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

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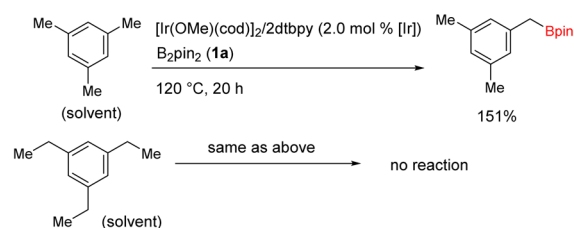
Ⓢ Supporting Information

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 toward 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 (Figure 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.[1e−i,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 (Figure 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 catalysis,[9] and functional polymers[10] (Figure 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.
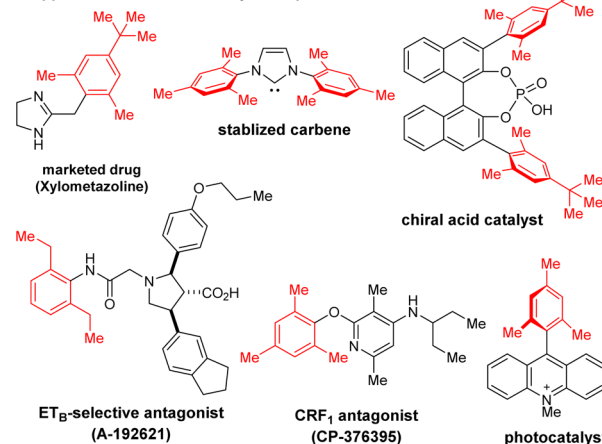

**Figure 1.** Challenges and importance of the C−H functionalization of hindered arenes.

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 group[11] or in improving meta/para regioselectivity for

monosubstituted 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,[14e] we investigated the reactivity of the corresponding platinum congener. Platinum complexes have been used in catalytic hydroboration[15] and diboration,[16] as well as in C−H activation,[17] but never in C−H borylation reactions. We initially examined the reaction of B_2pin_2 (**1a**) with benzene using Karstedt's catalyst $Pt_2(dvtms)_3$ (**3**, dvtms = divinyltetramethyldisiloxane),[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 bonds[19] 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 H_2PtCl_6 (see Supporting Information (SI)for details). As shown in Table S1 in the 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 B_2pin_2 (**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.
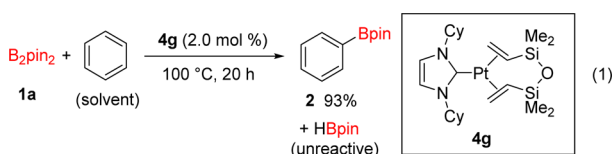
The platinum complex **4g** catalyzed the borylation of a broad range of arenes bearing electron-withdrawing and electron-donating substituents, including toluene, anisole, chlorobenzene, and trifluoromethylbenzene, affording a mixture of regioisomers (Figure 2A). A unique feature of this platinum system 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 toward 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 toward 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 Figure 1B).
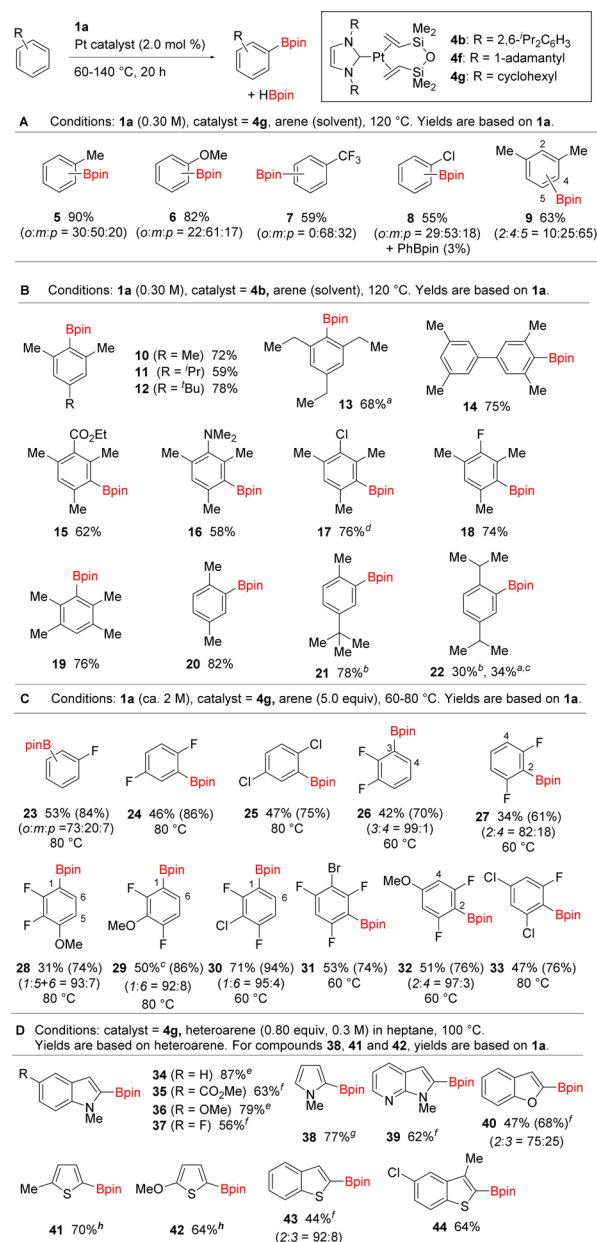
Figure 2. Platinum-catalyzed borylation of various arenes. Isolated yields are shown. The yields in parentheses are those determined by ¹H NMR. The ratio of regioisomers were determined by ¹H NMR spectroscopy or GC analysis. [a]At 140 °C. [b]Compound **4f** was used as the catalyst. [c]The borylated product was isolated following its conversion to the corresponding phenol. [d]Dechlorinated product was also formed (4%). [e]Compound **1a** (2.0 equiv relative to heteroarene) was used. [f]Compound **4g** (4.0 mol %) was used. [g]*N*-Methylpyrrole (5.0 equiv to **1a**) was used. [h]Heteroarene 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** (Figure 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 (Figure 1B). *p*-Xylene was an excellent substrate for this borylation, giving **20** in good yield, indicating 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 were 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 reaction (Figure 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[22] 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 (Figure 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 dvtms 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 ($k_H/k_D \approx 4.8$), 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-disusutituted phenylboronic ester derivatives such as **12** (Figure 3). Hindered ArBpin
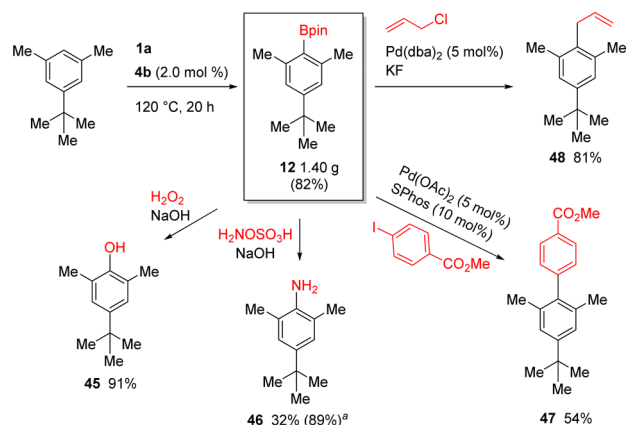

Figure 3. Scale-up of the borylation and synthetic utility of the product. Isolated yields are shown. [a]Yield based on the recovered starting material.

compounds were converted to a wide range of derivatives; for example, hindered phenol **45** and aniline **46** can be synthesized via known oxidation and amination[27] 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]

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

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b07677.

> Detailed experimental procedures, additional substrate scope, and characterization of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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