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Syntheses of Symmetric and Unsymmetric 2,6-Bis(phosphino)phenols

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ABSTRACT: *Compounds bearing the structural motif of 2,6-bis(phosphino)phenol have been synthesized via two general methods. Double lithium-halogen exchange occurred in low-temperature reactions of O-protected (by methyl- or tetrahydropyranyl groups) 2,6-dibromo-4-methylphenol derivatives with BuLi (2 equivalents); quenching the reaction mixtures with chlorophosphines $ClPR_2$ ($R = Ph, {}^iPr$) and corresponding O-deprotection yielded symmetrically substituted 2,6-bis(phosphino)phenols. Sequential incorporation of $-PR_2$ functionalities was accomplished via single lithium-halogen exchange (1 eq. of BuLi) of tetrahydropyranyl-protected 2,6-dibromo-4-methylphenol followed by $ClPR_2$ quenches, thus enabling the syntheses of unsymmetric 2,6-bis(phosphino)phenols. Such compounds were also obtained via sequential ortholithiations of tetrahydropyranyl-protected 4-tert-butylphenol, followed by $ClPR_2$ quenches. All of the new compounds have been characterized by spectrometric methods (^1H and ^{31}P NMR, and mass spectrometry). In addition, two of the compounds, 1-(diphenylphosphino)-3-(diphenylphosphoryl)-2-methoxy-5-methylbenzene (**3a-ox**) and 1,3-bis(diphenylphosphino)-2-methoxy-5-methylbenzene (**6a**) have also been characterized via single crystal X-ray diffraction experiments.* © 2006 Wiley Periodicals, Inc. Heteroatom Chem 17:656–663, 2006; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20251

INTRODUCTION

Various derivatives of *ortho*-phosphinophenol (**1**, Fig. 1) have found extensive use recently as mononucleating, monoanionic, bidentate [P,O] chelating ligands in transition metal chemistry [1–8]. Quite surprisingly, phenols featuring $-PR_2$ groups at both ortho positions (e.g., 2,6-bis(phosphino)phenol **2**, Fig. 1) have not yet been reported. Two [P,O] chelating sites possessed by such compounds may provide interesting platforms for bimetallic, O-bridged metal complexes, especially since a structurally similar ligand, 2,6-bis(diphenylphosphino)-*N*-methylaniline has been used to support the formation of an N-bridged dinuclear molybdenum complexes [9]. Herein we report the syntheses of 2,6-bis(phosphino)phenol derivatives, featuring symmetric (**3a, b, 4a**) or unsymmetric (**3c, 4b**) phosphine substitution patterns.

RESULTS AND DISCUSSION

A number of synthetic methods are known for the syntheses of *ortho*-phosphinophenols. Such methods typically involve metallations of *o*-bromophenols or O-protected phenols, followed by the reactions with dialkyl/diaryl chlorophosphines [10–13].

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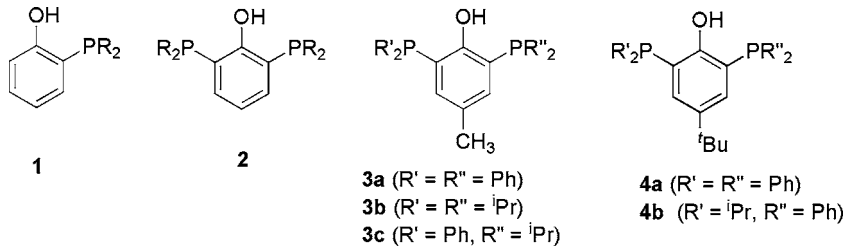
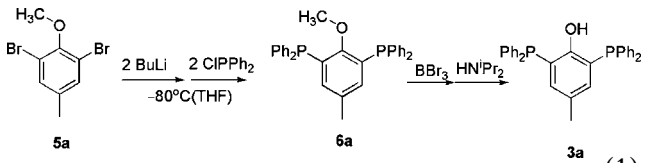


FIGURE 1 Generic structural drawings of *o*-phosphinophenol (**1**) and 2,6-bis(phosphino)phenol (**2**); Structural formulas of our synthesized compounds (**3a-c** and **4a-b**) bearing the structural motif of 2,6-bis(phosphino)phenol.

Following a similar strategy, we have established conditions for (1) one-step dilithiations of O-protected 2,6-dibromophenols via BuLi/Br exchange, leading to the syntheses of symmetric 2,6-bis(phosphino)phenol derivatives **3a,b**; (2) sequential single ortho-lithiations of suitable phenol precursors, leading to the syntheses of symmetric 2,6-bis(phosphino)phenol **4a** and unsymmetric phenols **3c** and **4b**.

Methyl-protected dibromophenol **5a** (obtained via reactions of 2,6-dibromo-4-methylphenol with dimethylsulfate) readily undergoes double lithium-halogen exchange upon exposure to 2 equivalents of butyl lithium at low temperature (−80°C); generation of a similar organodilithium intermediate has been reported earlier [14]. Quenching of the reaction mixture with $ClPPh_2$ produces 1,3-bis(diphenylphosphino)-2-methoxy-5-methylbenzene **6a** in 73% yield (Eq. (1)).



(1)

Compound **6a** is an air-stable, crystalline substance, and we have been able to obtain X-ray quality crystals and characterize it via single-crystal X-ray diffraction methods (Fig. 2). Most of the structural parameters of **6a** are similar to those determined for related compounds featuring (*ortho*-methoxyphenyl)diphenylphosphine fragments [15,16]. Some notable differences observed for **6a** are the longer C1–O1 distance (by ∼0.02 Å) and the smaller C1–O1–C11 angle (by ∼5°), with both probably resulting from steric pressure from the two $-PPh_2$ groups.

Treatment of **6a** with BBr_3 followed by amine results in demethylation, yielding 2,6-bis(diphenylphosphino)-4-methylphenol **3a** in excellent yield (95%); similar procedures have been used

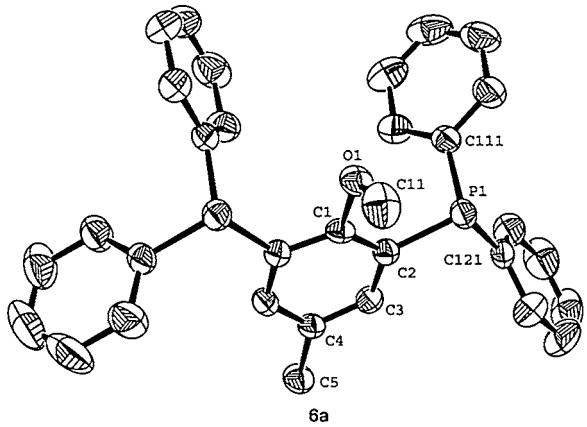


FIGURE 2 Thermal ellipsoid plot of **6a**. Selected data: C1-O1 1.394(4) Å; C2-P1 1.838(2) Å; O1-C11 1.440(4) Å; C1-C2-P1 116.79(17)°; C3-C2-P1 125.79(16)°; C2-C1-O1 118.60(14)°; C1-O1-C11 112.2(3)°.

for the syntheses of *o*-phosphinophenols [17]. Our attempts to obtain X-ray quality crystals of **3a** were only partially successful. The presence of adventitious oxygen in the system resulted in partial oxidation at one of the phosphorus centers of **3a**. The crystals deposited from THF/hexane (1:25) solution were composed of **3a** (37(1)%) and the mono oxidation product, **3a-ox** (63(1)%), according to the analysis of the X-ray diffraction data. Such data are supported by ^{31}P NMR ($CDCl_3$; **3a-ox**: δ 38.8, −14.6; **3a**: δ −21.0; the approximate ratios of peak intensities ∼1:1:1) and GC/MS (**3a**: $m/z = 476$ (M^+); **3a-ox**: $m/z = 492$ (M^+)) analyses of the crystals.

The structural features displayed by **3a-ox** (Fig. 3) are somewhat different from the ones reported for related *o*-(diphenylphosphoryl)phenols; the main difference being the nature of P=O···H—O hydrogen bond. While predominately intermolecular hydrogen bonding has been determined for (2-hydroxyphenyl)diphenylphosphine oxide [18] and (2-hydroxy-5-methylphenyl)diphenylphosphine oxide [19], an exclusively intramolecular P=O···H—O interaction is present in **3a-ox**. Other structural parameters are not exceptional.

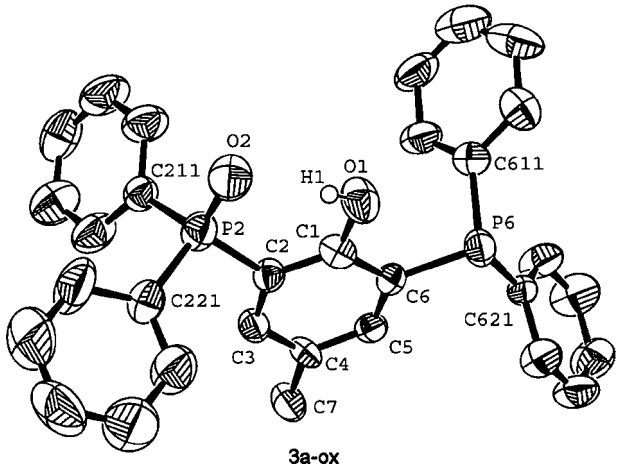
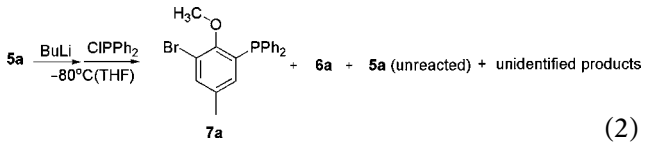


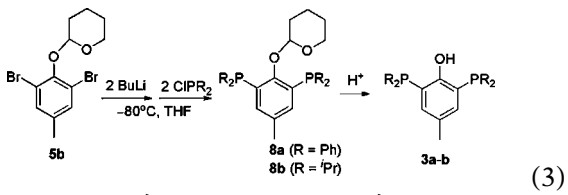
FIGURE 3 Thermal ellipsoid plot of **3a-ox**. Selected data: P2-O2 1.420(8) Å; P2-C2 1.818(7) Å; P6-C6 1.816(7) Å; O1-C1 1.358(8) Å; O2-P2-C2 109.8(4)°; O1-C1-C2 123.6(7)°; O1-C1-C6 114.9(8)°; C1-C2-P2 118.1(6)°; C1-C6-P6 118.0(6)°.

Reactions of **5a** with 1 equivalent of BuLi followed by a $ClPPh_2$ quench were expected to produce (3-bromo-2-methoxy-5-methylphenyl)-diphenylphosphine **7a** (Eq. (2)). However, selective mono BuLi/Br exchange followed by a clean formation of **7a** could not be achieved, and only moderate yields (~40–50%) of the desired product were observed by GC/MS ($M^+ = 384$) and ^{31}P NMR (δ –13.9) analyses of the reaction mixtures. We were not able to separate **7a** from the other components of the reaction mixtures via crystallization or extractions by various solvents. Changing the reaction media to Et_2O or hexane did not result in significant improvements. Yet, **7a** or its analogues may serve as starting materials for the entire family of unsymmetric 2,6-bis(phosphino)phenols, or other related compounds. Thus we examined different approaches to such compounds.



(2)

The dual usage of tetrahydropyranyl (THP) group as an O-protector and an ortho-lithiation facilitator has been well documented in the chemistry of phenols [20] and in the syntheses of *o*-phosphinophenols [2,6]. More importantly, the O-protecting THP group can be easily removed under mild acidic conditions [21], whereas the demethylation of **6a** with BBr_3 takes several days, and sometimes results in the formation of unwanted phosphine-BBr_3 adducts [22]. Thus, we found that 1-[(2-tetrahydropyranyl)oxy]-2,6-dibromo-4-methylphenol (**5b**) readily undergoes a double lithium-halogen exchange upon reaction with 2 equivalents of *n*-BuLi or *sec*-BuLi. Quenching of the reaction mixtures with $ClPR_2$ (R = Ph or ^{i}Pr) yields the THP-protected symmetric 2,6-bis(phosphino)phenols **8a,b** as moderately air-sensitive solids (Eq. (3)). The deprotection of the phenol group proceeds smoothly for **8a**, with only catalytic quantities of H^+ (TsOH as H^+ donor) required. Higher than stoichiometric quantities of stronger H^+ donors (anhydrous HCl) were required for the deprotection of **8b**, resulting in the formation of a phosphonium salt, as judged by the new ^{31}P NMR signal at δ 29.1; the formation of phosphonium salts under such conditions has been reported earlier [23,24]. Treatment of this phosphonium salt with NEt_3 led to the isolation of 2,6-bis(diisopropylphosphino)-4-methylphenol **3b** as an extremely air-sensitive colorless oil.



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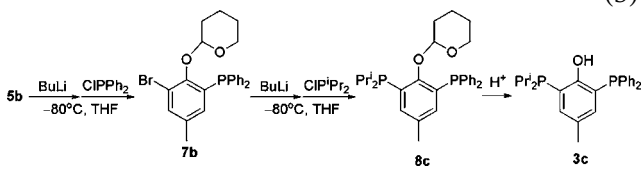
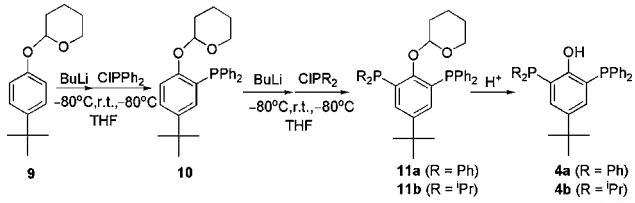


(4)

Reactions of **5b** with 1 equivalent of BuLi proceed differently from those of **5a**. We observed relatively clean lithium-halogen exchange involving only one of the bromines (Eq. (4)), and quenching of the reaction mixture with $ClPPh_2$ followed by a workup yields the (3-bromo-5-methyl-2-(tetrahydro-2*H*-pyran-2-yloxy)phenyl)diphenylphosphine **7b** in 51% isolated yield. The presence of bromine in **7b** makes it an attractive starting material for further syntheses. We briefly investigated this by synthesizing unsymmetric 2,6-bis(phosphino)phenol derivatives **8c** and **3c** via repeating the BuLi/$ClPR_2$ steps on **7b** (Eq. (4)). Deprotection of the phenol group (**8c** → **3c**) also requires higher than stoichiometric quantities of HCl, but only the $-P^iPr_2$ group is believed to form phosphonium salt under such conditions, as judged by the presence of two peaks in the ^{31}P NMR (δ 37.4, −21.8) spectrum of the reaction mixture.

Since phenols protected by the THP group readily undergo ortho-lithiations via deprotonation

by organolithium bases [2,6,20,25], compounds containing the structural motif of 2,6-bis(phosphino)phenol can also be constructed via a different synthetic approach, avoiding 2,6-dibromophenol derivatives as starting materials. We have successfully implemented this feature for the syntheses of symmetric and unsymmetric 2,6-bis(phosphino)phenols **4a,b** (Eq. (5)). Thus, prolonged exposure of the THP-protected *p-tert*-butylphenol (**9**) to 1 equivalent of *sec*-BuLi followed by a $ClPPh_2$ quench yields the THP-protected *ortho*-phosphinophenol **10** in >70% yield. Repeating the BuLi/$ClPR_2$ reaction sequence on **10** allows the introduction of the second $-PR_2$ group, forming symmetric (**11a**) and unsymmetric (**11b**) 2,6-bis(phosphino)phenol cores.



(5)

The deprotection of **11a,b** proceeds similarly to those described for **8a–c**. Thus, only catalytic quantities of H^+ are required for the synthesis of powdery **4a**. Higher than stoichiometric quantities of HCl were used for the deprotection of **11b**; the phosphonium salt formed (^{31}P NMR δ 38.4, −20.7) under such conditions is probably analogous to the one observed in the synthesis of **3c**.

The yields of the products containing 2,6-bis(phosphino)phenol fragments obtained via the latter synthetic method are comparable to those obtained starting from the 2,6-dibromophenol derivative. The synthetic utility of the latter method can be significantly expanded, as a large number of phenols are readily available commercially, and an entire family of 2,6-bis(phosphino)phenols or other related compounds can be envisioned.

EXPERIMENTAL

Manipulations requiring inert atmospheres were carried out by using Schlenk techniques or in a dry box under nitrogen atmosphere. Low-temperature reactions were performed in Schlenk flasks immersed in hexane/N_2 (liq.) or ethanol/N_2 (liq.) slush, contained in a Dewar flask. Solvents were purified before use by distillation from Na-benzophenone ketyl (ether, THF, hexane, benzene) or CaH_2 (toluene, acetonitrile) under nitrogen atmosphere. Methanol was distilled from magnesium methoxide under N_2; deoxygenated (by bubbling N_2 for at least 1 h) methanol was used where dry solvent was not required. Commercially available chlorophosphines $ClPR_2$ were purified prior to use: $ClPPh_2$ was vacuum distilled, and ClP^iPr_2 was frozen and degassed while thawing under vacuum (repeated three times). Diisopropylamine and triethylamine were distilled from CaH_2 under nitrogen atmosphere. Other reagents were obtained from commercial suppliers and were used as received. ^1H and ^{31}P NMR measurements were obtained on Varian INOVA spectrometer operating at 400 and 161.85 MHz, respectively. Spectra are referenced to tetramethylsilane (^1H) and 85% H_3PO_4 (^{31}P) (external reference). Low-resolution mass spectrometric measurements were performed on a Shimadzu QP5050A instrument; high-resolution measurements were performed at Mass Spectrometric Facility of Michigan State University (East Lansing, MI).

SYNTHESES

O-Protected Phenols

2,6-Dibromo-4-methylanisole (**5a**). The compound was synthesized according to the previously published synthetic procedure [26] (with minor modifications); identical spectroscopic characterizations were observed.

1-[2-Tetrahydropyranyl)oxy]-2,6-dibromo-4-methylbenzene (**5b**) and 1-[2-Tetrahydropyranyl) oxy]-4-tert-butylbenzene (**9**) were synthesized via the same general procedure; thus only one (for **5b**) is described in detail.

1-[2-Tetrahydropyranyl)oxy]-2,6-dibromo-4-methylbenzene (**5b**). 2,6-Dibromo-4-methylphenol (26.6 g, 0.1 mol) and 3,4-dihydro-2*H*-pyran (11.3 g, 0.13 mol) were mixed in a 100-mL flask, kept at −20°C. The cooling was removed, 0.15 mL of 37% HCl (aq.) was added, and the reaction mixture was stirred for 1 h at 0°C. After stirring overnight resulting in solution attaining room temperature, the reaction mixture was extracted with ether (250 mL), the organic layer was washed with 150 mL of 5% NaOH (aq.) and dried over K_2CO_3. All volatiles were removed on a rotary evaporator, and the remaining oily residue was crystallized from pentane (50 mL) at −20°C, yielding **5b** (20.6 g, 59%) as colorless crystals. Melting point: 38–40°C; ^1H NMR ($CDCl_3$): δ 1.64 (m, 3H, THP), 1.85 (m, 2H, THP), 2.10 (m, 1H, THP), 2.44 (s, 3H, CH_3), 3.60 (m, 1H, THP), 4.20 (m, 1H, THP), 5.38 (m, 1H, THP), 7.30 (s, 2H, arom).

*1-[2-Tetrahydropyranyl)oxy]-4-tert-butylbenzene (**9**).* Same procedure as described for **5b** was used. Protected phenol **9** was isolated as a colorless liquid after distillation of the crude reaction mixture under reduced pressure (yield: 22.0 g, 94%). Boiling point: 82–84°C (0.05 mmHg). ^{1}H NMR ($CDCl_3$): δ 1.05 (s, 9H, ^{t}Bu), 1.54 (m, 3H, THP), 1.75 (m, 2H, THP), 1.95 (m, 1H, THP), 3.60 (m, 1H, THP), 3.79 (m, 1H, THP), 5.25 (m, 1H, THP), 6.85 (d, 2H, arom, $^3J_{HH} = 8$ Hz), 7.15 (d, 2H, arom, $^3J_{HH} = 8$ Hz). (A similar synthesis of this compound has been reported in [27].)

Syntheses of Symmetric 2,6-Bis(phosphino)-phenols

*Syntheses of O-Protected 2,6-Bis(phosphino)-phenols. 1,3-Bis(diphenylphosphino)-2-methoxy-5-methylbenzene (**6a**).* To a stirred THF (80 mL) solution of 2,6-dibromo-4-methylmethoxybenzene (2.80 g, 10 mmol) at −80°C was added 12.5 mL (20 mmol) of *n*-butyl lithium solution (1.6 M in hexane). The reaction mixture was stirred for 2 h at −80°C, then a solution of 3.68 mL (20 mmol) of $ClPPh_2$ in THF (20 mL) was added. The reaction mixture was left to stir overnight and slowly warmed up to room temperature. The resulting yellow solution was filtered, and the volume of the solution was reduced under vacuo resulting in the precipitation of **6a** as a white powder, which was isolated by filtration; more product was obtained upon adding hexane to the filtrate. Combined yield: 3.58 g (73%). ^{1}H NMR ($CDCl_3$): δ 2.00 (s, 3H, C$\underline{H}_3$), 3.84 (s, 3H, OC$\underline{H}_3$), 6.53 (s, 2H, arom), 7.29 (m, 20H, arom). ^{31}P NMR ($CDCl_3$): δ −16.0 (s). HRMS (FAB): 491.1697 (MH^+) (Calcd for $C_{32}H_{29}OP_2$: 491.1694).

Compounds **8a,b** were obtained by the same general procedure, thus only one detailed description (for **8a**) is provided: To a stirred solution of **5b** (2.0 g, 5.7 mmol) in THF (80 mL) at −80°C was added a solution of 1.6 M *n*-butyl lithium in hexane (7.81 mL, 12.5 mmol). The reaction mixture was stirred at −80°C for 1 h. A solution of corresponding $ClPR_2$ (2 equivalents) in THF (5 mL) was added dropwise over 15 min. The reaction mixture was stirred at −80°C for 15 min and then allowed to warm up to room temperature overnight. After removal of the volatiles, benzene (50 mL) was added and the inorganic salt was removed by filtration.

*2-(2,6-Bis(diphenylphosphino)-4-methylphenoxy)-tetrahydro-2H-pyran (**8a**).* Benzene was removed, and the crude product was dissolved in THF (10 mL). After addition of hexane (50 mL), the white powdery **8a** was filtered off and dried in vacuo. Yield: 2.26 g (71%). Melting point: 126–128°C. ^{1}H NMR (C_6D_6): δ 1.18 (m, 3H, THP), 1.68 (s, 3H, CH_3), 1.70 (m, 2H, THP), 2.10 (m, 1H, THP), 3.47 (m, 1H, THP), 4.20 (m, 1H, THP), 5.85 (m, 1H, THP), 6.90–7.44 (m, 22H, arom). ^{31}P NMR (C_6D_6): δ −13.9 (s). HRMS (FAB): 561.2110 (MH^+) (Calcd for $C_{36}H_{35}O_2P_2$: 561.2112).

*2-(2,6-Bis(diisopropylphosphino)-4-methylphenoxy)-tetrahydro-2H-pyran (**8b**).* Evaporation of the benzene yielded **8b** as oil. Yield: 2.0 g (82%). ^{1}H NMR (C_6D_6): δ 0.82 (m, 12H, CH(C$\underline{H}_3$)$_2$), 0.98 (m, 12H, CH(C$\underline{H}_3$)$_2$), 1.18 (m, 3H, THP), 1.70 (m, 2H, THP), 1.67 (s, 3H, C$\underline{H}_3$), 1.97 (m, 4H, C$\underline{H}$(CH$_3$)$_2$), 2.19 (m, 1H, THP), 3.27(m, 1H, THP), 4.25 (m, 1H, THP), 5.80 (m, 1H, THP), 6.90–7.40 (m, 2H, arom). ^{31}P NMR (C_6D_6): δ −4.7 (s). HRMS (FAB): 425.2737 (MH^+) (Calcd for $C_{24}H_{43}O_2P_2$: 425.2738).

*2-(4-Tert-butyl-2,6-bis(diphenylphosphino)phenoxy)-tetrahydro-2H-pyran (**11a**).* To a stirred solution of **10** (1.40 g 3.3 mmol) in THF (60 mL) at −80°C was added a solution of 1.6 M *n*-butyl lithium in hexane (2.28 mL, 3.6 mmol). The resulting yellow solution was stirred for 10 min at −80°C before the cooling bath was removed, and the reaction mixture was stirred while warmed up to room temperature for 1 h. The reaction mixture was then recooled to −80°C, and a solution of diphenylchlorophosphine (0.74 mL, 3.4 mmol) in THF (5 mL) added dropwise over 20 min. The reaction mixture was stirred at −80°C for 15 min and then allowed to warm up to room temperature overnight. After reducing the reaction volume by about a half, the solution was filtered, and the remaining volatiles removed. The residue was crystallized from THF/hexane (1:10). Yield: 1.38 g (68%). Melting point: 123–125°C. ^{1}H NMR (C_6D_6): δ 0.90 (s, 9H, ^{t}Bu), 1.10 (m, 1H, THP), 1.30–1.75 (m, 5H, THP), 3.15 (m, 1H, THP), 3.90 (m, 1H, THP), 5.25 (s, 1H, THP), 6.75 (s, 2H, arom), 7.21–7.32 (m, 20H, arom). ^{31}P NMR (C_6D_6): δ –12.9 (s). HRMS (FAB): 603.2577 (MH^+) (Calcd for $C_{39}H_{41}O_2P_2$: 603.2582).

*O-Deprotection. 2,6-Bis(diphenylphosphino)-4-methylphenol (**3a**).* The compound was obtained via two separate routes, thus both preparations are described.

To a stirred solution of **6a** (2.33 g, 4.74 mmol) in CH_2Cl_2 (50 mL) at −80°C, BBr_3 was added (1.8 mL, 18.96 mmol). The resulting mixture was stirred for 12 h, all volatiles were removed under reduced pressure, and methanol (50 mL) was added to the residue. After stirring the suspension for 48 h, all volatiles were removed, and the residue was

suspended in toluene and diisopropylamine (2.65 mL, 18.96 mmol) was added. After stirring for 2 h, the mixture was filtered, and removal of volatiles precipitated **3a** as a white solid. Yield: 2.14 g (95%). Melting point: 132–134°C. ^{1}H NMR (C_6D_6): δ 2.05 (s, 3H, CH_3), 6.75 (s, 2H, arom), 7.24–7.40 (m, 20H, arom). ^{31}P NMR (C_6D_6): δ –19.5 (s). HRMS (FAB): 477.1539 (MH^+) (Calcd for $C_{31}H_{27}OP_2$: 477.1537).

To a stirred solution of **8a** (1.0 g, 1.78 mmol) in THF (20 mL) and methanol (50 mL) was added *p*-TsOH hydrate (0.12 g, 0.65 mmol) at room temperature. The reaction mixture was stirred overnight, solvents were removed under reduced pressure, and THF (3 mL) was added. A white solid was obtained after the solution was allowed to stand overnight at room temperature; this was recrystallized from THF/hexane (1:25) to give **3a** as white powder. Yield: 0.52 g (61%).

*2,6-Bis(diisopropylphosphino)-4-methylphenol (**3b**).* The solution of **8b** (1.0 g, 2.35 mmol) in deoxygenated methanol (30 mL) was treated with O_2-free anhydrous 2 N HCl solution in ether (4 mL, 8.0 mmol) at room temperature. The reaction mixture was stirred overnight, volatiles removed in vacuo, and the resulting oil dissolved in CH_2Cl_2 (10 mL). Addition of Et_2O (30 mL) precipitated a phosphonium salt (^{31}P NMR δ 29.1) as a white solid (isolated by filtration). Stirring of a suspension of this solid in benzene (20 mL) and NEt_3 (2.2 mL, 18.00 mmol) overnight yielded **3b** as a colorless oil after filtration and evaporation of all volatiles. Yield: 0.45 g (56%). ^{1}H NMR (C_6D_6): δ 0.95 (m, 12H, –CH($C\underline{H}_3$)$_2$), 1.05 (m, 12H, –CH($C\underline{H}_3$)$_2$), 1.75 (s, 3H, $C\underline{H}_3$), 1.95 m (m, 4H, $C\underline{H}(CH_3)_2$), 7.09–7.21 (m, 2H, arom). ^{31}P NMR (C_6D_6): δ –4.7 (s (br)). HRMS (FAB): 341.2162 (MH^+) (Calcd for $C_{19}H_{35}OP_2$: 341.2163).

*2,6-Bis(diphenylphosphino)-4-tert-butylphenol (**4a**).* To a stirred solution of **11a** (1.0 g, 1.66 mmol) in THF (20 mL) and methanol (50 mL) was added *p*-TsOH hydrate (0.17 g, 0.88 mmol). The reaction mixture was stirred overnight, volatiles were removed under reduced pressure, and the residue was extracted with benzene (30 mL). Benzene was removed under reduced pressure and following crystallization from a THF/hexane mixture (1:30), white powdery **4a** was obtained. Yield: 0.58 g (67%). Melting point: 102–104°C. ^{1}H NMR ($CDCl_3$): δ 0.91 (s, 9H, ^{t}Bu), 6.88 (s, 2H, arom), 7.19–7.43 (m, 20H, arom). ^{31}P NMR ($CDCl_3$): δ –19.5 (s). HRMS (FAB): 519.2004 (MH^+) (Calcd for $C_{34}H_{33}OP_2$: 519.2007).

Syntheses of Unsymmetric 2,6-Bis(phosphino)-phenols

*Syntheses of Precursors. (3-Bromo-5-methyl-2-(tetrahydro-2H-pyran-2-yloxy)phenyl)diphenylphosphine (**7b**).* To a stirred solution of **5b** (2.0 g, 5.7 mmol) in THF (80 mL) at –80°C was added a solution of 1.6 M *n*-butyl lithium in hexane (3.56 mL, 5.7 mmol). The reaction mixture was allowed to stir at –80°C for 1 h, and a solution of diphenylchlorophosphine (1.0 mL, 5.7 mmol) in THF (5 mL) was added dropwise over 15 min. The reaction mixture was stirred at –80°C for 15 min and then allowed to warm up to room temperature overnight. After removal of all the volatiles under reduced pressure, hexane (30 mL) was added and the insoluble inorganic salts were removed by filtration. Cooling of the filtrate afforded **7b** as a yellow solid. Yield: 1.32 g (51%). Melting point: 73–75°C. ^{1}H NMR (C_6D_6): δ 1.15 (m, 3H, THP), 1.61 (s, 3H, CH_3), 1.70 (m, 2H, THP), 2.10 (m, 1H, THP), 3.47 (m, 1H, THP), 4.28 (m, 1H, THP), 5.7 (m, 1H, THP), 6.67–7.33 (m, 12H, arom). ^{31}P NMR (C_6D_6): δ –13.1 (s). HRMS (FAB): 455.0774 (MH^+) (Calcd for $C_{24}H_{25}BrO_2P$: 455.0776).

*(5-Tert-butyl-2-(tetrahydro-2H-pyran-2-yloxy)-phenyl)diphenylphosphine (**10**).* To a stirred solution of **9** (4.6 g 19.6 mmol) in THF (150 mL) at –80°C was added a solution of 1.3 M *sec*-butyl lithium in hexane (17.0 mL, 22.0 mmol). The resulting yellow solution was stirred for 10 min at –80°C before the cooling bath was removed, and the reaction mixture was stirred while warming up to room temperature for 1 h. The reaction mixture was recooled to –80°C, and a solution of diphenylchlorophosphine (3.50 mL, 20.0 mmol) in THF (10 mL) was added dropwise over 20 min. The reaction mixture was stirred at –80°C for 15 min and then allowed to warm up to room temperature overnight. After removal of the volatiles in vacuo, hexane (50 mL) was added. The extract was filtered; volatiles were removed under vacuo to yield an oil. Yield: 6.1 g (74%). ^{1}H NMR ($CDCl_3$): δ 0.99 (s, 9H, ^{t}Bu), 1.25 (m, 3H, THP), 1.45 (m, 3H, THP), 3.35 (m, 2H, THP), 5.25 (s, 1H, THP), 6.75 (m, 1H, arom), 6.95 (m, 1H arom), 7.15–7.30 (m, 11H, arom). ^{31}P NMR ($CDCl_3$): δ –12.2 (s). HRMS (FAB): 419.2138 (MH^+) (Calcd for $C_{27}H_{32}O_2P$: 419.2140).

*Syntheses of O-Protected Unsymmetric 2,6-Bis(phosphino)phenols. 2-(2-(Diisopropylphosphino)-6-(diphenylphosphino)-4-methylphenoxy)-tetrahydro-2H-pyran (**8c**).* To a stirred solution of **7b** (1.2 g, 2.6 mmol) in THF (40 mL) at –80°C was added

a solution of 1.6 M *n*-butyl lithium in hexane (1.75 mL, 2.8 mmol). The reaction mixture was allowed to stir at −80°C for 1 h, and a solution of diisopropylchlorophoshine (0.42 mL, 2.8 mmol) in THF (5 mL) was added dropwise over 15 min. The reaction mixture was stirred at −80°C for 15 min and then allowed to warm up to room temperature overnight. After removal of the volatiles under reduced pressure, the remaining oily residue was extracted with hexane (30 mL). After filtering of the hexane extract and removal of the volatiles in vacuo, **8c** was obtained as oil. Yield: 0.53 g (41%). ^{1}H NMR (C_6D_6): δ 0.85 (m, 6H, CH(C$\underline{H}_3$)$_2$, 0.98 (m, 6H, CH(C$\underline{H}_3$)$_2$) 1.26 (m, 3H, THP), 1.84 (m, 2H, THP), 1.91 (s, 3H, C$\underline{H}_3$), 1.97 (m, 2H, CH(C$\underline{H}_3$)$_2$), 2.09 (m, 1H, THP), 3.28 (m, 1H, THP), 4.23 (m, 1H, THP), 5.78 (m, 1H, THP), 6.99–7.41 (m, 12H, arom). ^{31}P NMR (C_6D_6): δ ^{31}P NMR (C_6D_6): δ −4.7 (s), −13.3 (s). HRMS (FAB): 493.2426 (MH^+) (Calcd for $C_{30}H_{39}O_2P_2$: 493.2425).

*2-(4-Tert-butyl-2-(diisopropylphosphino)-6-(diphenylphosphino)phenoxy)-tetrahydro-2H-pyran (***11b***).* To a stirred solution of **10** (1.5 g 3.60 mmol) in THF (40 mL) at −80°C was added a solution of 1.3 M *sec*-butyl lithium in hexane (3.0 mL, 3.90 mmol). The resulting yellow solution was stirred for 10 min at −80°C; the cooling bath was removed, and the reaction mixture was stirred while warming up to room temperature for 1 h. The reaction mixture was recooled to −80°C, and the solution of diisopropylchlorophosphine (0.58 mL, 3.60 mmol) in THF (10 mL) was added dropwise over 20 min. The reaction mixture was stirred at −80°C for 15 min and then allowed to warm up to room temperature overnight. After removal of the volatiles under vacuo, hexane (50 mL) was added and the extract was filtered. After removal of all the volatiles under vacuo, **11b** was obtained as oil. Yield: 1.0 g (52%). ^{1}H NMR ($CDCl_3$): δ 0.80 (m, 6H, CH(C$\underline{H}_3$)$_2$), 0.91 (m, 6H, CH(C$\underline{H}_3$)$_2$), 1.01 (s, 9H, ^{t}Bu), 1.22 (m, 3H, THP), 1.45 (m, 2H, THP), 1.80 (m, 1H, THP), 1.97 (m, 2H, C$\underline{H}$(CH$_3$)$_2$), 3.40 (m, 1H, THP), 4.20 (m, 1H, THP), 5.50 (s, 1H, THP), 6.65 (m, 1H arom), 6.75 (m, 1H arom), 7.10–7.36 (m, 10H, arom). ^{31}P NMR ($CDCl_3$): δ −4.2 (s), −12.6 (s). HRMS (FAB): 535.2897 (MH^+) (Calcd for $C_{33}H_{45}O_2P_2$: 535.2895).

*O-Deprotection. 2-(Diisopropylphosphino)-6-(diphenylphosphino)-4-methylphenol (***3c***).* A solution of **8c** (1.60 g, 3.25 mmol) in deoxygenated methanol (30 mL) was treated with O_2-free anhydrous 2 N HCl solution in ether (6.5 mL, 13.0 mmol) at room temperature. The reaction mixture was stirred overnight, methanol was removed, and the resulting oil was dissolved in CH_2Cl_2 (10 mL). Addition of Et_2O (30 mL) precipitated a white solid phosphonium salt (^{31}P NMR: δ 37.4, –21.8). Solvents were removed, the phosphonium salt was suspended in benzene (20 mL), and NEt_3 (2.2 mL, 18.0 mmol) was added. The resulting mixture was stirred overnight; filtration and evaporation of all volatiles produced a solid residue. The crude product was crystallized two times from hexane (30 mL). Yield: 0.65 g (49%). ^{1}H NMR ($CDCl_3$): δ 0.95 (m, 6H, CH(C$\underline{H}_3$)$_2$), 1.05 (m, 6H, CH(C$\underline{H}_3$)$_2$), 2.0 (s, 3H, CH$_3$), 2.05 (m, 2H, CH(C$\underline{H}_3$)$_2$), 6.40 (s, 1H, OH) 7.00–7.34 (m, 12H, arom). ^{31}P NMR ($CDCl_3$): δ −16.6 (s), −21.71 (s). HRMS (FAB): 409.1852 (MH^+) (Calcd for $C_{25}H_{31}OP_2$: 409.1850).

*2-(Diisopropylphosphino)-6-(diphenylphosphino)-4-tert-butylphenol (***4b***).* The solution of **11b** (1.0 g, 1.87 mmol) in deoxygenated methanol (15 mL) was treated with O_2-free 4 M HCl solution in dioxane (1.8 mL, 7.4 mmol) at room temperature. The reaction mixture was stirred overnight, methanol was removed, and the resulting oil dissolved in CH_2Cl_2 (10 mL). The addition of Et_2O (30 mL) precipitated a white solid phosphonium salt (^{31}P NMR: δ 38.4, −20.7). Solvents were removed under reduced pressure, and the phosphonium salt was suspended in benzene/NEt_3 (20/1.2 mL) mixture. The resulting mixture was stirred overnight, filtered and all volatiles were removed under reduced pressure, yielding oil. Yield: 0.43 g (51%). ^{1}H NMR (C_6D_6): δ 0.90 (m, 6H, CH(C$\underline{H}_3$)$_2$), 1.05 (m, 6H, CH(C$\underline{H}_3$)$_2$), 1.8 (s, 9H, ^{t}Bu), 2.02 (m, 2H, C$\underline{H}$(CH$_3$)$_2$), 7.10–7.54 (m, 12H, arom). ^{31}P NMR (C_6D_6): δ −13.7 (s), −20.3 (s). HRMS (FAB): 451.2319 (MH^+) (Calcd for $C_{28}H_{37}OP_2$: 451.2320).

STRUCTURAL CHARACTERIZATIONS

X-Ray structure determinations of **6a** *and* **3a-ox**. **6a:** crystal (THF/hexane): colorless prism, 0.40 mm × 0.20 mm × 0.15 mm; orthorhombic *Pbnm* (no. 62), $a = 8.407(2)$ Å, $b = 12.488(3)$ Å, $c = 25.742(6)$ Å, $V = 2702.6(11)$ Å^3, $Z = 4$, $\lambda = 0.71073$ Å, $\rho_{calcd} = 1.205$ g/cm^3, $F(000) = 1032$, θ range 1.58–22.46. Final indices [$I > 2\sigma(I)$] $R_1 = 0.036$, $wR_2 = 0.0863$; R indices (all data) $R_1 = 0.056$, $wR_2 = 0.095$. **3a-ox:** crystal (THF/hexane): white prism, 0.15 mm × 0.10 mm × 0.10 mm; orthorhombic *Pbca* (no. 61), $a =$ 15.702(3) Å, $b = 15.782(4)$ Å, $c = 21.059(8)$ Å, $V = 5219(3)$ Å^3, $Z = 8$, $\lambda = 0.71073$, $\rho_{calcd} = 1.239$ g/cm^3, $F(000) = 2040$, θ range 1.93–22.47. Final indices [$I > 2\sigma(I)$] $R_1 = 0.067$, $wR_2 = 0.102$; R indices (all data) $R_1 = 0.282$, $wR_2 = 0.154$. Suitable crystals

were identified, rolled in epoxy resin and mounted on glass fibers.

Data for **6a** and **3a-ox** were collected at 293 K on an Enraf-Nonius Turbo CAD-4 X-ray diffractometer. Various crystallographic programs were used to refine the structure. The data collection and reduction were accomplished using procedures described previously [28]. The MS-Windows program WinGX was used as an interface for the solution and refinement of the models [29]. The data were first reduced and corrected for absorption using psi-scans [30] and then solved using the program SIR97 [31]. **6a** was arranged on a mirror plane with disorder in the arrangement of the H-atoms in the para-methyl group. Complex **3a-ox** did not contain any disorder, but the occupancy of the O atom (O2, which had an abnormally large thermal parameter when defined at full occupancy) bonded to the P2 atom was freely refined and this converged to a value of 63(1)%. This occupancy is reasonable in light of the intensities in the ^{31}P NMR spectrum of the crystals indicative of a 2:1 mixture of **3a-ox** (around 66%) and pure diphosphine compound **3a** (around 33%). The models were refined with SHELXL97 [32]. All non-H atoms were refined with anisotropic thermal parameters, and H-atoms were constrained to the carbon atoms to which they were attached.

CCDC 283562 for **6a** and CCDC 283563 for **3a-ox** contain the supplementary crystallographic data. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

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