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# A C–H Borylation Approach to Suzuki–Miyaura Coupling of Typically Unstable 2–Heteroaryl and Polyfluorophenyl Boronates

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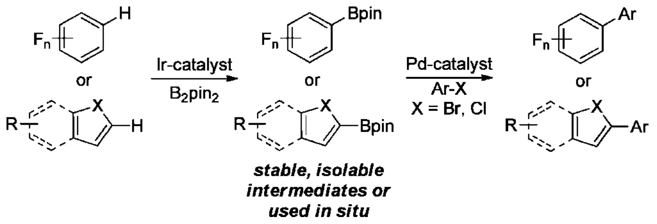
## ABSTRACT



**A method for the synthesis of biaryls and heterobiaryls from arenes and haloarenes without the intermediacy of unstable boronic acids is described. Pinacol boronate esters that are analogous to unstable boronic acids are formed in high yield by iridium-catalyzed C–H borylation of heteroarenes and fluoroarenes. These boronates are stable in the solid state or in solution and can be generated and used *in situ*. They couple with aryl halides in the presence of simple palladium catalysts, providing a convenient route to biaryl and heteroaryl products that have been challenging to prepare via boronic acids.**

Suzuki–Miyaura coupling is one of the most commonly used methods to construct carbon–carbon bonds, in part because of the stability of arylboronic acids.[1] However, coupling with several classes of organoboronates, such as 2-heteroaryl and polyfluoroaryl boronates, is challenging because the boronic acids are unstable to protodeborylation. Several approaches to enable cross-coupling of these organoboronates have been reported, including conversion to a boronic acid derivative, such as a trifluoroborate salt,[2] a cyclic triolborate,[3] a lithium borate,[4] or a MIDA boronate (MIDA = *N*-methyliminodiacetic acid)[5] and hydrolysis *in situ* to the boronic acid. Although valuable, these approaches require initial synthesis of the unstable boronic acid, often via lithiation at low temperatures. Alternatively, the coupling step is conducted with a highly reactive catalyst.[6] While the latter approach gives good yields of the coupled products, it does not address the problem of isolating, handling, and storing the boronic acid.

We report an alternative, one-pot method for the arylation of heteroarenes and fluorinated arenes by Ir-catalyzed C–H borylation, followed by Pd-catalyzed cross-coupling with pinacol boronate esters as surrogates for unstable boronic acids. This method rests upon the simplicity of forming pinacol boronates by C–H borylation that creates gaseous $H_2$ as the sole byproduct, the enhanced stability of pinacol boronates, relative to their corresponding boronic acids, and the rapid transmetalation of the resulting

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(1) (a) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(2) (a) Darses, S.; Genet, J.-P. *Chem. Rev.* **2007**, *108*, 288. (b) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275.

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

(4) (a) Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358. (b) Billingsley, K. L.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4695.

(5) Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961.

(6) (a) Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14073. (b) Han, S.; Movassaghi, M. *J. Am. Chem. Soc.* **2011**, *133*, 10768.

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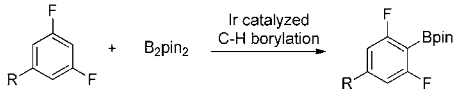
pinacol boronates with palladium complexes bearing simple phosphine ligands.

We chose to address the challenge of the Suzuki–Miyaura coupling of 2-heteroaryl boronates and polyfluoroaryl boronates because these aromatic groups are common substructures in medicinal chemistry but have been difficult to introduce by cross-coupling. While these classes of (hetero)aryl pinacol boronates can be synthesized by lithiation, followed by quenching with an alkoxyborate, or by the catalytic borylation of aryl halides, the borylation of the arene or heteroarene itself is a direct method to access these pinacol boronates.[10]

Unlike the corresponding boronic acids, the 2-heteroaryl and fluoroaryl pinacol boronate esters are stable in air at room temperature for at least 60 days without decomposition. Because these compounds can be stored without the need for cryogenic or anaerobic conditions, the corresponding pinacol boronate esters should be useful synthetic building blocks.

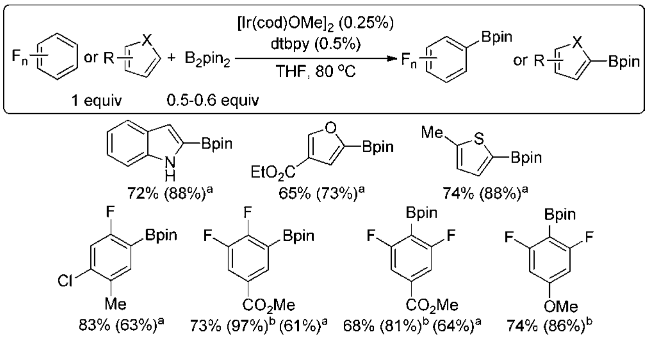
To form the 2-heteroaryl pinacol boronates, we utilized the established regioselectivity of the C–H borylation of five-membered heteroarenes at the 2-position. Reaction of five-membered or benzofused heteroarenes with bis(pinacolato)diboron ($B_2pin_2$) or pinacolborane (HBpin) in the presence of the catalyst formed *in situ* from a combination of $[Ir(cod)OMe]_2$ and 4,4′-di-*tert*-butylbipyridine (dtbpy). While the isolated yields of the 2-heteroaryl pinacol boronates are generally moderate to good, previous work has demonstrated that the GC yield of the pinacol boronate in the crude reaction mixture is high.[11] Thus a method to utilize these boronates *in situ* could potentially give higher yields of the coupled product than of the isolated pinacolboronate.

Mono- and di-*ortho*-fluoroaryl pinacol boronates also form by iridium-catalyzed C–H borylation and are stable both in the solid state and in solution.[12] Because the regioselectivity of the C–H borylation of arenes occurs at the least hindered C–H bond, we hypothesized that the reaction of a 3,5-difluoroarene with $B_2pin_2$ in the presence of the same Ir catalyst would yield a 2,6-difluoroaryl pinacol boronate (eq 1). This borylation should occur at the C–H bond *ortho* to both fluorine atoms due to the small size of fluorine.



(1)

Scheme 1. Borylation of Heteroarenes and Fluoroarenes



[a] Isolated yield obtained when 1.1 equiv of HBpin was used as the boron source. [b] GC yield.

Indeed, the borylation of polyfluorinated arenes occurred ortho to the fluorine atom with $B_2pin_2$ or HBpin as the boron source (Scheme 1). These reactions occur with 4-fluoroarenes, 3,4-difluoroarenes, and 3,5-difluoroarenes containing electron-donating or -withdrawing substituents. Similar to 2-heteroaryl pinacol boronates, these fluoroarylpinacol boronates are stable to chromatography. Again, yields of the borylation product from the crude reaction mixture determined by GC are high, suggesting that a method to utilize these boronates *in situ* could give coupled products in higher yield than sequences in which the boronate is isolated.

If the stability of these boronates is to be an asset, however, they must undergo cross-coupling under mild conditions with accessible catalysts. After examining several catalysts, we found that the classic catalyst generated from 1 mol % $Pd(dba)_2$ and 2 mol % $P(o\text{-tol})_3$ led to the coupling of these organoboronates with a variety of aryl bromides at room temperature with $Na_2CO_3$ as base in a 10:1 mixture of $THF/H_2O$.[13]

Having identified a suitable catalyst and reaction conditions for the Suzuki–Miyaura coupling of 2-heteroaryl boronates with aryl bromides, we developed a one-pot process for heteroarene borylation and Pd-catalyzed coupling. The scope of this sequence is shown in Scheme 2.

A variety of heterocycles, including pyrroles, indoles, furans, benzofurans, and thiophenes containing a variety of substituents, underwent the combination of borylation and coupling with a series of electron-rich and -poor aryl and heteroaryl bromides. In addition, *ortho*-substituted

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(7) (a) Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2116. (b) Amatore, C.; Jutand, A.; Le Duc, G. *Chem.—Eur. J.* **2011**, *17*, 2492.

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(10) (a) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508. (b) Billingsley, K. L.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 5589. (c) Kleeberg, C.; Dang, L.; Lin, Z.; Marder, T. B. *Angew. Chem., Int. Ed.* **2009**, *48*, 5350.

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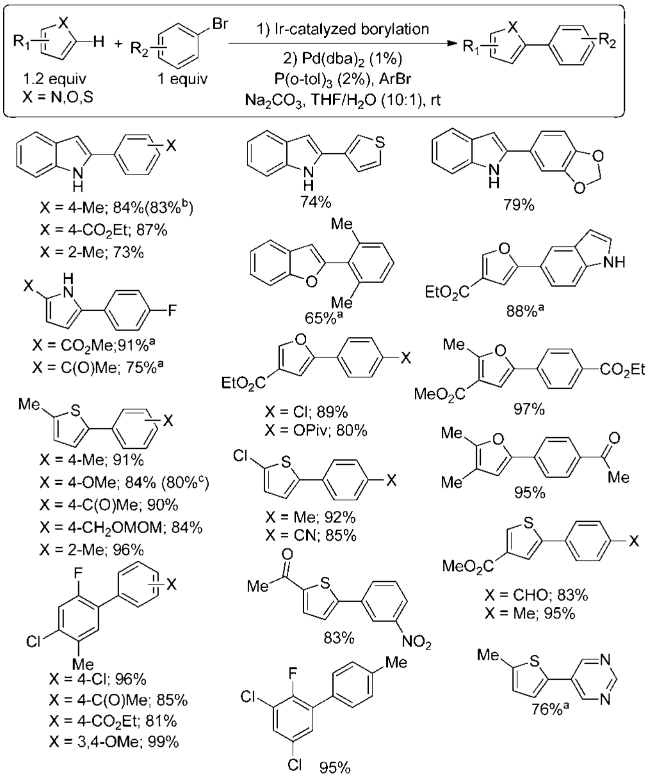
**Scheme 2.** Scope of the Combined Ir-Catalyzed Borylation and Pd-Catalyzed Cross-Coupling of Heteroarenes and Monofluoroarenes with Aryl Bromides



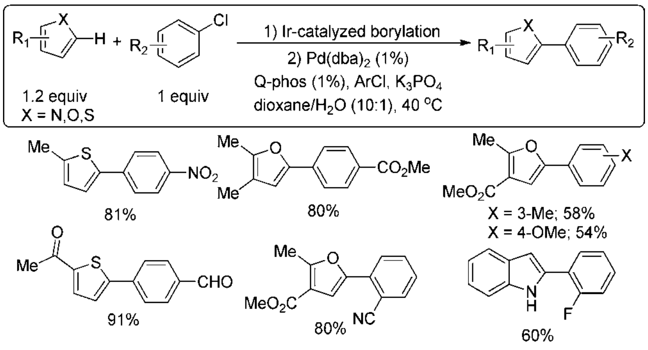
[a] Pd-catalyzed coupling at 50 °C. [b] Yield with 50 ppm Ir catalyst, 0.5% Pd catalyst, and 1.05 equiv of indole. [c] Yield without use of a drybox.

and *ortho*-disubstituted aryl bromides reacted with the intermediate heteroarylboronic ester in good yield. Esters, aldehydes, aryl halides, trifluoromethyl groups, and ketones with enolizable hydrogens were well tolerated. A MOM-protected alcohol and an aryl pivalate, which can be used for orthogonal Ni-catalyzed cross-coupling,[14] also underwent the one-pot sequence in good yield. The combination of heteroarene borylation and cross-coupling occurred on a larger 5 mmol scale with lower catalyst loadings than the reactions on a smaller scale. In addition, decreasing the amount of the starting heteroarene to 1.05 equiv did not diminish the yield of the biaryl product.

In addition to heteroarenes, fluoroarenes underwent the combination of C−H borylation and coupling with aryl bromides in high yield. With appropriate substitution on the fluoroarene, the borylation occurs *ortho* to fluorine. The resulting pinacol boronates couple in high yield with several aryl bromides at room temperature in the presence of the Pd−P(*o*-tol)$_3$ catalyst (Scheme 2).

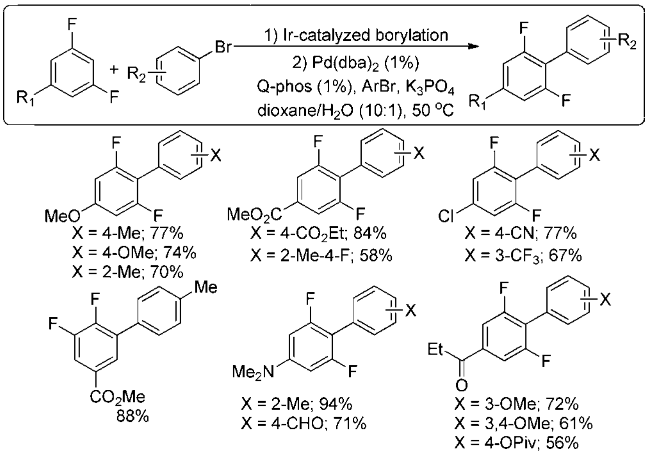
The coupling of 2-heteroaryl pinacol boronate esters with less reactive aryl chlorides also occurred in good yield (Scheme 3). Coupling of these less reactive aryl chlorides was conducted with 1 mol % Pd(dba)$_2$ and 1 mol % of the hindered alkylphosphine Q-phos (1,2,3,4,5-pentaphenyl-1′-(di-*tert*-butylphosphino)ferrocene)[15] and K$_3$PO$_4$ as a base in a 10:1 mixture of 1,4-dioxane/H$_2$O at 40 °C. Similar to the borylation and coupling sequence with aryl bromides, this method tolerates a variety of functional groups and occurred with electronically varied aryl chlorides.

**Scheme 3.** Scope of Ir-Catalyzed Borylation/Pd-Catalyzed Cross-Coupling of Heteroarenes with Aryl Chlorides



The coupling of 2,3-difluoroaryl and 2,6-difluoroaryl pinacol boronate esters with aryl bromides was conducted in the presence of 1 mol % of the Pd-Q-phos catalyst with K$_3$PO$_4$ as the base in a 10:1 mixture of 1,4-dioxane/H$_2$O at 50 °C to outpace protodeborylation. As shown in Scheme 4, the two-step, one-pot procedure for borylation of a difluoroarene and coupling occurred without isolation of the fluoroarylboronate with a variety of aryl bromides, including electron-rich, electron-poor, and *ortho*-substituted aryl bromides. This method tolerates a variety of functional groups but proceeded in higher yield with arylboronates containing an electron-donating substituent than with pinacolboronates containing an electron-withdrawing substituent at the *para* position.

**Scheme 4.** Scope of Ir-Catalyzed Borylation/Pd-Catalyzed Cross-Coupling of Polyfluorophenyl Derivatives with Aryl Bromides



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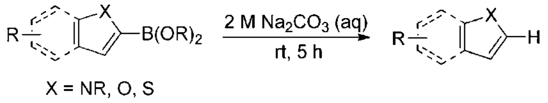
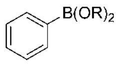
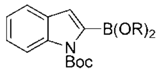
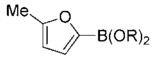
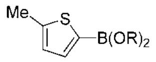
[14] Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2010**, *111*, 1346.

**Table 1.** Decomposition of Heteroaryl Pinacol Boronate Esters with Aqueous Base at Room Temperature



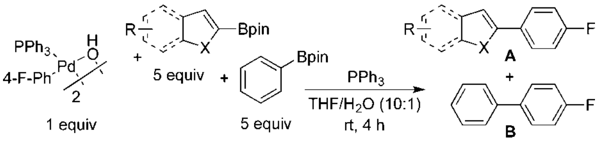
| entry | aryl boronate | %Ar-Bpin remaining | % ArB(OH)$_2$ remaining |
|---|---|---|---|
| 1 |  | 87% | - |
| 2 |  | 73%[a] | <2% |
| 3 |  | 72% | 9% |
| 4 |  | 88% | 74% |

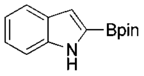
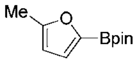
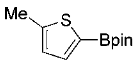
[a] The analogous reaction with the corresponding indolylboronic ester left 87% of the ArBpin unreacted.

Several experiments revealed the factors that enable the coupling of the pinacol boronate esters in high yields. The rate of decomposition of the pinacol boronate esters, relative to that of the coupling reaction, was determined by treating a THF solution of three different 2-heteroaryl pinacol boronate esters with the 2 M aqueous $Na_2CO_3$ used in the catalytic reaction (Table 1). A majority of the 2-heteroaryl pinacol boronate esters remained in solution after 5 h, the approximate time of the catalytic reaction. The amount of decomposition of the nitrogen and sulfur heteroaryl boronates was approximately the same as that of phenyl pinacol boronate. The 2,6-difluorophenyl pinacol boronate esters decomposed within 30 min at 50 °C. This greater lability explains the need to use a modern catalyst to achieve high yields for the Suzuki–Miyaura coupling reaction with these boronates.

This greater stability of pinacolboronate esters is only beneficial if transmetalation of the boronic ester, which is commonly proposed to be turnover-limiting, is faster than the other steps of the mechanism of cross-coupling. To assess the rates of transmetalation of the heteroaryl and fluoroaryl boronates, we conducted a series of competition experiments involving the reaction of an arylpalladium(II) hydroxide complex, shown recently to be the species that reacts with arylboronates,[7] with 5 equiv of a 2-heteroaryl pinacol boronate ester and phenyl pinacol boronate. These reactions formed > 90% of the product derived from the 2-heteroaryl pinacol boronate ester (Table 2); negligible amounts of product from coupling of the phenyl boronate ester ( < 5%) were observed. Thus, transmetalation of the 2-heteroaryl pinacol boronate esters is significantly faster than that of standard aryl pinacol boronate esters. The origin of this greater reactivity awaits further study.

**Table 2.** Competition Experiments between 2-Heteroaryl and Phenyl Pinacol Boronate Esters



| entry | heteroaryl Bpin | yield of A | yield of B |
|---|---|---|---|
| 1 |  | 93% | 5% |
| 2 |  | >98% | 1% |
| 3 |  | >98% | 1% |

Similar competition experiments showed that the 2, 6-difluorophenylboronic ester reacts faster than the corresponding phenylboronic ester. The competition reaction yielded almost exclusively the product from the 2,6-difluorophenyl pinacol boronate ester (see Supporting Information).[16] These competition experiments, in combination with the data on the stability of the boronic esters, indicate that the high yields for coupling of 2-heteroaryl pinacol boronates and fluoroaryl pinacol boronates result from the combination of their stability under aqueous conditions, but rapid transmetalation.

In summary, 2-heteroaryl and polyfluoroaryl pinacol boronate esters form in good yield by Ir-catalyzed C–H borylation, and Suzuki–Miyaura cross-coupling of these boronates generated *in situ* occurs with simple palladium catalysts. Although useful as formed *in situ*, the pinacol boronate esters are isolable and stable in air at room temperature, as opposed to the corresponding boronic acids, which require cold, anaerobic storage. Because of its generality, this method should be useful for the preparation of heteroaryl and fluoroaryl compounds with diverse applications.

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**Supporting Information Available.** Detailed experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(15) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.

(16) This finding with the boronic esters is consistent with previously reported kinetic data on transmetalation of fluorinated aryl boronic acids. See ref 6a.