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Preparation of New Buchwald-Type Secondary Phosphine Oxide Ligands and Applications in Suzuki−Miyaura Reactions

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Two air- and moisture-stable secondary phosphine oxides (SPOs), namely, 2-(*tert*-butylhydrophosphoryl)-1-(2-R-phenyl)-1*H*-imidazole (**3a**, R = H; **3b**, R = OMe) were prepared and characterized. A tautomeric equilibrium exists between the secondary phosphine oxide **3a** (or **3b**) and its corresponding phosphinous acid **3a′** (or **3b′**). The reaction of phosphinous acid **3a′** (or **3b′**) with $Pd(COD)Cl_2$ (or $PdBr_2$) yielded the corresponding monopalladium complex bis(2-(*tert*-butylhydrophosphoryl)-1-(2-R-phenyl)-1*H*-imidazole)PdX_2 (**5a**, R = H, X = Cl; **5b**, R = OMe, X = Br) in *cis*-form as well as dipalladium complex $[(\mu_2$-2-(*tert*-butylhydrophosphoryl)-1-(2-R-phenyl)-1*H*-imidazole-N,P)Pd(I)X$]_2$ (**6a**, R = H, X = Cl; **6b**, R = OMe, X = Br). The phosphinous acids **3a′** and **3b′** act as P,N-chelating ligands in the formation of **6a** and **6b**, which feature direct Pd(I)−Pd(I) bonds. Good to excellent reactivities were observed by applying these ligand-chelated palladium complexes in Suzuki−Miyaura coupling reactions.

1. Introduction

The diverse forms of metal-catalyzed cross-coupling reactions have probably been the most widely used methods for the formation of C−X (X = C, N, O, S, etc.) bonds in modern synthetic chemistry for the past few decades.[1] Palladium complexes have been extensively used as catalysts for the coupling reactions in combination with numerous supporting ligands, which acquire the desired reactivity and selectivity. Among all the factors that affect the catalytic performance of a transition metal complex catalyzed reaction, a well-designed ligand is doubtless the most essential one to the success of a catalytic reaction.[2] Therefore, considerable efforts have been made to search for more efficient and affordable ligands. As a result, various ligands with different shapes and functions had been explored and reported in the literature.[3] Although recent applications of so-called "eco-friendly" ligands, such as amines, imines, diazabutadienes, oximes, and N-heterocyclic carbenes, are having merits regarding low environmental impact and catalytic performances,[4] for many years, various kinds and shapes of organophosphines and derivatives remain the most frequently employed ligands.[5] Mainly, the electronically and sterically tunable capacities of phosphines make this type of ligand one of the most favorite choices among all ligands available.[6]

In general, the phosphorus atoms of organophosphine ligands are rich in electron density and vulnerable to oxidation. It is certainly not an agreeable character for long-term storage of phosphine ligands. In addition, the oxidized phosphine thereafter loses its coordination capability toward soft atoms such as Pd(II) or Pd(0) in complexes and subsequently leads to a great reduction in its catalytic performance. On the other hand, secondary phosphine oxides

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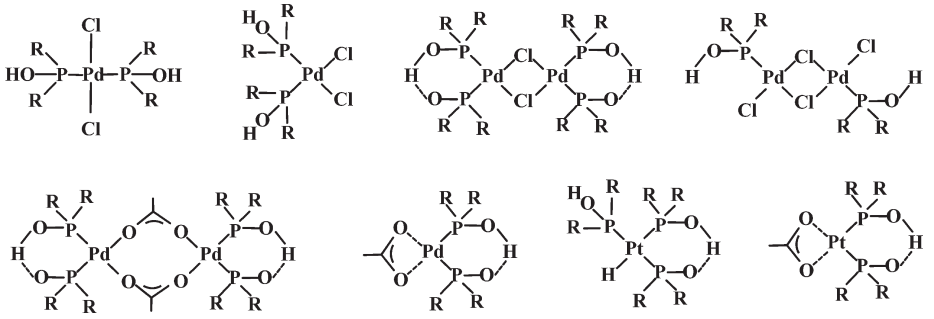

Figure 1. Selected phosphinous acid-coordinated palladium and platinum complexes.

(SPOs) ($R'R''PH(=O)$) are already in oxidized form and therefore stable toward moisture and air. The equilibrium existing between a secondary phosphine oxide ($R'R''PH(=O)$) and its tautomeric form, phosphinous acid ($R'R''POH$), is well documented.[7] Various structural forms of phosphinous acid (PAs)-coordinated palladium or platinum complexes had been reported as precatalysts in various C−C bond formation reactions (Figure 1).[8]

Recently, Buchwald-type phosphines, 2′-R′-biphenyl-2-yl-di-R″-phosphanes (R′ = OMe, NMe_2, etc.; R″ = ^{t}Bu, Ph, Cy, etc.) are gaining a reputation as efficient ligands in various palladium complex-catalyzed cross-coupling reactions.[9] As shown in Figure 2, one of the most distinguishing features of Buchwald-type phosphine is the existence of a weak interaction between its substituent of biaryl −R′ (with

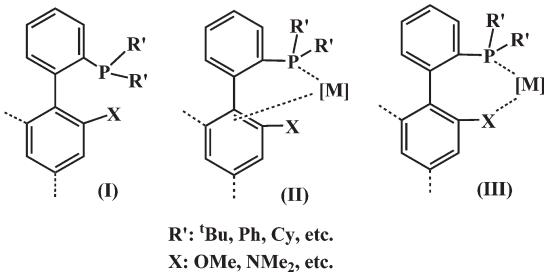

Figure 2. Buchwald-type phosphines (**I**) and two bonding modes (**II** and **III**) of phosphine-coordinated palladium complexes.

electron-donating capacity) and the metal, besides the strong P−M bonding, a brilliant application of the concept of hemilabile ligand.[10] This bonding mode provides flexibility around the coordination sphere of the metal center.

Lately, we have been interested in exploring a new type of stable SPO ligand thus to enhance the catalytic performance in coupling reactions. Our approach is thereby through the modification on Buchwald-type phosphine both by incorporating the notion of secondary phosphine oxide on phosphorus site as well as replacing the featureless phenyl ring by a more versatile heterocyclic ring, such as imidazole.[11] Presumably, it will bring about a new dimension of bonding capacity of the newly designed SPO ligands and hopefully improve their reactivities. Recently, Ackermann demonstrated the potential of the application of (*N*-aryl)azolyl-substituted secondary phosphine oxides, a new type of modified SPOs, in palladium-catalyzed cross-coupling reactions.[12] Herein we report the preparation of several modified Buchwald-type secondary phosphine oxides and their ligated palladium complexes. In addtion, their capacities as efficient mono- or bidentate ligands in palladium-catalyzed cross-coupling reactions were investigated.

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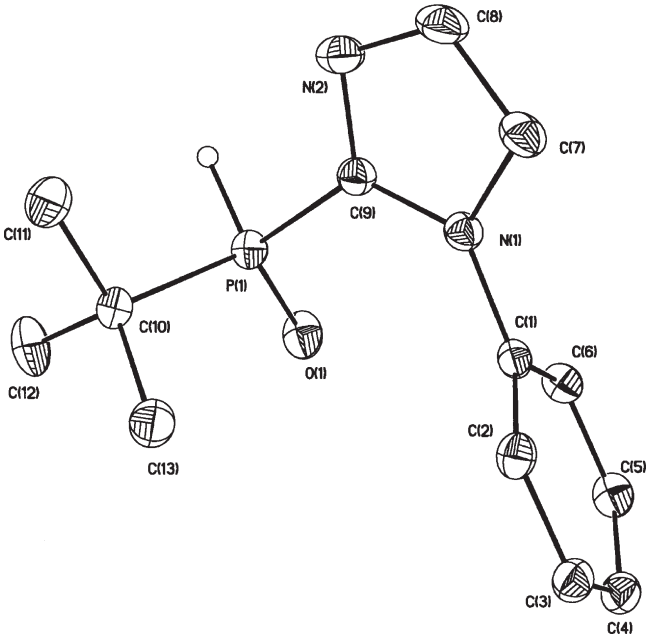

Figure 3. ORTEP diagram of **3a**. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (deg): P(1)−O(1) 1.4742(11); P(1)−C(9) 1.8055(15); P(1)−C(10) 1.8250(15); N(1)−C(7) 1.3751(19); N(1)−C(9) 1.3739(19); N(1)−C(1) 1.4407(17); C(9)−N(2) 1.3252(18); O(1)−P(1)−C(9) 114.74(7); O(1)−P(1)−C(10) 114.06(7); C(9)−P(1)−C(10) 108.04(7); N(2)−C(9)−N(1) 111.29(13); N(2)−C(9)−P(1) 121.03(12); N(1)−C(9)−P(1) 127.51(11).

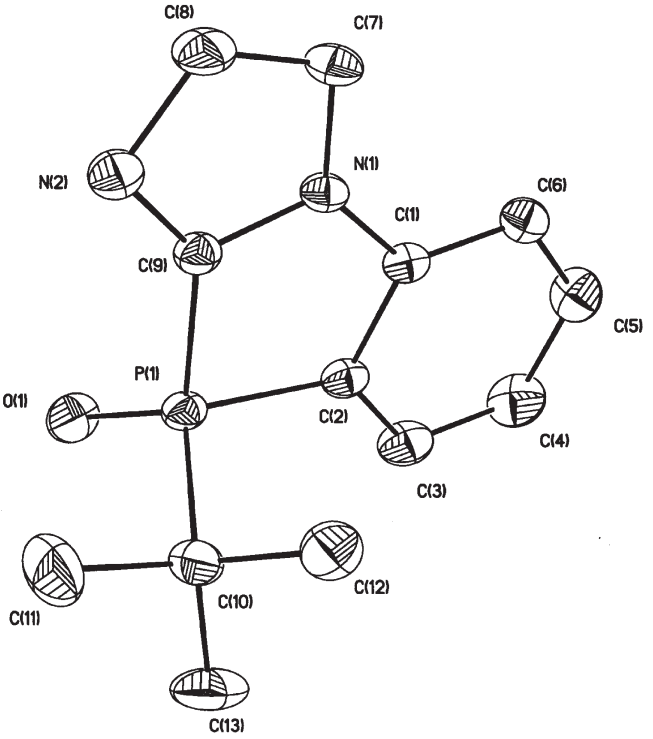

Figure 4. ORTEP diagram of **4**. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (deg): P(1)−O(1) 1.4819(12); P(1)−C(2) 1.8114(17); P(1)−C(9) 1.8118(16); P(1)−C(10) 1.8267(19); O(1)−P(1)−C(2) 117.37(9); O(1)−P(1)−C(9) 117.04(8); C(2)−P(1)−C(9) 89.92(7); O(1)−P(1)−C(10) 114.03(9); C(2)−P(1)−C(10) 109.05(8); C(9)−P(1)−C(10) 106.69(8).

2. Results and Discussion

2.1. Preparation of Buchwald-Type Secondary Phosphine Oxides (SPOs) 3a and 3b. First, the heterocyclic compound **1a** (or **1b**) was prepared in good yield by a Cu(I)-catalyzed coupling reaction between imidazole and bromobenzene (or 2-bromoanilsole), which was then treated with BuLi and P(^{t}Bu)Cl_2 to give **2a** (or **2b**). Subsequently, acidic workup gave **3a** in 45% or **3b** in 67% yield, respectively.[13]

The formation of compound **3a** was confirmed by single-crystal X-ray diffraction methods. The ORTEP diagram of **3a** is depicted in Figure 3. A distinctly large coupling constant, $J_{P-H} = 482$ Hz, between P(1) and its attached proton strongly suggests the existence of a P−H bond. The presence of a double bond between P(1) and O(1) is also evidenced by its short bond length, 1.4742(11) (Å). The geometric parameters of **3a** surrounding the phosphorus atom indeed supports the presence of a secondary phosphine oxide. Unexpectedly, a cyclic phosphine oxide **4** was isolated as well during the chromatographic process. The formation of **4** is presumably caused by further deprotonation from aryl by excess *n*-BuLi and then followed by cyclization and oxidation thereafter. The crystal structure reveals that it is cyclic in nature, with the phosphorus atom been oxidized (Figure 4).

2.3. Reaction of 3a or 3b with Palladium Salts. Generally, the catalytic efficiency of a bis-tertiary phosphine ligand coordinated $Pd(OAc)_2$ complex in *cis*-form is superior to that of bis-ligand-coordinated PdX_2 (X = Cl, Br) complex in cross-coupling reactions. Presumably this is due to its solubility in organic solvents and the ready reduction of the former complex in the presence of reducing agents such as excess phosphine and base.[14] Unfortunately, attempts to crystallize a **3a**- or **3b**-coordinated $Pd(OAc)_2$ complex were not successful. Therefore, unambiguous identification of the composition of *in situ* **3b**/$Pd(OAc)_2$ is not possible. In contrast to the palladium acetates, it is relatively convenient to grow crystals of palladium halide complexes in a not strictly moisture-free environment. The composition of the products including the ratio of ligand to metal could be readily identified after structural determination by X-ray diffraction methods. Thereby, the preparation of **3a**- or **3b**-coordinated palladium halide complexes was pursued.

The reaction of phosphinous acid **3a** (or **3b**) with one molar equivalent of either $Pd(COD)Cl_2$ or $PdBr_2$ at 60 °C for a designated number of hours gave palladium complex **5a** (R = H, X = Cl) or **5b** (R = OMe, X = Br) (Scheme 2). The complex **5a** (or **5b**) was observed in *cis*-form of a bis-phosphine ligands coordinated $Pd(II)X_2$ complex. The chemical shifts for **5a** and **5b** are 92.7 and 96.3 ppm, respectively, in ^{31}P NMR. The distinctly large coupling constant (J_{P-H}) between the phosphorus atom and its attached proton of **3a** (or **3b**) no longer exists in **5a** (or **5b**), which corresponds to the formation of a phosphinous acid form of the ligand. Interestingly, the formation of **6a** (R = H, X = Cl) or **6b** (R = OMe,

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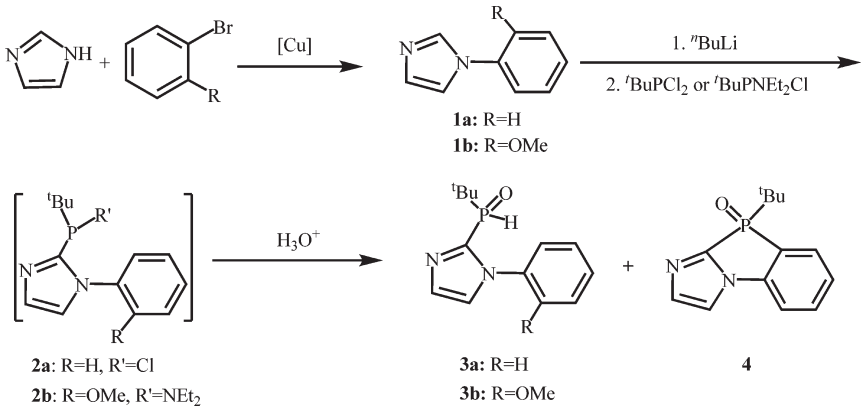
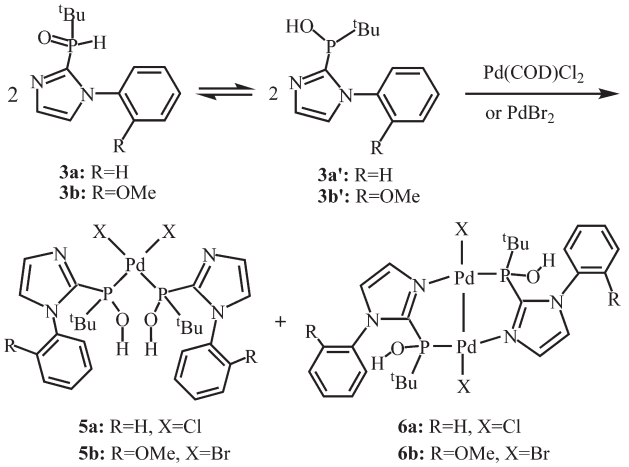
Scheme 1



Scheme 2



X = Br) was observed in the ^{31}P NMR, accompanied with some unidentified signals, by gradual conversion of the signal to 104.0 or 107.9 ppm, respectively. Purification of **6a** (or **6b**) from the mixture containing **5a** (or **5b**) by a chromatographic process in silica was not achievable presumably due to the fragility of the former. Fortunately, suitable crystals were obtained for structural determination. It was later confirmed that both **6a** and **6b** are unusual bimetallic compounds with direct Pd(I)−Pd(I) bonds.[15] For prolonged reaction time during the formation of **5a** or **5b**, it was accompanied with the formation of a new palladium complex, with an even further downfield shifted signal at 124.1 and 125.7 ppm, respectively, for **7a** or **7b**, in the ^{31}P NMR.[16]

All four compounds **5a**, **5b**, **6a**, and **6b** were crystallized in CH_2Cl_2 solution, and their structures were determined by single-crystal X-ray diffraction methods. The ORTEP diagrams of **5a**, **5b**, **6a**, and **6b** are shown in Figure 5−8, respectively. The tautomeric shift of the secondary phosphine oxide **3a** (or **3b**) to its phosphinous acid form **3a′** (or **3b′**) during the coordination is further evidenced by the structures of **5a** (or **5b**) and **6a** (or **6b**). We noticed that the expected intramolecular hydrogen bonding between deprotonated and non-deprotonated secondary phosphine oxides in *cis*-form of a bis-phosphine ligand coordinated palladium complex was not detected.[17] As shown, there are two molar equivalents of **3a′** (or **3b′**), each in its phosphinous acid form, coordinated to palladium in **5a** (or **5b**). In **5a**, the bond lengths of P(1)−O(1) and P(2)−O(2) are 1.529(4) and 1.553(4) Å, respectively. Both are typical single bonds. Notably, two molar equivalents of **3a′** (or **3b′**) ligands are each in its *R*- and *S*-forms. Recently, asymmetric synthesis using enantiopure SPOs as ligands has gained more and more attention.[18] Presumably, **3a′** (or **3b′**) is a potential candidate for asymmetric synthesis as a ligand after resolution of two enantiomers. In **5a**, the palladium is situated in an approximately square-planar environment. Similar structural parameters are observed for **5b** except the attached −OMe group. The framework of **6a** (or **6b**) can be regarded as a bis-**3a′** (or **3b′**)-bridged dipalladium complex. Both the phosphorus atom from phosphinous acid and the nitrogen atom from imidazole of **3a′** (or **3b′**) act as the coordinating sites, and **3a′** (or **3b′**) can be regarded as an authentic P,N-chelating ligand. It is particularly noteworthy that a nitrogen atom of imidazole acts as a coordinating site as well. In a closely related work, Beller did not mention the formation of a complex with a Pd(I)−Pd(I) bond.[19] Two molecules of **3a′**

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(16) The ^{31}P NMR signal shifts from 107.9 ppm of **6b** to 125.7 ppm of the new compound **7b**. The structure of **7b** was determined by single-crystal X-ray diffraction methods. For details, see the Supporting Information.

(17) Intramolecular hydrogen bonding of related cases: (a) Xu, H.; Ekoue-Kovi, K.; Wolf, C. *J. Org. Chem.* **2008**, *73*, 7638–7650. (b) Wolf, C.; Lerebours, R. *Org. Lett.* **2004**, *6*, 1147–1150. (c) Cobley, C. J.; van den Heuvel, M.; Abbadi, A.; de Vries, J. G. *Tetrahedron Lett.* **2000**, *41*, 2467–2470.

(18) (a) Gatineau, D.; Moraleda, D.; Naubron, J.-V.; Bürgi, T.; Giordano, L.; Buono, G. *Tetrahedron: Asymmetry* **2009**, *20*, 1912–1917. (b) Ackermann, L. In *Phosphorus Ligands in Asymmetric Catalysis*; Börner, A., Ed.; Wiley-VCH: Weinheim, 2008; Vol. *2*, pp 831−847. (c) Ackermann, L.; Born, R.; Spatz, J. H.; Althammer, A.; Gschrei, C. J. *Pure Appl. Chem.* **2006**, *78*, 209–214. (d) Ackermann, L. *Synthesis* **2006**, 1557–1571. (e) Nemoto, T.; Jin, L.; Nakamura, H. *Tetrahedron Lett.* **2006**, *47*, 6577–6581. (f) Bigeault, J.; Giordano, L.; Buono, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4753–4757. (g) Dubrovina, N. V.; Börner, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5883–5886. (h) Chan, E. Y. Y.; Zhang, Q.-F.; Sau, Y.-K.; Lo, S. M. F.; Sung, H. H. Y.; Williams, I. D.; Haynes, R. K.; Leung, W. H. *Inorg. Chem.* **2004**, *43*, 4921–4926. (i) Jiang, X.; van den Berg, M.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. *Tetrahedron: Asymmetry* **2004**, *15*, 2223–2229. (j) Dai, W.-M.; Yeung, K. K. Y.; Leung, W. H.; Haynes, R. K. *Tetrahedron: Asymmetry* **2003**, *14*, 2821–2826.

(19) (a) Schulz, T.; Torborg, C.; Schäffner, B.; Huang, J.; Zapf, A.; Kadyrov, R.; Börner, A.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 918–921. (b) Sergeev, A. G.; Schulz, T.; Torborg, C.; Spannenberg, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 7595–7599.

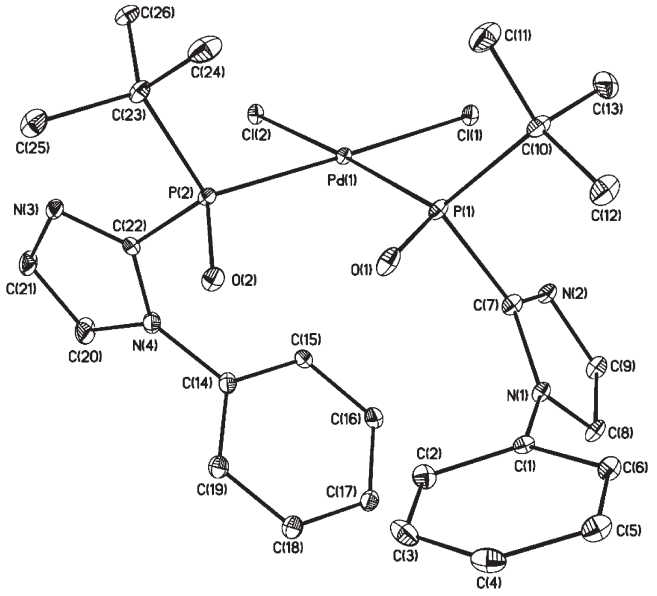


Figure 5. ORTEP diagram of **5a**. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (deg): Pd(1)−P(1) 2.258(1); Pd(1)−P(2) 2.261(1); Pd(1)−Cl(2) 2.364(1); Pd(1)−Cl(1) 2.388(1); P(1)−O(1) 1.529(4); P(2)−O(2) 1.553(4); P(1)−Pd(1)−P(2) 92.11(5); P(1)−Pd(1)−Cl(1) 92.57(5); Cl(2)−Pd(1)−Cl(1) 87.64(4); P(2)−Pd(1)−Cl(2) 87.61(5); O(1)−P(1)−Pd(1) 117.58(16); O(2)−P(2)−Pd(1) 115.61(16).

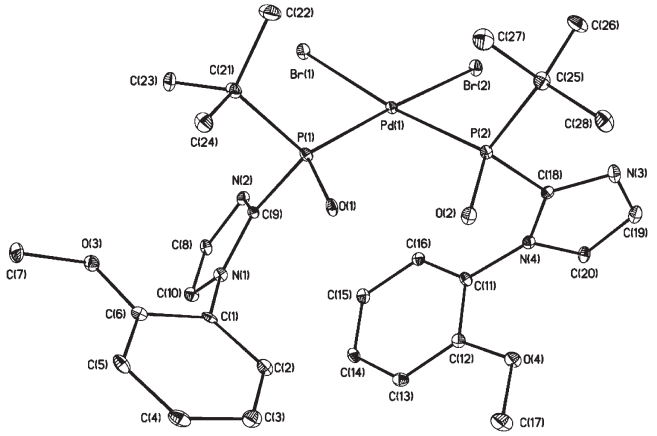


Figure 6. ORTEP diagram of **5b**. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (deg): Pd(1)−P(1) 2.278(1); Pd(1)−P(2) 2.269(1); Pd(1)−Br(2) 2.499(1); Pd(1)−Br(1) 2.509(1); P(1)−O(1) 1.521(2); P(2)−O(2) 1.565(3); P(2)−Pd(1)−P(1) 93.38(4); P(2)−Pd(1)−Br(2) 87.04(3); P(1)−Pd(1)−Br(1) 91.77(3); Br(2)−Pd(1)−Br(1) 88.07(2); O(1)−P(1)−Pd(1) 116.74(11); O(2)−P(2)−Pd(1) 115.47(11).

(or **3b′**) as chelating ligands, each in its *R*- or *S*-form, are arranged in opposite formats, while two halide atoms are located in terminal positions. Each palladium atom remains in a nearly square-planar environment. In **6a**, the bond lengths of Pd(1)−Pd(2) and P(1A)−O(1A) are 2.5649(5) and 1.608(4) Å, respectively. Both are typical single bonds. The bond angle of O(1A)−P(1A)−Pd(1) is 109.87(15)°, which is a typical sp^3 hybridization of the phosphorus atom center. The five atoms Pd(1), Pd(2), N(2A), C(9A), and P(1A) are not coplanar. Rather, they form a twisted pentagon such as cyclopentane. The formal charges of both of the

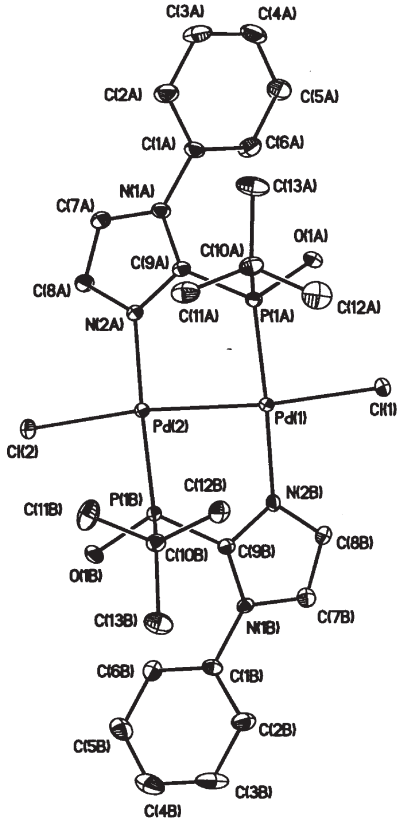


Figure 7. ORTEP diagram of **6a**. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (deg): Pd(1)−N(2B) 2.093(4); Pd(1)−P(1A) 2.1917(13); Pd(1)−Cl(1) 2.4477(12); Pd(1)−Pd(2) 2.5649(5); N(2B)−Pd(1)−P(1A) 176.88(11); N(2B)−Pd(1)−Cl(1) 92.68(11); P(1A)−Pd(1)−Cl(1) 89.98(4); N(2B)−Pd(1)−Pd(2) 91.52(11); P(1A)−Pd(1)−Pd(2) 85.63(3); Cl(1)−Pd(1)−Pd(2) 171.24(3); N(2A)−Pd(2)−Pd(1) 92.08(11); P(1B)−Pd(2)−Pd(1) 85.52(3); Cl(2)−Pd(2)−Pd(1) 167.62(3); O(1A)−P(1A)−Pd(1) 109.87(15).

palladium atoms can be regarded as +1, which is noteworthy. A probable conformation with P,N-chelated monopalladium complex by **3a** was not observed. This can be understood by the fact that the formation of a four-membered ring is not preferable due to severe internal strain. As for the structure of **6b**, rather similar structural parameters are observed to those of **6a** except the attached −OMe group. To our best knowledge, these two compounds are the first reported SPO-coordinated bimetallic complexes with direct Pd(I)−Pd(I) bonds.

The formation of the dipalladium complex **6a** (or **6b**) with a direct Pd(I)−Pd(I) bond is notable since the initial palladium source is a Pd(II) salt. Barder also observed the formation of a dipalladium complex with a direct Pd(I)−Pd(I) bond from a reduction of a Buchwald-type phosphine coordinated palladium dichloride complex.[14a] He proposed a disproportionation mechanism for the dimeric compound, which disintegrates into a Pd(II) plus a Pd(0) species through the reduction process by $PhB(OH)_2$. On the basis of Barder's assumption, it seems reasonable to postulate that the formation of **6** is first through the reduction of **5**, followed by addition of another molar equivalent of **5** and eventually accompanied by elimination of two molar equivalents of **3′** as shown in Scheme 3. Conversely, the formation of an active Pd(0) species might be possible through the disproportionation

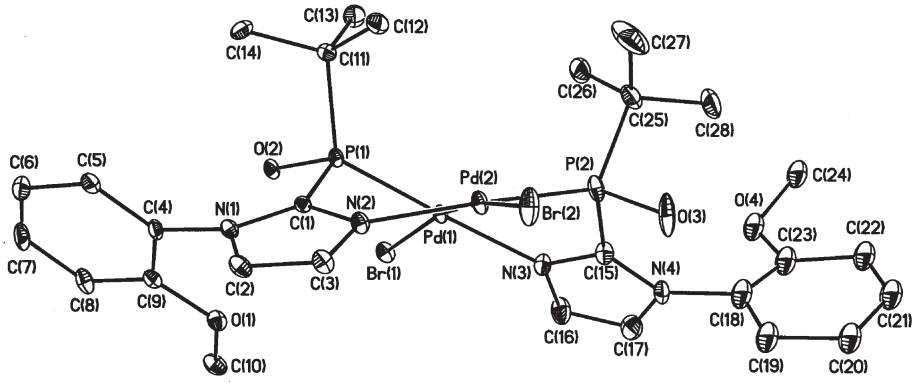
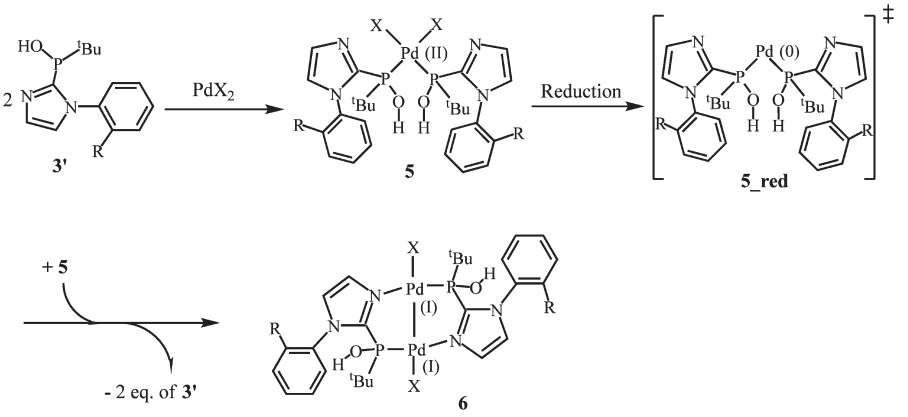


Figure 8. ORTEP diagram of **6b**. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (deg): Pd(1)−N(3) 2.111(4); Pd(1)−P(1) 2.1997(11); Pd(1)−Br(1) 2.5466(5); Pd(1)−Pd(2) 2.5738(4); P(1)−O(2) 1.601(3); O(1)−C(9) 1.361(5); O(1)−C(10) 1.422(5); N(3)−Pd(1)−P(1) 173.82(10); N(3)−Pd(1)−Br(1) 92.48(10); P(1)−Pd(1)−Br(1) 93.63(3); N(3)−Pd(1)−Pd(2) 91.32(10); P(1)−Pd(1)−Pd(2) 82.54(3); Br(1)−Pd(1)−Pd(2) 163.899(18); O(2)−P(1)−C(1) 106.83(16); O(2)−P(1)−C(11) 100.23(18); C(1)−P(1)−C(11) 104.86(19); O(2)−P(1)−Pd(1) 112.13(12); C(1)−P(1)−Pd(1) 106.88(13); C(11)−P(1)−Pd(1) 124.60(14); C(9)−O(1)−C(10) 117.8(3).

Scheme 3



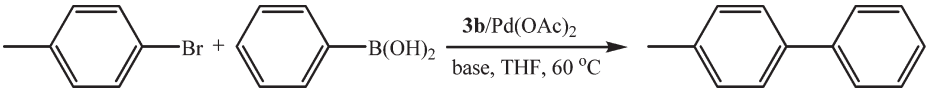
of **6** in solution. Presumably, it is this Pd(0) species that is responsible mostly for the catalytic performance in the cross-coupling reaction using **3′** as the ligand. Recently, several works on the preparation and structural determination of dipalladium complexes with a direct Pd(I)−Pd(I) bond were reported. Most of the dipalladium complexes contain a bridging ligand,[20] which are often hyride, CO, halides, isonitriles, olefins, and phosphines (chelating or nonchelating) between the dinuclear palladium centers. Hartwig also demonstrated that a dinuclear complex $[Pd_2(\mu\text{-}Br)_2(P'Bu_3)_2]$ is a suitable precatalyst for amination of various aryl halides.[21] Recently, the discovery of a bimetallic palladium(III) complex that can catalyze the formation of carbon−heteroatom bonds adds a new facet to our understanding of the chemistry of one of the most widely used metals in catalysis.[22]

2.3. Palladium-Catalyzed Suzuki−Miyaura Reactions Using SPOs as Ligand. Palladium-catalyzed Suzuki−Miyaura cross-coupling reactions of aryl halides and phenylboronic acid were carried out by employing the newly made SPOs (**3a** or **3b**) as ligands. Although the X-ray determined crystal structures of **3a**- or **3b**-coordinated $Pd(OAc)_2$ complexes were not available, $Pd(OAc)_2$ was chosen as the palladium source rather than PdX_2 (X = Cl, Br) due to its creditable catalytic performance in most palladium-catalyzed cross-coupling reactions. Several factors that affect the efficiency of the reactions, including temperature, time, concentration, bases, transition metal−ligand ratios, and solvent, had been evaluated. First, the catalytic performance was found to be better for **3b** than **3a** through a series of deliberate experiments by using these two ligands.[23] Presumably, the enhanced reaction rate of **3b** over **3a** is due to the additional −OMe group, which is consistent with Buchwald's observation.[9a] Since, the catalytic performance of **3b** is superior to **3a**, the following optimizations of the reaction conditions were all employing **3b** rather than **3a**. The results for the Suzuki−Miyaura coupling reactions are summarized in Tables 1−3.

(20) Murahashi, T.; Kurosawa, H. *Coord. Chem. Rev.* **2002**, *231*, 207.
(21) (a) Christmann, U.; Vilar, R.; White, A. J.; Williams, D. J. *Chem. Commun.* **2004**, 1294–1295. (b) Stambuli, J. P.; Kuwano, R.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 4746.
(22) Powers, D. C.; Ritter, T. *Nat. Chem.* **2009**, *1*, 302–309.

(23) The conversion rates are 40% and 60%, respectively, for employing **3a** and **3b** as the ligands under the following conditions: 4-bromotoulene (0.5 mmol), phenylboronic acid (0.6 mmol), NaOH (1.5 mmol), THF (1 mL), $Pd(OAc)_2$ (0.5 mol %), ligand (1 mol %), 60 °C, 2 h. Yield of the produced 4-phenyltoluene was determined by GC-MS using undecane as internal standard.
(24) (a) Dubbaka, S. R.; Vogel, P. *Org. Lett.* **2004**, *6*, 95–98. (b) Grasa, G. A.; Hillier, A. C.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 1077–1080. (c) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972–980.

Table 1. Suzuki−Miyaura Coupling Reactions Employing Various Bases[a]



entry	base	yield (%)[b]
1	NaOH	80
2	KOH	> 99
3	$CsOH \cdot H_2O$	17
4	NaO*t*-Bu	34
5	KO*t*-Bu	17
6	Na_2CO_3	18
7	K_2CO_3	35
8	Cs_2CO_3	< 1
9	KF	< 1
10	CsF	22
11	K_3PO_4	24
12	$K_3PO_4 \cdot nH_2O$	81

[a] Reaction conditions: 4-bromotoluene (0.5 mmol), phenylboronic acid (0.6 mmol), base (1.5 mmol), THF (1.0 mL), $Pd(OAc)_2$ (1.0 mol %), **3b** (2.0 mol %), 60 °C, 1 h. [b] Yield was determined by GC-MS.

Table 2. Effect of Reaction Time and Pd/L Ratios on Suzuki−Miyaura Reaction[a]

entry	Pd:L	time (h)	yield (%)[a]
1	1:2	1.0	> 99
2	1:2	1.0	76[b]
3	1:2	0.5	98
4	1:2	15.0	12[c]
5	1:1	0.25	29
6	1:2	0.25	55
7	1:3	0.25	< 5

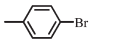
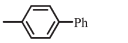
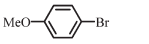
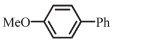
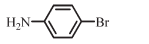
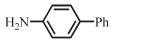
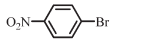
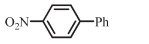
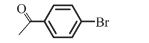
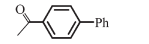
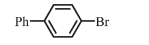
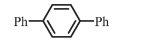
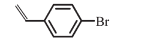
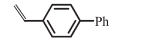
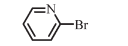
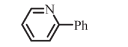
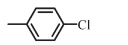
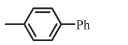
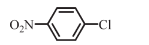
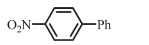
[a] Reaction conditions the same as in the footnote of Table 1 except using KOH as base. [b] Toluene as the solvent. [c] At room temperature.

Among all the influential factors that affect the catalytic efficiency of the cross-coupling reactions, the role played by base probably is the most unpredictable one.[24] Thereby, the impacts of employing different bases on the reaction yields were first investigated, and the results are shown in Table 1. Among all the bases screened, it was found that potassium hydroxide in THF is the most effective (Table 1, entry 2), while the other bases such as cesium hydroxide and sodium and potassium *tert*-butoxide gave poor yields of product. However, the bases NaOH and $K_3PO_4 \cdot nH_2O$ gave good yields of coupled product. We suspect that the cation of the base could be one of the key factors in Suzuki−Miyaura reactions with aryl bromides and using the SPO **3b** as ligand.

In order to achieve optimized reactivity, we carried out studies on variables such as solvent, temperature, and Pd:L ratio. The results are presented in Table 2. It was found that the combination of Pd:L (1:2) gave almost quantitative yield of coupled product in THF for 1 h (Table 2, entry 1). When the reaction was carried out using toluene as a solvent, it gave 76% yield, whereas reducing the reaction time to 15 min at 60 °C suppressed the corresponding yield. A better efficiency was observed for the composition of **3b**/$Pd(OAc)_2$ *in situ* equal to 2:1 (Table 2, entries 5−7). An attempt to run the reaction at lower temperature gave poor results (Table 2, entry 4). The optimal reaction condition is using **3b**/$Pd(OAc)_2$ (2:1) as the catalyst precursor in a solution of THF (1.0 mL) and KOH (1.5 mmol) and under 60 °C for reacting at least 1 h.

Employing the optimal reaction conditions, the scope of this reaction using various aryl bromides was examined, and the results are presented in Table 3. The Suzuki−Miyaura coupling reaction for electron-rich and electron-deficient aryl bromides was carried out smoothly to give the corresponding coupled products. Reactions of 4-bromoanisole and 4-nitrobromobenzene with phenylboronic acid gave 67% and 83% yields, respectively (Table 3, entries 2 and 4). The other heterocyclic substrate, 2-bromopyridine, gave only 10% yield of product, which is presumably due to its coordination with the palladium complex (Table 3, entry 8). In addition, the aryl chlorides in the presence of potassium carbonate as base forms a product (Table 3, entry 10).

Table 3. Suzuki−Miyaura Coupling Reactions Employing Various Aryl Halides[a]

Entry	Aryl halide	Product	Time (h)	Yield(%)[b]
1			1	98
2			3	67
3			3	-
4			3	83
5			3	90
6			10	67
7			10	70
8			10	-
9			24	18[c]
10			24	69[c]

[a] Reaction conditions: aryl halide (0.5 mmol), phenylboronic acid (0.6 mmol), KOH (1.5 mmol), THF (1.0 mL), $Pd(OAc)_2$ (1.0 mol %), **3b** (2.0 mol %), 60 °C. [b] Yield of isolated product. [c] K_2CO_3 (1.5 mmol), $Pd(OAc)_2$ (2.0 mol %), **3b** (4.0 mol %), toluene, 90 °C.

2.4. Summary. Two new air- and moisture-stable secondary phosphine oxides containing the aryl-1*H*-imidazole group were prepared. Applications of these ligands in palladium-catalyzed Suzuki−Miyaura cross-coupling reactions exhibited good to excellent efficiencies toward aryl bromides. Only moderate performances were observed for aryl chlorides. While the catalytic performances of theses SPOs are compatible with their trialkyl or triaryl counterparts, these

compounds show an advantage over the other known ligands, being stable toward air and moisture. The formation of the dipalladium complex **6a** or **6b** with a direct Pd(I)−Pd(I) bond is noteworthy. It is proposed that an active Pd(0) species is responsible for the catalytic performance through the disproportionation of **6a** or **6b** in solution.

3. Experimental Section

3.1. General Procedures. All reactions were carried out under a nitrogen atmosphere using standard Schlenk techniques or in a nitrogen-flushed glovebox. Freshly distilled solvents were used. All processes of separations of the products were performed by centrifugal thin layer chromatography (CTLC, Chromatotron, Harrison model 8924) or column chromatography. GC-MS analysis was performed on an Agilent 5890 gas chromatograph (Restek Rtx-5MS fused silica capillary column: 30 m, 0.25 mm, 0.5 μm) with an Agilent 5972 mass selective detector. Routine ^{1}H NMR spectra were recorded on a Varian-400 spectrometer at 400.00 MHz. The chemical shifts are reported in ppm relative to internal standard TMS ($\delta = 0.0$). ^{31}P and ^{13}C NMR spectra were recorded at 121.44 and 75.46 MHz, respectively. The chemical shifts for the former and the latter are reported in ppm relative to internal standards H_3PO_4 (δ = 0.0) and $CHCl_3$ (δ = 77) or CH_2Cl_2 ($\delta = 53$), respectively. Mass spectra were recorded on a JEOL JMS-SX/SX 102A GC/MS/MS spectrometer. Electrospray ionization high-resolution mass spectra (ESI-HRMS) were recorded on a Finnigan/Thermo Quest Mat 95 XL mass spectrometer.

3.2. Synthesis and Characterization of 1-Phenyl-1*H*-imidazole (1a) and 1-(2-Methoxyphenyl)-1*H*-imidazole (1b). Into a 250 mL round-bottomed flask were placed copper iodide (1.14 g, 6.0 mmol), 1,10-phenanthroline (1.08 g, 6.0 mmol), tripotassium phosphate (19.10 g, 90.0 mmol), imidazole (2.86 g, 42.0 mmol), and *N*,*N*-dimethylformamide (50 mL). After stirring at 25 °C for a few minutes, 30.0 mmol of bromobenzene (3.16 mL) was added. The solution was then heated and stirred at 120 °C for 48 h. After cooling to 25 °C, the solution was diluted with ethyl acetate (20 mL), filtered through silica gel, and washed with ethyl acetate. The organic layer was washed twice with brine (40 mL), then dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (hexane/ethyl acetate, 3:1) to afford **1a** in 78% yield (3.37 g, 23.40 mmol). Similar procedures were carried out for the preparation of **1b** except for the replacement of bromobenzene by 2-bromoanisole (3.74 mL, 30 mmol). The yield of **1b** is 85% (4.43 g, 24.89 mmol).

Selected spectroscopic data for 1a: ^{1}H NMR ($CDCl_3$, δ/ppm) 7.86 (s, 1H, N=CH-N), 7.51−7.47 (t, 2H, Ar), 7.40−7.36 (d, 3H, Ar), 7.29 (s, 1H, N-CH=C), 7.21 (s, 1H, C=CH-N); ^{13}C NMR ($CDCl_3$, δ/ppm) 136.4, 134.9, 129.8, 129.2, 126.8, 120.8, 120.7, 117.6; MS (EI, *m*/*z*) 144.1 $[M]^+$.

Selected spectroscopic data for 1b: ^{1}H NMR ($CDCl_3$, δ/ppm) 7.76 (s, 1H, N=CH-N), 7.35−7.30 (t, 1H, Ar), 7.24−7.22 (d, 1H, Ar), 7.19 (s, 1H, N−CH=C), 7.14 (s, 1H, C=CH-N), 7.04−6.98 (m, 2H, Ar); ^{13}C NMR ($CDCl_3$, δ/ppm) 152.1, 137.3, 128.5, 128.4, 126.1, 125.0, 120.6, 119.8, 112.0, 55.3; MS (EI, *m*/*z*) 174.0 $[M]^+$.

3.3. Preparation of 2-(*tert*-Butylhydrophosphoryl)-1-phenyl-1*H*-imidazole (3a). Into a N_2-flushed 100 mL round-bottomed flask were placed 1.0 mmol of **1a** (0.144 g) and 10 mL of THF. The solution was cooled to −78 °C before 1.1 mmol of *n*-BuLi (0.44 mL, 2.5 M in hexane) was added. The suspension was slowly warmed to 0 °C and stirred for another 30 min. Subsequently, the solution was slowly transferred to another flask, which contained 1.0 mmol of *tert*-butyldichlorophosphine (0.159 g) in 10 mL of THF at 0 °C. The reaction mixture was heated gradually from 0 to 60 °C and stirred for another 2 h. After completion, the solution was diluted with 5 mL of ethyl acetate at 0 °C and quenched with NH_4Cl solution (10 mL, 1.0 M). After stirring for a few minutes, the organic layer was separated and the aqueous layer was extracted twice with ethyl acetate (2 × 5 mL). The combined organic layer was dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (ethyl acetate/methanol, 20:1) to afford a white solid **3a** in 45% yield (0.45 mmol, 111.0 mg).

Selected spectroscopic data for 3a: ^{1}H NMR ($CDCl_3$, δ/ppm) 7.703, 6.499 (d, 1H, P-H, $^1J_{P-H} = 482$ Hz), 7.605−7.585 (d, 2H), 7.532−7.472 (m, 3H), 7.354 (s, 1H), 7.309 (s, 1H), 1.137−1.093 (d, 9H, $^3J_{P-H} = 17.6$); ^{13}C NMR ($CDCl_3$, δ/ppm) 140.6, 139.3 (d, C−P, $^1J_{P-C} = 203$), 136.8, 130.7, 130.6, 129.4, 129.1, 125.9, 125.0, 121.4, 33.0, 32.2 (d, C-P, $^1J_{P-C} = 118$); ^{31}P NMR ($CDCl_3$, δ/ppm) 32.0 (d, P-H, $^1J_{P-H} = 482$ Hz); MS (EI, *m*/*z*) 248.0 $[M]^+$.

3.4. Preparation of 2-(*tert*-Butylhydrophosphoryl)-1-(2-methoxyphenyl)-1*H*-imidazole (3b). Unexpectedly, the procedures for the preparation of **3a** did not work for **3b**. Therefore, another reaction pathway was pursued as follows.

To a N_2-flushed 100 mL round-bottomed flask, charged with 1.0 mmol of (^{t}Bu)PCl_2 (0.318 g) and 10 mL of hexane, was gradually added 2.0 mmol of Et_2NH (207 μL) at 0 °C. The suspension was then slowly warmed to 25 °C and stirred for 3 h. After filtration, the solvent was removed under reduced pressure at 0 °C before 10 mL of THF was added. Precaution against exposure to air had been taken. To another flask containing a solution of 2-(1*H*-imidazol-1-yl)anisole (0.174 g, 1.0 mmol) with 10 mL of THF was added 1.1 mmol of *n*-BuLi (0.44 mL, 2.5 M in hexane) at −78 °C for 1 h and then was warmed to 0 °C. Subsequently, the solution in the latter flask was slowly transferred to the former flask at 0 °C. The mixed solution was then heated to 60 °C for 2 h. After cooling to 0 °C, the reaction was quenched by water (2 mL). Subsequently, the resulting solution was washed with HCl (3.0 M, 2 mL) and NaOH (3.0 M, 2.5 mL), and then the aqueous layer was extracted twice with ethyl acetate (2 × 5 mL). The combined organic solution was dried over $MgSO_4$. Finally, the residue was purified through column chromatography (1:10 to 20:1 ethyl acetate/hexane to ethyl acetate/methanol) to afford white power **3b** in 67% yield (0.67 mmol, 186 mg).

Selected spectroscopic data for 3b: ^{1}H NMR ($CDCl_3$, δ/ppm) 7.55, 6.36 (d, 1H, P-H, $^1J_{P-H} = 476$ Hz), 7.47−7.43 (m, 2H, Ar), 7.35, 7.19 (s, 2H, C=C), 7.08−7.03 (m, 2H, Ar), 3.82 (s, 3H, OMe), 1.15, 1.11 (d, 9H, t-Bu, $^3J_{P\text{-}CC3H9} = 16$ Hz); ^{13}C NMR ($CDCl_3$, δ/ppm) 153.8, 140.5, 139.2, 130.7, 130.2, 130.0, 128.6, 125.6, 120.5, 111.6, 55.6, 32.74, 32.0, 23.65; ^{31}P NMR ($CDCl_3$, δ/ppm) 29.5 (d, P-H, $^1J_{P-H} = 476$ Hz); MS (EI, *m*/*z*) 278.1 $[M]^+$.

3.5. Formations of 5a and 6a from the Reaction of 3a with $Pd(COD)Cl_2$. Into a N_2-flushed 20 cm^3 Schlenk tube were placed $Pd(COD)Cl_2$ (57 mg, 0.2 mmol), **3a** (99 mg, 0.4 mmol), and THF (1.0 mL). The solution was stirred at 60 °C for 40 min. An alternative way is to stir at 25 °C for several hours in dichloromethane (1.0 mL). Recrystallization from dichloromethane gave light yellow **5a** in 86% yield (0.176 mmol, 116 mg). For a prolonged reaction time, the formation of **6a** was observed by gradual conversion of the ^{31}P NMR signal from 92.7 ppm of **5a** to 104.0 ppm for **6a**. Purification of **6a** from a mixture containing **5a** and some unidentified products by the chromatographic process was not achievable probably due to the fragility of the former. ^{1}H and ^{13}C NMR spectra of the mixture exhibit too many signals that are uninformative for structural assignment of **6a**.

Selected spectroscopic data for 5a: ^{1}H NMR ($CDCl_3$,δ/ppm) 7.904 (s, 2H), 7.506 (m, 6H), 7.378 (m, 4H), 7.278 (s, 2H), 7.155 (s, 2H), 1.321, 1.265 (d, 18H, J = 22.4 Hz); ^{13}C NMR ($CDCl_3$, δ/ppm) 144.08, 143.60, 136.80, 129.236, 129.00, 128.60, 127.93, 125.84, 125.48, 24.70; ^{31}P NMR ($CDCl_3$,δ/ppm) 92.7; MS (APCI, *m*/*z*) 670.7 $[M]^+$.

3.6. Formation of 5b and 6b from the Reaction of 3b with $PdBr_2$. Similar steps to those shown in section 3.5 for the reaction of **3b** with $PdBr_2$ had been proceeded. A N_2-flushed 20 cm^3 Schlenk tube contained a mixture of $PdBr_2$ (53.0 mg, 0.2 mmol), **3b** (110.0 mg, 0.4 mmol), and THF (1.0 mL). The mixture was stirred at 25 °C for 1 h until the unsoluble powder

$PdBr_2$ was consumed. Recrystallization from dichloromethane gave light yellow **5b** in 73% yield (0.146 mmol, 120.0 mg). Similar to the previous case, for prolonged reaction times, the formation of **6b** was observed by the ^{31}P NMR signal at 107.9 ppm besides the 96.3 ppm of **5b**. Complex **6b** is vulnerable to chromatographic processes; therefore, its purification from a mixture was not actualized. Too many signals were observed in teh ^{1}H and ^{13}C NMR spectra for the mixture, which caused the structural assignment of **6b** to not be credible.

Selected spectroscopic data for 5b: ^{1}H NMR (CD_2Cl_2, δ/ppm) 7.524 (s, 2H), 7.396 (s, 2H), 7.256 (s, 2H), 7.187 (s, 2H), 7.003−6.982 (d, 2H, J = 8.4 Hz), 6.701 (s, 2H), 3.811 (s, 6H), 1.336−1.207 (d, 18H); ^{13}C NMR (CD_2Cl_2, δ/ppm) 154.7, 131.0, 126.9, 125.8, 123.4, 119.7, 112.3, 56.3, 28.3; ^{31}P NMR (CD_2Cl_2, δ/ppm) 96.3; MS (ESI, m/z) 821.2 $[M]^+$.

3.7. General Procedure for the Suzuki−Miyaura Cross-Coupling Reactions. Suzuki−Miyaura cross-coupling reactions were performed according to the following procedures. The four reactants, $Pd(OAc)_2$, **3b**, boronic acid, and base, were placed in a suitable oven-dried Schlenk flask. It was evacuated for 0.5 h and backfilled with nitrogen gas before adding solvent and aryl halide through a rubber septum. The aryl halides being solids at room temperature were added prior to the evacuation/backfill cycle. The flask was sealed with a rubber septum, and the solution was stirred at the required temperature for the designated number of hours. Then, the reaction mixture was diluted with ethyl acetate (3 mL) and the cooled solution poured into a separatory funnel. The mixture was washed with aqueous NaOH (1.0 M, 5 mL), and the aqueous layer was extracted with ethyl acetate (2×5 mL). The combined organic layer were washed with brine and dried with anhydrous magnesium sulfate. The dried organic layer was concentrated *in vacuo*. The residue was purified by column chromatography to give the desired product.

3.8. X-ray Crystallographic Studies. Suitable crystals of **3a**, **4**, **5a**, **5b**, **6a**, and **6b** were sealed in thin-walled glass capillaries under a nitrogen atmosphere and mounted on a Bruker AXS SMART 1000 diffractometer. Intensity data were collected in 1350 frames with increasing ω (width of 0.3° per frame). The absorption correction was based on the symmetry equivalent reflections using the SADABS program. The space group determination was based on a check of the Laue symmetry and systematic absences and was confirmed using the structure solution. The structure was solved by direct methods using the SHELXTL package.[25] All non-H atoms were located from successive Fourier maps, and hydrogen atoms were refined using a riding model. Anisotropic thermal parameters were used for all non-H atoms, and fixed isotropic parameters were used for H atoms.[26] Crystallographic data for compounds **3a**, **4**, **5a**, **5b**, **6a**, and **6b** are available from the Supporting Information.

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Supporting Information Available: Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Center, CCDC no. 759451, 759450, 759453, 793730, 759452, and 759454 for compounds **3a**, **4**, **5a**, **5b**, **6a**, and **6b**, respectively. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk). This material is available free of charge via the Internet at http://pubs.acs.org.

(25) Sheldrick, G. M. *SHELXTL PLUS User's Manual*, Revision 4.1; Nicolet XRD Corporation: Madison, WI, 1991.

(26) The hydrogen atoms were riding on carbons or oxygens in their idealized positions and held fixed with C−H distances of 0.96 Å.