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Highly Efficient Monophosphine-Based Catalyst for the Palladium-Catalyzed Suzuki−Miyaura Reaction of Heteroaryl Halides and Heteroaryl Boronic Acids and Esters

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Abstract: A highly active and efficient catalyst system derived from a palladium precatalyst and monophosphine ligands **1** or **2** for the Suzuki−Miyaura cross-coupling reaction of heteroaryl boronic acids and esters has been developed. This method allows for the preparation of a wide variety of heterobiaryls in good to excellent yields and displays a high level of activity for the coupling of heteroaryl chlorides as well as hindered aryl and heteroaryl halides. Specific factors that govern the efficacy of the transformation for certain heterocyclic motifs were also investigated.

Since its discovery,[1] the Suzuki−Miyaura reaction has become one of the most powerful and synthetically valuable processes for the construction of carbon−carbon bonds.[2] Its importance in organic synthesis is evident from its application in a number of areas, ranging from natural product synthesis to materials chemistry.[3] Much recent work has been directed toward the development of new catalyst systems that efficiently process challenging substrates such as aryl chlorides[4] and hindered aryl boronic acids while still using relatively mild reaction conditions and low catalyst loadings.[5]

The recent realization of more active catalyst systems can be attributed to an increased focus on ligand design. Phosphine ligands have become one standard for palladium-catalyzed carbon−carbon and carbon−nitrogen bond-forming processes, and our recent report utilizing the highly effective biaryl monophosphine ligand SPhos (**1**) continues this trend.[5a] Suzuki−Miyaura reactions employing **1** as the supporting ligand have displayed exceptional reactivity while maintaining a broad substrate scope, facilitating the coupling of extremely hindered substrate combinations as well as aryl chlorides. Catalyst systems based on palladium precatalysts and trialkyl phosphines[6] or N-heterocyclic carbenes[7] to generate biaryls have also proven to be highly effective.

Despite considerable effort in developing more active catalysts for the Suzuki−Miyaura reaction over the past two decades, many limitations remain. For example, whereas simple aryl halides and aryl boronic acids are successful coupling partners, reactions involving their heteroaryl analogues are less straightforward.[8] In addition, problems with these coupling processes limit the application of the method, especially in the context of drug development. Therefore, the development of a "universal" method for the cross-coupling of heteroaryl substrates would be highly advantageous.[9] Herein, we report a general catalyst system based upon a palladium precatalyst and dialkyl phosphine ligands **1** and **2** (Figure 1) for the Suzuki−Miyaura reaction of heteroaryl boronic acids and esters.

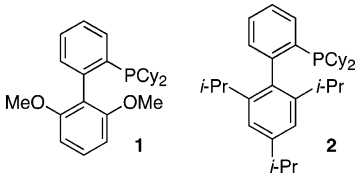

Figure 1. Structures of ligands **1** and **2**.

Results and Discussion

Thiophene Boronic Acids. Thiophenes are found in a variety of natural products as well as pharmaceutically interesting

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(2) Recent reviews: (a) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, *15*, 2419. (b) Miyaura, N. In *Metal-Catalyzed Cross-Coupling Reaction*; Diederich, F., de Meijere, A., Eds.; Wiley−VCH: New York, 2004; Chapt. 2.
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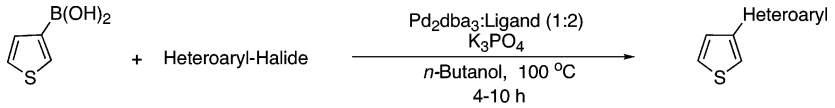
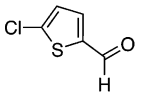
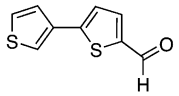
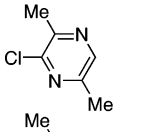
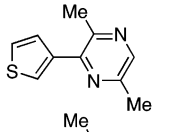
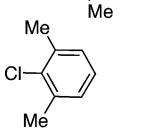
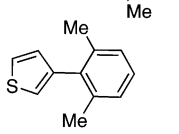
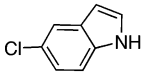
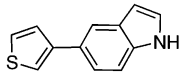
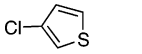
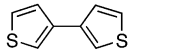
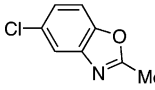
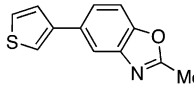
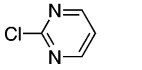
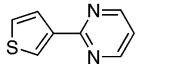
(8) Tyrell, E.; Brookes, P. *Synthesis* **2004**, *4*, 469−483.
(9) For recent reports on Suzuki−Miyaura reactions of heterocyclic substrates, see (a) Barder, T. E.; Buchwald, S. L. *Org. Lett.* **2004**, *6*, 2649−2652. (b) Kondolff, I.; Doucet, H.; Santelli, M. *Synlett* **2005**, *13*, 2057−2061. (c) Thompson, A. E.; Hughes, G.; Batsanov, A. S.; Bryce, M. R.; Parry, P. R.; Tarbit, B. *J. Org. Chem.* **2005**, *70*, 388−390. (d) Kudo, N.; Pereghini, M.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1282−1284. (e) Guram, A. S.; King, A. O.; Allen, J. G.; Wang, X.; Schenkel, L. B.; Chan, J.; Bunel, E. E.; Faul, M. M.; Larsen, R. D.; Martinelli, M. J.; Reider, P. J. *Org. Lett.* **2006**, *8*, 1787−1789. (f) A portion of this work has been communicated: Billingsley, K. L.; Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 3484−3488.

10.1021/ja068577p CCC: $37.00

Table 1. Suzuki−Miyaura Reactions of 3-Thiophene Boronic Acids **A**[a]



Entry	Aryl Chloride	Product	Ligand	Pd (mol%)	Yield (%)[b]
1			**1**	0.25	71[c]
2			**1**	0.25	97[c,d]
3			**2**	2.0	77
4			**2**	2.0	90[e]
5			**2**	2.0	96
6			**2**	2.0	91
7			**2**	2.0	84[f,g]

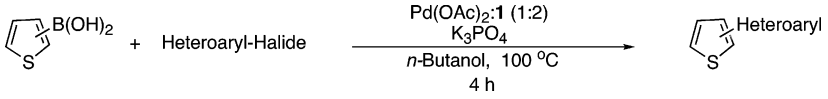
[a] Reaction conditions: 1 equiv of aryl or heteroaryl chloride, 1.5 equiv of boronic acid, 2 equiv of K_3PO_4, n-butanol (2 mL/mmol of halide), cat. Pd_2dba_3, L:Pd = 2:1. [b] Isolated yield based upon an average of two runs. [c] $Pd(OAc)_2$ was used instead of Pd_2dba_3. [d] s-Butanol was used as the solvent. [e] The boronic acid was added slowly via syringe pump over the first hour of the reaction. [f] Molecular sieves (4 Å) were added to the reaction. [g] t-Amyl alcohol was used as the solvent.

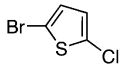
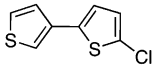
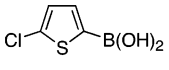
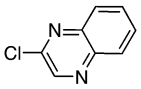
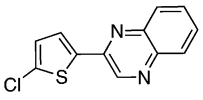
compounds.[10] In addition, polythiophenes, which are often prepared via Suzuki−Miyaura processes, have shown numerous applications as highly conducting polymers.[11] Despite the wealth of literature focused on the Suzuki−Miyaura reactions of thiophene boronic acids, the reaction of these substrates is plagued by several limitations.[12] For example, although polar solvents are often employed to facilitate the reaction of thiophene boronic acids, they are prone to decomposition under these conditions; their tendency to undergo protodeboronation is the likely reason. In addition, there are no general systems that effectively couple thiophene boronic acids with unactivated aryl chlorides. This is presumably due to the relatively slow rate of oxidative addition to aryl chlorides, which exacerbates the problems with stability of the thiophene boronic acids.

Our initial studies revealed that a catalyst system composed of $Pd(OAc)_2$/**1** proved to be highly effective for the coupling of thiophene boronic acids with heteroaryl bromides and activated heteroaryl chlorides at low catalyst loadings. For example, by use of 0.25% $Pd(OAc)_2$, the reaction of 3-thiophene boronic acid (**A**) with 5-chloro-2-thiophene carbaldehyde proceeded in 71% yield (Table 1, entry 1). A similar process allowed the combination of **A** with 3-chloro-2,5-dimethylpyrazine to provide an excellent yield of the product (Table 1, entry 2). However, for the reactions of **A** with unactivated heteroaryl chlorides, the $Pd(OAc)_2$/**1** catalyst was inefficient. In general, these failed to go to completion and gave low yields of the desired biaryl product. As the $Pd(OAc)_2$/**1** system has been shown to be extremely effective in the coupling of aryl chlorides, we found this inefficiency to be puzzling.[5a] In order to further probe this behavior, the reaction of excess **A** with 2-bromo-5-chlorothiophene was examined. As anticipated, only the coupling product resulting from oxidative addition at the 2-position was observed in the crude reaction product (Table 2, entry 1). Similarly, the reaction of excess 5-chloro-2-thiophene boronic acid with 2-chloroquinoxaline resulted only in the coupling of the activated heteroaryl chloride (Table 2, entry 2). These results indicate that unactivated heteroaryl chlorides were particularly challenging coupling partners for thiophene boronic acids under our conditions. Despite unsuccessful attempts to use $Pd(OAc)_2$/**1** in the coupling of **A** with a number of heteroaryl chlorides, in all cases we observed the formation of 3,3′-bithiophene **(3)** as a byproduct. We wondered whether the presence of **3** could have a deleterious effect on the process. In order to probe this possibility, we examined the reaction of **A** with 1-chloro-3,4-

(10) *Heterocyclic Chemistry*; Joule, J. A., Mills, K., Eds.; Blackwell Science: Malden, MA, 2000.
(11) Skotheim, T. S., Elsenbaumer, R. L., Reynolds, J. R., Eds. *Handbook of Conducting Polymers*; Marcel Dekker: New York, 1998.
(12) (a) Carpita, A.; Rossi, R. *Gazz. Chim. Ital.* **1985**, *115*, 575. (b) Gronowitz, S.; Bobosik, V.; Lawtz, K. *Chem. Scr.* **1984**, *23*, 120. (c) Yang, Y.; Hornfeldt, A.-B.; Gronwitz, S. *Chem. Scr.* **1988**, *28*, 275. (d) Gronowitz, S.; Peters, D. *Heterocycles* **1990**, *30*, 645. (e) Malm, J.; Rehn, B.; Hornfeldt, A.; Gronowitz, S. *J. Heterocycl. Chem.* **1994**, *31*, 11−15. (f) Hark, R. R.; Hauze, D. B.; Petrovskaia, O.; Joullie, M. M. *Tetrahedron Lett.* **1994**, *35*, 7719−7722. (g) Andrieu-Malapel, B.; Merour, J.-Y. *Tetrahedron* **1998**, *54*, 11079. (h) Haddach, M.; McCarthy, J. R. *Tetrahedron Lett.* **1999**, *40*, 3109. (i) Melucci, M.; Barbarella, G.; Sotgiu, G. *J. Org. Chem.* **2002**, *67*, 8877−8884.

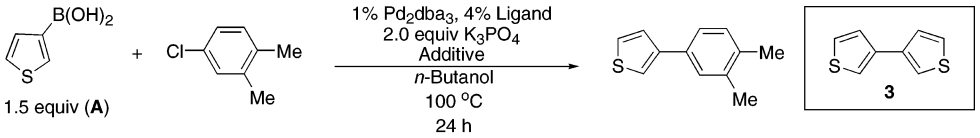
Table 2. Suzuki−Miyaura Reactions of Thiophene Boronic Acids Employing $Pd(OAc)_2$/**1**[a]



Entry	Boronic Acid	Aryl Halide	Product	Pd (mol%)	Yield (%)[b]
1	**A**			0.25	92
2				2.0	96[c]

[a] Reaction conditions: 1 equiv of aryl or heteroaryl chloride, 1.5 equiv of boronic acid, 2 equiv of K_3PO_4, n-butanol (2 mL/mmol of halide), cat. $Pd(OAc)_2$, L:Pd = 2:1. [b] Isolated yield based upon an average of two runs. [c] Reaction was conducted in t-amyl alcohol.

Table 3. Inhibition by 3,3′-Bithiophene[a]



Entry	Ligand	Additive	Conversion to Product (%)[b]
1	**1**	None	93[c]
2	**1**	25 mol% **3**	7
3	**2**	None	100[c]
4	**2**	25 mol% **3**	100[c]

[a] Reaction conditions: 1 equiv of aryl or heteroaryl chloride, 1.5 equiv of boronic acid, 2 equiv of K_3PO_4, *n*-butanol (2 mL/mmol of halide), cat. Pd_2dba_3, L:Pd = 2:1. [b] GC conversion based upon an average of two runs. [c] Approximately 10% *o*-xylene detected.

dimethylbenzene in the presence of 25 mol % **3**; only 7% conversion of the aryl chloride to product was seen (Table 3). In contrast, in the absence of **3**, the reaction proceeded to 93% conversion. Further experimentation led to the finding that a catalyst system employing **2** as the supporting ligand did not show similar loss of activity in the presence of **3**, even though **3** was formed under these reaction conditions. We have been unable to ascertain why **3** inhibits a catalyst system based upon **1** but not **2**. When **2** was used, however, coupling processes of **A** with unactivated heteroaryl chlorides were efficient. Similar byproducts were not readily produced in the reactions of related reagents (i.e., pyrrole, furan, 2-thiophene boronic acids).

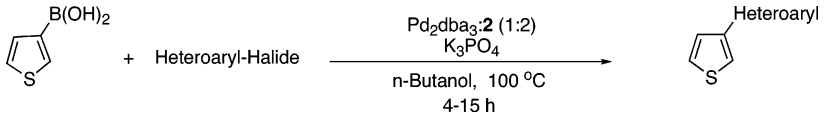
Reactions of **A** with unactivated aryl and heteroaryl chlorides by use of **2** as the supporting ligand proceeded in good to excellent yields. The coupling between 2-chloro-*m*-xylene and **A** smoothly produced the biaryl in 77% yield (Table 1, entry 3). In addition, **A** combined with a variety of heteroaryl chlorides in greater than 90% yield. In certain instances, slow addition of **A** increased the overall yield of the process. This presumably slows the decomposition of **A** over the course of the procedure. For example, the coupling of **A** with 5-chloroindole proceeded in 72% yield under standard conditions, while using the slow addition procedure increased the yield to 90% (Table 1, entry 4).

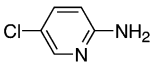
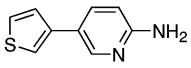
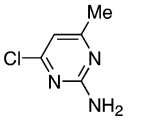
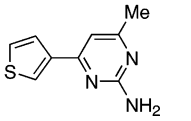
Azines are attractive targets for cross-coupling methodology due to their prevalence in biologically active compounds.[10] However, nitrogen-derived heterocycles have been particularly difficult to employ in palladium catalysis.[9f] In addition, it has been demonstrated that aminopyridines as well as aminopyrimidines can competitively bind to the Pd(II) center intermediate, leading to poor results when monodentate ligands are employed.[13] Thus it is of interest that a catalyst derived from Pd_2dba_3/**2** provided good to excellent yields for the Suzuki−Miyaura reaction of thiophene boronic acids with a variety of chloroazines. For example, **A** was allowed to react with 2-amino-5-chloropyridine (Table 4, entry 1) and 2-amino-4-choro-6-methylpyrimidine (Table 4, entry 2) to provide the desired products in 95% and 80% yield, respectively. In addition, 2-thiophene boronic acid (**B**) could be efficiently combined with 2-chloropyrimidine (Table 5, entry 3) and 2-chloro-4,6-dimethoxy-1,3,5-triazine (Table 5, entry 4) in 85% and 84% yield, respectively. A thiophene boronic acid possessing an electron-withdrawing group also smoothly reacted with 3-chloro-2,5-dimethylpyrazine in excellent yield (Table 5, entry 5).

One drawback of our protocol was that it did not effect the efficient coupling of **B** with unactivated aryl or heteroaryl chlorides by the above-described protocol. Under these conditions the decomposition of **B** became more rapid than the cross-coupling process, resulting in the incomplete conversion of the aryl chloride. The use of less polar solvents (e.g., toluene, dioxane) reduced the degree of decomposition of **B** but also slowed the rate of the desired reaction. Attempts to use

(13) Itoh, T.; Mase, T. *Tetrahedron Lett.* **2005**, *46*, 3573.
(14) (a) Ishikura, M.; Kamada, M.; Terashima, M. *Heterocycles* **1984**, *22*, 265−288. (b) Parry, P. R.; Wang, C.; Batsanov, A. S.; Bryce, M. R.; Tarbit, B. *J. Org. Chem.* **2002**, *67*, 7541−7543. (c) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302−4314. (d) Cioffi, C. L.; Spencer, W. T.; Richards, J. J.; Herr, R. J. *J. Org. Chem.* **2004**, *69*, 2210−2212. (e) Hodgson, P. B.; Salingue, F. H. *Tetrahedron Lett.* **2004**, *45*, 685−687.

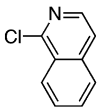
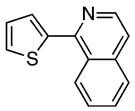
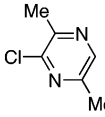
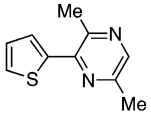
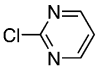
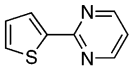
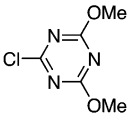
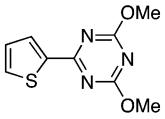
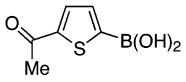
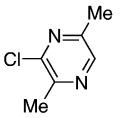
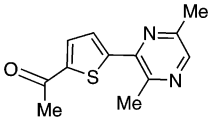
Table 4. Suzuki−Miyaura Reactions of Thiophene Boronic Acids with Chloroaminoazines[a]



Entry	Aryl Chloride	Product	Yield (%)[b]
1			95
2			80[c,d]

[a] Reaction conditions: 1 equiv of aryl or heteroaryl chloride, 1.5 equiv of boronic acid, 2 equiv of K_3PO_4, *n*-butanol (2 mL/mmol of halide), cat. Pd_2dba_3, L:Pd = 2:1. [b] Isolated yield based upon an average of two runs. [c] Molecular sieves (4 Å) were added to the reaction. [d] *t*-Amyl alcohol was used as the solvent.

Table 5. Suzuki−Miyaura Reactions of 2-Thiophene Boronic Acids[a]

Entry	Boronic Acid	Aryl Chloride	Product	Ligand	Pd (mol%)	Yield (%)[b]
1	**B**			**1**	0.25	96[c,d]
2	**B**			**1**	2.0	96[c,d]
3	**B**			**2**	2.0	85[e]
4	**B**			**2**	2.0	84[e]
5				**2**	2.0	98[f]

[a] Reaction conditions: 1 equiv of aryl or heteroaryl chloride, 1.5 equiv of boronic acid, 2 equiv of K_3PO_4, *n*-butanol (2 mL/mmol of halide), cat. Pd_2dba_3, L:Pd = 2:1, 4−10 h. [b] Isolated yield based upon an average of two runs. [c] $Pd(OAc)_2$ was used instead of Pd_2dba_3. [d] Reaction was conducted in *s*-butanol. [e] Molecular sieves (4 Å) were added to the reaction mixture. [f] Reaction was conducted in *t*-amyl alcohol.

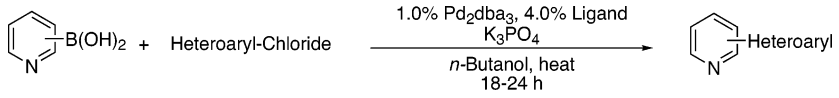
potassium trifluoroborate salts were unsuccessful due to their lack of stability under the reaction conditions employed. In addition, irreproducible results were seen with the pinacol boronate ester of **B**.

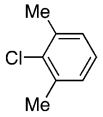
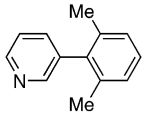
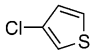
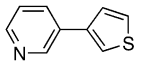
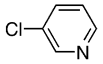
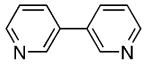
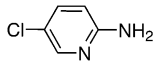
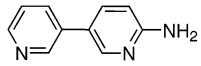
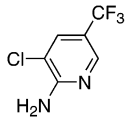
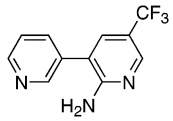
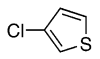
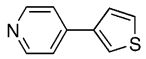
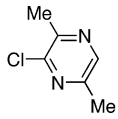
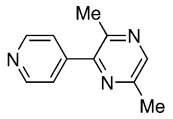
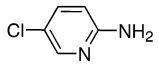
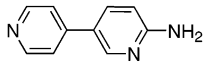
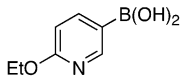
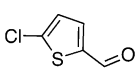
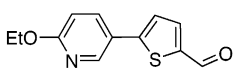
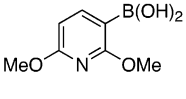
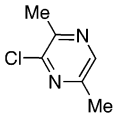
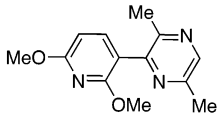
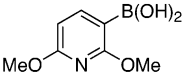
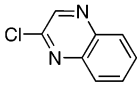
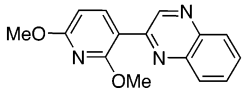
Pyridine Boronic Acids. The Suzuki−Miyaura reaction of pyridine-derived boronic acids has proven to be particularly challenging,[9b,14] and as a result, only a few relevant studies can be found.[5a,9a,d,f] The primary problem associated with these boronic acids is their slow rate of transmetalation, which is attributed to the electron deficiency of the heteroaromatic ring.[5a] Recognizing the importance of the pyridine-containing products in pharmaceutically active compounds, we sought to develop a general method for employing these substrates.

Despite our previous success[5a] with the Pd_2dba_3/**1** catalyst system for the reactions of pyridine-derived boronic acids with aryl chlorides, only modest yields of the desired biaryl could be obtained for the corresponding heteroaryl chlorides. Employing **2** as the supporting ligand, however, provided a highly active catalyst for this transformation. Higher temperatures (100−120 °C) and longer reaction times (18−24 h) were required in many instances to overcome the lower reactivity of the heteroaryl boronic acids.

Pyridine boronic acids reacted in good to excellent yield with sterically hindered as well as unactivated aryl chlorides. The reaction of 2-chloro-*m*-xylene with 3-pyridine boronic acid (**C**) proceeded smoothly to provide the desired biaryl in 81% yield (Table 6, entry 1). In addition, challenging substrates, such as those with halopyridines and halo-2-aminopyridines, combined with both **C** and 4-pyridine boronic acid (**D**) in greater than 95% yield (Table 6, entries 3−5, 8). Similarly, alkoxypyridine boronic acids reacted in high yield with several heteroaryl chlorides (Table 6, entries 9−11). This protocol offered a general method for the preparation of pyridine-derived heterobiaryls.

Table 6. Suzuki−Miyaura Reactions of Pyridine Boronic Acids[a]



Entry	Boronic Acid	Aryl Chloride	Product	Ligand	Temp (°C)	Yield (%)[b]
1	**C**			**2**	100	81
2	**C**			**2**	100	90
3	**C**			**2**	120	97
4	**C**			**2**	120	95
5	**C**			**2**	120	95
6	**D**			**2**	100	90
7	**D**			**1**	100	83[c,d]
8	**D**			**2**	120	95
9				**2**	100	91
10				**2**	100	85[e]
11				**2**	100	91[e]

[a] Reaction conditions: 1 equiv of aryl or heteroaryl chloride, 1.5 equiv of boronic acid, 2 equiv of K_3PO_4, *n*-butanol (2 mL/mmol of halide), cat. Pd_2dba_3, L:Pd = 2:1. [b] Isolated yield based upon an average of two runs. [c] $Pd(OAc)_2$ was used instead of Pd_2dba_3. [d] Reaction was conducted in *s*-butanol. [e] Reaction was conducted in *t*-amyl alcohol.

We note, however, that these protocols were not successful for the reaction of 2-pyridine boronic acids.

Pyrrole-Containing Boronic Acids and Esters. Pyrroles are components of numerous medicinally interesting compounds, but pyrrole-based boronic acids and borane derivatives have found limited application in organic synthesis.[8] One explanation for this, as described in previous reports, is the inability of pyrrole-based nucleophiles to react with hindered or heterocyclic aryl halides under standard Suzuki−Miyaura conditions.[15] In addition, the synthesis of pyrrole-based boronic acids is heavily reliant on the proper selection of the nitrogen-protecting group. However, to date, there is no single report that investigates preparative methods of protected pyrrole-derived organoboranes. Further, the effect that the pyrrole-protecting group displays on the efficiency of cross-coupling had yet to be thoroughly investigated.

Our first challenge was to prepare a stable pyrrole-based boron reagent. A previous synthesis of *N*-(triisopropylsilyl)-pyrrole-3-boronic acid has been reported, but it was realized in low yield.[15a] Further, reactions utilizing this reagent were plagued by competitive protodeboronation and were therefore limited to couplings with aryl iodides and activated aryl bromides. We hypothesized that the corresponding boronate ester would offer increased stability relative to the boronic acid. Several protected 3-pyrrole boronate esters were prepared in

(15) (a) Alzarez, A.; Guzmen, A.; Ruiz, A.; Velards, E.; Muchowski, J. *J. Org. Chem.* **1992**, *57*, 1653−1656. (b) Johnson, C.; Stemp, G.; Anand, N.; Stephen, S.; Gallagher, T. *Synlett* **1998**, 1025−1027.

Scheme 1. Synthesis of Pyrrole Boronate Ester Derivatives

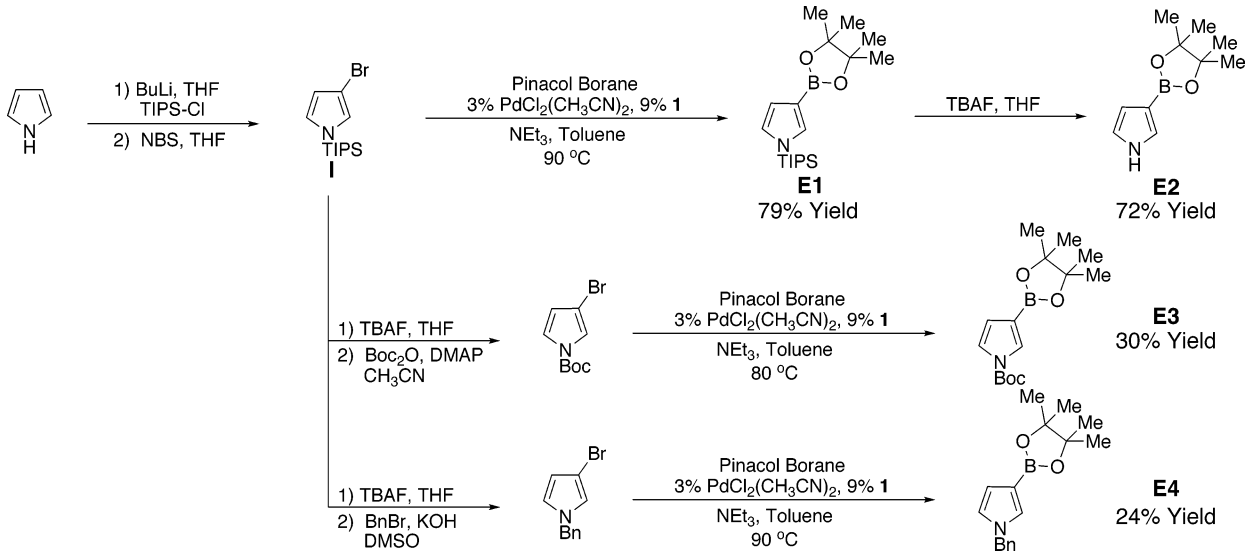
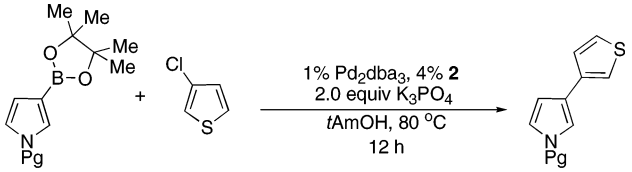


Table 7. Effect of Nitrogen-Protecting Group on the Reaction of Pyrrole-Derived Nucleophiles

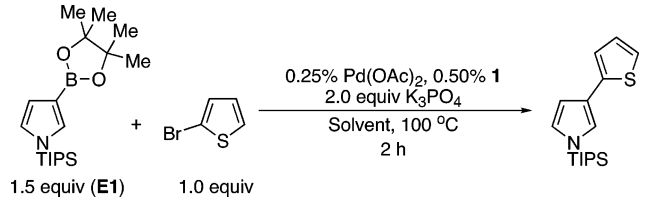


Entry	Protecting Group	Isolated Yield (%)
1	TIPS (**E1**)	58
2	None (**E2**)	Trace
3	BOC (**E3**)	51
4	Benzyl (**E4**)	55

order to determine whether the nitrogen protecting group played a significant role in the success of the coupling process. The three N-protected pyrrole-3-boronate esters were prepared from pyrrole in 24−79% overall yield (Scheme 1). The syntheses proceeded via the known triisopropylsilyl-3-bromopyrrole **(I)**.[15a] From **I**, **E1** was prepared via palladium-catalyzed carbon−boron bond formation in 79% overall yield from pyrrole, and **E2** was obtained after deprotection of **E1** in 72% overall yield from pyrrole. Boronate esters **E3** and **E4** were prepared by desilylation of **I** and immediate reprotection of 3-bromopyrrole under the appropriate conditions. Some decomposition was detected in each case resulting from the unstable 3-bromopyrrole intermediate. The final step again relied upon Pd-catalyzed borylation to produce the derivatives in 30% and 24% overall yield from pyrrole, respectively.

With **E1**−**E4** in hand, we next examined their coupling reactions with 3-chlorothiophene. We found little variation in yield among the four boronate esters for this reaction with the exception that **E2** yielded only a trace amount of product (Table 7). Of the four, **E1** is the easiest to prepare and is stable at elevated temperatures. In addition, its reaction provides yields equal to or better than those employing **E2**−**E4**.

Our preliminary studies revealed that, in reactions employing **E1**, $Pd(OAc)_2$/**1** provided a highly active catalyst for processing heteroaryl bromides. However, the success of these coupling reactions was dependent on the alcoholic solvent utilized. With *n*-butanol as the solvent, **E1** combined efficiently with a variety of heteroaryl bromides, whereas for reactions in *sec*-butanol or *tert*-amyl alcohol the aryl halide was not completely processed. In addition, we discovered that the addition of water to reactions conducted in *n*-butanol minimized the amount of reduced aryl halide produced and increased the overall yield. To further probe the effect of water on these coupling reactions, we carried out a series of experiments in which the ratio of *n*-butanol:water was varied. We found that the optimum ratio was 2.5:1; a procedure utilizing this solvent mixture gave quantitative yield of the biaryl (Figure 2).



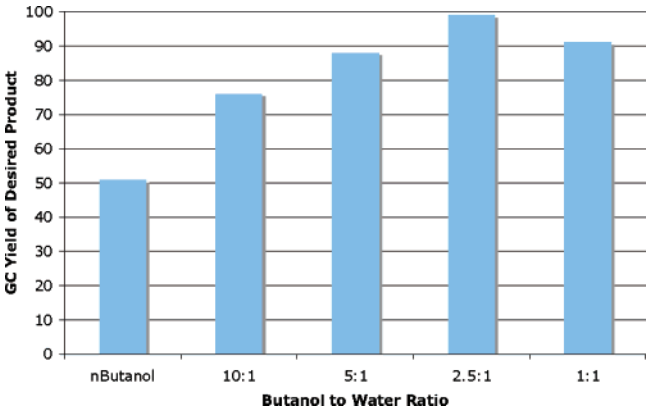
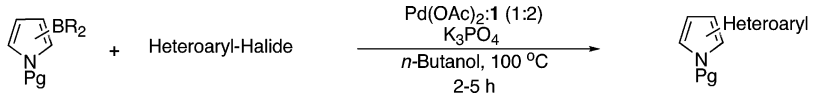


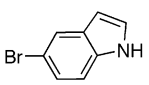
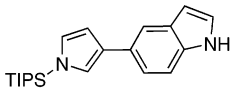
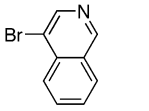
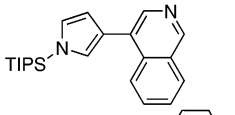
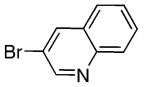
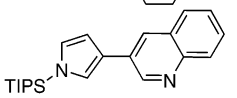
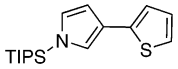
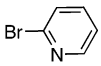
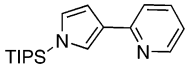
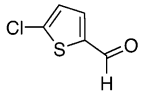
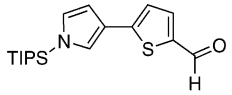
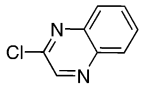
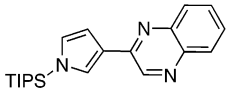
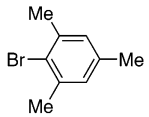
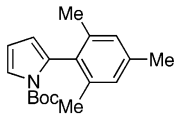
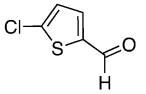
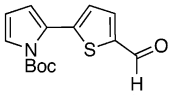
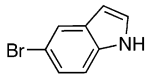
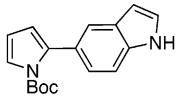
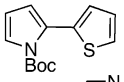
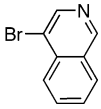
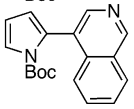
Figure 2. Effects of varying *n*-butanol:water.

A catalyst system based upon $Pd(OAc)_2$/**1** afforded good to excellent yields for the coupling of **E1** with heteroaryl bromides and activated heteroaryl chlorides at low catalyst loadings. By use of 0.25% $Pd(OAc)_2$, 5-bromoindole (Table 8, entry 1) and 4-bromoisoquinoline (Table 8, entry 2) were

(16) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875−2911.
(17) Yang, Y.; Martin, A. R. *Heterocycles* **1992**, *34*, 1395−1398.

Table 8. Suzuki−Miyaura Reactions of Pyrrole-Based Nucleophiles[a]



Entry	Boron Derivative	Aryl Halide	Product	Pd (mol%)	Yield (%)[b]
1	**E**			0.25	97[c]
2	**E**			0.25	93[c]
3	**E**			0.25	83[c]
4	**E**			0.25	99[c]
5	**E**			0.25	91[c]
6	**E**			0.25	82[c,d]
7	**E**			0.25	83[c,d]
8	**F**			2.0	89
9	**F**			2.0	84
10	**F**			2.0	79
11	**F**			2.0	84
12	**F**			2.0	95

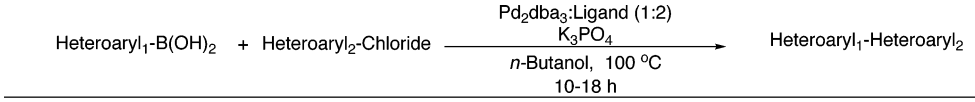
[a] Reaction conditions: 1 equiv of aryl or heteroaryl chloride, 1.5 equiv of boronic acid, 2 equiv of K_3PO_4, *n*-butanol (2 mL/mmol of halide), cat. $Pd(OAc)_2$, L:Pd = 2:1. [b] Isolated yield based upon an average of two runs. [c] *n*-Butanol:water (2.5:1) used as the solvent. [d] Temperature was 80 °C.

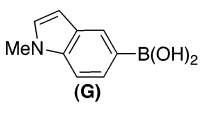
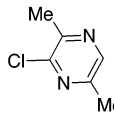
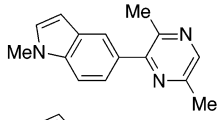
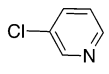
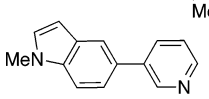
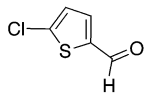
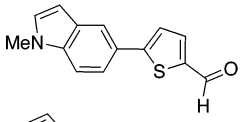
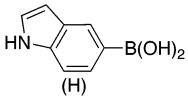
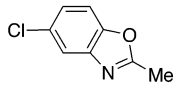
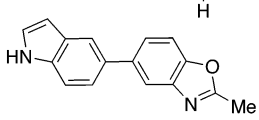
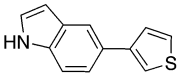
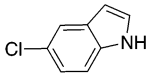
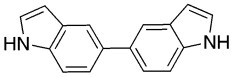
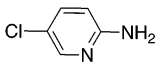
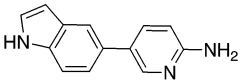
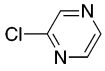
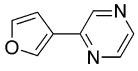
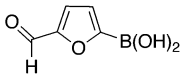
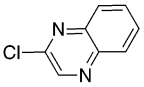
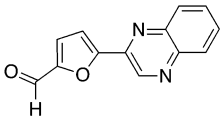
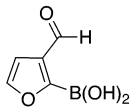
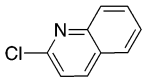
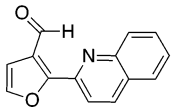
successfully combined with **E1** to produce the corresponding heterobiaryls in 90% yield. The combination of **E1** with 2-bromothiophene resulted in a nearly quantitative yield of the desired biaryl (Table 8, entry 4). In addition, the coupling of the activated heteroaryl chlorides 5-chloro-2-thiophenecarbaldehyde (Table 8, entry 6) and 2-chloroquinoxaline (Table 8, entry 7) led to 82% and 83% yield of the desired biaryls, respectively.

While **E1** provided a useful nucleophilic component for the preparation of 3-arylated pyrroles, a similar reagent was needed to provide 2-heteroaryl pyrrole analogues. The known *N*-(*t*-butoxycarbonyl)pyrrole-2-boronic acid **(F)** is a stable solid and easily purified by flash column chromatography. *n*-Butanol proved to be the ideal solvent for the cross-coupling of aryl as well as heteroaryl bromides; the addition of water resulted in poor yields due to a increased production of reduced aryl halide.

The $Pd(OAc)_2$/**1** system produced a highly active catalyst for the combination of **F** with aryl and heteroaryl bromides (Table 8, entries 8−12). The protocol outlined in Table 8 allowed for aryl halides possessing a variety of functional groups as well as different degrees of steric hindrance ortho to the halogen to be efficiently processed. Contrary to the literature reports, significant homocoupling or protodeboronation of **F** was not readily detected.[15b] Currently, this is the most general method for the Suzuki−Miyaura cross-coupling reaction of pyrrole boronic acids. However, the reactions of **E** and **F** remain problematic with unactivated aryl and heteroaryl chlorides. This

Table 9. Suzuki−Miyaura Reactions of Indole and Furan Boronic Acids[a]



Entry	Boronic Acid	Aryl Chloride	Product	Ligand	Pd (mol%)	Yield (%)[b]
1	 (G)			**1**	2.0	90[c,d]
2	G			**1**	2.0	77[c]
3	G			**1**	0.25	96[c]
4	 (H)			**2**	2.0	91[e]
5	H			**2**	2.0	90[e]
6	H			**2**	2.0	71[e]
7	H			**2**	2.0	77[e]
8	J			**1**	2.0	96[c]
9				**2**	2.0	82[f]
10				**2**	2.0	70[f]

[a] Reaction conditions: 1 equiv of aryl or heteroaryl chloride, 1.5 equiv of boronic acid, 2 equiv of K_3PO_4, *n*-butanol (2 mL/mmol of halide), cat. Pd_2dba_3, L:Pd = 2:1. [b] Isolated yield based upon an average of two runs. [c] $Pd(OAc)_2$ was used instead of Pd_2dba_3. [d] *s*-Butanol was used as the solvent. [e] Reaction was conducted at 120 °C. [f] *t*-Amyl alcohol was used as the solvent.

limitation, in general, can be attributed to rapid decomposition of these reagents in alcoholic media at elevated temperatures.

Indole Boronic Acids. Indoles are found throughout nature and their derivatives display a broad spectrum of biological activity.[16] Due to their significance, the development of efficient methods for the derivatization of indole building blocks is an important research topic. Several groups have investigated the reactivity of indole-derived boronic acids,[15b,17] but only a few protocols allow for the cross-coupling of heteroaryl chlorides with these substrates.[9d,f]

By utilization of the $Pd(OAc)_2$/**1** catalyst system, activated heteroaryl chlorides were successfully coupled to 5-indole boronic acids. *N*-Methyl-5-indole boronic acid (**G**) smoothly reacted with 3-chloro-2,5-dimethylpyrazine (Table 9, entry 1) and 3-chloropyridine (Table 9, entry 2) to afford the heterobiaryl products in 90% and 77% yield, respectively. In addition, with 0.25% $Pd(OAc)_2$, the reaction of 5-chloro-2-thiophenecarbaldehyde with **G** resulted in 96% yield of the desired biaryl (Table 9, entry 3).

5-Indole boronic acid (**H**) reacted with unactivated heteroaryl chlorides in greater than 75% yield. However, it was necessary to raise the reaction temperature to 120 °C for the reaction to proceed to completion. The reaction of **H** with 5-chlorobenzoxazole (Table 9, entry 4) and 3-chlorothiophene (Table 9, entry 5) produced the desired heterobiaryl products in 91% and 90% yield, respectively. In addition, **H** smoothly reacted with 2-amino-5-chloropyridine in 77% yield (Table 9, entry 7). This protocol represents an efficient method for the Suzuki−Miyaura reaction of indole boronic acids with unactivated heteroaryl chlorides.

Furan Boronic Acids. The use of furan boronic acids is well precedented in Suzuki−Miyaura literature.[18] However, due to the instability of many of these reagents, the Suzuki−Miyaura couplings of furan boronic acids have been limited to reactions employing aryl iodides and bromides.

By use of a catalyst system based upon $Pd(OAc)_2$/**1**, 3-furan boronic acid (**J**) was coupled to a variety of activated heteroaryl chlorides in good to excellent yield. The reaction of **J** with

2-chloropyrazine (Table 9, entry 8) resulted in 96% yield of the heterobiaryl. In addition, electron-deficient furan boronic acids were good coupling partners (Table 9, entries 9 and 10). Unactivated aryl chlorides, unfortunately, did not react in high yields with these furan boronic acids; under the reaction conditions, they underwent rapid decomposition. Reactions with 2-furan boronic acid were similarly unsuccessful.

Conclusions

In summary, we have developed a highly active catalyst system for the Suzuki−Miyaura cross-coupling of heteroaryl boronic acids and esters based on ligands **1** and **2**. This method represents a quite general procedure for the production of heterobiaryl compounds, an architectural motif that is ubiquitous in biologically active molecules. In addition, we have uncovered factors that govern the efficiency of the cross-coupling for individual heterocyclic boronic acid. These catalyst systems expand the substrate scope for the coupling of heteroaryl boronic acids with activated and unactivated aryl chlorides as well as hindered aryl halides.

Experimental Section

Representative Procedure for the Suzuki−Miyaura Coupling Reaction: Coupling of 3-Chlorothiophene and 3-Thiophene Boronic Acid (Table 1, Entry 5). An oven-dried Schlenk tube was charged with $Pd_2(dba)_3$ (2.3 mg, 0.0025 mmol), **2** (4.8 mg, 0.01 mmol), 3-thiophene boronic acid (48 mg, 0.375 mmol), and powdered, anhydrous K_3PO_4 (106 mg, 0.50 mmol). The Schlenk tube was capped with a rubber septum and then evacuated and backfilled with argon (this sequence was carried out two times). *n*-Butanol (0.50 mL) was added via syringe, through the septum, followed by addition of 3-chlorothiophene (23.2 μL, 0.25 mmol) in a like manner (aryl halides that were solids were added with other reagents before evacuation). The septum was then replaced with a Teflon screwcap and the Schlenk tube was sealed. The reaction mixture was heated to 100 °C until aryl halide had been completely consumed as determined by gas chromatography. At this point the reaction mixture was allowed to cool to room temperature. The reaction solution was then filtered through a thin pad of silica gel (eluted with ethyl acetate) and the eluent was concentrated under reduced pressure. The crude product was purified via flash column chromatography on silica gel (hexanes) to provide the title compound in 96% yield (36 mg) as a white solid, mp 119−121 °C. ^{1}H NMR (300 MHz, $CDCl_3$) 7.39 (dd, J = 3, 2 Hz, 1H), 7.35−7.36 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) 137.2, 126.3, 126.1, 119.7. IR (neat, cm^{-1}) 3414, 1652, 1465, 1418, 1089. Anal. Calcd. for $C_8H_6S_2$: C, 57.79; H, 3.64. Found: C, 57.98; H, 3.60.

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Supporting Information Available: Experimental procedures and spectral 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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