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# C–H Borylation by Platinum Catalysis

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## Abstract

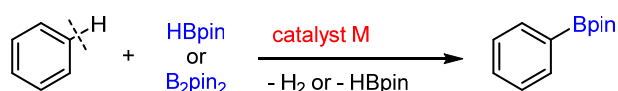
Herein, we describe the platinum-catalyzed borylation of aromatic C–H bonds. *N*-Heterocyclic carbene-ligated platinum catalysts are found to be efficient catalysts for the borylation of aromatic C(sp<sup>2</sup>)–H bonds when bis(pinacolato)diboron is used as the boron source. The most remarkable feature of these Pt catalysts is their lack of sensitivity towards the degree of steric hindrance around the C–H bonds undergoing the borylation reaction. These Pt catalysts allow for the synthesis of sterically congested 2,6-disubstituted phenylboronic esters, which are otherwise difficult to synthesize using existing C–H borylation methods. Furthermore, platinum catalysis allows for the siteselective borylation of the C–H bonds *ortho* to fluorine substituents in fluoroarene systems. Preliminary mechanistic studies and work towards the synthetic application of this platinum catalyzed C–H borylation process are described.

## 1. Introduction

Catalytic C–H bond functionalization is one of the simplest and most straightforward methods for the synthesis of complex organic molecules from readily available hydrocarbons and their derivatives.<sup>1</sup> One of the most reliable methods for C–H functionalization involves the use of a substrate containing a preinstalled coordinating group, which can direct a metal catalyst to react with a targeted C–H bond in a siteselective manner (directed methodology).<sup>1a,c,d,f,i,j</sup> Although this method works well for the activation of C–H bonds that are located in close proximity to a directing group (normally C–H bonds positioned *ortho* to a directing group in an aromatic system), it cannot be applied to substrates without a directing group or C–H bonds that are remote from a directing group.<sup>2</sup> C–H functionalization methods that do not rely on a directing group (i.e., undirected methodology) are highly desired because they could be used to achieve unique patterns of siteselectivity that would be otherwise unattainable using directed methods. Methods of this type would therefore to expand the substrate scope of these reactions considerably.<sup>3</sup> The siteselectivity of undirected C–H functionalization reactions is predominantly controlled by steric effects, which generally result in the direct functionalization of the least hindered C–H bond.<sup>4,5,6</sup>

C–H borylation is currently recognized as one of the most powerful methods for the undirected functionalization of C–H bonds (Figure 1).<sup>4,5</sup> The catalytic borylation of C–H bonds allows for the direct introduction of a synthetically useful boron functionality from readily available starting materials.<sup>5</sup> Among the variety of catalysts reported for C–H borylation, the Ir/dtbpy-based complexes developed by Miyaura, Ishiyama and Hartwig can catalyze the borylation of aromatic C–H bonds with high efficiency and selectivity in an undirected manner.<sup>4</sup> The siteselectivity of C–H borylation reactions is normally controlled by the steric environment surrounding the reacting C–H bonds. For example, the C–H borylation of 1,3-

disubstituted benzene substrates occurs exclusively at the 5-position. The outstanding catalytic activity and selectivity of iridium systems has resulted in their practical application in various areas of materials science and fine chemical synthesis. Since the first report on Ir/dtbpy catalysts, considerable progress has been made in the field of C–H borylation by modifying the properties of the ligands attached to the iridium complex. For example, phosphine ligands, such as bisphosphines and pincer-type ligands, can also be employed for iridium-catalyzed C–H borylation.<sup>7</sup> Furthermore, phenanthroline ligands have been reported to improve catalytic activity of iridium systems compared with dtbpy.<sup>8</sup> Several other N–N and N–B bidentate ligands have also been employed as effective ligands for iridium catalysis.<sup>9</sup> Several supported iridium systems have also been developed as catalysts for C–H borylation reactions.<sup>10</sup> In addition to improvements in catalytic efficiency, novel levels of siteselectivity that go beyond simple steric control can be achieved by tuning the properties of the ligand. For example, the appropriate choice of ligand allowed for the iridium-catalyzed C–H borylation of arenes to occur in a directed manner to give the *ortho* borylated product selectively.<sup>10a,11</sup> *Meta*-selective borylation can be accomplished using elaborate ligands containing a secondary interaction site through hydrogen bonding,<sup>12a</sup> electrostatic<sup>11c</sup> and ionic interactions.<sup>12b</sup> The *para*-selective borylation of monosubstituted benzene systems has also been reported using bulky phosphine ligands.<sup>13</sup> Addition of a catalytic amount of base was reported to be effective for the selective multiborylation of arenes.<sup>14</sup>



Known: M = Ir, Rh, Co, Fe, Ni

This Work: M = Pt

**Figure 1.** Transition Metal-Catalyzed Borylation of Aromatic C–H Bonds

Another promising approach for the development of new C–H borylation catalysts would involve the replacement of iridium with another metal. The catalytic activity of rhodium for C–H borylation reactions has long been established,<sup>15</sup> especially for the borylation of C(sp<sup>3</sup>)–H bonds.<sup>16</sup> Cobalt-based catalysts have been studied extensively by Chirik, who demonstrated that well-defined pincer cobalt complexes could effectively promote C–H borylation reactions.<sup>17</sup> Iron complexes have also been shown to be suitable metal centers for C–H borylation reactions when they are combined with hydrogen acceptors or performed under photochemical conditions.<sup>18</sup> Our group as well as Itami's group reported that nickel can catalyze the borylation of C–H bonds in arenes and 5-membered heteroarenes.<sup>19</sup> These developments are important in the sense that they highlight the possibility of replacing precious iridium with base metal

alternatives. An even more important aspect of these works is that varying the central metal can be used as the general strategy to provide new opportunities for the development of C–H borylation catalysts with new reactivity and/or selectivity profiles from existing iridium catalysts.<sup>20</sup>

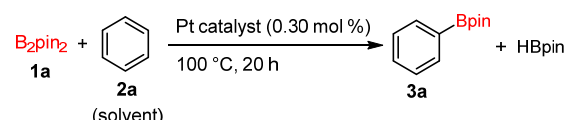
Based on our previous results for the nickel-catalyzed C–H borylation of arenes, we became interested in the reactivity of its heavier congener platinum for the C–H borylation of arenes. When we initiated this study, there were, to the best of our knowledge, no other reports in the literature describing the use of a platinum complex in a C–H borylation reaction. The catalytic C–H functionalization reactions of arenes using platinum catalysts have been studied to a much lesser extent<sup>21</sup> than those involving palladium and nickel catalysts, and only a few examples can be found in C–H silylation,<sup>22</sup> intramolecular C–H amination,<sup>23</sup> hydroarylation<sup>24</sup> and arylation.<sup>25</sup> In contrast, platinum complexes are well known as efficient catalysts for hydroboration and diboration reactions,<sup>26</sup> which have been postulated to be mediated by a platinum-boryl intermediate.<sup>27</sup> We hypothesized that a platinum-boryl species could also mediate C–H borylation reactions if it was used with an appropriate choice of the ligand and/or additives. Herein, we report that *N*-heterocyclic carbene (NHC)-ligated platinum catalysts can efficiently borylate aromatic C–H bonds (Figure 1).<sup>28</sup> The most fascinating feature of this platinum catalyst system is its high tolerance for steric hindrance, which allows for the borylation of mesitylene derivatives at their C(sp<sup>2</sup>)–H bonds. It is noteworthy that Takaya and Iwasawa independently reported that platinum catalysts bearing a pincer ligand can effect the C–H borylation of polyfluorinated arenes.<sup>29</sup>

## 2. Results and Discussion

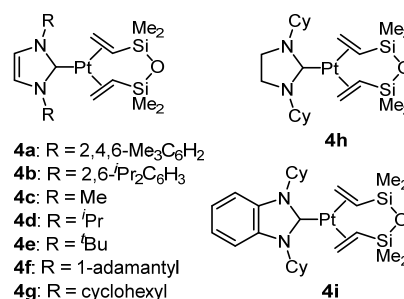
**C–H Borylation with Pt/NHC Complexes.** We initially evaluated the performance of Karstedt's catalyst **4** [Pt<sub>2</sub>(dvtms)<sub>3</sub>, dvtms = 1,3-divinyltetramethyldisiloxane] for the reaction of benzene with bis(pinacolato)diboron (**1a**), and found that this system produced a small amount of the target borylated product **3a** (TON = 5, Table 1, Entry 1). Our ongoing interest in the use of NHC ligands<sup>30</sup> and the effectiveness of NHCs as ligands in our previously reported nickel-catalyzed C–H borylation reaction<sup>19a</sup> led us to investigate the catalytic activity of Pt/NHC catalysts. We selected Pt(NHC)(dvtms) complexes in this particular case because they are air stable and easy to handle platinum catalyst precursors, which can be prepared in two steps from H<sub>2</sub>PtCl<sub>6</sub> (see SI for details). The Pt(NHC)(dvtms) complexes have been reported to be effective catalysts for hydrosilylation.<sup>31</sup> In the current study, the introduction of NHCs generally led to an improvement in the turnover number (TON) values of the catalysts. For example, the IMes-ligated platinum complex **4a** resulted in an 8-fold improvement in the TON to 40 (Entry 2), whereas the IPr complex **4b** gave none of the desired borylated product (Entry 3). Among the NHCs examined in this study, the ICy-ligated complex **4g** was determined to be optimal in terms of its TON for the borylation of benzene (Entry 8). In the presence of 2 mol% of **4g**, the borylated product **3a** was isolated in 93% yield (Scheme 1). In contrast, phosphine and bipyridine ligands were much less effective than **4g** (Entries 11–13). Diboron reagent **1a** was determined the most effective boron source for this platinum-catalyzed C–H borylation reaction. The use of other boron reagents such as pinacolborane (HBpin) or bis(neopentylglycolato)diboron (B<sub>2</sub>nep<sub>2</sub>) gave insufficient results (1% and 6% yield, respectively, in the presence of 2 mol% **4g**).

With the optimized conditions in hand, we proceeded to investigate the borylation of a series of substituted arenes to examine the site selectivity of this platinum-catalyzed

**Table 1.** Platinum-Catalysts for the C–H Borylation of Benzene<sup>a</sup>

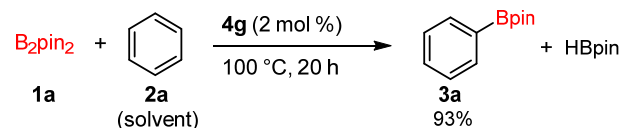


Entry	Catalyst	NHC	TON <sup>b</sup>
1	Pt <sub>2</sub> (dvtms) <sub>3</sub> ( <b>4</b> )	-	5
2	<b>4a</b>	IMes	40
3	<b>4b</b>	IPr	0
4	<b>4c</b>	IMe	6
5	<b>4d</b>	<i>i</i> Pr	69
6	<b>4e</b>	<i>t</i> Bu	16
7	<b>4f</b>	I(1-Ad)	58
8	<b>4g</b>	ICy	157
9	<b>4h</b>	SICy	106
10	<b>4i</b>	BICy	102
11	Pt(PPh <sub>3</sub> ) <sub>4</sub>	-	0
12 <sup>c</sup>	<b>4</b> + PCy <sub>3</sub>	-	2
13 <sup>c</sup>	<b>4</b> + 2,2'-bipyridine	-	13



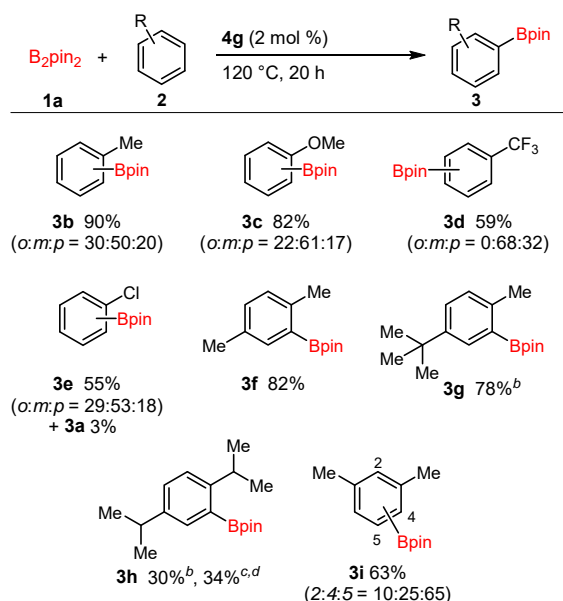
<sup>a</sup>Reaction conditions: **1a** (0.30 mmol), catalyst (0.90 μmol) in benzene (1.0 mL) at 100 °C for 20 h. <sup>b</sup>TON: molar amount of **3a** formed per molar amount of catalyst. <sup>c</sup>**4** (6.0 μmol) and PCy<sub>3</sub> or 2,2'-bipyridine (6.0 μmol), if indicated, were used.

**Scheme 1.** Platinum-Catalyzed Borylation of Benzene



borylation reaction (Figure 2). The borylation of toluene was conducted at 120 °C with 2 mol% of the ICy catalyst **4g**, leading to the formation of a mixture of *o*-, *m*- and *p*-borylated products **3b** without any of the benzylic borylation product. The formation of a significant amount of the *ortho*-borylated isomer indicated that our platinum catalyst system was not particularly sensitive to steric effects. Catalyst **4g** was also used to borylate anisole, trifluorobenzene and chlorobenzene, resulting in *o*- and *p*-borylated mixtures of the corresponding products **3c–3e**, respectively, indicating that this catalyst system was insensitive to the electronic properties of the arene substrate. The borylation of *p*-xylene proceeded efficiently to give the 2-borylated product **3f**, as a single product. In the case of 4-*tert*-butyltoluene (**2g**), the borylation proceeded at the least hindered 2-position to give **3g**. This platinum catalyst system was also used to borylate the C–H bond *ortho* to the isopropyl group in **2h**, albeit in a low yield. *m*-Xylene was also borylated under these platinum-catalyzed conditions to give a mixture of 2-, 4- and 5-borylated isomers. Surprisingly, some borylation was observed at the sterically congested 2-position of *m*-xylene, in addition to borylation at the 4- and 5-positions (2:4:5 = 10:25:65, **3i**). This reactivity contrasts sharply with the selectivity observed for iridium catalysts, where the least hindered 5-position is borylated exclusively.<sup>4</sup>

**Figure 2.** Platinum-Catalyzed Borylation of Substituted Arenes<sup>a</sup>



<sup>a</sup>Reaction conditions: arene (1.0 mL), **1a** (0.30 mmol), **4g** (2 mol%), 120 °C, 20 h. Yields are based on **1a**. The isomeric ratios were determined by <sup>1</sup>H NMR spectroscopy or GC analysis. <sup>b</sup>**4f** (2 mol%) was used instead of **4g**. <sup>c</sup>At 140 °C. <sup>d</sup>Isolated yield determined by the conversion of the product to the corresponding phenol.

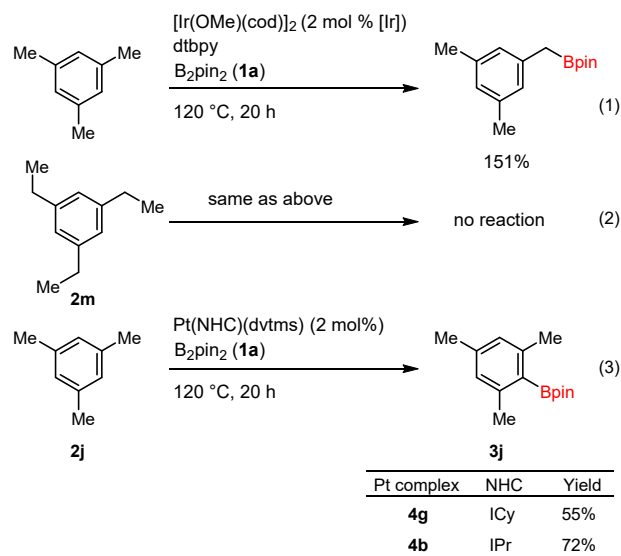
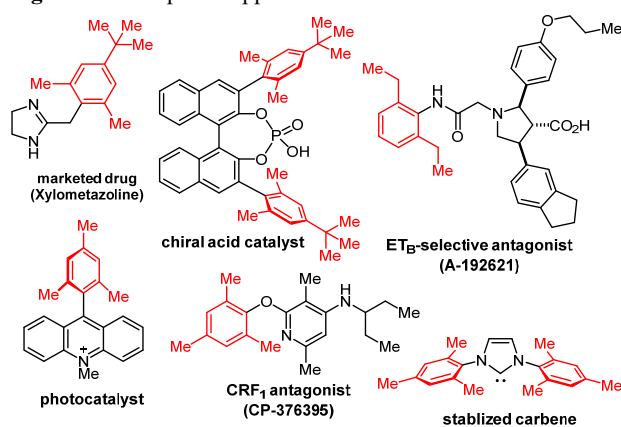
**Borylation of Sterically Congested C–H Bonds.** The high sensitivity of iridium catalysts to steric hindrance allows for the selective borylation of the least hindered C–H bond in an arene substrate. However, this sensitivity can become a problem for the borylation of sterically congested C–H bonds such as those of mesitylene. For instance, the borylation of mesitylene in the presence of an Ir/dtbpy catalyst occurs exclusively at the sterically more accessible benzylic C–H bond (eq 1). To the best of our knowledge, the only reported example of the C(sp<sup>2</sup>)–H borylation of mesitylene involved the use of a heterogeneous iron catalyst (41% GC yield after 4 days).<sup>18b</sup> Furthermore, the more sterically hindered substrate 1,3,5-triethylbenzene (**2m**) failed to react under the iridium-catalyzed conditions (eq 2). The development of new methods for the C–H borylation of hindered arenes is therefore highly desired because these systems are common structural motifs in a variety of different fields, including pharmaceuticals,<sup>32</sup> photocatalyst,<sup>33</sup> steric protection of reactive chemical species,<sup>34</sup> chiral catalysts,<sup>35</sup> and functional polymers<sup>36</sup> (Figure 3).

The low sensitivity exhibited by our platinum catalyst towards the steric hindrance exerted by neighboring substituents prompted us to examine the borylation of mesitylene. Pleasingly, catalyst **4g** allowed for the successful borylation of the sterically hindered C(sp<sup>2</sup>)–H bond in mesitylene to give **3j** in 55% yield as the sole product (eq 3). In an attempt to improve the yield of this reaction, we investigated the effect of the ligand (See SI for details about the effect of the ligand). In this regard, the IPr-bound platinum complex **4b** was found to be more effective than **4g**, leading to a considerable improvement in the yield of **3j** to 72%. As shown in Entry 3 of Table 1, catalyst **4b** was completely ineffective for the borylation of benzene. Monitoring of the reaction of **4b** by NMR revealed that the dtvms ligand of **4b** did not decompose under the catalytic conditions at 100 °C, while at 120 °C the decomposition was observed. In contrast, the dtvms ligand of the ICy-bound complex **4g** dissociated at 100 °C (see

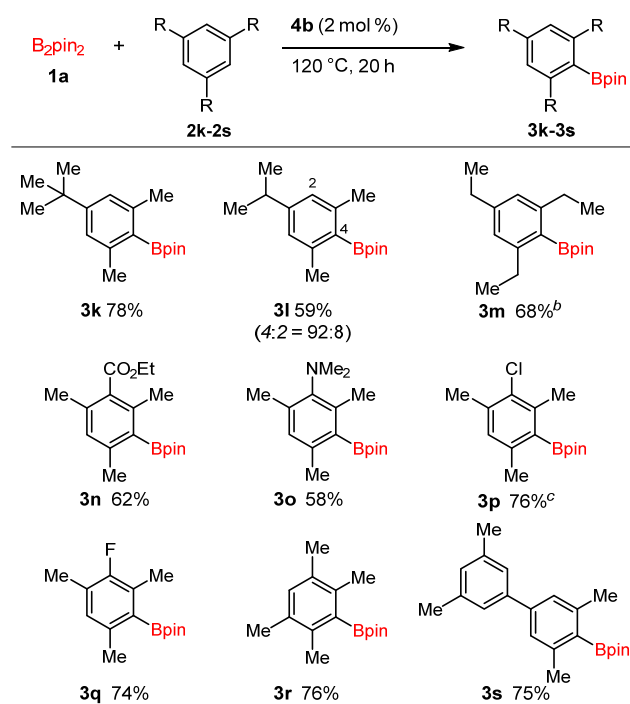
eq 6). Therefore, the nature of the ligand affects, not only the catalytic activity for the borylation reaction, but also the efficiency of the generation of active catalytic species (i.e., the efficiency of the dissociation of dtvms), and both effects would lead to an improved yield of the borylated product.

Catalyst **4b** effectively borylated a series of 1,3,5-trisubstituted arenes to give the corresponding arylboronic ester bearing two *ortho* substituents (Figure 4). A *tert*-butyl group was sufficiently large to block borylation at its *ortho* position in **2k**, as evidenced by the exclusive formation of **3k**. Similarly, 1-isopropyl-3,5-dimethylbenzene (**2l**) was siteselectively borylated at its 4-position (the least hindered position) to give **3l**, although some borylation was also observed at the C–H bond *ortho* to the isopropyl group (positions 2:4 = 92:8), further highlighting that platinum is much less sensitive to steric hindrance than iridium. It is noteworthy that 1,3,5-triethylbenzene (**2m**) was successfully borylated through the activation of its C(sp<sup>2</sup>)–H bonds, which were shielded by two *ortho*-ethyl groups to give the corresponding borylated product **3m**. The iridium/dtbpy catalyst was completely inactive against **2m** (eq 2). This result therefore clearly highlights the unique properties of platinum catalyst systems for the borylation of

**Figure 3.** Widespread Applications of Hindered Arenes



**Figure 4.** Platinum-Catalyzed Borylation of C–H Bonds in Sterically Congested Arenes<sup>a</sup>



<sup>a</sup>Reaction conditions: arene (1.0 mL), **1a** (0.30 mmol), **4b** (2 mol%), 120 °C, 20 h. Yields are based on **1a**. The isomeric ratios were determined by <sup>1</sup>H NMR spectroscopy. <sup>b</sup>At 140 °C, <sup>c</sup>The dechlorinated product **3j** was also formed (4%).

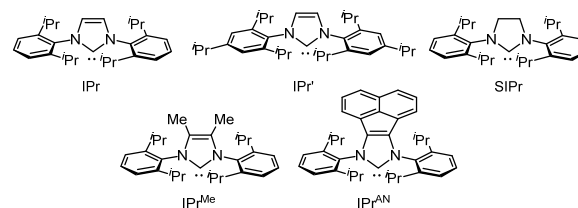
sterically hindered C(sp<sup>2</sup>)–H bonds. Furthermore, several functional groups, including esters, amines, chlorides and fluorides were tolerated under these conditions, which allows access to a series of elaborate hindered arylboronic esters **3n-3q**.

Although this platinum-catalyzed borylation requires an excess (ca. 20–35 equiv) of the arene substrate to obtain satisfactory levels of conversion, the unreacted substrate can be recovered quantitatively and used for another borylation reaction. However, the need for such a large excess of substrate clearly limits the application of this method to more elaborate substrates. To address this issue, we conducted a series of optimization to identify much more practical conditions. The effect of the ligand was investigated in much greater detail using hindered arene **2k** as a limiting agent in the presence of 1.0 equiv of **1a** under neat conditions (Table 2). The IPr-ligated catalyst **4b** was still active under these conditions and gave the borylated product **3k** in 51% yield (Entry 1). Although the yield of **3k** was moderate, **1a** was completely consumed, indicating that **1a** was also involved in some undesired pathways. There have been several reports pertaining to C–H borylation reactions, where the catalyst is deactivated through the C–H borylation of the ligand.<sup>17b</sup> These reports led us to investigate the use of IPr derivatives with fewer C–H bonds capable of being borylated. Whilst the use of an NHC bearing 1,3,5-triisopropylphenyl groups (IPr', **4j**) was less effective than IPr (Entry 2), the use of IPr derivatives with modifications on the imidazole backbone, such as SIPr (**4k**), IPr<sup>Me</sup> (**4l**) and IPr<sup>AN</sup> (**4m**), all improved the yield of the borylated product **3k** (Entries 3–5). These results therefore suggested that the higher efficiency of catalysts **4k-4m** could be attributed to their larger size<sup>37</sup> or limited rotation around their C(aryl)–N bonds,<sup>38</sup> rather than suppressing the C–H borylation of the imidazole ring. To develop conditions applicable to various arene substrates, we subsequently investigated the use of several

solvents with platinum catalyst **4k** (Entries 6–10). The borylation was found to be highly sensitive to the concentration of the aromatic substrate. For example, concentration of 0.3 and 3.0 M resulted in yields of 18 and 58% for the borylation of **2k** in octane (Entries 6 and 7, respectively). Several other nonpolar solvents, such as cyclooctane, decane and triisopropylbenzene (TIPB) were also used without any discernible loss of catalytic activity, thereby expanding the scope of this borylation procedure to solid arene substrates.

**Table 2.** Optimization towards Practical C–H Borylation of Hindered Arenes<sup>a</sup>

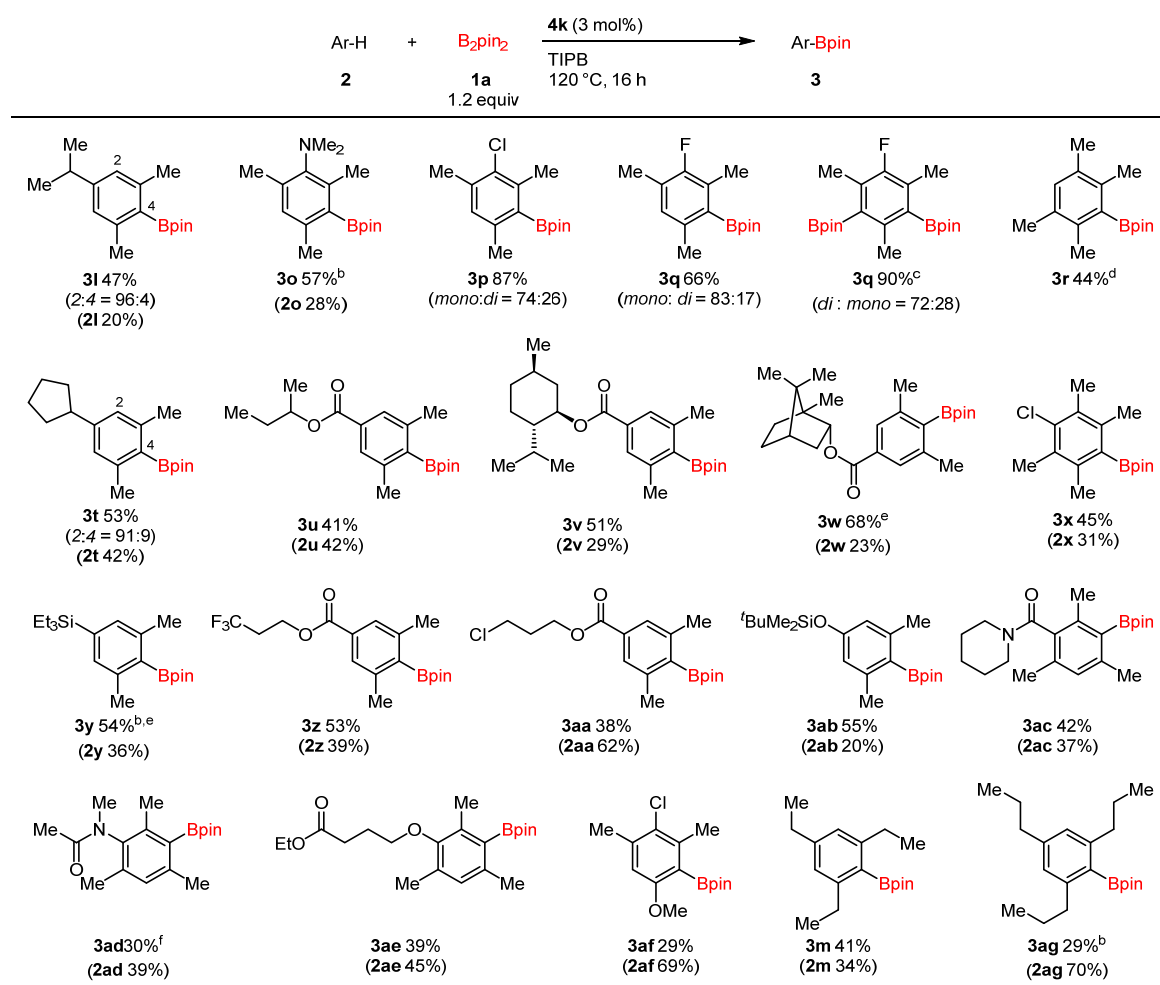
Entry	Catalyst	NHC	Solvent	Yields <sup>b</sup>
1	<b>4b</b>	IPr	neat	51
2	<b>4j</b>	IPr'	neat	39
3	<b>4k</b>	SIPr	neat	72 (65) <sup>c</sup>
4	<b>4l</b>	IPr <sup>Me</sup>	neat	76
5	<b>4m</b>	IPr <sup>AN</sup>	neat	72
6	<b>4k</b>	SIPr	octane (0.30 M)	18
7	<b>4k</b>	SIPr	octane (3.0 M)	58
8	<b>4k</b>	SIPr	cyclooctane (3.0 M)	57
9	<b>4k</b>	SIPr	decane (3.0 M)	58
10	<b>4k</b>	SIPr	TIPB (3.0 M)	53



<sup>a</sup>Reaction conditions: **2k** (0.30 mmol), **1a** (0.30 mmol for Entries 1–5; 0.36 mmol in Entries 6–10), Pt(NHC)(dvtms) (3 mol%), 120 °C, 16 h. <sup>b</sup>Yields determined by GC based on **2k**. <sup>c</sup>Isolated yield. TIPB = 1,3,5-triisopropylbenzene.

This new protocol was initially applied to arenes **2l**, **2o** and **2r**, and the results were compared with those obtained under the neat conditions described above (Figure 5). Although the yields of the borylated products were slightly lower than those obtained under the neat conditions (see Figure 4), they were still satisfactory considering that no other catalytic methods are currently available for the borylation of these arenes. It is noteworthy that diborylated products were only observed under these platinum-catalyzed conditions, when reactive substrates were used. For example, chloromesitylene underwent borylation to give a mixture of mono- and diborylated product (87% combined yield, **3p-mono**: **3p-di** = 74:26). Fluoromesitylene was also reacted to form mono- and diborylated products under these conditions (66% combined yield, **3q-mono**: **3q-di** = 83:17). Furthermore, the diborylated product **3q-di** was obtained as the major isomer when the borylation reaction was repeated (90% combined yield, **3q-mono**: **3q-di** = 28:72). The new protocol developed above allowed for the borylation of several relatively complicated arenes, such as those containing menthol (**3v**) and borneol (**3w**) substructures. Our protocol was capable of siteselectively borylating a silyl-substituted substrate to form an arene bearing both boron and silicon functionalities (**3y**), which are amenable to orthogonal functionalization (*vide infra*). Trifluoromethyl (**3z**),

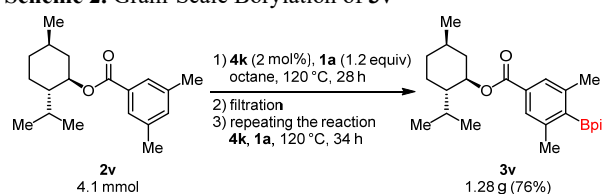
**Figure 5.** Substrate Scope for Sterically Congested Arenes under the Improved Conditions<sup>a</sup>



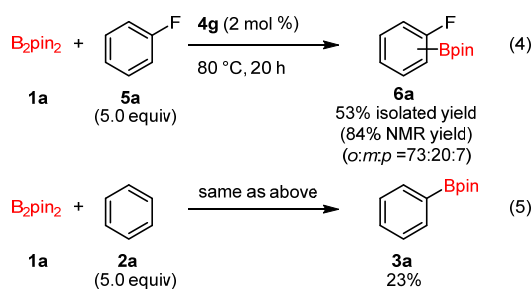
<sup>a</sup>Reaction conditions: **2** (0.30 mmol), **1a** (0.36 mmol) and **4k** (3 mol%) in TIPB (0.10 mL) at 120 °C for 16 h. Yields are the isolated yield based on **2**. Yields in parentheses refer to those of the recovered starting materials. <sup>b</sup> Octane (0.10 mL) was used instead of TIPB. <sup>c</sup> **2q** (0.15 mmol), **1a** (0.36 mmol), **4k** (6 mol%) were used and the reaction was repeated twice. <sup>d</sup> **2r** (0.60 mmol) and **1a** (0.30 mmol) were used; the yield is based on **1a**. See SI for details. <sup>e</sup>The reaction was repeated twice. See SI for details. <sup>f</sup> Isolated yield determined by the conversion of the product to the corresponding phenol.

alkyl chloride (**3aa**) and TBDMS ether (**3ab**) groups were also found to be compatible with these reaction conditions. Carbonyl functionalities such as benzamide (**3ac**), anilide (**3ad**) and alkyl ester (**3ae**) groups were also tolerated under these conditions. It is noteworthy that this platinum-catalyzed methodology is not limited to the borylation of C–H bonds surrounded by two methyl groups. For example, C–H bonds between methyl and methoxy groups (**3af**), two ethyl groups (**3m**) and two *n*-propyl groups (**3ag**) were all successfully borylated under these modified conditions to form the corresponding products. Although the yields of these products were moderate, most of the unreacted substrates could be recovered in good yields. It was therefore possible to improve the yields of these borylated products by simply repeating the borylation reaction. For example, the elaborate boronic ester **3v** was successfully synthesized on a gram scale by simply repeating the borylation reaction (Scheme 2). It is noteworthy that increasing the loading of the platinum catalyst did not generally lead to improvements in the yields of the borylated products.

**Scheme 2.** Gram-Scale Borylation of **3v**

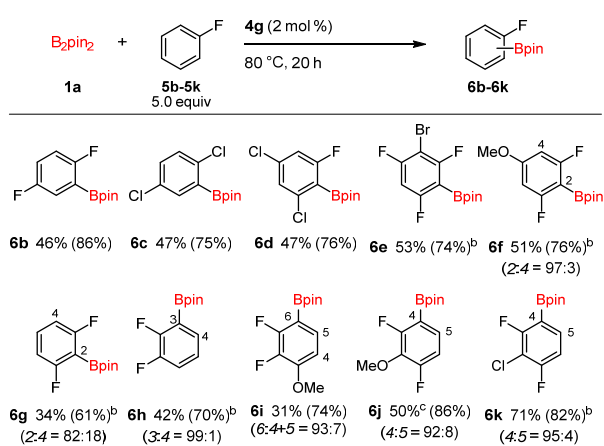


**Borylation of Fluorinated Arenes.** The introduction of a fluorine atom to the benzene ring had a profound effect on both the reactivity and selectivity of the platinum-catalyzed C–H borylation reaction. For example, the borylation of fluorobenzene (**5a**) proceeded efficiently even when the amount of the substrate was decreased to 5.0 equiv to give **6a** (eq 4). In contrast, the reaction of benzene under the same conditions afforded very little of the desired product (eq 5).



Notably, the C–H borylation of **5a** proceeded with a high level of *ortho* selectivity (73%), suggesting that fluorine atom exhibited an *ortho*-directing effect. Fluorine has been reported to behave as a directing group in C–H borylation reactions involving rhodium<sup>39</sup> and cobalt<sup>17a</sup> catalyzed systems, although the scope of this directing effect has not been extensively investigated. Takaya and Iwasawa reported a similar *ortho*-directing effect for fluorine when they investigated the C–H borylation of polyfluorinated benzene substrates with platinum catalysts bearing a pincer ligand.<sup>29</sup> A similar activating effect was also observed for chloroarenes, as exemplified by the formation of **6c** and **6d** (Figure 6). Several 1,3-difluorobenzene derivatives were also borylated to give the 2-borylated products as the major isomers, although this position was the most congested among the C–H bonds available (**6e–6g**). Most notably, 1,2-difluorobenzene derivatives bearing a C–H bond *ortho* to a fluorine atom were selectively borylated at this position to form **6h** and **6i**, rather than being borylated at their much less hindered C–H bonds. The two difluorinated arenes **5j** and **5k** also showed high *ortho* selectivity to form the corresponding polysubstituted aryl boronic esters **6j** and **6k**. Although the isolated yields of these fluorinated phenylboronic esters were found to be modest because of their poor stability during chromatographic isolation, these borylated products could be used directly without isolation as useful building blocks for the synthesis of fluorinated aromatic compounds. For example, **6j** was directly converted to the corresponding phenol without isolation.

**Figure 6.** Substrate Scope of Fluorinated Arenes<sup>a</sup>

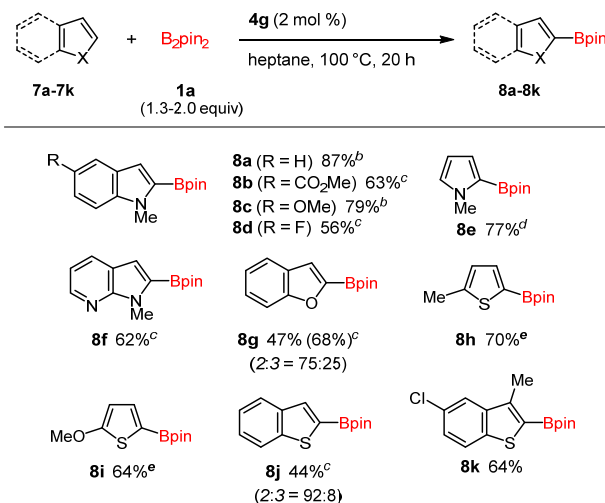


<sup>a</sup>Reaction conditions: **1a** (0.30 mmol), **5** (5 equiv), **4g** (2 mol%), 80 °C, 20 h. Yields are based on **1a**. The isomeric ratios were determined by <sup>1</sup>H NMR spectroscopy or GC analysis. Yields in parentheses refer to the NMR yields. <sup>b</sup>At 60 °C. <sup>c</sup>Isolated yield determined by the conversion of the product to the corresponding phenol (aqueous H<sub>2</sub>O<sub>2</sub>, NaOH, rt).

**Borylation of 5-Membered Heteroarenes.** 5-Membered heteroarenes are generally considered to be highly reactive

substrates for C–H borylation reactions.<sup>5,40</sup> A similar trend was also observed in our platinum-catalyzed system. For example, *N*-methylindole **7a** was sufficiently reactive to undergo borylation in the presence of 2.0 equiv of **1a** and 2.0 mol% of platinum catalyst **4g** in heptane to afford the 2-borylated product **8a** in 87% isolated yield (Figure 7). Indoles bearing a variety of different substituents, including an ester (**7b**), ether (**7c**) and fluoride (**7d**) were also successfully borylated to give the corresponding 2-borylated indoles **8b–8d**, respectively. The exclusive formation of **8d** suggested that an indole C–H bond is more susceptible to borylation than a C–H bond *ortho* to a fluorine atom. Although pyrrole **7e** was also successfully borylated under our newly developed platinum-catalyzed conditions, the reaction needed to be conducted in the presence of a large excess of pyrrole to suppress the undesired diborylation reaction. Although 6-membered heteroarenes such as pyridine and quinoline were found to be unsuitable for this type of platinum catalysis, they were not detrimental to the C–H borylation of azoles, as evidenced by the successful formation of the borylated azaindole **8f**. Benzofuran **7g** was also borylated under these conditions, albeit with decreased reactivity and poor 2-/3-selectivity. Thiophenes and benzothiophenes served as good substrates for the platinum-catalyzed borylation and afforded the corresponding borylated products **8h–8k** in moderate to good yields.

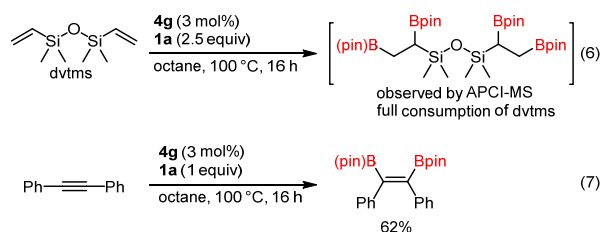
**Figure 7.** Substrate Scope of 5-Membered Heteroarenes<sup>a</sup>



<sup>a</sup>Reaction conditions: **7** (0.30 mmol), **1a** (1.2 equiv), **4g** (2 mol%), heptane (1.0 mL), 80 °C, 20 h. Yields are based on **7**. The isomeric ratios were determined by <sup>1</sup>H NMR spectroscopy or GC analysis. Yields in parentheses refer to the NMR yields. <sup>b</sup>**1a** (2.0 equiv) was used. <sup>c</sup>**4g** (4 mol%) was used. <sup>d</sup>*N*-Methylpyrrole **7e** (5.0 equiv to **1a**) was used. <sup>e</sup>Heteroarene was used as the solvent.

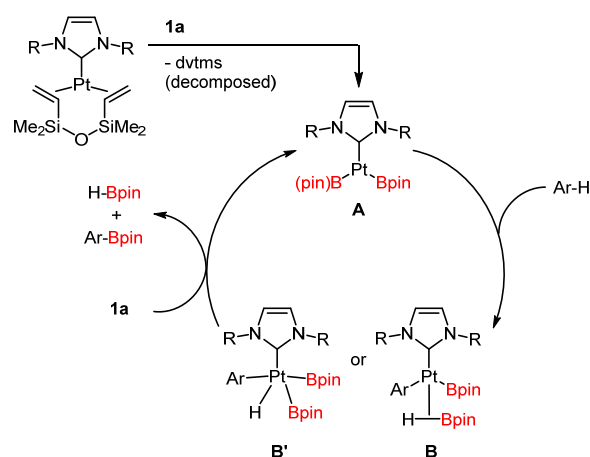
**Mechanistic Considerations.** Several experiments were conducted to gain a deeper insight into the nature of the catalytically active platinum species involved in this C–H borylation reaction. It was previously proposed that the dtvms ligand in the platinum precursor decomposed prior to the formation of the catalytically active platinum species in hydrosilylation reactions involving Pt(NHC)(dtvms).<sup>31,41</sup> With this in mind, we investigated the reaction of dtvms with **1a** in the presence of Pt(ICy)(dtvms) **4g** to examine the reactivity of dtvms under the catalytic conditions used in the current C–H borylation reaction. APCI-MS analysis revealed that the dtvms was completely consumed under the reaction conditions to give the corresponding tetraborylated product (eq 6). This observation

clearly demonstrated that the dtvms ligand could dissociate from the platinum center via the diboration of its alkene moieties to generate a coordinatively unsaturated platinum species, which could subsequently react with **1a**. It has been reported that several platinum(0) complexes can react with diboron reagents to afford platinum(II) diboryl species. For example, platinum diboryl complexes bearing phosphine ligands have been isolated and characterized, and their catalytic activity towards the diboration of alkenes and alkynes have been reported in detail.<sup>27</sup> It has also been reported that the Pt(NHC)(dvtms) complex, where NHC is <sup>i</sup>Bu or a triazole-based carbene, can catalyze the diboration of alkynes and alkenes, most likely through the formation of a Pt(NHC)(Bpin)<sub>2</sub> species.<sup>26d,e</sup> We also confirmed in our own hands that Pt(ICy)(dvtms) **4g** catalyzed the diboration of diphenylacetylene (eq 7). This observation suggested that **4g** could also generate a platinum diboryl species via its reaction with **1a**.



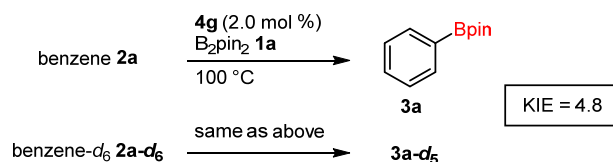
**Scheme 2.** Diboration of an Alkene and an Alkyne with Pt(ICy)(dvtms) Complex

Based on these experiments, we proposed a possible reaction mechanism for the Pt(NHC)-catalyzed borylation of arenes, which is shown in Scheme 3. The Pt(NHC)(dvtms) complex would be activated by its reaction with **1a** to give the platinum diboryl species **A** via the decomposition of the dtvms ligand. Complex **A** would then function as an active species to activate the C–H bond in the arenes. With regard to the subsequent C–H bond cleavage step, we considered two different mechanisms. The first of these mechanisms involve a  $\sigma$ -bond metathesis reaction between **A** and one of the Ar–H bonds of the substrate to form the Ar–Pt(II)–Bpin species **B**. The other mechanism would involve the oxidative addition of one of the C–H bonds to **A**, leading to the formation of the platinum(IV) species **B'**. It is noteworthy that  $\sigma$ -bond metathesis pathways have been proposed for rhodium- and iron-catalyzed C–H borylation reactions, based on DFT calculations,<sup>16b,42</sup> whereas oxidative addition pathways have been proposed for iridium-catalyzed C–H borylation reactions.<sup>43</sup> However, there is currently no evidence to discriminate these two pathways. The subsequent reaction of **B** or **B'** with **1a** would result in the release of HBpin and ArBpin with the regeneration of **A**.<sup>44</sup>



**Scheme 3.** Proposed Mechanism for the Pt-Catalyzed Borylation Reaction

The platinum-catalyzed borylation of benzene was monitored by GC and <sup>1</sup>H-NMR spectrometry and the results revealed that there was an induction period before the borylation started to occur. The decomposition of the dtvms ligand most likely occurred during the induction period to generate the catalytically active platinum species. Other experiments revealed that HBpin was generated during the borylation of benzene, and that this material remained unreacted (see SI for details). Initial rate experiments for the borylation of benzene revealed a large KIE value (4.8), which indicated that the cleavage of the C–H bond was most likely the turnover-limiting step of the catalytic cycle (Scheme 4). A similarly large KIE value (2.7) was also observed for the platinum-catalyzed borylation of *N*-methylindole under dilute conditions.



**Scheme 4.** KIE Experiments

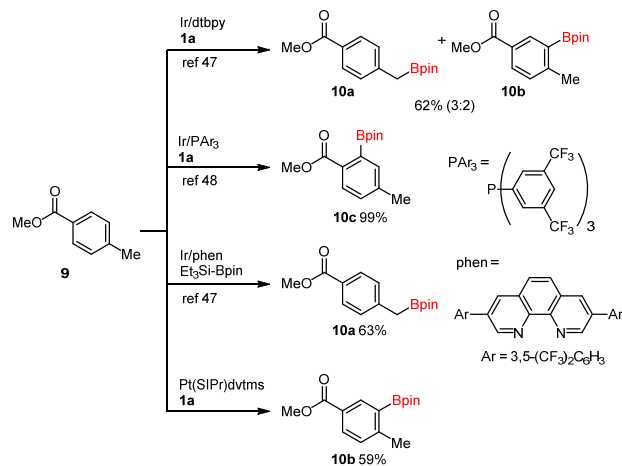
The origin of the unique sitespecificity by platinum catalysis currently remains elusive. Unlike the iridium catalyst system, the lack of the present platinum system in the activity toward C(sp<sup>3</sup>)–H bond activation should be a key to the successful borylation of mesitylene derivatives. The *ortho* directing effect of the fluorine atom in the present platinum system can be attributed to the increased acidity of the *ortho* C–H bond fluoroarene derivatives,<sup>45</sup> as well as the stronger C(aryl)–platinum bond when a fluorine atom is present at the *ortho* position.<sup>46</sup>

**Synthetic Applications.** As demonstrated in Figure 4-7, the platinum catalysts developed in the current study afforded unique levels of sitespecificity that are different to those observed with other catalysts. The complementary sitespecificities of these different systems is best exemplified by the borylation of *p*-methylbenzoate **9** (Scheme 5). The use of the standard Ir/dtbpy catalyst led to a mixture of products, including the benzylic borylation product **10a** and the 3-borylated product **10b**.<sup>47</sup> Selective borylation at the 2-position was only achieved with an Ir/P(3,5-(CF<sub>3</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>)<sub>3</sub> system, where the ester group of the substrate acted as an *ortho*-directing group to form **10c**.<sup>48</sup> Selective borylation at the benzylic position was possible with an iridium/phenanthroline system when silylborane was used as



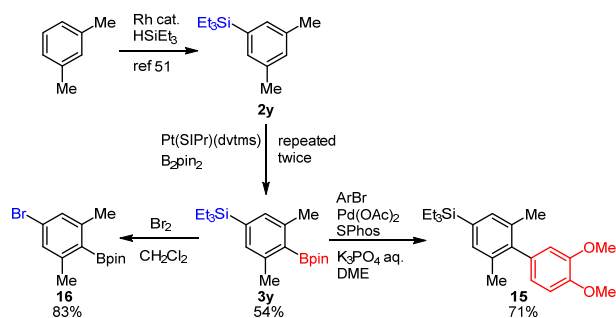
the borylating agent to deliver **10a**.<sup>47</sup> In contrast, the robust Pt catalyst developed in the current study was found to be insensitive to the steric hindrance suffered by the other systems to allow for the exclusive C–H borylation of **9** at its 3-position to provide **10b**.

**Scheme 5.** Comparison of Siteselectivity for the C–H Borylation of Methyl *p*-Methylbenzoate Using Different Catalysts



The current platinum-catalyzed borylation was found to be amenable to scale up, as exemplified by the gram-scale synthesis of **3k**, which could be used as a versatile building block for the introduction of different groups (Scheme 6). For example, the steric demand around the boron moiety in **3k** did not hamper its reactivity towards a standard palladium-catalyzed Suzuki–Miyaura cross-coupling reactions for the introduction of aryl (**11**) and alkyl (**12**) groups. Compound **3k** also afforded a hindered aniline **13** and a hindered phenol **14** via known amination<sup>49</sup> and oxidation methods, respectively.

Sequential C–H functionalization reactions were also evaluated in this study (Scheme 7). The rhodium-catalyzed silylation of *m*-xylene is known to occur at the least hindered 5-position to form **2y**.<sup>50,51</sup> The subsequent borylation of **2y** under our platinum-catalyzed conditions led to the activation of the C–H bond surrounded by two methyl groups to form **3y**. The silyl and boryl groups in **3y** could be converted to other functionalities in an orthogonal manner.<sup>50</sup> For example, the selective transformation of the boryl functionality in **3y** to an aryl group was successfully accomplished under standard Suzuki–Miyaura reaction conditions whilst leaving the silyl group unchanged to form **15**. Conversely, the silyl group in **3y** was brominated without the loss of the Bpin group to generate **16**. These examples further demonstrated the tolerance of our platinum catalyst towards steric demand, as well highlighting how it can be used in combination with existing methods to generate new synthetic strategy for the siteselective functionalization of hindered arenes.



**Scheme 7.** Sequential C–H Functionalization of *m*-Xylene and

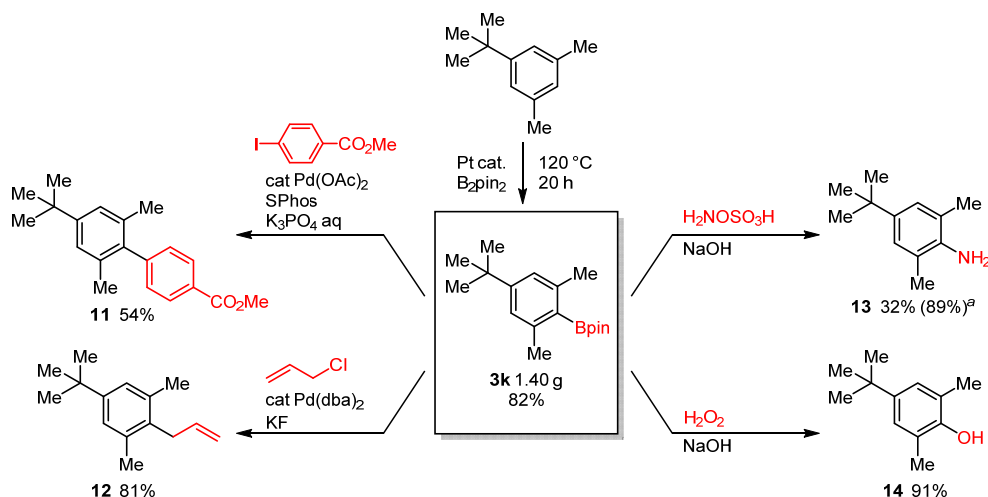
Divergent Functionalization of **3y**

### 3. Conclusion

We have developed a Pt/NHC complex-catalyzed C–H borylation of aromatic substrates. The use of a platinum complex in conjunction with NHC ligands, such as ICy and IPr, resulted in effective catalysts for the C–H borylation of a wide range of arenes and heteroarenes. Notably, this platinum system was found to be largely insensitive to steric hindrance, allowing for the borylation of the sterically hindered aromatic C–H bond in a series of mesitylene derivatives to give the corresponding phenylboronic ester derivatives bearing two *ortho* substituents. Further ligand screening determined that SIPr was as a suitable ligand for the borylation of sterically hindered arenes, whilst avoiding the need for a large excess of the substrate, thereby broadening the scope of this reaction. Another feature of this platinum catalyst system is that it exhibited a pronounced *ortho*-directing effect in the presence of fluorine substituents, providing facile access to a wide range of *ortho*-fluorophenylboronic esters directly from fluoroarenes. It is noteworthy that iridium catalyst system cannot be used in this way to achieve siteselective borylation of both types of substrates. It is therefore envisaged that the unique features of our platinum catalyst system for C–H borylation will allow for the development of new synthetic strategies for the siteselective functionalization of arenes, especially those with steric demand. Additional studies towards platinum-catalyzed C–H functionalization, as well as studies aimed at the development of C–H borylation reactions using other central metals, are currently underway in our laboratories.

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**Scheme 6.** Gram-Scale Synthesis of **3k** and Its Transformations <sup>a</sup>Yield based on the recovered starting material.

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## Graphical Abstract

<Title>

C–H Borylation by Platinum Catalysis

<Authors' names>

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<Summary>

The platinum-catalyzed borylation of aromatic C–H bonds is described. *N*-Heterocyclic carbene-ligated platinum catalysts are found to be efficient catalysts for the borylation of aromatic C–H bonds. The most remarkable feature of these Pt catalysts is their lack of sensitivity towards the degree of steric hindrance around the C–H bonds undergoing the borylation reaction.

<Diagram>

