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Note

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Synthesis of P-Chiral Dihydrobenzooxaphosphole (BOP) Core for BI Ligands in Asymmetric Transformations

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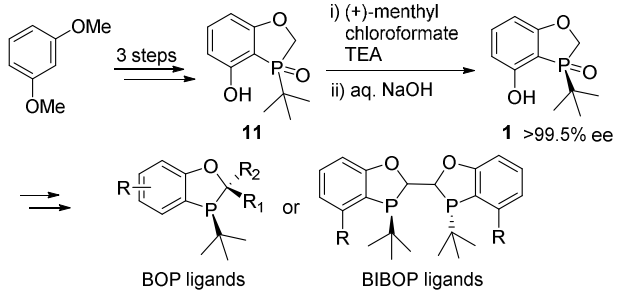
***Abstract*:** An efficient and practical synthesis of enantiomerically pure P-chiral dihydrobenzooxaphosphole (BOP) core **1** is developed which is amendable for large scale preparation of the related ligand series. The unique epimerization of P-chiral center of the undesired (*R*,*R*)-diastereomeric phosphine oxide **19** through chlorination followed by crystallization makes this chemical resolution method achieve 65% yield of the desired (*R*,*S*)-diastereomer **12**.



In the past decades, metal-catalyzed reactions with chiral phosphine ligands are widely utilized and advanced for variety of asymmetric transformations.[1] In 2010, our laboratories discovered a new series of P-chiral mono- and bis-phosphine ligands[2] containing a unique dihydrobenzooxaphosphole (BOP) core **1** which are structurally rigid, electronically and sterically tunable, and air-stable. These unique chiral BOP ligands have demonstrated superior reactivity and selectivity for various asymmetric transformations (Scheme 1) including 1) asymmetric Suzuki-Miyaura cross-coupling reaction,[3] 2) asymmetric hydrogenation of enamide,[2,4] ketones,[5] unfunctionalized alkenes,[6] and substituted pyridine,[7] 3) asymmetric

proprogylation,[2b,8] and allenylation,[9,10] 4) asymmetric addition to ketone,[10] imine, and nitroalkene, 5) asymmetric ring-opening,[11] 6) asymmetric hydroboration,[12] 7) asymmetric dearomative and reductive alkynone cyclization,[12] 8) asymmetric hydroformylation,[13] and 9) asymmetric alkene oxyarylation.[12] More significantly, these chiral BOP ligands were successfully applied to the syntheses of complex chiral drug candidates for Cholesteryl Ester Transfer Protein (CETP) inhibitor,[5] HIV Integrase Inhibitor,[3]and 11-beta-HSD-1 inhibitor[7] programs at Boehringer-Ingelheim (Figure 1). Also these ligands are effectively used for other non-asymmetric transformations such as sterically hindered Suzuki[14] and Negishi[15] cross-coupling, amination,[16] and borylation.[17]

Scheme 1. Asymmetric transformations using the P-chiral BOP ligand families

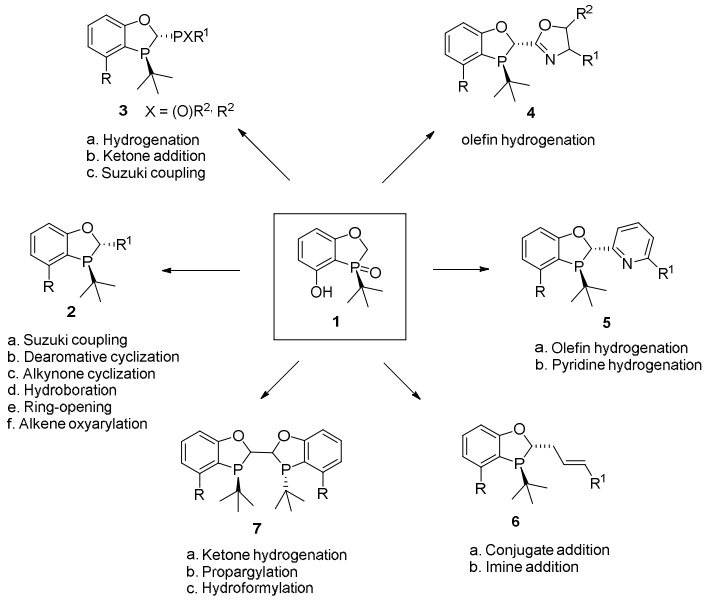
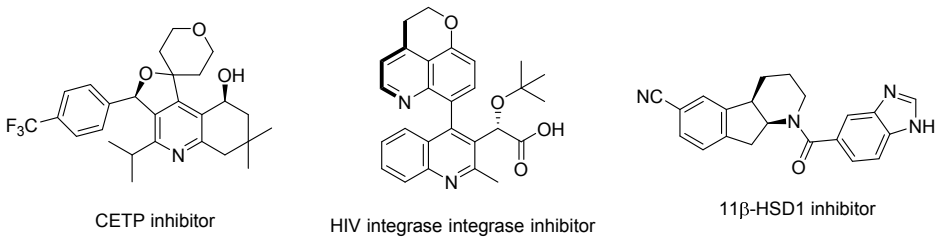


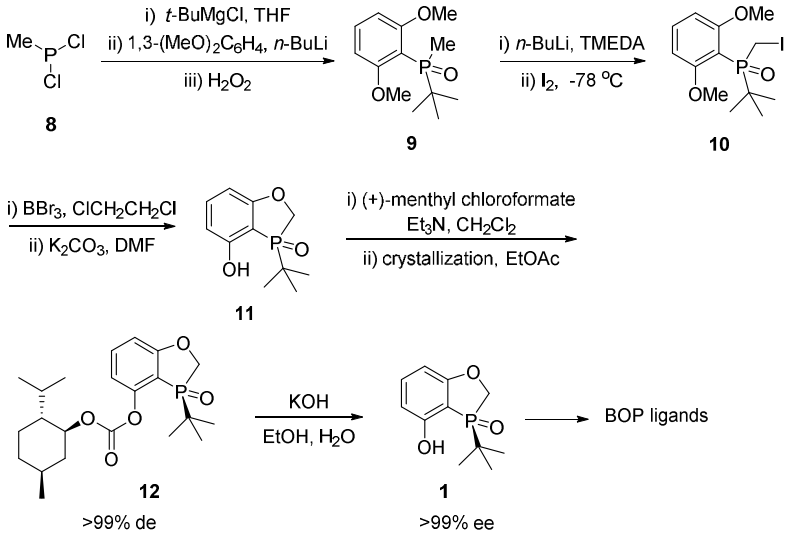
Figure 1.



Due to the versatile and important utilities of these P-chiral BOP ligands for various asymmetric transformations, it becomes very important to have an efficient, practical, and cost-effective synthesis of this class of chiral ligands, particular for its applications on industrial scale. While our original synthesis[2b] (Scheme 2) of BOP core **1** was already used to produce kilogram

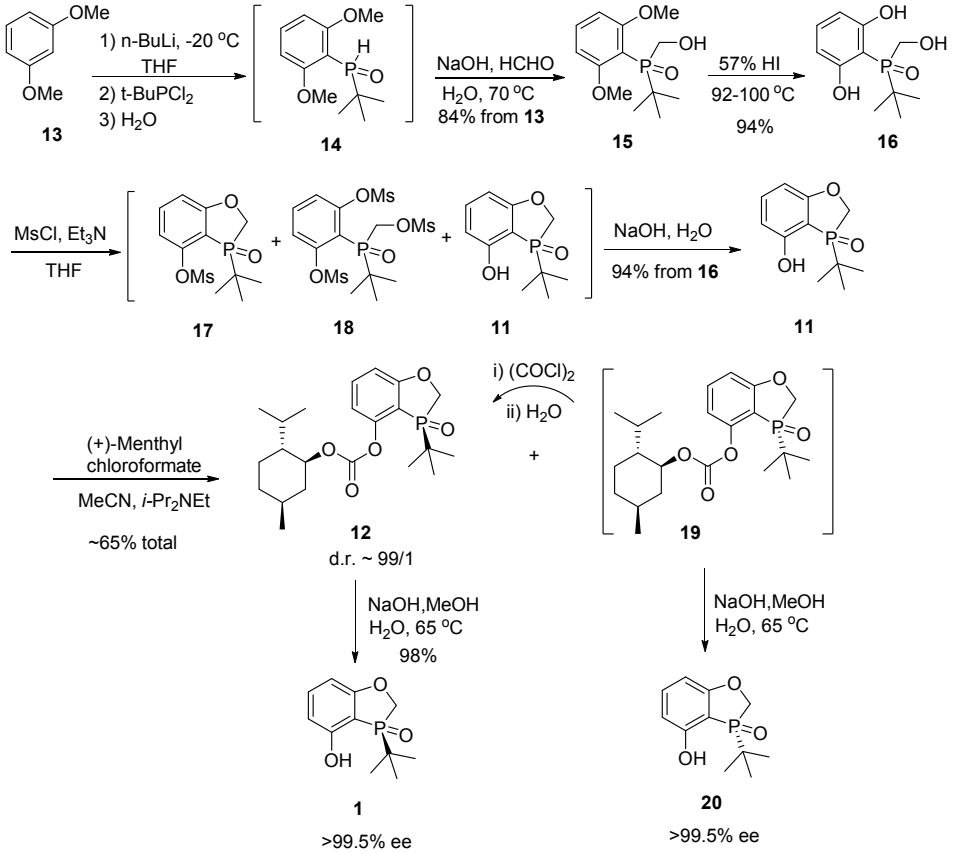
quantity of these ligands, there are some drawbacks hindering its further scale up. At first, the deprotonation of phosphanate **9** with n-BuLi at low temperatures (-78 ^{o}C) followed by iodination is not desirable because the good in-process controls of the reaction conditions are required to achieve reproducible results. Secondly, excess boron tribromide (BBr_3, 3 eq.) used in the demethylation of iodide **10** is a hazardous reagent in its handling on scale. Also, large amount of by-product HBr generated during the quenching and workup of this demethylation reaction are very problematic. In addition, chemical resolution of the menthyl ester has its inherent limitation because its potential maximum yield is 50%.

Scheme 2. Original Synthesis of Dihydrobenzooxaphosphole Core **1**



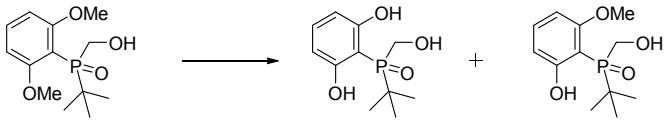
Herein, we describe a greatly improved synthesis of P-chiral 3-tert-butyl-2,3-dihydrobenzo(d)[1,3]oxaphosphol-4-ol oxide **1** in terms of efficiency, practicality, and cost-effectiveness. The preparation of racemic phenol **11** started from commercially available 1,3-dimethoxybenzene (**13**) (Scheme 3). 1,3-Dimethoxybenzene was first lithiated (n-BuLi, -20 ^{o}C to 0 ^{o}C, THF) and then reacted with t-butyl dichlorophosphine (- 20 ^{o}C to 0 ^{o}C). In the same pot, the reaction mixture was quenched with water to give phosphinate **14**. The crude **14** in aqueous layer was directly treated with 25% aq. NaOH and aq. 37% formaline. The desired hydroxyl phosphinate **15** was isolated as solids in 84% overall yield from 1,3-dimethoxybenzene (**13**).

Scheme 3. Improved Synthesis of Dihydrobenzooxaphosphole Core **1**



Demethylation of hydroxymethyl-phosphine oxide **15** was not trivial, a number of reaction conditions was explored to avoid the use of BBr_3 (Table 1). Treatment of **15** with 4 eq. BBr_3 in 1,2-dichloroethane (DCE) from rt to 60 °C gave **16** as major product (~60% yield) along with other minor products. Lithium benzenethiolate (PhSLi) in THF cleanly provided the monodemethylated product **21** only. Other conditions such as aq. 48% HBr (entry 3), 85% H_3PO_4/NaI (entry 4), and aq. 47% HI (entry 5) gave moderate yields (74-83%) of triol **16**. In these cases, mono-demethylation occurred smoothly in a few hours, while the second demethylation was slow and higher temperatures were required for complete conversion of **15** to **16**. Eventually, the demethylation of hydroxymethyl-phosphine oxide **15** was best accomplished with aq. 57% HI at 92 to 100 °C to give triol **16** in 94% yield as crystalline solids on cooling and neutralization with aq. NaOH.

Table 1: Demethylation of **15**



15 **16** **21**

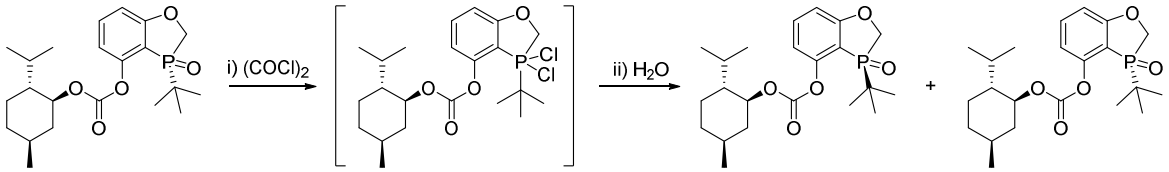
entry	Reagent/Solvent (eq)	Temp (^{o}C)	Time (h)	Yield (%)
1	BBr_3/CH_2Cl_2 (3)	60	1	60
2	PhSLi/THF (3)	0-40	17	0
3	48% HBr (10)	92-100	37	74
4	85% H_3PO_4/NaI (8/6)	92-100	38	75
5	47% HI (8)	92-100	24	83
6	57% HI (8)	92-100	24	94

Propylphosphonic anhydride (T3P) was first evaluated for dehydration of triol **16** to produce dihydrobenzooxaphosphole **11**. A mixture of **16** and 50% T3P in DMF was heated at 100 ^{o}C for 1.5 h followed by treatment with aq NaOH, the desired **11** was obtained in about 90% which contaminated with 10% unidentified by-products. On the other hand, treatment of **16** with methanesulfonyl chloride (MsCl) in presence of triethylamine (Et_3N) at room temperature, triol **16** was completely converted to a mixture of the desired hydroxyl dihydrobenzooxaphosphole **11**, its mono-mesylate **17**, and tri-mesylate **18**. Addition of aq. NaOH to this mixture led to selective hydrolysis of phenol mesylate functional group in **17** and **18** with concurrent cyclization to give exclusively dihydrobenzooxaphosphole **11** in 94% yield. Treatment of **11** with (+)-menthyl chloroformate (98.5% ee) and diisopropylethylamine (i-Pr_2NEt) in MeCN gave a mixture of diastereomers **12** and **19**, in which the desired diastereomer **12** (d.r. = 99:1) was directly crystallized from the reaction mixture in ~48% yield (>98% dr) while the undesired diastereomer **19** remained in the mother liquor, simply due to different solubility of these two diasteromers **12** and **19** in this solvent system. The diastereomerically pure (*R*,*R*)-**12** was hydrolyzed by aq. NaOH in MeOH to give enantiomerically pure hydroxyl-dihydrobenzooxaphosphole **1** (>99.5% ee) in 98% yield. On the other hand, simple concentration of the resulting mother liquor containing the diastereomeric (*R*,*S*)-**19** followed by hydrolysis and crystallization gave (*R*,*S*)-**20** (>99% ee) in 95% yield.

If ones only desire to have single enantiomer for specific asymmetric transformation, chemical resolution of a racemic mixture typically needs to sacrifice one of the enantiomer. In this case, however, by taking the advantage of the observed solubility difference of these two

diastereomers **12**/**19** as described above, the possibility of converting the undesired diastereomeric (*R*,*S*)-**19** into desired (*R*,*R*)-**12** via epimerization of phosphine oxide was envisioned. Treatment of the undesired diastereomer **19** (d.r. ~98/2) with 1.5 eq of oxalyl chloride[18] in CH_2Cl_2 at rt for about 20 h followed by quenching with water give a 42:58 mixture of **12** and **19** as indicated by ^{31}P NMR. Crystallization of this resulting mixture from MeCN provide additional ~17% of the desired **12** (d.r. = 99:1). Therefore, the combined yields of this chemical resolution protocol were ~65%. One can repeat this epimerization/crystallization protocol to obtain additional desired diastereomer if needed.

Scheme 4. Epimerization of **19**



The syntheses of various mono- and bis-phosphine ligands (**2**, **3**, **4**, **5**, **6**, and **7** in Scheme 1) using this key building block **1** have been previously reported from our laboratories and others.[2-17]

In summary, an efficient and practical synthesis of enantiomerically pure P-chiral dihydrobenzooxaphosphole core **1** is developed, which has been used to produce multikilogram quantities of this ligand series for asymmetric transformations on large scale. These unique chiral phosphine ligand families have been successfully applied to the asymmetric syntheses of drug candidates[3,5,7] on scale.

EXPERIMENTAL SECTION

General Method. All reactions were carried out under an atmosphere of argon or nitrogen in dry glassware with magnetic stirring or magnetic stirring. All commercially available reagents and solvents were used without further purification. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker DRX400 MHz spectrometer with solvent resonance as the internal standard (^{1}H

NMR: DMSO-d_6 at 2.50 ppm, $CDCl_3$ at 7.26 ppm, CD_3OD at 3.31 ppm; ^{13}C NMR: DMSO-d_6 at 39.52 ppm, $CDCl_3$ at 77.16 ppm, CD_3OD at 49.00). ^1H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant and integration. ^{31}P NMR spectra were referenced to 85% H_3PO_4 in D_2O at 0.0 ppm as external standard and obtained with ^1H decoupling. High resolution mass spectra were obtained on Agilent 85 LC-TOF mass analyzer with electrospray ionization. Chiral analyses were performed on an Agilent HP 1100 Series HPLC system.

tert-Butyl(2,6-dimethoxyphenyl)phosphine oxide (14). To a solution of 1,3-dimethoxybenzene (**13**) (25.00 g, 180.94 mmol) in anhydrous THF (25 mL) was charged 2.5 M *n*-BuLi in hexane (52.67 g, 190.00 mol, 1.05 eq) over 0.5 h between −20 to −10 ^oC. The resulting mixture was warmed to 10 ^oC and stirred for 1 h. The mixture was transferred into a solution of *t*-$BuPCl_2$ (30.21 g, 190.00 mmol, 1.05 eq) in anhydrous THF (30.21 g) cooled at −20 ^oC while the internal temperature was controlled below 5 ^oC. The mixture was stirred at 0 ^oC for about 1 h. Water (50 mL) was added below 20 ^oC. The volatiles (~50 mL) were distilled under reduced pressure. Hexane (50 mL) was added and the mixture was stirred for ~20 min. The aqueous phase was separated and the organic phase was extracted with water (25 mL). The combined aqueous extracts (~104 g, containing 41.64 g of product, 171.90 mmol, 95% yield) were used in the next step without further purification. Analytical data for **14**: ^1H (400 MHz, $CDCl_3$) δ = 7.52 [d, 1H, *J* (P, H) = 487.7 Hz], 7.42-7.37 (m, 1H), 6.58-6.53 (m, 2H), 3.84-3.81 (m, 6H), 1.17 [d, 1H, *J* (P, H) = 17.4 Hz, 9H]. ^{13}C NMR (125 MHz, $CDCl_3$) δ =163.1, 134.6, 104.1, 104.1, 55.8, 33.1 [d, *J* (P, C) = 89.95 Hz], 24.5, 24.5. ^{31}P (162 MHz, $CDCl_3$) δ = 32.77.

tert-Butyl(2,6-dimethoxyphenyl)(hydroxymethyl)phosphine oxide (15). To the crude product **14** (41.64 g, 171.90 mmol) in water from previous step was added 6 M NaOH (42.97 mL, 257.82 mmol, 1.50 eq). The solution was heated to ~65 ^oC and 37% formaline solution (69.76 g, 859.50 mmol, 5.00 eq) was added slowly to maintain the internal temperature between 65−75 ^oC. The mixture was stirred for 0.5 h at this temperature and cooled to room temperature. Concentrated hydrochloric acid (22.20 mL, 266.43 mmol, 1.55 eq) was added below 30 ^oC to adjust pH to 3−4. The mixture was extracted with CH_2Cl_2 (3 x 70 mL) and the combined extracts were

concentrated to remove ~170 mL of solvents. The residual mixture was diluted with MeOH (120 mL) and treated with 6 M HCl in 2-propanol (0.57 mL, 0.02 eq) for ~1 h at 55−60 °C. Solvents (120 mL) were removed under reduced pressure. 2-Butanone (120 mL) was charged and solvents (120 mL) was removed under reduced pressure. This process was repeated twice. The mixture was cooled to rt. Isopropyl acetate (80 mL) was charged over 0.5 h and the mixture was stirred for at least 0.5 h. The solid was filtered, rinsed with a mixed solution of 2-butanone (40 mL) and isopropyl acetate (80 mL), and dried to give white solid (32.33 g, 69%). Crystallization of the concentrated filtrate from 2-butanone and isopropyl acetate (1/2, v/v) gave the 2nd crop as white solid (9.48 g, 20%) with high purity similar to the first crop. Analytical data for **15**: M.P. 116-118 °C. ^{1}H (400 MHz, $CDCl_3$) δ = 7.45 (t, *J* = 8.4 Hz, 1H), 6.58 (dd, *J* = 4.0, 8.4 Hz, 2H), 5.36 (bs, 1H), 4.45 (d, *J* =14.2 Hz, 1H), 4.26 (dd, *J* = 3.0, 14.2 Hz, 1H), 3.83 (s, 6H), 1.21 [d, *J* (P, H) = 16.0 Hz, 9H] . ^{13}C NMR (125 MHz, $CDCl_3$) δ = 163.1, 135.3, 104.6, 104.5, 58.5 [d, *J* (P, C) = 82.4 Hz], 55.9, 3438 [d, *J* (P, C) = 81.8 Hz], 24.3 [d, *J* (P,C) = 1.25 Hz]. ^{31}P (162 MHz, $CDCl_3$) δ = 58.84. HRMS (ESI^+) calcd for $C_{13}H_{21}O_4P$+H, 273.1256; found, 273.1266.

tert-Butyl(2,6-dihydroxyphenyl)(hydroxymethyl)phosphine oxide (16). The mixture of **15** (14.60 g, 53.62 mmol) and 57% HI (96.26 g, 428.96 mmol, 8.00 eq) was stirred at ~92 °C for 5 h, at ~95 °C for 5 h, and 97−100 °C for 14 h for complete demethylation. The resulting solution was cooled to 0−5 °C and stirred for 1 h. Dichloromethane (50 mL) was added and 50% NaOH (25.31 g, 316.38 mmol, 5.90 eq) was added slowly to maintain the temperature below 15 °C. The slurry was aged at 15−20 °C for 2 h, filtered, rinsed with water (~100 mL) to pH ~7. The solid was dried in a vacuum oven at 40 °C until water content was < 0.1% to give white solid (12.30 g, 94%). Analytical data for **16**: M.P. 176-178 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.16 (t, *J* = 8.1 Hz, 1H), 6.25 (dd, *J* = 8.1, 3.6 Hz, 2H), 4.31 (s, 2H), 1.14 (d, *J* = 1.47 Hz, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 134.5, 107.0 (br), 96.4 (d, *J* (P, C) = 81.6 Hz), 58.0 (d, *J* (P, C) = 73.7 Hz), 34.3 (d, *J* (P, C) = 63.2 Hz), 24.5; ^{31}P NMR (162 MHz, DMSO-d_6) δ 64.3; HRMS (ESI^+) calcd for $C_{11}H_{17}O_4P$ +H, 245.0943; found, 245.0934.

3-(tert-Butyl)-4-hydroxy-2H-benzo[d][1,3]oxaphosphole 3-oxide (11).[2b] To the suspension of triol **16** (100.00 g, 0.41 mol) in THF (200 mL) was added Et_3N (124.30 g, 1.23 mol, 3.00 eq) and the resulting solution was cooled to −5 °C. Methanesulfonyl chloride (107.88 g, 0.94 mol, 2.30

eq) was added slowly to control the internal temperature below 20 °C. After addition, the mixture was warmed up and stirred at 25 °C for 0.5 h. A solution of NaOH (98.27 g, 2.46 mol, 6.00 eq) in water (500 mL) was charged. The mixture was heated to 60 °C, stirred for 1 h, then cooled to 25 °C and neutralized with a solution of concentrated HCl (201.71 g, 2.05 mol, 5.00 eq) in water (170 mL) to pH <2. The mixture was distilled at ~50 °C under reduced pressure to remove volatiles (180 mL). MeOH (200 mL) was added and the mixture was distilled at ~50 °C under reduced pressure to remove solvents (220 mL). The suspension was cooled to 10 °C, rinsed with water (200 mL) and heptane (100 mL). The wet cake was dried in a vacuum oven at ~40 °C to constant weight to give white solid (88.40 g, 95%). Analytical data are identical to those in the literature.[2b]

(*R*)-3-(tert-Butyl)-3-oxido-2H-benzo[d][1,3]oxaphosphol-4-yl ((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl) carbonate (12).[2b] To the suspension of **11** (40.00 g, 176.83 mmol) in CH_3CN (120 mL) was added *i*-Pr_2NEt (29.71 g, 229.88 mmol, 1,30 eq), followed by (+)-menthyl chloroformate (41.00 g, 187.44 mmol, 1.06 eq). The mixture was heated to 60 °C in ~0.5 h and held for ~1 h. The slurry was cooled to ~5 °C in 1 h and held for 2 h. The solid was filtered, rinsed with chilled MeCN (80 mL), and dried at ~40 °C under vacuum to give white solid (34.92 g, 48%). Chiral HPLC conditions for separation of the four diastereomers: Chiralcel IA-3, 4.6 x 150 mm, 3 μm, *n*-heptane/isopropanol = 90/10, isocratic, 40 °C, 1.2 mL/min; The ratio of the four diastereomers was determined as follows: 3.2 min (**19**, 0.5%), 4.2 min (*ent*-**12**, 0.1%), 4.6 min (*ent*-**19**, 0.2%), 5.8 min (**12**, 99.2%). Analytical data of **12** are identical to those in the literature.[2b]

(*R*)-3-(tert-Butyl)-3-oxido-2H-benzo[d][1,3]oxaphosphol-4-yl ((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl) carbonate (12) via epimerization of (19). The filtrate from previous experiment was concentrated under reduced pressure. The residue was dissolved in EtOAc (200 mL) and extracted with 0.5 N HCl (100 mL). The organic layer was extracted with water (2 x 50 mL), dried over $MgSO_4$, filtered and concentrated to give brownish oil (~40 g, ~97.93 mmol). The ratio of the four diastereomers was determined by chiral HPLC (same conditions as above): 3.2 min (**19**, 97.8%), 4.2 min (*ent*-**12**, 0.9%), 4.6 min (*ent*-**19**, 0.2%), 5.8 min (**12**, 1.1%). The oil was dissolved in CH_2Cl_2 (200 mL) and cooled to ~0 °C. Oxalyl chloride (18.64 g, 146.89 mmol, 1.50 eq) was added in ~15 min. The mixture was stirred at rt for 20 h. Solvents were removed

under vacuum. MeCN (50 mL) and water (5 mL) were added. The mixture was stirred at 60 ^{o}C for 2 h, and the resulting suspension was cooled to ~3 ^{o}C in an ice-water bath for 1 h. The solid was filtered, rinsed with chilled MeCN (10 mL) and dried to give **12** as white solid (11.86 g, 17% based on **11**) with 99.2% chiral purity. Another round of epimerization of **19** from the filtrate provided additional amount of **12** (8.25 g, 11%) with chiral purity of 99.5%.

(*R*)-3-(tert-Butyl)-4-hydroxy-2H-benzo[d][1,3]oxaphosphole 3-oxide (1).[2b] To the suspension of **12** (60.36 g, 144.49 mmol) in MeOH (240 mL) was added a solution of NaOH (11.56 g, 288.97, 2.00 eq) in water (60 mL). The mixture was heated to 65 ^{o}C and stirred for 2 h. The mixture was cooled to 30 ^{o}C and acidified with a solution of 37% HCl (29.9 g, 303.42, 2.10 eq) in water (25 mL) to pH <2. The mixture was distilled at normal pressure to remove volatiles (190 mL). Heptane (300 mL) was added and solvents (150 mL) were distilled at normal pressure. The suspension was cooled to ~3 ^{o}C and filtered. The solid was rinsed with water (120 mL), heptane (120 mL), and dried to give **1** as white solid (32.15 g, 98%) with >99.5% ee (the enantiomer **20** was not detected). Chiral HPLC conditions for separation of enantiomers of **5**: Chiralcel IA-3, 4.6 x 150 mm, 3 μm, n-heptane/isopropanol = 90/10, isocratic, 40 ^{o}C, 1.2 mL/min; 4.2 min (**1**), 5.8 min (**20**). Analytical data of **1** are identical to those in the literature.[2b]

Supporting Information

Copies of ^{1}H, ^{13}C NMR and/or ^{31}P spectra of the compounds are available free of charge via the Internet at http://pubs.acs.org.

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