Organometallics **2003,** *22,* 523−528 523

Coupling of Aryl Halides with Aryl Boronic Acids with $P(C_6H_5)(2\text{-}C_6H_4Cl)_2$ as the Supporting Ligand

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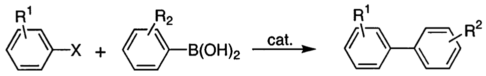
The chlorinated triarylphosphine $P(C_6H_5)(2\text{-}C_6H_4Cl)_2$ (**1**) has been used as a supporting ligand in the Suzuki−Miyaura coupling of aryl boronic acids with aryl halides. Aryl bromides without ortho substituents were successfully coupled at room temperature, while reactions involving sterically hindered aryl bromides required slight heating (70 °C). Electron-deficient aryl chlorides were also successfully coupled with heating (90 °C). Key reaction parameters such as order of addition, choice of mineral base, solvent volume, temperature, **1**/Pd ratio, as well as electronic and steric variation of the aryl halide have been investigated and are reported.

The coupling of aryl boronic acids with aryl halides (Suzuki−Miyaura reaction) has become one of the most widely used methods for preparation of biaryls due to a wide range of functional group tolerance and straightforward separation of products (eq 1).[1] These reactions are typically carried out with phosphine-based palladium catalysts at elevated temperatures and aryl bromides and iodides as substrates.[2] Despite the intense amount of attention this area has received, few systems have been found that promote this reaction under mild conditions.[3] Aryl chlorides are attractive substrates for this reaction; however, only a small number of successful catalysts have been found that promote these reactions.[4] Some of the more recent advances in this area involve the use of electron-rich or functionalized phosphine ligands (Figure 1).[5] Buchwald has shown that 2-dicyclohexylphosphanyl-2′-dimethylaminobiphenyl is an effective ligand for the room temperature coupling of aryl bromides and chlorides with aryl boronic acids.[6] Bei reported that a P$^{\cap}$O compound (Figure 1) is also an effective ligand for this reaction.[7] Additionally, few examples are known where triarylphosphines were used in Suzuki−Miyaura couplings employing aryl chlorides.[8] To determine if the simple addition of a halogen at the ortho position of two of the phenyl rings of PPh_3 could lead to a active catalyst, we have investigated Suzuki−Miyaura coupling reactions mediated by $P(C_6H_5)(2\text{-}C_6H_4Cl)_2/Pd_2(dba)_3$.



(1)

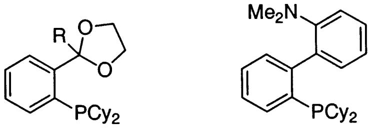
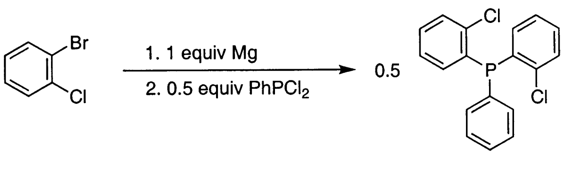


Figure 1. Functionalized phosphine ligands used in coupling reactions.

The chlorinated triphenylphosphine, $P(C_6H_5)(2\text{-}C_6H_4Cl)_2$ (**1**), was synthesized by treatment of 2-bromochlorobenzene with magnesium followed by addition of 0.5 equiv of $PhPCl_2$ (eq 2; 57.5% isolated yield).[9] Compound **1** was isolated as a colorless solid and was stable in air for extended periods of time. The molecular structure of **1** is shown in Figure 2 and crystallographic data and



(2)

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(1) (a) Miyaura, N.; Yanagi, N.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513. (b) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972. (c) Suzuki, A. *Pure Appl. Chem.* **1991**, *63*, 419. (d) Suzuki, A. *Pure Appl. Chem.* **1994**, *66*, 213.

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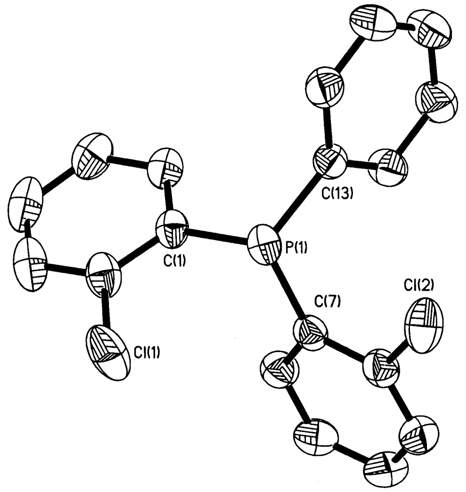

Figure 2. Molecular structure of **1** with thermal ellipsoids at 50% probability. Selected bond distances (Å) and angles (deg): P(1)−C(7) = 1.835(3), P(1)−C(1) = 1.840 (3), P(1)−C(13) = 1.834(3), C(13)−P(1)−C(7) = 101.59(13), C(13)−P(1)−C(1) = 102.08(13), C(7)−P(1)−C(1) = 101.04(13).

Table 1. Crystallographic Data and Refinement for Compound 1

empirical formula	$C_{18}H_{13}Cl_2P$
fw	331.15
temp (K)	298(2)
wavelength (Å)	0.71073
cryst system	monoclinic
space group	$P2(1)/c$
a (Å)	9.3807(18)
b (Å)	9.9582(15)
c (Å)	18.028(4)
α, γ (deg)	90
β (deg)	103.259(19)
vol (Å^3)	1639.2(5)
Z	4
density (calcd) (Mg/m^3)	1.342
abs coeff (mm^{-1})	0.483
F(000)	680
cryst size (mm^3)	0.65 × 0.44 × 0.30
θ range for data collection (deg)	2.23−27.50
index ranges	$-1 \leq h \leq 12$, $-1 \leq k \leq 12$, $-23 \leq l \leq 23$
no. of reflns collected	4956
no. of independent reflns	3770 [R(int) = 0.0286]
completeness to θ = 27.50° (%)	100.0
abs correction	empirical
max and min transmission	0.8771 and 0.7457
refinement method	full-matrix least-squares on F^2
no. of data/restraints/parameters	3770/0/190
goodness-of-fit on F^2	1.011
final R indices [$I > 2\sigma(I)$]	$R1 = 0.0570$, $wR2 = 0.1230$
R indices (all data)	$R1 = 0.1088$, $wR2 = 0.1447$
largest diff peak and hole	0.460 and −0.314 eÅ^{-3}

refinement parameters are listed in Table 1. The cone angle of **1** (183°) is significantly larger than that of PPh_3 (145°) due to the presence of the chlorine atoms in the ortho positions.[10]

The results of coupling reactions employing aryl bromides are summarized in Table 2. Reactions involving electron-deficient and electron-rich aryl bromides were typically complete within 20 h at 25 °C or 1 h at 70 °C. The catalytic system investigated consisted of 1 equiv of aryl halide, 1.1 equiv of aryl-boronic acid, $Pd_2(dba)_3$ (**2**, 1 mol % of Pd based upon aryl halide), **1** (**1**/Pd = 2), THF (1 mL), and KF (3.3 equiv). Increasing the **1**/Pd ratio resulted in decreased yields of the biaryl in room temperature reactions, but reactions carried out at 70 °C were not significantly affected.[11] Decreasing the **1**/Pd ratio to 1 did not adversely affect couplings carried out at 70 °C, but room temperature reactions were sluggish. Sterically hindered substrates were also coupled by using this system, although high yields were only obtained at 70 °C. The order in which **1** was added to the reaction was a critical reaction parameter and was investigated by using the coupling of 4-bromotoluene with phenyl boronic acid as the test case. When **1** was added prior to the aryl bromide, yields of room temperature couplings fell significantly (62% after 15 h). Similar reactions carried out at 70 °C were not as dramatically affected (82% conversion). The amount of solvent used in the reaction affected the reaction rate. When 7 mL of THF was used for the coupling of phenylboronic acid with bromobenzene, the coupling reactions were sluggish (<25% conversion). Decreasing the amount of solvent to 1 mL resulted in high yields of the biaryl (>90%). With this amount of solvent, the reactions are visibly heterogeneous; thus, the reactivity of these systems may vary.

The ability to use small amounts of catalyst and still achieve high conversions is a great concern in cross-coupling reactions due to the high cost of metals and ligands. We have investigated various catalyst loadings using the coupling of 4-bromoacetophenone with phenyl boronic acid as a test case. As shown in Table 3, high yields of the biaryl were obtained by using catalyst loadings of as low as 0.01 mol % of Pd (0.005 mol % of $Pd_2(dba)_3$). This corresponds to ∼10 000 turnovers. Reactions with 0.001 mol % of Pd (0.0005 mol % of $Pd_2(dba)_3$) afforded 4-phenylacetophenone in 70% yield (70 °C, 1 h).

Self-coupling of the aryl boronic acid as well as aryl−aryl exchange reactions between Pd−Ar and P−Ar are typical side reactions encountered when triarylphosphine ligands are employed in coupling reactions.[12] When **1** was employed as the supporting ligand, trace amounts of 2-chlorobiphenyls were observed (<0.1% by GC) as the result of aryl−aryl exchange followed by coupling with an aryl boronic acid.[13] The self-coupling of the phenyl boronic acid was not significant when reactions were carried out in the absence of oxygen. The addition of small amounts of air (1 mL) resulted in significant amounts of the self-coupling product. This was consistent with the previous observation that air accelerates this process.[14]

The effect of different mineral bases on this reaction was investigated by using the coupling of 4-bromotoluene with phenyl boronic acid as a test case. Using KF·

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[10] The cone angle of **1** was determined using the method of Coville: Smith, J. M.; Coville, N. J. *Organometallics* **2001**, *20*, 1210.

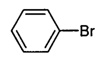
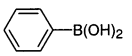
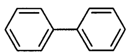
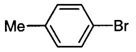
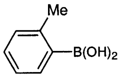
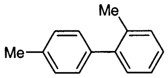
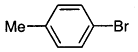
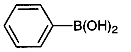
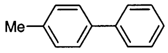
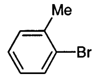
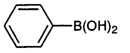
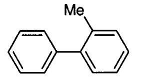
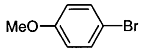
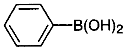
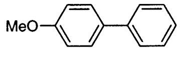
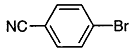
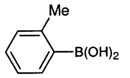
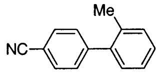
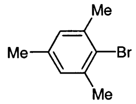
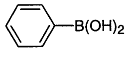
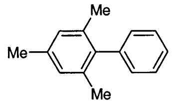
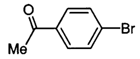
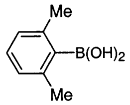
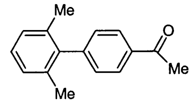
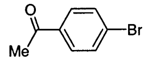
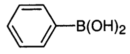
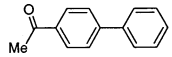
[11] The coupling of bromobenzene with phenyl boronic acid was used as a test reaction for investigating the effect of variation of the **1**/Pd ratio on the coupling reaction. When **1**/Pd = 4, 70% of the bromobenzene was consumed (48 h, 25 °C). Reactions carried out at 70 °C afforded 90% conversion. Reducing the ratio (**1**/Pd = 1) resulted in 41% consumption of bromobenzene (48 h, 25 °C). Reactions carried out at 70 °C afforded 84% conversion.

[12] (a) Kong, K. C.; Cheng, C. H. *J. Am. Chem. Soc.* **1991**, *113*, 6313. (b) Marcial, M. M.; Perez, M.; Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346.

[13] O'Keefe, D. F.; Dannock, M. C.; Marcuccio, S. M. *Tetrahedron Lett.* **1992**, *33*, 6679.

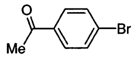
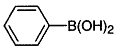
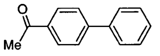
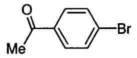
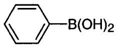
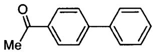
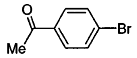
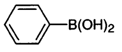
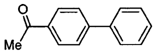
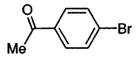
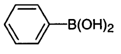
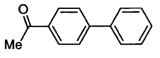
[14] Moreno-Manas, M.; Perez, M.; Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346.

Table 2. Coupling Reactions with Aryl Bromides[a]

#	Aryl Bromide	Boronic Acid	Product	% Yield
1				91 (94)
2				86^b $(95)^a$
3				90 (96)
4				86^b $(94)^a$
5				93^b $(93)^a$
6				88 (93)
7				$50^{b,c}$ $(87)^d$
8				$(91)^d$
9				94 (96)

[a] Reactions were stirred at 25 °C for 20 h or 70 °C for 1 h with 1 equiv of aryl bromide, 1.1 equiv of aryl boronic acid, 3.3 equiv of KF, $Pd_2(dba)_3$ (1 mol % Pd), **1** (2 mol %), and THF (1 mL). Yields are based upon isolated material with the value in parentheses referring to reactions at 70 °C; a = heated for 2 h, b = stirred for 30 h, c = GC yield; d = heated for 8 h.

Table 3. Influence of Low Catalyst Loading on the Coupling Reaction[a]

Entry	Aryl Halide	Boronic Acid	Product	Pd (mole %)	Yield
1				1	95
2				0.1	96
3				0.01	94
4				0.001	70^a

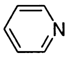
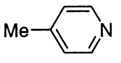
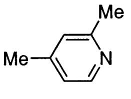
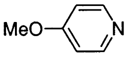
[a] Reactions were heated to 70 °C for 1 h using 1 equiv of aryl bromide, 1.1 equiv of aryl boronic acid, 3.3 equiv of KF, $Pd_2(dba)_3$, **1** (**1**/Pd = 2), and THF (1 mL). Results are based upon isolated material (average of two runs) unless specified. a = GC yield.

$2H_2O$, K_3PO_4, Na_2CO_3, or NaOH as the base did not significantly affect reactions carried out at 70 °C. However, the yields of room temperature reactions were lowered when Na_2CO_3 was used.

While a variety of substrates were coupled with the catalyst system of **1**/**2**, reactions employing aryl bromides containing heteroatoms such as 2-bromopyridine did not proceed to completion. It was possible that the nitrogen donor of the reagent or product could displace **1** from palladium resulting in the formation of pyridine-containing palladium compounds. Similar complexes have been reported by Nolan to be much less active in coupling reactions.[15] To probe this further, we investigated how easily **1** was displaced from a discrete palladium complex, $PdCl_2(P(C_6H_5)(2\text{-}C_6H_4Cl)_2)_2$ (**3**).[16] While no displacement of **1** was observed upon addition of excess 2-bromopyridine, benzonitrile, 4-bromobenzonitrile, 4-chlorobenzonitrile, or 2-acetopyridine, the addition of pyridine, 4-phenylpyridine, 4-methylpyridine, 2,4-dimethylpyridine, and 4-methoxypyridine displaced a significant amount of **1** from Pd (Table 4).[17] These data suggested that a possible reason for the reduced activity of **1**/**2** toward heteroaromatic systems could stem from the formation of L_nPd (L = pyridine-containing ligand) species.

Table 4. Treatment of 3 with Nitrogen Donors

$$\mathbf{3} \xrightarrow{2\,L} L_2PdCl_2 + 2\text{ equiv } \mathbf{1}$$

entry	L	equiv L	% **1** displaced
1		2	41
2		2	44
3		2	43
4		2	43

While aryl bromides and aryl iodides are the typical substrates used in Suzuki–Miyaura couplings, aryl chlorides are attractive substrates. The results of the coupling reactions involving aryl chlorides are summarized in Table 5. While aryl bromides were coupled by using a **1**/Pd ratio of 2, reactions employing aryl chlorides required slight heating and a **1**/Pd ratio of 4 for high yields of the biaryl. Electron-deficient aryl chlorides such as 4-chloroacetophenone and 4-chlorobenzonitrile are effectively coupled with phenyl boronic acid at 90 °C.[18] This process was also tolerant of ortho substituents as evidenced by the successful coupling of *o*-tolyl boronic acid with 4-chloroacetophenone and 4-chlorobenzonitrile. The sluggish reactivity of **1**/**2** toward deactivated aryl chlorides was presumably due to the weaker donor ability of **1** resulting in reduced electron density on palladium.

While **1**/**2** was successful in catalyzing the coupling reactions, the precise role of the chlorine substituent in **1** was not known. The reduced basicity of the phosphine due to the presence of the electron-withdrawing chlorine atoms and the larger cone angle could facilitate the formation of a coordinatively unsaturated palladium species that would promote the initial oxidative addition reaction. This process could be aided by intramolecular coordination of one of the chlorines to palladium. Such coordination of ortho-halogenated aryl

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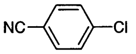
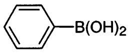
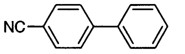
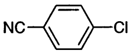
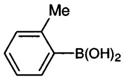
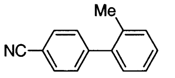
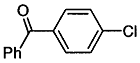
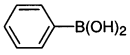
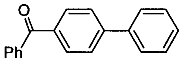
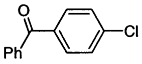
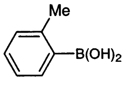
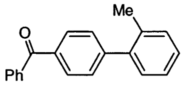
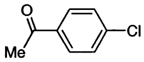
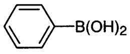
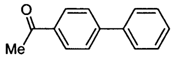
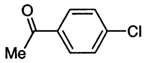
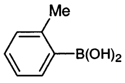
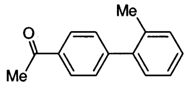
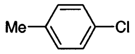
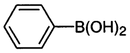
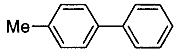
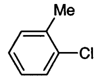
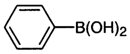
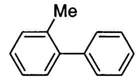
(15) Grasa, G. A.; Hillier, A. C.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 1077.

(16) We have recently reported that various monodentate phosphine and bidentate nitrogen-containing ligands (2,2′-bipyridine, 4,4′-dinonyl-2,2′-bipyridine, and 1,10-phenanthroline) readily displace **1** from **3**: Stone, J. J.; Stockland, R. A., Jr.; Rath, N. P. *Inorg. Chim. Acta.* In press.

(17) Using 20 equiv of 2,4-dimethyl pyridine or 4-phenylpyridine (test cases) resulted in almost quantitative (>95%) displacement of **1** from palladium.

(18) There is no evidence for coupling of the chloride of the ligand under the conditions used.

Table 5. Coupling Reactions Involving Aryl Chlorides[a]

#	Aryl Chloride	Boronic Acid	Product	% Yield
1				89
2				92
3				95
4				90
5				90
6				92
7				57[a]
8				50[a]

[a] Reactions were heated to 90 °C for 30 h with 1 equiv of aryl chloride, 1.1 equiv of aryl boronic acid, 3.3 equiv of KF, $Pd_2(dba)_3$ (1 mol % Pd), **1** (4 mol %), and THF (1 mL). Yields are based upon isolated material (average of two runs) unless specified. a = GC yield.

groups is known.[19] An additional possibility entails intramolecular oxidative addition of the C_6H_4-Cl bond across Pd to generate a four-membered palladacycle that catalyzes the reaction.[20]

In summary, we have outlined a system for the coupling of aryl bromides and chlorides with arylboronic acids using a chlorinated triarylphosphine as the supporting ligand. While the precise role of the chlorine substituent of **1** is not known, this work demonstrates that halogenated phosphine compounds can be successfully used as supporting ligands in the palladium-mediated coupling of aryl boronic acids with aryl halides. Furthermore, the ease in which **1** is displaced from palladium suggests that **1** may be an attractive alternative to PPh_3 in reactions where loss of a phosphine is a critical step. Work is currently underway to determine the effectiveness of **1** as well as other chlorinated phosphine ligands such as $PCy_2(2\text{-}C_6H_4Cl)$ in metal-catalyzed transformations.

Experimental Section

General Considerations. All experiments were carried out under an atmosphere of nitrogen with a Schlenk line or glovebox. The boronic acids, KF, and phenyldichlorophosphine were purchased from Aldrich and used as received. The aryl halides were dried and purified prior to use. $Pd_2(dba)_3$ was prepared as described in the literature.[21] THF was dried over sodium and distilled under nitrogen. Diethyl ether and hexane were dried by passage through a Grubbs-type solvent purification system.[22] Yields were determined based upon isolated material and relative to the amount of starting aryl halide. Elemental analyses were performed by Midwest Analytics. NMR spectra were recorded on a Bruker Avance-300 MHz spectrometer at 25 °C; chemical shifts are reported relative to residual solvent resonances (^1H and ^{13}C). ^{31}P NMR spectra were referenced with external 85% H_3PO_4 (0 ppm). Quantitative ^{31}P NMR spectra were obtained with use of the inverse-gated pulse program with a recycle delay of 30 s.

Synthesis of $P(C_6H_5)(2\text{-}C_6H_4Cl)_2$ (1).[7] A round-bottom flask was charged with Mg (1.48 g, 60.9 mmol) and an iodide crystal. 2-Bromochlorobenzene (13.0 g, 68.0 mmol; dissolved in ether (100 mL)) was added dropwise. The reaction proceeded rapidly and was gently warmed to maintain reflux. Once all the magnesium was consumed, $PPhCl_2$ (5.37 g, 30.0 mmol; dissolved in ether (20 mL)) was added dropwise with vigorous stirring. After aqueous workup, **1** was separated from the residue by distillation (220 °C) under vacuum (0.2 mmHg). Compound **1** was recrystallized from ethanol and dried in vacuo overnight affording 5.71 g (57.5%) of a colorless solid. Anal. Calcd for $C_{18}H_{13}Cl_2P$: C, 65.27; H, 3.93. Found: C, 64.97; H, 4.00. ^1H NMR ($CDCl_3$, 25 °C): δ 6.89−7.5 (m 13H). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 25 °C): −16.7 (s).

Molecular Structure Determination of 1. X-ray quality crystals were grown by slow evaporation of a diethyl ether solution containing **1**. A suitable sample was selected, mounted, and optically centered. Data collection was performed with a Bruker P-4 diffractometer with Mo radiation Kα (λ = 0.71073 Å). 3770 independent reflections were collected over the range of $2\theta = 2.50-55.00°$. The positions and anisotropic thermal parameters of the non-hydrogen atoms were refined on F^2 with use of direct methods with the SHELXTL97 package using 190 parameters yielding $R = 0.0570$. The hydrogen atoms were placed in calculated positions.

General Procedure for the Coupling Reaction. Method A (aryl bromides): A flask was charged in air with arylboronic acid, KF, $Pd_2(dba)_3$ (0.0029 g, 3.17 μmol), and the aryl halide. The flask was evacuated and refilled with nitrogen, and THF (0.5 mL) was added by syringe. After the mixture was stirred for 10 min, **1** (0.0042 g, 12.6 μmol, dissolved in 0.5 mL of THF) was added by syringe. The reaction was stirred at the desired temperature under nitrogen until GC analysis revealed the consumption of the aryl halide. The reaction mixture was diluted with 30 mL of ether and washed with dilute NaOH (1 M), dilute HCl (1 M), and water. After drying over $MgSO_4$, the solvent was removed under vacuum and the biaryl purified by column chromatography on silica. **Method B (aryl chlorides):** The same as method A with the exception that **1** (0.0084 g, 25.4 μmol, 4 mol %) was added in the air prior to evacuation and addition of the solvent (THF, 1.0 mL).

Synthesis of Biphenyl. **Method A:** The general procedure was followed with bromobenzene (0.100 g, 0.64 mmol), phenyl boronic acid (0.086 g, 0.71 mmol), and KF (0.12 g, 2.1 mmol). After the mixture was stirred at 25 °C for 20 h, workup and purification of the residue by column chromatography (silica gel; hexane) afforded 0.090 g (91%) of biphenyl as a colorless solid. Reactions carried out at 70 °C (1 h) afforded 0.093 g (94%). The formation of biphenyl was confirmed by comparison of the ^1H and ^{13}C NMR spectra of the purified material with an authentic sample (Aldrich).

Synthesis of 2-methylbiphenyl. Method A: The general procedure was followed with 2-bromotoluene (0.11 g, 0.64 mmol), phenylboronic acid (0.086 g, 0.71 mmol), and KF (0.12 g, 2.1 mmol). After the mixture was stirred at 25 °C for 30 h,

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[19] (a) Lahuerta, P.; Martinez, R.; Sanz, F.; Cantarero, A.; Torrens, F. *J. Chem. Res.* **1988**, *22*, 261. (b) Estevan, F.; Garcia-Bemabe, A.; Garcia-Granda, S.; Lahuerta, P.; Moreno, E.; Perez-Prieto, J.; Sanau, M.; Ubeda, M. A. *J. Chem. Soc., Dalton Trans.* **1999**, 3493. (c) Burk, M. J.; Crabtree, R. H.; Holt, E. M. *J. Organomet. Chem.* **1988**, *341*, 495.

[20] Dupont, J.; Pfeffer, M.; Spencer, J. *Eur. J. Inorg. Chem.* **2001**, 1917.

[21] Hegedus, L. Palladium in Organic Synthesis. In *Organometallics in Synthesis*; Schlosser, M., Ed.; Wiley and & Sons: Chichester, England, 1994; p 448.

[22] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

workup and purification of the residue by column chromatography (silica gel; hexane) afforded 0.093 g (86%) of 2-methylbiphenyl. Reactions carried out at 70 °C (2 h) yielded 0.102 g (94%). The formation of 2-methylbiphenyl was confirmed by ^{1}H and ^{13}C NMR spectroscopy.[7]

Synthesis of 4-Methylbiphenyl. Method A: The general procedure was followed with 4-bromotoluene (0.11 g, 0.64 mmol), phenylboronic acid (0.086 g, 0.71 mmol), and KF (0.12 g, 2.1 mmol). After the mixture was stirred at 25 °C for 20 h, workup and purification of the residue by column chromatography (silica gel; hexane) afforded 0.097 g (90%) of 4-methylbiphenyl. Reactions carried out at 70 °C (1 h) afforded 0.104 g (96%). The formation of 4-methylbiphenyl was confirmed by ^{1}H and ^{13}C NMR spectroscopy.[23]

Synthesis of 4-Phenylanisole. Method A: The general procedure was followed with 4-bromoanisole (80.3 μL, 0.64 mmol), phenylboronic acid (0.086 g, 0.71 mmol), and KF (0.12 g, 2.1 mmol). After the mixture was stirred at 25 °C for 30 h, workup and purification of the residue by column chromatography (silica gel; 15% ethyl acetate/hexane) afforded 0.11 g (93%) of 4-phenylanisole. Reactions carried out at 70 °C (1 h) yielded 0.11 g (93%). The formation of 4-phenylanisole was confirmed by ^{1}H and ^{13}C NMR spectroscopy.[23]

Synthesis of 4-Acetylbiphenyl. Method A: The general procedure was followed with 4-bromoacetophenone (0.127 g, 0.65 mmol), phenylboronic acid (0.086 g, 0.71 mmol), and KF (0.12 g, 2.1 mmol). After the mixture was stirred at 25 °C for 20 h, workup and purification of the residue by column chromatography (silica gel; 5% ethyl acetate/hexane) afforded 0.118 g (94%) of 4-acetylbiphenyl. Reactions carried out at 70 °C (1 h) yielded 0.120 g (96%). **Method B:** The general procedure was followed with 4-chloroacetophenone (0.099 g, 0.64 mmol), phenylboronic acid (0.086 g, 0.71 mmol), and KF (0.12 g, 2.1 mmol). After the mixture was stirred at 90 °C for 30 h, workup and purification by column chromatography (silica gel; 5% ethyl acetate/hexane) afforded 0.113 g (90%). The formation of 4-acetylbiphenyl was confirmed by ^{1}H and ^{13}C NMR spectroscopy.[24]

Synthesis of 4-Phenylbenzonitrile. Method B: The general procedure was followed with 4-chlorobenzonitrile (0.091 g, 0.66 mmol), phenylboronic acid (0.086 g, 0.71 mmol), and KF (0.12 g, 2.1 mmol). After the mixture was stirred at 90 °C for 30 h, workup and purification of the residue by column chromatography (silica gel; 5% ethyl acetate/hexane) afforded 0.105 g (89%) of 4-phenylbenzonitrile. The formation of 4-phenylbenzonitrile was confirmed by ^{1}H and ^{13}C NMR spectroscopy.[6c]

Synthesis of 2,4′-Dimethylbiphenyl. Method A: The general procedure was followed with 4-bromotoluene (0.109 g, 0.64 mmol), *o*-tolylboronic acid (0.097 g, 0.71 mmol), and KF (0.12 g, 2.1 mmol). After the mixture was stirred at 25 °C for 17 h, workup and purification of the residue by column chromatography (silica gel; hexane) afforded 0.10 g (86%) of 2,4′-dimethylbiphenyl. Reactions carried out at 70 °C (1 h) afforded 0.11 g (95%). The formation of 2,4′-dimethylbiphenyl was confirmed by ^{1}H and ^{13}C NMR spectroscopy.[5]

Synthesis of 2,4,6-Trimethylbiphenyl. Method A: The general procedure was followed with 2- bromomesitylene (0.13 g, 0.65 mmol), phenylboronic acid (0.086 g, 0.71 mmol), and KF (0.12 g, 2.1 mmol). Analysis of the reaction mixture after 24 h by GC revealed 50% conversion. Reactions carried out at 70 °C (8 h) afforded 0.11 g (87%) of 2,4,6-trimethylbiphenyl after workup and purification by column chromatography (silica gel; hexane). The formation of 2,4,6-trimethylbiphenyl was confirmed by ^{1}H and ^{13}C NMR spectroscopy.[25]

Synthesis of 2,6-Dimethyl-4′-acetylbiphenyl. Method A: The general procedure was followed with 4-bromoacetophenone (0.13 g, 0.65 mmol), 2,6-dimethylphenylboronic acid (0.106 g, 0.710 mmol), and KF (0.12 g, 2.1 mmol). After the mixture was stirred at 70 °C for 8 h, workup and purification of the residue by column chromatography (silica gel; 5% ethyl acetate in hexane) afforded 0.133 g (91%) of 2,6-dimethyl-4′-acetylbiphenyl. The formation of 2,6-dimethyl-4′-acetylbiphenyl was confirmed by ^{1}H and ^{13}C NMR spectroscopy.[6c]

Synthesis of 4-Phenylbenzophenone. Method B: The general procedure was followed with 4-chlorobenzophenone (0.14 g, 0.65 mmol), phenylboronic acid (0.086 g, 0.71 mmol), and KF (0.12 g, 2.1 mmol). After the mixture was stirred at 90 °C for 30 h, workup and purification of the residue by column chromatography (silica gel; 10% ethyl acetate in hexane) afforded 0.160 g (95%) of 4-phenylbenzophenone. The identity of the product was confirmed by comparison of the ^{1}H and ^{13}C NMR spectra with an authentic sample (Aldrich).

Synthesis of 2′-Methyl-4-acetylbiphenyl. Method B: The general procedure was followed with 4-chloroacetophenone (0.100 g, 0.65 mmol), *o*-tolylboronic acid (0.097 g, 0.71 mmol), and KF (0.12 g, 2.1 mmol). After the mixture was stirred at 90 °C for 30 h, workup and purification of the residue by column chromatography (silica gel; 10% ethyl acetate in hexane) afforded 0.126 g (92%) of 2′-methyl-4-acetylbiphenyl. The formation of 2′-methyl-4-acetylbiphenyl was confirmed by ^{1}H and ^{13}C NMR spectroscopy.[5]

Synthesis of 2′-Methyl-4-cyanobiphenyl. Method A: The general procedure was followed with 4-bromobenzonitrile (0.12 g, 0.66 mmol), *o*-tolylboronic acid (0.097 g, 0.71 mmol), and KF (0.12 g, 2.1 mmol). After the mixtue was stirred at 25 °C for 20 h, workup and purification of the residue by column chromatography (silica gel; 15% ethyl acetate in hexane) afforded 0.112 g (88%) of 2′-methyl-4-cyanobiphenyl. Reactions carried out at 70 °C afforded 0.118 g (93%). **Method B:** The general procedure was followed with 4-chlorobenzonitrile (0.088 g, 0.64 mmol), *o*-tolylboronic acid (0.097 g, 0.71 mmol), and KF (0.12 g, 2.1 mmol). After the mixture was stirred at 90 °C for 30 h, workup and purification of the residue by column chromatography (silica gel; 15% ethyl acetate in hexane) afforded 0.117 g (92%). The formation of the title compound was confirmed by ^{1}H and ^{13}C NMR spectroscopy.[3f]

Synthesis of 2′-Methyl-4-benzoylbiphenyl. Method B: The general procedure was followed with 4-chlorobenzophenone, (0.14 g, 0.65 mmol), *o*-tolylboronic acid (0.097 g, 0.71 mmol), and KF (0.12 g, 2.1 mmol). After the mixture was stirred at 90 °C for 30 h, workup and purification of the residue by column chromatography (silica gel; 15% ethyl acetate in hexane) afforded 0.159 g (90%) of 2′-methyl-4-benzoylbiphenyl. The formation of 2′-methyl-4-benzoylbiphenyl was confirmed by H and ^{13}C NMR spectroscopy.[3f]

Loading Experiments. Method A was followed with 4-bromoacetophenone (0.127 g, 0.64 mmol), phenylboronic acid (0.086 g, 0.71 mmol), and KF (0.12 g, 2.1 mmol). The appropriate amounts of $Pd_2(dba)_3$ and **1** were added by syringe (solutions were prepared by successive dilution of 0.67 mM THF solutions). After the mixture was stirred at 70 °C for 1 h, workup and purification of the residue by column chromatography (silica gel; 15% ethyl acetate in hexane) afforded 4-acetylbiphenyl.

Displacement of 1 from 3 by Nitrogen-Containing Lewis Bases. An NMR tube was charged with $(CH_3CN)_2PdCl_2$ (0.25 mL of a stock $CDCl_3$ solution; 0.046 M) and **1** (0.25 mL of a stock $CDCl_3$ solution (0.092 M) also containing $P(O)Ph_3$ as an internal standard; 0.092 M). A $^{31}P\{^1H\}$ NMR spectrum was recorded confirming formation of **3**.[26] The Lewis base was added and the tube shaken for 2 min. A $^{31}P\{^1H\}$ NMR spectrum from an inverse gaited decoupling pulse program

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with a recycle delay of 30 s was recorded and the signals for free **1** (δ −16.7 ppm) were integrated vs $P(O)Ph_3$ to provide the percent displacement of **1**.

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Supporting Information Available: Molecular structure information for **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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