Recent Advances in Palladium-Catalyzed Carbon-Carbon and Carbon-Boron Bond-Forming Processes

By

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B.S. Chemistry
University of South Carolina – Columbia, 2002

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ABSTRACT

Chapter 1.

Highly active and efficient catalyst systems derived from palladium precatalysts and monophosphine ligands 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.

Chapter 2.

A highly efficient method for the palladium-catalyzed Suzuki-Miyaura reaction of lithium triisopropyl 2-pyridylborates has been developed. Catalysts comprised of Pd_2dba_3 and either diaryl or dialkyl phosphine oxide supporting ligands were found to be ideal for the transformation. This report represents one of the most general systems for the cross-coupling of aryl and heteroaryl bromides and chlorides with 2-pyridyl-derived nucleophiles.

Chapter 3.

Catalysts comprised of Pd and dialkylmonophosphinobiaryl ligands provide highly active systems for the borylation of aryl and heteroaryl chlorides. The direct preparation of symmetrical and unsymmetrical biaryls from two aryl chlorides without the need to isolate the intermediate boronate esters is also described. Additionally, computational studies provide insight into the roles of the biaryl phosphine ligand as well as KOAc in the catalytic cycle.

Chapter 4.

A highly efficient method for the palladium-catalyzed borylation of aryl halides with an inexpensive and atom-economical boron source, pinacol borane, has been developed. This system allows for the conversion of aryl and heteroaryl iodides, bromides and several chlorides, containing a variety of functional groups, to the corresponding pinacol boronate esters. In addition to the increase in substrate scope, this is the first general method where relatively low quantities of catalyst and short reaction times can be employed.

Thesis Supervisor: Stephen L. Buchwald
Title: Camille Dreyfus Professor of Chemistry

ACKNOWLEDGMENTS

This thesis is dedicated to my mother whose love and support has carried me throughout my life.

PREFACE

This thesis has been adapted from the following published articles co-written by the author:

"A General and Efficient Method for the Suzuki-Miyaura Coupling of 2-Pyridyl Nucleophiles" Billingsley, K.; Buchwald, S. L. Accepted to *Angew. Chem. Int. Ed.*

"An Improved System for the Palladium-Catalyzed Borylation of Aryl Halides with Pinacol Borane" Billingsley, K.; Buchwald, S. L. Accepted to *J. Org. Chem.*

"Palladium-Catalyzed Borylation of Aryl Chlorides: Scope, Applications, and Computational Studies" Billingsley, K.; Barder, T. E.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5359-5363.

"Highly Efficient Monophosphine-Based Catalyst for the Palladium-Catalyzed Suzuki-Miyaura Reaction of Heteroaryl Halides and Heteroaryl Boronic Acids and Esters" Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358-3366.

"A Highly Active Catalyst for Suzuki-Miyaura Cross-Coupling Reactions of Heteroaryl Compounds" Billingsley, K.; Anderson, K. W.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 3484-3488.

Respective Contributions

This thesis contains work that is the result of collaborative efforts between the author and other workers at MIT. An overview detailing the specific contributions of the author is included below.

The work described in Chapter 3 was the result of a collaborative between Dr. Tim Barder and the author. The author is responsible for all experiments included in this chapter. Dr. Barder conducted the computational studies that provided insight into the roles of the biaryl phosphine ligand as well as KOAc in the catalytic cycle.

TABLE OF CONTENTS

Introduction

Throughout the past several decades, advancements in the field of transition metal catalysis have provided numerous efficient methods for carbon-carbon bond formation and, in turn, have allowed for new innovative strategies for the synthesis of complex organic molecules.[1] In particular, the Pd-catalyzed Suzuki-Miyaura cross-coupling reaction has become one of the most widely employed of these processes.[2] Its impact on organic synthesis is largely attributed to the fact that it provides a general and applicable method for the formation of biaryls, which are found in polymers,[3] biologically active compounds,[4] ligands[5] and various materials.[6]

The Suzuki-Miyaura reaction, in general, combines an aryl halide or sulfonate with an aryl boronic acid or ester under palladium catalysis to form a new carbon-carbon bond. The proposed catalytic cycle is shown in Figure 1. The mechanism is believed to occur in three sequential steps: 1)

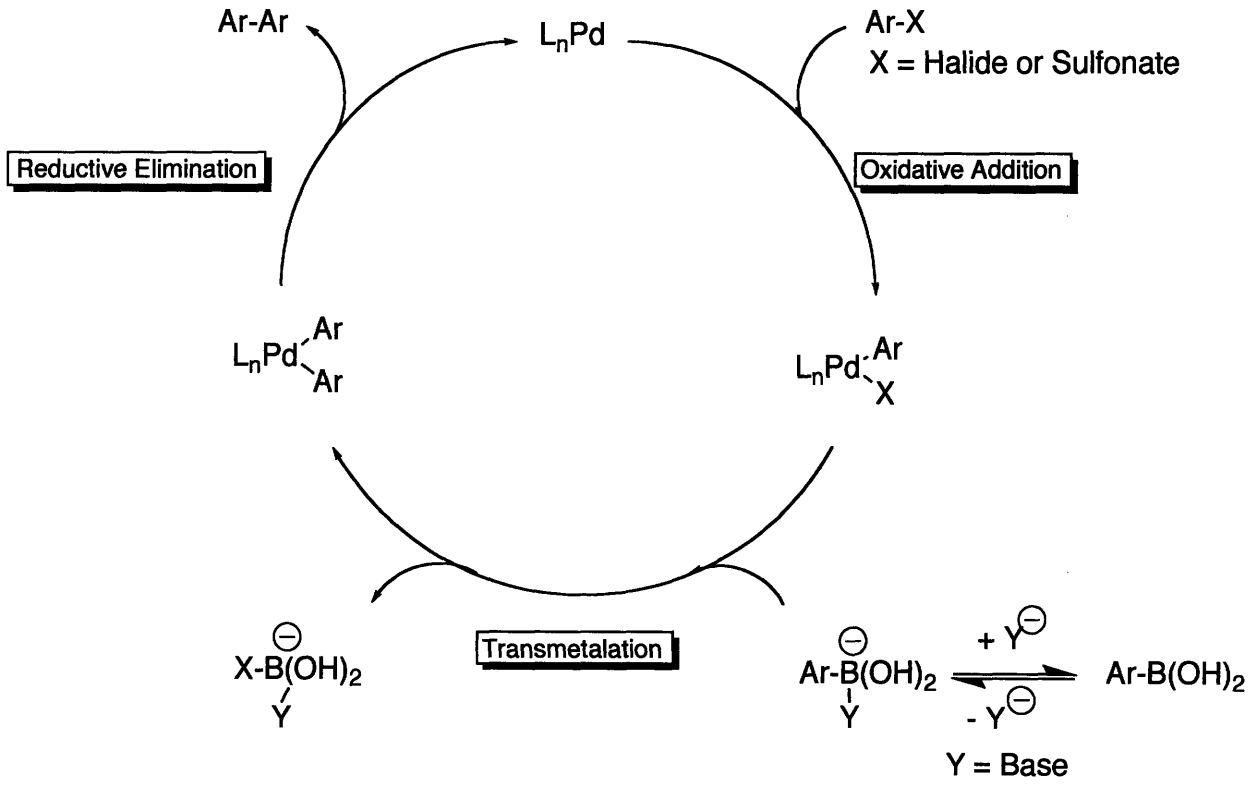

Figure 1. Proposed Catalytic Cycle of the Suzuki-Miyaura Reaction.

oxidative addition of the aryl electrophile to a ligated Pd(0) species, 2) a base-induced transmetalation with the aryl boronic acid or ester and 3) reductive elimination to form the product and regenerate the active catalyst. Importantly, the supporting ligand utilized in the reaction can play a significant role on each individual step of the cycle as well as on catalyst activity and stability. Furthermore, an increased focus on ligand design has directly contributed to the production of highly active catalyst systems, which allow for couplings to occur with more challenging substrates such as unactivated aryl chlorides and hindered boronic acids.[7] For example, a variety of catalyst-based upon dialkylbiaryl monophosphines have been shown to improve the efficacy of the overall cross-coupling process (Figure 2).[7b,8] These ligands have several key attributes that contribute to this enhancement in catalyst activity: 1) The size of the ligand provides access to monoligated $L_1Pd(0)$ intermediates, which promote oxidative addition of the aryl electrophile. 2) The formation of $L_1Pd(Ar)(X)$ species, which can more rapidly undergo transmetalation due to a decrease in steric congestion about the metal center, is favored. 3) The bottom aryl ring can provide a secondary interaction with palladium to facilitate reductive elimination and prevent catalyst decomposition.

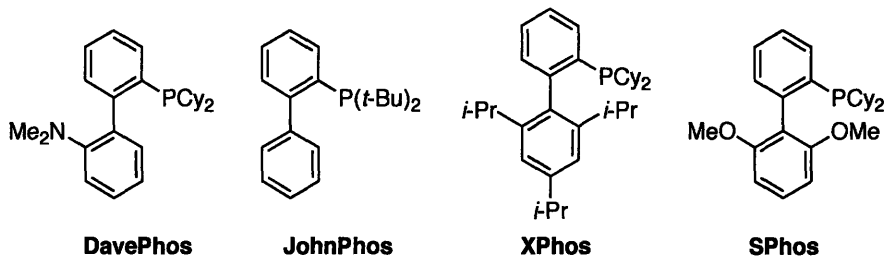

Figure 2. Examples of Dialkylbiaryl Monophosphine Ligands.

The ubiquity of the Suzuki-Miyaura reaction throughout organic synthesis exists, in part, due to the high stability and low toxicity of the organoborane nucleophiles. However, despite their advantages, aryl boronic acids and esters are typically prepared via the intermediacy of alkyl and aryllithiums or

Grignard reagents, processes that are not compatible with numerous functional groups.[9] Thus, this synthetic limitation prevents the preparation of a significant number of aryl boronic acids and esters.

Recently, transition-metal catalysis has offered an alternative to the classical methods for the preparation of carbon-boron bonds.[10] In the palladium-catalyzed process, an aryl halide is reacted with a boron reagent (i.e., bis(pinacolato)diboron or pinacol borane) and transformed into the corresponding boronate ester.[11] The mechanism of this process is believed to be closely related to that described for the Suzuki-Miyaura reaction. In the catalytic cycle, the metal again must undergo oxidative addition of the aryl halide, transmetalation with the boron reagent and reductive elimination to form the product. Due to the relative mildness of the conditions, these methods have been utilized in a variety of context such as natural product synthesis[12] and the preparation of high molecular weight π-conjugated dendrimers.[13]

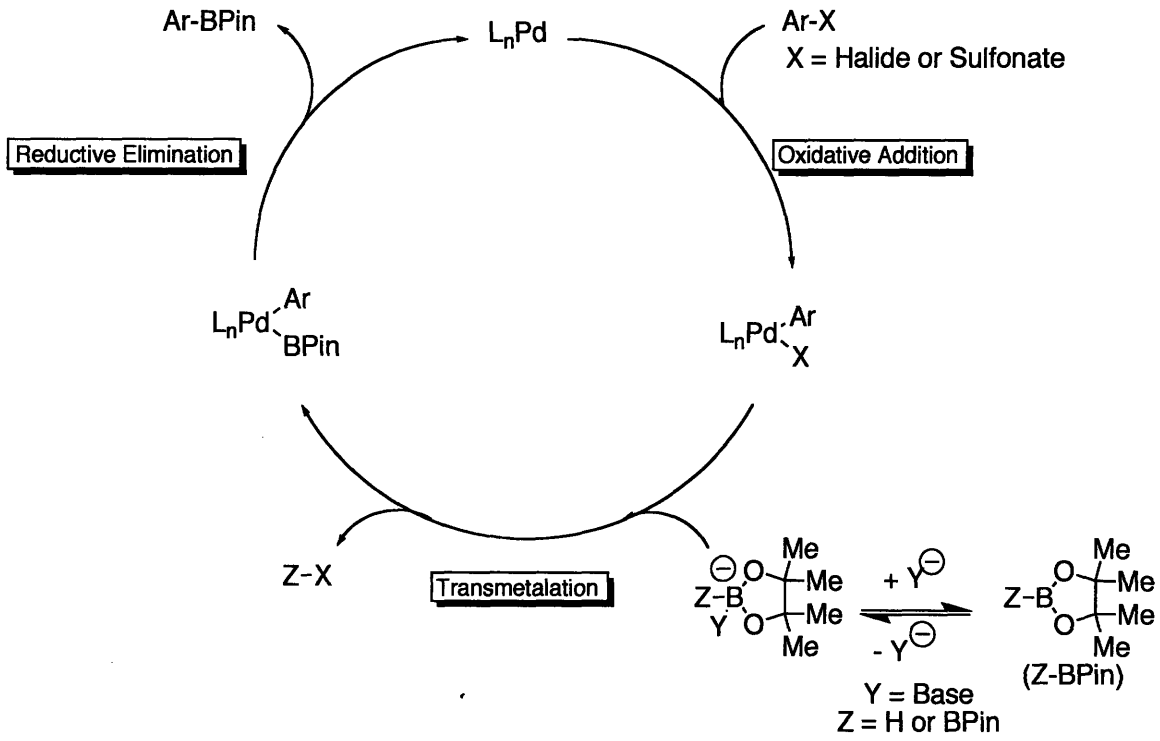

Figure 2. Proposed Catalytic Cycle of the Palladium-Catalyzed Borylation of Aryl Halides.

The work presented in this thesis represents recent advances in palladium-catalyzed processes. The work is described in four chapters. Chapters 1 and 2 focus on the development of catalyst systems for the Suzuki-Miyaura reaction of a variety of heteroaryl boronic acids and esters. The scope of the method is discussed in depth, and in many instances, the factors the govern the efficacy of the process are elaborated. Chapters 3 and 4 describe work conducted on the topic of the palladium-catalyzed borylation of aryl halides. A variety of conditions were developed to accomplish this transformation. In addition, "one-pot" procedures for the preparation of a wide range of biaryls from two aryl chlorides are presented.

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Chapter 1.

The Suzuki-Miyaura Reaction of Heteroaryl Boronic Acids and Esters

1.1 Introduction

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 towards 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[5b,7] to generate biaryls have also proven to be highly effective.

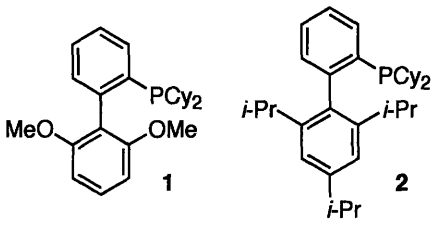


Figure 1. Structures of Ligands **1** and **2**.

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 XPhos (**2**) for the Suzuki-Miyaura reaction of heteroaryl boronic acids and esters.

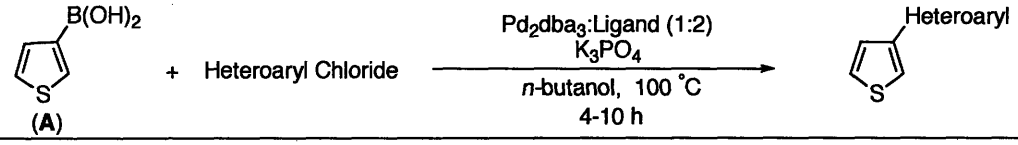
1.2 Results and Discussion

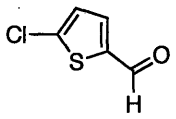
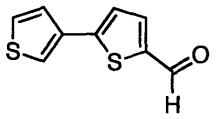
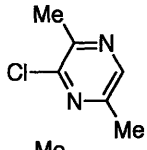
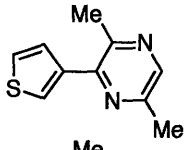
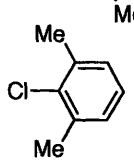
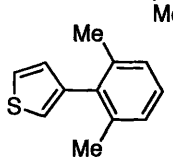
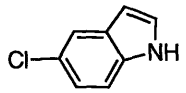
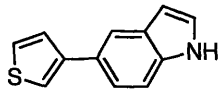
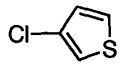
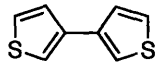
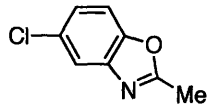
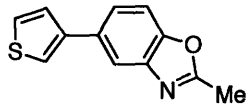
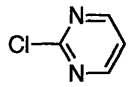
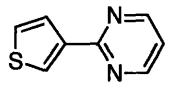
1.1.1 Thiophene Boronic Acids.

Thiophenes are found in a variety of natural products as well as pharmaceutically interesting 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 are plagued by several limitations.[9b,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; the tendency of these 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 of the stability of the thiophene boronic acids.

Our initial studies revealed that a catalyst system comprised 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, using 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

Table 1. Suzuki-Miyaura Reactions of **A**.[a]



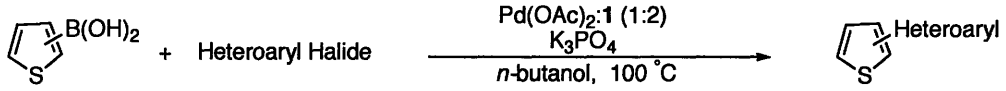
Entry	Heteroaryl Chloride	Product	Ligand	Pd (mol%)	Yield (%)[b]
1			**1**	0.25	71[c]
2			**1**	0.25	97[c,d]
3			**2**	2.0	77
4			**2**	2.0	90[e]
5			**2**	2.0	96
6			**2**	2.0	91
7			**2**	2.0	84[f,g]

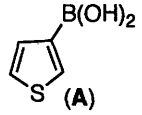
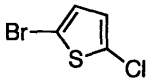
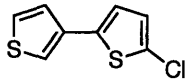
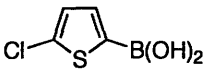
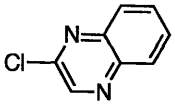
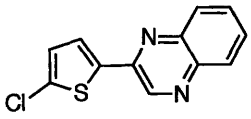
[a]Reaction Conditions: 1 equiv of aryl or heteroaryl chloride, 1.5 equiv of boronic acid, 2 equiv of K_3PO_4, *n*-butanol (2 mL/mmol halide), cat. Pd_2dba_3, L:Pd = 2:1. [b]Isolated yield based upon an average of two runs. [c]$Pd(OAc)_2$ was used instead of Pd_2dba_3. [d]*s*-Butanol was used as the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

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 3-chloro-2,5-dimethylpyrazine resulted in only 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, we, in all cases,

observed the formation of 3,3'-bithiophene (**3**) as a byproduct. We wondered whether the presence of **3** could be having a deleterious effect on the process. In order to probe this possibility, we examined the

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



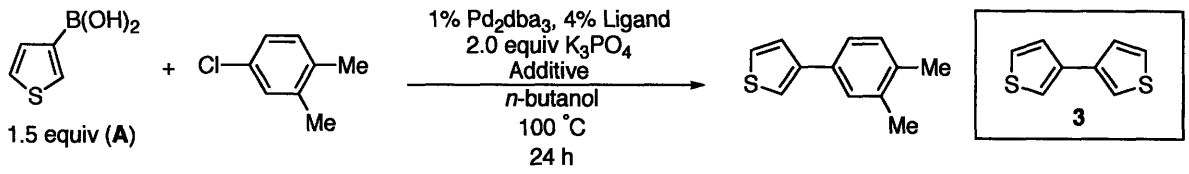
Entry	Boronic Acid	Heteroaryl Halide	Product	Pd (mol%)	Yield (%)[b]
1	 (**A**)			0.25	92
2				2.0	96[c]

[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 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.

reaction of **A** with 1-chloro-3,4-dimethylbenzene in the presence of 25 mol% **3**; only a 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 using **2**, however, coupling processes of **A** with unactivated heteroaryl chlorides were efficient. Significant homocoupling for related substrates (i.e., pyrrole, furan, 2-thiophene boronic acids) was not observed.

The reaction of **A** with unactivated aryl and heteroaryl chlorides using **2** as the supporting ligand proceeded in good to excellent yield. 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

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



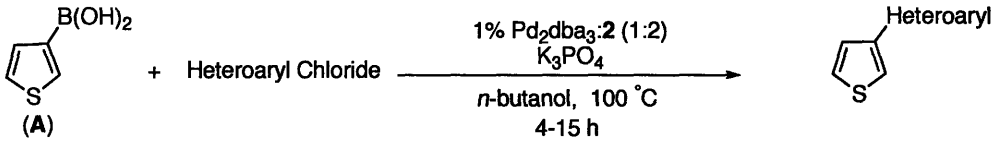
Entry	Ligand	Additive	Conversion to Product (%)[b]
1	**1**	None	93[c]
2	**1**	25 mol% **3**	7
3	**2**	None	100[c]
4	**2**	25 mol% **3**	100[c]

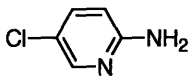
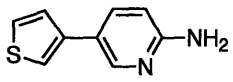
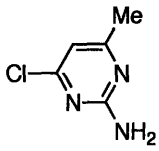
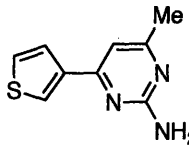
[a]Reaction Conditions: 1 equiv of aryl or heteroaryl chloride, 1.5 equiv of boronic acid, 2 equiv of K_3PO_4, *n*-butanol (2 mL/mmol halide), cat. Pd_2dba_3, L:Pd = 2:1. [b]GC conversion based upon an average of two runs. [c]ca. 10% *o*-xylene detected.

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 the yield for the process increased 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 product 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).

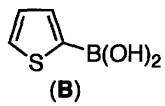
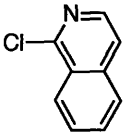
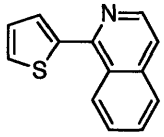
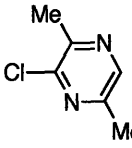
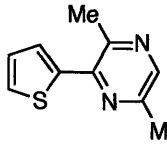
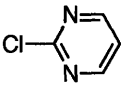
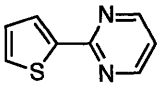
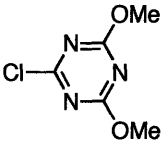
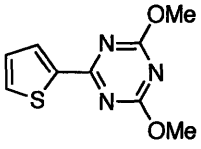
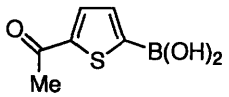
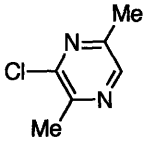
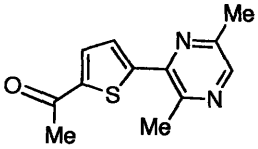
Table 4. Suzuki-Miyaura Reactions of Thiophene Boronic Acids with Chloroaminoazines.[a]



Entry	Heteroaryl 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 halide), cat. Pd_2dba_3, L:Pd = 2:1. [b]Isolated yield based upon an average of two runs. [c]4 Å Molecular sieves 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	Heteroaryl 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 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]4 Å Molecular sieves were added to the reaction mixture. [f]Reaction was conducted in *t*-amyl alcohol.

One drawback of our protocol was that it did not affect the efficient coupling of **B** with unactivated aryl or heteroaryl chlorides using 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 or dioxane) reduced the degree of decomposition of **B** but also slowed the rate of the desired reaction. Attempts to use potassium aryl 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**.

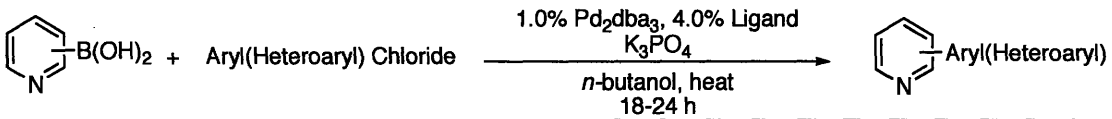
1.1.2 Pyridine Boronic Acids

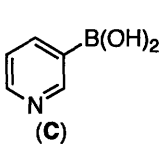
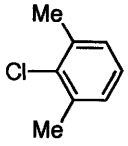
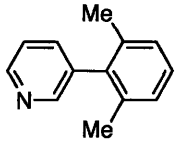
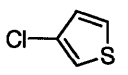
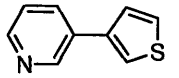
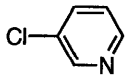
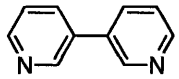
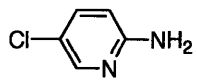
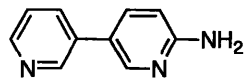
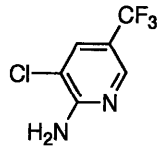
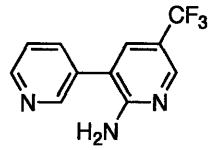
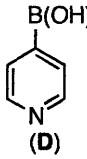
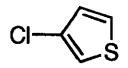
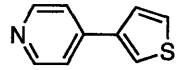
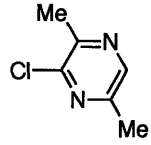
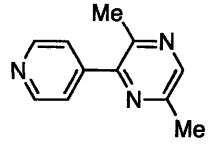
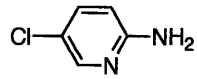
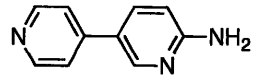
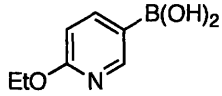
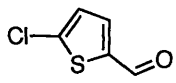
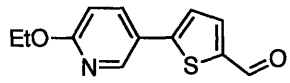
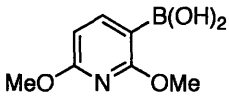
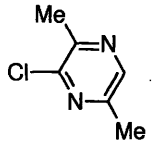
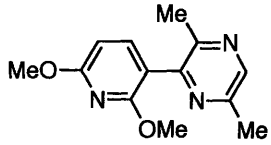
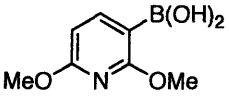
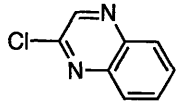
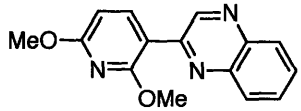
The Suzuki-Miyaura reaction of pyridine-derived boronic acids has proven to be particularly challenging,[9b,14] and as result, only a few relevant studies can be found.[5a,9a,d,f] The primary problem associated with these boronic acids is their slow rate of transmetalation, which is attributed to the 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, Entry 9-11). This protocol

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



Entry	Boronic Acid	Aryl(Heteroaryl) 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 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.

offered a general method for the preparation of pyridine-derived heterobiaryls. We note, however, that these protocols were not successful for the reaction of 2-pyridine boronic acids.

1.1.3 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 the cross-coupling has 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 its under going competitive protodeboronation. As such, its use was 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, thus, prepared in order to determine whether the nature of 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

Scheme 1. Synthesis of Pyrrole Boronate Ester Derivatives.

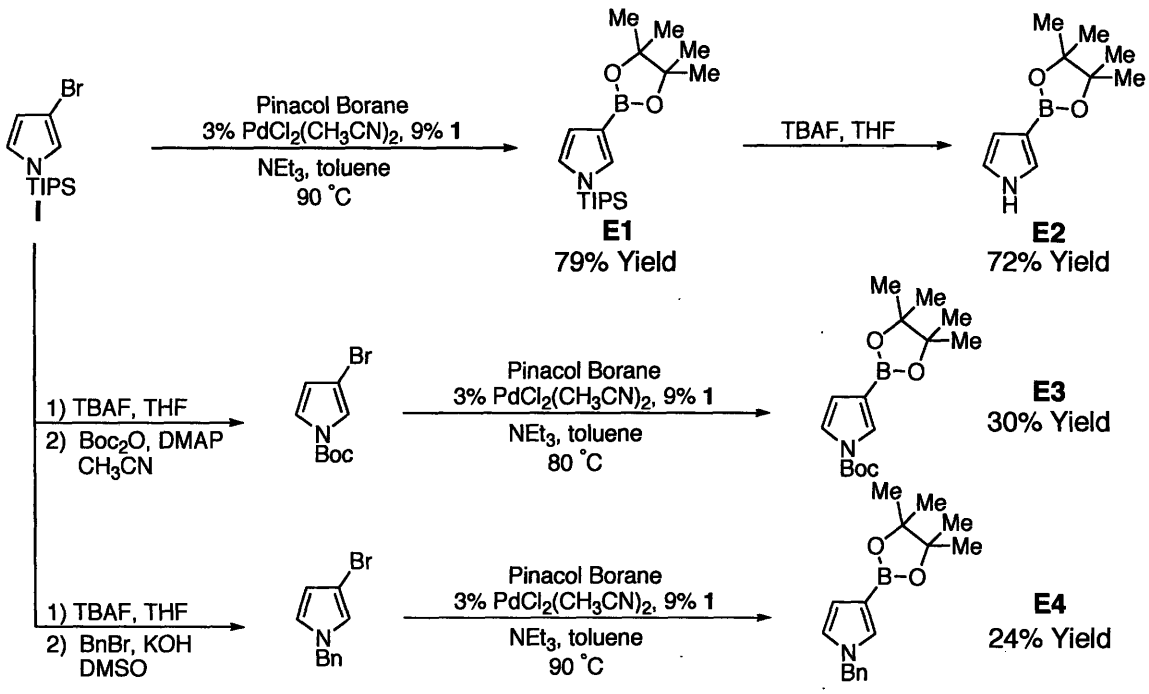
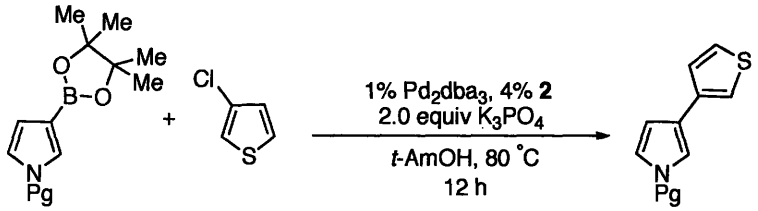


Table 7. Effect of Nitrogen-Protecting Group on the Reaction of Pyrrole-Derived Nucleophiles.



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

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 reaction 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 equal to or better yields 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 nature of the alcohol employed. 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 reaction 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 to 1; a procedure utilizing this solvent mixture gave quantitative yield of the biaryl (Figure 2).

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. Using 0.25% $Pd(OAc)_2$, 5-bromoindole (Table 8, Entry 1) and 4-bromoisoquinoline (Table 8, Entry 2) were 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-chloroquinaxoline (Table 8, Entry 7) led to a 82% and 83% yield of the desired biaryl, respectively.

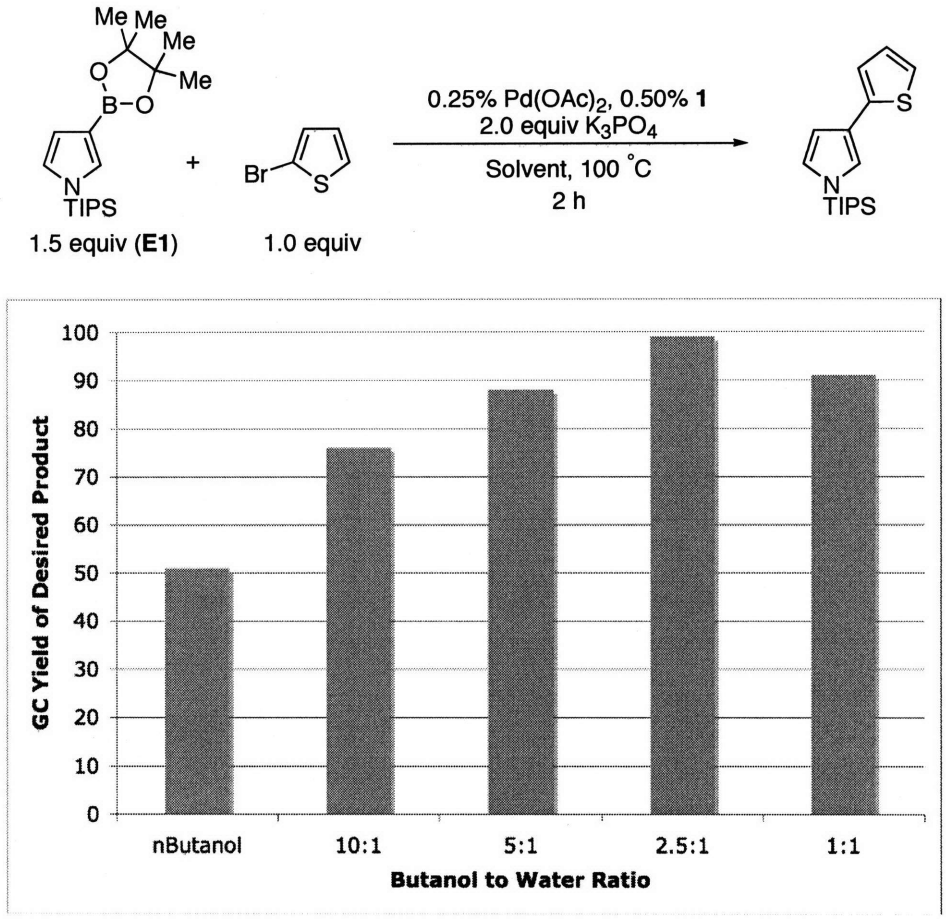
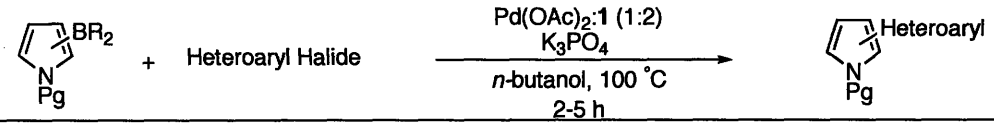


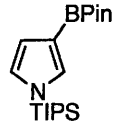
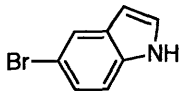
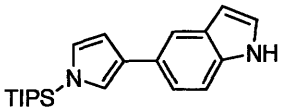
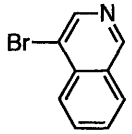
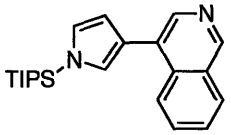
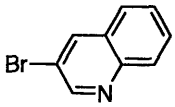
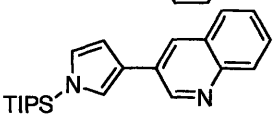
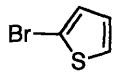
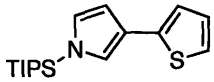
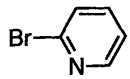
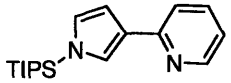
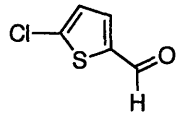
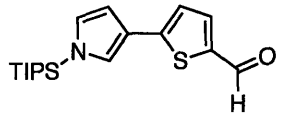
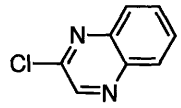
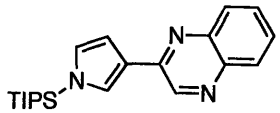
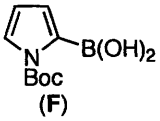
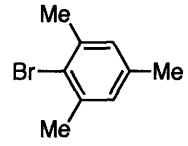
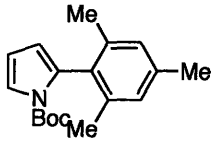
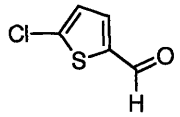
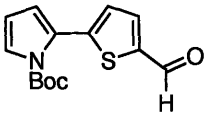
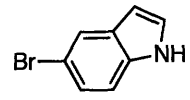
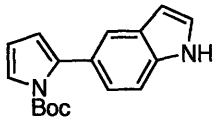
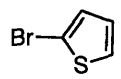
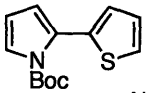
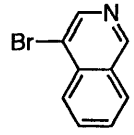
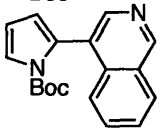
Figure 2. Effect of *n*-Butanol to Water Solvent Ratio on the Reation of **E1**.

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

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



Entry	Boron Derivative	Heteroaryl 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 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]Temperatue was 80 °C.

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 limitation, in general, can be attributed to rapid decomposition of these reagents when alcohols are employed as the solvent at elevated temperatures.

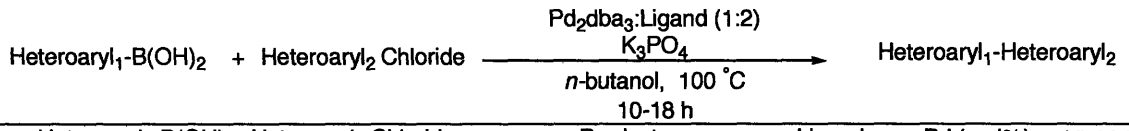
1.1.4 Indole Boronic Acids

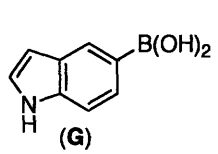
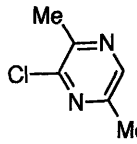
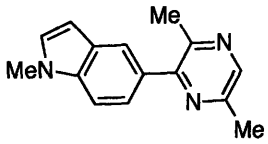
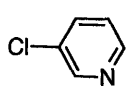
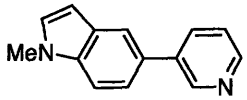
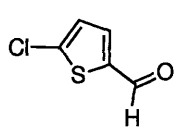
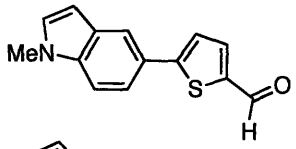
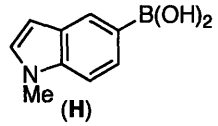
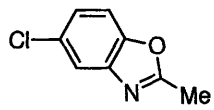
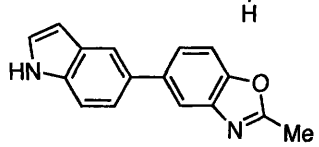
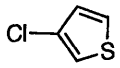
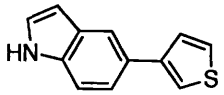
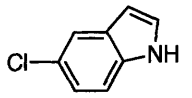
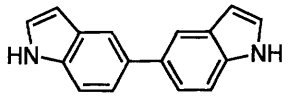
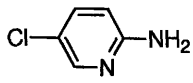
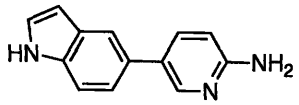
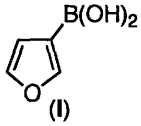
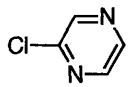
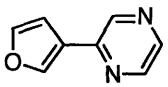
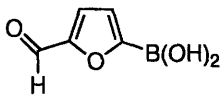
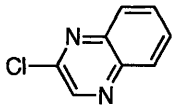
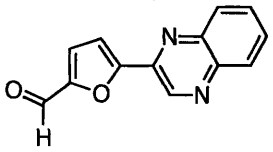
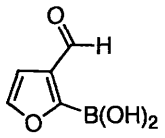
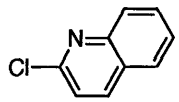
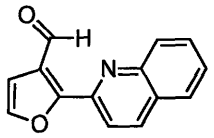
Indoles are found throughout nature and their derivatives display a broad spectrum of biological activity.[16] Due to their significance, the development of efficient methods for the derivatization of indole building blocks is an important research topic. Several groups have investigated the reactivity 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]

Utilizing 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, using 0.25 mol% $Pd(OAc)_2$, the reaction of 5-chloro-2-thiophene carbaldehyde 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.

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



Entry	$Heteroaryl_1$-$B(OH)_2$	$Heteroaryl_2$ 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	 (I)			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 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.

1.1.5 Furan Boronic Acids

The use of furan boronic acids are well precedented in Suzuki-Miyaura literature.[9b,12d,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.

Using a catalyst system based upon $Pd(OAc)_2$/**1**, 3-furan boronic acid (**I**) was coupled to a variety of activated heteroaryl chlorides in good to excellent yield. The reaction of **I** 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 9-10). Unactivated aryl chlorides, unfortunately, did not react in high yields with these furan boronic acids as under the reaction conditions, they underwent rapid decomposition. Reactions with 2-furan boronic acid were similarly unsuccessful.

1.3 Conclusion

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.

1.4 Experimental

1.4.1 General

All reactions were stirred with the aid of a magnetic stirrer and carried out under an argon atmosphere. *n*-Butanol (anhydrous), *sec*-butanol (anhydrous) and *tert*-amyl alcohol (reagent grade) were purchased from Aldrich Chemical Co. Commercially available materials were used without further

purification unless otherwise noted. SPhos (**1**) and XPhos (**2**) were synthesized in our laboratories but are commercially available from Aldrich Chemical Co. or Strem Chemicals, Inc. Aryl halides were purchased from Aldrich Chemical Co. Liquid aryl bromides were purified by passing through a pad of basic alumina prior to use. Boron reagents were purchased from Aldrich Chemical Co. or Frontier Scientific. Anhydrous granular potassium phosphate was purchased from Alfa Aesar and ground with a mortar and pestle and stored in a bench-top desiccator.

All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR spectroscopy and, in some cases, elemental analysis. Known compounds were characterized by ^{1}H NMR and melting points (for solids) and compared to their literature values. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300. Infrared spectra were recorded on an ASI Applied Systems ReactIR 1000 (neat samples were placed directly on the DiComp probe). Elemental analyses were preformed by Atlantic Microlabs Inc., Norcross, GA. All ^{1}H NMR experiments are reported in δ units, parts per million (ppm) downfield of TMS and were measured relative to the signals for the residual benzene (7.16 ppm), chloroform (7.26 ppm), dimethylsulfoxide (2.50 ppm) or methanol (3.31 ppm). All ^{13}C NMR spectra were reported in ppm relative to residual chloroform (77 ppm), dimethylsulfoxide (39.5 ppm) or methanol (49 ppm) and were obtained with ^{1}H decoupling. Melting points were obtained on a Mel-Temp capillary melting point apparatus. Gas chromatographic analyses were preformed on Hewlett-Packard 6890 gas chromatography instrument with a FID detector using 25 m x 0.20 mm capillary column with cross-linked methyl siloxane as a stationary phase.

The yields in tables 1-2 and 4-9 refer to isolated yields (average of two runs) of compounds estimated to be ≥ 95% pure as determined by ^{1}H NMR and/or combustion analysis.

1.4.2 Experimental for Reactions of Thiophene Boronic Acids

General Procedure A: Pd-Catalyzed Suzuki-Miyaura Couplings of Thiophene Boronic Acids.

An oven-dried Schlenk tube was charged with $Pd_2(dba)_3$ (2.3 mg, 0.0025 mmol), ligand (0.01 mmol), 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 a total of two times). *n*-Butanol (0.50 mL) was added via syringe, through the septum, followed by the addition of the aryl halide (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 (eluting with ethyl acetate) and the eluent was concentrated under reduced pressure. The crude material so obtained was purified via flash chromatography on silica gel.

General Procedure B: Pd-Catalyzed Suzuki-Miyaura Couplings of Thiophene Boronic Acids at Low Catalyst Loading.

Procedure A was followed with the following changes: A separate vial was initially charged with $Pd(OAc)_2$ (1.0 mol%) and SPhos (2.0 mol%). The vial was sealed with a Teflon-coated screwcap, a needle was inserted through the cap and the vial was then evacuated and backfilled with argon. *n*-Butanol (1 mL) was added and the mixture was briefly heated. 250 μL of this solution (0.25% Pd, 0.50% SPhos) was then added to the Schlenk flask containing the base, boronic acid and aryl halide. *n*-Butanol (250 μL) was added in the final solvent addition.

2,3'-Bithiophene-5-carbaldehyde (Table 1, entry 1). Following general procedure B, a mixture of 5-chlorothiophene-2-carbaldehyde (26.6 μL, 0.25 mmol), 3-thiophene boronic acid (48 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), $Pd(OAc)_2$ (0.25 mol%) and SPhos (0.50 mol%) was heated to 100 °C in *tert*-amyl alcohol with stirring for 4 h. The crude product was purified via flash column chromatography on silica gel (10% EtOAc/Hexanes) to provide the title compound in a 78% yield (38 mg) as a yellow solid, mp 122-123 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.84 (s, 1H), 7.67 (d, J= 3 Hz, 1H), 7.56 (dd, J = 3, 1 Hz, 1H), 7.37 (dd, J = 5, 3 Hz, 1H), 7.33 (dd, J = 5, 1 Hz, 1H), 7.26 (d, J = 5 Hz, 1H). ^{13}C NMR (75

MHz, $CDCl_3$) δ: 182.7, 148.7, 141.5, 137.5, 134.4, 127.2, 125.9, 124.0, 122.7. IR (neat, cm^{-1}): 3087, 1653, 1456, 1232. Anal. Calcd. for $C_8H_6OS_2$: C, 55.64; H, 3.11. Found C, 55.59; H, 3.02.

2,5-Dimethyl-3-(thiophen-3-yl)pyrazine (Table 1, entry 2). Following general procedure B, a mixture of 3-chloro-2,5-dimethylpyrazine (30.2 μL, 0.25 mmol), 3-thiophene boronic acid (48 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), $Pd(OAc)_2$ (0.25 mol%) and SPhos (0.50 mol%) was heated to 100 °C in *tert*-amyl alcohol with stirring for 4 h. The crude product was purified via flash column chromatography on silica gel (15% EtOAc/Hexanes) to provide the title compound in a 97% yield (42 mg) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.26 (s, 1H), 7.64 (ddd, J= 3, 2, 1 Hz, 1H) 7.49 (ddd, J = 5, 2, 1 Hz, 1H), 7.40 (ddd, J = 5, 3, 1 Hz, 1H), 2.67 (s, 3H), 2.55 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 150.3, 147.9, 147.7, 139.9, 128.4, 125.7, 125.6, 23.1, 21.1. IR (neat, cm^{-1}): 2921, 1564, 1530, 1435, 1372, 1329, 1166. ^1H NMR spectrum included.

3-(2,6-Dimethylphenyl)thiophene (Table 1, entry 3). Following general procedure A, a mixture of 2-chloro-m-xylene (33.1 μL, 0.25 mmol), 3-thiophene boronic acid (48 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), Pd_2dba_3 (2.3 mg, 0.0025 mmol) and XPhos (4.8 mg, 0.01 mmol) was heated to 100 °C in *n*-butanol with stirring for 10 h. The crude product was purified via flash column chromatography on silica gel (Hexanes) to provide the title compound in a 77% yield (36 mg) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.41 (dd, J = 5, 3 Hz, 1H), 7.18 (dd, J= 8, 7 Hz, 1H), 7.11 (t, J = 1 Hz, 2H), 7.05 (dd, J = 3, 1 Hz, 1H), 6.96 (dd, J = 5, 1 Hz, 1H), 2.11 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 140.7, 137.1, 128.7, 127.2, 125.2, 122.2, 20.8. IR (neat, cm^{-1}): 2924, 2851, 1678, 1527, 1435, 1372, 1166. ^1H NMR spectrum included.

5-(Thiophen-3-yl)-1*H*-indole (Table 1, entry 4). An oven-dried Schlenk tube was charged with a mixture of 5-chloroindole (37.9 mg, 0.25 mmol), $Pd_2(dba)_3$ (2.3 mg, 0.0025), XPhos (4.8 mg, 0.01 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, and the reaction mixture was heated to 100 °C. 3-thiophene boronic acid (48 mg, 0.375 mmol) in *n*-butanol (1.00 mL) was added via syringe pump through the

septum over 1 h. The septum was then replaced with a Teflon screwcap under argon and the Schlenk tube was sealed. The reaction mixture was heated at 100 °C for 15 h. 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 eluting with ethyl acetate and the eluent was concentrated under reduced pressure. The crude product was purified via flash column chromatography on silica gel (5% EtOAc/Hexanes) to provide the title compound in a 90% yield (45 mg) as a yellow solid, mp 80-82 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.12 (bs, 1H), 7.90 (t, J = 1 Hz, 1H), 7.48 (dd, J = 8, 2 Hz, 1H), 7.46 (dd, J = 5, 1 Hz, 1H), 7.40-7.44 (m, 2H), 7.22 (t, J = 3 Hz, 1H), 6.60 (t, J = 3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 143.6, 135.1, 128.2, 128.1, 126.8, 125.8, 124.8, 121.3, 118.8, 118.5, 111.2, 102.9. IR (neat, cm^{-1}): 2951, 2920, 1463, 854, 785. Anal. Calcd. for $C_{12}H_9NS$: C, 72.33; H, 4.55. Found C, 72.10; H, 4.72.

3,3'-Bithiophene (Table 1, entry 5).[19] Following general procedure A, a mixture of 3-chlorothiophene (23.2 μL, 0.25 mmol), 3-thiophene boronic acid (48 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), Pd_2dba_3 (2.3 mg, 0.0025 mmol) and XPhos (4.8 mg, 0.01 mmol) was heated to 100 °C in *n*-butanol with stirring for 10 h. The crude product was purified via flash column chromatography on silica gel (Hexanes) to provide the title compound in a 96% yield (36 mg) as a white solid, mp 119-121 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39 (dd, J = 3, 2 Hz, 1H), 7.35-7.36 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 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.

2-Methyl-5-(thiophen-3-yl)benzo[*d*]oxazole (Table 1, entry 6). Following general procedure A, a mixture of 5-chloro-2-methylbenzoxazole (41.9 mg, 0.25 mmol), 3-thiophene boronic acid (48 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), Pd_2dba_3 (2.3 mg, 0.0025 mmol) and XPhos (4.8 mg, 0.01 mmol) was heated to 100 °C in *n*-butanol with stirring for 10 h. The crude product was purified via flash column chromatography on silica gel (5% EtOAc/Hexanes) to provide the title compound in a 91% yield (49 mg) as a white solid, mp 85-87 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.84 (d, J = 2 Hz, 1H), 7.52-7.54 (dd, J = 8, 2 Hz, 1H) 7.47 (d, J = 8 Hz, 1H), 7.44 (t, J = 3 Hz, 1H), 7.41 (d, J = 1 Hz, 1H), 7.40 (d, J = 1 Hz, 1H), 2.65 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.5, 150.3, 142.1, 132.6, 126.6, 126.3, 123.3, 120.2,

117.1, 110.2, 14.6. IR (neat, cm^{-1}): 3075, 1621, 1578, 1268, 920. Anal. Calcd. for $C_{12}H_9NOS$: C, 66.95; H, 4.21. Found C, 66.81; H, 4.37.

2-(Thiophen-3-yl)pyrimidine (Table 1, entry 7).[20] Following general procedure A, a mixture of 2-chloropyrimidine (28.6 mg, 0.25 mmol), 3-thiophene boronic acid (48 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), 4Å molecular sieves (62.5 mg), Pd_2dba_3 (2.3 mg, 0.0025 mmol) and XPhos (4.8 mg, 0.01 mmol) was heated to 100 °C in *tert*-amyl alcohol with stirring for 4 h. The crude product was purified via flash column chromatography on silica gel (10% EtOAc/Hexanes) to provide the title compound in a 84% yield (38 mg) as a white solid, mp 92-94 °C. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.72 (dd, J = 5,1 Hz, 2H), 8.28 (dd, J = 5, 2 Hz, 1H), 7.88 (dd, J = 5, 1 Hz, 1H), 7.37 (dt, J = 4, 1 Hz, 1H), 7.10 (dt, J = 4, 1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.8, 157.2, 141.5, 127.9, 127.3, 126.1, 118.6. IR (neat, cm^{-1}): 3120, 1636, 1556, 1526, 1433, 1377. 1089. ^1H NMR spectrum included.

5-Chloro-2,3'-bithiophene (Table 2, entry 1). Following general procedure B, a mixture of 2-bromo-5-chlorothiophene (27.4 μL, 0.25 mmol), 3-thiophene boronic acid (48 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), $Pd(OAc)_2$ (0.25 mol%) and SPhos (0.50 mol%) was heated to 100 °C in *n*-butanol with stirring for 4 h. The crude product was purified via recrystallization (Hexanes) to provide the title compound in a 82% yield (41 mg) as a white solid, mp 74-76 °C. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.35 (dd, J = 5, 3 Hz, 1H), 7.31 (dd, J= 3, 2 Hz, 1H) 7.23 (dd, J = 5, 2 Hz, 1H), 6.95 (d, J = 4 Hz, 1H), 6.85 (d, J = 4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 137.8, 134.8, 128.1, 126.7, 126.4, 125.6, 122.2, 119.7. IR (neat, cm^{-1}): 3089, 1446, 769. ^1H NMR spectrum included.

2-(5-Chloro-thiophen-2-yl)quinoxaline (Table 2, entry 2). Following general procedure A, a mixture of 2-chloroquinoxaline (41.2 mg, 0.25 mmol), 5-chloro-2-thiophene boronic acid (60.9 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), Pd_2dba_3 (2.3 mg, 0.0025 mmol) and XPhos (4.8 mg, 0.01 mmol) was heated to 100 °C in *tert*-amyl alcohol with stirring for 4 h. The crude product was purified via recrystallization (Hexanes) to provide the title compound in a 96% yield (59 mg) as a yellow solid, mp 71-73 °C. ^1H NMR (300 MHz, $CDCl_3$) δ: 9.13 (s, 1H), 8.05 (dd, J = 8, 1 Hz, 1H), 8.01 (dd, J = 8, 1 Hz, 1H), 7.59 (d, J =4 Hz, 1H), 6.99 (d, J= 4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 146.4, 141.9, 141.3, 141.1, 141.0, 134.9,

130.6, 129.4, 129.1, 129.0, 127.6, 126.0. IR (neat, cm^{-1}): 3075, 2924, 2851, 1611, 1549, 1432, 1227. Anal. Calcd. for $C_{12}H_8N_2SCl$: C, 58.42; H, 2.86. Found C, 58.39; H, 2.82.

3-(3,4-Dimethylphenyl)thiophene (Table 3, entry 1). Following general procedure A, a mixture of 3,4-dimethylchlorobenzene (0.25 mmol), 3-thiophene boronic acid (48 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), Pd_2dba_3 (2.3 mg, 0.0025 mmol) and SPhos (4.1 mg, 0.01 mmol) was heated to 100 °C in *n*-butanol with stirring for 24 h. The crude product was analyzed via gas chromatography with dodecane as an internal standard. A 93% conversion of the aryl chloride was detected.

3-(3,4-Dimethylphenyl)thiophene (Table 3, entry 2). Following general procedure A, a mixture of 3,4-dimethylchlorobenzene (0.25 mmol), 3-thiophene boronic acid (48 mg, 0.375 mmol), 3,3'-bithiophene (41 mg, 0.0625 mmol), K_3PO_4 (106 mg, 0.50 mmol), Pd_2dba_3 (2.3 mg, 0.0025 mmol) and SPhos (4.1 mg, 0.01 mmol) was heated to 100 °C in *n*-butanol with stirring for 24 h. The crude product was analyzed via gas chromatography with dodecane as an internal standard. A 7% conversion of the aryl chloride was detected.

3-(3,4-Dimethylphenyl)thiophene (Table 3, entry 3). Following general procedure A, a mixture of 3,4-dimethylchlorobenzene (0.25 mmol), 3-thiophene boronic acid (48 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), Pd_2dba_3 (2.3 mg, 0.0025 mmol) and XPhos (4.1 mg, 0.01 mmol) was heated to 100 °C in *n*-butanol with stirring for 24 h. The crude product was analyzed via gas chromatography with dodecane as an internal standard. A 100% conversion of the aryl chloride was detected.

3-(3,4-Dimethylphenyl)thiophene (Table 3, entry 4). Following general procedure A, a mixture of 3,4-dimethylchlorobenzene (0.25 mmol), 3-thiophene boronic acid (48 mg, 0.375 mmol), 3,3'-bithiophene (41 mg, 0.0625 mmol), K_3PO_4 (106 mg, 0.50 mmol), Pd_2dba_3 (2.3 mg, 0.0025 mmol) and XPhos (4.1 mg, 0.01 mmol) was heated to 100 °C in *n*-butanol with stirring for 24 h. The crude product was analyzed via gas chromatography with dodecane as an internal standard. A 100% conversion of the aryl chloride was detected.

5-(Thiophen-3-yl)pyridin-2-amine (Table 4, entry 1). Following general procedure A, a mixture of 2-amino-5-chloropyridine (32.1 mg, 0.25 mmol), 3-thiophene boronic acid (48 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), Pd_2dba_3 (2.3 mg, 0.0025 mmol) and XPhos (4.8 mg, 0.01 mmol) was heated to 100 °C in *n*-butanol with stirring for 15 h. The crude product was purified via flash column chromatography on silica gel (40% EtOAc/Hexanes) to provide the title compound in a 95% yield (42 mg) as a white solid, mp 141-143 °C. ^{1}H NMR (300 MHz, CD_3OD) δ: 8.18 (d, J = 2 Hz, 1H), 7.77 (dd, J = 8, 2 Hz, 1H), 7.44-7.48 (m, 2H), 7.35 (dd, J = 5, 2 Hz, 1H), 6.64 (d, J = 8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.3, 145.8, 139.3, 136.0, 126.4, 125.7, 122.6, 118.7, 108.5. IR (neat, cm^{-1}): 3439, 2924, 2851, 1653, 1500, 1201, 1089. ^{1}H NMR spectrum included.

4-Methyl-6-(thiophen-3-yl)pyrimidin-2-ylamine (Table 4, entry 2). Following general procedure A, a mixture of 2-amino-4-chloro-6-methylpyrimidine (35.9 mg, 0.25 mmol), 3-thiophene boronic acid (48 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), 4 Å molecular sieves (62.5 mg), Pd_2dba_3 (2.3 mg, 0.0025 mmol) and XPhos (4.8 mg, 0.01 mmol) was heated to 100 °C in *tert*-amyl alcohol with stirring for 4 h. The crude product was purified via flash column chromatography on silica gel (40% EtOAc/Hexanes) to provide the title compound in a 80% yield (37 mg) as a yellow solid, mp 182-184 °C. ^{1}H NMR (300 MHz, CD_3OD) δ: 8.15 (dd, J = 3, 1 Hz, 1H), 7.68 (dd, J = 5, 1 Hz, 1H), 7.49 (dd, J = 5, 3 Hz, 1H), 6.96 (s, 1H), 2.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 203.5, 170.0, 162.7, 127.8, 127.7, 127.4, 122.1, 107.5, 23.8. IR (neat, cm^{-1}): 3350, 3187, 1645, 1580, 1552, 1466, 1418, 1238, 1089. ^{1}H NMR spectrum included.

1-(Thiophen-2-yl)isoquinoline (Table 5, entry 1).[21] Following general procedure B, a mixture of 1-chloroisoquinoline (40.9 mg, 0.25 mmol), 2-thiophene boronic acid (48 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), $Pd(OAc)_2$ (0.25 mol%) and SPhos (0.50 mol%) was heated to 100 °C in *sec*-butanol with stirring for 10 h. The crude product was purified via flash column chromatography on silica gel (10% EtOAc/Hexanes) to provide the title compound in a 96% yield (51 mg) as a yellow solid, mp 67-69 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.56 (d, J = 7 Hz, 1H), 8.51 (d, J= 8 Hz, 1H), 7.86 (dd, J = 8, 1 Hz, 1H), 7.68-7.71 (dt, J = 7, 1 Hz, 1H), 7.62 (m, 2H), 7.58 (d, J = 6 Hz, 1H), 7.53-7.54 (dt, J = 6, 1 Hz, 1H),

7.20-7.22 (ddd, J = 6, 3, 1, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.5, 142.7, 142.1, 130.1, 128.7, 127.9, 127.6, 127.4, 127.1, 126.8, 126.1, 119.9. IR (neat, cm^{-1}): 3053, 2918. 2851, 1617, 1550, 1434, 1340. Anal. Calcd. for $C_{13}H_9NS$: C, 73.90; H, 4.29. Found C, 73.69; H, 4.17.

2,5-Dimethyl-3-(thiophen-2-yl)pyrazine (Table 5, entry 2). Following general procedure A, a mixture of 3-chloro-2,5-dimethylpyrazine (30.2 μL, 0.25 mmol), 2-thiophene boronic acid (48 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol) and SPhos (4.1 mg, 0.01 mmol) was heated to 100 °C in *sec*-butanol with stirring for 4 h. The crude product was purified via flash column chromatography on silica gel (15% EtOAc/Hexanes) to provide the title compound in a 96% yield (45 mg) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.21 (s, 1H), 7.53 (dd, J= 4, 1 Hz, 1H), 7.46 (dd, J = 5, 1 Hz, 1H), 7.14 (dd, J = 5, 4 Hz, 1H), 2.77 (s, 3H), 2.54 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 150.2, 146.2, 146.1, 143.0, 141.0, 128.4, 127.8, 127.5, 23.9, 21.0. IR (neat, cm^{-1}): 2921, 1564, 1530, 1435, 1372, 1329, 1166. Anal. Calcd. for $C_8H_6N_2S$: C, 59.23; 3.73. Found C, 59.35; H, 3.72.

2-(Thiophen-2-yl)pyrimidine (Table 5, entry 3). Following general procedure A, a mixture of 2-chloropyrimidine (28.6 mg, 0.25 mmol), 2-thiophene boronic acid (48 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), 4Å molecular sieves (62.5 mg), Pd_2dba_3 (2.3 mg, 0.0025 mmol) and XPhos (4.8 mg, 0.01 mmol) was heated to 100 °C in *tert*-amyl alcohol with stirring for 6 h. The crude product was purified via flash column chromatography on silica gel (5% EtOAc/Hexanes) to provide the title compound in a 85% yield (34 mg) as a white solid, mp 79-80 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.67 (dd, J = 5, 1 Hz, 2H), 8.00 (dd, J= 5, 2 Hz, 1H), 7.47 (dd, J = 5, 1 Hz, 1H), 7.14 (dt, J = 4, 1 Hz, 1H), 7.06 (dt, J = 4, 1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.4, 157.1, 143.1, 129.9, 128.9, 128.3, 118.4. IR (neat, cm^{-1}): 3120, 1636, 1556, 1526, 1433, 1377. ^{1}H NMR spectrum included.

2,4-Dimethoxy-6-(thiophen-2-yl)-1,3,5-triazine (Table 5, entry 4). Following general procedure A, a mixture of 2-chloro-4,6-dimethoxy-1,3,5-triazine (43.9 mg, 0.25 mmol), 2-thiophene boronic acid (48 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), 4Å molecular sieves (62.5 mg),), Pd_2dba_3 (2.3 mg, 0.0025 mmol) and XPhos (4.8 mg, 0.01 mmol) was heated to 100 °C in *tert*-amyl alcohol with stirring for 6 h. The crude product was purified via flash column chromatography on silica gel (10%

EtOAc/Hexanes) to provide the title compound in a 84% yield (48 mg) as a white solid, mp 81-83 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.11 (dd, J = 4, 1 Hz, 1H), 7.56 (dd, J= 5, 1 Hz, 1H), 7.12 (dd, J = 5, 4 Hz, 1H), 4.06 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.4, 170.5, 140.5, 132.4, 131.8, 128.2, 55.1. IR (neat, cm^{-1}): 2998, 2951, 2873, 1555, 1497, 1378, 1359, 1335, 1105, 1045, 817. ^{1}H NMR spectrum included.

1-[5-(3,6-Dimethyl-pyrazin-2-yl)thiophen-2-yl]ethanone (Table 5, entry 5). Following general procedure A, a mixture of 3-chloro-2,5-dimethylpyrazine (30.2 μL, 0.25 mmol), 5-acetyl-2-thiophene boronic acid (63.8 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), Pd_2dba_3 (2.3 mg, 0.0025 mmol) and XPhos (4.8 mg, 0.01 mmol) was heated to 100 °C in *tert*-amyl alcohol with stirring for 6 h. The crude product was purified via flash column chromatography on silica gel (25% EtOAc/Hexanes) to provide the title compound in a 98% yield (57 mg) as a white solid, mp 85-87 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.27 (s, 1H), 7.69 (d, J = 5 Hz, 1H), 7.53 (d, J = 5 Hz, 1H), 2.76 (s, 3H), 2.57 (s, 3H), 2.54 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 190.8, 150.7, 150.4, 146.9, 145.2, 145.0, 142.5, 132.5, 128.0, 26.9, 23.8, 21.0. IR (neat, cm^{-1}): 2922, 2851, 1658, 1526m 1445, 1362, 1271, 1166. ^{1}H NMR spectrum included.

1.4.3 Experimental for Reactions of Pyridine Boronic Acids

General Procedure C: Pd-Catalyzed Suzuki-Miyaura Couplings of Pyridine Boronic Acids.

An-oven dried Schlenk tube was charged with $Pd_2(dba)_3$ (2.3 mg, 0.0025 mmol), ligand (0.01 mmol), pyridine boronic acid (46.1 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 the addition of the aryl halide (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 (eluting with ethyl acetate) and the eluent was concentrated under reduced pressure. The crude material so obtained was purified via flash chromatography on silica gel.

3-(2,6-Dimethylphenyl)pyridine (Table 6, entry 1).[22] Following general procedure C, a mixture of 2-chloro-*m*-xylene (33.1 μL, 0.25 mmol), 3-pyridine boronic acid (46.1 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), Pd_2dba_3 (2.3 mg, 0.0025 mmol) and XPhos (4.8 mg, 0.01 mmol) was heated to 100 °C in *n*-butanol with stirring for 18 h. The crude product was purified via flash column chromatography on silica gel (15% EtOAc/Hexanes) to provide the title compound in an 81% yield (37 mg) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.60 (dd, J = 5, 1 Hz, 1H), 8.44 (d, J = 2 Hz, 1H), 7.51 (dt, J = 8, 2 Hz, 1H) 7.37 (dd, J = 8, 5 Hz, 1H) 7.21 (dd, J = 8, 7 Hz, 1H), 7.13 (d, J = 7 Hz, 2H), 2.03 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 150.0, 148.1, 137.8, 136.7, 136.3, 127.8, 127.5, 123.3, 20.9. IR (neat, cm^{-1}): 3023, 2921, 1653, 1565, 1463, 1406. ^{1}H NMR spectrum included.

3-(Thiophen-3-yl)pyridine (Table 6, entry 2).[20] Following general procedure C, a mixture of 3-chlorothiophene (23.2 μL, 0.25 mmol), 3-pyridine boronic acid (46.1 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), Pd_2dba_3 (2.3 mg, 0.0025 mmol) and XPhos (4.8 mg, 0.01 mmol) was heated to 100 °C in *n*-butanol with stirring for 18 h. The crude product was purified via flash column chromatography on silica gel (10% EtOAc/Hexanes) to provide the title compound in a 90% yield (36 mg) as a white solid, mp 70-72 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.87 (d, J = 2 Hz, 1H), 8.53 (dd, J = 5, 2 Hz, 1H), 7.84-7.86 (ddd, J = 8, 3, 2 Hz, 1H), 7.52 (dd, J = 3, 1 Hz, 1H), 7.44 (dd, J = 5, 3 Hz, 1H), 7.39 (dd, J = 5, 2 Hz, 1H), 7.30-7.33 (ddd, J = 8, 5, 1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 148.2, 147.6, 138.7, 133.4, 131.5, 126.9, 125.8, 123.6, 121.4. IR (neat, cm^{-1}): 3100, 3077, 2925, 1574, 1431, 1322, 1222. Anal. Calcd. for C_9H_7NS: C, 67.05; H, 4.38. Found C, 66.93; H, 4.55.

3,3'-Bipyridinyl (Table 6, entry 3).[23] Following general procedure C, a mixture of 3-chloropyridine (23.8 μL, 0.25 mmol), 3-pyridine boronic acid (46.1 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), Pd_2dba_3 (2.3 mg, 0.0025 mmol) and XPhos (4.8 mg, 0.01 mmol) was heated to 120 °C in *n*-butanol with stirring for 18 h. The crude product was purified via flash column chromatography on silica gel (EtOAc)

to provide the title compound in a 97% yield (38 mg) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.83 (d, J = 2 Hz, 1H), 8.64 (dd, J = 5, 1 Hz, 1H), 7.87 (dt, J = 8, 2 Hz, 1H), 7.40 (dd, J = 8, 5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 149.2, 148.1, 134.4, 133.4, 123.7. IR (neat, cm^{-1}): 3031, 2962, 1585, 1465, 1425, 1396, 1260, 1024. ^{1}H NMR spectrum included.

3,3'-Bipyridin-6-amine (Table 6, entry 4).[9f] Following general procedure C, a mixture of 2-amino-5-chloropyridine (32.1 mg, 0.25 mmol), 3-pyridine boronic acid (46.1 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), Pd_2dba_3 (2.3 mg, 0.0025 mmol) and XPhos (4.8 mg, 0.01 mmol) was heated to 120 °C in *n*-butanol with stirring for 24 h. The crude product was purified via flash column chromatography on silica gel (10% Methanol/EtOAc) to provide the title compound in a 95% yield (40 mg) as a yellow solid, mp 134-136 °C. ^{1}H NMR (300 MHz, DMSO) δ: 8.63 (t, J = 1 Hz, 1H), 8.60 (dt, J = 5, 1 Hz, 1H), 8.31 (t, J = 1 Hz, 1H), 7.88 (dt, J = 8, 1 Hz, 1H), 7.61 (s, 1H), 7.48 (dd, J = 8, 5 Hz, 1H), 6.62 (bs, 2H). ^{13}C NMR (75 MHz, DMSO) δ: 159.5, 149.3, 148.9, 145.4, 136.4, 134.6, 132.5, 123.9, 116.7. IR (neat, cm^{-1}): 3328, 3198, 1624, 1511, 1474, 1425, 1384. ^{1}H NMR spectrum included.

5-(Trifluoromethyl)-3,3'-bipyridin-2-amine (Table 6, entry 5).[9f] Following general procedure C, a mixture of 2-amino-3-chloro-5-trifluoromethylpyridine (49.1 mg, 0.25 mmol), 3-pyridine boronic acid (46.1 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), Pd_2dba_3 (2.3 mg, 0.0025 mmol) and XPhos (4.8 mg, 0.01 mmol) was heated to 120 °C in *n*-butanol with stirring for 24 h. The crude product was purified via flash column chromatography on silica gel (10% Methanol/EtOAc) to provide the title compound in a 95% yield (57 mg) as a white solid, mp 167-169 °C. ^{1}H NMR (300 MHz, DMSO) δ: 8.63 (t, J = 1 Hz, 1H), 8.60 (dt, J = 5, 2 Hz, 1H), 8.31 (t, J = 1 Hz, 1H), 7.88 (dt, J = 8, 2 Hz, 1H), 7.60 (d, J = 2 Hz, 1H), 7.48 (dd, J = 8, 5 Hz, 1H), 6.62 (bs, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ: 160.9, 150.2, 150.0, 146.7, 146.6, 138.8, 136.6, 136.5, 134.9, 125.8, 119.0. IR (neat, cm^{-1}): 3407, 2254, 2128, 1649, 1269, 1049, 1025, 1003. ^{1}H NMR spectrum included.

4-(Thiophen-3-yl)pyridine (Table 6, entry 6). Following general procedure C, a mixture of 3-chlorothiophene (23.2 μL, 0.25 mmol), 4-pyridine boronic acid (46.1 mg, 0.375 mmol), K_3PO_4 (106 mg,

0.50 mmol), Pd_2dba_3 (2.3 mg, 0.0025 mmol) and XPhos (4.8 mg, 0.01 mmol) was heated to 100 °C in *n*-butanol with stirring for 18 h. The crude product was purified via flash column chromatography on silica gel (10% EtOAc/Hexanes) to provide the title compound in a 90% yield (36 mg) as a white solid, mp 124-126 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.60 (d, J = 5 Hz, 2H), 7.65 (t, J = 3 Hz, 1H), 7.45-7.47 (m, 2H), 7.43 (d, J = 5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 150.3, 142.5, 139.4, 127.1, 125.6, 123.0, 120.7. IR (neat, cm^{-1}): 3092, 3036, 2924, 1594, 1553, 1425. Anal. Calcd. for C_9H_7NS: C, 67.05; H, 4.38. Found C, 67.03; H, 4.53.

2,5-Dimethyl-3-(pyridin-4-yl)pyrazine (Table 6, entry 7).[9f] Following general procedure C, a mixture of 3-chloro-2,5-dimethylpyrazine (30.2 μL, 0.25 mmol), 4-pyridine boronic acid (46.1 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol) and SPhos (4.1 mg, 0.01 mmol) was heated to 100 °C in *n*-butanol with stirring for 12 h. The crude product was purified via flash column chromatography on silica gel (20% EtOAc/Hexanes) to provide the title compound in a 83% yield (39 mg) as a yellow solid, mp 56-58 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.73 (d, J = 4 Hz, 2H), 8.39 (s, 1H), 7.49 (d, J = 4 Hz, 2H), 2.58 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 150.8, 149.9, 148.1, 146.4, 143.1, 130.5, 123.5, 22.3, 21.1. IR (neat, cm^{-1}): 2925, 2857, 1724, 1598, 1449, 1404, 1370. Anal. Calcd. for $C_{11}H_{11}N_3$: C, 71.33; H, 5.99. Found C, 71.22; H, 6.16.

3,4'-Bipyridin-6-amine (Table 6, entry 8).[9f] Following general procedure C, a mixture of 2-amino-5-chloropyridine (32.1 mg, 0.25 mmol), 4-pyridine boronic acid (46.1 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), Pd_2dba_3 (2.3 mg, 0.0025 mmol) and XPhos (4.8 mg, 0.01 mmol) was heated to 120 °C in *n*-butanol with stirring for 24 h. The crude product was purified via flash column chromatography on silica gel (10% Methanol/EtOAc) to provide the title compound in a 95% yield (40 mg) as a yellow solid, mp 171-173 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.43 (d, J = 6 Hz, 2H), 8.29 (d, J = 2 Hz, 1H), 7.80 (dd, J = 8, 3 Hz, 1H), 7.55 (d, J = 6 Hz, 2H), 6.63 (d, J = 8 Hz, 1H), 4.90 (bs, 2H). ^{13}C NMR (75 MHz, CD_3OD) δ: 161.8, 151.3, 150.6, 148.1, 147.0, 137.6, 123.3, 123.1, 121.6, 110.5. IR (neat, cm^{-1}): 3428, 2925, 2856, 1633, 1519, 1488, 1394, 1221. Anal. Calcd. for $C_{10}H_9N_3$: C, 70.16; H, 5.30. Found C, 70.00; H, 5.49.

5-(6-Ethoxypyridin-3-yl)thiophene-2-carbaldehyde (Table 6, entry 9).[9f] Following general procedure C, a mixture of 5-chloro-2-thiophenecarbaldehyde (26.6 μL, 0.25 mmol), 2-ethoxy-5-pyridine boronic acid (62.6 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), Pd_2dba_3 (2.3 mg, 0.0025 mmol) and XPhos (4.8 mg, 0.01 mmol) was heated to 100 °C in *tert*-amyl alcohol with stirring for 12 h. The crude product was purified via flash column chromatography on silica gel (15% EtOAc/Hexanes) to provide the title compound in a 91% yield (53 mg) as a orange solid, mp 62-64 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.83 (s, 1H), 8.43 (d, J = 3 Hz, 1H), 7.76 (dd, J = 8, 2 Hz, 1H), 7.68 (t, J = 2 Hz, 1H), 7.26 (d, J = 4 Hz, 1H), 6.73 (d, J = 8 Hz, 1H), 4.35 (q, J = 7 Hz, 2H), 1.37 (t, J = 7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 182.5, 164.4, 150.8, 144.7, 142.1, 137.5, 136.4, 123.5, 122.4, 111.4, 62.2, 14.5. IR (neat, cm^{-1}): 2977, 2900, 1598, 1564, 1446, 1381, 1287, 1236, 1064. Anal. Calcd. for $C_{12}H_{11}NO_2S$: C, 61.78; H, 4.75. Found C, 61.78; H, 4.91.

3-(2,6-Dimethoxypyridin-3-yl)-2,5-dimethylpyrazine (Table 6, entry 10). Following general procedure C, a mixture of 3-chloro-2,5-dimethylpyrazine (30.2 μL, 0.25 mmol), 2,6-dimethoxy-5-pyridine boronic acid (68.6 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol Pd_2dba_3 (2.3 mg, 0.0025 mmol) and XPhos (4.8 mg, 0.01 mmol) was heated to 100 °C in *tert*-amyl alcohol with stirring for 12 h. The crude product was purified via flash column chromatography on silica gel (20% EtOAc/Hexanes) to provide the title compound in a 85% yield (52 mg) as a white solid, mp 86-88 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.28 (s, 1H), 7.55 (d, J = 8 Hz, 1H), 6.42 (d, J = 8 Hz, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 2.53 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.4, 159.3, 150.1, 150.0, 149.5, 142.1, 141.8, 113.3, 101.4, 53.6, 53.2, 21.5, 21.0. IR (neat, cm^{-1}): 2997, 2946, 1602, 1582, 1485, 1441, 1378, 1318, 1235, 1103, 1021. Anal. Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16. Found C, 63.82; H, 6.17.

2-(2,6-Dimethoxypyridin-3-yl)quinoxaline (Table 6, entry 11).[9f] Following general procedure C, a mixture of 2-chloroquinozaline (41.2 mg, 0.25 mmol), 2,6-dimethoxy-5-pyridine boronic acid (68.6 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), Pd_2dba_3 (2.3 mg, 0.0025 mmol) and XPhos (4.8 mg, 0.01 mmol) was heated to 100 °C in *tert*-amyl alcohol with stirring for 12 h. The crude product was purified

via recrystallization (Hexanes) to provide the title compound in a 91% yield (61 mg) as a yellow solid, mp 95-96 °C.. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.48 (s, 1H), 8.37 (d, J = 8 Hz, 1H), 8.07 (d, J = 8 Hz, 2H), 7.67-7.73 (m, 2H), 6.51 (d, J = 8 Hz, 1H), 4.07 (s, 3H), 3.99 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.1, 160.4, 150.3, 146.4, 142.7, 142.4, 140.7, 129.7, 129.1, 129.0, 128.9, 111.6, 102.8, 53.8, 53.6. IR (neat, cm^{-1}): 2947, 1600, 1578, 1483, 1383, 1305, 1267, 1226, 1030, 1014. ^{1}H NMR spectrum included.

1.4.4 Experimental for the Synthesis of Pyrrole Boronate Esters.

3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1-(triisopropyl-silanyl)-1*H*-pyrrole, E1.[9f] An oven-dried Schlenk tube was charged with $PdCl_2(CH_3CN)_2$ (59 mg, 3.0 mol%) and SPhos (278 mg, 9.0 mol%). The Schlenk tube was capped with a rubber septum and then evacuated and backfilled with argon (this sequence was carried out two times). Toluene (10 mL) was added via syringe, through the septum, followed by the addition of 3-bromo-1-(triisopropyl-silanyl)-1*H*-pyrrole[24] (2.27 g, 7.52 mmol), pinacol borane (1.15 g, 1.31 mL, 9.02 mmol) and triethylamine (2.64 mL, 18.8 mmol). Additional toluene (4 mL) was then added and the vessel was sealed with a Teflon screwcap. The reaction mixture was heated to 90 °C and stirred for 18 h. At this point the reaction mixture was allowed to cool to room temperature. The solution was then filtered though a thin pad of silica gel (eluting with ethyl acetate) and the eluent was concentrated under reduced pressure. The crude product was purified via flash column chromatography on silica gel (5% EtOAc/Hexanes) to provide the title compound in a 85% yield (2.25 g) as a light yellow solid, m.p. 59 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.24 (dd, J = 2, 1 Hz, 1H), 6.81 (dd, J= 3, 2 Hz, 1H) 6.63 (dd, J = 3, 1 Hz, 1H), 7.00 (dd, J = 7, 1 Hz, 1H), 1.46 (sept, J = 7 Hz, 3H), 1.33 (s, 12H), 1.09 (d, J= 7 Hz, 18H).^{13}C NMR (75 MHz, $CDCl_3$) δ: 133.6, 124.9, 115.6, 110.0, 82.6, 24.8, 17.7, 11.6. IR (neat, cm^{-1}): 2949, 2873, 1540, 1466, 1381, 1296, 1142. Anal. Calcd. for $C_{19}H_{36}BNO_2Si$: C, 65.31; H, 10.39. Found C, 65.32; H, 10.30.

3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-pyrrole, E2. An oven dried 10-mL round bottom flask was charged with **E** (174.5 mg, 0.500 mmol). The flask was capped with a rubber septum and then evacuated and backfilled with argon. Anhydrous THF (2 mL) was added via syringe, through the septum,

followed by the slow addition of 1.0 M TBAF in THF (0.525 mL, 0.525 mmol) over five minutes at room temperature. After 2 h, 10 mL of water was added to the reaction and the extracted with 10 mL portions of diethyl ether (this process was repeated three times). The organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The crude product was purified via flash column chromatography on silica gel (10% EtOAc/Hexanes) to provide the title compound in 91% yield (88 mg) as a white solid, mp 77-79 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.71 (bs, 1H), 7.25 (dd, J = 3, 2 Hz, 1H), 6.84 (dd, J= 4, 2 Hz, 1H) 6.56 (dd, J = 4, 3 Hz, 1H), 1.32 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ:130.5, 127.0, 118.7, 113.7, 82.9, 24.8. IR (neat, cm^{-1}): 3149, 2979, 2933, 1747, 1561, 1490, 1371, 1329, 1292, 1181, 1066. ^{1}H NMR spectrum included.

3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1-(carboxylic acid *tert*-butyl ester)-1*H*-pyrrole, E3. An oven-dried Schlenk tube was charged with $PdCl_2(CH_3CN)_2$ (15.6 mg, 0.06 mmol) and SPhos (74 mg, 0.18 mmol). The Schlenk tube was capped with a rubber septum and then evacuated and backfilled with argon (this sequence was carried out two times). Toluene (4 mL) was added via syringe, through the septum, followed by the addition of 3-bromo-1-(carboxylic acid *tert*-butyl ester)-1*H*-pyrrole[25] (488 mg, 1.99 mmol), pinacol borane (306 mg, 0.347 mL, 2.39 mmol) and triethylamine (0.694 mL, 4.98 mmol). Additional toluene (1 mL) was then added and the vessel was sealed with a Teflon screwcap. The reaction mixture was heated to 80 °C and stirred for 24 h. At this point the reaction mixture was allowed to cool to room temperature. The solution was then filtered though a thin pad of silica gel (eluting with ethyl acetate) and the eluent was concentrated under reduced pressure. The crude product was purified via flash column chromatography on silica gel (5% EtOAc/Hexanes) to provide the title compound in a 50% yield (265 mg) as a light yellow solid, m.p. 76-77 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.63 (d, J = 1 Hz, 1H), 7.25 (d, J= 3 Hz, 1H), 6.46 (dd, J = 3, 1 Hz, 1H), 1.57 (s, 9H), 1.31 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 148.5, 128.7, 120.7, 116.1, 83.8, 83.2, 27.9, 24.7. IR (neat, cm^{-1}): 2979, 2933, 1747, 1561, 1459, 1371, 1329, 1143. ^{1}H NMR spectrum included.

3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1-(benzyl)-1*H*-pyrrole, E4. An oven dried 25-mL round bottom flask was charged with 3-bromo-1-(triisopropyl-silanyl)-1*H*-pyrrole[15a] (795 mg, 2.62

mmol). The flask was capped with a rubber septum and then evacuated and backfilled with argon. Anhydrous THF (8 mL) was added via syringe, through the septum, followed by the slow addition of 1.0 M TBAF in THF (2.75 mL, 0.525 mmol) over 5 min at room temperature. After 2 h, 10 mL of water was added to the reaction and then extracted with 10 mL portions of diethyl ether (this process was repeated three times). The organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The crude product is unstable and was immediately transferred to an oven dried 25-mL round bottom flask. The flask was capped with a rubber septum and then evacuated and backfilled with argon. Anhydrous DMSO (6 mL) was added via syringe, through the septum, followed by the addition of KOH (294 mg, 5.24 mmol) and benzyl bromide (0.467 mL, 3.93 mmol). After 1 h, 10 mL of water was added to the reaction and the extracted with 10 mL portions of diethyl ether (this process was repeated three times). The organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The crude product was purified via flash column chromatography on silica gel (Hexanes) to provide 3-bromo-1-(benzyl)-pyrrole as a white solid. 3-bromo-1-(benzyl)-pyrrole, $PdCl_2(CH_3CN)_2$ (9.9 mg, 0.09 mmol) and SPhos (47 mg, 0.11 mmol) were charged into an oven dried Schlenk tube. The Schlenk tube was capped with a rubber septum and then evacuated and backfilled with argon (this sequence was carried out two times). Toluene (2 mL) was added via syringe, through the septum, followed by the addition of pinacol borane (195 mg, 0.221 mL, 1.52 mmol) and triethylamine (0.443 mL, 3.18 mmol). Additional toluene (1 mL) was then added and the vessel was sealed with a Teflon screwcap. The reaction mixture was heated to 90 °C and stirred for 24 h. At this point the reaction mixture was allowed to cool to room temperature. The solution was then filtered though a thin pad of silica gel (eluting with ethyl acetate) and the eluent was concentrated under reduced pressure. The crude product was purified via flash column chromatography on silica gel (5% EtOAc/Hexanes) to provide the title compound as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.26-7.34 (m, 3H), 7.14-7.17 (m, 3H), 6.72 (dd, J= 2, 1 Hz, 1H) 6.54 (dd, J = 2, 1 Hz, 1H), 5.06 (s, 2H), 1.33 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 137.4, 130.2, 128.6, 127.7, 127.2, 122.2, 11.4.4, 82.7, 53.2, 24.7. IR (neat, cm^{-1}): 2977, 2929, 2865, 1587, 1543, 1497, 1454, 1294, 1214, 1150, 1108. ^{1}H NMR spectrum included.

1.4.5 Experimental for Reactions of Pyrrole Boronate Esters.

General Procedure D: Pd-Catalyzed Suzuki-Miyaura Couplings of Heteroaryl Halides with E1.

An oven-dried Schlenk tube was charged with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), SPhos (4.1 mg, 0.01 mmol), **E1** (131 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 (0.45 mL) and water (0.05 mL) were added via syringe, through the septum, followed by the addition of the aryl halide (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 (eluting with ethyl acetate) and the eluent was concentrated under reduced pressure. The crude material so obtained was purified via flash chromatography on silica gel.

General Procedure E: Pd-Catalyzed Suzuki-Miyaura Couplings Heteroaryl Halides with E1 at Low Catalyst Loadings.

Procedure E was followed with the following changes: A separate vial was initially charged with $Pd(OAc)_2$ (1.0 mol%) and SPhos (2.0 mol%). The vial was sealed with Teflon coated screwcap, a needle was inserted through the cap and the vial was then evacuated and backfilled with argon. *n*-Butanol (1 mL) was added and the mixture as briefly heated. 250 μL of this solution (0.25% Pd, 0.50% SPhos) was then added to the Schlenk flask containing the base and boronic acid. 107 μL of *n*-butanol and 143 μL of water were added in the final solvent addition. The temperature was raised to 100 °C.

5-[1-(Triisopropylsilyl)-1*H*-pyrrol-3-yl]-1*H*-indole (Table 8, entry 1).[9f] Following general procedure E, a mixture of 5-bromoindole (49 mg, 0.25 mmol), **E1** (131 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), $Pd(OAc)_2$ (0.25 mol%) and SPhos (0.50 mol%) was heated to 100 °C in 2.5:1 *n*-butanol/water with stirring for 2 h. The crude product was purified via flash column chromatography on silica gel (10%

EtOAc/Hexanes) to provide the title compound in a 97% yield (82 mg) as a red oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.01 (bs, 1H), 7.82 (d, J= 1 Hz, 1H) 7.46 (dd, J = 8, 1 Hz, 1H), 7.36 (d, J = 8 Hz, 1H), 7.16 (t, J = 3 Hz, 1H), 7.10 (t, J = 1 Hz, 1H), 6.86 (t, J = 2 Hz, 1H), 6.71 (dd, J = 2, 1 Hz, 1H), 6.56 (m, 1H), 1.55 (sept, J = 7 Hz), 1.20 (d, J= 7 Hz, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 134.4, 128.3, 128.1, 127.8, 125.0, 124.3, 120.3, 120.0, 116.8, 111.0, 108.8, 102.5, 17.8, 11.7. IR (neat, cm^{-1}): 3481, 3400, 2949, 2867, 1709, 1467, 1327, 1119. ^{1}H NMR spectrum included.

4-[1-(Triisopropylsilyl)-1*H*-pyrrol-3-yl]isoquinoline (Table 8, entry 2). Following general procedure E, a mixture of 4-bromoisoquinoline (52 mg, 0.25 mmol), **E1** (131 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), $Pd(OAc)_2$ (0.25 mol%) and SPhos (0.50 mol%) was heated to 100 °C in 2.5:1 *n*-butanol/water with stirring for 2 h. The crude product was purified via flash column chromatography on silica gel (10% EtOAc/Hexanes) to provide the title compound in a 93% yield (82 mg) as a yellow solid, mp 74-75 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.12 (s, 1H), 8.66 (s, 1H) 8.31 (d, J = 8 Hz, 1H), 7.97 (d, J = 8 Hz, 1H), 7.67 (ddd, J = 8, 7, 1 Hz, 1H), 7.56 (ddd, J = 8, 7, 1 Hz, 1H), 7.02 (t, J = 1 Hz, 1H), 6.92 (t, J = 2 Hz, 1H), 6.62 (dd, J = 2, 1 Hz, 1H), 1.55 (sept, J= 7 Hz, 3H), 1.19 (d, J = 7 Hz, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 150.3, 142.3, 134.4, 130.0, 128.8, 128.6, 127.7, 126.7, 125.1, 124.8, 123.6, 121.5, 112.1, 17.8, 11.5. IR (neat, cm^{-1}): 3149, 1709, 1362, 1224. Anal. Calcd. for $C_{22}H_{30}N_2Si$: C, 75.4; H, 8.6. Found C, 75.62; H, 8.83.

3-[1-(Triisopropylsilyl)-1*H*-pyrrol-3-yl]quinoline (Table 8, entry 3). Following general procedure E, a mixture of 3-bromoquinoline (34 μL, 0.25 mmol), **E1** (131 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), $Pd(OAc)_2$ (0.25 mol%) and SPhos (0.50 mol%) was heated to 100 °C in 2.5:1 *n*-butanol/water with stirring for 2 h. The crude product was purified via flash column chromatography on silica gel (10% EtOAc/Hexanes) to provide the title compound in 83% yield (73 mg) as a white solid, mp 103-104 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.17 (d, J = 2 Hz, 1H), 8.17 (d, J = 2 Hz, 1H), 8.06 (d, J = 8 Hz, 1H), 7.78 (dd, J = 8, 1 Hz, 1H), 7.56-7.62 (ddd, J = 8, 7, 2 Hz, 1H), 7.45-7.51 (ddd, J = 7, 7, 1 Hz, 1H), 7.23 (t, J = 1 Hz, 1H), 6.87 (dd, J = 2, 1 Hz, 1H), 6.75 (dd, J = 2, 1 Hz, 1H), 1.55 (sept, J = 7 Hz, 3H), 1.20 (d, J = 7 Hz, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 149.4, 146.3, 129.4, 129.0, 128.4, 127.9, 127.4, 126.5, 125.8,

123.4, 121.3, 108.6, 99.6, 17.7, 11.5. IR (neat, cm^{-1}): 2953, 2871, 2366, 1713, 1497, 1123. ^1H NMR spectrum included.

3-(Thiophen-2-yl)-1-(triisopropylsilyl)-1*H*-pyrrole (Table 8, entry 4).[9f,26] Following general procedure E, a mixture of 2-bromothiophene (0.25 mmol, 24.2 μL), **E1** (131 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), $Pd(OAc)_2$ (0.25 mol%) and SPhos (0.50 mol%) was heated to 100 °C in 2.5:1 *n*-butanol/water with stirring for 2 h. The crude product was purified via flash column chromatography on silica gel (5% EtOAc/Hexanes) to provide the title compound in 99% yield (75 mg) as a red oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.04-7.08 (ddd, J = 5, 5, 1 Hz, 1H), 6.96-7.00 (m, 1H) 6.81 (t, J = 2 Hz, 1H), 6.76 (dd, J = 3, 2 Hz, 1H), 6.51 (dd, J = 3, 2 Hz, 1H), 6.32 (t, J = 2 Hz, 1H), 1.49 (sept, J = 7 Hz, 3H), 1.15 (d, J = 7 Hz, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 139.7, 127.4, 125.1, 121.4, 120.8, 120.7, 120.5, 109.2, 17.8, 11.6. IR (neat, cm^{-1}): 2949, 2867, 1706, 1462, 1112. Anal. Calcd. for $C_{17}H_{27}NSSi$: C, 65.45; H, 8.24. Found C, 65.43; H, 8.77.

2-[1-(Triisopropylsilyl)-1*H*-pyrrol-3-yl]pyridine (Table 8, entry 5).[9f] Following general procedure E, a mixture of 2-bromopyridine (23.8 μL, 0.25 mmol), **E1** (131 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), $Pd(OAc)_2$ (0.25 mol%) and SPhos (0.50 mol%) was heated to 100 °C in 2.5:1 *n*-butanol/water with stirring for 2 h. The crude product was purified via flash column chromatography on silica gel (10% EtOAc/Hexane) to provide the title compound in a 91% yield (68 mg) as a white solid, mp 74-75 °C. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.52-8.55 (ddd, J = 7, 2, 1 Hz, 1H), 7.56-7.61 (m, 1H), 7.48 (dt, J = 7, 1 Hz, 1H), 7.43 (t, J = 1 Hz, 1H), 7.00 (ddd, J = 7, 5, 1 Hz, 1H), 6.80 (ddd, J = 8, 3, 1 Hz, 1H), 1.55 (sept, J = 7 Hz, 3H), 1.10 (d, J = 7 Hz, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 154.7, 149.2, 136.2, 127.0, 125.4, 123.3, 120.0, 119.2, 108.9, 17.8, 11.6. IR (neat, cm^{-1}): 2946, 2867, 1635, 1591, 1541, 1488, 1464, 1429, 1145, 1082. Anal. Calcd. for $C_{18}H_{28}N_2Si$: C, 71.94; H, 9.39. Found C, 72.07; H, 9.35.

5-[1-(Triisopropylsilyl)-1*H*-pyrrol-3-yl]thiophene-2-carbaldehyde (Table 8, entry 6). Following general procedure E, a mixture of 5-chlorothiophene-2-carbaldehyde (26.6 μL, 0.25 mmol), **E1** (131 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), $Pd(OAc)_2$ (0.25 mol%) and SPhos (0.50 mol%) was heated to

100 °C in 2.5:1 *n*-butanol/water with stirring for 2 h. The crude product was purified via recrystallization (Hexanes) to provide the title compound in an 82% yield (68 mg) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.80 (s, 1H), 7.64 (d, J = 3 Hz, 1H), 7.13 (s, 1H), 7.12 (d, J = 1 Hz, 2H), 6.79 (t, J = 2 Hz, 1H), 6.56 (dd, J = 3, 1 Hz, 1H), 1.46 (sept, J = 7 Hz, 3H), 1.12 (d, J= 7 Hz, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 182.3, 150.8, 139.1, 138.0, 125.9, 122.6, 121.8, 120.1, 109.3, 17.6, 11.5. IR (neat, cm^{-1}): 3001, 2365, 1709, 1362, 1223. ^{1}H NMR spectrum included.

2-[1-(Triisopropylsilyl)-1*H*-pyrrol-3-yl]quinoxaline (Table 8, entry 7). Following general procedure E, a mixture of 2-chloroquinoxaline (41.2 mg, 0.25 mmol), **E1** (131 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), $Pd(OAc)_2$ (0.25 mol%) and SPhos (0.50 mol%) was heated to 100 °C in 2.5:1 *n*-butanol/water with stirring for 2 h. The crude product was purified via recrystallization (Hexanes) to provide the title compound in a 83% yield (73 mg) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.10 (s, 1H), 8.03 (dt, J = 7, 1 Hz, 2H), 7.68 (dt, J = 7, 1 Hz, 1H), 7.59-7.62 (m, 2H), 7.03 (dd, J = 3, 2 Hz, 1H), 6.89 (dd, J = 3, 2 Hz, 1H), 1.52 (sept, J = 7 Hz, 3H), 1.14 (d, J = 7 Hz, 18 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 149.6, 143.7, 142.6, 140.6, 129.7, 128.9, 128.8, 127.8, 126.2, 125.1, 124.8, 109.5, 17.7, 11.6. IR (neat, cm^{-1}): 3061, 2947, 2867, 1713, 1577, 1552, 1498, 1463, 1385, 1257, 1100. ^{1}H NMR spectrum included.

General Procedure F: Pd-Catalyzed Suzuki-Miyaura Couplings of Aryl and Heteroaryl Bromides with F.

An oven-dried Schlenk tube was charged with $Pd(OAc)_2$ (1.1 mg, 2.0 mol%), SPhos (4.1 mg, 4.0 mol%), **F** (79.1 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 (0.5 mL) were added via syringe, through the septum, followed by the addition of the aryl halide (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 (eluting with ethyl acetate) and the eluent was concentrated under reduced pressure. The crude material so obtained was purified via flash chromatography on silica gel.

***Tert*-Butyl 2-mesityl-1*H*-pyrrole-1-carboxylate (Table 8, entry 8).**[9f] Following general procedure F, a mixture of 2-bromomesitylene (38.3 μL, 0.25 mmol), **F** (79.1 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol) and SPhos (4.1 mg, 0.01 mmol) was heated to 100 °C in *n*-butanol with stirring for 5 h. The crude product was purified via flash column chromatography on silica gel (5% EtOAc/Hexanes) to provide the title compound in a 89% yield (63 mg) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39 (d, J = 3, 1H), 6.87 (s, 2H) 6.27 (t, J = 3 Hz, 1H), 5.99 (d, J = 3 Hz, 1H), 2.30 (s, 3H), 2.02 (s, 6H), 1.21 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 149.4, 137.8, 137.1, 131.9, 131.8, 127.5, 130.8, 113.1, 110.6, 82.7, 27.3, 21.1, 20.2. IR (neat, cm^{-1}): 2979, 1733, 1339. Anal. Calcd. for $C_{18}H_{23}NO_2$: C, 75.8; H, 8.1. Found C, 75.82; H, 8.25.

***Tert*-Butyl 2-(5-formyl-thiophen-2-yl)-1*H*-pyrrole-1-carboxylate (Table 8, entry 9).**[9f] Following general procedure E, a mixture of 5-chlorothiophene-2-carbaldehyde (26.6 μL, 0.25 mmol), **F** (79.1 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol) and SPhos (4.1 mg, 0.01 mmol) was heated to 100 °C in *n*-butanol with stirring for 3 h. The crude product was purified via flash column chromatography on silica gel (10% EtOAc/Hexanes) to provide the title compound in a 77% yield (53 mg) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.87 (s, 1H), 7.67 (d, J = 4 Hz, 1H), 7.40 (dd, J = 4, 2 Hz, 1H), 7.19 (d, J = 4 Hz, 1H), 6.44 (dd, J = 3, 2 Hz, 1H), 6.24 (t, J = 3 Hz, 1H), 1.48 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 183.6, 149.3, 145.8, 143.3, 136.7, 129.1, 126.8, 125.3, 118.7, 111.8, 85.4, 28.4. IR (neat, cm^{-1}): 2979, 1745, 1664, 1475, 1431, 1337, 1317, 1139. ^{1}H NMR spectrum included.

***Tert*-Butyl 2-(1*H*-indol-5-yl)-1*H*-pyrrole-1-carboxylate (Table 8, entry 10).** Following general procedure F, a mixture of 5-bromoindole (49 mg, 0.25 mmol), **F** (79.1 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol) and SPhos (4.1 mg, 0.01 mmol) was heated to 100 °C in *n*-butanol with stirring for 5 h. The crude product was purified via flash column chromatography on silica

gel (10% EtOAc/Hexanes) to provide the title compound in a 79% yield (55 mg) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.18 (bs, 1H), 7.62 (dd, J= 4, 2 Hz, 1H) 7.36 (dd, J = 4, 2 Hz, 1H), 7.33 (s, 1H), 7.20 (t, J = 3 Hz, 1H), 7.17 (d, J = 2 Hz, 1H), 6.55 (m, 1H), 6.25 (t, J = 3 Hz, 1H), 6.20 (dd, J = 3, 2 Hz, 1H), 1.30 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 149.6, 136.4, 135.0, 127.3, 125.9, 124.5, 123.9, 121.8, 121.1, 113.9, 110.4, 110.0, 102.5, 83.1, 27.5. IR (neat, cm^{-1}): 3180, 2979, 1731, 1323. Anal. Calcd. for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45. Found C, 60.87; H, 5.49.

***Tert*-Butyl 2-(thiophen-2-yl)-1*H*-pyrrole-1-carboxylate (Table 8, entry 11).**[27] Following general procedure F, a mixture of 2-bromothiophene (24.2 μL, 0.25 mmol), **F** (79.1 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol) and SPhos (4.1 mg, 0.01 mmol) was heated to 100 °C in *n*-butanol with stirring for 5 h. The crude product was purified via flash column chromatography on silica gel (5% EtOAc/Hexanes) to provide the title compound in an 84% yield (52 mg) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39 (dd, J = 3, 2 Hz, 1H), 7.31 (dd, J= 6, 2 Hz, 1H) 7.07 (dd, J = 4, 2 Hz, 1H), 7.01 (dd, J = 5, 3 Hz, 2H), 6.33 (dd, J = 4, 2 Hz, 1H), 6.23 (t, J = 3 Hz, 1H), 1.43 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 149.0, 134.9, 127.7, 126.8, 126.3, 125.5, 123.1, 116.5, 110.5, 83.7, 27.6. IR (neat, cm^{-1}): 3452, 2980, 1738, 1636, 1475, 1396, 1370, 1327, 1308, 1143. ^{1}H NMR spectrum included.

***Tert*-Butyl 2-(isoquinolin-4-yl)-1*H*-pyrrole-1-carboxylate (Table 8, entry 12).**[9f] Following general procedure F, a mixture of 4-bromoisoquinoline (52 mg, 0.25 mmol), **F** (79.1 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol) and SPhos (4.1 mg, 0.01 mmol) was heated to 100 °C in *n*-butanol with stirring for 5 h. The crude product was purified via flash column chromatography on silica gel (10% EtOAc/Hexanes) to provide the title compound in a 95% yield (70 mg) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.23 (s, 1H), 8.47 (s, 1H) 8.00 (dd, J = 7, 2 Hz, 1H), 7.54-7.67 (m, 4H), 6.37 (t, J = 3 Hz, 1H), 6.33 (dd, J = 3, 2 Hz, 1H), 0.90 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 148.4, 147.9, 137.0, 134.4, 132.4, 131.2, 126.8, 123.5, 123.4, 119.4, 115.7, 107.3, 83.9, 28.2. IR (neat, cm^{-1}): 2979, 1733, 1462, 1370. Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16. Found C, 73.19; H, 6.21.

1.4.6 Experimental for Reactions of Indole Boronic Acids.

General Procedure G: Pd-Catalyzed Suzuki-Miyaura Couplings of Indole Boronic Acids.

An oven-dried Schlenk tube was charged with $Pd_2(dba)_3$ (2.3 mg, 0.0025 mmol), ligand (0.01 mmol), indole boronic acid (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 the addition of the aryl halide (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 (eluting with ethyl acetate) and the eluent was concentrated under reduced pressure. The crude material so obtained was purified via flash chromatography on silica gel.

5-(3,6-Dimethyl-pyrazin-2-yl)-1-methyl-1*H*-indole (Table 9, entry 1).[9f] Following general procedure G, a mixture of 3-chloro-2,5-dimethylpyrazine (30.2 μL, 0.25 mmol), 1-methyl-5-indole boronic acid (65.3 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol) and SPhos (4.1 mg, 0.01 mmol) was heated to 100 °C in *n*-butanol with stirring for 12 h. The crude product was purified via flash column chromatography on silica gel (25% EtOAc/Hexanes) to provide the title compound in a 90% yield (53 mg) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.29 (s, 1H), 7.82 (s, 1H), 7.43 (t, J = 8 Hz, 1H), 7.40 (t, J = 8 Hz, 1H), 7.10 (d, J = 3 Hz, 1H), 6.54 (d, J = 3 Hz, 1H), 3.83 (s, 3H), 2.59 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 154.1, 150.0, 148.3, 136.6, 130.1, 129.6, 128.3, 122.6, 121.7, 109.1, 101.5, 32.9, 22.9, 21.2. IR (neat, cm^{-1}): 3099, 2959, 1923, 2824, 1617, 1514, 1449, 1426, 1331, 1245, 1150, 1105. ^{1}H NMR spectrum included.

1-Methyl-5-(pyridin-3-yl)-1*H*-indole (Table 9, entry 2). Following general procedure G, a mixture of 3-chloropyridine (23.8 μL, 0.25 mmol), 1-methyl-5-indole boronic acid (65.3 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol) and SPhos (4.1 mg, 0.01 mmol) was heated to 100 °C in *n*-butanol with stirring for 12 h. The crude product was purified via flash column

chromatography on silica gel (25% EtOAc/Hexanes) to provide the title compound in a 77% yield (40 mg) as a brown solid, mp 81-83 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.92 (d, J = 2 Hz, 1H), 8.55 (dd, J = 5, 1 Hz, 1H), 7.93 (dt, J = 7, 1 Hz, 1H), 7.84 (s, 1H), 7.45 (t, J = 7 Hz, 1H), 7.43 (t, J = 7 Hz, 1H), 7.35 (dd, J = 8, 5 Hz, 1H), 7.11 (d, J = 3 Hz, 1H), 6.56 (d, J = 3 Hz, 1H), 3.83 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 148.5, 147.4, 137.9, 136.5, 134.4, 129.8, 129.2, 129.2, 129.0, 123.4, 121.0, 119.5, 109.8, 101.4, 32.9. IR (neat, cm^{-1}): 3094, 3026, 2926, 1615, 1512, 1472, 1410, 1341, 1247. ^{1}H NMR spectrum included.

5-(1-Methyl-1*H*-indol-5-yl)thiophene-2-carbaldehyde (Table 9, entry 3).[9f] Following general procedure G, a mixture of 5-chloro-2-thiophenecarbaldehyde (26.6 μL, 0.25 mmol), 1-methyl-5-indole boronic acid (65.3 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), $Pd(OAc)_2$ (0.25 mol%) and SPhos (0.50 mol%) was heated to 100 °C in *n*-butanol with stirring for 12 h. The crude product was purified via flash column chromatography on silica gel (10% EtOAc/Hexanes) to provide the title compound in a 96% yield (57 mg) as a yellow solid, mp 138-140 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.87 (s, 1H), 7.96 (d, J = 2 Hz, 1H), 7.74 (d, J = 4 Hz, 1H), 7.56 (dd, J = 8, 2 Hz, 1H), 7.39 (d, J = 4 Hz, 1H), 7.35 (d, J = 8 Hz, 1H), 7.10 (d, J = 3 Hz, 1H), 6.55 (d, J = 3Hz, 1H), 2.68 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 182.7, 156.9, 141.1, 137.9, 137.3, 130.3, 128.8, 124.6, 122.8, 120.5, 119.3, 109.9, 101.8, 33.0. IR (neat, cm^{-1}): 3020, 2854, 1741, 1659, 1607, 1512, 1446, 1377, 1231, 1056. ^{1}H NMR spectrum included.

5-(1*H*-Indol-5-yl)-2-methylbenzooxazole (Table 9, entry 4).[9f] Following general procedure G, a mixture of 5-chloro-2-methylbenzoxazole (41.8 mg, 0.25 mmol), 5-indole boronic acid (60.4 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), Pd_2dba_3 (2.3 mg, 0.0025 mmol) and XPhos (4.8 mg, 0.01 mmol) was heated to 120 °C in *n*-butanol with stirring for 18 h. The crude product was purified via flash column chromatography on deactivated silica gel (10% Triethylamine/Hexanes) and eluent (40% EtOAc/Hexanes) to provide the title compound in a 91% yield (56 mg) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.35 (bs, 1H), 7.90 (d, J = 1 Hz, 1H), 7.87 (d, J = 1Hz, 1H), 7.60 (dd, J = 8, 2 Hz, 1H), 7.53 (dd, J = 8, 1 Hz, 1H), 7.47 (d, J = 1 Hz, 1H), 7.46 (d, J = 1Hz, 1H), 7.26 (t, J = 3 Hz, 1H), 6.63 (t, J

= 3 Hz, 1H), 2.68 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.3, 150.0, 142.0, 139.4, 135.2, 133.2, 128.4, 124.9, 124.3, 122.1, 119.5, 118.0, 111.3, 110.0, 102.9, 14.6. IR (neat, cm^{-1}): 3411, 3238, 2963, 2929, 1577, 1458, 1275. ^{1}H NMR spectrum included.

5-(Thiophen-3-yl)-1*H*-indole (Table 9, entry 5). Following general procedure G, a mixture of 3-chlorothiophene (23.2 μL, 0.25 mmol), 5-indole boronic acid (60.4 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), Pd_2dba_3 (2.3 mg, 0.0025 mmol) and XPhos (4.8 mg, 0.01 mmol) was heated to 120 °C in *n*-butanol with stirring for 18 h. The crude product was purified via flash column chromatography on silica gel (5% EtOAc/Hexanes) to provide the title compound in a 90% yield (45 mg) as a yellow solid, mp 80-82 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.12 (bs, 1H), 7.90 (t, J = 1 Hz, 1H), 7.48 (dd, J = 8,2 Hz, 1H), 7.46 (dd, J = 5, 1 Hz, 1H), 7.40-7.44 (m, 2H), 7.22 (t, J = 3 Hz, 1H), 6.60 (t, J = 3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 143.6, 135.1, 128.2, 128.1, 126.8, 125.8, 124.8, 121.3, 118.8, 118.5, 111.2, 102.9. IR (neat, cm^{-}1): 2951, 2920, 1463, 854, 785. Anal. Calcd. for $C_{12}H_9NS$: C, 72.33; H, 4.55. Found C, 72.10; H, 4.72.

1*H*,1'*H*-5,5'-Biindolyl (Table 9, entry 6). Following general procedure G, a mixture of 5-chloroindole (37.9 mg, 0.25 mmol), 5-indole boronic acid (60.4 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), Pd_2dba_3 (2.3 mg, 0.0025 mmol) and XPhos (4.8 mg, 0.01 mmol) was heated to 120 °C in *n*-butanol with stirring for 18 h. The crude product was purified via flash column chromatography on deactivated silica gel (10% Triethylamine/Hexanes) and eluent (40% EtOAc/Hexanes) to provide the title compound in a 71% yield (41 mg) as a red oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.14 (bs, 1H), 7.90 (d, J = 1 Hz, 1H), 7.53 (dd, J = 8, 2 Hz, 1H), 7.46 (dd, J = 8, 1 Hz, 1H), 7.26 (d, J = 1 Hz, 1H), 7.24 (d, J = 3 Hz, 1H), 6.62 (d, J = 3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 134.8, 134.7, 128.4, 124.6, 122.4, 119.3, 111.0, 102.9. IR (neat, cm^{-1}): 3411, 1637, 1456, 1415, 1293, 1092. ^{1}H NMR spectrum included.

5-(1*H*-Indol-5-yl)pyridin-2-amine (Table 9, entry 7).[9f] Following general procedure G, a mixture of 2-amino-5-chloropyridine (32.1 mg, 0.25 mmol), 5-indole boronic acid (60.4 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), Pd_2dba_3 (2.3 mg, 0.0025 mmol) and XPhos (4.8 mg, 0.01 mmol) was heated to 120 °C in *n*-butanol with stirring for 18 h. The crude product was purified via flash column chromatography on

silica gel (EtOAc) to provide the title compound in a 77% yield (40 mg) as a red oil. ^{1}H NMR (300 MHz, CD_3OD) δ: 8.14 (dd, J = 2, 1 Hz, 1H), 7.77 (dd, J = 8, 3 Hz, 1H), 7.67 (dd, J = 2, 1 Hz, 1H), 7.41 (dt, J = 8, 1 Hz, 1H), 7.26 (dd, J = 8, 1 Hz, 1H), 7.24 (d, J = 3 Hz, 1H), 6.67 (dd, J = 8, 1 Hz, 1H), 6.46 (dd, J = 3, 1 Hz, 1H). ^{13}C NMR (75 MHz, CD_3CN) δ: 159.0, 147.0, 137.2, 136.2, 130.9, 129.6, 128.6, 126.5, 121.3, 118.5, 112.6, 109.0, 102.7. IR (neat, cm^{-1}): 3394, 3025, 2924, 2532, 1620, 1499, 1468, 1389, 1316. ^{1}H NMR spectrum included.

1.4.7 Experimental for Reactions of Furan Boronic Acids.

General Procedure H: Pd-Catalyzed Suzuki-Miyaura Couplings of Furan Boronic Acids.

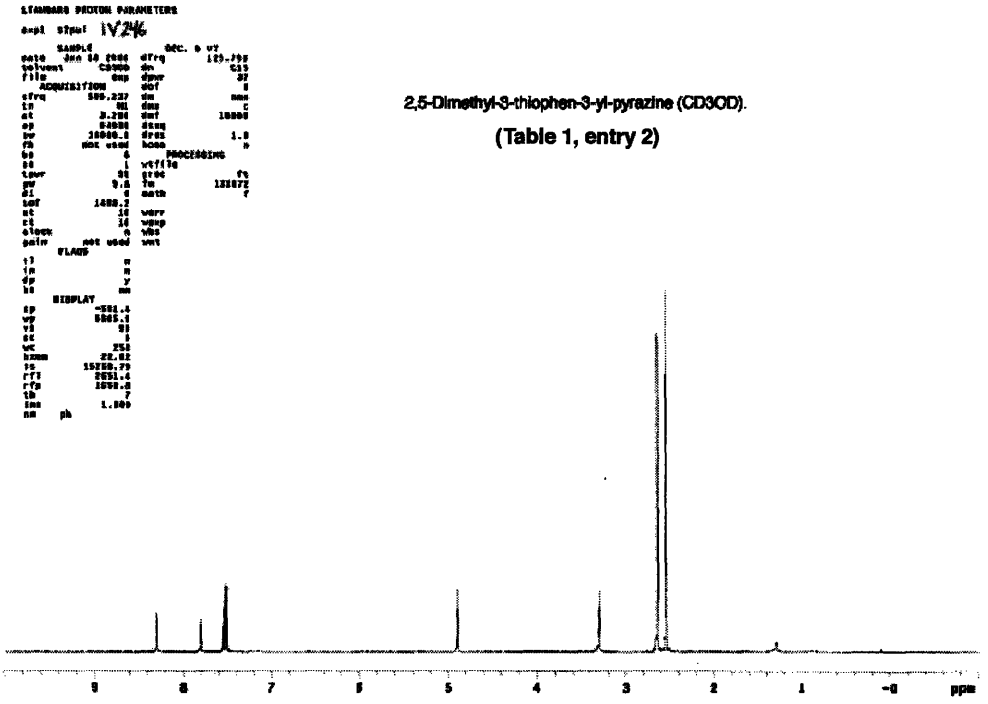
An oven-dried Schlenk tube was charged with $Pd_2(dba)_3$ (2.3 mg, 0.0025), ligand (0.01 mmol), furan boronic acid (42 mg, 0.375 mmol) and powdered, anhydrous K_3PO_4 (106 mg, 0.50 mmol). The Schlenk tube was capped with a rubber septum and then evacuated and backfilled with argon (this sequence was carried out two times). *tert*-Amyl alcohol (0.50 mL) was added via syringe, through the septum, followed by the addition of the aryl halide (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 (eluting with ethyl acetate) and the eluent was concentrated under reduced pressure. The crude material so obtained was purified via flash chromatography on silica gel.

2-(Furan-3-yl)pyrazine (Table 9, entry 8). Following general procedure H, a mixture of 2-chloropyrazine (28.6 mg, 0.25 mmol), 3-furan boronic acid (42 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), $Pd(OAc)_2$ (2.3 mg, 0.005 mmol) and SPhos (4.1 mg, 0.01 mmol) was heated to 100 °C in *sec*-butanol with stirring for 12 h. The crude product was purified via flash column chromatography on silica gel (15% EtOAc/Hexanes) to provide the title compound in a 96% yield (35 mg) as a brown solid, mp 64-66 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.76 (s, 1H), 8.52 (dd, J = 3, 1 Hz, 1H), 8.08 (dd, J = 2, 1 Hz, 1H),

7.53 (dd, J = 3, 1 Hz, 1H), 6.93 (dd, J = 3, 1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 147.7, 144.3, 144.2, 142.4, 141.8, 141.7, 124.1, 108.2. IR (neat, cm^{-1}): 3135, 3111, 3080, 2924, 1863, 1588, 1577, 1510, 1417, 1299, 1071. Anal. Calcd. for $C_8H_6N_2O$: C, 65.75; H, 4.23. Found C, 65.61; H, 4.23.

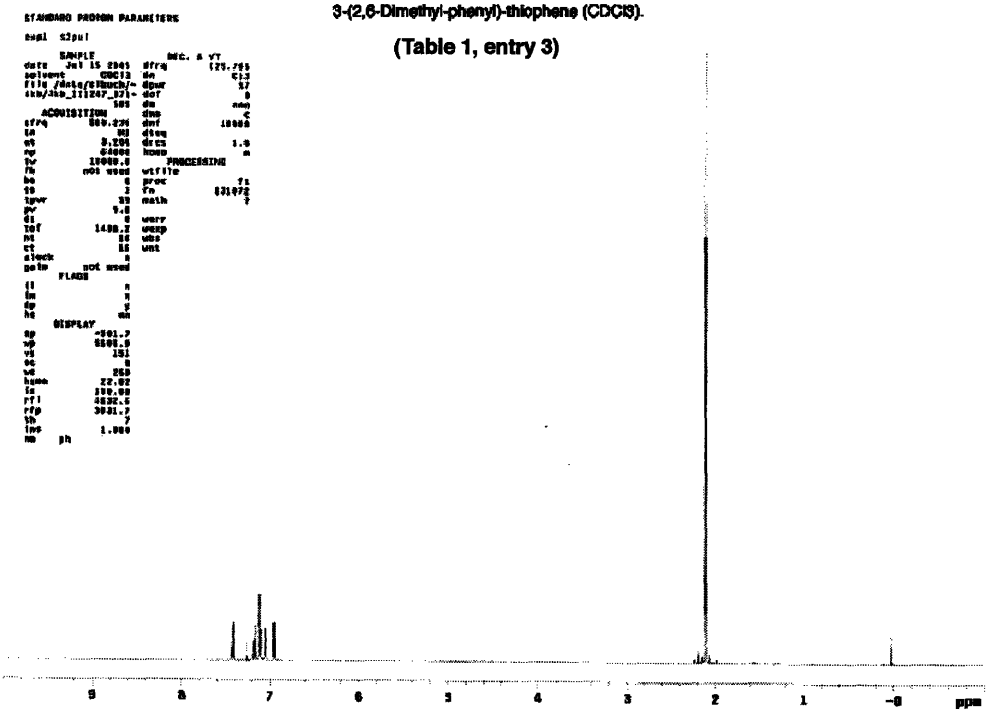
5-(Quinoxalin-2-yl)furan-2-carbaldehyde (Table 9, entry 9). Following general procedure H, a mixture of 2-chloroquinoxaline (41.2 mg, 0.25 mmol), 5-formyl-2-furan boronic acid (52.5 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), Pd_2dba_3 (2.3 mg, 0.0025 mmol) and XPhos (4.8 mg, 0.01 mmol) was heated to 100 °C in *tert*-amyl alcohol with stirring for 10 h. The crude product was purified via recrystallization (Hexanes) to provide the title compound in a 82% yield (46 mg) as a brown solid, mp 140-142 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.82 (s, 1H), 9.42 (s, 1H), 8.09-8.12 (m, 2H), 7.76-7.82 (m, 2H), 7.49 (d, J = 4 Hz, 1H), 7.42 (d, J = 4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 177.9, 156.1, 153.4, 142.5, 142.1, 142.0, 141.9, 130.9, 130.6, 129.4, 129.3, 122.1, 113.1. IR (neat, cm^{-1}): 2834, 1667, 1635, 1483, 1256, 1073. ^{1}H NMR spectrum included.

2-(Quinolin-2-yl)furan-3-carbaldehyde (Table 9, entry 10). Following general procedure H, a mixture of 2-chloroquinoline (40.9 mg, 0.25 mmol), 3-formyl-2-furan boronic acid (52.5 mg, 0.375 mmol), K_3PO_4 (106 mg, 0.50 mmol), Pd_2dba_3 (2.3 mg, 0.0025 mmol) and XPhos (4.8 mg, 0.01 mmol) was heated to 100 °C in *tert*-amyl alcohol with stirring for 10 h. The crude product was purified via flash column chromatography on silica gel (10% EtOAc/Hexanes) to provide the title compound in a 70% yield (39 mg) as a yellow solid, mp 104-105 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 11.21 (s, 1H), 8.25 (d, J = 8 Hz, 1H), 8.08 (d, J = 8 Hz, 1H), 7.97 (d, J = 8 Hz, 1H), 7.83 (d, J = 8 Hz, 1H), 7.75 (dt, J = 8, 1 Hz, 1H), 7.58 (dt, J = 8,1 Hz, 1H), 7.52 (d, J = 2 Hz, 1H), 7.00 (d, J = 2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 189.5, 157.6, 148.3, 147.1, 136.9, 130.2, 129.7, 128.3, 127.6, 127.3, 126.2, 118.3, 110.0. IR (neat, cm^{-1}): 3120, 2885, 1674, 1594, 509, 1411, 1274, 1165. ^{1}H NMR spectrum included.



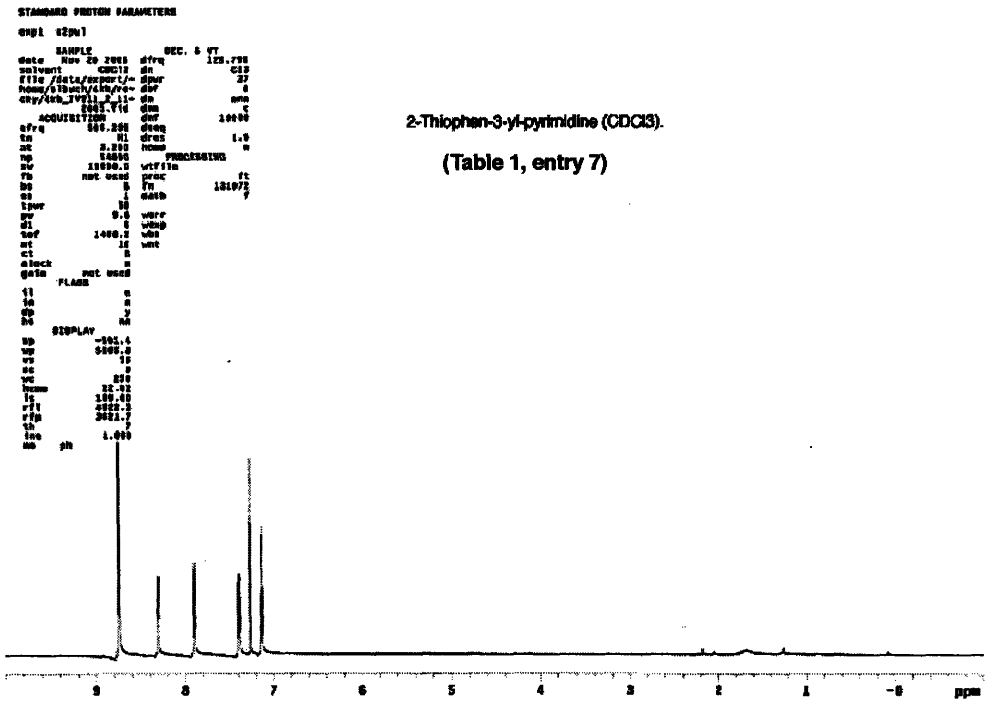
2,5-Dimethyl-3-thiophen-3-yl-pyrazine (CD3OD).

(Table 1, entry 2)



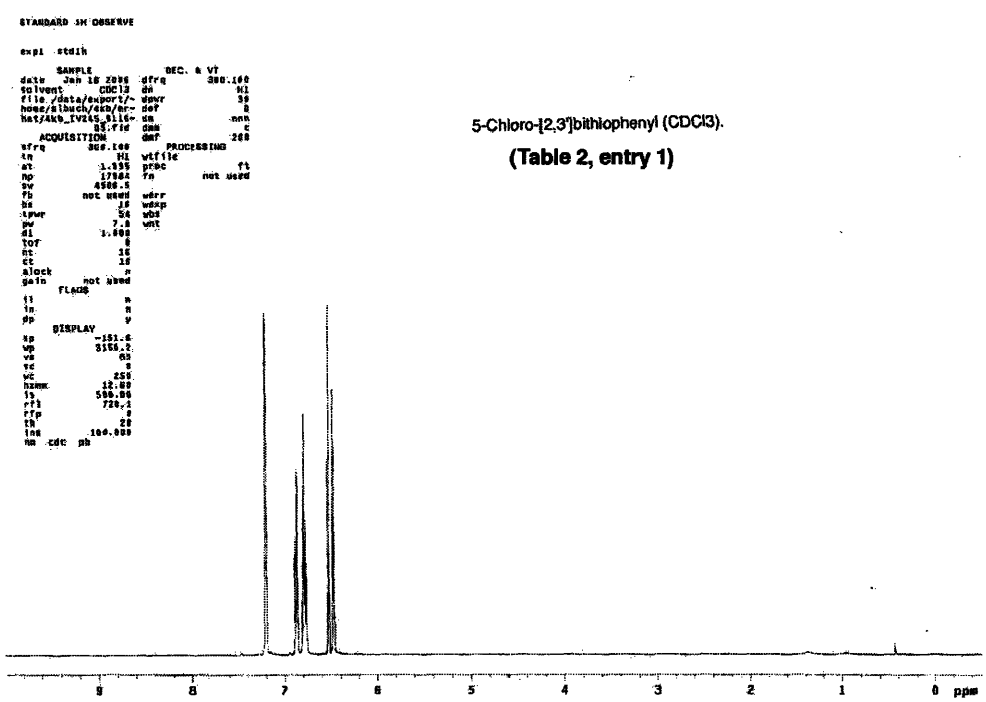
3-(2,6-Dimethyl-phenyl)-thiophene (CDCl3).

(Table 1, entry 3)



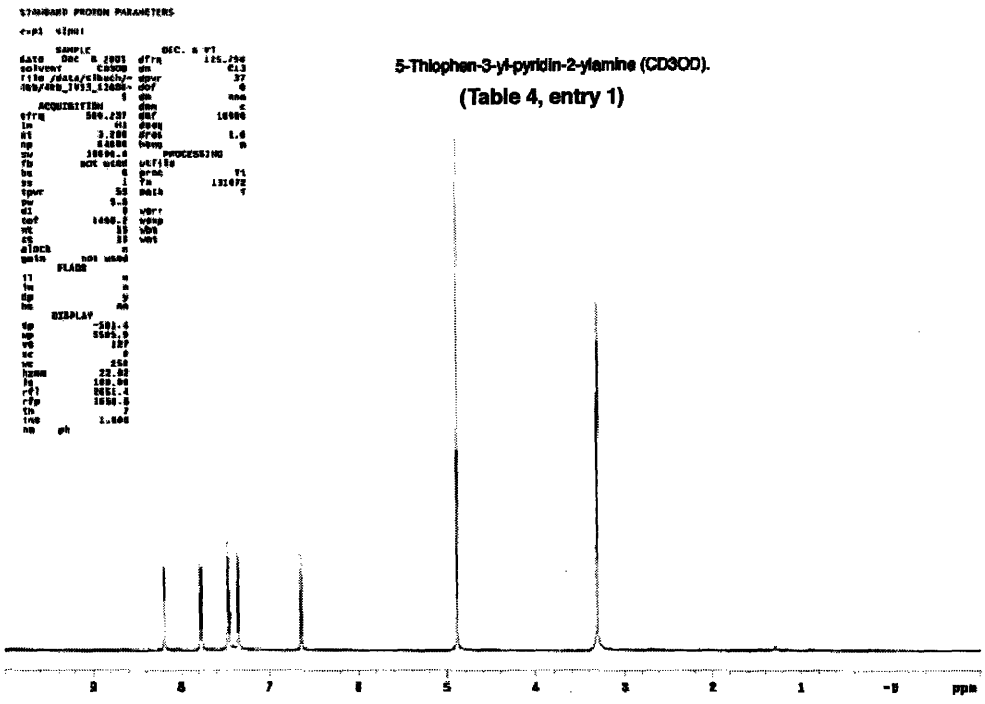
2-Thiophen-3-yl-pyrimidine (CDCl3).

(Table 1, entry 7)



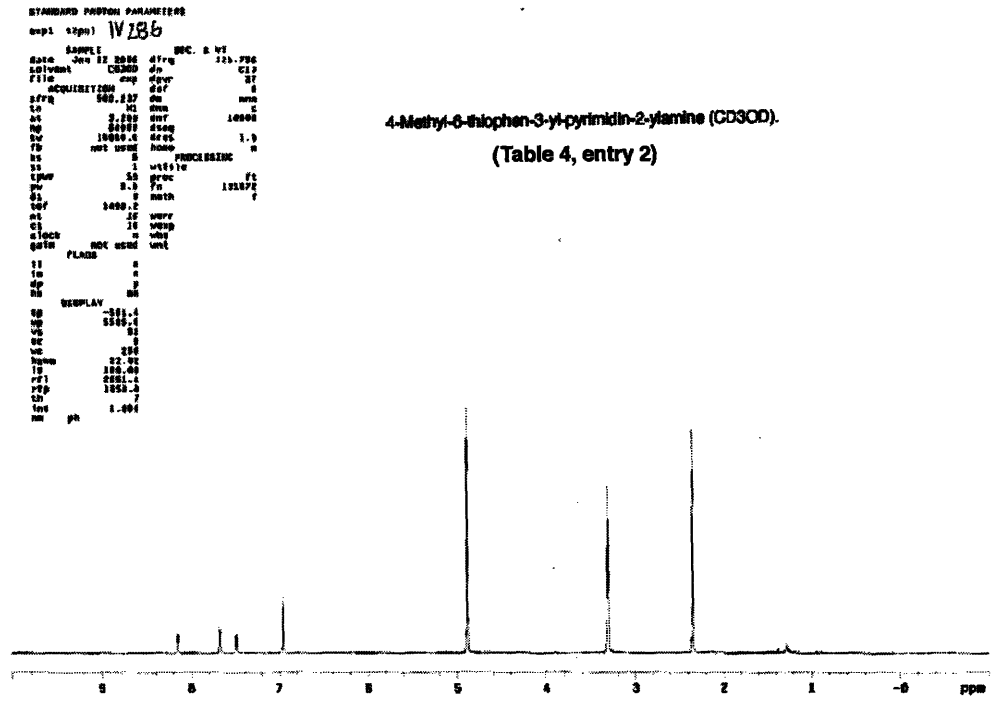
5-Chloro-[2,3']bithiophenyl (CDCl3).

(Table 2, entry 1)



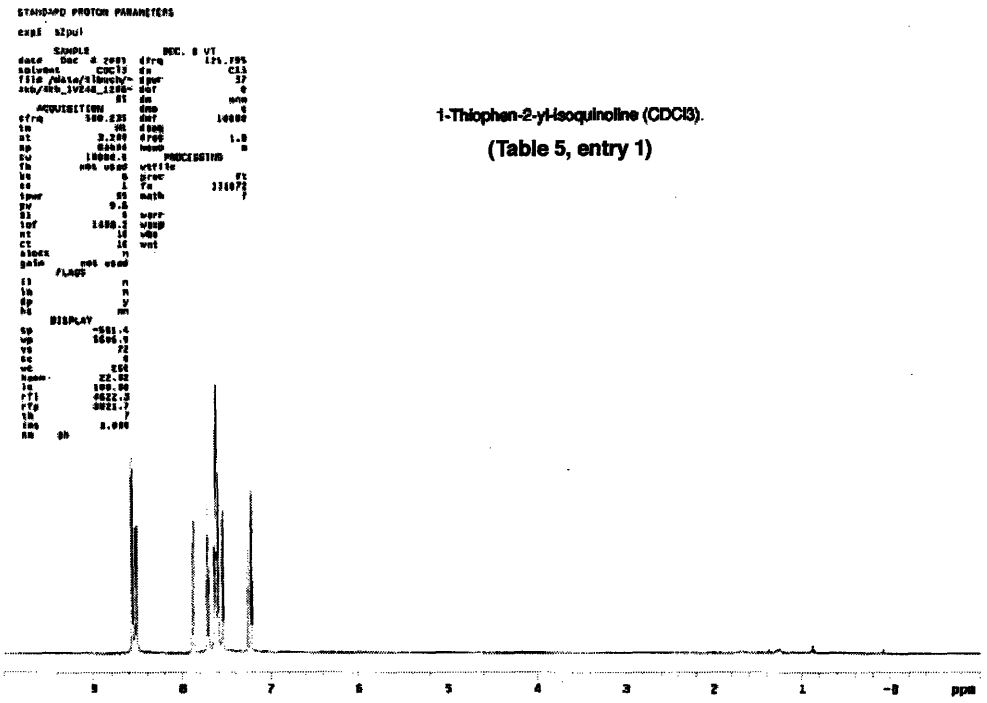
5-Thiophen-3-yl-pyridin-2-ylamine (CD3OD).

(Table 4, entry 1)



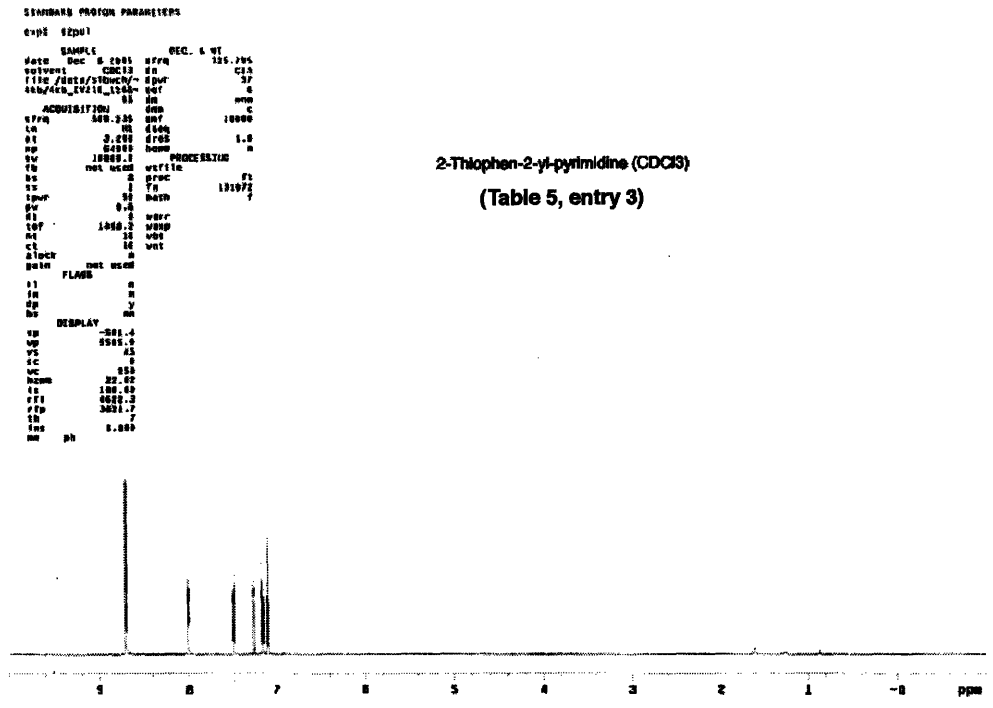
4-Methyl-6-thiophen-3-yl-pyrimidin-2-ylamine (CD3OD).

(Table 4, entry 2)



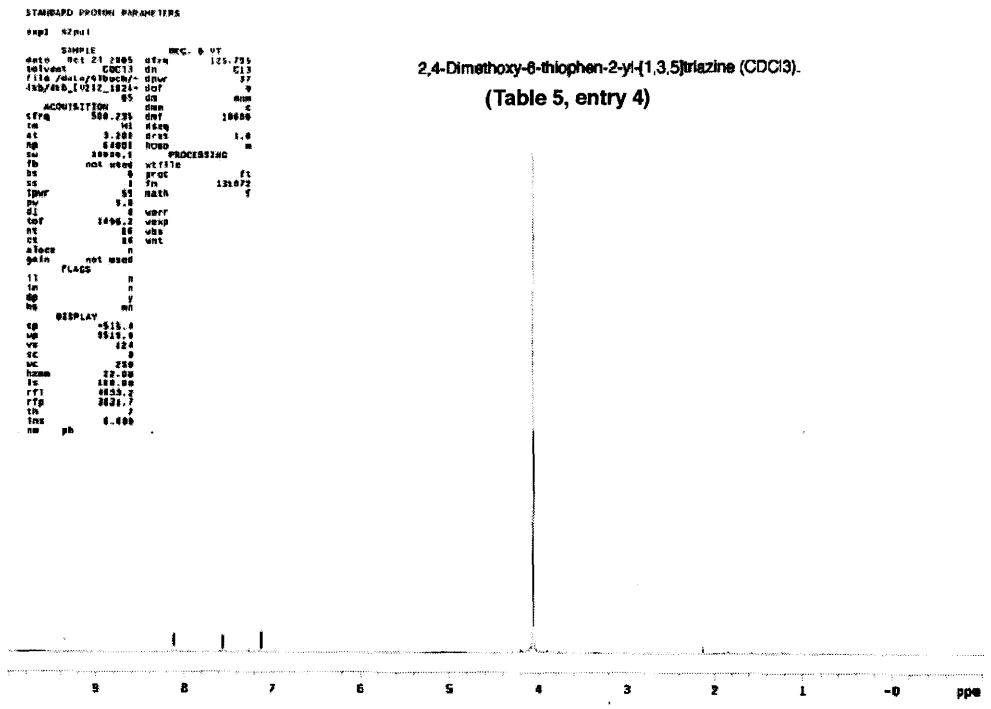
1-Thiophen-2-yl-isoquinoline (CDCl3).

(Table 5, entry 1)



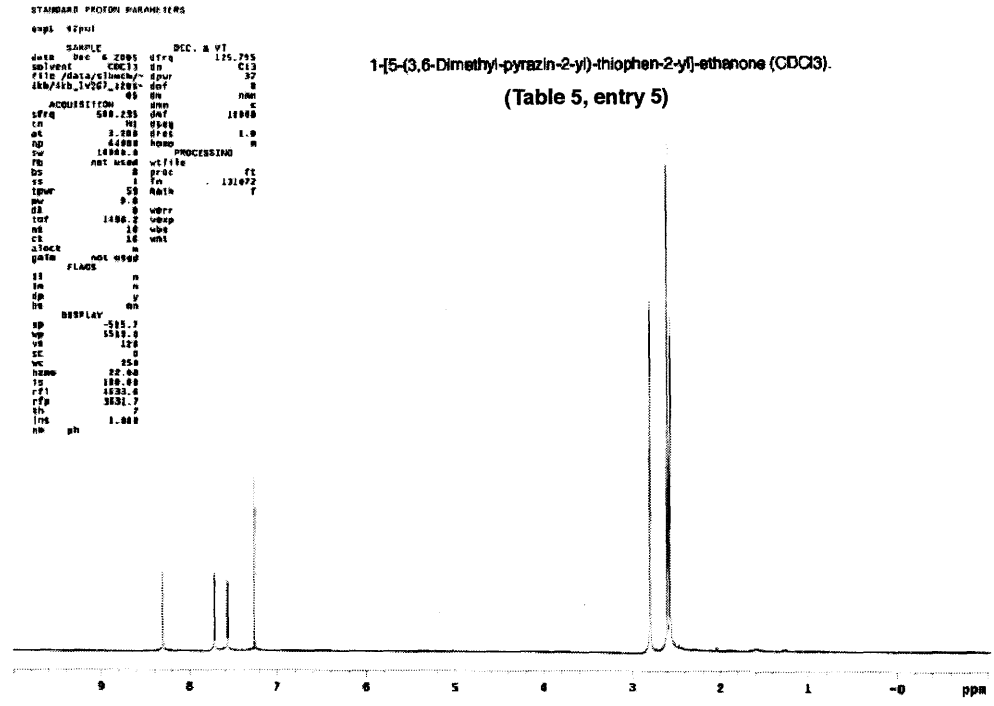
2-Thiophen-2-yl-pyrimidine (CDCl3)

(Table 5, entry 3)



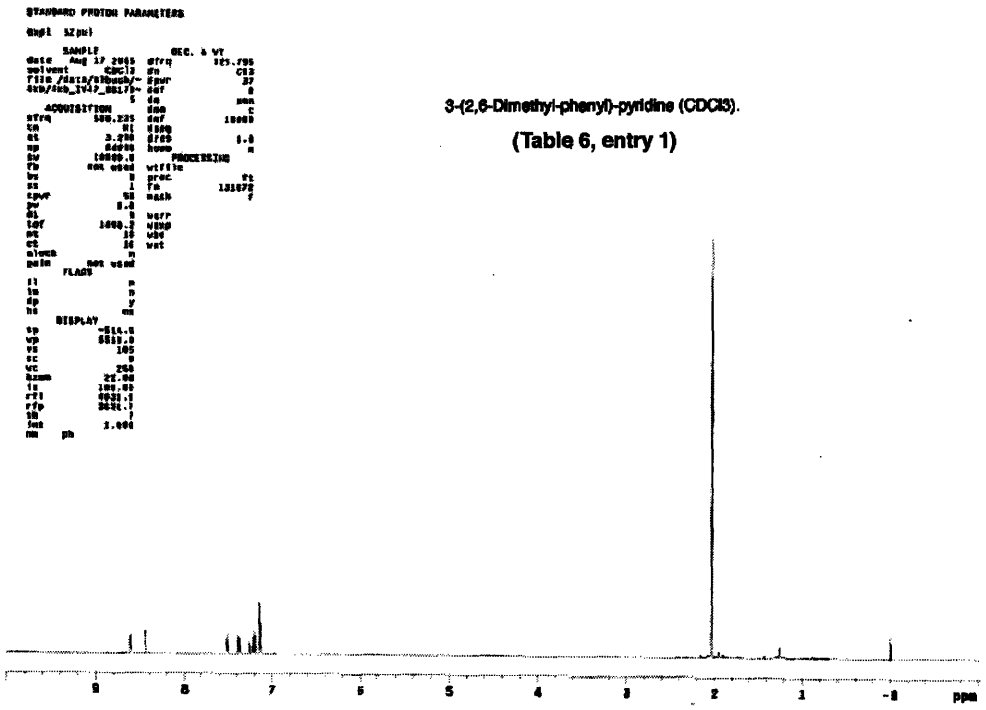
2,4-Dimethoxy-6-thiophen-2-yl-[1,3,5]triazine (CDCl3).

(Table 5, entry 4)



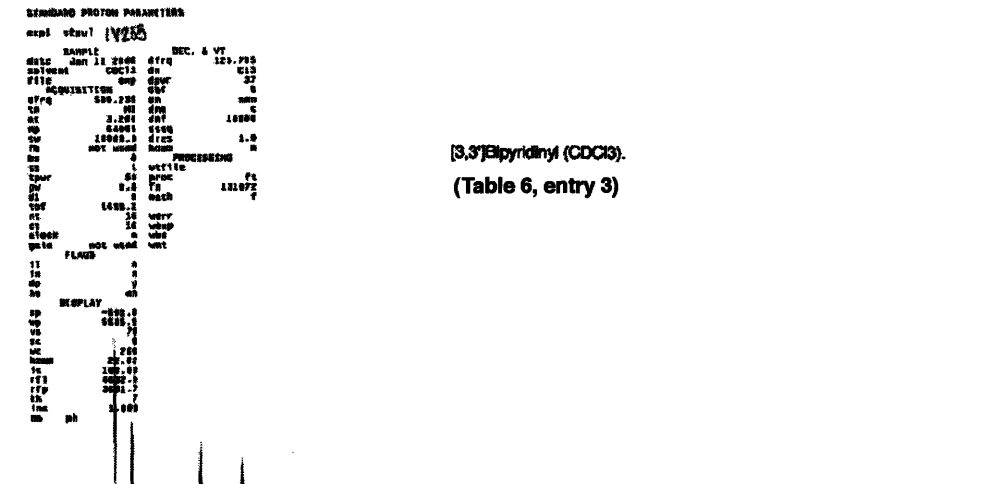
1-[5-(3,6-Dimethyl-pyrazin-2-yl)-thiophen-2-yl]-ethanone (CDCl3).

(Table 5, entry 5)



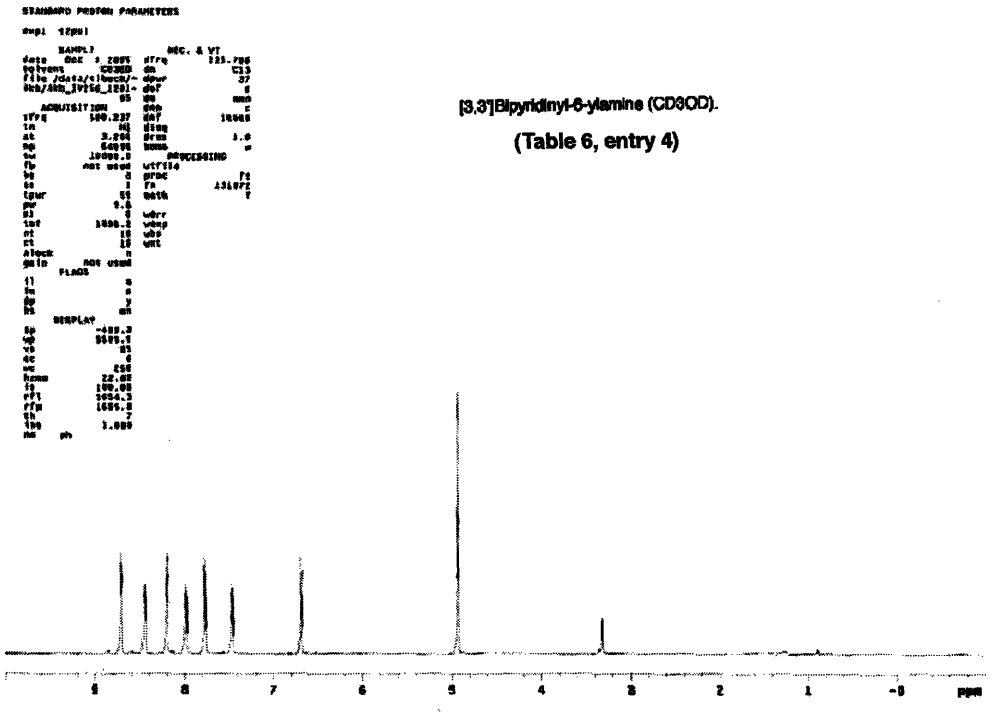
3-(2,6-Dimethyl-phenyl)-pyridine (CDCl3).

(Table 6, entry 1)



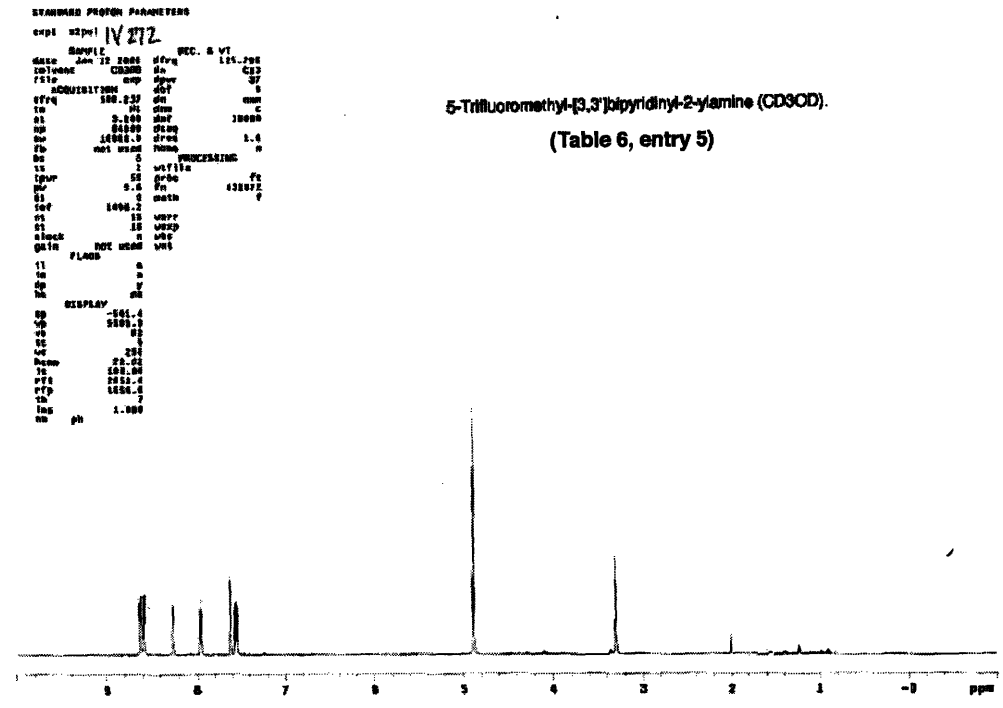
[3,3']Bipyridinyl (CDCl3).

(Table 6, entry 3)



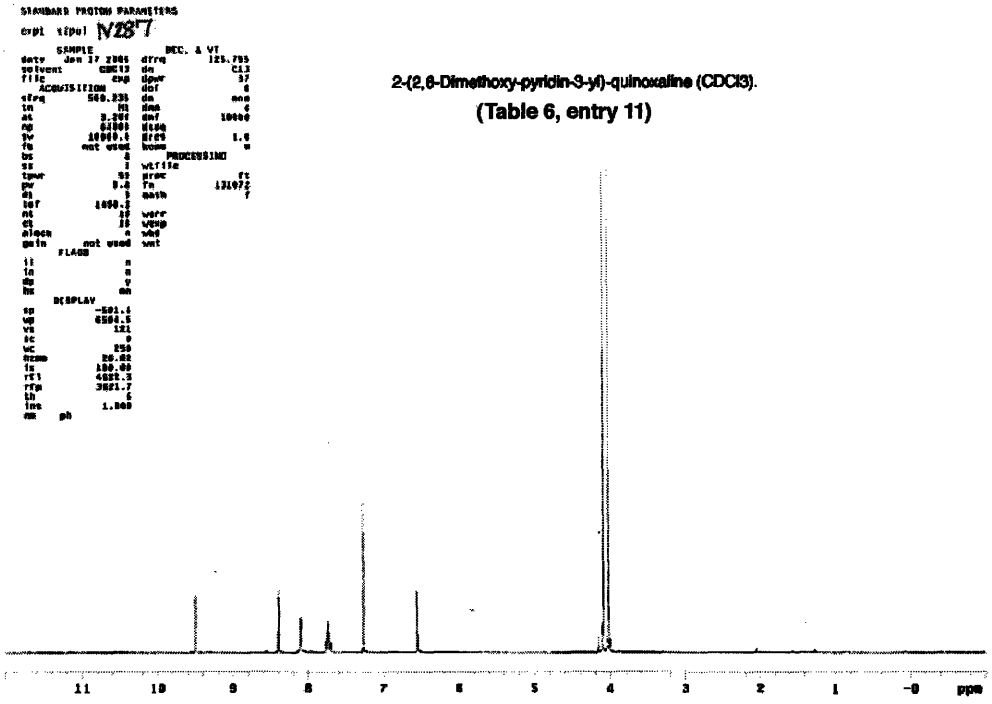
[3,3']Bipyridinyl-6-ylamine (CD3OD).

(Table 6, entry 4)



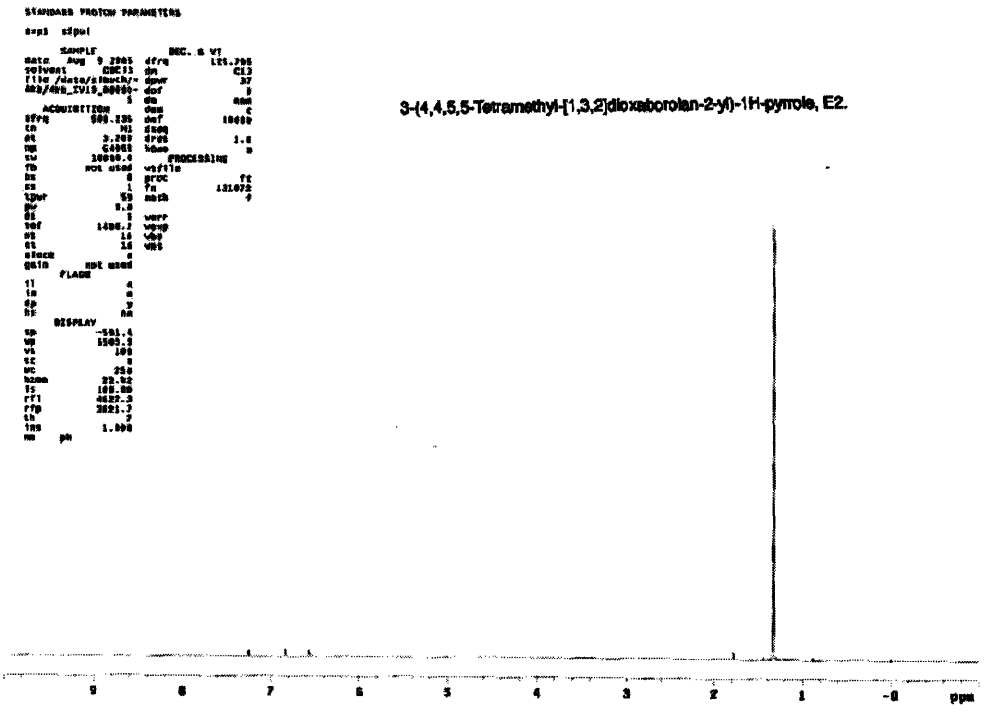
5-Trifluoromethyl-[3,3']bipyridinyl-2-ylamine (CD3OD).

(Table 6, entry 5)

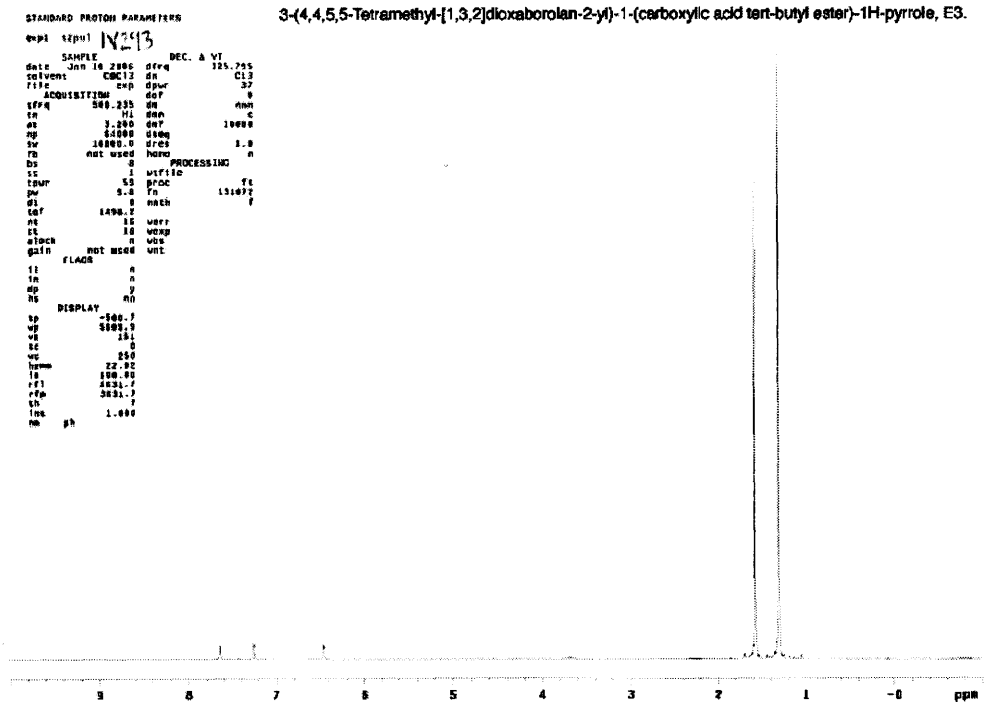


2-(2,6-Dimethoxy-pyridin-3-yl)-quinoxaline (CDCl3).

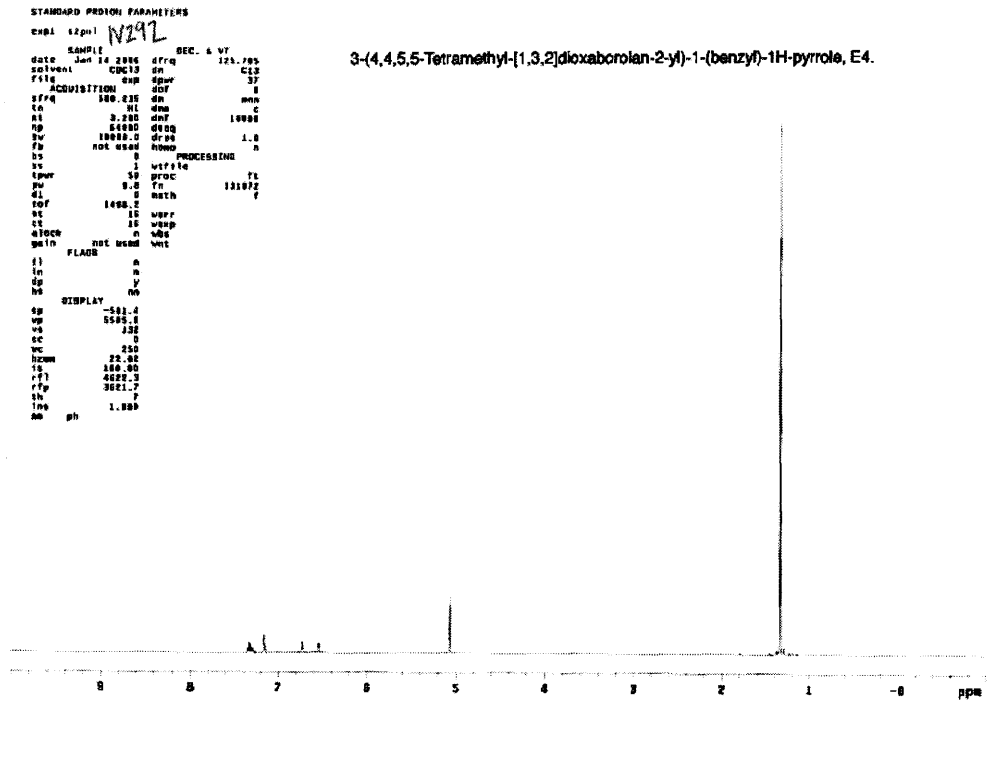
(Table 6, entry 11)



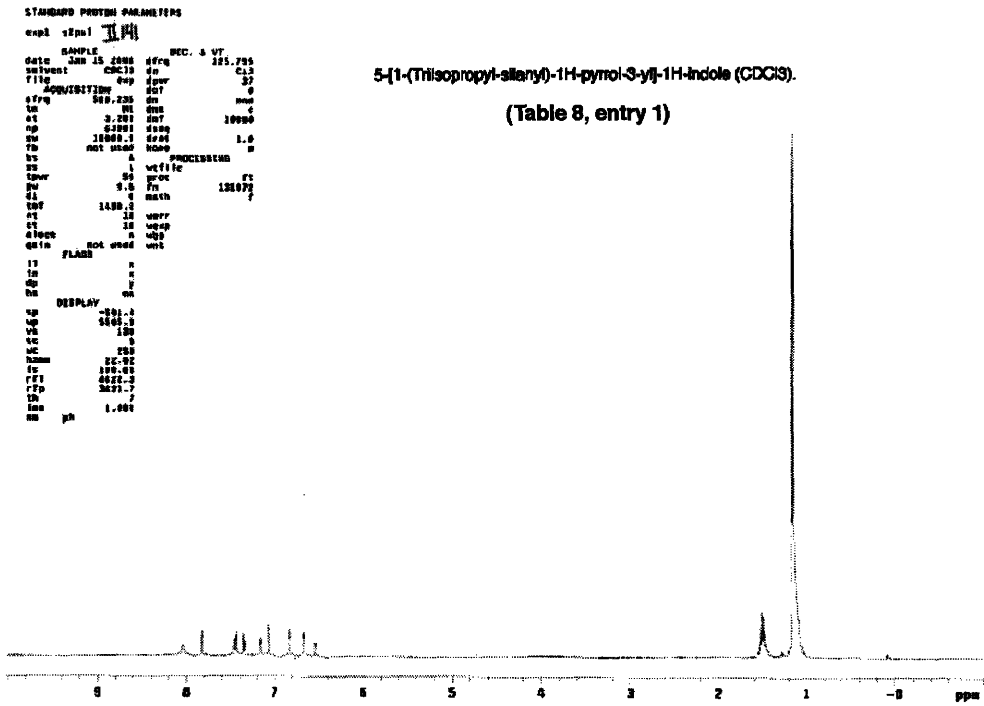
3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrrole, E2.



3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1-(carboxylic acid tert-butyl ester)-1H-pyrrole, E3.

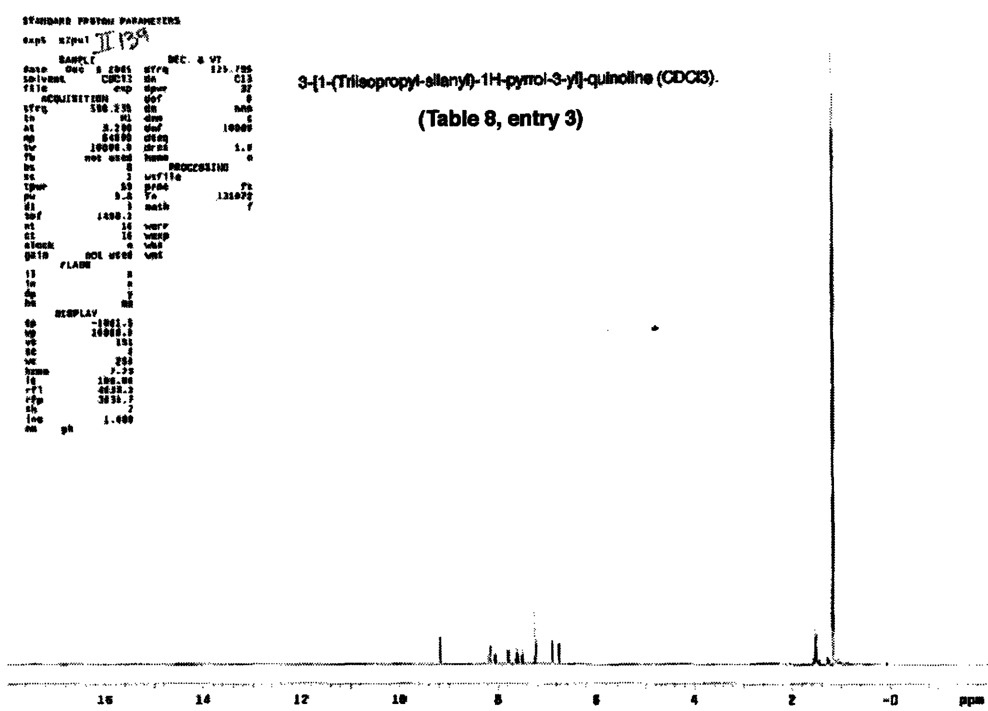


3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1-(benzyl)-1H-pyrrole, E4.



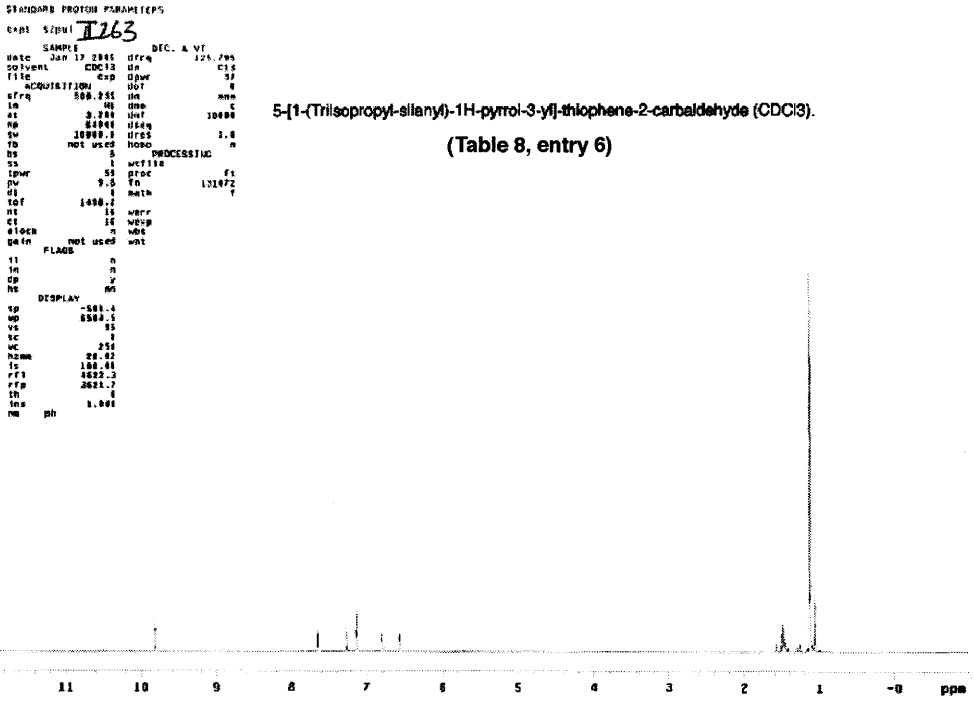
5-[1-(Triisopropyl-silanyl)-1H-pyrrol-3-yl]-1H-indole (CDCl3).

(Table 8, entry 1)



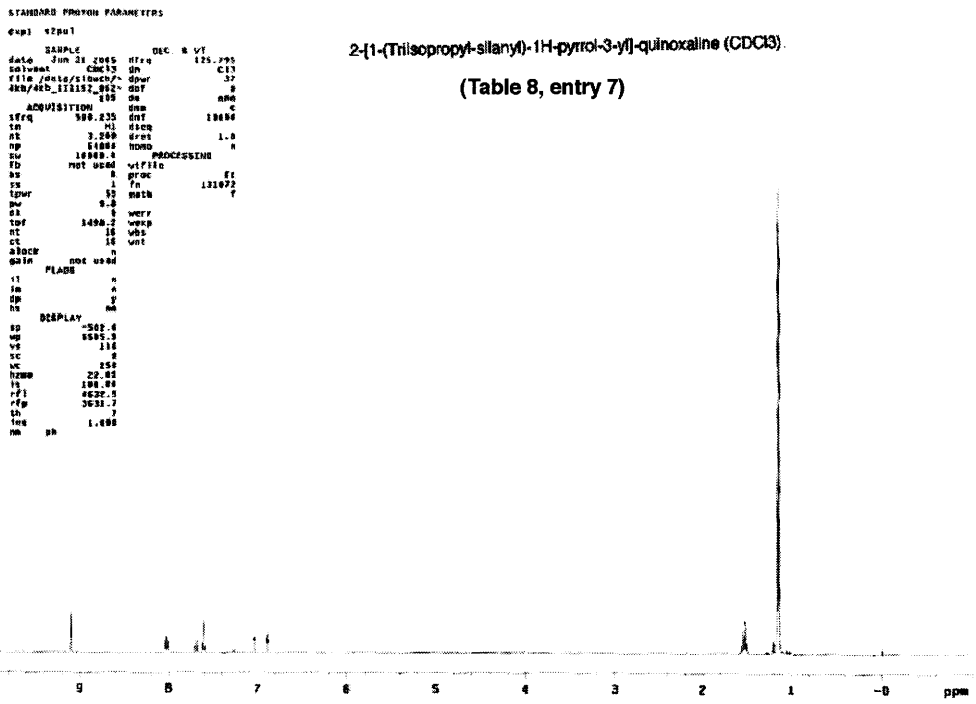
3-[1-(Triisopropyl-silanyl)-1H-pyrrol-3-yl]-quinoline (CDCl3).

(Table 8, entry 3)



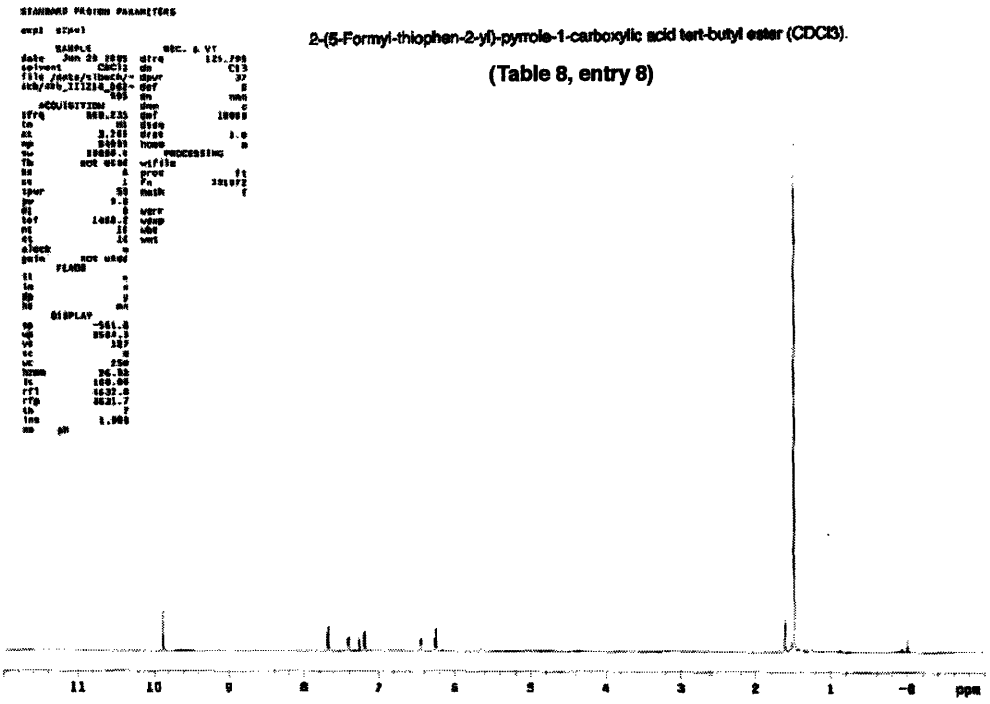
5-[1-(Triisopropyl-silanyl)-1H-pyrrol-3-yl]-thiophene-2-carbaldehyde (CDCl3).

(Table 8, entry 6)



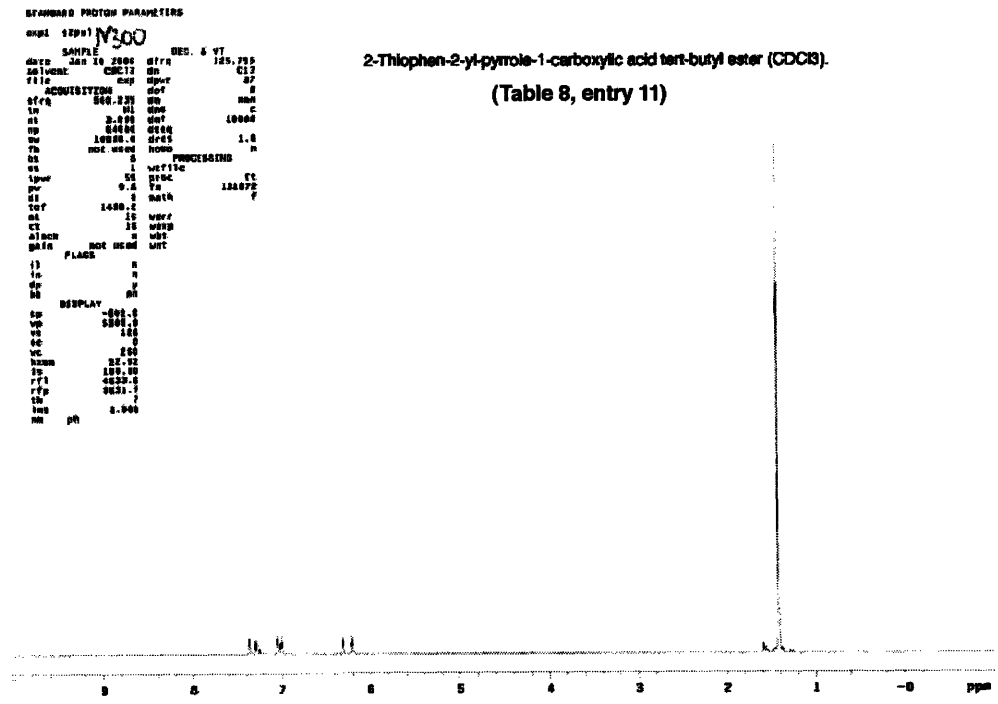
2-[1-(Triisopropyl-silanyl)-1H-pyrrol-3-yl]-quinoxaline (CDCl3).

(Table 8, entry 7)



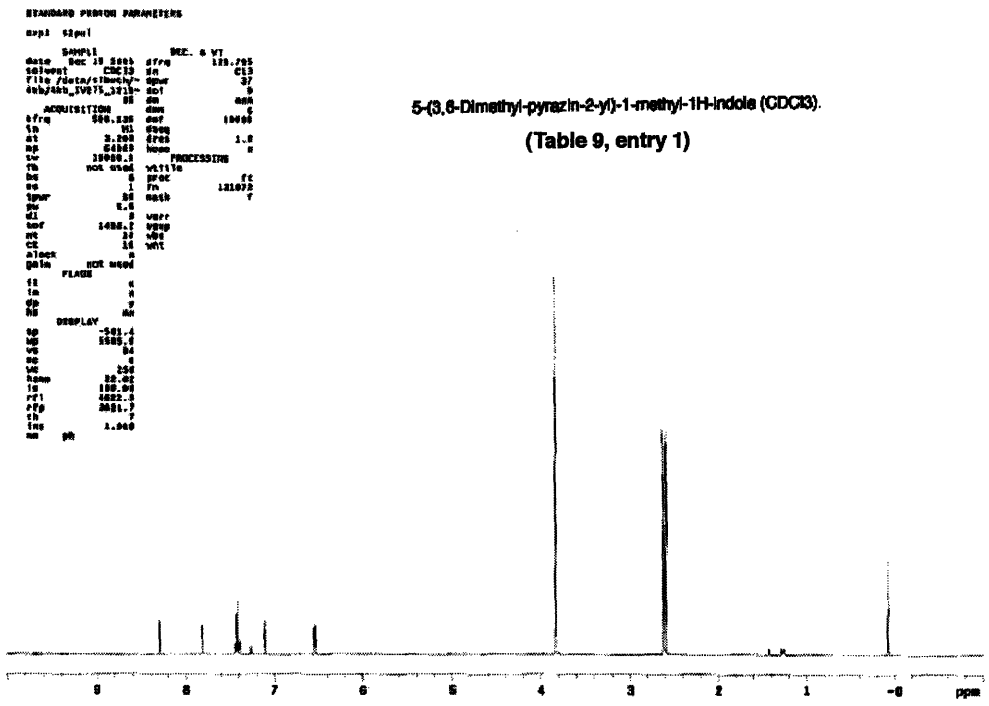
2-(5-Formyl-thiophen-2-yl)-pyrrole-1-carboxylic acid tert-butyl ester (CDCl3).

(Table 8, entry 8)



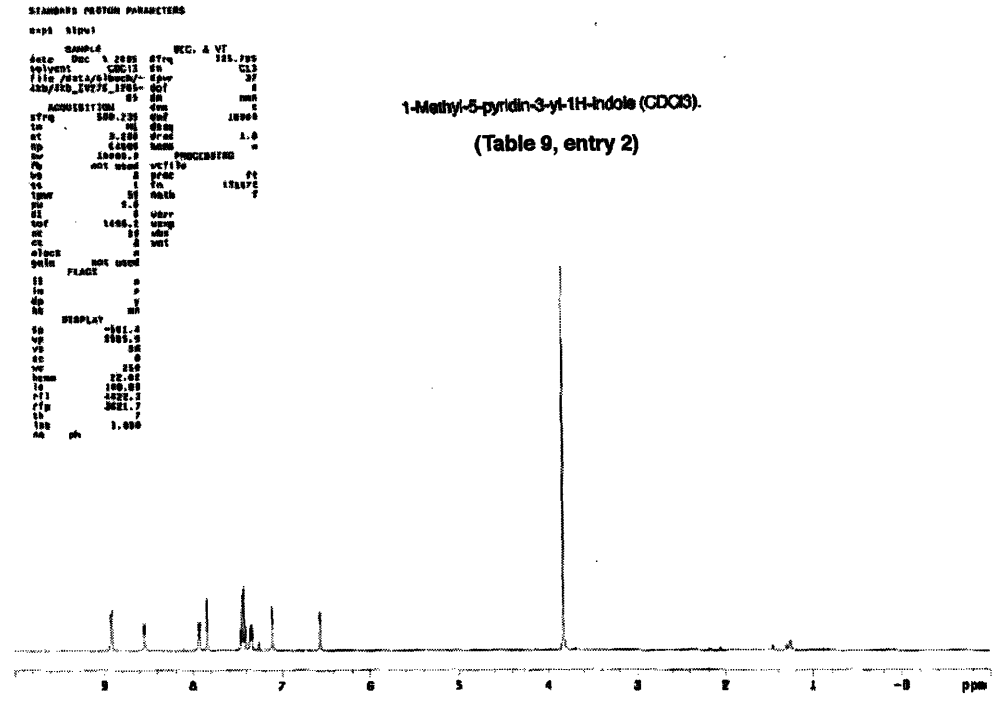
2-Thiophen-2-yl-pyrrole-1-carboxylic acid tert-butyl ester (CDCl3).

(Table 8, entry 11)



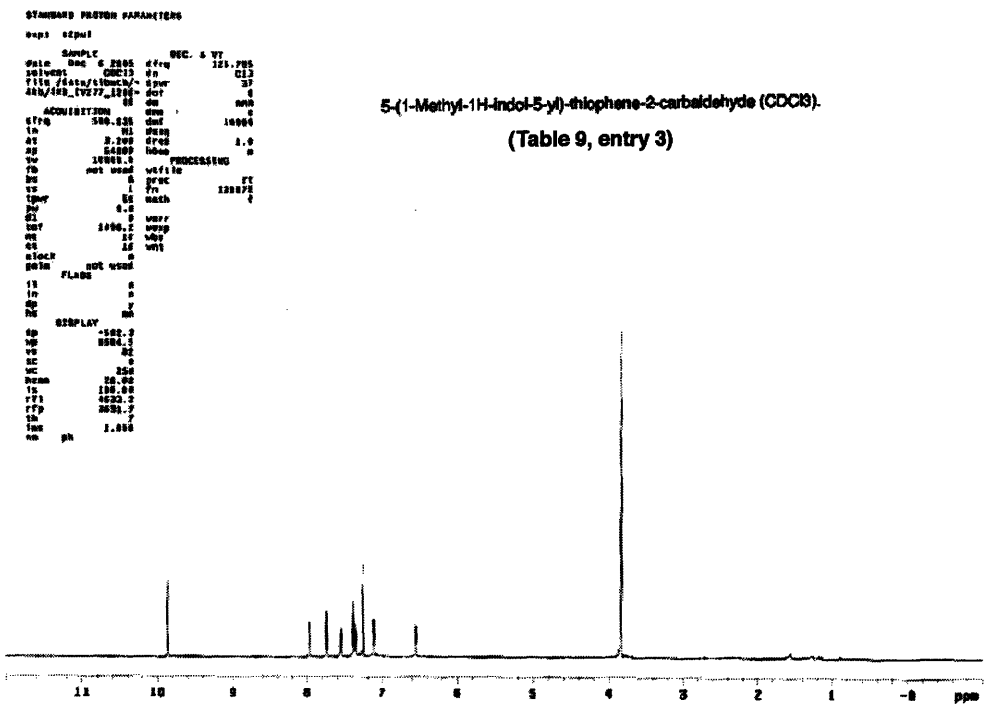
5-(3,6-Dimethyl-pyrazin-2-yl)-1-methyl-1H-indole (CDCl3).

(Table 9, entry 1)



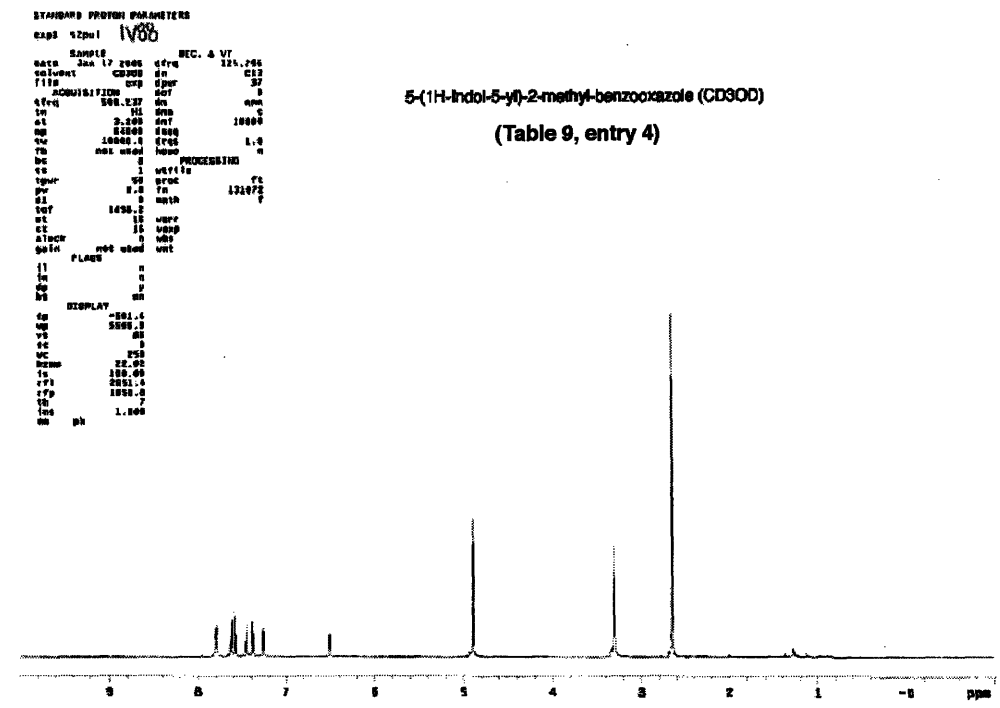
1-Methyl-5-pyridin-3-yl-1H-indole (CDCl3).

(Table 9, entry 2)



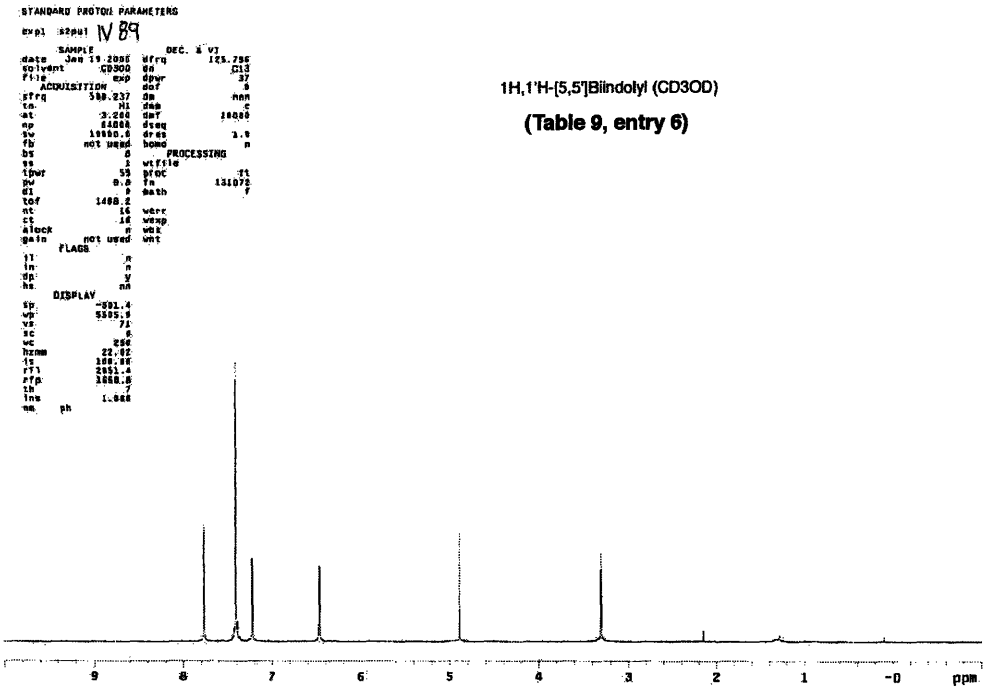
5-(1-Methyl-1H-indol-5-yl)-thiophene-2-carbaldehyde (CDCl3).

(Table 9, entry 3)



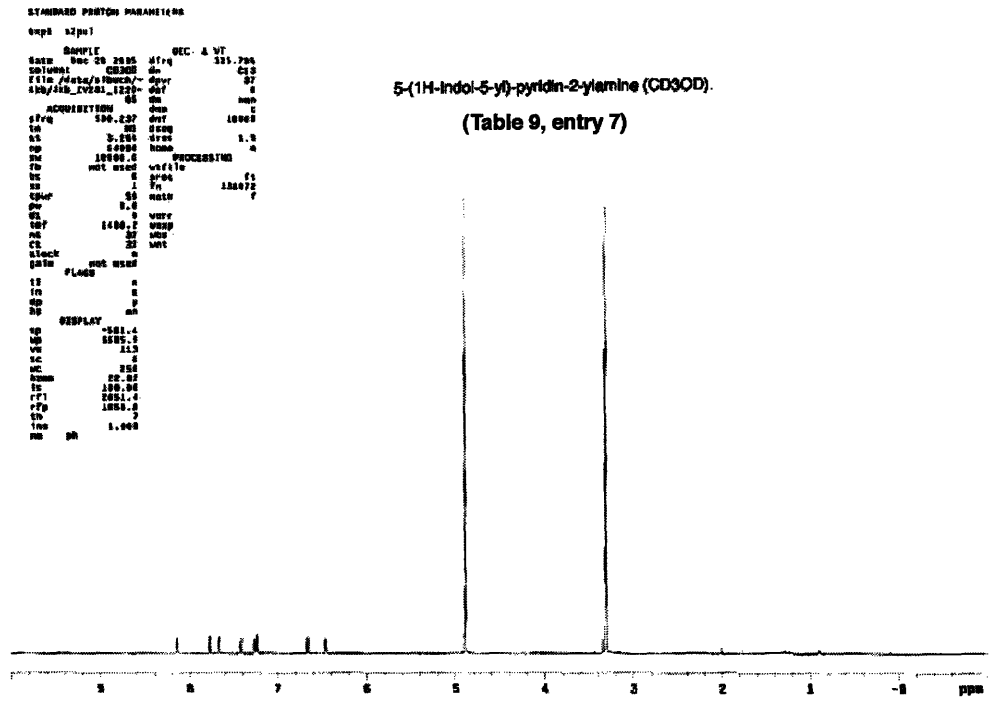
5-(1H-Indol-5-yl)-2-methyl-benzooxazole (CD3OD)

(Table 9, entry 4)



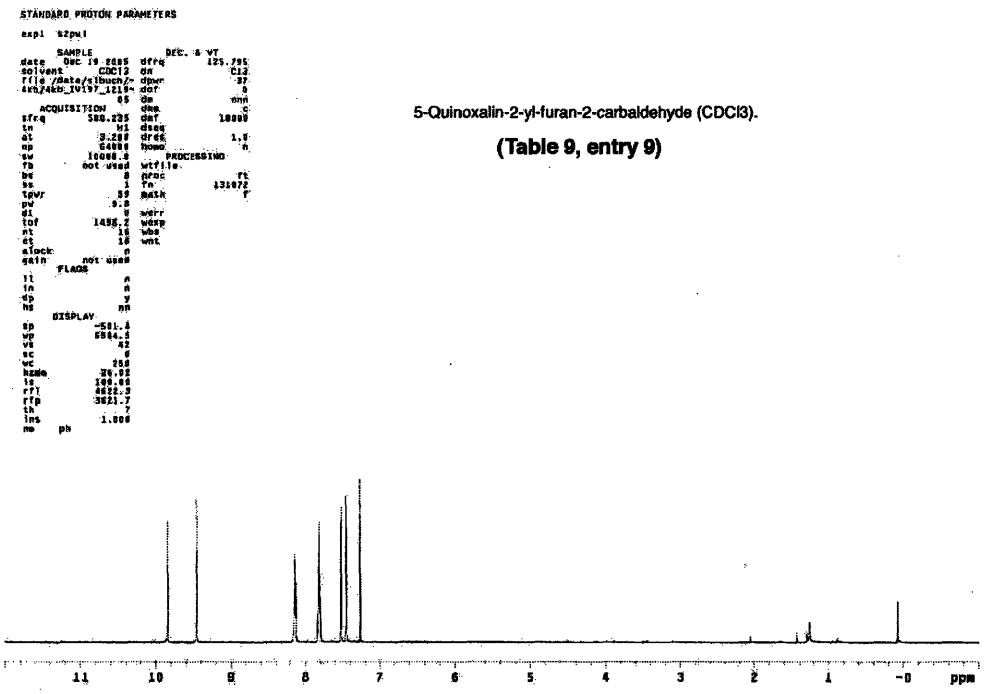
1H,1'H-[5,5']Biindolyl (CD3OD)

(Table 9, entry 6)



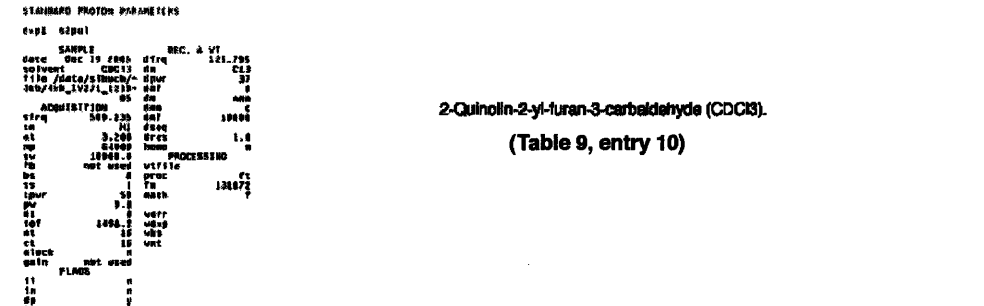
5-(1H-Indol-5-yl)-pyridin-2-ylamine (CD3OD)

(Table 9, entry 7)



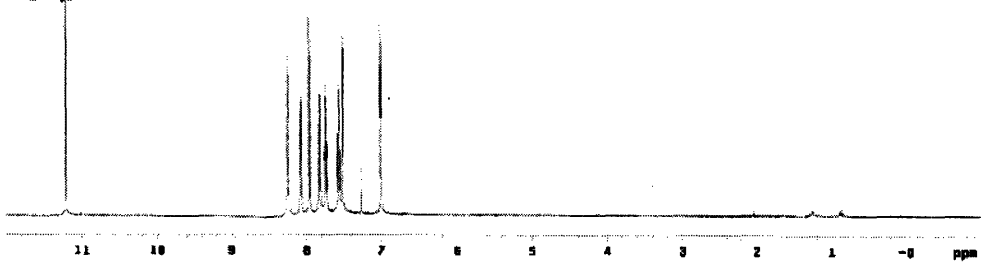
5-Quinoxalin-2-yl-furan-2-carbaldehyde (CDCl3).

(Table 9, entry 9)



2-Quinolin-2-yl-furan-3-carbaldehyde (CDCl3).

(Table 9, entry 10)



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Chapter 2.

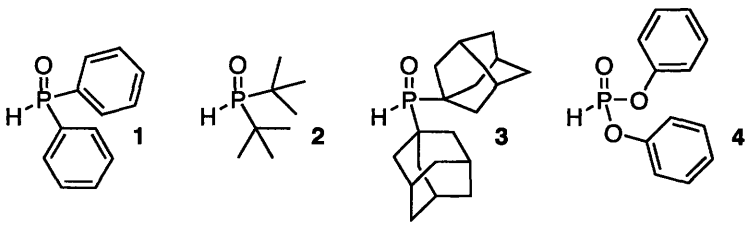
An Efficient Method for the Cross-Coupling of 2-Pyridyl Nucleophiles.

2.1 Introduction

The Suzuki-Miyaura reaction has become one of the most valuable synthetic processes for the construction of carbon-carbon bonds,[1] and our laboratory has developed many highly active catalyst systems that efficiently process challenging combinations of aryl halides and boronic acids.[2] Recently, we have been able to extend our methodology to the cross-coupling of heteroaryl boronic acids and esters, which serve as important building blocks for the assembly of biologically active molecules.[3,4] However, 2-substituted nitrogen-containing heteroaryl organoboranes, which are of importance for the construction of numerous natural products and pharmaceutically interesting compounds,[5] were not effectively transformed using our standard conditions. Further examination of the literature indicated that only a few reports of the Suzuki-Miyaura reaction of 2-pyridyl nucleophiles with aryl halides have appeared, and in these examples, only aryl iodides have been demonstrated as suitable coupling partners.[3,6-10] The difficulty can be attributed to several factors: (1) Electron-deficient heteroaryl boron derivatives undergo transmetalation at a relatively slow rate and (2) These reagents rapidly decompose via a protodeboronation pathway. The lack of an efficient method to process this class of nucleophiles led us to develop a technique specifically designed to accomplish this transformation.

2.2 Results and Discussion

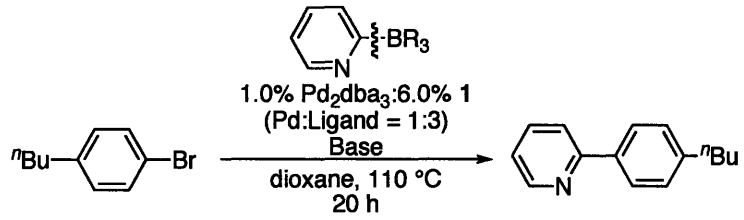
We found that catalysts based upon phosphite or phosphine oxide ligands (**1-4**) were highly active for the Suzuki-Miyaura reaction of 2-pyridyl boron derivatives with 1-bromo-4-butylbenzene (Scheme 1). The use of these has been pioneered by Li, and elegant applications by Ackermann and Wolf have

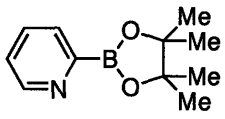
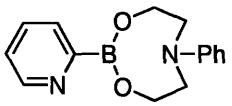


Scheme 1. Effective Phosphite and Phosphine Oxide Ligands

appeared more recently.[11] However, the reaction remained sensitive to the nature of the nucleophile and base. For example, the reaction of commercially-available reagents, such as 2-pyridyl boronic acid,[6] pinacol boronate ester[7] or *N*-phenyl diethanolamine boronate ester,[8] with 4-*n*-butylbromobenzene produced low yields of the desired biaryl product (Table 1, Entries 1-3). Similarly, attempts to use organotrifluoroborates resulted in a low conversion of the aryl bromide (Table 1, Entry 4).[9] Although 2-pyridylborates have been used in Suzuki-Miyaura reactions, the cross-coupling processes result in only

Table 1. The Effects of the Base and Nucleophile[a]

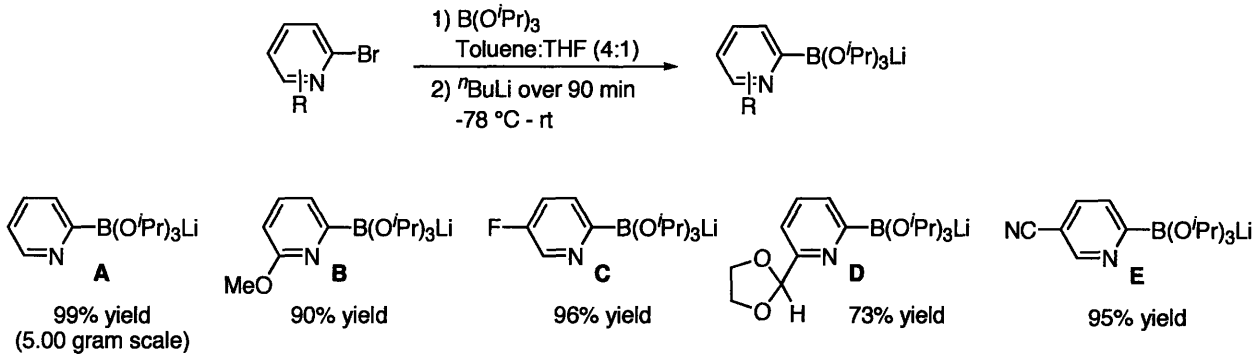


Entry	Ar—BR_3	Base	GC Yield (%)	Conversion (%)
1	—$B(OH)_2$	KF NaO^tBu	0 8	<10 36
2		KF NaO^tBu	0 49	<10 73
3		KF NaO^tBu	6 15	43 100
4	—BF_3K	KF NaO^tBu	0 10	<10 37
5	—$B(O^iPr)_3Li$	KF NaO^tBu	85 68	100 100

[a]Reaction Conditions: 1 equiv of aryl or heteroaryl bromide, 1.5 equiv of 2-pyridylborate, 3.0 equiv of base, dioxane (3 mL/mmol halide), cat. Pd_2dba_3, L:Pd = 3:1.

poor to modest yields of the desired biaryl product.[12] However, when lithium triisopropyl 2-pyridylborate (**A**) was employed as the nucleophile, the desired product could be obtained in an 85% yield with 100%

conversion of the aryl halide (Table 1, Entry 5). Although **A** is not yet commercially available, it is stable under an argon atmosphere for up to a month, and it can be prepared in near quantitative yield from 2-bromopyridine via lithium halogen exchange and immediate *in situ* quenching of the resulting anion with triisopropylborate. In addition, **A** can be prepared in multigram quantities with



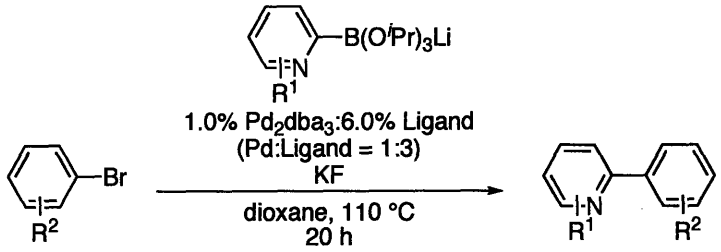
Scheme 2. Synthesis of Lithium Triisopropyl 2-Pyridylborates

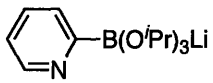
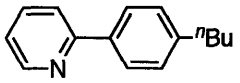
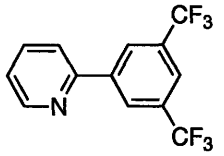
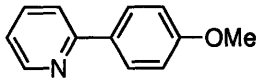
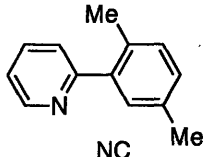
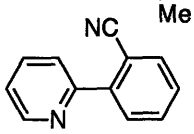
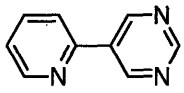
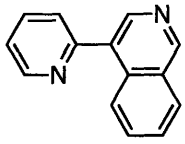
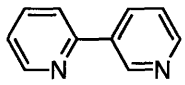
an excellent yield. Lithium triisopropyl 2-(6-methoxypyridyl)borate (**B**) and lithium triisopropyl 2-(5-fluoropyridyl)borate (**C**) were also prepared employing this protocol in 90% and 96% yield, respectively. Similarly, under these conditions, 2-bromopyridines possessing a protected aldehyde (**D**) or a nitrile (**E**) could be efficiently transformed to the corresponding borates.[13]

A catalyst based upon Pd_2dba_3/**1** proved to be highly effective for the Suzuki-Miyaura reactions of **A** with aryl and heteroaryl bromides. For example, this system efficiently combined 3,5-(bis-trifluoromethyl)bromobenzene (Table 2, Entry 2) and 4-bromoanisole (Table 2, Entry 3) with **A** to furnish the desired biaryl in 82% and 74% yield, respectively. In addition, *ortho*-substituted aryl bromides were coupled in good to excellent yields (Table 2, Entries 4-5). Heteroaryl bromides were also suitable coupling partners as seen in the reactions of **A** with 5-bromopyrimidine (Table 2, Entry 6) and 4-bromoisoquinoline (Table 2, Entry 7) which resulted in a 91% and 82% yield, respectively, of the desired heterobiaryl compound. Utilizing a Pd_2dba_3/**2** catalyst, a range of lithium triisopropyl 2-pyridylborates possessing functional groups were successfully cross-coupled with aryl bromides. Indeed, this catalyst

system allowed for the reaction of **B** and **C** with a variety of electron-poor, -neutral, -rich and *ortho*-substituted aryl bromides (Table 2, Entries 9-12).

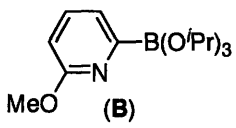
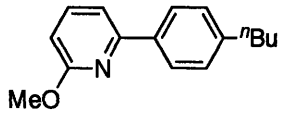
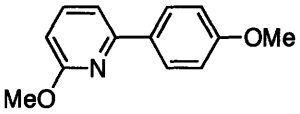
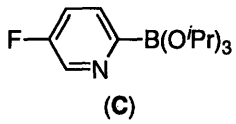
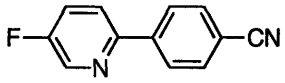
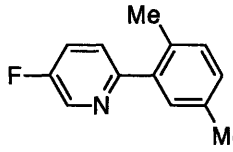
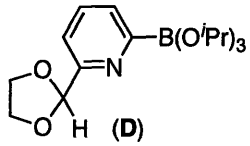
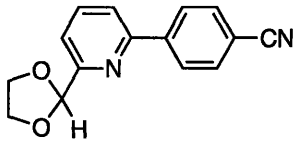
Table 2. The Reaction of **A-D** with Aryl Bromides[a]



Entry	Borate	Ligand	Product	Yield (%)[b]
1	 (A)	1		85
2	A	1		82
3	A	1		74
4	A	1		87
5	A	1		90
6	A	1		91
7	A	1		82
8	A	1		73

[a]Reaction Conditions: 1 equiv of aryl or heteroaryl bromide, 1.5 equiv of 2-pyridylborate, 3.0 equiv of KF, dioxane (3 mL/mmol halide), cat. Pd_2dba_3, L:Pd = 3:1. [b]Isolated yield based upon an average of two runs. [c]1.5% Pd_2dba_3 used instead of 1.0%.

Table 2 (cont). The Reaction of **A-D** with Aryl Bromides[a]

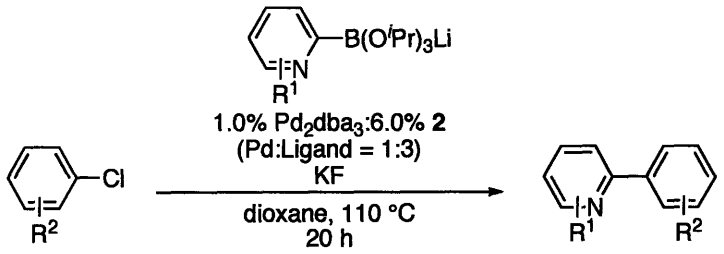
Entry	Borate	Ligand	Product	Yield (%)[b]
9	 (**B**)	**2**		90[c]
10	**B**	**2**		61[c]
11	 (**C**)	**2**		65[c]
12	**C**	**2**		40[c]
13	 (**D**)	**1**		63[c]

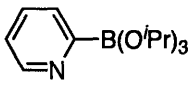
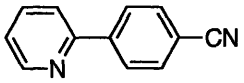
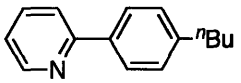
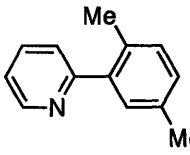
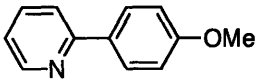
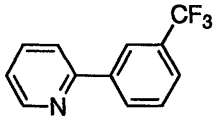
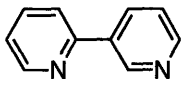
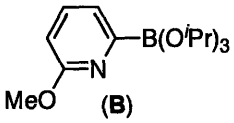
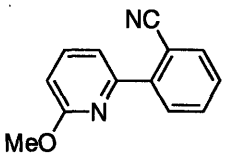
[a]Reaction Conditions: 1 equiv of aryl or heteroaryl bromide, 1.5 equiv of 2-pyridylborate, 3.0 equiv of KF, dioxane (3 mL/mmol halide), cat. Pd_2dba_3, L:Pd = 3:1. [b]Isolated yield based upon an average of two runs. [c]1.5% Pd_2dba_3 used instead of 1.0%.

In addition, the reaction of 4-bromobenzonitrile and **D** furnished the desired biaryl in a 63% yield (Table 2, Entry 13). However, the cross-coupling reactions utilizing **E** resulted in incomplete conversion in its reaction with a variety of aryl bromides. We attributed this difficulty to the relatively slow rate of transmetalation of the highly electron deficient 2-pyridylborate. Overall, however, this protocol still represents the most general available method for the Suzuki-Miyaura reaction of 2-pyridyl nucleophiles with aryl or heteroaryl bromides.

Despite the efficacy of the Pd_2dba_3/**1** catalyst system for the reactions of lithium triisopropyl 2-pyridylborates with aryl bromides, more modest yields of the desired biaryls were obtained in the reactions of the corresponding aryl or heteroaryl chlorides. Employing **2** as the supporting ligand, however, provided a more active catalyst for this transformation. For example, the reaction of **A** with 4-chlorobenzonitrile furnished the desired product in 73% yield (Table 3, Entry 1). In addition, unactivated

Table 3. The Reaction of **A** and **B** with Aryl Chlorides[a]



Entry	Borate	Product	Yield (%)[b]
1	 (**A**)		73
2	**A**		76
3	**A**		70
4	**A**		78
5	**A**		57
6	**A**		92
7	 (**B**)		76[c]

[a]Reaction Conditions: 1 equiv of aryl or heteroaryl chlroide, 1.5 equiv of 2-pyridylborate, 3.0 equiv of KF, dioxane (3 mL/mmol halide), cat. Pd_2dba_3, L:Pd = 3:1. [b]Isolated yield based upon an average of two runs. [c]1.5% Pd_2dba_3 used instead of 1.0%.

aryl chlorides were efficiently coupled as the reactions of 4-*n*-butylchlorobenzene (Table 3, Entry 2) and 4-chloroanisole (Table 3, Entry 4) with **A** resulted in a 76% and 78% yield, respectively, of the desired product. Similarly, under these conditions, *ortho*-substituted aryl chlorides were suitable substrates as the reaction of 2-chloro-*p*-xylene and **A** proceeded in a 70% yield (Table 3, Entry 3). In addition, a heteroaryl

chloride, 3-chloropyridine, was coupled with **A** in an excellent yield to give *o,m*-bipyridine (Table 3, Entry 6).

2.3 Conclusion

In summary, we have developed an efficient method for the Suzuki-Miyaura reaction of lithium triisopropyl 2-pyridylborates. The borates can be readily prepared in one step from the corresponding 2-bromo- or 2-iodopyridine derivatives. This represents the first relatively general Suzuki-Miyaura cross-coupling reaction of these substrates with aryl and heteroaryl bromides and chlorides.

2.4 Experimental

2.4.1 General

All reactions were stirred with the aid of a magnetic stirrer and carried out under an argon atmosphere. 1,4-Dioxane (anhydrous) was purchased from Aldrich Chemical Co. in a SureSeal® bottle. Commercially available materials were used without further purification unless otherwise noted. Diphenylphosphine oxide was purchased from Alfa Aesar, and di-*tert*-butylphosphine oxide was purchased from Strem Chemicals, Inc. Both ligands are hygroscopic and must be stored in a benchtop desiccator. Aryl halides were purchased from Aldrich Chemical Co. Liquid aryl halides were purified by passage through a pad of basic alumina prior to use. Potassium fluoride (anhydrous, Alfa Aesar) and Pd_2dba_3 (Strem Chemicals, Inc.) were stored in a benchtop desiccator. All lithium triisopropyl 2-pyridylborates were prepared in our laboratories via the procedure described in this experimental (Page 2). These were stored inside a benchtop desiccator for up to a month.

All new compounds were characterized by ^1H NMR, ^{13}C NMR, IR spectroscopy, melting points (for solids) and, in most cases, elemental analysis. Known compounds were characterized by ^1H NMR, ^{13}C NMR and melting points (for solids) and compared to their literature values. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 300. Infrared spectra were recorded on an ASI Applied Systems

ReactIR 1000 (neat samples were placed directly on the DiComp probe). Elemental analyses were preformed by Atlantic Microlabs Inc., Norcross, GA. All ^{1}H NMR experiments are reported in δ units, parts per million (ppm) downfield of TMS and were measured relative to the signals for the residual benzene (7.16 ppm), chloroform (7.26 ppm), dimethylsulfoxide (2.50 ppm) or methanol (3.31 ppm). All ^{13}C NMR spectra were reported in ppm relative to residual chloroform (77 ppm), dimethylsulfoxide (39.5 ppm) or methanol (49 ppm) and were obtained with ^{1}H decoupling. Melting points were obtained on a Mel-Temp capillary melting point apparatus and are uncorrected. Gas chromatographic analyses were performed on Hewlett-Packard 6890 gas chromatography instrument with a FID detector using 25 m x 0.20 mm capillary column with cross-linked methyl siloxane as a stationary phase.

The yields in tables 2 and 3 refer to isolated yields (average of two runs) of compounds estimated to be ≥ 95% pure as determined by ^{1}H NMR and/or combustion analysis.

2.4.2 Experimental for Preparation of Lithium Triisopropyl 2-Pyridylborates

General Procedure for the Preparation of Lithium Triisopropyl 2-Pyridylborates.[13]

An oven-dried round-bottomed flask equipped with a magnetic stir bar and fitted with a rubber septum was charged with toluene (60 mL) and THF (15 mL) and placed under an argon atmosphere. The flask was charged with triisopropylborate (3.81 mL, 3.10 g, 16.5 mmol) and the heteroaryl bromide (15.0 mmol). The reaction mixture was cooled to -78 °C using a dry ice/acetone bath. *n*-Butyllithium (2.5 M in hexanes, 6.6 mL, 16.5 mmol) was added dropwise via a syringe pump over 1.5 h, and the mixture was stirred for an additional 0.5 h while the temperature was held at -78 °C. The reaction mixture was then allowed to warm to room temperature overnight (15 h). The resulting solution was then concentrated under reduced pressure, followed by further drying under high vacuum at 110 °C for 12 h to yield the desired borate.

Lithium Triisopropyl 2-Pyridyl Borate (A). The general procedure was followed on a larger scale using toluene (120 mL), THF (30 mL), triisopropylborate (8.03 mL, 6.55 g, 34.8 mmol), 2-bromopyridine (31.6 mmol), *n*-Butyllithium (2.5 M in hexanes, 13.9 mL, 34.8 mmol) to provide the title compound in a

99% yield (8.67 g) as a brown solid, mp >250 °C. ^{1}H NMR (300 MHz, CD_3OD) δ: 8.38 (d, J = 5 Hz, 1H), 7.58 (dt, J = 8, 1 Hz, 1H), 7.54 (t, J = 8 Hz, 1H), 7.07 (dt, J = 8, 1 Hz, 1H), 3.93 (sept, J = 6 Hz, 3H), 1.15 (d, J = 6 Hz, 18H). ^{13}C NMR (75 MHz, CD_3OD) δ: 148.2, 135.5, 128.5, 121.7, 64.7, 25.4. (No C-B Signal) IR (neat, cm^{-1}): 3372, 2941, 2913, 1653, 1557, 1538, 1421, 1149, 1004, 931. ^{1}H NMR spectrum included.

Lithium Triisopropyl 2-(6-Methoxypyridyl) Borate (B). The general procedure was followed to provide the title compound in a 90% yield (4.10 g) as a white solid, mp 226-227 °C. ^{1}H NMR (300 MHz, CD_3OD) δ: 7.52 (t, J = 8 Hz, 1H), 7.13 (d, J = 8 Hz, 1H), 6.52 (d, J = 8 Hz, 1H), 3.93 (sept, J = 6 Hz, 3H), 3.87 (s, 3H), 1.15 (d, J = 6 Hz, 18H). ^{13}C NMR (75 MHz, CD_3OD) δ: 165.4, 138.9, 121.9, 105.3, 64.7, 54.4, 25.3. (No C-B Signal) IR (neat, cm^{-1}): 3284, 2952, 2901, 2851, 1647, 1589, 1559, 1487, 1425, 1401, 1282, 1226, 1043, 934, 903. ^{1}H NMR spectrum included.

Lithium Triisopropyl 2-(5-fluoropyridyl) Borate (C). The general procedure was followed on a smaller scale using toluene (40 mL), THF (10 mL), triisopropylborate (2.88 mL, 2.35 g, 12.5 mmol), 2-bromo-5-fluoropyridine (2.00 g, 11.4 mmol), *n*-Butyllithium (2.5 M in hexanes, 5.00 mL, 12.5 mmol) to provide the title compound in a 96% yield (3.24 g) as a brown solid, mp >250 °C. ^{1}H NMR (300 MHz, CD_3OD) δ: 8.26 (s, 1H), 7.55 (dd, J = 8, 6 Hz, 1H), 7.39 (dt, J = 8, 6 Hz, 1H), 3.93 (sept, J = 6 Hz, 3H), 1.15 (d, J = 6 Hz, 18H). ^{13}C NMR (75 MHz, CD_3OD) δ: 161.0, 159.0, 135.8, 129.4, 122.6, 64.7, 25.5. IR (neat, cm^{-1}): 3282, 2959, 171, 1471, 1375, 1326, 1171, 1129, 950. ^{1}H NMR spectrum included.

Lithium Triisopropyl 2-(6-(1,3-dioxolan-2-yl)pyridin-2-yl) Borate (D). The general procedure was followed on a smaller scale using toluene (16.0 mL), THF (4.0 mL), triisopropylborate (1.05 mL, 0.856 g, 4.55 mmol), 2-bromo-6-(1,3-dioxolan-2-yl)pyridine (0.952 g, 4.14 mmol), *n*-Butyllithium (2.5 M in hexanes, 1.82 mL, 4.55 mmol) to provide the title compound in a 73% yield (1.04 g) as a brown solid, mp 159-161 °C. ^{1}H NMR (300 MHz, CD_3OD) δ: 7.64 (t, J = 8 Hz, 1H), 7.55 (dd, J = 8, 1 Hz, 1H), 7.30 (dd, J = 8, 1 Hz, 1H), 5.81 (s, 1H), 3.95-4.10 (m, 4H), 3.92 (sept, J = 6 Hz, 3H), 1.15 (d, J = 6 Hz, 18H). ^{13}C NMR (75 MHz, CD_3OD) δ: 155.9, 136.2, 128.7, 121.0, 119.0, 105.2, 66.4, 64.7, 25.5. IR (neat, cm^{-1}): 2964, 2892, 1593, 1464, 1376, 1202, 1127, 1007. ^{1}H NMR spectrum included.

Lithium Triisopropyl 2-(5-cyanopyridyl) Borate (E). The general procedure was followed on a smaller scale using toluene (20.0 mL), THF (5.0 mL), triisopropylborate (1.27 mL, 1.03 g, 5.50 mmol), 6-bromopyridine-3-carbonitrile (0.915 g, 5.00 mmol), *n*-Butyllithium (2.5 M in hexanes, 2.20 mL, 5.50 mmol) to provide the title compound in a 95% yield (1.42 g) as a brown solid, mp >250 °C. ^{1}H NMR (300 MHz, CD_3OD) δ: 8.73 (d, J = 3 Hz, 1H), 7.93 (dd, J = 8, 3 Hz, 1H), 7.71 (d, J = 8 Hz, 1H), 3.93 (sept, J = 6 Hz, 3H), 1.15 (d, J = 6 Hz, 18H). ^{13}C NMR (75 MHz, CD_3OD) δ: 151.1, 138.3, 132.0, 128.8, 118.6, 107.8, 64.8, 25.4. IR (neat, cm^{-1}): 2952, 2862, 2218, 1591, 1448, 1363, 1126, 999. ^{1}H NMR spectrum included.

2.4.3 Experimental for the Reactions with Aryl Bromides

General Procedure A: Pd-Catalyzed Suzuki-Miyaura Reaction of Lithium Triisopropyl 2-Pyridylborates with Aryl Halides.

An oven-dried resealable Schlenk tube possessing a Teflon screw valve was charged with Pd_2dba_3 (2.0-3.0%), ligand (6.0-9.0%), lithium triisopropyl 2-pyridylborate (0.375 mmol) and anhydrous KF (43.5 mg, 0.75 mmol). The Schlenk tube was capped with a rubber septum and then evacuated and backfilled with argon (this sequence was carried out two times). 1,4-Dioxane (0.75 mL) was added via syringe, through the septum, followed by the addition of the aryl halide (0.25 mmol) in a like manner (aryl halides that were solids were added with the other solid reagents). The septum was then replaced with a Teflon screw valve and the Schlenk tube was sealed. The reaction mixture was heated to 110 °C until the aryl halide had been completely consumed as determined by gas chromatography and was allowed to cool to room temperature. The reaction solution was then filtered through a thin pad of silica gel (eluting with ethyl acetate) and the eluent was concentrated under reduced pressure. The crude material so obtained was purified via flash chromatography on silica gel.

2-(4-butylphenyl)pyridine (Table 2, Entry 1).[14] Following general procedure A, a mixture of 4-*n*-butylbromobenzene (44.1 μL, 53.3 mg, 0.25 mmol), lithium triisopropyl 2-pyridylborate (104 mg, 0.375 mmol), KF, Pd_2dba_3 (2.3 mg, 0.0025 mmol) and **1** (3.0 mg, 0.015 mmol) was heated for 20 h. Flash

column chromatography (10% EtOAc/Hexanes) yielded the title compound in 45 mg (85% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.66 (dt, J = 6,1 Hz, 1H), 7.88 (d, J = 8 Hz, 2H), 7.67-7.71 (m, 2H), 7.26 (d, J = 8 Hz, 2H), 7.16 (dt, J = 6,1 Hz, 1H), 2.64 (t, J = 8 Hz, 2H), 1.62 (pent, J = 8 Hz, 2H), 1.36 (sext, J = 8 Hz, 2H), 0.92 (t, J = 8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.4, 149.5, 143.9, 136.7, 136.6, 128.8, 126.7, 121.7, 120.2, 35.4, 33.5, 22.3, 13.9. ^{1}H NMR spectrum included.

2-(3,5-bis(trifluoromethyl)phenyl)pyridine (Table 2, Entry 2).[15] Following general procedure A, a mixture of 3,5-bis(trifluoromethyl)bromobenzene (43.1 μL, 73.3 mg, 0.25 mmol), lithium triisopropyl 2-pyridylborate (104 mg, 0.375 mmol), KF, Pd_2dba_3 (2.3 mg, 0.0025 mmol) and **1** (3.0 mg, 0.015 mmol) was heated for 20 h. Flash column chromatography (10% EtOAc/Hexanes) yielded the title compound in 60 mg (82% yield) as a white solid, mp 45-46 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.75 (dt, J = 5, 1 Hz, 1H), 8.48 (s, 2H), 7.91 (s, 1H), 7.81-7.86 (m, 2H), 7.35 (dt, J = 5,1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 154.1, 150.1, 141.3, 137.2, 132.1, 126.9, 124.4, 123.6, 122.4, 120.6. ^{1}H NMR spectrum included.

2-(4-methoxyphenyl)pyridine (Table 2, Entry 3).[16] Following general procedure A, a mixture of 4-bromoanisole (31.3 μL, 46.8 mg, 0.25 mmol), lithium triisopropyl 2-pyridylborate (104 mg, 0.375 mmol), KF, Pd_2dba_3 (2.3 mg, 0.0025 mmol) and **1** (3.0 mg, 0.015 mmol) was heated for 20 h. Flash column chromatography (15% EtOAc/Hexanes) yielded the title compound in 34 mg (74% yield) as a white solid, mp 47-48 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.65 (dt, J = 5, 1 Hz, 1H), 7.96 (d, J = 9 Hz, 2H), 7.71 (dt, J = 8, 2 Hz, 1H), 7.66 (dt, J = 8, 1 Hz, 1H), 7.17 (dd, J = 5, 1 Hz, 1H), 7.00 (d, J = 9 Hz, 2H), 3.86 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.4, 157.0, 149.4, 136.6, 132.0, 128.1, 121.4, 119.8, 114.1, 55.3. ^{1}H NMR spectrum included.

2-(2,5-dimethylphenyl)pyridine (Table 2, Entry 4). Following general procedure A, a mixture of 2-bromo-*p*-xylene (34.5 μL, 46.3 mg, 0.25 mmol), lithium triisopropyl 2-pyridylborate (104 mg, 0.375 mmol), KF, Pd_2dba_3 (2.3 mg, 0.0025 mmol) and **1** (3.0 mg, 0.015 mmol) was heated for 20 h. Flash column chromatography (10% EtOAc/Hexanes) yielded the title compound in 39 mg (87% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.71 (dt, J = 5, 1 Hz, 1H), 7.74 (dt, J = 7, 1 Hz, 1H), 7.42 (dt, J = 8, 1 Hz, 1H), 7.23-7.26 (m, 2H), 7.16 (dt, J = 6, 1 Hz, 1H), 7.20 (d, J = 8 Hz, 1H), 7.14 (dt, J = 8,

1 Hz, 1H), 2.38 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.0, 149.2, 140.2, 135.9, 135.2, 132.4, 130.6, 130.2, 128.9, 124.0, 121.5, 20.9, 19.7. IR (neat, cm^{-1}): 3394, 3014, 2922, 1598, 1563, 1501, 1471, 1426, 1378, 1149, 1039, 992, 792, 749. ^1H NMR spectrum included.

2-(pyridin-2-yl)benzonitrile (Table 2, Entry 5).[17] Following general procedure A, a mixture of 2-bromobenzonitrile (45.5 mg, 0.25 mmol), lithium triisopropyl 2-pyridylborate (104 mg, 0.375 mmol), KF, Pd_2dba_3 (2.3 mg, 0.0025 mmol) and **1** (3.0 mg, 0.015 mmol) was heated for 20 h. Flash column chromatography (25% EtOAc/Hexanes) yielded the title compound in 41 mg (90% yield) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.77 (dt, J = 5, 1 Hz, 1H), 7.76-7.84 (m, 4H), 7.79 (dt, J = 8, 2 Hz, 1H), 7.50 (dt, J = 8, 2 Hz, 1H), 7.35 (ddd, J = 8, 5, 1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.2, 149.9, 143.4, 136.8, 134.1, 132.8, 129.9, 128.7, 123.3, 123.2, 118.7, 111.0. ^1H NMR spectrum included.

5-(pyridin-2-yl)pyrimidine (Table 2, Entry 6).[18] Following general procedure A, a mixture of 5-bromopyrimidine (39.7 mg, 0.25 mmol), lithium triisopropyl 2-pyridylborate (104 mg, 0.375 mmol), KF, Pd_2dba_3 (2.3 mg, 0.0025 mmol) and **1** (3.0 mg, 0.015 mmol) was heated for 20 h. Recrystallization (Hexanes) yielded the title compound in 36 mg (91% yield) as a brown solid, mp 129-130 °C. ^1H NMR (300 MHz, $CDCl_3$) δ: 9.33 (s, 2H), 9.25 (s, 1H), 8.75 (dt, J = 5, 1 Hz, 1H), 7.83 (dt, J = 8, 2 Hz 1H), 7.76 (dt, J = 8, 1 Hz, 1H), 7.35 (ddd, J = 8, 5, 2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.6, 155.1, 152.0, 150.4, 137.2, 132.4, 123.6, 120.5. ^1H NMR spectrum included.

4-(pyridin-2-yl)isoquinoline (Table 2, Entry 7).[19] Following general procedure A, a mixture of 4-bromoisoquinoline (52.0 mg, 0.25 mmol), lithium triisopropyl 2-pyridylborate (104 mg, 0.375 mmol), KF, Pd_2dba_3 (2.3 mg, 0.0025 mmol) and **1** (3.0 mg, 0.015 mmol) was heated for 20 h. Flash column chromatography (50% EtOAc/Hexanes) yielded the title compound in 42 mg (82% yield) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 9.29 (s, 1H), 8.82 (dt, J = 5, 1 Hz, 1H), 8.64 (s, 1H), 8.20 (d, J = 8 Hz, 1H), 8.03 (d, J = 8 Hz, 1H), 7.86 (dt, J = 8, 1 Hz, 1H), 7.70 (dt, J = 8, 1 Hz, 1H), 7.63 (t, J = 8 Hz, 1H), 7.37 (ddd, J = 8, 5, 1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.3, 153.0, 149.7, 143.4, 136.8, 133.7, 131.5, 130.9, 128.5, 127.9, 127.3, 124.9, 124.7, 122.5. ^1H NMR spectrum included.

2,3'-bipyridine (Table 2, Entry 8).[20] Following general procedure A, a mixture of 3-bromopyridine (24.1 μL, 39.5 mg, 0.25 mmol), lithium triisopropyl 2-pyridylborate (104 mg, 0.375 mmol), KF, Pd_2dba_3 (2.3 mg, 0.0025 mmol) and **1** (3.0 mg, 0.015 mmol) was heated for 20 h. Flash column chromatography (EtOAc) yielded the title compound in 29 mg (73% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.17 (d, J = 3 Hz, 1H), 8.71 (dt, J = 5, 1 Hz, 1H), 8.64 (dt, J = 5, 1 Hz, 1H), 8.31 (dt, J = 8, 1 Hz, 1H), 7.79 (dt, J = 8, 1 Hz, 1H), 7.75 (dt, J = 8, 1 Hz, 1H), 7.39 (dd, J = 8, 3 Hz, 1H), 7.28 (ddd, J = 8, 5, 1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 154.7, 150.0, 149.9, 148.2, 136.9, 134.8, 134.3, 123.5, 122.8, 120.6. ^{1}H NMR spectrum included.

2-(4-butylphenyl)-6-methoxypyridine (Table 2, Entry 9). Following general procedure A, a mixture of 4-*n*-butylbromobenzene (44.1 μL, 53.3 mg, 0.25 mmol), lithium triisopropyl 2-(6-methoxypyridyl)borate (114 mg, 0.375 mmol), KF, Pd_2dba_3 (3.4 mg, 0.00375 mmol) and **2** (3.6 mg, 0.0225 mmol) was heated for 20 h. Flash column chromatography (5% EtOAc/Hexanes) yielded the title compound in 54 mg (90% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.97 (d, J = 8 Hz, 2H), 7.62 (t, J = 8 Hz, 1H), 7.32 (d, J = 8 Hz, 1H), 7.28 (d, J = 8 Hz, 2H), 6.67 (d, J = 8 Hz, 1H), 4.05 (s, 3H), 2.67 (t, J = 8 Hz, 2H), 1.65 (pent, J = 8 Hz, 2H), 1.39 (sext, J = Hz, 2H), 0.96 (t, J = 8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.6, 154.7, 143.8, 139.1, 136.5, 128.7, 126.5, 112.4, 108.8, 53.1, 35.4, 33.6, 22.3, 14.0. IR (neat, cm^{-1}): 3060, 2955, 2929, 2857, 1587, 1514, 1463, 1435, 1398, 1324, 1302, 1255, 1151, 1075, 1025, 795. ^{1}H NMR spectrum included.

2-methoxy-6-(4-methoxyphenyl)pyridine (Table 2, Entry 10).[21] Following general procedure A, a mixture of 4-bromoanisole (31.3 μL, 46.8 mg, 0.25 mmol), lithium triisopropyl 2-(6-methoxypyridyl)borate (114 mg, 0.375 mmol), KF, Pd_2dba_3 (3.4 mg, 0.00375 mmol) and **2** (3.6 mg, 0.0225 mmol) was heated for 20 h. Flash column chromatography (5% EtOAc/Hexanes) yielded the title compound in 33 mg (61% yield) as a white solid, mp 120-121 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.01 (d, J = 7 Hz, 2H), 7.59 (dt, J= 7, 2 Hz, 1H), 7.27 (d, J = 7 Hz, 1H), 6.98 (d, J = 7 Hz, 2H), 6.63 (d, J = 7 Hz, 2H), 4.03 (s, 3H), 3.86 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.6, 160.3, 154.4, 139.1, 131.7, 127.9, 113.9, 111.9, 108.2, 55.3, 53.1. ^{1}H NMR spectrum included.

4-(5-fluoropyridin-2-yl)benzonitrile (Table 2, Entry 11). Following general procedure A, a mixture of 4-bromobenzonitrile (45.5 mg, 0.25 mmol), lithium triisopropyl 2-(5-fluoropyridyl)borate (109 mg, 0.375 mmol), KF, Pd_2dba_3 (3.4 mg, 0.00375 mmol) and **2** (3.6 mg, 0.0225 mmol) was heated for 20 h. Recrystallization (Hexanes) yielded the title compound in 32 mg (65% yield) as a brown solid, mp 61-62 °C. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.57 (d, J = 3 Hz, 1H), 8.06 (d, J = 8 Hz, 2H), 7.78 (dd, J = 8, 3 Hz, 1H), 7.75 (d, J = 8 Hz, 2H), 7.52 (dt, J = 8, 3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.3, 158.3, 142.3, 138.3, 132.6, 127.2, 123.7, 121.8, 118.6, 112.4. IR (neat, cm^{-1}): 2917, 2226, 1585, 1476, 1225, 1069, 1014, 791. Anal. Calcd. For $C_{12}H_7N_2F$: C, 72.72; H, 3.56. Found C, 72.52; H, 3.55.

2-(2,5-dimethylphenyl)-5-fluoropyridine (Table 2, Entry 12). Following general procedure A, a mixture of 2-bromo-*p*-xylene (34.5 μL, 46.3 mg, 0.25 mmol), lithium triisopropyl 2-(5-fluoropyridyl)borate (109 mg, 0.375 mmol), KF, Pd_2dba_3 (3.4 mg, 0.00375 mmol) and **2** (3.6 mg, 0.0225 mmol) was heated for 20 h. Flash column chromatography (5% EtOAc/Hexanes) yielded the title compound in 20 mg (40% yield) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.55 (d, J = 3 Hz, 1H), 7.45 (dt, J = 8, 3 Hz, 1H), 7.39 (dd, J = 8, 3 Hz, 1H), 7.20 (s, 1H), 7.17 (d, J = 8 Hz, 1H), 7.12 (d, J = 8 Hz, 1H), 2.36 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.3, 157.2, 139.1, 137.2, 135.4, 132.5, 130.7, 130.2, 129.1, 124.8, 122.8, 20.9, 19.8. IR (neat, cm^{-1}): 3019, 2923, 2862, 1630, 1580, 1479, 1380, 1237, 1220, 1020, 812. ^1H NMR spectrum included.

4-(6-(1,3-dioxolan-2-yl)pyridin-2-yl)benzonitrile (Table 2, Entry 13). Following general procedure A, a mixture 4-bromobenzonitrile (45.5 mg, 0.25 mmol), lithium triisopropyl 2-(6-(1,3-dioxolan-2-yl)pyridin-2-yl)borate (129 mg, 0.375 mmol), KF, Pd_2dba_3 (3.4 mg, 0.00375 mmol) and **1** (4.5 mg, 0.0225 mmol) was heated for 20 h. Flash column chromatography (25% EtOAc/Hexanes) yielded the title compound in 38 mg (63% yield) as a white solid, mp 80-81 °C. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.14 (d, J = 8 Hz, 2H), 7.85 (t, J = 8 Hz, 1H), 7.73-7.76 (m, 3H), 7.57 (d, J = 8 Hz, 1H), 5.92 (s, 1H), 4.11-4.22 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.6, 154.6, 143.0, 137.9, 132.4, 127.5, 121.0, 120.1, 118.8, 112.4, 103.7, 65.7. IR (neat, cm^{-1}): 2955, 2876, 2223, 1593, 1459, 1367, 1110. ^1H NMR spectrum included.

2.4.4 Experimental for the Reactions with Aryl Chlorides

4-(pyridin-2-yl)benzonitrile (Table 3, Entry 1).[22] Following general procedure A, a mixture of 4-chlorobenzonitrile (34.4 mg, 0.25 mmol), lithium triisopropyl 2-pyridylborate (104 mg, 0.375 mmol), KF, Pd_2dba_3 (2.3 mg, 0.0025 mmol) and **2** (3.0 mg, 0.015 mmol) was heated for 20 h. Flash column chromatography (15% EtOAc/Hexanes) yielded the title compound in 33 mg (73% yield) as a white solid, mp 91-92 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.72 (dt, J= 8, 1 Hz, 1H), 8.11 (d, J = 8 Hz, 2H), 7.81 (dt, J = 8, 1 Hz, 1H), 7.74-7.77 (m, 3H), 7.31 (dt, J = 8, 1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.1, 150.0, 143.4, 137.0, 132.5, 127.4, 123.3, 120.9, 118.8, 112.3. ^{1}H NMR spectrum included.

2-(4-butylphenyl)pyridine (Table 3, Entry 2).[14] Following general procedure A, a mixture of 4-*n*-butylchlorobenzene (41.0 μL, 42.2 mg, 0.25 mmol), lithium triisopropyl 2-pyridylborate (104 mg, 0.375 mmol), KF, Pd_2dba_3 (2.3 mg, 0.0025 mmol) and **2** (2.4 mg, 0.015 mmol) was heated for 20 h. Flash column chromatography (10% EtOAc/Hexanes) yielded the title compound in 39 mg (76% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.66 (dt, J = 6, 1 Hz, 1H), 7.88 (d, J = 8 Hz, 2H), 7.67-7.71 (m, 2H), 7.26 (d, J = 8 Hz, 2H), 7.16 (dt, J = 6, 1 Hz, 1H), 2.64 (t, J = 8 Hz, 2H), 1.62 (pent, J = 8 Hz, 2H), 1.36 (sext, J = 8 Hz, 2H), 0.92 (t, J = 8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: δ: 157.4, 149.5, 143.9, 136.7, 136.6, 128.8, 126.7, 121.7, 120.2, 35.4, 33.5, 22.3, 13.9. ^{1}H NMR spectrum included.

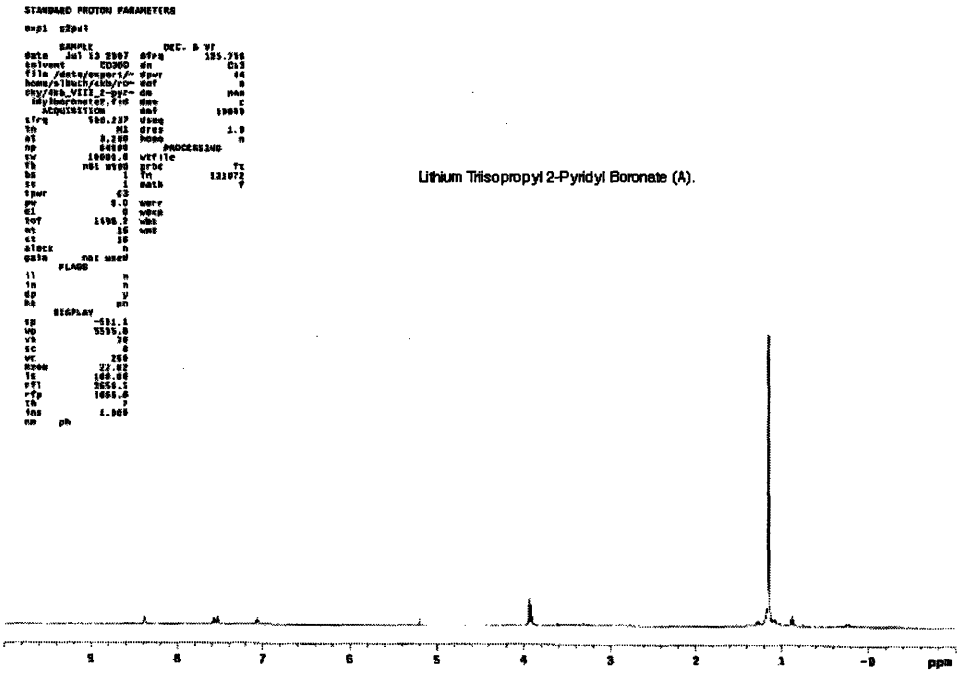
2-(2,5-dimethylphenyl)pyridine (Table 3, Entry 3). Following general procedure A, a mixture of 2-chloro-*p*-xylene (33.5 μL, 35.1 mg, 0.25 mmol), lithium triisopropyl 2-pyridylborate (104 mg, 0.375 mmol), KF, Pd_2dba_3 (2.3 mg, 0.0025 mmol) and **2** (2.4 mg, 0.015 mmol) was heated for 20 h. Flash column chromatography (10% EtOAc/Hexanes) yielded the title compound in 32 mg (70% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.71 (dt, J = 5,1 Hz, 1H), 7.74 (dt, J = 7, 1 Hz, 1H), 7.42 (dt, J = 8, 1 Hz, 1H), 7.23-7.26 (m, 2H), 7.16 (dt, J = 6, 1 Hz, 1H), 7.20 (d, J = 8 Hz, 1H), 7.14 (dt, J = 8, 1 Hz, 1H), 2.38 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.0, 149.2, 140.2, 135.9, 135.2, 132.4, 130.6, 130.2, 128.9, 124.0, 121.5, 20.9, 19.7. IR (neat, cm^{-1}): 3394, 3014, 2922, 1598, 1563, 1501, 1471, 1426, 1378, 1149, 1039, 992, 792, 749. ^{1}H NMR spectrum included.

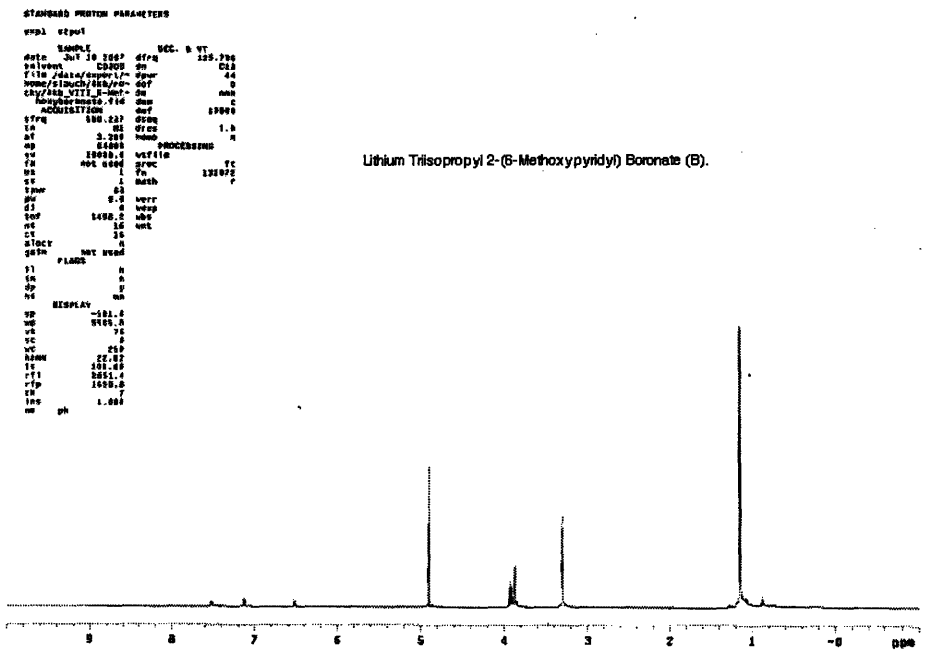
2-(4-methoxyphenyl)pyridine (Table 3, Entry 4).[15] Following general procedure A, a mixture of 4-chloroanisole (30.4 μL, 35.6 mg, 0.25 mmol), lithium triisopropyl 2-pyridylborate (104 mg, 0.375 mmol), KF, Pd_2dba_3 (2.3 mg, 0.0025 mmol) and **2** (2.4 mg, 0.015 mmol) was heated for 20 h. Flash column chromatography (15% EtOAc/Hexanes) yielded the title compound in 36 mg (78% yield) as a white solid, mp 47-48 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.65 (dt, J = 5, 1 Hz, 1H), 7.96 (d, J = 9 Hz, 2H), 7.71 (dt, J = 8, 2 Hz, 1H), 7.66 (dt, J = 8, 1 Hz, 1H), 7.17 (dd, J = 5, 1 Hz, 1H), 7.00 (d, J = 9 Hz, 2H), 3.86 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.4, 157.0, 149.4, 136.6, 132.0, 128.1, 121.4, 119.8, 114.1, 55.3. ^{1}H NMR spectrum included.

2-(3-(trifluoromethyl)phenyl)pyridine (Table 3, Entry 5). Following general procedure A, a mixture of 3-chlorobenzotrifluoride (33.9 μL, 45.1 mg, 0.25 mmol), lithium triisopropyl 2-pyridylborate (104 mg, 0.375 mmol), KF, Pd_2dba_3 (2.3 mg, 0.0025 mmol) and **2** (2.4 mg, 0.015 mmol) was heated for 20 h. Flash column chromatography (10% EtOAc/Hexanes) yielded the title compound in 32 mg (57% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.70 (dt, J = 5, 1 Hz, 1H), 8.26 (s, 1H), 8.15 (d, J = 8 Hz, 1H), 7.71-7.77 (m, 2H), 7.64 (d, J = 8 Hz, 1H), 7.56 (t, J = 8 Hz, 1H), 7.26 (ddd, J = 8, 5, 1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.8, 149.9, 140.1, 137.0, 130.5, 130.0, 129.2, 125.5, 123.7, 122.8, 120.6, 112.3. IR (neat, cm^{-1}): 2963, 2913, 1631, 1586, 1464, 1437, 1417, 1301, 1262, 1166, 1123, 1073, 775. Anal. Calcd. for $C_{12}H_8NF_3$: C, 64.58; H, 3.61. Found C, 64.68; H, 3.56.

2,3'-bipyridine (Table 3, Entry 6).[20] Following general procedure A, a mixture of 3-chloropyridine (23.8 μL, 28.3 mg, 0.25 mmol), lithium triisopropyl 2-pyridylborate (104 mg, 0.375 mmol), KF, Pd_2dba_3 (2.3 mg, 0.0025 mmol) and **2** (2.4 mg, 0.015 mmol) was heated for 20 h. Flash column chromatography (EtOAc) yielded the title compound in 36 mg (92% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.17 (d, J = 3 Hz, 1H), 8.71 (dt, J = 5, 1 Hz, 1H), 8.64 (dt, J = 5, 1 Hz, 1H), 8.31 (dt, J = 8, 1 Hz, 1H), 7.79 (dt, J = 8, 1 Hz, 1H), 7.75 (dt, J = 8, 1 Hz, 1H), 7.39 (dd, J = 8, 3 Hz, 1H), 7.28 (ddd, J = 8, 5, 1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 154.7, 150.0, 149.9, 148.2, 136.9, 134.8, 134.3, 123.5, 122.8, 120.6. ^{1}H NMR spectrum included.

2-(6-methoxypyridin-2-yl)benzonitrile (Table 3, Entry 7). Following general procedure A, a mixture of 2-chlorobenzonitrile (34.4 mg, 0.25 mmol), lithium triisopropyl 2-(6-methoxypyridyl)borate (114 mg, 0.375 mmol), KF, Pd_2dba_3 (3.4 mg, 0.00375 mmol) and **2** (3.6 mg, 0.0225 mmol) was heated for 20 h. Flash column chromatography (5% EtOAc/Hexanes) yielded the title compound in 40 mg (76% yield) as a white solid, mp 48-49 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.79-7.83 (m, 2H), 7.63-7.70 (m, 2H), 7.48 (dt, J = 8, 1 Hz, 1H), 7.31 (d, J = 8 Hz, 1H), 6.80 (d, J = 8 Hz, 1H), 4.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.8, 152.4, 142.9, 139.2, 134.7, 132.5, 129.4, 128.5, 119.2, 115.2, 111.0, 99.7, 54.0. IR (neat, cm^{-1}): 2969, 2946, 2223, 1602, 1574, 1461, 1426, 1406, 1325, 1247, 1152, 1017, 804, 780. ^{1}H NMR spectrum included.

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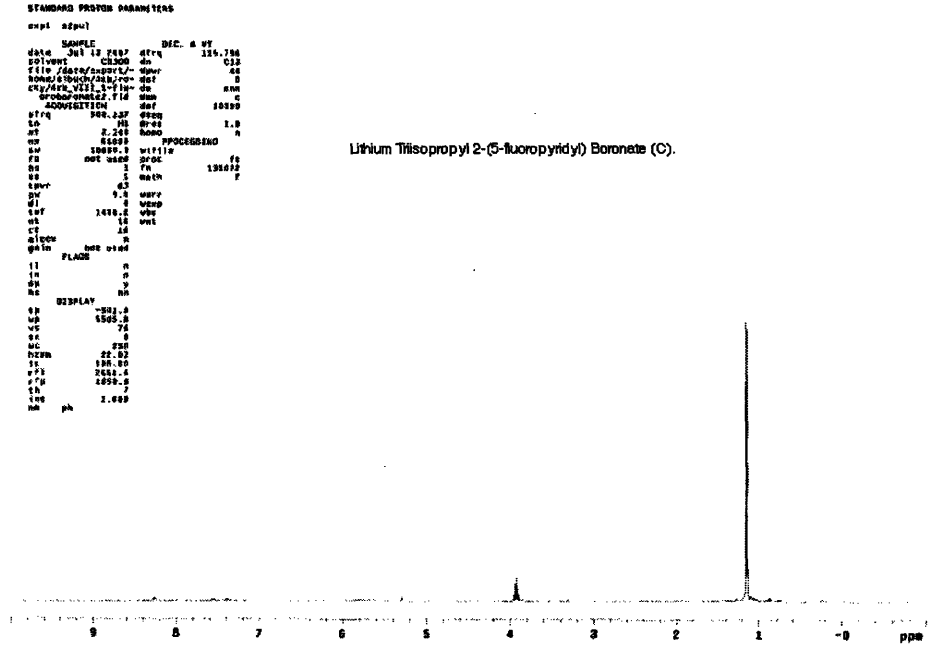
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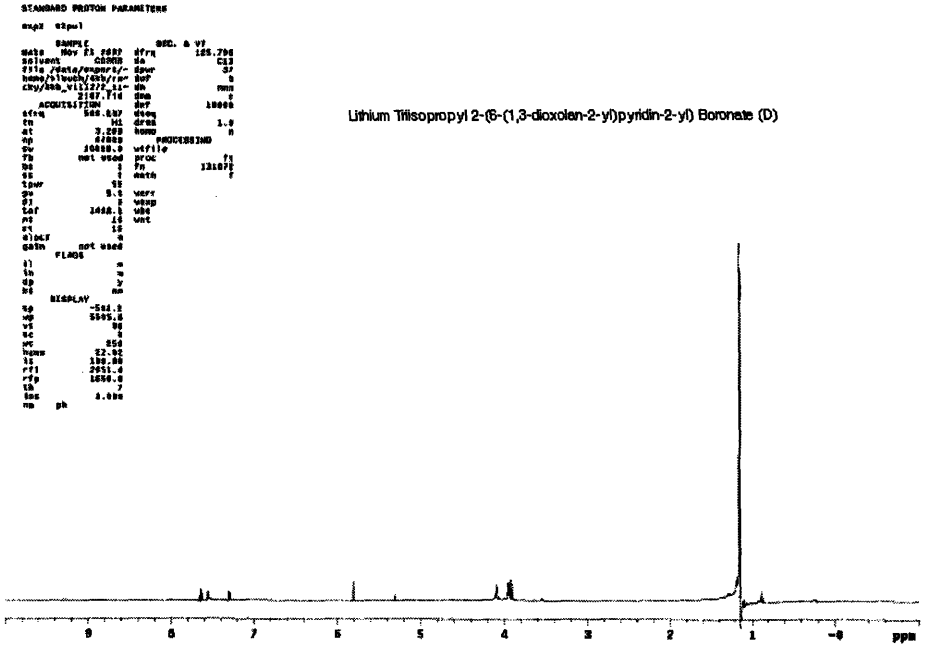
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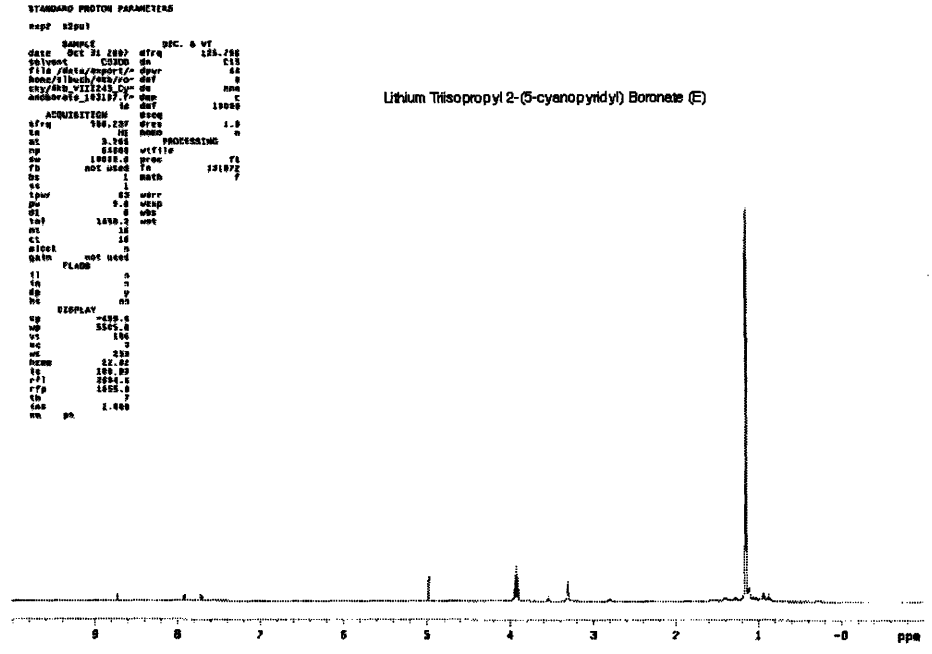
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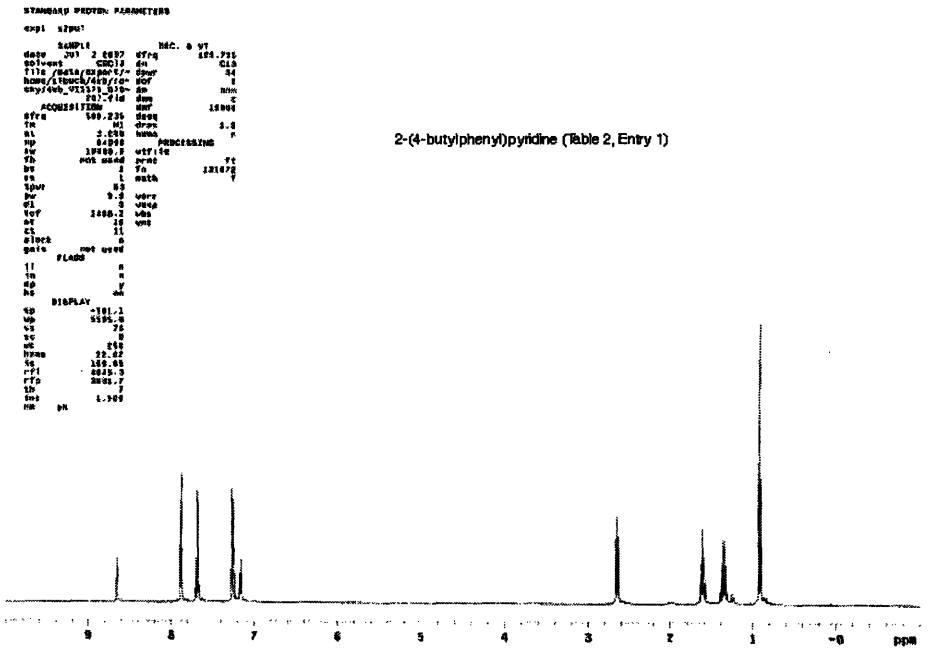
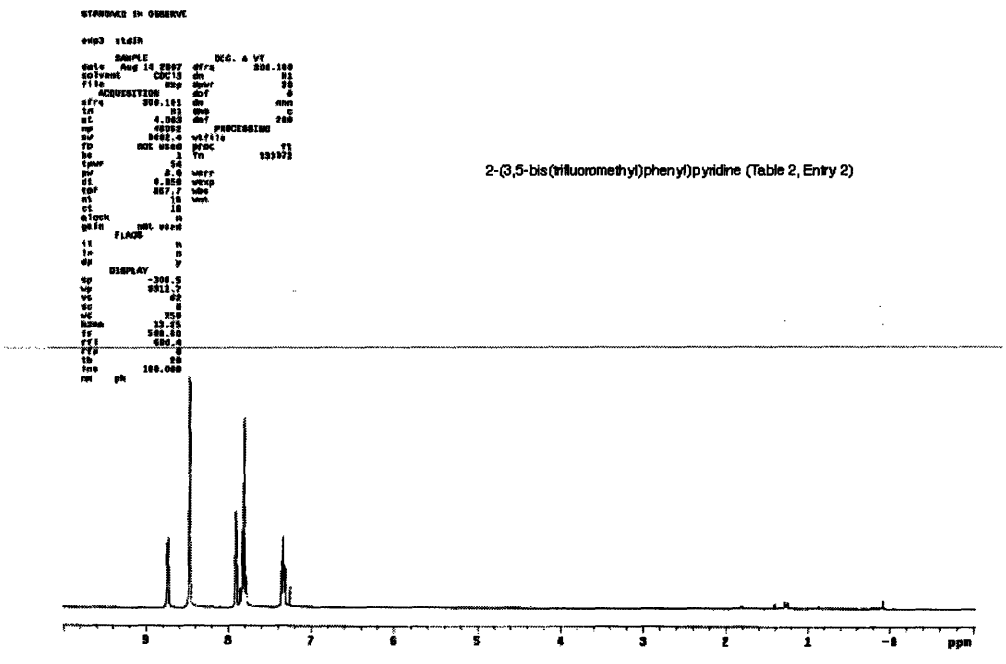
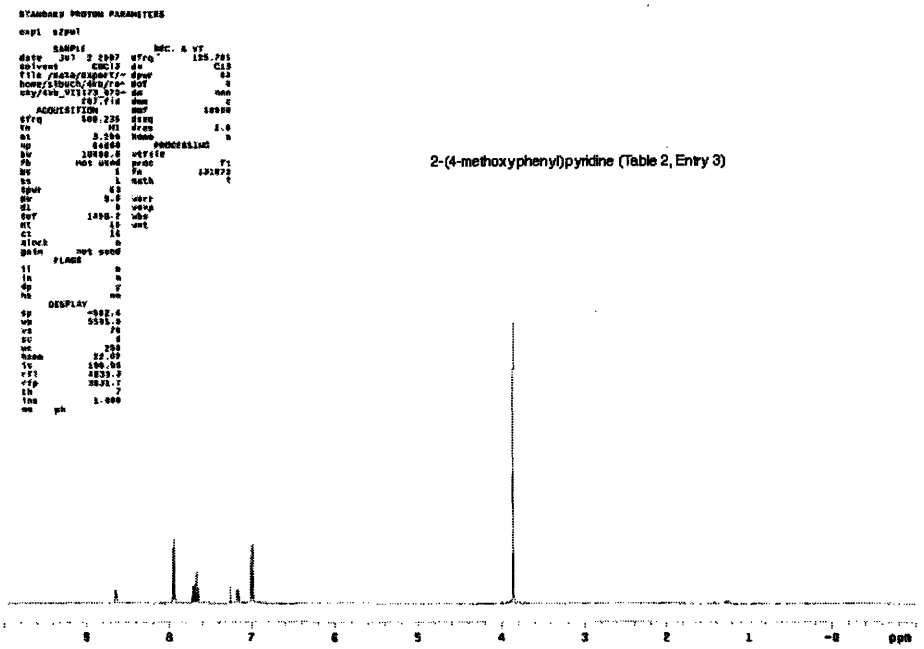


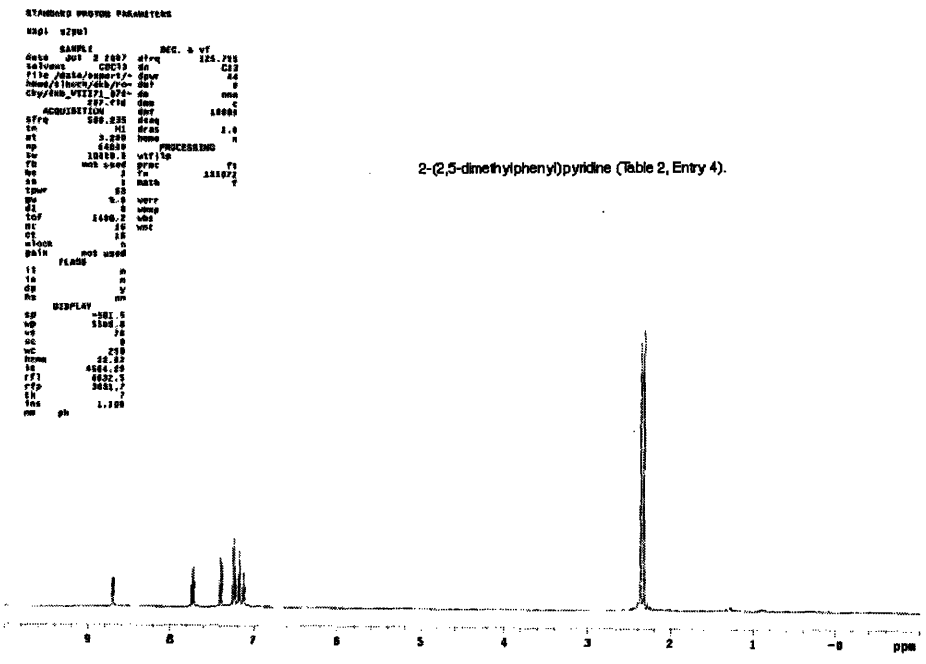
2-(4-butylphenyl)pyridine (Table 2, Entry 1)



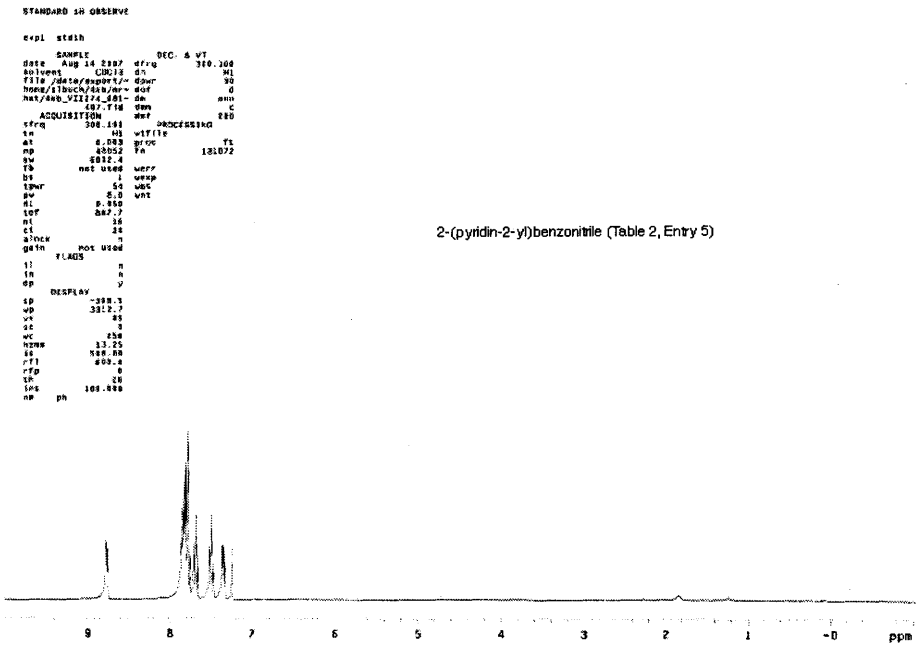
2-(3,5-bis(trifluoromethyl)phenyl)pyridine (Table 2, Entry 2)



2-(4-methoxyphenyl)pyridine (Table 2, Entry 3)



2-(2,5-dimethylphenyl)pyridine (Table 2, Entry 4).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dmm c
dmf 220
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wexp
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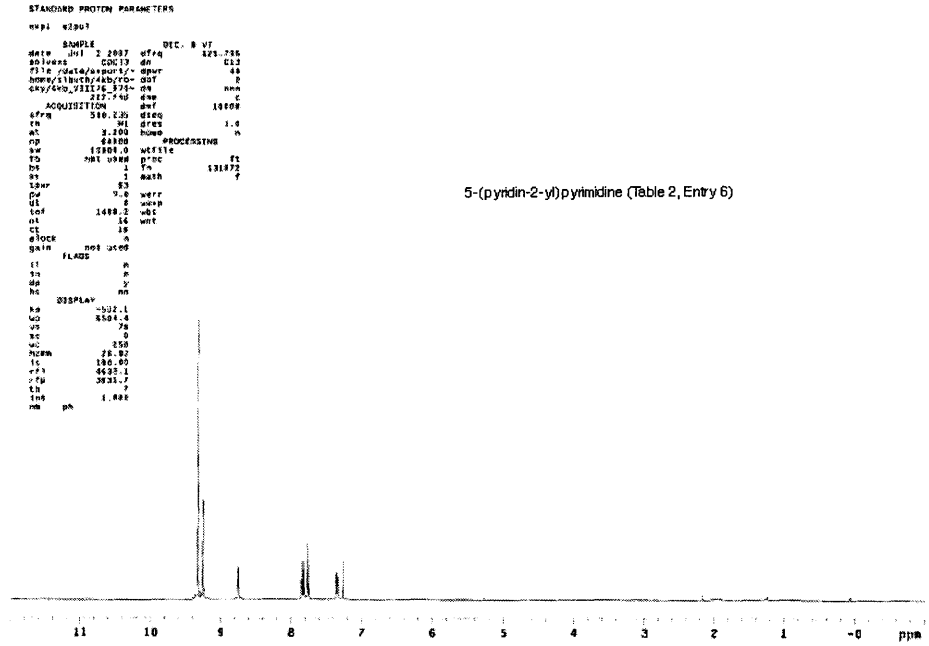
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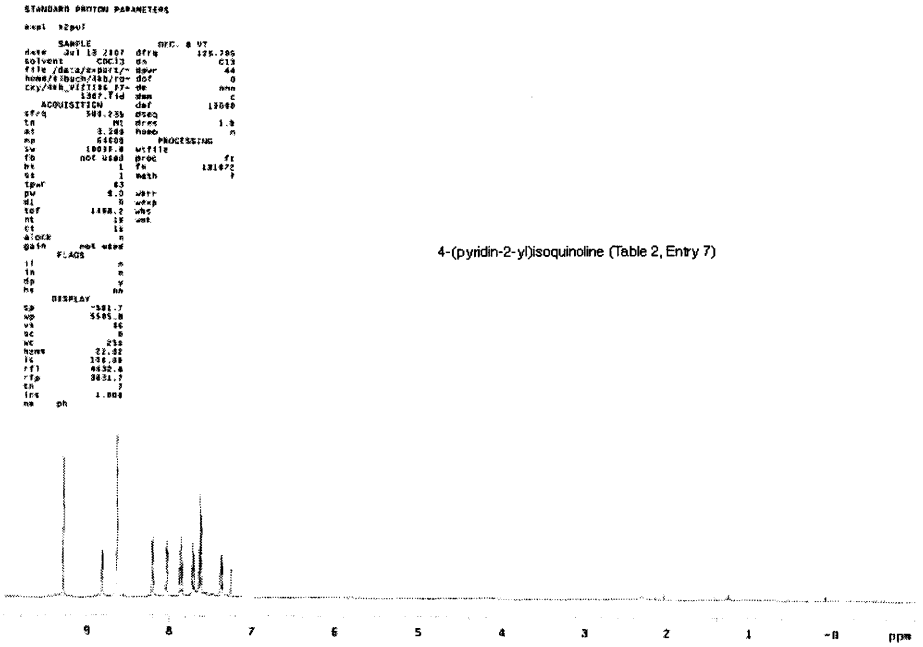
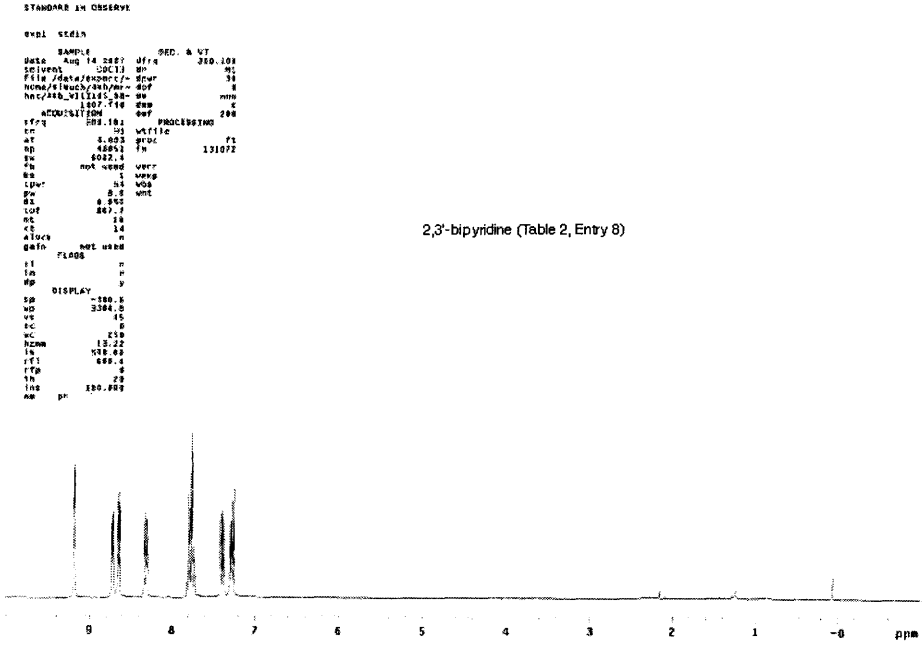
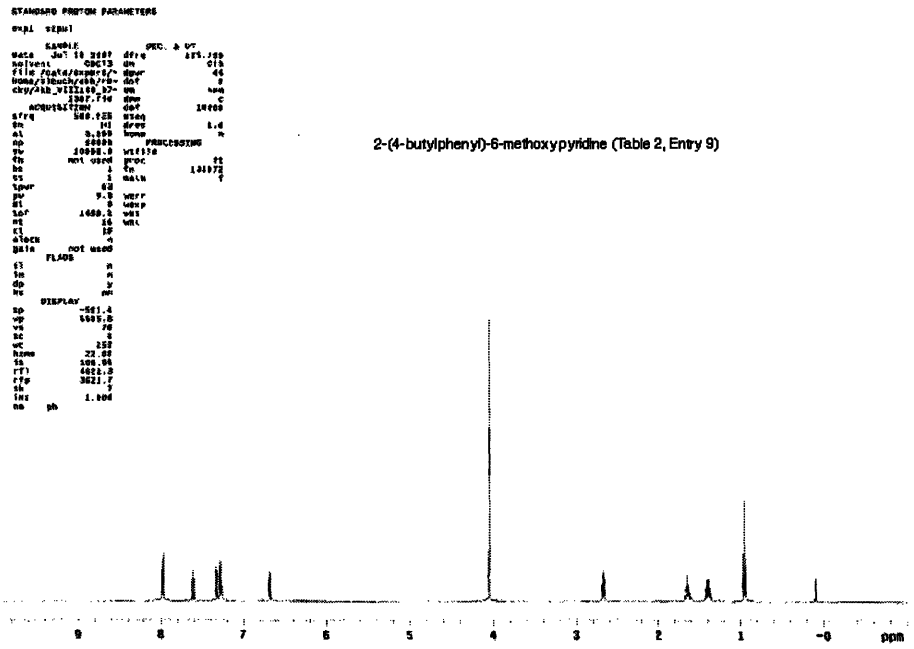


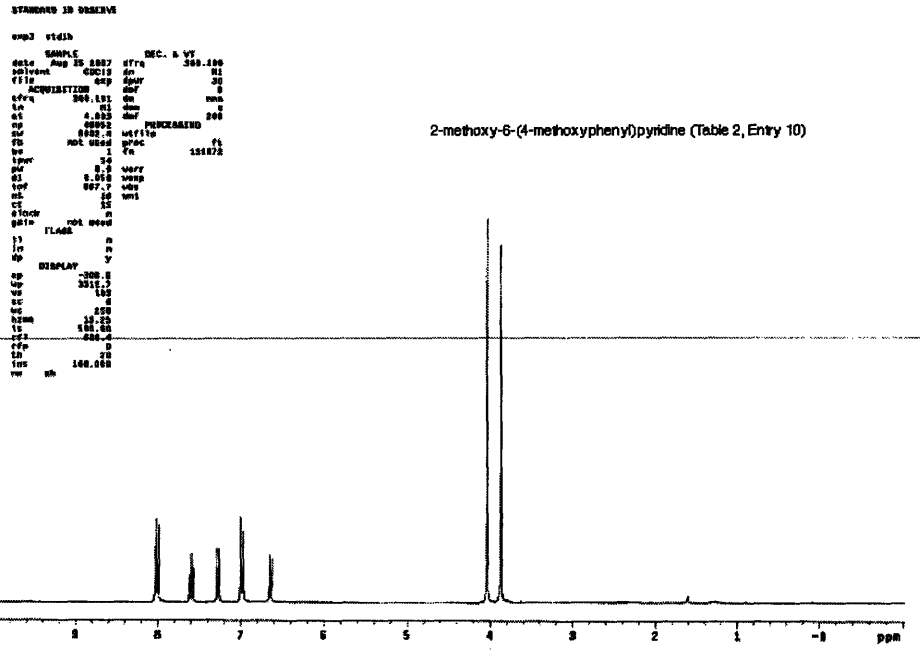
4-(pyridin-2-yl)isoquinoline (Table 2, Entry 7)



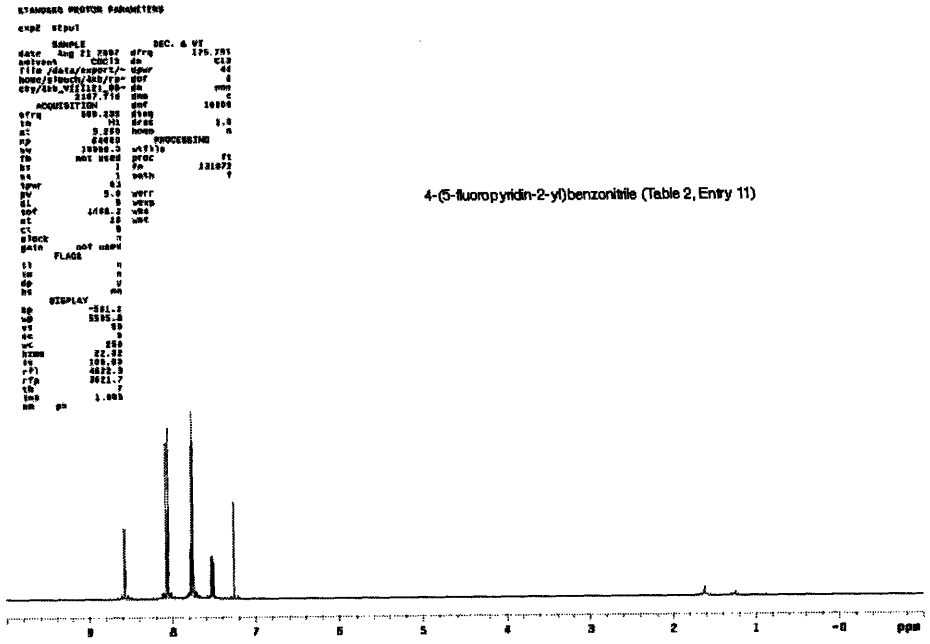
2,3'-bipyridine (Table 2, Entry 8)



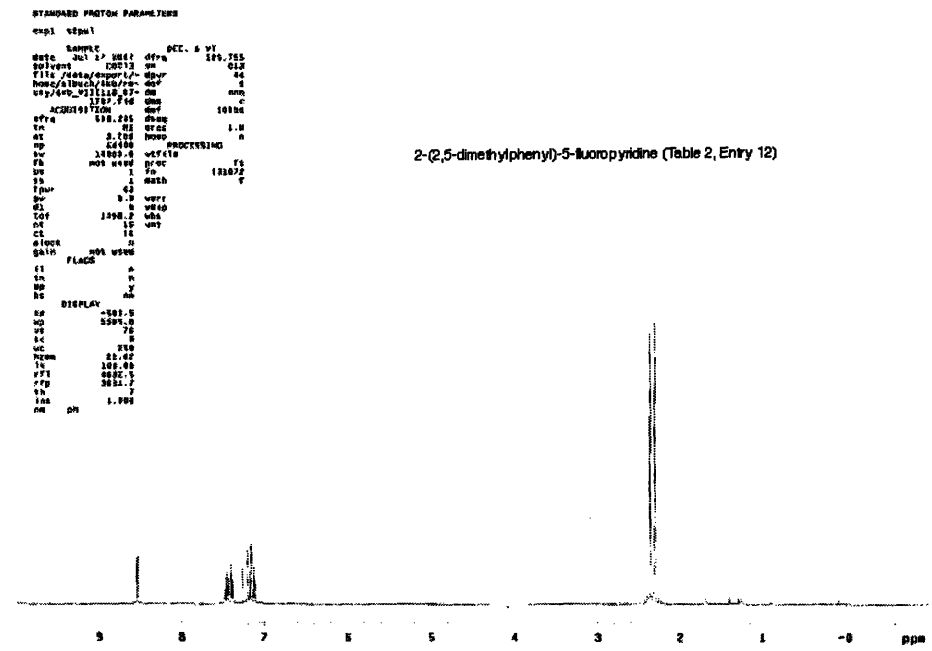
2-(4-butylphenyl)-6-methoxypyridine (Table 2, Entry 9)



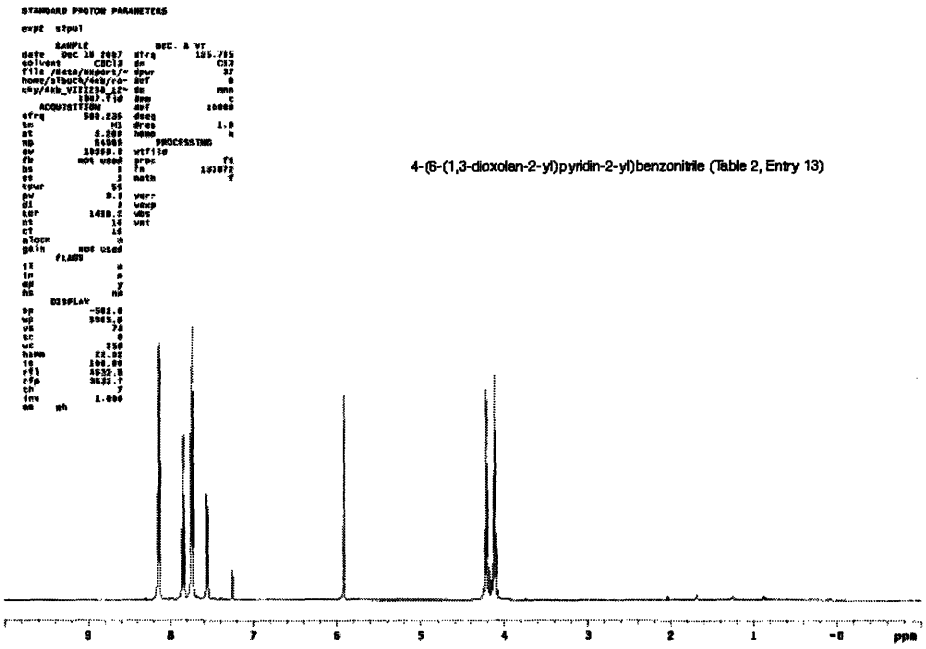
2-methoxy-6-(4-methoxyphenyl)pyridine (Table 2, Entry 10)



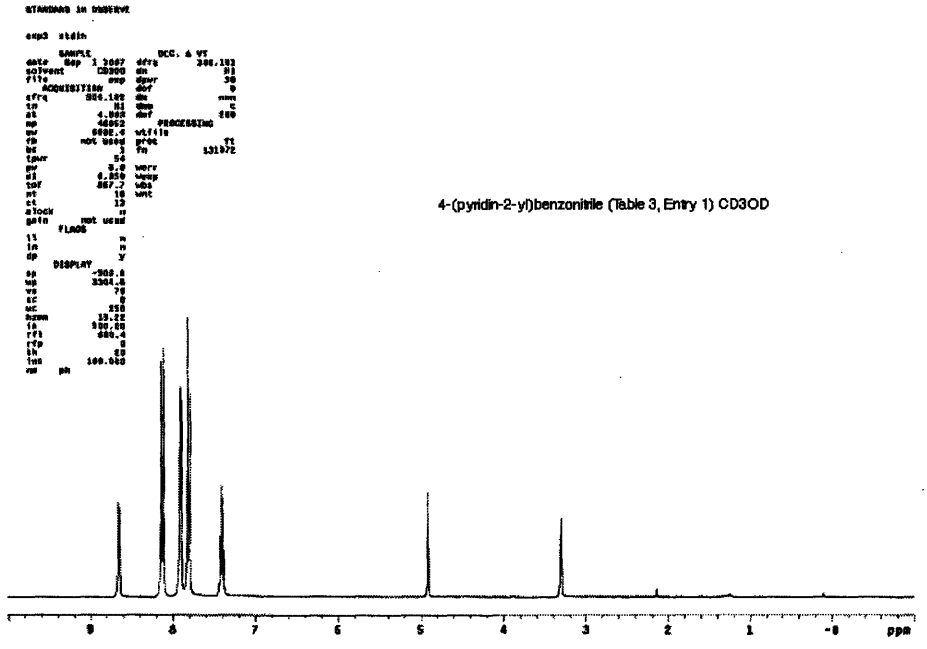
4-(5-fluoropyridin-2-yl)benzonitrile (Table 2, Entry 11)



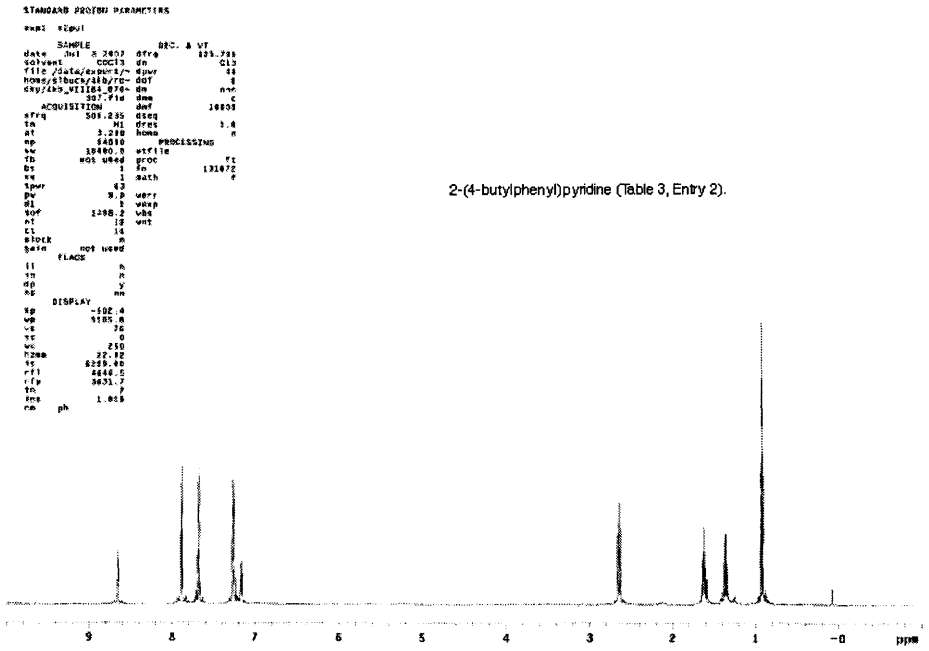
2-(2,5-dimethylphenyl)-5-fluoropyridine (Table 2, Entry 12)



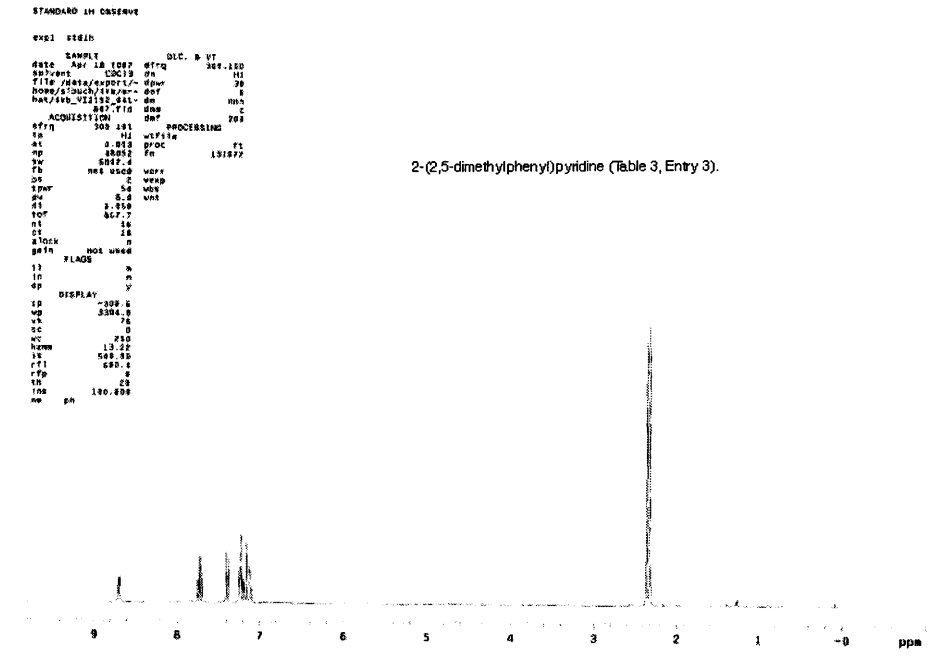
4-(6-(1,3-dioxolan-2-yl)pyridin-2-yl)benzonitrile (Table 2, Entry 13)



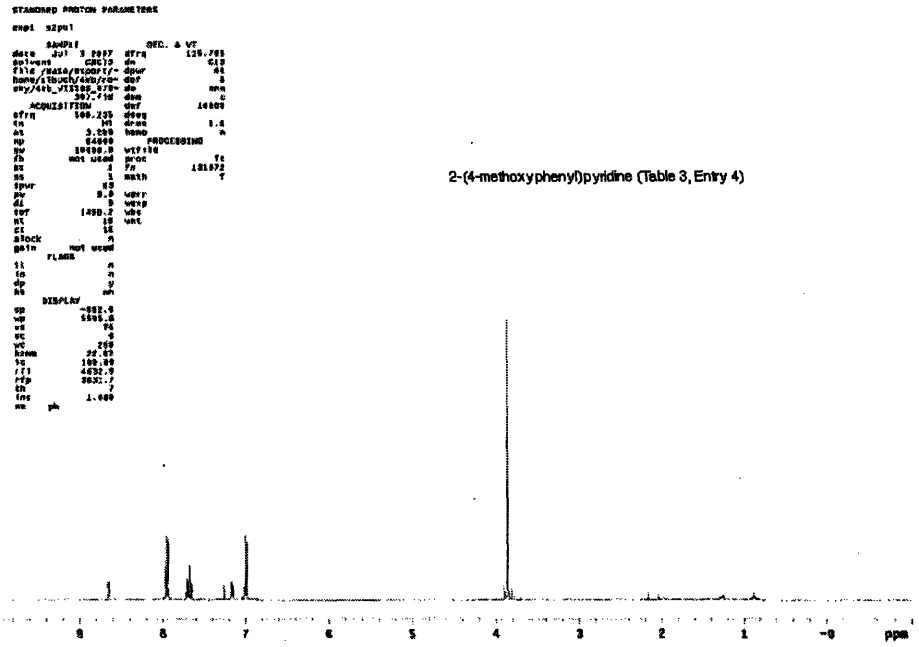
4-(pyridin-2-yl)benzonitrile (Table 3, Entry 1) CD3OD



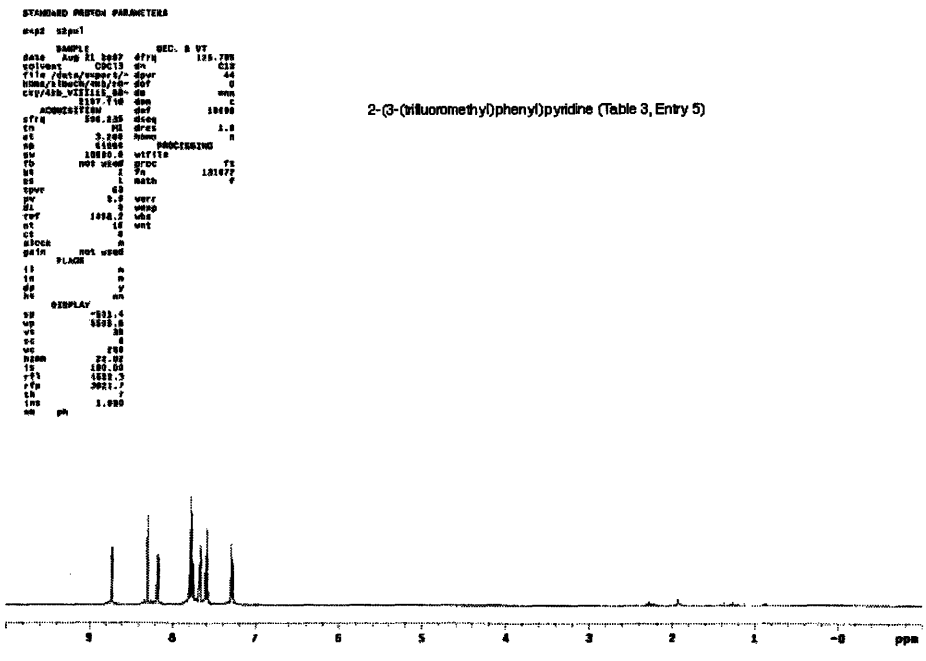
2-(4-butylphenyl)pyridine (Table 3, Entry 2).



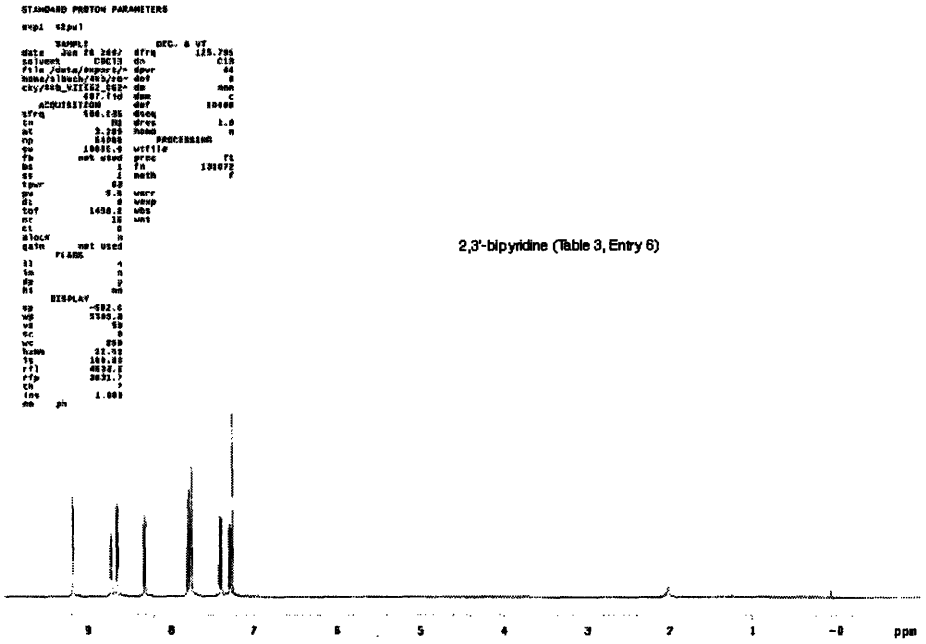
2-(2,5-dimethylphenyl)pyridine (Table 3, Entry 3).



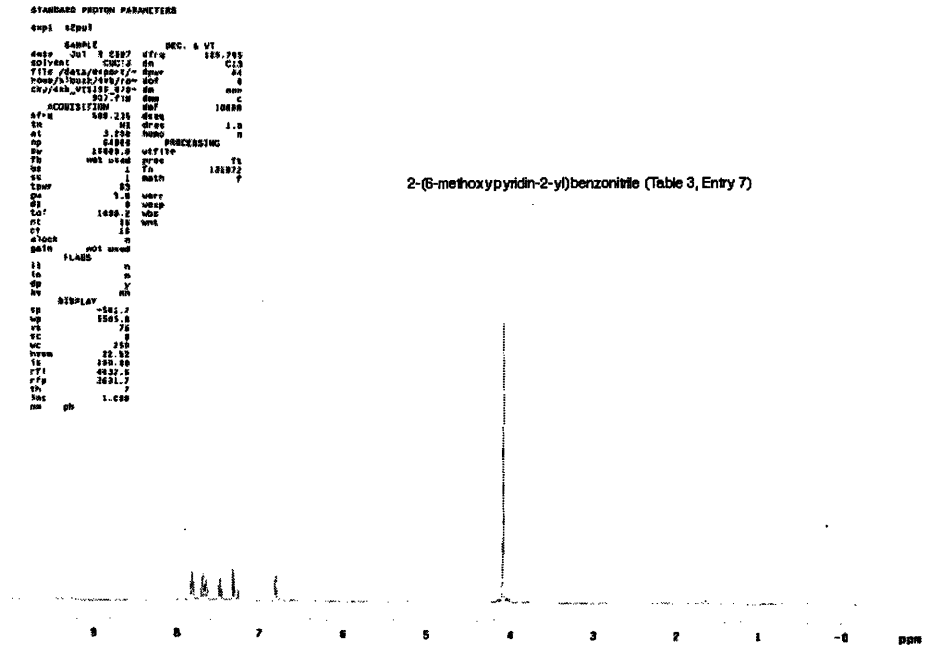
2-(4-methoxyphenyl)pyridine (Table 3, Entry 4)



2-(3-(trifluoromethyl)phenyl)pyridine (Table 3, Entry 5)



2,3'-bipyridine (Table 3, Entry 6)



2-(6-methoxypyridin-2-yl)benzonitrile (Table 3, Entry 7)

2.5 References

(1) Recent Reviews: (a) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11-59. (b) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, *15, 2419.* (c) Miyaura, N. In *Metal-Catalyzed Cross-Coupling Reaction*; Diederich, F., de Meijere, A., Eds.; Wiley-VCH: Weinheim, 2004; Chapter 2.

(2) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685-4696.

(3) For a review of the Suzuki-Miyaura reaction of heteroaryl nucleophiles, see: Tyrell, E.; Brookes, P. *Synthesis* **2004**, *4*, 469-483.

(4) Billingsley, K. L. Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358-3366.

(5) (a) Richardson, C. M.; Gillespie, R. J.; Williamson, D. S.; Jordan, A. M.; Fink, A.; Knight, Antony R.; Sellwood, D. M.; Misra, A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5993-5997. (b) Gellibert, F.; De Gouville, A.-C.; Woolven, J.; Mathews, N.; Nguyen, V.-L.; Bertho-Ruault, C.; Patikis, A.; Grygielko, E. T.; Laping, N. J.; Huet, S. *J. Med. Chem.* **2006**, *49*, 2210-2221. (c) Salama, I.; Hocke, C.; Utz, W.; Prante, O.; Boeckler, F.; Huebner, H.; Kuwert, T.; Gmeiner, P. *J. Med. Chem.* **2007**, *50*, 489-500. (d) Meyers, K. M.; Kim, N.; Mendez-Andino, J. L.; Hu, X. E.; Mumin, R. N.; Klopfenstein, S. R.; Wos, J. A.; Mitchell, M. C.; Paris, J. L.; Ackley, D. C.; Holbert, J. K.; Mittelstadt, S. W.; Reizes, O. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 814-818. (e) Anderson, D. R.; Meyers, M. J.; Vernier, W. F.; Mahoney, M. W.; Kurumbail, R. G.; Caspers, N.; Poda, G. I.; Schindler, J. F.; Reitz, D. B.; Mourey, R. J. *J. Med. Chem.* **2007**, *50*, 2647-2654.

(6) For examples of Suzuki-Miyaura reactions of 2-pyridyl boronic acids, see: (a) Deshayes, K.; Broene, R. D.; Chao, I.; Knobler, C. B.; Diederich, F. *J. Org. Chem.* **1991**, *56*, 6887-6895. (b) Sindkhedkar, M. D.; Mulla, H. R.; Wirth, M. A.; Cammers-Goodwin, A. *Tetrahedron* **2001**, *57*, 2991-2996. (c) Mandolesi, S. D.; Vaillard, S. E.; Podestá, J. C.; Rossi, R. A. *Organometalllics* **2002**, *21*, 4886-4888. (d) Bouillon, A.; Lancelot, J.-C.; Sopkova de Oliveira Santos, J.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2003**, *59*, 10043-10049. (e) Shinozuka, T.; Shimada, K.; Matsui, S.; Tamane, T.; Ama, M.; Fukuda, T.; Taki, M.; Takeda, Y.; Otsuka, E.; Yamato, M.; Naito, S. *Bioorg. Med. Chem.* **2006**, *14*, 6807-6819.

(7) During the development of this work, we discovered unpublished results from CombiPhos Catalysts, Inc. utilizing 2-pyridyl pinacol boronate esters. Chlorodialkyl phosphines and dialkyl phosphine oxides were used as supporting ligands. However, we found that 2-pyridyl pinacol boronate ester was not effectively coupled under our conditions as seen in Table 1.

(8) For examples of Suzuki-Miyaura reactions of 2-pyridyl *N,N*-diethanolamine boronate esters, see: (a) Hodgson, P. B.; Salingue, F. H. *Tetrahedron Lett.* **2004**, *45*, 685-687. (b) Gros, P.; Doudouh, A.; Fort, Y. *Tetrahedron Lett.* **2004**, *45*, 6239-6241.

(9) For work with 2-pyridyltrifluoroborates, see: Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302-4314.

(10) Yamamoto, Y.; Takizawa, M.; Yu, X.-Q.; Miyaura. N. *Angew. Chem., Int. Ed.* **2008**, *47*, 928-931.

(11) For selected examples of phosphine oxides ligands in carbon-carbon bond forming cross-coupling processes, see: (a) Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513-1516. (b) Li, G. Y.; Marshall, W. J. *Organometallics* **2002**, *21*, 590-591. (c) Wolf, C.; Lerebours, R. *J. Org. Chem.* **2003**, *68*, 7551-7554. (d) Wolf, C.; Lerebours, R. *Org. Lett.* **2004**, *6*, 1147-1150. (e) Lerebours, R.; Camacho-Soto, A.; Wolf, C. *J. Org. Chem.* **2005**, *70*, 8601-8604. (f) Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 7216-7219. (g) Ackermann, L.; Althammer, A. *Org. Lett.* **2006**, *8*, 3457-3460. (h) Wolf, C.; Ekoue-Kovi, K. *Eur. J. Org. Chem.* **2006**, 1917-1925.

(12) (a) Dube, D.; Fortin, R.; Friesen, R.; Wang, Z.; Gauthier, J. (Merck Frost Canada Inc.). Substituted Pyridines as Selective Cyclooxygenase-2 Inhibitors. WO 98/03484, 1998. (b) O'Neill, B. T.; Yohannes, D.; Bundesmann, M. W.; Arnold, E. P. *Org. Lett.* **2000**, *2*, 4201-4204. (c) Ahman, B.; Hodgson, P.; Lewandowski, S.; Walton, R. (Pfizer Inc.). Process for the Production of Quinazolines. WO 02/094815, 2002.

(13) For a related protocol for the synthesis of 3-pyridine boronic acid, see: Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Cai, D.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 5394-5397.

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(15) Coppo, P.; Plummer, E. A.; Cola, L. D. *Chem. Commun.* **2004**, 1774.

(16) Andersson, H.; Almqvist, F.; Olsson, R. *Org. Lett.* **2007**, *9*, 1335.

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(20) Cioffi, C. L.; Spencer, W. T.; Richards, J. J.; Herr, R. J. *J. Org. Chem.* **2004**, *69*, 2210.

(21) Gosmini, C.; Nédélec, J. Y.; Périchon, R. *Tetrahedron Lett.* **2000**, *41*, 5039.

(22) Gosmini, C.; Lasry, S.; Nedelec, J.-Y.; Perichon, J. *Tetrahedron* **1998**, *54*, 1289.

Chapter 3.

Palladium-Catalyzed Borylation of Aryl Chlorides.

3.1 Introduction

Aryl boronic acids and esters are versatile reagents for organic synthesis that are utilized in the preparation of various carbon-oxygen, carbon-nitrogen and carbon-carbon bonds.[1] In addition, the use of organoboranes for cross-coupling processes is particularly attractive due to their high stability and low toxicity. However, boronic acids and esters usually are prepared via the intermediacy of alkyl and aryllithiums or Grignard reagents, processes that are not compatible with numerous functional groups.[2] In addition, the use of aryl iodides or bromides are often necessary, while the more readily available aryl chlorides[3] are often unsuitable precursors.

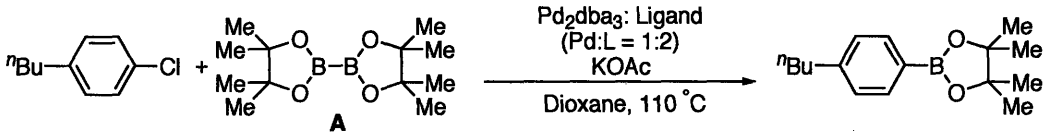
In recent years, the development of a variety of transition metal-catalyzed processes has allowed for the preparation of aryl boronate esters under milder conditions.[4] In particular, numerous palladium-catalyzed methods have emerged for the conversion of aryl iodides, bromides, and triflates to the corresponding pinacol or catechol boronate esters.[5] However, only two reports[6] can be found in which unactivated aryl chlorides are suitable coupling partners, and these methods have several disadvantages: (1) High quantities of palladium catalysts (5-6 mol%) are required for many substrates. (2) Long reaction times (24-48 h) are necessary. (3) Limited substrate scope and functional group tolerance (e.g., few or no examples with *ortho*-substituents, phenols, anilines) is exhibited. Herein, we report an active catalyst composed of Pd and dialkylphosphinobiphenyl ligands **1** or **2** that efficiently converts aryl chlorides to pinacol boronate esters and allows for the first time the direct "one-pot"-synthesis of symmetrical and unsymmetrical biaryls from two aryl chlorides. In addition, computational studies are presented that provide insight into the efficacy of biaryl monophosphine ligands on the palladium-catalyzed borylation process.

3.2 Results and Discussion

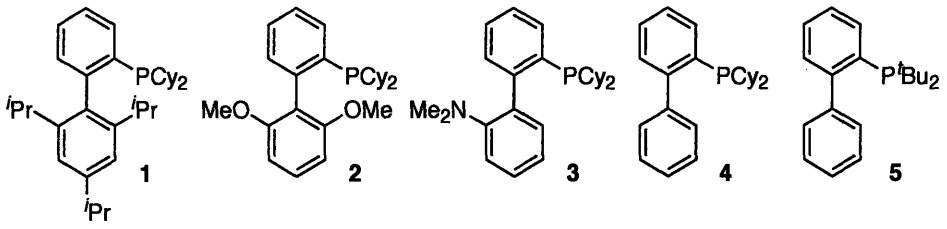
We began our work by optimizing the reaction parameters. We found that a variety of dialkylphosphinobiphenyl ligands could be employed to afford highly active catalysts for the borylation

of 4-*n*-butylchlorobenzene (Table 1). In each instance, the desired aryl boronate ester was obtained in good to excellent yield. The optimum system, based upon Pd_2dba_3 and XPhos (**1**), allowed for the use of relatively low quantities of catalyst and provided a quantitative yield of product in just two hours (Table 1, Entry 6). We found KOAc to be the optimal base, although a variety of inorganic bases could be utilized. However, the use of K_3PO_4 or fluoride bases, despite resulting in full conversion of the aryl chloride, also led to the formation of ~15-20% of homocoupling product (4,4'-*n*-butylbiphenyl).

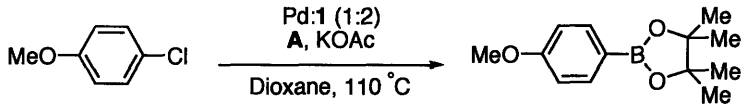
Table 1. Ligand Optimization for the Pd-Catalyzed Borylation of Aryl Chlorides.



Entry	Ligand	Pd (mol%)	Time (h)	GC Yield
1	**1**	2.0	24	99
2	**2**	2.0	24	94
3	**3**	2.0	24	97
4	**4**	2.0	24	95
5	**5**	2.0	24	82
6	**1**	0.50	2	99



To illustrate the activity of the catalyst, the borylation of an electron-rich aryl chloride, 4-chloroanisole, was examined (Scheme 1). The previous best result for the transformation of this substrate combination required 5 mol% $Pd(dba)_2$ and a 24 hour reaction time to obtain a 86% yield of the pinacol boronate ester.[5a] However, it was found that a catalyst based upon $Pd(OAc)_2$/**1** resulted in an extremely rapid conversion (10 min) of the aryl chloride and a 97% yield of the desired product. In addition, the process remained efficient at lower levels of palladium as the boronate ester was produced in 94% yield after 24 hours when 0.05 mol% Pd_2dba_3 was utilized.



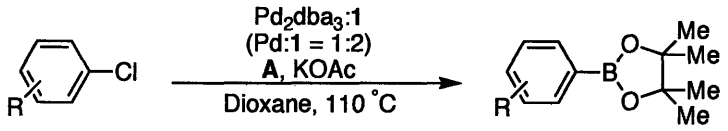
2.0% $Pd(OAc)_2$: 97% isolated yield; *10 min*
0.05% Pd_2dba_3 (0.10% Pd): 94% isolated yield; 24 h

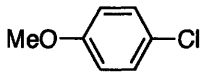
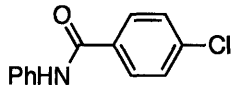
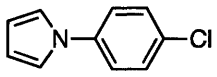
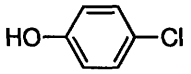
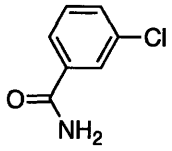
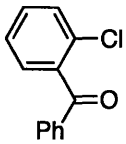
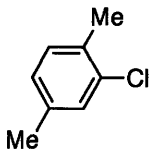
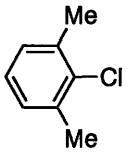
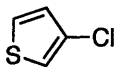
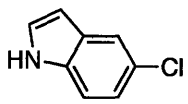
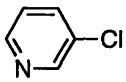
Scheme 1. Pd-Catalyzed Borylation of 4-Chloroanisole.

Catalyst systems based upon $Pd(OAc)_2$ or Pd_2dba_3 and **1** as the supporting ligand proved to be highly active for the borylation of a variety aryl chlorides. In general, employing $Pd(OAc)_2$ as a precatalyst offered faster reaction rates but also resulted in the production in a greater quantity of reduced aryl halide as a byproduct relative to when Pd_2dba_3 was employed. The Pd_2dba_3/**1** system efficiently transformed activated aryl chlorides, such as 4-chlorobenzanilide, to the corresponding boronate ester in excellent yield and in only thirty minutes (Table 2, Entry 2). In addition, the system proved to be highly active in the borylation of 4-chlorophenol (Table 2, Entry 4) as well as 3-chlorobenzamide (Table 2, Entry 5) as the desired pinacol boronate esters were furnished in 82% and 89% yield, respectively. Although *ortho*-substituted aryl halides are known to be particularly challenging substrates, the borylation of 2-chloro-*p*-xylene (Table 2, Entry 7) as well as 2-chloro-*m*-xylene (Table 2, Entry 8) under standard conditions successfully produced the corresponding boronate esters in moderate to high yield. In addition, many heteroaryl chlorides were also efficiently transformed to the desired products (Table 2, Entry 9-10). In contrast, the borylation of 3-chloropyridine under the standard reaction conditions resulted in only a 60% conversion of the heteroaryl chloride. However, if the aryl halide was slowly added over the course of the reaction, a 100% conversion was observed resulting in an 82% yield of the boronate ester (Table 2, Entry 11).

Although palladium-catalyzed borylation methods offer a higher degree of functional group tolerance, these processes still rely upon employing elevated temperatures. Therefore, we sought to develop a system that could efficiently accomplish such a transformation.

Table 2. Pd-Catalyzed Borylation of Aryl Chlorides at Elevated Temperatures.[a]

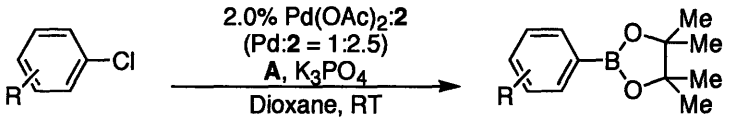


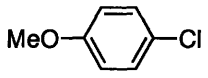
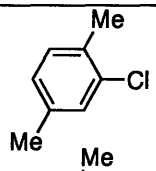
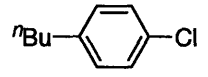
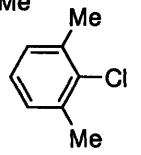
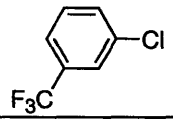
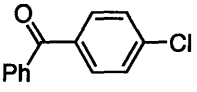
Entry	Aryl Chloride	mol% Pd	Time	Yield (%)[b]
1		2.0 0.10	10 min 24 h	97[c] 94
2		0.50	30 min	96
3		1.0	30 min	83
4		2.0	30 min	82
5		2.0	30 min	89
6		2.0	1 h	87
7		2.0	1 h	88
8		4.0	5 h	62[d]
9		1.0	2 h	76
10		2.0	1 h	95[c]
11		2.0	5 h	82[e]

[a]Reaction Conditions: 1 equiv of aryl or heteroaryl chloride, 1.2-3.0 equiv of **A**, 3 equiv of KOAc, dioxane (2 mL/mmol halide), cat. Pd_2dba_3, 1:Pd = 2:1. [b]Isolated yield based upon an average of two runs. [c]$Pd(OAc)_2$ used instead of Pd_2dba_3. [d]Dioxane:H_2O (10:1) used as the solvent. [e]3-Chloropyridine was added via syringe pump over the course of 1 h.

We discovered that our standard conditions for the borylation of aryl chlorides at elevated temperatures were inefficient at room temperature. However, when $Pd(OAc)_2$ and K_3PO_4 were employed in lieu of Pd_2dba_3 and KOAc, this process proceeded in an efficient manner. Although $Pd(OAc)_2$/**1** was a suitable catalyst, SPhos (**2**) proved to be a better supporting ligand for the room temperature version of this transformation. For example, a catalyst based upon $Pd(OAc)_2$/**2** allowed for the borylation of 4-chloroanisole in 97% yield at room temperature (Table 3, Entry 1). This process was also applicable to sterically hindered aryl chlorides, such as 2-chloro-*p*-xylene and 2-chloro-*m*-xylene (Table 3, Entry 4-5). Noteworthy, with the latter substrate, is that a significantly higher yield was obtained, using one-half the amount of palladium precatalyst than when the reaction was carried out at 110 °C.[7] In addition, activated aryl chlorides such as 4-chlorobenzophenone were efficiently converted to the corresponding pinacol boronate ester (Table 3, Entry 6). This protocol represents the first Pd-catalyzed method for transforming aryl chlorides to aryl boronate esters at room temperature.

Table 3. Pd-Catalyzed Borylation of Aryl Chlorides at Room Temperature.[a]



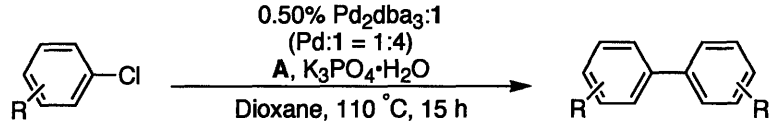
Entry	Aryl Chloride	Time (h)	Yield (%)[b]	Entry	Aryl Chloride	Time (h)	Yield (%)[b]
1		24	97	4		48	79
2		48	91[c]	5		48	86
3		48	64[c]	6		48	91[c,d]

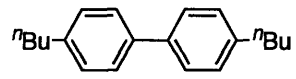
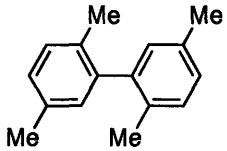
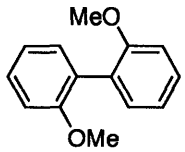
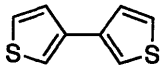
[a]Reaction Conditions: 1 equiv of aryl or heteroaryl chloride, 3.0 equiv of **A**, 3 equiv of K_3PO_4, dioxane (2 mL /mmol halide), cat. $Pd(OAc)_2$, **2**:Pd = 2.5:1. [b]Isolated yield based upon an average of two runs. [c]$K_3PO_4 \cdot H_2O$ used instead of K_3PO_4. [d]3.0% $Pd(OAc)_2$ used instead of 2.0%.

Although aryl boronate esters can be precursors to a variety of compounds, their primary application is in the synthesis of biaryls via the Suzuki-Miyaura reaction with an aryl halide or sulfonate.[1] However, the boronate ester is typically prepared and isolated prior to the cross-coupling step. Although a few reports have utilized a two-step "one-pot" borylation/Suzuki-Miyaura reaction protocol to synthesize biaryls, these methods employ catalysts that neither display prolonged stability nor a high level of activity.[8] Consequently, previous efforts have been unsuccessful when attempting to utilize aryl chlorides, which are relatively unreactive, for the "one-pot" biaryl synthesis. Further, the addition of a second "dose" of palladium catalyst is necessary for the reaction to go to completion.

As noted, in our initial studies on the borylation of aryl chlorides, we found that when employing bases such as K_3PO_4, ~15-20% of the aryl halide was converted directly to the symmetrical biaryl.[9] In addition, if $K_3PO_4 \cdot H_2O$ was utilized, this product was isolated in high yield. A Pd to ligand ratio of 1:4 was found to be optimal in order to maintain catalyst stability. Using the conditions shown, 4-*n*-butylchlorobenzene was directly converted to the symmetrical biaryl in near-quantitative yield (Table 4,

Table 4. Pd-Catalyzed Preparation of Symmetrical Biaryls.[a]



Entry	Product	Yield (%)[b]	Entry	Product	Yield (%)[b]
1		98[c,d]	3		77[c,d]
2		70	4		87

[a]Reaction Conditions: 1 equiv of aryl or heteroaryl chloride, 0.50 equiv of **A**, 3 equiv of $K_3PO_4 \cdot H_2O$, dioxane (4 mL/mmol halide), cat. Pd_2dba_3, 1:Pd = 4:1. [b]Isolated yield based upon an average of two runs. [c] K_3PO_4 used instead of $K_3PO_4 \cdot H_2O$. [d] H_2O (0.50 mL) added to the reaction mixture by syringe after 6 h.

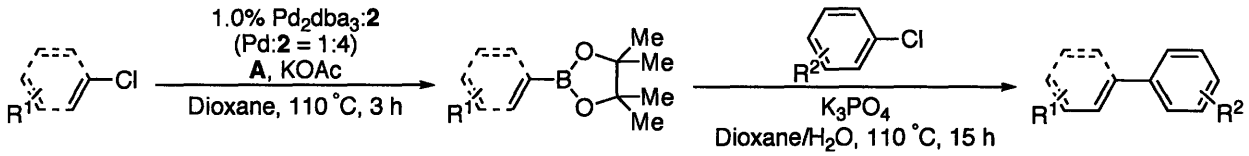
Entry 1). This method was then applied to the homocoupling of an electron-rich (2-chloroanisole, Entry 2), a relatively hindered (2-chloro-*p*-xylene, Entry 3) and a heteroaryl chloride (3-chlorothiophene, Entry 4), all of which were readily converted to the corresponding symmetrical biaryls.

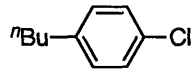
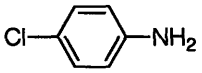
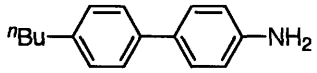
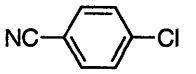
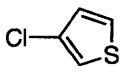
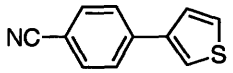
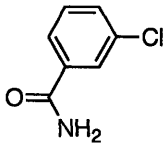
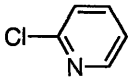
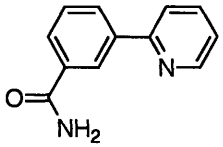
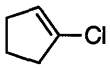
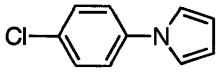
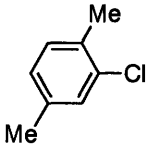
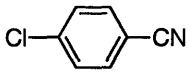
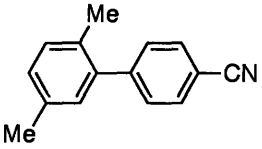
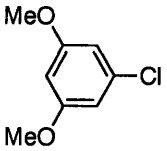
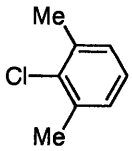
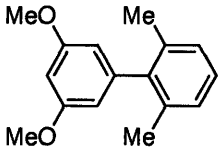
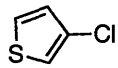
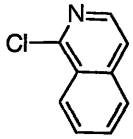
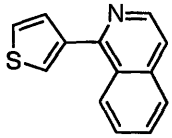
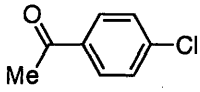
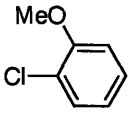
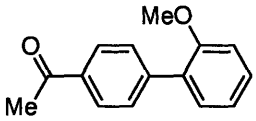
Although this method was useful for the preparation of symmetrical biaryls, we sought to develop conditions for the direct synthesis of unsymmetrical ones. It was found that a catalyst system based upon Pd_2dba_3/**2** proved to be effective for the borylation as well as for the subsequent Suzuki-Miyaura reaction. In this process, the substrate was subjected to standard Pd-catalyzed borylation conditions followed by the addition of the second aryl chloride and aqueous K_3PO_4. No workup was performed nor was catalyst added prior to conducting the second reaction of the sequence. This protocol could be used with a variety of aryl chlorides and with a vinyl chloride (Table 5). In addition, heteroaryl chlorides could be employed in the first (Table 5, Entry 7) or second step (Table 5, Entry 2-3) while maintaining good to excellent yields of the biaryls. However, these standard conditions could not be used with many ketones as significant α-arylation of the substrate was observed.[10] If KOAc was replaced with K_3PO_4, however, in the first step, then the biaryl was obtained in good yield (Table 5, Entry 8). These methods represent the first processes for the direct synthesis of symmetrical and unsymmetrical biaryls from two aryl chlorides.

In order to help determine what effect(s) biaryl phosphine ligands may impart on the Pd-catalyzed borylation of aryl halides with **A**, we turned to computational chemistry. Specifically, we were interested in the common use of KOAc in Pd-catalyzed borylation reactions. All of the calculated structures below were optimized using Gaussian 03[11] and the B3LYP[12] functional in combination with the 6-31G(d) basis set for all non-metal atoms and LANL2DZ+ECP[13] for the Pd center.

It is possible that the use of KOAc in Pd-catalyzed borylation reactions facilitates the formation of a $L_1Pd(Ar)OAc$ compound from an oxidative addition species (e.g., $L_1Pd(Ar)Cl$ - complex **6**). This type of metathesis was shown to occur in the Pd-catalyzed borylation reactions of aryl iodides and bromides by Miyaura in 1995.[14] Although the calculated free energy of reaction is +9.2 kcal/mol, this

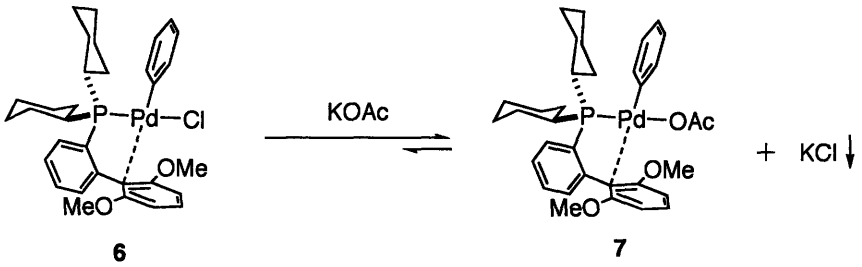
Table 5. Pd-Catalyzed Preparation of Unsymmetrical Biaryls.[a]



Entry	Aryl[1] (Vinyl[1]) Chloride	Aryl[2]Chloride	Product	Yield[b]
1				89
2				92
3				92
4				62
5				70
6				95
7				71
8				65[c,d]

[a]Reaction Conditions: 1.2 equiv of the first aryl or heteroaryl chloride, 1.0 equiv of the second aryl chloride, 1.2 equiv of **A**, 2 equiv of KOAc, 5 equiv K_3PO_4, dioxane (4 mL/mmol halide), cat. Pd_2dba_3, **2**:Pd = 4:1. [b]Isolated yield based upon an average of two runs. [c]K_3PO_4 used instead of KOAc in step one. [d]2.0% Pd_2dba_3 used instead of 1.0%.

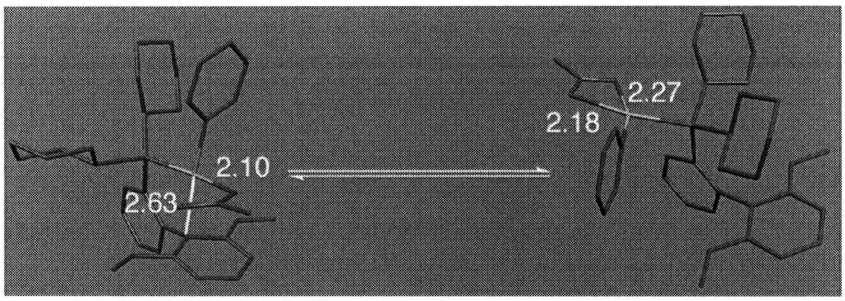
metathesis may still occur due to concurrent generation and precipitation of KCl thus shifting the reaction equilibrium to product (Scheme 2).

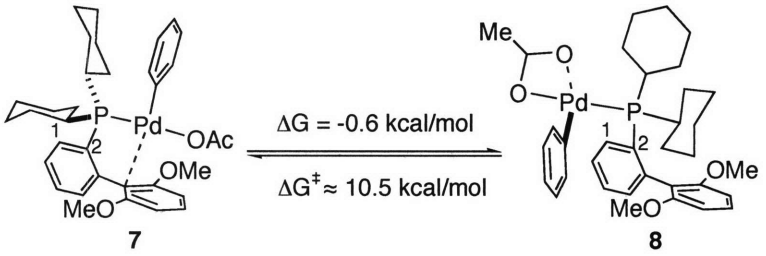


6 7

Scheme 2. Formation of $L_1Pd(Ar)OAc$.

Based upon our previous study of oxidative addition intermediates involving biaryl phosphine ligands, it is very likely that transmetalation of bis(pinacolato)diboron must occur when complex **7** is in a geometry such that the Pd center is distal from the non-phosphine-containing ring of the ligand.[15] The necessity for this is the extreme crowding around the Pd center when the Pd center is coordinated to the non-phosphine-containing ring of the ligand (Scheme 3). Specifically, a free coordination site on the Pd center needs to be made available such that coordination of the diboron species can occur. We have previously demonstrated that rotation of an oxidative addition complex (complex **6**) around C2-P to a geometry such that the Pd center is distal to the bulk of the ligand is viable at room temperature ($\Delta G^{\ddagger} \approx 14$ kcal/mol).[16] We postulated that the barrier to rotation in complex **7** is likely similar to the barrier of rotation in complex **6**. This was determined to be correct by conducting a potential energy surface scan varying the C1-C2-P-Pd dihedral angle in **7** to afford **8**. From this scan, the activation energy for rotation is approximated to be 10.5 kcal/mol.[17] Hence, an advantage of using KOAc in borylation reactions catalyzed by biaryl phosphine-Pd complexes may be that once the metathesis occurs to form **7**, rotation of the Pd center such that it is distal to the non-phosphine-containing ring of the ligand can readily occur to form **8**. This rotation is thermodynamically favored by 0.6 kcal/mol which is due to the acetate ligand forming an κ^2 complex with the Pd center (*cf.* $L_1Pd(Ph)Cl$ where $\Delta G_{rotamers} = +3.8$ kcal/mol as the chloride ligand is unable to stabilize the Pd center when the metal center is distal to the non-phosphine-containing ring of the ligand).[16] It is very likely that binding of the diboron species and subsequent transmetalation





7 8

Scheme 3. Kinetic and thermodynamic parameters for the rotation around the C2-P bond. Red = oxygen, turquoise = palladium, purple = phosphorous and green = carbon.

must occur from a species with the Pd center distal to the non-phosphine-containing ring of the ligand (e.g., complex **8**). Hence, as complex **8** is more favored relative to **7**, the binding of bis(pinacolato)diboron may occur more readily in $L_1Pd(Ph)OAc$ than in a complex composed of $L_1Pd(Ph)Cl$ in which the structure analogous to **8** is thermodynamically unfavored relative to complex **6**.

From these computational studies, we attribute two features of biaryl phosphine ligands to their efficacy in promoting Pd-catalyzed borylation reactions: 1) the large nature of the ligand promotes formation of the highly reactive $L_1Pd(0)$ complex vs. the much less reactive $L_2Pd(0)$ species[18] and 2) the ability for $L_1Pd(Ph)OAc$ (derived from the oxidative addition product + KOAc) to easily access a geometry such that the Pd-arene interaction is no longer present. This creates an open coordination site on the Pd center and facilitates the binding of the diboron species and subsequent transfer of the borylate moiety to the Pd(II) center with concurrent generation of pinacol boryl acetate.

3.3 Conclusion

In summary, we have demonstrated that use of catalysts comprised of Pd and ligands **1** or **2** provide highly stable and active catalysts for the borylation of aryl chlorides at elevated as well as room temperatures. We have also shown that these methods are applicable to the direct synthesis of symmetrical and unsymmetrical biaryls. Further, mechanistic aspects of Pd-catalyzed borylation of aryl halides with bis(pinacolato)diboron were elucidated by computational chemistry, and the effects of biaryl phosphine ligands and KOAc on the catalytic cycle were presented.

3.4 Experimental

3.4.1 General

All reactions were stirrer with aid of a magnetic stirrer and carried out under an argon atmosphere. 1,4-Dioxane (anhydrous) was purchased from Aldrich Chemical Co. in SureSeal® bottles. Commercially available materials were used without further purification unless otherwise noted. XPhos (**1**) was donated by Saltigo, and SPhos (**2**) was synthesized in our laboratories. Both ligands are commercially available from Aldrich Chemical Co. or Strem Chemicals, Inc. Aryl halides were purchased from Aldrich Chemical Co. Liquid aryl bromides were purified by passage through a pad of basic alumina prior to use. Bis(pinacolato)diboron was purchased from Aldrich Chemical Co. Potassium phosphate (anhydrous) and potassium phosphate (monohydrate) were purchased from Alfa Aesar and ground with a mortar and pestle and stored in a bench-top desiccator. $Pd(OAc)_2$ was donated by BASF, and Pd_2dba_3 was purchased from Strem Chemicals, Inc. Both palladium precatalysts were stored in a bench-top desiccator.

All new compounds were characterized by ^1H NMR, ^{13}C NMR, IR spectroscopy and, in most cases, elemental analysis. Known compounds were characterized by ^1H NMR and melting points (for solids) and compared to their literature values. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 300. Infrared spectra were recorded on an ASI Applied Systems ReactIR 1000 (neat samples

were placed directly on the DiComp probe). Elemental analyses were preformed by Atlantic Microlabs Inc., Norcross, GA. All ^{1}H NMR experiments are reported in δ units, parts per million (ppm) downfield of TMS and were measured relative to the signals for the residual benzene (7.16 ppm), chloroform (7.26 ppm), dimethylsulfoxide (2.50 ppm) or methanol (3.31 ppm). All ^{13}C NMR spectra were reported in ppm relative to residual chloroform (77 ppm), dimethylsulfoxide (39.5 ppm) or methanol (49 ppm) and were obtained with ^{1}H decoupling. Melting points were obtained on a Mel-Temp capillary melting point apparatus. Gas chromatographic analyses were performed on Hewlett-Packard 6890 gas chromatography instrument with a FID detector using 25 m x 0.20 mm capillary column with cross-linked methyl siloxane as a stationary phase.

The yields in tables 2-5 refer to isolated yields (average of two runs) of compounds estimated to be ≥ 95% pure as determined by ^{1}H NMR and GC analysis and/or combustion analysis.

3.4.3 Experimental for the Borylation of Aryl Chlorides

General Procedure A: Pd-Catalyzed Borylation of Aryl Chlorides at Elevated Temperatures.

An oven-dried Schlenk tube was charged with Pd_2dba_3 (2.3 mg, 0.0025 mmol), **1** (4.8 mg, 0.01 mmol), bis(pinacolato)diboron (190 mg, 0.75 mmol) and KOAc (73.6 mg, 0.75 mmol). The Schlenk tube was capped with a rubber septum and then evacuated and backfilled with argon (this sequence was carried out two times). 1,4-Dioxane (0.50 mL) was added via syringe, through the septum, followed by the addition of the aryl chloride (0.25 mmol) in a like manner (aryl halides that were solid 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 110 °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 celite (eluting with ethyl acetate) and the eluent was concentrated under reduced pressure. The crude material so obtained was purified via flash chromatography on silica gel.

2-(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 2, entry 1a).[19] Following general procedure A, a mixture of 4-chloroanisole (35.6 mg, 30.4 μL, 0.25 mmol), bis(pinacolato)diboron (76 mg, 0.30 mmol), KOAc (73.6 mg, 0.75 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol) and **1** (4.8 mg, 0.010 mmol) was heated to 110 °C in 1,4-dioxane with stirring for 10 min. The crude product was purified via flash column chromatography on silica gel (5% EtOAc/Hexanes) to provide the title compound in a 97% yield (57 mg) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.75 (d, J = 9 Hz, 2H), 6.90 (d, J = 9 Hz, 2H), 3.83 (s, 3H), 1.34 (s, 12H). ^{1}H NMR spectrum included.

2-(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 2, entry 1b).[19] Following general procedure A, a mixture of 4-chloroanisole (143 mg, 121.7 μL, 1.00 mmol), bis(pinacolato)diboron (381 mg, 1.50 mmol), KOAc (294 mg, 3.00 mmol), Pd_2dba_3 (0.46 mg, 0.50 μmol) and **1** (0.95 mg, 0.0020 mmol) was heated to 110 °C in 1,4-dioxane with stirring for 24 h. The crude product was purified via flash column chromatography on silica gel (5% EtOAc/Hexanes) to provide the title compound in a 94% yield (219 mg) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.75 (d, J = 9 Hz, 2H), 6.90 (d, J = 9 Hz, 2H), 3.83 (s, 3H), 1.34 (s, 12H). ^{1}H NMR spectrum included.

***N*-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (Table 2, entry 2).** Following general procedure A, a mixture of 4-chlorobenzanilide (115.8 mg, 0.50 mmol), bis(pinacolato)diboron (152 mg, 0.60 mmol), KOAc (147 mg, 1.50 mmol), Pd_2dba_3 (1.1 mg, 0.00125 mmol) and **1** (2.4 mg, 0.0050 mmol) was heated to 110 °C in 1,4-dioxane with stirring for 30 min. The crude product was purified via recrystallization (Hexanes) to provide the title compound in a 96% yield (155 mg) as a white solid, mp 202-203 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.05 (bs, 1H), 7.89 (d, J = 8 Hz, 2H), 7.84 (d, J = 8 Hz, 2H), 7.64 (d, J = 7 Hz, 2H), 7.34 (t, J = 8 Hz, 2H), 7.13 (t, J = 8 Hz, 1H), 1.36 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.7, 137.8, 137.1, 135.0, 130.5, 129.0, 126.1, 124.5, 120.3, 84.1, 24.8. IR (neat, cm^{-1}): 3298, 2978, 2931, 1652, 1600, 1535, 1442, 1398, 1361, 1324, 1144, 1086. ^{1}H NMR spectrum included.

1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrrole (Table 2, entry 3). Following general procedure A, a mixture of *N*-(4-chorophenyl)pyrrole (44.4 mg, 0.25 mmol),

bis(pinacolato)diboron (190 mg, 0.75 mmol), KOAc (73.6 mg, 0.75 mmol), Pd_2dba_3 (1.1 mg, 0.00125 mmol) and **1** (2.4 mg, 0.0050 mmol) was heated to 110 °C in 1,4-dioxane with stirring for 30 min. The crude product was purified via flash column chromatography on silica gel (5% EtOAc/Hexanes) to provide the title compound in a 83% yield (56 mg) as a white solid, mp 83-84 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.88 (d, J = 8 Hz, 2H), 7.41 (d, J = 8 Hz, 2H), 7.16 (t, J = 2 Hz, 2H), 6.37 (t, J = 2 Hz, 2H), 1.38 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 142.8, 136.2, 119.2, 119.0, 110.7, 83.9, 24.8. (No C-B signal) IR (neat, cm^{-1}): 2978, 2930, 1608, 1481, 1362, 1329, 1144. Anal. Calcd. for $C_{16}H_{20}BNO_2$: C, 71.40; H, 7.49. Found C, 71.51; H, 7.58.

4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (Table 2, entry 4).[19] Following general procedure A, a mixture of 4-chlorophenol (32.1 mg, 0.25 mmol), bis(pinacolato)diboron (190 mg, 0.75 mmol), KOAc (73.6 mg, 0.75 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol) and **1** (4.8 mg, 0.010 mmol) was heated to 110 °C in 1,4-dioxane with stirring for 30 min. The crude product was purified via flash column chromatography on silica gel (10% EtOAc/Hexanes) to provide the title compound in a 82% yield (45 mg) as a white solid, mp 106-107 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.70 (d, J = 7 Hz, 2H), 6.82 (d, J = 7 Hz, 2H), 5.82 (bs, 1H), 1.34 (s, 12H). ^{1}H NMR spectrum included.

3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (Table 2, entry 5). Following general procedure A, a mixture of 3-chlorobenzamide (38.9 mg, 0.25 mmol), bis(pinacolato)diboron (76 mg, 0.30 mmol), KOAc (73.6 mg, 0.75 mmol), Pd_2dba_3 (2.3 mg, 0.0025 mmol) and **1** (4.8 mg, 0.010 mmol) was heated to 110 °C in 1,4-dioxane with stirring for 30 min. The crude product was purified via recrystallization (Hexanes) to provide the title compound in an 89% yield (55 mg) as a white solid, mp 182-183 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.18 (s, 1H), 7.99 (d, J = 7 Hz, 1H), 7.94 (d, J = 7 Hz, 1H), 7.45 (t, J = 7 Hz, 1H), 6.36 (bs, 1H), 6.29 (bs, 1H), 1.34 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.5, 138.2, 132.9, 132.6, 130.7, 128.1, 84.1, 24.8. (No C-B signal) IR (neat, cm^{-1}): 3416, 3199, 2978, 1651, 1618, 1602, 1381, 1353, 1322. Anal. Calcd. for $C_{13}H_{18}BNO_3$: C, 63.19; H, 7.34. Found C, 62.96; H, 7.32.

phenyl(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanone (Table 2, entry 6). Following general procedure A, a mixture of 2-chlorobenzophenone (54.2 mg, 0.25 mmol), bis(pinacolato)diboron (190 mg, 0.75 mmol), KOAc (73.6 mg, 0.75 mmol), Pd_2dba_3 (2.3 mg, 0.0025 mmol) and **1** (4.8 mg, 0.010 mmol) was heated to 110 °C in 1,4-dioxane with stirring for 1 h. The crude product was purified via flash column chromatography on silica gel (10% EtOAc/Hexanes) to provide the title compound in a 87% yield (67 mg) as a white solid, mp 101-102 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.77 (d, J = 7 Hz, 2H), 7.74 (dt, J = 7, 1 Hz, 1H), 7.35-7.55 (m, 6H), 1.19 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 198.1, 143.5, 138.1, 133.7, 132.4, 130.3, 130.0, 129.7, 128.9, 128.2, 84.0, 24.5. IR (neat, cm^{-1}): 3060, 2978, 1667, 1596, 1485, 1448, 1380, 1352, 1284, 1145. ^{1}H NMR spectrum included.

2-(2,5-dimethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 2, entry 7).[20] Following general procedure A, a mixture of 2-chloro-*p*-xylene (33.5 μL, 0.25 mmol), bis(pinacolato)diboron (190 mg, 0.75 mmol), KOAc (73.6 mg, 0.75 mmol), Pd_2dba_3 (2.3 mg, 0.0025 mmol) and **1** (4.8 mg, 0.010 mmol) was heated to 110 °C in 1,4-dioxane with stirring for 1 h. The crude product was purified via flash column chromatography on silica gel (2.5% EtOAc/Hexanes) to provide the title compound in an 88% yield (52 mg) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.60 (s, 1H), 7.15 (d, J = 8 Hz, 1H), 7.08 (d, J = 8 Hz, 1H), 2.52 (s, 3H), 2.32 (s, 3H), 1.36 (s, 12H). ^{1}H NMR spectrum included.

2-(2,6-dimethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 2, entry 8).[8b] Following general procedure A, a mixture of 2-chloro-*m*-xylene (33.1 μL, 0.25 mmol), bis(pinacolato)diboron (190 mg, 0.75 mmol), KOAc (73.6 mg, 0.75 mmol), Pd_2dba_3 (4.6 mg, 0.0050 mmol) and **1** (9.6 mg, 0.020 mmol) was heated to 110 °C in 1,4-dioxane:water (10:1) with stirring for 5 h. The crude product was purified via flash column chromatography on silica gel (2.5% EtOAc/Hexanes) to provide the title compound in a 62% yield (36 mg) as a white solid, mp 46-47 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.13 (t, J = 7 Hz, 1H), 6.95 (d, J = 7 Hz, 2H), 2.41 (s, 6H), 1.40 (s, 12H). ^{1}H NMR spectrum included.

4,4,5,5-tetramethyl-2-(thiophen-3-yl)-1,3,2-dioxaborolane (Table 2, entry 9).[21] Following general procedure A, a mixture of 3-chlorothiophene (29.6 mg, 23.2 μL, 0.25 mmol), bis(pinacolato)diboron (190

mg, 0.75 mmol), KOAc (73.6 mg, 0.75 mmol), Pd_2dba_3 (1.1 mg, 0.00125 mmol) and **1** (2.4 mg, 0.005 mmol) was heated to 110 °C in 1,4-dioxane with stirring for 1 h. The crude product was purified via flash column chromatography on silica gel (Hexanes) to provide the title compound in a 76% yield (40 mg) as a white solid, mp 72-73 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.92 (dt, J = 3, 1 1H), 7.41 (dt, J = 5, 1 Hz, 1H), 7.34 (dt, J = 5, 3 Hz, 1H), 1.33 (s, 12H). ^{1}H NMR spectrum included.

5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (Table 2, entry 10).[22] Following general procedure A, a mixture of 5-chloroindole (37.9 mg, 0.25 mmol), bis(pinacolato)diboron (190 mg, 0.75 mmol), KOAc (73.6 mg, 0.75 mmol), $Pd(OAc)_2$ (1.1 mg, 0.0050 mmol) and **1** (4.8 mg, 0.010 mmol) was heated to 110 °C in 1,4-dioxane with stirring for 1 h. The crude product was purified via flash column chromatography on silica gel (10% EtOAc/Hexanes) to provide the title compound in a 95% yield (58 mg) as a white solid, mp 91-92 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.38 (bs, 1H), 8.23 (s, 1H), 7.67 (d, J = 8 Hz, 1H), 7.36 (d, J = 8 Hz, 1H), 7.16 (t, J = 3 Hz, 1H), 6.57 (t, J = 3 Hz, 1H), 1.39 (s, 12H). ^{1}H NMR spectrum included.

3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (Table 2, entry 11).[23] Following general procedure A, a mixture of bis(pinacolato)diboron (190 mg, 0.75 mmol), KOAc (73.6 mg, 0.75 mmol), Pd_2dba_3 (2.3 mg, 0.0025 mmol) and **1** (4.8 mg, 2.0 mol%) was heated to 110 °C in 1,4-dioxane. 3-Chloropyridine (28.4 mg, 23.8 μL, 0.25 mmol) in 1,4-dioxane (1.0 mL) was added via syringe pump over 1 h. After addition of the aryl halide, the reaction was allowed to stir for 4 h at 110 °C. The crude product was purified via recrystallization (Hexanes) to provide the title compound in a 82% yield (42 mg) as a yellow solid, mp 85-86 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.94 (s, 1H), 8.66 (dd, J = 5, 2 Hz, 1H), 8.04 (dt, J = 7, 1 Hz, 1H), 7.26 (ddd, J = 7, 5, 1 Hz, 1H), 1.35 (s, 12H). ^{1}H NMR spectrum included.

3.4.4 Experimental for the Borylation of Aryl Chlorides

General Procedure B: Pd-Catalyzed Borylation of Aryl Chlorides at Room Temperature.

An oven-dried Schlenk tube was charged with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), **2** (5.1 mg, 0.0125 mmol), bis(pinacolato)diboron (190 mg, 0.75 mmol) and K_3PO_4 (159 mg, 0.75 mmol). The Schlenk tube was capped with a rubber septum and then evacuated and backfilled with argon (this sequence was carried out two times). 1,4-Dioxane (0.50 mL) was added via syringe, through the septum, followed by the addition of the aryl chloride (0.25 mmol) in a like manner (aryl halides that were solid 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 stirred at room temperature 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 celite (eluting with ethyl acetate) and the eluent was concentrated under reduced pressure. The crude material so obtained was purified via flash chromatography on silica gel.

2-(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 3, entry 1).[19] Following general procedure B, a mixture of 4-chloroanisole (35.6 mg, 30.4 μL, 0.25 mmol), bis(pinacolato)diboron (190 mg, 0.75 mmol), K_3PO_4 (159 mg, 0.75 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol) and **2** (5.1 mg, 0.0125 mmol) in 1,4-dioxane was stirred at room temperature for 24 h. The crude product was purified via flash column chromatography on silica gel (5% EtOAc/Hexanes) to provide the title compound in a 97% yield (57 mg) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.75 (d, J = 9 Hz, 2H), 6.90 (d, J = 9 Hz, 2H), 3.83 (s, 3H), 1.34 (s, 12H). ^{1}H NMR spectrum included.

2-(4-butylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 3, entry 2).[24] Following general procedure B, a mixture of 4-*n*-butylchlorobenzene (42.2 mg, 41.0 μL, 0.25 mmol), bis(pinacolato)diboron (190 mg, 0.75 mmol), $K_3PO_4 \cdot H_2O$ (173 mg, 0.75 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol) and **2** (5.1 mg, 0.0125 mmol) in 1,4-dioxane was stirred at room temperature for 48 h. The crude product was purified via flash column chromatography on silica gel (2.5% EtOAc/Hexanes) to provide the title compound in a 91% yield (59 mg) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.75 (d, J = 8 Hz, 2H), 7.22 (d, J = 8 Hz, 2H), 2.64 (t, J = 8 Hz, 2H), 1.62 (pent, J = 8 Hz, 2H), 1.37 (sext, J = 8 Hz, 2H), 1.36 (s, 12H), 0.94 (t, J = 8 Hz, 3H). ^{1}H NMR spectrum included.

4,4,5-trimethyl-2-(3-(trifluoromethyl)phenyl)-1,3,2-dioxaborolane (Table 3, entry 3).[19] Following general procedure B, a mixture of 3-chlorobenzotrifluoride (45.1 mg, 33.8 μL, 0.25 mmol), bis(pinacolato)diboron (190 mg, 0.75 mmol), $K_3PO_4 \cdot H_2O$ (173 mg, 0.75 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol) and **2** (5.1 mg, 0.0125 mmol) in 1,4-dioxane was stirred at room temperature for 48 h. The crude product was purified via flash column chromatography on silica gel (2.5% EtOAc/Hexanes) to provide the title compound in a 64% yield (44 mg) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.07 (s, 1H), 7.97 (d, J = 7 Hz, 1H), 7.69 (d, J = 7 Hz, 1H), 7.48 (t, J = 7 Hz, 1H), 1.36 (s, 12H). ^1H NMR spectrum included.

2-(2,5-dimethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 3, entry 4).[20] Following general procedure B, a mixture of 2-chloro-*p*-xylene (33.5 μL, 0.25 mmol), bis(pinacolato)diboron (190 mg, 0.75 mmol), K_3PO_4 (159 mg, 0.75 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol) and **2** (5.1 mg, 0.0125 mmol) in 1,4-dioxane was stirred at room temperature for 40 h. The crude product was purified via flash column chromatography on silica gel (2.5% EtOAc/Hexanes) to provide the title compound in a 79% yield (46 mg) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.60 (s, 1H), 7.15 (d, J = 8 Hz, 1H), 7.08 (d, J = 8 Hz, 1H), 2.52 (s, 3H), 2.32 (s, 3H), 1.36 (s, 12H). ^1H NMR spectrum included.

2-(2,6-dimethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 3, entry 5).[8b] Following general procedure B, a mixture of 2-chloro-*m*-xylene (33.1 μL, 0.25 mmol), bis(pinacolato)diboron (190 mg, 0.75 mmol), K_3PO_4 (159 mg, 0.75 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol) and **2** (5.1 mg, 0.0125 mmol) in 1,4-dioxane was stirred at room temperature for 48 h. The crude product was purified via flash column chromatography on silica gel (2.5% EtOAc/Hexanes) to provide the title compound in a 86% yield (50 mg) as a white solid, mp 46-47 °C. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.13 (t, J = 7 Hz, 1H), 6.95 (d, J = 7 Hz, 2H), 2.41 (s, 6H), 1.40 (s, 12H). ^1H NMR spectrum included.

phenyl(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanone (Table 3, entry 6).[5a] Following general procedure B, a mixture of 4-chlorobenzophenone (54.2 mg, 0.25 mmol), bis(pinacolato)diboron (190 mg, 0.75 mmol), $K_3PO_4 \cdot H_2O$ (173 mg, 0.75 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol) and **2** (5.1 mg, 0.0125 mmol) in 1,4-dioxane was stirred at room temperature for 48 h. The crude

product was purified via flash column chromatography on silica gel (10% EtOAc/Hexanes) to provide the title compound in a 87% yield (67 mg) as a white solid, mp 75-76 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.91 (d, J = 8 Hz, 2H), 7.79 (dd, J = 8, 1 Hz, 2H), 7.76 (d, J = 8 Hz, 2H), 7.59 (dt, J = 8, 1 Hz, 1H), 7.48 (t, J = 8 Hz, 2H), 1.37 (s, 12H). ^{1}H NMR spectrum included.

3.4.5 Experimental for the Preparation of Symmetrical Biaryls

General Procedure C: Experimental for the Preparation of Symmetrical Biaryls.

An oven-dried Schlenk tube was charged with Pd_2dba_3 (4.6 mg, 0.0050 mmol), **1** (19 mg, 0.040 mmol), bis(pinacolato)diboron (127 mg, 0.50 mmol) and $K_3PO_4 \cdot H_2O$ (460 mg, 2.00 mmol). The Schlenk tube was capped with a rubber septum and then evacuated and backfilled with argon (this sequence was carried out two times). Dioxane (2.00 mL) was added via syringe, through the septum, followed by the addition of the aryl chloride (1.00 mmol) in a like manner (aryl halides that were solid 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 110 °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 celite (eluting with ethyl acetate) and the eluent was concentrated under reduced pressure. The crude material so obtained was purified via flash chromatography on silica gel.

4,4'-dibutylbiphenyl (Table 4, entry 1).[25] Following general procedure C, a mixture of 4-*n*-butylchlorobenzene (168 mg, 164 μL, 1.00 mmol), bis(pinacolato)diboron (127 mg, 0.50 mmol), $K_3PO_4 \cdot H_2O$ (460 mg, 2.00 mmol), Pd_2dba_3 (4.6 mg, 0.0050 mmol) and **1** (19 mg, 0.040 mmol) was heated to 110 °C in 1,4-dioxane with stirring for 6 h. At this point, H_2O (0.50 mL) was added via syringe, through the septum, into the reaction flask. The reaction mixture remained heated to 110 °C for 15 h. The crude product was purified via flash column chromatography on silica gel (Hexanes) to provide the title compound in a 98% yield (131 mg) as a white solid, mp 44-45 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.56

(d, J = 8 Hz, 2H), 7.29 (d, J = 8 Hz, 2H), 2.72 (t, J = 7 Hz, 2H), 1.69 (pent, J = 7 Hz, 2H), 1.45 (sext, J = 7 Hz, 2H), 1.01 (t, J = 7 Hz, 3H). ^{1}H NMR spectrum included.

2,2'-dimethoxybiphenyl (Table 4, entry 2).[25] Following general procedure C, a mixture of 4-chloroanisole (142.6 mg, 127 μL, 1.00 mmol), bis(pinacolato)diboron (127 mg, 0.50 mmol), $K_3PO_4 \cdot H_2O$ (460 mg, 2.00 mmol), Pd_2dba_3 (4.6 mg, 0.0050 mmol) and **1** (19 mg, 0.040 mmol) was heated to 110 °C in 1,4-dioxane with stirring for 15 h. The crude product was purified via flash column chromatography on silica gel (5% EtOAc/Hexanes) to provide the title compound in a 70% yield (80 mg) as a white solid, mp 153-154 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37 (dt, J = 8, 2 Hz, 1H), 7.30 (dd, J = 7, 2 Hz, 1H), 7.06 (t, J = 7 Hz, 1H), 7.02 (d, J = 8 Hz, 1H), 3.82 (s, 6H). ^{1}H NMR spectrum included.

2,2',5,5'-tetramethylbiphenyl (Table 4, entry 3).[26] Following general procedure C, a mixture of 2-chloro-*p*-xylene (140.6 mg, 134 μL, 1.00 mmol), bis(pinacolato)diboron (127 mg, 0.50 mmol), K_3PO_4 (424 mg, 2.00 mmol), Pd_2dba_3 (4.6 mg, 0.0050 mmol) and **2** (19 mg, 0.040 mmol) was heated to 110 °C in 1,4-dioxane with stirring for 6 h. At this point, H_2O (0.50 mL) was added via syringe, through the septum, into the reaction flask. The reaction mixture remained heated to 110 °C for 15 h. The crude product was purified via flash column chromatography on silica gel (Hexanes) to provide the title compound in a 77% yield (81 mg) as a white solid, mp 51-52 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.22 (d, J = 8 Hz, 2H), 7.14 (d, J = 8 Hz, 2H), 7.01 (s, 2H), 2.41 (s, 6H), 2.10 (s, 6H). ^{1}H NMR spectrum included.

3,3'-bithiophene (Table 4, entry 4).[27] Following general procedure C, a mixture of 3-chlorothiophene (118.6 mg, 92.9 μL, 1.00 mmol), bis(pinacolato)diboron (127 mg, 0.50 mmol), $K_3PO_4 \cdot H_2O$ (460 mg, 2.00 mmol), Pd_2dba_3 (4.6 mg, 0.0050 mmol) and **1** (19 mg, 0.040 mmol) was heated to 110 °C in 1,4-dioxane with stirring for 15 h. The crude product was purified via flash column chromatography on silica gel (Hexanes) to provide the title compound in a 87% yield (72 mg) as a white solid, mp 119-121 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39 (dd, J = 3, 2 Hz, 1H), 7.35-7.36 (m, 2H). ^{1}H NMR spectrum included

3.4.6 Experimental for the Preparation of Unsymmetrical Biaryls

General Procedure D: Experimental for the Preparation of Unsymmetrical Biaryls.

An oven-dried 25-mL round bottom flask was charged with Pd_2dba_3 (4.6 mg, 0.005 mmol), **2** (16.4 mg, 0.040 mmol), bis(pinacolato)diboron (152 mg, 0.60 mmol) and KOAc (98 mg, 1.00 mmol). The flask, equipped with reflux condenser, was capped and then evacuated and back-filled with argon (this was repeated two additional times). 1,4-Dioxane (2.00 mL) was added via syringe, through the septum, followed by the addition of the first aryl chloride (0.60 mmol) in a like manner (aryl halides that were solid were added with other reagents before evacuation). The reaction mixture was heated to 110 °C until aryl halide had been completely consumed as determined by gas chromatography. At this point the second aryl chloride (0.50 mmol) in dioxane (0.50 mL) and 5 M K_3PO_4 (aq) (0.50 mL) were added via syringe, through the septum, into the reaction flask. The reaction mixture remained heated to 110 °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 celite (eluting with ethyl acetate) and the eluent was concentrated under reduced pressure. The crude material so obtained was purified via flash chromatography on silica gel (eluting with hexanes/ethyl acetate mixtures).

4'-butylbiphenyl-4-amine (Table 5, entry 1). Following general procedure D, a mixture of 4-*n*-butylchlorobenzene (101.2 mg, 98.4 μL, 0.60 mmol), bis(pinacolato)diboron (152 mg, 0.60 mmol), KOAc (98 mg, 1.00 mmol), Pd_2dba_3 (4.6 mg, 0.005 mmol) and **2** (16.4 mg, 0.040 mmol) was heated to 110 °C in 1,4-dioxane with stirring for 3 h. At this point the 4-chloroaniline (63.8 mg, 0.50 mmol) in dioxane (0.50 mL) and 5 M K_3PO_4 (aq) (0.50 mL) were added via syringe, through the septum, into the reaction flask. The reaction mixture remained heated to 110 °C for 15 h. The crude product was purified via flash column chromatography on silica gel (20% EtOAc/Hexanes) to provide the title compound in a 89% yield (100 mg) as a brown solid, mp 50-51 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.49 (d, J = 8 Hz, 2H), 7.44 (d, J = 8 Hz, 2H), 7.25 (d, J = 8 Hz, 2H), 6.77 (d, J = 8 Hz, 2H), 2.67 (t, J = 7 Hz, 2H), 1.67

(pent, J = 7 Hz, 2H), 1.43 (sext, J = 7 Hz, 2H), 1.00 (t, J = 7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 145.5, 140.9, 138.4, 131.5, 128.7, 127.7, 126.2, 115.3, 35.2, 33.7, 22.4, 14.0. IR (neat, cm^{-1}): 3561, 3387, 3218, 2957, 2925, 2855, 1619, 1499, 1265. ^{1}H NMR spectrum included.

4-(thiophen-3-yl)benzonitrile (Table 5, entry 2).[28] Following general procedure D, a mixture of 4-chlorobenzonitrile (82.5 mg, 0.60 mmol), bis(pinacolato)diboron (152 mg, 0.60 mmol), KOAc (98 mg, 1.00 mmol), Pd_2dba_3 (4.6 mg, 0.005 mmol) and **2** (16.4 mg, 0.040 mmol) was heated to 110 °C in 1,4-dioxane with stirring for 3 h. At this point the 3-chlorothiophene (59.3 mg, 46.5 μL, 0.50 mmol) in dioxane (0.50 mL) and 5 M K_3PO_4 (aq) (0.50 mL) were added via syringe, through the septum, into the reaction flask. The reaction mixture remained heated to 110 °C for 15 h. The crude product was purified via flash column chromatography on silica gel (10% EtOAc/Hexanes) to provide the title compound in a 92% yield (85 mg) as a white solid, mp 100-101 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.68 (m, 4H), 7.57 (dd, J = 3, 1 Hz, 1H), 7.44 (dd, J = 5, 3 Hz, 1H), 7.40 (dd, J = 5, 1 Hz, 1H). ^{1}H NMR spectrum included.

3-(pyridin-2-yl)benzamide (Table 5, entry 3). Following general procedure D, a mixture of 3-chlorobenamide (93.3 mg, 0.60 mmol), bis(pinacolato)diboron (152 mg, 0.60 mmol), KOAc (98 mg, 1.00 mmol), Pd_2dba_3 (4.6 mg, 0.005 mmol) and **2** (16.4 mg, 0.040 mmol) was heated to 110 °C in 1,4-dioxane with stirring for 3 h. At this point the 2-chloropyridine (56.8 mg, 47.3 μL, 0.50 mmol) in dioxane (0.50 mL) and 5 M K_3PO_4 (aq) (0.50 mL) were added via syringe, through the septum, into the reaction flask. The reaction mixture remained heated to 110 °C for 15 h. The crude product was purified via flash column chromatography on silica gel (80% EtOAc/Hexanes) to provide the title compound in a 92% yield (91 mg) as a white solid, mp 152-153 °C. ^{1}H NMR (300 MHz, DMSO) δ: 8.70 (d, J = 4 Hz, 1H), 8.57 (s, 1H), 8.23 (d, J = 8 Hz, 1H), 8.13 (s, 1H), 8.04 (d, J = 8 Hz, 1H), 7.93 (s, 1H), 7.92 (s, 1H), 7.57 (t, J = 8 Hz, 1H), 7.46 (s, 1H), 7.39 (dd, J = 8, 4 Hz, 1H). ^{13}C NMR (75 MHz, DMSO) δ: 167.8, 155.4, 149.6, 138.7, 137.4, 134.9, 129.2, 128.8, 128.1, 125.7, 122.9, 120.5. IR (neat, cm^{-1}): 3354, 2921, 1653, 1610, 1577, 1384, 1091. Anal. Calcd. for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.12. Found C, 72.63; H, 5.12.

1-(4-cyclopentenylphenyl)-1*H*-pyrrole (Table 5, entry 4). Following general procedure D, a mixture of 1-chlorocyclopentene (61.5 mg, 59.5 μL, 0.60 mmol), bis(pinacolato)diboron (152 mg, 0.60 mmol), KOAc (98 mg, 1.00 mmol), Pd_2dba_3 (4.6 mg, 0.005 mmol) and **2** (16.4 mg, 0.040 mmol) was heated to 110 °C in 1,4-dioxane with stirring for 3 h. At this point the *N*-(4-chorophenyl)pyrrole (88.8 mg, 0.50 mmol) in dioxane (0.50 mL) and 5 M K_3PO_4 (aq) (0.50 mL) were added via syringe, through the septum, into the reaction flask. The reaction mixture remained heated to 110 °C for 15 h. The crude product was purified via flash column chromatography on silica gel (5% EtOAc/Hexanes) to provide the title compound in a 62% yield (65 mg) as a white solid, mp 142-143 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48 (d, J = 8 Hz, 2H), 7.34 (d, J = 8 Hz, 2H), 7.09 (t, J = 2 Hz, 2H), 6.34 (6.34, J = 2 Hz, 2H), 6.19 (m, 1H), 2.72 (m, 2H), 2.55 (m, 2H), 2.05 (pent, J = 8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 141.4, 139.2, 134.3, 126.6, 126.2, 120.1, 119.1, 110.3, 33.4, 33.2, 23.3. IR (neat, cm^{-1}): 2923, 2851, 1641, 1605, 1521, 1329. ^{1}H NMR spectrum included.

2',5'-dimethylbiphenyl-4-carbonitrile (Table 5, entry 5). Following general procedure D, a mixture of 2-chloro-*p*-xylene (84.4 mg, 80.4 μL, 0.60 mmol), bis(pinacolato)diboron (152 mg, 0.60 mmol), KOAc (98 mg, 1.00 mmol), Pd_2dba_3 (4.6 mg, 0.005 mmol) and **2** (16.4 mg, 0.040 mmol) was heated to 110 °C in 1,4-dioxane with stirring for 3 h. At this point the 4-chlorobenzonitrile (68.8 mg, 0.50 mmol) in dioxane (0.50 mL) and 5 M K_3PO_4 (aq) (0.50 mL) were added via syringe, through the septum, into the reaction flask. The reaction mixture remained heated to 110 °C for 12 h. The crude product was purified via flash column chromatography on silica gel (5% EtOAc/Hexanes) to provide the title compound in a 70% yield (72 mg) as a white solid, mp 62-63 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.70 (d, J = 8 Hz, 2H), 7.43 (d, J = 8 Hz, 2H), 7.19 (d, J = 8 Hz, 1H), 7.13 (d, J = 8 Hz, 1H), 7.02 (s, 1H), 2.36 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 146.9, 139.8, 135.6, 131.9, 131.8, 130.6, 130.1, 129.9, 128.9, 119.0, 110.5, 20.9, 19.8. IR (neat, cm^{-1}): 2953, 2923, 2227, 1607, 1493, 1453, 1393, 843, 813. ^{1}H NMR spectrum included.

3',5'-dimethoxy-2,6-dimethylbiphenyl (Table 5, entry 6).[29] Following general procedure D, a mixture of 1-chloro-3,5-dimethoxybenzene (103.6 mg, 0.60 mmol), bis(pinacolato)diboron (152 mg, 0.60 mmol), KOAc (98 mg, 1.00 mmol), Pd_2dba_3 (4.6 mg, 0.005 mmol) and **2** (16.4 mg, 0.040 mmol) was heated to 110 °C in 1,4-dioxane with stirring for 3 h. At this point the 2-chloro-*m*-xylene (70.3 mg, 66.3 μL, 0.50 mmol) in dioxane (0.50 mL) and 5 M K_3PO_4 (aq) (0.50 mL) were added via syringe, through the septum, into the reaction flask. The reaction mixture remained heated to 110 °C for 15 h. The crude product was purified via flash column chromatography on silica gel (5% EtOAc/Hexanes) to provide the title compound in a 95% yield (115 mg) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.11-7.16 (m, 3H), 6.48 (t, J = 3 Hz, 1H), 6.34 (d, J = 3 Hz, 2H), 3.82 (s, 6H), 2.11 (s, 6H). ^{1}H NMR spectrum included.

1-(thiophen-3-yl)isoquinoline (Table 5, entry 7). Following general procedure D, a mixture of 3-chlorothiophene (71.1 mg, 55.8 μL, 0.60 mmol), bis(pinacolato)diboron (152 mg, 0.60 mmol), KOAc (98 mg, 1.00 mmol), Pd_2dba_3 (4.6 mg, 0.005 mmol) and **2** (16.4 mg, 0.040 mmol) was heated to 110 °C in 1,4-dioxane with stirring for 3 h. At this point the 1-chloroisoquinoline (81.8 mg, 0.50 mmol) in dioxane (0.50 mL) and 5 M K_3PO_4 (aq) (0.50 mL) were added via syringe, through the septum, into the reaction flask. The reaction mixture remained heated to 110 °C for 15 h. The crude product was purified via flash column chromatography on silica gel (10% EtOAc/Hexanes) to provide the title compound in a 71% yield (75 mg) as a yellow solid, mp 74-75 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.58 (d, J = 6 Hz, 1H), 8.29 (d, J = 8 Hz, 1H), 7.87 (d, J = 8 Hz, 1H), 7.72 (dt, J = 3, 1 Hz, 1H), 7.69 (dt, J = 8, 1 Hz, 1H), 7.62 (d, J = 6 Hz, 1H), 7.57 (dt, J = 8, 1 Hz, 1H), 7.55 (dt, J = 6, 1 Hz, 1H), 7.49 (ddd, J = 6, 3, 1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.8, 142.1, 140.6, 136.7, 130.5, 130.0, 129.1, 127.3, 127.1, 126.9, 126.0, 125.6, 119.8. IR (neat, cm^{-1}): 3105, 3049, 1620, 1582, 1555, 1498, 1418, 1337, 1309. Anal. Calcd. for $C_{13}H_9NS$: C, 73.90; H, 4.29. Found C, 73.79; H, 4.25.

1-(2'-methoxybiphenyl-4-yl)ethanone (Table 5, entry 8). Following general procedure D, a mixture of 4-chloroacetophenone (92.8 mg, 77.8 μL, 0.60 mmol), bis(pinacolato)diboron (152 mg, 0.60 mmol), K_3PO_4 (466 mg, 2.20 mmol), Pd_2dba_3 (4.6 mg, 0.005 mmol) and **2** (16.4 mg, 0.040 mmol) was heated to

110 °C in 1,4-dioxane with stirring for 6 h. At this point the 2-chloroanisole (71.3 mg, 63.5 μL, 0.50 mmol) in dioxane (0.50 mL) and H_2O (0.50 mL) were added via syringe, through the septum, into the reaction flask. The reaction mixture remained heated to 110 °C for 15 h. The crude product was purified via flash column chromatography on silica gel (10% EtOAc/Hexanes) to provide the title compound in a 65% yield (74 mg) as a white solid, mp 105-106 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.00 (d, J = 8 Hz, 2H), 7.65 (d, J = 8 Hz, 2H), 7.38 (dt, J = 8, 2 Hz, 1H), 7.35 (dd, J = 8, 2 Hz, 1H), 7.06 (dt, J = 8, 2 Hz, 1H), 7.01 (d, J = 8 Hz, 1H), 3.83 (s, 3H), 2.64 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 197.9, 156.4, 143.5, 135.4, 130.6, 130.5, 129.7, 129.4, 129.3, 128.0, 120.9, 111.2, 55.5, 26.6. IR (neat, cm^{-1}): 2938, 2836, 1680, 1604, 1486, 1402, 1267, 1237, 1026. Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found C, 79.55; H, 6.26.

3.4.7 Computational Methods

All calculations were conducted on a home-built Linux cluster consisting of 12 dual Opteron processors. Ground state geometry optimizations, using all-atom DFT without any approximations, were conducted using Gaussian 03[11] with the B3LYP hybrid functional.[12] For all non-metal atoms, the 6-31G(d) basis set was used and for the Pd center, LANL2DZ+ECP[13] was employed. All calculated structures were verified to be local minima (all positive eigenvalues) for ground state structures. The unscaled Gibbs free energies were calculated at 298.15 K and 1 atm and based upon ideal gas-phase conditions.

Cartesian coordinates for all optimized structures:

6

C	2.59977800	-0.06871400	0.44026500
C	2.93037200	-1.36640500	0.91492400
C	3.73434100	-2.22645200	0.16092200
C	4.20436300	-1.80468300	-1.07721200
C	3.91091100	-0.53897700	-1.58132000

C	3.13083400	0.33063200	-0.81468000
C	2.11246300	0.96601600	1.41799500
C	0.79055400	1.44808400	1.50887800
C	0.49043200	2.42195900	2.47898400
C	1.46406000	2.91625700	3.34403800
C	2.77129700	2.44114900	3.25082800
C	3.08303000	1.47814300	2.29580500
H	3.95603300	-3.22683900	0.50751900
H	4.29211400	-0.24368900	-2.55052700
H	-0.52093000	2.80128300	2.57488700
H	1.19912700	3.66483900	4.08578000
H	3.54314000	2.81410000	3.91860000
H	4.09916400	1.10125600	2.22239600
P	-0.49626300	0.82722000	0.32773700
Pd	0.23384600	-1.23027600	-0.53679500
C	3.40360600	2.10579700	-2.39837900
H	3.01233500	1.54806900	-3.25834100
H	3.08928700	3.14872300	-2.46759300
H	4.49955600	2.05533500	-2.40089600
C	2.54342500	-3.02436700	2.59060800
H	2.08791200	-3.71173100	1.86864000
H	3.58923300	-3.30831400	2.76562600
H	1.99857900	-3.06411700	3.53530800
H	4.80425700	-2.48507900	-1.67397700
O	2.86759400	1.62199900	-1.17402400
O	2.43782000	-1.67595200	2.14441200

C	-2.09723100	0.98799600	1.30134800
C	-3.37441800	0.78998900	0.45404300
C	-2.09035200	0.03718500	2.51893000
H	-2.12341900	2.02064100	1.67677300
C	-4.63549200	0.96621000	1.31946200
H	-3.37716200	-0.20895500	0.00901400
H	-3.40093000	1.50603200	-0.37488900
C	-3.36367000	0.20062000	3.36696800
H	-2.02340600	-0.99629000	2.16064500
H	-1.20409900	0.21702300	3.13777600
C	-4.63317800	0.01504500	2.52341900
H	-5.52602300	0.79731800	0.70113300
H	-4.69391200	2.00586100	1.67666000
H	-3.34495000	-0.51742400	4.19672400
H	-3.37276400	1.20283300	3.82193400
H	-5.52698000	0.17781200	3.13922800
H	-4.68067300	-1.02166900	2.16144400
C	-0.48547000	2.18681000	-0.98473300
C	-1.07277000	1.73426500	-2.33809300
C	-1.07518300	3.54059300	-0.54068800
H	0.59434000	2.32273100	-1.13157400
C	-0.88011200	2.81754900	-3.41368200
H	-2.14333500	1.51394000	-2.23587100
H	-0.58941900	0.80261200	-2.65251400
C	-0.87472300	4.61248300	-1.62806700
H	-2.15085100	3.43609700	-0.34471100

H	-0.60812400	3.87385400	0.39290400
C	-1.46225100	4.16884400	-2.97527200
H	-1.33905500	2.48952000	-4.35493500
H	0.19508500	2.93640900	-3.61558600
H	-1.32949500	5.55720400	-1.30338400
H	0.20139000	4.80760400	-1.74643700
H	-1.27507300	4.93179500	-3.74162000
H	-2.55494100	4.08028200	-2.88251300
C	-1.59879100	-1.98401800	-0.83196400
C	-2.30369300	-1.75699000	-2.01647800
C	-2.14396200	-2.81726700	0.15022900
C	-3.56930800	-2.32810700	-2.19680700
H	-1.87522000	-1.15012800	-2.80643300
C	-3.41036400	-3.38397700	-0.03560000
H	-1.58384000	-3.04286400	1.05243600
C	-4.13083900	-3.13458100	-1.20549400
H	-4.11086200	-2.14348500	-3.12193300
H	-3.82418800	-4.03161900	0.73416600
Cl	1.03346600	-3.22672600	-1.54753200
H	-5.11305600	-3.57712700	-1.34947700

E = -2322.26575318

7

C	2.17425700	-1.21355800	-0.57211900

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C	4.45466700	0.42495600	-0.46967700
C	3.95603100	-0.11248200	0.70921300
C	2.81831200	-0.93228900	0.66300900
C	1.26316900	-2.40426000	-0.71582700
C	-0.13546000	-2.37640600	-0.55314800
C	-0.87272600	-3.55259300	-0.77680200
C	-0.24681300	-4.74312300	-1.13954700
C	1.14056200	-4.77596200	-1.27919800
C	1.88027700	-3.61540400	-1.07069900
H	4.26353600	0.62557800	-2.60184000
H	4.43092000	0.11892400	1.65330600
H	-1.95290900	-3.54449500	-0.67560600
H	-0.84016800	-5.63729000	-1.31047800
H	1.64420900	-5.69805200	-1.55659600
H	2.95957300	-3.63407800	-1.19364800
P	-0.92841300	-0.81204200	0.02736100
Pd	0.63628200	0.88536800	-0.18521000
C	2.69997400	-1.06915200	3.04321200
H	2.55898300	0.01492800	3.10337800
H	2.05159000	-1.57793100	3.75902900
H	3.74261800	-1.33752500	3.25520400
C	2.54166500	-0.41312700	-4.12740100
H	2.45990200	0.68047400	-4.10060700
H	3.57820700	-0.69626700	-4.35149700

H	1.88372300	-0.80973800	-4.90240800
H	5.33024200	1.06675700	-0.42889500
O	2.29814500	-1.54983400	1.75570500
O	2.09624500	-0.99378500	-2.90958400
C	-2.60960700	-0.82102100	-0.80594900
C	-3.56796600	0.27198400	-0.28277000
C	-2.45795400	-0.73353800	-2.34095900
H	-3.06162600	-1.79322100	-0.56301100
C	-4.93021100	0.19359000	-0.99432700
H	-3.12628400	1.25920100	-0.44824700
H	-3.71454300	0.16945100	0.79808300
C	-3.82443800	-0.79479300	-3.04414900
H	-1.96246500	0.21124500	-2.59480900
H	-1.81133400	-1.53909000	-2.70733700
C	-4.77908500	0.28657200	-2.51889800
H	-5.57997700	0.99710100	-0.62544300
H	-5.42602000	-0.75442400	-0.73511700
H	-3.68400100	-0.68958400	-4.12762700
H	-4.27358100	-1.78657400	-2.88319700
H	-5.75890700	0.19902000	-3.00566100
H	-4.38276400	1.27813600	-2.78032900
C	-1.19015600	-1.18767800	1.86479600
C	-1.31086900	0.08424000	2.73161700
C	-2.31421400	-2.19934300	2.16985900
H	-0.23054000	-1.65849000	2.11931500
C	-1.39332300	-0.26981000	4.22685100

H	-2.20318700	0.65768800	2.44673900
H	-0.44524700	0.73019300	2.55292600
C	-2.37518000	-2.53154300	3.67201000
H	-3.28414700	-1.78546300	1.86216800
H	-2.16359400	-3.12335200	1.60031500
C	-2.52252000	-1.26513000	4.52553500
H	-1.52344000	0.64825600	4.81338200
H	-0.43516200	-0.70742200	4.54477900
H	-3.20603100	-3.22368900	3.86113800
H	-1.45524200	-3.06070400	3.96115500
H	-2.53249800	-1.52471800	5.59194200
H	-3.49252000	-0.79244900	4.30954100
C	-0.69592400	2.37405700	-0.37787200
C	-1.13697100	3.12108700	0.71847400
C	-1.07872100	2.75504500	-1.66980000
C	-1.98562200	4.21749300	0.52282100
H	-0.80013500	2.87261200	1.71888700
C	-1.92446600	3.85471300	-1.85971900
H	-0.71423500	2.20784300	-2.53470800
C	-2.38906500	4.58307900	-0.76288500
H	-2.32368700	4.79112400	1.38329900
H	-2.21359100	4.14107400	-2.86882300
H	-3.04835100	5.43482000	-0.90991500
O	2.06015800	2.43137800	-0.06977500
C	2.33084400	2.72022200	1.16413900
C	3.25291100	3.92671900	1.33008300

H	3.58701600	4.01358300	2.36657100
H	4.11639900	3.84650800	0.66162500
H	2.71064100	4.83718400	1.04959500
O	1.90046600	2.11567300	2.16110600

E = -2090.52988631

8

C	3.03528100	-0.20168800	-0.88537100
C	3.92680100	0.80852700	-0.47355300
C	5.05085100	0.51004600	0.30982500
C	5.31219200	-0.81756000	0.64056000
C	4.48306000	-1.84875400	0.20579700
C	3.35462800	-1.53712400	-0.56642400
C	1.90738100	0.09434300	-1.83252000
C	0.55100900	0.34688500	-1.50951600
C	-0.35376600	0.55341400	-2.57477500
C	0.04202300	0.54018900	-3.90783700
C	1.37892000	0.30200600	-4.22017400
C	2.28393300	0.07896700	-3.18935300
H	5.72396800	1.29096100	0.64139100
H	4.71969300	-2.87506800	0.45731300
H	-1.40463400	0.71677800	-2.34744700
H	-0.69315500	0.70534400	-4.69044600
H	1.71369900	0.28049000	-5.25375600

H	3.32558400	-0.12076700	-3.42402700
P	-0.32113700	0.53864100	0.13719900
Pd	-2.47254200	-0.31238500	-0.06484700
C	2.75843300	-3.84695200	-0.79939000
H	2.75372200	-4.05423700	0.27789400
H	1.94120900	-4.39474100	-1.26896300
H	3.71718300	-4.16456800	-1.22918600
C	4.49975000	3.13387000	-0.55565200
H	4.55419800	3.27697900	0.53130900
H	5.51018600	2.96606800	-0.94970300
H	4.07528600	4.02773500	-1.01582900
H	6.18606900	-1.05413600	1.24150500
O	2.50141700	-2.47500600	-1.06716400
O	3.62565700	2.07036000	-0.90103500
C	0.79942100	0.03814300	1.56559300
C	0.41183400	0.72643700	2.89440000
C	0.81822000	-1.49292200	1.76346300
H	1.80620200	0.37416900	1.29089600
C	1.34744600	0.30019500	4.04097000
H	-0.62578700	0.47179400	3.15272600
H	0.45855200	1.81343700	2.79667500
C	1.76965500	-1.90680800	2.89852400
H	-0.19524200	-1.82710700	2.00897700
H	1.08580700	-2.00013600	0.83429500
C	1.39499800	-1.22157700	4.21875500
H	1.02456600	0.78768000	4.96995700

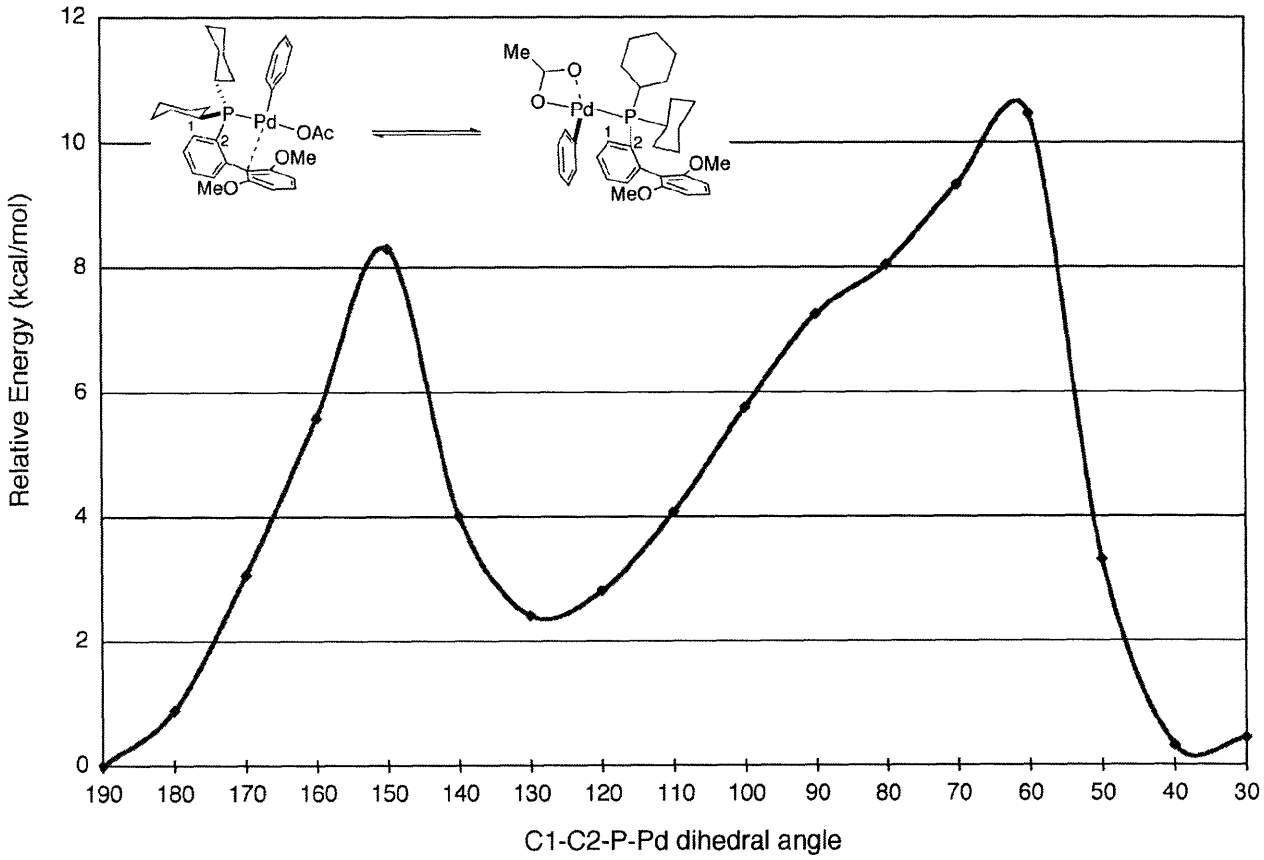
H	2.36136400	0.67129600	3.82921000
H	1.73931700	-2.99823200	3.01465800
H	2.80303300	-1.64664600	2.62991800
H	2.10735800	-1.48972000	5.00966100
H	0.40883600	-1.58030400	4.54810300
C	-0.57169900	2.41770700	0.17136700
C	-1.58996300	2.93342600	1.21473400
C	0.72859700	3.24456600	0.20179600
H	-1.03793600	2.57108700	-0.81265600
C	-1.88138600	4.42610200	0.97538800
H	-1.19671200	2.81189100	2.22974200
H	-2.52039400	2.36544300	1.14748300
C	0.42891500	4.74019200	-0.01230800
H	1.22862300	3.11609500	1.17265300
H	1.42880100	2.89236900	-0.56003500
C	-0.59948100	5.27106700	0.99607000
H	-2.58732400	4.78571200	1.73495800
H	-2.38369600	4.54054300	0.00437600
H	1.36199300	5.31621100	0.05230200
H	0.04392600	4.88366900	-1.03255700
H	-0.83034100	6.32324100	0.78468400
H	-0.16327700	5.24343200	2.00614500
C	-1.92828100	-2.23080500	0.00427400
C	-2.48263500	-3.02431400	1.01889900
C	-1.22593500	-2.84717900	-1.03821800
C	-2.33367700	-4.41475800	0.99037100

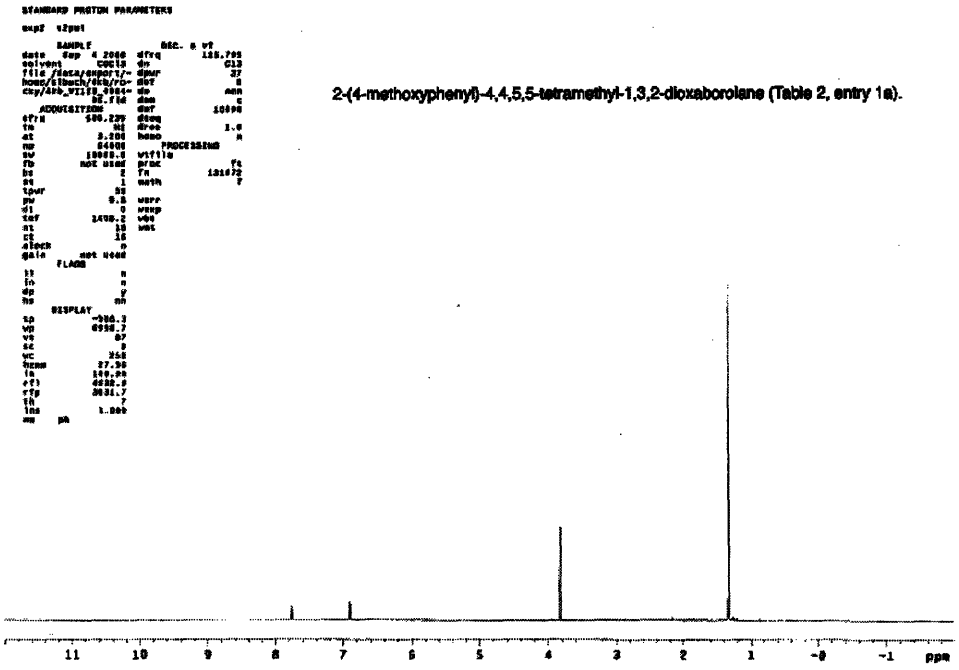
H	-3.04974000	-2.56587600	1.82510200
C	-1.09518300	-4.24164500	-1.07087300
H	-0.78421800	-2.25521900	-1.83440200
C	-1.64016800	-5.02879300	-0.05530200
H	-2.77174300	-5.01764900	1.78294900
H	-0.57236500	-4.71003100	-1.90292700
H	-1.53520000	-6.11059600	-0.08233600
O	-4.62089900	-0.61162700	-0.32421000
C	-4.81618900	0.63680700	-0.48539500
C	-6.22441500	1.14881100	-0.69289700
H	-6.62363900	1.49916000	0.26670200
H	-6.22034100	1.99722300	-1.38266900
H	-6.87248400	0.35384300	-1.06852200
O	-3.84372100	1.45721200	-0.44615800

E = -2090.52951912

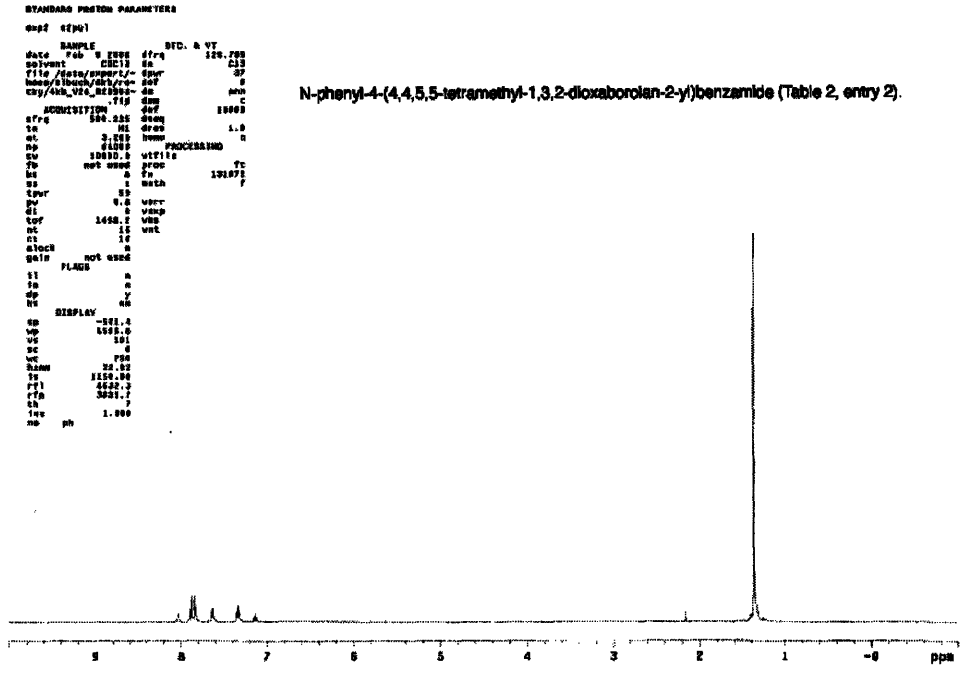
Potential Energy Surface Scan

A PES scan was conducted to approximate the activation energy required for rotation from **7** to **8**. 17 structures were optimized ranging from a C1-C2-P-Pd dihedral angle of -170° to 30° with a step size of 10°. A maximum of 30 optimization cycles was imposed on each structure. Gaussian 03[14] was used in conjunction with the B3LYP functional[15] with the 6-31G(d) basis set for all non-metal atoms and the LANL2DZ+ECP[16] basis set was employed for Pd.

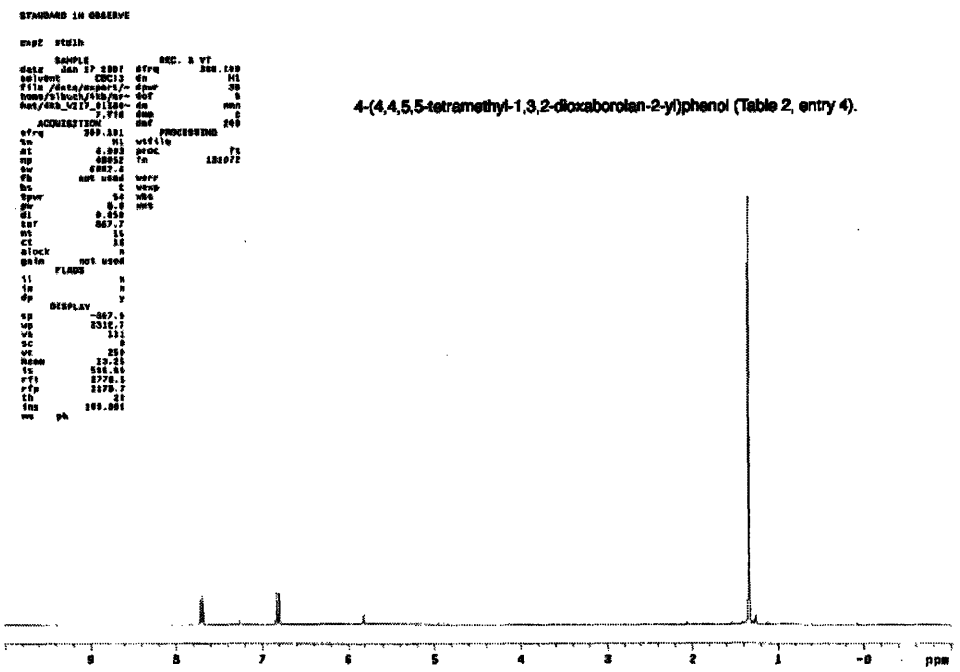

Relative Energy (kcal/mol)
12
10
8
6
4
2
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
C1-C2-P-Pd dihedral angle
P
Pd
OAc
OMe
MeO
Me
O
O
Pd
P
OMe
MeO



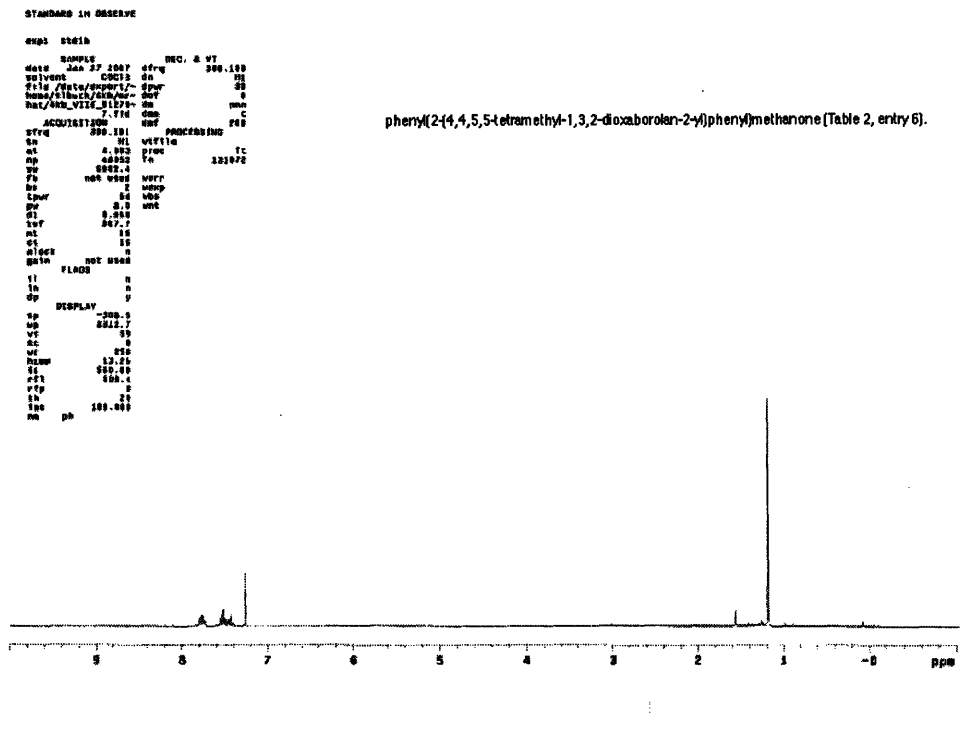
2-(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 2, entry 1a).



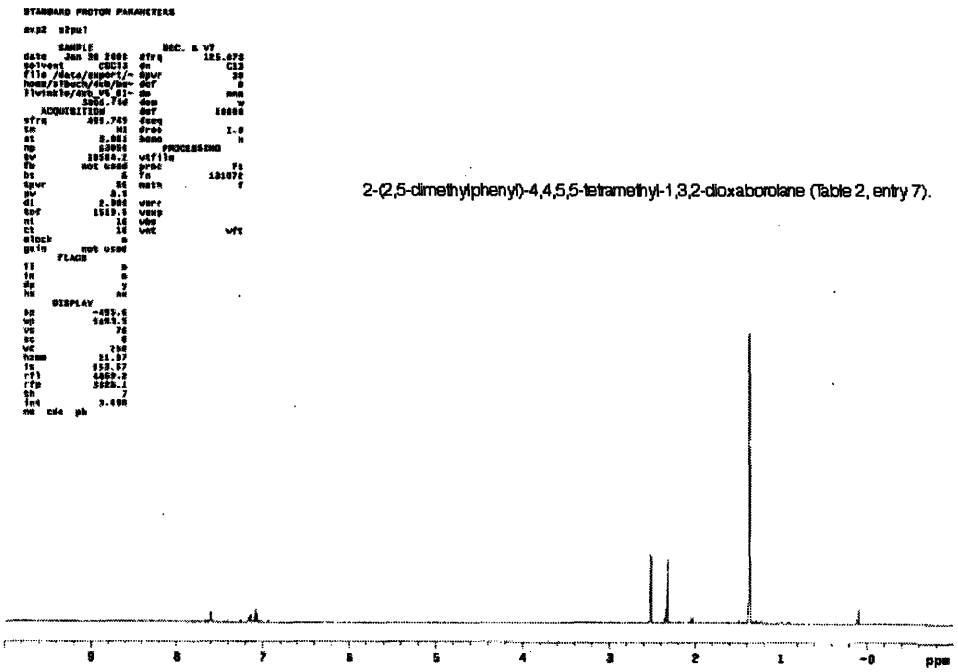
N-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (Table 2, entry 2).



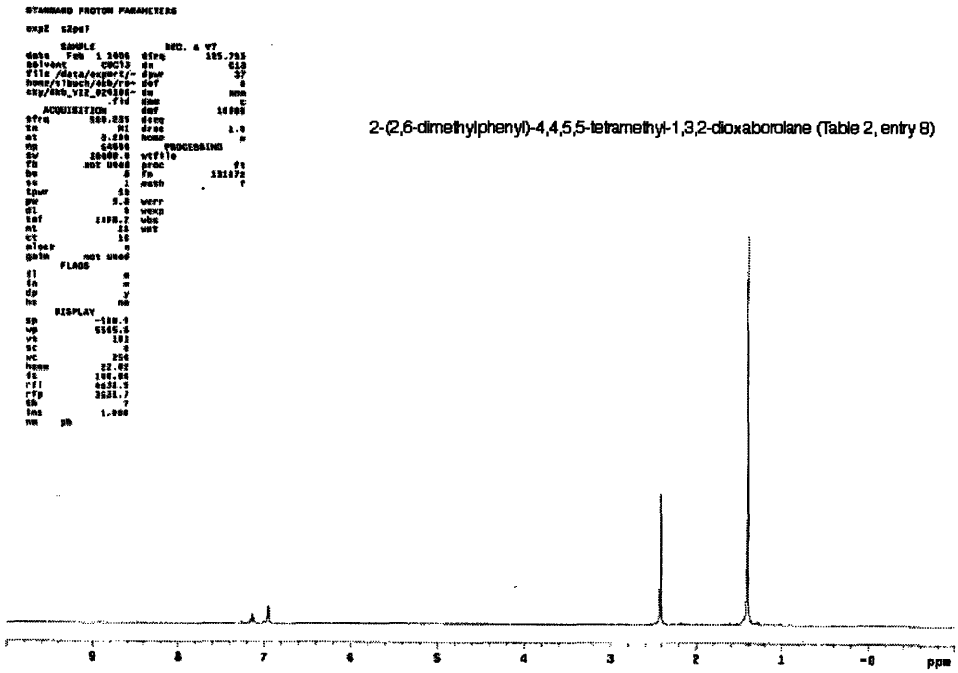
4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (Table 2, entry 4).



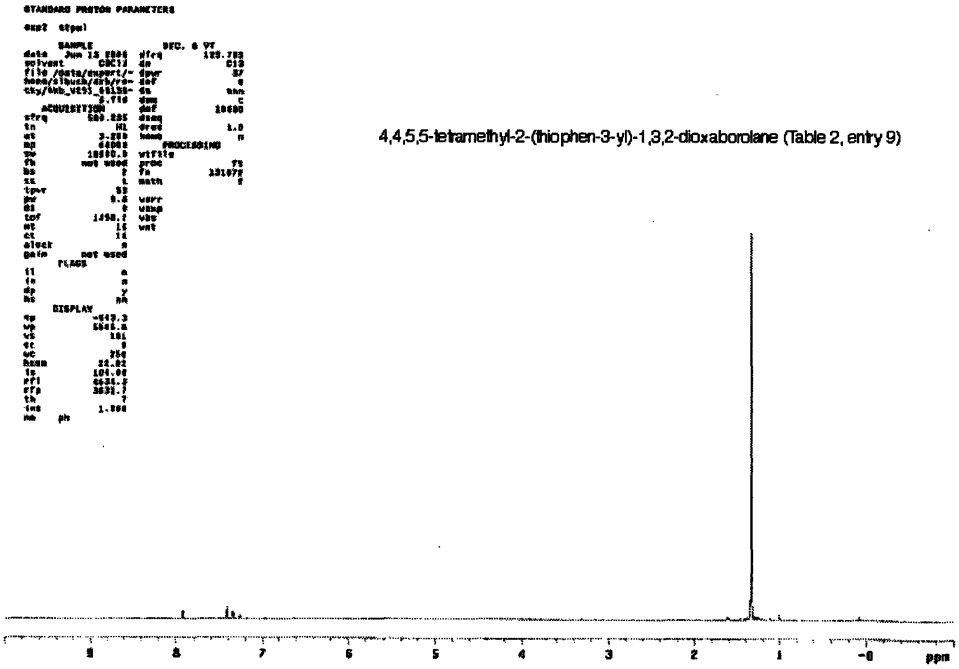
phenyl(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanone (Table 2, entry 6).



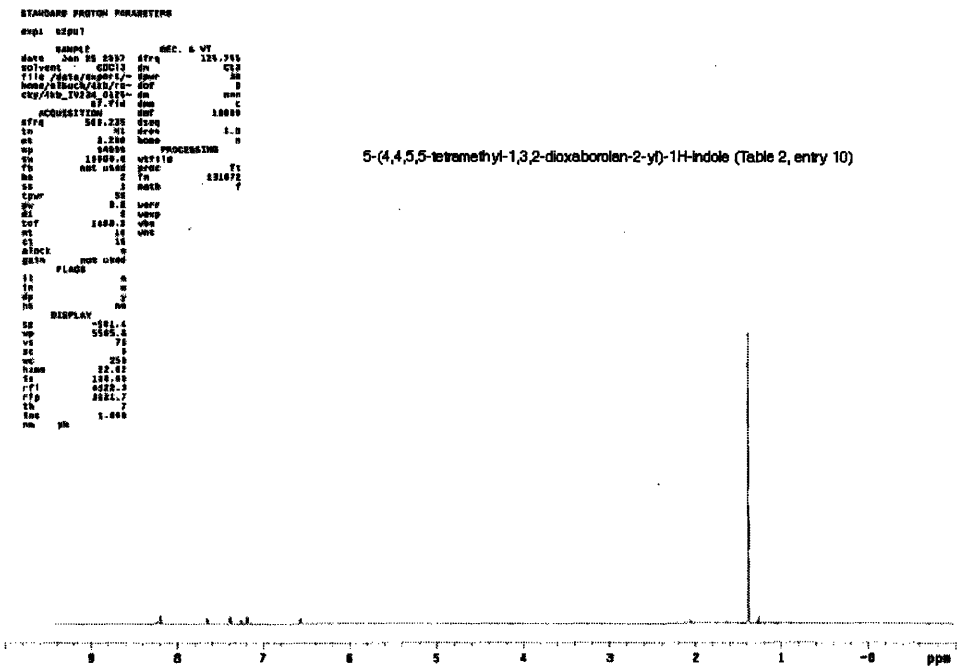
2-(2,5-dimethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 2, entry 7).



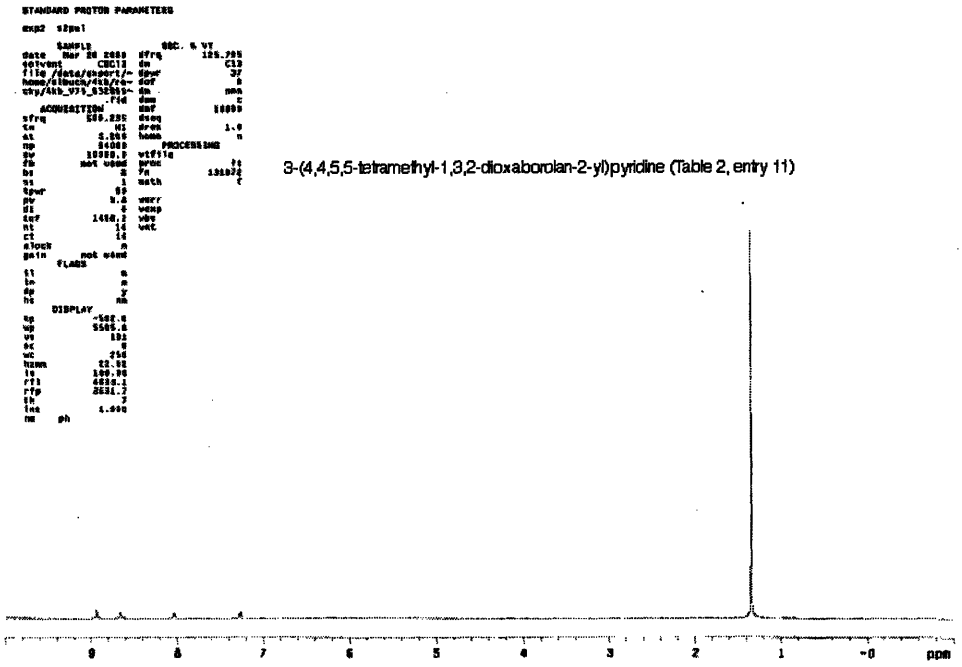
2-(2,6-dimethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 2, entry 8)



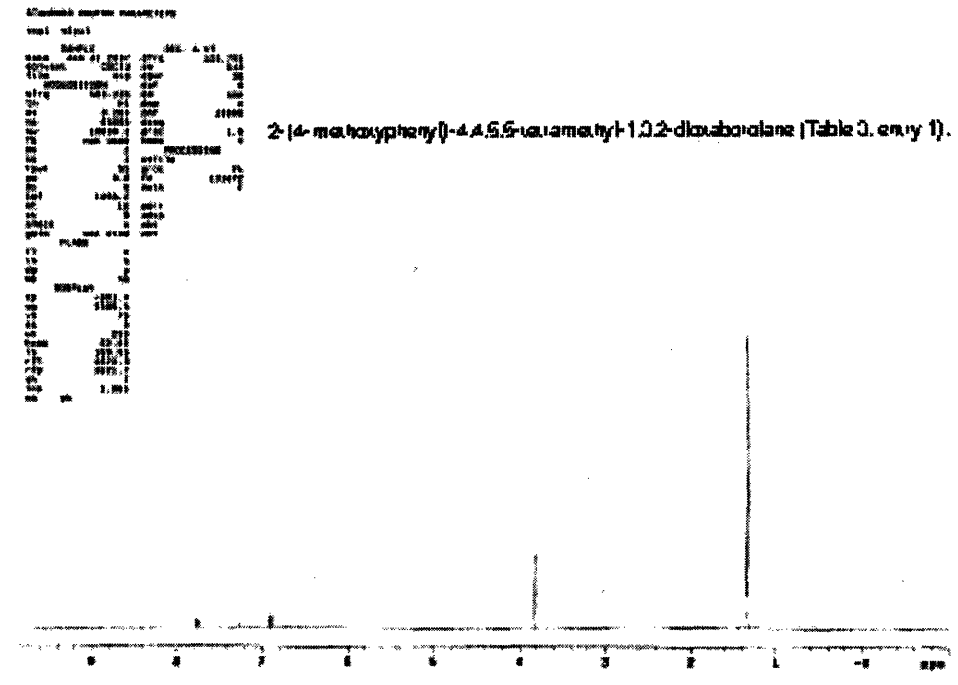
4,4,5,5-tetramethyl-2-(thiophen-3-yl)-1,3,2-dioxaborolane (Table 2, entry 9)



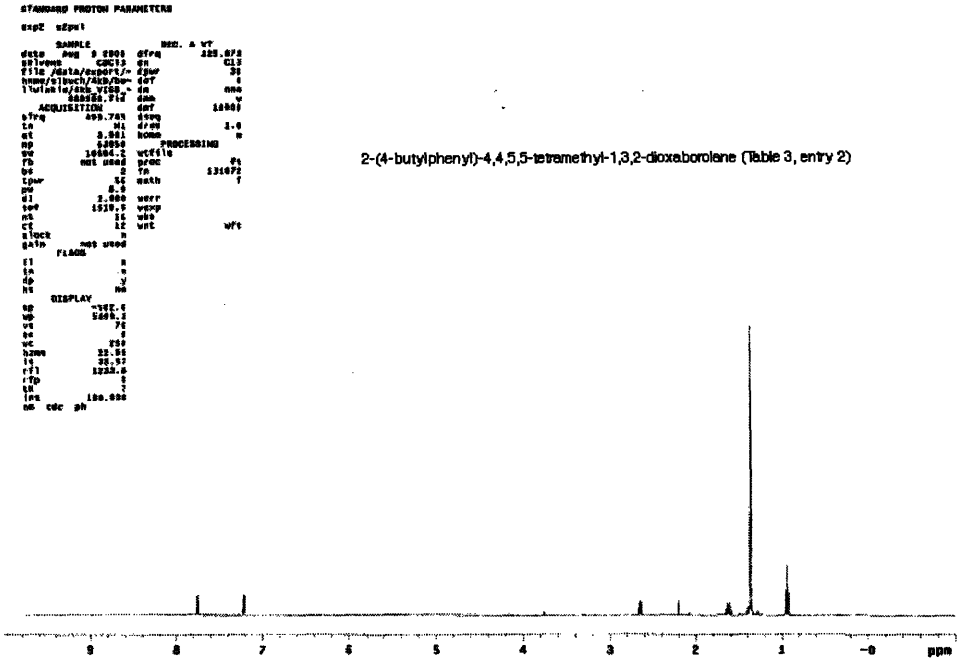
5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (Table 2, entry 10)



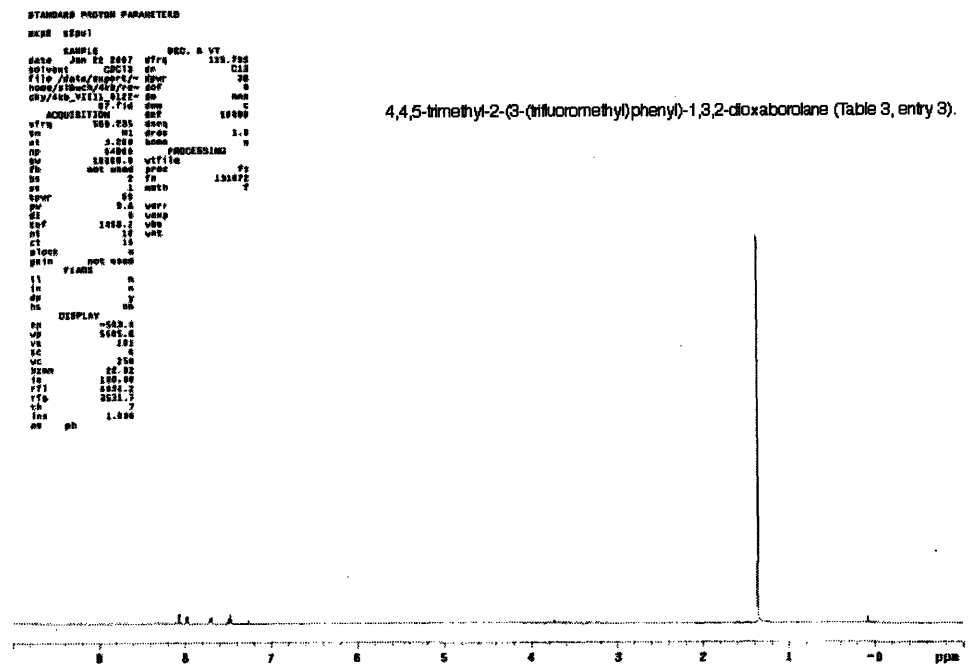
3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (Table 2, entry 11)



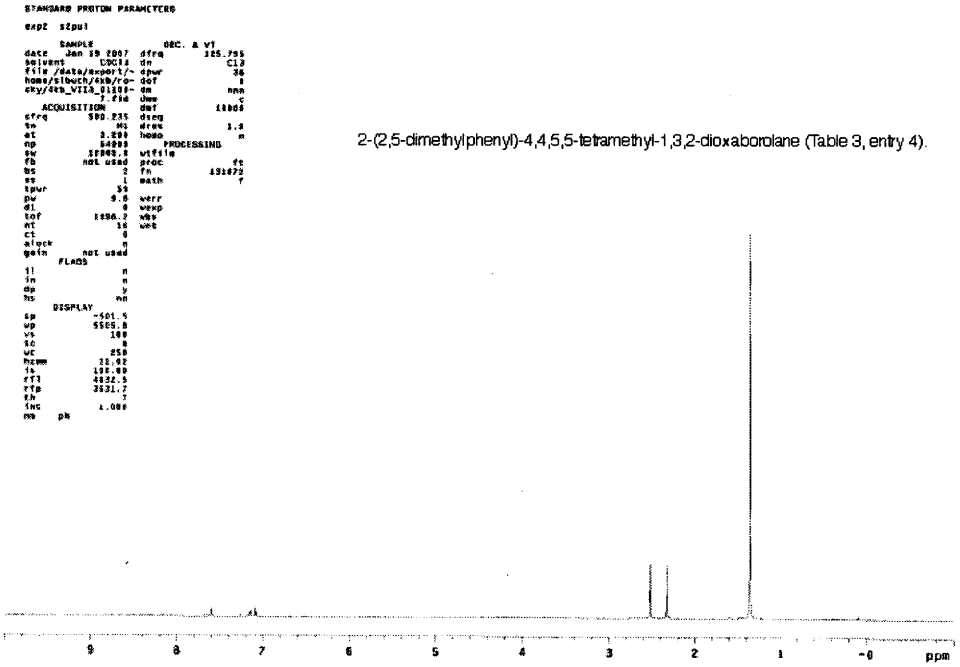
2-(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 3, entry 1).



2-(4-butylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 3, entry 2)



4,4,5-trimethyl-2-(3-(trifluoromethyl)phenyl)-1,3,2-dioxaborolane (Table 3, entry 3).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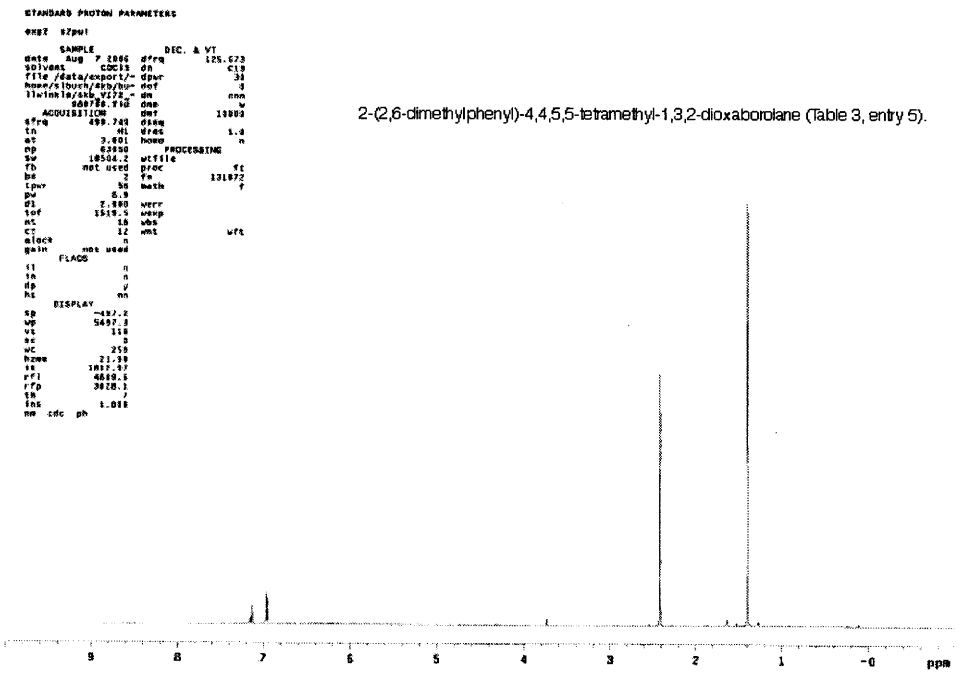
sfrq 599.735
tn H1
at 3.280
np 64000
sw 19969.8
fb not used
bs 2
ss 1
tpwr 55
pw 9.6
pl 0
tof 1496.2
nt 16
ct 0
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -501.5
wp 5505.8
vs 160
sc 0
wc 250
hzmm 18.62
is 199.89
rfl 4852.5
rfp 3831.7
th 7
ins 1.000
ns 8 ph
DEC. & VT
dfrq 125.755
dn C13
dpwr 36
dof 0
dm nnn
dmm c
dmf 18868
dseq
dres 1.8
homo n
PROCESSING
wtfile
proc ft
fn 131072
math f
werr
wexp
wbs
wnt
2-(2,5-dimethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 3, entry 4).
9
8
7
6
5
4
3
2
1
-0
ppm


STANDARD PROTON PARAMETERS
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date Aug 7 2006
solvent CDCl3
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llwinkle/skb_VI72.-
608758.fid
ACQUISITION
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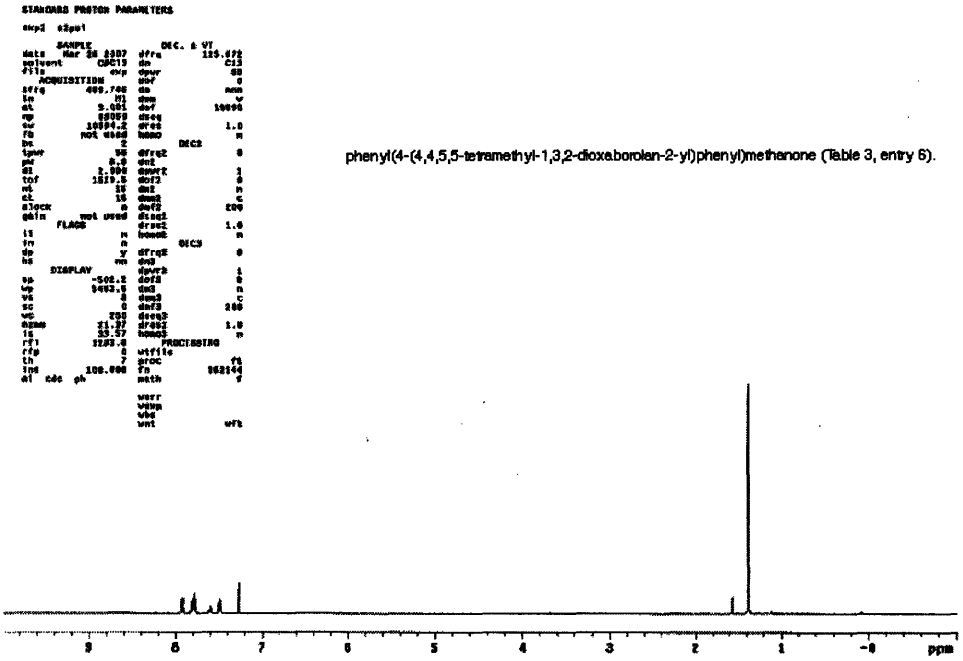
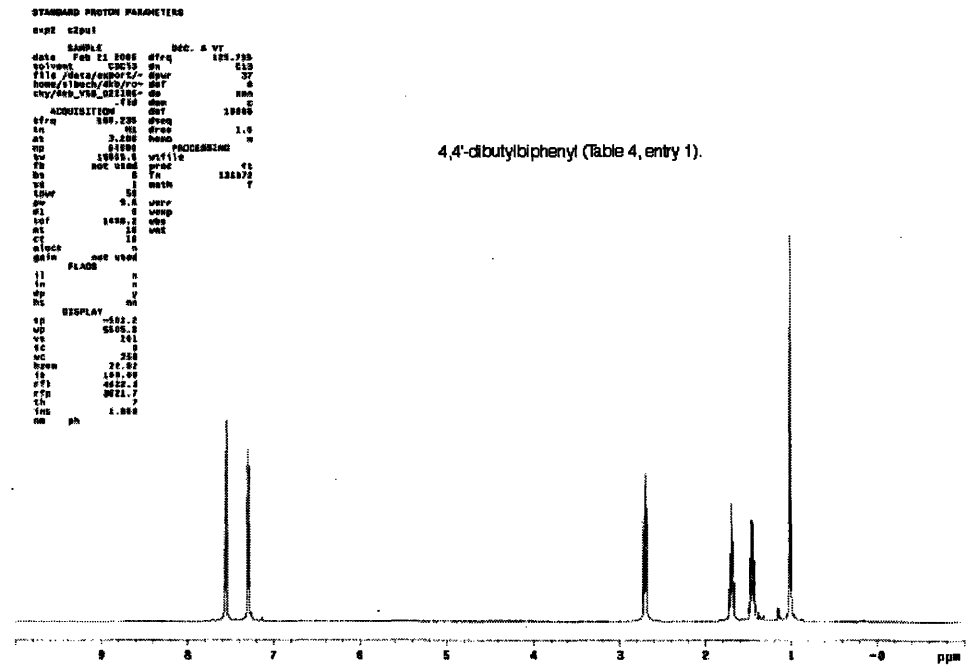
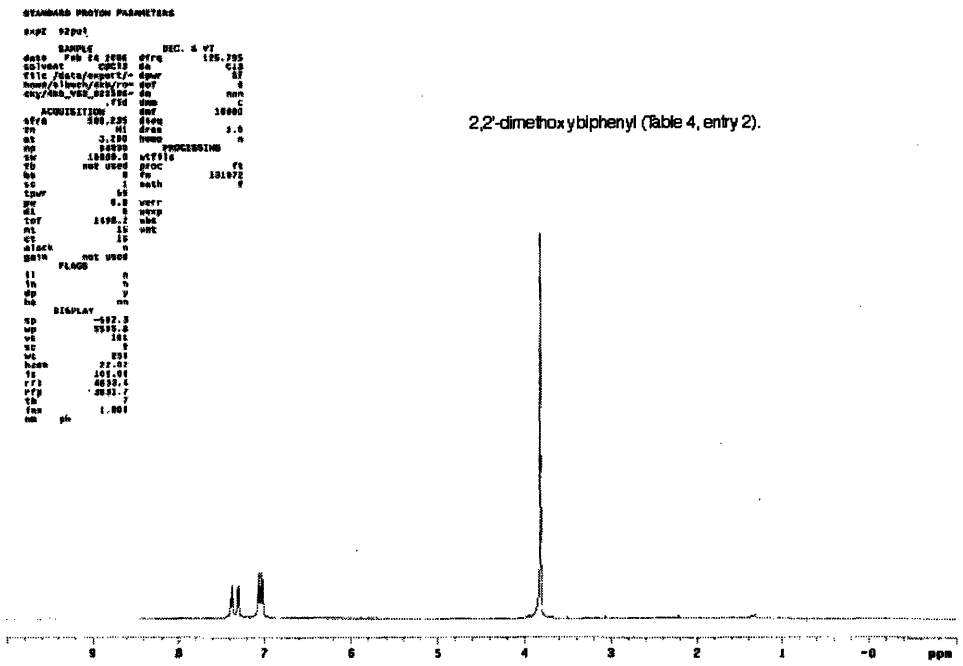
tn H1
at 3.601
np 63890
sw 18504.2
fb not used
bs 2
tpwr 55
pw 8.9
pl 2.980
tof 1519.5
nt 16
ct 12
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -497.2
wp 5497.3
vs 110
sc 0
wc 250
hzmm 21.99
is 1817.87
rfl 4819.5
rfp 3828.1
th 7
ins 1.000
ns 16 cdc ph
DEC. & VT
dfrq 125.673
dn C13
dpwr 31
dof 0
dm nnn
dmm w
dmf 13803
dseq
dres 1.8
homo n
PROCESSING
wtfile
proc ft
fn 131072
math f
werr
wexp
wbs
wnt wft
2-(2,6-dimethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 3, entry 5).
9
8
7
6
5
4
3
2
1
-0
ppm



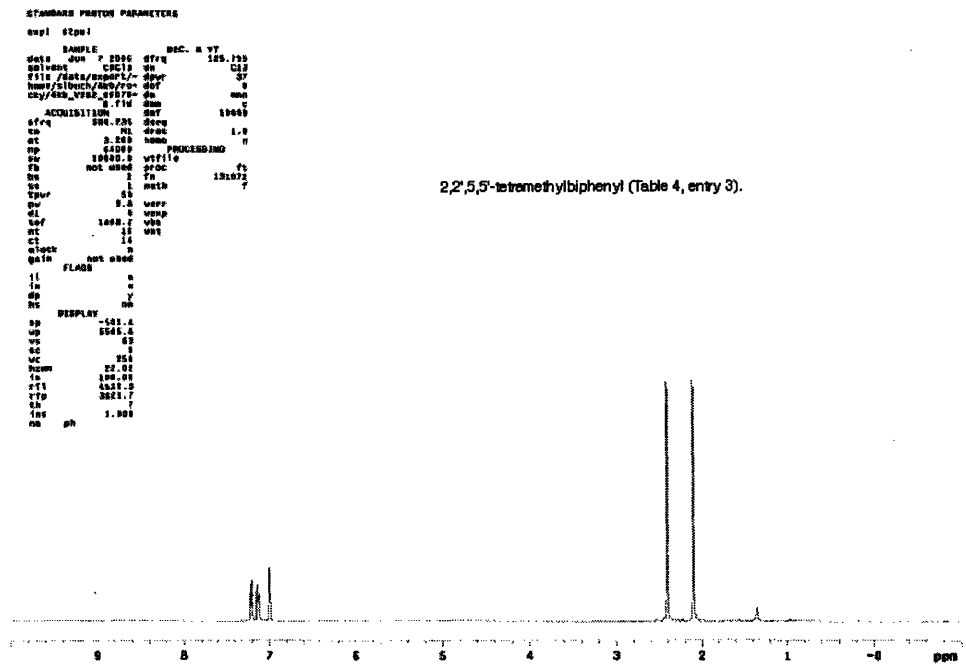
phenyl(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanone (Table 3, entry 6).



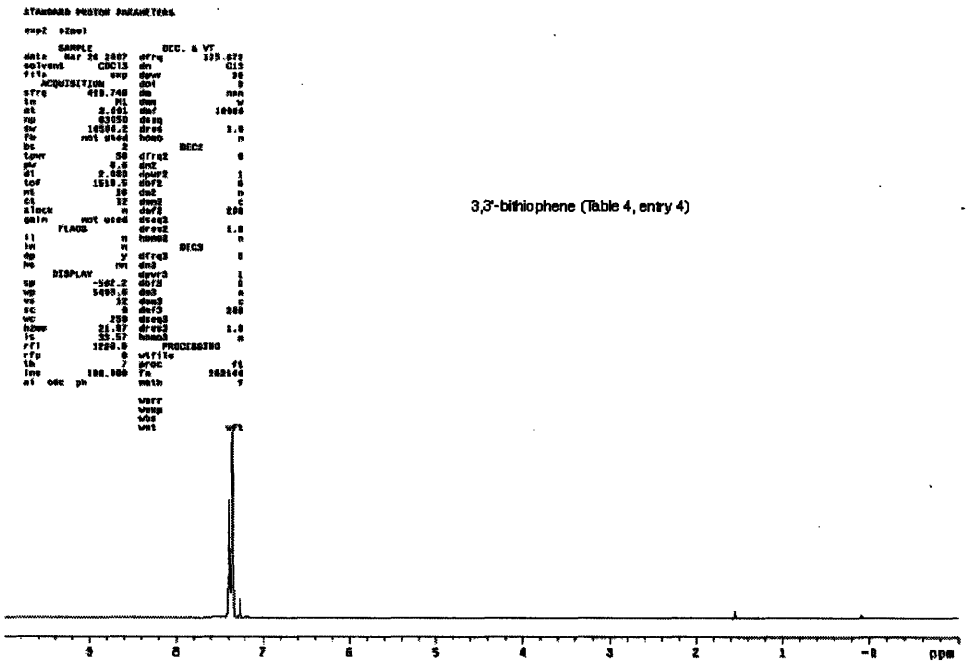
4,4'-dibutylbiphenyl (Table 4, entry 1).



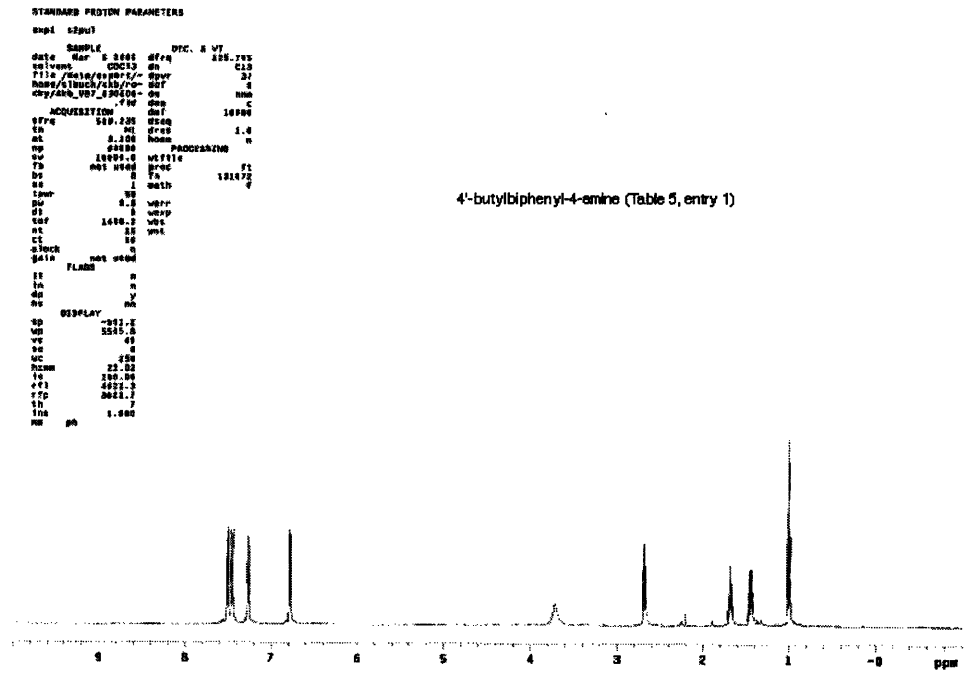
2,2'-dimethoxybiphenyl (Table 4, entry 2).



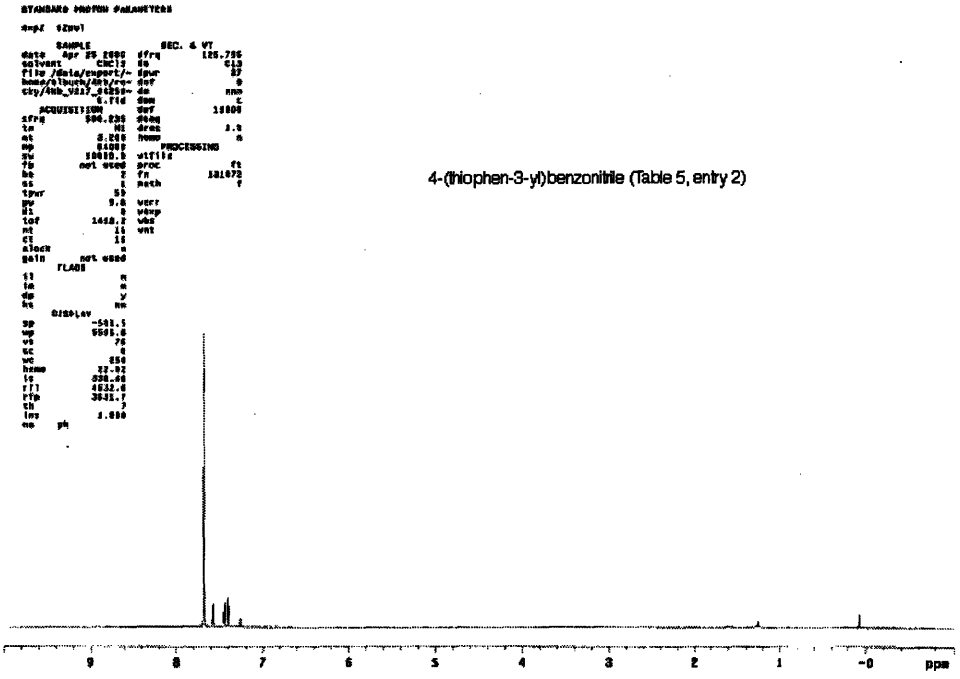
2,2',5,5'-tetramethylbiphenyl (Table 4, entry 3).



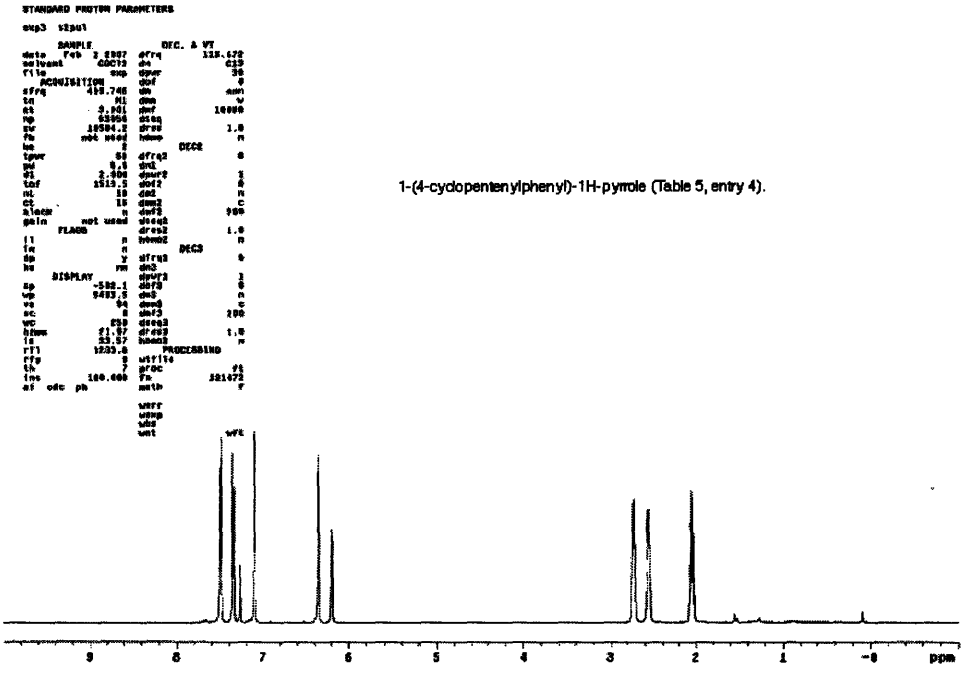
3,3'-bithiophene (Table 4, entry 4)



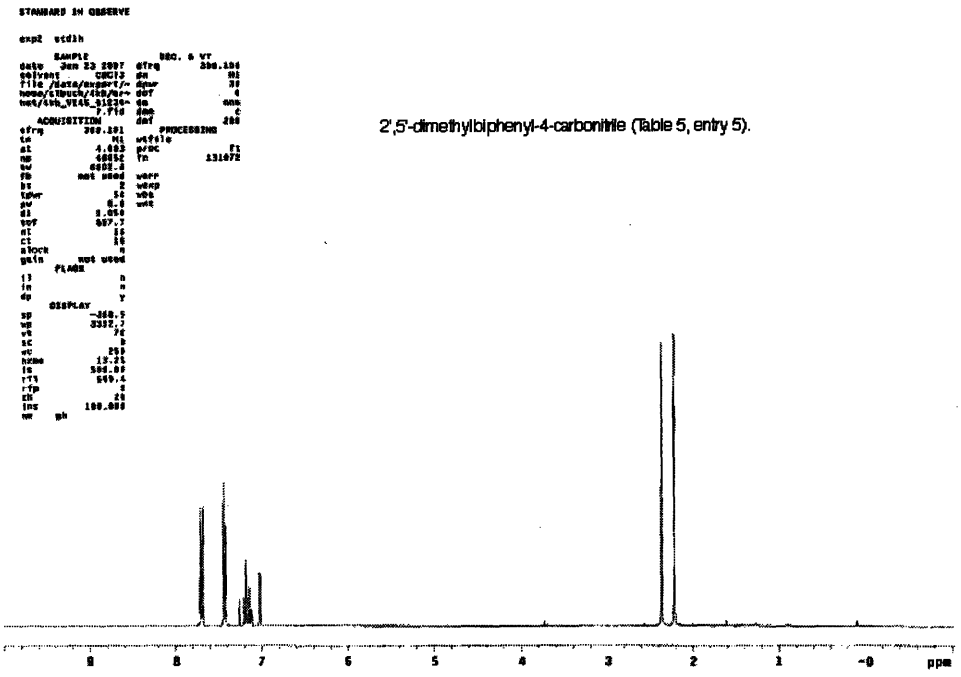
4'-butylbiphenyl-4-amine (Table 5, entry 1)



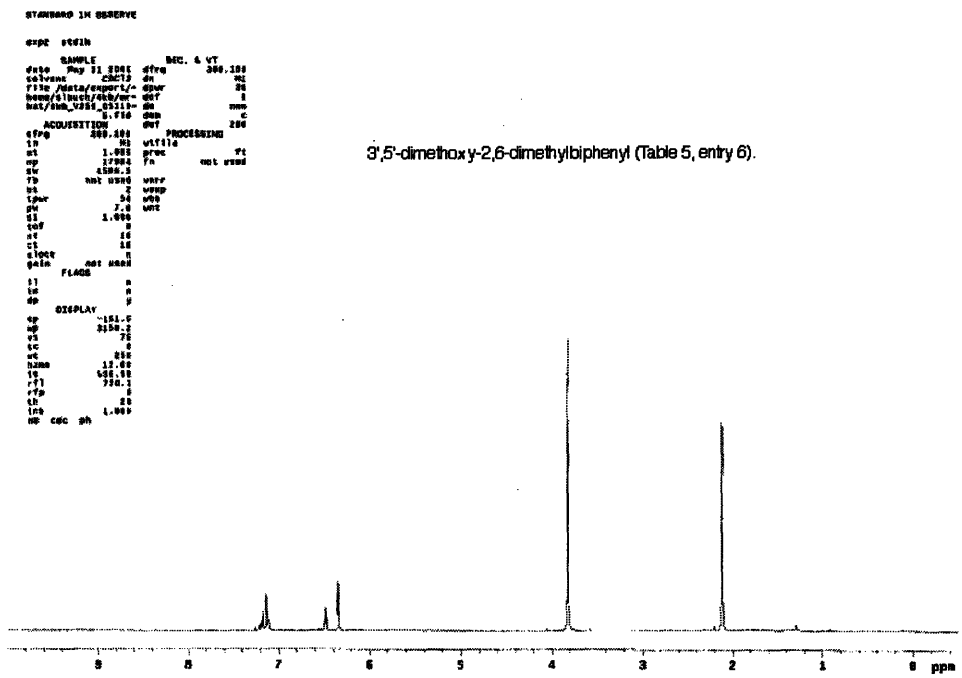
4-(thiophen-3-yl)benzonitrile (Table 5, entry 2)



1-(4-cyclopentenylphenyl)-1H-pyrrole (Table 5, entry 4).



2',5'-dimethylbiphenyl-4-carbonitrile (Table 5, entry 5).



3',5'-dimethoxy-2,6-dimethylbiphenyl (Table 5, entry 6).

3.5 References

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(7) Although H_2O is necessary for the borylation of 2-chloro-*m*-xylene (Table 2, Entry 8) at 110 °C to proceed to completion, an increased amount of reduced starting material is observed under these conditions. When the reaction of this substrate is conducted under the standard room temperature conditions (Table 3, Entry 5), catalyst decomposition (palladium black) is not observed, and a higher yield of the desired product is obtained.

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(9) For a previous method for the preparation of symmetrical biaryls via one-pot borylation/Suzuki-Miyaura reaction, see: Nising, C. F.; Schmid, U. K.; Nieger, M.; Bräse, S. *J. Org. Chem.* **2004**, *69*, 6830.

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(11) Gaussian 03, Revision D.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A.; Gaussian, Inc., Wallingford CT, 2004.

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Chapter 4.

Synthesis of Aryl Boronate Esters from Aryl Halides with Pinacol Borane.

4.1 Introduction

The utility of aryl boronic acids and esters throughout organic synthesis is seen by their use as key intermediates in the preparation of a wide range of synthetic targets.[1] Despite their versatility, standard methods for the preparation of these compounds can be harsh and, hence, be incompatible with a variety of functional groups.[2] However, various techniques have recently emerged that provide access to aryl boronate esters under milder reaction conditions.[3] In particular, palladium-based systems for the conversion of aryl halides to the corresponding carbon-boron bonds have proved to be a powerful synthetic tool. Recently, we reported a highly active catalyst for transforming aryl chlorides into aryl pinacol-derived boronate esters.[4] However, this system required the use of an expensive boron source, bis(pinacolato)diboron ($1.59/mmol from Aldrich).[5] In addition, the reactions of sterically hindered aryl chlorides were less efficient as they required higher quantities of Pd as well as an increase in the number of equivalents of the expensive boron reagent.

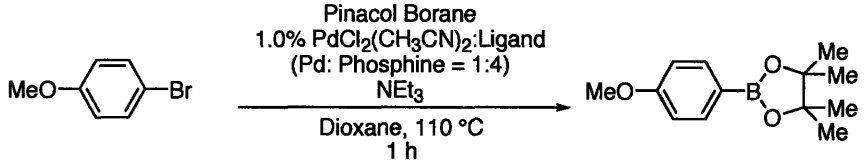
In order to address these issues, we sought to develop a system where pinacol borane ($0.48/mmol from Aldrich), a cheaper and more atom-economical boron source, could be employed in the borylation of aryl halides and concurrently to produce a method applicable to sterically hindered substrates. Although several systems have been developed for the borylation of aryl halides with pinacol borane, these methods have several limitations.[6] In general, aryl iodides and bromides are necessary, while the cheaper and more readily available aryl chlorides are unsuitable substrates.[7] We are aware of only one report in which aryl chlorides are efficiently transformed to the corresponding boronate esters when using pinacol borane as the boron source.[8] However, this method had a limited substrate scope as only *para*-substituted electron-rich aryl chlorides were efficiently converted to the desired products. In addition, all Pd-catalyzed borylation methods employing pinacol borane rely upon high quantities of palladium catalyst (>3.0 mol%) in order to efficiently process the aryl halides. Herein, we report a highly active catalyst system based upon $PdCl_2(CH_3CN)_2$ and SPhos (**1**) as the supporting ligand for the borylation of aryl and heteroaryl iodides and bromides with pinacol borane. This method not only allows

for the use of lower amounts of Pd catalyst with shorter reaction times but also proved general for the borylation of a range of aryl, heteroaryl and vinyl chlorides.

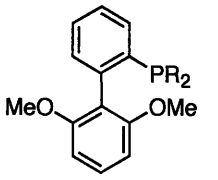
4.2 Results and Discussion

We began our work by examining the optimization of the reaction shown in Table 1. We found that a variety of dialkylbiarylphosphine ligands could be employed to afford highly active catalysts. In general, dicyclohexylphosphino biphenyl ligands resulted in higher conversion and yield for this process as compared to the corresponding diphenyl- or di-*tert*-butylphosphino compounds. For example, a catalyst based upon **8** allowed for an 86% conversion and yield for the borylation of 4-bromoanisole

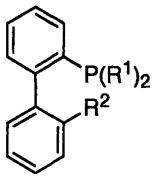
Table 1. Reaction of 4-Bromoanisole with Pinacol Borane.



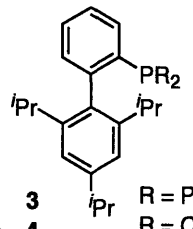
Entry	Ligand	GC Yield (%)	Conversion (%)
1	***1***	*99*	*100*
2	**2**	<10	28
3	**3**	94	100
4	**4**	81	87
5	**5**	<10	15
6	**6**	84	100
7	**7**	46	53
8	**8**	86	86
9	**9**	<10	14
10	**10**	<10	16



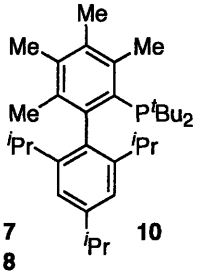
R = Cy **1**
R = ^{t}Bu **2**



R^1 = Cy, R^2 = H **3**
R^1 = Cy, R^2 = NMe_2 **4**
R^1 = Cy, R^2 = ^{i}Pr **5**
R^1 = ^{t}Bu, R^2 = H **6**



R = Ph **7**
R = Cy **8**
R = ^{t}Bu **9**



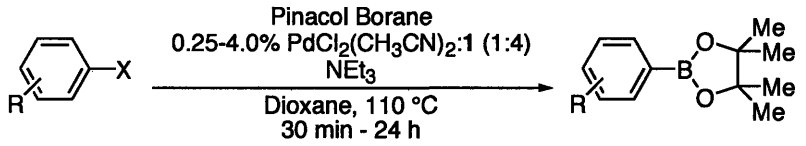
10

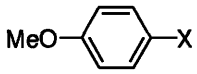
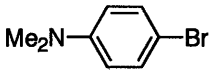
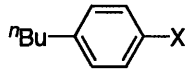
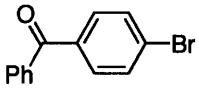
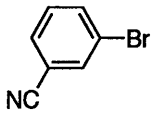
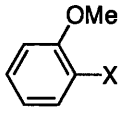
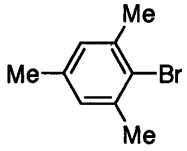
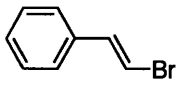
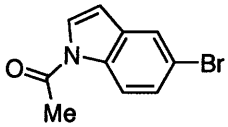
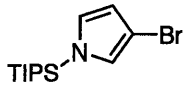
while **7** or **9** resulted in only 53% and 14% conversion of the aryl halide, respectively. In addition, highly active systems were observed when **3** (Table 1, Entry 3) or **6** (Table 1, Entry 6) was employed. The catalyst system derived from $PdCl_2(CH_3CN)_2$ and **1**, however, produced a near quantitative yield of the aryl boronate ester (Table 1, Entry 1).

Initially, we examined the borylation of aryl iodides. Despite the fact that aryl iodides are more reactive than the corresponding aryl bromides or chlorides, there are no methods, to our knowledge, for their borylation with low catalyst loadings (i.e., <3.0 mol%) or reaction times under one hour. The $PdCl_2(CH_3CN)_2$/**1** combination proved to be highly active in the borylation of 4-iodoanisole producing the desired aryl boronate ester in 94% yield in only 30 minutes (Table 2, Entry 1). The process remained efficient at lower levels of catalyst as the boronate ester was produced in 91% yield after 5 hours when 0.10 mol% Pd was utilized (Table 2, Entry 2).

The same catalyst system was highly efficient in the borylation of a range of aryl and heteroaryl bromides. For example, electron-rich aryl bromides, such as 4-bromoanisole (Table 2, Entry 3) and 4-bromo-*N*,*N*-dimethylaniline (Table 2, Entry 5), were successfully transformed into the desired pinacol boronate esters in 97% and 85% yield, respectively. Although electron-deficient aryl halides are known to be more challenging substrates for Pd-catalyzed carbon-boron bond-forming processes, 4-bromobenzophenone was smoothly converted to the desired product in five hours of reaction time with 1 mol% Pd (Table 2, Entry 8). Importantly, this method was also applicable to a variety of *ortho*-substituted aryl bromides as the borylation of the sterically hindered aryl halide, 2-bromomesitylene, resulted in 90% yield of the corresponding aryl boronate ester (Table 2, Entry 12). In addition, a substrate possessing an *ortho*-functional group, 2-bromoanisole, efficiently furnished the desired product in a high yield (Table 2, Entry 10). The $PdCl_2(CH_3CN)_2$/**1** catalyst system was also suitable in the borylation of a vinyl bromide to produce the alkenyl pinacol boronate in 68% yield (Table 2, Entry 13).[9] In addition, heteroaryl bromides were efficiently transformed to the desired products (Table 2, Entries 14-15). This catalyst system offers a general method for the conversion of aryl and vinyl bromides to pinacol boronate ester while maintaining low Pd loadings and minimal reaction times.

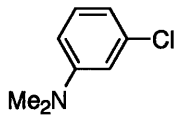
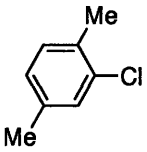
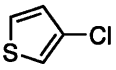
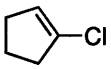
Table 2. Pd-Catalyzed Borylation of Aryl Halides with Pinacol Borane.[a]



Entry	Aryl Halide		Pd (mol%)	Time	Yield[b]
1		X = I	1.0	30 min	94
2		X = I	0.10	5 h	91
3		X = Br	1.0	1 h	97
4		X = Cl	3.0	24 h	96[c]
5			1.0	3 h	85
6		X = Br	1.0	4 h	84
7		X = Cl	3.0	24 h	62[c]
8			1.0	5 h	70
9			1.0	3 h	57
10		X = Br	2.0	4 h	89
11		X = Cl	4.0	24 h	51[c]
12			2.0	4 h	90
13			2.0	4 h	68
14			2.0	4 h	97
15			2.0	4 h	74

[a]Reaction Conditions: 1 equiv of aryl or heteroaryl halide, 1.5 equiv of pinacol borane, 3 equiv of NEt_3, 1,4-Dioxane (0.60 mL/mmol halide), cat. $PdCl_2(CH_3CN)_2$, 1:Pd = 4:1. [b]Isolated yield based upon an average of two runs. [c]NEt_3 (1.00 mL/mmol halide) used as solvent instead of 1,4-Dioxane.

Table 2 (cont). Pd-Catalyzed Borylation of Aryl Halides with Pinacol Borane.[a]

Entry	Aryl Halide	Pd (mol%)	Time	Yield[b]
16		3.0	24 h	80[c]
17		3.0	24 h	87[c]
18		3.0	24 h	59[c]
19		3.0	24 h	73[c]

[a]Reaction Conditions: 1 equiv of aryl or heteroaryl halide, 1.5 equiv of pinacol borane, 3 equiv of NEt_3, 1,4-Dioxane (0.60 mL/mmol halide), cat. $PdCl_2(CH_3CN)_2$, 1:Pd = 4:1. [b]Isolated yield based upon an average of two runs. [c]NEt_3 (1.00 mL/mmol halide) used as solvent instead of 1,4-Dioxane.

Despite the economic advantages of employing aryl chlorides in Pd-catalyzed borylation chemistry, there remains only one report, to our knowledge, of the successful combination of an aryl chloride with pinacol borane.[9] However, as previously stated, this method was only applicable to *para*-substituted electron-rich aryl chlorides (i.e., 4-chloroanisole and 4-chloro-*N*-methylaniline). We were pleased to discover that the $PdCl_2(CH_3CN)_2$/**1** catalyst system was efficient in the reaction of similar substrates as 4-chloroanisole was successfully converted to the pinacol boronate ester in greater than 95% yield (Table 2, Entry 4). Furthermore, this method was also general for a wide range of aryl chlorides as an electron-neutral aryl halide, 4-*n*-butylchlorobenzene, resulted in a 62% yield of the desired product (Table 2, Entry 7). Although *ortho*-substituted aryl chlorides have proven to be challenging substrates for a variety of systems, the $PdCl_2(CH_3CN)_2$/**1** catalyst also remained applicable in these couplings as modest to good yields resulted in both cases (Table 2, Entries 11 and 17). In addition, this method represents the only process employing pinacol borane as the boron source by which a heteroaryl chloride (Table 2, Entry 18) or vinyl chloride (Table 2, Entry 19) has been successfully converted to the corresponding pinacol

boronate ester. Despite the success of the catalyst system for a variety of aryl chlorides, electron-poor substrates still remain problematic. In general, reactions of these substrates resulted in incomplete conversion of the aryl chloride as well as an increase in reduced arene byproduct.

4.3 Conclusion

In summary, we have demonstrated the utility of the $PdCl_2(CH_3CN)_2$/**1** catalyst system in the borylation of a variety of aryl and heteroaryl halides. The reactions of aryl iodides and bromides can be conducted with relatively low Pd loadings and short reaction times while still maintaining a wide substrate scope. In addition, the method represents the first general system for the borylation of aryl and heteroaryl chlorides whereby a range of substrates can be converted to the desired pinacol boronate esters using pinacol borane.

4.4 Experimental

4.4.1 General

All reactions were stirred with the aid of magnetic stirring and carried out under an argon atmosphere. 1,4-Dioxane (anhydrous), triethylamine (≥99.5%) and pinacol borane (97%) were purchased from Aldrich Chemical Co. in SureSeal® bottles. Commercially available materials were used without further purification unless otherwise noted. SPhos (**1**) and aryl halides were purchased from Aldrich Chemical Co. Liquid aryl halides were purified by passage through a pad of basic alumina prior to use. $PdCl_2(CH_3CN)_2$ was purchased from Strem Chemicals, Inc. and stored in a benchtop desiccator.

All new compounds were characterized by ^1H NMR, ^{13}C NMR, IR spectroscopy, melting points (for solids) and, in most cases, elemental analysis. Known compounds were characterized by ^1H NMR, ^{13}C NMR and melting points (for solids) and compared to their literature values. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 300. Infrared spectra were recorded on an ASI Applied Systems ReactIR 1000 (neat samples were placed directly on the DiComp probe). Elemental analyses were

preformed by Atlantic Microlabs Inc., Norcross, GA. All ^{1}H NMR experiments are reported in δ units, parts per million (ppm) downfield of TMS and were measured relative to the signals for the residual benzene (7.16 ppm), chloroform (7.26 ppm), dimethylsulfoxide (2.50 ppm) or methanol (3.31 ppm). All ^{13}C NMR spectra were reported in ppm relative to residual chloroform (77 ppm), dimethylsulfoxide (39.5 ppm) or methanol (49 ppm) and were obtained with ^{1}H decoupling. Melting points were obtained on a Mel-Temp capillary melting point apparatus and are uncorrected. Gas chromatographic analyses were performed on Hewlett-Packard 6890 gas chromatography instrument with a FID detector using 25 m x 0.20 mm capillary column with cross-linked methyl siloxane as a stationary phase.

The yields in table 2 refer to isolated yields (average of two runs) of compounds estimated to be ≥ 95% pure as determined by ^{1}H NMR and GC analysis and/or combustion analysis.

4.4.2 Experimental for the Borylation of Aryl Halides.

General Procedure A: Pd-Catalyzed Borylation of Aryl Iodides and Bromides.

An oven-dried resealable Schlenk tube possessing a Teflon screw valve was charged with $PdCl_2(CH_3CN)_2$ (0.25%-2.0%) and SPhos (1.0-8.0%). The Schlenk tube was capped with a rubber septum and then evacuated and backfilled with argon (this sequence was carried out a total of two times). 1,4-Dioxane (0.30 mL) was added via syringe, through the septum, followed by the addition of the aryl halide (0.50 mmol), NEt_3 (0.209 mL, 152 mg, 1.50 mmol) and pinacol borane (0.109 mL, 96.1 mg, 0.75 mmol) in a like manner (aryl halides that were solids were added with the other solid reagents). The septum was then replaced with a Teflon screw valve and the Schlenk tube was sealed. The reaction mixture was heated to 110 °C until the aryl halide had been completely consumed as determined by gas chromatography and was then allowed to cool to room temperature. The reaction solution was filtered through a thin pad of celite (eluting with ethyl acetate) and the eluent was concentrated under reduced pressure. The crude material so obtained was purified via flash chromatography on silica gel.

General Procedure B: Pd-Catalyzed Borylation of Aryl Chlorides.

An oven-dried resealable Schlenk tube possessing a Teflon screw valve was charged with $PdCl_2(CH_3CN)_2$ (3.0-4.0%) and SPhos (12.0-16.0%). The Schlenk tube was capped with a rubber septum and then evacuated and backfilled with argon (this sequence was carried out two times). NEt_3 (0.500 mL) was added via syringe, through the septum, followed by the addition of the aryl chloride (0.50 mmol) and pinacol borane (0.109 mL, 96.1 mg, 0.75 mmol) in a like manner (aryl halides that were solids were added with the other solid reagents). The septum was then replaced with a Teflon screw valve and the Schlenk tube was sealed. The reaction mixture was heated to 110 °C until the aryl halide had been completely consumed as determined by gas chromatography and was then allowed to cool to room temperature. The reaction solution was filtered through a thin pad of celite (eluting with ethyl acetate) and the eluent was concentrated under reduced pressure. The crude material so obtained was purified via flash chromatography on silica gel.

2-(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 1, Entry 1).[10] Following general procedure A, a mixture of 4-iodoanisole (127 mg, 0.50 mmol), pinacol borane, NEt_3, $PdCl_2(CH_3CN)_2$ (1.3 mg, 0.0050 mmol) and SPhos (8.2 mg, 0.020 mmol) was heated in 1,4-dioxane with stirring for 30 min. Flash column chromatography (5% EtOAc/Hexanes) yielded the title compound in 110 mg (94% yield) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.75 (d, J = 9 Hz, 2H), 6.90 (d, J = 9 Hz, 2H), 3.83 (s, 3H), 1.34 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.1, 136.4, 113.2, 102.7, 83.4, 55.0, 24.8. ^1H NMR spectrum included.

2-(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 1, Entry 2).[10] Following general procedure A on a larger scale, a mixture of 4-iodoanisole (234 mg, 1.00 mmol), pinacol borane (0.218 mL, 192 mg, 1.50 mmol), NEt_3 (0.418 mL, 354 mg, 3.00 mmol), $PdCl_2(CH_3CN)_2$ (0.26 mg, 0.0010 mmol) and SPhos (1.6 mg, 0.0040 mmol) was heated in 1,4-dioxane with stirring for 30 min. Flash column chromatography (5% EtOAc/Hexanes) yielded the title compound in 212 mg (91 % yield) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.75 (d, J = 9 Hz, 2H), 6.90 (d, J = 9 Hz, 2H), 3.83 (s, 3H), 1.34 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.1, 136.4, 113.2, 102.7, 83.4, 55.0, 24.8. ^1H NMR spectrum included.

2-(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 1, Entry 3).[10] Following general procedure A, a mixture of 4-bromoanisole (62.5 μL, 93.5 mg, 0.50 mmol), pinacol borane, NEt_3, $PdCl_2(CH_3CN)_2$ (1.3 mg, 0.0050 mmol) and SPhos (8.2 mg, 0.020 mmol) was heated in 1,4-dioxane with stirring for 1 h. Flash column chromatography (5% EtOAc/Hexanes) yielded the title compound in 113 mg (97% yield) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.75 (d, J = 9 Hz, 2H), 6.90 (d, J = 9 Hz, 2H), 3.83 (s, 3H), 1.34 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.1, 136.4, 113.2, 102.7, 83.4, 55.0, 24.8. ^1H NMR spectrum included.

2-(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 1, Entry 4).[10] Following general procedure B, a mixture of 4-chloroanisole (61.2 μL, 71.3 mg, 0.50 mmol), pinacol borane, NEt_3 (0.500 mL), $PdCl_2(CH_3CN)_2$ (3.9 mg, 0.015 mmol) and SPhos (24.6 mg, 0.060 mmol) was heated with stirring for 24 h. Flash column chromatography (5% EtOAc/Hexanes) yielded the title compound in 112 mg (96% yield) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.75 (d, J = 9 Hz, 2H), 6.90 (d, J = 9 Hz, 2H), 3.83 (s, 3H), 1.34 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.1, 136.4, 113.2, 102.7, 83.4, 55.0, 24.8. ^1H NMR spectrum included.

***N,N*-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (Table 1, Entry 5).**[6a] Following general procedure A, a mixture of 4-bromo-*N,N*-dimethylaniline (100.0 mg, 0.50 mmol), pinacol borane, NEt_3, $PdCl_2(CH_3CN)_2$ (1.3 mg, 0.0050 mmol) and SPhos (8.2 mg, 0.020 mmol) was heated in 1,4-dioxane with stirring for 3 h. Recrystallization (Hexanes) yielded the title compound in 105 mg (85% yield) as a white solid, mp 116-117 °C. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.71 (d, J = 8 Hz, 2H), 6.70 (d, J = 8 Hz, 2H), 3.00 (s, 6H), 1.34 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 152.5, 136.1, 111.2, 83.1, 40.1, 24.8 (No C-B Signal). ^1H NMR spectrum included.

2-(4-butylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 1, Entry 6).[11] Following general procedure A, a mixture of 4-bromo-*n*-butylbenzene (106.5 mg, 0.50 mmol), pinacol borane, NEt_3, $PdCl_2(CH_3CN)_2$ (1.3 mg, 0.0050 mmol) and SPhos (8.2 mg, 0.020 mmol) was heated in 1,4-dioxane with stirring for 4 h. Flash column chromatography (2.5% EtOAc/Hexanes) yielded the title compound in 109 mg (84% yield) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.75 (d, J = 8 Hz, 2H), 7.22 (d, J = 8

Hz, 2H), 2.64 (t, J = 8 Hz, 2H), 1.62 (p, J = 8 Hz, 2H), 1.37 (sext, J = 8 Hz, 2H), 1.36 (s, 12H), 0.94 (t, J = 8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 146.3, 134.8, 127.9, 83.5, 35.8, 33.5, 24.8, 22.3, 13.9 (No C-B Signal). ^{1}H NMR spectrum included.

2-(4-butylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 1, Entry 7).[11] Following general procedure B, a mixture of 4-*n*-butylchlorobenzene (82.0 μL, 84.4 mg, 0.50 mmol), pinacol borane, NEt_3 (0.50 mL), $PdCl_2(CH_3CN)_2$ (3.9 mg, 0.015 mmol) and SPhos (24.6 mg, 0.060 mmol) was heated in 1,4-dioxane with stirring for 24 h. Flash column chromatography (2.5% EtOAc/Hexanes) yielded the title compound in 81 mg (62% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.75 (d, J = 8 Hz, 2H), 7.22 (d, J = 8 Hz, 2H), 2.64 (t, J = 8 Hz, 2H), 1.62 (p, J = 8 Hz, 2H), 1.37 (sext, J = 8 Hz, 2H), 1.36 (s, 12H), 0.94 (t, J = 8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 146.3, 134.8, 127.9, 83.5, 35.8, 33.5, 24.8, 22.3, 13.9 (No C-B Signal). ^{1}H NMR spectrum included.

phenyl(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanone (Table 1, Entry 8).[5a] Following general procedure A, a mixture of 4-bromobenzophenone (130 mg, 0.50 mmol), pinacol borane, NEt_3, $PdCl_2(CH_3CN)_2$ (1.3 mg, 0.0050 mmol) and SPhos (8.2 mg, 0.020 mmol) was heated in 1,4-dioxane with stirring for 5 h. Flash column chromatography (10% EtOAc/Hexanes) yielded the title compound in 108 mg (70% yield) as a yellow solid, mp 96-97 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.91 (d, J = 8 Hz, 2H), 7.79 (dd, J = 8, 1 Hz, 2H), 7.76 (d, J = 8 Hz, 2H), 7.59 (dt, J = 8, 1 Hz, 1H), 7.48 (t, J = 8 Hz, 2H), 1.37 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 196.9, 139.7, 137.4, 134.5, 132.5, 130.1, 129.0, 128.3, 84.2, 24.9 (No C-B Signal). ^{1}H NMR spectrum included.

3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (Table 1, Entry 9).[12] Following general procedure A, a mixture of 3-bromobenzonitrile (91 mg, 0.50 mmol), pinacol borane, NEt_3, $PdCl_2(CH_3CN)_2$ (1.3 mg, 0.0050 mmol) and SPhos (8.2 mg, 0.020 mmol) was heated in 1,4-dioxane with stirring for 3 h. Flash column chromatography (5% EtOAc/Hexanes) yielded the title compound in 65 mg (57% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.08 (s, 1H), 7.99 (d, J = 7 Hz, 1H), 7.71 (d, J = 7 Hz, 1H), 7.46 (t, J = 7 Hz, 1H), 1.34 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.7, 138.4, 134.4, 128.4, 118.8, 112.0, 84.4, 24.8 (No C-B Signal). ^{1}H NMR spectrum included.

2-(2-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 1, Entry 10).[6a] Following general procedure A, a mixture of 2-bromoanisole (62.3 μL, 93.5 mg, 0.50 mmol), pinacol borane, NEt_3, $PdCl_2(CH_3CN)_2$ (2.6 mg, 0.010 mmol) and SPhos (16.4 mg, 0.040 mmol) was heated in 1,4-dioxane with stirring for 4 h. Flash column chromatography (5% EtOAc/Hexanes) yielded the title compound in 104 mg (89% yield) as a white solid, mp 77-78 °C. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.67 (dd, J = 7, 2 Hz, 1H), 7.39 (dt, J = 8, 2 Hz, 1H), 6.94 (dt, J = 7, 2 Hz, 1H), 6.85 (d, J = 8 Hz, 1H), 3.83 (s, 3H), 1.35 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.8, 137.4, 133.2, 120.9, 111.1, 84.1, 56.5, 25.5 (No C-B Signal). ^1H NMR spectrum included.

2-(2-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 1, Entry 11).[6a] Following general procedure B, a mixture of 2-chloroanisole (62.3 μL, 93.5 mg, 0.50 mmol), pinacol borane, NEt_3 (0.50 mL), $PdCl_2(CH_3CN)_2$ (5.2 mg, 0.020 mmol) and SPhos (32.8 mg, 0.080 mmol) was heated with stirring for 24 h. Flash column chromatography (5.0% EtOAc/Hexanes) yielded the title compound in 60 mg (51% yield) as a white solid, mp 76-77 °C. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.67 (dd, J = 7, 2 Hz, 1H), 7.39 (dt, J = 8, 2 Hz, 1H), 6.94 (dt, J = 7, 2 Hz, 1H), 6.85 (d, J = 8 Hz, 1H), 3.83 (s, 3H), 1.35 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.8, 137.4, 133.2, 120.9, 111.1, 84.1, 56.5, 25.5 (No C-B Signal). ^1H NMR spectrum included.

2-mesityl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 1, Entry 12).[13] Following general procedure A, a mixture of 2-bromomesitylene (76.5 μL, 99.5 mg, 0.50 mmol), pinacol borane, NEt_3, $PdCl_2(CH_3CN)_2$ (2.6 mg, 0.010 mmol) and SPhos (16.4 mg, 0.040 mmol) was heated in 1,4-dioxane with stirring for 4 h. Flash column chromatography (2.5% EtOAc/Hexanes) yielded the title compound in 111 mg (90% yield) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 6.82 (s, 2H), 2.42 (s, 6H), 2.29 (s, 3H), 1.41 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 142.0, 138.8, 127.4, 83.3, 24.9, 22.1, 21.2 (No C-B Signal). ^1H NMR spectrum included.

***(E)*-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane (Table 1, Entry 13).**[14] Following general procedure A, a mixture of b-bromostyrene (64.1 μL, 91.5 mg, 0.50 mmol), pinacol borane, NEt_3, $PdCl_2(CH_3CN)_2$ (2.6 mg, 0.010 mmol) and SPhos (16.4 mg, 0.040 mmol) was heated in 1,4-dioxane with

stirring for 4 h. Flash column chromatography (2.5% EtOAc/Hexanes) yielded the title compound in 79 mg (69% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.49 (d, J = 8 Hz, 2H), 7.41 (d, J = 18 Hz, 1H), 7.29-7.36 (m, 3H), 6.18 (d, J = 18 Hz, 1H), 1.33 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 149.5, 137.4, 128.9, 128.5, 127.0, 126.5, 83.3, 24.8. ^{1}H NMR spectrum included.

1-acetyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (Table 1, Entry 14). Following general procedure A, a mixture of *N*-acetyl-5-bromoindole (119 mg, 0.50 mmol), pinacol borane, NEt_3, $PdCl_2(CH_3CN)_2$ (2.6 mg, 0.010 mmol) and SPhos (16.4 mg, 0.040 mmol) was heated in 1,4-dioxane with stirring for 4 h. Flash column chromatography (15% EtOAc/Hexanes) yielded the title compound in 138 mg (97% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.41 (d, J = 7 Hz, 1H), 8.06 (s, 1H), 7.80 (d, J = 7 Hz, 1H), 7.40 (d, J = 2 Hz, 1H), 6.63 (d, J = 2 Hz, 1H), 2.63 (s, 3H), 1.37 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.7, 137.4, 131.4, 129.8, 125.2, 115.8, 109.4, 83.7, 24.9, 24.1 (No C-B Signal). IR (neat, cm^{-1}): 3149, 3109, 2978, 1712, 1610, 1539, 1471, 1430, 1352, 1231, 1145. Anal. Calcd. for $C_{16}H_{20}BNO_3$: C, 67.39; H, 7.07. Found C, 67.15; H, 7.08. ^{1}H and ^{13}C NMR spectrum included.

3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(triisopropylsilyl)-1*H*-pyrrole (Table 1, Entry 15).[15] Following general procedure A, a mixture of 3-bromo-1-(triisopropyl-silanyl)-1*H*-pyrrole[16] (156 mg, 0.50 mmol), pinacol borane, NEt_3, $PdCl_2(CH_3CN)_2$ (2.6 mg, 0.010 mmol) and SPhos (16.4 mg, 0.040 mmol) was heated in 1,4-dioxane with stirring for 4 h. Flash column chromatography (15% EtOAc/Hexanes) yielded the title compound in 119 mg (74% yield) as a light yellow solid, m.p. 59 °C. ^{1}H NMR (300 MHz, $CDCl_3$) ≥: 7.24 (dd, J = 2, 1 Hz, 1H), 6.81 (dd, J= 3, 2 Hz, 1H) 6.63 (dd, J = 3, 1 Hz, 1H), 7.00 (dd, J = 7, 1 Hz, 1H), 1.46 (sept, J = 7 Hz, 3H), 1.33 (s, 12H), 1.09 (d, J = 7 Hz, 18H).^{13}C NMR (75 MHz, $CDCl_3$) ≥: 133.6, 124.9, 115.6, 110.0, 82.6, 24.8, 17.7, 11.6. ^{1}H NMR spectrum included.

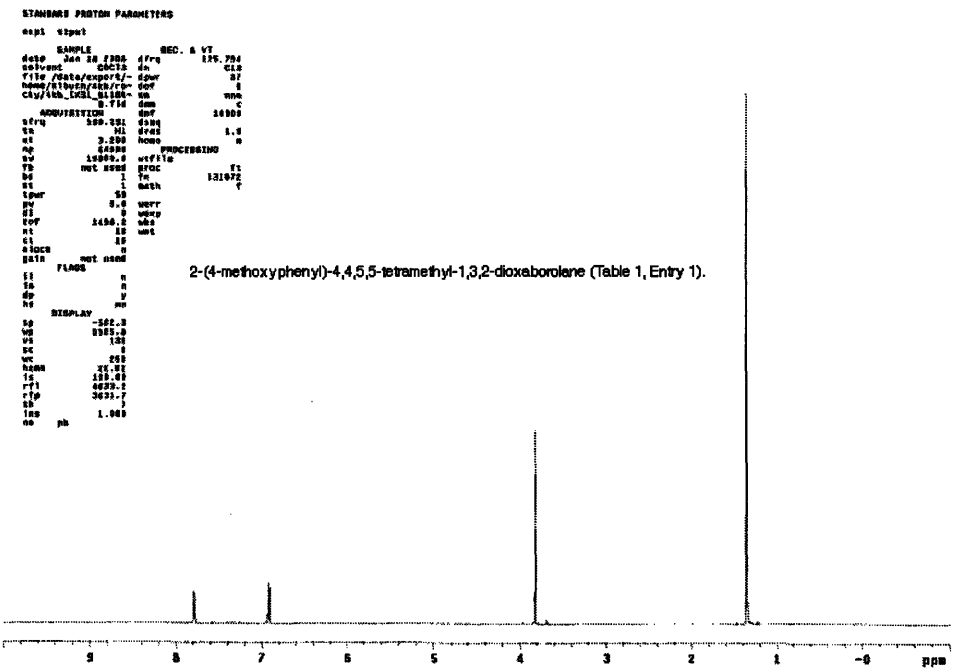
***N,N*-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (Table 1, Entry 16).**[6a] Following general procedure B, a mixture of 3-chloro-*N,N*-dimethylaniline (77.8 mg, 0.50 mmol), pinacol borane, NEt_3 (0.50 mL), $PdCl_2(CH_3CN)_2$ (3.9 mg, 0.015 mmol) and SPhos (24.6 mg, 0.060 mmol) was heated with stirring for 24 h. Flash column chromatography (10% EtOAc/Hexanes) yielded the title compound

in 99 mg (80% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.27 (t, J = 8 Hz, 1H), 7.19-7.22 (m, 2H), 6.87 (dd, J = 8, 3 Hz, 1H), 2.97 (s, 6H), 1.35 (s, 12 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 150.1, 128.5, 123.2, 118.6, 115.8, 83.6, 40.8, 24.8 (No C-B Signal). ^{1}H NMR spectrum included.

2-(2,5-dimethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 1, Entry 17).[17] Following general procedure B, a mixture of 2-chloro-*p*-xylene (67.0 μL, 70.3 mg, 0.50 mmol), pinacol borane, NEt_3 (0.50 mL), $PdCl_2(CH_3CN)_2$ (3.9 mg, 0.015 mmol) and SPhos (24.6 mg, 0.060 mmol) was heated with stirring for 24 h. Flash column chromatography (2.5% EtOAc/Hexanes) yielded the title compound in 101 mg (87% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.60 (s, 1H), 7.15 (d, J = 8 Hz, 1H), 7.08 (d, J = 8 Hz, 1H), 2.52 (s, 3H), 2.32 (s, 3H), 1.36 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 141.7, 136.3, 133.9, 131.5, 129.8, 83.3, 24.8, 21.7, 20.8 (No C-B Signal). ^{1}H NMR spectrum included.

4,4,5,5-tetramethyl-2-(thiophen-3-yl)-1,3,2-dioxaborolane (Table 1, Entry 18).[18] Following general procedure B, a mixture of 3-chlorothiophene (59.2 mg, 46.4 μL, 0.50 mmol), pinacol borane, NEt_3 (0.50 mL), $PdCl_2(CH_3CN)_2$ (3.9 mg, 0.015 mmol) and SPhos (24.6 mg, 0.060 mmol) was heated with stirring for 24 h. Flash column chromatography (2.5% EtOAc/Hexanes) yielded the title compound in 62 mg (59% yield) as brown solid, mp 55-56 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.92 (dt, J = 3, 1 1H), 7.41 (dt, J = 5, 1 Hz, 1H), 7.34 (dt, J = 5, 3 Hz, 1H), 1.33 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 131.2, 132., 126.1, 103.8, 84.4, 25.6. ^{1}H NMR spectrum included.

2-cyclopentenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 1, Entry 19).[19] Following general procedure B, a mixture of 1-chlorocyclopentene (49.6 μL, 51.3 mg, 0.50 mmol), pinacol borane, NEt_3 (0.50 mL), $PdCl_2(CH_3CN)_2$ (3.9 mg, 0.015 mmol) and SPhos (24.6 mg, 0.060 mmol) was heated with stirring for 24 h. Flash column chromatography (2.5% EtOAc/Hexanes) yielded the title compound in 71 mg (73% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.54 (t, J = 2 Hz, 1H), 2.37-2.41 (m, 4H), 1.83 (pent, J = 7 Hz, 2H), 1.28 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 147.6, 83.0, 34.7, 34.5, 24.8, 23.9. ^{1}H NMR spectrum included.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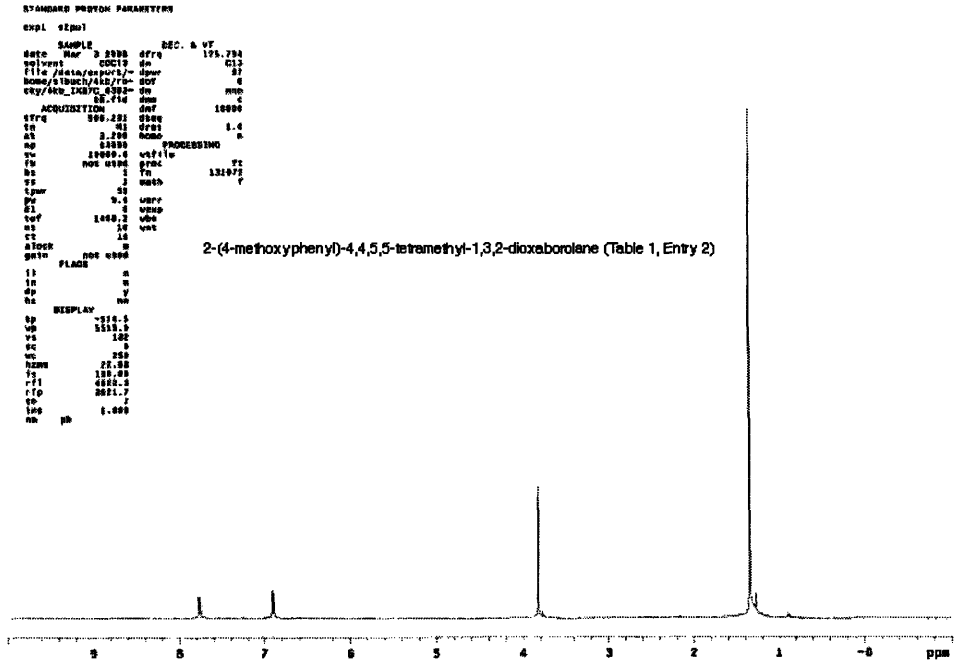
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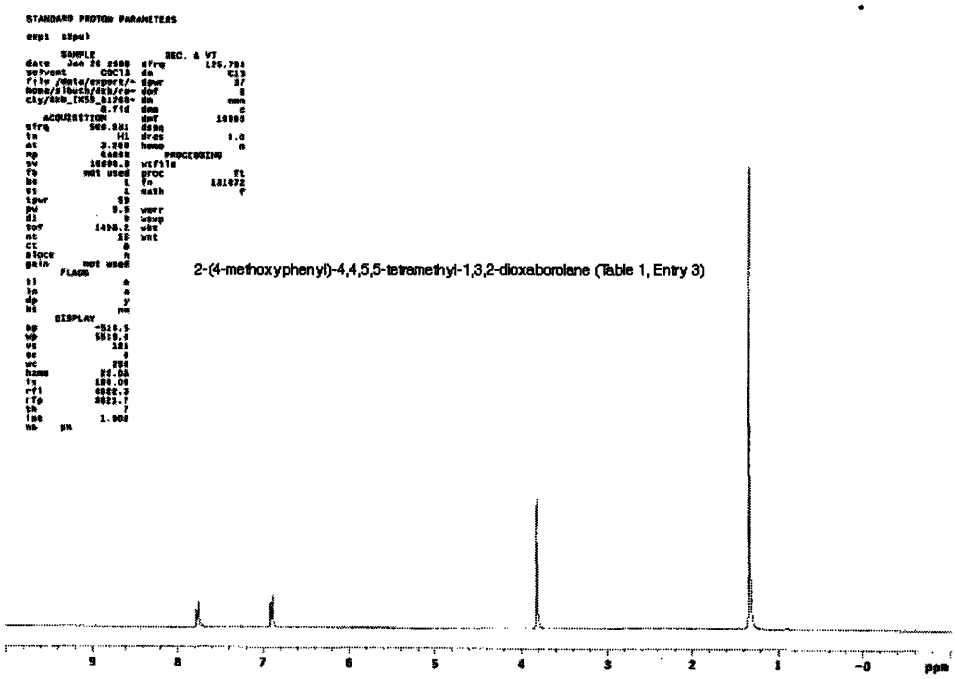
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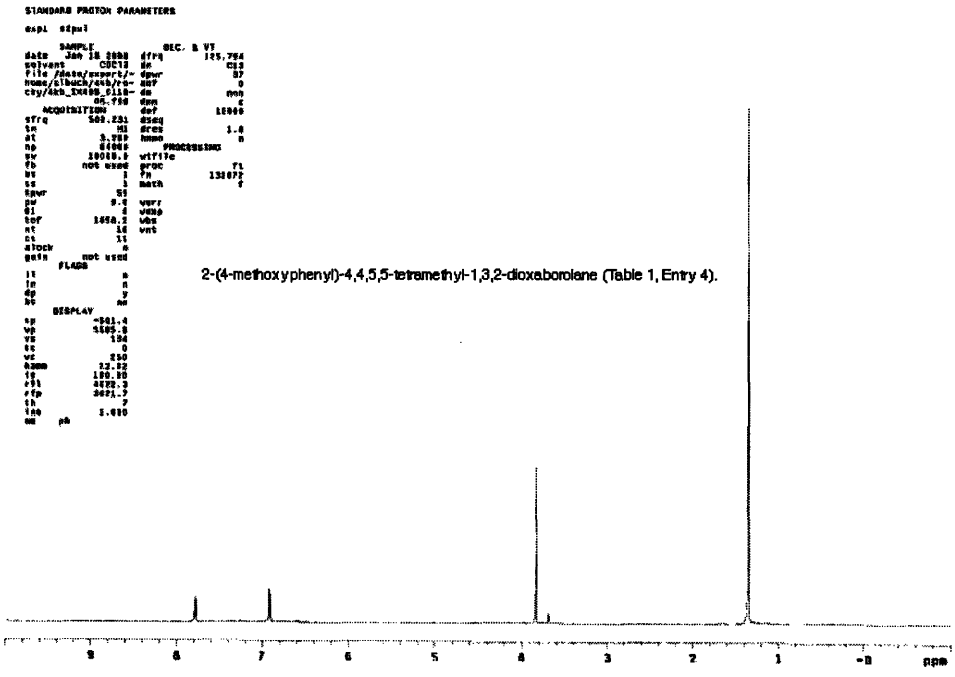
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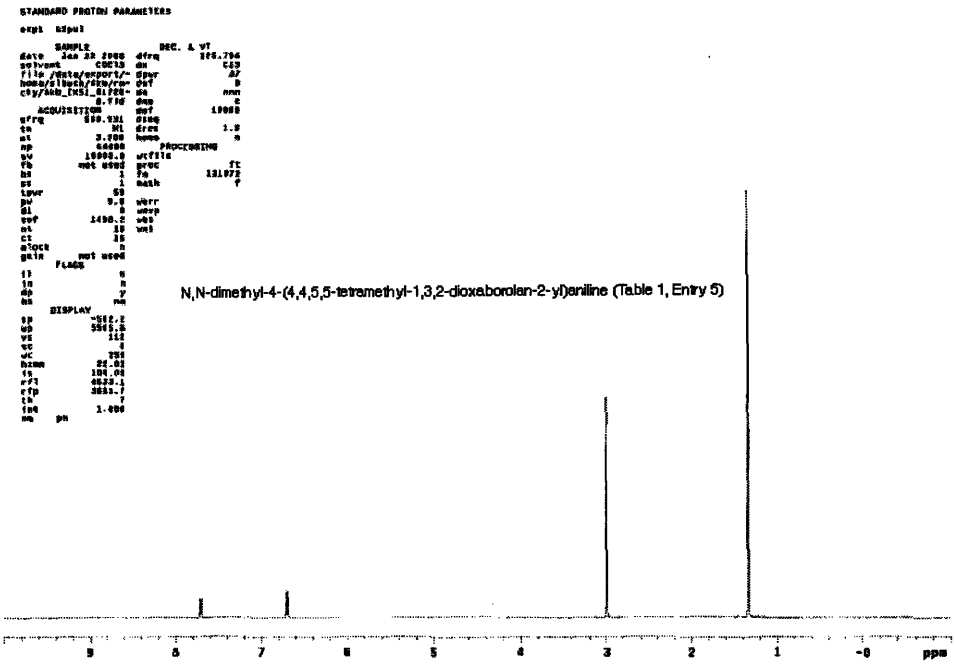
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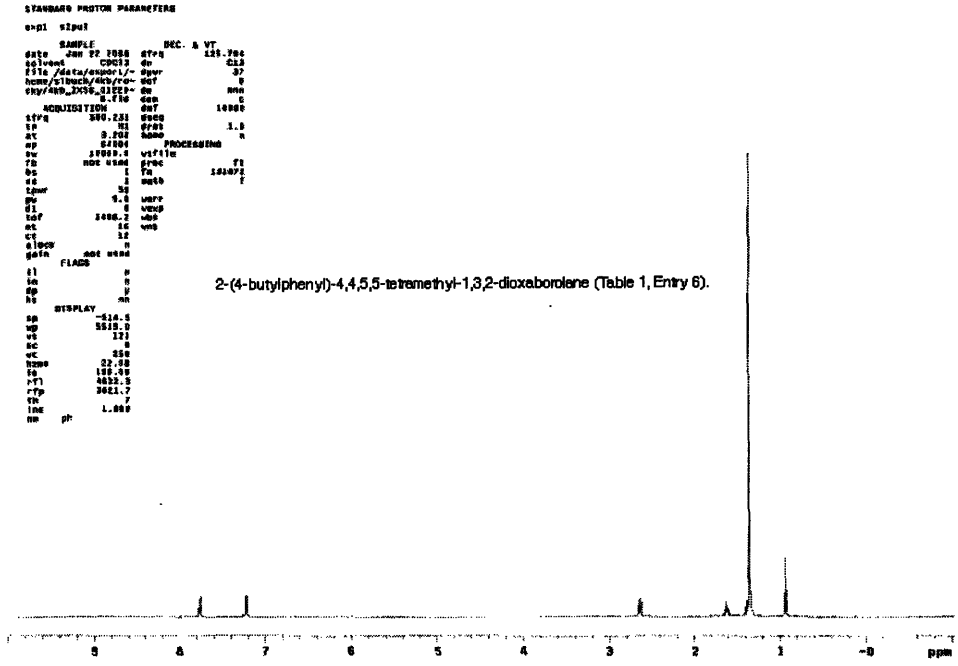
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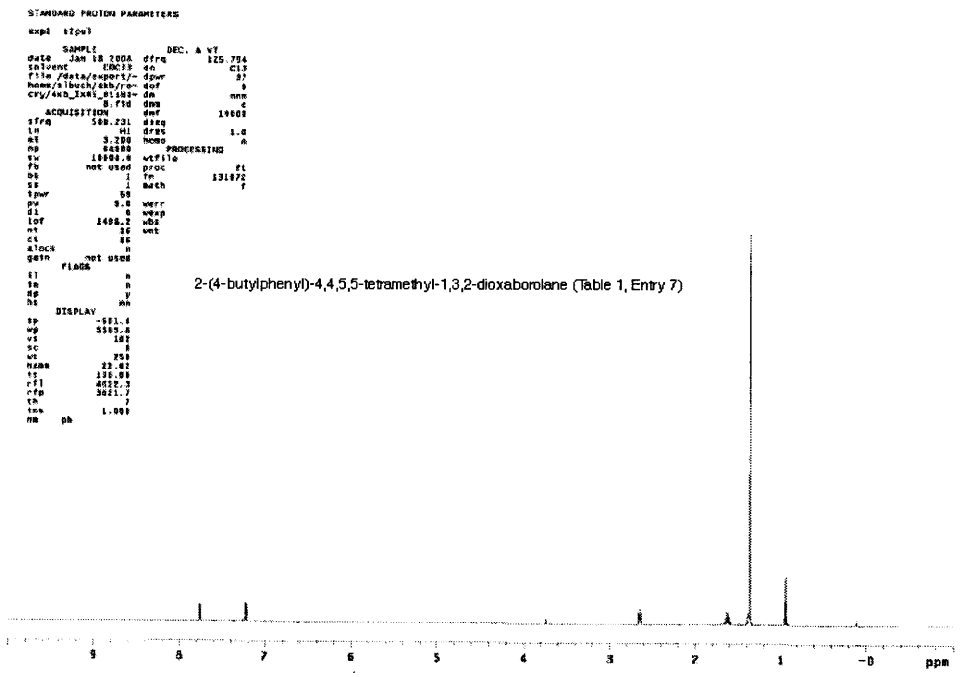
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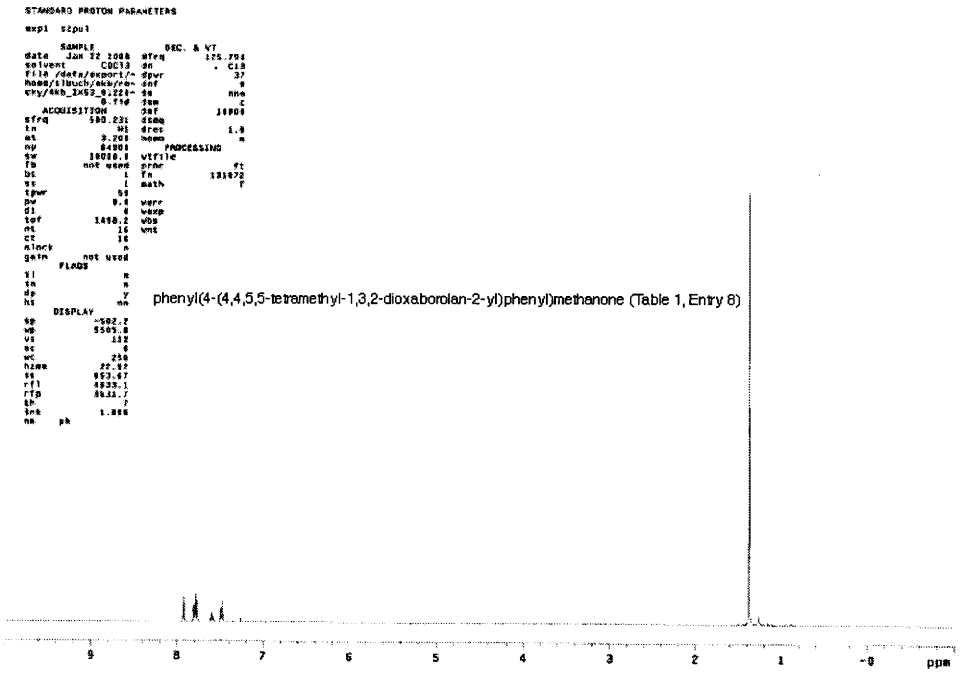
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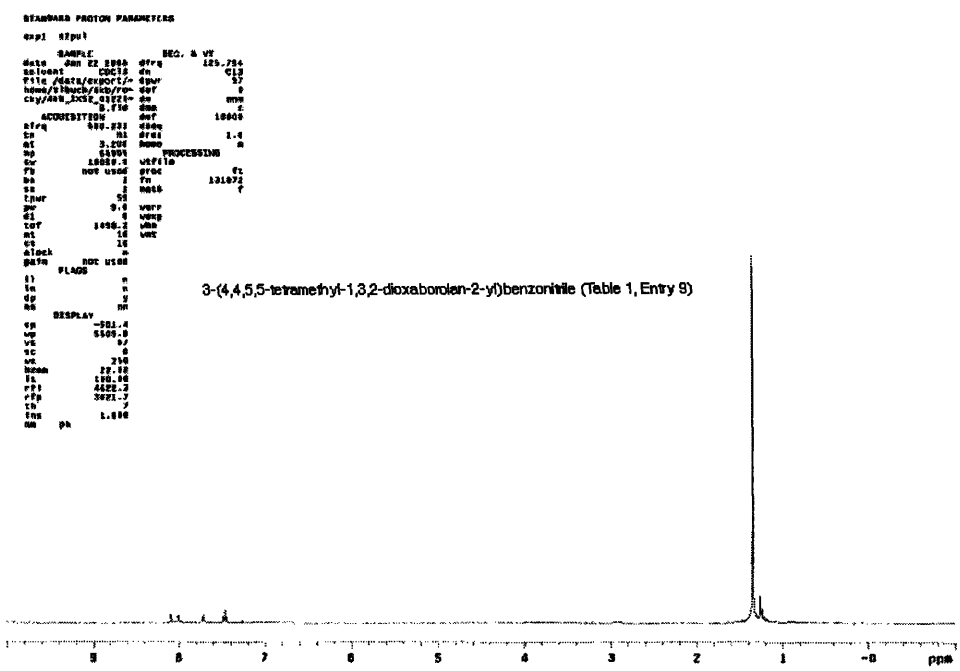
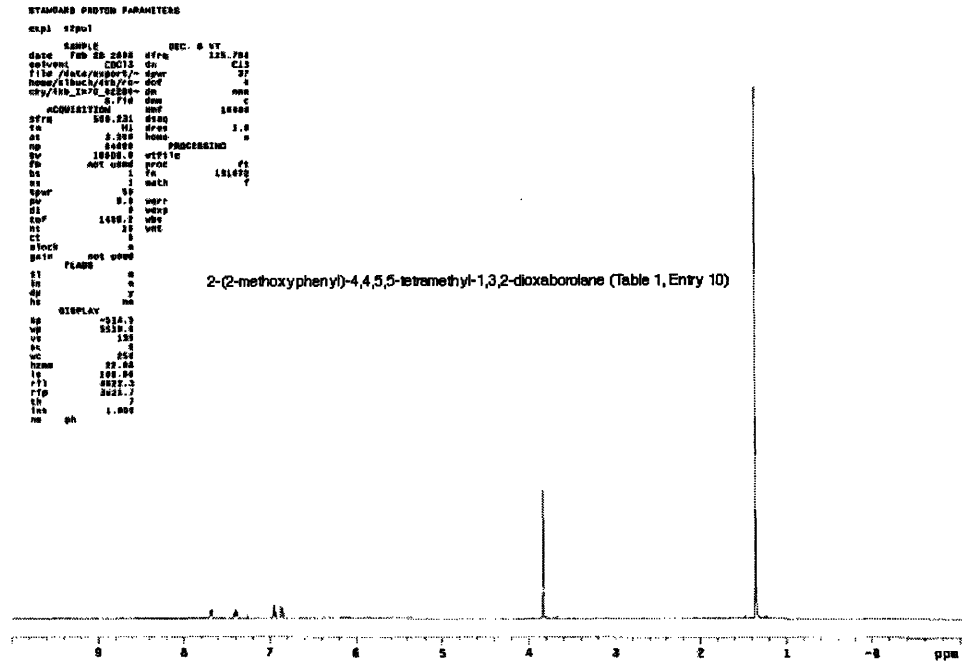
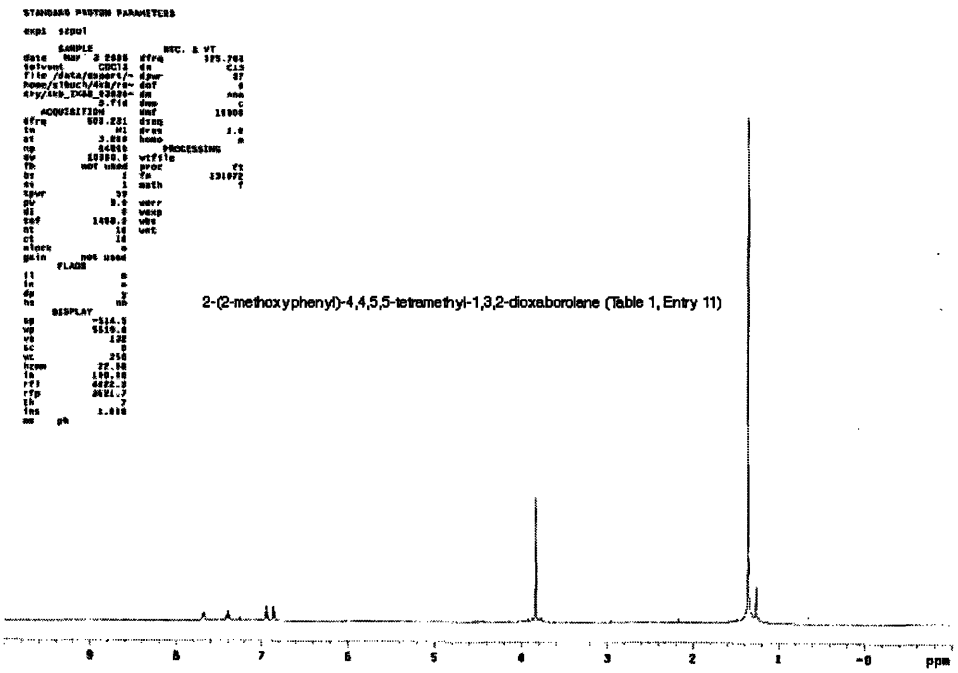
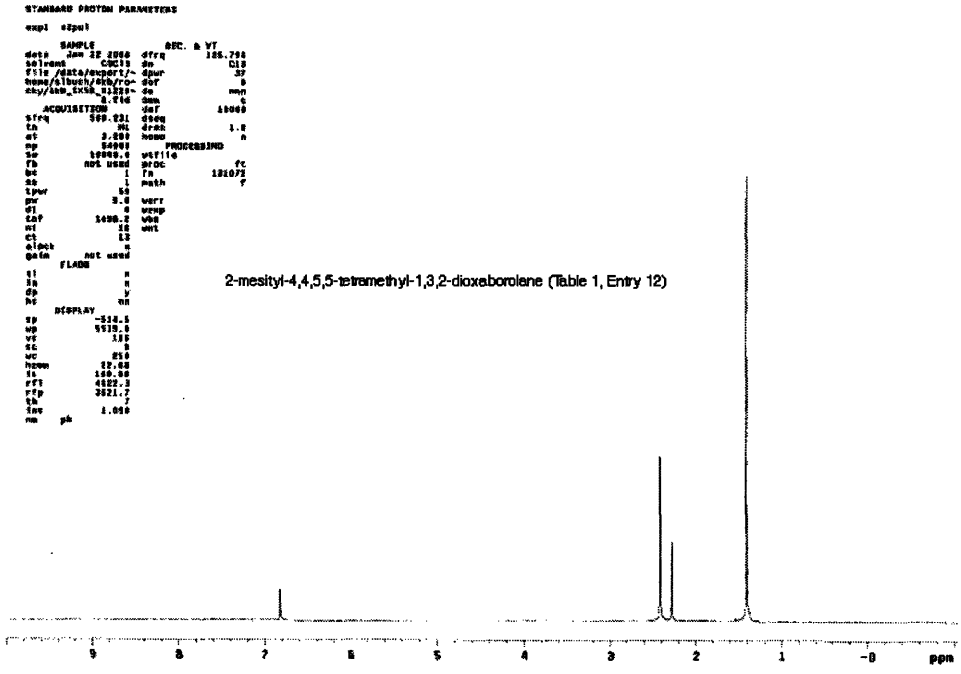


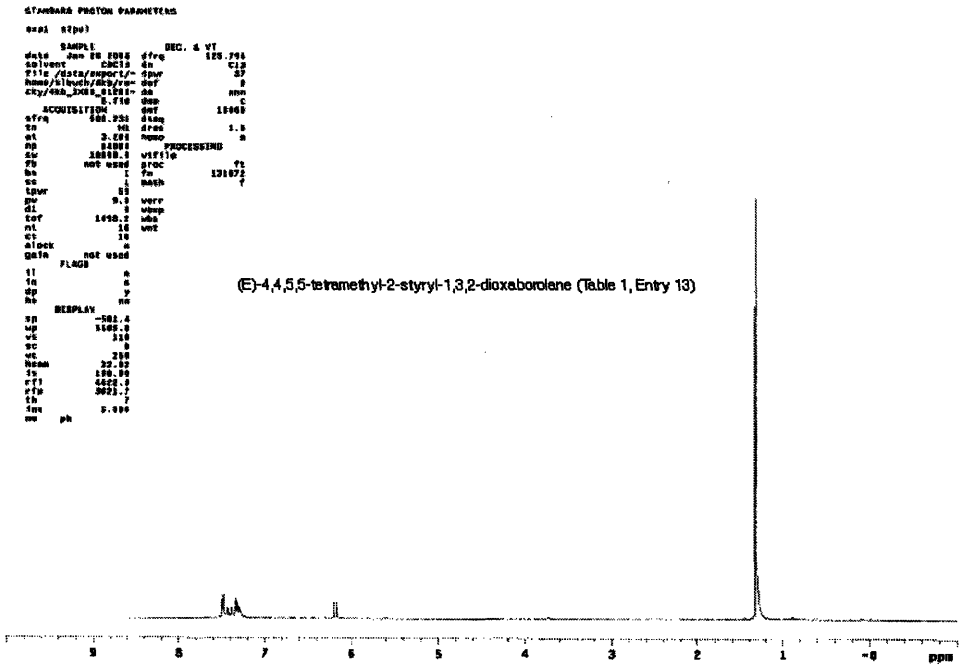
3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (Table 1, Entry 9)

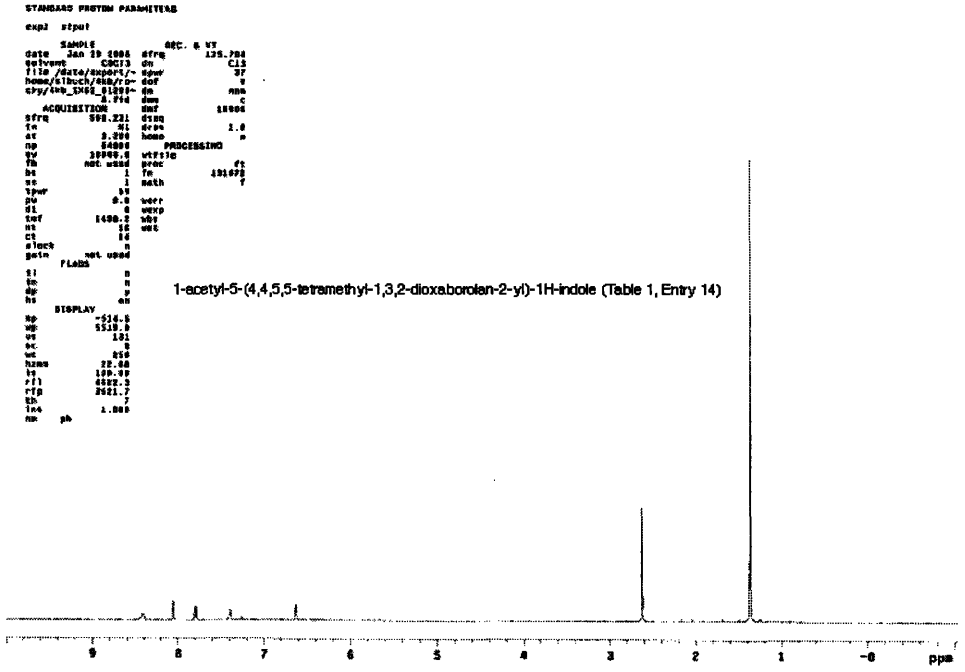


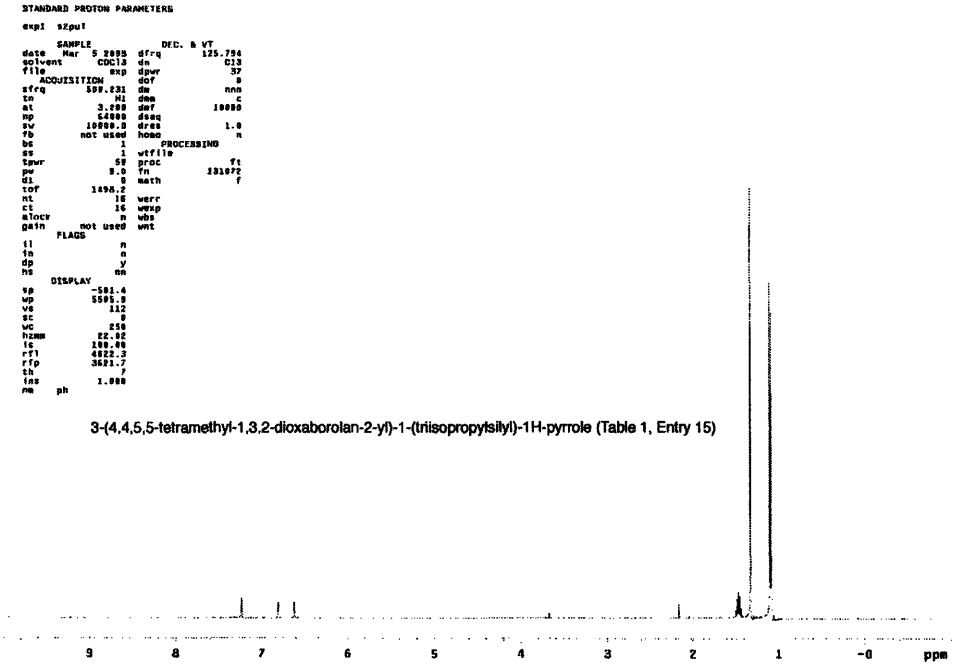
2-(2-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 1, Entry 10)

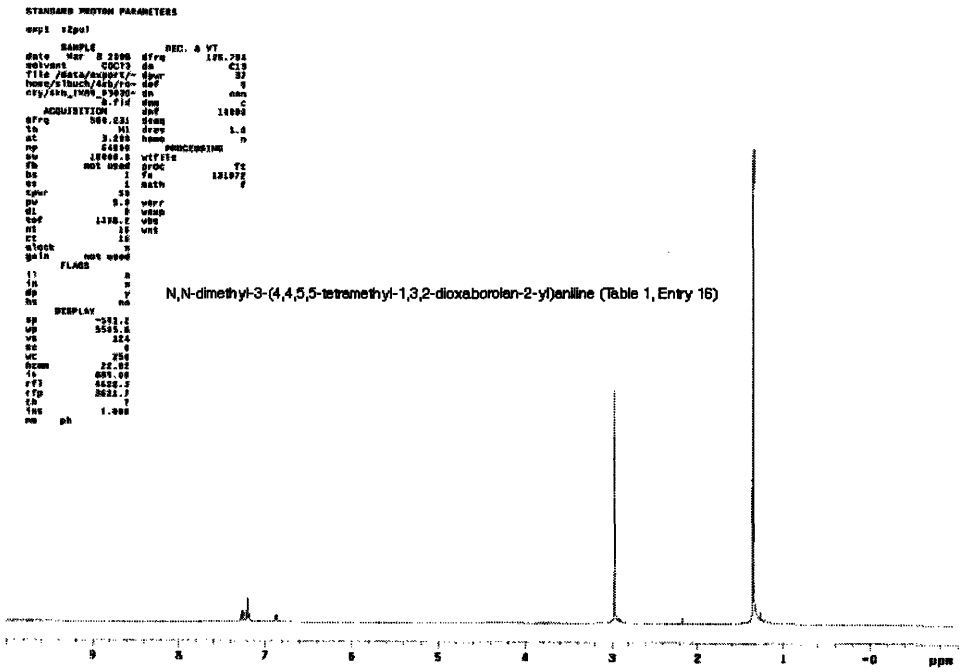

STANDARD PROTON PARAMETERS
2-(2-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 1, Entry 11)
9
8
7
6
5
4
3
2
1
-0
ppm

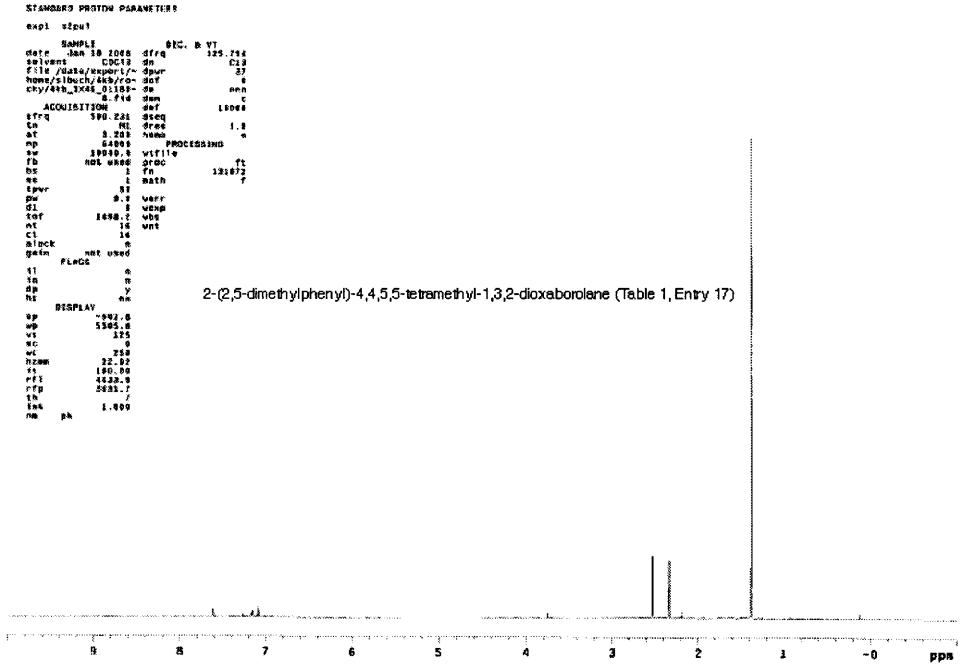

STANDARD PROTON PARAMETERS
2-mesityl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 1, Entry 12)
9
8
7
6
5
4
3
2
1
-0
ppm

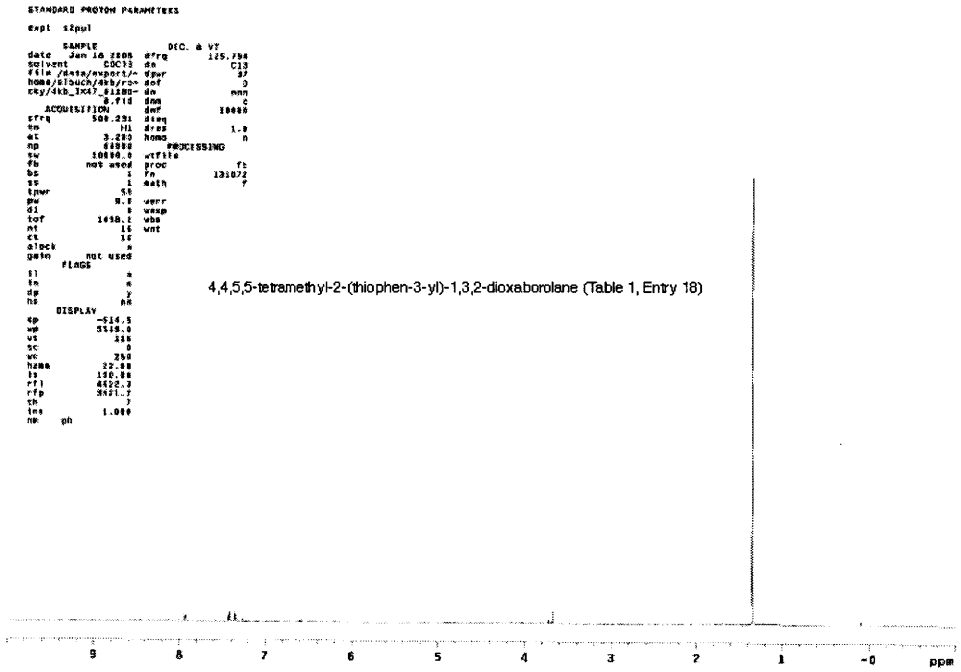

STANDARD PROTON PARAMETERS
SAMPLE
DEC. & VT
ACQUISITION
PROCESSING
DISPLAY
(E)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane (Table 1, Entry 13)
9
8
7
6
5
4
3
2
1
-0
ppm

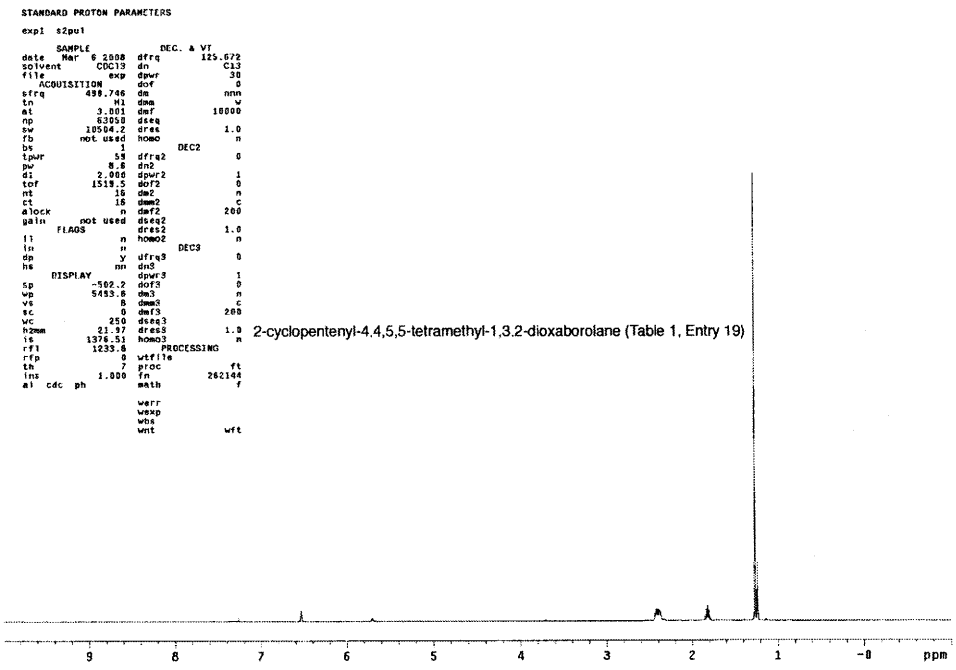

STANDARD PROTON PARAMETERS
SAMPLE
DEC. & VT
ACQUISITION
PROCESSING
DISPLAY
1-acetyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (Table 1, Entry 14)
9
8
7
6
5
4
3
2
1
-0
ppm


STANDARD PROTON PARAMETERS
expl sZpul
SAMPLE
date Mar 5 2005
solvent CDCl3
file exp
ACQUISITION
sfrq 599.831
tn H1
at 3.288
np 64000
sw 19999.8
fb not used
bs 1
ss 1
tpwr 59
pw 9.0
dl 0
tof 1496.2
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -581.4
wp 5591.9
vs 112
sc 0
wc 250
hzmm 22.82
is 100.00
rfl 4822.3
rfp 3621.7
th 7
ins 1.000
ap ph
DEC. & VT
dfrq 125.794
dn C13
dpwr 37
dof 0
dm nnn
dmm c
dmf 10000
dseq
drev
homo n
PROCESSING
wtfile
proc ft
fn 131072
math f
werr
wexp
wbs
wnt
3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(triisopropylsilyl)-1H-pyrrole (Table 1, Entry 15)
9
8
7
6
5
4
3
2
1
-0
ppm


STANDARD PROTON PARAMETERS
expl sZpul
SAMPLE
date Mar 8 2005
solvent CDCl3
file /data/export/~
home/sthuch/445/ro~
rty/sth_1N09_03020~
9.fid
ACQUISITION
sfrq 500.231
tn H1
at 3.286
np 64000
sw 10000.0
fb not used
bs 1
ss 1
tpwr 59
pw 9.0
dl 0
tof 1398.6
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -391.1
wp 5585.5
vs 124
sc 0
wc 250
hzmm 22.82
is 695.00
rfl 4628.7
rfp 3622.7
th 7
ins 1.000
ap ph
DEC. & VT
dfrq 125.794
dn C13
dpwr 37
dof 0
dm nnn
dmm c
dmf 10000
dseq
drev
homo n
PROCESSING
wtfile
proc ft
fn 131072
math f
werr
wexp
wbs
wnt
N,N-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (Table 1, Entry 16)
9
8
7
6
5
4
3
2
1
-0
ppm


STANDARD PROTON PARAMETERS
expt szpu1
SAMPLE
date Jan 18 2005
solvent CDCl3
file /data/export/~
home/slbuch/4kb/ro~
cky/4kb_1X45_01180~
8.fid
ACQUISITION
sfrq 500.231
tn H1
at 3.283
np 64000
sw 10000.0
fb not used
bs 1
ss 1
tpwr 57
pw 9.0
dl 1
tof 1498.1
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -992.6
wp 5305.8
vs 125
sc 0
wc 250
hzmm 22.02
is 150.00
rfl 4532.9
rfp 3031.7
th 7
lm 1.000
nm ph
DEC. & VT
dfrq 125.794
dn C13
dpwr 37
dof 0
dm nnn
dmm c
def 10000
dres 1.0
homo n
PROCESSING
wtfile
proc ft
fn 131072
math f
werr
wexp
wbs
wnt
2-(2,5-dimethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 1, Entry 17)
9
8
7
6
5
4
3
2
1
-0
ppm


STANDARD PROTON PARAMETERS
expt szpu1
SAMPLE
date Jan 18 2005
solvent CDCl3
file /data/export/~
home/slbuch/4kb/ro~
cky/4kb_1X47_01180~
8.fid
ACQUISITION
sfrq 500.231
tn H1
at 3.283
np 64000
sw 10000.0
fb not used
bs 1
ss 1
tpwr 55
pw 8.5
dl 1
tof 1498.1
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -514.5
wp 5518.8
vs 115
sc 0
wc 250
hzmm 22.88
is 150.00
rfl 4422.3
rfp 3421.7
th 7
lm 1.000
nm ph
DEC. & VT
dfrq 125.794
dn C13
dpwr 37
dof 0
dm nnn
dmm c
def 10000
dres 1.0
homo n
PROCESSING
wtfile
proc ft
fn 131072
math f
werr
wexp
wbs
wnt
4,4,5,5-tetramethyl-2-(thiophen-3-yl)-1,3,2-dioxaborolane (Table 1, Entry 18)
9
8
7
6
5
4
3
2
1
-0
ppm



4.5 References

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Undergraduate Research with Prof. Uwe H. F. Bunz — 2000-2003
University of South Carolina - Columbia
Teaching Assistant
Massachusetts Institute of Technology — 2003-2004
University of South Carolina-Columbia — 2002-2003

Awards

- MIT Presidential Graduate Fellowship (2003)
- Phi Beta Kappa (2002)
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- State of South Carolina Palmetto Fellowship (1998)

Publications

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"A Highly Active Catalyst for Suzuki-Miyaura Cross-Coupling Reactions of Heteroaryl Compounds" Billingsley, K.; Anderson, K. W.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 3484-3488.

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"Palladium-Catalyzed Borylation of Aryl Chlorides: Scope, Applications, and Computational Studies" Billingsley, K.; Barder, T. E.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5359-5363.

"A General and Efficient Method for the Suzuki-Miyaura Coupling of 2-Pyridyl Nucleophiles" Billingsley, K.; Buchwald, S. L. Accepted to *Angew. Chem. Int. Ed.*

"An Improved System for the Palladium-Catalyzed Borylation of Aryl Halides with Pinacol Borane" Billingsley, K.; Buchwald, S. L. Accepted to *J. Org. Chem.*