SYNTHESIS AND RESOLUTION OF A NEW C_2-SYMMETRIC CHIRAL BIS-ANILINE, *trans*-1,2-BIS(2-AMINOPHENYL)CYCLOPENTANE

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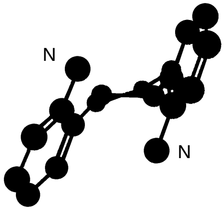
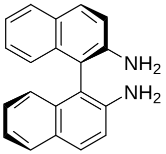
Dedicated to Professor Otakar Červinka on the occasion of his 75th birthday in recognition of his outstanding contributions to the area of organic stereochemistry.

New C_2-symmetric *trans*-1,2-bis(2-aminophenyl)cyclopentanes **2a** and **2b** were synthesized in optically pure forms (99% ee) from the known racemic *trans*-1,2-bis(2-hydroxyphenyl)cyclopentane (**3**) by the conversion to its bis-triflate **4** followed by the Buchwald amination and resolution.

Key words: Amines; Chiral bis-anilines; C_2-Symmetry; N-Ligand; Asymmetric catalysis; Axial chirality.

Recently, optically active [1,1′-binaphthalene]-2,2′-diamine (**1**) and its derivatives have been the focus of attention in asymmetric synthesis[1,2]. However, very little effort has been reported to develop bis-arylamines with markedly different core structures, and so we became very interested in the development of a new class of bis-arylamine. We would like to report herein the first synthesis of optically pure *trans*-1,2-bis(2-aminophenyl)cyclopentanes **2a** and **2b** with the following characteristic: an orientation of aromatic groups capable of producing cyclic structures bearing an enveloping C_2-symmetric chiral wall (Fig. 1, calculated by MOPAC (ref.[3]): PM3, precise mode).





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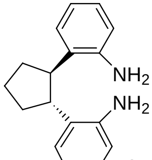
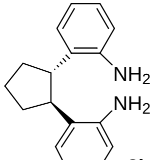


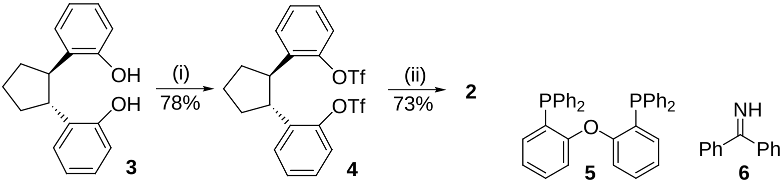
2a



2b

FIG. 1
Possible structure for **2a**. H atoms are omitted for clarity

We first selected the optically pure *trans*-1,2-bis(2-hydroxyphenyl)cyclopentane (**3**) as the starting material for the synthesis of the optically pure bis-aniline **2**, and our attempt is shown in Scheme 1. Treatment of optically pure **3**, which has been reported by Whitesell[4], with trifluoromethanesulfonic anhydride (Tf_2O) and pyridine in CH_2Cl_2 at –20 °C afforded the optically pure bis-triflate **4** in 89% yield. We examined the Buchwald amination[5,6] of optically pure **4**, but our efforts were unsuccessful because this amination afforded completely racemic **2**.

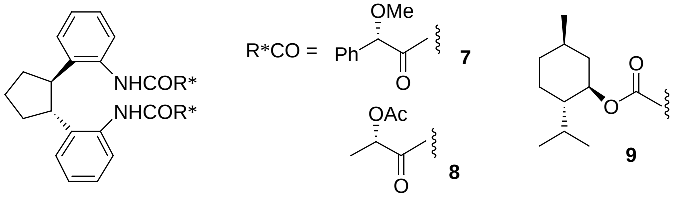


Reagents and conditions: (i) Tf_2O, pyridine, CH_2Cl_2, -20 °C; (ii) $Pd(OAc)_2$, ligand **5**, benzophenone imine **6**, molecular sieves 4A, Cs_2CO_3, Et_3N, toluene, 120 °C, 20 h; then 10% aqueous HCl, EtOH/THF

SCHEME 1

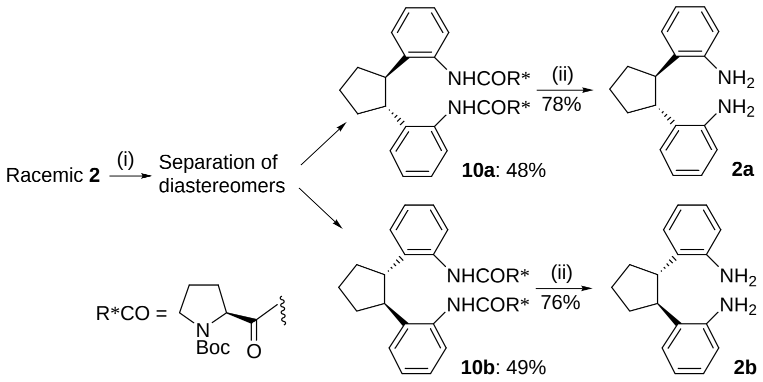
We then planned elaboration of the method with the racemic **3** as the starting material. This involves the Buchwald amination of racemic **4** and subsequent optical resolution of racemic **2**. After trifluoromethanesulfonylation of racemic **3**, racemic **4** underwent amination to afford racemic **2** in 73% yield.

With racemic **2** in hand, its resolution was investigated. Many attempts to resolve racemic **2** *via* the salts of (1*S*)-camphor-10-sulfonic acid and (2*R*,3*R*)-2,3-di(benzoyloxy)succinic acid or *via* the (*S*)-2-methoxy-2-phenylacetamide (**7**), (*S*)-2-acetoxypropionamide (**8**), and (1*R*)-menthyl carbamate (**9**) were unsuccessful.



However, we finally found that the resolution could be accomplished *via* its bis-*N*-*tert*-butoxycarbonyl-L-prolinylamide (Scheme 2). The amidation of racemic **2** with *N*-Boc-L-proline afforded the diastereomers **10a** and **10b** as a

1 : 1 mixture. The diastereomers were separable by preparative TLC on silica gel (ether–hexane 3 : 1). The hydrolysis of the separated diastereomers **10a** and **10b** was accomplished by treatment with 20% aqueous HCl to afford the analytically pure bis-anilines **2a** and **2b** with >99% ee, as determined by HPLC analysis (Daicel Chiralpak AD). The assignment of their absolute configurations was achieved by comparison with (1*S*,2*S*)-**2**, which was independently prepared from (1*S*,2*S*)-**4** of known configuration[7]. As a result, the configuration of (+)-**2a** with $[\alpha]_D^{25}$ +62 (*c* 1.12, $CHCl_3$) and (–)-**2b** with $[\alpha]_D^{25}$ –62 (*c* 1.08, $CHCl_3$) was determined to be 1*R*,2*R* and 1*S*,2*S*, respectively.



Reagents and conditions: (i) *N*-Boc-L-proline, 1,3-dicyclohexylcarbodiimide (DCC), 4-(*N*,*N*-dimethylamino)pyridine (DMAP), CH_2Cl_2; (ii) 20% aqueous HCl, reflux

SCHEME 2

In conclusion, we have succeeded in synthesizing *trans*-1,2-bis(2-aminophenyl)cyclopentanes **2a** and **2b** in optically pure form (>99% ee), respectively. Ongoing efforts are focused on the development of an application of optically pure **2a**, **2b** and its derivatives to asymmetric syntheses.

EXPERIMENTAL

Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were measured on a Jasco FT/IR-230 diffraction grating IR spectrophotometer (wavenumbers are given in cm^{-1}). ^1H and ^{13}C NMR spectra were measured on a JEOL GX-400 NMR spectrometer, operating at 400 MHz for ^1H NMR and at 100 MHz for ^{13}C NMR. All ^1H and ^{13}C NMR spectra were reported in δ-scale (ppm) downfield from tetramethylsilane (δ 0). Coupling constants *J* are given in Hz. Electron impact (EI) mass spectra were obtained from JEOL JMS-DX-303 instrument. Specific rotations (in deg cm^3 g^{-1} l^{-1}) were measured on a Jasco DIP-1000 Digital Polarimeter.

In general, all reactions were carried out in dry solvents under argon atmosphere. Pyridine was distilled under argon atmosphere from CaH_2. Toluene was distilled under argon atmosphere from sodium. All reagents were available from commercial sources and were used without further purification. Silica gel column chromatography and preparative TLC were performed on Kanto Chemical silica gel 60 (spherical, 100–200 μm) and Merck silica gel $60F_{254}$, respectively.

(±)-*trans*-1,2-Bis[2-(trifluoromethanesulfonyloxy)phenyl]cyclopentane (**4**)

To a stirred solution of racemic **3** (1.40 g, 5.50 mmol) in CH_2Cl_2 (15.0 ml) were added pyridine (2.68 ml, 33.1 mmol) and Tf_2O (2.78 ml, 16.5 mmol) dropwise at –20 °C. The reaction mixture was stirred for 30 min at the same temperature, quenched by an addition of water (10 ml), and extracted with EtOAc (3 × 20 ml). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column (EtOAc–hexane 1 : 20) to give the racemic bis-triflate **4** (2.53 g, 89%) as a colorless solid. Recrystallization from EtOAc–hexane gave colorless prisms, m.p. 64–66 °C. IR (Nujol): 1 417, 1 215, 1 139. ^1H NMR ($CDCl_3$): 1.73–1.86 m, 2 H; 1.98–2.06 m, 2 H; 2.36–2.45 m, 2 H; 3.52–3.62 m, 2 H; 7.11 dd, 2 H, *J* = 8.2, 1.3; 7.20 ddd, 2 H, *J* = 8.2, 8.2, 1.7; 7.32 ddd, 2 H, *J* = 7.3, 7.3, 1.3; 7.47 dd, 2 H, *J* = 8.2, 1.7. ^{13}C NMR ($CDCl_3$): 24.06; 34.51; 45.55; 118.2 q, *J* = 319; 120.8; 127.6; 128.1; 128.5; 135.5; 147.5. EI-MS, *m/z*: 518 (M^+), 385, 252, 133, 83 (bp). For $C_{19}H_{16}F_6O_6S_2$ (518.5) calculated: 44.02% C, 3.11% H; found: 44.10% C, 3.15% H.

(±)-*trans*-1,2-Bis(2-aminophenyl)cyclopentane (**2**)

A mixture of the racemic bis-triflate **4** (1.00 g, 1.93 mmol), $Pd(OAc)_2$ (52.1 mg, 0.232 mmol), ligand **5** (187 mg, 0.347 mmol), Et_3N (0.14 ml, 1.00 mmol), benzophenone imine **6** (6.38 ml, 38.0 mmol), and molecular sieve 4A (2.00 g) in toluene (5.00 ml) was stirred for 20 min at 25 °C. To this mixture was then added Cs_2CO_3 (6.19 g, 19.0 mmol). The whole mixture was stirred for 20 h under reflux, allowed to cool, and diluted with EtOAc. The resulting mixture was filtered to remove the solid material. The filtrate was washed with brine, dried over Na_2SO_4, and concentrated. The residue was dissolved in a mixture of THF (12. 0 ml) and EtOH (12.0 ml), and treated with aqueous 10% HCl (18.0 ml). The solution was stirred for 3 h at 25 °C and then concentrated. The residue was diluted with EtOAc (30 ml) and water (30 ml). The combined organic layer was washed with aqueous 10% NaOH and brine, dried over Na_2SO_4, and concentrated. Purification by silica gel column chromatography (EtOAc–benzene 1 : 4) and subsequent recrystallization (EtOAc–hexane) gave the racemic bis-aniline **2** (353 mg, 73%) as colorless needles, m.p. 114–116 °C. IR (Nujol): 3 391. ^1H NMR (C_6D_6): 1.64–1.74 m, 4 H; 1.96–2.04 m, 2 H; 2.86 br s, 4 H; 3.05–3.12 m, 2 H; 6.28 dd, 2 H, *J* = 7.3, 1.2; 6.74 ddd, 2 H, *J* = 7.3, 7.3, 1.2; 6.94 ddd, 2 H, *J* = 7.3, 7.3, 1.7; 7.10 dd, 2 H, *J* = 7.3, 1.7. ^{13}C NMR ($CDCl_3$): 25.28; 33.13; 47.10; 116.2; 119.2; 126.0; 126.5; 129.3; 144.4. EI-MS, *m/z*: 253 (M^+ + 1), 252 (M^+), 159 (bp), 118. For $C_{17}H_{20}N_2$ (252.4) calculated: 80.91% C, 7.99% H, 11.10% N; found: 80.93% C, 8.16% H, 10.98% N.

trans-(1*R*,2*R*)-Bis(2-{[*N*-Boc-(*S*)-prolyl]amino}phenyl)cyclopentane (**10a**) and *trans*-(1*S*,2*S*)-Bis(2-{[*N*-Boc-(*S*)-prolyl]amino}phenyl)cyclopentane (**10b**)

To a stirred solution of the racemic bis-aniline **2** (151 mg, 0.60 mmol) in CH_2Cl_2 (5.00 ml) were added *N*-Boc-L-proline (452 mg, 2.10 mmol), DCC (433 mg, 2.10 mmol), and DMAP (7.3 mg, 0.06 mmol) at room temperature. The reaction mixture was stirred for 3 h at room temperature, washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by preparative TLC on silica gel (Et_2O–hexane 3 : 1) to give **10a** (187 mg, 48%) as a colorless amorphous solid and **10b** (189 mg, 49%) as a colorless solid, respectively. Recrystallization of **10b** from Et_2O–hexane gave pure form of **10b** as colorless needles, m.p. 177–179 °C.

Compound **10a**: $[\alpha]_D^{25}$ –34 (*c* 1.00, $CHCl_3$). IR (Nujol): 3 325, 1 695, 1 661. ^{1}H NMR (DMSO-d_6, 100 °C): 1.35–1.55 m, 2 H; 1.42 s, 18 H; 1.78–1.97 m, 8 H; 2.12–2.22 m, 2 H; 2.31–2.37 m, 2 H; 3.35–3.45 m, 4 H; 3.48–3.56 m, 2 H; 4.33 dd, 2 H, *J* = 8.1, 3.2; 7.00–7.09 m, 4 H; 7.20–7.36 m, 4 H; 8.80 br s, 2 H. ^{13}C NMR (DMSO-d_6, 100 °C): 23.00; 23.11; 27.77; 29.89; 33.86; 44.58; 46.25; 59.66; 78.22; 124.9; 125.0; 125.1; 125.6; 135.3; 137.8; 153.1; 170.5. EI-MS, *m/z*: 647 (M^+ + 1), 547, 446, 250, 57 (bp). For $C_{37}H_{50}N_4O_6$ (646.84) calculated: 68.71% C, 7.79% H, 8.66% N; found: 68.83% C, 7.93% H, 8.49% N.

Compound **10b**: $[\alpha]_D^{25}$ –140 (*c* 1.00, $CHCl_3$). IR (Nujol): 3 381, 1 667, 1 652. ^{1}H NMR (DMSO-d_6, 100 °C): 1.30–1.50 m, 2 H; 1.41 s, 18 H; 1.75–2.04 m, 8 H; 2.15–2.24 m, 2 H; 2.30–2.38 m, 2 H; 3.36–3.47 m, 4 H; 3.51–3.59 m, 2 H; 4.37 dd, 2 H, *J* = 8.5, 3.9; 7.00–7.09 m, 4 H; 7.25–7.30 m, 4 H; 8.91 br s, 2 H. ^{13}C NMR (DMSO-d_6, 100 °C): 23.02; 23.58; 28.20; 30.23; 33.88; 44.34; 46.72; 60.13; 78.69; 125.4; 125.5; 125.6; 126.0; 135.9; 138.0; 153.6; 171.0. EI-MS, *m/z*: 647 (M^+ + 1), 547, 446, 57 (bp). For $C_{37}H_{50}N_4O_6$ (646.8): 68.71% C, 7.79% H, 8.66% N; found: 68.42% C, 7.98% H, 8.47% N.

trans-(1*R*,2*R*)-Bis(2-aminophenyl)cyclopentane (**2a**)

A mixture of **10a** (210 mg, 0.325 mmol) and aqueous 20% HCl (5.0 ml) was refluxed for 12 h, allowed to cool, alkalinized with saturated aqueous Na_2CO_3, and extracted with EtOAc (3 × 10 ml). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by preparative TLC on silica gel (EtOAc–hexane 1 : 2) to give **2a** (64.1 mg, 78%, >99% ee) as a colorless solid. Recrystallization from Et_2O–hexane gave **2a** as colorless prisms, m.p. 121–122 °C. $[\alpha]_D^{25}$ +62 (*c* 1.12, $CHCl_3$). Other spectral data of **2a** were identical to those of racemic **2**.

trans-(1*S*,2*S*)-Bis(2-aminophenyl)cyclopentane (**2b**)

A mixture of **10b** (130 mg, 0.201 mmol) and aqueous 20% HCl (5.0 ml) was refluxed for 12 h, allowed to cool, alkalinized with saturated aqueous Na_2CO_3, and extracted with EtOAc (3 × 10 ml). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by preparative TLC on silica gel (EtOAc–hexane 1 : 2) to give **2b** (38.5 mg, 76%, >99% ee) as a colorless solid. Recrystallization from Et_2O–hexane gave **2b** as colorless prisms, m.p. 122–123.5 °C. $[\alpha]_D^{25}$ –62 (*c* 1.08, $CHCl_3$). Other spectral data of **2b** were identical to those of racemic **2**.

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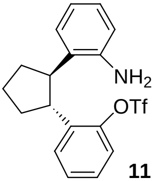
7. By shortening the time of palladium-catalyzed reaction from 20 to 9 h, the Buchwald amination of (1*S*,2*S*)-**4** was carried out to afford (1*S*,2*S*)-**2** in 4% yield with 95% ee, along with the mono-aniline **11** in 19% yield and the starting bis-triflate **4** in 45% yield (see below).



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