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Metal–free directed C–H bond activation and borylation

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Organoboron reagents are important synthetic intermediates that play 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 opens a route to diverse substances.[2–5] Here we show a general method of directed C–H activation for site-selective C–H borylation of arenes and heteroarenes avoiding the use of metal catalysts. C7 and C4-borylated indoles are produced by a mild approach with broad functional group compatibility. The mechanism involves BBr_3 as both reagent and catalyst and is established with DFT calculations. Downstream transformation of the formed boron species to natural products and drug scaffolds highlights the potential utility of this strategy.

To achieve excellent site-selectivity, directed *ortho*-metalation (usually lithiation)[6] has been typically used to synthesize organoboron compounds, 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 to build C-B bonds (Fig. 1b).[9–11] However, these reactions rely mostly on precious metal catalysts with ligands; this requirement can be a significant limitation, particularly for large-scale syntheses and the necessity of removal of toxic trace metals in pharmaceutical products. Early studies involving directed C-H borylation without transition metal catalysts assisted by strongly coordinating groups like pyridine have been reported.[12–14] While achieving very good levels of regioselectivity, harsh conditions using high reaction temperature (up to 300 °C),[12] and aluminium salts were usually needed.[13]Replacing the transition metal-catalysed process by a mild metal-free strategy (Fig. 1c) offers an alternative pathway for C-H activation which is practical, inexpensive and environmentally benign.[15]

The indole moiety is an important structural motif,[16,17] and several recent studies report indole C-H functionalization without transition metals (Fig. 1d, left). For example, Fontaine and co-workers described a FLP-catalysed C-H borylation of indoles at the most electron-rich C3 position.[18] Grubbs and Stoltz reported a novel method to access C2-silylated indoles by KO^{t}Bu-catalysed C-H silylation.[19] Installation of pivaloyl groups at the N1 or C3 position of indoles allows selective delivery of the boron species to the unfavourable C7 or C4 positions (Fig. 1d, right). [20-25]

The reaction of *N*-pivaloyl indole **1a** (1.0 equiv) with BBr_3[26] (1.1 equiv) in dry DCM without any additive for 1 hour at room temperature produced the dibromoborane product **1b**, as confirmed by X-ray analysis (Fig. 2a). The central B atom is tetrahedral, and a C-B bond is formed at the indole C7 position chelated by O. In situ formation of the pinacol boronate ester was facile, and product **1c** was isolated in 78% yield after reaction with pinacol using pyridine as a base (see 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 Me (**2c**-**4c**), Ph (**5c**), OMe (**6c**), OTBS (**7c**), F, Cl, Br, and I (**8**-**13c**) substituents at the C4-6 positions underwent borylation and gave the corresponding products in 56-91% yield. In addition, indole **14a** bearing 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); these reacted with high regioselectivity to produce C4-borylated indoles. Treatment of the indole **15a** bearing an *N*-Ts group in the system provided an 88% isolated yield of the desired C4-borylation product **15c**. N-Bn indole **16a** gave a much lower yield for C4-borylation. Notably, even the N-H free indole **17a** provided the desired product **17c** in modest yield. Various substituents, including methyl (**18c**), methoxy (**19c**), phenyl (**20c**), F, Cl, Br, I (**21**-**25c**), and alkenyl (**26c**), were tolerated. A complex substrate **27a** underwent C-H borylation at the C4-position of the indole motif as well.

The strategy is not restricted to indoles; other arenes are also viable substrates for the reaction (Fig. 2c). When *N*-pivaloyl aniline **28a** was employed 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 only occurs 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. Particularly noteworthy is the tolerance of electron-withdrawing groups such as CF_3 (**45**-**46a**), and CN (**47a**); these substrates produced *ortho*-borylated products **45**-**47c** as well. The reaction is compatible with heterocyclic motifs such as thiophene (**48c**). In addition, 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.

Based on the diverse boron conversion, our C-H borylation strategy provides a simple way to construct various C-C and C-heteroatom

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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/DG 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 to the reported C−H hydroxylation by transition metal catalysts,[28] we developed an entirely transition-metal-free route for the transformation of amide **29a** to product **56** in 82% yield. Besides that, base-mediated alkylation between an indole-boroxine **1d** and tosylhydrazone **57** provided a $C(sp^2)$-$C(sp^3)$ coupling product **58** in a moderate yield (Fig. 3b).[29] Subjection of the dibromoborane **1b** to Cu-catalysed C-N bond coupling conditions could afford N-H free C7-azided indole **59** in a 67% yield. Treatment of K_2CO_3 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-b** and 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 (M062X/6-311++G(d,p), SMD(CH_2Cl_2)//B3LYP/6-31G(d)) 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 due to the unfavourable entropy of association. Br transfers from **IN1** to a second BBr_3 leads to a borenium cation[30] intermediate **IN2** through **TSI** with an active free energy of 19.4 kcal/mol. Intramolecular electrophilic attack at the C7 position of the indole by the borenium cation via a six-membered cyclic transition state $\mathbf{TSII}^{\beta}$ gives a Wheland intermediate $\mathbf{IN3}^{\beta}$ with a barrier of 6.0 kcal/mol relative to **IN2**. The subsequent deprotonation by BBr_4^- is a facile process with a barrier of only 3.0 kcal/mol with respect to $\mathbf{IN3}^{\beta}$. Based on the computed energy profile, C-H borylation is the rate determining step with an overall free energy barrier of 20.9 kcal/mol (For mechanistic investigation of amide **29a**, see Supplementary Information, section 6.2). On the other hand, electrophilic attack at the C3 position of the indole via a five-membered cyclic transition state $\mathbf{TSII}^{\alpha}$ has a much higher barrier ($\mathbf{TSII}^{\alpha}$, 27.1 kcal/mol vs $\mathbf{TSII}^{\beta}$, 20.9 kcal/mol), which is consistent with our experimental observation that $\mathbf{1b}^{\alpha}$ was not detected. The site-selectivity of the C-H borylation in indoles at the C7 position over the C2 position is likely a result of a larger distortion energy suffered by the latter, reflected in the ∠COB which is 118° in the disfavoured $TSII^{\alpha}$ (Fig. 4b). The mechanism suggests its broader application to other arenes and the ability to synthesize previously inaccessible organoboron as substrates for the synthesis of natural products and drug discovery.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, statements of data availability and associated accession codes are available at https://doi.org/10.1038/s41586-019-1640-2.

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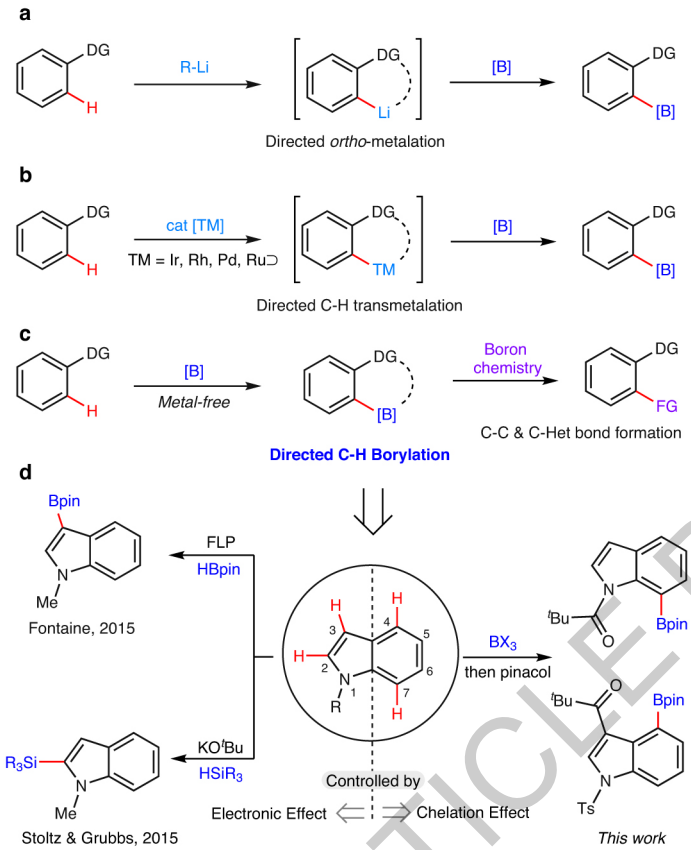

Fig. 1 | Strategies for directed C-H bond borylation. a, Directed *ortho*-metallation. **b**, Transition metal-catalysed C-H borylation. **c**, Metal-free directed C-H borylation. **d**, Metal-free site-selective C-H functionalization of indoles. DG, directing group; FG, functional group; TM, transition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

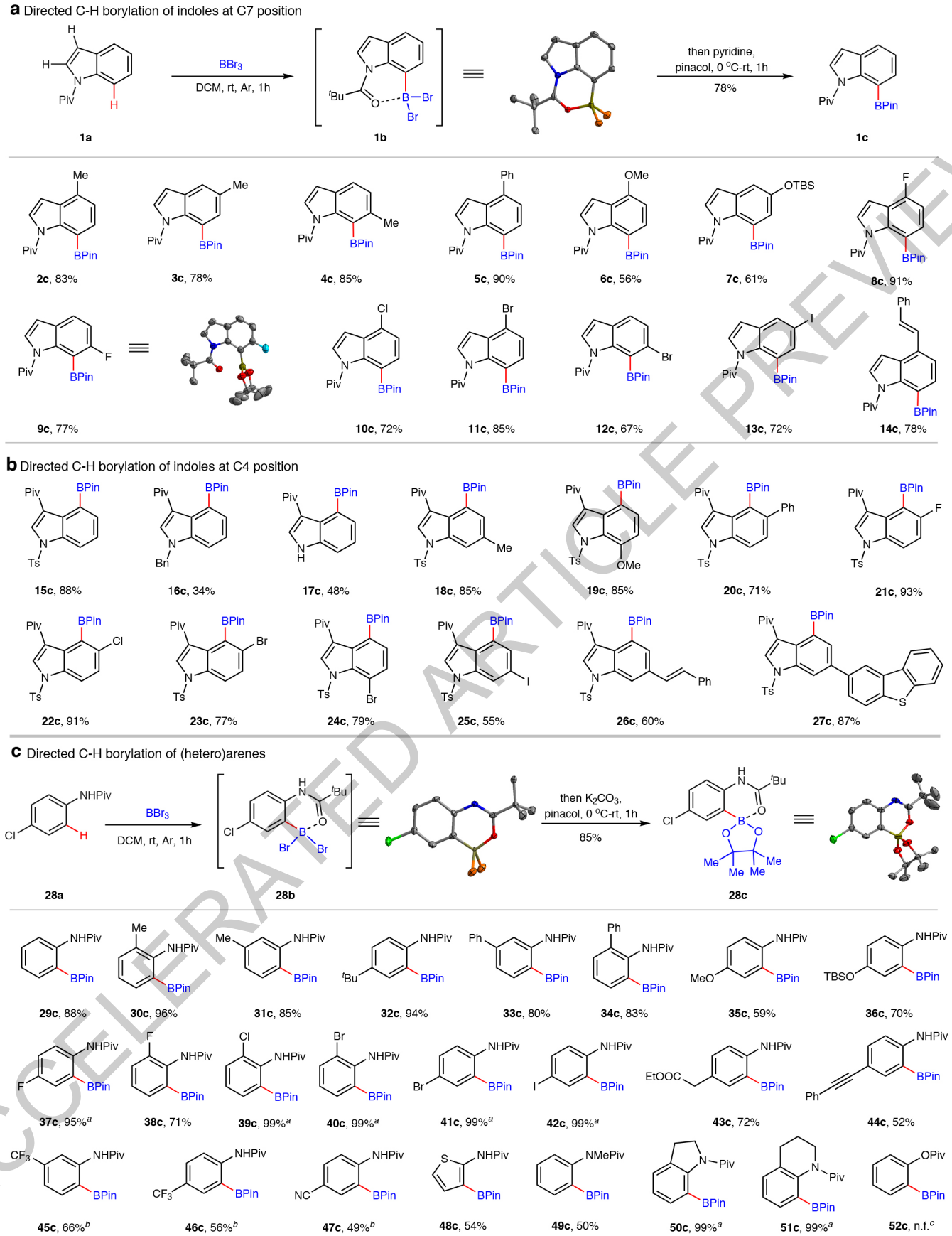

Fig. 2 | See next page for caption.

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, 1-9 hours, 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 hour. [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. Piv, pivaloyl; DCM, dichloromethane; TBS, *tert*-butyldimethylsilyl; Ts, 4-toluenesulfonyl. The B-O coordination bonds in the products and all hydrogens in X-ray structures are omitted for clarity.

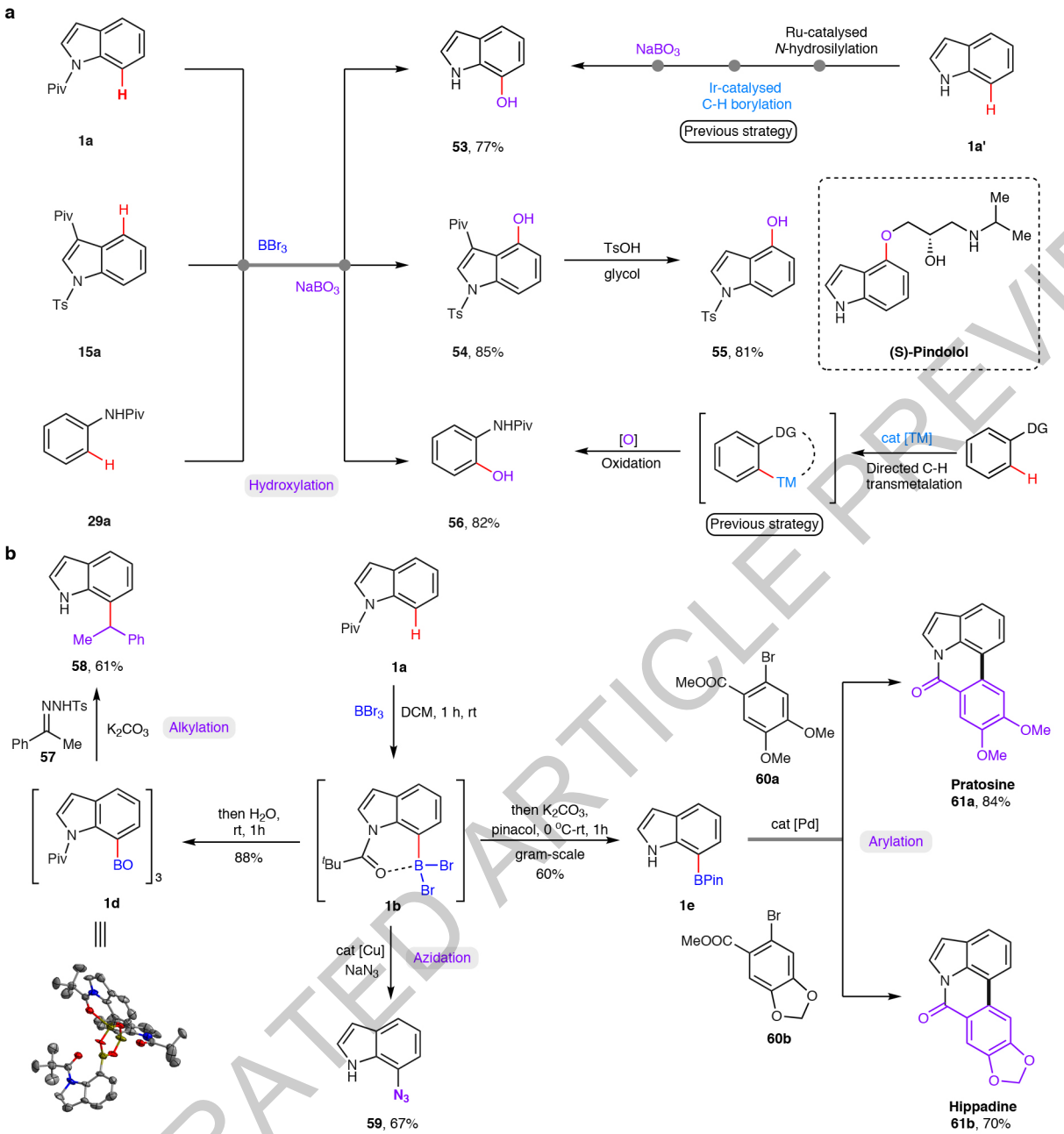

Fig. 3 | Applications of metal-free directed C-H borylation strategy. a, Directed C-H hydroxylation mediated by boron species. **b**, Cascade C-H borylation/C-C & C-Het bond formation.

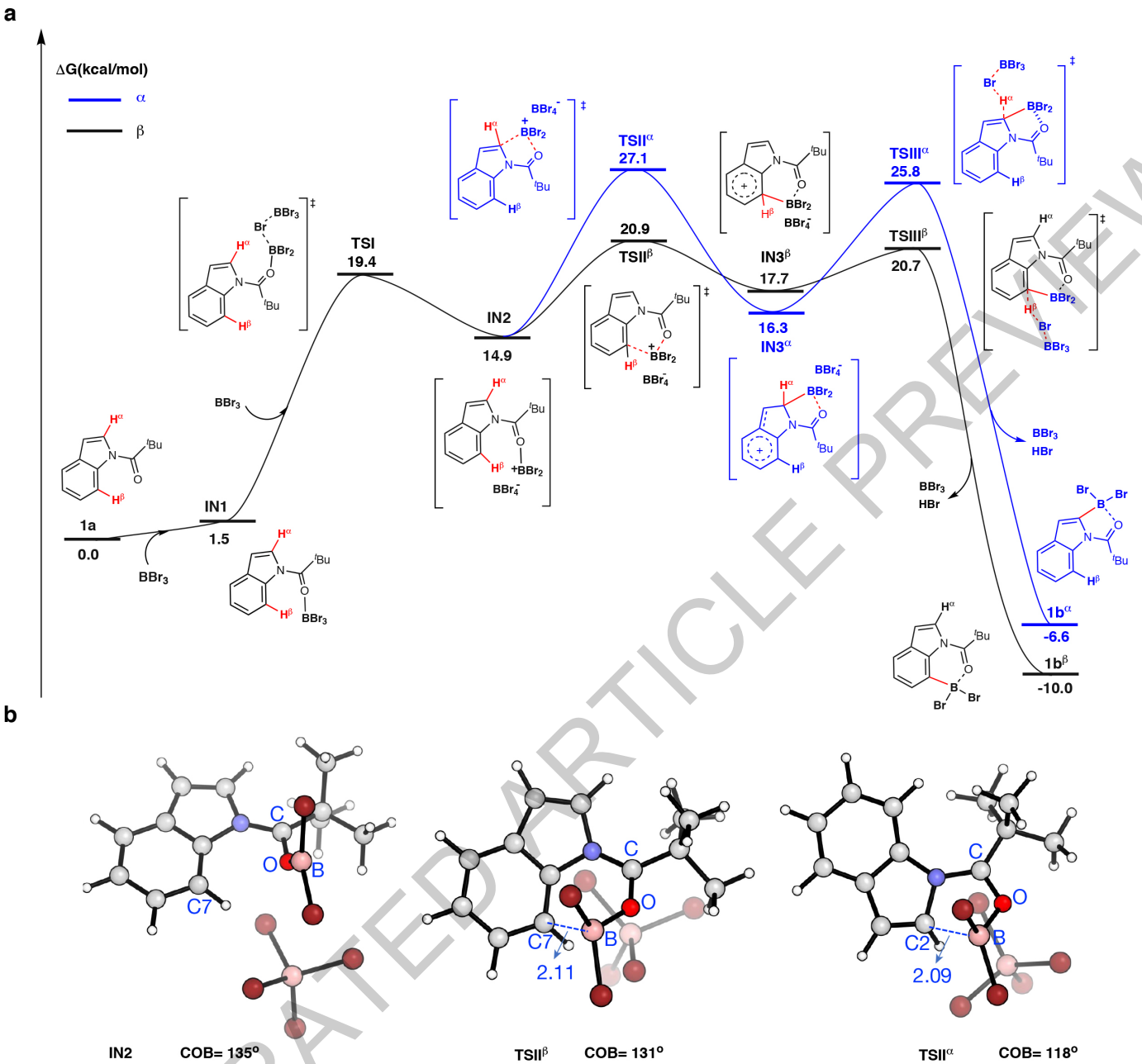

Fig. 4 | DFT calculations for the reaction of 1a with BBr_3. a, Free energy profiles for C-H borylation of indole **1a**. **b**, Optimized structures of **IN2**, **TSII**$^{\alpha}$ (292i cm^{-1}) and **TSII**$^{\beta}$ (287i cm^{-1}). BBr_4^- and all hydrogens are omitted for clarity. Bond lengths are in Å.

METHODS

General procedure for C7-selective C-H borylation of indoles. To 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 argon atmosphere. The reaction mixture was stirred at room temperature for 1 hour and then quenched with a solution of pinacol (23.6 mg, 0.2 mmol, 1.0 equiv), 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 continued to stir for another 1 hour. After that, the solvent was removed under vaccum directly 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, 1910137.

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Author contributions Z.S. conceived the project and directed the research. K.N.H and Y. L 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 IR experiments. Y.Z. performed the crystallographic studies. Y.Y., Y. H., Y.L., J.Z. and W.Y.S. discussed the results.

Competing interests The authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to K.N.H. or Z.S.

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