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Synthesis of (+)-CP-99,994 via Pd(0)-Catalyzed Asymmetric Allylic and Homoallylic C−H Diamination of Terminal Olefin

Renzhong Fu, Baoguo Zhao, and Yian Shi*

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

yian@lamar.colostate.edu

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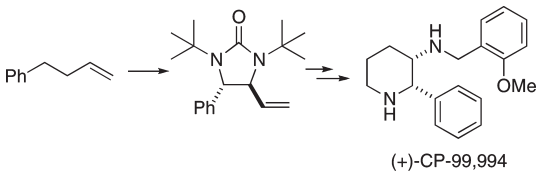


This paper describes an asymmetric synthesis of the potent substance P receptor antagonist (+)-CP-99,994 from 4-phenyl-1-butene via Pd(0)-catalyzed asymmetric allylic and homoallylic C−H diamination.

(+)-CP-99,994 (**1**) is a potent and selective nonpeptide substance P receptor antagonist (Figure 1).[1] Its biological activity has led to the development of various syntheses of this molecule and related analogues.[2−5] Recently, we reported that terminal olefins can be enantioselectively diaminated at allylic and homoallylic carbons via C−H activation using di-*tert*-butyldiaziridinone (**3**) as nitrogen source with a catalyst derived from $Pd_2(dba)_3$ and the tetramethylpiperidine-based phosphorus amidite ligand **5** (Scheme 1).[6,7] Herein, we wish to report the extension of this diamination process to the synthesis of (+)-CP-99,994.

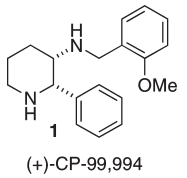
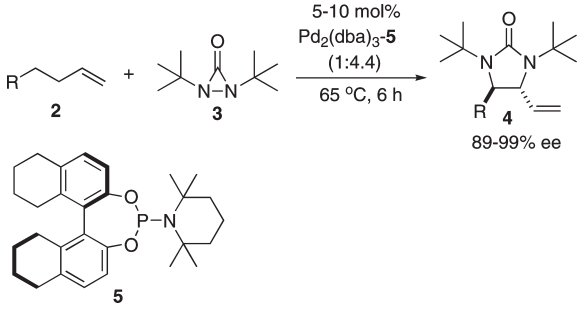


FIGURE 1. The structure of (+)-CP-99,994.

SCHEME 1



The retrosynthetic plan for (+)-CP-99,994 is outlined in Scheme 2. Compound **1** can be obtained from diamino acid **7** via lactam **6**. Compound **7** can be derived from diamination of 4-phenyl-1-butene (**10**).

The synthesis of (+)-CP-99,994 is described in Scheme 3. Allylic and homoallylic C−H diamination of 4-phenyl-1-butene (**10**) with di-*tert*-butyldiaziridinone (**3**), $Pd_2(dba)_3$, and ligand *ent*-**5** gave imidazolidinone **9** in 78% yield and 90% ee. Compound **9** was oxidized to aldehyde **11** in 90% yield via dihydroxylation with OsO_4−NMO, followed by oxidative cleavage with $NaIO_4$.[8] The olefination[3b] of aldehyde **11**, followed by hydrogenation[3b] gave ester **13** in high yields.

One of the *tert*-butyl groups on the imidazolidinone of **13** was selectively removed with CF_3CO_2H in CH_2Cl_2 to give compound **14** along with very small amounts of **15** in 98% yield.[9] At this point, compounds **14** and **15** could not be separated by flash column chromatography. Treating compounds **14** and **15** with sodium bis(trimethylsilylamide) and subsequently with nosyl chloride[10] gave compound **16** in 72% yield after recrystallization from hexanes and ethyl acetate. The remaining *tert*-butyl group of compound **16** was removed with methanesulfonic acid to give compound **17** in 95% yield and >99% ee. Cleavage of the imidazolidinone

(1) For leading references, see: (a) Desai, M. C.; Lefkowitz, S. L.; Thadeio, P. F.; Longo, K. P.; Snider, R. M. *J. Med. Chem.* **1992**, *35*, 4911. (b) Rosen, T.; Seeger, T. F.; McLean, S.; Desai, M. C.; Guarino, K. J.; Bryce, D.; Pratt, K.; Heym, J. *J. Med. Chem.* **1993**, *36*, 3197.

(2) For leading references on racemic synthesis of CP-99,994, see: (a) Desai, M. C.; Rosen, T. J. WO 9301170. (b) Desai, M. C.; Thadeio, P. F.; Lefkowitz, S. L. *Tetrahedron Lett.* **1993**, *34*, 5831. (c) Reference 1b. (d) Tsai, M.-R.; Chen, B.-F.; Cheng, C.-C.; Chang, N.-C. *J. Org. Chem.* **2005**, *70*, 1780.

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(6) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2008**, *130*, 8590.

(7) For leading references on the preparation of di-*tert*-butyldiaziridinone (**3**), see: (a) Greene, F. D.; Stowell, J. C.; Bergmark, W. R. *J. Org. Chem.* **1969**, *34*, 2254. (b) Du, H.; Zhao, B.; Shi, Y. *Org. Synth.* In press.

(8) Oshitari, T.; Akagi, R.; Mandai, T. *Synthesis* **2004**, 1325.

(9) (a) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 762. (b) Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 11688.

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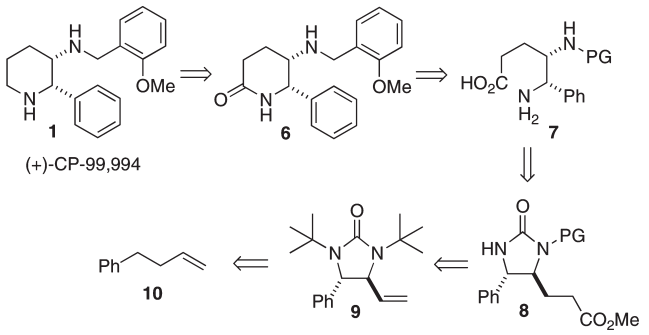
SCHEME 2



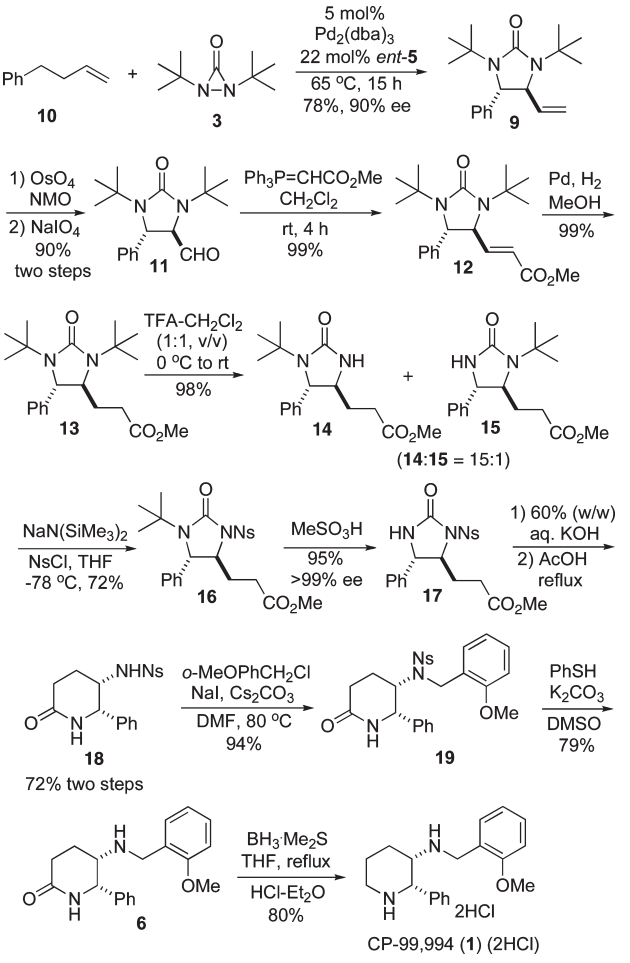
ring of **17** with potassium hydroxide solution,[11] followed by cyclization in refluxing AcOH[12] led to lactam **18** in 72% yield in two steps. It was found that the nosyl group of **18** could not be removed with thiophenol under basic conditions. Compound **18** was then transformed to compound **19** in 94% yield by alkylation with 2-methoxybenzyl chloride. The removal of the nosyl group was realized by treating **19** with thiophenol and K_2CO_3 to give compound **6** in 79% yield.[13] Based on a known procedure,[1b,2a,2b] reduction of compound **6** with borane dimethyl sulfide (THF, reflux, 15 h) and subsequent treatment with saturated HCl−Et_2O gave (+)-CP-99,994 (**1**) as its dihydrochloride salt in 80% yield and >99% ee. The spectroscopic data and optical rotation were consistent with literature data.[1a,3c,3e,4b,4f] The X-ray structure of (+)-CP-99,994 (**1**) dihydrochloride salt is shown in the Supporting Information.[1a]

In conclusion, (+)-CP-99,994 (2HCl) was synthesized from 4-phenyl-1-butene in overall 20% yield and >99% ee. The vicinal diamine moiety was introduced onto a readily available terminal olefin with our recently developed asymmetric allylic and homoallylic C−H diamination process. The selective removal of one of the *tert*-butyl groups allows ready differentiation of the two nitrogens. Further application of the diamination strategy to other biologically significant molecules is in progress.

Experimental Section

Synthesis of Compound 9. A 50-mL flask containing $Pd_2(dba)_3$ (0.345 g, 0.38 mmol) and ligand *ent*-**5** (0.769 g, 1.66 mmol) was evacuated and then filled with argon three times. Upon addition of benzene (2.0 mL, distilled from sodium), the resulting mixture was immersed in an oil bath (65 °C), stirred for 45 min, and then concentrated under vacuum at room temperature. 4-Phenyl-1-butene (1.0 g, 7.6 mmol) was then added. The resulting mixture was immersed in an oil bath (65 °C) with stirring. Then di-*tert*-butyldiaziridinone (3.21 g, 18.9 mmol) was added by syringe pump at a rate of 1.89 mmol/h. Upon completion of addition (10 h), the reaction mixture was stirred for an additional 5 h and purified by flash chromatography (silica gel, hexane:ethyl acetate = 30:1, v/v) to give the diamination product along with a small amount of dba, which was further purified by flash chromatography (silica gel, toluene then hexane:ethyl acetate = 30:1, v/v) to give diamination product **9** as a colorless oil (1.75 g, 78% yield, 90% ee). The enantioselectivity was determined by HPLC (Chiralpak AD Column, NO. AD00CE-EA001, hexanes:2-propanol = 90:10, v/v). $[\alpha]^{20}_D$ −29.2 (*c* 1.0, $CHCl_3$) (90% ee); IR (KBr) 1689 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.26 (m, 5H), 6.04 (ddd, J = 17.7, 10.2, 8.4 Hz, 1H), 5.20 (d, J = 17.7 Hz, 1H), 4.16 (s, 1H), 3.65 (d, J = 8.4 Hz, 1H), 1.34 (s, 9H), 1.28 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 144.0, 140.9, 128.9, 127.8, 125.8, 115.7, 64.9, 63.3, 53.6, 53.4, 29.0, 28.8; HRMS calcd for $C_{19}H_{29}N_2O$ (M + 1) 301.2274, found 301.2279.

SCHEME 3



Synthesis of Compound 11. To a solution of compound **9** (2.33 g, 7.8 mmol) in 1,4-dioxane (140 mL)−H_2O (45 mL) was added $Me_3NO\cdot 2H_2O$ (1.73 g, 15.6 mmol) and aqueous OsO_4 (2.75 mL, 0.45 mmol, 4% w/w). Then the resulting mixture was stirred at rt for 14 h. Upon addition of $NaIO_4$ (5.81 g, 27.2 mmol), the reaction mixture was stirred at rt for 4 h, quenched with saturated aqueous $Na_2S_2O_3$, and extracted with ethyl acetate (3 × 50 mL), washed with brine, dried ($MgSO_4$), filtered, concentrated, and recrystallized from hexane to give aldehyde **11** as a yellow crystal (2.12 g, 90% yield). Mp 120−122 °C; $[\alpha]^{20}_D$ −10.0 (*c* 1.0, $CHCl_3$); IR (KBr) 1728, 1674 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.77 (d, J = 3.3 Hz, 1H), 7.40−7.26 (m, 5H), 4.56 (d, J = 1.8 Hz, 1H), 3.66 (dd, J = 3.3, 1.8 Hz, 1H), 1.37 (s, 9H), 1.27 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0, 159.0, 142.7, 129.1, 128.4, 125.8, 68.9, 57.6, 54.3, 53.8, 29.0, 28.8. Anal. Calcd for $C_{18}H_{26}N_2O_2$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.29; H, 8.54; N, 9.12.

Synthesis of Compound 12. To a solution of aldehyde **11** (2.10 g, 6.9 mmol) in CH_2Cl_2 (40 mL) was added methyl

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(12) (a) Elworthy, T. R.; Brill, E. R.; Caires, C. C.; Kim, W.; Lach, L. K.; Tracy, J. L.; Chiou, S.-S. *Bioorg. Med. Chem.* **2005**, *15*, 2523. (b) Garrido, N. M.; García, M.; Díez, D.; Sánchez, M. R.; Sanz, F.; Urones, J. G. *Org. Lett.* **2008**, *10*, 1687.
(13) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373.

(triphenylphosphoranylidene)acetate (2.55 g, 7.6 mmol). Upon stirring at rt for 4 h, the reaction mixture was concentrated and purified by flash chromatography (silica gel, hexane:ethyl acetate = 8:1, v/v) to give compound **12** as a colorless oil (2.44 g, 99% yield). $[\alpha]^{20}_D$ −66.9 (*c* 1.0, $CHCl_3$); IR (KBr) 1728, 1690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.25 (m, 5H), 7.04 (dd, *J* = 15.6, 7.8 Hz, 1H), 5.97 (d, *J* = 15.6 Hz, 1H), 4.18 (d, *J* = 1.5 Hz, 1H), 3.81 (dd, *J* = 7.8, 1.5 Hz, 1H), 3.78 (s, 3H), 1.32 (s, 9H), 1.27 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 158.9, 149.1, 143.4, 129.1, 128.2, 125.8, 121.5, 62.7, 62.3, 53.9, 53.7, 52.0, 28.7; HRMS calcd for $C_{21}H_{31}N_2O_3$ (M + 1) 359.2329, found 359.2332.

Synthesis of Compound 13. A suspension of compound **12** (2.40 g, 6.7 mmol) and palladium on activated carbon (10 wt %) (0.24 g) in MeOH (100 mL) was stirred under H_2 atmosphere (ballon) at rt for 2 h. The reaction mixture was filtered through Celite and concentrated to give compound **13** as a colorless oil (2.41 g, 99% yield). $[\alpha]^{20}_D$ +6.0 (*c* 1.0, $CHCl_3$); IR (KBr) 1739, 1686 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36−7.21 (m, 5H), 4.18 (s, 1H), 3.69 (s, 3H), 3.21 (dd, *J* = 7.5, 2.4 Hz, 1H), 2.58−2.36 (m, 2H), 2.06−1.84 (m, 2H), 1.36 (s, 9H), 1.28 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 158.7, 144.2, 128.9, 127.8, 125.6, 61.1, 60.9, 53.5, 52.9, 52.0, 30.7, 29.0; HRMS calcd for $C_{21}H_{33}N_2O_3$ (M + 1) 361.2486, found 361.2490.

Synthesis of Compounds 14 and 15. To a solution of compound **13** (2.30 g, 6.4 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added CF_3CO_2H (25 mL) dropwise over 30 min. The reaction mixture was then warmed to room temperature slowly, stirred at room temperature for 10 h, and concentrated. The resulting residue was dissolved in CH_2Cl_2 (100 mL), washed with saturated aqueous Na_2CO_3 and brine, dried ($MgSO_4$), filtered, and concentrated to give a mixture of compounds **14** and **15** as a colorless oil (1.91 g, 98% yield) (the ratio of compound **14** to **15** is 15 to 1 based on ^1H NMR). $[\alpha]^{20}_D$ −13.4 (*c* 1.0, $CHCl_3$); IR (KBr) 1737, 1688 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.26 (m, 5H), 4.64 (br s, 1H), 4.37 (d, *J* = 3.3 Hz, 1H), 3.67 (s, 3H), 3.23−3.16 (m, 1H), 2.45−2.36 (m, 2H), 1.99−1.81 (m, 2H), 1.28 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 161.7, 144.2, 128.9, 127.8, 125.9, 65.4, 58.2, 54.0, 51.8, 31.5, 29.7, 28.8; HRMS calcd for $C_{17}H_{25}N_2O_3$ (M + 1) 305.1860, found 305.1861.

Synthesis of Compound 16. To a stirred solution of compounds **14** and **15** (1.76 g, 5.8 mmol) in THF (12 mL) at −78 °C was added dropwise sodium bis(trimethylsilyl)amide (1.0 M solution in THF, 6.1 mL, 6.1 mmol) over 10 min. After 15 min of stirring at −78 °C, a solution of 4-nitrobenzenesulfonyl chloride (1.54 g, 6.9 mmol) in THF (8 mL) was added dropwise at −78 °C over 10 min. The reaction mixture was stirred at −78 °C for another 2 h and allowed to warm to 0 °C slowly. Upon addition of water (30 mL), the mixture was extracted with ethyl acetate (3 × 50 mL), washed with brine, dried ($MgSO_4$), filtered, concentrated, and purified by flash chromatography (silica gel, hexane:ethyl acetate = 6:1, v/v) to give a white solid (2.45 g, 86% yield) that was recrystallized from hexanes (15 mL) and ethyl acetate (10 mL) to give compound **16** as a white crystal (2.05 g, 72%). Mp 131−132 °C; $[\alpha]^{20}_D$ +37.6 (*c* 1.0, $CHCl_3$); IR (KBr) 1727, 1532, 1397, 1350, 1174 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, *J* = 9.0 Hz, 2H), 8.19 (d, *J* = 9.0 Hz, 2H), 7.34−7.22 (m, 3H), 6.92 (d, *J* = 6.9 Hz, 2H), 4.42 (s, 1H), 3.98−3.93 (m, 1H), 3.71 (s, 3H), 2.49 (t, *J* = 7.5 Hz, 2H), 2.25−2.12 (m, 2H), 1.24 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 152.1, 150.6, 144.6, 141.3, 129.8, 129.4, 128.8, 125.1, 124.1, 62.6, 62.2, 55.6, 52.1, 30.6, 29.0, 28.2. Anal. Calcd for $C_{23}H_{27}N_3O_7S$: C, 56.43; H, 5.56; N, 8.58. Found: C, 56.66; H, 5.68; N, 8.72.

Synthesis of Compound 17. To $MeSO_3H$ (5 mL) was added compound **16** (1.69 g, 3.5 mmol) at rt. After being stirred for 1 h, the reaction mixture was added dropwise to saturated aqueous Na_2CO_3 (30 mL) with vigorous stirring. The white precipitate was collected by suction filtration, dried under vacuum, and recrystallized from hexane and EtOAc to give compound **17** as a white solid (1.46 g, 95% yield, > 99% ee) (the enantioselectivity was determined by HPLC, Chiralpak AD-H Column, NO. ADH0CE-FD069, hexanes:2-propanol = 85:15, v/v). Mp 123−125 °C; $[\alpha]^{20}_D$ +47.9 (*c* 1.0, $CHCl_3$); IR (KBr) 3314, 1730, 1532, 1351, 1175 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.7 Hz, 2H), 8.07 (d, *J* = 8.7 Hz, 2H), 7.36−7.22 (m, 3H), 6.94 (d, *J* = 7.5 Hz, 2H), 5.59 (s, 1H), 4.39 (s, 1H), 4.23−4.21 (m, 1H), 3.72 (s, 3H), 2.60−2.52 (m, 2H), 2.37−2.26 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 155.1, 150.6, 143.6, 140.5, 129.4, 129.0, 125.0, 124.1, 65.7, 58.3, 52.1, 30.6, 29.0. Anal. Calcd for $C_{19}H_{19}N_3O_7S$: C, 52.65; H, 4.42; N, 9.69. Found: C, 52.42; H, 4.65; N, 9.68.

Synthesis of Compound 18. A suspension of compound **17** (1.38 g, 3.2 mmol) in 60% (w/w) aqueous KOH (50 mL) was stirred at room temperature for 36 h. The resulting clear solution was diluted with water (20 mL) and adjusted to pH 5−6 with 12 N HC1. The yellow precipitate was collected by suction filtration, washed with water, and dried under vacuum to give a yellow solid (0.985 g, 79% yield). A suspension of the above yellow solid (0.860 g, 2.2 mmol) in AcOH (50 mL) was heated at reflux for 3 h. The resulting clear solution was concentrated under vacuum to give the crude product, which was recrystallized from EtOAc and MeOH to give compound **18** as a yellow solid (0.751 g, 91% yield) (72% yield for two steps). Mp 149−151 °C; $[\alpha]^{20}_D$ −7.75 (*c* 0.40, CH_3OH); IR (KBr) 3103, 1653, 1527, 1350, 1162 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 8.18 (d, *J* = 9.0 Hz, 2H), 7.76 (d, *J* = 9.0 Hz, 2H), 7.26−7.14 (m, 5H), 4.78 (d, *J* = 4.2 Hz, 1H), 3.93−3.87 (m, 1H), 2.64−2.37 (m, 2H), 2.04−1.78 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 174.5, 151.0, 148.2, 139.0, 129.3, 128.9, 128.8, 125.3, 60.6, 52.8, 28.5, 26.6; HRMS calcd for $C_{17}H_{18}N_3O_5S$ (M + 1) 376.0962, found 376.0964.

Synthesis of Compound 19. A suspension of compound **18** (0.60 g, 1.6 mmol), 2-methoxybenzyl chloride (0.376 g, 2.4 mmol), sodium iodide (0.024 g, 0.16 mmol), and cesium carbonate (0.78 g, 2.4 mmol) in DMF (4 mL) was heated at 80 °C for 5 h. The resulting reaction mixture was diluted with water (50 mL), extracted with EtOAc (3 × 50 mL), washed with brine, dried ($MgSO_4$), filtered, concentrated, and purified by flash chromatography (silica gel, CH_2Cl_2:MeOH = 100:1, v/v) to give compound **19** as a yellow solid (0.751 g, 94% yield). Mp 135−137 °C; $[\alpha]^{20}_D$ −100.2 (*c* 1.0, $CHCl_3$); IR (KBr) 3206, 1666 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.7 Hz, 2H), 7.59 (d, *J* = 8.7 Hz, 2H), 7.50−7.36 (m, 5H), 7.05 (t, *J* = 7.2 Hz, 1H), 6.85 (d, *J* = 7.5 Hz, 1H), 6.66 (t, *J* = 7.5 Hz, 1H), 6.37 (d, *J* = 7.8 Hz, 1H), 6.21 (s, 1H), 5.09−5.07 (m, 1H), 4.77−4.72 (m, 1H), 3.66 (d, *J* = 15.6 Hz, 1H), 3.46 (s, 3H), 3.26 (d, *J* = 15.6 Hz, 1H), 2.67−2.63 (m, 2H), 2.26−2.15 (m, 1H), 2.00−1.85 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 156.8, 149.4, 147.2, 137.8, 131.3, 129.4, 128.9, 128.8, 127.9, 123.7, 123.0, 120.0, 109.6, 59.6, 58.6, 54.7, 44.4, 31.4, 20.4; HRMS calcd for $C_{25}H_{26}N_3O_6S$ (M + 1) 496.1537, found 496.1541.

Synthesis of Compound 6. A mixture of compound **19** (0.731 g, 1.5 mmol), PhSH (0.25 g, 2.3 mmol), K_2CO_3 (0.21 g, 1.5 mmol), and DMSO (4 mL) was stirred at room temperature for 3 h. The reaction mixture was diluted with water (20 mL), extracted with EtOAc (3 × 30 mL), washed with brine, dried ($MgSO_4$), filtered, concentrated, and purified by flash chromatography (silica gel, CH_2Cl_2:MeOH = 25:1, v/v) to give compound **6** as a yellow oil (0.368 g, 79% yield). $[\alpha]^{20}_D$ +40.5 (*c* 1.0, $CHCl_3$); IR (KBr) 3201, 3063, 1660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42−7.25 (m, 5H), 7.19 (td, *J* = 8.1, 1.5 Hz, 1H), 7.07 (d, *J* = 7.5 Hz, 1H), 6.85 (t, *J* = 7.2 Hz, 1H), 6.73 (d, *J* = 8.1 Hz, 1H), 5.90 (br s, 1H), 4.74 (d, *J* = 3.3 Hz, 1H), 3.77 (d, *J* = 13.8 Hz, 1H), 3.56 (d, *J* = 13.8 Hz, 1H), 3.50 (s, 3H), 3.08−3.00 (m, 1H), 2.79−2.66 (m, 1H), 2.43−2.33 (m, 1H), 2.10−2.00 (m, 1H), 1.91−1.80 (m, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 157.5, 138.6, 129.5, 128.7, 128.3, 128.1, 127.6, 127.0, 120.3, 110.0, 60.7, 54.9, 52.9, 46.4, 27.5, 23.5. Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.80; H, 6.97; N, 9.19.

Synthesis of (+)-CP-99,994. To a solution of compound **6** (0.328 g, 1.06 mmol) in THF (3 mL) was added borane dimethyl sulfide in THF (2.0 M, 2.8 mL, 5.6 mmol) under argon. The reaction mixture was heated at reflux for 18 h. After the reaction mixture was cooled to room temperature, MeOH (5 mL) was added dropwise (cautiously) to decompose the excess borane dimethyl sulfide. The resulting mixture was then concentrated. EtOH (9 mL) and powdered K_2CO_3 (0.311 g, 2.25 mmol) were added. The resulting mixture was heated at reflux for 18 h, cooled, and concentrated. Water (20 mL) was added to the resulting residue. The mixture was extracted with CH_2Cl_2 (4 $\times$ 20 mL), dried ($MgSO_4$), filtered, and concentrated. Then the residue was dissolved in a minimum amount of CH_2Cl_2 (2 mL), followed by addition of saturated HCl-ether (50 mL). After the solution was stirred for 2 h, white solids were collected by filtration and recrystallized from hot MeOH−EtOH (1:1, v/v) to give the 2HCl salt of (+)-CP-99,994 (**1**) as a white crystalline solid (0.31 g, 80% yield). Mp 253−255 °C; $[\alpha]^{20}_D$ +77.3 (*c* 1.0, MeOH); IR (KBr) 3461, 3386, 1603, 1491, 1440 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 7.76−7.68 (m, 2H), 7.62−7.52 (m, 3H), 7.40 (td, J = 7.8, 1.5 Hz, 1H), 7.21 (dd, J = 7.8, 1.5 Hz, 1H), 6.98−6.92 (m, 2H), 5.03 (d, J = 3.6 Hz, 1H), 4.14 (d, J = 13.2 Hz, 1H), 4.06−3.98 (m, 1H), 3.87 (d, J = 13.2 Hz, 1H), 3.70 (s, 3H), 3.72−3.62 (m, 1H), 3.38−3.28 (m, 1H), 2.55−2.40 (m, 2H), 2.34−2.22 (m, 1H), 2.06−1.94 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 159.0, 133.0, 132.84, 132.80, 131.2, 130.9, 128.4, 122.0, 119.0, 111.9, 60.4, 58.4, 56.1, 49.1, 45.6, 25.3, 17.8. Anal. Calcd for $C_{19}H_{26}Cl_2N_2O$: C, 61.79; H, 7.10; N, 7.58. Found: C, 61.53; H, 6.96; N, 7.74.

A suspension of the 2HCl salt of (+)-CP-99,994 (**1**) (0.105 g, 0.28 mmol) in CH_2Cl_2 (5 mL) and 1 N NaOH (10 mL) was stirred at room temperature for 15 min. Then the mixture was extracted with CH_2Cl_2 (3 $\times$ 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to give (+)-CP-99,994 as a yellow oil (0.075 g, 89% yield, >99% ee) (the enantioselectivity was determined by HPLC, Chiralcel OD-H Column, NO. ODHOCE-ME069, hexanes:2-propanol = 90:10). $[\alpha]^{20}_D$ + 69.8 (*c* 1.0, $CHCl_3$); IR (KBr) 3329, 1492, 1461, 1241 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.18 (m, 5H), 7.15 (td, J = 8.1, 1.5 Hz, 1H), 6.97 (dd, J = 7.2, 1.2 Hz, 1H), 6.80 (t, J = 7.8 Hz, 1H), 6.67 (d, J = 8.1 Hz, 1H), 3.87 (d, J = 2.1 Hz, 1H), 3.68 (d, J = 13.8 Hz, 1H), 3,43 (s, 3H), 3.41 (d, J = 13.8 Hz, 1H), 3.31−3.24 (m, 1H), 2.85−2.73 (m, 2H), 2.19−2.10 (m, 1H), 2.01−1.82 (m, 3H), 1.65−1.53 (m, 1H), 1.44−1.34 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 142.3, 129.7, 128.2, 127.9, 126.6, 126.3, 120.0, 109.8, 64.0, 54.8, 54.6, 47.8, 46.8, 28.1, 20.3; HRMS calcd for $C_{19}H_{25}N_2O$ (M + 1) 297.1961, found 297.1965.

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Supporting Information Available: The synthetic procedure for ligand *ent*-**5**, the X-ray structure of (+)-CP-99,994 (**1**) (2HCl), and the data for the determination of the enantiomeric excess of compounds **9**, **17**, and **1** along with the NMR spectra for ligand *ent*-**5** and compounds **1**, **6**, **9**, and **11**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.