Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 09 Sep 2008.

To cite this article: Y.-Q. Fu , L.-N. Ding , L.-G. Wang & J.-C. Tao (2008) Synthesis and Application of Novel Proline-Derived Chiral Piperazinones and Sulfamide-Amine Alcohols, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 38:15, 2672-2683, DOI: 10.1080/00397910701392400

To link to this article: http://dx.doi.org/10.1080/00397910701392400

Synthetic Communications®, 38: 2672–2683, 2008

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910701392400

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Synthesis and Application of Novel Proline-Derived Chiral Piperazinones and Sulfamide-Amine Alcohols

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Abstract: Several novel chiral piperazinone and sulfamide-amine alcohols were synthesized starting from inexpensive and readily available L-proline and trans-4-hydroxy-L-proline. The catalytic activity of the sulfamide-amine alcohols for the asymmetric addition of diethylzinc to benzaldehyde were evaluated preliminarily.

Keywords: Catalysis, piperazinone, proline derivatives, synthesis, sulfamide-amine alcohol

Proline and proline derivatives have attracted much attention from chemists in recent years because of their special biological functions and extensive application in asymmetric synthesis. For example, cyclodipeptides derived from L-proline and 4-hydroxy-L-proline are plant growth regulators,[1–3] and some proline derivatives have been used as highly efficient chiral auxiliaries,[4] chiral ligands,[5–7] or organocatalysts[8,9] in asymmetric synthesis.

The piperazinone ring and chiral β-amino alcohol moiety are widely used structures in medicinal chemistry. Because of the similarity of piperazinone (Fig. 1) to a conformationally constrained cyclodipeptide, it serves as an effective and versatile template for the construction of biologically active molecules[10,11] (e.g., some substituted piperazinone anologues have been demonstrated as inhibitors of farnesyltransferase,[12] growth hormone secretagogue,[13] etc). Chiral β-amino alcohol moieties

Received in the U.S.A. September 22, 2006
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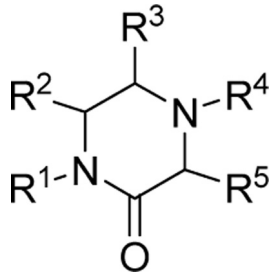
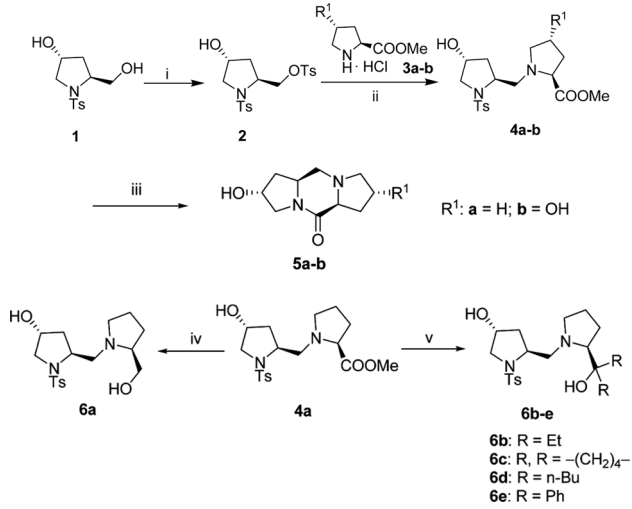


Figure 1. Substituted piperazinone.

are critical structural segments of some natural or synthesized biologically active compounds such as adrenergic agonists or antagonists,[14,15] inhibitors for HIV protease,[16] and anticancer agents.[17] Moreover, some chiral β-amino alcohols have been successfully used as chiral ligands in asymmetric synthesis (e.g., asymmetric alkylation,[5–7] reductions,[18–20] and epoxylation.)[21–23]

In this report, we prepared two piperazinone derivatives **5a,b** and five sulfamide-amine alcohols **6a-e** (Scheme 1) via simple methods using commercially available, inexpensive L-proline and *trans*-4-hydroxyl-L-proline as main materials.



Scheme 1. Reagents and conditions: i) TsCl, dry pyridine, $-10\,^{\circ}C$ to rt, 12 h; ii) Na_2CO_3, CH_3CN, $80\,^{\circ}C$, 36 h; iii) 40% HBr, HOAc, phenol, reflux, 2–4 h; iv) $NaBH_4$, CH_3OH, t-BuOH, reflux, 3 h; v) RMgBr, THF, $0\,^{\circ}C$ to rt, 0.5–2 h.

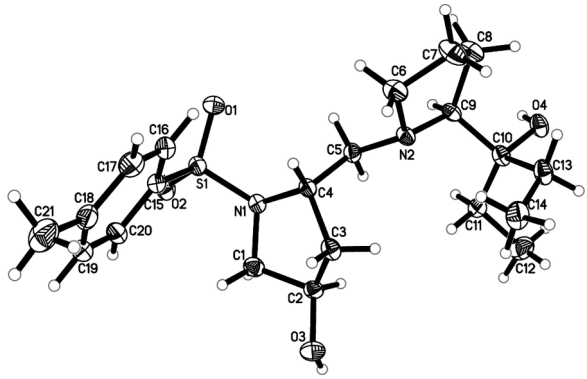


Figure 2. Single crystal structure of compound **6b**.

Compound **1** is an intermediate of the synthetic veterinary drug danofloxacin mesylate, derived from *trans*-4-hydroxyl-L-proline.[24] The primary hydroxyl group could be selectively transformed into sulfonate **2** in good yield at $-10\,^{\circ}C$ to room temperature. The sulfonate group of compound **2** was substituted conveniently by methyl L-prolinate **3a** or methyl 4-hydroxyl-L-prollinate **3b** in the presence of excess Na_2CO_3 to give compounds **4a** and **4b** respectively. In this step, the use of an inorganic base instead of organic base made the reaction easily treated after reaction and environmentally green. By the action of HBr/HOAc/phenol,[25] **4a,b** detosylated and cyclized in one step to furnish chiral 1,3,4,6-tetrasubstitued tricycle piperazinone derivatives **5a,b.** By reduction of **4a** with $NaBH_4$ in *t*-butyl alcohol and methanol[26] or routine Grignard reagent addition of alkyl magnesium bromide to **4a**, compounds **6a-e** were obtained. The single crystals of compound **6b** suitable for X-ray analysis were obtained by recrystallization from ethanol at room temperature. From the single-crystal structure of **6b**, we can see that the three chiral centers keep their original configurations (C(4)$-S$, C(2)$-R$, and C(9)$-S$) in *trans*-4-hydroxyl-L-proline and L-proline (Fig. 2) because the configuration of C (2) could not change.

Many prolinol analogues have been demonstrated as highly efficient catalysts for various kinds of asymmetric transformations.[5–7] The catalytic functions of these compounds are mainly attributed to the unique structure of the strained five-membered pyrrolidine ring, the chirality, and the coordinative capabilities of N, O atoms. Cho and Chun found that the zinc complexes chirally modified by β-sulfonamidoalchohol alone without the use of $Ti(O^iPr)_4$ are effective as chiral catalysts for the addition of diethylzinc to aldehydes to afford secondary alcohols with moderate enantioselectivity.[27] Recently, Wan and coworkers[28]

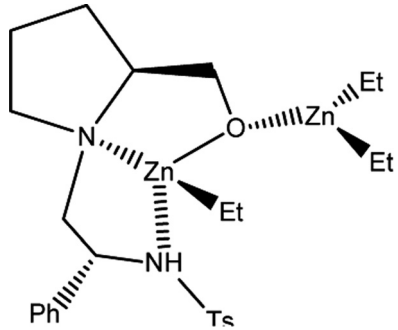


Figure 3. Proposed trivalent binding modes of the Zn with the sulfamide-amino alcohols derived from L-proline.[29]

synthesized a series of proline-derived sulfamide-amine alcohols to promote the addition of diethylzinc to aldehyde with high enantioselectivities. From the experimental results, they reasoned that the nitrogen atom from the sulfonamide served as another weakly coordinative site besides the coordination of the nitrogen and oxygen atoms from the prolinol moiety (Fig. 3). Considering that compounds **6a-e** have structures similar to Wan's catalyst, we presumed that they should be potential catalysts to promote the reaction of alkylation of aldehyde.

Therefore, the catalytic activity of **6a-e** for the addition of diethylzinc to benzaldehyde was first evaluated at room temperature, and the results are summarized in Table 1. When 5 mol% of catalyst were used to promote the reaction for 3 days at room temperature, the products were furnished in moderate yields with poor enantioselectivity. The activity

Table 1. Addition of diethylzinc to benzaldehyde catalyzed by **6a-e**

Entry	Cat.	Cat. loading (mol%)	Yield (%)[a]	Ee (%)[b]	Config.[c]
1	**6a**	5	Trace	—	—
2	**6b**	5	26	6	*S*
3	**6c**	5	32	27	*R*
4	**6d**	5	31	11	*R*
5	**6e**	5	63	27	*S*
6	**6e**	10	62	26	*S*
7	**6e**	20	60	26	*S*

[a]Isolated yields.

[b]Determined by chiral high performance liquid chromatography (HPLC) on chiralcel OD-H column.

[c]Determined by comparison with literature.[29]

of **6e** (R = Ph) was higher than that of others (entry 5). The configuration of the major product depended on the substituent group R of the catalyst. When R = $-(CH_{-2})_{4-}$ (**6c**) or *n*-Bu (**6d**), *R*-enantiomer was excess (entries 3 and 4), whereas when R = Et (**6b**) or Ph (**6e**), *S*-enantiomer was the major product (entries 2 and 5). Increasing the catalyst loading did not improve the activity and enantioselectivity (entries 6 and 7).

In conclusion, the present work describes the synthesis of several novel L-proline derivatives—two chiral piperazinones and five sulfamide-amine alcohols—and provides candidate compounds for the screening of new drug. Primary investigation demonstrated that **6b-e** could catalyze the asymmetric addition of diethylzinc to benzaldehyde with moderate yield. Other applications of these compounds, such as asymmetric catalysis in other reactions and biological activity, are now in progress in our laboratory.

EXPERIMENTAL

General

Tetrahydrofuran (THF) was distilled from sodium-benzophenone immediately prior to use. All other chemicals were used as received unless otherwise noted. ^{1}H NMR spectra were collected on a Bruker DPX (400 MHz) with TMS as an internal stantard. IR spectra were recorded on a Thermo Nicolet IR200 unit. High-resolution mass spectra (HRMS) were carried out on a Waters Micromass Q-Tof Micro^{TM} instrument using the electrospray ionization (ESI) technique. Melting points were determined using an XT5A apparatus and are uncorrected. Specific rotatory power was determined on a Perkin Elmer 341 polarimeter. The single-crystal structure was determined on a Rigaku R-AXIS-IV image area detector.

Synthesis of Compound 2

A solution of compound 1 (8.140 g, 30 mmol) in anhydrous pyridine (50 mL) was added p-TsCl (6.100 g, 32 mmol) portion wise at $-10\,^{\circ}C$. The mixture was stirred for 12 h, during which the temperature was allowed to rise to room temperature. Then the mixture was poured into 50 mL of cool water. The aqueous phase was extracted with $CHCl_3$ (3×30 mL), and the organic layer was washed with 2 M aq. HCl, saturated aq. Na_2CO_3, and water, then dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified through column chromatography on silica gel (eluent: ethyl acetate/petroleum ether = 1:2, v/v) to give 2 as a white solid.

(2*S*, 4*R*)-4-Hydroxyl-1-tosyl-2-*p*-tosyloxymethyl-pyrrolidine 2

Yield: 86%, mp 103–105 °C; $[\alpha]_D^{20} = -87.9$ (c 1.80, EtOH); IR (KBr disc) cm^{-1}: 3514, 3089, 1597, 1362, 818; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.95 (m, 1H), 2.02 (m, 1H), 2.43 (s, 3H), 2.45 (s, 3H), 3.23 (dd, $J = 11.6$ Hz, 1H), 3.48 (dd, $J = 11.6$ Hz, 1H), 3.94 (m, 1H), 4.13 (dd, $J = 10.4$, 6.4 Hz, H), 4.33 (dd, $J = 10.4$, 2. °Hz, 2H), 7.30 (d, $J = 8.0$ Hz, 2H), 7.39 (d, $J = 8.0$ Hz, 2H), 7.67 (d, $J = 8.0$ Hz, 2H), 7.81 (d, $J = 8.0$ Hz, 2H).

Synthesis of Compound 4a,b

General Procedures for Preparation of **4a** and **4b**

To the stirring mixture of methyl prolinate hydrochloride **3a**. (1.507 g, 9 mmol), Na_2CO_3 (5.774 g, 54 mmol), and anhydrous CH_3CN (50 mL), compound 2 (7.765 g, 1 °mmol) was added. After stirring at 80 °C for 36 h and filtering off the solid, the filtrate was evaporated in vacuo. By column chromatography on silica gel (ethyl acetate as eluent), compound **4a** was obtained as a slabby, and the excess **2** was recovered also. A similar procedure afforded **4b** as a sllaby.

(2*S*,2′*S*,4′*R*)-Methyl 1-[(1′-*p*-Tosyl-4′-hydroxypyrolidin-2′-yl)methyl] pyrrolidine-2-carboxylate **4a**

Yield: 78%, $[\alpha]_D^{20} = -126.0$ (c 1.20, $CHCl_3$), IR (KBr disc) cm^{-1}: 3513, 1741, 1598, 1494, 817; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.84 (m, 4H), 2.16 (m, 2H), 2.41 (s, 3H), 2.45 (m, 2H), 2.77 (m, 1H), 2.90 (dd, $J = 12.0$, 3.6 Hz, 1H), 3.17 (dd, $J = 11.2$, 3.2 Hz, 2H), 3.26 (m, 1H), 3.50 (dd, $J = 11.2$, 4.4 Hz, 1H), 3.70 (s, 3H), 3.75 (m, 1H), 4.32 (t, $J = 4.4$ Hz, 1H), 7.30 (d, $J = 8.0$ Hz, 2H), 7.71 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.0, 24.8, 30.4, 40.4, 53.2, 55.0, 57.7, 59.3, 61.8, 67.7, 70.8, 129.1 (2Ar-C), 131.0 (2Ar-C), 135.5, 145.0, 176.1. MS (ESI) m/z: 383 $(M + H^+)$, 405 $(M + Na^+)$; HRMS (ESI) m/z: calcd. for $C_{18}H_{27}N_2O_5S$ $(M + H)^+$ 383.1640, found 383.1654.

(2*S*,2′*S*,4′*R*,4′*R*)-Methyl 4-Hydroxy-1-[(1′-p-tosyl-4′-hydroxypyrolidin-2′-yl)methyl] pyrrolidine-2-carboxylate **4b**

Yield 47%, $[\alpha]_D^{20} = -100.0$ (c 1.30, acetone); IR (KBr, cm^{-1}): 3461, 3064, 2951, 1734, 1598, 817; ^1H NMR (400 MHz, $CDCl_3$) δ 1.77 (m,

1H), 2.04–2.12 (m, 3H), 2.40 (s, 3H), 2.59 (dd, $J = 10.0$, 2.8, 1H), 2.75 (dd, $J = 12.0$, 9.6, 1H), 2.98 (dd, $J = 12.0$, 4.0, 1H), 3.14 (dd, $J = 11.2$, 4.0, 1H), 3.39 (dd, $J = 10.0$, 5.2, 1H), 3.49 (dd, $J = 10.0$, 4.8, 1H), 3.64 (t, $J = 8.0$, 1H), 3.71 (s, 3H), 3.76 (m, 1H), 4.33 (m, 1H), 4.42 (m, 1H), 7.30 (d, $J = 8.0$, 2H), 7.70 (d, $J = 8.0$, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.3, 38.4, 38.6, 51.6, 55.9, 57.7, 59.7, 61.5, 64.5, 69.0, 70.1, 127.4 (2Ar-C), 129.4 (2Ar-C), 133.9 (Ar-C), 143.4 (Ar-C), 174.2 (C=O); MS (ESI) m/z: 399 ($M + H^+$), 421 ($M + Na^+$), 437 ($M + K^+$); HRMS (ESI) m/z: calcd for $C_{18\text{-}27}N_2O_6S$ $(M + H)^+$ 399.1590, found 399.1592.

Synthesis of 5a,b

General Procedures for Preparation of **5a** and **5b**

The mixture of **4a** (382 mg, 1 mmol), phenol (113 mg, 1.2 mmol), acetic acid (0.13 mL, 2.4 mmol), and 40% HBr (1 mL) was refluxed for 2–4 h, then extracted with ethyl ether to remove most of the phenol. The aqueous phase was evaporated, and the solid was extracted with acetone to give 153 mg of **5a** (hydrobromide) as a white solid.

(3*S*,9*S*,11*R*,)-11-Hydroxy-1,7-diaza-2-oxo-tricyclo[7.3.0.0^{3,7}]dodecane **5a** (Hydrobromide)

Yield 55%, mp 245 °C (decompose); $[\alpha]_D^{20} = -50.5$ (c 1.09, H_2O); IR (KBr disc) cm^{-1}: 3507 (br), 2956, 2808, 1641; ^{1}H NMR (400 MHz, D_2O) δ: 1.85 (td, $J = 12.8$, 4.0, 1H), 2.08 (m, 1H), 2.16–2.27 (m, 3H), 2.52 (m, 1H,), 3.14 (m, 1H), 3.38 (m, 1H), 3.45 (d, $J = 13.6$, 1H), 3.75 (dd, $J = 13.6$, 4.8, 1H), 3.87 (m, 1H), 3.92 (dd, $J = 12.4$, 2.8, 1H), 4.20 (m, 1H), 4.44 (t, $J = 9.6$, 1H), 4.51 (t, $J = 4.0$, 1H); ^{13}C NMR (100 MHz, D_2O) δ: 22.0, 27.4, 37.7, 52.2, 53.2, 54.2, 57.1, 62.1, 67.8, 165.2; MS (ESI) m/e: 197 ($M + H^+$); HRMS (ESI) m/z: calcd. for $C_{10}H_{17}N_2O_2S$ $(M + H)^+$ 213.1239, found 213.1239.

(3*S*, 5*R*, 9*S*, 11*R*)–5,11-Dihydroxy-1,7-diaza-2-oxo-tricyclo[7.3.0.0^{3,7}] dodecane **5b** (Hydrobromide)

Yield 51%, mp 205–207 °C; $[\alpha]_D^{20} = -35.5$ (c 1.36, H_2O); IR (KBr disc) cm^{-1}: 3372, 3007, 2950, 2933, 2815, 2672, 2631, 1650; ^{1}H NMR (400 MHz, D_2O) δ: 1.76–1.84 (m, 1H), 2.20 (dd, $J = 13.5$, 5.6, 1H), 2.34–2.48 (m, 2H), 3.04 (m, 1H), 3.40 (dd, $J = 12.8$, 3.6, 1H), 3.44 (d, $J = 12.4$, 1H), 3.67 (dd, $J = 13.4$, 4.3, 1H), 3.82 (dd, $J = 12.8$, 1.2, 1H), 3.98 (dd, $J = 12.2$, 2.6, 1H), 4.16 (m, 1H), 4.55–4.59 (m, 2H), 4.66–4.71

(m, 1H); ^{13}C NMR (100 MHz, D_2O) δ: 36.1, 37.7, 53.4, 53.4, 54.3, 60.4, 64.3, 68.1, 68.2, 165.3; MS (ESI) m/e: M + H^+ (213); HRMS: (ESI) m/z: calcd. for $C_{10}H_{17}N_2O_3S$ $(M+H)^+$ 197.1291, found 197.1279.

Synthesis of 6a

To the mixture of **4a** (0.661 g, 1.7 mmol), $NaBH_4$ (0.772 g, 20 mmol), and *t*-BuOH (10 mL), MeOH (7 mL) was added over 7.5 h at 80 °C. The reaction mixture was stirred overnight at this temperature. Then most of the solvent was evaporated and extracted with *n*-BuOH, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified through column chromatography on silica gel to give compound 6a as a white solid (chloroform/methanol = 7:1, v/v).

(2*S*,2′*S*,4′*R*)-2-Hydroxylmethyl-1-[(1′-*p*-tosyl-4′-hydroxypyrolidin-2′-yl) methyl] pyrrolidine (**6a**)

Yield: 56%, mp 114–116 °C, $[\alpha]_D^{20} = -123.0$ (c 0.60, EtOH); IR (KBr disc) cm^{-1}: 3412, 1596, 817; ^{1}H NMR (400 MHz, DMSO) δ: 1.46–1.50 (m, 2H), 1.61–1.67 (m, 2H), 1.76–1.79 (m, 1H), 1.88–1.92 (m, 1H), 2.18 (m, 1H), 2.40 (s, 3H), 2.50 (m, 1H), 2.70–2.74 (m, 2H), 2.91 (dd, $J = 10.0$, 5.2 Hz, 1H), 3.21 (m, 1H), 3.37 (m, 1H), 3.41–3.45 (m, 2H), 3.55 (m, 1H), 4.16–4.21 (m, 1H), 4.38 (s, 1H), 4.78 (d, $J = 3.8$Hz, 1H), 7.42 (d, $J = 8.0$ Hz, 2H), 7.67 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.9, 22.7, 27.6, 38.2, 54.0, 55.9, 57.5, 60.6, 64.2, 65.5, 67.4, 127.5 (2 × C), 129.5 (2 x C), 133.7, 143.0; HRMS (ESI) m/z: calcd. for $C_{17}H_{27}N_2O_4S$ $(M+H)^+$ 355.1691, found 355.1676.

Synthesis of 6b-e

General Procedure for Preparation of Sulfamide-Amine alcohols **6b**-e

Under an argon atmosphere, a solution of alkyl bromide (16 mmol) and 1,4-dibromobutane (°mmol) was used to prepare **6c** in THF (10 mL). It was added slowly to a three-necked flask containing magnesium scraps (16 mmol). The reaction mixture was stirred for another 20 min at room temperature, then cooled to 0 °C, and a solution of compound **4a** (2 mmol) in THF (6 mL) was added dropwise. After stirring the mixture for 0.5–2 h, it was acidified with 2 M aq. HCl and extracted with EtOAc. The organic layer was successively washed with saturated

Na_2CO_3, water, and brine, then dried over Na_2SO_4, filtrated, and evaporated in vacuo. The crude product was purified through column chromatography to furnish sulfamide amino alcohols **6b-e.**

(2*S*,2′*S*,4′*R*)-2-(1″ 0-Hydroxy-1″0-ethylpropyl)-1-[(1′-p-tosyl-4′-hydroxy-pyrolidin-2′-yl)methyl]pyrrolidine **6b**

Colorless crystal, yield 91%, mp 220–222 °C, $[\alpha]_D^{20} = -95.6$ (*c* 1.30, ethanol); IR (KBr, cm^{-1}): 3423, 3336, 1598, 1456, 816; ^1H NMR (400 MHz, D_2O) δ: 0.79 (t, $J = 7.2$ Hz, 3H), 0.85 (t, $J = 7.2$ Hz, 3H), 1.43–1.59 (m, 4H), 1.75–2.12 (m, 6H), 2.32 (s, 3H), 3.24 (m, 1H), 3.38 (m, 1H), 3.42–3.54 (m, 4H), 3.75 (m, 1H), 4.19 (m, 2H), 7.36 (d, $J = 8.0$ Hz, 2H), 7.68 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (100 Hz, D_2O) δ: 6.3, 6.3, 20.5, 23.1, 25.6, 26.2, 28.1, 37.8, 55.8, 55.9, 58.2, 63.0, 68.8, 74.9, 77.8, 127.7 (2Ar-C), 129.8 (2Ar-C), 131.3, 145.8; HRMS (ESI) m/z: calcd for $C_{21}H_{35}N_2O_4S$ $(M + H)^+$ 411.2317, found 411.2321.

(2*S*,2′*S*,4′*R*)-2-(1″-Hydroxy-cyclopenta-1″-yl)-1-[(1′-*p*-tosyl-4′-hydroxy-pyrolidin-2′-yl)methyl] pyrrolidine **6c**

White solid, yield: 75%, mp 128.9–130.8 °C, $[\alpha]_D^{20} = -116.5$ (c 0.54, EtOH); IR (KBr disc) cm^{-1}: 3383, 1597, 816; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.45–1.68 (m, 5H), 1.75–1.92 (m, 7H), 2.02 (dd, $J = 6.4$, 5.2 Hz, 2H), 2.43 (s, 3H), 2.73 (m, 1H), 2.85 (m, 1H), 2.98 (t, $J = 11.2$ Hz, 1H), 3.19 (dd, $J = 11.2$, 3.6 Hz, 1H), 3.29 (dd, $J = 12.0$, 3.2 Hz, 1H), 3.34 (m, 1H), 3.53 (dd, $J = 11.2$,4.4 Hz, 1H), 3.86–3.89 (m, 4H), 4.32 (m, 1H), 7.33 (d, $J = 8.0$ Hz, 2H), 7.73 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.5, 23.0, 24.1, 24.5, 24.7, 36.8, 39.5, 40.5, 54.9, 56.1, 57.4, 62.9, 69.3, 74.2, 82.1, 127.8 (2 C), 129.7 (2 C), 133.8, 143.8; HRMS (ESI) m/z: calcd. for $C_{21}H_{33}N_2O_4S^+$ $(M + H)^+$ 409.2161, found 409.2152.

(2*S*,2′*S*,4′*R*)-2-(1″-Hydroxy-1″-butylpentyl)-1-[(1′-*p*-tosyl-4′-hydroxy-pyrolidin-2′-yl)methyl] pyrrolidine **6d**

White solid, yield: 72%, mp 155–156 °C, $[\alpha]_D^{20} = -100.6$ (c 1.67, EtOH); IR (KBr disc) cm^{-1}: 3436, 3335, 1599, 812; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.91 (t, $J = 6.8$, 3H, CH_3), 0.94 (t, $J = 7.2$, 3H, CH_3), 1.07 (m, 1H, C*H*H), 1.21–1.70 (m, 11H, CH*H*, $5CH_2$), 1.92–2.33 (m, 8H, $4CH_2$), 2.44 (s, 3H, Ar-CH_3), 2.91 (br, 1H, OH), 3.26 (m, 2H, CH_2), 3.38–3.52 (m, 3H, C*H*H, CH_2), 3.83–3.95 (m, 2H, CH*H*, CH), 4.05 (m, 1H, CH), 4.32 (m, 1H, CH), 7.34 (d, $J = 8.0$, 2H, Ar-H), 7.70 (d, $J = 8.0$, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ14.0, 14.1, 21.6,

23.1, 23.1, 24.1, 25.3, 25.6, 26.1, 35.0, 35.9, 42.6, 55.5, 55.9, 56.2, 65.1, 69.3, 74.4, 79.9, 128.0, 129.9, 132.8, 144.5; HRMS (ESI) m/z: calcd. for $C_{25}H_{43}N_2O_4S$ $(M+H)^+$ 467.2943, found 467.2943.

(2*S*,2′*S*,4′*R*)-2-(1″-Hydroxy-1″-phenylbenzyl)-1-[(1′-*p*-tosyl-4′-hydroxypyrolidin-2′-yl)methyl]pyrrolidine **6e**

White solid, yield: 70%, mp 214–216 °C, $[\alpha]_D^{20} = -52.8$ (c 0.5, $CHCl_3$); IR (KBr disc) cm^{-1}: 3496, 3420, 1598, 814; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.38–1.46 (m, 3H CH_2CHH), 1.63–1.73 (m, 3H, CH_2CHH), 1.87 (m, 1H), 2.01 (t, $J = 11.6$ Hz, 1H), 2.41 (s, 3H, CH_3), 2.57 (m, 1H), 2.82 (dd, $J = 11.6$, 4.0 Hz, 1H), 2.91 (dd, $J = 10.8$, 4.8 Hz, 1H), 3.11 (dd, $J = 10.8$, 4.8 Hz, 1H), 3.19 (m, 1H), 3.58 (m, 1H), 3.98 (dd, $J = 8.8$, 4.8 Hz, 1H), 4.53 (s, 1H), 7.14 (m, 2H, Ar-H), 7.25–7.30 (m, 6H, Ar-H), 7.52 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.65 (m, 4H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ21.6, 24.8, 29.1, 37.9, 55.2, 55.6, 62.3, 69.4, 71.5, 77.9, 125.2 (2 C), 126.0 (2 C), 126.3 (2 C), 127.6 (2 C), 128.1 (4 C), 129.7 (2 C), 134.1, 143.7, 146.2, 147.9; HRMS: (ESI) m/z: calcd. for $C_{29}H_{35}N_2O_4S$ $(M+H)^+$ 507.2314, found 507.2317.

General Procedure for the Addition of Diethylzinc to Benzaldehyde and Conditions for the Analysis of Chiral Secondary Alcohol

Under a dry argon atmosphere, chiral ligand (0.05 mmol) in dry toluene (1 mL) was cooled to 0 °C, and a solution of Et_2Zn (0.9 M in hexane, 1.1 mL, 1.0 mmol) was added. 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 3 days at room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with ether (3×8 mL). The combined organic phase was washed with brine, dried with Na_2SO_4, filtered, and concentrated. The residue was purified by thin-layer chromatography on silica gel (petroleum ether/ethyl acetate = 6:1) to give the carbinol. The enantiomeric purity of the product was determined by HPLC. The absolute configuration of the product was assigned by comparison to literature values.[29]

Chiral HPLC: Chiralcel OD-H, UV 216 nm, *i*-PrOH/hexane = 2/100, flow rate 1.0 mL/min, t_R 12.4 min (*R*-isomer), t_R 14.7 min (*S*-isomer).

ACKNOWLEDGMENT

We are grateful for financial support from the National Natural Science Foundation of China (Grant 20372059). We also thank Jian-Xun Kang and Wei-Guo Zhu for the NMR data and Shao-Min Wang for HRMS.

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