

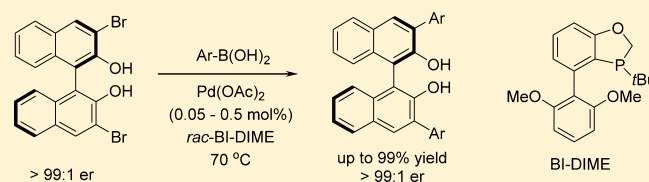
# Ligand-Accelerated Stereoretentive Suzuki–Miyaura Coupling of Unprotected 3,3'-Dibromo-BINOL

Bo Qu,\* Nizar Haddad,\* Sonia Rodriguez, Joshua D. Sieber, Jean-Nicolas Desrosiers, Nitinchandra D. Patel, Yongda Zhang, Nelu Grinberg, Heewon Lee, Shengli Ma, Uwe Jörg Ries, Nathan K. Yee, and Chris H. Senanayake

Chemical Development, Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, Ridgefield, Connecticut 06877, United States

**S** 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)<sub>2</sub>/BI-DIME has enabled mild reaction conditions at palladium loads as low as 500 ppm.

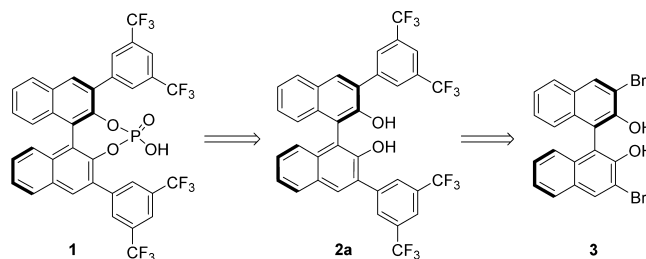


## INTRODUCTION

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.<sup>1</sup> 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.<sup>2,3</sup> 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.<sup>4</sup> 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.<sup>5</sup> 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.<sup>6</sup> 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.<sup>7</sup> 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.<sup>7</sup> 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**).

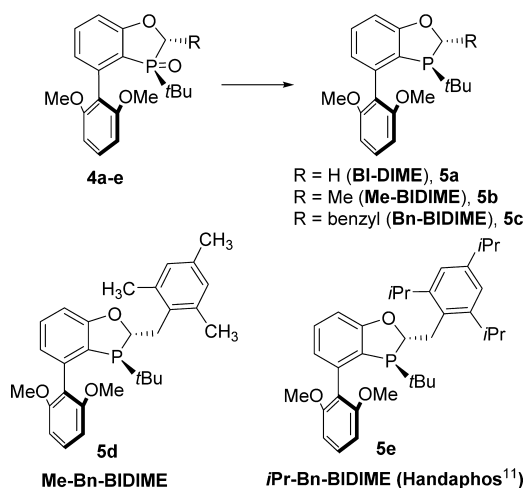
## RESULTS AND DISCUSSION

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

Received: October 13, 2015

Published: January 12, 2016

Scheme 2. BI-DIME Ligand and Derivatives

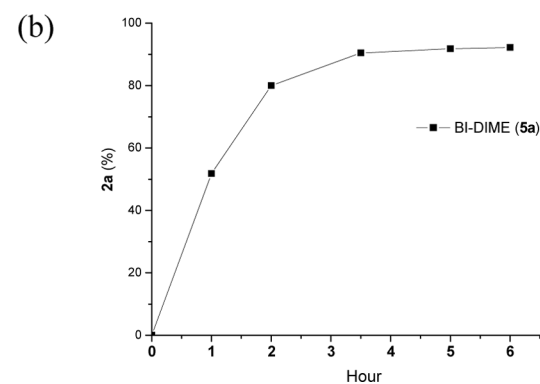
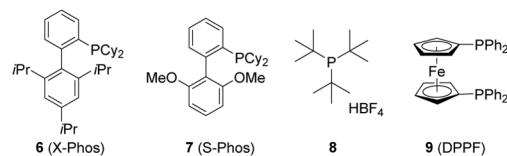
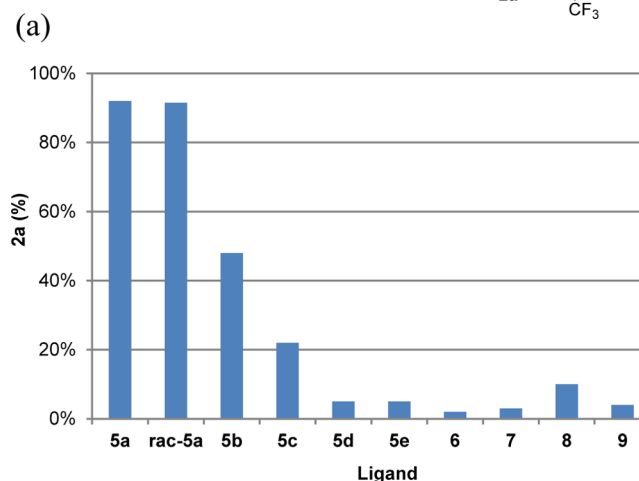
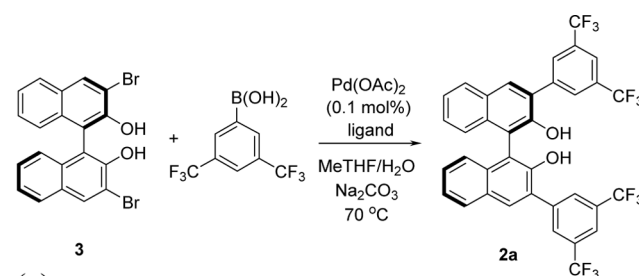


phosphine ligands were derived from this key building block.<sup>8</sup> BI-DIME and derivatives have been demonstrated to be highly effective ligands<sup>9</sup> for palladium-catalyzed cross-coupling reactions, especially the Suzuki–Miyaura reaction.<sup>10</sup> It was envisioned that these highly 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)<sub>2</sub> (2 mol %) and (*S*)-BI-DIME ligand **5a** (2.2 mol %) in MeTHF/H<sub>2</sub>O at 70 °C using Na<sub>2</sub>CO<sub>3</sub> 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.<sup>10a,c</sup> 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)<sub>2</sub> (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).<sup>13</sup> 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<sup>11</sup> (**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,<sup>12</sup> X-Phos, *P*-*t*-Bu<sub>3</sub>-HBF<sub>4</sub>, 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**)<sup>a</sup>

<sup>a</sup>(*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)<sub>2</sub> (1.52 mg, 0.0068 mmol) and ligand (0.0074 mmol), Na<sub>2</sub>CO<sub>3</sub> (2.15 g, 20.26 mmol), MeTHF (22.5 mL), H<sub>2</sub>O (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<sub>2</sub>CO<sub>3</sub>, which leads to high enantiopurity of

Table 1. Effect of Base on the Coupling Product 2a<sup>a</sup>

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

<sup>a</sup>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)<sub>2</sub> (1.3 mg, 0.0056 mmol) and *rac*-BI-DIME (2.1 mg, 0.0062 mmol), 20 v% of H<sub>2</sub>O was added (total 5 mL of solvent mixture). <sup>b</sup>20 h. <sup>c</sup>Yield of product 2a is reported in HPLC area percent at 220 nm wavelength (see the Supporting Information for details).

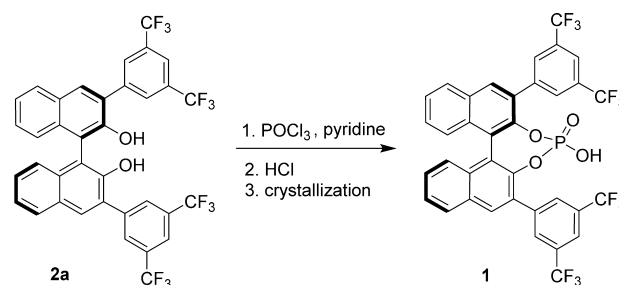
the product even after prolonged heating. Most phosphine ligands require the use of a stronger base to favor the coupling reaction; however, in the meantime, chiral degradation of the isolated products resulted.<sup>6,7</sup> Furthermore, the effect of base on the enantiopurity of the product was studied (Table 1). It was shown that the enantiopurity of the product 2a remained the same in the presence of K<sub>2</sub>CO<sub>3</sub> and K<sub>3</sub>PO<sub>4</sub> 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<sub>2</sub>CO<sub>3</sub> and K<sub>3</sub>PO<sub>4</sub>, 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)<sub>2</sub>/BI-DIME catalyst system was then applied for the Suzuki coupling of unprotected (*R*)-3,3'-dibromo-BINOL with various boronic acids with Na<sub>2</sub>CO<sub>3</sub> 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)<sub>2</sub> (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.<sup>7</sup>

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 monoposphoric 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<sup>14</sup> 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 monoposphoric acids.

## EXPERIMENTAL SECTION

**General Methods.** Unless otherwise stated, all reactions were carried out under strictly N<sub>2</sub> inert atmosphere. MeTHF and HPLC-grade water were used as received and N<sub>2</sub>-sparged before usage. <sup>1</sup>H and <sup>13</sup>C NMR spectra were acquired in CDCl<sub>3</sub> at 23 °C. The <sup>1</sup>H and <sup>13</sup>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<sub>2</sub>O (10 mL) were added to quench the reaction. The layers were separated, and the organic layer was extracted with 5 mL of CH<sub>2</sub>Cl<sub>2</sub> and dried with Na<sub>2</sub>SO<sub>4</sub> and compound 4d was purified on silica with 10–35% EtOAc in hexanes to give white crystalline solid after dryness.

(2*S*,3*R*)-3-*tert*-Butyl-4-(2,6-dimethoxyphenyl)-2-(2,4,6-trimethylbenzyl)-2*H*-benzo[*d*][1,3]oxaphosphole 3-oxide (4d): 0.84 g, 61% yield; mp 210–212 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) 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

**Table 2. Palladium-Catalyzed Suzuki Coupling of 3,3'-Dibromo-BINOL (3)<sup>a</sup>**

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

<sup>a</sup>Reaction conditions: (R)-3,3'-dibromo-BINOL (0.5 g, 1.126 mmol), boronic acid (2.5 equiv), Na<sub>2</sub>CO<sub>3</sub> (358 mg, 3.38 mmol), catalyst solution containing Pd(OAc)<sub>2</sub> (1.3 mg, 0.0056 mmol) and *rac*-BI-DIME (2.1 mg, 0.0062 mmol), MeTHF/H<sub>2</sub>O 3/1 (5 mL), 70 °C, 2–4 h. <sup>b</sup>Isolated yield of average two runs with (R)- and (S)-isomers. <sup>c</sup>500 ppm Pd(OAc)<sub>2</sub> at 10 g scale, 7 h. <sup>d</sup>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); <sup>31</sup>P NMR (202 MHz, CDCl<sub>3</sub>) δ 59.97 ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 163.4 (d, *J*<sub>C–P</sub> = 19.5 Hz), 158.8, 157.4, 138.5 (d, *J*<sub>C–P</sub> = 5.1 Hz), 137.0, 136.0, 134.2 (d, *J*<sub>C–P</sub> = 1.8 Hz), 132.2 (d, *J*<sub>C–P</sub> = 10.4 Hz), 129.8, 129.2, 125.0 (d, *J*<sub>C–P</sub> = 8.3 Hz), 117.3 (d, *J*<sub>C–P</sub> = 2.4 Hz), 114.3 (d, *J*<sub>C–P</sub> = 90.3 Hz), 112.6 (d, *J*<sub>C–P</sub> = 5.7 Hz), 104.5, 103.0, 74.5 (d, *J*<sub>C–P</sub> = 59.6 Hz), 56.2, 55.4, 33.8 (d, *J*<sub>C–P</sub> = 71.0 Hz), 29.0, 23.6, 20.9, 20.5 ppm; HRMS(EI) *m/z* calcd for C<sub>29</sub>H<sub>36</sub>O<sub>4</sub>P [M + H<sup>+</sup>] 479.2346, found 479.2329.

(2*S*,3*R*)-3-*tert*-Butyl-4-(2,6-dimethoxyphenyl)-2-(2,4,6-triisopropylbenzyl)-2*H*-benzo[*d*][1,3]oxaphosphole 3-oxide (**4e**): 1.023 g of white crystalline solid, 63% yield; mp 232–233 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) 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); <sup>31</sup>P NMR (202 MHz, CDCl<sub>3</sub>) δ 59.8 ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 163.4 (d, *J*<sub>C–P</sub> = 19.7 Hz), 158.8, 157.4, 147.4, 147.0, 138.6 (d, *J*<sub>C–P</sub> = 5.0 Hz), 134.2 (d, *J*<sub>C–P</sub> = 1.8 Hz), 129.9, 129.4 (d, *J*<sub>C–P</sub> = 10.6 Hz), 125.0 (d, *J*<sub>C–P</sub> = 8.4 Hz), 121.3, 117.3 (d, *J*<sub>C–P</sub> = 2.2 Hz), 114.5 (d, *J*<sub>C–P</sub> = 89.8 Hz), 112.6 (d, *J*<sub>C–P</sub> = 5.8 Hz), 104.5, 103.0, 76.0 (d, *J*<sub>C–P</sub> = 59.0 Hz), 56.2, 55.4, 34.1, 33.8 (d, *J*<sub>C–P</sub> = 71.0 Hz), 29.3, 26.9, 24.7, 24.2, 24.1, 24.0, 23.6 ppm (d, *J*<sub>C–P</sub> = 0.6 Hz); HRMS(EI) *m/z* calcd for C<sub>35</sub>H<sub>48</sub>O<sub>4</sub>P [M + H<sup>+</sup>] 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)<sub>4</sub> (742 mg, 2.61 mmol). The mixture was stirred at 65 °C for 14 h. Upon complete conversion by <sup>31</sup>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<sub>2</sub> 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<sub>4</sub> on the top. **5d** was obtained as a white crystalline solid after dryness.

(2*S*,3*S*)-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; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) 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); <sup>31</sup>P NMR (162 MHz, CDCl<sub>3</sub>) δ 8.03 ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 162.9, 157.8, 157.1, 138.8 (d, *J*<sub>C–P</sub> = 17.2 Hz), 136.7, 135.7, 132.8 (d, *J*<sub>C–P</sub> = 12.6 Hz), 130.5, 129.1, 129.0, 125.5, 124.5 (d, *J*<sub>C–P</sub> = 15.3 Hz), 123.7 (d, *J*<sub>C–P</sub> = 4.0 Hz), 119.7, 110.1, 104.4, 103.6, 83.4 (d, *J*<sub>C–P</sub> = 26.0 Hz), 56.0, 55.4, 35.2 (d, *J*<sub>C–P</sub> = 31.0 Hz), 31.2 (d, *J*<sub>C–P</sub> = 18.5 Hz), 30.3, 26.7 (d, *J*<sub>C–P</sub> = 14.4 Hz), 20.9, 20.5 ppm (d, *J*<sub>C–P</sub> = 1.6 Hz); HRMS(EI) *m/z* calcd for C<sub>29</sub>H<sub>36</sub>O<sub>3</sub>P [M + H<sup>+</sup>] 463.2397, found 463.2369.

(2*S*,3*S*)-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; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) 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 Hz, 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, 2H), 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); <sup>31</sup>P NMR (202 MHz, CDCl<sub>3</sub>) δ 9.59 ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 162.8, 157.8, 157.1, 147.1, 146.8, 138.7 (d, *J*<sub>C–P</sub> = 16.8 Hz), 130.6, 130.5 (d, *J*<sub>C–P</sub> = 14.2 Hz), 129.1, 124.7 (d, *J*<sub>C–P</sub> = 14.9 Hz), 123.7 (d, *J*<sub>C–P</sub> = 4.1 Hz),



## ■ ASSOCIATED CONTENT

## S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02368.

<sup>1</sup>H and <sup>13</sup>C NMR spectra and HPLC chromatograms of the enantiomeric ratio analyses (PDF)

## ■ AUTHOR INFORMATION

## Corresponding Authors

\*E-mail: bo.qu@boehringer-ingenheim.com.

\*E-mail: nizar.haddad@boehringer-ingenheim.com.

## Notes

The authors declare no competing financial interest.

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