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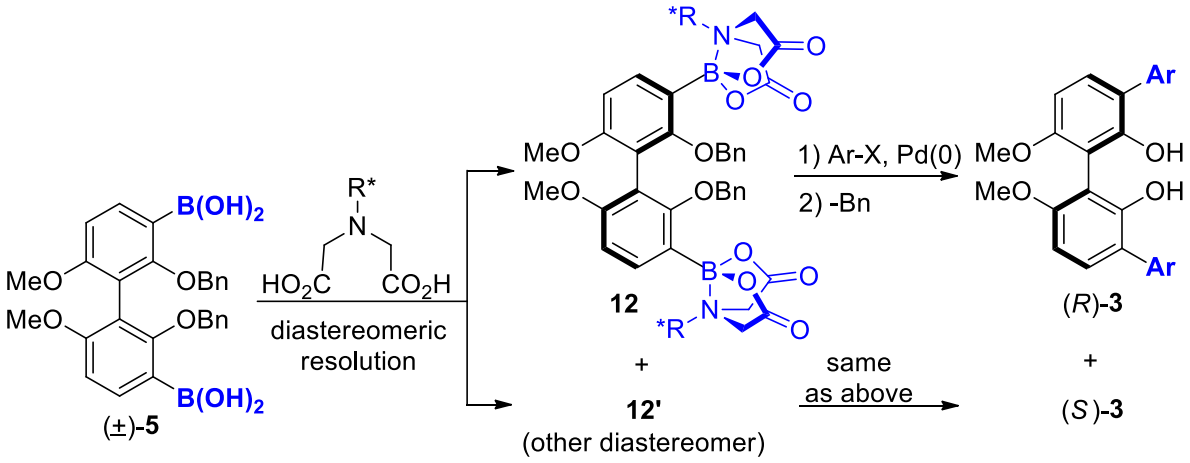
Synthesis of Optically Pure 3,3'-Disubstituted-1,1'-Bi-6-Methoxy-2-Phenol (BIPhOL) Derivatives via Diastereomeric Resolution

Jung-Min Yoon, Chun-Young Lee, Young-In Jo, and Cheol-Hong Cheon*

Department of Chemistry, Korea University, 145 Anam-ro, Seongbuk-gu, Seoul 02841, Republic of Korea, Phone: +82-2-3290-3147; Fax: +82-2-3290-3121; E-mail: cheon@korea.ac.kr



Abstract: A new protocol for the enantioselective synthesis of 3,3'-disubstituted-1,1'-bi-6-methoxy-2-phenol (BIPhOL) derivatives is described. Diastereomeric resolution of racemic BIPhOL boronic acid using a boronic acid moiety as a resolving group generated two diastereomers and subsequent Suzuki-Miyaura coupling reaction of the resulting diastereomers with aryl halides provided BIPhOL derivatives without any loss of enantioselectivity. In addition, the absolute stereochemistry of chiral BIPhOL was determined by comparison of the optical rotation with the reported value.

Introduction

Since the first use of chiral 1,1'-bi-2-naphthol (BINOL, **1**) as a ligand in metal-mediated asymmetric catalysis in 1979,[1] optically active 2,2'-dihydroxy-1,1'-biaryls (**A**, Figure 1) have been widely used as privileged ligands in various transition metal-catalyzed asymmetric reactions.[2,3] More recently, they have been utilized in asymmetric organocatalysis as either hydrogen bonding catalysts or chiral frameworks in chiral phosphoric acid catalysts.[4,5] Since the outcomes of given asymmetric transformations with axially chiral biaryl diols (**A**) show a strong dependence on their steric and electronic natures, considerable efforts have been made to control the steric and electronic properties of these axially chiral compounds.

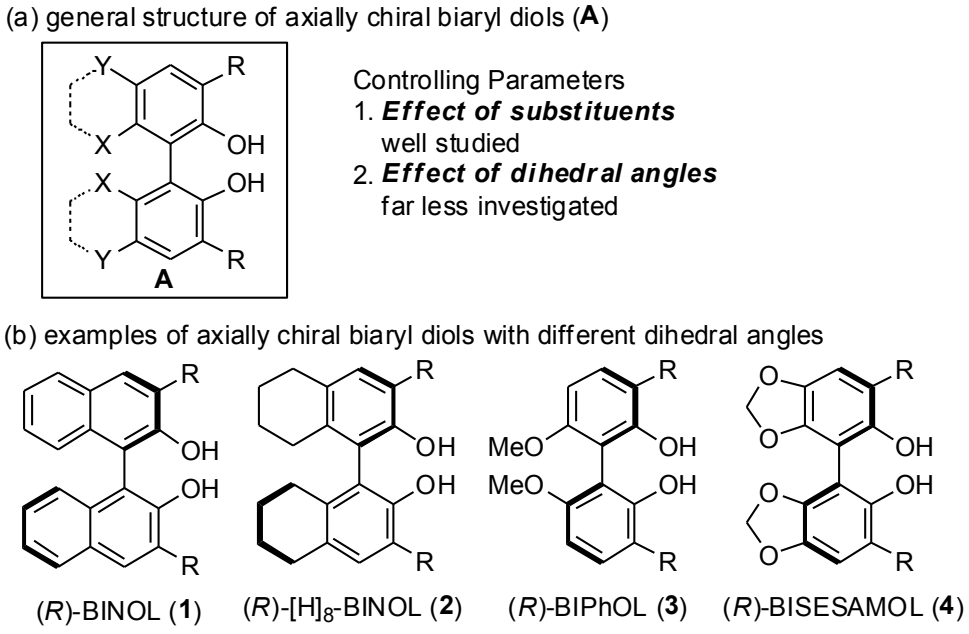


Figure 1. (a) General Structure of Axially Chiral Biaryl Diols (A) and (b) Representative Examples of Axially Chiral Biaryl Diols

One of the ways to tune the steric and electronic natures of axially chiral biaryl diols (**A**) is incorporation of different substituents at the periphery of the chiral axis, particularly at

the 3,3'-positions; as such, various axially chiral biaryl diol derivatives bearing different substituents have been prepared and applied to a number of asymmetric protocols.[6] In addition to substituent effects, the dihedral angle along the chiral axis in axially chiral biaryl diols has been found to exert a pronounced influence on the outcome of asymmetric transformations with these compounds. For instance, chiral phosphoric acids, derived from BINOL (**1**) and 1,1'-bi(5,5,6,6,7,7,8,8-octahydro-2-naphthol) ($[H]_8$-BINOL, **2**) derivatives bearing the same substituents at the 3,3'-positions afforded significantly different results in asymmetric synthesis.[7]

However, the effects of the dihedral angles on the efficiency of asymmetric reactions with axially chiral biaryl diols (**A**) have been far less investigated as compared to substituent effects on the efficiency of asymmetric reactions. This poor exploration of the influence of dihedral angles in axially chiral biaryl diols (**A**) on the asymmetric reactions might be due to the lack of reliable synthetic routes to access axially chiral biaryl diol derivatives other than BINOL and $[H]_8$-BINOL derivatives; although the enantioselective synthesis of the parent 1,1'-bi-6-methoxy-2-phenol (BIPhOL, **3**) and 1,1'-bi-2-sesamol (BISESAMOL, **4**) have been reported a couple of times,[8-11] there are few general synthetic routes that can be used to access these axially chiral biaryl diol derivatives, and thus few derivatives of chiral BIPhOL **3** and BISESAMOL **4** have been prepared.

Herein, we describe the development of a new synthetic route to access optically pure 3,3'-disubstituted BIPhOL derivatives **3**. Diastereomeric resolution of racemic BIPhOL boronic acid using a boronic acid moiety as a resolving group generated two diastereomers, which could be readily separable by a conventional separation technique. Subsequent Suzuki-Miyaura coupling reaction of the resulting diastereomers with aryl halides provided the desired BIPhOL derivatives in good yields. The absolute stereochemistry of chiral BIPhOL was determined by comparison of the optical rotation of the resulting optically active BIPhOL

with the reported value and the absolute stereochemistry of all other derivatives was assigned by analogy.

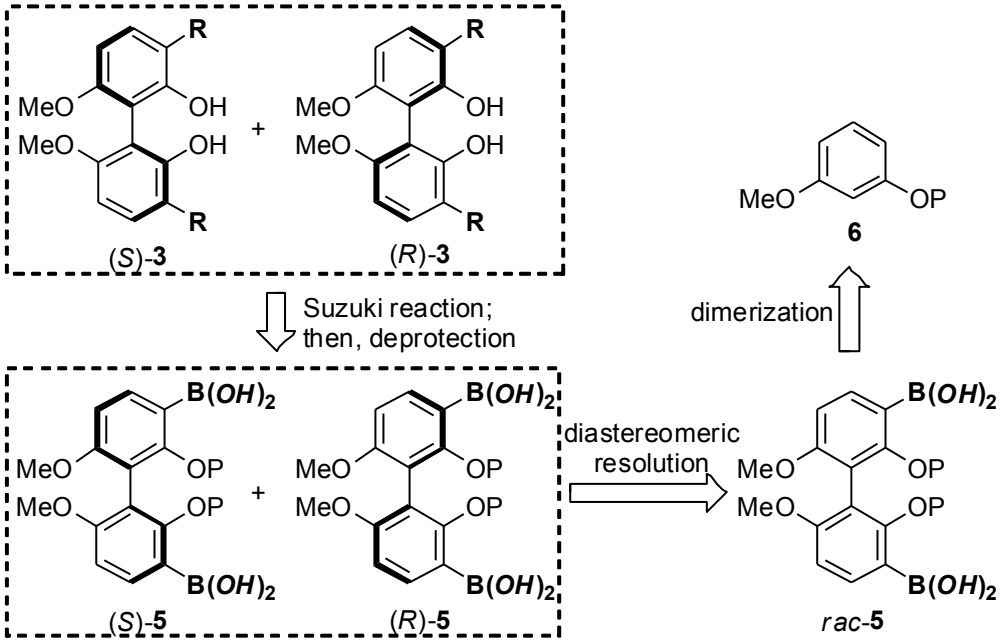
Results and Discussion

To date, the enantioselective synthesis of chiral BIPhOL itself has been reported several times[8-11] mainly via diastereoselective resolution[8,9] or kinetic resolution[10] of *rac*-BIPhOL, where the phenolic hydroxy groups are used as resolving groups. However, it might be difficult to develop a protocol to access optically pure BIPhOL derivatives bearing substituents at the 3,3'-positions based on previous methods since these previous methods required multistep synthetic sequences to access parent chiral BIPhOL and additional synthetic steps are needed to introduce substituents at the 3,3'-positions. Thus, it is desired to develop a new approach to access these derivatives.

Our group developed a new approach to access axially chiral biaryl compounds via the diastereomeric resolution where a boronic acid moiety acts as a diastereomeric resolving group and a masked functional group to introduce other functional groups.[12] This protocol was successfully applied to the synthesis of (*R*)- and (*S*)-3,3'-diaryl BINOL derivatives[12(a)], and oxidation-divergent total syntheses of some natural products,[12(b)] respectively. In an effort to enantioselectively synthesize biaryl compounds bearing an axial chirality using this approach, we attempted to further apply our diastereomeric resolution protocol to the synthesis of chiral 3,3'-disubstituted BIPhOL derivatives **3**.

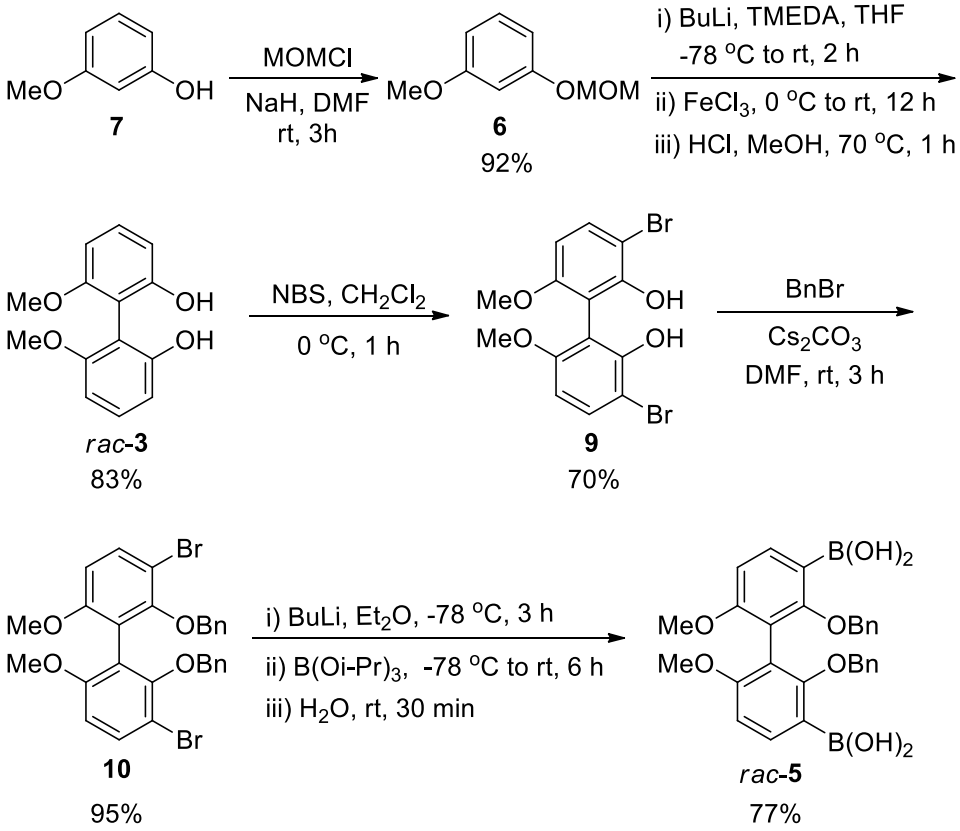
The retrosynthetic analysis of the enantioselective synthesis of 3,3'-disubstituted BIPhOL derivatives **3** is depicted in Scheme 1. Both (*R*)- and (*S*)-BIPhOL derivatives could be prepared by Suzuki-Miyaura coupling reaction of the optically pure boronic acids, (*R*)- and (*S*)-**5**, which could be prepared by the diastereomeric resolution of racemic biaryl boronic acid (*rac*-**5**) using a boronic acid moiety as a resolving group. *rac*-**5** could be prepared via

dimerization of resorcinol **6** with a proper protecting group, followed by the installation of boronic acid moieties at the 3,3'-position. We initially planned to introduce the boronic acid functional groups at the 3,3'-positions in *rac*-**5** via directed *ortho*-metalation followed by electrophilic borylation with a trialkyl borate. Since a methoxymethyl (MOM) group is known to exhibit a stronger *ortho* directing ability than a methoxy group,[13] we decided to use a MOM group as the protecting group in compound **6**.



Scheme 1. Retrosynthetic Analysis

Based on these considerations, our synthesis commenced with the preparation of *rac*-**5** (Scheme 2). The reaction of methoxy-protected resorcinol **7** with MOM chloride in the presence of a base provided MOM-protected compound **6** in 92% yield. Directed lithiation at the 2-position of **6** with *n*-BuLi and subsequent dimerization of the resulting organolithium species in the presence of $FeCl_3$ afforded biaryl compound **8**[14] after an acidic aqueous work-up. Unfortunately, some of the MOM group in compound **8** was hydrolyzed under the acidic conditions, leading to the concomitant formation of *rac*-BIPhOL (*rac*-**3**).



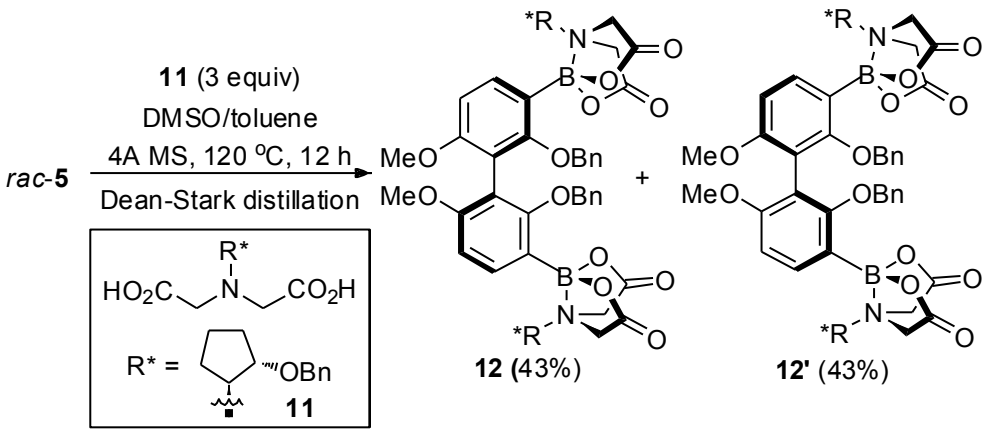
Scheme 2. Synthesis of *rac*-Boronic Acid, *rac*-**5**. TMEDA = 1,1,2,2-tetramethylethylenediamine, NBS = N-bromosuccinimide, DMF = N,N-dimethylformamide, Bn = benzyl.

Next, we investigated the possibility of introducing a boronic acid moiety via directed *ortho*-metalation of **8** with *n*-BuLi using the MOM group as the *ortho*-directing group followed by trapping the resulting organolithium species with trimethyl borate. However, the directed *ortho*-metalation protocol was not successful; most of starting compound **8** remained unreacted and only a trace amount of mono-boronic acid was obtained. Alternatively, a boronic acid functional group could be introduced from the corresponding halide via metal-halogen exchange followed by electrophilic borylation of the resulting organometallic species with a trialkyl borate, and thus we decided to introduce bromide groups at the 3,3'-positions

as precursors for boronic acid moieties. When compound **8** was treated with NBS, unfortunately, bromination took place without any regioselectivity, leading to a complex mixture of different regioisomers.

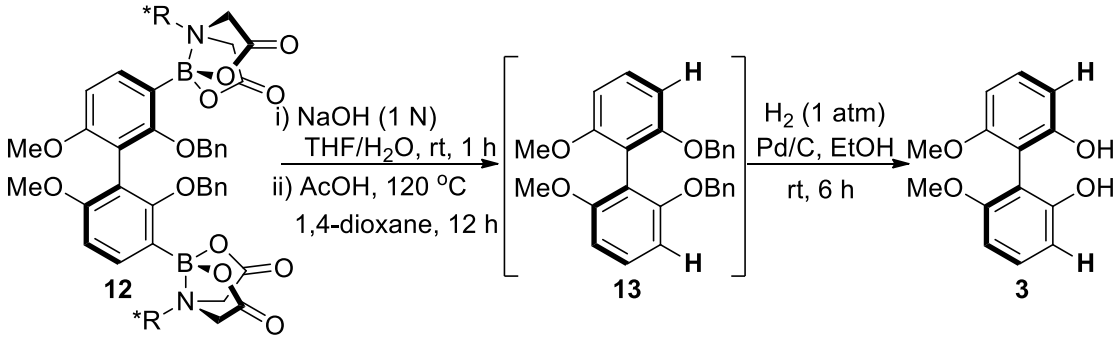
Since a phenolic hydroxy group is known as a better directing group than the corresponding alkoxy group in electrophilic aromatic substitution (EAS) reactions[15] and some of the MOM group in compound **8** was hydrolyzed during the acidic work-up, the MOM group was converted into a free hydroxy group via treatment with aqueous acidic solution affording parent BIPhOL **3** as a racemate in 83% yield from compound **6** over two steps. When compound **3** was subjected to bromination with NBS, 3,3'-dibrominated compound **9** was obtained in 70% yield with perfect regioselectivity. Subsequent protection of the phenolic hydroxy group with benzyl bromide afforded compound **10** in 95% yield. Bromide-lithium exchange of **10** with *n*-BuLi followed by trapping of the resulting organolithium species with $B(Oi\text{-}Pr)_3$ afforded *rac*-**5** in 77% yield.

With *rac*-**5** in hand, we explored the diastereomeric resolution of *rac*-**5** with chiral ligand **11**[16-18] using a boronic acid as a resolving group (Scheme 3).[12] To our delight, the reaction of *rac*-**5** with chiral ligand **11** provided the two diastereomers (**12** and **12'**), both in 43 % yields, which could be readily separated by column chromatography on silica. [19] Furthermore, this diastereomeric resolution could be performed on a gram-scale (10 mmol scale) without any loss in efficiency.[20]



Scheme 3. Diastereomeric Resolution of *rac*-**5** with Chiral Ligand **11**.

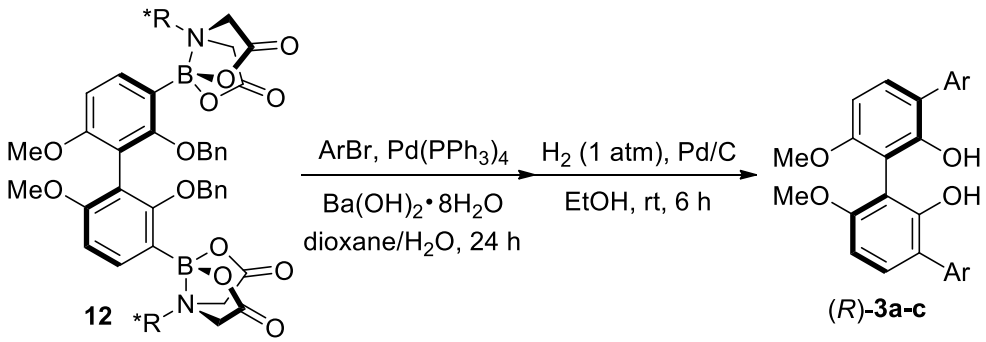
In order to determine the absolute stereochemistry of the resulting diastereomeric compounds (**12** and **12'**), the resulting diastereomers were converted into the enantiomers of BIPhOL **3**, since the absolute stereochemistry of the parent chiral BIPhOL was reported[11] (Scheme 4).

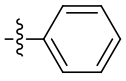
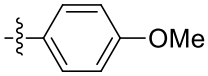
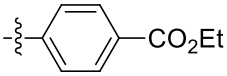


compound	R_f values[a] of **12** or **12'**	% ee of **3**[b]	$[\alpha]_D$ of **3** measured	$[\alpha]_D$ of **3** reported[c]	configuration (**3**)
12	0.6	99.1	+ 153.6		(*R*)
12'	0.4	98.6	- 144.0	- 144.0 (*S*)	(*S*)

Scheme 4. Determination of Absolute Stereochemistry of the Resulting Enantiomers. [a] A mixture of hexanes/ethyl acetate (1:1) was used as the eluent. [b] % ee was determined by HPLC analysis using a Chiralcel AS-H column. [c] For the reported $[\alpha]_D$ value of (*S*)-**3**, see ref. 11.

Treatment of each diastereomer (either **12** or **12'**) with a basic solution provided the corresponding chiral boronic acid. Subsequent thermal protodeboronation of the resulting boronic acid with acetic acid in 1,4-dioxane,[21] followed by the removal of a benzyl group via hydrogenolysis provided the parent BIPhOL with excellent enantioselectivity (>98% ee for each enantiomer). Comparison of the optical rotation of the resulting enantiomer with the reported value of the known enantiomer[22] allowed us to assign the absolute stereochemistry of the resulting enantiomers of the parent BIPhOL; the less polar diastereomer **12** was derived from (*R*)-BIPhOL, while the more polar diastereomer **12'** was from (*S*)-BIPhOL.



Ar =			
with **12**	(*R*)-**3a** 82% yield (99.1% ee)[a]	(*R*)-**3b** 67% yield	(*R*)-**3c** 60% yield
with **12'**	(*S*)-**3a** 80% yield (98.6% ee)[a]		

Scheme 5. Synthesis of Chiral BIPhOL Derivatives. [a] Ee was determined by HPLC analysis using a Chiralcel AD-H column.

Next, we further attempted to prepare chiral BIPhOL derivatives through Suzuki-Miyaura coupling reaction of the resulting diastereomers with aryl bromides, followed by deprotection of the benzyl group (Scheme 5). When chiral boronate **12** was subjected to Suzuki-Miyaura coupling reaction with phenyl bromide, to our delight, the Suzuki reaction

proceeded smoothly to provide the desired (*R*)-BIPhOL derivative, (*R*)-**3a**, in a good yield and excellent enantiopurity[12a] after the removal of the benzyl group. In addition, when the other diastereomer **12'** was subjected to Suzuki-Miyaura coupling reaction with phenyl bromide, the (*S*)-BIPhOL derivative, (*S*)-**3a**, was obtained with a similar efficiency. It should be noted that all transformations could be accomplished without any loss of enantioselectivity. Under these conditions, other aryl bromides were subjected to Suzuki-Miyaura coupling reaction with **12** and the chiral BIPhOL derivatives, (*R*)-**3b** and (*R*)-**3c**, were obtained in similar efficiencies regardless of electronic natures of the aryl groups. Furthermore, chiral ligand **11** used for the resolution could be readily recovered in quantitative yield by re-dissolving chiral ligand **11** with acetone from the concentrated crude product of **11** from the aqueous layer after the extraction.[20] The recovered chiral ligand could be directly re-applied to diastereomeric resolution of *rac*-**5** without any loss of efficiency.

Conclusions

In conclusion, we have developed a new synthetic protocol to access chiral 3,3'-disubstituted BIPhOL derivatives via the diastereomeric resolution of racemic BIPhOL boronic acid using a boronic acid moiety as a resolving group followed by Suzuki-Miyaura coupling reaction of the resulting diastereomers with aryl bromides. The desired BIPhOL derivatives bearing aryl groups at the 3,3'-positions were obtained in good yields and with excellent enantioselectivities. Furthermore, the absolute stereochemistry of the resulting chiral BIPhOL derivatives was determined by comparison of the optical rotation of the resulting BIPhOLs with the reported value. Further development of the synthesis of novel axially chiral biaryl diols and novel asymmetric transformations with these diol compounds are currently underway in our laboratory.

Experimental Section

General. All reactions were carried out in oven- or flame-dried glassware under an argon atmosphere unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin layer chromatography (TLC) using pre-coated silica gel glass plates (0.25 mm) with F254 indicator. Visualization was accomplished by UV light (254 nm), with combination of potassium permanganate and/or phosphomolybdic acid solution as an indicator. Flash column chromatography was performed using silica gel 60 (230 – 400 mesh). Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise noted. Commercial grade reagents and solvents were used without further purification. ^{1}H NMR and ^{13}C{1H} NMR spectra were recorded on 300/400 MHz, 75/100 MHz, respectively. Tetramethylsilane and $CDCl_3$ were used as internal standards for ^{1}H NMR (δ: 0.0 ppm) and ^{13}C NMR (δ: 77.0 ppm), respectively. The proton spectra are reported as follows: chemical shift ppm, multiplicity, coupling constant *J*, number of protons. Multiplicities are indicated by s (singlet), d (doublet), t (triplet), m (multiplet) and br (broad). High performance liquid chromatography (HPLC) was performed by using chiral columns (0.46 cm x 250 mm) with 2-propanol/hexane as the eluent. High resolution mass spectra (HRMS) were measured on a Q-TOF spectrometer using electron spray ionization (ESI) as the ionization method. Optical rotations were measured using a 1 mL cell with 10 mm path length on an automatic polarimeter and reported as follows: $[\alpha]^{25}_{D}$ (c: g/100 mL, in solvent).

*Synthesis of 1-methoxy-3-(methoxymethoxy)benzene (**6**)*: To a solution of 3-methoxyphenol **7** (12.4 g, 100 mmol) in DMF (300 mL) was added NaH (4.8 g, 120 mmol; 60 wt% powder) at 0 ^{o}C and the reaction mixture was warmed up to room temperature and stirred for additional 1 h. Then, methoxymethyl (MOM) chloride (8.4 mL, 110 mmol) was added dropwise to the reaction mixture. After complete consumption of compound **7**, the reaction mixture was

quenched by the addition of H_2O and extracted with ethyl acetate. The organic layer was combined, dried over $MgSO_4$, and concentrated. The crude mixture was purified by short flash column chromatography on silica (hexanes/ethyl acetate=3:1) to provide the desired product **6** as colorless oil in 92% yield (16 g). The spectroscopic data were in good agreement with the literature.[23] ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.18 (t, J = 8.1 Hz, 1H), 6.52 - 6.68 (m, 3H), 5.16 (s, 2H), 3.78 (s, 3H), 3.47 (s, 3H).

*Synthesis of rac-BIPhOL (rac-**3**)*: To a mixture of compound **6** (7.1 g, 42 mmol) and TMEDA (6.9 mL, 46 mmol) in THF was slowly added a solution of *n*-BuLi (2.5 M in hexane, 19 mL, 46 mmol) at -78 ^{o}C. Then, the reaction mixture was warmed up to room temperature and stirred for additional 2 h at the same temperature. Then the reaction mixture was cooled to 0 ^{o}C and $FeCl_3$ (8.2 g, 50 mmol) was added to the reaction mixture in one portion at 0 ^{o}C. The reaction mixture was warmed to room temperature and stirred for 12 h. After 12 h, aqueous HCl solution (1 *N,* 50 mL) was added to the reaction mixture to quench the remaining $FeCl_3$. The organic phase was extracted with ethyl acetate and the organic layers were combined, dried over $MgSO_4$, and concentrated to provide the desired product **8** along with *rac*-BIPhOL (*rac*-**3**). To a solution of the crude mixture in MeOH was added 3*N* HCl solution, and the reaction mixture was stirred at 70 ^{o}C for 1 h. After complete conversion of compound **8** into *rac*-**3**, the reaction mixture was cooled to room temperature, concentrated under reduced pressure, and extracted with ethyl acetate. The organic layer was combined, dried over $MgSO_4$, and concentrated. The crude mixture was purified by short flash column chromatography on silica (hexanes/ethyl acetate=3:1) to afford the desired product *rac*-**3** as a yellowish green solid in 83% yield from compound **6** over two steps (4.3 g). The spectroscopic data were in good agreement with the literature.[8-11] mp 144-146 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.31 (t, J = 8.3 Hz, 2H), 6.72 (d, J = 8.3 Hz, 2H), 6.62 (d, J = 8.3 Hz, 2H), 5.05 (s, 2H), 3.77 (s, 6H).

*Synthesis of 3,3'-dibromo-6,6'-dimethoxy-(1,1'-biphenyl)-2,2'-diol (**9**)*: A solution of *N*-bromosuccimide (NBS, 5.7 g, 32 mmol) in dichloromethane (50 mL) was added dropwise to a suspension of in *rac*-**3** (3.9 g, 16 mmol) in dichloromethane (100 mL) at 0 ^{o}C. The reaction mixture stirred at 0 ^{o}C for 1 h and monitored by TLC. After complete consumption of *rac*-**3**, the reaction mixture was quenched with saturated $NaHSO_4$ aqueous solution and extracted with dichloromethane. The organic layer was combined, dried over $MgSO_4$, and concentrated. The crude mixture was purified by flash column chromatography on silica (hexanes/ethyl acetate=3:1) to provide the desired product **9** in 70% yield (4.5 g). The spectroscopic data were in good agreement with the literature.[9a] mp 186-188 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.48 (d, J = 8.8 Hz, 2H), 6.54 (d, J = 9.1 Hz, 2H), 5.44 (s, 2H), 3.74 (s, 6H).

*Synthesis of 2,2'-bis(benzyloxy)-3,3'-dibromo-6,6'-dimethoxy-1,1'-biphenyl (**10**)*: A solution of compound **9** (4.4 g, 11 mmol) and $CsCO_3$ (7.5 g, 23 mmol) in DMF (100 mL) was stirred for 30 min at room temperature. Benzyl bromide (2.8 mL, 23 mmol) was added dropwise to the above reaction mixture, and the reaction mixture was stirred at room temperature. After complete consumption of compound **9**, the reaction mixture was poured into H_2O, and extracted with ethyl acetate. The organic layers were combined, dried over $MgSO_4$, and concentrated. The crude mixture was purified by short column chromatography flash on silica (hexanes/ethyl acetate=4:1) to yield the desired product **10** in 95% yield as a white solid (6.1 g). mp 92-94 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.55 (d, J = 8.8 Hz, 2H), 7.15 - 7.25 (m, 6H), 6.95 - 7.05 (m, J = 2.6, 6.5 Hz, 4H), 6.64 (d, J = 9.1 Hz, 2H), 4.89 (d, J = 10.4 Hz, 2H), 4.67 (d, J = 10.7 Hz, 2H), 3.65 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 157.5, 154.3, 136.6, 132.3, 127.7, 127.6, 127.3, 119.4, 108.3, 108.0, 74.3, 55.7. HRMS (ESI) calcd for $C_{28}H_{24}Br_2O_4Na$ 604.9941, found 604.9937.

*Synthesis of (2,2'-bis(benzyloxy)-6,6'-dimethoxy-[1,1'-biphenyl]-3,3'-diyl)diboronic acid (rac-**5**)*: To a solution of compound **10** (11 g, 19 mmol) in Et_2O was added slowly a solution of *n*-

BuLi (2.5 M in hexane, 16 mL, 39 mmol) at -78 °C and the reaction mixture was stirred for 3 h at -78 °C. After complete consumption of compound **10**, triisopropyl borate (10 mL, 94 mmol) was added dropwise to the reaction mixture at -78 °C. After the reaction mixture was stirred for 1 h at -78 °C, the reaction mixture was warmed up to room temperature and stirred for additional 6 h. After 6 h, the reaction mixture was quenched with H_2O, and extracted with ethyl acetate. The organic layers were combined, dried over $MgSO_4$, and concentrated. The crude mixture was purified by flash column chromatography on silica (hexanes/ethyl acetate=1:1) to provide the desired product *rac*-**5** in 77% yield as a white solid (7.4 g). mp not unavailable due to decomposition of **10** during the measurement. ^{1}H NMR (300 MHz, acetone-d_6, ppm) 7.94 (d, J = 8.2 Hz, 2H), 7.20 (m, J = 5.8 Hz, 4H), 6.98 - 7.05 (m, 4H), 6.88 - 6.94 (m, 4H), 4.65 (d, J = 10.2 Hz, 2H), 4.51 (d, J = 10.2 Hz, 2H), 3.83 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6, ppm) 205.6, 163.9, 161.6, 137.2, 136.8, 128.7, 128.4, 128.3, 117.4, 107.6, 76.4, 55.7. HRMS (ESI) calcd for $C_{28}H_{28}B_2O_8$ 514.1970, unable to be measured due to decomposition of compound **10** during the analysis.

*Synthesis of Compounds **12** and **12'***: Chiral ligand **11** (9.2 g, 30 mmol) and 4 Å molecular sieves were added to a solution of *rac*-**5** (5.1 g, 10 mmol) in a mixture of DMSO and toluene (1:20) (200 mL). The reaction mixture was refluxed with azeotropic removal of water using a Dean-stark condenser under an argon atmosphere. After stirring for 12 h, the reaction mixture was cooled to room temperature. The reaction mixture was quenched by water and extracted with ethyl acetate. The organic layer was combined, dried over $MgSO_4$, and concentrated. The crude mixture was purified by flash silica gel column chromatography (hexanes/ethyl acetate=1:2) to provide the desired products **12** and **12'** in both 43% yields (4.5 g).

In order to recover unreacting chiral ligand **11** used for the diastereomeric resolution, the aqueous layer was combined and concentrated under reduced procedure. Then, chiral ligand **11** in the resulting crude solid mixture was separated by re-dissolving it with excess of

acetone. The acetone solution was combined and concentrated *in vacuo* to provide chiral lignad **11** in a pure form without further purification (2.8 g, 91%).

Compound **12**: a white solid. mp 150-152 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.74 (d, J = 8.5 Hz, 2H), 7.27 - 7.37 (m, 6H), 7.04 - 7.20 (m, 6H), 6.84 - 7.01 (m, 8H), 6.79 (d, J = 8.0 Hz, 2H), 4.83 - 5.10 (m, 4H), 4.27 (d, J = 11.3 Hz, 2H), 3.93 - 4.16 (m, 4H), 3.73 - 3.83 (m, 2H), 3.71 (br. s., 6H), 3.29 (d, J = 16.5 Hz, 8H), 0.73 - 2.02 (m, 12H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) 168.4, 161.4, 160.8, 137.6, 137.0, 136.6, 128.9, 128.8, 128.7, 128.4, 128.3, 128.0, 127.9, 126.9, 118.0, 107.0, 79.8, 74.3, 71.2, 62.0, 56.0, 29.7, 26.2, 21.8. HRMS (ESI) calcd for $C_{60}H_{62}B_2N_2O_{14}Na$ 1079.4287, found 1079.4299.

Compound **12'**: a white solid. mp 170-172 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.68 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 5.5 Hz, 6H), 7.20 (d, J = 7.2 Hz, 2H), 7.03 - 7.16 (m, 8H), 6.97 (d, J = 7.2 Hz, 6H), 6.73 (d, J = 8.5 Hz, 2H), 4.89 (d, J = 10.2 Hz, 2H), 4.47 - 4.62 (m, 4H), 4.22 - 4.35 (m, 4H), 3.79 (d, J = 9.9 Hz, 4H), 3.71 (br. s., 2H), 3.66 (s, 6H), 3.37 - 3.51 (m, 2H), 3.17 (d, J = 15.95 Hz, 2H), 1.03 - 2.01 (m, 12H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) 169.2, 168.2, 161.0, 159.6, 136.9, 136.7, 136.1, 128.8, 128.5, 128.3, 128.1, 127.9, 127.8, 107.1, 80.4, 74.2, 73.7, 72.0, 62.8, 57.0, 55.9, 30.6, 26.7, 22.1. HRMS (ESI) calcd for $C_{60}H_{62}B_2N_2O_{14}Na$ 1079.4287, found 1079.4299.

Synthesis of (R)-BIPhOL ((R)-3): To a suspension of compound **12** (0.11 g, 0.10 mmol) in THF (10 mL) was added 1 N NaOH (0.50 mL), and the reaction mixture was stirred for 1 h. The reaction mixture was quenched with saturated NH_4Cl, and the crude product was extracted with ethyl acetate. The organic layer was combined, dried over $MgSO_4$, and concentrated. Acetic acid (1.0 mL) was added to a solution of the crude product in 1,4-dioxane (10 mL) and the reaction mixture was stirred at 100 ^{o}C in an open flask. After stirring for 12 h, the reaction mixture was quenched with saturated NH_4Cl, and the crude product was extracted with ethyl acetate. The organic layer was combined, dried over $MgSO_4$, and

concentrated. Pd/C powder (0.050 g) was added to a solution of crude mixture in EtOH (10 mL). The above mixture was stirred at room temperature under a hydrogen atmosphere and monitored by TLC. After stirring for 6 h, the reaction mixture was filtered through celite, and washed with dichloromethane. Then, the filtrate was concentrated, and purified by flash column chromatography on silica (hexanes/ethyl acetate=3:1) to provide the desired product (*R*)-**3** in 90% yield over three steps (0.022 g). The spectroscopic data were in good agreement with the literature.[8-11] ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.31 (t, J = 8.25 Hz, 2H), 6.72 (d, J = 8.25 Hz, 2H), 6.62 (d, J = 8.25 Hz, 2H), 5.05 (s, 2H), 3.77 (s, 6H). Enantiomeric excess (ee) was determined by HPLC with a Chiralcel AS-H column (hexane:2-propanol = 90:10, flow rate = 1.0 mL/min, λ = 254 nm), t_r(major) = 20.4 min., t_r(minor) = 23.2 min. $[\alpha]^{20}_D$ = +153.6 (*c* 0.77, $CHCl_3$).

Synthesis of (S)-BIPhOL ((S)-3): Similar reaction with **12'** provided (*S*)-BIPhOL. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.31 (t, J = 8.25 Hz, 2H), 6.72 (d, J = 8.25 Hz, 2H), 6.62 (d, J = 8.25 Hz, 2H), 5.05 (s, 2H), 3.77 (s, 6H). Enantiomeric excess (ee) was determined by HPLC with a Chiralcel AS-H column (hexane:2-propanol = 90:10, flow rate = 1.0 mL/min, λ= 254 nm), t_r(major) = 21.2 min., t_r(minor) = 19.3 min. $[\alpha]^{20}_D$= -144.0 (*c* 0.77, $CHCl_3$) (Lit.[11] $[\alpha]^{20}_D$= -144.0 (*c* 0.77, $CHCl_3$)).

Synthesis of 3,3'-disubstituted-6,6'-dimethoxy-2,2'-biphenol: To a solution of compound **12** (0.21 g, 0.20 mmol), $Ba(OH)_2 \cdot 8H_2O$ (0.18 g, 0.58 mmol, 2.9 equiv.), and $Pd(PPh_3)_4$ (0.012 g, 0.010 mmol, 0.050 equiv) in 1,4-dioxane (5.0 mL) and H_2O (2.0 mL) was added aryl bromide (0.60 mmol, 3.0 equiv). The above mixture was stirred at room temperature under an argon atmosphere for 10 min, then heated to 120 ^{o}C and stirred for 24 h. After stirring for 24 h, the reaction mixture was cooled to room temperature. The reaction mixture was quenched by 1 N HCl aqueous solution, and extracted with dichloromethane. The organic layer was combined, dried over $MgSO_4$, and concentrated. The crude mixture was re-dissolved in EtOH (10 mL)

and Pd/C powder was added to the reaction mixture. The above mixture was stirred at room temperature under a hydrogen atmosphere, and monitored by TLC. After complete consumption of the starting material, the reaction mixture was filtered through celite, and washed with dichloromethane. Then, the filtrate was concentrated, and the crude product was purified by flash column chromatography on silica to provide the desired product. For the recovery of chiral ligand **11**, the aqueous layer after Suzuki-Miyaura reaction was combined and concentrated under reduced procedure. Then, the chiral ligand **11** in the resulting crude solid mixture was separated by re-dissolving it with excess of acetone (20 mL/mmol of **11** X 3 times). The acetone solution was combined and concentrated in vacuo to provide chiral **11** in a pure form without further purification (0.11 g, 90%).

*(R)-3,3'-Diphenyl BIPhOL ((R)-**3a**)*: The product was obtained in 82% yield as an off-white solid (0.065 g) with 99.1% ee. mp 134-136 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 7.58 (d, J = 7.4 Hz, 4H), 7.18 - 7.50 (m, 8H), 6.72 (d, J = 8.5 Hz, 2H), 5.31 (s, 2H), 3.80 (s, 6H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 157.8, 152.0, 138.1, 131.7, 129.5, 128.6, 127.1, 122.4, 107.9, 104.0, 56.3. HRMS (ESI) calcd for $C_{26}H_{22}O_4Na$ 421.1418, found 421.1410. Enantiomeric excess (ee) was determined by HPLC with a Chiralcel AD-H column (hexane:2-propanol = 90:10, flow rate = 1.0 mL/min, λ= 254 nm), t_r(major) = 19.7 min., t_r(minor) = 29.8 min. $[\alpha]^{20}_{D}$ = -17.3 (*c* 1.0, $CHCl_3$).

*(S)-3,3'-Diphenyl BIPhOL ((S)-**3a**)*: The reaction of the other diastereomer **12'** under the above conditions provided (*S*)-**3a**. The product was obtained in 80% yield (0.063 g) as an off-white solid with 98.6% ee. mp 133-135 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 7.58 (d, J = 7.4 Hz, 4H), 7.18 - 7.50 (m, 8H), 6.72 (d, J = 8.5 Hz, 2H), 5.31 (s, 2H), 3.80 (s, 6H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 157.8, 152.0, 138.1, 131.7, 129.5, 128.6, 127.1, 122.4, 107.9, 104.0, 56.3. HRMS (ESI) calcd for $C_{26}H_{22}O_4Na$ 421.1418, found 421.1410. Enantiomeric excess (ee) was determined by HPLC with a Chiralcel AD-H column (hexane:2-propanol =

90:10, flow rate = 1.0 mL/min, λ= 254 nm), t_r(minor) = 19.7 min., t_r(major) = 29.8 min. $[\alpha]^{20}_D$ = +17.2 (*c* 1.0, $CHCl_3$).

*(R)-3,3'-Di(4-methoxyphenyl) BIPhOL ((R)-**3b**)*: The product was obtained as an off-white solid in 67% yield (0.061 g). mp 120-122 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 7.50 (d, *J* = 8.8 Hz, 4H), 7.34 (d, *J* = 8.5 Hz, 2H), 6.97 (d, *J* = 8.5 Hz, 4H), 6.70 (d, *J* = 8.5 Hz, 2H), 5.29 (s, 2H), 3.84 (s, 6H), 3.79 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) 158.8, 157.5, 152.0, 131.4, 130.6, 130.4, 122.1, 114.1, 107.9, 103.9, 56.3, 55.5. HRMS (ESI) calcd for $C_{28}H_{26}O_6Na$ 481.1629, found 481.1623. $[\alpha]^{20}_D$ = +11.3 (*c* 0.20, $CHCl_3$).

*(R)-3,3'-Di(4-(ethoxycarbonyl)phenyl) BIPhOL ((R)-**3c**)*: The product was obtained in 60% (0.065 g) yield as an off-white solid. mp 110-112 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 8.09 (d, *J* = 8.0 Hz, 4H), 7.67 (d, *J* = 7.7 Hz, 4H), 7.43 (d, *J* = 8.5 Hz, 2H), 6.74 (d, *J* = 8.5 Hz, 2H), 5.33 (br. s., 2H), 4.39 (q, *J* = 6.7 Hz, 4H), 3.81 (s, 6H), 1.40 (t, *J* = 7.0 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) 166.8, 158.3, 152.3, 142.8, 132.1, 129.8, 129.4, 128.9, 121.5, 107.5, 104.2, 61.1, 56.3, 14.6. HRMS (ESI) calcd for $C_{32}H_{30}O_8Na$ 565.1841, found 565.1832. $[\alpha]^{20}_D$ = +4.5 (*c* 0.50, $CHCl_3$).

Notes

The authors declare no competing financial interests.

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Supporting Information

^{1}H NMR and $^{13}C\{^{1}H\}$ NMR spectra for compounds **3, 5, 6, 8, 9,10, 12,** and **12'** and HPLC traces for compounds **3** and **3a**. The Supporting Information is available free of charge via the Internet at http://pubs.acs.org.

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19. For a picture of the TLC of the resulting diastereomers, see Supporting Information.

20. Since chiral ligand **11** is soluble in water, all **11** remained in the aqueous layer after extraction. The aqueous layer should be concentrated to provide the crude product of **11**, from which **11** could be recovered by re-dissolving **11** in excess of acetone. The acetone solution was combined and concentrated to provide chiral ligand **11**.

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