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## Introduction

Simple boranes, such as  $\text{BH}_3$  and  $\text{BF}_3$ , denoted as **B**, cannot exist stably due to the electron deficiency of the boron atom. Usually they form a Lewis acid–base adduct  $\text{L} \cdot \text{B}$  with a Lewis base (**L** = THF,  $\text{Me}_2\text{S}$ ,  $\text{NH}_3$ ,  $\text{Me}_3\text{N}$ , etc.) through a dative bond. There is no doubt that the interplay between the Lewis acid and base exists in these adducts (Scheme 1a). However, while the influence of **L** on the properties and reactivity of **B** has been extensively explored (Scheme 1a I)<sup>1</sup> and the steric interrelationship results in frustrated Lewis pair (FLP) complexes that are also well-known (Scheme 1a II),<sup>2</sup> the influence of boranes (**B**) on a Lewis base (**L**) has been relatively underexplored (Scheme 1a III).

Most studies on the influence of boranes (**B**) on a Lewis base (**L**) have mainly focused on the impacts of  $\text{BF}_3$ ,  $\text{BAR}_3$ , and  $\text{B}_2\text{pin}_2$  on pyridine derivatives.  $\text{BF}_3$  mediated C-2 or C-4 selective functionalization,<sup>3</sup> C-2 methyl group deprotonation,<sup>4</sup> and asymmetric synthesis of pyridine derivatives<sup>5</sup> have been extensively studied.  $\text{BAR}_3$  and  $\text{B}_2\text{pin}_2$  mediated C-3 alkylation,<sup>6</sup> trifluoromethylthiolation,<sup>7</sup> allylation,<sup>8</sup> and cyanation<sup>9</sup> of pyridine

# Triborane ( $\text{B}_3\text{H}_7$ )-mediated regioselective substitution reactions of pyridine derivatives†

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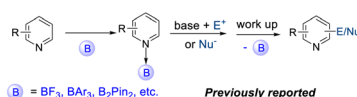
There exists an interplay between borane and a Lewis base in their adducts. However, studies on these adducts so far have mainly focused on the different reactions of B–H bonds with limited attention given to the influence of borane on the chemistry of the Lewis base, except for  $\text{BF}_3$  and  $\text{BAR}_3$ . Herein, we have synthesized novel borane adducts with pyridine derivatives,  $\text{Py} \cdot \text{B}_3\text{H}_7$ , in which the coordination of  $\text{B}_3\text{H}_7$  efficiently achieved the intra-molecular charge transfer. The strong B–N bond in these adducts resulted in the formation of stable dearomatic intermediates of pyridine derivatives, confirmed by  $^1\text{H}$  and  $^{11}\text{B}$  NMR spectroscopy, from which different reactions have transpired to realize  $\text{C}(\text{sp}^3)\text{--H}$  and  $\text{C}(\text{sp}^2)\text{--H}$  functionalization under mild conditions. The  $\text{B}_3\text{H}_7$  pyridine derivatives are stable and do not dissociate or decompose during the reaction process. The high stability of the B–N bond makes this method a good option for boron-containing drugs with potential for use in boron neutron capture therapy (BNCT).

have become hot research fields recently (Scheme 1b). In contrast, the effects of the boron hydrogen complexes, such as  $\text{BH}_3$ , on the Lewis base have rarely been reported because of their strong reducing ability<sup>10</sup> and weak Lewis acidity. Recent studies from our group have found that  $\text{NaNH}_2\text{BH}_3$  could directly react with esters to form amides,<sup>11</sup> which did not work for  $\text{NaNH}_2$  (Scheme 1c).<sup>12</sup> This result suggested that  $\text{BH}_3$  could change the reactivity of the Lewis base of adducts.

(a) The interplay between L and B in the Lewis acid–base pairs



(b) The effect of boranes on the Lewis base



(c) The effect of boranes on synthesis of amides



(d) Triborane ( $\text{B}_3\text{H}_7$ ) mediated regioselective substitution reactions (this work)



Scheme 1 Properties and reactions of borane Lewis base adducts.

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Multinuclear boranes are usually used as reducing agents in organic synthesis.<sup>13</sup> Recently, multinuclear boranes, such as carborane,  $[\text{B}_{10}\text{H}_{10}]^{2-}$ ,  $[\text{B}_6\text{H}_6]^{2-}$ , and  $[\text{HCB}_{11}\text{Cl}_{11}]^-$  have also been used as borylation reagents<sup>14</sup> or catalysts.<sup>15</sup> However, there has been hardly any research into the influence of the Lewis acid properties of multinuclear boranes on reactions.

We have systematically studied the syntheses and properties of octahydridotriborate ( $\text{B}_3\text{H}_8^-$ ) and its neutral derivatives ( $\text{L}\cdot\text{B}_3\text{H}_7$ ), indicating that  $\text{B}_3\text{H}_7$  as a Lewis acid possesses remarkable features.<sup>16</sup> Compared with  $\text{BH}_3$ ,  $\text{B}_3\text{H}_7$  exhibits greater stability, weaker reducing ability, and a higher ability to coordinate with metals.<sup>17</sup> Compared with  $\text{BF}_3$ ,  $\text{B}_3\text{H}_7$  has relatively low acidity. In addition,  $\text{B}_3\text{H}_7$  has a steric effect and  $\sigma$  aromaticity. All these properties may enable the  $\text{B}_3\text{H}_7$  group to mediate different organic reactions (Scheme 1d).

## Results and discussion

### Synthesis and properties of $\text{Py}\cdot\text{B}_3\text{H}_7$

To explore the effects of  $\text{B}_3\text{H}_7$  on a Lewis base, we selected pyridine, which is widely used in pharmaceutical chemistry, functional materials, and natural products as a Lewis base.<sup>18</sup> We synthesized  $\text{Py}\cdot\text{B}_3\text{H}_7$  through a reaction of pyridine with  $\text{THF}\cdot\text{B}_3\text{H}_7$ , formed *in situ* by reacting  $\text{KB}_3\text{H}_8$  with  $\text{HCl}\cdot\text{Et}_2\text{O}$ . The  $\text{Py}\cdot\text{B}_3\text{H}_7$  adduct **1a** was obtained as a white solid in 91% yield (Scheme 2). This novel compound showed excellent stability towards both acid and base in aqueous solutions at room temperature (see ESI, Fig. S1†), offering an opportunity to examine their reactivity. The results indicated that a rapid dearomatic reaction of pyridine derivatives occurred, which then further reacted with electrophiles or oxidants to provide the rearomatic products (Scheme 1d).

### $\text{B}_3\text{H}_7$ mediated dearomatic reaction of Py derivatives

A direct dearomatic reaction of pyridine is impossible under mild conditions. The dearomatic intermediates of  $\text{BF}_3$  coordinated pyridine derivatives are potential products in most situations.<sup>19</sup> We found that the  $\text{B}_3\text{H}_7$  mediated dearomatic reaction of 4-methylpyridine rapidly proceeded by reacting with  $\text{KO}^t\text{Bu}$  to form 4-methylene dihydropyridine at low temperatures. This intermediate was identified spectrally (Fig. 1e) but not isolated, which indicated that  $\text{B}_3\text{H}_7$  could stabilize the dihydropyridine derivatives. To explore the universality of such an effect, we conducted a reaction of the  $\text{B}_3\text{H}_7$  mediated addition of Grignard reagents to pyridines bearing an electron-withdrawing substituent. Similarly, the dihydropyridine intermediates were stable under these conditions, which could also be characterized by  $^{11}\text{B}$ ,  $^1\text{H}$ , and  $^1\text{H}\{^{11}\text{B}\}$  NMR spectra (ESI, Fig. S7–S9†).



Scheme 2 Synthesis of the pyridine  $\text{B}_3\text{H}_7$  adduct.



Fig. 1  $^1\text{H}$  NMR in  $\text{CDCl}_3$  of (a) 4-methylpyridine, (b) **1b**, (c) **1c**, (d) **1d**, and (e) 4-methylene dihydropyridine **3a** in  $\text{THF-d}_8$  at  $-78^\circ\text{C}$ .

These observations differ from the  $\text{BF}_3$  mediated similar reactions of pyridine derivatives under the same conditions where no dihydropyridine derivative intermediates were detected. We further set up control experiments to explore the different influences of  $\text{BH}_3$ ,  $\text{BF}_3$ , and  $\text{B}_3\text{H}_7$  on pyridine in their adducts. The  $^1\text{H}$  NMR spectra of 4-methylpyridine of the corresponding  $\text{B}_3\text{H}_7$  adduct **1b**,  $\text{BH}_3$  adduct **1c**, and  $\text{BF}_3$  adduct **1d** showed that the chemical shifts of the protons at the C3 and C5 position and the methyl downfield-shifted in the adducts in comparison with 4-methylpyridine.

The impact of the  $\text{BF}_3$  group was the most significant and those of the  $\text{BH}_3$  and  $\text{B}_3\text{H}_7$  groups were almost the same, but the  $\text{B}_3\text{H}_7$  group was slightly larger than that of  $\text{BH}_3$  (Fig. 1a–d). Therefore, we speculated that the impacts of these three Lewis acids on their coordinated Lewis base should be  $\text{BF}_3 > \text{B}_3\text{H}_7 > \text{BH}_3$ .

Surprisingly, the  $^{11}\text{B}\{^1\text{H}\}$  NMR signals of the  $\text{B}_3\text{H}_7$  coordinated 4-methylene dihydropyridine anion **3a** and ethyl 4-isopropyl 3-carboxylate dihydropyridine complex **3b** changed significantly in comparison with those of their parent complexes. The top boron atom connected with the nitrogen atom shifted to a lower field and the two base boron atoms to a higher field (Fig. 2), in contrast to the general B-signals of the  $\text{B}_3\text{H}_7$  adducts.<sup>13a</sup> Furthermore, the signal shifts in **3a** and **3b** are different (Fig. 2b and d). The exploration of the reason for such a difference is underway in our laboratory.

### $\text{B}_3\text{H}_7$ mediated the nucleophilic substitution reaction of 4-alkylpyridine

Based on the formation of the dearomatic intermediates, we further explored the  $\text{B}_3\text{H}_7$  mediated nucleophilic substitution reactions of pyridine derivatives by selecting the 4-ethylpyridine  $\text{B}_3\text{H}_7$  adduct **1e** as the model substrate, reacting with methyl iodide (Table S4†). After systematically screening reactions with different bases in various solvents, we found that the methylation product **4a** was obtained at an 88% yield in  $\text{CH}_3\text{CN}$  when a mild base  $\text{KO}^t\text{Bu}$  was used (entry 1 in Table S4†). In contrast,





Fig. 2 (a)  $^{11}\text{B}\{^1\text{H}\}$  NMR of **1b** in  $\text{CDCl}_3$ . (b)  $^{11}\text{B}\{^1\text{H}\}$  NMR of 4-methylene dihydropyridine **3a** in  $\text{THF-d}_8$  at  $-78^\circ\text{C}$ . (c)  $^{11}\text{B}\{^1\text{H}\}$  NMR of ethyl nicotinate· $\text{B}_3\text{H}_7$  **6a** in  $\text{CDCl}_3$ . (d)  $^{11}\text{B}\{^1\text{H}\}$  NMR of ethyl 4-isopropyl 3-carboxylate dihydropyridine complex **3b** in  $\text{THF-d}_8$  at room temperature.

no reaction occurred when the  $\text{BH}_3$  adduct **1f** was used (entry 18 in Table S4<sup>†</sup>) and the product decomposed when the  $\text{BF}_3$  adduct **1g** was used (entry 19 in Table S4<sup>†</sup>). Only a trace amount of the

product was detected. The reaction with 4-ethyl pyridine, without  $\text{B}_3\text{H}_7$  coordinated, was also conducted at similar conditions and no reaction occurred (entry 20 in Table S4<sup>†</sup>). As expected, the starting material 4-ethyl pyridine was collected. These results suggested that the  $\text{Py}\cdot\text{B}_3\text{H}_7$  adducts have a unique stability and reactivity.

Considering the excellent stability of the  $\text{Py}\cdot\text{B}_3\text{H}_7$  adducts and the importance of boron-containing compounds in BNCT, we further examined the scope of the electrophiles (Table 1). Firstly, different alkyl iodides were detected. As shown in Table 1, regardless of whether the alkyl iodides were primary or secondary, products (**4b–4r**) were obtained in moderate to good yields. Additionally, this transformation shows a high functional group tolerance, such as allyl, ester, trifluoromethyl, cyclopropyl, and alkoxy were all compatible. We also found that the yields of the reactions using the alkyl bromides were significantly low compared to the alkyl iodides. Encouraged by these results, we further screened other electrophilic reagents and found that acyl chlorides could also be used in this reaction to produce stable  $\text{Py}\cdot\text{B}_3\text{H}_7$  derivatives (**4s–4w**). The scope for the pyridine core was assessed next (**4x–4ae**). Gratifyingly, our method showed a good C4 regioselectivity for the pyridines that

Table 1 Reaction scope<sup>a</sup>



<sup>a</sup> Conditions: **1** (0.5 mmol, 1.0 eq.), **2** (1.25 mmol, 2.5 eq.), and base (1.25 mmol, 2.5 eq.) in  $\text{CH}_3\text{CN}$  (15 mL) at room temperature for 1 hour. Isolated yield. The d.r. value was determined by  $^1\text{H}$  NMR analysis of the crude reaction mixture. <sup>b</sup> Conditions: **4** (0.5 mmol, 1.0 eq.),  $\text{MeOH}:\text{H}_2\text{O}$  (5 : 0.5 mL),  $60^\circ\text{C}$ , 12 h.



contained multiple methyl groups at C2, C3, or C6 (**4z–4ab**). We thought this was because the high steric hindrance of  $B_3H_7$  decreased the reactivity of the C2 and C6 positions, and the acidity of the methyl group at the C3 position is relatively weak. It was worth noting that the reaction of 4-methyl  $Py \cdot B_3H_7$  with methyl iodide gave a mixture of 4-ethyl  $Py \cdot B_3H_7$ , 4-isopropyl  $Py \cdot B_3H_7$ , and 4-*tert*-butyl  $Py \cdot B_3H_7$ . Introducing methyl groups to the C2 and C6 positions could weaken the acidity of the C4 methyl to give the mono-methylation products (**4z**, **4aa**) in high yields. The structure of **4aa** was determined by single-crystal X-ray diffraction. Regardless of whether the substituent group at the C4 position was the primary, secondary, or tertiary alkyl group, the reactions transpired smoothly in high yields. In addition, the halogen atom (**4x**, **4y**) and ester group (**4ad**, **4ae**) were compatible in this transformation.

To remove  $B_3H_7$  from pyridine derivatives has also been explored to expand the application of this protocol. After a series of explorations for the reaction conditions, the  $B_3H_7$  unit was successfully removed with MeOH and  $H_2O$  at 60 °C, and the corresponding pyridine compounds were obtained in almost quantitative yields (**5a**, **5b**).<sup>20</sup>

### The $B_3H_7$ mediated nucleophilic addition of Grignard reagents to electron deficient pyridines and their subsequent oxidation

The  $BF_3$  promoted C4 direct alkylation of functionalized pyridines has been reported, in which  $BF_3$ -mediated 4-isopropyl-dihydropyridine was considered a potential intermediate.<sup>4a</sup> We have obtained the dearomatic dihydropyridine intermediate by the nucleophilic addition of  $^iPrMgCl \cdot LiCl$  to ethyl nicotinate  $B_3H_7$  adduct (Fig. 2d), further oxidation aromatization mediated by chloranil provided the 4-alkylated product **8a** in 71% yield (Table 2). Based on this, we examined the scope of Grignard reagents and pyridine derivatives and successfully introduced different alkyl and aryl groups into the C4 position of electron-deficient pyridines (Table 2). In these reactions, moderate yields of products could be obtained (**8b–8g**). The low yields of **8h** and **8i** are probably due to using strong bases such as organic lithium reagents. The ethyl nicotinate  $B_3H_7$  adduct would be destroyed by strong bases to produce the pyridine  $BH_3$  adduct, decreasing the yield. In addition, the electronic effects also played an important role in this reaction. The strength and stability of the electron-withdrawing group at the C3 position would affect the yields of products (**8j**, **8k**, **8m**, **8o**, and **8s**). When the pyridine had electron-donating groups, the yield would decrease due to the increase of the electron density at the C4 position (**8l**, **8n**, **8p–8r**). For all the low-yield reactions, the starting materials could be detected and recovered, such as the starting material for **8l** could be recovered in 72%.

### Mechanistic studies

To gain insight into the reaction mechanism, quantum chemical studies using density functional theory (DFT) have been performed. From the theoretical data, the reaction mechanism is proposed, as shown in Fig. 3.

Table 2 The C-4 substitution reaction scope<sup>a</sup>



<sup>a</sup> Conditions: **6** (0.5 mmol, 1.0 eq.), **7** (0.5 mmol, 1 eq.), and chloranil (1 mmol, 2 eq.). Isolated yield. <sup>b</sup> R-Li (0.5 mmol, 1 eq.).



Fig. 3 The energy profile of the reaction calculated at M06-2X-D3-SMD/def2-QZVP//B3LYP-D3(BJ)/6-311G(d,p)/SDD level of theory.

First, the reactants 4-methyl  $Py \cdot B_3H_7$  and potassium *tert*-butoxide form the reaction complex RC. The relative free energy of RC is 6.8 kcal mol<sup>-1</sup>. In RC, the  $K^+$  cation interacted with the H of the  $B_3H_7$  fragment, the K–H bond is 2.80 and 2.84 Å, and a hydrogen bond exists between the O of *tert*-butoxy and the H of the methyl group with a bond length of 2.10 Å. Subsequently, RC traverses transition state TS1 to yield a complex of intermediate (IM) and a *tert*-butanol with a relative free energy of –6.1 kcal mol<sup>-1</sup>. From RC to TS1, the K–H bond shortened to 2.77 Å and the O–H bond shortened from 2.10 Å to 1.37 Å. At the same time, the C–H bond enlarged from 1.11 Å to 1.29 Å. The relative free energy of TS1 is 10.4 kcal mol<sup>-1</sup>, indicating a modest energy



barrier of 3.6 kcal mol<sup>-1</sup> for this step. Then *tert*-butanol dissociates, leaving behind IM. Following this, a new complex, IM with CH<sub>3</sub>I, formed with a relative energy of 0.9 kcal mol<sup>-1</sup> with the I-C bond of 2.23 Å. The subsequent reaction of IM and CH<sub>3</sub>I *via* transition state TS2 results in the final product. During this step, the I-C bond enlarged to 2.53 Å, and the C-C bond formed with a bond length of 2.47 Å. The relative energy of TS2 is 14.3 kcal mol<sup>-1</sup>, implying a barrier of 13.4 kcal mol<sup>-1</sup> for the second step. With the Walden inversion of CH<sub>3</sub>, the final product formed and exhibits a relative free energy of -52.5 kcal mol<sup>-1</sup>. The negative  $\Delta G$  of the whole reaction and the low energy barrier indicate that this reaction will easily proceed spontaneously. The charge distribution of CH<sub>3</sub>Py, CH<sub>3</sub>PyB<sub>3</sub>H<sub>7</sub>, KCH<sub>3</sub>PyB<sub>3</sub>H<sub>7</sub><sup>+</sup>, and CH<sub>2</sub>PyB<sub>3</sub>H<sub>7</sub><sup>-</sup> was further analysed by using Natural Population Analysis (NPA). As delineated in Table S5,<sup>†</sup> the formation of the N-B dative bond and the preferential association of the K ions near the B<sub>3</sub>H<sub>7</sub> fragment caused the electron concentration to be towards the B<sub>3</sub>H<sub>7</sub> fragment. Such intramolecular charge transfer facilitates the deprotonation.

The proposed mechanism is supported by the experimental results of the capture of the reaction intermediate (Scheme 3a-c). The <sup>1</sup>H NMR spectroscopy showed that the B<sub>3</sub>H<sub>7</sub> coordinated 4-methylene dihydropyridine anion intermediate **3a** (IM) was formed in an almost quantitative yield by the deprotonation of 4-methyl Py·B<sub>3</sub>H<sub>7</sub> **1b** with KO<sup>t</sup>Bu in THF-d<sub>8</sub> at -78 °C (Fig. 1e).<sup>21</sup> The intermediate of 4-alkalene dihydropyridine was frequently discussed in the literature.<sup>22</sup> However, the BH<sub>3</sub> and BF<sub>3</sub> coordinated 4-methylene dihydropyridine anion intermediates **3c** and **3d** could not be formed in similar reactions (Scheme 3b and c).

These results were consistent with the theoretical prediction that the interaction between the alkali metal cation and the NB<sub>3</sub>H<sub>7</sub> moiety induced the additional intramolecular charge transfer from CH<sub>3</sub>/CH<sub>2</sub> to the B<sub>3</sub>H<sub>7</sub> end to facilitate the reaction and also stabilized the formed 4-methylene dihydropyridine intermediate (Table S5<sup>†</sup>). This result was further confirmed by the fact that the addition of 18-C-6 to the reaction mixture would decrease the yields from 88% to 54% (Fig. S2<sup>†</sup>) because the formation of the K-18-C-6 complex weakened the interaction between the K cation and the B<sub>3</sub>H<sub>7</sub> moiety.

### <sup>10</sup>B-labeled <sup>10</sup>B<sub>3</sub>H<sub>7</sub> reactions

To evaluate the potential of this protocol in BNCT,<sup>23</sup> a <sup>10</sup>B-labeled <sup>10</sup>B<sub>3</sub>H<sub>7</sub> was introduced to the pyridine core (Scheme 4). Firstly,



Scheme 3 A mechanism study.



Scheme 4 <sup>10</sup>B-labeled experiments.

the <sup>10</sup>B-labeled Na<sup>10</sup>B<sub>3</sub>H<sub>8</sub> was synthesized by the reaction of Na<sup>10</sup>BH<sub>4</sub> with I<sub>2</sub>. The reaction of 4-ethyl pyridine with the THF·<sup>10</sup>B<sub>3</sub>H<sub>7</sub> formed the *in situ* produced 4-ethyl Py·<sup>10</sup>B<sub>3</sub>H<sub>7</sub> **9** in 60% yield.<sup>24</sup> The <sup>10</sup>B-labeled 4-ethyl Py·<sup>10</sup>B<sub>3</sub>H<sub>7</sub> could also react with alkyl iodide under KO<sup>t</sup>Bu to afford the alkylated product **10** in a good yield.

## Conclusions

In summary, we have synthesized a novel class of Py·B<sub>3</sub>H<sub>7</sub> compounds and studied the reactions of 4-alkyl Py·B<sub>3</sub>H<sub>7</sub> with different electrophiles and pyridine bearing an electron-withdrawing group with nucleophiles. The relatively high stability of the Py·B<sub>3</sub>H<sub>7</sub> adducts results in the formation of stable dearomatic intermediates, dihydropyridine, under mild conditions, from which the rearomatization has further transpired to form different alkylation and acylation products. The mechanistic study reveals that the coordination of the B<sub>3</sub>H<sub>7</sub> unit led to the intra-molecular charge transfer from the pyridine ring to borane, realizing the alkylation and acylation reactions of the C(sp<sup>3</sup>)-H bond of the C-4 position with excellent regioselectivity and high yields under mild reaction conditions. The B<sub>3</sub>H<sub>7</sub> coordinated dihydropyridine intermediate was obtained in solution and characterized by <sup>1</sup>H and <sup>11</sup>B NMR. Such an intra-molecular charge transfer also promoted C-4 direct alkylation of the pyridines bearing an electron-withdrawing group to provide the 4-alkylated products. Compared with BH<sub>3</sub> and BF<sub>3</sub>, B<sub>3</sub>H<sub>7</sub> possesses remarkable features, such as relatively higher stability, a weaker reducing ability, and a higher ability to coordinate with metals, as well as steric effects and  $\sigma$  aromaticity. All these properties will enable the B<sub>3</sub>H<sub>7</sub> group to mediate different organic reactions. In addition, stable Py·B<sub>3</sub>H<sub>7</sub> will play a significant role in boron-containing drugs and organic synthesis. Further research into the effect of B<sub>3</sub>H<sub>7</sub> on other series of Lewis bases and the reaction mechanisms is underway in our laboratory.

## Data availability

Data for all compounds in this manuscript are available in the ESI,<sup>†</sup> which includes experimental details, characterisation data, computational data and copies of <sup>1</sup>H, <sup>13</sup>C, <sup>19</sup>F, and <sup>11</sup>B NMR spectra. The data supporting this article have been included as part of the ESI.<sup>†</sup> Crystallographic data have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-2308054 (**1a**) and CCDC-2308050 (**4aa**).



## Author contributions

Y.-N. M. and X. C. conceived and designed the study; Z.-H. F., Q.-J. P., L. C., S. J., and X.-M. C. performed the experiments. J.-X. K. and C.-Q. X. performed the mechanistic and DFT studies. Y.-N. M. and X. C. prepared the manuscript.

## Conflicts of interest

There are no conflicts to declare.

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