Synthesis and Resolution of Quinazolinone Atropisomeric Phosphine Ligands†,‡

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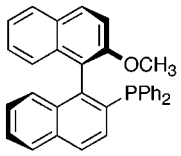
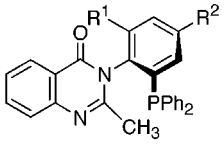
The syntheses of 2-methyl-3-[2'-(diphenylphosphino)phenyl]-4(3*H*)-quinazolinone (MPQ, **1a**) and methyl-substituted analogues were achieved in good yield by coupling *N*-acetylanthranilic acid with the corresponding phosphinoanilines. Resolution of ligand **1b** was achieved using (−)-di-μ-chlorobis-[(*S*)-dimethyl-(1-phenylethyl)aminato-C^2,*N*]dipalladium(II) (**5**). The resulting crystalline complex (*S*,*R*)-**6** served to unambiguously assign the absolute configuration of antipode (*R*)-(−)-**1b**. A practical resolution of this series of ligands **1a**−**c** was accomplished using the (benzenesulfonyl-)hydrazone derivative of camphorsulfonic acid (**7**) as a resolving agent.

Introduction

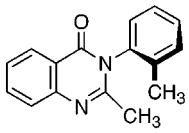
Asymmetric catalysis has been advanced in many areas by the discovery and application of the atropisomeric ligand BINAP.[1] The chiral environment imposed by the orthogonal naphthalene rings as well as the chelating nature of this ligand has proven effective for inducing high stereoselectivity in a variety of asymmetric reactions.[2] More recently, the binaphthylmonophosphines (MOP's) and related ligands have also found use in catalytic asymmetric reactions.[3] As an addition to this class of atropisomeric phosphine ligands, we have developed an efficient synthesis and resolution of the quinazolinone-containing atropisomeric phosphine ligands **1a**−**c**.



(+)-MOP



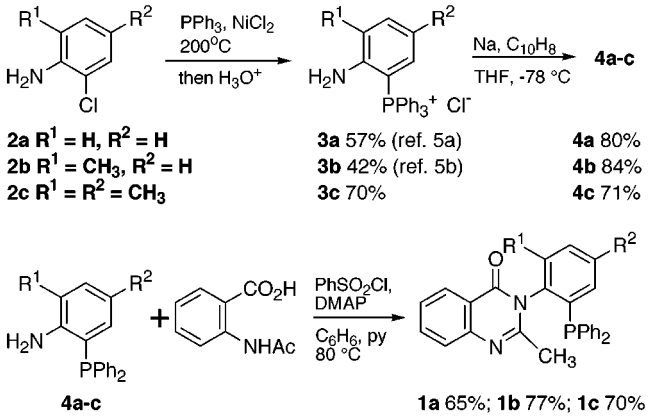
1a R^1, R^2 = H
1b R^1 = H, R^2 = CH_3
1c R^1, R^2 = CH_3



Methaqualone

The atropisomeric nature of substituted quinazolinones has been studied in connection with their medicinal properties. In particular, the activation barrier for racemization of 2-methyl-3-*o*-tolyl-4(3*H*)-quinazolinone (methaqualone) was found to be 31.5 kcal/mol at 135 °C in diphenyl ether.[4] We therefore expected that ligand **1a** would possess a suitable activation barrier to racemization to allow resolution and that the methyl-substituted ligands **1b** and **1c** would be essentially inert to racemization by N−C_{aryl} bond rotation.

Scheme 1. Preparation of the Racemic Ligands 1a−c



Results and Discussion

Two-Stage Synthesis of Ligand 1a−c. Our synthesis begins with the preparation of phosphinoanilines **4a**−**c** from the commercially available chloroanilines by Cooper's method (Scheme 1).[5] The anilines **2a**−**c** were reacted with triphenylphosphine and anhydrous nickel(II) chloride to afford the phosphonium salts **3a**−**c** after aqueous acidic workup and recrystallization from tetrahydrofuran. Reduction of **3a**−**c** with sodium naphthalenide at −78 °C afforded the phosphinoanilines **4a**−**c** in 71−84% yield after recrystallization. We found the removal of naphthalene by sublimation allowed a more straightforward isolation and higher yields than Cooper's reported two-step procedure.

Reaction of the phosphinoanilines **4a**−**c** with *N*-acetylanthranilic acid and benzenesulfonyl chloride[6] as the coupling agent afforded the racemic ligands **1a**−**c** in 65−

† Dedicated to Professor E. J. Corey with deep respect on the occasion of his 70th birthday.

‡ Presented at the 214th National American Chemical Society Meeting, Las Vegas, NV, Sep 1997; ORGN 224.

(1) Takaya, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629.

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(3) (a) Uozumi, Y.; Tanahashi, A.; Lee, S.-Y.; Hayashi, T. *J. Org. Chem.* **1993**, *58*, 1945. (b) Hayashi, T.; Iwamura, H.; Uozumi, Y.; Matsumoto, Y.; Ozawa, F. *Synthesis* **1994**, *15*, 526. (c) Alcock, N. W.; Brown, J. M.; Hulmes, D. I. *Tetrahedron: Asymmetry* **1993**, *4*, 743.

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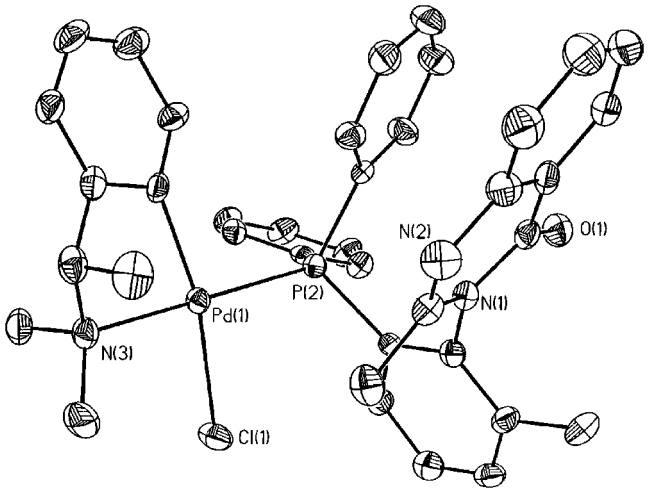
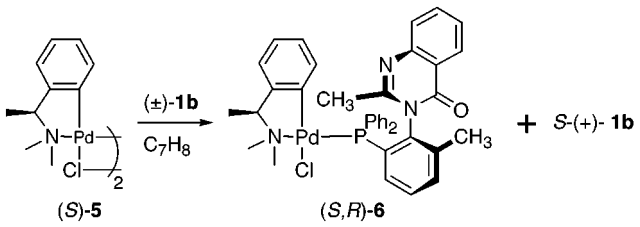


Figure 1. ORTEP plot of complex (*S*,*R*)-**6**.

77% yield. In particular, ligand **1c** was prepared on a 25 g scale from the readily available dimethylchloroaniline **2c**.

Conventional Resolution of 1b and Absolute Configuration of Palladium Complex 6. Ligand **1b** was resolved on a 6 g scale using (−)-di-μ-chlorobis[(*S*)-dimethyl-(1-phenylethyl)aminato-C^2,*N*]dipalladium(II) (**5**), which is a conventional resolving agent for monophosphines.[7] Reacting dimer (*S*)-**5** with 4 equiv of racemic **1b** yielded palladium complex **6** as a yellow crystalline precipitate that was collected by filtration. The (+)-**1b** was recovered from the filtrate in good yield (82%) and high enantiomeric excess (96% ee as determined by chiral HPLC). Treatment of the complex **6** with ethylenediamine in CH_2Cl_2 released the ligand (−)-**1b**, which was isolated in 91% yield and 99% ee (HPLC). The resulting palladium ethylenediamine complex was converted back to complex **5** in nearly quantitative yield using 2 *N* aqueous hydrochloric acid.[8]



The X-ray structure[9] of complex **6** displays a significant π-stacking between one phenyl ring on phosphorus and the quinazolinone ring system with the palladium center oriented to the side of the quinazolone methyl group (Figure 1). On the basis of the known *S*-stereochemistry of the phenethylamine ligand, the absolute stereochemistry of the phosphine ligand chiral axis is assigned as *R* according to the Cahn−Ingold−Prelog rule.[10]

Rotational Barrier of Ligands 1a,b. A study on the thermal racemization of **1a** and **1b** was conducted by heating their toluene solutions to reflux under argon. Small portions of the solutions were taken out at regular time intervals up to 96 h and analyzed by chiral HPLC analysis. For **1a**, the $t_{1/2}$ was found to be 40 h at 110 °C, which corresponds to a rotational barrier ($\Delta G^{\ddagger}$) of 32 kcal/mol. As for **1b**, which has an extra *o*-methyl group, there was no detectable racemization after 96 h at relux in toluene.

Resolution of the Ligands 1a−c Using a New Resolving Agent. To achieve larger scale and economical resolution of the ligands **1a**−**c**, a suitable acid-resolving agent was sought to ionize the nitrogen of the quinazolinone ring. Since quinazolinone derivatives are only weakly basic ($pK_a \approx 2.2$), the field of possible resolving acids has been limited to camphorsulfonic acid.[11,12] When ligand **1a** and (*S*)-camphorsulfonic acid ((*S*)-CSA) were combined in equimolar proportions in ethyl acetate, large hexagonal-shaped crystals were obtained. Upon neutralization of the 1:1 salt, only racemic **1a** was obtained. Similar results were obtained for the ligand **1b** using (*S*)-CSA, and no crystalline salt was obtained using π-bromocamphorsulfonic acid.

X-ray diffraction analysis of the hexagonal salt above confirmed the composition as ((*S*)-CSA)$_2$·((*R*)-**1a**)·((*S*)-**1a**) and further revealed the structural features of this salt (Figure 2).[13] The monoclinic P_{21} unit cell is divided into adjacent domains of homotopic salt cores extending along the crystallographic 2_1 screw axes. This led us to surmise that the stronger ionic interactions in the crystal had achieved the segregation of the two enantiomers of the ligand **1a** while the weaker interactions between the aromatic rings and (*S*)-CSA had allowed the quasi-racemate unit cell to form.[14] Indeed, the hydrophobic and roughly spherical nature of the bicyclic portion of (*S*)-CSA seems to adopt analogous positions in the two salt bridge motifs.

Our solution to the resolution of ligands **1a**−**c** was to investigate a simple derivative of camphorsulfonic acid that would more distinctly define the chirality about the bicyclic core without affecting the ability of the salt bridge formation. The (benzenesulfonyl)hydrazone of (*S*)-camphorsulfonic acid (*S*-CSZ, **7**) is readily prepared in 99% yield by combination of solutions of the two reagents in

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(9) Complex **6** ($C_{38}H_{37}ClN_3OPPd$; $M_w = 724.53$) crystallized in the orthorhombic $P2_12_12_1$ space group with cell dimensions $a = 10.4822(7)$ Å, $b = 17.3192(12)$ Å, $c = 18.5003(12)$ Å, and $Z = 4$. A total of 13 752 reflections were collected at −85 °C using a Siemens SMART/CCD diffractometer. Least-squares refinement of the data using 4839 reflections converged upon the structure shown in Figure 1 with $R = 0.0308$ and a goodness of fit = 1.114.

(10) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994.

(11) Perrin, D. D. *Dissociation Constants of Organic Bases in Aqueous Solution*; International Union of Pure and Applied Chemistry: London, 1965; p 227.

(12) Kashima, C.; Katoh, A. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1599.

(13) Crystalline salt ((*S*)-CSA)$_2$·((*R*)-**1a**)·((*S*)-**1a**) ($C_{74}H_{74}N_4O_{10}P_2S_2$; $M_w = 1305.58$ crystallized in the monoclinic $P2_1$ space group with cell dimensions $a = 11.1602(5)$ Å, $b = 10.8868(5)$ Å, $c = 27.2325(12)$ Å, $\beta = 95.132°$, and $Z = 2$. A total of 8796 reflections were collected at 20 °C using a Siemens SMART/CCD diffractometer. Least-squares refinement of the data using 4690 reflections converged upon the structure shown in Figure 2 with $R = 0.1176$ and a goodness of fit = 1.044.

(14) For examples of quasi-racemates, see: (a) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; Chapter 5. (b) Fredga, A. *Tetrahedron* **1960**, *8*, 126. (c) Auburn, M.; Ciriano, M.; Howard, J. A. K.; Murry, M.; Pugh, N. J.; Spencer, J. L.; Stone, F. G. A.; Woodward, P. *J. Chem. Soc., Dalton Trans.* **1980**, 659. (d) Schurig, V.; Pille, W.; Winter, W. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 327. (e) Alcock, N. W.; Hulmes, D. I.; Brown, J. M. *J. Chem. Soc., Chem. Commun.* **1995**, 395. (f) Vedejs, E.; Donde, Y. *J. Am. Chem. Soc.* **1997**, *119*, 9293.

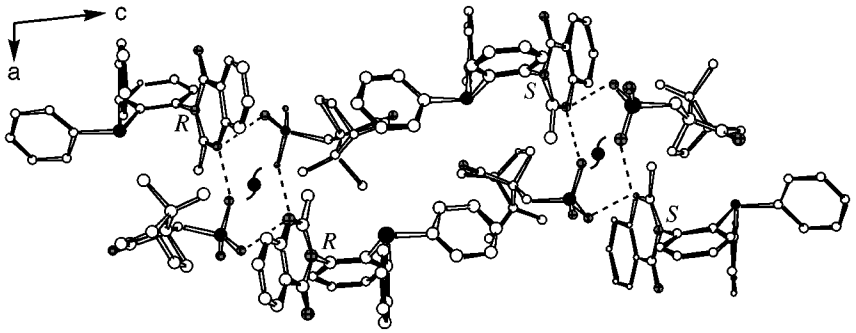
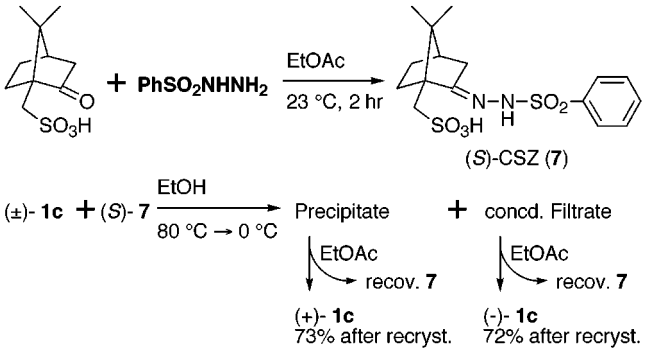


Figure 2. X-ray structure of the salt ((*S*)-CSA)$_2$·((*R*)-**1a**)·((*S*)-**1a**) showing adjacent crystallographic screw axes. Antipode (*R*)-**1a** and (*S*)-CSA comprise the extended salt core on the left, while (*S*)-**1a** and (*S*)-CSA are seen at right.

Scheme 2. Resolution of Ligand 1c Using the (*S*)-CSZ (7) Resolving Agent



ethyl acetate and filtration of the resulting precipitate (Scheme 2). Addition of a solution of **1c** to 1 equiv of (*S*)-CSZ (**7**) in hot ethanol and slow cooling to 0 °C caused precipitation of one antipode as the sulfonate salt that was collected by filtration. Trituration of the crystalline salt with ethyl acetate freed the ligand into solution, leaving behind the recovered (*S*)-CSZ (**7**). After washing with aqueous sodium bicarbonate and recrystallization, the ethyl acetate solution afforded optically pure (+)-**1c** in 73% yield. The concentrated ethanol filtrate treated in the same manner afforded the antipode (−)-**1c** in 72% yield. The above procedure, which can be performed on a 25 g scale for ligand **1c** and also proceeds favorably for ligands **1a**,**b**, represents the first preparation of CSA derivatives such as **7** and their use as resolving agents. The enantiomeric excess of both resolved samples in each case was greater than 96%.[15]

In conclusion, our ligand system represents the first example of an atropisomeric biaryl phosphine ligand about a central N−C$_{aryl}$ bond. The quinazolinone ring structure facilitates a straightforward synthesis that may be applied to related ligands. The weakly basic imine nitrogen of this heterocycle is a unique feature allowing the convenient resolution of **1a**−**c** using a new class of camphorsulfonic acid (benzenesulfonyl)hydrazone resolving agents. Furthermore, although poorly positioned for chelation, the same nitrogen may have an effect on the asymmetric reactions of chiral ligands based on the quinazolinone ring system. Further work will be disclosed on the catalytic reactions using the ligands described above.

(15) After the palladium resolution, determination of the ee value of ligands **1a**−**c** was conducted by addition of a slight excess of the reagent **5** and ^{1}H NMR analysis of the ratio of the palladium complex **6** and its diastereomer in the region of 3.5−7.0 ppm.

Experimental Section

Tetrahydrofuran was distilled from sodium benzophenone ketyl under nitrogen. TLC was carried out on silica gel 60-F$_{254}$ plates (0.25 mm, E. Merck) and visualized with UV light and phosphomolybdic acid stain. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian XL-300, Varian Unity-300, or a Varian VXR-500 spectrometer. ^{31}P NMR spectra were measured on a Varian XL-300 (121.4 MHz) spectrometer, and chemical shifts were reported in ppm relative to 85% H_3PO_4 external standard. HPLC analyses were performed using a Daicel CHIRALCEL OJ column. 2-Diphenylphosphinoaniline (**4a**) and 6-methyl-2-diphenylphosphinoaniline (**4b**) were prepared according to Cooper's procedure with modifications as described below for **4c**.[5] (−)-Di-μ-chlorobis[(*S*)-dimethyl(1-phenylethyl)aminato-C^2,*N*]dipalladium(II) was prepared according to the literature procedure.[7]

4,6-Dimethyl-2-(diphenylphosphino)aniline (4c).[5] 2-Chloro-4,6-dimethylaniline (25.0 g, 0.16 mol), triphenylphosphine (42.6 g, 0.16 mol), and anhydrous nickel chloride (10.5 g, 0.08 mol) were combined and heated to 200 °C with stirring and removal of residual water over 4 h. The blue melt was poured into water (300 mL) and concd HCl (2 mL) and stirred to dissolve. The aqueous phase was extracted with diethyl ether (4 × 40 mL) and then with dichloromethane (4 × 50 mL). The combined CH_2Cl_2 extracts were dried ($MgSO_4$) and evaporated to an oil. After addition of tetrahydrofuran (300 mL) and cooling at 4 °C overnight, the resulting white crystals were collected by filtration, washed with ether, and vacuum-dried to afford 47.0 g (70%) of phosphonium salt **3c** (mp 131.3−132.5 °C).

An oven-dried, three-neck, 1-L round-bottom flask equipped with a mechanical stirrer was charged with naphthalene (34.7 g, 0.27 mol) in THF (300 mL) under argon, and sodium metal pieces (5.7 g, 0.25 mol) were added. After the solution was stirred for 3 h at room temperature, the solution was cooled to −78 °C. The powdered phosphonium salt **3c** (47.0 g, 0.11 mol) was added with stirring, and the mixture was left overnight to warm to room temperature. Acetic acid (2.8 mL) was added dropwise followed by a 20% aqueous ammonium chloride solution (69 mL). The resulting phases were separated, and the aqueous layer was extracted with diethyl ether (2 × 100 mL). The combined organic phases were dried ($MgSO_4$) and evaporated to a brown oil. The naphthalene was removed by sublimation at 60 °C and 0.1 mmHg using a Kugelrohr apparatus. Recrystallization from ethyl acetate and hexane (2:3) afforded 24.44 g (71%) of the phosphinoaniline **4c**: mp 58.5−59.5 °C; R_f = 0.47 (silica, 1:2 ethyl acetate/hexane); FTIR (thin film, cm^{-1}) 3455, 3354, 3050, 2913, 1616, 1585, 1473, 1434, 1236, 743, 696, 490; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21−7.46 (m, 10 H), 6.92 (br s, 1 H), 6.48 (dd, 1 H, J = 1.5, 5.5 Hz), 4.07 (br s, 2 H), 2.16 (s, 3 H), 2.10 (s, 3 H); ^{31}P NMR (121.4 MHz) −19.83 (s); HRMS calcd for $C_{20}H_{20}NP$ (M^+) 305.1334, found: 305.1332.

2-Methyl-3-[6′-methyl-2′-(diphenylphosphino)phenyl]-4(3*H*)-quinazolinone (1b). To a solution of *N*-acetylanthranilic acid (16.58 g, 92.5 mmol) and 4-(dimethylamino)pyridine (50 mg) in pyridine (27 mL) was added dropwise benzene-

sulfonyl chloride ($PhSO_2Cl$, 9.64 mL, 75.5 mmol). The resulting slurry was treated with a solution of aminophosphine **4b** (10.0 g, 34.4 mmol) in benzene (100 mL), and the mixture was heated at reflux for 36 h. After cooling, the solvent was evaporated, and the residue was partitioned with ethyl acetate (250 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (50 mL), and the combined ethyl acetate fractions were dried ($MgSO_4$). After removal of the solvent, crystallization from ethyl acetate (80 mL) and hexane (80 mL) afforded ligand **1b** (11.48 g, 77%) as white needles: mp 169−170 °C; R_f = 0.28 (silica, 1:2 ethyl acetate/hexane); FTIR (thin film, cm^{-1}) 3054, 1683, 1603, 1569, 1472, 1434, 1377, 1326, 1267, 1116, 774, 743, 696; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (dd, 1 H, J = 1.2, 7.8 Hz), 7.74 (ddd, 1 H, J = 1.5, 6.9, 8.4 Hz), 7.67 (d, 1 H, J = 7.8 Hz), 7.33−7.42 (m, 8 H), 7.10−7.25 (m, 6 H), 2.13 (s, 3 H), 2.04 (s, 3 H); ^{31}P NMR (121.4 MHz) −18.2 (s); HRMS 434.1548 (calcd for $C_{28}H_{23}N_2OP$ 434.1548). Anal. C 77.33, H 5.49, N 6.30 (calcd for $C_{28}H_{23}N_2OP$: C 77.41, H 5.34, N 6.45).

2-Methyl-3-[2′-(diphenylphosphino)phenyl]-4(3*H*)-quinazolinone (1a). Ligand **1a** was obtained as white needles (65%) under the above conditions: mp 181−182 °C; R_f = 0.21 (silica, 1:2 ethyl acetate/hexane); FTIR (thin film, cm^{-1}) 3053, 1684, 1604, 1566, 1471, 1435, 1377, 1340, 1275, 771, 744, 696; ^1H NMR (300 MHz, $CDCl_3$) δ 8.12 (dd, 1 H, J = 1.3, 8.1 Hz), 7.73 (ddd, 1 H, J = 1.3, 6.9, 8.2 Hz), 7.66 (d, 1 H, J = 8.1 Hz), 7.53 (ddd, 1 H, J = 1.5, 7.6, 7.6 Hz), 7.30−7.47 (m, 8 H), 7.15−7.29 (m, 6 H), 2.05 (s, 3 H); ^{31}P NMR (121.4 MHz) −16.87 (s); HRMS 420.1392 (calcd for $C_{27}H_{21}N_2OP$: 420.1392).

2-Methyl-3-[4′,6′-dimethyl-2′-(diphenylphosphino)-phenyl]-4(3*H*)-quinazolinone (1c). Ligand **1c** was obtained as white needles (79%) under the above conditions: mp 179−180 °C; R_f = 0.34 (silica, 1:2 ethyl acetate/hexane); FTIR (thin film, cm^{-1}) 3052, 1682, 1602, 1570, 1471, 1434, 1377, 1340, 1325, 773, 741, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (dd, 1 H, J = 1.2, 7.9 Hz), 7.73 (ddd, 1 H, J = 1.4, 6.9, 6.9 Hz), 7.66 (d, 1 H, J = 7.3 Hz), 7.1−7.4 (m, 13 H), 6.91 (br s, 1 H), 2.28 (s, 3 H), 2.08 (s, 3 H), 2.05 (s, 3 H); ^{31}P NMR (121.4 MHz) −16.27 ppm (s); HRMS 448.1704 (calcd for $C_{29}H_{25}N_2OP$ 448.1705).

Resolution of Ligand 1b Using (−)-Di-μ-chlorobis[(*S*)-dimethyl-(1-phenylethyl)aminato-C^2,*N*]dipalladium(II) (5). To a solution of complex **5** (2.00 g, 3.44 mmol) in toluene (80 mL) was added **1b** (6.00 g, 13.8 mmol), and the solution was stirred for 4 h at ambient temperature. The mixture was treated with hexane (50 mL) and stored at 0 °C overnight. Yellow crystals of (*S*, *R*)-**6** were collected by filtration (4.79 g, 96% yield): mp 185 °C (dec); R_f = 0.67 (silica, ethyl acetate); FTIR (thin film, cm^{-1}) 3448, 1676, 1601, 1474, 1437, 1340, 1267, 1092, 774, 731, 697; ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (dd, 2 H, J = 7.2, 11.6 Hz), 7.81 (dd, 1 H, J = 1.4, 8.0 Hz), 7.74 (dd, 2 H, J = 7.7, 12.1 Hz), 7.54−7.67 (m, 2 H), 7.22−7.52 (m, 7 H), 6.87 (dd, 1 H, J = 2.0, 7.2 Hz), 6.71 (t, 1 H, J = 7.3 Hz), 6.61 (ddd, 2 H, J = 2.0, 7.3, 7.3 Hz), 6.45 (ddd, 1 H, J = 1.3, 7.2, 7.2 Hz), 6.16 (ddd, 1 H, J = 1.2, 7.5, 7.5 Hz), 5.86 (t, 1 H, J = 6.9 Hz), 3.78 (quin, 1 H, J = 5.5 Hz), 2.86 (d, 3 H, J = 1.7 Hz), 2.75 (d, 3 H, J = 3.0 Hz), 2.67 (s, 3 H), 1.93 (s, 3 H), 1.74 (d, 3 H, J = 6.4 Hz); ^{31}P NMR (121.4 MHz) 45.53 (s); $[\alpha]^{23}_D$ = −10.5° (c = 1.04, $CHCl_3$); HRMS (FAB, 3-nitrobenzyl alcohol) 723.1397 (calcd for $C_{38}H_{37}ClN_3OPPd$ 723.1398).

The mother liquor was concentrated, and the residue was recrystallized from ethyl acetate/hexanes (1:3) to afford (*S*)-(+)-**1b** (2.45 g, 82%) (96% ee based on chiral HPLC analyses; 98:2 hexane/2-propanol, flow rate 1.5 mL/min, t_R = 13.5 min).

Treatment of the complex (*S*,*R*)-**6** with ethylenediamine (0.115 mL, 1.72 mmol) in CH_2Cl_2 (30 mL), followed by filtration and crystallization from ethyl acetate−hexanes (1:3) solvent mixture, gave 2.73 g (91%) of free ligand (*R*)-(−)-**1b** as white needles (99% ee based on chiral HPLC analyses, 98:2 hexane/2-propanol, flow rate 1.5 mL/min, t_R = 8.9 min).

Camphorsulfonic Acid (Benzenesulfonyl)hydrazone (7). To a solution of (1*S*)-(+)-camphorsulfonic acid (10.73 g, 46.2 mmol) in ethyl acetate (170 mL) and ethanol (30 mL) was added a solution of (benzenesulfonyl)hydrazine (7.95 g, 46.2 mmol) in ethyl acetate (130 mL). After being stirred for 2 h, the mixture was filtered to afford **7** as a white solid (17.8 g, 99%): mp 266−268 °C dec; R_f = 0.58 (silica, 1:2 methanol/ethyl acetate); FTIR (thin film, cm^{-1}) 3436, 2964, 1673, 1359, 1231, 1174, 1041; ^1H NMR (300 MHz, DMF-d_7) δ 8.3−9.8 (br s, 2 H), 7.78 (d, 2 H, J = 8.3 Hz), 7.49 (t, 1 H, J = 7.3 Hz), 7.42 (t, 2 H, J = 7.6 Hz), 3.22 (d, 1 H, J = 14.7 Hz), 2.66 (d, 1 H, J = 15.1 Hz), 2.46 (m, 1 H), 2.31 (dt, 1 H, J = 18.1, 3.9 Hz), 1.84 (d, 1 H, J = 17.6 Hz), 1.6−1.7 (m, 2 H), 1.21 (m, 1 H), 0.96 (m, 1 H), 0.89 (s, 3 H), 0.46 (s, 3 H); ^{13}C NMR (75 MHz, $CF_3COOH-CDCl_3$) δ 212.3, 137.1, 135.0, 131.1, 129.1, 60.3, 55.7, 50.7, 43.8, 40.6, 30.6, 26.4, 19.6, 18.4; $[\alpha]^{23}_D$ = −9.5° (c = 1.01, DMF); HRMS 386.0972 (calcd for $C_{16}H_{22}N_2S_2O_5$ (M^+) 386.0970).

Resolution of 1c Using Resolving Agent 7. In a 200-mL, round-bottom flask 21.6 g (56.0 mmol, 1.00 equiv) of acid **7** was dissolved in 1200 mL of ethanol at reflux, and 25.1 g (56.0 mmol, 1.00 equiv) of racemic **1c** was added. The clear solution was cooled slowly to 0 °C and kept at 0 °C overnight. The crystals were filtered, washed with ethanol (3 × 20 mL), and air-dried to afford 22.4 g (96%) of white (*S*)-**1c**·**7** salt. Trituration of this salt in ethyl acetate (100 mL) and filtration freed the ligand. Acid **7** was recovered as a white solid. After washing with aqueous sodium bicarbonate (2 × 30 mL) and recrystallization, the ethyl acetate solution afforded optically pure (+)-**1c** (9.05 g, 73%): mp 167−169 °C; $[\alpha]^{23}_D$ = +186° (c = 0.90, $CHCl_3$) (>96% ee).[15]

The ethanolic mother liquor was concentrated to dryness. The residue was triturated, neutralized, and crystallized as above to give 9.05 g of white prisms (72%): mp 166−167 °C; $[\alpha]^{23}_D$ = −193° (c = 0.90, $CHCl_3$) (>96% ee).[15]

Resolution of 1b Using Resolving Agent 7. Compound **1b** was resolved analogously to that described for **1c**, starting from racemic **1b** (2.33 g, 5.36 mmol) and acid **7** (2.08 g, 5.39 mmol) in 120 mL of ethanol. The white (*S*)-**1b**·CSZ salt provided 0.862 g of white prisms (74%): mp 143−145 °C; $[\alpha]^{23}_D$ = +172° (c = 0.93, $CHCl_3$) (>96% ee).[15] The ethanolic mother liquor affored 1.07 g of white prisms (91%): mp 142−144 °C; $[\alpha]^{23}_D$ = −176° (c = 0.97, $CHCl_3$) (>96% ee).[15]

Resolution of 1a Using Resolving Agent 7. Compound **1a** was resolved analogously to that described for **1c**, starting from racemic **1a** (2.44 g, 5.81 mmol) and acid **7** (2.27 g, 5.88 mmol) in 140 mL of ethanol. The white (*S*)-**1a**·CSZ salt provided 0.935 g of white prisms (77%): mp 142−144 °C; $[\alpha]^{23}_D$ = +229° (c = 1.29, $CHCl_3$) (>96% ee).[15] The ethanolic mother liquor affored 1.06 g of white prisms (87%): mp 138−141 °C; $[\alpha]^{23}_D$ = −245° (c = 1.31, $CHCl_3$) (>96% ee).[15]

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Supporting Information Available: Tables of atomic coordinates and thermal parameters for complex **6** and the salt ((*S*)-CSA)$_2$·((*R*)-**1a**)·(*S*)-**1a**). ^1H NMR and ^{13}C NMR spectra of compounds **4c**, **1a**−**c**, **6**, and **7** as well as the use of **5** for analysis of the ee of **1c** (28 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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