# Metal-free directed $sp^2$-C–H borylation

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Organoboron reagents are important synthetic intermediates that have a key role in the construction of natural products, pharmaceuticals and organic materials[1]. The discovery of simpler, milder and more efficient approaches to organoborons can open additional routes to diverse substances[2–5]. Here we show a general method for the directed C–H borylation of arenes and heteroarenes without the use of metal catalysts. C7- and C4-borylated indoles are produced by a mild approach that is compatible with a broad range of functional groups. The mechanism, which is established by density functional theory calculations, involves $BBr_3$ acting as both a reagent and a catalyst. The potential utility of this strategy is highlighted by the downstream transformation of the formed boron species into natural products and drug scaffolds.

In order to achieve excellent site-selectivity, organoboron compounds have typically been synthesized by directed *ortho*-metalation (usually lithiation)[6]—a process that is not compatible with many sensitive functional groups (Fig. 1a). During the past two decades, transition-metal-catalysed directed C–H activation[7,8] has emerged as a powerful tool for the construction of C–B bonds[9–11] (Fig. 1b). However, these reactions rely mostly on precious-metal catalysts with ligands, which can be a substantial limitation—particularly when considering large-scale syntheses and the need to remove toxic trace metals in pharmaceutical products. Early studies involving directed C–H borylation without transition-metal catalysts, assisted by strongly coordinating groups such as pyridine, have been reported[12–14]. Although very good levels of regioselectivity can be achieved, such reactions usually require harsh conditions (including temperatures of up to 300 °C)[12] and the use of aluminium salts[13]. Replacing the transition-metal-catalysed process by a mild metal-free strategy (Fig. 1c) offers an alternative pathway to C–H borylation that is practical, inexpensive and environmentally benign[15].

The indole moiety is an important structural motif[16,17]. Several recent studies have reported indole C–H functionalization without the use of transition metals (Fig. 1d), including a frustrated-Lewis-pair-catalysed C–H borylation of indoles at the most electron-rich C3 position[18] and a method to access C2-silylated indoles by KO$^t$Bu-catalysed C–H silylation[19]. Installation of pivaloyl groups at the N1 or C3 positions of indoles enables selective delivery of the boron species to the unfavourable C7 or C4 positions[20–25] (Fig. 1d).

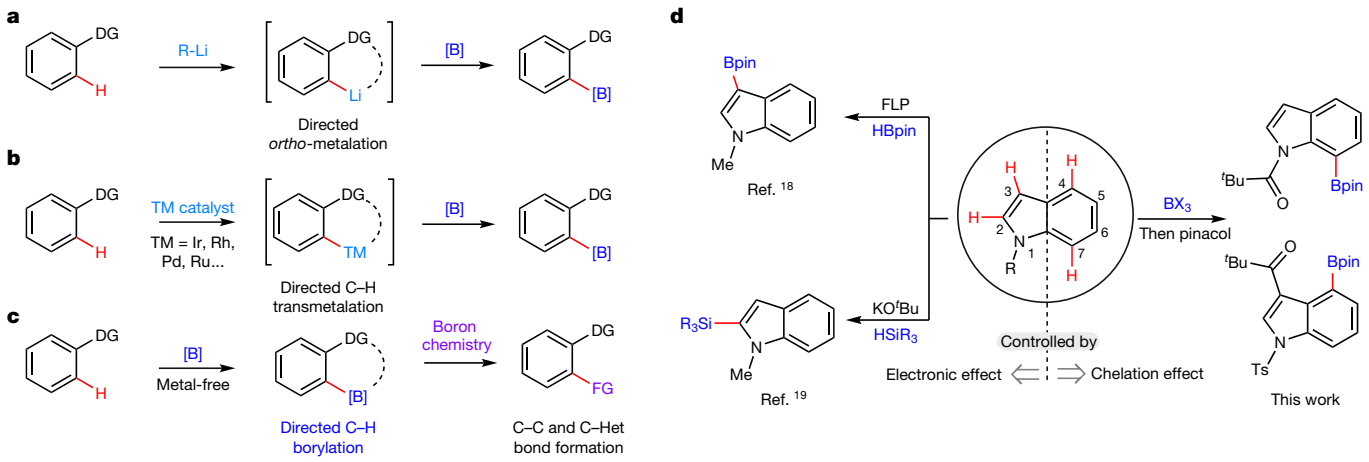


**Fig. 1 | Strategies for directed C–H bond borylation. a**, Directed *ortho*-metalation. **b**, Transition-metal-catalysed C–H borylation. **c**, Metal-free directed C–H borylation. **d**, Transition-metal-free site-selective C–H functionalization of indoles. DG, directing group; FG, functional group; FLP, frustrated Lewis pair; Het, heteroatom; pin, pinacolate; TM, transition metal.

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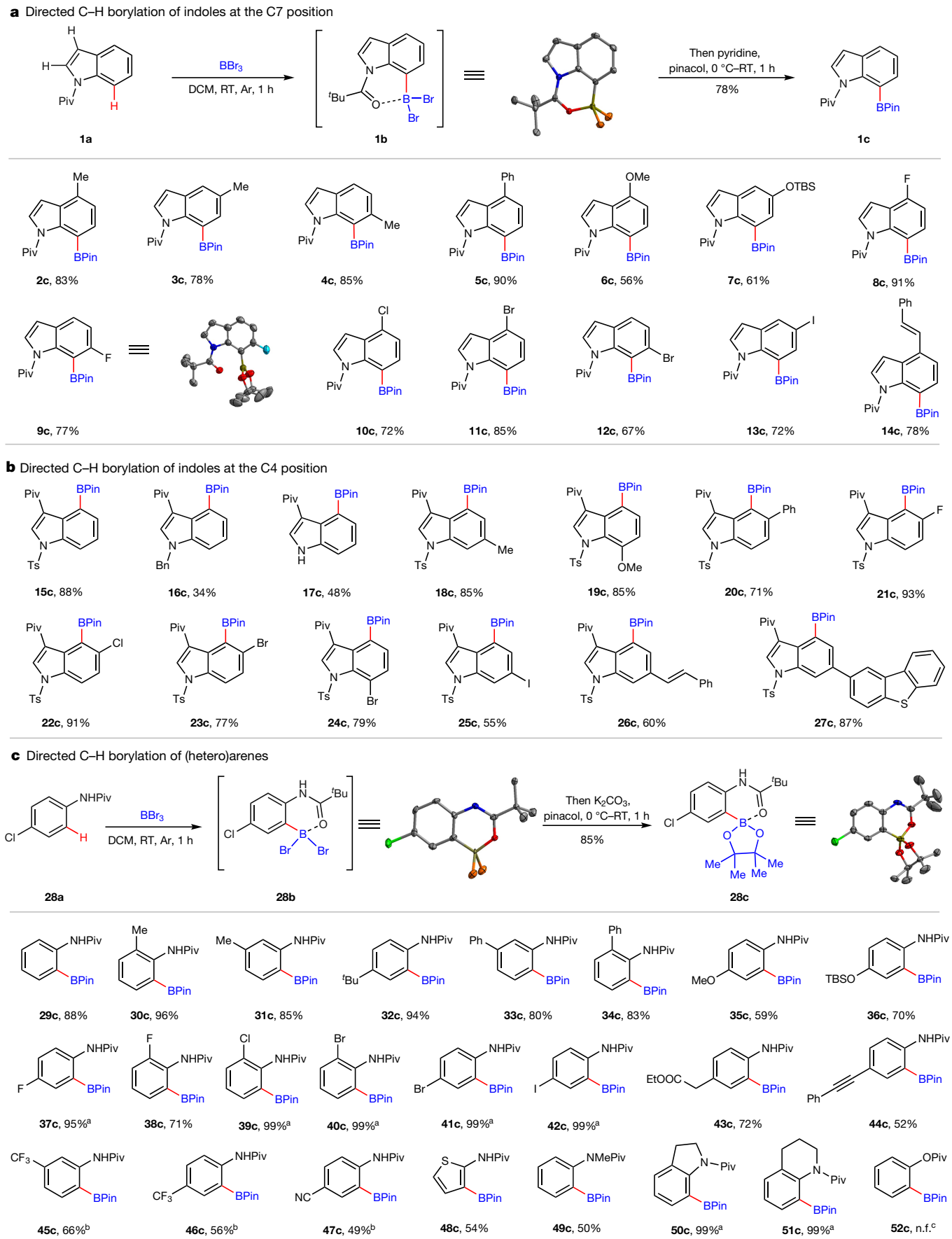


**Fig. 2** | See next page for caption.

**Fig. 2 | Substrate scope of directed C–H borylation of (hetero)arenes. a**, C7-selective C–H borylation of indoles. **b**, C4-selective C–H borylation of indoles. **c**, *Ortho*-selective C–H borylation of arenes. Reaction conditions: substrates **1**–**52a** (0.20 mmol), $BBr_3$ (0.22 mmol) in 1.0 ml of DCM at room temperature (RT), 1–9 h, under Ar; then base (**1**–**14a**, pyridine; **15**–**27a**, $Et_3N$; **28**–**52a**, $K_2CO_3$) and pinacol were added to the mixture, and the temperature was increased from 0 °C to room temperature over 1 h. [a]Without further purification by column chromatography on silica gel. [b]Using $BBr_3$ (2.0 mmol) in 0.1 ml of DCM. [c]Not formed (n.f.). Piv, pivaloyl; Ts, 4-toluenesulfonyl. The B–O coordination bonds in the products and all hydrogens in X-ray structures are omitted for clarity.

The reaction of *N*-pivaloyl indole **1a** (1.0 equiv.) with $BBr_3$ (1.1 equiv.)[26] in dry dichloromethane (DCM) without any additive for 1 h at room temperature produced the dibromoborane product **1b**, as confirmed by X-ray analysis (Fig. 2a). A C–B bond is formed at the indole C7 position, and the central B atom is tetrahedral and is chelated by O. In situ formation of the pinacol boronate ester was facile: product **1c** was isolated in 78% yield after reaction with pinacol using pyridine as a base (Supplementary Information, section 3). Indole C2- and C3-borylation products were not detected. Using these conditions, we first examined the scope of the C7-selective C–H borylation of indoles (**2**–**14a**). Indoles bearing methyl (**2c**–**4c**), phenyl (**5c**), methoxy (**6c**), OTBS (TBS, *tert*-butyldimethylsilyl; **7c**), F, Cl, Br, and I (**8**–**13c**) substituents at the C4–C6 positions underwent borylation and gave the corresponding products in 56–91% yield. In addition, indole **14a**—which bears an alkenyl substituent—was also compatible. Next, we examined the scope of C3-pivaloyl indoles[23] (**15**–**27a**) as coupling partners with $BBr_3$ (Fig. 2b), and found that they reacted with high regioselectivity to produce C4-borylated indoles. Treatment of the indole **15a**—which

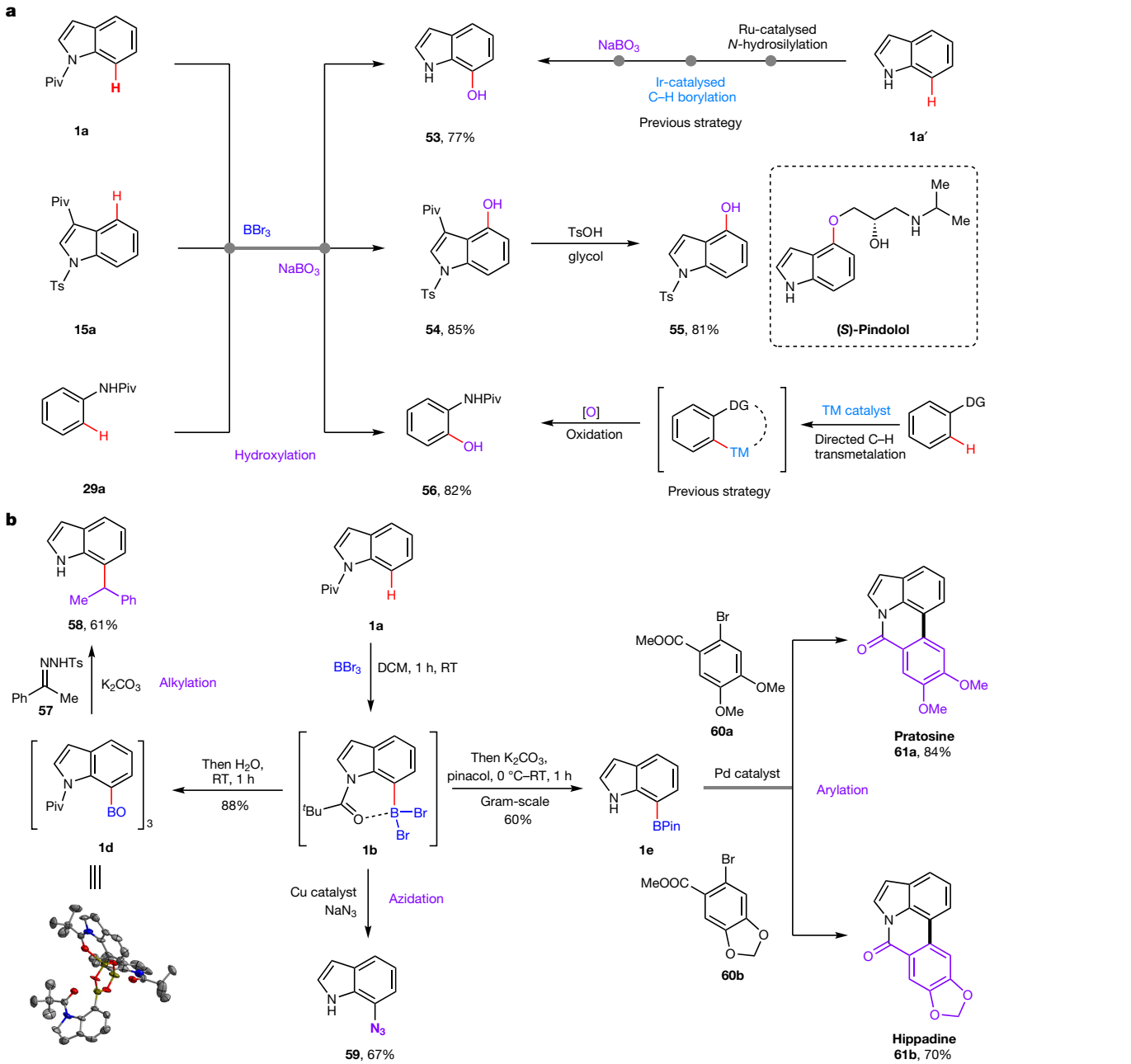


**Fig. 3 | Applications of the metal-free directed C–H borylation strategy. a**, Directed C–H hydroxylation mediated by boron species. **b**, Cascade C–H borylation/C–C and C–Het bond formation.

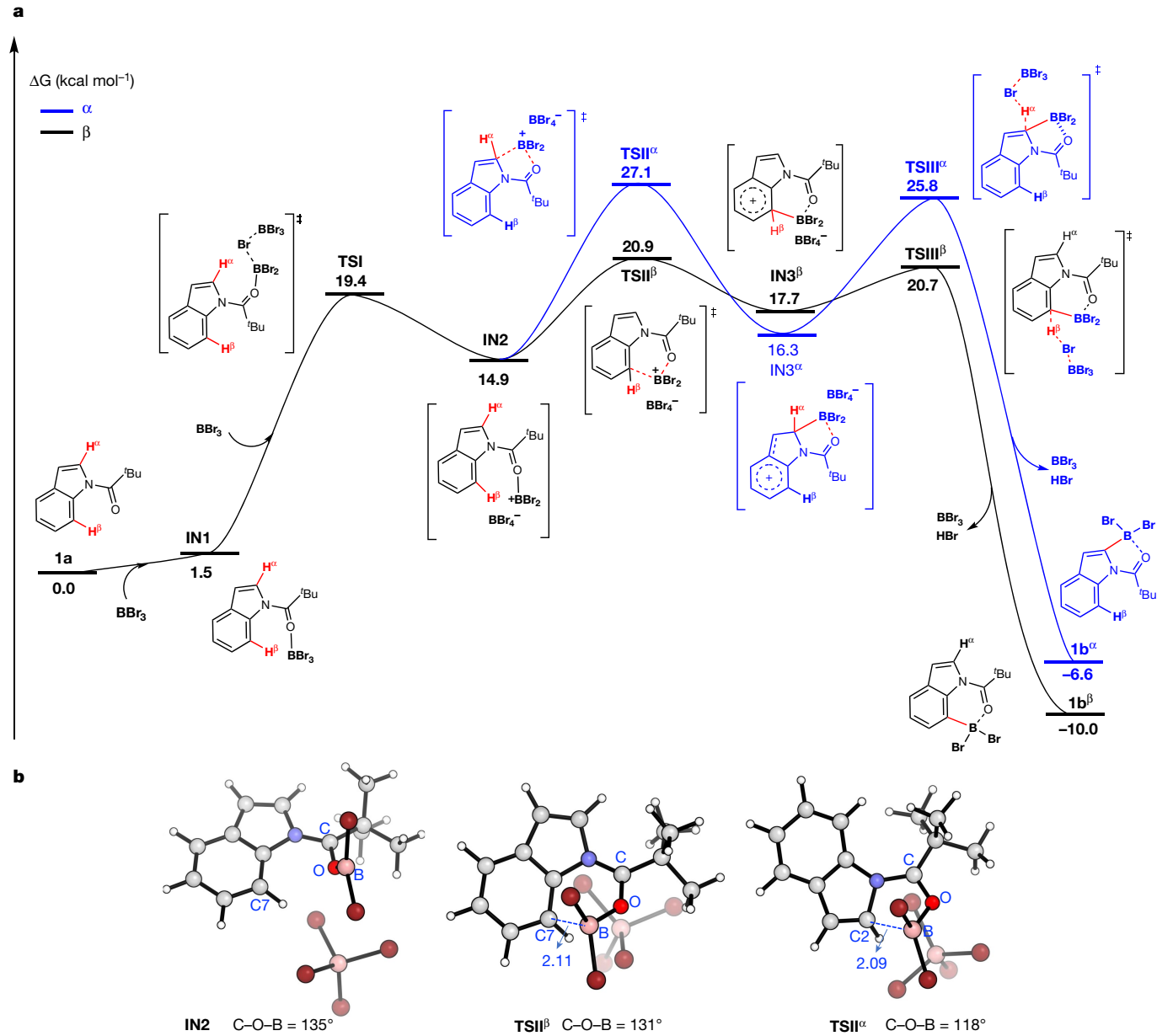


**Fig. 4 | DFT calculations for the reaction of 1a with $BBr_3$. a**, Free energy profiles for the C–H borylation of indole **1a**. **b**, Optimized structures of **IN2**, **TSII**$^{\alpha}$ (292i $cm^{-1}$) and **TSII**$^{\beta}$ (287i $cm^{-1}$). Bond lengths are in Å.

bears an *N*–Ts group—with $BBr_3$ resulted in an 88% isolated yield of the desired C4-borylation product **15c**. The *N*–Bn indole **16a** gave a much lower yield of the C4-borylation product. Notably, even the free indole **17a**, bearing an N–H group, provided the desired product **17c** in a modest yield. Various substituents—including methyl (**18c**), methoxy (**19c**), phenyl (**20c**), F, Cl, Br, I (**21**–**25c**) and alkenyl (**26c**) groups—were tolerated. Substrate **27a**, containing a dibenzothiophene moiety as an example of additional functionality, also underwent C–H borylation at the C4-position of the indole motif.

The strategy is not restricted to indoles; other arenes are also viable substrates for the reaction (Fig. 2c). When *N*-pivaloyl aniline **28a** was used as a substrate, borylation proceeded at the *ortho* C–H bond. Pinacol was added to facilitate formation of the easily isolated pinacol boronic ester **28c** in 85% yield. The intermediate **28b** and product **28c** were confirmed by X-ray analysis. This approach has a good substrate scope and is tolerant of a range of substituents in all positions of the aromatic ring. For example, *ortho*-substituted pivanilides readily produce multi-substituted aryl boronate esters, in which borylation has taken place in the *ortho* position of the amido group regardless of the electronic properties of the substituent (**30c**, **34c**, **38**–**40c**). When the pivanilide was substituted in the *meta* position, C–H borylation occurs only at the less sterically hindered *ortho* position (**31c**, **33c**). Halogens (**37**–**42c**) remain unaffected during the reaction. This system is tolerant of ester (**43c**) and alkynyl (**44c**) groups. Of particular note is the tolerance of this reaction to electron-withdrawing groups such as $CF_3$ (**45**–**46a**) and CN (**47a**); these substrates also reacted and produced *ortho*-borylated products **45**–**47c**. The reaction is compatible with heterocyclic motifs such as thiophene (**48c**), and other amides including *N*-methylaniline (**49c**), indoline (**50c**) and tetrahydroquinoline (**51c**) are also tolerated. However, the phenyl pivalate **52a** failed to react under the current reaction conditions.

Our C–H borylation strategy therefore provides a simple way to construct various C–C and C–heteroatom bonds. As a key intermediate for the synthesis of natural indolequinone, 7-hydroxyindole **53**[27] could be rapidly prepared from indole **1a** in 77% yield by a cascade C–H borylation–oxidation–directing-group-removal process, in which

oxidation can be performed directly from the dibromoborane intermediate (Fig. 3a). Similarly, the reaction of **15a** gave the C4-hydroxylation product **54** in 85% yield. By a reverse Friedel–Crafts process, the directing group in **54** was removed to provide compound **55** in good yield, providing the core of the beta-blocker (*S*)-pindolol. Compared with the reported C–H hydroxylation by transition-metal catalysts[28], we developed a transition-metal-free route for the transformation of amide **29a** to product **56** in 82% yield. In addition, base-mediated alkylation between an indole-boroxine **1d** and tosylhydrazone **57** provided the C($sp^2$)–C($sp^3$) coupling product **58** in a moderate yield[29] (Fig. 3b). Subjection of the dibromoborane **1b** to copper-catalysed C–N bond coupling conditions afforded the free indole with a C7-azide group (**59**) in a 67% yield. Treatment with potassium carbonate successfully converted indole **1a** to deprotected product **1e** on a gram scale in a 60% yield. Further cascade Suzuki–Miyaura coupling of *o*-bromobenzoates **60a** and **60b** followed by lactamization produced the natural products pratosine (**61a**) and hippadine (**61b**) in good yields[20].

To establish the mechanism of this C–H borylation, density functional theory (DFT) calculations (at the M062X/6-311++G(d,p), SMD($CH_2Cl_2$)//B3LYP/6-31G(d) level of theory) were conducted on the model reaction of indole **1a** and $BBr_3$ (Fig. 4a). The complexation of **1a** with $BBr_3$ to form **IN1** is endergonic by 1.5 kcal mol$^{-1}$ owing to the unfavourable entropy of association. Bromine transfer from **IN1** to a second $BBr_3$, through the transition state **TSI**, leads to a borenium cation[30] intermediate **IN2** with an active free energy of 19.4 kcal mol$^{-1}$. Intramolecular electrophilic attack at the C7 position of the indole by the borenium cation—via a six-membered cyclic transition state **TSII**$^{\beta}$—gives a Wheland intermediate **IN3**$^{\beta}$ with a barrier of 6.0 kcal mol$^{-1}$ relative to **IN2**. The subsequent deprotonation by $BBr_4^-$ is a facile process with a barrier of only 3.0 kcal mol$^{-1}$ with respect to **IN3**$^{\beta}$. On the basis of the computed energy profile, C–H borylation is the rate-determining step with an overall free-energy barrier of 20.9 kcal mol$^{-1}$ (for mechanistic investigation of amide **29a**, see Supplementary Information, section 6.2). Conversely, electrophilic attack at the C2 position of the indole via a five-membered cyclic transition state **TSII**$^{\alpha}$ has a much higher barrier (**TSII**$^{\alpha}$, 27.1 kcal mol$^{-1}$ compared with **TSII**$^{\beta}$, 20.9 kcal mol$^{-1}$), which is consistent with our experimental observation that **1b**$^{\alpha}$ was not detected. The selectivity of the C–H borylation of indoles for the C7 position over the C2 position is probably a result of a larger distortion energy suffered by the latter; this is reflected in the C–O–B bond angle, which is 118° in the disfavoured TSII$^{\alpha}$ (Fig. 4b). The mechanism suggests that this reaction could be applied more broadly to other arenes, and could enable the synthesis of previously inaccessible organoborons as substrates for the preparation of natural products and for drug discovery.

## Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41586-019-1640-2.


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# Methods

### General procedure for the C7-selective C–H borylation of indoles

A flame-dried 25 ml Schlenk tube was flushed with argon and charged with *N*-pivaloyl indoles (0.2 mmol, 1.0 equiv.) and dry DCM (1.0 ml, 0.2 M). A solution of $BBr_3$ (1 M in DCM, 0.22 ml, 1.1 equiv.) was added slowly under an argon atmosphere. The reaction mixture was stirred at room temperature for 1 h and then quenched with a solution of pinacol (23.6 mg, 0.2 mmol, 1.0 equiv.) and pyridine (79.1 mg, 1.0 mmol, 5.0 equiv.) in dry DCM (1.0 ml) at 0 °C. The resulting mixture was allowed to warm to ambient temperature and stirring was continued for another 1 h. Next, the solvent was removed under vacuum and the crude product was further purified by flash column chromatography over silica to give the products.

## Data availability

The data supporting the findings of this study are available within the article and its Supplementary Information. Additional data are available from the corresponding authors upon request. Metrical parameters for the structures of **1b**, **9c**, **28b**, **28c** and **1d** are available free of charge from the Cambridge Crystallographic Data Centre (https://www.ccdc.cam.ac.uk/) under reference numbers CCDC 1910131, 1910132, 1910134, 1910135 and 1910137, respectively.

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**Author contributions** Z.S. conceived the project and directed the research. K.N.H. and Y. Liang supervised the mechanistic study. Z.S. and K.N.H. wrote the paper. J.L., B.Z. and M.W. performed the experiments. X.C. and X.-S.X. performed the DFT calculations. L.J. assisted with operando infrared spectroscopy experiments. Y.Z. performed the crystallographic studies. Y.Y., Y.H., Y. Lu, J.Z. and W.-Y.S. discussed the results.

**Competing interests** The authors declare no competing interests.

**Additional information**
**Supplementary information** is available for this paper at https://doi.org/10.1038/s41586-019-1640-2.
**Correspondence and requests for materials** should be addressed to K.N.H. or Z.S.
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