Catalytic Asymmetric Synthesis of Piperidine Derivatives Through the [4+2] Annulation of Imines with Allenes

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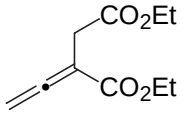
SUPPORTING INFORMATION

I. General

Me-BPE, Et-BPE, TANGPHOS, and BINAPINE were purchased from Strem Chemicals. Phosphines **1-4** were provided by Degussa (we also prepared phosphines **1**, **5**, and **6** according to previously reported procedures[1]). The imines were synthesized according to the method of Obrecht.[2] The allenes (Table 2, entries 2 and 4) were prepared according to the method of Kwon.[3] All other materials were purchased from commercial suppliers. CH_2Cl_2 was purified by passage through a neutral alumina column under argon.

II. Preparation of Allenes[4]

The yields have not been optimized.



General procedure: 2-Vinylidenesuccinic acid diethyl ester. (Carbethoxymethylene)triphenylphosphorane (5.24 g, 15.0 mmol, 1.0 equiv), anhydrous $CHCl_3$ (50 mL), and ethyl bromoacetate (2.76 g, 16.6 mmol, 1.10 equiv) were added to a 250-mL round-bottom flask. The flask was fitted with a condenser, and the reaction mixture was heated to reflux for 45 h. The reaction mixture was then cooled to room temperature, treated with NEt_3 (4.40 mL, 3.35 g, 33.1 mmol, 2.20 equiv), and stirred at room temperature for 1.5 h. Acetyl chloride (1.07 mL, 1.18 g, 15.0 mmol, 1.00 equiv) was then added dropwise over 40 min. The reaction mixture was stirred overnight, and then it was concentrated under reduced pressure. The residue was filtered through a short column of silica gel (25% EtOAc/hexanes), which removed most of the triphenylphosphine oxide. The material was then carefully purified by chromatography (3→10% EtOAc/hexanes), which yielded a clear colorless oil (1.97 g, 66%).

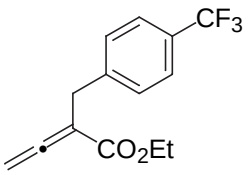
R_f 0.48 (30% EtOAc / hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24 (t, *J* = 2.2 Hz, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.28 (t, *J* = 2.2 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 214.6, 170.6, 166.4, 94.7, 79.6, 61.5, 61.1, 34.9, 14.30, 14.28.

IR (film) 1972, 1738, 1712, 1264 cm^{-1}.

HRMS (EI) calcd for $C_{10}H_{15}O_4$ [M+H^+] 199.0970, found: 199.0965.



2-(4-(Trifluoromethyl)benzyl)buta-2,3-dienoic acid ethyl ester. The general procedure was followed (phosphorane: 3.52 g, 10.1 mmol, 1.0 equiv; $CHCl_3$: 50 mL; benzyl bromide: 2.54 g, 10.6 mmol, 1.05 equiv; NEt_3: 3.10 mL, 2.25 g, 22.2 mmol, 2.2 equiv; AcCl: 0.72 mL, 0.79 g, 10.1 mmol, 1.0 equiv), except that the reaction was refluxed for 64 h. The desired allene was isolated as a clear, colorless oil (1.55 g, 57%).

R_f 0.84 (30% EtOAc / hexanes).

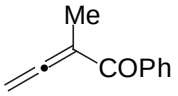
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 5.14 (m, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.56-3.63 (m, 2H), 1.27 (t, *J* = 7.0 Hz, 3H).

^{19}F NMR (377 MHz, $CDCl_3$) δ –66.7.

^{13}C NMR (100 MHz, $CDCl_3$) δ 214.6, 166.8, 143.4, 129.4, 129.1, 125.8, 125.4, 99.8, 79.8, 61.5, 35.0, 14.4.

IR (film) 2987, 1969, 1939 (C=O), 1713, 1619, 1327, 1260, 1163, 1111, 1067, 1020, 853 cm^{-1}.

HRMS (ESI) calcd for $C_{14}H_{13}F_3NaO_2$ [M+Na^+] 293.0760, found: 293.0754.



2-Methyl-1-phenyl-buta-2,3-dien-1-one. The general procedure was followed, except that benzoylmethylenetriphenylphosphorane (1.46 g, 3.84 mmol, 1.0 equiv) and MeI (0.68 g, 4.80 mmol, 1.25 equiv) were used. The reaction mixture allowed to reflux for 40 h, and the product was purified by column chromatography (5→8% EtOAc / hexanes), which furnished a clear, colorless oil (202 mg, 33%).

R_f 0.74 (30% EtOAc / hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77-7.79 (m, 2H), 7.50-7.52 (m, 1H), 7.28-7.43 (m, 2H), 5.04 (m, 2H), 2.04 (m, 2H).

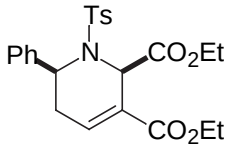
^{13}C NMR (100 MHz, $CDCl_3$) δ 217.8, 195.3, 138.3, 132.1, 129.2, 128.0, 102.2, 78.6, 14.9.

IR (film) 1934, 1651, 1281, 1003 cm^{-1}.

HRMS (ESI) calcd for $C_{11}H_{10}NaO$ [M+Na^+] 181.0624, found: 181.0620.

III. Catalytic Asymmetric Synthesis of Piperidine Derivatives

General Procedure. In a glove box, the imine (0.250 mmol, 1.0 equiv) and then catalyst **1** (4.6 mg, 0.012 mmol, 5%) were added to an oven-dried 25-mL vial. These solids were dissolved in anhydrous CH_2Cl_2 (1.5 mL), and then a solution of the allene (0.300 mmol, 1.2 equiv) in CH_2Cl_2 (0.9 mL) was added dropwise over 2 min. The vessel that had originally contained the allene was washed with CH_2Cl_2 (0.1 mL), and this CH_2Cl_2 solution was added to the reaction mixture. The vial was capped and removed from the glove box, and the reaction mixture was stirred for 16 h. It was then concentrated, and the diastereomeric ratio was determined by ^{1}H NMR analysis. The tetrahydropyridine was purified by column chromatography (10→30% EtOAc / hexanes; in most instances, it was possible to separate the diastereomers).



(2*R*,6*S*)-6-Phenyl-1-(toluene-4-sulfonyl)-1,2,5,6-tetrahydro-pyridine-2,3-dicarboxylic acid diethyl ester (Table 2, entry 1). Catalyst: (*R*)-**1**. Viscous, colorless oil; run 1: 104 mg (91%; 98% ee, 91:9 dr); run 2: 108 mg (94%; 98% ee, 91:9 dr).

R_f 0.25 (30% EtOAc / hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 6.6 Hz, 2H), 7.33 (d, *J* = 9.2 Hz, 2H), 7.18-7.21 (m, 4H), 7.10-7.12 (m, 2H), 5.64 (s, 1H), 5.15 (d, *J* = 7.1 Hz, 1H), 4.18-4.26 (m, 2H), 3.47-3.54 (m, 1H), 3.34-3.39 (m, 1H), 2.65-2.70 (m, 1H), 2.46-2.52 (m, 1H), 2.46 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.96 (t, *J* = 7.1 Hz, 3H).

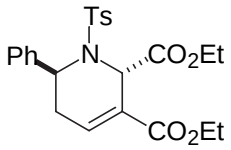
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 164.8, 144.1, 137.3, 137.1, 136.5, 129.9, 128.7, 128.22, 128.19, 128.15, 127.9, 61.6, 61.1, 52.12, 52.09, 26.2, 21.8, 14.3, 13.8.

IR (film) 2983, 1740, 1713 (C=O), 1452, 1347, 1260, 1163, 1101, 1029, 895, 816, 724, 660 cm^{-1}.

HRMS (EI) calcd for $C_{24}H_{27}NO_6S$ [M^+] 457.1554, found: 457.1573.

The enantiomeric excess was determined by chiral HPLC analysis: Chiracel AD-H, 5.0% *i*-PrOH:hexanes, 1.0 mL / min; (2*S*,6*R*): t_r: 38.8 min; (2*R*,6*S*): t_r: 42.4 min.

$[\alpha]^{22}_D$ +81.7° (*c* = 1.00, $CHCl_3$).



***trans*-6-Phenyl-1-(toluene-4-sulfonyl)-1,2,5,6-tetrahydro-pyridine-2,3-dicarboxylic acid diethyl ester**. The pure trans diastereomer can be isolated by crystallization from EtOAc / Et_2O / hexanes of diastereomerically enriched samples from column chromatography.

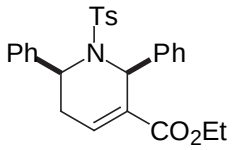
Mp 117-118 °C.

R_f 0.36 (30% EtOAc / hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.26 (m, 3H), 7.10-7.12 (m, 1H), 6.97-7.05 (m, 6H), 5.90 (s, 1H), 4.92-4.97 (m, 1H), 4.26-4.33 (m, 4H), 3.08-3.16 (m, 1H), 2.79-2.84 (m, 1H), 2.33 (s, 3H), 1.33-1.37 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 164.5, 142.8, 140.1, 138.5, 137.5, 129.3, 128.9, 128.6, 127.9, 127.7, 127.3, 62.2, 61.4, 57.3, 56.4, 30.4, 21.6, 14.4.

IR (film) 2982, 1739, 1717 (C=O), 1454, 1291, 1248, 1157, 1094, 1031, 814, 751, 697, 670 cm^{-1}.

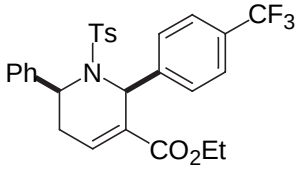


(2*S*,6*S*)-2,6-Diphenyl-1-(toluene-4-sulfonyl)-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid ethyl ester (Table 2, entry 2) [528853-89-6]. Catalyst: (*R*)-**1**. White crystalline solid; run 1: 91 mg (78%; 89% ee, >99:1 dr); run 2: 90 mg (78%; 85% ee, >99:1 dr).

Mp 160-162 °C.

The enantiomeric excess was determined by chiral HPLC analysis: Chiracel AD-H, 5.0% *i*-PrOH:hexanes, 1.0 mL / min; (2*S*,6*S*): t_r: 36.3 min; (2*R*,6*R*): t_r: 41.9 min.

$[\alpha]^{21}_D$ +148° (*c* = 1.00, $CHCl_3$).



(2*S*,6*S*)-6-Phenyl-1-(toluene-4-sulfonyl)-2-(4-trifluoromethylphenyl)-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid ethyl ester (Table 2, entry 3). Catalyst: (*R*)-**1**. Clear, colorless crystals; run 1: 107 mg (81%; 91% ee, >99:1 dr); run 2: 106 mg (80%; 85% ee, >99:1 dr).

Mp 168 °C.

R_f 0.60 (30% EtOAc / hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.23-7.26 (m, 1H), 7.12 (d, *J* = 8.2 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.88-6.97 (m, 5H), 6.15 (s, 1H), 5.27 (d, *J* = 6.9 Hz, 1H), 4.05-4.13 (m, 2H), 2.72-2.77 (m, 1H), 2.46 (s, 3H), 2.13-2.19 (m, 1H), 1.09 (t, *J* = 7.1 Hz, 3H).

^{19}F NMR (282 MHz, $CDCl_3$) δ 97.9.

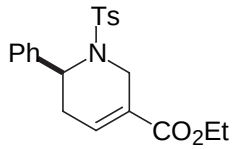
^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 144.1, 142.9, 138.4, 137.6, 137.3, 130.2, 130.0, 128.8, 128.1, 128.0, 127.3, 125.6, 124.5, 124.4, 122.9, 61.2, 53.9, 51.9, 25.0, 21.8, 14.2.

IR (film) 3061, 1641 (C=O), 1342, 1162, 1093, 702 cm^{-1}.

HRMS (EI) calcd for $C_{28}H_{27}F_3NO_4S$ [M+H$^+$] 530.1613, found: 530.1734.

The enantiomeric excess was determined by chiral HPLC analysis: Chiracel AD-H, 5.0% *i*-PrOH:hexanes, 1.0 mL / min; (2*S*,6*S*): t_r: 15.6 min; (2*R*,6*R*): t_r: 37.4 min.

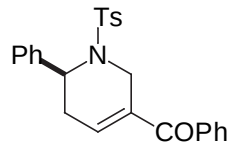
$[\alpha]^{21}_D$ +152° (*c* = 1.00, $CHCl_3$).



(6*S*)-Phenyl-1-(toluene-4-sulfonyl)-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid ethyl ester (Table 2, entry 4) [528853-66-9]. Catalyst: (*R*)-**1**. Oily semi-solid; run 1: 71 mg (74%; 69% ee); run 2: 68 mg (70%; 67% ee).

The enantiomeric excess was determined by chiral HPLC analysis: Chiracel AS, 20.0% *i*-PrOH:hexanes, 1.0 mL / min; (6*R*): t_r: 19.6 min; (6*S*): t_r: 25.7 min.

$[\alpha]^{22}_D$ +29.9° (*c* = 1.00, $CHCl_3$).



(6*S*)-Phenyl-[6-phenyl-1-(toluene-4-sulfonyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-methanone (Table 2, entry 5). Catalyst: (*R*)-**1**. White amorphous solid; run 1: 103 mg (99%; 77% ee); run 2: 98 mg (94%; 74% ee).

Mp 148-149 °C.

R_f 0.36 (30% EtOAc / hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.49-7.55 (m, 3H), 7.44 (d, *J* = 7.3 Hz, 2H), 7.28-7.33 (m, 7H), 6.62-6.66 (m, 1H), 5.46-5.48 (m, 1H), 4.62 (d, *J* = 18.6 Hz, 1H), 3.64 (d, *J* = 18.6 Hz, 1H), 2.73 (br s, 2H), 2.45 (s, 3H).

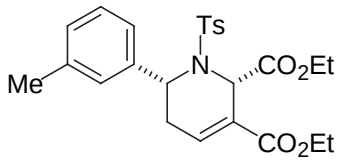
^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 143.6, 139.8, 138.5, 137.4, 137.2, 135.4, 132.3, 129.9, 129.3, 128.8, 128.4, 128.2, 128.0, 127.3, 52.6, 39.9, 27.3, 21.7.

IR (film) 3061, 1641 (C=O), 1342, 1162, 1093, 702 cm^{-1}.

HRMS (EI) calcd for $C_{25}H_{23}NO_3S$ [M^+] 417.1393, found: 417.1390.

The enantiomeric excess was determined by chiral HPLC analysis: Chiracel AS, 20.0% *i*-PrOH:hexanes, 1.0 mL / min; (6*R*): t_r: 43.7 min; (6*S*): t_r: 68.4 min.

$[\alpha]^{22}_D$ +66.3° (*c* = 1.00, $CHCl_3$).



(2*S*,6*R*)-1-(Toluene-4-sulfonyl)-6-*m*-tolyl-1,2,5,6-tetrahydro-pyridine-2,3-dicarboxylic acid diethyl ester (Table 3, entry 2). Catalyst: (*S*)-**1**. Viscous, colorless oil; run 1: 117 mg (99%; 98% ee, 93:7 dr); run 2: 113 mg (96%; 97% ee, 93:7 dr).

R_f 0.35 (30% EtOAc / hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.16-7.18 (m, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.80 (s, 1H), 5.65 (s, 1H), 5.09 (d, *J* = 6.9 Hz, 1H), 4.17-4.28 (m, 2H), 3.51-3.55 (m, 1H), 3.33-3.38 (m, 1H), 2.62-2.64 (m, 1H), 2.46-2.50 (m, 1H), 2.46 (s, 3H), 2.21 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 0.96 (t, *J* = 7.1 Hz, 3H).

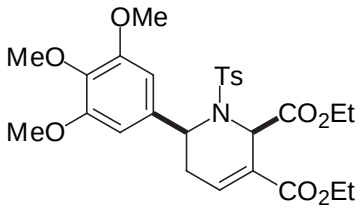
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 164.8, 144.0, 137.7, 137.4, 137.1, 136.7, 129.8, 129.6, 128.8, 128.0, 127.9, 125.4, 61.5, 61.1, 52.1, 51.9, 26.3, 21.7, 21.5, 14.3, 13.8.

IR (film) 2982, 1739, 1715 (C=O), 1261, 1162, 1100, 1029, 720, 659 cm^{-1}.

HRMS (EI) calcd for $C_{25}H_{29}NO_6S$ [M^+] 471.1710, found: 471.1722.

The enantiomeric excess was determined by chiral HPLC analysis: Chiracel OD, 5.0% *i*-PrOH:hexanes, 1.0 mL / min; (2*R*,6*S*): t_r: 24.2 min; (2*S*,6*R*): t_r: 35.6 min.

$[\alpha]^{22}_D$ –72.3° (*c* = 1.00, $CHCl_3$).



(2*R*,6*S*)-1-(Toluene-4-sulfonyl)-6-(3,4,5-trimethoxyphenyl)-1,2,5,6-tetrahydro-pyridine-2,3-dicarboxylic acid diethyl ester (Table 3, entry 3). Catalyst: (*R*)-**1**. White amorphous solid; run 1: 125 mg (83%; 97% ee, 96:4 dr); run 2: 132 mg (88%; 95% ee, 96:4 dr). The product can be recrystallized from Et_2O / EtOAc / hexanes, which affords white microcrystals.

Mp 129 °C.

R_f 0.41 (60% EtOAc / hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 6.6 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.20-7.22 (m, 1H), 6.26 (s, 2H), 5.76 (s, 1H), 5.03-5.06 (m, 1H), 4.23-4.29 (m, 2H), 3.78 (s, 3H), 3.70 (s, 6H), 3.62-3.67 (m, 1H), 3.51-3.56 (m, 1H), 2.64-2.66 (m, 2H), 2.46 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 0.97 (t, *J* = 7.2 Hz, 3H).

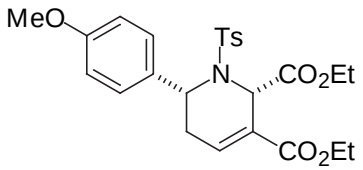
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 164.8, 152.8, 144.0, 137.6, 137.5, 136.3, 132.9, 129.8, 128.5, 128.0, 105.7, 61.6, 61.1, 60.7, 56.1, 52.5, 51.9, 27.2, 21.7, 14.3, 13.8.

IR (film) 2982, 1734, 1714 (C=O), 1594, 1510, 1463, 1336, 1254, 1162, 1128, 1030, 817, 729, 659 cm^{-1}.

HRMS (EI) calcd for $C_{27}H_{33}NO_9S$ [M^+] 547.1871, found: 547.1878.

The enantiomeric excess was determined by chiral HPLC analysis: Chiracel OD, 15.0% *i*-PrOH:hexanes, 1.0 mL / min; (2*S*,6*R*): t_r: 21.4 min; (2*R*,6*S*): t_r: 38.4 min.

$[\alpha]^{22}_D$ +34.4° (*c* = 1.00, $CHCl_3$).



(2*S*,6*R*)-6-(4-Methoxyphenyl)-1-(toluene-4-sulfonyl)-1,2,5,6-tetrahydro-pyridine-2,3-dicarboxylic acid diethyl ester (Table 3, entry 4). Catalyst: (*S*)-**1**. Viscous, pale-yellow oil; run 1: 52 mg (43%; 98% ee, 93:7 dr); run 2: 49 mg (40%; 98% ee, 93:7 dr). Unreacted imine and allene comprised the balance of the material.

R_f 0.32 (30% EtOAc / hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 6.6 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.16 (br s, 1H), 7.01 (d, *J* = 6.8 Hz, 2H), 6.71 (d, *J* = 6.7 Hz, 2H), 5.63 (s, 1H), 5.10 (d, *J* = 6.8 Hz, 1H), 4.17-4.25 (m, 2H), 3.73 (s, 3H), 3.55-3.59 (m, 1H), 3.40-3.45 (m, 1H), 2.60-2.62 (m, 1H), 2.48-2.51 (m, 1H), 2.46 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.99 (t, *J* = 7.2 Hz, 3H).

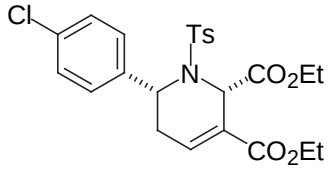
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 164.9, 159.4, 144.0, 137.4, 136.6, 130.0, 129.9, 129.0, 128.1, 127.9, 113.4, 61.6, 61.1, 55.4, 52.0, 51.6, 26.4, 21.8, 14.3, 13.8.

IR (film) 2983, 1738, 1714 (C=O), 1514, 1299, 1256, 1163, 1101, 1030, 895, 830, 722, 660, 552 cm^{-1}.

HRMS (EI) calcd for $C_{25}H_{29}NO_7S$ [M^+] 487.1659, found: 487.1693.

The enantiomeric excess was determined by chiral HPLC analysis: Chiracel AD-H, 7.0% *i*-PrOH:hexanes, 1.0 mL / min; (2*S*,6*R*): t_r: 39.6 min; (2*R*,6*S*): t_r: 48.9 min.

$[\alpha]^{21}_D$ –54.8° (*c* 1.00, $CHCl_3$).



(2*S*,6*R*)-6-(4-Chlorophenyl)-1-(toluene-4-sulfonyl)-1,2,5,6-tetrahydro-pyridine-2,3-dicarboxylic acid diethyl ester (Table 3, entry 5). Catalyst: (*S*)-**1**. White amorphous solid; run 1: 122 mg (99%; 96% ee, 91:9 dr); run 2: 120 mg (98%; 96% ee, 91:9 dr). The product can be recrystallized from Et_2O / EtOAc / hexanes, which affords a white feathery solid.

Mp 110-111 °C.

R_f 0.38 (30% EtOAc / hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 6.5 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.15 (d, *J* = 6.8 Hz, 2H), 7.12-7.14 (m, 1H), 7.06 (d, *J* = 6.8 Hz, 2H), 5.64 (s, 1H), 5.08 (d, *J* = 6.4 Hz,

1H), 4.16-4.27 (m, 2H), 3.56-3.61 (m, 1H), 3.45-3.50 (m, 1H), 2.57-2.61 (m, 1H), 2.45-2.49 (m, 1H), 2.45 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.00 (t, *J* = 7.2 Hz, 3H).

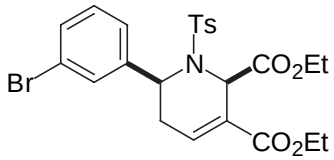
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 164.7, 144.2, 137.1, 136.2, 135.9, 134.1, 130.1, 130.0, 128.4, 128.3, 127.8, 61.7, 61.2, 52.2, 51.7, 26.3, 21.8, 14.3, 13.8.

IR (film) 2983, 1740, 1714 (C=O), 1493, 1347, 1260, 1163, 1099, 1029, 895, 817, 716, 659 cm^{-1}.

HRMS (EI) calcd for $C_{24}H_{26}ClNO_6S$ [M^+] 491.1164, found: 491.1154.

The enantiomeric excess was determined by chiral HPLC analysis: Chiracel AD-H, 5.0% *i*-PrOH:hexanes, 1.0 mL / min; (2*S*,6*R*): t_r: 39.2 min; (2*R*,6*S*): t_r: 43.3 min.

$[\alpha]^{22}_D$ –56.6° (*c* = 1.00, $CHCl_3$).



(2*R*,6*S*)-6-(3-Bromophenyl)-1-(toluene-4-sulfonyl)-1,2,5,6-tetrahydro-pyridine-2,3-dicarboxylic acid diethyl ester (Table 3, entry 6). Catalyst: (*R*)-**1**. Foamy white solid; run 1: 133 mg (99%; 98% ee, 89:11 dr); run 2: 130 mg (97%; 99% ee, 89:11 dr).

Mp 50-53 °C.

R_f 0.35 (30% EtOAc / hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 6.5 Hz, 2H), 7.31-7.36 (m, 3H), 7.16-7.18 (m, 1H), 7.06-7.08 (m, 3H), 5.68 (s, 1H), 5.06 (d, *J* = 5.6 Hz, 1H), 4.18-4.29 (m, 2H), 3.62-3,67 (m, 1H), 3.48-3.53 (m, 1H), 2.60-2.65 (m, 1H), 2.54-2.59 (m, 1H), 2.48 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.06 (t, *J* = 7.2 Hz, 3H).

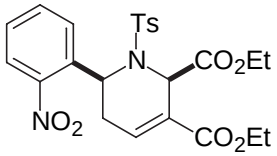
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 164.6, 144.3, 139.7, 136.9, 136.1, 132.0, 131.2, 130.0, 129.8, 128.3, 127.9, 126.8, 122.2, 61.9, 61.2, 52.0, 51.8, 26.2, 21.8, 14.3, 13.9.

IR (film) 2982, 1738, 1714 (C=O), 1261, 1163, 1098, 1028, 728, 660 cm^{-1}.

HRMS (EI) calcd for $C_{24}H_{26}BrNO_6S$ [M-CO_2Et^+] 464.0531, found: 464.0359.

The enantiomeric excess was determined by chiral HPLC analysis: Chiracel OD, 10% *i*-PrOH:hexanes, 1.0 mL / min; (2*S*,6*R*): t_r: 16.1 min; (2*R*,6*S*): t_r: 27.5 min.

$[\alpha]^{22}_D$ +64.4° (*c* = 1.00, $CHCl_3$).



(2*R*,6*S*)-6-(2-Nitrophenyl)-1-(toluene-4-sulfonyl)-1,2,5,6-tetrahydro-pyridine-2,3-dicarboxylic acid diethyl ester (Table 3, entry 7). Catalyst: (*R*)-**1**. Viscous, yellow oil; run 1: 125 mg (99%; 66% ee, 94:6 dr); run 2: 121 mg (96%; 69% ee, 97:3 dr).

R_f 0.22 (30% EtOAc / hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 7.9 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.59-7.62 (m, 3H), 7.38-7.42 (m, 1H), 7.23-7.25 (m, 2H), 7.11-7.14 (m, 1H), 5.73 (s, 1H), 5.22-5.26 (m, 1H), 4.19-4.25 (m, 2H), 3.98-4.05 (m, 2H), 2.83-2.89 (m, 1H), 2.39-2.43 (m, 1H), 2.43 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.16 (t, *J* = 7.1 Hz, 3H).

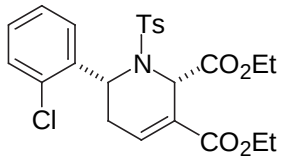
^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 163.7, 148.6, 144.4, 139.0, 136.8, 134.2, 133.5, 130.6, 129.8, 128.7, 128.5, 128.1, 124.3, 62.2, 61.4, 55.0, 52.2, 30.6, 21.7, 14.3, 14.0.

IR (film) 2983, 1740, 1716 (C=O), 1528 (NO_2), 1352 (NO_2), 1258, 1208, 1166, 1096, 1033, 816, 730, 661 cm^{-1}.

HRMS (EI) calcd for $C_{21}H_{21}N_2O_6S$ [M-CO_2Et^+] 429.1120, found: 429.1181.

The enantiomeric excess was determined by chiral HPLC analysis: Chiracel OD, 10% *i*-PrOH:hexanes, 1.0 mL / min; (2*S*,6*R*): t_r: 14.1 min; (2*R*,6*S*): t_r: 18.5 min.

$[\alpha]^{22}_D$ +86.5° (*c* = 1.00, $CHCl_3$).



(2*S*,6*R*)-6-(2-Chlorophenyl)-1-(toluene-4-sulfonyl)-1,2,5,6-tetrahydro-pyridine-2,3-dicarboxylic acid diethyl ester (Table 3, entry 8). Catalyst: (*S*)-**1**. White solid; run 1: 93 mg (76%; 61% ee, 79:21 dr); run 2: 91 mg (74%; 59% ee, 79:21 dr).

Mp 78-79 °C.

R_f 0.37 (30% EtOAc / hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.4 Hz, 2H), 7.70-7.74 (m, 1H), 7.32-7.35 (m, 1H), 7.25-7.28 (m, 2H), 7.16-7.22 (m, 3H), 5.60 (s, 1H), 5.30-5.35 (m, 1H), 4.19-4.27 (m, 2H), 3.75-3.80 (m, 1H), 3.61-3.65 (m, 1H), 2.80-2.85 (m, 1H), 2.46-2.42 (m, 1H), 2.41 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.07 (t, *J* = 7.1 Hz, 3H).

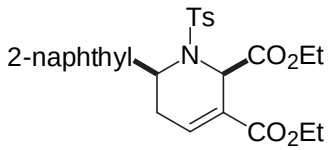
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 164.3, 144.1, 138.2, 137.1, 135.5, 134.0, 129.8, 129.65, 129.60, 129.4, 128.53, 128.48, 127.0, 61.9, 61.3, 54.0, 52.2, 29.3, 21.8, 14.4, 13.9.

IR (film) 2983, 1740, 1716 (C=O), 1354, 1259, 1167, 1096, 1034, 662 cm^{-1}.

HRMS (EI) calcd for $C_{24}H_{26}ClNO_6S$ [M^+] 491.1164, found: 491.1192.

The enantiomeric excess was determined by chiral HPLC analysis: Chiracel OD, 10% *i*-PrOH:hexanes, 1.0 mL / min; (2*R*,6*S*): t_r: 12.7 min; (2*S*,6*R*): t_r: 18.7 min.

$[\alpha]^{22}_D$ –41.3° (*c* = 1.00, $CHCl_3$).



(2*R*,6*S*)-6-Naphthalen-2-yl-1-(toluene-4-sulfonyl)-1,2,5,6-tetrahydro-pyridine-2,3-dicarboxylic acid diethyl ester (Table 3, entry 9). Catalyst: (*R*)-**1**. White amorphous solid; run 1: 123 mg (97%; 99% ee, 93:7 dr); run 2: 119 mg (94%; 98% ee, 93:7 dr). The

product can be recrystallized from Et_2O / EtOAc / hexanes, which affords a clear, colorless crystalline solid.

Mp 140-143 °C.

R_f 0.28 (30% EtOAc / hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.3 Hz, 2H), 7.69-7.75 (m, 2H), 7.67 (d, *J* = 8.6 Hz, 1H), 7.43-7.48 (m, 3H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.23-7.27 (m, 1H), 7.22 (dd, *J* = 8.6, 2.0 Hz, 1H), 5.67 (s, 1H), 5.31 (d, *J* = 7.1 Hz, 1H), 4.17-4.28 (m, 2H), 3.03-3.09 (m, 2H), 2.82-2.91 (m, 1H), 2.49-2.65 (m, 1H), 2.49 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.69 (t, *J* = 7.1 Hz, 3H).

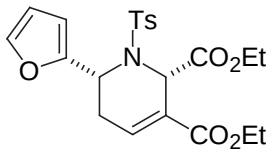
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 164.9, 144.2, 137.3, 136.6, 134.5, 133.0, 132.8, 130.0, 128.3, 128.2, 128.0, 127.9, 127.5, 127.2, 127.1, 126.7, 126.4, 61.4, 61.2, 52.4, 52.2, 26.3, 21.8, 14.4, 13.4.

IR (film) 2982, 1740, 1712 (C=O), 1261, 1164, 1100, 1029, 817, 714, 660 cm^{-1}.

HRMS (EI) calcd for $C_{28}H_{29}NO_6S$ [M^+] 507.1710, found: 507.1724.

The enantiomeric excess was determined by chiral HPLC analysis: Chiracel AD-H, 7.0% *i*-PrOH:hexanes, 1.0 mL / min; (2*S*,6*R*): t_r: 36.6 min; (2*R*,6*S*): t_r: 41.0 min.

$[\alpha]^{22}_D$ –30.4° (*c* = 1.00, $CHCl_3$).



(2*S*,6*R*)-6-Furan-2-yl-1-(toluene-4-sulfonyl)-1,2,5,6-tetrahydro-pyridine-2,3-dicarboxylic acid diethyl ester (Table 3, entry 10). Catalyst: (*S*)-**1**. Pale-yellow oil; run 1: 111 mg (99%; 97% ee, 87:13 dr); run 2: 107 mg (96%; 97% ee, 87:13 dr).

R_f 0.22 (30% EtOAc / hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 6.6 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 7.22 (s, 1H), 7.10 (br s, 1H), 6.18 (br s, 1H), 6.03 (br s, 1H), 5.61 (s, 1H), 5.21 (d, *J* = 6.5 Hz, 1H), 4.18-4.25 (m, 2H), 3.67-3.74 (m, 2H), 2.61-2.70 (m, 2H), 2.43 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.02 (t, *J* = 7.2 Hz, 3H).

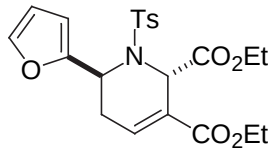
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 164.8, 150.8, 143.9, 142.5, 137.3, 135.9, 129.6, 128.0, 127.5, 110.4, 109.6, 61.7, 61.1, 51.9, 46.7, 26.8, 21.7, 14.3, 13.8.

IR (film) 2983, 1739, 1714 (C=O), 1367, 1294, 1260, 1162, 1101, 1027, 893, 816, 715, 659 cm^{-1}.

HRMS (ESI) calcd for $C_{22}H_{25}NNaO_7S$ [$M+Na^+$] 470.1244, found: 470.1260.

The enantiomeric excess was determined by chiral HPLC analysis: Chiracel OD, 5.0% *i*-PrOH:hexanes, 1.0 mL / min; (2*R*,6*S*): t_r: 26.8 min; (2*S*,6*R*): t_r: 41.8 min.

$[\alpha]^{23}_D$ –49.9° (*c* = 1.00, $CHCl_3$).



***trans*-6-Furan-2-yl-1-(toluene-4-sulfonyl)-1,2,5,6-tetrahydro-pyridine-2,3-dicarboxylic acid diethyl ester.** The trans diastereomer was isolated as a white solid after column chromatography.

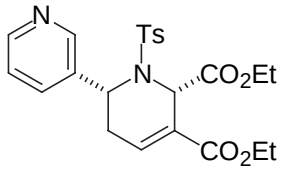
Mp 80-82 °C.

R_f 0.30 (30% EtOAc / hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.4 Hz, 2H), 7.22 (t, *J* = 4.8 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.90 (br s, 1H), 6.20 (d, *J* = 3.6 Hz, 1H), 6.13 (br s, 1H), 5.77 (s, 1H), 4.82-4.86 (m, 1H), 4.15-4.38 (m, 4H), 3.01-3.09 (m, 1H), 2.50 (m, 1H), 2.36 (s, 3H), 1.32-1.59 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 164.5, 150.2, 142.9, 142.3, 139.5, 137.6, 129.1, 128.8, 127.6, 110.3, 110.2, 62.2, 61.3, 56.6, 50.1, 29.3, 21.7, 14.4, 14.3.

IR (film) 2983, 1739, 1717 (C=O), 1301, 1256, 1158, 1094, 1070, 1029, 814, 743, 715, 657 cm^{-1}.



(2*S*,6*R*)-1-(Toluene-4-sulfonyl)-1,2,3,6-tetrahydro-[2,3']bipyridinyl-5,6-dicarboxylic acid diethyl ester (Table 3, entry 11). Catalyst: (*S*)-**1**. Isolated as an inseparable mixture of diastereomers as a viscous, pale-orange oil; run 1: 88 mg (77%; 97% ee, 91:9 dr); run 2: 86 mg (75%; 97% ee, 91:9 dr).

R_f 0.29 (EtOAc).

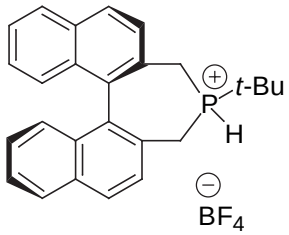
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 4.8 Hz, 1H), 8.25 (d, *J* = 2.4 Hz, 1H), 7.87 (d, *J* = 6.6 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.13-7.18 (m, 2H), 5.66 (s, 1H), 5.11 (d, *J* = 5.4 Hz, 1H), 4.18-4.25 (m, 2H), 3.58-3.60 (m, 1H), 3.43-3.49 (m, 1H), 2.60-2.66 (m, 2H), 2.46 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.00 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 164.4, 150.3, 149.2, 144.4, 136.8, 135.9, 133.0, 130.0, 129.2, 128.5, 127.8, 127.0, 123.0, 61.8, 61.2, 52.1, 50.4, 26.0, 14.3, 13.7.

IR (film, 9:1 cis:trans) 2983, 1739, 1714 (C=O), 1262, 1164, 1100, 1027, 816, 727, 563 cm^{-1}.

HRMS (EI) calcd for $C_{23}H_{27}N_2O_6S$ [M+H$^+$] 459.1590, found: 459.1570.

The enantiomeric excess was determined by chiral HPLC analysis: Chiracel AD-H, 20.0% *i*-PrOH:hexanes, 1.0 mL / min; (2*S*,6*R*): t_r: 24.8 min; (2*R*,6*S*): t_r: 42.2 min.



1·HBF$_4$. Phosphine **1** (43 mg, 0.12 mmol, 1.0 equiv) was added under a nitrogen atmosphere to a 25-mL flask. The phosphine was dissolved in CH_2Cl_2 (4.0 mL), and then 48% HBF_4 (0.1 mL) was added in one portion via syringe to the rapidly stirred solution. The reaction mixture was stirred for 15 min and then dried over anhydrous Na_2SO_4, filtered, and concentrated, yielding a fine white powder (53 mg, 99%). This phosphonium salt can be used without further purification.

Mp 278-280 ^{o}C.

^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.12 (dd, *J* = 8.4, 5.3 Hz, 2H), 8.04 (t, *J* = 7.8 Hz, 2H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.67 (d, *J* = 8.5 Hz, 1H), 7.55-7.62 (m, 2H), 7.35 (t, *J* = 8.2 Hz, 1H), 7.28 (t, *J* = 7.1 Hz, 1H), 7.19 (d, *J* = 8.6 Hz, 1H), 7.05 (d, *J* = 78.6 Hz, 1H), 6.00 (br s, 1H), 3.83-3.88 (m, 1H), 3.69-3.75 (m, 1H), 3.52 (t, *J* = 16.5 Hz, 1H), 3.23-3.30 (m, 1H), 1.45 (d, *J* = 17.9 Hz, 9H).

^{13}C NMR (100 MHz, CD_2Cl_2) δ 135.0, 134.46, 134.41, 134.21, 132.69, 132.66, 132.60, 132.59, 131.1, 130.7, 129.1, 129.0, 128.02, 127.99, 127.8, 127.63, 127.58, 127.53, 127.34, 127.27, 127.0, 30.8, 30.5, 26.1.

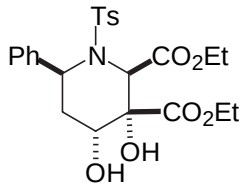
^{31}P {^{1}H} NMR (162 MHz, CD_2Cl_2) δ 44.5.

IR (film) 3411, 2918, 1384, 1053 (broad), 831, 749, 533, 522 cm^{-1}.

HRMS (ESI) calcd for $C_{26}H_{26}P$ [M^+] (no BF_4 counterion) 369.1772, found: 369.1773.

$[\alpha]^{23}_{D}$ –161° (*c* = 1.00, $CHCl_3$).

IV. Eq 2 and Scheme 1



(2*R*,3*S*,4*R*,6*S*)-3,4-Dihydroxy-6-phenyl-1-(toluene-4-sulfonyl)piperidine-2,3-dicarboxylic acid diethyl ester (eq 2).[5] $NaIO_4$ (88 mg, 0.41 mmol, 1.5 equiv) and then distilled water (0.22 mL) were added to a 50-mL flask. After the $NaIO_4$ had dissolved, the solution was cooled in an ice bath, and H_2SO_4 (6 drops of a 2 N solution) and then $RuCl_3 \cdot 2H_2O$ (2 or 3 small crystals) were added. The solution was stirred for 5 min, and then EtOAc (0.4 mL) was added. The solution was solution stirred for an additional 5 min, and then CH_3CN (0.8 mL) was added. The solution was stirred for 5 more minutes, and then a solution of the substrate (126 mg, 0.28 mmol) in EtOAc (0.6 mL) was added in one portion. The solution was stirred for 6 min at 0 °C, and then it was transferred by pipet into a solution of 10% $NaHCO_3$ (2.0 mL) and saturated Na_2SO_3 (4.6 mL). The solution was stirred for 30 min, and then it was extracted with EtOAc (3x25 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The crude diol was chromatographed on silica gel (15→50% EtOAc/hexanes). The desired product was isolated as a white crystalline solid: run 1: 108 mg (80%; racemic material); run 2: 87 mg (82%; starting material: 98% ee; product: 98% ee).

Mp 60-65 °C.

R_f 0.33 (30% EtOAc/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 6.6 Hz, 2H), 7.43 (d, *J* = 7.8 Hz, 2H), 7.22-7.32 (m, 5H), 5.37 (s, 1H), 5.26 (d, *J* = 5.4 Hz, 1H), 4.93-4.96 (m, 1H), 4.20-4.25 (m, 1H), 4.07-4.12 (m, 1H), 3.74 (d, *J* = 2.6 Hz, 1H), 3.58-3.62 (m, 1H), 3.26-3.30 (m, 1H), 3.20 (s, 1H), 2.46 (s, 3H), 2.34-2.38 (m, 1H), 1.64-1.72 (m, 1H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.11 (t, *J* = 7.1 Hz, 3H).

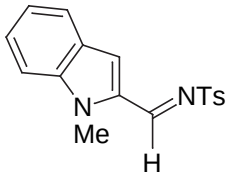
^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 168.9, 143.9, 137.3, 137.1, 129.5, 128.7, 128.3, 128.0, 127.9, 73.1, 64.3, 61.9, 61.7, 59.3, 54.3, 26.8, 21.8, 13.9, 13.8.

IR (film) 3492 (br; OH), 2982, 1734 (C=O), 1449, 1349, 1268, 1162, 1098, 1022, 989, 939, 734, 665 cm^{-1}.

HRMS (ESI) calcd for $C_{24}H_{29}NNaO_8S$ [M+Na^+] 514.1506, found: 514.1528.

The enantiomeric excess was determined by chiral HPLC analysis: Chiracel AD-H, 20% *i*-PrOH:hexanes, 0.9 mL/min; (2*S*,3*R*,4*S*,6*R*): t_r: 22.4 min; (2*R*,3*S*,4*R*,6*S*): t_r: 54.0 min.

$[\alpha]^{21}_D$ +49.3° (*c* = 1.00, $CHCl_3$).



4-Methyl-*N*-(1-methyl-1*H*-indol-2-ylmethylene)benzenesulfonamide. The title compound was prepared according to the method of Bhat.[6] To a round-bottom flask equipped with a Dean-Stark assembly was added 1-methylindole-2-carboxyaldehyde (1.30 g, 8.19 mmol, 1.0 equiv), *p*-toluenesulfonamide (1.40 g, 8.19 mmol, 1.0 equiv), powdered molecular sieves (4 Å, 0.60 g) and Amberlite (IR120 hydrogen form) in anhydrous toluene (30 mL). The reaction mixture was heated to reflux for 12 h with azeotropic removal of water. The mixture was then cooled to room temperature, filtered through a pad of Celite (washing with CH_2Cl_2), and concentrated in vacuo. The product was isolated as a bright-orange solid (2.53 g, 99%) in 98% purity. If desired, the imine can be recrystallized from EtOAc / hexanes, yielding a bright-orange solid.

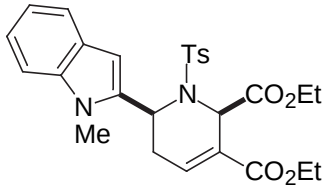
Mp 165-167 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 7.91 (d, *J* = 8.2 Hz, 2H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.32-7.43 (m, 5H), 7.17-7.19 (m, 1H), 4.12 (s, 3H), 2.46 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 144.4, 142.5, 136.2, 131.7, 129.9, 127.9, 127.8, 126.9, 123.3, 121.4, 120.3, 110.6, 32.5, 21.8.

IR (film) 2951, 1584 (C=N), 1472, 1324, 1311, 1156, 1087, 822, 715, 663 cm^{-1}.

HRMS (ESI) calcd for $C_{17}H_{16}N_2NaO_2S$ [M+Na^+] 335.0825, found 335.0816.



(2*R*,6*S*)-6-(1-Methyl-1*H*-indol-2-yl)-1-(toluene-4-sulfonyl)-1,2,5,6-tetrahydro-pyridine-2,3-dicarboxylic acid diethyl ester. This was prepared according to the standard reaction protocol, except that 10% of catalyst **1** was used. The title compound was isolated by chromatography as a pale-yellow crystalline solid. The minor diastereomer could not be removed by chromatography, but crystallization from EtOAc / hexanes furnished the diastereomerically pure cis tetrahydropyridine. Clear, colorless crystals; run 1: 126 mg (99%; 97% ee, 93:7 dr); run 2: 125 mg (98%; 97% ee, 93:7 dr).

Mp 187-188 °C.

R_f 0.29 (30% EtOAc / hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 4.9 Hz, 2H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.31 (d, *J* = 7.0 Hz, 3H), 7.19-7.23 (m, 1H), 7.02-7.05 (m, 1H), 6.80-6.85 (m, 1H), 6.28 (s, 1H), 5.59 (d, *J* = 7.4 Hz, 1H), 5.46 (s, 1H), 4.24-4.26 (m, 2H), 3.90 (s, 3H), 3.05-3.09 (m, 1H), 2.90-2.94

(m, 1H), 2.67-2.71 (m, 1H), 2.46 (s, 3H), 2.44-2.47 (m, 1H), 1.30 (t, J = 7.1 Hz, 3H), 0.77 (t, J = 7.2 Hz, 3H).

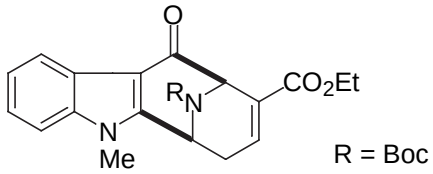
^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 165.2, 144.5, 138.2, 136.8, 135.6, 134.5, 130.0, 127.7, 127.6, 126.4, 122.6, 120.8, 119.7, 109.3, 103.4, 61.8, 61.2, 52.7, 46.4, 30.2, 26.7, 21.8, 14.4, 13.6.

IR (film) 2982, 1734, 1713 (C=O), 1470, 1350, 1303, 1258, 1165, 1098, 1067, 1026, 907, 726 cm^{-1}.

HRMS (ESI) calcd for $C_{27}H_{30}N_2NaO_6S$ [M+Na$^+$] 533.1717, found: 533.1698.

The enantiomeric excess was determined by chiral HPLC analysis: Chiracel AD-H, 20% *i*-PrOH:hexanes, 0.9 mL / min; minor diastereomer: t_r: 12.4 min; (2*S*,6*R*): t_r: 13.6 min; (2*R*,6*S*): t_r: 25.8 min.

$[\alpha]^{22}_D$ +134.8° (*c* = 1.00, $CHCl_3$).



In a 25-mL flask, (2*R*,6*S*)-6-(1-methyl-1*H*-indol-2-yl)-1-(toluene-4-sulfonyl)-1,2,5,6-tetrahydro-pyridine-2,3-dicarboxylic acid diethyl ester (125 mg, 0.25 mmol, 1.0 equiv) was treated with anhydrous $MeSO_3H$ (0.65 mL). The flask was fitted with a reflux condenser and heated to 80 °C for 1 h. Then, the reaction mixture was cooled in an ice bath and diluted with distilled water (2.0 mL). The pH of the solution was increased to pH=10 by the addition of saturated aq $NaHCO_3$. The reaction mixture was then extracted with EtOAc (3x20 mL), and the organic extracts were washed with brine (1x20 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in anhydrous THF (3.0 mL), cooled in an ice bath, and treated with NEt_3 (27 mg, 0.27 mmol, 1.1 equiv) and Boc_2O (80 mg, 0.37 mmol, 1.5 equiv). After 1 h, the ice bath was removed, and the reaction mixture was allowed to stir at room temperature for 12 h. Then, it was diluted with EtOAc and brine and extracted with EtOAc (3x25 mL). The combined organic extracts were washed with brine (1x25 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (20→60% EtOAc / hexanes), which furnished the desired product as a viscous, clear colorless oil that crystallized upon standing: 86 mg (86%; starting material: 99% ee; product: 99% ee).

Mp 218-219 °C.

R_f 0.77 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 6.6 Hz, 1H), 7.28-7.36 (m, 3H), 6.91 (br s, 1H), 5.86 (d, J = 6.7 Hz, 1H), 5.55 (s, 1H), 4.28 (q, J = 7.1 Hz, 2H), 3.79 (s, 3H), 3.11-3.18 (m, 1H), 2.37-2.43 (m, 1H), 1.48 (s, 9H), 1.33 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 188.8, 164.1, 153.8, 149.9, 137.6, 135.3, 130.3, 124.6, 123.8, 123.2, 121.9, 109.7, 108.1, 82.1, 61.3, 57.8, 43.5, 30.3, 28.9, 28.4, 14.4.

IR (film) 2979, 1714, 1668 (C=O), 1479, 1394, 1313, 1248, 1164, 1085, 1050, 906, 735 cm^{-1}.

HRMS (ESI) calcd for $C_{23}H_{26}N_2NaO_5$ [M+Na^+] 433.1734, found: 433.1747.

The enantiomeric excess was determined by chiral HPLC analysis: Chiracel AD-H, 20.0% *i*-PrOH:hexanes, 0.9 mL / min; (2*S*,6*R*): t_r: 9.50 min; (2*R*,6*S*): t_r: 14.5 min.

$[\alpha]^{22}_D$ +63.7° (*c* = 1.00, $CHCl_3$).

V. Determination of Stereochemistry

An X-ray crystal structure was obtained of the product of Table 3, entry 9 (formed through the use of (*R*)-**1**).

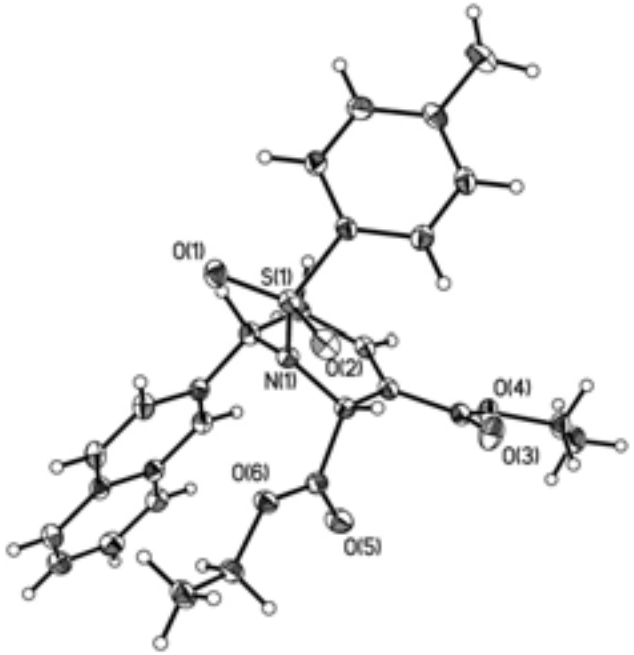


Table 1. Crystal data and structure refinement for 05043.

Identification code	05043	
Empirical formula	C28 H29 N O6 S	
Formula weight	507.58	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 8.1162(2) Å	a= 90°.
	b = 12.8118(5) Å	b= 90°.
	c = 24.3250(7) Å	g = 90°.
Volume	2529.39(14) $Å^3$	
Z	4	
Density (calculated)	1.333 Mg/m^3	
Absorption coefficient	0.172 mm^{-1}	
F(000)	1072	
Crystal size	0.25 x 0.15 x 0.15 mm^3	
Theta range for data collection	1.80 to 30.03°.	
Index ranges	-11<=h<=11, 0<=k<=18, 0<=l<=34	
Reflections collected	57382	
Independent reflections	7401 [R(int) = 0.0349]	
Completeness to theta = 30.03°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9747 and 0.9583	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7401 / 0 / 328	
Goodness-of-fit on F^2	1.080	
Final R indices [I>2sigma(I)]	R1 = 0.0389, wR2 = 0.0972	
R indices (all data)	R1 = 0.0402, wR2 = 0.0983	
Absolute structure parameter	0.00(5)	
Largest diff. peak and hole	0.594 and -0.199 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x10^3) for 05043. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
S(1)	-4958(1)	-5235(1)	-1802(1)	16(1)
N(1)	-4422(1)	-5752(1)	-1214(1)	15(1)
O(1)	-5741(1)	-4258(1)	-1679(1)	22(1)
O(2)	-3505(1)	-5260(1)	-2141(1)	22(1)
O(3)	-2044(1)	-8454(1)	-1664(1)	29(1)
O(4)	-3350(1)	-9441(1)	-1033(1)	21(1)
O(5)	-1110(1)	-6945(1)	-520(1)	26(1)
O(6)	-1241(1)	-5325(1)	-875(1)	19(1)
C(1)	-6438(2)	-6052(1)	-2104(1)	17(1)
C(2)	-8106(2)	-5788(1)	-2086(1)	22(1)
C(3)	-9256(2)	-6445(1)	-2324(1)	25(1)
C(4)	-8770(2)	-7372(1)	-2583(1)	22(1)
C(5)	-7092(2)	-7622(1)	-2596(1)	21(1)
C(6)	-5926(2)	-6979(1)	-2357(1)	20(1)
C(7)	-10006(2)	-8091(1)	-2842(1)	32(1)
C(8)	-5610(2)	-5729(1)	-752(1)	16(1)
C(9)	-6402(2)	-6804(1)	-658(1)	18(1)
C(10)	-5322(2)	-7713(1)	-789(1)	18(1)
C(11)	-3887(2)	-7626(1)	-1053(1)	17(1)
C(12)	-3180(1)	-6574(1)	-1208(1)	15(1)
C(13)	-4761(2)	-5227(1)	-260(1)	16(1)
C(14)	-4227(2)	-4173(1)	-329(1)	20(1)
C(15)	-3468(2)	-3655(1)	89(1)	21(1)
C(16)	-3198(2)	-4139(1)	606(1)	19(1)
C(17)	-2428(2)	-3621(1)	1053(1)	24(1)
C(18)	-2207(2)	-4121(1)	1546(1)	27(1)
C(19)	-2746(2)	-5154(1)	1618(1)	26(1)
C(20)	-3489(2)	-5684(1)	1194(1)	22(1)
C(21)	-3727(2)	-5189(1)	678(1)	18(1)
C(22)	-4506(2)	-5721(1)	233(1)	18(1)
C(23)	-2980(2)	-8537(1)	-1279(1)	19(1)
C(24)	-2694(2)	-10375(1)	-1299(1)	23(1)
C(25)	-2787(2)	-11248(1)	-887(1)	28(1)
C(26)	-1739(2)	-6311(1)	-821(1)	17(1)
C(27)	9(2)	-5002(1)	-478(1)	20(1)
C(28)	673(2)	-3965(1)	-665(1)	25(1)

Table 3. Bond lengths [Å] and angles [°] for 05043.

S(1)-O(1)	1.4355(10)
S(1)-O(2)	1.4393(10)
S(1)-N(1)	1.6340(10)
S(1)-C(1)	1.7552(13)
N(1)-C(12)	1.4586(15)
N(1)-C(8)	1.4815(15)
O(3)-C(23)	1.2091(17)
O(4)-C(23)	1.3375(16)
O(4)-C(24)	1.4620(16)
O(5)-C(26)	1.2077(16)
O(6)-C(26)	1.3334(15)
O(6)-C(27)	1.4589(15)
C(1)-C(2)	1.3963(18)
C(1)-C(6)	1.4002(17)
C(2)-C(3)	1.3836(19)
C(3)-C(4)	1.400(2)
C(4)-C(5)	1.399(2)
C(4)-C(7)	1.502(2)
C(5)-C(6)	1.3822(19)
C(8)-C(13)	1.5219(17)
C(8)-C(9)	1.5368(17)
C(9)-C(10)	1.4926(17)
C(10)-C(11)	1.3339(17)
C(11)-C(23)	1.4870(18)
C(11)-C(12)	1.5122(17)
C(12)-C(26)	1.5376(17)
C(13)-C(22)	1.3719(17)
C(13)-C(14)	1.4282(18)
C(14)-C(15)	1.3618(19)
C(15)-C(16)	1.4190(18)
C(16)-C(17)	1.4182(18)
C(16)-C(21)	1.4232(18)
C(17)-C(18)	1.372(2)
C(18)-C(19)	1.406(2)
C(19)-C(20)	1.3741(19)
C(20)-C(21)	1.4200(17)
C(21)-C(22)	1.4268(17)
C(24)-C(25)	1.504(2)
C(27)-C(28)	1.5040(19)
O(1)-S(1)-O(2)	120.04(6)

O(1)-S(1)-N(1)	106.82(6)
O(2)-S(1)-N(1)	105.91(6)
O(1)-S(1)-C(1)	107.71(6)
O(2)-S(1)-C(1)	107.94(6)
N(1)-S(1)-C(1)	107.89(6)
C(12)-N(1)-C(8)	117.16(10)
C(12)-N(1)-S(1)	119.05(8)
C(8)-N(1)-S(1)	118.88(8)
C(23)-O(4)-C(24)	115.39(10)
C(26)-O(6)-C(27)	114.51(10)
C(2)-C(1)-C(6)	120.48(12)
C(2)-C(1)-S(1)	120.40(10)
C(6)-C(1)-S(1)	119.11(10)
C(3)-C(2)-C(1)	119.53(12)
C(2)-C(3)-C(4)	120.94(13)
C(5)-C(4)-C(3)	118.58(13)
C(5)-C(4)-C(7)	120.03(13)
C(3)-C(4)-C(7)	121.38(14)
C(6)-C(5)-C(4)	121.36(12)
C(5)-C(6)-C(1)	119.11(12)
N(1)-C(8)-C(13)	108.08(10)
N(1)-C(8)-C(9)	111.54(10)
C(13)-C(8)-C(9)	116.82(10)
C(10)-C(9)-C(8)	114.94(10)
C(11)-C(10)-C(9)	123.36(11)
C(10)-C(11)-C(23)	123.01(12)
C(10)-C(11)-C(12)	121.77(11)
C(23)-C(11)-C(12)	114.75(11)
N(1)-C(12)-C(11)	112.53(10)
N(1)-C(12)-C(26)	111.94(10)
C(11)-C(12)-C(26)	109.34(10)
C(22)-C(13)-C(14)	119.47(12)
C(22)-C(13)-C(8)	124.08(11)
C(14)-C(13)-C(8)	116.45(11)
C(15)-C(14)-C(13)	120.78(12)
C(14)-C(15)-C(16)	121.20(12)
C(17)-C(16)-C(15)	122.80(12)
C(17)-C(16)-C(21)	118.81(12)
C(15)-C(16)-C(21)	118.38(11)
C(18)-C(17)-C(16)	120.58(13)
C(17)-C(18)-C(19)	120.56(13)
C(20)-C(19)-C(18)	120.53(13)
C(19)-C(20)-C(21)	120.21(13)

C(20)-C(21)-C(16)	119.29(12)
C(20)-C(21)-C(22)	121.20(12)
C(16)-C(21)-C(22)	119.50(11)
C(13)-C(22)-C(21)	120.66(12)
O(3)-C(23)-O(4)	124.32(12)
O(3)-C(23)-C(11)	121.91(12)
O(4)-C(23)-C(11)	113.72(11)
O(4)-C(24)-C(25)	107.18(11)
O(5)-C(26)-O(6)	124.63(12)
O(5)-C(26)-C(12)	123.05(11)
O(6)-C(26)-C(12)	112.27(10)
O(6)-C(27)-C(28)	107.41(10)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2x10^3$) for 05043. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U11	U22	U33	U23	U13	U12
S(1)	22(1)	15(1)	13(1)	2(1)	-1(1)	-1(1)
N(1)	18(1)	17(1)	11(1)	2(1)	-1(1)	1(1)
O(1)	32(1)	14(1)	21(1)	1(1)	-4(1)	1(1)
O(2)	26(1)	25(1)	16(1)	4(1)	3(1)	-4(1)
O(3)	35(1)	24(1)	29(1)	1(1)	13(1)	3(1)
O(4)	27(1)	14(1)	22(1)	-1(1)	3(1)	0(1)
O(5)	29(1)	20(1)	29(1)	6(1)	-10(1)	-2(1)
O(6)	19(1)	17(1)	21(1)	2(1)	-4(1)	-2(1)
C(1)	22(1)	14(1)	13(1)	0(1)	-3(1)	0(1)
C(2)	26(1)	22(1)	18(1)	-4(1)	-4(1)	6(1)
C(3)	21(1)	31(1)	23(1)	-3(1)	-3(1)	2(1)
C(4)	27(1)	23(1)	15(1)	-1(1)	-3(1)	-4(1)
C(5)	30(1)	15(1)	18(1)	-1(1)	-1(1)	1(1)
C(6)	23(1)	19(1)	17(1)	1(1)	0(1)	3(1)
C(7)	33(1)	35(1)	27(1)	-7(1)	-5(1)	-10(1)
C(8)	17(1)	18(1)	14(1)	0(1)	1(1)	0(1)
C(9)	17(1)	18(1)	18(1)	0(1)	1(1)	-2(1)
C(10)	21(1)	16(1)	16(1)	0(1)	-1(1)	-3(1)
C(11)	19(1)	15(1)	16(1)	0(1)	-2(1)	-1(1)
C(12)	16(1)	15(1)	15(1)	1(1)	0(1)	0(1)
C(13)	18(1)	16(1)	15(1)	-1(1)	1(1)	1(1)
C(14)	26(1)	16(1)	17(1)	2(1)	2(1)	1(1)
C(15)	29(1)	14(1)	20(1)	0(1)	2(1)	-1(1)
C(16)	20(1)	20(1)	16(1)	-3(1)	1(1)	3(1)
C(17)	26(1)	24(1)	23(1)	-7(1)	-2(1)	0(1)
C(18)	27(1)	33(1)	22(1)	-8(1)	-5(1)	3(1)
C(19)	29(1)	32(1)	17(1)	0(1)	-3(1)	6(1)
C(20)	25(1)	23(1)	17(1)	2(1)	1(1)	3(1)
C(21)	19(1)	20(1)	15(1)	-1(1)	1(1)	2(1)
C(22)	19(1)	17(1)	16(1)	0(1)	2(1)	0(1)
C(23)	20(1)	17(1)	19(1)	-2(1)	-2(1)	-1(1)
C(24)	29(1)	15(1)	26(1)	-4(1)	-1(1)	2(1)
C(25)	32(1)	19(1)	31(1)	0(1)	-1(1)	2(1)
C(26)	17(1)	17(1)	17(1)	1(1)	0(1)	0(1)
C(27)	20(1)	20(1)	20(1)	-1(1)	-3(1)	-1(1)
C(28)	28(1)	18(1)	29(1)	-1(1)	-4(1)	-4(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x10^3) for 05043.

	x	y	z	U(eq)
H(2)	-8450	-5161	-1911	26
H(3)	-10390	-6265	-2312	30
H(5)	-6747	-8246	-2772	25
H(6)	-4793	-7163	-2365	24
H(7A)	-10726	-8381	-2557	48
H(7B)	-9429	-8660	-3031	48
H(7C)	-10671	-7701	-3109	48
H(8)	-6518	-5246	-863	19
H(9A)	-6743	-6854	-268	21
H(9B)	-7410	-6851	-886	21
H(10)	-5674	-8389	-679	21
H(12)	-2724	-6635	-1589	18
H(14)	-4403	-3829	-670	24
H(15)	-3113	-2956	34	25
H(17)	-2063	-2921	1010	29
H(18)	-1684	-3766	1841	32
H(19)	-2596	-5489	1963	31
H(20)	-3844	-6384	1246	26
H(22)	-4853	-6424	279	21
H(24A)	-1537	-10259	-1414	28
H(24B)	-3352	-10549	-1630	28
H(25A)	-2064	-11092	-575	41
H(25B)	-2436	-11902	-1061	41
H(25C)	-3924	-11320	-757	41
H(27A)	906	-5525	-462	24
H(27B)	-483	-4937	-108	24
H(28A)	1114	-4033	-1039	37
H(28B)	1552	-3740	-416	37
H(28C)	-216	-3447	-663	37

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