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J. Am. Chem. Soc., **Just Accepted Manuscript** • Publication Date (Web): 15 Sep 2015

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C-H Functionalization at Sterically Congested Positions by the Platinum-Catalyzed Borylation of Arenes

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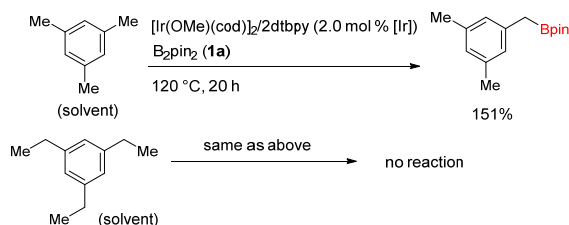
Supporting Information Placeholder

ABSTRACT: Despite significant progress in the area of C-H bond functionalization of arenes, no general method has been reported for the functionalization of C-H bonds at the sterically encumbered positions of simple arenes, such as mesitylene. Herein, we report the development of the first platinum-based catalyst for C-H borylation of arenes and heteroarenes. Notably, this method exhibited high tolerance towards steric hindrance and provided rapid access to a series of 2,6-disubstituted phenylboronic esters, valuable building blocks for further elaborations.

Catalytic C-H bond functionalization is one of the most simple and straightforward methods for the synthesis of complex organic molecules from readily available hydrocarbons and their derivatives,¹ and two general strategies have been established to date for this process (Fig. 1A). One involves the use of a substrate containing a preinstalled coordinating group, which can direct a metal catalyst to a targeted C-H bond in a regioselective manner.^{1c-1.2} In contrast, the second strategy involves the use of steric control, which allows for the direct functionalization of the least hindered C-H bond of an aromatic system.³⁻⁵ However, neither of these two strategies can be applied to the catalytic functionalization of the C-H bonds located at the sterically congested positions of simple arenes, such as mesitylene. For example, the application of iridium-catalyzed borylation, the state-of-the-art method for the functionalization of simple arenes, to mesitylene only resulted in the functionalization of the more accessible benzylic C-H bond (Fig. 1B).⁴ Furthermore, it is not possible to functionalize the more hindered C(sp²)-H bonds found in 1,3,5-triethylbenzene using existing catalytic systems. Based on these limitations, the development of new methods for the C-H functionalization of hindered arenes is highly desired because the unusual steric properties exerted by hindered arenes can be used in a variety of different fields, including pharmaceuticals,⁶ photocatalysis,⁷ steric protection of reactive chemical species,⁸ chiral catalysis⁹ and functional polymers¹⁰ (Fig. 1C). Herein, we report the development of the first platinum catalyst for the C-H borylation of arenes and heteroarenes. This new platinum system was found to be highly tolerant to steric hindrance and allowed for the borylation of 1,3,5-trisubstituted arenes. Notably, the 2,6-disubstituted phenylboronic esters generated in this way are useful building blocks for the synthesis of hindered arene derivatives.

Iridium/bipyridine-based complexes are currently recognized as the most reliable catalysts for C-H borylation of arenes.⁴ The exploration of new catalytic systems continue to be important in addressing the remaining challenges in C-H borylation reactions. Ligand modification is a viable approach and has been successful, for example, in achieving otherwise difficult ortho-selective borylations of arenes containing an appropriate directing group¹¹ or in improving meta/para regioselectivity for mono-substituted benzenes.¹² Another rewarding approach for the development of new C-H borylation catalysts involves the use of other suitable central metals. Although this approach has focused primarily on replacing precious iridium with base metal alternatives,^{13,14} varying the central metal could also provide opportunities for the development of C-H borylation catalysts with new reactivity and/or selectivity profiles.

On the basis of our previous identification of a nickel catalyst for the C-H borylation of arenes,^{14c} we investigated the reactivity of the corresponding platinum congener. Platinum complexes have been used in catalytic hydroboration¹⁵ and diboration,¹⁶ as well as in C-H activation,¹⁷ but never in C-H borylation reactions. We initially examined the reaction of B₂pin₂ (**1a**) with benzene using Karstedt's catalyst Pt₂(dvtms)₃ (**3**, dvtms = divinyltetramethylsiloxane),¹⁸ which is a commercially available platinum(0) source. We found that **3** exhibited slight activity (TON = 5). Our ongoing interest in the use of N-heterocyclic carbene (NHC) ligands for the catalytic transformations of strong bonds¹⁹ prompted us to examine the catalytic activity of a series of Pt(NHC)(dvtms) complexes, which are air stable and readily prepared in two steps from H₂PtCl₆ (See SI for details). As shown in Table S1 in the Supporting Information (SI), the introduction of NHCs improved the turnover number (TON) of the catalysts with the ICy-ligated complex **4g** being optimal under these conditions (TON = 157). A 2.0 mol % loading of **4g** provided the borylated product **2** in 93% yield when B₂pin₂ (**1a**) was used as the boron source (eq 1). The use of HBpin (**1b**) did not give an appreciable amount of **2** under these platinum-catalyzed conditions.

A. Strategies for C(sp²)-H FunctionalizationB. Attempted C(sp²)-H Borylation of Hindered Arenes

C. Applications of Hindered Aryl Groups

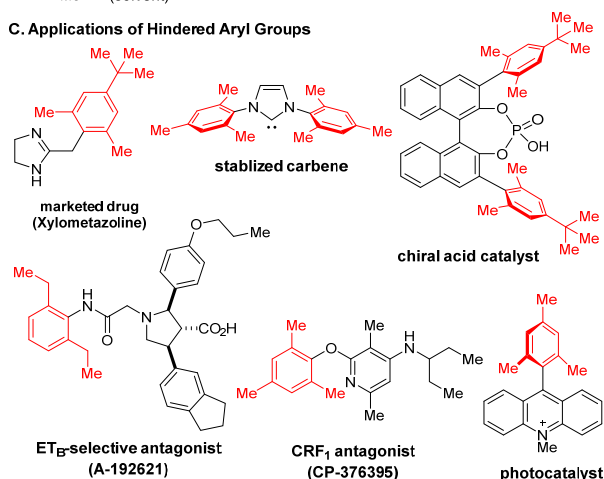
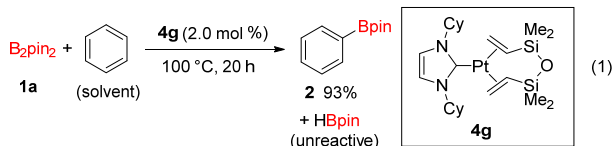


Fig. 1. Challenges and Importance of the C-H Functionalization of Hindered Arenes



The platinum complex **4g** catalyzed the borylation of a broad range of arenes bearing electron-withdrawing and electron-donating substituents, including toluene, anisole, chlorobenzene and trifluoromethylbenzene, affording a mixture of regioisomers (Fig. 2A). A unique feature of this platinum system is its lower sensitivity to steric effects, as exemplified by the formation of significant amounts of the ortho isomers of **5**, **6** and **8**. The **4g**-catalyzed borylation of m-xylene occurred at its most congested position (i.e., 2-position), in addition to its 4- and 5-positions. This is in sharp contrast to the results obtained using an iridium catalyst, which gave the least hindered 5-borylated product exclusively.²⁰ The robustness of this platinum catalyst towards the steric demands posed by ortho substituents prompted us to examine the borylation of a mesitylene substrate. Pleasingly, the borylation of the C(sp²)-H bond of mesitylene was successfully accomplished to form **10** as the sole product. Reinvestigation of the ligands showed that the IPr-bound platinum complex **4b** exhibited higher activity towards the reactions of congested arenes, and gave an improved yield of **10** (72%). To the best of our knowledge, there have been no reports in the literature pertaining to C(sp²)-H borylation of mesitylene, except in the presence of a heterogeneous iron catalyst (41% GC yield after 4 days).^{14b} This difficulty can be attributed in part to the benzylic C-H bonds of

mesitylene being more accessible than the hindered C(sp²)-H bonds and therefore activated with greater ease (see Fig. 1B).

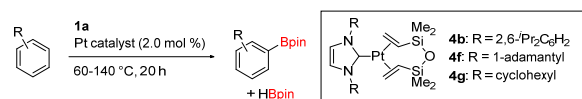
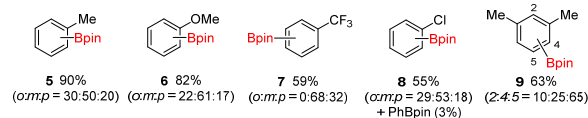
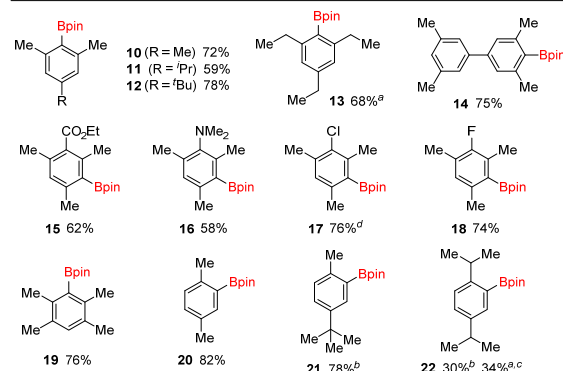
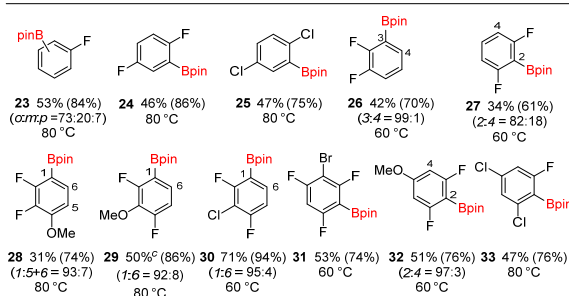
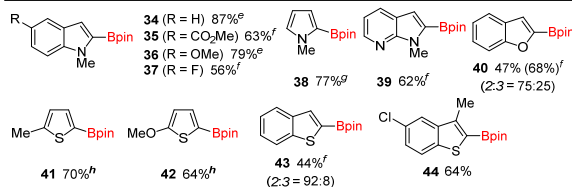
A. Conditions: **1a** (0.30 M), catalyst = **4g**, arene (solvent), 120 °C. Yields are based on **1a**.B. Conditions: **1a** (0.30 M), catalyst = **4b**, arene (solvent), 120 °C. Yields are based on **1a**.C. Conditions: **1a** (ca. 2 M), catalyst = **4g**, arene (5.0 equiv), 60-80 °C. Yields are based on **1a**.D. Conditions: catalyst = **4g**, heteroarene (0.80 equiv, 0.3 M) in heptane, 100 °C. Yields are based on heteroarene. For compounds **38**, **41** and **42**, yields are based on **1a**.

Fig. 2. Platinum-Catalyzed Borylation of Various Arenes Isolated yields are shown. The yields in parentheses are those determined by ¹H NMR. The ratio of regioisomers were determined by ¹H NMR spectroscopy or GC analysis. ^aAt 140 °C. ^b**4f** was used as the catalyst. ^cThe borylated product was isolated following its conversion to the corresponding phenol. ^dDechlorinated product was also formed (4%). ^e**1a** (2.0 equiv relative to heteroarene) was used. ^f**4g** (4.0 mol %) was used. ^gN-Methylpyrrole (5.0 equivalent to **1a**) was used. ^hHeteroarene was used as the solvent.

The platinum/NHC catalyst effectively borylated a series of 1,3,5-trisubstituted arenes to form the corresponding arylboronic esters bearing two ortho substituents, as in **10-18** (Fig. 2B). It is noteworthy that 1,3,5-triethylbenzene was borylated through the activation of one of its C(sp²)-H bonds shielded by two ortho ethyl groups to generate **13**. The use of an iridium/dtbpy catalyst instead resulted in no conversion (Fig. 1B). p-Xylene was an excellent substrate for this borylation, giving **20** in good yield, indicat-

ing that the approach of the platinum species to the C(sp²)-H bond of the substrate was not inhibited by the ortho methyl group. A tert-butyl group was found to be sufficiently large to block the borylation of the ortho C(sp²)-H bonds, as shown by the selective formation of **21** from 1-tert-butyl-4-methylbenzene. In contrast, the C(sp²)-H bonds ortho to an isopropyl group was found to be reactive, which enabled the synthesis of **22**, again highlighting the robustness of this platinum catalyst to steric hindrance.

The introduction of a fluorine atom to the benzene ring had a significant impact on both the reactivity and selectivity of the platinum-catalyzed C-H borylation (Fig. 2C). For example, the **4g**-catalyzed borylation of fluorobenzene proceeded efficiently (84% NMR total yield), even when the amount of the substrate was decreased to 5.0 equiv relative to **1a**. Another prominent feature of the borylation of fluorobenzene was the ortho selectivity of 73%, which clearly suggests that the fluorine atom has an ortho directing effect.²¹ Although similar directing effects by fluorine have been observed with rhodium^{22a} and cobalt^{14d} catalysts, the scope of the directing effect was not explored extensively using different fluoroarene substrates in these studies. Notably, difluoro-substituted benzenes provided efficient access to the corresponding ortho borylated products **26-30** in a regioselective manner, even when the C-H bond was not the least hindered C-H bond in the fluoroarene substrate. In the case of 1,3-difluorobenzene, borylation occurred preferentially at the most-congested 2-position to give **27**. In contrast, the iridium-catalyzed borylation of 1,3-difluorobenzene has been reported to give all three regioisomers, with the least-hindered 5-borylated isomer being formed as the major product.²³ Although the isolated yields of **23-33** were modest because of the instabilities during chromatographic isolation, these borylated products can be used directly to the subsequent transformation without isolation. A similar activating effect was also observed with chloroarenes, as exemplified by the formation of **25** from 1,4-dichlorobenzene. 1,3,5-Trisubstituted fluoroarenes have also performed as good substrates, leading to the formation of the corresponding ortho-disubstituted fluorophenylboronic esters **31-33**, which are useful building blocks for the synthesis of fluorinated aromatic compounds.²⁴

Finally, **4g**-catalyzed borylation of a series of heteroarenes was examined (Fig. 2D). Indoles were excellent substrates for this borylation, enabling their use as limiting reagents. Esters (**35**) and ethers (**36**) were also well tolerated, providing the regioselective access to the corresponding 2-borylated products. Fluorine substitution did not affect the regioselectivity, and **37** was obtained. Although less reactive, pyrroles and thiophenes also underwent borylation, resulting in the formation of the corresponding 2-borylated products (**38**, **41** and **42**). Benzofused heteroarenes, including benzofurans and benzothiophenes also reacted successfully under the borylation conditions to give **40**, **43** and **44**.

Although further study is needed to clarify the detailed mechanism of platinum-catalyzed borylation, several preliminary observations are worthy of note. The presence of an induction period of 0.3-1.0 h implies that the platinum precatalyst needs to be activated, most likely involving the dissociation of the dtvms ligand, prior to its participation in the C-H borylation.²⁵ It was also confirmed that the HBpin generated in the reaction of benzene with **1a** in the presence of **4g** remained unreacted (See SI for details). A comparison of the initial rates for the separate reactions of benzene and benzene-*d*₆ showed that this borylation had a large kinetic isotope effect ($k_H/k_D \sim 4.8$), indicating that C-H bond cleavage occurred during the turnover-limiting step of the catalytic cycle.²⁶

The present platinum-catalyzed protocol can be successfully used for the gram scale synthesis of 2,6-disubstituted phenylboronic ester derivatives such as **12** (Fig. 3). Hindered ArBpin compounds were converted to a wide range of derivatives; for example, hin-

dered phenol **45** and aniline **46** can be synthesized via known oxidation and amination²⁷ methods, respectively. The steric demand in **12** did not hamper the cross-coupling processes, and therefore allowed for the introduction of aryl and alkyl groups, as in **47** and **48**.²⁸

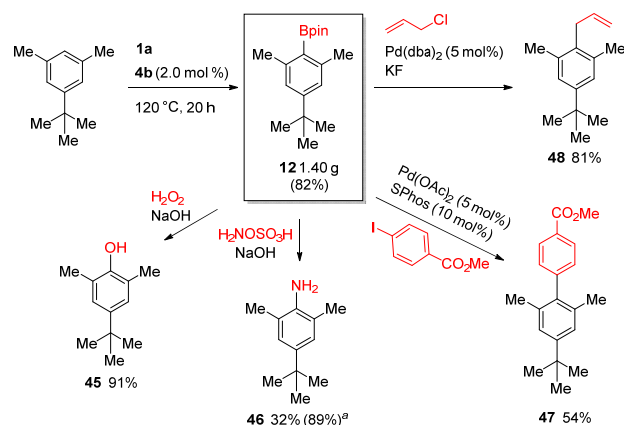


Fig. 3. Scale-Up of the Borylation and Synthetic Utility of the Product Isolated yields are shown. ^aYield based on the recovered starting material.

In summary, we have developed the first platinum catalyst for C-H borylation of arenes. Platinum complexes ligated with NHC ligands, such as ICy and IPr, performed as particularly effective catalysts for the borylation of a range of arenes and heteroarenes. This platinum system exhibited two useful features that have not been observed for common iridium-based catalysts. The first of these features was the high tolerance of the catalytic systems to steric hindrance, which allowed for the borylation of 1,3,5-trisubstituted arenes to give the corresponding 2,6-disubstituted phenylboronic ester derivatives. The second key feature was the ortho-directing effect of fluorine substituents, which allowed the facile synthesis of ortho-fluorophenylboronic ester derivatives. Both classes of ArBpin readily accessed by this platinum-catalyzed C-H borylation represent useful building blocks in organic synthesis. Further studies aimed at expanding upon the application of this platinum catalyst to other catalytic transformations and C-H borylations using other central metals are currently being investigated in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, additional substrate scope and characterization of new compounds are available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas "Molecular Activation Directed toward Straightforward Synthesis" from MEXT, Japan. M.T. was also supported by the "Elements Strategy Initiative to Form Core

Research Center⁷ from MEXT. T.F. expresses his special thanks for a JSPS Research Fellowship for Young Scientists. We also thank the Instrumental Analysis Center, Faculty of Engineering, Osaka University, for their assistance with HRMS.

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