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Manganese-Catalyzed C(sp²)-H Borylation of Furan and Thiophene Derivatives

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KEYWORDS Manganese, Earth-abundant, C-H borylation, Boron, Photocatalysis

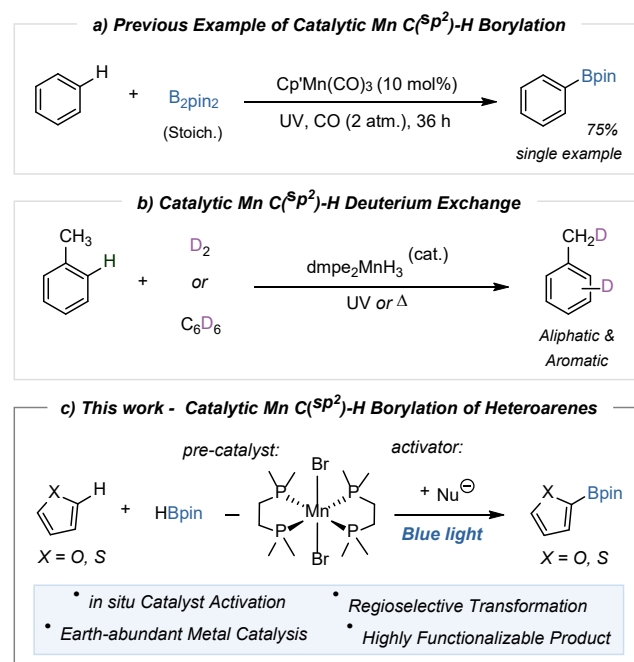
ABSTRACT: Aryl boronic esters are bench-stable, platform building-blocks that can be accessed through metal-catalyzed aryl C(sp²)-H borylation reactions. C(sp²)-H bond functionalization reactions using rare- and precious metal catalyst are well established and whilst examples utilizing Earth-abundant 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(sp²)-H bond borylation occurs through 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(sp²)-H functionalization of arenes, in particular C(sp²)-H borylation.¹ Direct C(sp²)-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(sp²)-H borylation is currently dominated by platinum-group metal catalysts, namely iridium and rhodium,³ with examples of C(sp²)-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(sp²)-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(sp²)-H borylation involving a manganese catalyst (Scheme 1a).¹⁰

Hartwig reported that stoichiometric quantities of a catecholborane-manganese carbonyl complex [(OC)₃MnBcat where Bcat = catecholborane] would mediate the C(sp²)-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' = C₅H₄Me) and the diboronic ester B₂pin₂ (B₂pin₂ = 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(sp²)-H Borylation

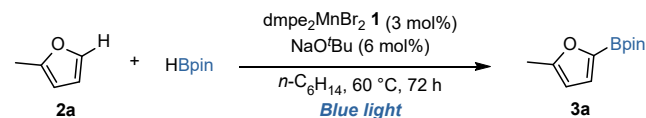


a) Previous example of manganese-catalyzed C(sp²)-H borylation. **b)** dmpe₂MnH₃ catalyzed C(sp²)-H deuterium exchange under thermal and photochemical conditions. **c)** This work - C(sp²)-H borylation using dmpe₂MnBr₂ **1** as a pre-catalyst, activated by exogenous nucleophiles, under blue light irradiation.

The manganese complex, bis[1,2-bis(dimethylphosphino)ethane]trihydridomanganese (dmpe₂MnH₃), has been used to catalyze hydrogen isotope exchange reactions of arene C(sp²)-H bonds using C₆D₆ and D₂ 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 = $\text{dmpe}_2\text{MnH}_3$ 4 No NaO'Bu	93
2	none	86
3	White light	30
4	UV light (CFL)	13
5	Furan : HBpin (1 : 1)	60
6	Pre-catalyst = $(\text{CO})_5\text{MnBr}$	0
7	Pre-catalyst = $\text{Cp}'\text{Mn}(\text{CO})_3$	0
8	No pre-catalyst	0
8	No NaO'Bu	0
10	No light (60 °C and 100 °C)	0

^a2-Methylfuran **2a** (2.8 equiv.), HBpin (1 equiv.), $\text{dmpe}_2\text{MnBr}_2$ **1** (3 mol%), NaO'Bu (6 mol%), $n\text{-C}_6\text{H}_{14}$ (1 M), 60 °C, 72 h. Yields determined by ¹H-NMR spectroscopy of the crude reaction mixtures using product:substrate ratio. Blue light (460 nm). Cp' = $\text{C}_5\text{H}_4\text{Me}$.

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 $\text{dmpe}_2\text{MnH}_3$ **4** (3 mol%) as a pre-catalyst (see SI for stoichiometric generation of $\text{dmpe}_2\text{MnH}_3$ **4**) and pinacolborane (HBpin) (1 equiv.) in $n\text{-C}_6\text{H}_{14}$ (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 $\text{dmpe}_2\text{MnH}_3$ **4** pre-catalyst for the manganese(II) halide precursor, $\text{dmpe}_2\text{MnBr}_2$ **1**, (3 mol%) and *in situ* activation using NaO'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'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-naphthalenediaminatoborane (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).

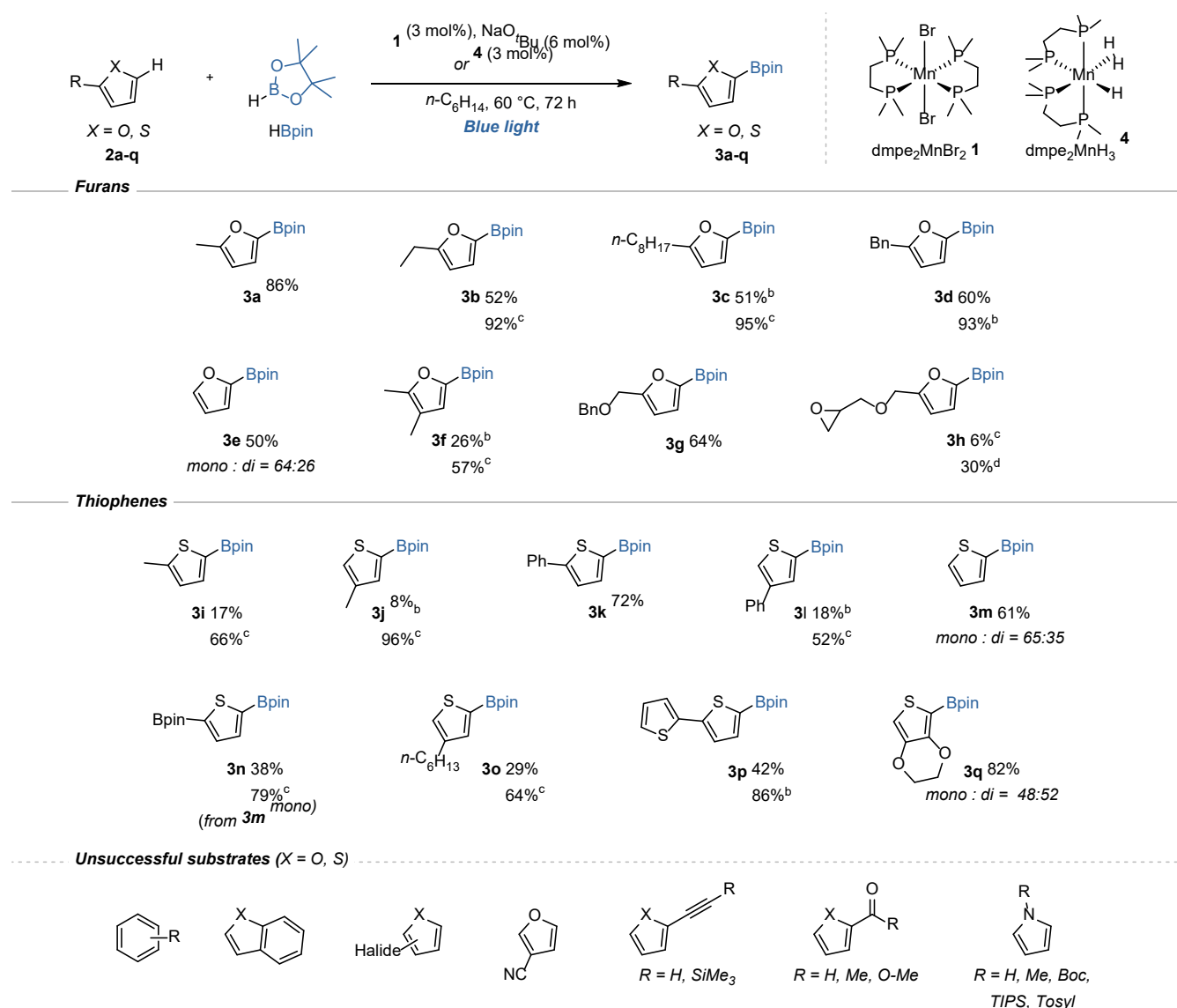
With optimized reaction conditions identified, the reactivity of the system was assessed by application to a selection of furan and thiophene derivatives (Table 2). 2-Methylfuran **2a** underwent efficient and regioselective C-H borylation to give the 5-substituted boronic ester regioisomer **3a** exclusively 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-substituted 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 $\text{dmpe}_2\text{MnH}_3$ **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 $\text{dmpe}_2\text{MnBr}_2$ **1** in $n\text{-C}_6\text{H}_{14}$, activation studies were performed in THF. Reaction of the activator, NaO'Bu, with HBpin and the $\text{dmpe}_2\text{MnBr}_2$ pre-catalyst **1** in the absence of light irradiation showed no observable formation of the $\text{dmpe}_2\text{MnH}_3$ **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 ¹H NMR spectroscopy (Scheme 2a). In combination with ¹¹B, ¹H-¹¹B HMBC, and variable temperature ¹H NMR spectroscopy, the structure was suggested to be a hydride bridged manganese borohydride complex $\text{dmpe}_2\text{Mn}(\mu\text{-H})_2\text{Bpin}$ **6**.^{4d, 14} Under both thermal and photochemical conditions, $\text{dmpe}_2\text{MnH}_3$ **4** is reported to readily dissociate dihydrogen to give a Mn(I) hydride species which was trapped here by HBpin to give $\text{dmpe}_2\text{Mn}(\mu\text{-H})_2\text{Bpin}$ **6**.¹² Blue light irradiation accelerated the formation of the manganese borohydride adduct $\text{dmpe}_2\text{Mn}(\mu\text{-H})_2\text{Bpin}$ **6** as observed by ¹H NMR spectroscopy, presumably by increasing the rate of H₂ dissociation.

To confirm the identity of any intermediate manganese hydride species, further mechanistic studies were performed using isolated $\text{dmpe}_2\text{MnH}_3$ **4**. The reaction of $\text{dmpe}_2\text{MnH}_3$ **4** with HBpin under blue light irradiation again showed the formation of $\text{dmpe}_2\text{Mn}(\mu\text{-H})_2\text{Bpin}$ **6**, as observed by ¹H and ¹¹B NMR spectroscopy (Scheme 2b, I). Single crystals suitable for X-ray analysis were obtained from a concentrated $n\text{-C}_6\text{H}_{14}$ 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



^aReaction conditions 1: Arene **2** (2.8 equiv.), HBpin (1 equiv.), dmpe₂MnBr₂ **1** (3 mol%), NaO^tBu (6 mol%), *n*-C₆H₁₄ (1 M), 60 °C, 72 h. Isolated yields reported. ^bYields determined by ¹H NMR spectroscopy of the crude reaction mixtures using product:substrate ratio (reaction conditions 1). ^cReaction conditions 2: Arene **2** (2.8 equiv.), HBpin (1 equiv.), dmpe₂MnH₃ **4** (3 mol%), *n*-C₆H₁₄ (1 M), 60 °C, 24 h. Isolated yields reported. ^dYields determined by ¹H 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.

dmpe₂Mn(μ-H)₂Bpin **6** (Scheme 2c). Substitution of HBpin for DBpin led to the deuterated borohydride adduct, dmpe₂Mn(μ-H/D)₂Bpin *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 dmpe₂Mn(μ-H)₂Bpin **6** with 2-methylfuran **2a** resulted in the formation of the 5-boryl product **3a**, and regeneration of dmpe₂MnH₃ **4** (Scheme 2b, **III**). Use of the deuterated complex, dmpe₂Mn(μ-H/D)₂Bpin *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.

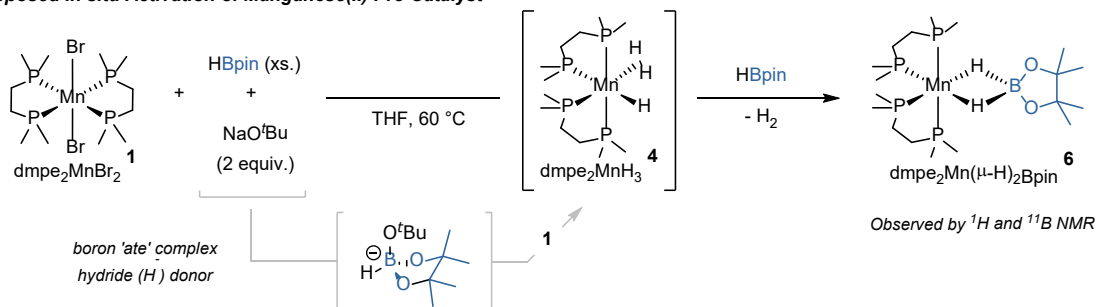
Further structural confirmation of the manganese-HBpin borohydride complex was gained through the synthesis, isolation

and characterization of the analogous HBdan and HBcat complexes, dmpe₂Mn(μ-H)₂Bdan **7** and dmpe₂Mn(μ-H)₂Bcat **8**. These complexes displayed comparative ¹H and ¹¹B NMR resonances as well as the characteristic ¹H-¹¹B cross peak (HMQC). Single crystals suitable for X-ray analysis of dmpe₂Mn(μ-H)₂Bdan **7** were obtained from a concentrated *n*-C₆H₁₄/C₆D₆ solution and again showed the bridging borohydride bonding arrangement (Scheme 2c).

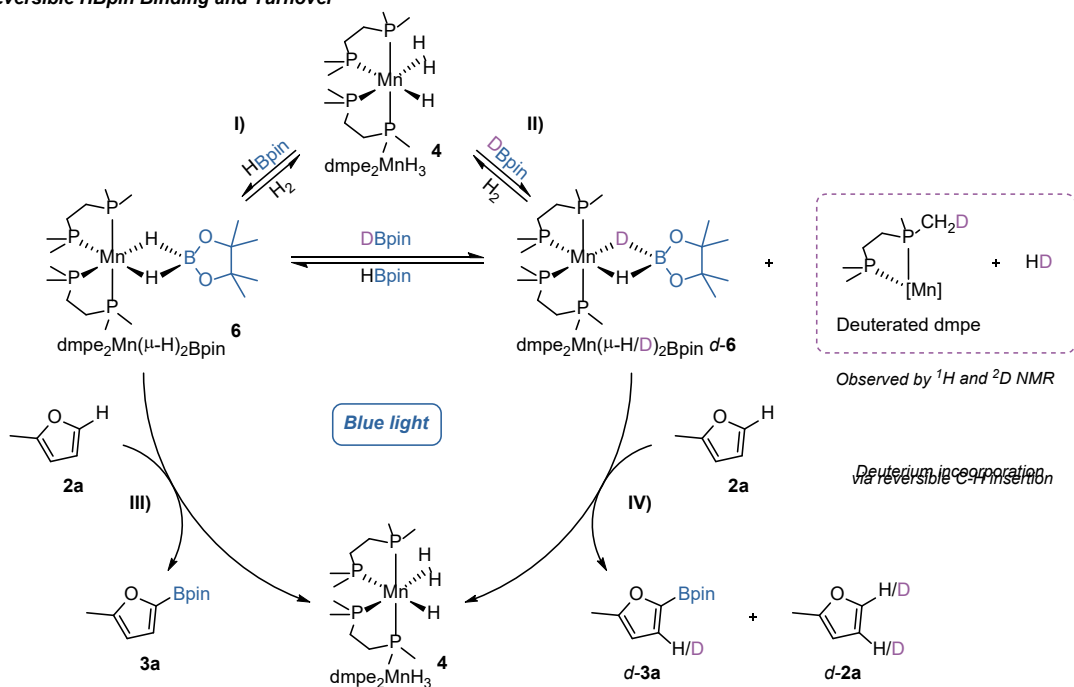
The relative stability of the manganese borohydride adducts **6**, **7**, and **8** was assessed through a series of exchange/competition reactions that showed a relationship corresponding to the relative Lewis acidity of each boron reagent. (Scheme 2c). Addition of HBpin to dmpe₂Mn(μ-H)₂Bdan **7** gave dmpe₂Mn(μ-H)₂Bpin **6** through the displacement of HBdan, as observed by ¹H and ¹¹B NMR spectroscopy. This reaction was found to be

Scheme 2. Mechanistic Investigations 1

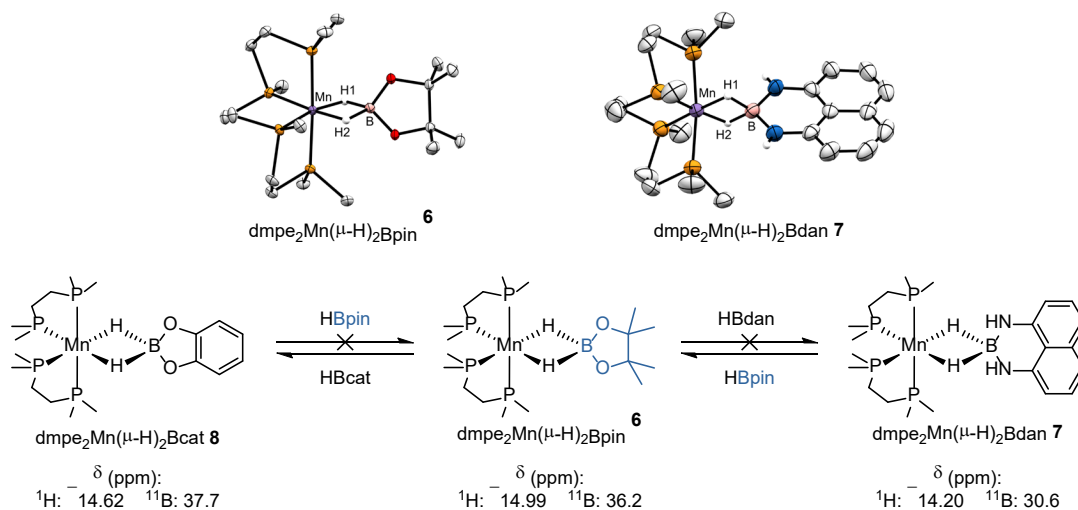
a) Proposed *in situ* Activation of Manganese(II) Pre-Catalyst



b) Reversible HBpin Binding and Turnover



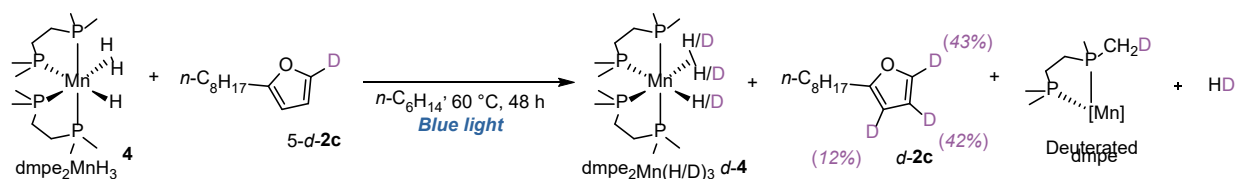
c) Identification and Relative Stability of Manganese Borohydride Adducts



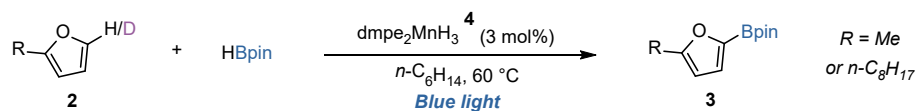
^aX-ray crystal structure of $\text{dmpe}_2\text{Mn}(\mu\text{-H})_2\text{Bpin}$ 6, ellipsoids are set at 50% probability. X-ray crystal structure of $\text{dmpe}_2\text{Mn}(\mu\text{-H})_2\text{Bdan}$ 7, ellipsoids set to 30% probability. C bound H atoms omitted for clarity

Scheme 3. Mechanistic Investigations 2

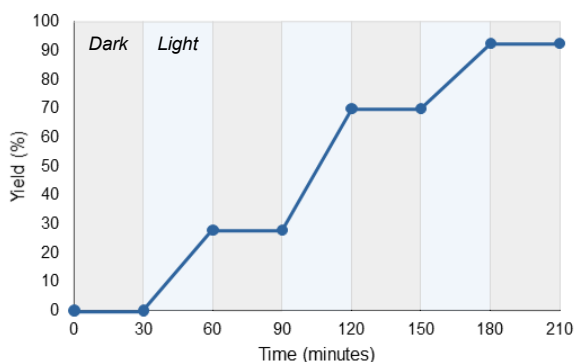
a) Reversible C-H Insertion - H/D Scrambling



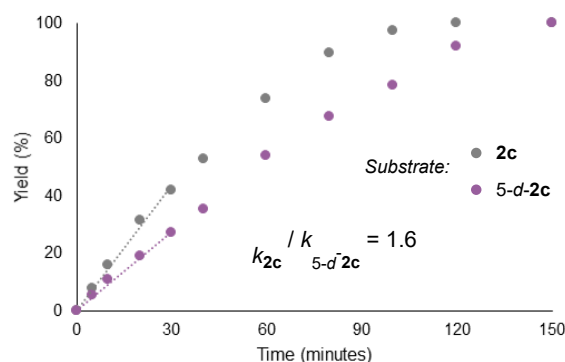
b) Determination of C-H Kinetic Isotope Effect



I) Light/Dark Experiment ($R = \text{Me}$)



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



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

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

Blue light irradiation of $\text{dmpe}_2\text{MnH}_3$ **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 $5\text{-}d\text{-}2\text{-octylfuran}$, $5\text{-}d\text{-}2\text{c}$, led to HD observed *in situ*, deuterium incorporation into the pre-catalyst, $\text{dmpe}_2\text{Mn}(\text{H}/\text{D})_3$ 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.

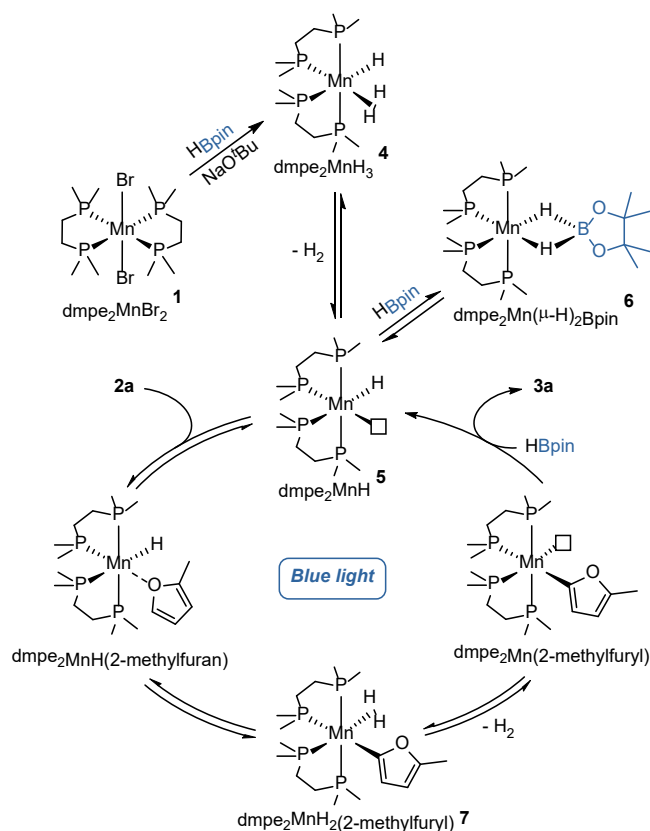
Irradiation of $\text{dmpe}_2\text{MnH}_3$ **4** in the presence of excess thiophene **2m** again led to no evidence of an isolatable C-H metallated manganese aryl complex. Instead, small quantities of a thiophene coordinated Mn(I) hydride complex, $\text{dmpe}_2\text{MnH}(\text{thiophene})$ **9**, were observed by ^1H NMR spectroscopy (See SI, Part 8). The ^1H - ^{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, $\text{dmpe}_2\text{Mn}(\mu\text{-H})_2\text{Bpin}$ **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, $(\text{dmpe}_2\text{MnH})_2(\mu\text{-dmpe})$ and $(\text{dmpe}_2\text{MnH})_2(\kappa^1\text{-dmpe})$ (See SI, Part 8). These complexes are presumably the product of thermal or irradiative degradation of $\text{dmpe}_2\text{MnH}_3$ **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 $5\text{-}d\text{-}2\text{-octylfuran}$ $5\text{-}d\text{-}2\text{c}$, 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 $\text{dmpe}_2\text{Mn}(\mu\text{-H})_2\text{Bpin}$ **6**. The concentration of this species was then observed to decrease as the reaction proceeded. The growth and subsequent depletion of $\text{dmpe}_2\text{Mn}(\mu\text{-H})_2\text{Bpin}$ **6** suggested this complex was an off-cycle resting-state. In support of this, using $\text{dmpe}_2\text{Mn}(\mu\text{-H})_2\text{Bpin}$ **6** as the pre-catalyst, in place of $\text{dmpe}_2\text{MnH}_3$ **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, $\text{dmpe}_2\text{MnH}_3$ **4**, could either be generated *in situ* from the corresponding dibromide precursor, $\text{dmpe}_2\text{MnBr}_2$ **1**, or used directly. Thermal or photochemical loss of dihydrogen gives a highly reactive Mn(I) hydride species, dmpe_2MnH **5** which is rapidly adducted by HBpin to give $\text{dmpe}_2\text{Mn}(\mu\text{-H})_2\text{Bpin}$ **6**, an off-cycle, resting-state and catalyst reservoir.

Alternatively, dmpe_2MnH **5** undergoes C(*sp*²)-H bond metallation, potentially by initial heteroatom coordination, producing the manganese aryl complex $\text{dmpe}_2\text{MnH}_2(2\text{-methylfuryl})$ **7**. Further dissociation of dihydrogen results in a highly reactive coordinately unsaturated manganese aryl complex, $\text{dmpe}_2\text{Mn}(2\text{-methylfuryl})$. Finally, in the presence of HBpin, $\text{dmpe}_2\text{Mn}(2\text{-methylfuryl})$ 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, dmpe_2MnH **5**. The addition of NaO'Bu and NaBr to a catalyzed reaction using $\text{dmpe}_2\text{MnH}_3$ **4** showed no inhibition of catalytic activity, thus, the reduced activity observed when performing reactions using $\text{dmpe}_2\text{MnBr}_2$ **1** and *in situ* activation can be attributed to incomplete activation of the $\text{dmpe}_2\text{MnBr}_2$ **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'Bu and HBpin provided an efficient means of accessing the photoactive species, $\text{dmpe}_2\text{MnH}_3$ **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, $\text{dmpe}_2\text{Mn}(\mu\text{-H})_2\text{Bpin}$ **6**, which acts as a catalyst resting-state and reservoir.

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Author Contributions

L.B., M.S. and J.H.D. performed the practical work. J.H.D. and S.P.T. conceived the reaction. S.P.T. and A.P.D. advised investigations. All authors contributed to the manuscript.

Notes

The authors declare no competing financial interest

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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