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Featured Article

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Ligand-Accelerated Stereoretentive Suzuki–Miyaura Coupling of Unprotected 3,3′-Dibromo-BINOL

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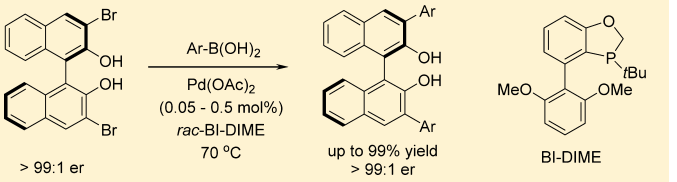
Supporting Information

ABSTRACT: An efficient synthesis of the enantiomerically pure 3,3′-bis-arylated BINOL derivatives is accomplished through the palladium-catalyzed Suzuki–Miyaura coupling of the unprotected 3,3′-dibromo-BINOL with complete retention of enantiopurity. The active catalyst system $Pd(OAc)_2$/BI-DIME has enabled mild reaction conditions at palladium loads as low as 500 ppm.

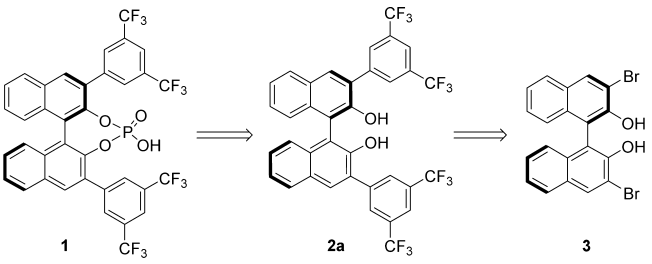


INTRODUCTION

Organocatalysts derived from 1,1′-binaphthalene-2,2′-diol (BINOL) are becoming increasingly versatile catalysts and have been shown to catalyze a plethora of asymmetric transformations using operationally simple and mild reaction conditions with diverse functional group tolerance.[1] Notably, the aryl substitution at the 3- and 3′- positions of the BINOL can significantly influence the catalytic activity by adjusting both the steric and electronic properties with different substituents.[2,3] Even though the enantioselective transformations employing 3,3′-bis-arylated BINOLs have seen exponential growth, the strategies for their synthesis have remained the same and require the cross coupling of an ether-protected 3,3′-bis-boronic acid or 3,3′-dihalo-BINOL to construct the aryl functionality. A deprotection step is then followed to generate the 3,3′-bis-arylated BINOLs. Furthermore, high catalyst load and prolonged reaction time are often required to achieve acceptable conversions, which renders these BINOL-derived catalysts not readily available for large-scale applications.

Recently, the enantiomerically pure BINOL-based phosphoric acid (**1**) was required in one of our programs. To identify an efficient and cost-effective synthetic strategy to access the intermediate 3,3′-diaryl-BINOL (**2a**), a streamlined protection-free Suzuki–Miyaura coupling process was sought starting from 3,3′-dibromo-BINOL (**3**) (Scheme 1). Despite the growing interest in these BINOL derivatives, coupling of the unprotected 3,3′-dihalo-BINOL is scarce in literature. The key challenge associated with this approach is the potential racemization of BINOLs and the corresponding coupling products, which is known to occur under both basic and acidic conditions, especially at elevated temperature.[4] As a result, there are few reports of direct palladium-catalyzed Suzuki–Miyaura coupling of the unprotected 3,3′-dibromo-BINOL. Beller and Köckritz reported the successful Suzuki coupling of partially hydrogenated 3,3′-dibromo-H8-BINOL.[5] However,

Scheme 1. Proposed Synthesis of Phosphoric Acid 1



Chiu and co-workers observed diminished enantiomeric excess (from >99% ee to 94% ee) with a low isolation yield when coupling the enantiomerically pure 3,3′-dibromo-BINOL with phenylboronic acid.[6] Clark et al. have reported an elegant synthesis of 3,3′-bis-arylated BINOL derivatives using a one-pot C–H borylation/Suzuki–Miyaura coupling sequence, yet the enantiopurity was preserved only for coupling of the phenyl halides without any substitution.[7] When coupling with the substituted phenyl halides with either an electron-donating or an electron-withdrawing group, the enantiopurities of the resulting 3,3′-diaryl-BINOLs are in the range of 87–97% ee.[7] Herein, we report an efficient synthesis to prepare enantiomerically pure 3,3′-bis-arylated BINOLs with the complete retention of optical purity through a palladium-catalyzed Suzuki–Miyaura coupling of the commercially available unprotected (*R*)-3,3′-dibromo-BINOL (**3**).

RESULTS AND DISCUSSION

We have recently reported a privileged dihydrobenzophosphole core structure (Scheme 2), and various effective chiral

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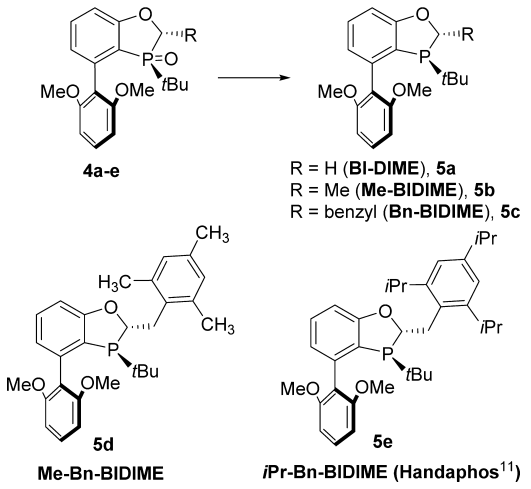
Scheme 2. BI-DIME Ligand and Derivatives



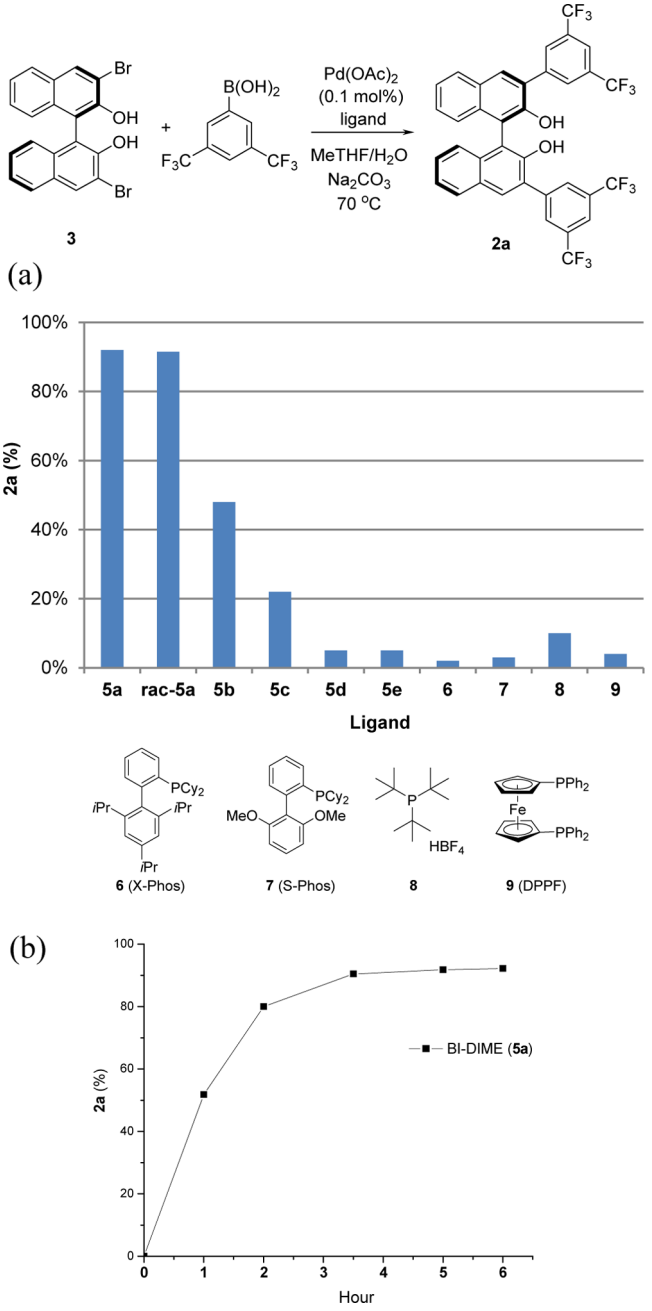
phosphine ligands were derived from this key building block.[8] BI-DIME and derivatives have been demonstrated to be highly effective ligands[9] for palladium-catalyzed cross-coupling reactions, especially the Suzuki–Miyaura reaction.[10] It was envisioned that these highly effective ligands could facilitate the coupling of the unprotected dibromo-BINOL under mild reaction conditions and therefore retain the stereoconfiguration.

The reaction of (*R*)-3,3′-dibromo-BINOL (**3**) and 3,5-bis(trifluoromethyl)phenylboronic acid was first examined with $Pd(OAc)_2$ (2 mol %) and (*S*)-BI-DIME ligand **5a** (2.2 mol %) in MeTHF/H_2O at 70 °C using Na_2CO_3 as the base. To our delight, the reaction completed in 30 min, and the desired product **2a** was isolated in 92% yield. Most importantly, the coupling product was analyzed on chiral HPLC, and no racemization was detected. The enantiomeric ratio of **2a** is >99.5:0.5, the same as that of the starting material **3**. Furthermore, the structural modification of the BIDIME ligand at the 2-position with increased steric hindrance was reported to increase the reactivity of the palladium-catalyzed Suzuki–Miyaura coupling reactions.[10a,c] Ligands **5b–e** were included into the screening together with several structurally diverse ligands. To compare the reactivity of the ligands, the reactions were carried out with 0.1 mol % of $Pd(OAc)_2$ (1000 ppm) as the catalyst precursor at 70 °C for 20 h (Scheme 3).

In the presence of BI-DIME ligand **5a**, desired product **2a** was observed in 92% yield together with the remaining monocoupling intermediate and monocoupling des-Br impurity (Scheme 3a).[13] The reaction progress was monitored by HPLC and is shown in Scheme 3b. Increasing the steric hindrance at the 2-position of the ligand slows down the reaction. A 48% yield was observed using the Me-BIDIME ligand with a methyl substitution (**5b**, Scheme 3a) after 20 h, 22% for Bn-BIDIME with a benzyl substitution (**5c**), and less than 5% for Me-Bn-BIDIME (**5d**) and *i*-Pr-Bn-BIDIME[11] (**5e**). The reactivity is irrelevant to the chirality of the ligand; both (*S*)- and racemic-BIDIME produced the same reaction profile. Racemic BI-DIME was then applied for further studies. On the other hand, S-Phos,[12] X-Phos, P-*t*-Bu_3·HBF_4, and DPPF ligands were all produced in less than 10% yield under 0.1 mol % catalyst load.

As revealed in the literature, racemization is an existing challenge for Suzuki–Miyaura coupling of the unprotected 3,3′-dibromo-BINOL; therefore, we evaluated whether any chiral erosion would occur after extended heating under our reaction

Scheme 3. Ligand Evaluation for Suzuki–Miyaura Coupling of (*R*)-Dibromo-BINOL (3)[a]



[a](*R*)-Dibromobinol (3.0 g, 6.755 mmol), 3,5-bis(trifluoromethyl)-phenylboronic acid (4.58 g, 16.887 mmol), catalyst stock solution containing $Pd(OAc)_2$ (1.52 mg, 0.0068 mmol) and ligand (0.0074 mmol), Na_2CO_3 (2.15 g, 20.26 mmol), MeTHF (22.5 mL), H_2O (7.5 mL), 70 °C, 20 h. Product **2a** is reported in HPLC area percent at 220 nm wavelength (see the Supporting Information for details). The plot 3b represents the reaction progress with ligand BI-DIME (**5a**) under the same conditions.

conditions. The reaction mixture of (*R*)-dibromo-BINOL and 3,5-bis(trifluoromethyl)phenylboronic acid was heated for 48 h at 70 °C after the reaction was completed. The desired product **2a** was isolated again with an enantiomeric ratio of >99.5:0.5 (Table 1, entry 1). The high reactivity of the BI-DIME ligand enables the coupling to occur under mild reaction conditions with a weak base Na_2CO_3, which leads to high enantiopurity of

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Table 1. Effect of Base on the Coupling Product 2a[a]

entry	base	solvent	T (°C)	mono des-Br (%) (2 h)	yield[c] (**2a**) (%) (2 h)	er (2 h)	er (48 h)
1	Na_2CO_3	MeTHF	70	2.4	97.6	>99.5:0.5	>99.5:0.5
2	K_2CO_3	MeTHF	70	5.5	94.5	>99.5:0.5	>99.5:0.5
3	K_3PO_4	MeTHF	70	6.5	93.5	>99.5:0.5	>99.5:0.5
4	NaO-*t*-Bu	MeTHF	70	20.0	80.0	>99.5:0.5	99.4:0.6[b]
5	Na_2CO_3	dioxane	70	2.5	97.5	>99.5:0.5	>99.5:0.5
6	K_3PO_4	dioxane	70	9.7	90.3	>99.5:0.5	>99.5:0.5
7	Na_2CO_3	dioxane	100	2.3	97.7	>99.5:0.5	99.2:0.8[b]
8	K_3PO_4	dioxane	100	6.0	94.0	99.5:0.5	99.2:0.8[b]
9	NaO-*t*-Bu	dioxane	100	18.0	82.0	98.2:1.8	94.2:5.8[b]

[a]Reaction conditions: (*R*)-dibromo-BINOL (0.5 g, 1.126 mmol), 3,5-bis(trifluoromethyl)phenylboronic acid (2.5 equiv), base (3.38 mmol), catalyst solution containing $Pd(OAc)_2$ (1.3 mg, 0.0056 mmol) and *rac*-BI-DIME (2.1 mg, 0.0062 mmol), 20 v% of H_2O was added (total 5 mL of solvent mixture). [b]20 h. [c]Yield of product **2a** is reported in HPLC area percent at 220 nm wavelength (see the Supporting Information for details).

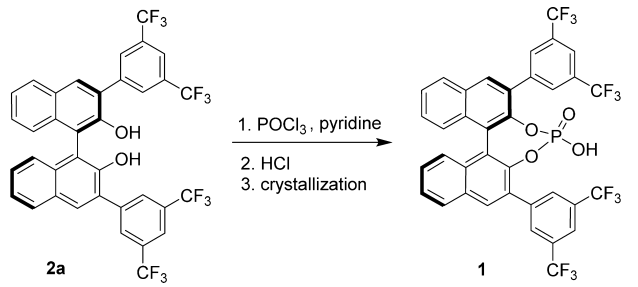
the product even after prolonged heating. Most phosphine ligands require the use of a stronger base to favor the coupling reaction; however, in the meantime, chiral degradation of the isolated products resulted.[6,7] Furthermore, the effect of base on the enantiopurity of the product was studied (Table 1). It was shown that the enantiopurity of the product **2a** remained the same in the presence of K_2CO_3 and K_3PO_4 after heating at 70 °C for 48 h (entries 2, 3 and 5, 6) and started to degrade slightly in the presence of NaO-*t*-Bu (entry 4). More importantly, stronger base also favors the formation of the monocoupling des-bromo impurity. The racemization starts to occur at a higher temperature of 100 °C. An enantiomeric ratio of 99.2:0.8 was obtained after 20 h in the presence of Na_2CO_3 and K_3PO_4, respectively (entries 7 and 8) and a ratio of 94.2:5.8 er with NaO-*t*-Bu as the base (entry 9).

The $Pd(OAc)_2$/BI-DIME catalyst system was then applied for the Suzuki coupling of unprotected (*R*)-3,3′-dibromo-BINOL with various boronic acids with Na_2CO_3 as the base (Table 2). At a catalyst load of 0.5 mol %, both electron-rich and electron-poor boronic acids were coupled successfully with dibromo-BINOL in 88−99% yields (entries 1−6). Catalyst amount can be further decreased; with 0.05 mol % $Pd(OAc)_2$ (500 ppm), the coupling of 3,3′-dibromo-BINOL with 3,5-bis(trifluoromethyl)phenylboronic acid was completed within 7 h, and an isolation yield of 85% resulted (entry 1). Ortho-substituted boronic acids were also obtained with 89−97% yields (entries 7−10). The catalyst system is applicable to the heteroaryl boronic acids as well. The Suzuki coupling with 1-methyl 5-indole boronic acid, 5-benzofuran boronic acid and 3-thiophene-ylboronic acid produced 86%, 81%, and 77% yield, respectively (entries 11−13). Chiral purity of all the isolated products has an enantiomeric ratio of >99:1. In contrast, Clark observed a 93% ee for the compound **2d**.[7]

The resulting 3,3′-diaryl-BINOLs can be conveniently converted to chiral phosphoric acids (Scheme 4) and other related BINOL Brønsted acids. The formation of the chiral monophosphoric acid **1** completed within 1.5 h by increasing the reaction temperature to 80 °C. A modified workup procedure allowed the preparation of the (*R*)-phosphoric **1** on kilogram scale with a 71% isolated yield[14] starting from the commercially available (*R*)-3,3′-dibromo-BINOL. The two-step synthesis significantly improves the efficiency of the overall process for this important BINOL-derived Brønsted acid.

In summary, a straightforward efficient Suzuki−Miyaura coupling process to prepare enantiomerically pure 3,3′-bis-aryl substituted BINOLs starting from the unprotected 3,3′-dibromo-BINOL is reported. The methodology eliminated

Scheme 4. Converting (*R*)-2a to Phosphoric Acid (*R*)-1



the deprotection process after the coupling step with an increased overall yield and excellent enantiopurity. The Pd-BI-DIME catalyst system enables low catalyst load of 500 ppm; which constitutes a cost-effective, efficient and high yielding process to access derivatives of substituted BINOLs, including chiral monophosphoric acids.

EXPERIMENTAL SECTION

General Methods. Unless otherwise stated, all reactions were carried out under strictly N_2 inert atmosphere. MeTHF and HPLC-grade water were used as received and N_2-sparged before usage. ^1H and ^{13}C NMR spectra were acquired in $CDCl_3$ at 23 °C. The ^1H and ^{13}C chemical shifts are given in parts per million (δ) with respect to an internal tetramethylsilane (TMS, δ 0.00 ppm) standard. High-resolution mass spectroscopy was performed on a TOF instrument with ESI positive or negative ionization modes. Flash chromatography was performed on an automated system with silica columns. Melting points of the crystalline compounds were measured on TA Instrument DSC Q1000. All starting materials are commercially available and used as received including (*R*)- and (*S*)-3,3′-dibromo-BINOL with chiral purity of >99.5% ee.

General Procedure for Alkylation Reactions. Phosphine oxide **4a** (1.0 g, 2.887 mmol) was dissolved in 15 mL of anhydrous THF under argon in a three-neck flask. The mixture was cooled to −78 °C, and 2.0 M LDA in THF/ethylbenzene (1.7 mL, 3.46 mmol) was added dropwise. The temperature was maintained under −70 °C for 1 h. 2-(Bromomethyl)-1,3,5-trimethylbenzene (646 mg, 3.03 mmol) was added, and the temperature was kept under −60 °C. The mixture was stirred at −78 °C for 1 h and then warmed to 23 °C, and stirring continued for 2 h. DCM (10 mL) and H_2O (10 mL) were added to quench the reaction. The layers were separated, and the organic layer was extracted with 5 mL of CH_2Cl_2 and dried with Na_2SO_4, and compound **4d** was purified on silica with 10−35% EtOAc in hexanes to give white crystalline solid after dryness.

*(2S,3R)-3-tert-Butyl-4-(2,6-dimethoxyphenyl)-2-(2,4,6-trimethylbenzyl)-2H-benzo[d][1,3]oxaphosphole 3-oxide (**4d**):* 0.84 g, 61% yield; mp 210−212 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.51 (t, J = 7.9 Hz, 1H), 7.34 (t, J = 8.4 Hz, 1H), 6.96 (dd, J = 7.2, 3.2 Hz, 1H), 6.93

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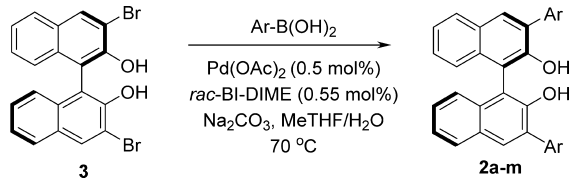
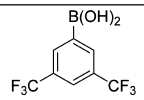
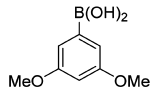
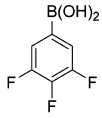
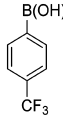
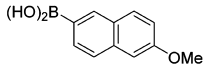
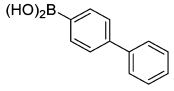
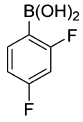
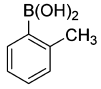
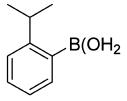
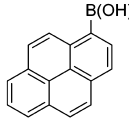
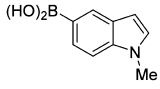
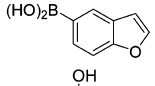
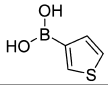
Table 2. Palladium-Catalyzed Suzuki Coupling of 3,3′-Dibromo-BINOL (3)[a]



Entry	Ar-B(OH)$_2$	Yield[b]
1		**2a**, 91% **2a**, 85%[c]
2		**2b**, 95%
3		**2c**, 93%
4		**2d**, 88%
5		**2e**, 88%
6		**2f**, 99%
7		**2g**, 93%
8		**2h**, 89%
9		**2i**, 91%[d]
10		**2j**, 97%
11		**2k**, 86%
12		**2l**, 81%
13		**2m**, 77%[d]

[a]Reaction conditions: (*R*)-3,3′-dibromo-BINOL (0.5 g, 1.126 mmol), boronic acid (2.5 equiv), Na_2CO_3 (358 mg, 3.38 mmol), catalyst solution containing $Pd(OAc)_2$ (1.3 mg, 0.0056 mmol) and *rac*-BI-DIME (2.1 mg, 0.0062 mmol), MeTHF/H_2O 3/1 (5 mL), 70 °C, 2−4 h. [b]Isolated yield of average two runs with (*R*)- and (*S*)-isomers. [c]500 ppm $Pd(OAc)_2$ at 10 g scale, 7 h. [d]14 h.

(s, 2H), 6.88 (dd, *J* = 8.0, 3.2 Hz, 1H), 6.71 (d, *J* = 8.6 Hz, 1H), 6.61 (d, *J* = 8.2 Hz, 1H), 4.58−4.62 (m, 1H), 3.85 (s, 3H), 3.75 (s, 3H), 3.16−3.29 (m, 2H), 2.34 (s, 6H), 2.31 (s, 3H), 0.92 (d, *J* = 15.6 Hz, 9H); ^{31}P NMR (202 MHz, $CDCl_3$) δ 59.97 ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4 (d, J_{C-P} = 19.5 Hz), 158.8, 157.4, 138.5 (d, J_{C-P} = 5.1 Hz), 137.0, 136.0, 134.2 (d, J_{C-P} = 1.8 Hz), 132.2 (d, J_{C-P} = 10.4 Hz), 129.8, 129.2, 125.0 (d, J_{C-P} = 8.3 Hz), 117.3 (d, J_{C-P} = 2.4 Hz), 114.3 (d, J_{C-P} = 90.3 Hz), 112.6 (d, J_{C-P} = 5.7 Hz), 104.5, 103.0, 74.5 (d, J_{C-P} = 59.6 Hz), 56.2, 55.4, 33.8 (d, J_{C-P} = 71.0 Hz), 29.0, 23.6, 20.9, 20.5 ppm; HRMS(EI) *m*/*z* calcd for $C_{29}H_{36}O_4P$ [M + H$^+$] 479.2346, found 479.2329.

*(2S,3R)-3-tert-Butyl-4-(2,6-dimethoxyphenyl)-2-(2,4,6-triisopropylbenzyl)-2H-benzo[d][1,3]oxaphosphole 3-oxide (**4e**):* 1.023 g of white crystalline solid, 63% yield; mp 232−233 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (t, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 8.4 Hz, 1H), 7.04 (s, 2H), 6.94 (dd, *J* = 7.4, 3.1 Hz, 1H), 6.84 (dd, *J* = 8.4, 3.4 Hz, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 6.59 (d, *J* = 8.4 Hz, 1H), 4.45−4.50 (m, 1H), 3.83 (s, 3H), 3.72 (s, 3H), 3.27 (dd, *J* = 6.5, 3.4 Hz, 2H), 3.17 (sep, *J* = 6.8 Hz, 2H), 2.90 (sep, *J* = 6.8 Hz, 1H), 1.26−1.29 (m, 2H), 1.21 (d, *J* = 6.8 Hz, 6H), 0.89 (d, *J* = 15.6 Hz, 9H); ^{31}P NMR (202 MHz, $CDCl_3$) δ 59.8 ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4 (d, J_{C-P} = 19.7 Hz), 158.8, 157.4, 147.4, 147.0, 138.6 (d, J_{C-P} = 5.0 Hz), 134.2 (d, J_{C-P} = 1.8 Hz), 129.9, 129.4 (d, J_{C-P} = 10.6 Hz), 125.0 (d, J_{C-P} = 8.4 Hz), 121.3, 117.3 (d, J_{C-P} = 2.2 Hz), 114.5 (d, J_{C-P} = 89.8 Hz), 112.6 (d, J_{C-P} = 5.8 Hz), 104.5, 103.0, 76.0 (d, J_{C-P} = 59.0 Hz), 56.2, 55.4, 34.1, 33.8 (d, J_{C-P} = 71.0 Hz), 29.3, 26.9, 24.7, 24.2, 24.1, 24.0, 23.6 ppm (d, J_{C-P} = 0.6 Hz); HRMS(EI) *m*/*z* calcd for $C_{35}H_{48}O_4P$ [M + H$^+$] 563.3285, found 563.3242.

General Procedure for Reduction of the Phosphine Oxides. To a Schlenk flask under argon were added **4d** (500 mg, 1.045 mmol), THF (10 mL), polymethylhydrosiloxane (1.5 g), and Ti(O-*i*-Pr)$_4$ (742 mg, 2.61 mmol). The mixture was stirred at 65 °C for 14 h. Upon complete conversion by ^{31}P NMR analysis, the mixture was concentrated under vacuum. Then the flask was cooled to 0 °C, and 20 mL of degassed 30% aqueous NaOH was added slowly with caution. Extreme H_2 gas evolution was observed in the beginning. After complete addition, the mixture was heated to 60 °C after addition of 10 mL of MeTHF and the mixture stirred for 1 h. The mixture was cooled to 23 °C, and the product was extracted with degassed MeTHF (3 × 10 mL) under argon. The combined organic layer was filtered through a plug of neutral alumina with anhydrous $MgSO_4$ on the top. **5d** was obtained as a white crystalline solid after dryness.

*(2S,3S)-3-tert-Butyl-4-(2,6-dimethoxyphenyl)-2-(2,4,6-trimethylbenzyl)-2,3-dihydrobenzo[d][1,3]oxaphosphole (**5d**):* 425 mg, 88% yield; mp 184−185 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (t, *J* = 7.8 Hz, 1H), 7.27 (t, *J* = 8.4 Hz, 1H), 6.82−6.85 (m, 4H), 6.65 (d, *J* = 8.2 Hz, 1H), 6.58 (d, *J* = 8.4 Hz, 1H), 4.99 (dd, *J* = 10.5, 4.6 Hz, 1H), 3.77 (s, 3H), 3.69 (s, 3H), 3.04−3.11 (m, 1H), 2.84−2.89 (m, 1H), 2.28 (s, 6H), 2.24 (s, 3H), 0.68 (d, *J* = 12.2 Hz, 9H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 8.03 ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 157.8, 157.1, 138.8 (d, J_{C-P} = 17.2 Hz), 136.7, 135.7, 132.8 (d, J_{C-P} = 12.6 Hz), 130.5, 129.1, 129.0, 125.5, 124.5 (d, J_{C-P} = 15.3 Hz), 123.7 (d, J_{C-P} = 4.0 Hz), 119.7, 110.1, 104.4, 103.6, 83.4 (d, J_{C-P} = 26.0 Hz), 56.0, 55.4, 35.2 (d, J_{C-P} = 31.0 Hz), 31.2 (d, J_{C-P} = 18.5 Hz), 30.3, 26.7 (d, J_{C-P} = 14.4 Hz), 20.9, 20.5 ppm (d, J_{C-P} = 1.6 Hz); HRMS(EI) *m*/*z* calcd for $C_{29}H_{36}O_3P$ [M + H$^+$] 463.2397, found 463.2369.

*(2S,3S)-3-tert-Butyl-4-(2,6-dimethoxyphenyl)-2-(2,4,6-triisopropylbenzyl)-2,3-dihydrobenzo[d][1,3]oxaphosphole (**5e**):* 442 mg of white crystalline solid, 91% yield; mp 195−196 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (t, *J* = 7.8 Hz, 1H), 7.28 (t, *J* = 8.2 Hz, 1H), 6.99 (s, 2H), 6.87 (dd, *J* = 7.8, 3.2 Hz, 1H), 6.83 (dd, *J* = 8.3, 0.9 Hz, 1H), 6.66 (d, *J* = 8.5, 1H), 6.59 (d, *J* = 8.6 Hz, 1H), 4.88 (dd, *J* = 11.1, 3.0 Hz, 1H), 3.77 (s, 3H), 3.70 (s, 3H), 3.10−3.19 (m, 3H), 2.96 (ddd, *J* = 15.1, 6.8, 3.0 Hz, 1H), 2.88 (sep, *J* = 6.8 Hz, 1H), 1.24 (m, 12H), 1.18 (d, *J* = 6.8 Hz, 6H), 0.70 (d, *J* = 12.0 Hz, 9H); ^{31}P NMR (202 MHz, $CDCl_3$) δ 9.59 ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.8, 157.8, 157.1, 147.1, 146.8, 138.7 (d, J_{C-P} = 16.8 Hz), 130.6, 130.5 (d, J_{C-P} = 14.2 Hz), 129.1, 124.7 (d, J_{C-P} = 14.9 Hz), 123.7 (d, J_{C-P} = 4.1 Hz),

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121.1, 119.8, 110.0, 104.6, 103.7, 85.1 (d, J_{C-P} = 26.1 Hz), 56.1 (d, J_{C-P} = 1.6 Hz), 55.4, 34.2, 33.3 (d, J_{C-P} = 32.0 Hz), 31.1 (d, J_{C-P} = 19.0 Hz), 29.3, 26.6, 26.5, 24.7, 24.2, 24.1 ppm (d, J_{C-P} = 4.6 Hz); HRMS(EI) m/z calcd for $C_{35}H_{48}O_3P$ [M + H$^+$] 547.3336, found 547.3348.

General Procedure for the Suzuki−Miyaura Coupling. (*R*)-3,3′-Dibromo-BINOL (500 mg, 1.126 mmol), (3,5-bis(trifluoromethyl)phenyl)boronic acid (95%, 764.2 mg, 2.815 mmol), Na_2CO_3 (378 mg, 3.38 mmol), MeTHF (3.75 mL), and H_2O (1.25 mL) were charged to a 25 mL flask. The mixture was purged with Ar for 10 min, and then catalyst stock solution containing $Pd(OAc)_2$ (1.3 mg, 0.0056 mmol) and racemic BI-DIME (2.1 mg, 0.0062 mmol) was added. The mixture was heated to 70 °C and stirred at this temperature for 2−14 h under argon. The reaction was monitored by LC−MS. After complete conversion to the desired product was observed, the mixture was cooled and 5 mL of H_2O was added. The layers were separated, and the aqueous layer was extracted three times with 10 mL of MeTHF. The organic layer was combined and dried with Na_2SO_4 and purified on silica with 5% EtOAc in hexanes to yield **2a** as white crystalline solid after dryness.

*(R)-3,3′-Bis(3,5-bis(trifluoromethyl)phenyl)[1,1′-binaphthalene]-2,2′-diol (**2a**):*[15] 760 mg of white crystalline solid, 92% yield, >99.5% ee; mp 217−219 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (s, 4H), 8.04 (s, 2H), 7.92 (d, J = 8.2 Hz, 2H), 7.84 (s, 2H), 7.40 (dt, J = 7.2, 1.0 Hz, 2H), 7.34 (dt, J = 8.0, 1.4 Hz, 2H), 7.16 (d, J = 8.5 Hz, 2H), 5.28 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.8, 139.4, 133.2, 132.3, 131.7 (q, J_{C-F} = 33.3 Hz), 129.9, 129.8, 129.4, 128.9, 128.6, 127.7, 125.2, 123.9, 122.3 (q, J_{C-F} = 272.9 Hz), 121.3 (sep, J_{C-F} = 3.8 Hz), 111.7 ppm.

*(R)-3,3′-Bis(3,5-dimethoxyphenyl)[1,1′-binaphthalene]-2,2′-diol (**2b**):* crystallized from 1:1 MeOH/water, 597 mg of white crystalline solid, 95% yield, >99.5% ee; mp 243−244 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 2H), 7.91 (d, J = 8.0 Hz, 2H), 7.38 (dt, J = 8.0, 2.0 Hz, 2H), 7.30 (dt, J = 8.0, 2.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 6.85 (d, J = 2.0 Hz, 2H), 6.52 (t, J = 2.0 Hz, 2H), 3.85 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 149.8, 139.3, 133.1, 131.0, 130.5, 129.3, 128.4, 127.3, 124.4, 124.3, 112.9, 107.7, 100.2, 55.5 ppm; HRMS(EI) m/z calcd for $C_{36}H_{31}O_6$ [M + H$^+$] 559.2115, found 559.2109.

*(R)-3,3′-Bis(3,4,5-trifluorophenyl)[1,1′-binaphthalene]-2,2′-diol (**2c**):* purified on silica with 0−40% EtOAc in hexanes, 589 mg of white crystalline solid, 93% yield, >99.5% ee; spectral data were in complete agreement with the published data;[3f] mp 198−201 °C.

*(R)-3,3′-Bis(4-(trifluoromethyl)phenyl)[1,1′-binaphthalene]-2,2′-diol (**2d**):* purified on silica with 0−10% EtOAc in hexanes, 567 mg of white crystalline solid, 88% yield, >99.5% ee; spectral data were in complete agreement with the published data;[7] mp 203−206 °C.

*(R)-6,6‴-Dimethoxy[2,2′:4′,1″:3″,2‴-quaternaphthalene]-2″,3′-diol (**2e**):* crystallized from 1:1 MeOH/water, 593 g of white crystalline solid, 88% yield, >99.5% ee; mp 153−154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, J = 9.6 Hz, 2H), 7.98 (d, J = 8.0 Hz, 2H), 7.88 (s, 4H), 7.84 (d, J = 10.0 Hz, 2H), 7.44 (dt, J = 6.7 Hz, 1.0 Hz, 2H), 7.37 (dt, J = 6.7 Hz, 1.0 Hz, 2H), 7.32 (d, J = 9.4 Hz, 2H), 7.24−7.20 (m, 4H), 5.49 (s, 2H), 3.98 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 150.3, 134.0, 133.0, 132.7, 131.5, 130.7, 129.8, 129.6, 129.0, 128.5, 128.4, 128.2, 127.3, 126.9, 124.4, 124.4, 119.2, 112.6, 105.7, 55.4 ppm; HRMS(EI) m/z calcd for $C_{42}H_{31}O_4$ [M + H$^+$] 599.2217, found 599.2209.

*(R)-3,3′-Bis(4-biphenyl)[1,1′-binaphthalene]-2,2′-diol (**2f**):* purified on silica with 10% EtOAc in hexanes, 732 mg of white crystalline solid, 99% yield, >99.5% ee; spectral data were in complete agreement with the published data;[16] mp 220−222 °C.

*(R)-3,3′-Bis(2,4-difluorophenyl)[1,1′-binaphthalene]-2,2′-diol (**2g**):*[3e] purified on silica with 10% EtOAc in hexanes, 600 mg of white solid isolated, 93% yield, >99.5% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.22 (s, 2H), 6.92−7.03 (m, 4H), 7.24 (d, J = 8.4 Hz, 2H), 7.34−7.44 (m, 4H), 7.73 (ddd, J = 15.0, 6.4, 1.7 Hz, 2H), 7.92 (d, J = 8.2 Hz, 2H), 7.98 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.3, 111.4, 111.6, 121.3, 121.4, 121.5 (2), 124.2, 124.4, 124.6, 127.9, 128.6, 129.2 (2), 129.3, 132.6, 123.7 (2), 132.8, 150.6, 159.1, 159.2, 161.5, 161.6, 161.7 (2), 164.0, 164.1.

*(R)-3,3′-Di-o-tolyl[1,1′-binaphthalene]-2,2′-diol (**2h**):* purified on silica with 0−20% EtOAc in hexanes, 470 mg of white solid isolated, 89% yield, >99.5% ee; spectral data were in complete agreement with the published data.[17]

*(R)-3,3′-Bis(2-isopropylphenyl)[1,1′-binaphthalene]-2,2′-diol (**2i**):* purified on silica with 5% EtOAc in hexanes, 535 mg of white crystalline solid isolated, 91% yield, >99.5% ee; spectral data were in complete agreement with the published data;[18] mp 218−220 °C.

*(R)-3-(1,9-Dihydropyren-4-yl)-3′-(pyren-4-yl)[1,1′-binaphthalene]-2,2′-diol (**2j**):* crystallized from 1:1 MeOH/water, 750 mg of off-white crystalline solid, 97% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40−7.90 (m, 22H), 7.35−7.35 (m, 6H), 5.38−5.2 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.2, 113.3, 113.6, 124.50, 124.53, 124.74, 124.77, 124.82, 124.85, 124.87, 124.92, 124.94, 124.99, 125.03, 125.1, 125.31, 125.36, 125.41, 125.47, 125.49, 125.53, 126.1, 126.21, 126.24, 127.46, 127.49, 127.55, 127.59, 127.63, 127.87, 127.92, 127.94, 128.05, 128.12, 128.2, 128.38, 128.45, 128.6, 128.7, 129.4, 129.5, 129.63, 129.66, 129.7, 129.90, 129.99, 130.01, 130.07, 130.99, 131.02, 131.04, 131.39, 131.4, 132.17, 132.24, 132.27, 132.74, 132.77, 132.9, 133.7, 133.8, 150.78, 150.80, 150.82 ppm (rotamers not assigned); HRMS(EI) m/z calcd for $C_{52}H_{29}O_2$ [M − H$^+$] 685.2173, found 685.2188.

*(R)-3,3′-Bis(1-methyl-1H-indol-6-yl)[1,1′-binaphthalene]-2,2′-diol (**2k**):* purified on silica with 30% EtOAc in hexanes, 527 mg of white solid isolated, 86% yield, 98.4% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 2H), 7.96 (d, J = 1.1 Hz, 2H), 7.91 (d, J = 8.0 Hz, 2H), 7.58 (dd, J = 8.5, 1.6 Hz, 2H), 7.44 (d, J = 8.5 Hz, 2H), 7.34−7.40 (m, 2H), 7.27−7.33 (m, 2H), 7.11 (d, J = 3.1 Hz, 2H), 5.51 (s, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 136.3, 132.9, 131.8, 130.9, 129.5, 129.4, 128.8, 128.4, 128.2, 126.7, 124.5, 123.9, 123.3, 122.0, 113.2, 109.3, 101.4, 33.0 ppm; HRMS(EI) m/z calcd for $C_{38}H_{29}N_2O_2$ [M + H$^+$] 545.2224, found 545.2221.

*(R)-3,3′-Di(benzofuran-5-yl)[1,1′-binaphthalene]-2,2′-diol (**2l**):* purified with 30% EtOAc in hexanes, 450 mg of white crystalline solid, 77% yield, 99.5% ee; mp 235−236 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 2H), 7.94 (d, J = 1.2 Hz, 2H), 7.91 (d, J = 8.0 Hz, 2H), 7.65 (dd, J = 8.8, 2.0 Hz, 4H), 7.61 (d, J = 8.8 Hz, 2H), 7.39 (td, J = 8.4, 1.6 Hz, 2H), 7.32 (td, J = 8.0, 1.2 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 6.82 (dd, J = 2.4, 0.8 Hz, 2H), 5.40 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 150.2, 145.6, 132.9, 132.2, 131.5, 130.9, 129.5, 128.4, 127.8, 127.2, 126.1, 124.37, 124.34, 122.3, 112.6, 111.4, 106.8 ppm; HRMS(EI) m/z calcd for $C_{36}H_{22}O_4$ [M + H$^+$] 519.1591, found 519.1584.

*(R)-3,3′-Di(thiophene-3-yl)[1,1′-binaphthalene]-2,2′-diol (**2m**):* purified on silica with 4% EtOAc in hexanes, 391 mg of white solid isolated, 77% yield, >99.5% ee; spectral data were in complete agreement with the published data.[19]

*(R)-3,3′-Bis[3,5-bis(trifluormethyl)phenyl]-1,1′-binaphthyl-2,2′-dihydrogen Phosphate (**1**).* (*R*)-3,3′-Bis(3,5-bis(trifluoromethyl)-phenyl)[1,1′-binaphthalene]-2,2′-diol (**2a**) (5.5 g, 7.40 mmol) and 15 mL of pyridine were added to a 250 mL reactor. A solution of phosphorus oxychloride (1.71 g, 11.152 mmol) in 7.5 mL of pyridine was slowly added while the reaction temperature was maintained below 30 °C. The reaction mixture was stirred at 80 °C for 1.5 h, cooled to 40 °C, and 7.5 mL of water was added followed after 10 min by addition of 37 mL of 6 N HCl aqueous solution. The mixture was heated to 100 °C for 1 h and cooled to 20 °C, and the solids were filtered. The solids were washed with 15 mL of water and then returned to the reactor. Toluene (60 mL) and 6 N HCl (15 mL) were added. The mixture was heated to 40 °C for 20 min, and then the aqueous fraction was separated. The organic layer was washed at 30−40 °C with 15 mL of 6 N HCl two times and then with 20 mL of water. The layer was distilled twice with toluene to reach 17 mL of the product solution and heated to 60 °C, and then 60 mL of heptane was added to crystallize the product. The mixture was cooled to 20 °C, filtered, washed with heptane, and then dried under reduced pressure at 70 °C for 20 h to yield 3.82 g of white crystalline solid, 66.4% yield, ee >99.5%; spectral data were in complete agreement with the published data;[15] mp 192−194 °C.

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■ ASSOCIATED CONTENT

Supporting Information

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^{1}H and ^{13}C NMR spectra and HPLC chromatograms of the enantiomeric ratio analyses (PDF)

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Notes

The authors declare no competing financial interest.

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