JOC*Note*

Facile Synthesis of Structurally Diverse 3,3′-Disubstituted 1,1′-Binaphthyl-2,2′-diamines in Optically Pure Forms

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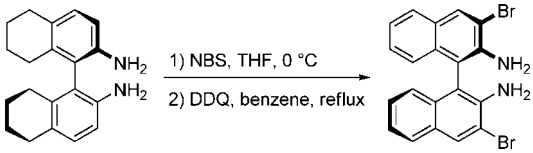
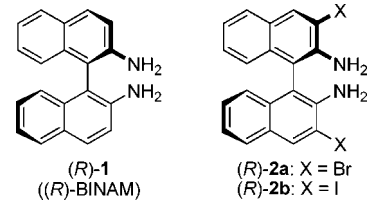


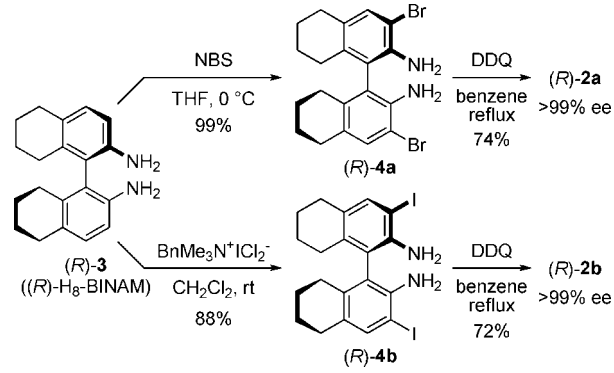
A new synthetic route to 3,3′-dihalo BINAMs based on the direct halogenation of H_8-BINAM and subsequent rearomatization to the binaphthyl core has been developed. The combination of this new procedure and Pd-catalyzed coupling reactions enabled us to synthesize various 3,3′-disubstituted BINAMs in only three steps starting from H_8-BINAM.

Axially chiral 2,2′-disubstituted derivatives of 1,1′-binaphthyl such as 1,1′-binaphthyl-2,2′-diol (BINOL) and 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) have been widely used in asymmetric synthesis.[1] Because BINOL[2] and BINAP[3] are readily modifiable, a wide variety of their derivatives have been synthesized and used as chiral ligands and organocatalysts.[4] On the other hand, although the nitrogen analogue 1,1′-binaphthyl-2,2′-diamine (BINAM) **1** and its N-substituted derivatives have also been frequently employed in asymmetric catalysis,[1,5,6] a limited number of 3,3′-substituted BINAMs are available due to the difficulty in their synthesis.[7,8] To our surprise, a general method to prepare 3,3′-dihalo BINAM **2**, which are expected



to be key intermediates for further derivatization of BINAM **1**, has not been reported to date. In this context, we are interested in the short-step synthesis of optically pure 3,3′-dihalo BINAMs **2a** (X = Br) and **2b** (X = I) and their synthetic application. Here we report a convenient procedure for obtaining 3,3′-substituted BINAMs.

SCHEME 1



3,3′-Dihalo BINAM (*R*)-**2** was selected as an initial target, aiming at the introduction of various functional groups at the 3,3′-positions. Since the direct halogenation of the 3,3′-positions of **1** is known to be difficult because of the high reactivity of the 6,6′-positions of **1**,[9] we decided to employ the partially hydrogenated H_8-BINAM (*R*)-**3** as a starting material, whose 6,6′-positions were temporally masked.[10] In addition, (*R*)-**3** would be expected to act as a simple aniline in aromatic substitution reactions. Accordingly, our synthetic approach for the preparation of (*R*)-**2** was to convert (*R*)-**3** to the 3,3′-dihalo H_8-BINAM (*R*)-**4**, and then rearomatize them to the desired 3,3′-dihalo BINAM (*R*)-**2** (Scheme 1). Thus, treatment of (*R*)-**3** with two equiv of *N*-bromosuccinimide in THF at 0 °C for 1 min furnished the desired dibromo H_8-BINAM (*R*)-**4a** in 99% yield. Unfortunately, however, the use of other standard halogenating agents such as *N*-chlorosuccinimide and *N*-iodosuccinimide resulted in a complex mixture of products. In the case of the

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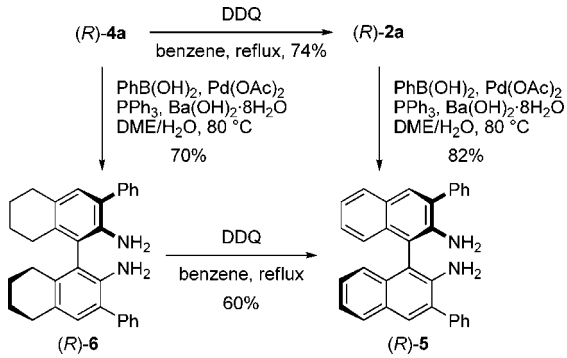
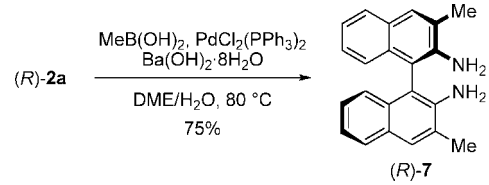
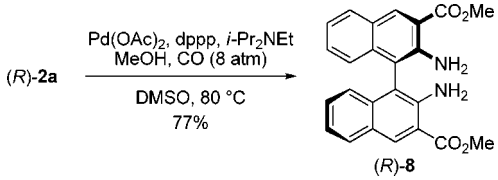
SCHEME 2



SCHEME 3



SCHEME 4



iodination of (*R*)-**3**, benzyltrimethylammonium dichloroiodate[11] was found to be effective, giving the diiodo H_8-BINAM (*R*)-**4b** in 88% yield. With these dihalo H_8-BINAM (*R*)-**4** in hand, we then turned our attention to their conversion to dihalo BINAM (*R*)-**2** by oxidative aromatization. To our delight, the reaction of (*R*)-**4** with 5 equiv of DDQ in benzene proceeded smoothly under reflux conditions to give the desired dihalo BINAM (*R*)-**2a** and (*R*)-**2b** in good yield, respectively. It should be noted that no loss of enantiopurity was observed in the case of (*R*)-**2a** and (*R*)-**2b**, as determined by HPLC analysis.

With the dibromo BINAM (*R*)-**2a**, various substituents could be installed on the 3,3′-positions of BINAM (*R*)-**1**. For instance, the Suzuki−Miyaura coupling[12] of (*R*)-**2a** with phenylboronic acid gave rise to the 3,3′-diphenyl BINAM (*R*)-**5** in 82% yield, which could also be obtained by the Suzuki−Miyaura coupling of (*R*)-**4a** and subsequent aromatization of the resulting (*R*)-**6** (Scheme 2).

Moreover, the Suzuki−Miyaura coupling of (*R*)-**2a** with methylboronic acid provided a convenient synthesis of 3,3′-dimethyl BINAM (*R*)-**7**, which is known as a chiral poison for the racemic Ru complex and has been prepared by the optical resolution of racemic **7** (Scheme 3).[8b,c] Finally, introduction of ester groups on the 3,3′-positions of (*R*)-**1** was achieved by Pd-catalyzed carbonylation of (*R*)-**2a** with CO and MeOH (Scheme 4).[7,13]

In summary, we have developed a new synthetic route to 3,3′-dihalo BINAMs based on the direct halogenation of H_8-BINAM and subsequent rearomatization to the binaphthyl as key steps. The combination of this new procedure and the Pd-catalyzed coupling reactions enabled us to synthesize various 3,3′-disubstituted BINAMs in only three steps starting from the readily available H_8-BINAM.

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Experimental Section

(*R*)-5,5′,6,6′,7,7′,8,8′-Octahydro-1,1′-binaphthyl-2,2′-diamine (*R*)-3.[10] H_8-BINAM (*R*)-**3** was prepared by a slightly modified procedure of Ding.[10b] To a stirred mixture of (*R*)-1,1′-binaphthyl-2,2′-diamine (*R*)-**1** (284 mg, 1.0 mmol) and Raney Ni-Al alloy (2.0 g) in isopropanol (100 mL) and water (100 mL) was gradually added 1% aqueous NaOH solution (200 mL) over 1 h at 90 °C. After 15 h of stirring, the reaction mixture was cooled to room temperature. The mixture was filtered through Celite, and the filter cake was washed with ethyl acetate. The filtrate was then exacted with ethyl acetate, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 3:1 as eluent) to afford (*R*)-**3** (278 mg, 0.95 mmol, 95% yield): ^{1}H NMR, ^{13}C NMR, IR, and HRMS data were consistent with previously reported values.[10a]

(*R*)-3,3′-Dibromo-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl-2,2′-diamine (*R*)-4a. To a stirred solution of (*R*)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl-2,2′-diamine (*R*)-**3** (292 mg, 1.00 mmol) in anhydrous THF (5 mL) was added NBS (356 mg, 2.00 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 min. The mixture was then quenched with saturated $NaHCO_3$ and saturated Na_2SO_3 at 0 °C, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 40:1 as eluent) to afford (*R*)-**4a** (446 mg, 0.99 mmol, 99% yield): [α] 30.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (2H, s), 3.72 (4H, br s), 2.70 (4H, t, J = 6.0 Hz), 2.16−2.25 (2H, m), 2.03−2.13 (2H, m), 1.60−1.74 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 135.6, 132.3, 129.0, 122.4, 107.0, 29.0, 26.7, 23.1, 22.9; IR (neat) 3472, 3375, 2930, 2855, 2359, 2332, 1601, 1456, 1013, 908, 733 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{20}H_{23}Br_2N_2$ 449.0223 ([M + H]$^+$), found 449.0211 ([M + H]$^+$).

(*R*)-3,3′-Diiodo-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl-2,2′-diamine (*R*)-4b. To a stirred solution of (*R*)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl-2,2′-diamine (*R*)-**3** (58.5 mg, 0.2 mmol) and $CaCO_3$ (60 mg, 0.6 mmol) in CH_2Cl_2 (1 mL) and MeOH (400 μL) was added benzyltrimethylammonium dichloroiodate (139 mg, 0.4 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. The mixture was then quenched with saturated $NaHCO_3$ and saturated Na_2SO_3 at 0 °C and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 30:1 as eluent) to afford (*R*)-**4b** (95.8 mg, 0.176 mmol, 88% yield): [α] −17.7 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (2H, s), 3.72 (4H, br s), 2.68 (4H, t, J = 6.0 Hz), 2.15−2.25 (2H, m), 2.03−2.14 (2H, m), 1.58−1.74 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 138.8, 136.7, 129.8, 121.8, 81.5, 28.9, 26.7, 23.1, 22.9; IR (neat) 3460, 3364, 2928, 2855, 2357, 1597, 1452, 908, 733 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{20}H_{23}I_2N_2$ 544.9945 ([M + H]$^+$), found 544.9935 ([M + H]$^+$).

(*R*)-3,3′-Dibromo-1,1′-binaphthyl-2,2′-diamine (*R*)-2a. To a stirred solution of (*R*)-**4a** (76.5 mg, 0.17 mmol) in benzene (3 mL) was added DDQ (193 mg, 0.85 mmol) at room temperature, and the mixture was refluxed for 5 min. Upon consumption of the starting material, the reaction mixture was directly purified by flash column chromatography (hexane/ethyl acetate = 30:1 as eluent) to afford (*R*)-**2a** (55.7 mg, 0.126 mmol, 74% yield, >99% ee): mp 217−222°; [α] 88.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (2H, s), 7.72 (2H, d, J = 8.0 Hz), 7.19−7.29 (4H, m), 6.98

(2H, d, J = 8.0 Hz), 4.12 (4H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3, 132.4, 132.2, 128.6, 127.4, 127.3, 123.8, 123.4, 113.4, 112.6; IR (neat) 3470, 3372, 2957, 2924, 2853, 2367, 1732, 1597, 1497, 1454, 1425, 1360, 1202, 997, 907, 880, 729 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{20}H_{15}Br_2N_2$ 440.9602 ([M + H]$^+$), found 440.9597 ([M + H]$^+$). HPLC analysis: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 19:1, flow rate = 0.5 mL/min, t_R = 21.6 min (*S*) and 25.9 min (*R*).

(*R*)-3,3′-Diiodo-1,1′-binaphthyl-2,2′-diamine (*R*)-2b. Compound (*R*)-**2b** was prepared in a similar manner as described above using (*R*)-**4b** instead of (*R*)-**4a** (72% yield, >99% ee): mp 265−268°; [α] 20.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (2H, s), 7.69 (2H, dd, J = 2.4, 6.4 Hz), 7.17−7.30 (4H, m), 6.98 (2H, dd, J = 2.4, 6.4 Hz), 4.10 (4H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 139.5, 133.0, 129.5, 127.6, 127.1, 123.8, 123.2, 112.7, 88.0; IR (neat) 3466, 3337, 3051, 2924, 2853, 2357, 1734, 1595, 1419, 1271, 881, 745 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{20}H_{15}I_2N_2$ 536.9319 ([M + H]$^+$), found 536.9316 ([M + H]$^+$). HPLC analysis: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 19:1, flow rate = 0.5 mL/min, t_R = 23.7 min (*R*) and 32.6 min (*S*).

(*R*)-3,3′-Diphenyl-1,1′-binaphthyl-2,2′-diamine (*R*)-5. A mixture of (*R*)-**2a** (88.4 mg, 0.2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), PPh_3 (21.0 mg, 0.08 mmol), $Ba(OH)_2 \cdot 8H_2O$ (252 mg, 0.8 mmol), and phenylboronic acid (73 mg, 0.6 mmol) in degassed DME (2 mL) and H_2O (200 μL) was refluxed for 20 h under an argon atmosphere. After cooling to room temperature, the resulting mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/diethyl ether = 25:1 to 10:1 as eluent) to afford (*R*)-**5** (71.6 mg, 0.164 mmol, 82% yield, >99% ee): ^{1}H NMR, ^{13}C NMR, IR, and HRMS data were consistent with previously reported values.[8a] HPLC analysis: Daicel Chiralcel OD, hexane/*i*-PrOH = 100:1, flow rate = 0.5 mL/min, t_R = 19.5 min (*R*) and 26.1 min (*S*).

(*R*)-3,3′-Diphenyl-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl-2,2′-diamine (*R*)-6. (*R*)-**6** was prepared in a similar manner as described above using (*R*)-**4a** instead of (*R*)-**2a** (70% yield): ^{1}H NMR, ^{13}C NMR, IR, and HRMS data were consistent with previously reported values.[6c]

(*R*)-3,3′-Dimethyl-1,1′-binaphthyl-2,2′-diamine (*R*)-7. A mixture of (*R*)-**2a** (68 mg, 0.154 mmol), $PdCl_2(PPh_3)_2$ (10.5 mg, 0.015 mmol), $Ba(OH)_2 \cdot 8H_2O$ (195 mg, 0.62 mmol), and methylboronic acid (28 mg, 0.46 mmol) in degassed DME (3 mL) and H_2O (300 μL) was stirred at 80 °C for 36 h under an argon atmosphere. After cooling to room temperature, the resulting mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 4:1 as eluent) to afford (*R*)-**7** (36 mg, 0.115 mmol, 75% yield, >99% ee): mp 250−252°; ^{1}H NMR, ^{13}C NMR, IR, and HRMS data were consistent with previously reported values.[8c] HPLC analysis: Daicel Chiralcel OD-H, hexane/*i*-PrOH = 4:1, flow rate = 1.0 mL/min, t_R = 8.6 min (*R*) and 13.5 min (*S*).

(*R*)-3,3′-Bis(methoxycarbonyl)-1,1′-binaphthyl-2,2′-diamine (*R*)-8. A mixture of (*R*)-**2a** (66.3 mg, 0.15 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), dppp (13.6 mg, 0.033mmol) and *i*-Pr_2NEt (115 μL, 0.66 mmol) in DMSO (6 mL) and MeOH (4 mL) was transferred into an autoclave. The autoclave was pressurized to 8 atm with CO gas, and the mixture was heated to 80 °C and stirred for 36 h with the pressure staying about 8 atm. After cooling of the autoclave to room temperature, the resulting mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 3:1 as eluent) to afford (*R*)-**8** (46.2 mg, 0.116 mmol, 77% yield): mp 250−254°; [α] 193.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR, ^{13}C NMR, IR, and HRMS data were consistent with previously reported values.[7]

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Supporting Information Available: Experimental details and ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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