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Manganese-Catalyzed C(*sp*^{2})-H Borylation of Furan and Thiophene Derivatives

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ABSTRACT: Aryl boronic esters are bench-stable, platform building-blocks that can be accessed through metal-catalyzed aryl C(*sp*^{2})-H borylation reactions. C(*sp*^{2})-H bond functionalization reactions using rare- and precious metal catalyst are well established and whilst examples utilizing Earth-abundant alternatives have emerged, manganese catalysis remains lacking. The manganese-catalyzed C-H borylation of furan and thiophene derivatives is reported alongside an *in situ* activation method providing facile access to the active manganese hydride species. Mechanistic investigations showed blue light irradiation directly affected catalysis by action at the metal centre, that C(*sp*^{2})-H bond borylation occurs though a C-H metallation pathway, and that the reversible coordination of pinacolborane to the catalyst gave a manganese borohydride complex which was as an off-cycle resting-state.

The development of catalytic protocols based on Earth-abundant metals underpins the sustainable future of chemical synthesis by providing a replacement for the ubiquitous rare and precious metals. A key target for sustainable catalysis is the selective C(*sp*^{2})-H functionalization of arenes, in particular C(*sp*^{2})-H borylation.[1] Direct C(*sp*^{2})-H borylation provides efficient access to aryl boronic esters which are highly versatile synthetic intermediates and a staple of the pharmaceutical industry.[1e, 2] Arene C(*sp*^{2})-H borylation is currently dominated by platinum-group metal catalysts, namely iridium and rhodium,[3] with examples of C(*sp*^{2})-H borylation using 1st-row transition metals being generally limited to Fe,[4] Co,[5] and Ni species.[6] Photoinduced borylations have also been reported.[7]

Manganese is the third most abundant transition metal and benefits from low physiological and environmental toxicity.[8] Manganese-catalyzed C(*sp*^{2})-H functionalization of arenes has shown promising development with examples including hydroarylation, alkenylation, and allylation, all of which were proposed to proceed through manganese aryl intermediates.[9] These were typically performed using Mn(0)/(I) carbonyl species and demonstrated high regioselectivity when using directing groups.[9a, 9b] Despite this, and to the best of our knowledge, there is currently only a single previous example of catalytic C(*sp*^{2})-H borylation involving a manganese catalyst (Scheme 1a).[10]

Hartwig reported that stoichiometric quantities of a catecholborane-managanese carbonyl complex [(OC)$_5$MnBcat where Bcat = catecholborane] would mediate the C(*sp*^{2})-H borylation of benzene under UV light irradiation (200-400 nm) to give phenyl-Bcat.[11] This was later followed by a single catalytic example using a manganese half-sandwich complex (Cp'Mn(CO)$_3$ where Cp' = C$_5$H$_4$Me) and the diboronic ester B$_2$pin$_2$ (B$_2$pin$_2$ = bis(pinacolato)diboron) (Scheme 1a). Under a pressure of CO (2 atm.) and irradiation (200-400 nm), phenyl-Bpin was observed in 75% yield after 36 hours.[10]

Scheme 1. Manganese-Catalyzed C(*sp*^{2})-H Borylation
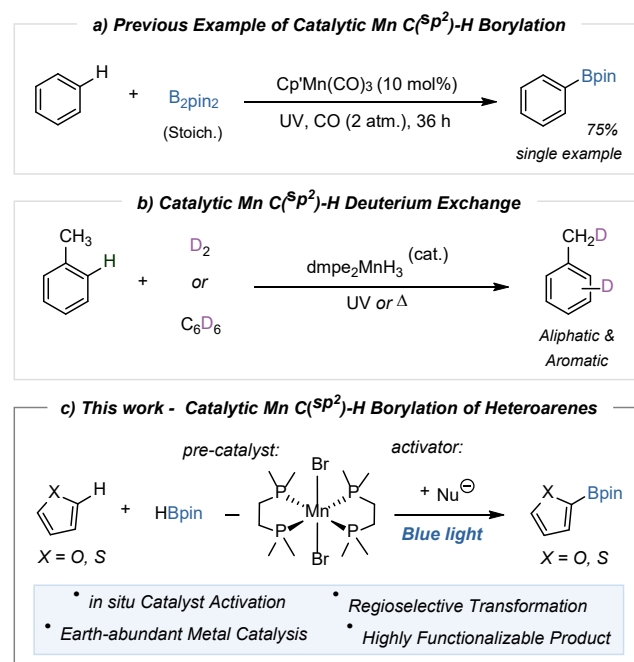
a) Previous example of manganese-catalyzed C(*sp*^{2})-H borylation. **b**) dmpe$_2$MnH$_3$ catalyzed C(*sp*^{2})-H deuterium exchange under thermal and photochemical conditions. **c**) This work - C(*sp*^{2})-H borylation using dmpe$_2$MnBr$_2$ **1** as a pre-catalyst, activated by exogenous nucleophiles, under blue light irradiation.

The manganese complex, bis[1,2-bis(dimethylphosphino)ethane]trihydridomanganese (dmpe$_2$MnH$_3$), has been used to catalyze hydrogen isotope exchange reactions of arene C(*sp*^{2})-H bonds using C$_6$D$_6$ and D$_2$ gas as the isotope

source (Scheme 1b).[12] As this was also proposed to proceed through a manganese aryl species, generated by arene C-H metallation, it was questioned if this manganese aryl species was long-lived enough to be intercepted with a suitable borane and trigger C-H borylation. Further, recent studies on the analogous iron complex had shown that the metal hydride could be accessed *in situ*,[4f, 4h] so possibly negating the need to generate and handle the manganese trihydride (Scheme 1c).

Table 1. Deviations from Optimized Conditions[a]
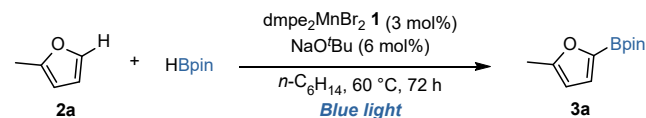
Entry	Deviation	Yield %
1	Pre-catalyst = dmpe$_2$MnH$_3$ **4** No NaO^{t}Bu	93
2	none	86
3	White light	30
4	UV light (CFL)	13
5	Furan : HBpin (1 : 1)	60
6	Pre-catalyst = (CO)$_5$MnBr	0
7	Pre-catalyst = Cp'Mn(CO)$_3$	0
8	No pre-catalyst	0
8	No NaO^{t}Bu	0
10	No light (60 °C and 100 °C)	0

[a]2-Methylfuran **2a** (2.8 equiv.), HBpin (1 equiv.), dmpe$_2$MnBr$_2$ **1** (3 mol%), NaO^{t}Bu (6 mol%), *n*-C$_6$H$_{14}$ (1 M), 60 °C, 72 h. Yields determined by ^{1}H-NMR spectroscopy of the crude reaction mixtures using product:substrate ratio. Blue light (460 nm). Cp' = C$_5$H$_4$Me .

The ubiquitous nature of borylated heterocycles in pharmaceutical development directed focus to the C-H borylation of simple heteroarenes with 2-methylfuran used as a model substrate. The potential for C-H borylation was tested using isolated dmpe$_2$MnH$_3$ **4** (3 mol%) as a pre-catalyst (see SI for stoichiometric generation of dmpe$_2$MnH$_3$ **4**) and pinacolborane (HBpin) (1 equiv.) in *n*-C$_6$H$_{14}$ (1 M) under blue light irradiation. This gave the borylation of 2-methylfuran **2a** with high yield (93%) and exclusive regioselectivity for the 5-borylated regioisomer **3a** (Table 1, entry 1). Exchange of the dmpe$_2$MnH$_3$ **4** pre-catalyst for the manganese(II) halide precursor, dmpe$_2$MnBr$_2$ **1**, (3 mol%) and *in situ* activation using NaO^{t}Bu (6 mol%) activator, gave equal catalytic activity and demonstrated the effectiveness of the strategy (entry 2). *in situ* Activation was used to further expedite development and negate the need for air- and moisture sensitive reagents/(pre-)catalysts.[4h, 13]

The use of blue light (460 nm) was found to be more effective than white light and higher energy ultraviolet light (<300 nm) (entries 3 and 4). An excess of furan **2a** (2.8 equiv.), relative to HBpin, was superior to stoichiometric quantities (entry 5), and substitution of NaO^{t}Bu for carboxylate, metal hydride, or alkyl lithium activators resulted in reduced yields (See SI, ST2). Alternative boranes and dioxaborolanes such as 9-borabicyclo[3.3.1]nonane (H-*B*-9-BBN), 1,8-naphthalenediaminatobo-

rane (HBdan), HBcat, were all unreactive towards C-H borylation (See SI, ST2). Variation of the diphosphine ligand (See SI, ST2), or exchange for Mn(I) carbonyl species showed no reactivity (entries 6 and 7). The requirement for manganese pre-catalyst, activator, and light irradiation were confirmed through a series of control experiments (entries 8-10).
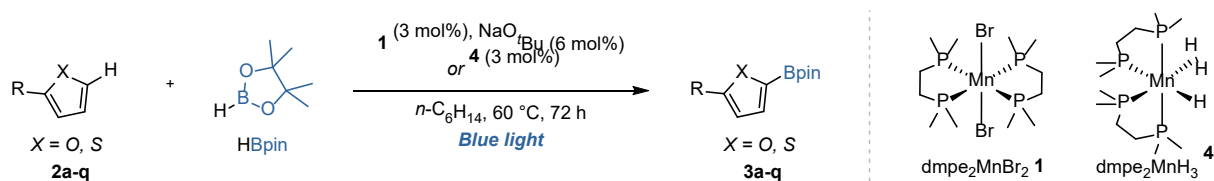
With optimized reaction conditions identified, the reactivity of the system was assessed by application to a selection of furan and thiophene derivatives (Table 2). 2-Methylfuran **2a** underwent efficient and regioselective C-H borylation to give the 5-substituted boronic ester regioisomer **3a** exclusively and in high isolated yield (85%). Substitution of the methyl group for ethyl, octyl, and benzyl groups all resulted in similar reactivity and regioselectivity to give the 5-boryl furans **3b**, **3c** and **3d** in 51%, 51%, and 60% yields, respectively. Borylation of the parent furan **2e** was also successful, but gave a 64:36 mixture of mono:di substituted boryl furans, with borylation occurring only at the 2- and 5-positions only.

Application to thiophene derivatives showed that reactivity was generally more efficient for 2-substitued thiophenes than the 3-substituted analogues. This was observed for the methyl and phenyl substituted 5-boryl thiophene derivatives **3i**, **3j**, **3k**, and **3l**, respectively. Unsubstituted thiophene **2m** showed similar reactivity to furan **2e**, with mono- and diboration observed in a similar ratio (65:35, cf. 64:36 for furan **2e**). For substrates that showed limited reactivity, borylations were performed using isolated dmpe$_2$MnH$_3$ **4**. Furans **2f** and **2h**, and thiophenes **2j**, **2l**, **2o**, and **2q**, all achieving a significant increase in reactivity and yield. Simple carboarenes, aryl halides, and pyrrole derivatives showed no reactivity, and the presence of nitrile, alkyne and carbonyl functionalities gave no observable C-H borylation.
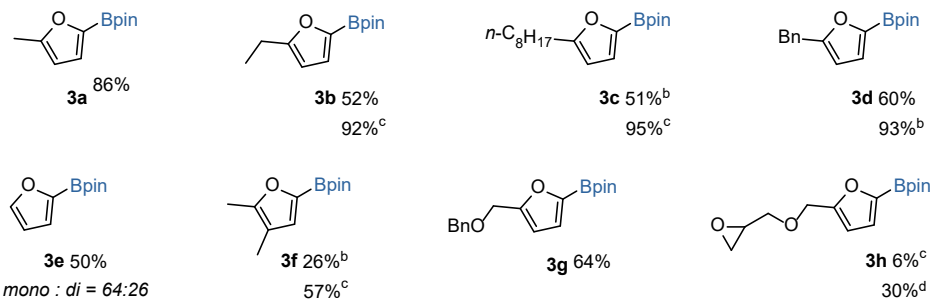
In order to gain mechanistic insight into the pre-catalyst activation and borylation reaction, a series of single-turnover experiments were carried out. Due to the poor solubility of dmpe$_2$MnBr$_2$ **1** in *n*-C$_6$H$_{14}$, activation studies were performed in THF. Reaction of the activator, NaO^{t}Bu, with HBpin and the dmpe$_2$MnBr$_2$ pre-catalyst **1** in the absence of light irradiation showed no observable formation of the dmpe$_2$MnH$_3$ **4** at room temperature or 60 °C. Instead, a new manganese hydride species was produced and observed to increase in concentration over time, as determined by ^{1}H NMR spectroscopy (Scheme 2a). In combination with ^{11}B, ^{1}H-^{11}B HMBC, and variable temperature ^{1}H NMR spectroscopy, the structure was suggested to be a hydride bridged manganese borohydride complex dmpe$_2$Mn(μ-H)$_2$Bpin **6**.[4d, 14] Under both thermal and photochemical conditions, dmpe$_2$MnH$_3$ **4** is reported to readily dissociate dihydrogen to give a Mn(I) hydride species which was trapped here by HBpin to give dmpe$_2$Mn(μ-H)$_2$Bpin **6**.[12] Blue light irradiation accelerated the formation of the manganese borohydride adduct dmpe$_2$Mn(μ-H)$_2$Bpin **6** as observed by ^{1}H NMR spectroscopy, presumably by increasing the rate of H$_2$ dissociation.

To confirm the identity of any intermediate manganese hydride species, further mechanistic studies were performed using isolated dmpe$_2$MnH$_3$ **4**. The reaction of dmpe$_2$MnH$_3$ **4** with HBpin under blue light irradiation again showed the formation of dmpe$_2$Mn(μ-H)$_2$Bpin **6**, as observed by ^{1}H and ^{11}B NMR spectroscopy (Scheme 2b, **I**). Single crystals suitable for X-ray analysis were obtained from a concentrated *n*-C$_6$H$_{14}$ solution at −40 °C, unambiguously confirming the structure of the hydride bridged manganese borohydride complex,
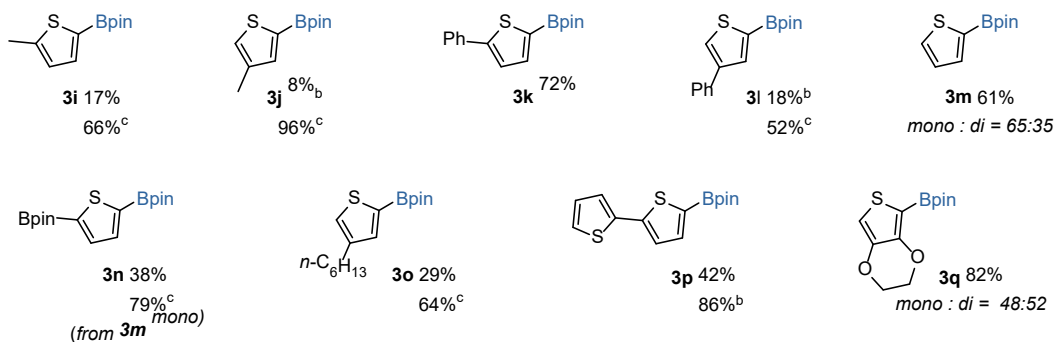
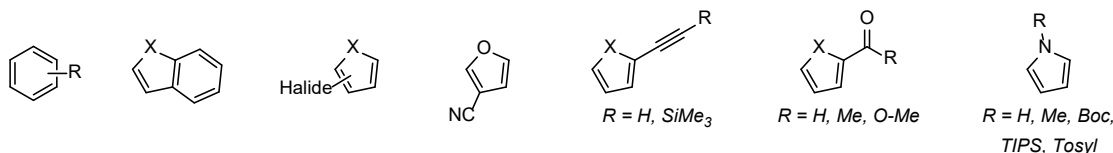**Table 2. Scope of Manganese-Catalyzed C-H Borylation of Furan and Thiophenes[a]**

Furans

3a 86%

3b 52%
92%[c]

3c 51%[b]
95%[c]

3d 60%
93%[b]

3e 50%
mono : di = 64:26

3f 26%[b]
57%[c]

3g 64%

3h 6%[c]
30%[d]

Thiophenes

3i 17%
66%[c]

3j 8%[b]
96%[c]

3k 72%

3l 18%[b]
52%[c]

3m 61%
mono : di = 65:35

3n 38%
79%[c] (mono)
(from 3m)

3o 29%
64%[c]

3p 42%
86%[b]

3q 82%
mono : di = 48:52

Unsuccessful substrates (X = O, S)

R = H, SiMe₃ → R = H, SiMe$_3$

R = H, Me, O-Me

R = H, Me, Boc, TIPS, Tosyl

[a]Reaction conditions 1: Arene **2** (2.8 equiv.), HBpin (1 equiv.), dmpe$_2$MnBr$_2$ **1** (3 mol%), NaO^{t}Bu (6 mol%), n-C$_6$H$_{14}$ (1 M), 60 °C, 72 h. Isolated yields reported. [b]Yields determined by ^{1}H NMR spectroscopy of the crude reaction mixtures using product:substrate ratio (reaction conditions 1). [c]Reaction conditions 2: Arene **2** (2.8 equiv.), HBpin (1 equiv.), dmpe$_2$MnH$_3$ **4** (3 mol%), n-C$_6$H$_{14}$ (1 M), 60 °C, 24 h. Isolated yields reported. [d]Yields determined by ^{1}H NMR spectroscopy of the crude reaction mixtures using product:substrate ratio (reaction conditions 2). Mono: 2-boryl product. Di: 2,5-diboryl product. Mono:Di = molar ratio of products.

dmpe$_2$Mn(μ-H)$_2$Bpin **6** (Scheme 2c). Substitution of HBpin for DBpin led to the deuterated borohydride adduct, dmpe$_2$Mn(μ-H/D)$_2$Bpin d-**6**, as well as the observation of HD *in situ* and the incorporation of deuterium to the dmpe ligands of the complex (Scheme 2b, **II**).[12]

Blue light irradiation of dmpe$_2$Mn(μ-H)$_2$Bpin **6** with 2-methylfuran **2a** resulted in the formation of the 5-boryl product **3a,** and regeneration of dmpe$_2$MnH$_3$ **4** (Scheme 2b, **III**). Use of the deuterated complex, dmpe$_2$Mn(μ-H/D)$_2$Bpin d-**6**, led to deuterium incorporation observed in both the furan substrate (d-**2a**) and 5-boryl product d-**3a** (Scheme 2b, **IV**), indicating a reversible C-H metallation process was occurring.
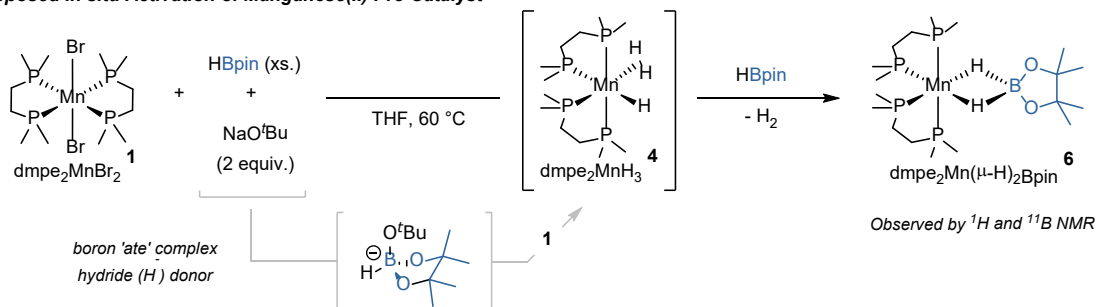
Further structural confirmation of the manganese-HBpin borohydride complex was gained through the synthesis, isolation

and characterization of the analogous HBdan and HBcat complexes, dmpe$_2$Mn(μ-H)$_2$Bdan **7** and dmpe$_2$Mn(μ-H)$_2$Bcat **8**. These complexes displayed comparative ^{1}H and ^{11}B NMR resonances as well as well the characteristic ^{1}H-^{11}B cross peak (HMQC). Single crystals suitable for X-ray analysis of dmpe$_2$Mn(μ-H)$_2$Bdan **7** were obtained from a concentrated n-C$_6$H$_{14}$/C$_6$D$_6$ solution and again showed the bridging borohydride bonding arrangement (Scheme 2c).

The relative stability of the manganese borohydride adducts **6**, **7**, and **8** was assessed through a series of exchange/competition reactions that showed a relationship corresponding to the relative Lewis acidity of each boron reagent. (Scheme 2c). Addition of HBpin to dmpe$_2$Mn(μ-H)$_2$Bdan **7** gave dmpe$_2$Mn(μ-H)$_2$Bpin **6** through the displacement of HBdan, as observed by ^{1}H and ^{11}B NMR spectroscopy. This reaction was found to be
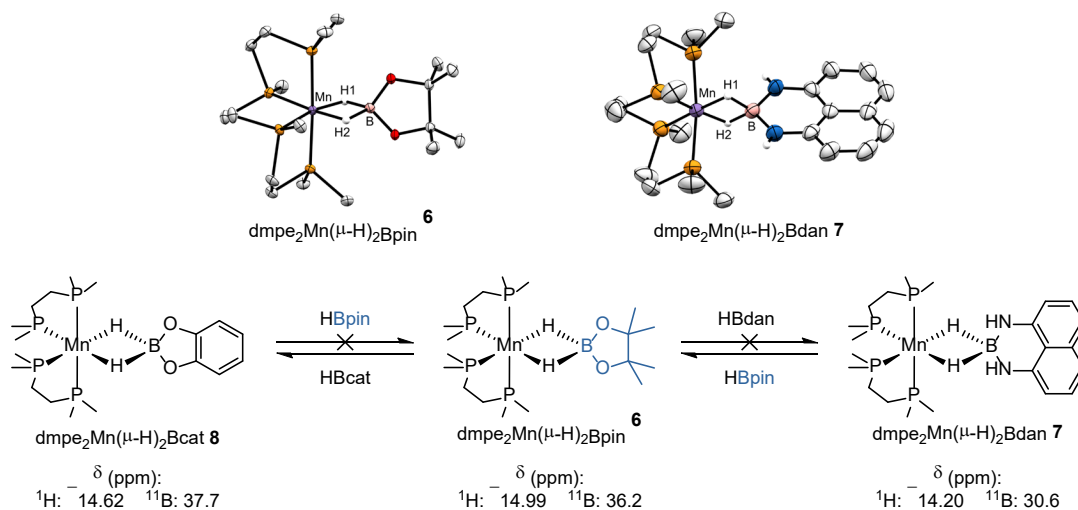
Scheme 2. Mechanistic Investigations 1

a) Proposed in situ Activation of Manganese(II) Pre-Catalyst

1 dmpe₂MnBr₂ + HBpin (xs.) + NaOᵗBu (2 equiv.) → THF, 60 °C → **4** dmpe₂MnH₃ → HBpin / - H₂ → **6** dmpe₂Mn(μ-H)₂Bpin

Observed by ¹H and ¹¹B NMR

boron 'ate' complex hydride (H⁻) donor

b) Reversible HBpin Binding and Turnover

4 dmpe₂MnH₃

I) HBpin / H₂   II) DBpin / H₂

6 dmpe₂Mn(μ-H)₂Bpin   ⇌ DBpin / HBpin ⇌   **d-6** dmpe₂Mn(μ-H/D)₂Bpin

Deuterated dmpe + HD

Observed by ¹H and ²D NMR

Deuterium incorporation via reversible C–H insertion

Blue light

III)   IV)

2a   **2a**

3a   **4** dmpe₂MnH₃   **d-3a**   +   **d-2a**
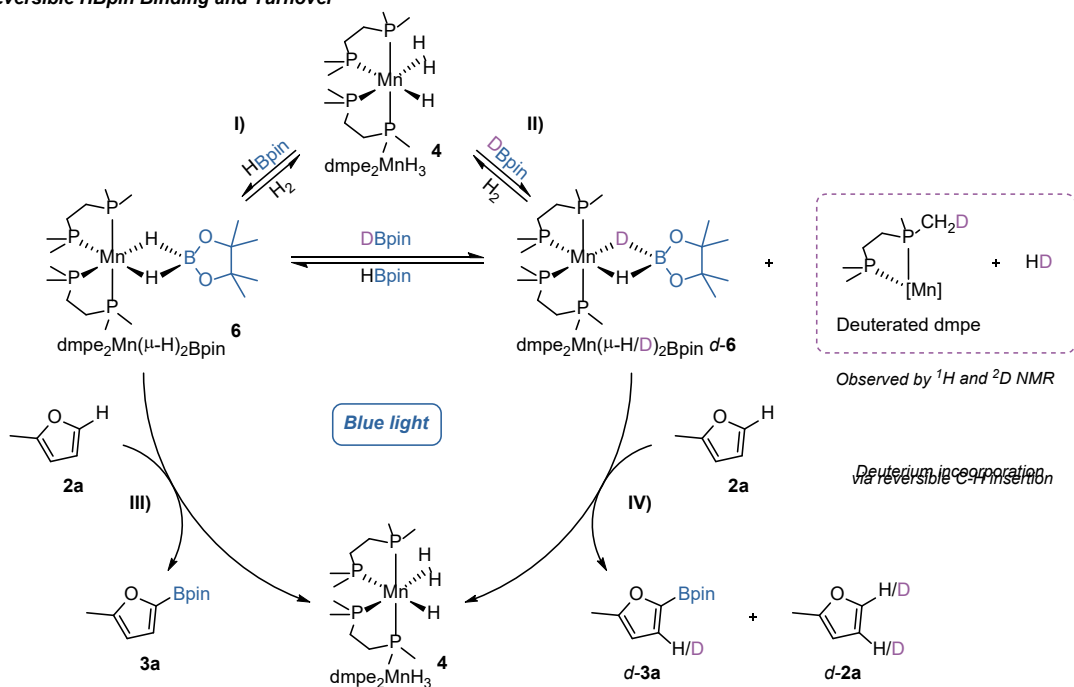
c) Identification and Relative Stability of Manganese Borohydride Adducts

dmpe₂Mn(μ-H)₂Bpin **6**   dmpe₂Mn(μ-H)₂Bdan **7**

dmpe₂Mn(μ-H)₂Bcat **8**   ⇌ HBpin ✕ / HBcat ⇌   dmpe₂Mn(μ-H)₂Bpin **6**   → HBdan ✕ / HBpin →   dmpe₂Mn(μ-H)₂Bdan **7**

δ (ppm):
¹H: ⁻14.62   ¹¹B: 37.7

δ (ppm):
¹H: ⁻14.99   ¹¹B: 36.2

δ (ppm):
¹H: ⁻14.20   ¹¹B: 30.6

[a]X-ray crystal structure of dmpe₂Mn(μ-H)₂Bpin **6**, ellipsoids are set at 50% probability. X-ray crystal structure of dmpe₂Mn(μ-H)₂Bdan **7**, ellipsoids set to 30% probability. C bound H atoms omitted for clarity

Scheme 3. Mechanistic Investigations 2

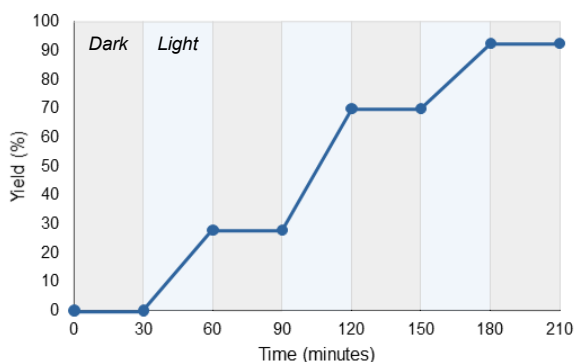*a) Reversible C-H Insertion - H/D Scambling*

dmpe$_2$MnH$_3$ **4** + 5-*d*-**2c** $\xrightarrow{\text{n-C}_6\text{H}_{14}\text{' 60 °C, 48 h, Blue light}}$ dmpe$_2$Mn(H/D)$_3$ *d*-**4** (12%) + n-C$_8$H$_{17}$ furan *d*-**2c** (43%) / (42%) + Deuterated dmpe + HD

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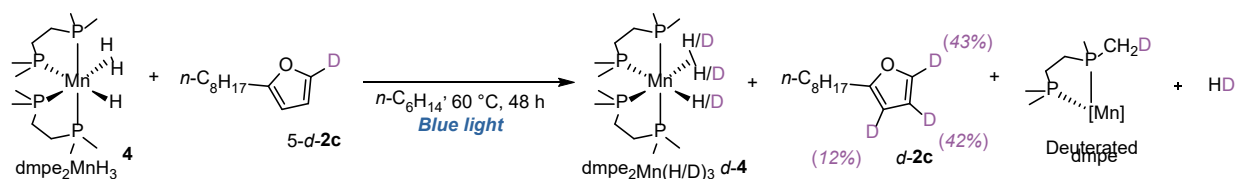
b) Determination of C-H Kinetic Isotope Effect

R–furan–H/D **2** + HBpin $\xrightarrow[\text{n-C}_6\text{H}_{14}, 60 °C, \text{Blue light}]{\text{dmpe}_2\text{MnH}_3 \ \mathbf{4} \ (3 \text{ mol\%})}$ R–furan–Bpin **3**   R = Me or n-C$_8$H$_{17}$
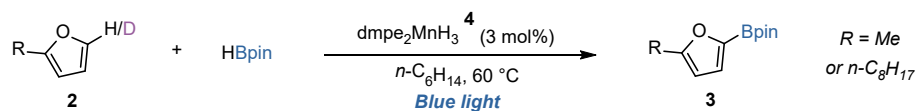
I) Light/Dark Experiment (R = Me)

II) C-H Kinetic Isotope Effect (R = n-C$_8$H$_{17}$)

Substrate: **2c**, 5-*d*-**2c**

$k_{2c} / k_{5\text{-}d\text{-}2c} = 1.6$
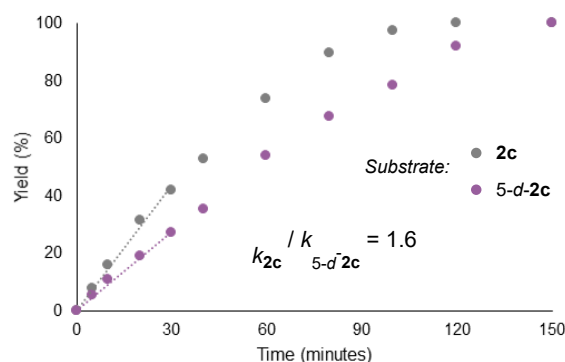
[a]Reaction conditions 1: dmpe$_2$MnH$_3$ **4** (1 equiv.), 5-*d*-**2c** (xs.), n-C$_6$H$_{14}$ (1 M), 60 °C, 48 h. Deuterium incorporation determined by ^{1}H and ^{2}D NMR spectroscopy. [b]Standard reaction conditions, arene: 2-methylfuran **2a**. [c]Standard reaction conditions, arene: 2-octylfuran **2c** or 5-*d*-2-octylfuran 5-*d*-**2c**.

irreversible by the addition of HBdan to dmpe$_2$Mn(μ-H)$_2$Bpin **6** giving no observable formation of dmpe$_2$Mn(μ-H)$_2$Bdan **7**. However, addition of, the more Lewis acidic, HBcat to dmpe$_2$Mn(μ-H)$_2$Bpin **6** gave dmpe$_2$Mn(μ-H)$_2$Bcat **8**.

Blue light irradiation of dmpe$_2$MnH$_3$ **4** in the presence of 2-methylfuran **2a** led to no observable manganese aryl complex, arising from C-H bond metallation. However, irradiation in the presence of 5-*d*-2-octylfuran, 5-*d*-**2c**, led to HD observed *in situ*, deuterium incorporation into the pre-catalyst, dmpe$_2$Mn(H/D)$_3$ *d*-**4**, and H/D scrambling of the furan, thus indicating a reversible C-H metallation process (Scheme 3a). Deuterium incorporation at the 3- and 4-positions of the furan was observed suggesting the catalyst was capable of insertion into all the C-H bonds, but only underwent C-B formation in the 5-position. These observations may suggest a necessity for arene-borane pre-coordination through the neighboring heteroatom to achieve C-B formation, and could explain the lack of reactivity with carboarenes.

Irradiation of dmpe$_2$MnH$_3$ **4** in the presence of excess thiophene **2m** again led to no evidence of an isolatable C-H metallated manganese aryl complex. Instead, small quantities of a thiophene coordinated Mn(I) hydride complex, dmpe$_2$MnH(thiophene) **9**, were observed by ^{1}H NMR spectroscopy (See SI, Part 8). The ^{1}H-^{31}P coupling within the associated hydride signal was akin to that of the *trans*-adducted Mn(I) hydride complexes prepared by Jones and co-workers,[12] although the exact configuration of the thiophene coordination was undetermined. When

reacted with HBpin, immediate and quantitative conversion to the borohydride complex, dmpe$_2$Mn(μ-H)$_2$Bpin **6**, was observed.

It was noted that during the mechanistic investigations, two further hydride signals were consistently observed despite changes in substrate and solvent. Attempts to isolate these species, alongside recent studies by Emslie and co-workers,[14d] confirmed these to be the phosphine complexes, (dmpe$_2$MnH)$_2$(μ-dmpe) and (dmpe$_2$MnH)$_2$(κ^1-dmpe) (See SI, Part 8). These complexes are presumably the product of thermal or irradiative degradation of dmpe$_2$MnH$_3$ **4**.

Finally, the rate-limiting step of the C-H borylation reaction was investigated. A light/dark experiment was used to confirm that the C-H borylation reaction could be accurately followed by NMR spectroscopy. The borylation of 2-methylfuran **2a** under alternating blue light irradiation and darkness confirmed that C-H borylation only occurred under irradiation and no persistent reaction was observed in the dark (Scheme 3b, **I**). A kinetic isotope effect (KIE) of 1.6 was found for the borylation of 2-octylfuran **2c** versus 5-*d*-2-octylfuran 5-*d*-**2c**, with the initial rates of reaction being determined by monitoring the formation of borylated furan product **3c** using 1H NMR spectroscopy (Scheme 3b, **II**). The reversibility of the C-H metallation step (Scheme 3a) presumably accounts for the smaller than average value for a typical primary KIE.[15] Use of higher power light sources (450 nm and 365 nm) increased the rate of reaction (See SI, Part 10).

Scheme 4. Proposed Mechanism for Manganese-Catalyzed C-H Borylation of Furan and Thiophenes.
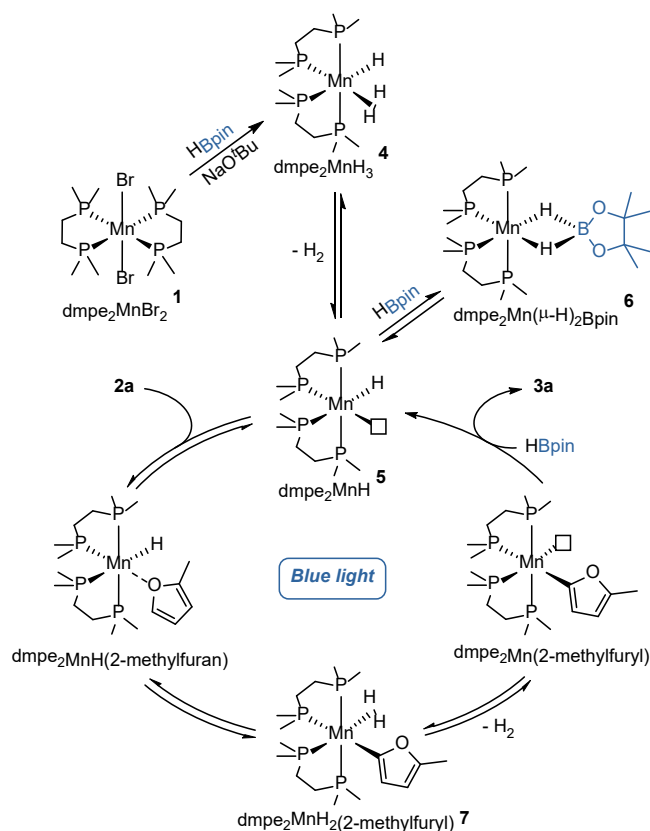
By monitoring reaction progression it was possible to determine the relative ratio of manganese species present throughout the borylation reaction (See SI, Part 10). In the early stages of the reaction, when the concentration of HBpin was high, the majority manganese species dmpe₂Mn(μ-H)₂Bpin **6**. The concentration of this species was then observed to decrease as the reaction proceeded. The growth and subsequent depletion of dmpe₂Mn(μ-H)₂Bpin **6** suggested this complex was an off-cycle resting-state. In support of this, using dmpe₂Mn(μ-H)₂Bpin **6** as the pre-catalyst, in place of dmpe₂MnH₃ **4**, gave equal activity in the borylation of 2-methylfuran **2a** (93% yield) under standard conditions.

Based on the accumulated mechanistic studies, a catalytic cycle was proposed (Scheme 4). Pre-catalyst, dmpe₂MnH₃ **4**, could either be generated *in situ* from the corresponding dibromide precursor, dmpe₂MnBr₂ **1**, or used directly. Thermal or photochemical loss of dihydrogen gives a highly reactive Mn(I) hydride species, dmpe₂MnH **5** which is rapidly adducted by HBpin to give dmpe₂Mn(μ-H)₂Bpin **6**, an off-cycle, resting-state and catalyst reservoir.

Alternatively, dmpe₂MnH **5** undergoes $C(sp^2)$-H bond metallation, potentially by initial heteroatom coordination, producing the manganese aryl complex dmpe₂MnH₂(2-methylfuryl) **7**. Further dissociation of dihydrogen results in a highly reactive coordinately unsaturated manganese aryl complex, dmpe₂Mn(2-methylfuryl). Finally, in the presence of HBpin, dmpe₂Mn(2-methylfuryl) can either undergo oxidative addition followed by a subsequent reductive elimination, or a single-step σ-bond metathesis reaction to give the aryl-boronic ester prod-

uct **3a**, whilst regenerating the catalyst, dmpe₂MnH **5**. The addition of NaO^{t}Bu and NaBr to a catalyzed reaction using dmpe₂MnH₃ **4** showed no inhibition of catalytic activity, thus, the reduced activity observed when performing reactions using dmpe₂MnBr₂ **1** and *in situ* activation can be attributed to incomplete activation of the dmpe₂MnBr₂ **1** pre-catalyst.

In summary, the first example of manganese-catalyzed $C(sp^2)$-H borylation of furan and thiophenes derivatives has been developed using the *in situ* activation of a bench-stable Mn(II) pre-catalyst. The combination of NaO^{t}Bu and HBpin provided an efficient means of accessing the photoactive species, dmpe₂MnH₃ **4**. Mechanistic investigations resulted in the identification of key reaction intermediates that suggest the boronic ester products are obtained exclusively through a C-H metallation pathway. Additional kinetic studies confirmed that C-H metallation was also the rate limiting step. Alternatively, coordination with pinacolborane results in the manganese borohydride adduct, dmpe₂Mn(μ-H)₂Bpin **6**, which acts as a catalyst resting-state and reservoir.

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ASSOCIATED CONTENT

Supporting information. General experimental, mechanistic and kinetic studies, characterization data, crystallographic data (CIF), and NMR spectra are available free of charge via the Internet at http://pubs.acs.org.

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