



Cite this: *Chem. Sci.*, 2021, **12**, 11447

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 31st May 2021  
 Accepted 22nd July 2021

DOI: 10.1039/d1sc02937a  
[rsc.li/chemical-science](http://rsc.li/chemical-science)

## Introduction

Directed C–H bond activation has emerged as one of the most powerful and reliable tools in synthetic organic chemistry.<sup>1</sup> A variety of directing groups are being designed for achieving a regioselective C–H bond functionalization reaction. Among them, the metal-catalyzed C–H functionalization of 2-pyrimidylanilines was investigated on a number of occasions.<sup>2,3</sup> In this regard, *ortho*-C–H alkylation,<sup>2</sup> alkyne annulation,<sup>3a</sup> alkynylation,<sup>3b,c</sup> chalcogenation,<sup>3d</sup> amidation<sup>3f–h</sup> and the alkenylation<sup>3i</sup> of aniline derivatives have been achieved using various metal catalysts (Fig. 1A). Nevertheless, given the importance of organoboron compounds in organic synthesis,<sup>4</sup> selective C–H borylation has not yet been achieved in the case of 2-pyrimidylanilines, which are key structural motifs that are found in numerous bioactive compounds that are used in crop protection and medicinal chemistry.<sup>5</sup> Considering the recent progress in metal-free directed C–H borylation, it would be predicted that this reaction could be used in conjunction with a broad spectrum of substrates to prepare a wide variety of synthetically important organoboron compounds without the use of any metal precursors. In this regard, notable contributions include the directed C–H borylation of various nitrogen-containing heterocycles,<sup>6</sup> such as benzimidazoles,<sup>6a</sup> pyridines,<sup>6c–e,h,k</sup> benzothiadiazoles,<sup>6f,i,j</sup> quinolines,<sup>6g</sup> benzoselenadiazoles,<sup>6l</sup> benzotriazoles,<sup>6l</sup> and indoles,<sup>6m</sup> a thio-directed

## Pyrimidine-directed metal-free C–H borylation of 2-pyrimidylanilines: a useful process for tetra-coordinated triarylborane synthesis†

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Convenient, easily handled, laboratory friendly, robust approaches to afford synthetically important organoboron compounds are currently of great interest to researchers. Among the various available strategies, a metal-free approach would be overwhelmingly accepted, since the target boron compounds can be prepared in a metal-free state. We herein present a detailed study of the metal-free directed *ortho*-C–H borylation of 2-pyrimidylaniline derivatives. The approach allowed us to synthesize various boronates, which are synthetically important compounds and various four-coordinated triarylborane derivatives, which could be useful in materials science as well as Lewis-acid catalysts. This metal-free directed C–H borylation reaction proceeds smoothly without any interference by external impurities, such as inorganic salts, reactive functionalities, heterocycles and even transition metal precursors, which further enhance its importance.

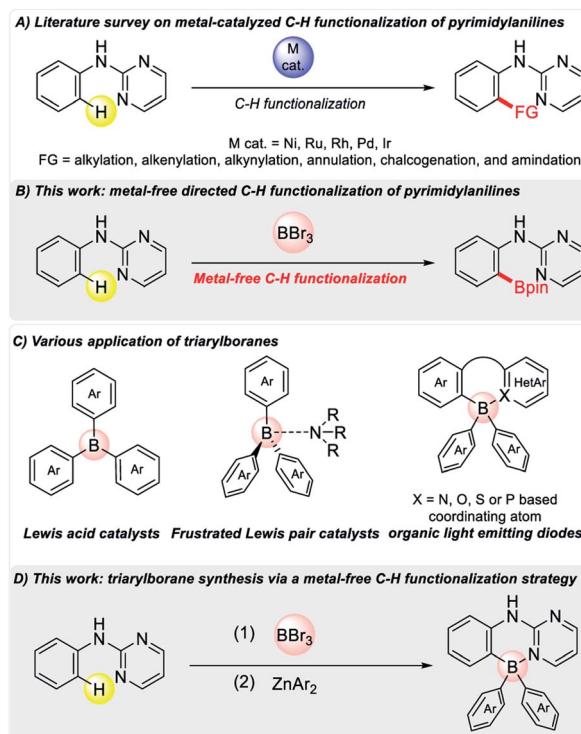


Fig. 1 (A) Literature survey of the directed *ortho*-C–H functionalization of 2-pyrimidylanilines. (B) Our work on the metal-free C–H borylation of 2-pyrimidylanilines. (C) The importance of triarylboranes in various fields and (D) our approach to accessing tetra-coordinated triarylboranes in a straightforward manner.

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† Electronic supplementary information (ESI) available: Experimental details and spectroscopic data. See DOI: [10.1039/d1sc02937a](https://doi.org/10.1039/d1sc02937a)



intramolecular C–H borylation of 2-mercaptobiphenyl,<sup>6b</sup> and pre-installing a directing group<sup>7</sup> assisted C–H borylation of phenol,<sup>7a,b</sup> aniline,<sup>7c–e</sup> indole,<sup>7c,d</sup> and pyrrole derivatives.<sup>7f</sup> We recently reported the transient imine-directed C–H borylation of benzaldehydes.<sup>8</sup> Having a continuous interest in this metal-free C–H borylation protocol, we were prompted to explore the selective C–H borylation of 2-pyrimidylanilines.

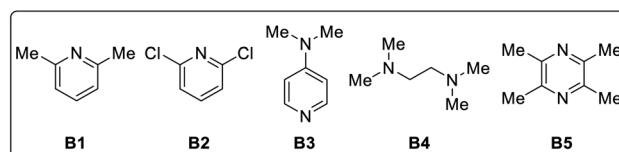
Triarylborane-based compounds have wide application as Lewis acid catalysts or frustrated Lewis pair catalysts in various catalyses such as hydrosilylation, hydroboration, Diels–Alder reactions and for small molecule activation.<sup>9</sup> In addition, there are widespread applications for tetra-coordinated triarylboranes as organic materials, such as anion sensors, organic light emitting devices, imaging and electron transport materials (Fig. 1C).<sup>10</sup> Four-coordinated organoboron compounds can function as electron-transport materials *via* the boron-stabilized p\* orbital of the donating ligands. Considering these wide applications, various strategies have emerged for their synthesis. One of the more recent strategies is cascade B–Cl/C–B cross-metathesis and C–H bond borylation.<sup>11</sup> While this strategy is interesting, it has some drawbacks, including the need for harsh conditions, the production of various waste by-products, and relatively poor yields of triarylboranes. Therefore, the most attractive strategy would involve the use of boron trihalide to construct tetra-coordinated fluorophores *via* activating a C–H bond using a directing atom of a heterocycle. Given our focus on metal-free C–H borylation reactions,<sup>8</sup> we developed a keen interest in accessing tetra-coordinated triarylboranes containing a 2-pyrimidylaniline group. In 2019, Shi/Houk and Ingleson independently reported the directed C–H borylation of anilides using an oxygen atom as a directing moiety with BBr<sub>3</sub> for preparing boronic esters of anilines.<sup>7c,d</sup> We hypothesized that, compared to an oxygen directing atom, a nitrogen moiety would provide access to more stable tetra-coordinated triarylboranes. Hence, nitrogen-based heterocycles were mainly used for organic materials due to their high stability. We herein report on the metal-free C–H borylation of 2-pyrimidylaniline scaffolds to afford synthetically important boronic esters (Fig. 1B) and the synthesis of tetra-coordinated triarylboranes (Fig. 1D).

## Results and discussion

We started the project by investigating the reaction conditions for the directed metal-free C–H borylation of 2-pyrimidylanilines. The reaction of *N*-(pyrimidine-2-yl)aniline (**1a**) and 1 equiv. of BBr<sub>3</sub> in dichloroethane (DCE) gave 21% NMR yield of the expected borylated product **1b** (entry 1, Table 1). Remarkably, the reaction proceeded even in the case of **1a**, which contains a free NH moiety. An increase in the amount of BBr<sub>3</sub> to 2 equiv. improved the product yield to 50% (entry 2). After a thorough screening of various bases, it was found that 2,3,5,6-tetramethylpyrazine (**5**) was the optimal base, giving **1b** in 84% yield (entry 10 *vs.* entries 3–9). Adjusting the amounts of base and BBr<sub>3</sub> used provided the optimal conditions in which the use of 3 equiv. of BBr<sub>3</sub> along with 1.2 equiv. of **5** gave **1b** in 77% isolated yield (entry 12). The reactivity was retained when the solvent was switched from DCE to CHCl<sub>3</sub> (entry 13).

Table 1 Optimization of the metal-free borylation of 2-pyrimidylaniline **1a**<sup>a</sup>

Entry	Base (YY equiv.)	BBr <sub>3</sub> (XX equiv.)	Solvent	Yield of
				<b>1b</b> (%)
1 <sup>b</sup>	—	1 equiv.	DCE	21
2	—	2 equiv.	DCE	50
3	<b>B1</b> (2 equiv.)	2 equiv.	DCE	71
4	<b>B2</b> (2 equiv.)	2 equiv.	DCE	66
5	Pyridine (2 equiv.)	2 equiv.	DCE	5
6	NEt <sup>i</sup> Pr <sub>2</sub> (2 equiv.)	2 equiv.	DCE	65
7	<b>B3</b> (2 equiv.)	2 equiv.	DCE	3
8	<b>B4</b> (2 equiv.)	2 equiv.	DCE	17
9	NEt <sub>3</sub> (2 equiv.)	2 equiv.	DCE	61
10	<b>B5</b> (2 equiv.)	2 equiv.	DCE	84
11 <sup>c</sup>	<b>B5</b> (3 equiv.)	3 equiv.	DCE	93
12 <sup>c</sup>	<b>B5</b> (1.2 equiv.)	3 equiv.	DCE	92 (77)
13 <sup>c</sup>	<b>B5</b> (1.2 equiv.)	3 equiv.	CHCl <sub>3</sub>	90 (76)

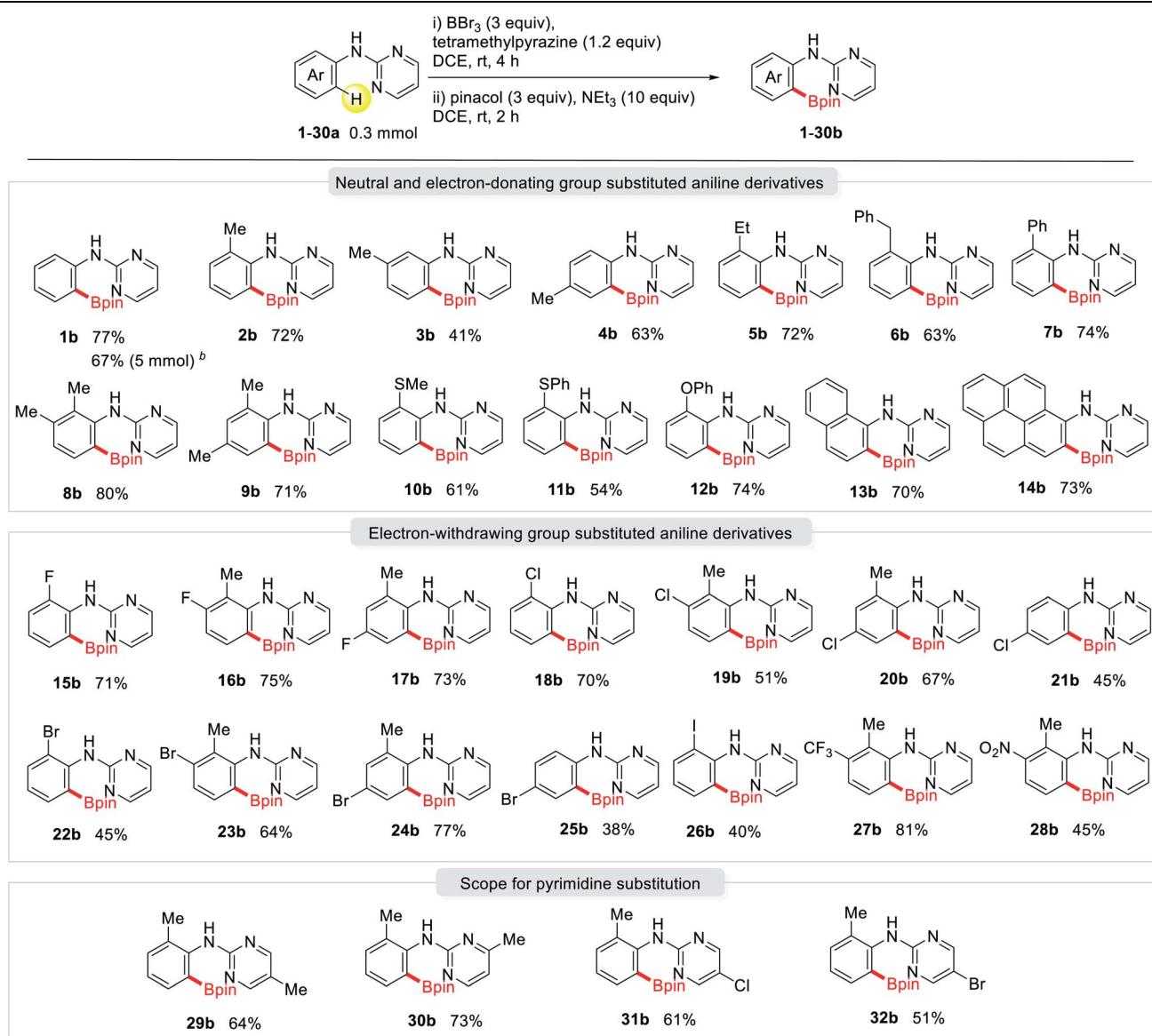


<sup>a</sup> Reaction conditions: 2-pyrimidylaniline (**1a**, 0.1 mmol, 1 equiv.), BBr<sub>3</sub> and base in DCE (0.5 mL) at r.t. for 4 h, then pinacol (0.2 mmol) and NEt<sub>3</sub> (1.0 mmol) in DCE (0.5 mL) for 2 h at r.t. Yields of the product were determined by <sup>1</sup>H NMR of the crude mixture using 1,1,2,2-tetrachloroethane as an internal standard. Isolated yields are given in parentheses. <sup>b</sup> 1 equiv. of pinacol was used in the final step. <sup>c</sup> 3 equiv. of pinacol was used in the final step.

With the optimized reaction conditions in hand, we explored the versatility of this *ortho*-directed metal-free borylation reaction using various substituted 2-pyrimidylaniline derivatives (Table 2). This protocol provided a broad scope of substrates and a high tolerance for various functional groups. Notably, a variety of substituted aniline derivatives containing an electron-donating group, such as methyl (**2b–4b**, **8b**, and **9b**), ethyl (**5b**), benzyl (**6b**), phenyl (**7b**), methylthio (**10b**), phenylthio (**11b**), and phenoxy (**12b**), reacted smoothly to afford the corresponding boronic esters in yields in the range of 41–80%. 1-Naphthylamine (**13a**) and 1-aminopyrene (**14a**) selectively produced the desired products (**13b** and **14b**) in high yields without the formation of any side products. In the case of the *meta*-Me-substituted aniline, the reaction occurred exclusively at the sterically less hindered site (**3b**). A variety of electron-withdrawing functional groups, such as F (**15b–17b**), Cl (**18b–21b**), Br (**22b–25b**), I (**26b**), CF<sub>3</sub> (**27b**), and even NO<sub>2</sub> (**28b**) were also tolerated in this metal-free C–H borylation reaction. The reaction proceeded readily in the case of substituents on the pyrimidine ring, as in Me (**29a** and **30a**), Cl (**31a**), and Br (**32a**) groups. Notably, this wide substrate applicability increases the



Table 2 Substrate scope for the metal-free borylation of 2-pyrimidylanilines



<sup>a</sup> Reaction conditions: 2-pyrimidylaniline derivative (0.3 mmol, 1 equiv.), BBr<sub>3</sub> (0.9 mmol, 3 equiv.) and tetramethylpyrazine (0.36 mmol, 1.2 equiv.) in DCE (1.0 mL) at r.t. for 4 h, then pinacol (0.9 mmol, 3 equiv.) and NEt<sub>3</sub> (3.0 mmol, 10 equiv.) in DCE (1.0 mL) at r.t. for 2 h. Isolated yields of the product are given. <sup>b</sup> Reaction was performed on a 5 mmol scale.

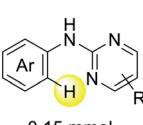
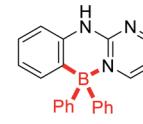
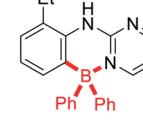
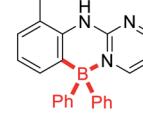
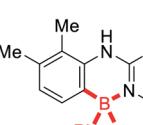
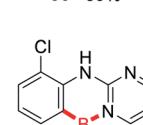
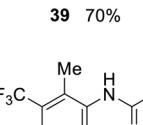
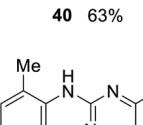
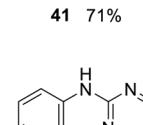
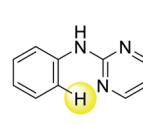
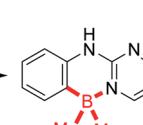
significance of this easily handled and convenient directed C–H borylation protocol to afford borylated synthetic intermediates.

Four-coordinated organoboron compounds have been extensively investigated in the past decade as emissive materials for use in organic light-emitting diodes, due to their high thermal and chemical stability.<sup>10</sup> We attempted to prepare a series of tetra-coordinated triarylborane derivatives using this metal-free *ortho*-C–H borylation of 2-pyrimidylaniline derivatives. A pyrimidine-directed borylation with BBr<sub>3</sub> gave a dibromoborane intermediate and the subsequent reaction with diarylzinc provided the desired four-coordinated triarylboranes. Various electron-donating or neutral group-substituted aniline derivatives (33–37), electron-withdrawing group substituted

aniline derivatives (38–42), and even a substrate with a substitution on the pyrimidine ring (43) reacted efficiently to afford the desired products in good to high yields (Table 3). These entities would be of value in terms of preparing many other pyrimidinyl-coordinated triarylborane compounds. A dentafluorophenyl substituted triarylborane (44) was also synthesized when bis(pentafluorophenyl)zinc was used. This protocol could lead to the production of various substituted boron-based Lewis acid catalysts. When trimethylaluminum was reacted with the dibromoborane intermediate, a dimethyl substituted aryl borane compound 45 was obtained. This convenient synthetic protocol for obtaining various substituted four-coordinated boranes clearly provides opportunities to



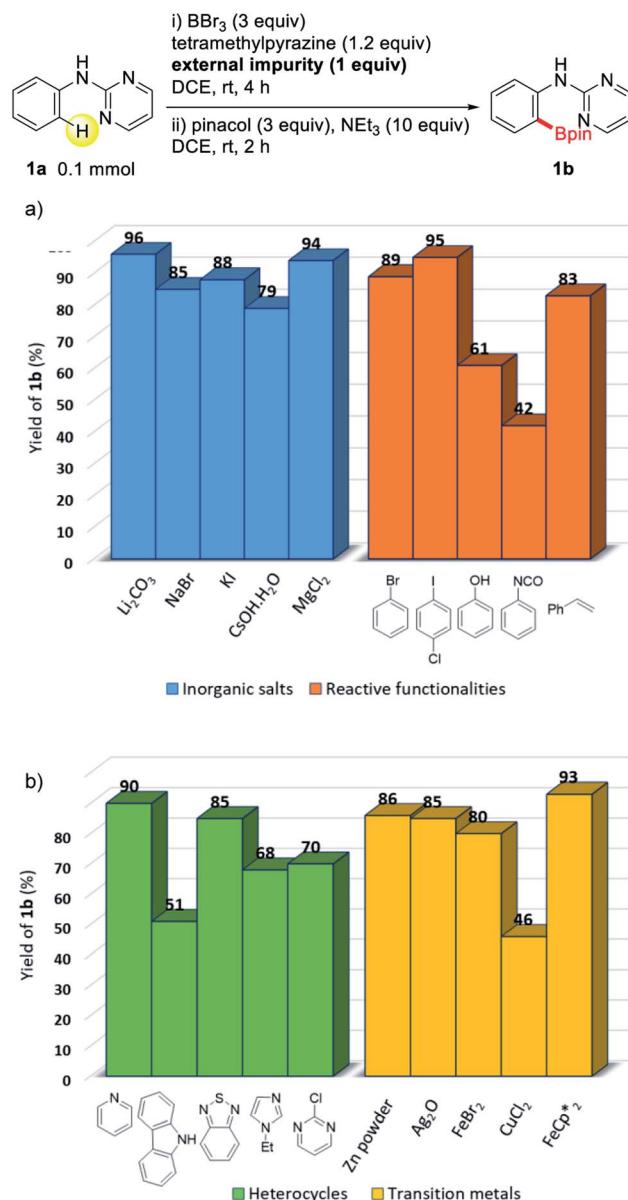
**Table 3** Synthesis of tetra-coordinated triarylborane via a metal-free C–H borylation<sup>a</sup>

 0.15 mmol	i) $\text{BBr}_3$ (3 equiv) tetramethylpyrazine (1.2 equiv) $\text{CHCl}_3$ , rt, 4 h  ii) $\text{ZnAr}'_2$ (3 equiv) toluene, 70 °C, 12 h	
		evaporate and then ii) $\text{ZnAr}'_2$ (3 equiv) toluene, 70 °C, 12 h
	33 82%	
	34 72%	
	35 60%	
	36 59%	
	37 59%	
	38 81%	
	39 70%	
	40 63%	
	41 71%	
	42 73%	
	43 66%	
	44 45%	
 0.15 mmol	i) $\text{BBr}_3$ (3 equiv) 2,6-lutidine (3 equiv) $\text{DCE}$ , rt, 4 h  ii) $\text{AlMe}_3$ (6 equiv) rt, 12 h	 45 74% <sup>b</sup>

<sup>a</sup> Reaction conditions: 2-pyridylaniline derivative (0.15 mmol, 1 equiv.),  $\text{BBr}_3$  (0.45 mmol, 3 equiv.), and tetramethylpyrazine (0.18 mmol, 1.2 equiv.) in  $\text{CHCl}_3$  (1.0 mL) at r.t. for 4 h, evaporated under reduced pressure, after which, toluene (1.5 mL) and  $\text{ZnAr}'_2$  (0.45 mmol, 3 equiv.) were added followed by heating at 70 °C for 12 h. <sup>b</sup> 2-Pyridylaniline (0.15 mmol, 1 equiv.),  $\text{BBr}_3$  (0.45 mmol, 3 equiv.) and 2,6-lutidine (0.45 mmol, 3 equiv.) in  $\text{DCE}$  (1.0 mL) at r.t. for 4 h, then  $\text{AlMe}_3$  (0.9 mmol, 6 equiv.) for 12 h at r.t. Isolated yields of the product are given.

produce a library of compounds containing the 2-pyridylaniline moiety, which would be useful as emissive materials.

The wide substrate applicability of this metal-free borylation prompted us to investigate the sustainability of this protocol in the presence of impurities. Although detail studies of robustness and sensitivity have been previously reported for metal-catalyzed organic synthetic procedures,<sup>12</sup> metal-free protocols

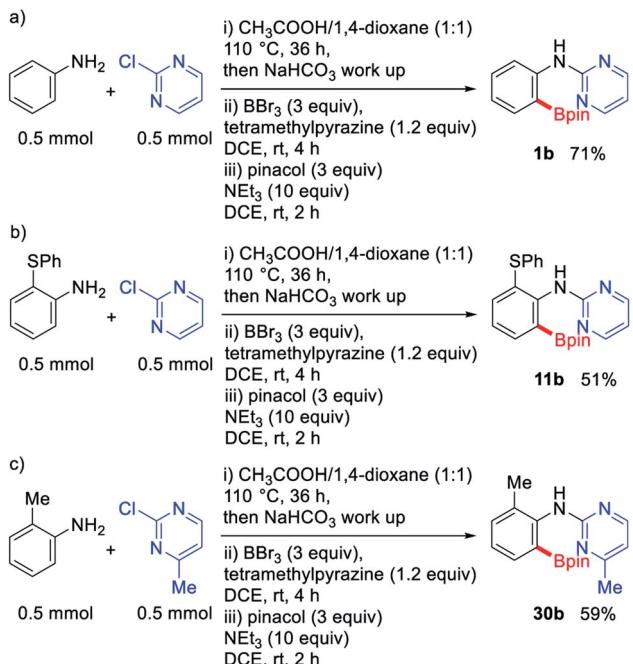


**Fig. 2** Metal-free directed borylation of 2-pyridylaniline in the presence of external impurities such as (a) inorganic salts and reactive functionalities, (b) heterocycles and transition metals.

have not gained much attention.<sup>8</sup> To examine this issue, we performed a series of borylation reactions using **1a** in the presence of 1 equiv. of various external impurities, such as inorganic salts, reactive functionalities, heterocycles, and transition metals (Fig. 2). To our delight, in most cases, the reaction proceeded smoothly to afford the desired product **1b** with negligible interference by external impurities. These observations further strongly support the sustainability of this protocol from a synthetic point of view. We anticipated that the robustness of the procedure would make this protocol useful in terms of large-scale organic synthesis.

Since various impurities were tolerated in this protocol, we performed a series of sequential reactions, in which the first step is the synthesis of the starting 2-pyridylanilines followed





Scheme 1 (a)–(c) Sequential one-pot reaction of starting material synthesis followed by metal-free directed borylation.

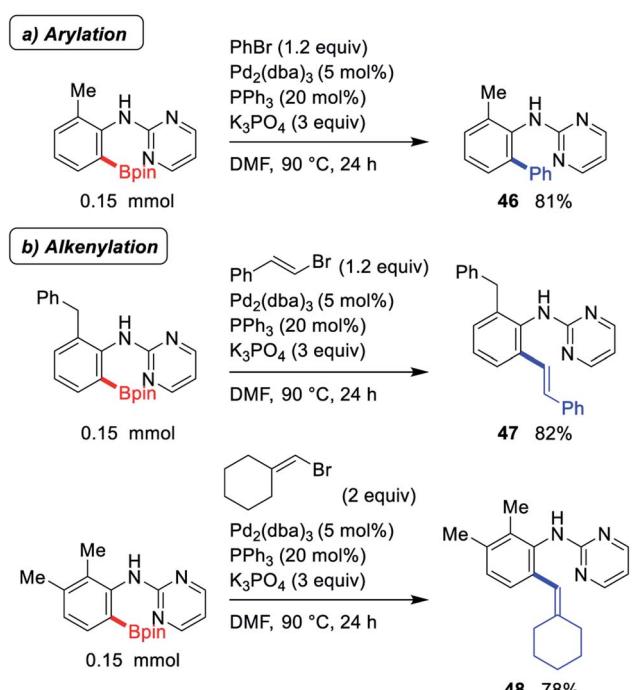
by directed C–H borylation without isolating the starting materials. The sequential reactions proceeded without any difficulties to afford the desired products **1b**, **11b**, and **30b**, despite the presence of various impurities such as aniline derivatives, 2-chloropyrimidine, traces of solvent and acetic acid

(Scheme 1). This experiment further confirms the efficacy of this protocol for use in a multi-step organic synthetic process.

To evaluate the synthetic utilities of *ortho*-borylated 2-pyrimidylaniline derivatives, some important synthetic transformations were performed and the results for reactions including arylation and alkenylation are presented in Scheme 2, which indicate the smooth formation of the desired products (46–48).

We predicted that one of the reasons for the wide substrate scope and high impurity tolerance of this metal-free directed borylation is that the reaction proceeds rapidly. To confirm this, we plotted the reaction profile for this reaction with yield *vs.* time (Fig. 3a), and were surprised to observe that the reaction gave the desired borylated product **1b** in 70% yield, even after a reaction time of 1 minute at room temperature. This finding can be attributed to the high reactivity of  $\text{BBr}_3$  and the electron-rich arene system. Similar to the previously reported metal-free directed borylation using  $\text{BBr}_3$ ,<sup>7,8</sup> the present reaction also appears to proceed through an electrophilic aromatic substitution pathway. To confirm this, two control experiments were performed, in which an electron-donating group substituted aniline derivative (**10a** or **2a**) and an electron-withdrawing group substituted aniline derivative (**18a** or **22a**) were reacted in a one-pot reaction. As expected, anilines with electron-donating groups gave higher product yields in both cases (Fig. 3b). However, the ratio of the product yields for electronically different sets of substrates were not as high as we expected. An additional substituent on the aniline substrate had only a minor influence on the reactivity because the substrate itself is an electron-rich system. To determine whether tetramethylpyrazine has any other role in this metal-free borylation except for abstracting a proton, we conducted  $^{11}\text{B}$  NMR studies. Unlike the previous observation in the reaction of 2,6-lutidine and  $\text{BBr}_3$ , in which the generation of a mixture of an adduct complex and a borenium ion was observed,<sup>8,13</sup> only one signal appeared in the negative region in the reaction of tetramethylpyrazine and  $\text{BBr}_3$ , which corresponds to the formation of the adduct complex (**49**) (Fig. 3c).<sup>14</sup> A similar signal was also observed in the reaction of 2-pyrimidylaniline **1a** with  $\text{BBr}_3$ . We were not able to confirm the exact species that is responsible for the reaction, due to the speed of the reaction.

A proposed mechanism for this *ortho*-C–H borylation of 2-pyrimidylanilines is shown in Scheme 3. A Lewis acid–base adduct is initially formed between  $\text{BBr}_3$  and the N atom of a pyrimidyl group in **1a**. A bromine transfer from **50** to another  $\text{BBr}_3$  molecule then leads to the formation of the borenium species **51**.<sup>15</sup> Due to the strong electrophilic nature of the aniline ring in **51**, an electrophilic aromatic substitution proceeds readily to give a Wheland intermediate **52**.<sup>7d</sup> Proton abstraction by a base then gives the dibromoboron complex **1c**, which, upon quenching with pinacol and triethyl amine, provides the desired borylated product **1b**. The results of  $^{11}\text{B}$  NMR experiments suggest that electrophilic borylation proceeds soon after a borenium species **51** is generated from the adduct **50**, because of the electron-rich nature of 2-pyrimidylaniline. However, the possibility that a base accelerates disproportionation between **50** and  $\text{BBr}_3$  cannot be excluded. It is noteworthy that due to the



Scheme 2 Representative synthetic application of C–H borylated products in terms of (a) phenylation and (b) alkenylation.

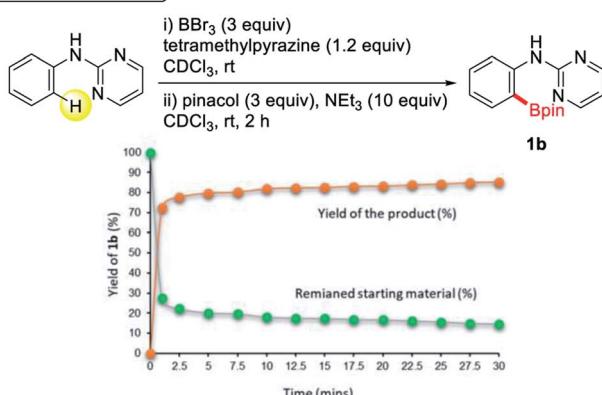
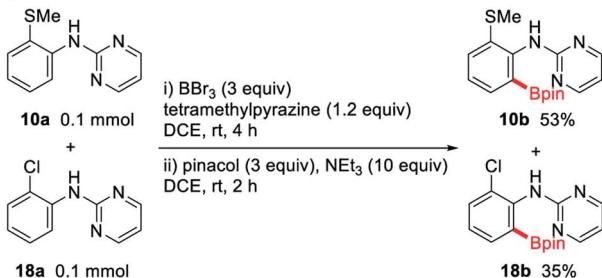
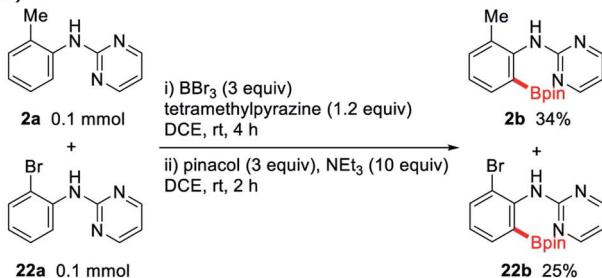
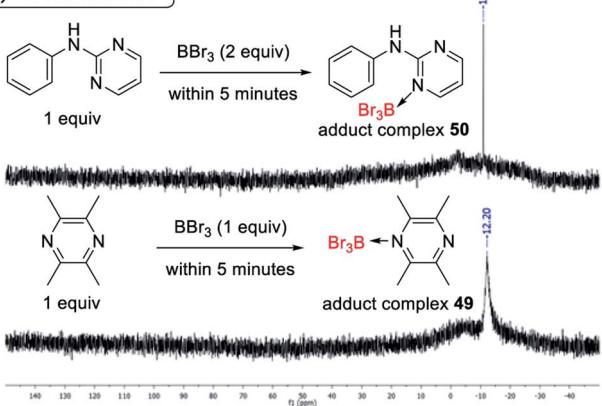
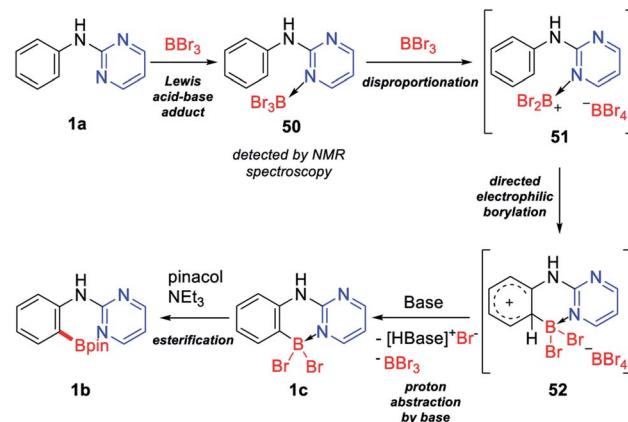
**a) Reaction profile****b) Reactivity comparison****b-I)****b-II)****c)  $^{11}\text{B}$  NMR studies**

Fig. 3 (a) Reaction profile of the metal-free directed borylation. (b) Reactivity comparison of electron rich and electron deficient functional group substituted anilines. (c) *In situ*  $^{11}\text{B}$  NMR studies.



Scheme 3 Plausible mechanism for metal-free directed C–H borylation of 2-pyrimidylaniline.

speed of this reaction, it is not possible to trap or detect any of the other reactive intermediates.

## Conclusions

In summary, we report that a biologically important key structural motif of a pyrimidyl moiety functions efficiently as a directing group for the *ortho*-C–H borylation of aniline derivatives. Despite being a highly significant structural component, the C–H borylation of 2-pyrimidylanilines has not yet been achieved, even by a metal-catalysed process. Moreover, the high impurity tolerance of this process makes it the first choice for the synthesis of organoboron compounds. This approach can also be a useful protocol for producing a series of four-coordinated triarylborane derivatives containing a pyrimidyl moiety, which are of importance in material chemistry for use in OLED devices or as a Lewis acid catalyst. The protocol involves the use of readily available starting materials, can be carried out at room temperature without the need for external additives, and reaction times are minimal, thus being potentially useful as an industrial process. Finally, we conclude that the detailed study presented here represents a notable contribution in the field of synthetic organic chemistry as well as in organic materials chemistry, since it permits libraries of compounds containing key structural scaffolds to be produced.

## Data availability

See ESI† for all experimental details including synthetic procedure and characterization.

## Author contributions

S. R. conceptualized the work. Experimental work and data analysis were performed by S. R. and A. D. N. C. supervised the project. The manuscript was written with discussion and approval of all authors.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

This work was supported by a Grant in Aid for Specially Promoted Research by MEXT (17H06091). S. R. wishes to express his special thanks for a JSPS Postdoctoral Research Fellowship. We also wish to thank the Instrumental Analysis Centre, Faculty of Engineering, Osaka University, for assistance with the HRMS.

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