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Short asymmetric synthesis of (*S*,*S*)-PDP using L-prolinol derivative as economic starting material

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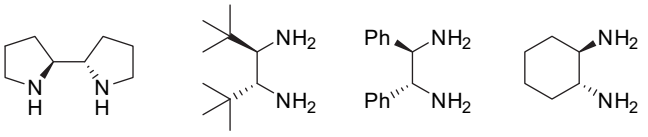
ABSTRACT

(*S*,*S*)-PDP (**5d**) and its backbone (2*S*,2′*S*)-bipyrrolidine (**1**) have been extensively applied as the scaffold of various chiral ligands in catalytic asymmetric syntheses. In this study, new short asymmetric syntheses of these two important C_2-symmetrical nitrogen heterocycles have been accomplished employing economically available L-prolinol derivative **10** as the starting material. Excellent diastereoselectivity was achieved of the key Grignard addition to imine intermediate utilizing (*S*)-*N*-*tert*-butanesulfinamide as the chiral auxiliary.

1. Introduction

Chiral C_2-symmetrical diamines have extensively served as the scaffolds of a large number of significant ligands or catalysts in organic synthesis.[1] Several representatives of the frequently used backbones are shown in Figure 1.



1 2 3 4

Figure 1. Some representative C_2-symmetrical diamines used in the asymmetric synthesis.

(*S*,*S*)-PDP (**5d**, 2-(((*S*)-2-((*S*)-1-(pyridin-2-ylmethyl)pyrrolidin-2-yl)pyrrolidin-1-yl)methyl)pyridine), a chiral ligand of non-heme iron catalysts developed from the diamine **1**, has exhibited excellent regio-, chemo-, and enantioselectivities in the catalytic aliphatic C–H oxidations in recent years.[2] Before the successful application of (*S*,*S*)-PDP (**5d**), several other amines **5a**, **5b**, and **5c** were also applied as the ligands (Fig. 2) in oxidizing sp^3 C–H bond,[2,3] although neither their efficiency of conversions nor their selectivities were satisfactory. In the presence of ligand **5d**, the metal center, iron (II), is considered to be on an energetically suitable state. It has been uncovered that some specific typologies were formed in the catalyst so as to explain its behaviors.[4] In order to further investigate the catalytic environment caused by such ligands in non-heme iron catalysts, it is necessary to deliver a convenient and efficient synthetic pathway to this chiral ligand.

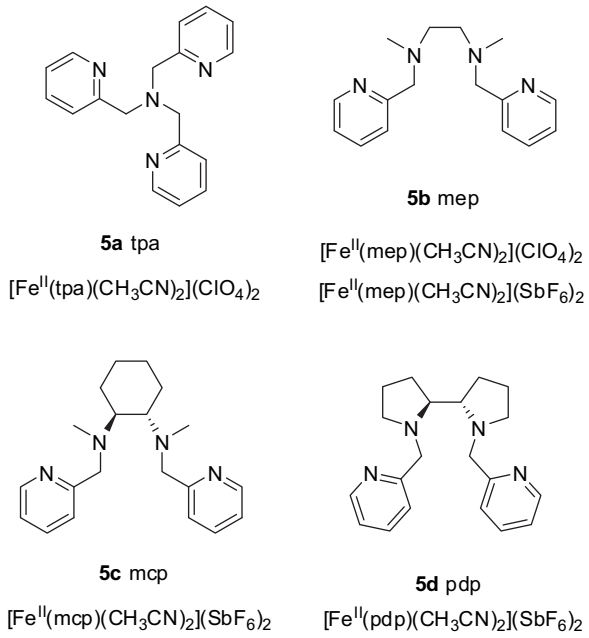


Figure 2. Some amine ligands of non-heme iron catalysts for oxidizing sp^3 C–H bond.

Syntheses of (2*S*,2′*S*)-bipyrrolidine (**1**), the backbone of **5d**, have been accomplished by several groups.[5] The first synthesis of this chiral pyrrolidines involved a photo-activated coupling and a subsequent resolution by optically active tartaric acid.[5a] Since the coupling of pyrrolidine occurred in the gas phase under refluxing conditions, the efficiency was considerably low. What was more, the radical mechanism of the reaction resulted in a mixture of three isomers, in which the yield of (*S*,*S*) or (*R*,*R*)-bipyrrolidine was

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limited to 25% upon complete conversion. A feasible asymmetric synthesis of diamine **1** with high stereoselectivity was published by Alexakis and co-workers in 2000.[5d] A substrate-controlled nucleophilic addition of organozinc reagent to C=N double bond[6-7] was utilized in constructing the chiral diamine functionality. Herein, we report an additional asymmetric pathway to furnish (*S*,*S*)-PDP (**5d**) with (2*S*,2′*S*)-bipyrrolidine hydrochloride as the precursor, using economically available L-proline derivative as the starting material.

Because of the economic availability of both L- and D-proline and their structural relevance to 2,2′-bipyrrolidine, we decided to start our work from a commercially available L-proline derivative to introduce the first optically pure pyrrolidine functionality, and then establish the second one by asymmetric manners. General requirements for constructing the second chiral pyrrolidine should at least include: (i) it should be a highly diastereoselective method; (ii) the *N*-atom can be easily introduced. For the uncertain diastereoselectivity in the synthesis, (*R*)- and (*S*)-*N*-*tert*-butanesulfinamide, a pair of commercially available and widely employed chiral auxiliaries,[8] were taken into our consideration.

According to the previous pioneer work by Ellman and coworkers, aldehydes were first condensed with *N*-*tert*-butanesulfinamide, to deliver the single *E* isomer.[8a] The highly diastereoselective addition of Grignard reagent was followed through a six-membered chair-like transition state to accomplish the chiral amine **8** as the major isomer (Fig. 3). Based on such predictable rules, we designed our retrosynthetic analysis of **5d** as shown in Figure 4. It is noteworthy that choosing (*R*)-*N*-*tert*-butanesulfinamide (**6**) as the chiral auxiliary was based on the above mentioned classical six-membered chair-like transition state.

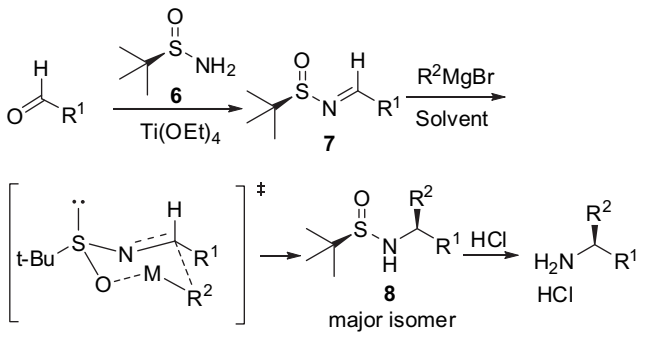


Figure 3. Asymmetric synthesis of chiral amines using *N*-*tert*-butanesulfinamide as the chiral auxiliary.

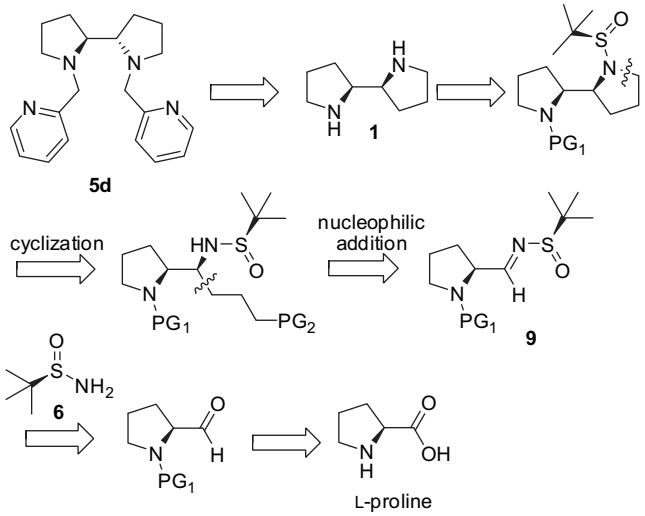
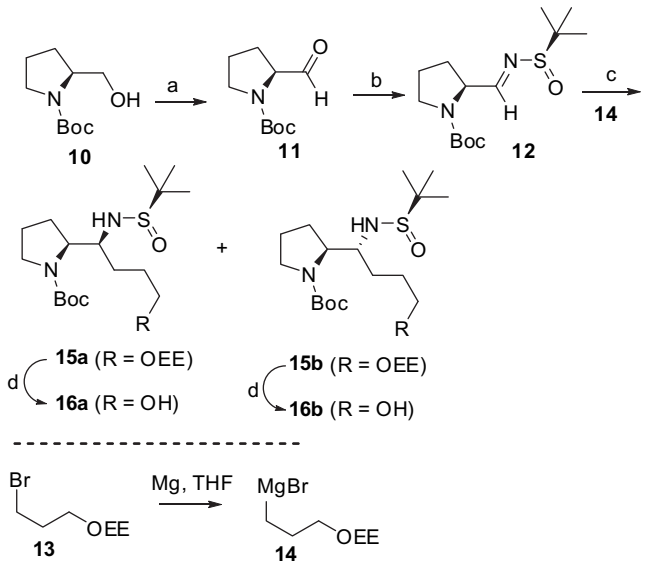


Figure 4. Retrosynthetic analysis of (*S*,*S*)-PDP (**5d**).

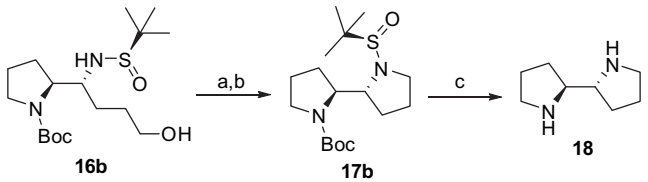
2. Results and discussion

At first, Swern oxidation of commercially available L-prolinol derivative **10** provided its corresponding aldehyde **11** in 94% yield after purification. In large-scale synthesis, the crude aldehyde **11** could be directly used in the next step without further purification. Condensation of aldehyde **11** and (*R*)-*N*-*tert*-butanesulfinamide (**6**) was carried out with 4 equiv $Ti(OEt)_4$ in THF at 0 °C to room temperature,[8a] affording 90% yield of sulfinylimine **12** (Scheme 1). Grignard reagent containing acetal protecting groups were usually well tolerated, and gave a high yield and diastereoselectivity in the nucleophilic additions.[9] However, our initial attempts in the nucleophilic addition of freshly prepared $BrMg(CH_2)_3OEE$ (**14**)[10,11] to sulfinylimine **12** in THF at −48 °C resulted in two inseparable diastereoisomers **15a** and **15b**. The ratio of these two isomers could be determined by HPLC. The crude mixture of **15a** and **15b** was further dissolved in propanol and treated with catalytic amount of PPTS, giving two isomers **16a** and **16b**. Fortunately, these two compounds exhibited sufficient difference in polarity, and could be separated by flash chromatography (8% isolated yield in two steps for **16a**, 65% for **16b**, **16b**/**16a**=8.1:1). Their stereochemistries were finally determined after further transformations (see text below).



Scheme 1. Reagents and conditions: (a) Oxalyl chloride (1.25 equiv), DMSO (2.67 equiv), Et_3N, DCM, −78 °C to rt, 1 h, 94%; (b) (*R*)-*N*-*tert*-butanesulfinamide (**6**, 1.0 equiv), $Ti(OEt)_4$ (4.0 equiv), THF, 0 °C to rt, 11 h, 90%; (c) THF, −48 °C, then **14** (2.0 equiv); (d) PPTS (25 mol %) in propanol, rt, 30 h; 8% for **16a**, 65% for **16b**, two steps; **16b**/**16a**=8.1:1 (based on silica gel separation).

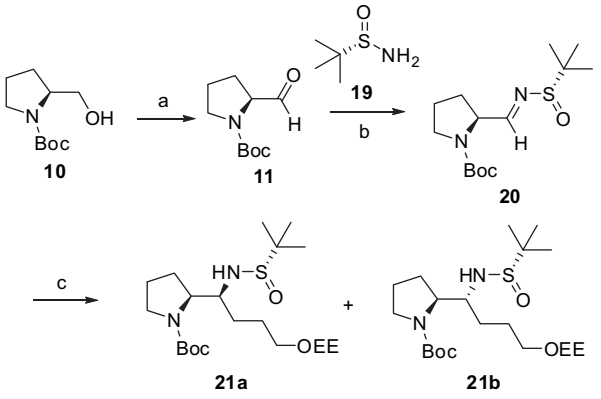
The major isomer **16b** (stereochemistry unknown at this stage) was then used in the following cyclization. The primary hydroxyl group of **16b** was first transformed to the corresponding mesylate with MsCl and Et_3N. Then, a number of bases including K_2CO_3, DBU, NaH, and *t*-BuOK[12] were screened for the intramolecular S_N2 cyclization. Among these, NaH and *t*-BuOK worked well to afford **17b** (Scheme 2). Both the *N*-Boc and *N*-*tert*-butanesulfinyl groups of **17b**



Scheme 2. Reagents and conditions: (a) MsCl (2.5 equiv), Et_3N (2.7 equiv), DCM, 0 °C to rt, 15 min; (b) NaH (8.0 equiv), THF, rt, 45% for two steps; (c) 4 M HCl in dioxane (10.0 equiv) and MeOH (1:1, v/v), rt, 4 h, 88%.

were removed by treatment with 4 M HCl in dioxane and MeOH (1:1, v/v).[8b] Characterizations including optical rotation at this stage clearly indicated that the obtained bipyrrolidine **18** was a *meso* compound, as well as by comparison with previously reported NMR data.[13] Obviously, the classical transition state previously mentioned in Figure 3 did not work in this case with substrate **12**.

To verify this speculation, we decided to apply the counter auxiliary (*S*)-*N*-*tert*-butanesulfinamide (**19**) to our synthesis. With the same procedures, Swern oxidation and condensation with (*S*)-*N*-*tert*-butanesulfinamide (**19**) afforded aldimine **20** in 65% yield (Scheme 3). In order to improve the yield and diastereoselectivity of Grignard addition to aldimine **20**, optimization of reaction conditions was performed (Table 1). It was found that non-coordinating solvents, toluene, and DCM, showed great improvement in the diastereoselectivities of Grignard additions of **14** to sulfinylimine **20** (Table 1, entry 3 and 4).[14] Changing the solvent from THF to DCM increased the diastereoselectivity of this reaction dramatically (**21a**/**21b**=30.9:1, measured by HPLC).



Scheme 3. Reagents and conditions: (a) Oxalyl chloride (1.25 equiv), DMSO (2.67 equiv), Et_3N, DCM, −78 °C to rt, 1 h; (b) (*S*)-*N*-*tert*-butanesulfinamide (**19**, 1.0 equiv), $Ti(OEt)_4$ (4.0 equiv), THF, 0 °C to rt, 11 h, 65% yield for two steps. (c) **14**, conditions see Table 1.

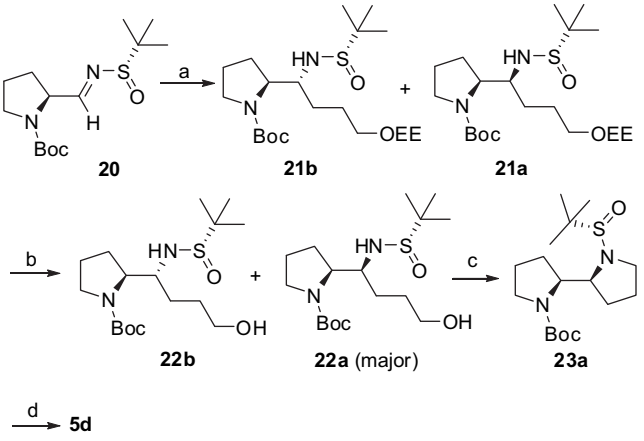
Table 1
Grignard additions of **14** to (*S*)-*tert*-butanesulfinyl aldimine **20**

Entry	Solvent	Temp[a]	Time	Results	**12a**/**21b**[b]
1	THF	−48 °C	6 h	Complete conversion	6.4:1
2	THF	−48 °C	12 h	Complete conversion	8.9:1
3	Toluene	−48 °C	6 h	Complete conversion	14.8:1
4	DCM	−48 °C	6 h	Complete conversion	30.9:1
5	THF	−78 °C	6 h	Low conversion	—

[a] The reactions were performed initially at listed temperatures, and warmed to room temperature before quenching.
[b] The ratios were determined by HPLC of the crude products **21a** and **21b**.

Treatment of the mixture of **21a** and **21b** with PPTS in propanol provided two separable diastereoisomers **22a** and **22b** (94% yield for **22a**, Scheme 4). Intramolecular cyclization of the major product **22a** was carried out with mesylation followed by intramolecular S_N2 substitution using *t*-BuOK as the base, affording **23a** in 74% yield in two steps. Global deprotection of **23a** with 4 M HCl in 1,4-dioxane and methanol (1:1, v/v) and subsequent substitution with 2-picolyl chloride hydrochloride were accomplished in 86% yield. Optical rotation and NMRs of the synthetic (*S*,*S*)-PDP (**5d**) are in good agreement with those reported.[2]

Notably, during our initial attempts (Scheme 1), the Grignard reaction underwent a pathway different from the classical one via transition state **24** (Fig. 5). The favored nucleophilic addition occurred on the opposite side of C=N and gave undesired **15b** predominantly.[15] Considering the existence of a β-*N*-Boc functionality in aldimine **12**, we postulate that the electrons on the oxygen of Boc-carbonyl group might play an important role in the transition states. Internal transformation to the other transition state **25** would lower the whole energy by corresponding chelating effects (Fig. 5).



Scheme 4. Reagents and conditions: (a) **20** in DCM (0.6 M), $BrMg(CH_2)_3OEE$ in THF (2.0 equiv), −48 °C, **21a**/**21b**=31.8:1 (by HPLC); (b) PPTS (25 mol %), propanol, rt, 30 h, 94% yield for **22a** for two steps. (c) (i) MsCl (2.5 equiv), Et_3N (2.7 equiv), DCM, 0 °C to rt, 15 min; (ii) *t*-BuOK (2.0 equiv), THF, rt, 30 min, 75% yield for two steps; (d) (i) 4 M HCl (10 equiv) in dioxane and MeOH (1:1, v/v), rt, 3–4 h; (ii) 2-picolyl chloride hydrochloride (2.2 equiv), NaOH (6.4 equiv) in H_2O and CH_2Cl_2, rt, 18 h, 86% for two steps.

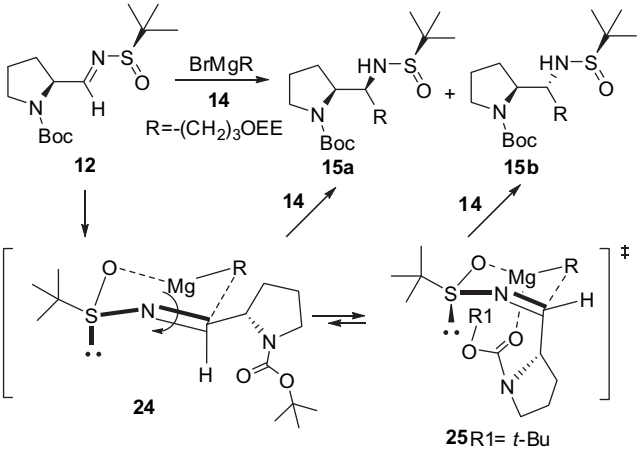


Figure 5. Proposed transition state for the addition of $BrMg(CH_2)_3OEE$ to (*R*)-*tert*-butanesulfinyl aldimine **12**.

3. Conclusion

In summary, a seven-step asymmetric synthesis of (*S*,*S*)-PDP (**5d**) has been accomplished in 39% overall yield. Uses of economic starting materials and commercially available chiral auxiliary make this newly established synthesis suitable for the future large-scale preparation. Up to 94% de was achieved in the key Grignard addition in the optimized solvent by using (*S*)-*N*-*tert*-butanesulfinamide as the chiral auxiliary. With an additional β-*N*-Boc functionality in *tert*-butanesulfinyl aldimine substrate, an opposite stereochemical pathway from the classical transition state was observed in the corresponding Grignard addition, and a reasonable alternative transition state was proposed to demonstrate such a phenomenon. Furthermore, the present methodology will be eligible to the synthesis of (*R*,*R*)-PDP by using D-proline derivative as the starting material and (*R*)-*N*-*tert*-butanesulfinamide (**6**) as the chiral auxiliary. Further applications of (*S*,*S*)-PDP and its analogues in catalytic reactions are under investigation and will be reported in due course.

4. Experimental section

4.1. (*S*)-*tert*-Butyl 2-formylpyrrolidine-1-carboxylate (11)

To a solution of oxalyl chloride (2.6 mL, 30 mmol) in CH_2Cl_2 (60 mL) was added DMSO (4.6 mL, 65 mmol) dropwise at −78 °C under nitrogen atmosphere. The mixture was stirred at the same temperature for 30 min, and alcohol **10** (5.01 g, 25 mmol) in CH_2Cl_2 (40 mL) was added slowly. The resulting mixture was stirred for 1 h under the same temperature. Et_3N (17.2 mL, 119 mmol) was added to quench the reaction at −78 °C. After stirring for additional 20 min under the same temperature, the mixture was warmed to room temperature. After being diluted with water, the resulting mixture was extracted with CH_2Cl_2. The organic layer was washed with aqueous saturated NH_4Cl, aqueous saturated Na_2CO_3, and brine successively, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate=4:1) to give **11** (4.74 g, 94%) as a colorless oil. $[\alpha]_D^{23}$ −90.1 (*c* 1.1, $CHCl_3$) (lit. [16] $[\alpha]_D^{24}$ −98.4 (*c* 0.66, $CHCl_3$)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 and 1.39 (s, 9H), 1.72–2.13 (m, 4H), 3.31–3.52 (m, 2H), 3.92–4.15 (m, 1H), 9.35–9.49 (m, 1H).

4.2. (*S*)-*tert*-Butyl 2-((*E*)-((*R*)-*tert*-butylsulfinylimino)-methyl)pyrrolidine-1-carboxylate (12)

To a dried 25 mL flask was added **11** (1.01 g, 5 mmol), (*R*)-*N*-*tert*-butanesulfinamide **6** (614 mg, 5 mmol) and THF (5 mL) under N_2 atmosphere. The mixture was cooled to 0 °C, and then $Ti(OEt)_4$ (4.2 mL, 20 mmol) in THF (5 mL) was added slowly via a syringe. The reaction was warmed to room temperature and stirred overnight. The excess of $Ti(OEt)_4$ was decomposed by slow addition of brine at 0 °C. The resulting suspension was filtered through a pad of Celite, and washed with ethyl acetate. The filtrate was separated and the aqueous layer was extracted with ethyl acetate for three times. The combined organic phased were dried over $MgSO_4$ and concentrated. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate=3:1) to give **12** (1.37 g, 90%) as a colorless oil. $[\alpha]_D^{28}$ −286.4 (*c* 1.01, $CHCl_3$). IR (neat): 2977, 1698, 1627, 1396, 1365 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (s, 9H), 1.41 and 1.45 (s, 9H), 1.76–2.01 (m, 3H), 2.03–2.23 (m, 1H), 3.31–3.59 (m, 2H), 4.48–4.71 (m, 1H), 7.88–8.00 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.5, 23.6 (24.0), 28.5, 29.2 (30.6), 46.6, 56.9 (57.2), 60.7 (60.9), 79.7 (80.3), 154.1 (154.3), 168.5 (169.6). HRMS (ESI) calcd for $C_{14}H_{26}N_2Na_1O_3S_1$ $[M+Na]^+$ 325.1556; found, 325.1555.

4.3. (*S*)-*tert*-Butyl 2-((*S*)-1-((*R*)-1,1-dimethylethylsulfinamido)-4-hydroxybutyl)-pyrrolidine-1-carboxylate (16a) and (*S*)-*tert*-butyl 2-((*R*)-1-((*R*)-1,1-dimethylethylsulfinamido)-4-hydroxybutyl)pyrrolidine-1-carboxylate (16b)

To a 250 mL flask containing magnesium turnings (5.01 g, 0.2 mol) in THF (50 mL) was added bromide **13** (30 mL, 0.2 mol) dropwise. The reaction was cooled in a water bath and kept the internal temperature at 25–30 °C. During this addition, an additional batch of THF (50 mL) was added in portions. After completion of addition of bromide **13**, the mixture was stirred at room temperature for 1 h. Concentration of the freshly prepared Grignard reagent **14** was titrated by the standard method (~0.80 M).[11]

To a solution of **14** (100 mL, 80 mmol), **12** (12.04 g, 39.8 mmol) in THF (40 mL) was added dropwise at −48 °C. The resulting solution was stirred at this temperature for 12 h, and then warmed to room temperature. The reaction was quenched with aqueous saturated NH_4Cl in an ice bath, and extracted with ethyl acetate for three times. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue (**15a** and **15b**) was treated with PPTS (2.75 g, 11 mmol) in propanol (100 mL). After being stirred for 30 h at rt, the reaction mixture was concentrated. The product was purified by flash chromatography (ethyl acetate) to afford **16a** (1.16 g, 8%) and **16b** (9.45 g, 65%) as white solids. **16a**: mp 96–99 °C. $[\alpha]_D^{28}$ −62.0 (*c* 0.94, $CHCl_3$). IR (KBr): 3484, 3154, 2981, 1686, 1378 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (s, 9H), 1.45 (s, 9H), 1.64–1.97 (m, 7H), 2.00–2.49 (br, 2H), 3.17–3.31 (m, 1H), 3.31–3.50 (m, 1H), 3.50–3.80 (m, 3H), 3.80–4.01 (m, 1H), 4.11–4.30 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.7, 23.9, 26.8 (27.1), 27.6 (27.9), 28.5, 29.5, 47.1, 56.0, 60.2, 61.1, 62.1, 79.7, 154.7 (156.0). HRMS (ESI) calcd for $C_{17}H_{34}N_2Na_1O_4S_1$ $[M+Na]^+$ 385.2132; found, 385.2115. **16b**: mp 105–106 °C. $[\alpha]_D^{28}$ −76.8 (*c* 0.94, $CHCl_3$). IR (KBr): 3392, 3144, 2974, 1656, 1414 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (s, 9H), 1.45 (s, 9H), 1.60–1.87 (m, 7H), 2.02–2.22 (m, 1H), 3.15–3.32 (m, 1H), 3.32–3.46 (m, 1H), 3.46–3.59 (m, 1H), 3.59–3.71 (m, 2H), 3.99–4.12 (m, 1H), 5.33–5.56 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.1, 24.2, 27.4, 28.6, 29.2, 29.6, 48.4, 56.3, 60.4, 62.4, 63.2, 79.9, 156.2. HRMS (ESI) calcd for $C_{17}H_{34}N_2Na_1O_4S_1$ $[M+Na]^+$ 385.2132; found, 385.2119.

4.4. (2*S*,2′*R*)-*tert*-Butyl 1′-((*R*)-*tert*-butylsulfinyl)-2,2′-bipyrrolidine-1-carboxylate (17b)

To a stirred solution of **16b** (8.76 g, 24 mmol) and Et_3N (9.6 mL, 66 mmol) in CH_2Cl_2 (100 mL) was added MsCl (4.8 mL, 62 mmol) in CH_2Cl_2 (30 mL) under nitrogen atmosphere at 0 °C. The resulting mixture was warmed to room temperature and stirred for 15 min. The reaction was then quenched with aqueous saturated $NaHCO_3$ and extracted with CH_2Cl_2 three times. The combined organic layers were dried over $MgSO_4$ and concentrated. The above ice-cooled crude product in THF (150 mL) was added slowly to a suspension of NaH (1.55 g, 39 mmol) in THF (5 mL). After being stirred at room temperature overnight, the reaction was quenched by addition of aqueous saturated NH_4Cl. The aqueous phase was extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate=1:1) to give **17b** (3.75 g, 45%) as a colorless oil. $[\alpha]_D^{29}$ −18.6 (*c* 1.00, $CHCl_3$). IR (neat): 2974, 2882, 1696, 1456, 1394 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (s, 9H), 1.46 (s, 9H), 1.69–2.00 (m, 8H), 2.69–2.81 (m, 1H), 3.15–3.29 (m, 1H), 3.31–3.62 (m, 1H), 3.64–3.89 (m, 2H), 3.94–4.06 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.8, 24.4, 26.3, 27.3, 28.7, 29.2, 42.8, 47.1, 57.9, 61.1, 68.2, 79.3, 155.1. HRMS (ESI) calcd for $C_{17}H_{32}N_2Na_1O_3S_1$ $[M+Na]^+$ 367.2026; found, 367.2010.

4.5. *meso*-(2*S*,2′*R*)-2,2′-Bipyrrolidine (18)

To a flask containing **17b** (70 mg, 0.20 mmol) was added MeOH (2 mL) and 4 M HCl solution in dioxane (2 mL, 4 mmol). The reaction was stirred at room temperature for 4 h and concentrated. Diethyl ether was then added to precipitate the amine hydrochloride. After several times of wash by diethyl ether, the product was purified by silica gel chromatography (CH_2Cl_2/MeOH/aqueous ammonia=20:1.5:1) to give free base **18** (25 mg, 88%) as a colorless liquid. IR (neat): 2965, 2875, 1400, 909, 732 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32–1.49 (m, 2H), 1.60–1.82 (m, 4H), 1.82–1.98 (m, 2H), 2.00–2.37 (br, 2H), 2.79–3.02 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.94, 29.59, 47.10, 63.56. HRMS (ESI) calcd for $C_8H_{16}N_2Na_1$ $[M+Na]^+$ 163.1206; found, 163.1206.

4.6. (*S*)-*tert*-Butyl 2-((*E*)-((*S*)-*tert*-butylsulfinylimino)methyl)pyrrolidine-1-carboxylate (20)

N-Boc prolinal, which was freshly prepared by Swern oxidation of alcohol **10** (66.1 g, 328 mmol) without purification, was dissolved in THF (100 mL). To this solution was added (*S*)-*N*-*tert*-butanesulfinamide **19** (44.04 g, 363 mmol) in THF (370 mL) and

$Ti(OEt)_4$ (331.6 g, 1.45 mol) in THF (450 mL) successively at 0 °C. The reaction mixture was warmed to room temperature and stirred overnight. The excess of $Ti(OEt)_4$ was decomposed by slow addition of brine at 0 °C. The resulting suspension was filtered through a pad of Celite and washed with ethyl acetate. The filtrate was separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried over $MgSO_4$ and concentrated. Purification on silica gel chromatography (petroleum ether/ethyl acetate=4:1) gave **20** (65.0 g, 65%) as a colorless oil. $[\alpha]_D^{30}$ 79.2 (*c* 1.64, $CHCl_3$). IR (neat): 2978, 2932, 1699, 1626, 1393 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.19 (s, 9H), 1.41 (s, 9H), 1.69–2.26 (m, 4H), 3.32–3.58 (m, 2H), 4.49–4.68 (m, 1H), 7.88, and 7.96 (s, 1H). Anal. Calcd for $C_{14}H_{26}N_2O_3S$: C, 55.60; H, 8.67; N, 9.26; S, 10.60. Found: C, 55.42; H, 8.90; N, 9.14; S, 10.67.

4.7. (*S*)-*tert*-Butyl 2-((*S*)-1-((*S*)-1,1-dimethylethylsulfinamido)-4-hydroxybutyl)-pyrrolidine-1-carboxylate (22a)

To a solution of Grignard reagent **14** in THF (0.75 M, 142 mL, 106.5 mmol) was added slowly **20** (17.1 g, 56.5 mmol) in CH_2Cl_2 (100 mL) at −48 °C. The resulting solution was stirred at this temperature for 15 h. The reaction was warmed to room temperature and quenched with aqueous saturated NH_4Cl at 0 °C. The aqueous phase was extracted with ethyl acetate three times. The combined organic layers was dried over $MgSO_4$ and concentrated. HPLC (Kromasil C_{18}, 5 μm, 4.6×150 mm, CH_3CN/H_2O=70:30, 1.0 mL/min): dr of **21a** (major, T_R 5.3 min) versus **21b** (minor, T_R 4.3 min)=31.8:1.

The crude product of **21a** and **21b** was treated with PPTS (3.4 g, 13.5 mmol) in propanol (250 mL) for 30 h. The mixture was concentrated, and the residue was purified by flash chromatography (petroleum ether/ethyl acetate=1:5 to pure ethyl acetate) to afford **22a** (19.3 g, 94%) as a colorless oil. $[\alpha]_D^{28}$ 10.5 (*c* 1.08, $CHCl_3$). IR (neat): 2976, 2875, 1672, 1403, 1367 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.20 (s, 9H), 1.45 (s, 9H), 1.55–2.03 (m, 8H), 2.51 (br, 1H), 3.10–3.29 (m, 1H), 3.30–3.49 (m, 2H), 3.54–3.74 (m, 2H), 3.78–4.00 (m, 1H), 4.91–5.09 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.2, 23.8, 28.2, 28.7, 30.6, 34.3, 46.8, 55.9, 60.4 (60.6) 61.7, 62.6, 80.1, 157.2. HRMS (ESI) calcd for $C_{17}H_{34}N_2Na_1O_4S_1$ $[M+Na]^+$ 385.2132; found, 385.2116.

4.8. (2*S*,2′*S*)-*tert*-Butyl 1′-((*S*)-*tert*-butylsulfinyl)-2,2′-bipyrrolidine-1-carboxylate (23a)

To a stirred solution of **22a** (20.45 g, 24.1 mmol) and Et_3N (20.4 mL, 141 mmol) in CH_2Cl_2 (160 mL) was added MsCl (8.8 mL, 114 mmol) in CH_2Cl_2 (40 mL) under nitrogen atmosphere at 0 °C. The resulting mixture was warmed to room temperature and stirred for 30 min. The reaction was quenched with aqueous saturated $NaHCO_3$ and extracted with CH_2Cl_2 three times. The combined organic layers were dried over $MgSO_4$ and concentrated. This crude product in THF (400 mL) was treated with *t*-BuOK (12.7 g, 113 mmol) at 0 °C. After being stirred for 1 h, the reaction was quenched by addition of saturated aqueous NH_4Cl. The aqueous phase was extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate=2:1 to 1:1) to give **23a** (14.49 g, 75%) as a colorless oil. $[\alpha]_D^{30}$ −69.9 (*c* 1.56, $CHCl_3$). IR (neat): 2970, 2869, 1693, 1393, 1362 m^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.16 (s, 9H), 1.37–1.56 (m, 9H), 1.63–2.05 (m, 8H), 3.18–3.76 (m, 4H), 3.76–4.19 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.8, 24.0, 26.5, 26.8, 27.4, 28.7, 42.5, 47.0, 57.4, 60.1, 67.2, 80.0, 154.9. HRMS (ESI) calcd for $C_{17}H_{32}N_2Na_1O_3S_1$ $[M+Na]^+$ 367.2026; found, 367.2010.

4.9. (*S*,*S*)-PDP (5d)

To a solution of **23a** (7.54, 21.9 mmol) in MeOH (55 mL) was added 4 M HCl solution in dioxane (60 mL, 240 mmol). The reaction was stirred at room temperature for 4 h and concentrated. Diethyl ether was added to precipitate the amine hydrochloride. After several washings by diethyl ether, the crude product was resolved in CH_2Cl_2 (45 mL) and H_2O (45 mL). Solid NaOH (5.6 g, 0.14 mol) was added, followed by 2-picolyl chloride hydrochloride (7.9 g, 48.1 mmol). After 18 h stirring at room temperature, the reaction mixture was diluted with 1 M NaOH. The aqueous layer was extracted with CH_2Cl_2. The organic extracts were combined, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography (CH_2Cl_2/MeOH/NH_4OH=40:2:1) to provide **5d** (6.07 g, 86%). $[\alpha]_D^{27}$ −89.1 (*c* 0.9, MeOH) (lit.[2] $[\alpha]_D^{25}$ −94.6 (*c* 1.0, MeOH)). ^1H NMR (300 MHz, $CDCl_3$): δ 1.61–1.93 (m, 8H), 2.14–2.33 (m, 2H), 2.80 (m, 2H), 3.00 (m, 2H), 3.50 (d, *J*=12.9 Hz, 2H), 4.19 (d, *J*=14.4 Hz, 2H), 7.10 (dd, *J*=5.7, 6.3 Hz, 2H), 7.40 (d, *J*=7.8 Hz, 2H), 7.59 (dd, *J*=7.2, 7.8 Hz, 2H), 8.47 (d, *J*=4.5 Hz, 2H). All data are identical to those reported.[2]

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Supplementary data

Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2010.02.048.

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