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# Manganese-Catalyzed C(sp<sup>2</sup>)–H Borylation of Furan and Thiophene Derivatives

Luke Britton, Maciej Skrodzki, Gary S. Nichol, Andrew P. Dominey, Piotr Pawluć, Jamie H. Docherty,\* and Stephen P. Thomas\*



providing facile access to the active manganese hydride species. Mechanistic investigations showed that blue light irradiation directly affected catalysis by action at the metal center, that  $C(sp^2)$ -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.

Earth-abundant Metal Catalysis

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derivatives is reported alongside an in situ activation method

T he development of catalytic protocols based on Earthabundant 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.<sup>1</sup> 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.<sup>1e,2</sup> Arene  $C(sp^2)$ -H borylation is currently dominated by platinum-group metal catalysts, namely, iridium and rhodium,<sup>3</sup> with examples of  $C(sp^2)$ -H borylation using first-row transition metals being generally limited to Fe,<sup>4</sup> Co,<sup>5</sup> and Ni species.<sup>6</sup> Photoinduced borylations have also been reported.<sup>7</sup>

Manganese is the third most abundant transition metal and benefits from low physiological and environmental toxicity.<sup>8</sup> 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.<sup>9</sup> These were typically performed using Mn(0)/(I) carbonyl species and demonstrated high regioselectivity when using directing groups.<sup>9a,b</sup> 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).<sup>10</sup>

Hartwig reported that a manganese-borylcarbonyl complex  $[(OC)_5MnBcat$ , where cat = catechol] would mediate the  $C(sp^2)$ -H borylation of benzene under UV light irradiation

(200–400 nm) to give phenyl-Bcat.<sup>11</sup> This was later followed by a single catalytic example using a manganese half-sandwich complex (Cp'Mn(CO)<sub>3</sub>, where Cp' = C<sub>5</sub>H<sub>4</sub>Me) and the diboronic ester B<sub>2</sub>pin<sub>2</sub> (B<sub>2</sub>pin<sub>2</sub> = 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 h.<sup>10</sup>

The manganese complex,  $bis[1,2-bis(dimethylphosphino)-ethane]trihydridomanganese (dmpe<sub>2</sub>MnH<sub>3</sub>), has been used to catalyze hydrogen isotope exchange reactions of arene <math>C(sp^2)-H$  bonds using  $C_6D_6$  and  $D_2$  as the isotope sources (Scheme 1b).<sup>12</sup> As this was proposed to proceed through a manganese aryl species, generated by arene C–H metallation, it was questioned if this manganese aryl species would be 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,<sup>4f,h</sup> so possibly negating the need to generate and handle the manganese trihydride (Scheme 1c).

The ubiquitous nature of borylated heterocycles in pharmaceutical development directed focus to the C-H borylation of simple heteroarenes with 2-methylfuran used as

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# Scheme 1. Manganese-Catalyzed $C(sp^2)$ -H Borylation



<sup>*a*</sup>Previous example of manganese-catalyzed  $C(sp^2)$ -H borylation  $(Cp' = C_5H_4Me)$ . <sup>*b*</sup>dmpe<sub>2</sub>MnH<sub>3</sub>-catalyzed  $C(sp^2)$ -H deuterium exchange under thermal and photochemical conditions (dmpe =  $Me_2P(CH_2)_2PMe_2$ ). <sup>*c*</sup>This work— $C(sp^2)$ -H borylation using dmpe<sub>2</sub>MnBr<sub>2</sub> 1 as a precatalyst, activated by NaO<sup>t</sup>Bu, under blue

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light irradiation.

a model substrate. The potential for C–H borylation was tested using isolated dmpe<sub>2</sub>MnH<sub>3</sub> 4 (3 mol %) as a precatalyst (see Supporting Information (SI) for stoichiometric generation of dmpe<sub>2</sub>MnH<sub>3</sub> 4) and pinacolborane (HBpin) (1 equiv) in *n*- $C_6H_{14}$  (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<sub>2</sub>MnH<sub>3</sub> **4** precatalyst for the manganese(II) halide precursor, dmpe<sub>2</sub>MnBr<sub>2</sub> **1** (3 mol

#### Table 1. Deviations from Optimized Conditions<sup>a</sup>

_0_H	dmpe <sub>2</sub> MnBr <sub>2</sub> <b>1</b> (3 mol%) NaO <sup>t</sup> Bu (6 mol%)	O Bpin
2a	<i>n</i> -C <sub>6</sub> H <sub>14</sub> , 60 °C, 72 h <i>Blue light</i>	3a
entry	deviation	yield (%)
1	precatalyst = dmpe <sub>2</sub> MnH <sub>3</sub> <b>4</b> No NaO <sup>t</sup> Bu	93
2	none	86
3	white light	30
4	UV light (CFL)	13
5	furan/HBpin (1:1)	60
6	precatalyst = (CO) <sub>5</sub> MnBr	0
7	$precatalyst = Cp'Mn(CO)_3$	0
8	no precatalyst	0
9	no NaO <sup>t</sup> Bu	0
10	no light (60 and 100 $^\circ C$ )	0

<sup>*a*</sup>2-Methylfuran **2a** (2.8 equiv), HBpin (1 equiv), dmpe<sub>2</sub>MnBr<sub>2</sub> **1** (3 mol %), NaO<sup>4</sup>Bu (6 mol %), *n*-C<sub>6</sub>H<sub>14</sub> (1 M), 60 °C, 72 h. Yields determined by <sup>1</sup>H NMR spectroscopy of the crude reaction mixtures using product:substrate ratio. Blue light (460 nm). Cp' = C<sub>5</sub>H<sub>4</sub>Me.

%), and in situ activation using NaO<sup>t</sup>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 the development and negate the need for air- and moisture-sensitive reagents/(pre-)catalysts.<sup>4h,13</sup>

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<sup>t</sup>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), catecholborane (HBcat), and 1,8-naphthalenediaminatoborane (HBdan)) were all unreactive toward 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 a manganese precatalyst, an 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 2aunderwent efficient and regioselective C–H borylation to give the 5-substituted boronic ester 3a exclusively in high isolated yield (86%). Substitution of the methyl group for ethyl, octyl, and benzyl groups all resulted in similar reactivity and regioselectivity to give the 5-boryl furan derivatives 3b, 3c, and 3d in 52, 51, and 60% yields, respectively. Borylation of the parent furan 2e was also successful but gave a 64:36mixture of mono/disubstituted boryl furans, with borylation occurring 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 methyland phenyl-substituted 5-boryl thiophene derivatives 3i, 3j, 3k, and 3l. Unsubstituted thiophene 2m showed similar reactivity to furan 2e, with mono- and diborations 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<sub>2</sub>MnH<sub>3</sub> 4. Furans 2f and 2h and thiophenes 2i, 2j, 2l, 2n, and 2o all achieved 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.

To gain mechanistic insight into the precatalyst activation and borylation reaction, a series of single-turnover experiments were carried out. Due to the poor solubility of dmpe<sub>2</sub>MnBr<sub>2</sub> 1 in  $n-C_6H_{14}$ , activation studies were performed in THF. Reaction of the activator, NaO'Bu, with HBpin and the dmpe<sub>2</sub>MnBr<sub>2</sub> precatalyst 1 in the absence of light irradiation showed no observable formation of dmpe2MnH3 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 <sup>1</sup>H NMR spectroscopy (Scheme 2a). In combination with <sup>11</sup>B, <sup>1</sup>H-<sup>11</sup>B HMQC, and variable-temperature <sup>1</sup>H NMR spectroscopies, the structure was suggested to be a hydride-bridged manganese borohydride complex dmpe<sub>2</sub>Mn( $\mu$ -H)<sub>2</sub>Bpin 6.<sup>4d,14</sup> Under both thermal and photochemical conditions, dmpe<sub>2</sub>MnH<sub>3</sub> 4 is reported to readily dissociate dihydrogen to give a Mn(I) hydride species,



## Table 2. Scope of Manganese-Catalyzed C-H Borylation of Furan and Thiophene Derivatives<sup>a</sup>

<sup>*a*</sup>Reaction conditions 1: arene **2** (2.8 equiv), HBpin (1 equiv), dmpe<sub>2</sub>MnBr<sub>2</sub> **1** (3 mol %), NaO<sup>t</sup>Bu (6 mol %), *n*-C<sub>6</sub>H<sub>14</sub> (1 M), 60 °C, 72 h. Isolated yields reported. <sup>*b*</sup>Yields determined by <sup>1</sup>H NMR spectroscopy of the crude reaction mixture using product:substrate ratio (reaction conditions 1). <sup>c</sup>Reaction conditions 2: arene **2** (2.8 equiv), HBpin (1 equiv), dmpe<sub>2</sub>MnH<sub>3</sub> **4** (3 mol %), *n*-C<sub>6</sub>H<sub>14</sub> (1 M), 60 °C, 72 h. Isolated yields reported. <sup>*d*</sup>Yield determined by <sup>1</sup>H NMR spectroscopy of the crude reaction mixture using product:substrate ratio (reaction conditions 2). Mono: 2-boryl product. Di: 2,5-diboryl product. Mono:Di = molar ratio of products.

which was trapped here by HBpin to give  $dmpe_2Mn(\mu-H)_2Bpin 6$ .<sup>12</sup> Blue light irradiation accelerated the formation of the manganese borohydride adduct  $dmpe_2Mn(\mu-H)_2Bpin 6$  as observed by <sup>1</sup>H NMR spectroscopy, presumably by increasing the rate of H<sub>2</sub> dissociation.

To confirm the identity of any intermediate manganese hydride species, further mechanistic studies were performed using isolated dmpe<sub>2</sub>MnH<sub>3</sub> **4**. The reaction of dmpe<sub>2</sub>MnH<sub>3</sub> **4** with HBpin under blue light irradiation again showed the formation of dmpe<sub>2</sub>Mn( $\mu$ -H)<sub>2</sub>Bpin **6**, as observed by <sup>1</sup>H and <sup>11</sup>B NMR spectroscopy (Scheme 2b, I). Single crystals suitable for X-ray analysis were obtained from a concentrated *n*-C<sub>6</sub>H<sub>14</sub> solution at -40 °C, unambiguously confirming the structure of the hydride-bridged manganese borohydride complex, dmpe<sub>2</sub>Mn( $\mu$ -H)<sub>2</sub>Bpin **6** (Scheme 2c). Substitution of HBpin for DBpin led to the deuterated borohydride adduct,  $dmpe_2Mn(\mu-H/D)_2Bpin$  *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).<sup>12</sup>

Blue light irradiation of  $dmpe_2Mn(\mu-H)_2Bpin$  6 with 2methylfuran 2a resulted in the formation of the 5-boryl product 3a and regeneration of  $dmpe_2MnH_3$  4 (Scheme 2b, III). Use of the deuterated complex,  $dmpe_2Mn(\mu-H/D)_2Bpin$ *d*-6, led to deuterium incorporation observed in both the furan substrate (*d*-2a) and 5-boryl product *d*-3a (Scheme 2b, IV), indicating that 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<sub>2</sub>Mn( $\mu$ -H)<sub>2</sub>Bdan 7 and dmpe<sub>2</sub>Mn( $\mu$ -

# Scheme 2. Mechanistic Investigations 1

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





(c) Identification and Relative Stability of Manganese Borohydride Adducts



<sup>c</sup>X-ray crystal structure of dmpe<sub>2</sub>Mn( $\mu$ -H)<sub>2</sub>Bpin **6**; ellipsoids are set at 50% probability. X-ray crystal structure of dmpe<sub>2</sub>Mn( $\mu$ -H)<sub>2</sub>Bdan 7; ellipsoids are set to 30% probability. C-bound H atoms are omitted for clarity.

#### Scheme 3. Mechanistic Investigations 2



(b) Determination of C-H Kinetic Isotope Effect



<sup>*a*</sup>Reaction conditions 1: dmpe<sub>2</sub>MnH<sub>3</sub> **4** (1 equiv), 5-*d*-**2c** (xs.), *n*-C<sub>6</sub>H<sub>14</sub> (1 M), 60 °C, 48 h. Deuterium incorporation determined by <sup>1</sup>H and <sup>2</sup>D NMR spectroscopy. <sup>*b*</sup>I) Standard reaction conditions, arene: 2-methylfuran **2a**. II) Standard reaction conditions, arene: 2-octylfuran **2c** or 5-*d*-octylfuran 5-*d*-**2c**.

H)<sub>2</sub>Bcat 8. These complexes displayed comparative <sup>1</sup>H and <sup>11</sup>B NMR resonances as well as the characteristic <sup>1</sup>H–<sup>1</sup>B cross peak (HMQC). Single crystals suitable for X-ray analysis of dmpe<sub>2</sub>Mn( $\mu$ -H)<sub>2</sub>Bdan 7 were obtained from a concentrated *n*-C<sub>6</sub>H<sub>14</sub>/C<sub>6</sub>D<sub>6</sub> solution and again showed the bridging borohydride bonding arrangement (Scheme 2c).

The relative stability of the manganese borohydride adducts **6–8** 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<sub>2</sub>Mn( $\mu$ -H)<sub>2</sub>Bdan 7 gave dmpe<sub>2</sub>Mn- $(\mu$ -H)<sub>2</sub>Bpin **6** through displacement of HBdan, as observed by <sup>1</sup>H and <sup>11</sup>B NMR spectroscopy. This reaction was found to be irreversible by the addition of HBdan to dmpe<sub>2</sub>Mn( $\mu$ -H)<sub>2</sub>Bpin **6** giving no observable formation of dmpe<sub>2</sub>Mn( $\mu$ -H)<sub>2</sub>Bdan 7. The addition of, the more Lewis acidic, HBcat to dmpe<sub>2</sub>Mn( $\mu$ -H)<sub>2</sub>Bpin **6** gave dmpe<sub>2</sub>Mn( $\mu$ -H)<sub>2</sub>Bcat **8**.

Blue light irradiation of dmpe<sub>2</sub>MnH<sub>3</sub> **4** in the presence of 2methylfuran **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 precatalyst, dmpe<sub>2</sub>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 that the catalyst was capable of insertion into all of the C–H bonds but only underwent C–B formation in the 5-position. These observations may suggest a necessity for arene-borane precoordination through the neighboring heteroatom to achieve C–B formation and could explain the lack of reactivity with carboarenes.

Irradiation of dmpe<sub>2</sub>MnH<sub>3</sub> **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<sub>2</sub>MnH-(thiophene) **9**, were observed by <sup>1</sup>H NMR spectroscopy (see SI, Part 8). The <sup>1</sup>H–<sup>31</sup>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,<sup>12</sup> although the exact configuration of the thiophene coordination was undetermined. When reacted with HBpin, immediate and quantitative conversion to the borohydride complex, dmpe<sub>2</sub>Mn( $\mu$ -H)<sub>2</sub>Bpin **6**, was observed.

It was noted that during the mechanistic investigations, two further hydride signals were consistently observed despite changes in the substrate and solvent. Attempts to isolate these species, alongside recent studies by Emslie and co-workers,<sup>14d</sup> confirmed these to be the phosphine complexes, (dmpe<sub>2</sub>MnH)<sub>2</sub>( $\mu$ -dmpe) and (dmpe<sub>2</sub>MnH)<sub>2</sub>( $\kappa$ <sup>1</sup>-dmpe) (see SI, Part 8). These complexes are presumably the product of thermal or irradiative degradation of dmpe<sub>2</sub>MnH<sub>3</sub> 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 5d-2c, with the initial rates of reaction being determined by monitoring the formation of borylated furan product 3c using <sup>1</sup>H NMR spectroscopy (Scheme 3b, II). The reversibility of the C–H metallation step (Scheme 3a) presumably accounts for the smaller than average value of a typical primary KIE.<sup>15</sup> Use of higher power light sources (450 and 365 nm) increased the rate of reaction (see SI, Part 10).

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 of manganese species were the borohydride adduct dmpe<sub>2</sub>Mn( $\mu$ -H)<sub>2</sub>Bpin 6. The concentration of this species was then observed to decrease as the reaction proceeded. The growth and subsequent depletion of dmpe<sub>2</sub>Mn( $\mu$ -H)<sub>2</sub>Bpin 6 suggested that this complex was an off-cycle resting state. In support of this, use of dmpe<sub>2</sub>Mn( $\mu$ -H)<sub>2</sub>Bpin 6 as the precatalyst, in place of dmpe<sub>2</sub>MnH<sub>3</sub> 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). Precatalyst,  $dmpe_2MnH_3$  4, could either be generated in situ from the corresponding dibromide precursor,  $dmpe_2MnBr_2$  1, or used directly. Thermal or photochemical loss of dihydrogen gives a highly reactive Mn(I) hydride species,  $dmpe_2MnH$  5, which is rapidly

# Scheme 4. Proposed Mechanism for Manganese-Catalyzed C–H Borylation of Furan and Thiophene Derivatives.



dmpe<sub>2</sub>MnH<sub>2</sub>(2-methylfuryl) 7

adducted by HBpin to give  $dmpe_2Mn(\mu-H)_2Bpin$  6, an offcycle, 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 dmpe<sub>2</sub>MnH<sub>2</sub>(2methylfuryl) 7. Further dissociation of dihydrogen results in a highly reactive coordinately unsaturated manganese aryl complex, dmpe<sub>2</sub>Mn(2-methylfuryl). Finally, in the presence of HBpin, dmpe<sub>2</sub>Mn(2-methylfuryl) can either undergo oxidative addition followed by a subsequent reductive elimination, or a single-step  $\sigma$ -bond metathesis reaction to give the aryl boronic ester product 3a while regenerating the catalyst, dmpe<sub>2</sub>MnH 5. The addition of NaO<sup>t</sup>Bu and NaBr to a standard catalysis reaction using dmpe<sub>2</sub>MnH<sub>3</sub> 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 precatalyst.

In summary, the manganese-catalyzed  $C(sp^2)$ -H borylation of furan and thiophene derivatives has been developed using the in situ activation of a Mn(II) precatalyst. The combination of NaO'Bu and HBpin provided an efficient means of accessing the photoactive species, dmpe<sub>2</sub>MnH<sub>3</sub> **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. Kinetic studies confirmed that C-H metallation was also the rate-limiting step. Alternatively, coordination with pinacolborane results in the manganese borohydride adduct, dmpe<sub>2</sub>Mn-( $\mu$ -H)<sub>2</sub>Bpin **6**, which acts as a catalyst resting state and reservoir.

# ASSOCIATED CONTENT

#### **Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c01563.

- General experimental, mechanistic and kinetic studies, characterization data, and crystallographic data (PDF) (CIF)
- (CIF)

#### AUTHOR INFORMATION

#### **Corresponding Authors**

- Jamie H. Docherty EaStCHEM School of Chemistry, University of Edinburgh, Edinburgh EH9 3FJ, United Kingdom; Email: jamie.docherty@ed.ac.uk
- Stephen P. Thomas EaStCHEM School of Chemistry, University of Edinburgh, Edinburgh EH9 3FJ, United Kingdom; orcid.org/0000-0001-8614-2947; Email: stephen.thomas@ed.ac.uk

#### Authors

- Luke Britton EaStCHEM School of Chemistry, University of Edinburgh, Edinburgh EH9 3FJ, United Kingdom
- Maciej Skrodzki EaStCHEM School of Chemistry, University of Edinburgh, Edinburgh EH9 3FJ, United Kingdom; Faculty of Chemistry, Adam Mickiewicz University, 61-614 Poznań, Poland
- Gary S. Nichol EaStCHEM School of Chemistry, University of Edinburgh, Edinburgh EH9 3FJ, United Kingdom
- Andrew P. Dominey GSK Medicines Research Centre, Stevenage SG1 2NY, United Kingdom

Piotr Pawluć – Faculty of Chemistry, Adam Mickiewicz University, 61-614 Poznań, Poland

Complete contact information is available at: https://pubs.acs.org/10.1021/acscatal.1c01563

#### Author Contributions

L.B., M.S., and J.H.D. performed the practical work. G.S.N. carried out X-ray crystallography. J.H.D. and S.P.T. conceived the reaction. S.P.T., P.P., and A.P.D. advised investigations. All authors contributed to the manuscript.

## Notes

The authors declare no competing financial interest.

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