J = 8.4 Hz, 2H, N*H*). [13] C NMR (75 MHz, $CDCl_3$) δ (ppm) 170.5 (C21), 143.1 (C20),140.2 (C19), 137.9 (18), 130.4 (C17), 130.3 (C16), 129.4 (C15), 129.2 (C14), 128.7 (C13), 128.3 (C12), 128.1 (C11), 127.7 (C10), 127.5 (C9), 106.1 (C8), 84.8 (C7), 77.6 (C6), 51.2 (C5), 49.9 (C4), 49.8 (C3), 48.8 (C2), 21.5 (C1). HRMS(ESI): calcd for (M^+ + 1) $C_{30}H_{31}N_2O_4S$: 515.6431; found: 515.6446. Anal. calcd for $C_{30}H_{30}N_2O_4S$: C, 70.01%; found: 70.09%; H, 5.88%; found: 6.02%, N%: 5.44%; found: 5.56%.

*(2S)-*N*-[(1R,2S)-1-hydroxy-1-phenylpropan-2-yl]-3-phenyl-2-(tosylamino)propanamide (**1e**); (2R)-*N*-[(1R,2S)-1-hydroxy-1-phenylpropan-2-yl]-3-phenyl-2- (tosylamino)propanamide (**1f**)*



1e was a white solid in 84% yield $[\alpha]_D^{22}$ −15.6 (0.5 M, CH_2Cl_2), m.p.184–186 °C. **1f** was a white solid in 89% yield; m.p. 175–178 °C; $[\alpha]_D^{22}$ −27.68 (c 0.2, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.83 (d, J = 6.9 Hz, 3H, -CHCH_3), 2.40(s, 3H, ArCH_3), 2.92–2.95 (m, 2H, PhCH_2CH-), 3.90 (br, 1H, -CHO*H*), 4.14–4.18 (dd, J_1 = 13.8 Hz, J_2 = 6.9 Hz, 1H, -NHCOC*H*-), 4.71 (m, 1H, CH_3CH-), 5.25 (d, J = 7.2 Hz, 1H, -*CH*OH), 6.26(d, J = 8.1 Hz, 2H, Ar*H*), 6.98–6.99 (m, 2H, Ar*H*), 7.16–7.34 (m, 10H, Ar*H*), 7.55 (d, J = 8.4 Hz, 2H, N*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 170.4 (C18), 143.9 (C17), 140.9 (C16), 135.3 (C15), 129.8 (C14), 129.2 (C13), 128.9 (C12), 128.2 (C11), 127.6 (C10), 127.3 (C9),126.0 (C8), 125.5 (C7), 81.0 (C6), 57.9 (C5), 51.1 (C4), 38.6 (C3), 21.6 (C2), 13.8 (C1). HRMS(ESI): calcd for (M^+ + 1) $C_{25}H_{29}N_2O_4S$: 453.5738; found: 453.5746. Anal. calcd for $C_{25}H_{28}N_2O_4S$: C, 66.35%; found: 66.46%; H, 6.24%; found: 6.38%, N, 6.19%; found: 6.32%.

*(2S)-*N*-[(S)-1-hydroxy-3-methylbutan-2-yl]-3-phenyl-2-(tosylamino)propanamide (**1g**); (2S)-*N*-[(R)-1-hydroxy-3-methylbutan-2-yl]-3-phenyl-2-(tosylamino)propanamide (**1h**)*



1g was a white solid in 83% yield. $[\alpha]_D^{22}$ −50.0 (0.5 M, CH_2Cl_2), m.p.119–121 °C. **1h** was a white solid in 88% yield. $[\alpha]_D^{22}$ −23.48 (0.5 M, CH_2Cl_2), m.p. 135–137 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.85 (d, J = 6.9 Hz, 3H, -CHCH_3), 0.90 (d, J = 6.6 Hz, 3H, -CHCH_3), 2.42 (s, 3H, TsCH_3), 2.39–2.45 [m, 1H, $(CH_3)_2$C*H*-], 2.86–2.96 [m, 2H, PhCH_2CH(TsNH)CO-], 3.62–3.65 [m, 1H, $(CH_3)_2$CHC*H*-], 3.81–3.88 (m,2H, HOCH_2-), 3.93–3.95 [m, 1H, PhCH_2C*H*(TsNH)CO-], 4.09(br, 1H, O*H*), 6.94–6.97 (m, 2H, Ar*H*), 7.16–7.23 (m, 7H, Ar*H*), 7.54(d, J = 8.4 Hz, 2H, N*H*). ^{13} C NMR (75 MHz, $CDCl_3$) δ (ppm) 171.4 (*C*16), 143.7 (C15), 136.1 (C14), 135.7 (C13), 129.8 (C12), 129.2 (C11), 128.7 (C10), 125.7 (C9), 125.4 (C8), 66.3 (C7), 58.3 (C6), 57.5 (C5), 38.3 (C4), 28.9 (C3), 19.4 (C2), 18.6 (C1). HRMS(ESI): calcd for ($M^+ + 1$) $C_{21}H_{29}N_2O_4S$: 405.5310; found: 405.5322. Anal. calcd for $C_{21}H_{28}N_2O_4S$: C, 62.35%; found: 62.46%; H, 6.98%; found: 7.09%, N%: 6.93%; found: 7.02%.

A Typical Procedure for the Catalytic Addition of Diethylzinc to Aromatic Aldehydes

To a solution of **1f** (11.4 mg, 0.025 mmol) in $PhCH_3$ (1.0 ml), a solution of diethylzinc (1.0 M in hexane, 0.375 ml, 0.375 mmol) was added under a nitrogen atmosphere at 0 °C, and the reaction mixture was stirred for 30 min at room temperature (about 22 °C). The reaction mixture was then cooled to 0 °C, and the corresponding aromatic aldehyde (0.25 mmol) was added and stirring was continued for stated times. The reaction mixture was quenched with HCl (1.0 M, 2.0 ml) at 0 °C, and the product was extracted with (3 × 5 ml) ethyl acetate. The combined ethyl acetate extracts were dried over Na_2SO_4 and evaporated to dryness under vacuum pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate, 10 : 1, v/v) to afford the secondary alcohol products. The enantioselectivities of the reactions were determined by chiral GC G-TA, OJ-H or OD-H columns. Compounds**3a–n** are known compounds; they were characterized by comparing their ^{1} H, ^{13}C NMR spectra with those published in the literature.[2a,7b,11,12]

*(S)-1-Phenyl-propan-1-ol (**3a**)*[2a,7b,11,12]

Enantiomeric excess was determined on a Chiral GC G-TA column (100 °C, 2.0 ml/min, t_R = 9.0 min, t_R = 9.2 min).

*(S)-1-*p*-Tolyl-propan-1-ol (**3b**)*[2a,7b,11,12]

Enantiomeric excess was determined on a Chiral GC G-TA column (115 °C, 2.0 ml/min, t_R = 13.7 min, t_R = 13.4 min).

*(S)-1-*o*-Tolyl-propan-1-ol (**3c**)*[2a,7b,11,12]

Enantiomeric excess was determined on a Chiral GC G-TA column (115 °C, 2.0 ml/min, t_R = 14.2 min, t_R = 12.7 min).

*(S)-1-(4-Methoxy-phenyl)-propan-1-ol (**3d**)*[2a,11,12]

Enantiomeric excess was determined on a Chiral GC G-TA column (110 °C, 2.0 ml/min, t_R = 41.1 min, t_R = 39.7 min).

*(S)-1-(3-Methoxy-phenyl)-propan-1-ol (**3e**)*[2a,12]

Enantiomeric excess was determined on a Chiral HPLC OD (UV detector, 254 nm, hexane–*i*-PrOH = 9 : 1, 1.0 ml/min, t_R = 10.8 min, t_R = 10.0 min).

*(S)-1-(4-Fluoro-phenyl)-propan-1-ol (**3f**)*[2a,7b,11,12]

Enantiomeric excess was determined on a Chiral GC G-TA column (110 °C, 2.0 ml/min, t_R = 10.9 min, t_R = 10.1 min).

*(S)-1-(4-Chloro-phenyl)-propan-1-ol (**3g**)*[2a,7b,11,12]

Enantiomeric excess was determined on a Chiral GC G-TA column (135 °C, 3.0 ml/min, t_R = 7.5 min, t_R = 8.3 min).

*(S)-1-(2-Chloro-phenyl)-propan-1-ol (**3h**)*[2a,7b,11,12]

Enantiomeric excess was determined on a Chiral GC G-TA column (135 °C, 3.0 ml/min, t_R = 11.2 min, t_R = 11.7 min).

*(S)-1-(4-Bromo-phenyl)-propan-1-ol (**3i**)*[2a]

Enantiomeric excess was determined on a Chiral GC G-TA column (130 °C, 3.0 ml/min, t_R = 15.9 min, t_R = 15.2 min).

*(S)-1-(4-Iodo-phenyl)-propan-1-ol (**3j**)*[2a]

Enantiomeric excess was determined on a Chiral GC G-TA column (130 °C, 3.0 ml/min, t_R = 29.5 min, t_R = 28.0 min).

*(S)-1-(4-Trifluoromethyl-phenyl)-propan-1-ol (**3k**)*[2a,7b]

Enantiomeric excess was determined on a Chiral HPLC OJ-H (UV detector, 254 nm, hexane–*i*-PrOH = 98 : 2, 1.0 ml/min, t_R = 17.9 min, t_R = 16.4 min).

*(S)-(E)-1-Phenyl-pent-1-en-3-ol (**3l**)*[2a,7b,11,12]

Enantiomeric excess was determined on a Chiral HPLC OD-H (UV detector, 254 nm, hexane–*i*-PrOH = 9 : 1, 1.0 ml/min, t_R = 13.5 min, t_R = 9.1 min).

*(S)-2-Naphthalen-2-yl-propan-1-ol (**3m**)*[2a,7b,11,12]

Enantiomeric excess was determined on a Chiral HPLC OD-H (UV detector, 254 nm, hexane–*i*-PrOH = 9 : 1, 1.0 ml/min, t_R = 10.1 min, t_R = 9.4 min).

*(S)-1-Naphthalen-2-yl-propan-1-ol (**3n**)*[2a,7b,11,12]

Enantiomeric excess was determined on a Chiral HPLC OD column (UV detector, 254 nm, 4 : 96 *i*-PrOH–hexane, 0.5 ml/min t_R = 31 min, t_R = 27 min).

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