Prediction of Suitable Catalyst by ^{1}H NMR: Asymmetric Synthesis of Multisubstituted Biaryls by Chiral Phosphoric Acid Catalyzed Asymmetric Bromination

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General experimental procedures.

All reactions utilizing air- and moisture-sensitive reagents were performed in dried glassware under an atmosphere of dry nitrogen. Ethereal solvents (THF, Et_2O) were distilled from benzophenone ketyl. Dichloromethane and 1,2-dichloroethane were distilled over CaH_2. Benzene and toluene were distilled over CaH_2, and stored over 4A molecular sieves. *N*,*N*-Dimethylformamide (DMF) was distilled over CaH_2, and stored over 4A molecular sieves.

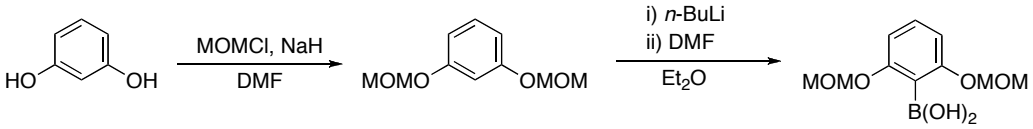
For thin-layer chromatography (TLC) analysis, Merck pre-coated plates (silica gel 60 F_{254}, Art 5715, 0.25 mm) were used. Column chromatography and preparative TLC (PTLC) were performed on PSQ 60B, Fuji Silysia Chemical Ltd. and Wakogel B-5F, Wako Pure Chemical Industries, respectively.

Melting point (mp) determinations were performed by using a AS ONE ATM-01 instrument and are uncorrected. ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and ^{31}P NMR were measured on a varian-400 MR (Varian Ltd., 400 MHz) spectrometer. Chemical shifts are expressed in parts per million (ppm) downfield from internal standard (tetramethylsilane for ^{1}H, C_6F_6 for ^{19}F, and H_3PO_4 for ^{31}P NMR, 0.00 ppm), and coupling constants are reported as hertz (Hz). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; sep, septet; m, multiplet. Infrared (IR) spectra were recorded on a FTIR-8600PC instrument (Shimadzu Co.). Elemental analysis (EA) was carried out on Flash2000 instrument (Amco Inc.).

1. Preparation of starting materials.

All starting materials were synthesized according to the reported procedure.[1,2] The preparation and data of new compounds are shown below.

Scheme 1. Preparation of MOM-protected boronic acid **s3**.[1]



s1 **s2** 68% (2 steps) **s3**

To a suspension of NaH (60% oil, 1.67 g, 41.8 mmol) in DMF (30.0 mL) were successively added a solution of resolcinol (**s1**) (2.01 g, 18.3 mmol) in DMF (30.0 mL) and MOMCl (3.04 mL, 40.2 mmol) at 0 °C. After being stirred for 4 h at room temperature, the reaction was stopped by adding 1 M aqueous HCl. The crude products were extracted with EtOAc (x4) and the combined organic extracts were washed with 1 M aqueous HCl (x6), brine, dried (Na_2SO_4), and concentrated in vacuo to give crude **s2** (3.71 g). This material was used to next reaction without further purification.

To a solution of **s2** in Et_2O (72.7 mL) was added *n*-BuLi (1.60 M in hexane, 13.6 mL, 21.8 mmol) at 0 °C. After stirring for 3 h at room temperature, $B(OMe)_3$ (3.04 mL, 27.4 mmol) was added to the reaction mixture at 0 °C. After being stirred for 1 h at room temperature, the reaction was acidified by 2 M HCl at 0 °C. After being stirred for 1 h at room temperature, the resulting white precipitates were filtered off and washed by H_2O to afford analytically pure **s3** (3.01 g, 68%) as a white solid.

Mp. 115–116 °C.

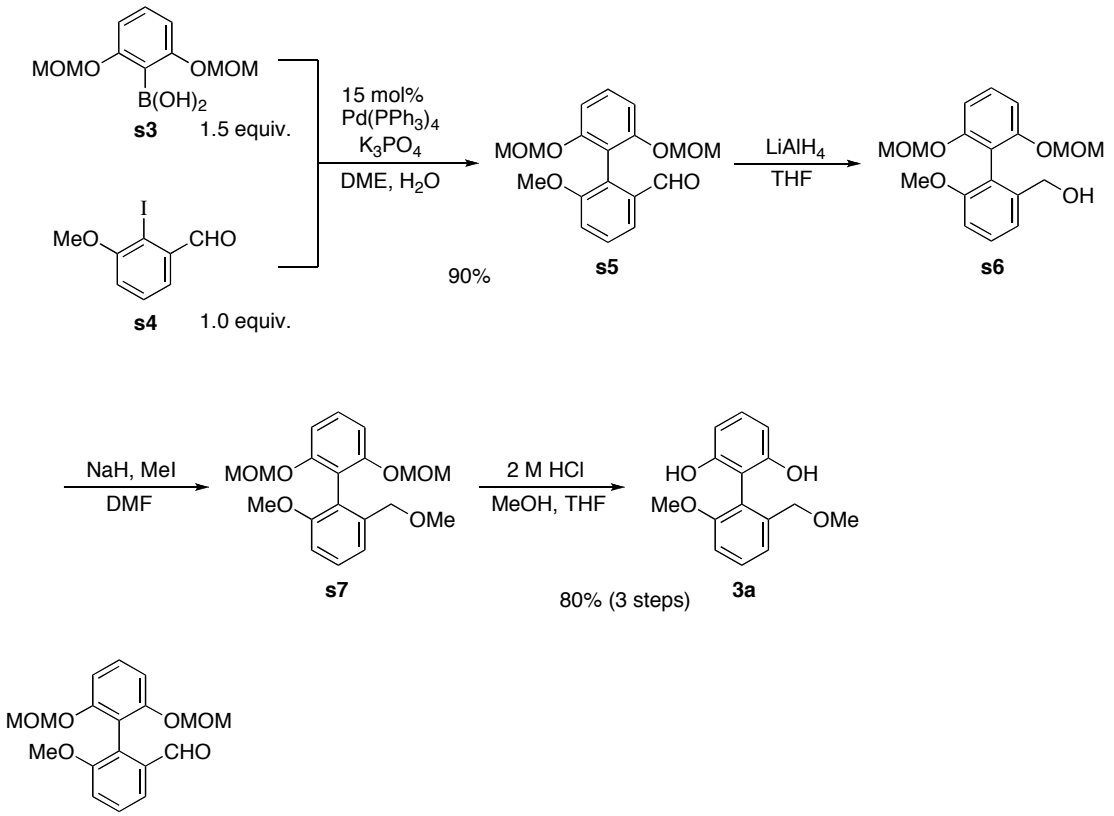
IR (KBr) 3316, 2951, 2898, 2826, 1600, 1585, 1461, 1441, 1397, 1370, 1337, 1308, 1241, 1199, 1152, 1097, 1044, 1008, 921, 893 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 3.51 (s, 6H), 5.30 (s, 4H), 6.88 (d, 1H, J = 8.0 Hz), 7.23 (brs, 2H), 7.35 (dd, 1H, J = 8.0, 8.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ 56.5, 94.8, 108.2, 133.0, 163.0.

Anal. Calcd for $C_{10}H_{15}BO_6$: C, 49.62; H, 6.25. Found: C, 49.45; H, 6.55.

Scheme 2. General synthetic route to biphenol **3a**.[2] Preparation of **3a** is shown as a representative example.



Synthesis of 6-methoxy-2',6'-bis(methoxymethoxy)biphenyl-2-carbaldehyde (s5):

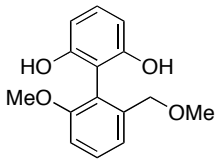
The mixture of boronic acid **s3** (530 mg, 2.18 mmol), iodobenzene **s4** (438 mg, 1.67 mmol),[2] $Pd(PPh_3)_4$ (290 mg, 0.250 mmol), K_3PO_4 (1.08 g, 5.09 mmol), DME (17.0 mL), and H_2O (5.6 mL) were heated at reflux for 4.5 h. After cooling to room temperature, the reaction was stopped by adding H_2O. The crude mixture was extracted with EtOAc (x3) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 2/1) to give **s5** (500 mg, 90%) as a colorless amorphous.

IR (neat) 2959, 2828, 1689, 1591, 1466, 1402, 1306, 1261, 1247, 1202, 1181, 1153, 1100, 1044, 918, 894, 783, 741, 727, 666 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 3.26 (s, 6H), 3.77 (s, 3H), 5.01 (d, 2H, J = 6.8 Hz), 5.05 (d, 2H, J = 6.8 Hz), 6.92 (d, 2H, J = 8.4 Hz), 7.20 (d, 1H, J = 8.0 Hz), 7.33 (dd, 1H, J = 8.4, 8.4 Hz), 7.46 (dd, 1H, J = 8.0, 8.0 Hz), 7.64 (dd, 1H, J = 1.2, 8.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ 55.8, 55.9, 94.6, 108.5, 113.1, 115.9, 118.6, 128.0, 128.7, 130.0, 135.4, 155.9, 157.5, 192.9.

Anal. Calcd for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07. Found: C, 64.93; H, 6.08.



Synthesis of 2'-methoxy-6'-(methoxymethyl)biphenyl-2,6-diol (3a):

To a solution of **s5** (2.55 g, 7.68 mmol) in THF (38.0 mL) was added $LiAlH_4$ (219 mg, 5.75 mmol) at 0 °C. After being stirred for 0.5 h at 0 °C, the reaction was stopped by adding $Na_2SO_4 \cdot 10H_2O$. After being stirred for another 1 h at room temperature, the crude material was filtered through Celite® pad and the resulting filtrate was concentrated in vacuo to give crude benzyl alcohol **s6** (2.57 g). The crude material was used for the next reaction without further purification.

To a solution of **s6** in DMF (38.0 mL) were successively added NaH (60% oil, 590 mg, 14.7 mmol) and MeI (0.90 mL, 14.5 mmol) at 0 °C. After being stirred for 4 h at room temperature, the reaction was stopped by adding aqueous 1 M HCl at 0 °C. The crude mixture was extracted with EtOAc (x3) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give methyl ether **s7** (2.75 g). The crude material was used for the next reaction without further purification.

To a solution of **s7** in THF (29.0 mL) and MeOH (38.5 mL) was added aqueous 2 M HCl (19.0 mL, 38.0 mmol) at 0 °C. After being stirred for 5.5 h at 50 °C, the reaction was stopped by adding saturated aqueous $NaHCO_3$ at 0 °C. The crude mixture was extracted with EtOAc (x3) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 2/1) to give **3a** (1.60 g, 96% from **s3**) as a white solid.

Mp. 110–111 °C.

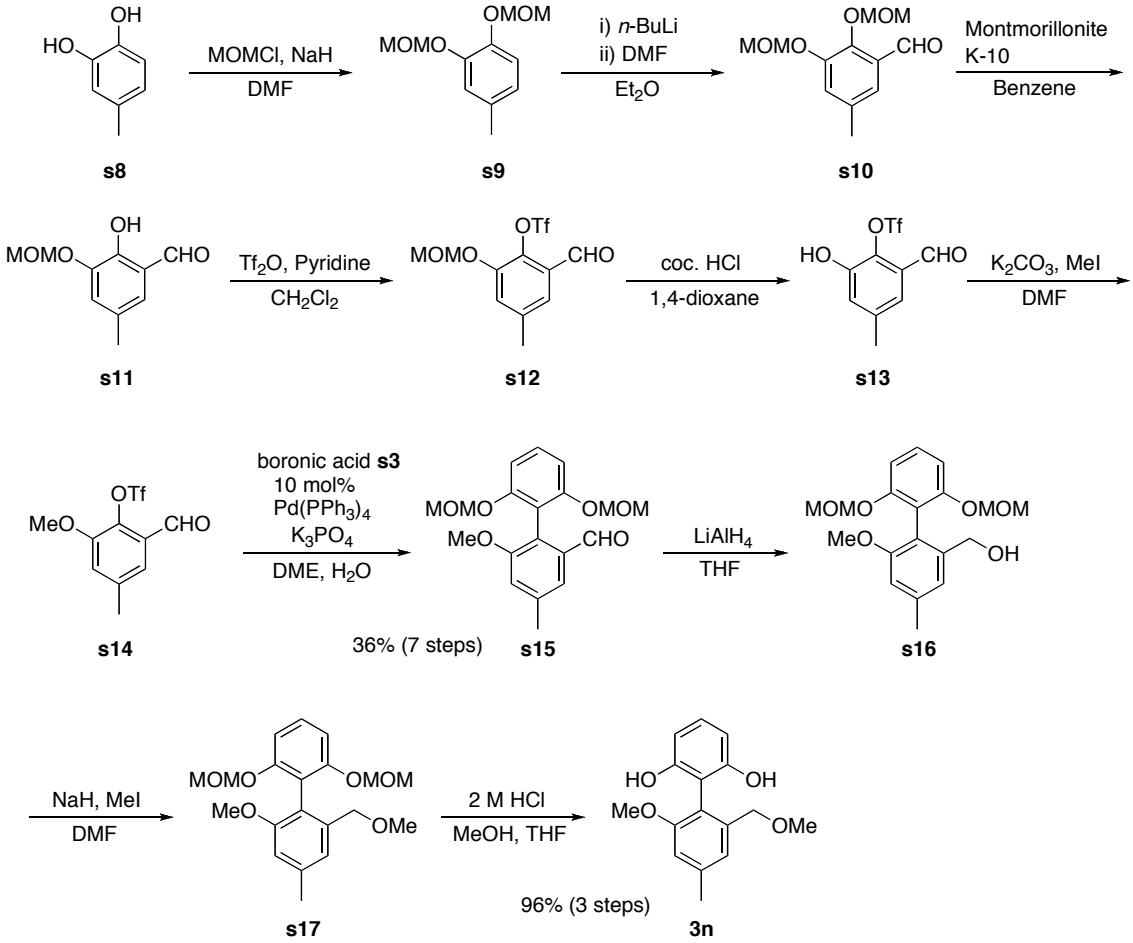
IR (neat) 3398, 2934, 2836, 1620, 1581, 1506, 1463, 1437, 1378, 1265, 1188, 1151, 1069, 1008, 911, 787, 732, 676, 645 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 3.27 (s, 3H), 3.72 (s, 3H), 4.16 (s, 2H), 5.29 (s, 2H), 6.59 (d, 2H, J = 8.4 Hz), 7.00 (d, 1H, J = 8.0 Hz), 7.16 (dd, 1H, J = 8.4, 8.4 Hz), 7.18 (d, 1H, J = 8.0 Hz), 7.43 (dd, 1H, J = 8.0, 8.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ 56.0, 58.5, 73.0, 108.5, 111.0, 111.5, 118.8, 122.1, 129.6, 130.6, 140.0, 154.1, 158.0.

Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found: C, 69.37; H, 6.09.

Scheme 3. General synthetic route to biphenol **3n**.



To a suspension of NaH (60% oil, 1.68 g, 41.9 mmol) in DMF (22.0 mL) were successively added a solution of 4-methylcatecol (**s8**) (2.00 g, 16.1 mmol) in DMF (22.0 mL) and MOMCl (2.81 mL, 37.1 mmol) at 0 °C. After being stirred for 10 h at room temperature, the reaction was stopped by adding 1 M aqueous HCl. The crude products were extracted with EtOAc(x4) and the combined organic extracts were washed with 1 M aqueous HCl (x6), brine, dried (Na_2SO_4), and concentrated in vacuo to give crude **s9** (3.70 g). This material was used to next reaction without further purification.

To a solution of **s9** in Et_2O (80.6 mL) was added *n*-BuLi (1.65 M in hexane, 11.7 mL, 19.3 mmol) at 0 °C. After stirring for 3 h at room temperature, DMF (3.17 mL, 32.2

mmol) was added to the reaction mixture at 0 °C. After being stirred for 10 min at 0 °C, the reaction was stopped by adding saturated aqueous NH_4Cl. The crude products were extracted with EtOAc (x3) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 6/1) to give **s10** (3.25g) as a pale yellow oil with inseparable impurities. This material was used to next reaction without further purification.

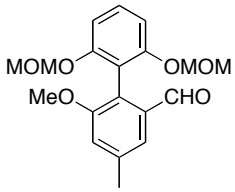
To a solution of **s10** in Benzene (120 mL) was added Montmorillonite K-10 (2.95 g) at room temperature. After being stirred for 20 min, the crude material was filtered through Celite® pad, and the resulting filtrate was concentrated in vacuo to give crude **s11** (2.56 g). This material was used to next reaction without further purification.

To a solution of **s11** in CH_2Cl_2 (124 mL) were successively added pyridine (2.99 mL, 37.0 mmol) and Tf_2O (3.10 mL, 18.5 mmol) at 0 °C. After being stirred for 5 h at room temperature, the reaction was stopped by adding saturated aqueous $NaHCO_3$ at 0 °C. The crude products were extracted with CH_2Cl_2 (x4) and the combined organic extracts were washed with 1 M aqueous HCl (x2), brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 8/1) to give **s12** (2.60 g) as a pale yellow oil with inseparable impurities. This material was used to next reaction without further purification.

To a solution of **s12** in 1,4-dioxane (50.2 mL) was added 1 M HCl (10. 0 mL, 10.0 mmol) at 0 °C. After being stirred for 5 h at room temperature, the reaction was stopped by adding saturated aqueous $NaHCO_3$ at 0 °C. The crude products were extracted with EtOAc (x5) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give crude **s13** (2.35 g). This material was used to next reaction without further purification.

To a solution of **s13** in DMF (37.0 mL) were successively added K_2CO_3 (2.05 g, 14.8 mmol) and MeI (0.70 mL, 11.2 mmol) at 0 °C. After being stirred for 5 h at room temperature, the reaction was stopped by adding 1 M aqueous HCl. The crude products were extracted with EtOAc(x4) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10/1) to give **s14** (2.09 g) as a white solid with inseparable impurities. This material was used to next reaction without further purification.

The mixture of boronic acid **s3** (1.96 g, 6.20 mmol), triflate **s14**, $Pd(PPh_3)_4$ (718 mg, 0.621 mmol), K_3PO_4 (3.96 g, 18.6 mmol), DME (27.0 mL), and H_2O (7.0 mL) were heated at reflux for 4 h. After cooling to room temperature, the reaction was stopped by adding H_2O. The crude mixture was extracted with EtOAc (x3) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 6/1) to give **s14** (2.01 g, 36% from **s8**) as a white solid.



6-Methoxy-2',6'-bis(methoxymethoxy)-4-methylbiphenyl-2-carbaldehyde (**s15**).

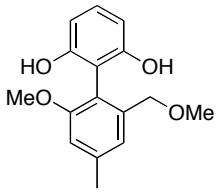
Mp. 117–119 °C.

IR (KBr) 2935, 2902, 2827, 1685, 1602, 1584, 1465, 1430, 1389, 1310, 1248, 1153, 1099, 1081, 1042, 922, 898 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 3.31 (s, 6H), 3.53 (s, 3H), 5.06 (d, 2H, *J* = 6.8 Hz), 5.09 (d, 2H, *J* = 6.8 Hz), 6.89 (d, 2H, *J* = 8.4 Hz), 7.26 (d, 1H, *J* = 2.4 Hz), 7.28 (dd, 1H, *J* = 8.4, 8.4 Hz), 7.65 (d, 1H, *J* = 2.4 Hz), 10.41 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 55.8, 62.3, 94.5, 108.5, 117.3, 127.4, 128.6, 128.7, 129.5, 132.9, 140.0, 155.4, 160.0, 190.5.

Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23. Found: C, 66.49; H, 6.95.



2'-Methoxy-6'-(methoxymethyl)-4'-methylbiphenyl-2,6-diol (**3n**).

White solid.

Yield: 96% (prepared from **s15**).

Mp. 115–116 °C.

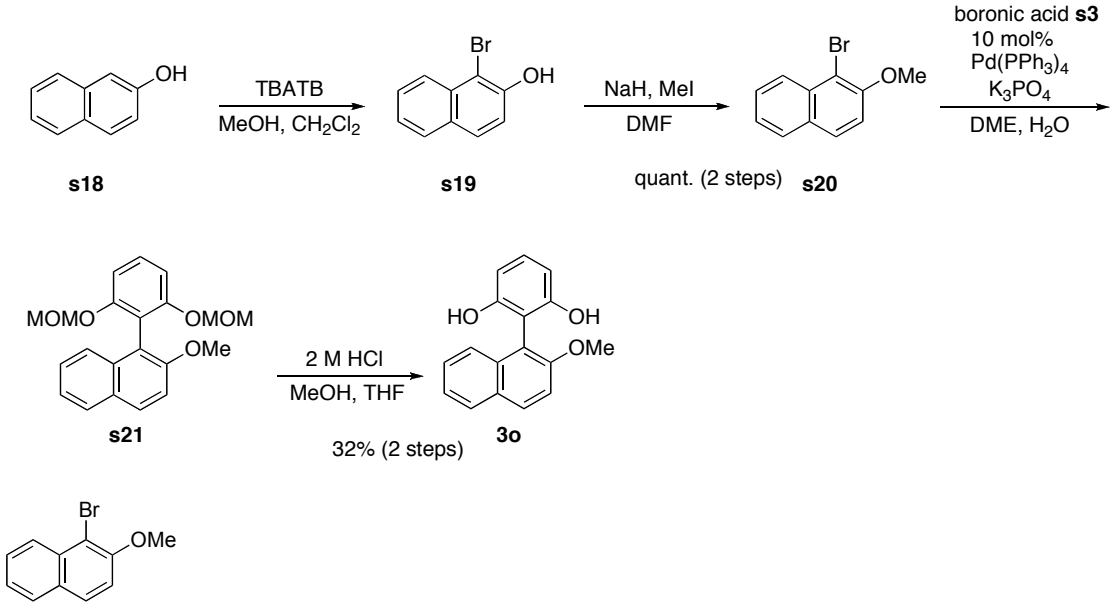
IR (KBr) 3334, 3001, 2977, 2961, 2937, 2873, 2830, 1614, 1582, 1500, 1463, 1371, 1299, 1259, 1224, 1198, 1178, 1161, 1116, 1066, 1011, 997, 963, 920, 893, 876, 860, 799 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 3.48 (s, 3H), 3.52 (s, 3H), 4.54 (s, 2H), 5.51 (brs, 2H), 6.61 (d, 2H, *J* = 8.0 Hz), 7.12 (d, 1H, *J* = 1.2 Hz), 7.16 (dd, 1H, *J* = 8.0, 8.0 Hz), 7.32 (d, 1H, *J* = 1.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 58.6, 62.0, 69.6, 108.7, 112.7, 124.3, 129.8, 131.3, 132.2, 132.7, 135.3, 153.8, 153.9.

Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.25; H, 6.43.

Scheme 4. Preparation of **3o**.



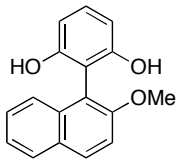
Synthesis of 1-bromo-2-methoxynaphthalene (s20):

To a solution of **s18** (1.00 g, 6.93 mmol) in CH_2Cl_2 (50.6 mL) and MeOH (34.0 mL) was added tetrabutylammonium bromide (3.34 g, 6.93 mmol) at 0 °C. After being stirred for 10 min at 0 °C, the reaction was stopped by adding H_2O. The crude products were extracted with EtOAc (x4) and the combined organic extracts were washed with 1 M aqueous HCl (x1), brine, dried (Na_2SO_4), and concentrated in vacuo to give crude **s19** (1.65 g). This material was used to next reaction without further purification.

To a solution of **s19** in DMF (34.7 mL) were successively added NaH (60% oil, 554 mg, 11.9 mmol) and MeI (0.86 mL, 11.9 mmol) at 0 °C. After being stirred for 3 h at room

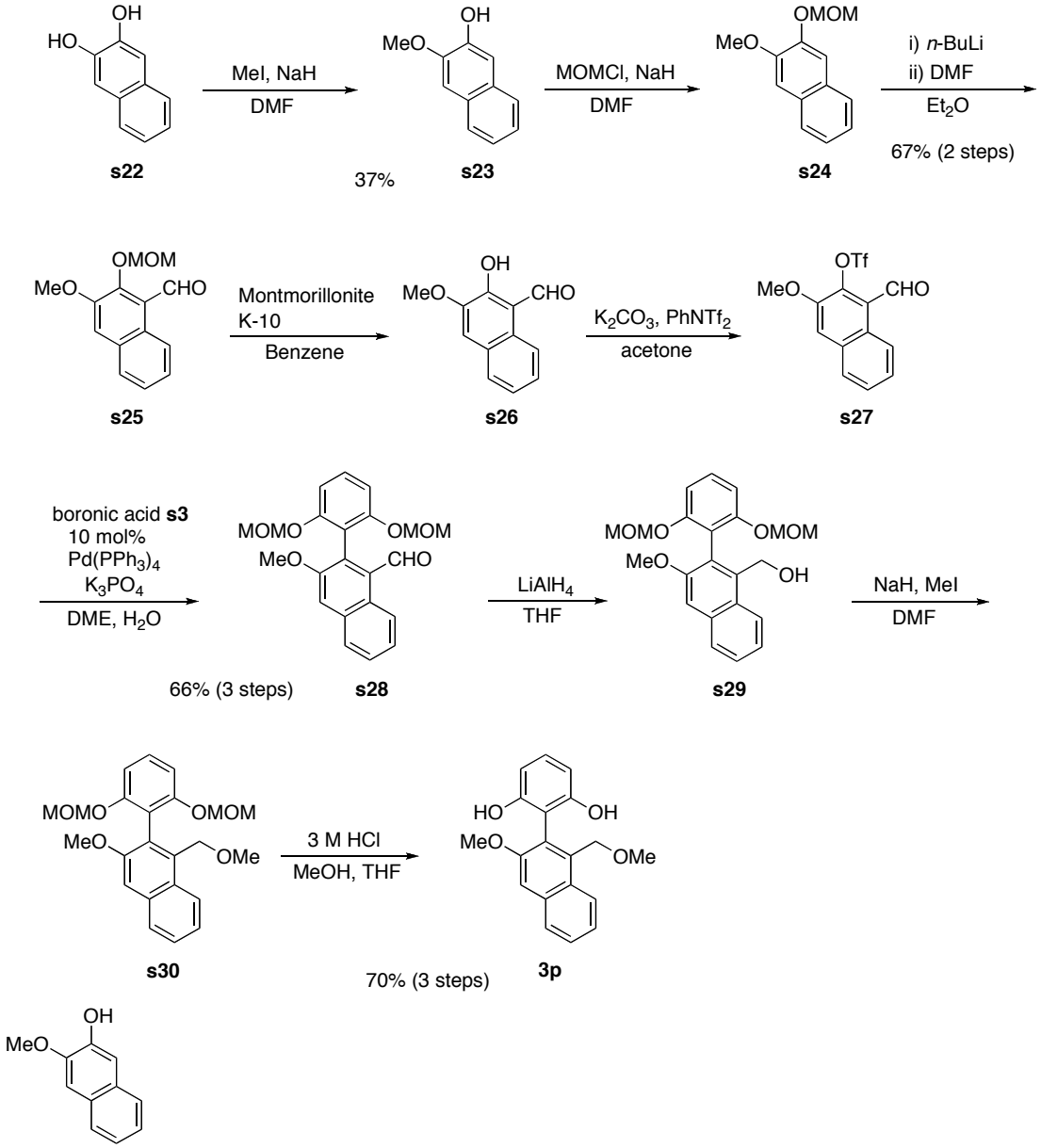
temperature, the reaction was stopped by adding 1 M aqueous HCl. The crude products were extracted with EtOAc (x4) and the combined organic extracts were washed with 1 M aqueous HCl (x6), brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 15/1) to give **s20** (1.65 g, quant. from **s18**) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.03 (s, 3H), 7.27 (d, 1H, *J* = 8.8 Hz), 7.40 (ddd, 1H, *J* = 0.8, 8.0, 8.0 Hz), 7.57 (ddd, 1H, *J* = 0.8, 8.0, 8.0 Hz), 7.78 (d, 1H, *J* = 8.0 Hz), 7.81 (d, 1H, *J* = 8.8 Hz), 8.23 (d, 1H, *J* = 8.0 Hz).
^{13}C NMR (100 MHz, $CDCl_3$) δ 57.0, 108.7, 113.6, 124.3, 126.1, 127.7, 128.0, 128.9, 129.8, 133.1, 153.8.
The ^{1}H and ^{13}C NMR spectra were in complete agreement with those in the literature.[3]



2-(2-methoxynaphthalen-1-yl)benzene-1,3-diol (**3o**).
Yield: 32% (prepared from **s20**).
Mp. 162–163 °C.
IR (KBr) 3477, 3059, 2933, 2835, 1621, 1591, 1507, 1463, 1432, 1384, 1334, 1308, 1255, 1174, 1148, 1120, 1073, 1061, 1007, 904, 812, 785 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (s, 3H), 4.63 (brs, 2H), 6.67 (d, 2H, *J* = 8.4 Hz), 7.26 (dd, 1H, *J* = 8.4, 8.4 Hz), 7.36–7.50 (m, 4H), 7.83–7.90 (m, 1H), 8.00 (d, 1H, *J* = 9.2 Hz).
^{13}C NMR (100 MHz, $CDCl_3$) δ 56.7, 107.8, 109.3, 111.2, 113.5, 124.2, 124.6, 128.0, 128.3, 129.5, 130.0, 131.9, 133.3, 154.3, 156.1.
Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30. Found: C, 76.55; H, 5.45.

Scheme 5. Preparation of **3p**.



Synthesis of 3-methoxynaphthalen-2-ol (s23):

To a solution of **s22** (2.00 g, 12.5 mmol) in DMF (62.0 mL) were successively added NaH (60% oil, 500 mg, 12.5 mmol) and MeI (0.82 mL, 13.1 mmol) at 0 °C. After being stirred for 3 h at room temperature, the reaction was stopped by adding 1 M aqueous HCl. The crude products were extracted with EtOAc (x4) and the combined organic extracts were washed with 1 M aqueous HCl (x6), brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 30/1) to give **s23** (805 mg, 37%) as a white solid.

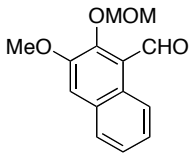
Mp. 128–129 °C.

IR (KBr) 3400, 3046, 2970, 2931, 1637, 1515, 1486, 1439, 1413, 1354, 1280, 1260, 1198, 1163, 1114, 1017, 951 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02 (s, 3H), 5.89 (s, 1H), 7.12 (s, 1H), 7.26 (s, 1H), 7.37–7.48 (m, 2H), 7.61–7.74 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 55.8, 105.7, 109.4, 123.8, 124.3, 126.3, 126.4, 128.9, 129.6, 145.6, 147.3.

Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.55; H, 5.90.



Synthesis of 3-methoxy-2-(methoxymethoxy)-1-naphthaldehyde (s25):

To a suspension of NaH (60% oil, 343 mg, 8.58 mmol) in DMF (12.0 mL) were successively added a solution of **s23** (830 mg, 16.1 mmol) in DMF (12.0 mL) and MOMCl (0.54 mL, 7.15 mmol) at 0 °C. After being stirred for 20 h at room temperature, the reaction was stopped by adding 1 M aqueous HCl. The crude products were extracted with EtOAc(x4) and the combined organic extracts were washed with 1 M aqueous HCl (x6), brine, dried (Na_2SO_4), and concentrated in vacuo to give crude **s24** (1.15 g). This material was used to next reaction without further purification.

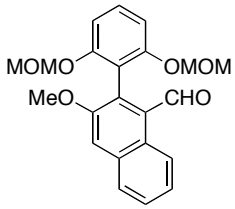
To a solution of **s24** in Et_2O (23.8 mL) was added *n*-BuLi (1.65 M in hexane, 4.30 mL, 7.10 mmol) at 0 °C. After stirring for 2.5 h at room temperature, DMF (0.74 mL, 9.56 mmol) was added to the reaction mixture at 0 °C. After being stirred for 10 min at 0 °C, the reaction was stopped by adding saturated aqueous NH_4Cl. The crude products were extracted with EtOAc (x3) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10/1) to give **s25** (759 mg, 67% from **s23**) as a yellow oil.

IR (neat) 3005, 2939, 2894, 2835, 1681, 1620, 1596, 1505, 1465, 1450, 1433, 1382, 1359, 1288, 1246, 1225, 1205, 1175, 1155, 1077, 1037, 1010, 941, 892 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (s, 3H), 3.99 (s, 3H), 5.30 (s, 2H), 7.40 (s, 1H), 7.41–7.58 (m, 2H), 7.71 (d, 1H, *J* = 8.0 Hz), 9.12 (dd, 1H, *J* = 0.8, 8.0 Hz), 10.88 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 55.9, 58.2, 100.0, 114.1, 123.8, 125.0, 125.8, 126.3, 126.7, 126.9, 131.0, 150.5, 153.9, 192.9.

Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.40; H, 5.55.



Synthesis of 2-(2,6-bis(methoxymethoxy)phenyl)-3-methoxy-1-naphthaldehyde (s28):

To a solution of **s25** (650 mg, 2.64 mmol) in Benzene (26.4 mL) was added Montmorillonite K-10 (650 mg) at room temperature. After being stirred for 0.5 h, the crude material was filtered through Celite® pad, and the resulting filtrate was concentrated in vacuo to give crude **s26** (583 mg). This material was used to next reaction without further purification.

To a solution of **s26** in acetone (20.0 mL) were successively added K_2CO_3 (547 mg, 3.96 mmol) and $PhNTf_2$ (1.13 g, 3.17 mmol) at 0 °C. After being stirred for 3 h at room temperature, the reaction was stopped by adding saturated aqueous $NaHCO_3$ at 0 °C. The crude products were extracted with EtOAc (x5) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give vrude **s27** (1.23 g). This material was used to next reaction without further purification.

The mixture of boronic acid **s3** (958 mg, 3.96 mmol), triflate **s27**, $Pd(PPh_3)_4$ (305 mg, 0.264 mmol), K_3PO_4 (1.68 g, 7.92 mmol), DME (16.0mL), and H_2O (4.0 mL) were heated at reflux for 8 h. After cooling to room temperature, the reaction was stopped by adding H_2O. The crude mixture was extracted with EtOAc (x3) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 6/1) to give **s28** (666 mg, 66% from **s25**) as a white solid.

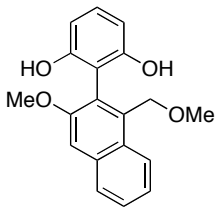
Mp. 198–200 °C.

IR (KBr) 3001, 2959, 2900, 2830, 1688, 1619, 1590, 1466, 1401, 1362, 1285, 1251, 1222, 1200, 1180, 1154, 1099, 1044, 921, 894, 854 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 3.25 (s, 6H), 3.86 (s, 3H), 5.00 (d, 2H, *J* = 6.8 Hz), 5.03 (d, 2H, *J* = 6.8 Hz), 6.92 (d, 2H, *J* = 8.4 Hz), 7.35 (dd, 1H, *J* = 8.4, 8.4 Hz), 7.44 (s, 1H), 7.48–7.59 (m, 2H), 7.78–7.86 (m, 1H), 9.13–9.22 (m, 1H), 10.11 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 55.8, 55.8, 94.4, 108.1, 111.4, 113.4, 125.7, 125.9, 126.2, 126.9, 130.2, 130.3, 134.4, 134.8, 155.0, 155.9, 195.1.

Anal. Calcd for $C_{22}H_{22}O_6$: C, 69.10; H, 5.80. Found: C, 68.85; H, 5.78.



2-(3-Methoxy-1-(methoxymethyl)naphthalen-2-yl)benzene-1,3-diol (**3p**).

White solid.

Yield: 55% (prepared from **s28**).

Mp. 169–171 °C.

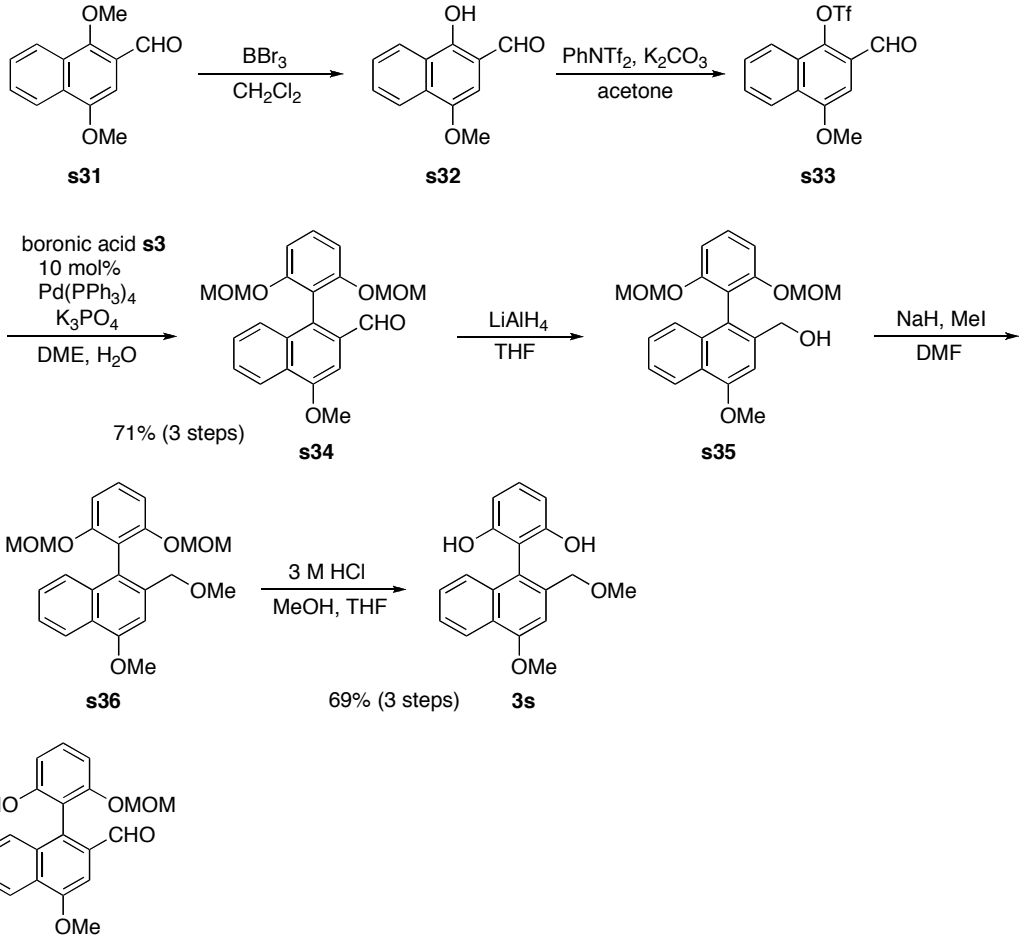
IR (neat) 3398, 3072, 2935, 2830, 1619, 1597, 1504, 1462, 1425, 1396, 1338, 1282, 1227, 1198, 1181, 1152, 1133, 1083, 1065, 1009, 953, 909, 866, 834, 813, 786, 733, 687, 647, 624 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 3.41 (s, 3H), 3.86 (s, 3H), 4.67 (s, 2H), 5.24 (brs, 2H), 6.67 (d, 2H, *J* = 8.4 Hz), 7.23 (dd, 1H, *J* = 8.4, 8.4 Hz), 7.32 (s, 1H), 7.43–7.60 (m, 2H), 7.83 (d, 1H, *J* = 8.0 Hz), 8.12 (d, 1H, *J* = 8.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ 56.0, 59.0, 69.4, 107.7, 108.8, 111.9, 122.4, 124.5, 124.9, 127.3, 127.4, 128.0, 129.9, 135.3, 136.0, 154.4, 155.1.

Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found: C, 73.56; H, 5.81.

Scheme 6. Preparation of **3r**. **3t** was also synthesized by this procedure.



Synthesis of 1-(2,6-bis(methoxymethoxy)phenyl)-4-methoxy-2-naphthaldehyde (s34):

To a solution of **s31**[4] (500 mg, 2.31 mmol) in CH_2Cl_2 (23.0 mL) was added BBr_3 (0.5 M in CH_2Cl_2, 5.10 mL, 2.55 mmol) at –20 °C. After being stirred for 1 h, the reaction was stopped by adding saturated aqueous $NaHCO_3$ at –20 °C. The crude products were extracted with CH_2Cl_2 (x4) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give crude **s32** (463 mg). This material was used to next reaction without further purification.

To a solution of **s32** in acetone (11.0 mL) were successively added K_2CO_3 (805 mg, 5.82 mmol) and $PhNTf_2$ (1.48 g, 4.14 mmol) at 0 °C. After being stirred for 13 h at room temperature, the reaction was stopped by adding saturated aqueous $NaHCO_3$ at 0 °C. The crude products were extracted with EtOAc (x5) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give crude **s33** (2.041 g). This material was used to next reaction without further purification.

The mixture of boronic acid **s3** (720 mg, 2.97 mmol), triflate **s33**, $Pd(PPh_3)_4$ (265 mg,

0.239 mmol), K_3PO_4 (2.20 g, 6.98 mmol), DME (11.5 mL), and H_2O (3.8 mL) were heated at reflux for 4 h. After cooling to room temperature, the reaction was stopped by adding H_2O. The crude mixture was extracted with EtOAc (x3) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 6/1) to give **s34** (627 mg, 71% from **s31**) as a pale orange solid.

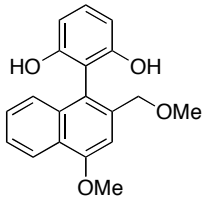
Mp. 159–160 °C.

IR (KBr) 2956, 2932, 2848, 1682, 1596, 1513, 1465, 1422, 1401, 1369, 1346, 1247, 1200, 1154, 1133, 1111, 1097, 1042, 922, 896 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 3.08 (s, 6H), 4.08 (s, 3H), 4.93 (s, 4H), 6.96 (d, 2H, J = 8.4 Hz), 7.36–7.48 (m, 3H), 7.52–7.61 (m, 2H), 8.34 (d, 1H, J = 8.4 Hz), 9.90 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 55.8, 94.1, 98.9, 108.0, 114.3, 122.3, 126.6, 126.9, 128.0, 128.7, 130.3, 131.7, 133.1, 133.4, 155.2, 156.4, 193.1.

Anal. Calcd for $C_{22}H_{22}O_6$: C, 69.10; H, 5.80. Found: C, 69.40; H, 5.77.



2-(4-Methoxy-2-(methoxymethyl)naphthalen-1-yl)benzene-1,3-diol (**3r**).

White solid.

Yield: 69% (prepared from **s34**).

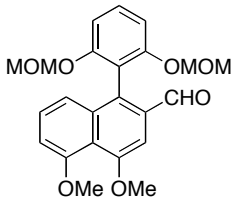
Mp. 180–182 °C.

IR (KBr) 3397, 2933, 1621, 1593, 1511, 1460, 1420, 1378, 1346, 1308, 1276, 1232, 1190, 1172, 1132, 1109, 1035, 1009, 969, 910, 849, 791 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 3.36 (s, 3H), 4.10 (s, 3H), 4.35 (s, 2H), 4.87 (brs, 2H), 6.69 (d, 2H, J = 8.0 Hz), 7.09 (s, 1H), 7.29 (dd, 1H, J = 8.0, 8.0 Hz), 7.38–7.59 (m, 3H), 8.34 (d, 1H, J = 8.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ 55.7, 58.8, 73.4, 104.6, 104.7, 108.2, 111.7, 117.5, 122.4, 125.0, 126.0, 128.0, 130.1, 133.5, 138.0, 154.6, 156.9.

Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found: C, 73.28; H, 5.77.



1-(2,6-bis(methoxymethoxy)phenyl)-4,5-dimethoxy-2-naphthaldehyde (**s37**).

Yield: 60% (prepared from known 1,4,5-trimethoxy-2-naphthaldehyde[5]).

Pale red solid.

Yield: 66%.

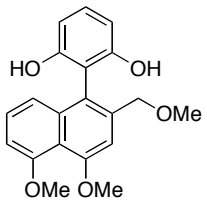
Mp. 140–142 °C.

IR (KBr) 2955, 2934, 2846, 1683, 1591, 1515, 1465, 1441, 1384, 1361, 1337, 1263, 1248, 1200, 1154, 1130, 1098, 1073, 1042, 922, 897, 849 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 3.09 (s, 6H), 4.00 (s, 3H), 4.08 (s, 3H), 4.95 (s, 4H), 6.95 (d, 2H, *J* = 8.4 Hz), 6.99 (d, 1H, *J* = 8.0 Hz), 7.17 (dd, 1H, *J* = 0.8, 8.4 Hz), 7.31 (dd, 1H, *J* = 8.4, 8.4 Hz), 7.36–7.46 (m, 2H), 9.84 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 55.8, 56.1, 56.6, 94.1, 100.4, 108.1, 109.4, 115.0, 119.5, 120.4, 126.9, 130.2, 131.9, 132.4, 136.3, 156.3, 157.1, 157.3, 192.9.

Anal. Calcd for $C_{23}H_{24}O_7$: C, 66.98; H, 5.87. Found: C, 66.71; H, 5.99.



2-(4,5-Dimethoxy-2-(methoxymethyl)naphthalen-1-yl)benzene-1,3-diol (**3t**).

White solid.

Yield: 66% (prepared from **s37**).

Mp. 255–257 °C.

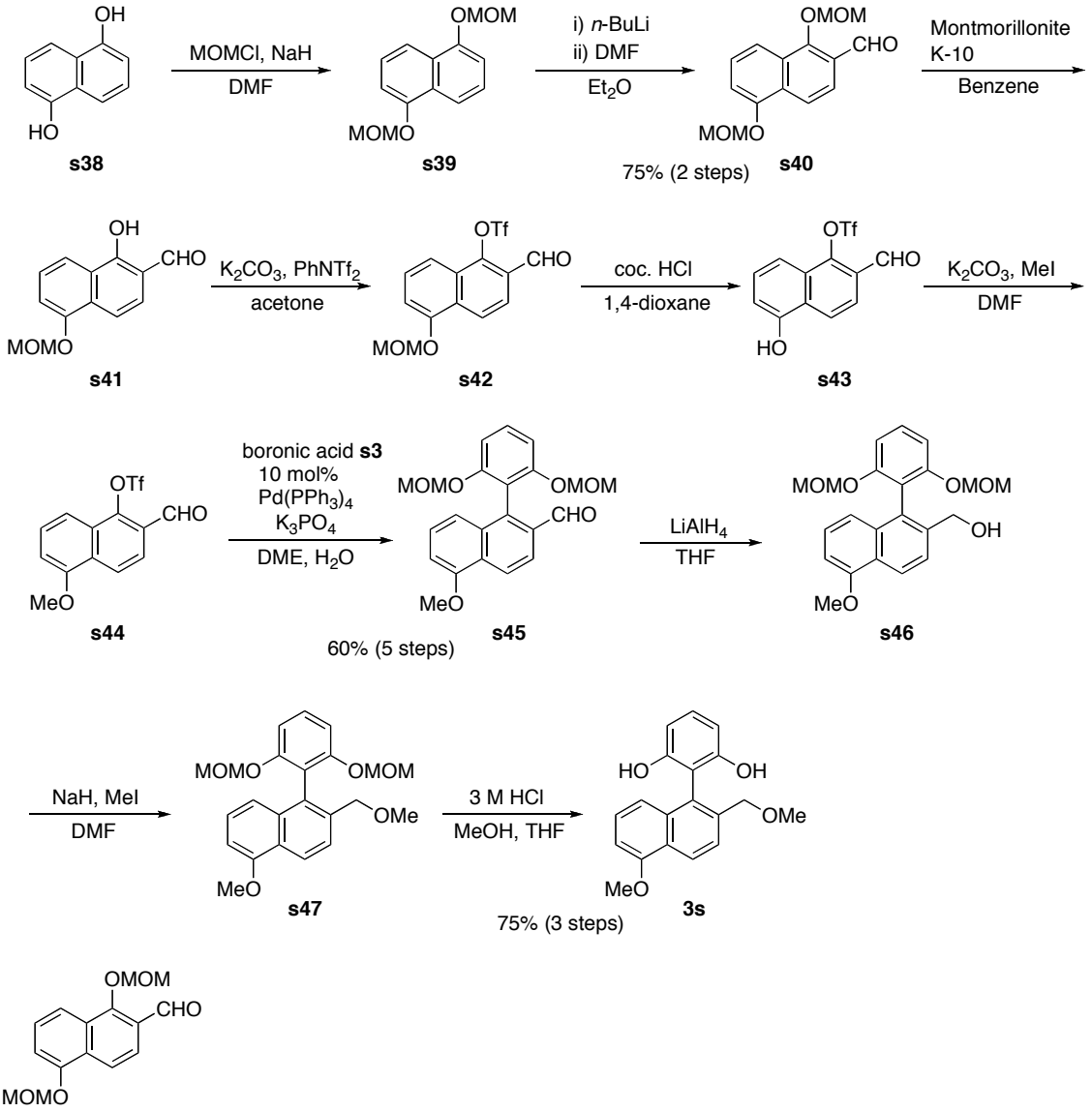
IR (KBr) 3439, 2947, 2837, 1621, 1591, 1469, 1393, 1341, 1324, 1259, 1200, 1167, 1144, 1127, 1106, 1093, 992, 968, 860, 827, 809, 794 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 3.33 (s, 3H), 3.92 (s, 3H), 3.95 (s, 3H), 4.29 (s, 2H), 5.01 (brs, 2H), 6.68 (d, 2H, *J* = 8.0 Hz), 6.82 (d, 1H, *J* = 8.0 Hz), 7.00 (s, 1H), 7.02 (dd, 1H, *J* = 1.2, 8.4 Hz), 7.24–7.33 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 56.2, 56.4, 58.8, 73.0, 105.9, 107.1, 108.1, 112.1, 116.9, 117.6, 117.7, 127.9, 130.1, 136.4, 138.7, 154.5, 157.5, 158.5.

Anal. Calcd for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Found: C, 70.76; H, 5.78.

Scheme 7. Preparation of **3s**.



Synthesis of 1,5-bis(methoxymethoxy)-2-naphthaldehyde (s40):

To a suspension of NaH (60% oil, 1.30 g, 32.5 mmol) in DMF (20.0 mL) were successively added a solution of 1,5-dihydroxynaphthalene (**s38**) (2.00 g, 12.5 mmol) in DMF (65.0 mL) and MOMCl (2.19 mL, 28.7 mmol) at 0 °C. After being stirred for 24 h at room temperature, the reaction was stopped by adding 1 M aqueous HCl. The crude products were extracted with EtOAc(x4) and the combined organic extracts were washed with 1 M aqueous HCl (x6), brine, dried (Na_2SO_4), and concentrated in vacuo to give crude **s39** (3.10 g). This material was used to next reaction without further

purification.

To a solution of **s39** in Et_2O (250.0 mL) was added *n*-BuLi (1.60 M in hexane, 10.1 mL, 16.2 mmol) at 0 °C. After stirring for 4 h at room temperature, DMF (2.45 mL, 25.0 mmol) was added to the reaction mixture at 0 °C. After being stirred for 10 min at 0 °C, the reaction was stopped by adding saturated aqueous NH_4Cl. The crude products were extracted with EtOAc (x3) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 6/1) to give **s40** (2.59 g, 75% from **s38**) as a pale yellow solid.

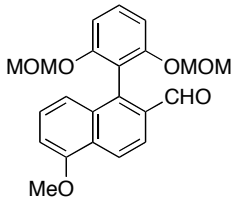
Mp. 95–97 °C.

IR (KBr) 2949, 2901, 2828, 1677, 1622, 1596, 1505, 1464, 1424, 1371, 1332, 1253, 1230, 1155, 1076, 1016, 932, 863 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 3.55 (s, 3H), 3.65 (s, 3H), 5.27 (s, 2H), 5.40 (s, 2H), 7.28 (d, 1H, *J* = 8.4 Hz), 7.49 (dd, 1H, *J* = 8.4, 8.4 Hz), 7.85 (d, 1H, *J* = 8.4 Hz), 7.87 (d, 1H, *J* = 8.8 Hz), 8.13 (d, 1H, *J* = 8.8 Hz), 10.54 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 56.2, 58.0, 94.6, 101.7, 111.2, 116.4, 118.9, 121.8, 125.9, 127.0, 129.2, 130.1, 153.1, 158.9, 190.4.

Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.44; H, 5.72.



Synthesis of 1-(2,6-bis(methoxymethoxy)phenyl)-5-methoxy-2-naphthaldehyde (s45):

To a solution of **s40** (1.32 g, 4.78 mmol) in Benzene (47.8 mL) was added Montmorillonite K-10 (1.32 g) at room temperature. After being stirred for 3 h, the crude material was filtered through Celite® pad, and the resulting filtrate was concentrated in vacuo to give crude **s41** (1.095 g). This material was used to next reaction without further purification.

To a solution of **s41** in acetone (45.0 mL) were successively added K_2CO_3 (1.32 g, 9.55 mmol) and $PhNTf_2$ (2.22 g, 6.21 mmol) at 0 °C. After being stirred for 7 h at room temperature, the reaction was stopped by adding saturated aqueous $NaHCO_3$ at 0 °C.

The crude products were extracted with EtOAc (x5) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10/1) to give **s42** (2.00 g) as a pale yellow oil with inseparable impurities. This material was used to next reaction without further purification.

To a solution of **s42** in 1,4-dioxane (30.0 mL) was added conc. HCl (6.0 mL) at 0 °C. After being stirred for 4 h at room temperature, the reaction was stopped by adding saturated aqueous $NaHCO_3$ at 0 °C. The crude products were extracted with EtOAc (x5) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give crude **s43** (1.90 g). This material was used to next reaction without further purification.

To a solution of **s43** in DMF (22.0 mL) were successively added K_2CO_3 (1.52 g, 11.0 mmol) and MeI (0.62 mL, 9.96 mmol) at 0 °C. After being stirred for 3.5 h at room temperature, the reaction was stopped by adding 1 M aqueous HCl. The crude products were extracted with EtOAc(x4) and the combined organic extracts were washed with 1 M aqueous HCl (x6), brine, dried (Na_2SO_4), and concentrated in vacuo to give crude **s44** (1.81 g). This material was used to next reaction without further purification.

The mixture of boronic acid **s3** (1.50 g, 6.20 mmol), triflate **s44**, $Pd(PPh_3)_4$ (276 mg, 0.239 mmol), K_3PO_4 (3.04 g, 14.3 mmol), DME (20.0 mL), and H_2O (5.0 mL) were heated at reflux for 4 h. After cooling to room temperature, the reaction was stopped by adding H_2O. The crude mixture was extracted with EtOAc (x3) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 6/1) to give **s45** (1.10 g, 60% from **s40**) as a pale yellow solid.

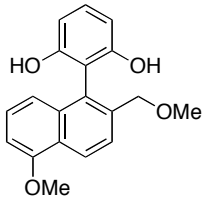
Mp. 83–85 °C.

IR (KBr) 2953, 2900, 2846, 1677, 1615, 1590, 1464, 1442, 1397, 1374, 1322, 1234, 1204, 1153, 1098, 1081, 1041, 986, 922, 897, 859, 815 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 3.16 (s, 6H), 4.20 (s, 3H), 4.93 (d, 1H, J = 6.8 Hz), 4.97 (d, 1H, J = 6.8 Hz), 6.95 (d, 2H, J = 8.0 Hz), 7.30–7.42 (m, 2H), 7.54 (dd, 1H, J = 1.2, 7.6 Hz), 7.65 (dd, 1H, J = 7.6, 7.6 Hz), 7.72 (d, 1H, J = 8.8 Hz), 8.29 (d, 1H, J = 8.0 Hz), 10.60 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 55.9, 65.8, 94.3, 108.6, 119.2, 122.0, 122.5, 123.0, 124.4, 126.3, 128.0, 129.6, 131.5, 133.7, 137.3, 155.7, 162.8, 189.8.

Anal. Calcd for $C_{22}H_{22}O_6$: C, 69.10; H, 5.80. Found: C, 68.88; H, 5.95.



2-(5-Methoxy-2-(methoxymethyl)naphthalen-1-yl)benzene-1,3-diol (**3s**).

White solid.

Yield: 75% (prepared from **s45**).

Mp. 213–215 °C.

IR (KBr) 3376, 3324, 2926, 2844, 1617, 1587, 1499, 1460, 1413, 1378, 1311, 1254, 1237, 1192, 1176, 1147, 1099, 1087, 1007, 980, 937, 861, 810, 794 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.44 (s, 3H), 4.02 (s, 3H), 4.60 (brs, 2H), 4.70 (s, 2H), 6.67 (d, 2H, J = 8.4 Hz), 7.26 (dd, 1H, J = 8.4, 8.4 Hz), 7.42 (d, 1H, J = 8.4 Hz), 7.53 (d, 1H, J = 8.4 Hz), 7.57 (dd, 1H, J = 1.2, 7.6 Hz), 7.67 (d, 1H, J = 7.6, 8.4 Hz), 8.31 (ddd, 1H, J = 1.2, 8.4, 8.4 Hz).

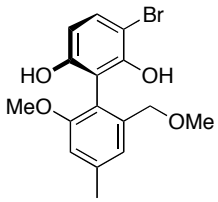
^{13}C NMR (100 MHz, $CDCl_3$) δ 58.4, 63.1, 69.1, 107.7, 113.2, 121.3, 124.3, 126.2, 127.7, 128.0, 128.5, 129.0, 130.0, 130.1, 133.5, 154.0, 154.6.

Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found: C, 73.75; H, 5.97.

2. Synthesis of chiral biaryls.

General Procedure for the formation of monobrominated-biaryls.

To a suspension of biphenol **3** (0.20 mmol), chiral phosphoric acid **2j** (0.02 mmol, 10 mol%) and powered MS13X (25 mg, activated) in CH_2Cl_2 (1.0 mL) and toluene (1.0 mL) was added *N*-bromophthalimide (0.20 mmol, 1 equiv.) at –20 °C. After completion of the reaction, the reaction was stopped by adding saturated aqueous $NaHCO_3$. The crude mixture was extracted with EtOAc (x3) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by preparative TLC to give monobromide **4**.



(*R*)-3-Bromo-2'-methoxy-6'-(methoxymethyl)-4'-methylbiphenyl-2,6-diol (**4n**).

Colorless amorphous.

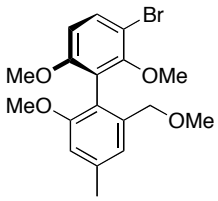
Yield: 70%, 17% ee (The enantioselectivity was determined after methylation of two hydoxy groups)

IR (neat) 3378, 2931, 2823, 1611, 1574, 1466, 1444, 1427, 1325, 1305, 1227, 1191, 1082, 1020, 867, 801 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 2.53 (s, 3H), 3.47 (s, 3H), 3.52 (s, 3H), 4.52 (d, 1H, *J* = 12.0 Hz), 4.56 (d, 1H, *J* = 12.0 Hz), 5.72 (s, 1H), 5.78 (brs, 1H), 6.57 (d, 1H, *J* = 8.8 Hz), 7.12 (d, 1H, *J* = 1.6 Hz), 7.31 (d, 1H, *J* = 1.6 Hz), 7.37 (d, 1H, *J* = 8.8 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 58.5, 62.1, 69.6, 101.4, 110.4, 114.0, 124.6, 131.3, 131.8, 132.1, 132.5, 134.8, 150.0, 153.6, 153.8.

Anal. Calcd for $C_{16}H_{17}BrO_4$: C, 54.41; H, 4.85. Found: C, 54.56; H, 4.65.



(*R*)-3-bromo-2,2',6-trimethoxy-6'-(methoxymethyl)-4'-methylbiphenyl (**s46**).

Colorless oil.

Yield: 90%, 17% ee.

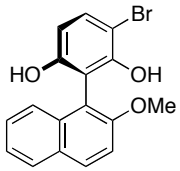
HPLC [DAICEL CHIRALPAK® AD-H, ϕ 0.46 x 25 cm, hexane/*i*-PrOH = 30/1, 0.2 mL/min, 254 nm, retention time (min) = 28.3 (41.6%), 30.3 (58.4%)].

IR (neat) 2935, 2832, 1567, 1461, 1428, 1401, 1382, 1284, 1265, 1225, 1191, 1167, 1142, 1091, 1011, 917, 866, 801 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 3.45 (s, 3H), 3.46 (s, 3H), 3.53 (s, 3H), 3.73 (s, 3H), 4.52 (d, 1H, *J* = 12.0 Hz), 4.55 (d, 1H, *J* = 12.0 Hz), 6.67 (d, 1H, *J* = 8.4 Hz), 6.93 (d, 1H, *J* = 2.0 Hz), 7.25 (d, 1H, *J* = 2.0 Hz), 7.51 (d, 1H, *J* = 8.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 56.0, 58.4, 60.7, 61.3, 69.7, 108.0, 108.4, 123.7, 127.0, 130.0, 130.9, 131.9, 132.3, 132.8, 154.1, 155.5, 157.5.

Anal. Calcd for $C_{18}H_{21}BrO_4$: C, 56.70; H, 5.55. Found: C, 56.95; H, 5.65.



(*S*)-4-Bromo-2-(2-methoxynaphthalen-1-yl)benzene-1,3-diol (**4o**).

White solid.

Yield: 89%, 1% ee.

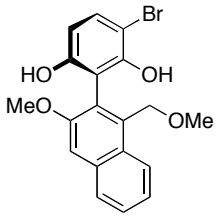
HPLC [DAICEL CHIRALCEL® OD-H, ϕ 0.46 x 25 cm, hexane/*i*-PrOH = 10/1, 0.5 mL/min, 220 nm, retention time (min) = 57.9 (50.4%), 64.9 (49.6%)].

IR (neat) 3498, 3059, 2938, 2840, 1619, 1593, 1573, 1508, 1480, 1466, 1446, 1381, 1334, 1306, 1277, 1258, 1173, 1148, 1108, 1066, 1018, 980, 907, 809, 732 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H), 4.70 (brs, 1H), 5.29 (s, 1H), 6.62 (d, 1H, *J* = 8.8 Hz), 7.32–7.52 (m, 5H), 7.82–7.90 (m, 1H), 8.00 (d, 1H, *J* = 8.8 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ 56.7, 100.7, 109.2, 110.7, 112.0, 113.4, 124.1, 124.4, 127.8, 128.3, 129.3, 131.8, 132.1, 133.1, 150.6, 154.1, 155.7.

Anal. Calcd for $C_{17}H_{13}BrO_3$: C, 59.15; H, 3.80. Found: C, 59.03; H, 4.07.



(*R*)-4-Bromo-2-(3-methoxy-1-(methoxymethyl)naphthalen-2-yl)benzene-1,3-diol (**4p**).

White solid.

Yield: 90%, 29% ee.

HPLC [DAICEL CHIRALCEL® OJ-H, ϕ 0.46 x 25 cm, hexane/*i*-PrOH = 10/1, 1.0 mL/min, 254 nm, retention time (min) = 44.2 (35.7%), 57.9 (64.3%)].

$[\alpha]_D^{25}$ +11.1 (c 1.000, CH_3COCH_3).

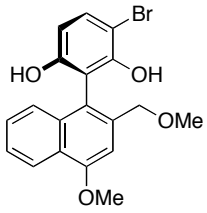
Mp. 195–197 °C.

IR (KBr) 3467, 3311, 3073, 2930, 2825, 1623, 1598, 1575, 1456, 1439, 1288, 1234, 1166, 1119, 1070, 1019, 998, 930, 865, 801, 745 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 3.40 (s, 3H), 3.85 (s, 3H), 4.47 (d, 1H, *J* = 10.4 Hz), 4.84 (d, 1H, *J* = 10.4 Hz), 5.52 (s, 1H), 5.64 (brs, 1H), 6.64 (d, 1H, *J* = 8.8 Hz), 7.30 (s, 1H) 7.36–7.60 (m, 3H), 7.82 (dd, 1H, *J* = 0.8, 8.4 Hz), 8.11 (d, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 56.0, 58.9, 69.4, 101.3, 107.4, 110.5, 113.0, 123.1, 124.5, 124.7, 127.1, 127.4, 127.8, 132.0, 135.1, 135.3, 150.5, 154.5, 155.1.

Anal. Calcd for $C_{19}H_{17}BrO_4$: C, 58.63; H, 4.40. Found: C, 58.43; H, 4.54.



(*S*)-4-Bromo-2-(4-methoxy-2-(methoxymethyl)naphthalen-1-yl)benzene-1,3-diol (**4r**).

Colorless solid.

Yield: 85%, 51% ee.

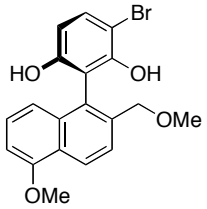
HPLC [DAICEL CHIRALCEL® OD-H, ϕ 0.46 x 25 cm, hexane/*i*-PrOH = 10/1, 0.5 mL/min, 254 nm, retention time (min) = 23.1 (75.5%), 32.4 (24.5%)].

IR (neat) 3502, 2935, 2850, 1621, 1592, 1576, 1510, 1443, 1375, 1347, 1309, 1233, 1191, 1162, 1136, 1105, 1023, 976, 909, 851, 802, 768 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.40 (s, 3H), 4.09 (s, 3H), 4.29 (d, 1H, *J* = 11.2 Hz), 4.36 (d, 1H, *J* = 11.2 Hz), 5.14 (brs, 1H), 5.41 (s, 1H), 6.64 (d, 1H, *J* = 8.4 Hz), 7.07 (s, 1H), 6.35 (d, 1H, *J* = 8.4 Hz), 7.40–7.58 (m, 3H), 8.33 (d, 1H, *J* = 8.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ 55.7, 58.7, 73.3, 100.9, 104.4, 109.8, 113.0, 118.1, 122.4, 124.8, 125.9, 126.0, 127.8, 132.4, 133.1, 137.2, 150.8, 154.5, 156.8.

Anal. Calcd for $C_{19}H_{17}BrO_4$: C, 58.63; H, 4.40. Found: C, 58.48; H, 4.68.



(*S*)-4-Bromo-2-(5-methoxy-2-(methoxymethyl)naphthalen-1-yl)benzene-1,3-diol (**4s**).

Colorless solid.

Yield: 88%, 15% ee.

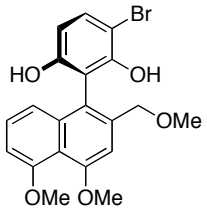
HPLC [DAICEL CHIRALCEL® OD-H, ϕ 0.46 x 25 cm, hexane/*i*-PrOH = 10/1, 0.5 mL/min, 254 nm, retention time (min) = 40.2 (57.4%), 48.1 (42.6%)].

IR (neat) 3418, 2931, 2853, 1613, 1576, 1444, 1409, 1376, 1308, 1190, 1170, 1075, 1019, 991, 909, 862, 811, 770 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.43 (s, 3H), 4.00 (s, 3H), 4.66 (d, 1H, *J* = 11.6 Hz), 4.70 (d, 1H, *J* = 11.6 Hz), 4.81 (brs, 1H), 5.37 (s, 1H), 6.61 (d, 1H, *J* = 8.4 Hz), 7.35 (d, 1H, *J* = 8.4 Hz), 7.40–7.56 (m, 3H), 7.63 (dd, 1H, *J* = 7.2, 8.4 Hz), 8.26 (d, 1H, *J* = 8.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ 58.3, 63.1, 69.1, 100.8, 109.3, 114.5, 121.3, 124.1, 126.1, 127.4, 128.3, 128.7, 128.8, 129.5, 132.1, 133.2, 150.4, 153.9, 154.5.

Anal. Calcd for $C_{19}H_{17}BrO_4$: C, 58.63; H, 4.40. Found: C, 58.92; H, 4.46.



(*S*)-4-Bromo-2-(4,5-dimethoxy-2-(methoxymethyl)naphthalen-1-yl)benzene-1,3-diol (**4t**).

Colorless solid.

Yield: 68%, 9% ee.

HPLC [DAICEL CHIRALPAK® AD-H, ϕ 0.46 x 25 cm, hexane/*i*-PrOH = 5/1, 1.0 mL/min, 220 nm, retention time (min) = 17.2 (45.5%), 31.0 (54.5%)].

IR (neat) 3420, 2931, 2842, 1613, 1591, 1463, 1389, 1339, 1262, 1166, 1090, 909, 809, 732 cm^{-1}.

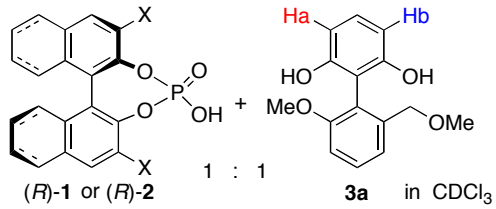
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.33 (s, 3H), 3.92 (s, 3H), 3.96 (s, 3H), 4.26 (d, 1H, *J* = 11.6 Hz), 4.31 (d, 1H, *J* = 11.6 Hz), 5.22 (brs, 1H), 5.50 (s, 1H), 6.64 (d, 1H, *J* = 8.0 Hz), 6.81 (d, 1H, *J* = 8.0 Hz), 6.95 (d, 1H, *J* = 8.0 Hz), 7.00 (s, 1H), 7.29 (dd, 1H, *J* = 8.0, 8.4 Hz), 7.48 (d, 1H, *J* = 8.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ 56.2, 56.4, 58.7, 72.9, 100.8, 105.7, 107.0, 109.7, 113.4, 117.5, 117.5, 127.8, 132.4, 136.0, 138.0, 150.8, 154.4, 157.4, 158.4.

Anal. Calcd for $C_{20}H_{19}BrO_5$: C, 57.29; H, 4.57. Found: C, 57.01; H, 4.74.

3. The results of ^{1}H NMR experiment.

All ^{1}H NMR experiments were conducted with substrate **3** (0.020 mmol) and chiral phosphoric acid **1** or **2** (0.020 mmol) in NMR solvent (0.40 mL).



(*R*)-**1** or (*R*)-**2** **3a** in $CDCl_3$

1a: X = Ph
1b: X = *p*-$NO_2C_6H_4$
1c: X = *p*-$CF_3C_6H_4$
1d: X = $SiPh_3$
1e: X = 2,4,6-(i-Pr)$_3C_6H_2$
1f: X = 1-naphthyl
1g: X = 2-naphthyl
1h: X = 9-phenanthryl
1i: X = 1-pyrenyl
1j: X = 9-anthryl
2j: X = 9-anthryl

(*R*)-**1** : binaphthyl skeleton
(*R*)-**2** : hydrogenated binaphthyl skeleton

Entry	Ar	Yield/ %	Ee/%	Δδ|Ha–Hb|/ ppm
1	Ph (**1a**)	80	9	0
2	4-(NO_2)C_6H_4 (**1b**)	82	6	0
3	4-$CF_3C_6H_4$ (**1c**)	94	8	0
4	$SiPh_3$ (**1d**)	89	2	0
5	2,4,6-(*i*-Pr)$_3C_6H_2$ (**1e**)	79	2	0.02
6	1-naphtyl (**1f**)	79	15	0.02
7	2-naphtyl (**1g**)	90	23	0
8	9-phenanthryl (**1h**)	89	17	0.02
9	1-pyrenyl (**1i**)	85	14	0.003
10	9-anthryl (**1j**)	93	34	016
11	9-anthryl (**2j**)	96	48	0.37

Figure 1. The correlation between the selectivity and the peak difference of Ha and Hb (Δδ|Ha–Hb|/).

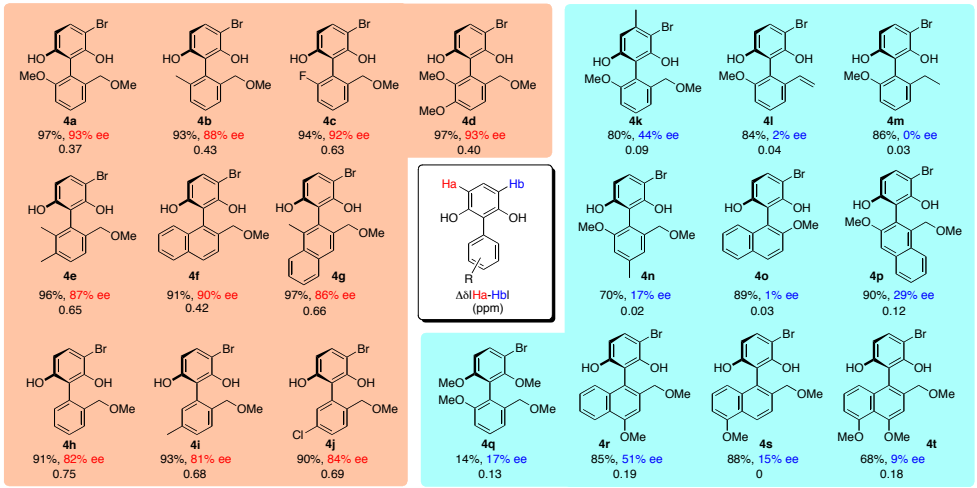
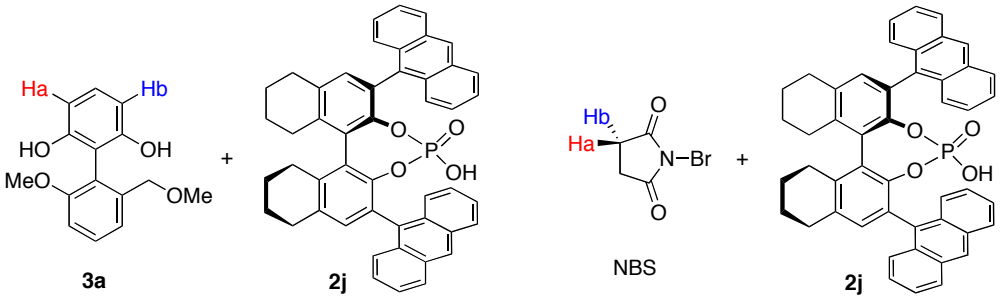
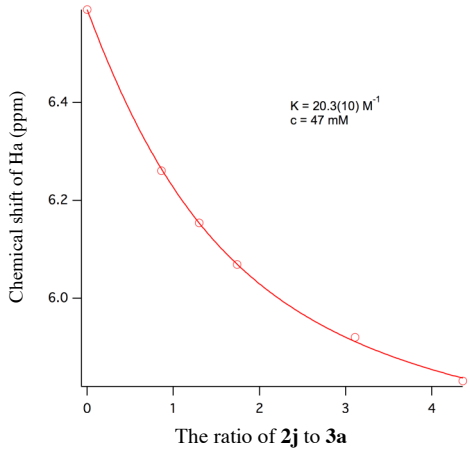


Figure 2. Substrate scope and the correlation between the selectivity and Δδ|Ha–Hb|.

4. Determination of the association constant.

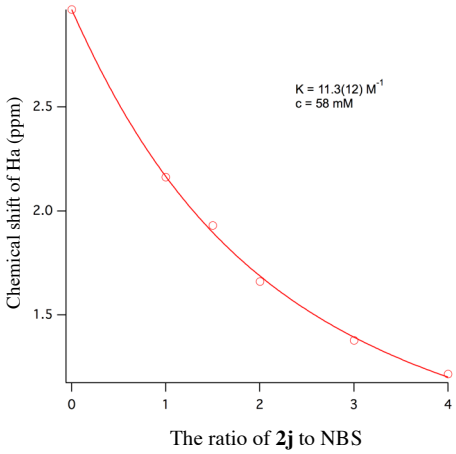
The association constants (K) of catalyst **2j** and substrate **3a**, catalyst **2j** and NBS were determined by ^{1}H NMR studies. The data were analyzed with Igor (WaveMetrics) running on a Macintosh computer fitted to the function reported previously.[6] In this experiment, NBS was used in place of NBP because the alternation of the chemical shift was easy to analyze. The association constant of catalyst **2j** and substrate **3a** (K = 20.3 M^{-1}) was larger than that of catalyst **2j** and NBS (K = 11.3 M^{-1}), which revealed the substrate **3a** was easier to interact with catalyst **2j** than NBS.





The ratio of **2j** to **3a**	chemical shift of Ha (ppm)
0	6.590
0.86	6.2605
1.30	6.154
1.74	6.069
3.11	5.920
4.36	5.831

Figure 3. The alternation of the chemical shift by changing the ratio of **2j** and **3a**.

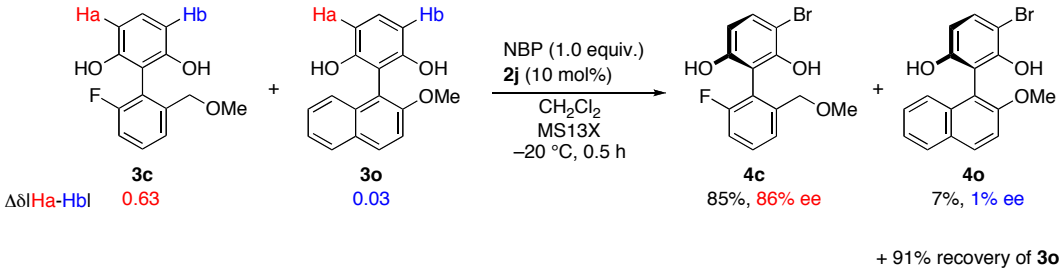


The ratio of **2j** to NBS	chemical shift of Ha (ppm)
0	2.969
1.02	2.163
1.53	1.930
2.00	1.661
3.00	1.377
4.00	1.215

Figure 4. The alternation of the chemical shift by changing the ratio of **2j** and NBS.

4. Control experiment.

The affinity difference between substrates enabled preferential bromination of high affinity substrate (eq. 1). When the mixture of high affinity substrate **3c** and low affinity substrate **3o** in CH_2Cl_2 was treated with 1 equivalent of NBP in the presence of catalyst **2j** and activated MS13X, the corresponding bromide **4c** was obtained in 85% whilst the chemical yield of **4o** was low (7%). This result also supports our assumption that the degree of affinity between the substrate and the catalyst could be estimated by the peak separation of the enantiotopic hydrogens (Ha and Hb).



5. Computational results.

Cartesian coordinates of each structure

Computational details are shown in ref. 9.

B

ONIOM: extrapolated energy = -3352.401292635451 A.U.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	3.370192	3.421950	0.672170
2	6	0	2.857244	2.663249	-0.373691
3	6	0	3.447374	1.432982	-0.666994
4	6	0	4.543267	0.974944	0.072562
5	6	0	5.045850	1.756817	1.112213
6	6	0	4.465484	2.986959	1.407623
7	1	0	2.897483	4.365283	0.913006
8	1	0	2.000499	2.996684	-0.941722
9	1	0	4.872551	3.560176	2.227503
10	8	0	2.995725	0.631017	-1.653176
11	1	0	1.585429	-0.822722	0.688377
12	8	0	6.069609	1.294099	1.916283
13	1	0	6.796232	0.934020	1.360922
14	6	0	4.997382	-0.435044	-0.144680
15	6	0	4.182232	-1.454730	0.317697
16	6	0	6.173901	-0.776686	-0.799379
17	6	0	4.494140	-2.780850	0.122146
18	6	0	6.500348	-2.110548	-0.990515
19	6	0	5.659093	-3.110972	-0.544253
20	1	0	3.826105	-3.531084	0.489202
21	1	0	7.413834	-2.363865	-1.491729
22	1	0	5.912935	-4.139436	-0.704793
23	6	0	7.111404	0.309523	-1.254402
24	1	0	6.566338	1.102651	-1.747616
25	1	0	7.860384	-0.083954	-1.929756
26	8	0	7.767396	0.841003	-0.071499
27	8	0	3.027041	-1.133043	1.035311
28	6	0	8.607469	1.987997	-0.310366
29	1	0	9.427818	1.729119	-0.969403
30	1	0	8.995447	2.292712	0.648816
31	1	0	8.037045	2.799410	-0.746380
32	6	0	3.233434	-0.877379	2.469855
33	1	0	3.386318	-1.820609	2.970883
34	1	0	2.329177	-0.403970	2.812551
35	1	0	4.086492	-0.231690	2.598402
36	1	0	2.041075	0.800318	-1.799963
37	8	0	0.329646	0.732512	-1.468065
38	15	0	-0.279644	0.028235	-0.322063
39	8	0	-1.257006	-1.135117	-0.895448
40	8	0	-1.286303	0.926086	0.580588
41	8	0	0.597208	-0.593002	0.800923
42	6	0	-2.183237	-1.702219	-0.037052
43	6	0	-2.435565	1.352451	-0.071590
44	6	0	-3.295603	-0.940528	0.323680
45	6	0	-2.007899	-3.012917	0.391461
46	6	0	-2.553113	2.678954	-0.471723
47	6	0	-3.451817	0.418064	-0.276860
48	6	0	-4.205113	-1.452418	1.268011
49	6	0	-2.977674	-3.529871	1.244670
50	6	0	-0.855840	-3.878241	-0.043412
51	6	0	-3.711203	3.025312	-1.159417
52	6	0	-1.542281	3.746613	-0.141717
53	6	0	-4.568418	0.772451	-1.057206
54	6	0	-4.047945	-2.769172	1.714179
55	6	0	-5.278662	-0.543566	1.889469
56	1	0	-2.868771	-4.554751	1.579147
57	6	0	-0.839258	-4.414052	-1.334746
58	6	0	0.131929	-4.229522	0.881506
59	6	0	-4.696588	2.095579	-1.491692
60	1	0	-3.828204	4.056324	-1.471587
61	6	0	-1.559013	4.326086	1.130824
62	6	0	-0.687584	4.235253	-1.132804
63	6	0	-5.563964	-0.301764	-1.525537
64	6	0	-5.046281	-3.425924	2.678182
65	1	0	-5.661460	0.146462	1.154754
66	1	0	-4.785237	0.049889	2.655069
67	6	0	-6.424611	-1.336203	2.535715
68	6	0	0.185613	-5.333528	-1.700523
69	6	0	-1.828678	-4.083113	-2.321339
70	6	0	1.135695	-5.172348	0.513359
71	6	0	0.182502	-3.676033	2.207272
72	6	0	-5.918718	2.576545	-2.286605
73	6	0	-0.706819	5.432993	1.409437
74	6	0	-2.416533	3.856934	2.182951
75	6	0	0.143134	5.359670	-0.850645
76	6	0	-0.597572	3.641165	-2.438541
77	1	0	-5.104755	-0.813231	-2.367640
78	1	0	-5.714891	-1.039479	-0.753607
79	6	0	-6.906630	0.292398	-1.976586
80	1	0	-5.733659	-4.031649	2.093861
81	1	0	-4.509599	-4.091834	3.343873
82	6	0	-5.851805	-2.397866	3.485986
83	1	0	-7.073145	-0.653430	3.073508
84	1	0	-7.019223	-1.820825	1.767057
85	6	0	0.191956	-5.878481	-3.027034
86	6	0	1.141005	-5.699005	-0.766789
87	6	0	-1.786184	-4.618929	-3.555873
88	1	0	-2.599460	-3.392331	-2.056552
89	6	0	2.113316	-5.564890	1.488303
90	6	0	1.120432	-4.069966	3.090263
91	1	0	-0.532563	-2.927369	2.471441
92	1	0	-5.598962	3.313649	-3.013863
93	1	0	-6.599007	3.069932	-1.597673
94	6	0	-6.661260	1.426512	-2.982624
95	6	0	-0.734794	6.021865	2.716667
96	6	0	0.114099	5.930919	0.410607
97	6	0	-2.410700	4.438763	3.397499
98	1	0	-3.059273	3.026844	1.982677
99	6	0	0.990035	5.876912	-1.886907
100	6	0	0.218393	4.154942	-3.378730
101	1	0	-1.158479	2.754109	-2.633724
102	1	0	-7.447365	0.679933	-1.118247
103	1	0	-7.511813	-0.488878	-2.423074
104	1	0	-5.208717	-1.917664	4.216414
105	1	0	-6.647747	-2.900988	4.023626
106	6	0	-0.753958	-5.536039	-3.920217
107	1	0	0.973059	-6.566072	-3.287430
108	1	0	1.898568	-6.408522	-1.040953
109	1	0	-2.529028	-4.356454	-4.282469
110	1	0	2.847860	-6.293507	1.202986
111	6	0	2.102705	-5.042918	2.729316
112	1	0	1.142633	-3.648219	4.075502
113	1	0	-6.066844	1.051624	-3.809498
114	1	0	-7.599321	1.791149	-3.386066
115	6	0	-1.551612	5.545381	3.673836
116	1	0	-0.085425	6.853570	2.910460
117	1	0	0.736584	6.781191	0.616947
118	1	0	-3.053280	4.072548	4.173326
119	1	0	1.600653	6.729933	-1.662545
120	6	0	1.021043	5.304341	-3.103913
121	1	0	0.287002	3.690029	-4.341674
122	1	0	-0.742512	-5.944977	-4.910805
123	1	0	2.830704	-5.347144	3.455045
124	1	0	-1.566313	5.989300	4.649275
125	1	0	1.658496	5.693034	-3.872832

C

ONIOM: extrapolated energy = -6284.065901895045 A.U.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.701059	-3.350558	3.535753
2	6	0	0.210699	-3.206614	4.757181
3	6	0	0.700928	-1.761980	4.684865
4	6	0	0.055479	-1.237205	3.414772
5	7	0	-0.708868	-2.143432	2.831370
6	1	0	1.010370	-3.939159	4.662329
7	1	0	0.384022	-1.141086	5.523425
8	8	0	0.265148	-0.056375	3.031549
9	8	0	-1.315217	-4.339828	3.228013
10	1	0	1.782167	-1.664673	4.586767
11	1	0	-0.360735	-3.438427	5.655148
12	35	0	-1.921133	-1.989241	0.968659
13	6	0	-3.930300	-3.014446	-0.689070
14	6	0	-3.004505	-1.930692	-0.924203
15	6	0	-3.563774	-0.594780	-0.953228
16	6	0	-4.903965	-0.350073	-0.618546
17	6	0	-5.723003	-1.439127	-0.322261
18	6	0	-5.220827	-2.775796	-0.365088
19	1	0	-3.535329	-4.019427	-0.730463
20	1	0	-2.168061	-2.109369	-1.589766
21	1	0	-5.918755	-3.562683	-0.125376
22	8	0	-2.822184	0.415257	-1.312815
23	1	0	0.015810	0.324971	1.846924
24	8	0	-7.020485	-1.337755	-0.006007
25	1	0	-7.493733	-0.561687	-0.401724
26	6	0	-5.324135	1.076058	-0.425300
27	6	0	-4.697823	1.777550	0.612833
28	6	0	-6.255861	1.732290	-1.212632
29	6	0	-5.000204	3.107339	0.831192
30	6	0	-6.571269	3.064413	-0.971366
31	6	0	-5.938817	3.746529	0.041789
32	1	0	-4.505680	3.649285	1.608475
33	1	0	-7.302746	3.555166	-1.581910
34	1	0	-6.170340	4.777227	0.223410
35	6	0	-6.986082	1.005431	-2.309371
36	1	0	-6.343483	0.296990	-2.813645
37	1	0	-7.386696	1.702854	-3.032520
38	8	0	-8.088601	0.295410	-1.675976
39	8	0	-3.802326	1.082019	1.360892
40	6	0	-8.922158	-0.471472	-2.570098
41	1	0	-9.397377	0.180939	-3.292099
42	1	0	-9.673322	-0.948071	-1.960771
43	1	0	-8.342474	-1.224317	-3.091059
44	6	0	-2.838627	1.766213	2.195362
45	1	0	-2.263940	2.471078	1.616261
46	1	0	-2.182329	1.003555	2.567843
47	1	0	-3.332275	2.267219	3.017511

48	1	0	-1.853385	0.158789	-1.438889
49	8	0	-0.316765	-0.203540	-1.543534
50	15	0	0.539771	0.320598	-0.439607
51	8	0	1.444077	1.517263	-1.072665
52	8	0	1.657239	-0.744627	0.091144
53	8	0	-0.105295	0.847869	0.843646
54	6	0	2.534221	1.936056	-0.331445
55	6	0	2.645645	-1.094648	-0.816828
56	6	0	3.660375	1.111917	-0.314756
57	6	0	2.496043	3.155860	0.334491
58	6	0	2.653290	-2.371179	-1.368271
59	6	0	3.629702	-0.150500	-1.113700
60	6	0	4.756674	1.452770	0.499069
61	6	0	3.629447	3.511453	1.058570
62	6	0	1.325803	4.101553	0.278420
63	6	0	3.631539	-2.641064	-2.318203
64	6	0	1.729016	-3.463029	-0.901209
65	6	0	4.550844	-0.417063	-2.143969
66	6	0	4.740487	2.677079	1.176020
67	6	0	5.894124	0.446131	0.739873
68	1	0	3.625825	4.464349	1.574422
69	6	0	1.131663	4.889447	-0.859530
70	6	0	0.516177	4.271046	1.405176
71	6	0	4.546496	-1.678492	-2.747537
72	1	0	3.660949	-3.633237	-2.753321
73	6	0	2.037074	-4.142077	0.282166
74	6	0	0.643155	-3.859695	-1.682355
75	6	0	5.465886	0.699466	-2.672803
76	6	0	5.929231	3.155811	2.021279
77	1	0	6.104548	-0.108939	-0.160181
78	1	0	5.534948	-0.268375	1.476465
79	6	0	7.171766	1.111259	1.273461
80	6	0	0.108790	5.880926	-0.861150
81	6	0	1.933760	4.749351	-2.042496
82	6	0	-0.485072	5.286016	1.402490
83	6	0	0.639652	3.450981	2.579443
84	6	0	5.560952	-2.064431	-3.833587
85	6	0	1.224717	-5.235408	0.695694
86	6	0	3.159641	-3.789500	1.106605
87	6	0	-0.137202	-4.983343	-1.280534
88	6	0	0.266996	-3.171381	-2.887291
89	1	0	4.862078	1.318132	-3.331633
90	1	0	5.796027	1.331097	-1.863036
91	6	0	6.666583	0.156129	-3.461585
92	1	0	6.516544	3.846088	1.421738
93	1	0	5.555537	3.704226	2.878088
94	6	0	6.832268	2.000933	2.478126
95	1	0	7.884335	0.343567	1.554712
96	1	0	7.626960	1.715332	0.494312
97	6	0	-0.080382	6.684450	-2.033963
98	6	0	-0.666644	6.063611	0.271485
99	6	0	1.722681	5.525392	-3.122465
100	1	0	2.701178	4.005753	-2.050862
101	6	0	-1.277282	5.486239	2.582360
102	6	0	-0.129990	3.668945	3.663049
103	1	0	1.326703	2.633789	2.565376
104	1	0	5.072656	-2.701004	-4.562272
105	1	0	6.352359	-2.646216	-3.368711
106	6	0	6.181377	-0.840994	-4.524233
107	6	0	1.540076	-5.916868	1.917341
108	6	0	0.161520	-5.635026	-0.096976
109	6	0	3.432718	-4.468300	2.237845
110	1	0	3.780473	-2.975409	0.799641
111	6	0	-1.216853	-5.416197	-2.121452
112	6	0	-0.761081	-3.606813	-3.641928
113	1	0	0.796593	-2.281953	-3.151292
114	1	0	7.358765	-0.340417	-2.787991
115	1	0	7.193303	0.982239	-3.926428
116	1	0	6.320686	1.409005	3.230276
117	1	0	7.735137	2.400262	2.926665
118	6	0	0.693159	6.515224	-3.121601
119	1	0	-0.857517	7.423890	-2.019915
120	1	0	-1.422752	6.825704	0.273044
121	1	0	2.326426	5.403379	-3.999680
122	1	0	-2.011260	6.268932	2.571154
123	6	0	-1.099179	4.719109	3.673897
124	1	0	-0.034120	3.034696	4.521346
125	1	0	5.441633	-0.360892	-5.156577
126	1	0	7.003256	-1.158541	-5.156234
127	6	0	2.605475	-5.555065	2.657062
128	1	0	0.901140	-6.720468	2.225621
129	1	0	-0.441651	-6.465565	0.215262
130	1	0	4.280172	-4.197842	2.836587
131	1	0	-1.777106	-6.280394	-1.819677
132	6	0	-1.511263	-4.762750	-3.261257
133	1	0	-1.033726	-3.079029	-4.534018
134	1	0	0.545191	7.117776	-3.995614
135	1	0	-1.689054	4.878877	4.554915
136	1	0	2.844231	-6.078346	3.561896
137	1	0	-2.314332	-5.095173	-3.888781

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