Article

Catalysts for Suzuki–Miyaura Coupling Processes: Scope and Studies of the Effect of Ligand Structure

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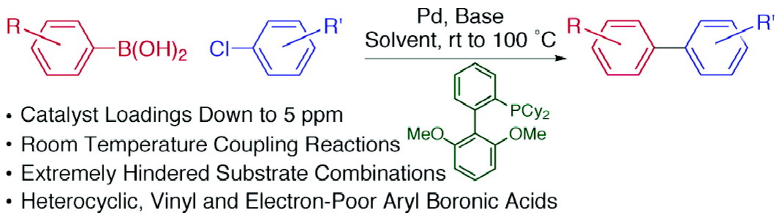

- Catalyst Loadings Down to 5 ppm
- Room Temperature Coupling Reactions
- Extremely Hindered Substrate Combinations
- Heterocyclic, Vinyl and Electron-Poor Aryl Boronic Acids

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Catalysts for Suzuki−Miyaura Coupling Processes: Scope and Studies of the Effect of Ligand Structure

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Abstract: Suzuki−Miyaura coupling reactions of aryl and heteroaryl halides with aryl-, heteroaryl- and vinylboronic acids proceed in very good to excellent yield with the use of 2-(2′,6′-dimethoxybiphenyl)-dicyclohexylphosphine, SPhos (**1**). This ligand confers unprecedented activity for these processes, allowing reactions to be performed at low catalyst levels, to prepare extremely hindered biaryls and to be carried out, in general, for reactions of aryl chlorides at room temperature. Additionally, structural studies of various **1**·Pd complexes are presented along with computational data that help elucidate the efficacy that **1** imparts on Suzuki−Miyaura coupling processes. Moreover, a comparison of the reactions with **1** and with 2-(2′,4′,6′-triisopropylbiphenyl)diphenylphosphine (**2**) is presented that is informative in determining the relative importance of ligand bulk and electron-donating ability in the high activity of catalysts derived from ligands of this type. Further, when the aryl bromide becomes too hindered, an interesting C−H bond functionalization-*cross*-coupling sequence intervenes to provide product in high yield.

In 1979, the seminal paper of Miyaura, Yamada, and Suzuki[1] laid the groundwork for what now is arguably the most important and useful transformation for construction of carbon−carbon bonds in modern day organic chemistry. Although the original paper reported coupling reactions of alkenyl boronates with alkenyl bromides, throughout the past 25 years contributions from myriad research groups[2] have led to vast improvements on what now is known as the Suzuki−Miyaura cross-coupling reaction. Advances have been made in the way of reaction scope, including the use of aryl chlorides[3] as substrates and the ability to conduct couplings at very low catalyst loadings[4] and at room temperature.[5] Moreover, it is now possible to couple hindered substrates,[6] and even asymmetric variations have been reported.[7] Improvements in Suzuki−Miyaura coupling reactions have relied a great deal on the increased reactivity and stability of the metal catalysts by use of increasing efficacious supporting ligands. The most common ligands used today are phosphine-based, although a variety of others, including *N*-heterocyclic carbenes (NHC), have been employed.[5f,h,i,8] Also of great importance are the procedures that utilize so-called "ligandless" conditions.[9] The ability to satisfy the diverse requirements of different Suzuki−Miyaura couplings with a single ligand, however, remains unrealized. Herein, we present a full report of a catalyst system that enables the coupling of heteroaryl-, both electron-rich and -poor aryl-, and vinylboronic acids with very hindered aryl halides and a variety of heteroaryl halides at exceptionally low catalyst loadings.[10] Additionally,

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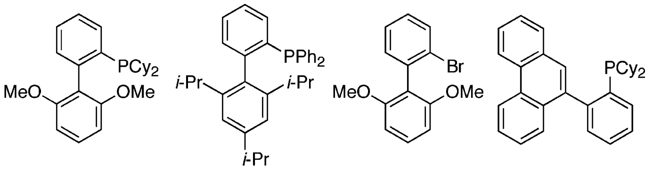
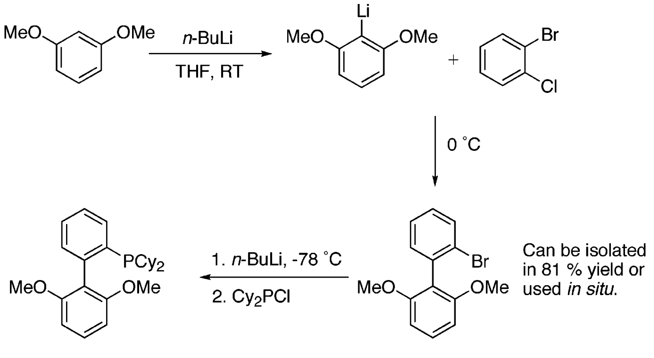


1 **2** **3** **4**

Figure 1. Ligands and a ligand precursor for Suzuki−Miyaura coupling reactions.

Scheme 1. One-Pot Synthesis of 1



1 **3**

we present crystallographic data and computational studies to help explain the efficacy that catalysts based on **1** (SPhos) (Figure 1) impart in Suzuki−Miyaura cross-coupling processes. Further, a simply prepared triarylphosphine, ligand **2**, is described that also demonstrates high activity in the coupling of electron-rich and hindered aryl chloride substrates.

Results

Synthesis of 2-(2′,6′-Dimethoxybiphenyl)dicyclohexylphosphine (1). We have developed a direct and experimentally convenient one-pot protocol for the construction of ligand **1** (Scheme 1), based upon a procedure developed by Schlosser, who had nicely modified our original procedure to provide aryl halides in a simple protocol.[11] Although our previous synthesis of dialkylbiarylphosphine ligands[12] required an aryl halide precursor, the selection of the 1,3-dimethoxybenzene moiety for the bottom (nonphosphine containing) ring offered the advantage that it can be installed by means of a directed metalation. The directed *ortho*-lithiation of 1,3-dimethoxybenzene with *n*-BuLi in THF at room temperature, followed by cooling the reaction mixture to 0 °C, and slow addition of neat 1-bromo-2-chlorobenzene generated 2-bromo-1′,3′-dimethoxybiphenyl (**3**). The latter, produced via a rapid, tandem benzyne condensation−bromine atom transfer sequence, could be isolated in 81% yield. Compound **3**, in THF at −78 °C, could be treated with *n*-BuLi and then chlorodicyclohexylphosphine. However, for expedient access to **1**, **3** was not isolated but was treated sequentially, at −78 °C, with *n*-BuLi and chlorodicyclohexylphosphine, followed by warming the reaction to room temperature. Following workup and crystallization, **1** was produced in 59% overall yield. This new procedure allows for the synthesis of **1** in a considerably shorter reaction time and with an easier isolation procedure (no CuCl is required) than the route used previously to access such ligands.

Suzuki−Miyaura Coupling Reactions of Hindered Substrates. The ability to prepare extremely hindered biaryls via Suzuki−Miyaura coupling reactions has historically proven to be a difficult task. Most challenging are examples with substrates that contain large *ortho*-substituents and/or *ortho,ortho′*-substituents. However, with the use of **1**, the coupling of an aryl bromide that possesses two large *ortho,ortho′*-substituents, 2,4,6-triisopropylbromobenzene, with boronic acids as hindered as 2-biphenylboronic acid proceeded in excellent yield (Table 1, entry 3, 93%). Unfortunately the reaction of 2,4,6-triisopropylbromobenzene and 2,6-dimethylphenylboronic acid with 1.5% $Pd_2(dba)_3$ and 6% **1** at 100 °C for 14 h provided no desired product. Relatively bulky 1-naphthylboronic acid required only 0.1% Pd for its efficient combination with 2,4,6-triisopropylbromobenzene in 12 h to give product in 96% isolated yield (Table 1, entry 2). We previously reported the preparation of biaryls possessing a 2,2′,6,6′ tetrasubstituted pattern with a phenanthrene-based phosphine ligand, **4**.[13] However, this system has several disadvantages, including the necessity of using between 4 and 10% Pd and the fact that **4** is not commercially available. Gratifyingly, the use of ligand **1** allowed for the coupling of 2,6-dimethoxybromobenzene with 2,6-dimethylphenylboronic acid with 3% Pd in 86% isolated yield (Table 1, entry 4). The difficulty of this particular transformation exists not only from the steric encumberance of both the aryl bromide and boronic acid, but also from the very electron-rich nature of the aryl bromide. Additionally, we were able to couple 2-methyl-4,6-di-*tert*-butylbromobenzene with phenyl- and 2-methylphenylboronic acid (Table 1, entries 6 and 7). Although 10% $Pd(OAc)_2$ was required to obtain full conversion of the aryl bromide, only a small amount of arene byproduct was observed, and isolated yields were greater than 80%. Taken together, the results shown in Table 1 represent, to our knowledge, the most hindered couplings of aryl halides and arylboronic acids to date.

Tandem C−H Functionalization/Suzuki−Miyaura Coupling Reactions. In hope of further pushing the limit of the degree of steric hindrance of the aryl bromide that could be successfully coupled, we examined the reaction of 2,4,6-tri-*tert*-butylbromobenzene with phenylboronic acid. We were surprised that only 2% Pd was required to promote full conversion of the aryl bromide. The relatively low quantity of catalyst required was initially puzzling, as 10% Pd was needed

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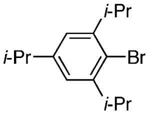
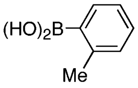
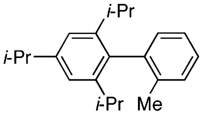
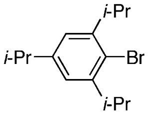
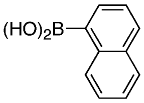
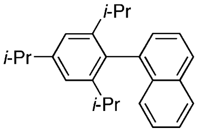
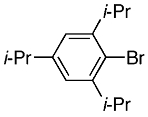
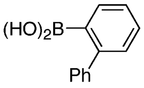
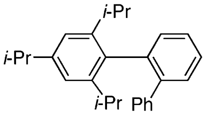
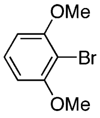
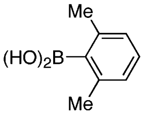
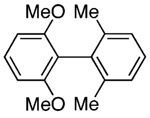
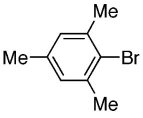
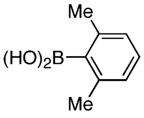
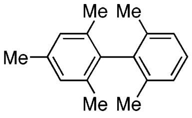
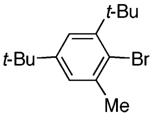
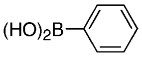
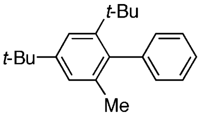
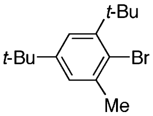
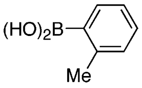
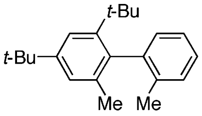
Table 1. Hindered Suzuki−Miyaura Couplings Using Ligand 1[a]

Entry	Halide	Boronic Acid	Product	mol% Pd	Conditions	Yield (%)[b]
1				3 0.1	100 °C, 2 h 100 °C, 24 h	94 95
2				0.1	100 °C, 12 h	96
3				3	100 °C, 18 h	93
4				3	100 °C, 10 h	86
5				4	110 °C, 18 h	82[c]
6				10	110 °C, 18 h	82
7				10	110 °C, 18 h	89

[a] Reaction conditions: 1 equiv of aryl bromide, 2 equiv of boronic acid, 3 equiv of K_3PO_4, toluene (2 mL/mol halide), cat. $Pd_2(dba)_3$, ligand **1**, L:Pd = 2:1. [b] Isolated yield based upon an average of two runs. [c] 4 equiv of K_3PO_4 was used.

for the much less hindered 2-methyl-4,6-di-*tert*-butylbromobenzene. Examination of the ^{1}H NMR spectrum of the product from this reaction indicated that instead of the desired biaryl, the α,α-dimethyl-β-aryl hydrostyrene derivative, **9** (Table 2, entry 1), was produced. More hindered boronic acids, such as 2-methylphenylboronic acid and 2-biphenylboronic acid, also proved to be excellent coupling partners in this type of transformation, with yields >96%. Scheme 2 contains a suggested mechanism for this transformation. Following oxidative addition to the aryl bromide to give **5**, cyclometalation occurs to form a five-membered palladacycle, **6**, via abstraction of one of the hydrogen atoms from the *tert*-butyl group. A mechanism of this type has previously been proposed in the reactions of similar aryl bromides.[14] Selective protonation of the weaker[15] and less hindered sp^3 C−Pd bond of **6** affords the alkyl Pd^{II} species, **7**. This can undergo transmetalation with the boronic acid, **8**. Finally, reductive elimination occurs with formation of a carbon−carbon bond to **9** with concomitant regeneration of LPd(0). One possible reason for the efficiency of this reaction is that **7** lacks β-hydrogens and therefore few side reactions are available to it. Further work is ongoing on our laboratories to investigate the scope of this tandem C−H activation/cross-coupling reaction.

Suzuki−Miyaura Coupling Reactions at Low Catalyst Loadings. The need to perform Suzuki−Miyaura coupling reactions at low catalyst loadings exists not only to minimize the amount of palladium and ligand for reasons of cost but as well as to allow for these types of coupling processes to be used on large scale while minimizing the effort required for the removal of palladium from the final product.[16] Using **1**, efficient coupling reactions with quantities of palladium at or below the allowable limit[16] can be achieved. For example, the coupling of 4-*tert*-butylbromobenzene with 2-methylphenylboronic acid using 10 ppm $Pd(OAc)_2$ at 100 °C for 1.5 h provides an 98% isolated yield of product. Using catalyst loadings as low as 10 ppm $Pd(OAc)_2$, the coupling of 4-*tert*-butylbromobenzene with the sterically demanding 2-biphenylboronic acid proceeds in 85% isolated yield in 24 h at 100 °C. These are, of course, very simple processes. However, these results

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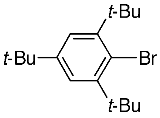
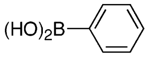
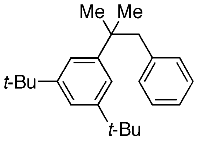
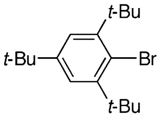
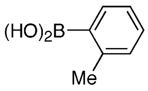
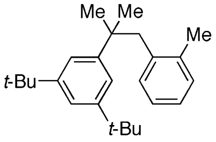
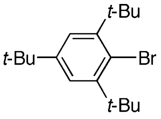
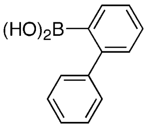
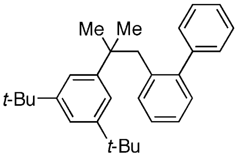
(14) For reviews of C−H activation, see: (a) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879−2932. (b) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698−1712. (c) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211−241.

(15) There is precedent for such chemoselectivity: Cámpora, J.; López, J. A.; Palma, P.; Valerga, P.; Spillner, E.; Carmona, E. *Angew. Chem., Int. Ed.* **1999**, *38*, 147−151.

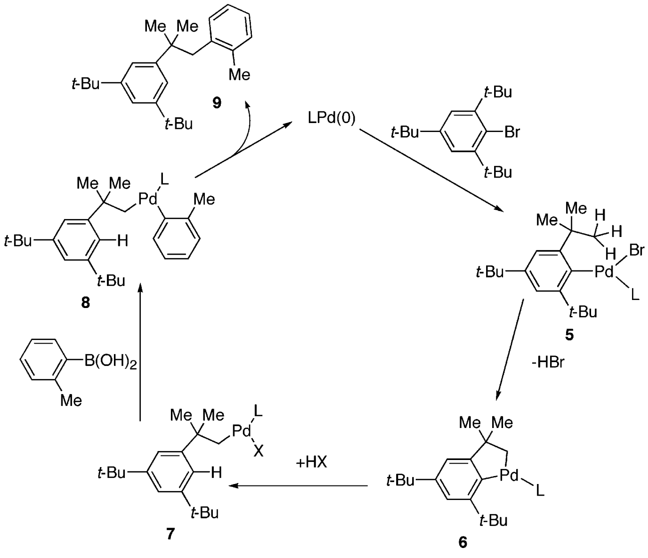
(16) (a) Garrett, C. E.; Prasad, K. *Adv. Synth. Catal.* **2004**, *346*, 889−900. (b) Bien, J. T.; Lane, G. C.; Oberholzer, M. R. *Top. Organomet. Chem.* **2004**, *6*, 263−283.

Table 2. C−H Activation Followed by Coupling with Arylboronic Acids Using Ligand 1[a]

Entry	Halide	Boronic Acid	Product	Conditions	Yield (%)[b]
1				100 °C, 18 h	95
2				100 °C, 18 h	96
3				100 °C, 18 h	99

[a] Reaction conditions: 1 equiv of aryl bromide, 2 equiv of boronic acid, 3 equiv of K_3PO_4, toluene (2 mL/mol halide), 1% $Pd_2(dba)_3$, 4% ligand **1**. [b] Isolated yield based upon an average of two runs.

Scheme 2. Suggested Mechanism of the Tandem C−H Functionalization Suzuki−Miyaura Coupling



represent the smallest amount of palladium used in Suzuki−Miyaura couplings of *unactivated* aryl bromides with boronic acids *aside from phenylboronic acid*. This latter point is important, as we find little degree of extrapolation of results using phenylboronic acid and those obtained with other arylboron derivatives. The coupling of 2,4,6-triisopropylbromobenzene and phenylboronic acid proceeded to 97% isolated yield at 0.01% Pd in 16 h (Table 3, entry 3). However, only 50% conversion of aryl bromide was observed under similar conditions when the catalyst loading was lowered to 0.001% Pd. Additionally, we have achieved the coupling of an unactivated aryl chloride, 4-*n*-butylchlorobenzene, with phenylboronic acid using 50 ppm $Pd(OAc)_2$ or 15 ppm $Pd_2(dba)_3$ at 100 °C to give 96% and 93% isolated yield of biaryl, respectively (Table 3, entry 4).

Suzuki−Miyaura Coupling Reactions Using Aryl Pinacol Boronate Esters. Although Suzuki−Miyaura coupling reactions are among the most mild and efficient methods to construct carbon−carbon bonds, a drawback of using boronic acids is the structural ambiguity associated with them. Under anhydrous conditions, boronic acids dimerize and trimerize to form anhydrides and boroxines.[17] Under normal laboratory conditions, a mixture of monomer, dimer, and boroxine exist. This drawback can be overcome by use of boronate esters or trifluoroborate salts,[18] both of which are air- and water-stable and exist only in a monomeric form. Further advantages of boronate esters include the ability to purify them via chromatography and the ability to observe them via gas and liquid chromatography. It is our belief that trace water, either from a hydrated base or through the addition of a small amount of water to the reaction mixture, most likely hydrolyzes the boronate ester either partially or fully to allow for transmetalation to occur efficiently.[19] Table 4 illustrates several examples of Suzuki−Miyaura coupling reactions with aryl boronate esters and aryl- and heteroaryl chlorides that all provide product in excellent isolated yield. For example, the coupling of 2-chloro-*m*-xylene with 3-hydoxyphenylboronic acid was accomplished in 94% isolated yield using 1% $Pd(OAc)_2$ as precatalyst at 100 °C in 30 min (Table 4, entry 2).

Suzuki−Miyaura Coupling Reactions at Room Temperature. Our initial communication describing the activity of **1** included Suzuki−Miyaura couplings at room temperature. Catalyst loadings as low as 0.5% $Pd(OAc)_2$ effected the reaction of *ortho*,*ortho′*-substituted and electron-rich aryl chlorides with *ortho*-substituted boronic acids in very good to excellent yield. Little or no effort was made to minimize the quantity of catalyst that was necessary.

The reason for the efficiency of bulky, electron-rich ligands is oftentimes ascribed to their proclivity to donate electron-density to the intermediate Pd(0) complex to facilitate the rate

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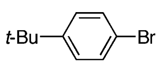
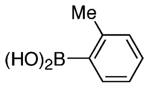
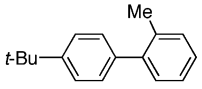
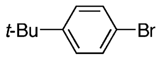
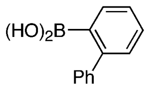
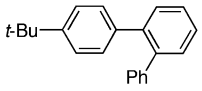
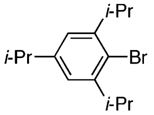
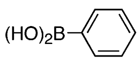
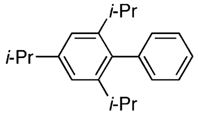
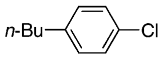
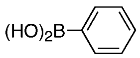
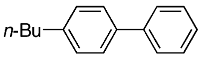
(17) Onak, T. *Organoborane Chemistry*; Academic Press: New York, New York 1975.

(18) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020−3027.

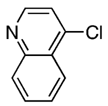
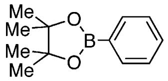
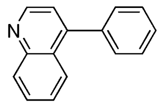
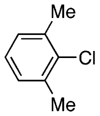
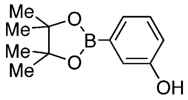
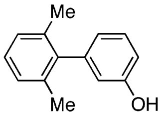
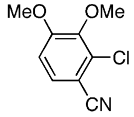
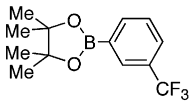
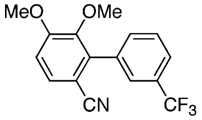
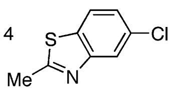
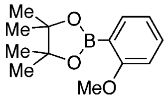
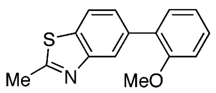
(19) We were under the impression that studies were conducted demonstrating the necessity of water for the efficient coupling of aryl boronate esters. We were, however, unable to locate any reports directly illustrating this theory.

Table 3. Suzuki−Miyaura Coupling at Low Catalyst Loadings Using Ligand 1[a]

Entry	Halide	Boronic Acid	Product	mol% Pd	Conditions	Yield (%)[b]
1				0.001 0.0005	110 °C, 1.5 h 100 °C, 24 h	98 89
2				0.001	100 °C, 24 h	85[c]
3				0.01	100 °C, 16 h	97[d]
4				0.005 0.003	100 °C, 10 h 100 °C, 24 h	96 93[d,e]

[a] Reaction conditions: 1 equiv of aryl halide, 1.5 equiv of boronic acid, 2 equiv of K_3PO_4, toluene (2 mL/mmol halide), cat. $Pd(OAc)_2$, ligand **1**, L:Pd = 2.5:1. [b] Isolated yield based upon an average of two runs. [c] L:Pd = 2:1. [d] Cat. Pd_2dba_3 used with L:Pd = 2:1. [e] $K_3PO_4{\cdot}H_2O$ used as base.

Table 4. Suzuki−Miyaura Couplings of Pinacol Aryl Boronates Using Ligand 1[a]

Entry	Halide	Pinacol Boronate Ester	Product	Conditions	Yield (%)[b]
1				100 °C, 0.5 h	88
2				100 °C, 0.5 h	94
3				100 °C, 0.5 h	94
4				RT, 24 h	91[c]

[a] Reaction conditions: 1 equiv of aryl chloride, 1.5 equiv of boronate ester, 2 equiv of K_3PO_4, toluene:H_2O (10:1) (2 mL/mol of halide), 1% $Pd(OAc)_2$, 2% ligand **1**. [b] Isolated yield based upon an average of two runs. [c] 1% $Pd(OAc)_2$ and 1% ligand **1** in THF:H_2O (10:1) was used.

of oxidative addition. Alternately, it has been proposed that these ligands cause a reasonable amount of highly reactive L_1Pd species to form.[20] To decipher the relative contribution of these two factors, we prepared the triarylphosphine **2**.[21] Ligand **2** was then employed in various coupling processes, and it was ascertained that it was an excellent supporting ligand for Suzuki−Miyaura coupling reactions, particularly those carried out at room temperature.

There have been several accounts of Suzuki−Miyaura coupling reactions of aryl chlorides at room temperature.[5h,i,6,22] Despite the success that has been realized, limitations still exist. For example, in the report of Nolan, NaO*t*-Bu was required as base, and slow addition of the aryl chloride was necessary as dehalogenation was observed as a side reaction.[5i] In a particularly impressive recent paper from Glorius, the use of KOH (from KO*t*-Bu and water) was required for boronic acids possessing two *o*-methyl substituents.[6] In this work, the scope of formation of tetra*ortho*-substituted biaryls was expanded to the highest level reported to date. Fu was able to employ KF, a milder base, in his work; only activated aryl chlorides (heterocyclic and electron-poor), however, were used.[22] Our reaction conditions using **2** allow the use of a mild base, $K_3PO_4{\cdot}H_2O$, very hindered boronic acids, and electron-rich aryl chlorides, without slow addition of any reagents. The generality of Suzuki−Miyaura couplings using this ligand is demonstrated by the results shown in Table 5. Catalyst levels as low at 0.05% $Pd(OAc)_2$ effected the reaction of 3-chlorobenzonitrile with 2-biphenylboronic acid in 93% isolated yield (Table 5, entry

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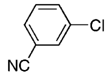
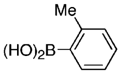
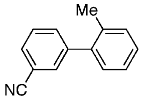
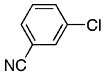
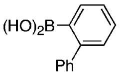
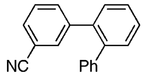
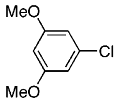
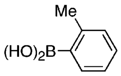
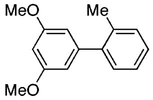
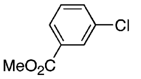
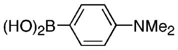
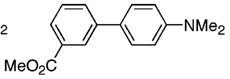
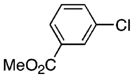
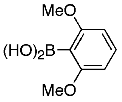
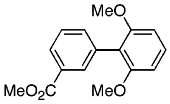
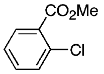
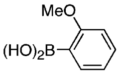
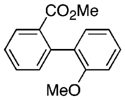
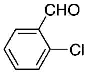
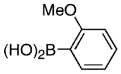
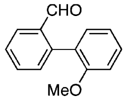
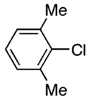
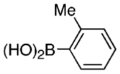
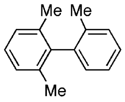
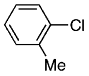
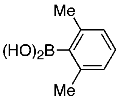
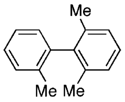
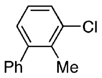
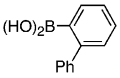
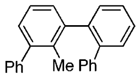
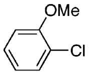
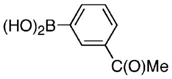
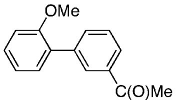
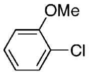
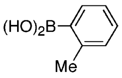
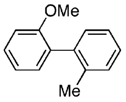
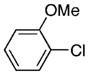
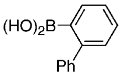
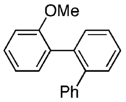
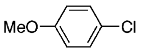
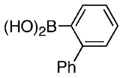
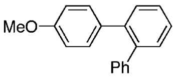
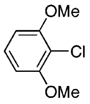
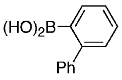
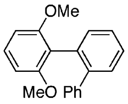
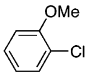
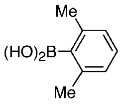
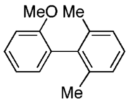
(20) (a) Paul, F.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969−5970. (b) Hartwig, J. F.; Paul, F. *J. Am. Chem. Soc.* **1995**, *117*, 5373−5374. (c) Galardon, E.; Ramdeehul, S.; Brown, J. M.; Cowley, A.; Hii, K. K.; Jutand, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1760−1763. (d) Hills, I. D.; Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5749−5752. (e) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 13978−13980.

(21) Liu, S.-H.; Choi, M. J.; Fu, G. C. *Chem. Commun.* **2001**, 2408−2409.

(22) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028.

Table 5. Suzuki−Miyaura Couplings of Aryl Chlorides at Room Temperature Using Ligand 2[a]

Entry	Halide	Boronic Acid	Product	mol% Pd	Yield (%)[b]
1				0.05	94
2				0.05	93
3				0.1	97
4				0.5	97
5				0.5	98[c]
6				0.5	98
7				0.5	98
8				0.5	94
9				0.5	93[c]
10				0.25	99

Entry	Halide	Boronic Acid	Product	mol% Pd	T (°C)	Yield (%)[b]
11				0.5	RT	89
12				0.25	RT	97
13				0.25	RT	97
14				0.25	40	93
15				0.5	40	99
16				0.5	40	98[c]

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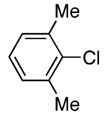
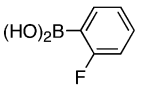
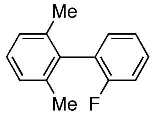
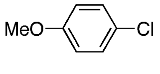
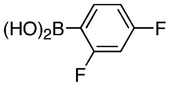
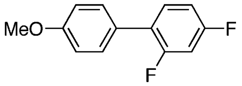
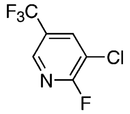
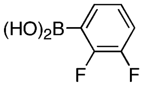
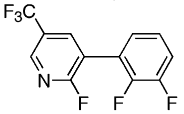
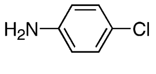
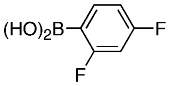
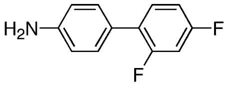
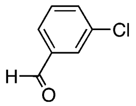
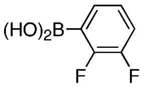
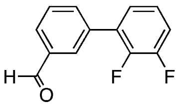
[a] Reaction conditions: 1 equiv of aryl chloride, 1.5 equiv of boronic acid, 3 equiv of $K_3PO_4 \cdot H_2O$, THF (1 mL/mmol of halide), cat. $Pd(OAc)_2$, ligand **2**, L:Pd = 3.1. [b] Isolated yield based upon an average of two runs. [c] 3 equiv of boronic acid was used.

Table 6. Suzuki−Miyaura Couplings of Mono- and Difluorophenylboronic Acids Using Ligand 1[a]

Entry	Halide	Boronic Acid	Product	mol% Pd	Conditions	Yield (%)[b]
1				0.5	90 °C, 1.5 h	91
2				0.5	80 °C, 16 h	99
3				1	90 °C, 16 h	96
4				1	80 °C, 10 h	96
5				0.5	90 °C, 3 h	80

[a] Reaction conditions: 1 equiv of aryl chloride, 1.5 equiv of boronic acid, 2 equiv of K_3PO_4, toluene (2 mL/mol of halide), cat. $Pd(OAc)_2$, ligand **1**, L:Pd = 2:1. [b] Isolated yield based upon an average of two runs.

2). Additionally, the formation of previously described 2,2′,6-trimethylbiphenyl can be achieved by the coupling of 2-chloro-*m*-xylene with *o*-tolylboronic acid or 2-chlorotoluene with 2,6-dimethylphenylboronic acid using 0.5% $Pd(OAc)_2$ in 94% and 93% isolated yields, respectively (Table 5, entries 8 and 9). In comparison, the reaction of 2-chloro-*m*-xylene with *o*-tolylboronic acid described by Nolan proceeded in 79% isolated yield with 2% of the preformed Pd complex,[5i] while Glorius used 3% Pd and a reaction temperature of 50 °C to give the product in 85% yield.[5h] Although most coupling reactions using 2-substituted boronic acids proceeded at room temperature in excellent yield with aryl chlorides, a reaction temperature of 40 °C was required for certain electron-rich aryl chlorides (Table 5, entries 14−16). This higher temperature is most likely necessary as oxidative addition is much slower for aryl chlorides that possess an electron donation group in the 2- or 4- positions of the arene relative to the chloride. For example, the coupling of very electron rich 2,6-dimethoxychlorobenzene with 2-biphenylboronic acid proceeded at 40 °C in 99% isolated yield using 0.5% $Pd(OAc)_2$ (Table 5, entry 15).

We believe that these results illustrate that the primary factor for the efficient Suzuki−Miyaura coupling of unactivated aryl chloride substrates is the ability of biaryl-derived phosphine ligands to maximize the concentration of monoligated palladium species within the catalytic cycle. Ligand **2**, which is nearly isostructural, but substantially less electron-rich than **1**, promotes the reaction of hindered substrates at low temperatures (≤40 °C) and relatively low catalyst loadings (down to 0.25% Pd) in excellent yields. In these studies, **1** is superior to **2** as the supporting ligand for all reactions described. As the cost of preparing **2** should be considerably less than that for **1**, **2** may have some advantage for large-scale reactions in cases where the procedure can be optimized to reduce the amount of palladium required. However, in most academic and industrial research laboratories, this cost differential is of minimal importance.

Suzuki−Miyaura Coupling Reactions of Electron-Deficient Arylboronic Acids. Our attention next shifted to reactions of mono- and difluoroarylboronic acids. The interest in the Suzuki−Miyaura coupling of these boronic acids exists, in part, because of the difficulty of coupling electron-poor boronic acids.[23] Fluorinated aromatic rings are often used in medicinally active compounds in which a fluorine is substituted for a hydrogen to help block oxidation of the aromatic ring,[24] alter routes of metabolism,[25] and increase lipophilicity which affects drug distribution.[26] Fortunately, nearly all combinations of *n*-fluorophenylboronic acids, where $n = 1-5$, are commercially available.[27] Despite the availability of this class of boronic acids, there exist only a few examples of Suzuki−Miyaura coupling reactions, all of which are with aryl bromides or iodides.[28] A particularly challenging example, the coupling of 2,4-difluorophenylboronic acid with 2,6-dimethylbromobenzene, has previously been reported.[28b] This reaction proceeded in 60% isolated yield; however, a reaction temperature of 130 °C and the use of a noncommercially available ligand were required. In our present work, a wide variety of substrates, including electron-rich, -poor, and heterocyclic aryl chlorides, were coupled with fluorophenyl- and difluorophenylboronic acids in very good to excellent yields. Of particular note is the reaction of 4-chloroaniline with 2,4-difluorophenylboronic acid, which

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(23) Electron-poor arylboronic acids are less nucleophilic and undergo transmetalation at a slower rate than electron-neutral and -rich arylboronic acids. Additionally, electron-poor boronic acids are prone to homocoupling. For a recent report, see: Wong, M. S.; Zhang, X. L. *Tetrahedron Lett.* **2001**, *42*, 4087−4089. Electron-poor arylboronic acids are more susceptible to metal-catalyzed protodeboronation. For a report, see: Kuivila, H. G.; Reuwer, J. F.; Mangravite, J. A. *J. Am. Chem. Soc.* **1964**, *86*, 2666−2670.

(24) For an example of aryl fluorides blocking oxidation, see: Rosenblum, S. B.; Huynh, T.; Afonso, A.; Davis, H. R., Jr.; Yumibe, N.; Clader, J. W.; Burnett, D. A. *J. Med. Chem.* **1998**, *41*, 97−980.

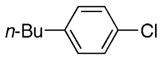
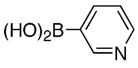
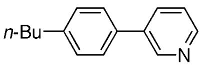
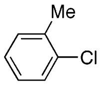
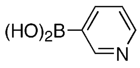
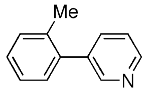
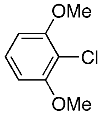
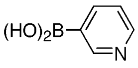
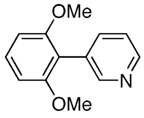
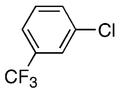
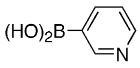
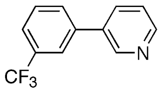
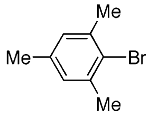
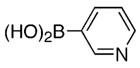
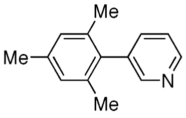
(25) (a) Bush, I. E.; Mahesh, V. B. *Biochem. J.* **1964**, *93*, 236−255. (b) Abel, S. M.; Back. D. J.; Maggs, J. L.; Park, B. K. *J. Steroid Biochem. Mol. Biol.* **1993**, *46*, 833−839.

(26) Park, B. K.; Kitteringham, N. R. *Drug Metab. Rev.* **1994**, *26*, 605−643.

(27) Prices from Sigma-Aldrich Co.: 2,3-difluorophenylboronic acid, \$52.40/5 g; 4-fluorophenylboronic acid, \$16.20/g.

(28) For examples of Suzuki−Miyaura couplings with 2,4-difluorophenylboronic acid, see: (a) Thiemann, T.; Umeno, K.; Wang, J.; Tabuchi, Y.; Arima, K.; Wantabe, M.; Tanaka, Y.; Gorohmaru, H.; Mataka, S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2090−2110. (b) Feuerstein, M.; Berthiol, F.; Doucet, H.; Santelli, M. *Synlett* **2002**, *11*, 1807−1810.

Table 7. Suzuki−Miyaura Couplings of 3-Pyridylboronic Acid Using Ligand 1[a]

Entry	Halide	Boronic Acid	Product	mol% Pd	Conditions	Yield (%)[b]
1				2	100 °C, 15 h	96
2				2	100°C, 20 h	88
3				3	100 °C, 24 h	81
4				2	90 °C, 24 h	87
5				2	90 °C, 24 h	83

[a] Reaction conditions: 1 equiv of aryl chloride, 1.5 equiv of boronic acid, 2 equiv of K_3PO_4, 1-butanol (2 mL/mmol of halide), cat. Pd_2dba_3, ligand **1**, L:Pd = 2:1.

proceeded at 80 °C to give a 96% isolated yield of product (Table 6, entry 4). Although the Suzuki−Miyaura coupling of 4-chloroaniline has been previously reported,[29] all accounts only use phenylboronic acid as the coupling partner. Hindered aryl chlorides also proved to be excellent coupling partners with 2-fluorophenylboronic acid (Table 6, entry 1). The reaction with 2-chloro-*m*-xylene gives a 91% isolated yield of product using 0.5 mol % $Pd(OAc)_2$ in only 90 min. Additionally, the coupling of a heteroaryl chloride, 2-fluoro-3-chloro-5-trifluoromethylpyridine, with 2,3-difluorophenylboronic acid provided a highly fluorinated heteroaromatic compound in 96% isolated yield (Table 6, entry 3). Disappointingly, reactions using 2,6-difluorophenylboronic acid and 2,4,6-trifluorophenylboronic acid did not proceed efficiently.

We recently reported the coupling of potassium 3-pyridyltrifluoroborate with a variety of aryl- and heteroaryl chlorides using **1**.[30] However, we were unable to efficiently couple this trifluoroborate salt with aryl chlorides possessing one or more *o*-methyl substituents. Since an improved means for the preparation of 3-pyridylboronic acid and/or the corresponding boroxine has been recently reported,[31] the coupling of 3-pyridylboronic acid with aryl chlorides was attempted. Using conditions similar to what we reported for the coupling of potassium 3-pyridyltrifluoroborate (i.e., 3% $Pd(OAc)_2$, K_2CO_3, ethanol at reflux), low conversion (<50%) of aryl chloride was observed. However, upon switching from ethanol to 1-butanol and increasing the reaction temperature to 90−100 °C, the coupling of 4-*n*-butylchlorobenzene with 3-pyridylboronic acid (Table 7, entry 1) produced the desired product in 96% yield. The higher temperature required for the coupling of 3-pyridylboronic acid is presumably due to the less nucleophilic nature of the boronic acid relative to the trifluoroborate salt.[32] Thus the transmetalation of the ligated (aryl)PdCl complex is slowed,[33] which therefore slows down the entire catalytic cycle, as transmetalation is usually the rate-limiting step for Suzuki−Miyaura couplings. Hindered aryl chlorides, such as 2-chlorotoluene and 2,6-dimethoxychlorobenzene (Table 7, entries 2 and 3), were also excellent coupling partners, giving product in isolated yields greater than 80%. The attempted combination of the more hindered 2-chloro-*m*-xylene with 3-pyridylboronic acid proved to be more difficult and 30% of *m*-xylene, from competitive reduction of the aryl halide, was observed. This limitation could be partially overcome as evidenced by the transformation of 2-bromomesitylene, which could be carried out at 90 °C (Table 7, entry 5). To the best of our knowledge, there are no other examples of the coupling of 3-pyridylboronic acid with aryl halides possessing an *ortho*,*ortho′*-substitution pattern nor any examples of its successful combination with unactivated aryl chlorides.

Usually electron-deficient arylboronic acids (e.g., *n*-fluorophenyl and 3-pyridyl) tend to be difficult coupling partners, as they are less nucleophilic and, hence, transmetalate more slowly than electron−neutral analogues. Although we have no direct evidence, we believe that the ability of **1** to maximize the concentration of a LPd(aryl) chloride species rather an a L_2Pd(aryl) chloride species is the key for successful coupling of these types of boronic acids. In reactions with poorly nucleophilic arylboronic acids, transmetalation may well be the rate-limiting step in Suzuki−Miyaura coupling reactions. Transmetalation processes are very sensitive to steric factors and should occur much more rapidly to a LPd(aryl) chloride intermediate than to a L'_2Pd(aryl) chloride intermediate, even when L′ is smaller than L. A more detailed discussion

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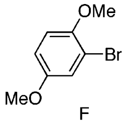
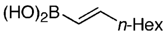
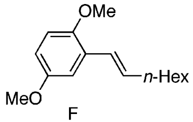
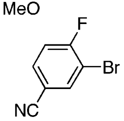
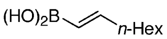
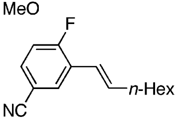
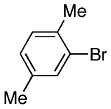
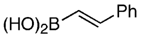
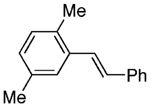
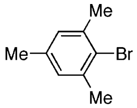
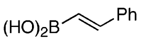
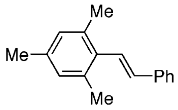
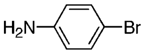
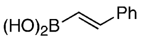
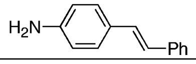
Table 8. Suzuki−Miyaura Couplings of Alkenylboronic Acid Using Ligand 1[a]

Entry	Halide	Boronic Acid	Product	Yield (%)[b]
1				97
2				97[c]
3				98
4				99
5				88

[a] Reaction conditions: 1 equiv of aryl bromide, 1.5 equiv of alkenylboronic acid, 2 equiv of K_3PO_4, THF (2 mL/mmol of halide), 1% $Pd(OAc)_2$, 2% ligand **1**, 40 °C, >99:1 trans:cis isomers.

on structural features of complexes derived from **1** follows below.

Suzuki−Miyaura Coupling Reactions of Vinylboronic Acids. Due to their aforementioned advantages, boronate esters are often the boron reagents of choice for Suzuki−Miyaura coupling reactions. For example, the use of vinyl boronates was recently described in Jacobsen's elegant asymmetric synthesis of quinine,[34] where **1** was utilized in the coupling of an (*E*)-alkenyl pinacol boronate ester with a 4-bromoquinoline derivative in excellent yield. To investigate the generality of **1** in the coupling of vinyl boronate derivatives with aryl halides, we examined the combination of (*E*)-octenylboronic acid and (*E*)-β-styrylboronic acid with aryl halides. Optimization of reaction conditions proved to be somewhat difficult, as reaction at temperatures that we often use (60−100 °C) produced a mixture of *E*- and *Z*-isomers. We found that a reaction temperature of 40 °C was optimal for aryl halide substrates containing an *ortho*-substituent and allowed full conversion of aryl halide with no detectable *Z*-isomer. For substrates without an *ortho*-substituent as large as methyl, the reactions proceeded at room temperature. For example, 2-fluoro-5-cyanobromobenzene reacted with (*E*)-octenylboronic acid at room temperature to give product in 97% isolated yield (Table 8, entry 1). However, the coupling of (*E*)-β-styrylboronic acid with 4-bromoaniline also required a reaction temperature of 40 °C, probably due to the very electron-rich nature of the aryl bromide. Aryl bromides possessing an *ortho*,*ortho′*-substitution pattern were also efficient coupling partners, as illustrated by the coupling of 2-bromomesitylene with (*E*)-β-styrylboronic acid (Table 8, entry 4), which proceeded in 99% isolated yield. A similar reaction has been reported by Molander using the potassium trifluoroborate salt of (*E*)-decenylboronic acid with 2-bromomesitylene.[35] However, under these conditions, the product was only isolated in 38% yield. Finally, we attempted to extend these conditions to the coupling of aryl chlorides with vinylboronic acids; however, reaction temperatures of >40 °C were required to promote full conversion of the aryl chloride, and alkene isomerization ensued.

Structural Studies of Palladium Complexes of 1. To gain further insight as to why the catalyst system based upon **1** is so effective in promoting Suzuki−Miyaura coupling processes, we turned to X-ray crystallography and computational chemistry to obtain structural information of various SPhos−Pd complexes.

We have previously reported, in our initial communication, the X-ray crystal structure of **1**·Pd(dba) (dba = dibenzylideneacetone), which possessed an unusual η^1 Pd−C(ipso) interaction (Figure 2). This type of interaction, as had been suggested by Kocovosky and Lloyd-Jones for a related Pd^{II} complex,[36] may help stabilize the complex and contribute in this way to the long-lived nature of the catalyst. We have no evidence that this interaction facilitates steps in the catalytic cycle, although it may help shift the equilibrium from $L_2Pd(0)$ to $L_1Pd(0)$. To probe the nature of this η^1 interaction, we performed ground-state geometry optimizations, using Gaussian 03,[37] on **1**/Pd(dba) using B3LYP[38] with several different basis set combinations, including 3-21G*, 6-31G*, and LANL2DZ+ECP[39] for the Pd center. The basis set that provided a structure nearly identical to the solid-state structure was 3-21G*. In the X-ray crystal structure the Pd−C(ipso) distance is 2.374(3) Å, whereas in the optimized structure the distance is 2.378 Å. Following the geometry optimization, a single point energy calculation using B3LYP/6-31++G(2d,2p) was preformed which allowed for an "atoms in molecules" analysis using AIM2000.[40] The atoms in molecules theory,[41] developed by Bader, allows for the determination of bonding by the presence of bond critical points. In the structure of **1**/Pd(dba), there exists a bond critical point between the Pd center and the ipso carbon of the lower aromatic ring, as seen in Figure 3. Additionally, there are no bond critical points between the Pd center and the two *ortho* carbons of the lower aromatic ring, which verifies that this observed interaction is truly η^1 (rather than the more common η^2 or η^3 interactions). Further support of this η^1 interaction is illustrated by the Pd−C(ortho) distances, 2.696 and 2.788 Å, in the X-ray crystal structure, as these distances are substantially greater than the Pd−C(ipso) distance of 2.374(3) Å. Additional studies are ongoing in our laboratories to gain a better under-

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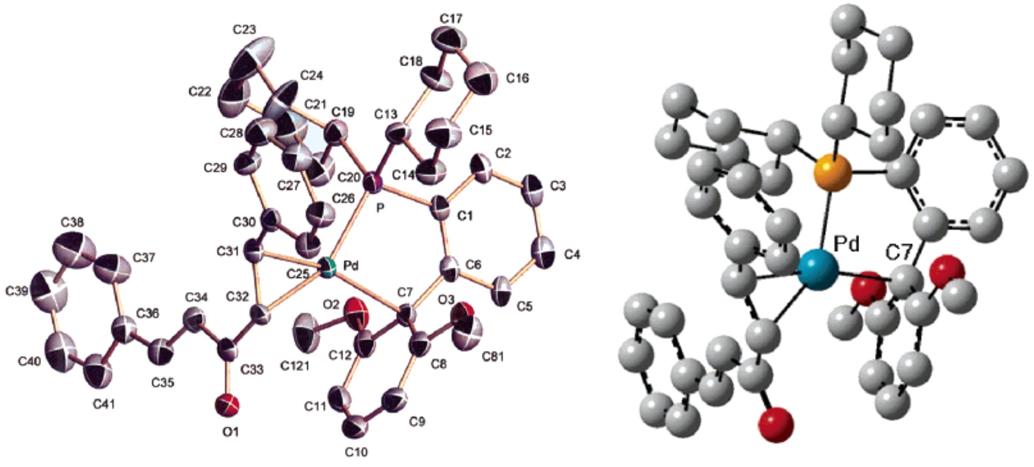
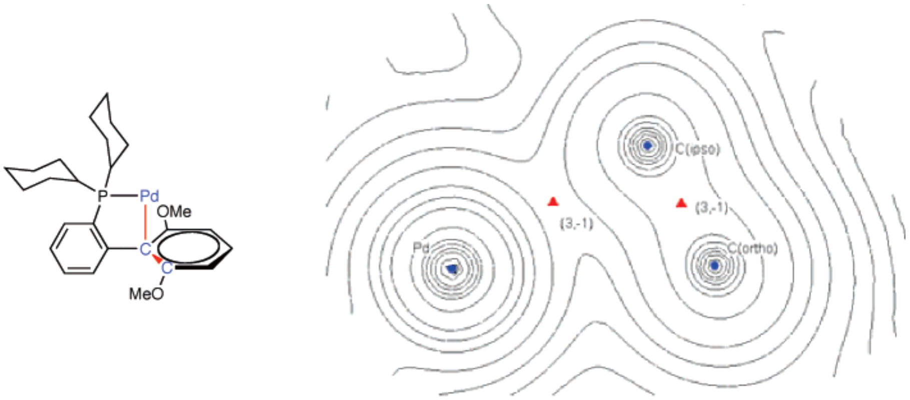


(a) (b)

Figure 2. (a) ORTEP diagram of **1**·Pd(dba) with hydrogens removed for clarity. Thermal ellipsoids are at 30% probability. (b) Calculated structure of **1**·Pd(dba) using the 3-21G* basis set.



(a) (b)

Figure 3. (a) Cartoon illustrating the Pd−C(ipso)−C(ortho) plane. (b) Electron density contour diagram of the Pd−C(ipso)−C(ortho) plane illustrating the bond critical points (3,−1).

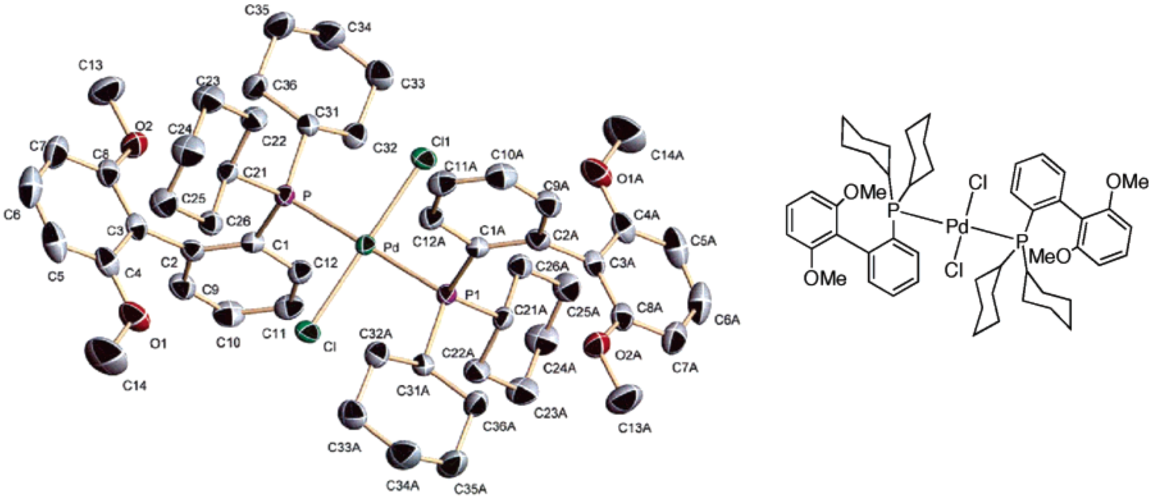


Figure 4. ORTEP diagram and drawing of **10** with hydrogen atoms omitted for clarity. Thermal ellipsoids are at 30% probability.

standing of the electronic nature and strength of the Pd−C(ispo) bond.

Additionally, two other palladium complexes of **1** were prepared and their X-ray crystal structures determined. First, a Pd(II) complex, $Cl_2Pd(\mathbf{1})_2$ (**10**), was prepared by stirring 2 equiv of **1** with $(CH_3CN)_2PdCl_2$ in CH_2Cl_2. A Pd(0) complex, $(\mathbf{1})_2Pd(0)$ (**11**), was prepared by heating 2 equiv of **1** with $(tmeda)PdMe_2$ in benzene at 55 °C.[42] X-ray crystal structures of these complexes are shown in Figures 4 and 5, respectively.

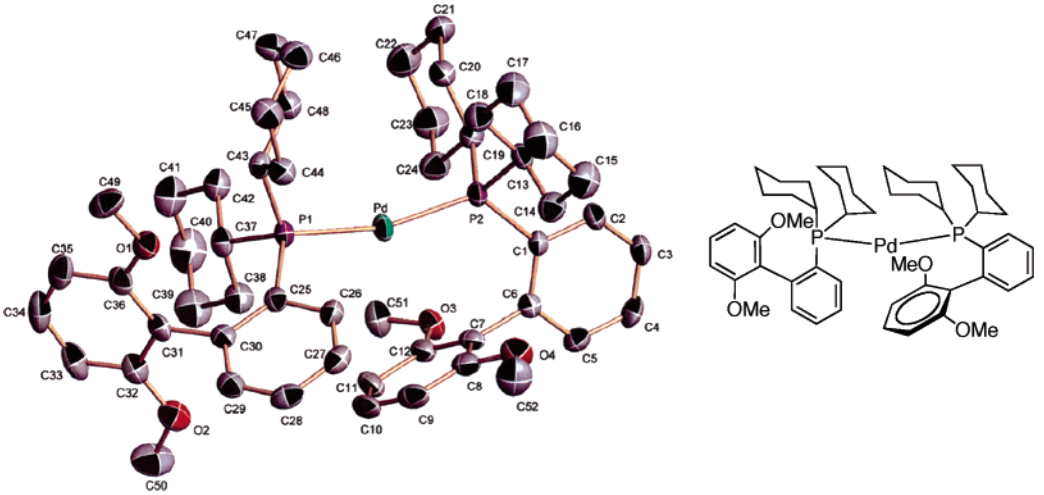
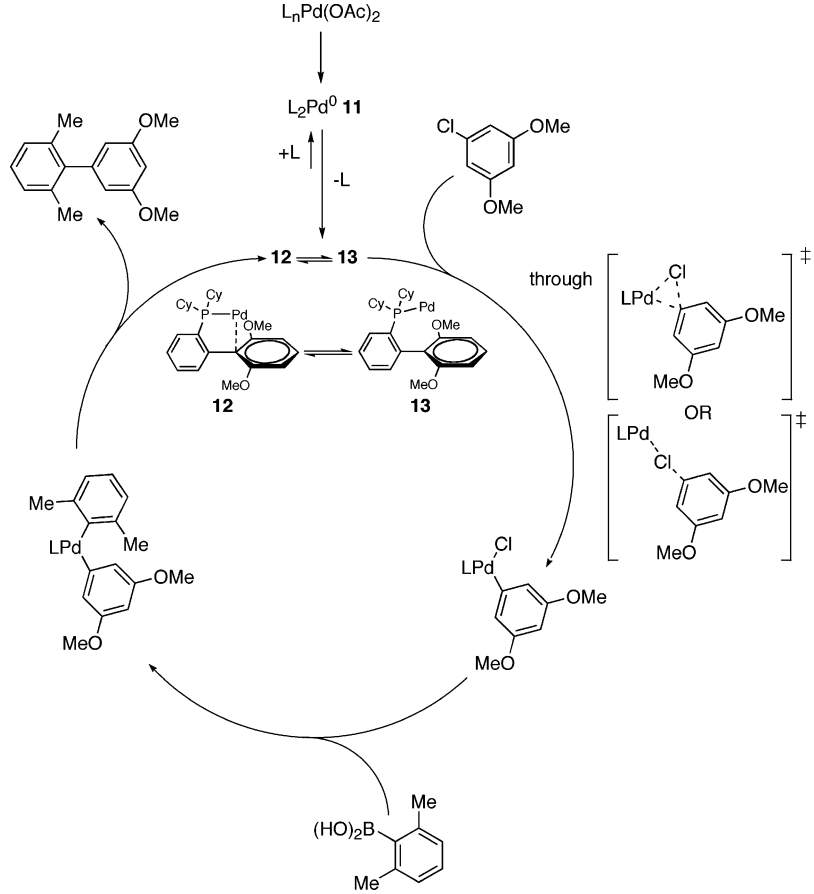


Figure 5. ORTEP diagram and drawing of **11** with hydrogen atoms omitted for clarity. Thermal ellipsoids are at 30% probability.

Scheme 3. Proposed Reaction Pathway for the Suzuki−Miyaura Coupling Reaction Using **1**·Pd(0)



Complex **10** possesses a trans square planar geometry, including a center of inversion about the palladium atom, in which the sterically demanding biaryl portion of the ligands are pointed away from the crowded palladium center. This complex is also amenable to purification via flash chromatography on silica gel (88% yield) and is indefinitely stable in air and in solution. It is important to note that **10** is *not* an intermediate in the catalytic cycle but a possible precursor to the active catalyst when PdCl$_2$ is used as the precatalyst.

A particularly noteworthy aspect of complex **11** is the large nonlinear P(1)−Pd−P(2) angle of 164.48(3)°, which is unusual in bisphosphine Pd(0) complexes.[43] A similar bis-phosphine complex was recently reported by Fink[44] (where PR$_3$ = 2-dicyclohexylphosphinobiphenyl) where the P(1)−Pd−P(2) angle deviated from linearity by 25.18°. However, in contrast to the structure reported in Fink's work, there are no obvious palladium−arene interactions, as shown in Figure 5. It is

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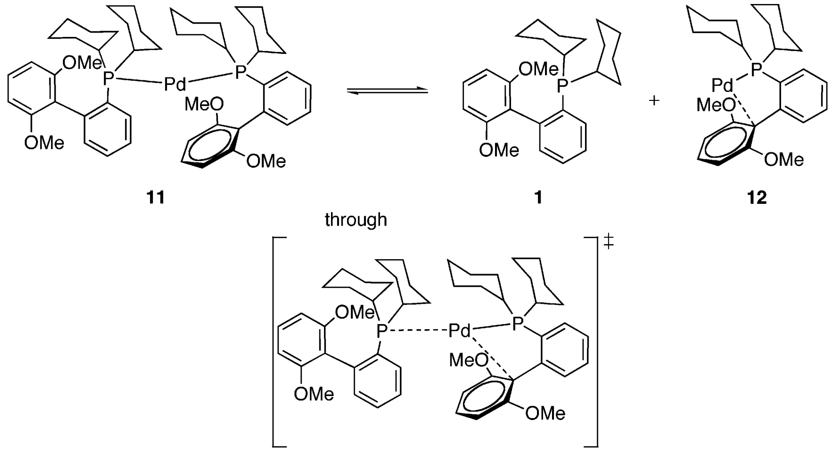
Scheme 4. Dissociation of One Phosphine from 11 with Concurrent Generation of a Pd−Arene Interaction



possible that the lack of a palladium η^1-arene interaction with an *ortho* carbon of the lower ring of the ligand may be beneficial to the lifetime of the catalyst in this system. The η^1 Pd−C(ortho) interaction that Fink observed led to the formation of a dibenzophospholane, presumably by cyclometalation of the *ortho* carbon followed by reductive elimination. A similar cyclometalation process is highly unlikely with **1**, as both *ortho* carbons of the lower ring are substituted, and products from this mode of catalyst decomposition have never been observed.

Furthermore, based upon the structure of **11**, it is our belief that the $L_2Pd(0)$ complex is too large to allow for the Pd−C(ipso) interaction (the Pd−C(ipso) distance is 3.371 Å), and is most likely much too hindered to participate in an oxidative addition process with an aryl halide. Therefore, one of the ligands must dissociate to arrive at a complex similar to **1**·Pd(dba), but lacking the dibenzylideneacetone ligand, prior to oxidative addition. This complex would contain a 12- or 14e$^-$ Pd center, depending on whether the Pd−C(ipso) interaction is present or not, respectively, which would be extremely reactive and undergo rapid oxidative addition. The existence of such intermediates has been often postulated, beginning with the work of Hartwig.[45] Additionally, complex **11** was shown to be chemically competent in Suzuki−Miyaura couplings. For example, the coupling of 5-chloro-1,3-dimethoxybenzene with 2,6-dimethylphenylboronic acid in the presence of 2 equiv of K_3PO_4 and 1 mol % **11** at 100 °C provided the product in 99% isolated yield in 1.75 h.

The size of **1** undoubtedly shifts the $L_2Pd(0)$/LPd(0) equilibrium toward the monoligated complex, which may be one cause for the highly reactive nature of these types of complexes. It is also ambiguous as to whether the palladium is coordinated to the aromatic ring, **12** versus **13** (or a combination of the two), when it interacts with the aryl halide (Scheme 3).[46] It is tempting to suggest, on the basis of the structure of **11**, that the Pd−C(ipso) interaction begins to take place as 1 equiv of **1** begins to dissociate from the palladium center (Scheme 4). This could lead to a higher ratio of the LPd(0):$L_2Pd(0)$ complexes and thus facilitate the oxidative addition process. Alternatively, the function of **12** may be to serve only as a nonreactive form of **1**·Pd(0) and may prevent catalyst decomposition while providing access to **13**. The importance of the Pd−C(ipso) interaction in intermediates and/or transition state structures within the catalytic cycle with **1**·Pd(0) as the catalyst is unknown, and further work is currently ongoing to gain a better understanding as to the oxidative addition and other processes with dialkylbiarylphosphine Pd complexes.

Conclusion

In conclusion, we report a new phosphine ligand that that can be used, in combination with a suitable Pd compound, to produce a catalyst system that overcomes many of the important limitations in Suzuki−Miyaura coupling processes. Specifically, 2-(2′,6′-dimethoxybiphenyl)dicyclohexylphosphine, **1**, imparts unprecedented activity in the coupling of extremely hindered arylboronic acids and aryl halides. Additionally, the coupling of boronic acids with aryl bromides and chlorides can be conducted in excellent yields with only 5 and 30 ppm Pd, respectively. Heterocyclic boronic acids, electron-deficient boronic acids, and vinylboronic acids can be coupled with a wide variety of aryl- and heteroaryl chlorides and bromides at minimal catalyst loadings using **1**. This ligand is an air stable crystalline solid that allows for extremely simple and rapid reaction setup. The wide scope and high reactivity that this ligand engenders in Suzuki−Miyaura coupling procesess is unprecedented. We have also prepared and studied reactions involving the triaryl phosphine **2**. From the results presented here, we are able to ascertain the relative contributions of size and electron-donating capacity to the efficacy of **1** and **2** as ligands. These results clearly show that while the electron-donating capacity of the phosphorus center is important, it is secondary to size for this class of ligand. We have also performed structural studies that provided insight into the highly reactive nature of these catalysts.

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Supporting Information Available: Experimental procedures, spectral data, and X-ray crystal structure data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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