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Iron-Catalysed C(sp²)-H Borylation with Expanded Functional Group Tolerance†

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Comprehensive Summary

Arene C(sp²)-H bond borylation offers direct and efficient access to aryl boronic esters. Using in situ catalyst activation and photoirradiation, the iron-catalysed C(sp²)-H borylation reaction of carboarenes, pyrroles, and indoles has been developed using only bench-stable pre-catalysts and reagents. Good functional group tolerance was observed including those not reported using previous methods (ArNH₂, ArOH, ArSiR₃, ArP(O)(OR)₂, ArC(O)NR₂). Mechanistic studies revealed iron-catalysed reductive deoxygenation, C—F protodefluorination, and a demethylation of aryl methyl ethers by C—O sigma bond hydroboration.

Keywords
Iron | Earth-abundant | C—H borylation | Boron | Photochemistry

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Iron-Catalysed C(sp²)-H Borylation

Background and Originality Content

The ever increasing need for sustainable processes and manufacturing requires a shift away from the use of rare and precious metals and the application of Earth-abundant metal catalysis. This requires the development of operationally simple methods to enable trialing and application by the wider community. The selective C(sp²)-H functionalisation of arenes, in particular C(sp²)-H borylation, offers a key transformation in this regard by giving direct and efficient access to highly versatile synthetic intermediates. Currently this process is dominated by rhodium and iridium-based catalysts, although a handful of Earth-abundant metal examples have been reported. Iron has high natural abundance, is inexpensive, and has low toxicity, so offers an ideal choice as a metal for catalysis.

Four examples of iron-mediated carboarene C(sp²)-H borylation using dioxaborolane reagents (H-B(OR)) have been disclosed, with further reports of the use of bis(pinacolato) diboron. Stoichiometric studies by Hartwig and co-workers, and independently by Tatsunami, Okhi and co-workers, demonstrated that this transformation could be achieved using half-sandwich iron complexes, [CpFe(CO)₂Bcat] (where cat = catechol) and [Cp³Fe(NHC)Ph] (where NHC = 1,3,4,5-tetramethyl-imidazol-2-ylidene) respectively. (Scheme 1a). Mankad and co-workers demonstrated the first catalytic examples of carboarene C(sp²)-H borylation using heterobimetallic Fe-Cu and Fe-Zn complexes under continuous ultraviolet irradiation (Scheme 1b). Darcel and co-workers achieved similar reactivity using a dimethyl- or dihydrido iron(II) bisphosphine complexes, again under continuous ultraviolet light irradiation (Scheme 1b).

Scheme 1  Iron-mediated C(sp²)-H borylation of carboarenes. Cp = C₅H₅

a) Iron-mediated Carboarene C(sp²)-H Borylation

\[
\begin{align*}
\text{Fe}^\text{II} & \quad \text{OC} \quad \text{OC} \quad \text{Bcat} \\
\text{PhH} & \quad \text{hv} \\
\text{B(OR)}_2 & \quad \Delta \\
\text{Tatsunami and Okhi} & \quad 2010
\end{align*}
\]

b) Iron-catalysed Carboarene C(sp²)-H Borylation

\[
\begin{align*}
\text{Fe}^\text{II} & \quad \text{OC} \quad \text{OC} \\
\text{R} & \quad \text{hv} \\
\text{Bpin} & \quad \Delta \\
\text{Mankad} & \quad 2013 \\
\text{Darcel} & \quad 2015
\end{align*}
\]

[catalyst, air- and moisture sensitive pre-catalyst]

This work - Expanding Iron-catalysed Carboarene Borylation

Although this represents an operationally simple system, there are several limitations to its widespread adoption: 1. The need to prepare and isolate sensitive organometallic pre-catalysts; 2. The requirement for large excesses of reagents (10 equiv. HBpin or 3 equiv. arene) 3. Limited functional tolerance beyond simple alkyl substituents (tolerated; -NMe₂ -CF₃ -OMe). It was postulated that these limitations could be overcome using the in situ activation of the benz-stable bisphosphino iron(II) halide complex, [dmpe₂FeCl₂], to access the dihydride pre-catalyst, [dmpe₂FeH₂]. This could be achieved through the addition of an exogenous nucophile which in combination with HBpin, would form an organometallic hydride donor in an operationally simple manner (Scheme 1c). This complex and the analogous manganese species have shown good activity for C(sp²)-H borylation under blue light irradiation, but these systems were limited to the borylation of heteroarenes. Additionally, free alcohols and amines would be tolerated by use of HBpin as a traceless protecting group.

Results and Discussion

Reaction optimisation for carboarene C(sp²)-H borylation was conducted using [dmpe₂FeCl₂] 1 (4 mol%), as the pre-catalyst, sodium 2-ethylhexanoate Na(2-ETH) as an exogenous activator, ortho-xylene 3g (1 equiv.), and pinacolborane (HBpin, 2 equiv.) (See Supporting Information, Table S2). In contrast to the C-H borylation of heterocycles, the use of ultraviolet light (365 nm) was required for efficient reaction, with the borylation reaction proceeding with complete regioselectivity to the 4-Bpin-ortho-xylene product 4g (78% by ²H NMR spectroscopy). Blue light irradiation (450 nm), including using a high-intensity LED lamp, showed limited stoichiometric borylation reactivity even under extended reaction times. With optimised reaction conditions established using [dmpe₂FeCl₂] 1 (4 mol%), Na(2-ETH) (8 mol%), arene (1.0 equiv.) and HBpin (2.0 equiv.) in THF under UV irradiation, the system was tested on a selection of simple benzene derivatives (Scheme 2). The borylation of alkyl substituted derivatives, 3a-3d, all proceeded in moderate to good isolated yield (49% to 75%) with meta selectivity, but as a mixture of borylated regioisomers (meta:para;di-meto). Recovery of non-volatile starting materials accounted for the remaining mass balance. Phenyl-Bpin 3e underwent efficient borylation in a para selective manner. The preference for the second -Bpin unit to be installed preferentially in the para position was also observed for benzene 3f which gave a 49 : 16 : 35 mixture of mono, di-meta, and di-para borylated products, respectively. Attempts to control the extent of borylation (mono vs. di), led only to reduced yields and incremental changes in the product regioisomer ratios. Exchange of HBpin for the more sterically demanding dioxaborolane, pinaneborane, gave no improvement in regioselectivity or yield (see SI, Table S2). The presence of alkyl and/or boryl substituents in either the 1,2-, or 1,3-positions, 3g-3l, led to entirely regioselective borylation with ortho- and meta-xylene being borylated in 73% and 48% isolated yields, respectively. The borylation of naphthalene 3j and fluorene 3k gave the mono-borylated products as the major product in both cases.

Application to arenes bearing N-alkyl- and N,N-dialkyl amine groups, 3m-3o, gave meta selective borylation in all cases. N,N-Dimethylbenzylamine 3p gave notably higher proportions of the di-meta borylated product (43% yield; 29 : 36 : 35 : m : p: di-m). The parent aniline 3l was also successfully borylated, after pre-protection with 1 equivalent of HBpin which acted as a traceless protecting group which was subsequently removed upon work-up. For the first time using Earth-abundant metals, phenol derivatives 4q-4t became accessible with either -Bpin or -SIMe₃ pre-protection resulting in the borylation of phenol 3q (80%) and 2-tert-butylphenol 3s (65%) in high isolated yields with high meta regioselectivity. 2,6-Diisopropylphenol (Propofol) 3t
Iron-catalysed C(sp^2)-H Borylation

**Scheme 2** Iron-catalysed C(sp^2)-H borylation of carboarenes^a

- **Simple arenes**

<table>
<thead>
<tr>
<th>Arene</th>
<th>HBpin (2 equiv.)</th>
<th>[dmpe]_2FeCl_2 (4 mol%), Na(2-EH) (8 mol%), THF (1 M), 60 °C, Ar, 24 h</th>
<th>Isolated yields</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>4a 63%</td>
<td>41:37:22</td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td>4b 75%</td>
<td>41:32:27</td>
<td></td>
</tr>
<tr>
<td>3c</td>
<td>4c 49%</td>
<td>35:22:43</td>
<td></td>
</tr>
<tr>
<td>3d</td>
<td>4d 53%</td>
<td>45:36:19</td>
<td></td>
</tr>
<tr>
<td>4a</td>
<td>4e 65%</td>
<td>36:61:3</td>
<td></td>
</tr>
<tr>
<td>4f</td>
<td>4f 61%</td>
<td>49:16:35</td>
<td></td>
</tr>
</tbody>
</table>

- **Amines and Alcohols**

<table>
<thead>
<tr>
<th>Arene</th>
<th>HBpin (2 equiv.)</th>
<th>[dmpe]_2FeCl_2 (4 mol%), Na(2-EH) (8 mol%), THF (1 M), 60 °C, Ar, 24 h</th>
<th>Isolated yields</th>
</tr>
</thead>
<tbody>
<tr>
<td>4g</td>
<td>4g 73%</td>
<td>41:32:27</td>
<td></td>
</tr>
<tr>
<td>4h</td>
<td>4h 48%</td>
<td>65:15:20</td>
<td></td>
</tr>
<tr>
<td>4i</td>
<td>4i 31%</td>
<td>65:15:20</td>
<td></td>
</tr>
</tbody>
</table>

- **Miscellaneous**

<table>
<thead>
<tr>
<th>Arene</th>
<th>HBpin (2 equiv.)</th>
<th>[dmpe]_2FeCl_2 (4 mol%), Na(2-EH) (8 mol%), THF (1 M), 60 °C, Ar, 24 h</th>
<th>Isolated yields</th>
</tr>
</thead>
<tbody>
<tr>
<td>4j</td>
<td>4j 36%</td>
<td>88:8:6</td>
<td></td>
</tr>
<tr>
<td>4k</td>
<td>4k 46%</td>
<td>66:34:0</td>
<td></td>
</tr>
<tr>
<td>4l</td>
<td>4l 49%</td>
<td>65:15:20</td>
<td></td>
</tr>
</tbody>
</table>

**Note:**
- Arene 3 (1.0 equiv.), HBpin (2.0 equiv.), [dmpe]_2FeCl_2 (4 mol%), Na(2-EH) (8 mol%), THF (1 M), 60 °C, UV irradiation (365 nm), 24 h. Isolated yields reported. Ratio of regioisomers determined by ^1H NMR spectroscopy. Regioselectivity expressed as the ratio of meta:para:di-meto boryl-substitution unless stated otherwise. ^48 h. ^Yields determined by ^1H NMR spectroscopy of the crude reaction mixture (internal standard: 1,3,5-trimethoxybenzene). ^Starting material pre-mixed with 1 equivalent of HBpin. ^Starting material 3x: 2,2,2-trimethylacetophenone. ^Ratio of regioisomers determined from crude reaction mixture.

underwent entirely regioselective borylation to give the para Bpin product. The isolated yields for benzylalcohol derivatives, 4u–4w, were consistently lower than the amine analogues 4l–4o, due to competitive reductive transformations to give borylated toluene (from 3u–3v) or styrenyl (from 3w) by-products. The use of a pre-installed trimethylsilyl protecting group gave little to no improvement in the yield of the C–H borylation for these substrates. Application to 2,2,2-trimethylacetophenone 3x led only to isolation of the C–H borylated benzyl alcohol derivative, presumably due to competitive (direct) hydroboration of the ketone group. The moderate borylation of anisole 3y was a result of significant levels of competing O-demethylation to give a mixture of phenolic side products. ^36–37 No evidence for C(sp^3)-H borylation of the MeO- group was observed. Arylboronic ester products containing trimethylsilyl (3z), phosphonate (3aa), ester (3ab–3ac), and amide (3ad) functional groups all gave good to high yields of the borylated products, which further demonstrated the functional group tolerance of the system. In contrast to iridium-catalysed borylation, ^38–40 no ortho-directed borylation was observed for the phosphonate, benzoate ester, and benzamide substrates.

Fluorobenzene 3ae also underwent borylation with meta regioselectivity. Orthogonal regioselectivity to cobalt-catalysed borylation ^21 was observed for 2-methylfluorobenzene 3af to give the meta borylated arene. The 3- or 4-methyl analogues, 3ag–3ah,
gave an increase of borylation products ortho to the fluoro substituents. All fluoroarenes, 3ae—3ah, showed some levels of competitive defluorination resulting in the isolation of protodehalogenated aryl-Bpin by-products. Only minimal levels of (sp²)-F defluorination were observed when α,α,α-trifluorotoluene 3ai was used. Other halide (Cl, Br, I) substituted arenes displayed no reactivity for C(sp²)-H borylation.

To better understand the side reactions that were leading to diminished yields in the borylation of benzyl alcohols and phenyl methyl ethers (anisole), mechanistic studies were conducted. Independently prepared O-Bpin-4-Bpin benzyl alcohol was reacted under standard reactions conditions to give a mixture of 4-Bpin toluene (para-4a) (72%) and the corresponding benzyl-Bpin product in trace quantities (Scheme 3a, i). 4-Bpin toluene was unreactive under standard reaction conditions, further indicating direct benzyllic C(sp²)-H borylation was not operative. Monitoring the reaction of the O-Bpin-4-Bpin benzyl alcohol, DBpin, and [dmpe-FeH]₂ (4 mol%) showed deuteration incorporation at the benzyllic position, as observed by 2H NMR spectroscopy (Scheme 3a, ii).

Monitoring the demethylation of 4-methylanisole under standard reaction conditions showed the formation of p-cresol, which was isolated in a 68% yield (Scheme 3b, i). Use of blue light irradiation (450 nm), in place of UV irradiation (350 nm), gave only 30% conversion to the p-cresol product as observed by 1H NMR spectroscopy. Reaction of 4-methylanisole, DBpin, and [dmpe-FeH]₂ (4 mol%), led to the formation of MeBpin, as observed by 1B NMR spectroscopy (Scheme 3b, ii). O-ethyl and O-’-octyl substituted 4-methyl phenyl ethers were both unreactive to de-etherification under standard reaction conditions. To gain insight into the defluorination observed for arenes 3ae—3ah, a series of stoichiometric reactions were conducted. Irradiation (UV, 365 nm) of [dmpe-FeH]₂ in the presence of either fluorobenzene or 4-Bpin-fluorobenzene led to complex mixtures of products as observed by 1H, 19F, and 31P NMR spectroscopy, likely due to competitive C-H metallation. Alternatively, [dmpe-FeH]₂ reacted cleanly with C₆F₆ at room temperature to give [dmpe-Fe(H)(C₆F₅)]₂ which was characterised in solution and the solid-state by 1H, 19F, and 31P NMR spectroscopy and single crystal X-ray crystallography, respectively (Scheme 3c). The formation of [dmpe-Fe(H)(C₆F₅)]₂ is proposed to proceed in a similar manner to that of the analogous ruthenium complex, [dmpe-Ru(H)(C₆F₅)]₄. This both polyfluoroaryl-iron complex 6 and the non-fluorinated analogue, [dmpe-Fe(H)(Ph)]₅ exist as mixtures of the cis and trans isomers in solution, but only the trans isomer was observed in the solid-state. However, unlike the parent phenyl complex 5 which reacted readily with HBpin at room temperature in the absence of light, the polyfluorophenoxy-iron complex 6 required UV irradiation to generate [dmpe-Fe(H)(Bpin)] and a mixture of C₆F₅H and C₆F₅Bpin (ca. 50:50) as observed by 19F NMR spectroscopy. The effect of fluorine substitution on the relative reactivity of the iron-aryl bonds for these complexes, 5 and 6, was directly reflected in the Fe—C bond lengths observed in the solid-state: 5 Fe—C [Å] = 2.276(9) and 6 Fe—C [Å] = 2.1064(16). The reaction of C₆F₆ under standard borylation conditions led to only trace amounts of protodefluorination, and defluorinative borylation products being isolated including C₆F₅H, C₆F₅Bpin, C₆F₅H₂, and C₆F₅BHPin.

Finally, the borylation system was applied to a series of heterocycles including pyrroles and indoles (Scheme 4). The borylations of N-Boc 7a and N-trisopropylsilyl 7b substituted pyrroles were entirely regioselective to give the 3-borylated pyrrole products in 72% and 80% isolated yields, respectively. The borylation of pyrrole 7c was achieved by nitrogen pre-protection using HBpin, which after work up gave a 11 : 60 : 29 mixture of 2-, 3- and 2,5-di-borylated products, respectively, in a 52% yield. The borylation of N-methylpyrrole 7d underwent borylation with similar levels of reactivity and regioselectivity (41% yield; 24 : 64 : 12 = 2 : 3 : 2,5-di). Borylation of benzofuran 7e led to the isolation of only the 2-substituted boronic ester. The application to a selection of indole derivatives, 7f—7j, gave moderate yields up to 39% and regioselectivity displaying a general trend for: 2 > 3 > 6 > 5. Regioselectivity could be further controlled through N- and/or aryl ring substitution. Pyridine derivatives were found to be poisonous to the catalytic system and attempts to block potential nitrogen coordination (2,6-di-tert-butylypyridine) also gave no C—H borylation.

Scheme 3  a) Reduction of benzyl alcohols, b) demethylation of anisole, and c) iron-aryl structures

---

a Standard reaction conditions: Arenes (1.0 equiv.), HBpin (2.0 equiv.), [dmpe-FeCl]₂ (4 mol%), Na(2-EH) (sodium 2-ethylhexanoate) (8 mol%), THF (1 M), 60 °C, UV irradiation (365 nm), 24 h. Isolated yields reported. See SI, S6 for full experimental details. X-ray ellipsoids are shown at 50% probability. Hydrogen atoms, with the exception of the Fe-hydride, have been omitted for clarity.
Iron-catalysed C(sp^3)-H Borylation

**Scheme 4** Iron-catalysed C(sp^3)-H borylation of heteroarenes

**Scheme 5** Proposed catalyst cycle for iron-catalysed C(sp^3)-H borylation of heteroarenes

**Conclusions**

In summary, the iron-catalysed C(sp^3)-H borylation of carboarenes, pyrroles and indoles has been demonstrated using an in situ activation method requiring only bench-stable reagents and pre-catalyst. The system displayed good functional group tolerance, expands the scope to previously disclosed iron-catalysed C(sp^3)-H borylation methodologies, and demonstrated orthogonal reactivity to precious metal-catalysed systems. Mechanistic studies revealed iron-catalysed reductive deoxygenation of benzyl alcohol derivatives, C—F protodefluorination, and a demethylation of aryl methyl ethers by C—O sigma bond hydroboration.

**Experimental**

All reactions were performed in oven (185 °C) and/or flame-dried glassware under an atmosphere of anhydrous nitrogen or argon, unless otherwise indicated. Reagents were purchased from commercial suppliers and used without further purification unless otherwise stated in the Supporting Information. UV irradiation was provided by a HepatoChem P301-30-1 365 nm lamp. NMR spectra were recorded on Bruker Avance III 400 and 500 MHz; Bruker AVI 400 MHz; Bruker Avance I 600 MHz spectrometers at 25 °C. Flash chromatography was performed on silica gel (Merck Kieselgel 60, 40—63 μm) or if specified, carried out on a Teledyne ISCO CombiFlash NextGen 300+ using RediSep Rf normal phase silica flash columns.

**General procedure for the borylation of simple carboarenes.**

In a glove box with a purified argon atmosphere, [dmpe,FeCl]_2 (1.6 mg, 0.020 mmol, 4 mol%), sodium (2-ethylhexanoate) (6.9 mg, 0.040 mmol, 8 mol%), pinacolborane (145 μL, 1.00 mmol, 2 equiv.) and anhydrous THF (0.5 mL) were added to a vial and stirred for 5 min. After addition of corresponding arene (3.0 mmol, 1 equiv.) the vial was sealed, removed from the glove box and irradiated with UV light for 24 h. The reaction mixture was exposed to air and washed through a silica plug (3 g SiO_2) with EtOAc. The products were purified on silica using flash column chromatography.

Full experimental procedures and data are given in the Supporting Information.

**Supporting Information**

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.202200465.

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