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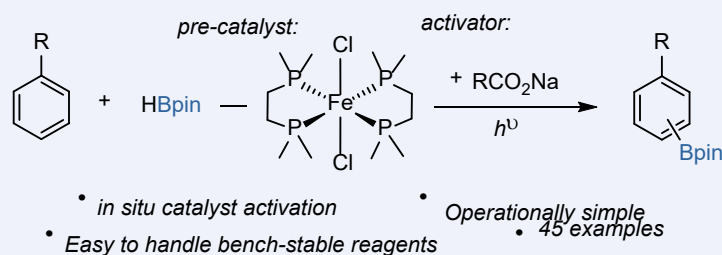
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# Iron-catalysed C(sp<sup>2</sup>)-H Borylation with Expanded Functional Group Tolerance

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## Comprehensive Summary

Arene C(sp<sup>2</sup>)-H bond borylation offers direct and efficient access to aryl boronic esters. Using *in situ* catalyst activation and photoirradiation, the iron-catalysed C(sp<sup>2</sup>)-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 tolerated under previous methods (ArNH<sub>2</sub>, ArOH, ArSiR<sub>3</sub>, ArP(O)(OR)<sub>2</sub>, ArC(O)NR<sub>2</sub>). Mechanistic studies revealed iron-catalysed reductive deoxygenation, C-F proto-defluorination, and a demethylation of aryl methyl ethers by C-O sigma bond hydroboration.



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## Keywords

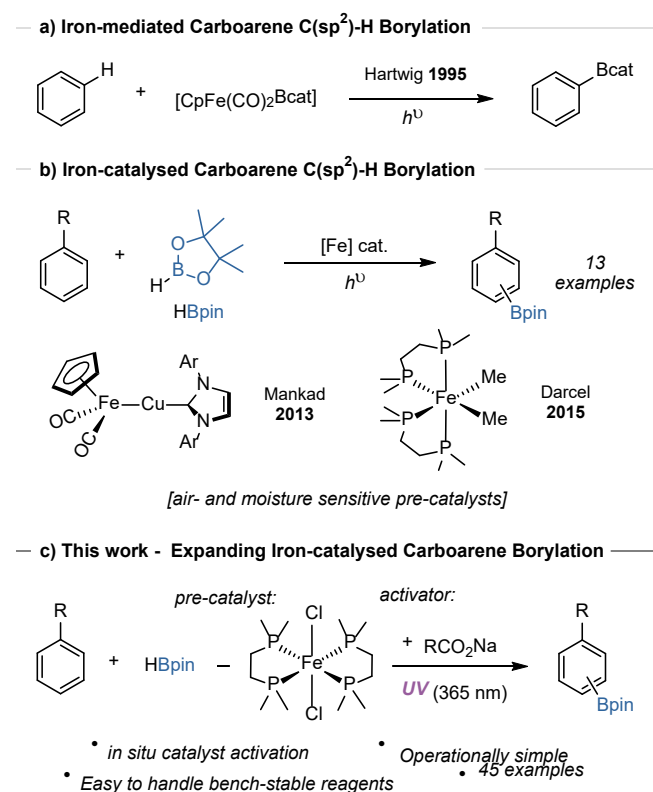
iron | earth-abundant | C-H borylation | boron | photochemistry

\*E-mail:

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## Background and Originality Content

**Scheme 1** Iron-mediated C(sp<sup>2</sup>)-H borylation of carboarenes. Cp = C<sub>5</sub>H<sub>5</sub>. Cat = catechol.



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(sp<sup>2</sup>)-H functionalisation of arenes, in particular C(sp<sup>2</sup>)-H borylation, offers a key transformation in this regard by giving direct and efficient access to highly versatile synthetic intermediates.<sup>1–7</sup> Currently this process is dominated by rhodium and iridium-based catalysts,<sup>8–16</sup> although a handful of Earth-abundant metal examples have been reported.<sup>17–23</sup> Iron has high natural abundance, is inexpensive, and has low toxicity, so offers an ideal choice as a metal for catalysis.<sup>24–26</sup>

Three examples of iron-mediated carboarene C(sp<sup>2</sup>)-H borylation using dioxaborolane reagents (H-B(OR)<sub>2</sub>) have been reported, with further reports of the use of bis(pinacolato)diboron.<sup>27–29</sup> Stoichiometric studies by Hartwig and co-workers demonstrated that this transformation could be achieved using an iron-boryl carbonyl complex, [CpFe(CO)<sub>2</sub>Bcat] (where cat = catechol), under ultraviolet irradiation (Scheme 1a).<sup>30</sup> Mankad and co-workers demonstrated the first catalytic examples of carboarene C(sp<sup>2</sup>)-H borylation using heterobimetallic Fe-Cu and Fe-Zn complexes under continuous ultraviolet irradiation (Scheme 1b).<sup>31</sup> Darcel and co-workers achieved similar reactivity using a dimethyl- or dihydrido iron(II) bisphosphine complexes, again under continuous ultraviolet light irradiation (Scheme 1b).<sup>32</sup>

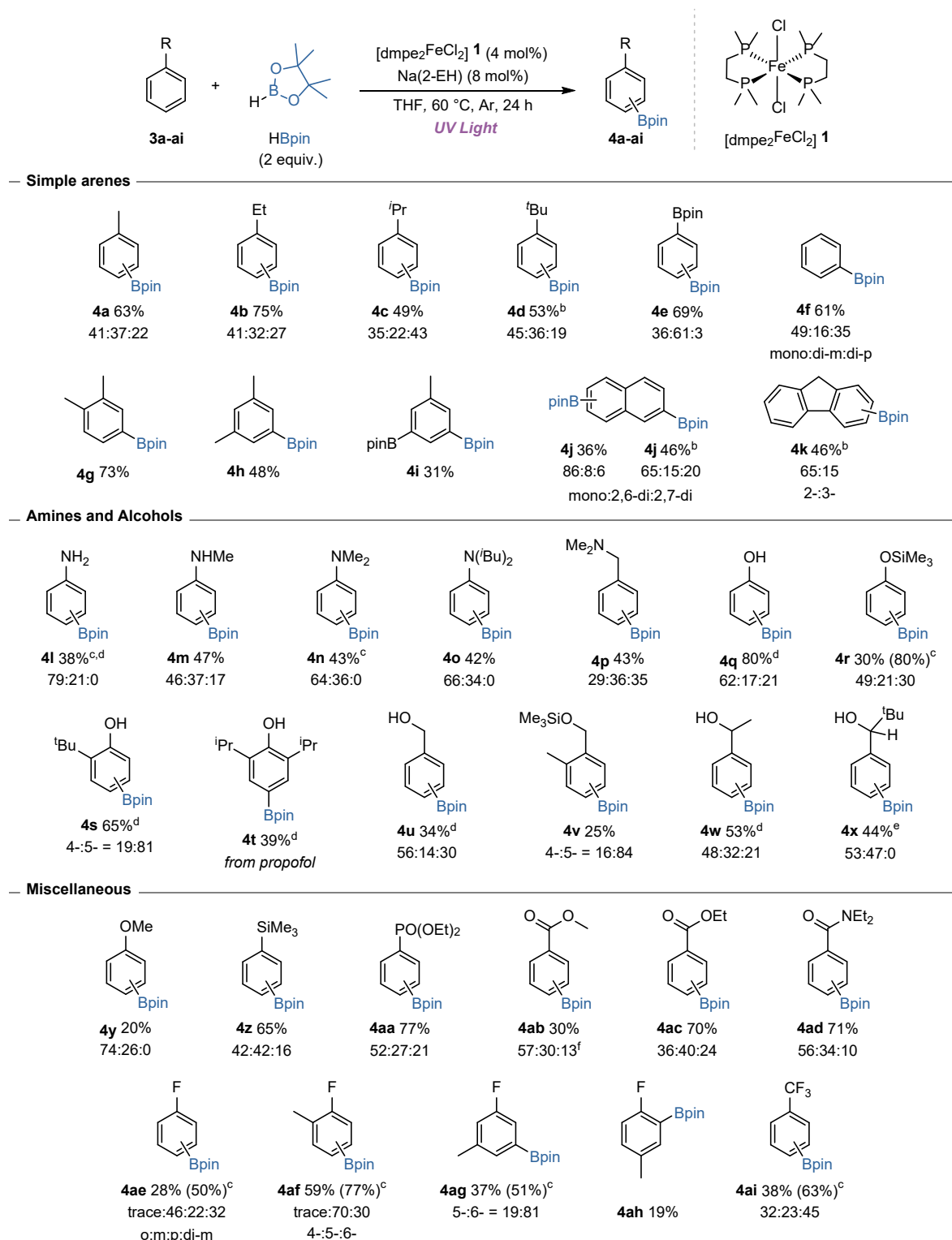
Despite the significance of these findings, both catalytic systems have similar limitations to widespread adoption: 1. The need to prepare and isolate sensitive organometallic pre-catalysts; 2. The requirement for large excesses of reagents (10 equiv. HBpin<sup>31</sup> or 3 equiv. arene<sup>32</sup>); 3. Limited functional tolerance beyond simple alkyl

substituents (tolerated; -NR<sub>2</sub>, -CF<sub>3</sub>, -OMe). It was postulated that these limitations could be overcome using our *in situ* activation of a bisdiphosphino iron(II) halide complex, [dmpe<sub>2</sub>FeCl<sub>2</sub>] **1**, to access the dihydride pre-catalyst, [dmpe<sub>2</sub>FeH<sub>2</sub>] **2**, in an operationally simple manner (Scheme 1c).<sup>18</sup> This complex and the analogous manganese species had shown good activity in the C(sp<sup>2</sup>)-H borylation of heteroarenes.<sup>17</sup> Additionally, free alcohols and amines would be tolerated by use of HBpin as a traceless protecting group.<sup>14,15,33</sup>

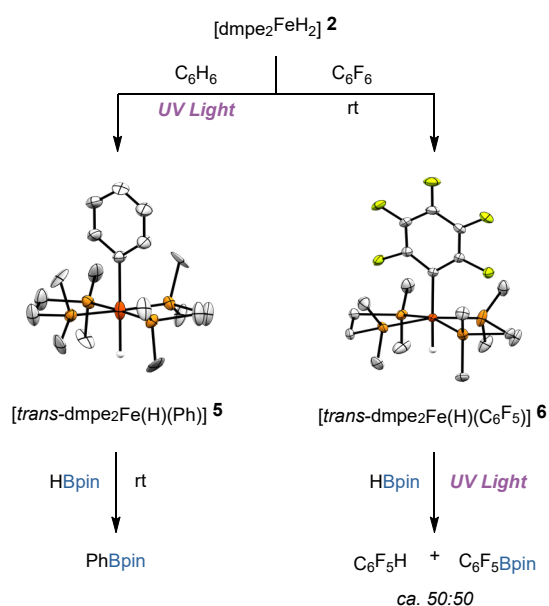
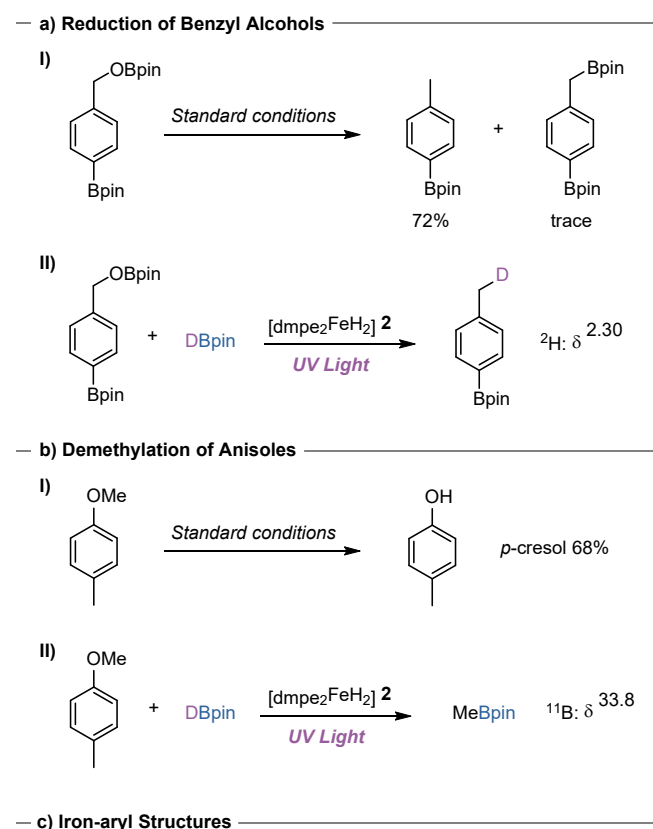
## Results and Discussion

Reaction optimisation for carboarene C(sp<sup>2</sup>)-H borylation was conducted using [dmpe<sub>2</sub>FeCl<sub>2</sub>] **1** (4 mol%) as the pre-catalyst, sodium 2-ethylhexanoate (Na-2-EH) 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,<sup>18</sup> 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 <sup>1</sup>H 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 [dmpe<sub>2</sub>FeCl<sub>2</sub>] (4 mol%), Na(2-EH) (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 (Table 1). The borylation of alkyl substituted derivatives, **3a–d**, all proceeded in moderate to good isolated yield (49% to 75%) with *meta* selectivity, but as a mixture of borylated regioisomers (*meta* : *para* : *di-meta*). 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–i**, led to entirely regioselective borylation with *ortho*- and *meta*-xylene being borylated to 73% and 48% isolated yield, 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–o**, 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.<sup>14,33</sup> For the first time using Earth-abundant metals, phenol derivatives **4q–t** became accessible with either -Bpin or -SiMe<sub>3</sub> 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** underwent entirely regioselective borylation to give the *para* Bpin product. The isolated yields for benzylalcohol derivatives, **4u–w**, were consistently lower than the amine analogues, **4l–o**, due to competitive reductive transformations to give borylated toluene (from **3u–v**) or styrenyl (from **3w**) by-products. The use of a pre-installed trimethylsilyl protecting group gave little-to-no improvement in the yield of C-H borylation for these substrates.

Scheme 2 Iron-catalysed C(sp<sup>2</sup>)-H borylation of carboarenes.<sup>a</sup>

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

Scheme 3 a) Reduction of benzyl alcohols b) Demethylation of anisole.<sup>a</sup>

<sup>a</sup>Standard reaction conditions: <sup>a</sup>Arene (1.0 equiv.), HBpin (2.0 equiv.), [dmpe<sub>2</sub>FeCl<sub>2</sub>] **1** (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, has been omitted for clarity.

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.<sup>34,35</sup> No evidence for C(sp<sup>3</sup>)-H borylation of the MeO-group was observed. Arylboronic ester products containing trimethylsilyl (**3z**), phosphonate (**3aa**), ester (**3ab-ac**), 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,<sup>36-38</sup> no *ortho*-directed borylation was observed for the phosphonate, benzoate ester, and benzamide substrates.

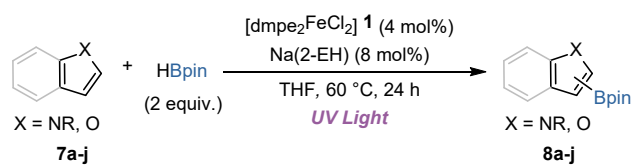
Fluorobenzene **3ae** also underwent borylation with *meta* regioselectivity. Orthogonal regioselectivity to cobalt-catalysed borylation<sup>21</sup> was observed for 2-methylfluorobenzene **3af** to give the *meta* borylated arene. The 3- or 4-methyl analogues, **3ag-ah**, gave an increase of borylation products *ortho* to the fluoro substituents. All fluoroarenes, **3ae-ah**, showed some levels of competitive defluorination resulting in the isolation of protodehalogenated aryl-Bpin by-products. Only minimal levels of C(sp<sup>3</sup>)-F defluorination were observed when  $\alpha,\alpha,\alpha$ -trifluorotoluene **3ai** was used.<sup>29</sup> Other halide (Cl, Br, I) substituted arenes displayed no reactivity for C(sp<sup>2</sup>)-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 reaction conditions to give a mixture of 4-Bpin toluene (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 benzylic C(sp<sup>3</sup>)-H borylation was not operative. Monitoring the reaction of the *O*-Bpin-4-Bpin benzyl alcohol, DBpin, and [dmpe<sub>2</sub>FeH<sub>2</sub>] **2** (4 mol%) showed deuterium incorporation at the benzylic position, as observed by <sup>2</sup>H NMR spectroscopy (Scheme 3a, II).

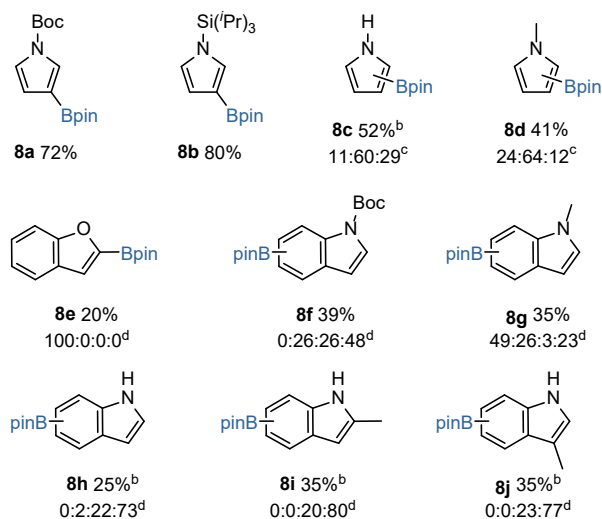
Monitoring the demethylation of 4-methylanisole under standard reaction conditions showed the formation of *p*-cresol, which was isolated in a 68% yield (Scheme 3b, I). Use of blue light irradiation (450 nm), in place of UV irradiation (350 nm), gave only 30% conversion to the *p*-cresol product as observed by <sup>1</sup>H NMR spectroscopy. Reaction of 4-methylanisole, DBpin, and [dmpe<sub>2</sub>FeH<sub>2</sub>] **2** (4 mol%), led to the formation of MeBpin, as observed by <sup>11</sup>B 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-ah**, a series of stoichiometric reactions were conducted. Irradiation (UV, 365 nm) of [dmpe<sub>2</sub>FeH<sub>2</sub>] **2** in the presence of either fluorobenzene or 4-Bpin-fluorobenzene led to complex mixtures of products as observed by <sup>1</sup>H, <sup>19</sup>F, and <sup>31</sup>P NMR spectroscopy, likely due to competitive C-H metallation. Alternatively, [dmpe<sub>2</sub>FeH<sub>2</sub>] **2** reacted cleanly with C<sub>6</sub>F<sub>6</sub> at room temperature to give [dmpe<sub>2</sub>Fe(H)(C<sub>6</sub>F<sub>5</sub>)] **6** which was characterised in solution and the solid-state by <sup>1</sup>H, <sup>19</sup>F, <sup>31</sup>P NMR spectroscopy and single crystal X-ray crystallography, respectively (Scheme 3c). The formation of [dmpe<sub>2</sub>Fe(H)(C<sub>6</sub>F<sub>5</sub>)] **6** is proposed to proceed in a similar manner to that of the analogous ruthenium complex, [dmpe<sub>2</sub>Ru(H)(C<sub>6</sub>F<sub>5</sub>)].<sup>39</sup> Both this polyfluoroaryl-iron complex **6** and the non-fluorinated analogue, [dmpe<sub>2</sub>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,<sup>32</sup> the polyfluoroaryl-iron complex **6** required UV irradiation to generate [dmpe<sub>2</sub>Fe(H)(Bpin)] and a mixture of C<sub>6</sub>F<sub>5</sub>H and C<sub>6</sub>F<sub>5</sub>Bpin (ca. 50:50) as observed by <sup>19</sup>F NMR spectroscopy.<sup>40</sup> 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] = 2.1046(16).



Scheme 4 Iron-catalysed C(sp<sup>2</sup>)-H borylation of heteroarenes<sup>a</sup>

## Heteroarenes



<sup>a</sup>Arene **8** (1.0 equiv.), HBpin (2.0 equiv.), [dmpe<sub>2</sub>FeCl<sub>2</sub>] **1** (4 mol%), Na(2-EH) (sodium 2-ethylhexanoate) (8 mol%), THF (1 M), 60 °C, UV irradiation (365 nm), 24 h. Isolated yields reported. Ratio of regioisomers determined by <sup>1</sup>H NMR spectroscopy. <sup>b</sup>Starting material pre-mixed with 1 equivalent of HBpin and triethylamine. <sup>c</sup>Regioselectivity expressed as the ratio of 2-:3-:2,5-di boryl-substitution. <sup>d</sup>Regioselectivity expressed as the ratio of 2-:3-:5-:6-boryl-substitution.

Finally, the borylation system was applied to a series of heterocycles including pyrroles and indoles (Scheme 4). The borylation of *N*-Boc **7a** and *N*-triisopropylsilyl **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-j**, 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*-butylpyridine) also gave no C-H borylation.

## Conclusions

In summary, the iron-catalysed C(sp<sup>2</sup>)-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<sup>2</sup>)-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 flamed-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 column 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<sub>2</sub>FeCl<sub>2</sub>] **1** (8.6 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 minutes. After addition of corresponding arene **3** (0.5 mmol, 1 equiv.) the vial was sealed, removed from the glove box and irradiated with UV light for 24 hours. The reaction mixture was exposed to air and washed through a silica plug (*ca.* 3 g SiO<sub>2</sub>) with EtOAc. The products **4** 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.2021xxxx>.

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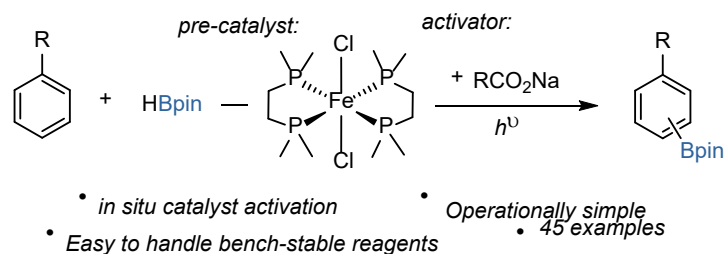
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## Entry for the Table of Contents

Iron-catalysed C(sp<sup>2</sup>)-H Borylation with Expanded Functional Group ToleranceLuke Britton,<sup>a</sup> Jamie H. Docherty,<sup>a</sup> Andrew P. Dominey,<sup>b</sup> and Stephen P. Thomas.\*<sup>a</sup>*Chin. J. Chem.* **2022**, *40*, XXX–XXX. DOI: 10.1002/cjoc.202200XXX

Using in situ catalyst activation and photoirradiation, the iron-catalysed C(sp<sup>2</sup>)-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 tolerated under previous methods (ArNH<sub>2</sub>, ArOH, ArSiR<sub>3</sub>, ArP(O)(OR)<sub>2</sub>, ArC(O)NR<sub>2</sub>).